Aspects of the chemistry of species with carbon–polonium bonds

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I. INTRODUCTION AND SCOPE

The current volume in Patai's 'The Chemistry of Functional Groups' is devoted to the organic chemistry of compounds containing the group 16 elements, most notably the

PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0564

'middle chalcogens' selenium and tellurium. Some twenty-five years ago there were two volumes in this series of monographs on this topic[1,2]—sufficient progress has been made to warrant additional books now. The chemistry of the two lighter elements of this column, oxygen and sulfur, multiply appears elsewhere in this series as well—the intense interest and importance of these elements both in this source and elsewhere makes reference citations all but superfluous. The heaviest congener, polonium, is all but unfound in these earlier volumes and anywhere else in the series. To remedy this omission, the current and admittedly brief chapter is devoted to some aspects of this missing organic chemistry. As chronicled by earlier reviews, much remains unstudied: polonium chemistry remains a largely unexplored discipline despite some earlier well-written and well-motivated reviews, like a study within the context of general inorganic chemistry[3], a general study of radiochemical synthesis and onium ions and related neutrals[4] and of the novel, albeit quite systematic, chemistry of elements with high atomic number and nuclear charges[5], defined in this reference as $Z \geq 55$.

Despite our personal enjoyment of the theoretical aspects of our discipline, we will nonetheless limit our attention almost exclusively to the experimental literature where we acknowledge that measurements have been few, calculational data are sparse and that theory and experiment have rarely studied the same polonium-containing species. Despite our enthusiasm for chemical analysis, we find it here almost totally limited to paper and thin layer chromatography and radiochromatography. Despite the general power arising from the interplay of structure and energetics, we will nonetheless limit our attention almost exclusively to chronicling what carbon–polonium bonded species have been observed. Plausible structural assignments have often been given as well, mostly by use of isoelectronic reasoning on the related tellurium species. However, we must emphasize the word 'plausible' because spectroscopic and/or crystallographic determinations of polonium-containing species are almost always absent because of the absence of suitable samples. Understanding of energetics whether defined by enthalpies and Gibbs free energies of formation, or even that 'compound A rearranges to form B and so B is more stable than A' are all but absent.

This is not to say that calculationally inclined theoretical chemists have been unconcerned about the structure and energies of polonium-containing species. Theoretical studies of compounds of the middle chalcogens selenium and tellurium have often been extended to corresponding species containing either sulfur and/or polonium: these investigations are natural extensions up and down the periodic table (i.e. S $\leftarrow$ Se, Te $\rightarrow$ Po). Recent (chronologically arranged) calculational studies include comparisons of heteroatoms and dipole moments[6], resonance structures, oxidation states and acidity[7] (cf. sulfide, sulfoxide and sulfone analogs), unexpected chalcogen-rich heterocycles[8], uranium(VI) bis(imido) chalcogenide complexes[9] and proton and methyl cation affinities of main group hydrides[10]. Then we sadly recall that there are no corroborative, or even comparative, experimental data for these polonium species to accompany those of other chalcogens. As such, these papers and their conclusions will be ignored in the current study.

Some simpler questions, at least conceptually, have also been addressed by the theoretical and computational community. For example, consider the spectroscopic and thermodynamic constants associated with small molecules from group 14 and group 16. These are valence isoelectronic counterparts of CO and CO_2, two of the best and widest studied molecules of any type. These CPo and CPo_2 species are discussed[11,12], and again, experimental data are absent. (Were one value known for these seemingly simple diatomic and triatomic molecules, we could plausibly use the simple semiempirical equality relating dissociation energies of 10-valence electron AB and 16-valence electron AB_2 species[13,14] to derive the other.) The reader should note that we implicitly spoke of gas-phase diatomic and triatomic molecules. Nonetheless, many binary species formed from group 14 and 16 elements are 'naturally' solids under conventional conditions, such as the oxides and

sulfides of tin and lead. Using classical techniques for synthesis and characterization, no carbon polonide (polonium carbide) is formed from direct combination of the elements[15].

Consider now the question of the length of the various bonds containing polonium (and of course, other interatomic distances in larger molecules). While such Po-containing bonds have been studied by theorists, many times in fact, experiment is absent for corroboration, and indeed, the findings are sorely contentious[11, 12, 16–18].

A key problem in studying polonium and its compounds is seen to be both elementary and elemental; a solution seemingly evades us. As found for all of the manifold isotopes of polonium, having masses of the exceptionally large range of 187 to 220, inclusive[19], the element is inherently highly radioactive, it is 'hot'. Some seventy years ago, however, there was an unsubstantiated spectroscopic claim of a stable isotope of polonium[20]. Indeed, had this paper been correct, we are convinced that this chapter, indeed all of polonium chemistry, would have been more substantial. The element polonium and all of its compounds are therefore quite inaccessible as well as unavoidably toxic. This discourages experimental investigation because of the inseparably coupled concerns of undesired inconvenience, expense and danger. The radioactivity also complicates experimental studies because the emitted radiation damages the species itself. Not only is there 'direct impact' and kinetic energy transfer from the decaying nucleus to the rest of the sample *per se*, but also there is heating involved when the radiation is absorbed that will decompose thermally labile compounds. More precisely, this radiation damage is a 'multiple whammy' in that the most commonly studied isotope of polonium (^{210}Po) is generally synthesized *in situ* by neutron irradiation of a formally related compound containing bismuth, polonium's neighbor in the periodic table that is naturally found solely as the nonradioactive ^{209}Bi. Let us note that strictly speaking, this statement is not true but its absolute validity, in fact, is irrelevant. Recently it was convincingly shown that ^{209}Bi has a half-life of *ca* $2 \cdot 10^{19}$ years, i.e. rather much larger than a billion times the generally accepted age of the universe[21]. What remains surprising, if not particularly relevant save acknowledging our frustration here however, is that 83 protons in a nucleus can result in an essentially 'infinitely' stable arrangement while any arrangement of 84 protons always results in a rather short-lived isotope (even by human standards of elapsed time). The neutron irradiation can additionally damage the sample in the same way as the emitted radiation accompanying the subsequent transformation of the intermediate ^{210}Bi to ^{210}Po. Finally, in that the oxidation state of Bi is almost always 3 or 5, this is chemically incompatible with the even numbers expected for the chalcogen Po, 2, 4 or 6. That is, chemically reactive intermediates (both radicals and ions) will be formed accompanying any desired, cold closed-shell organopolonium compound produced. This suggests 'high energy' products (even as defined by conventional chemistry) will be formed because these reactive intermediates that accompany the synthesis of the polonium generally precede, *in situ*, the synthesis of any conventional organometalloid compound of interest.

We note now this problem would be, in part, ameliorated by using a more stable (more long-lived, less radioactive) isotope of polonium than ^{210}Po and synthesizing the compound subsequent to synthesizing and isolating the element[22, 23], but this strategy has largely been ignored by both the radiochemically and synthetically inclined communities.

Alternatively, elemental polonium can be synthesized and separated prior to the chemical synthesis, but then tracer and carrier techniques must be used that are not part of most organic chemists' skill set. Tellurium is the most sensible tracer, used as the radioactive isotope ^{127}Te, and even if tellurium and polonium chemistry parallel (usually assumed but again, inadequately documented), tellurium chemistry has problems. These studies are troubled by the horrible smell and chemical toxicity associated with many of the simplest compounds of tellurium, most notably most those that are derived from H_2Te and the weakly basic Te^{2-} and TeH^-, although clearly tellurium organic chemistry is rich enough

to warrant the current volume it shares with selenium. A quick perusal of organopolonium chemistry shows it is dominated by arylated species as opposed to those with alkyl or acyl groups. As such, the chemistry of these tellurium-containing anions seemingly has not helped us as they are not particularly relevant as they would for alkyl and acyl derivatives such as ethers, esters and their heavier chalcogen analogs; simple aryl halides generally do not undergo facile halogen displacement reactions unlike alkyl and acyl halides.

We remind the reader that polonium has a high nuclear charge (+84), and accordingly with its many electrons, this element lies in the bottom reaches of the periodic table. Accordingly we remind the reader that this is discussed in Reference 5, spin orbit and relativistic effects are unavoidably large and so, both the beginning chemistry course description of an s^2p^4 electron configuration for a naturally divalent atom with six valence electrons, and standard quantum chemical computational protocols for an atom with a ^{3}P term symbol are unavoidably confounded. An example of this is the formally simple crystal structure of the element. Unlike the almost one hundred other elements studied crystallographically, the most stable form (at STP) of polonium, α-Po, has a simple cubic structure[24, 25] with a largely unprecedented 6-coordination for neutral polonium. We recall that the heavier chalcogens form stable hexafluorides with 6-coordinated S, Se and Te and so probably does polonium (cf. Reference 23); there are no hexahydrides or hexachlorides and only tellurium forms the hexamethyl derivative[26]. As such, a lattice composed of only polonium atoms so joined to six other polonium atoms seems simultaneously simple, strange and suspect. We now note that there is another elemental form, the so-called β allotrope that is the more stable at higher temperatures[27]. We also note no allotrope of any other element has this simple cubic structure of α-polonium. To perform this crystallographic measurement the use of either of two uncommon methodologies was required. The first required a macroscopic sample that had to be cooled because of radiation-derived self-heating and resultant self-contamination and self-destruction of the crystal lattice[24]. This study used the most available isotope of polonium, ^{210}Po. The other study[25] used a mixture of two much longer-lived, but much more inaccessible and still significantly radioactive, isotopes of polonium ^{208}Po and ^{209}Po. This simple but hard-won simple cubic structure[28] has been related to the ring and chain structures of the lighter chalcogens (sulfur, selenium and tellurium) that are also solids and even to the common diatomic form of elemental oxygen, normally gaseous, but also requiring cooling to form a crystallographically relevant solid. In general, going up a column in the periodic table for main group elements usually is accompanied by decrease of coordination numbers and loss of metallic character. We recall metallic lead and tin (with two nearly equally stable forms, 'white' and 'gray', differing[29] by *ca* 2 kJ mol^{-1}), germanium and silicon (both stolidly tetrahedrally based solids under essentially 'human conditions'[30]) up to carbon (again with two nearly equally stable forms, diamond and graphite, differing[29] by *ca* 2 kJ mol^{-1}). A convincing explanation for this cubic structure of elemental polonium has yet to be achieved—indeed, this subject like so much else for polonium is contentious; some references to the condensed matter (solid state) physics literature are given now without details (e.g. References 31–35).

Given all of these uncertainties, is it obvious how to describe C–Po, Po–H and Po–O bonds? These are the three most important building blocks for organopolonium chemistry should we make analogies with that of the majority of the known organochalcogen species. Our problem is hardly lessened should we ask only about C–Po and Po–H bonds; we note that because of their mode of synthesis, many organopolonium compounds have Po–halogen (almost exclusively Po–Cl or Po–Br) bonds as well.

We now proceed, more to chronicle than to explain organopolonium chemistry. It is now sadly acknowledged that from the above, it is evident that so many of the techniques of the armamentarium of the organic chemist are not available for this study. May we now add two more instrument-driven technical issues, or should we say limitations. The first

notes that polonium—as its most commonly investigated A (sum of protons and neutrons) = 210 isotope, ^{210}Po—cannot have a nuclear spin equal to $^1/_2$ because A is even and so one more powerful technique, namely NMR, is also of lessened use for the student of polonium chemistry. In fact, the nuclear spin of this isotope is 0[36] and so this isotope is invisible to NMR as opposed to the plausible alternative integer values $I \geq 1$ with merely undesired signal broadening in NMR and the possibility of NQR. And finally, seemingly no use has been made for organopolonium chemistry to date of Mössbauer spectroscopy, that wonderful technique that taught the inorganic chemist much about noble gas compounds[37–39]. This was through the radiochemical association of xenon with its special iodine isotope counterpart, ^{129}I: we seemingly have no such comfortable pillow here interrelating ^{210}Bi and ^{210}Po and hence their compounds. After all, the chemistry of iodine-containing anions such as IO_4^- and ICl_2^- is well-established and so immediately relates to isoelectronic xenon-containing neutral species such as XeO_4 and $XeCl_2$ (and thereby relates to the more stable, easier to make, and thereby more commonly studied XeF_2). However, there are no such organobismuth anions to help us in understanding isoelectronically related polonium-containing species. This statement is however not completely correct. We note the preparation of the yellow hexaphenylbismuthate anion $(Ph_6Bi)^-$ that is synthetically derived from the blue pentaphenyl bismuth (Ph_5Bi)[40]. The colors are explicitly noted now to herald the unusual nature of these species as they would most plausibly be colorless given the absence of obvious chromophores. Additionally, one must be careful in reading: on searching in SciFinder® for 'Mössbauer' and 'polonium', one finds a reference sharing both words but that relates to a study of a set of species with an α-polonium lattice, namely $[Cp_2^*M][M'(dca)_3]$ with diverse metals, trivalent M and divalent M′ ($Cp^* \equiv C_5Me_5$, dca $\equiv [N(CN)_2]^-$, M = Fe, Co; M′ = Mn, Fe, Co, Ni, Cd[41]).

II. DIALKYL POLONIDES

In this section we discuss species of the generic formula R_2Po, there being no data on compounds of the type RPoH nor R_2Po_2 and so our study does not parallel that of dialkylselenides and tellurides accompanied by selenols and tellurols, and diselenides and ditellurides, nor the much more common sulfides, thiols (mercaptans) and disulfides.

A. Nucleophilic Displacement Reactions

We start the more detailed chemical discussion of this chapter with alkyl derivatives because they are in many ways simpler than their aryl counterparts. In principle, species with the generic formula R_2Po may be expected to be simply synthesized using nucleophilic displacement, i.e. S_N2, reaction (equation 1)

$$2RX + Po^{2-} \rightarrow R_2Po + 2X^- \quad (1)$$

Related chemistry has been observed. Paralleling the accompanying tellurium species[42], the simple binary salt Na_2Po was synthesized by sequentially reacting elemental polonium with NaOH to form Na_2Po_2 and then reducing this dipolonide salt with $Na_2S_2O_4$ in the next step. Dimethyl and dibenzylpolonide were accordingly synthesized by the simple alkylation of the Na_2Po product. Unfortunately, no reaction was done nor subsequently reported with Na_2Po_2 or any other Po_2^{2-} salt. As such, we are deprived of information about the related organic dipolonide, R_2Po_2. We wonder if this species can be isolated or does it immediately decompose into elemental polonium and the corresponding polonide, R_2Po. There is no evidence from experiment to guide us. Indeed, save the various phases

of elemental polonium, Po−Po bonds are all but unknown to the experimentalist. We also note (with admitted 'sour grapes') that any accompanying presence of tellurium allows for the possibility that the dichalcogenide chemistry would have been dominated by the mixed anion, $(PoTe)^{2-}$.

B. Bioalkylation (Plausibly Electrophilic) Displacement Reactions

Dimethyl polonide has also been suggested as the product of bioalkylation reactions in diverse biological media[43] including seawater[44]. This assertion was made on the basis of production of a volatile polonium-containing species whose synthesis is thwarted when reactions of the powerful, if not quite ubiquitous, biomethylating agent methylcobalamin were inhibited. We note the absence of corresponding bioethylation reactions, or indeed, reactions involving benzyl or other 'large' alkyl groups[45]. We note the Te/Po analogy again and, as with numerous other metalloids and metals, we may assume this purported biosynthesis of an organopolonium species to proceed through an electrophilic displacement or S_E2 reaction.

C. Radical Reactions

We note the synthesis of a volatile polonium species by the reaction of gas-phase ethyl radicals with polonium that had been formed as a radioactive decay product of solid thorium. In the particular, the following radical reaction[46] was suggested (equation 2),

$$2Et^{\bullet}(g) + \text{'Po(s)'} \rightarrow Et_2Po(g) \tag{2}$$

Admittedly, the chemical identities of the polonium, both as starting material and as final product, are ill-defined. That is, we cannot preclude the initial existence of thorium polonide paralleling known metal polonium species. Also, while Et_2Po is most assuredly precedented by the stable and isolable, dialkyl derivatives of selenium and tellurium, we note the existence of stable, but not isolable, monoalkyl derivatives of these elements, $RSe^{\bullet}$ and $RTe^{\bullet}$. These radicals are readily formed by homolysis (i.e. thermolysis and/or photolysis) of the more conventional dialkyl monochalcogenides or their dichalcogenide analogs. As such, the product from the reaction of gas-phase ethyl radical with solid polonium need not be Et_2Po as opposed to $EtPo^{\bullet}$.

We recall a study[22] of the high volatility of electroplated polonium formed from acetic acid solution. These authors noted an initially formed 'bright deposit' and yellow solution of elemental and complexed polonium that darkened and then disappeared. The authors suggested 'the formation of a volatile methylpolonium formed by the reaction of the elementary polonium with free radicals, liberated in the solution, or at the electrode.' The solution-phase organopolonium species (suggested to be $Po(OAc)_4$ and related ions with their Po−O bonds) formed by complexation reactions of preformed aqueous polonium hydroxide solution chemically decompose with subsequent rapidly blackening and continue darkening as a precipitate forms on standing. This darkening was attributed to radiation-induced carbonization of the initially formed polonium-containing acetate or corresponding ion. Related formation of formate, tartrate and cyanide was also reported with associated darkening but no concomitant volatilization. This makes sense: While the acetate would be expected to form acetoxy radical either radiochemically or electrochemically and then the acetoxy radical rapidly decomposes into methyl radical, no analogous radical would be expected from the other anions or their polonium complex. One may now ask about other anions such as propionate that would likewise form ethyl radicals

and so volatilize the polonium, and diversely substituted benzoates that would form the relatively stable aryl polonium species (see below). However, we sadly know of no current investigators that we can convince to perform these new experiments.

III. ARYL POLONIUM DERIVATIVES

A. Unhalogenated Species and their Chlorides and Bromides

There are several generic synthetic approaches to aryl polonium chloride and bromide derivatives, Ar_mPoX_n (X = Cl, Br). We will not attempt to be systematic or complete as to which compound is produced by which method. Furthermore, without any disrespect to the original authors or distress of the curious reader, we are loathe to discuss the systematics[47,48] of the product distribution or even total yield as a function of Ar, X, *m* and *n* (note *n* can equal 0). As noted[47], yields of substituted phenylpolonium compounds have been related to bond energies in the parent bismuth compounds, which in turn are related to the Hammett σ_p constant of the substituents on the phenyl ring; in the current case *o*-Me, *p*-Cl and *p*-Br were compared. However, we are pessimistic as there are few enthalpy of formation data for organobismuth compounds of any type, or even indirect thermochemical inferences[49]. We are loathe to make the analysis suggested above as triphenylbismuth is the sole relevant species in the organometallic literature. Relatedly, we recall[48] discussion of the stability of conjugated ions is offered for the understanding of mesitylpolonium derivatives. However, we fail to see any conjugation save that in the benzene ring of the mesityl group, and no more in this case than in any other substituted phenylpolonium species that is also discussed in the current section. This was but rarely given by the original authors of the papers cited. Perhaps with greater optimism than we have, a summary of classical aryl polonium species and associated yields was earlier given by Nefedov and his coworkers[4] as befits these authors' combined radiochemistry and synthetic chemistry orientation.

Likewise unreported in this chapter, and unameliorated elsewhere, is any direct structural determination or confirmation save analogy to the isoelectronic tellurium species. No such information was given by the original authors. As found in the primary references we cite, the separation of the diverse polonium species from each other, and occasionally any precursor or carrier, very often involved solely the use of paper and thin layer radiochromatography. It is largely this lack of information, both synthetic and structural, that encouraged our lack of attention to detail. The data are simply too incomplete to encourage us to try to derive chemical regularities or even attempt explanations. Indeed, we generally lack information as to simpler, more classic, species to use as analogies or guidelines. To be more precise, the only aryl selenium and aryl tellurium species for which there is direct (i.e. calorimetric) information[50] as to their energetics are diphenyl selenide and telluride, the corresponding dichalcogenides, and the halogen containing phenyl selenium bromide and tribromide. There are no such data on any selenium or tellurium compounds with any substituted phenyl group.

We note one more reason for our pessimism—not enough is known about substituted phenyl derivatives of elements other than selenium, tellurium and *a fortiori*, polonium. Suppose we wanted to discuss the energetics of aryl halogen compounds, and making this discussion even simpler, consider the isomeric tolyl halides, more commonly known as the monohalotoluenes and we wish to consider relative isomeric stabilities in terms of enthalpies of formation of organohalogen species[51]. Let us start the discussion with the fluorinated species. The sole data for the *o*-species is from the 'prehistory' of the discipline[52]. There are no experimental thermochemical data at all for the *m*-isomer. The data for the *p*-isomer are trustworthy[53], but with what do we compare it now? We admit

now that Swarts[52] also gives data for this species, and indeed there is a $30\,kJ\,mol^{-1}$ disparity for the two results. There is a common, quite trustworthy, reference[54] for all three chlorotoluenes, and the three values are found to be the same—within the measured uncertainties of $ca \pm 10\,kJ\,mol^{-1}$. These data are therefore without use for our study. A recent quantum chemical study[55] corroborates the near equality of the enthalpies of formation of the three fluorotoluenes, and likewise of the three chlorotoluenes. For the bromotoluenes, there are no relevant data for the *o*- and *m*-isomers, and so, how useful for us is just the *p*-isomer[56]? Finally, we turn to the iodotoluenes and rejoice that there are data for all three isomers[57]. It is found that the *p*-isomer is the most stable and that the *o*- and *m*-isomers have quite indistinguishable values. Then it is noticed that within recorded uncertainties, all three values can be assumed to be the same. We are able to conclude that essentially nothing can be learned from this exercise.

So, let us return to synthetic concerns and methodology. The first general approach starts with elemental polonium that has been admixed with tellurium carrier. From this, there is the synthesis of some Po^{IV}-containing inorganic species, typically $PoCl_4$ or $PoBr_4$, that is most generally likewise accompanied by the corresponding tellurium halide. In order of reaction steps, the tellurium and polonium halides are reduced by appropriate aryl Grignard reagent to the corresponding divalent chalcogen derivative and additionally, the halogen is replaced by an aryl group. This results in the diaryl polonide, Ar_2Po. Subsequent rehalogenation then yields the desired diarylpolonium dihalides Ar_2PoCl_2 and Ar_2PoBr_2.

The alternative method uses arylbismuth derivatives of the type Ar_3Bi, Ar_3BiX_2 (almost always X = Cl, Br) and even Ar_5Bi which are irradiated with neutrons to transmute their bismuth nuclei into polonium, some classical halogenation chemistry often follows, and thereby convert organobismuth into organopolonium compounds.

For a composite of these synthetic approaches wherein one or both methods were used, diverse aryl groups have been investigated including phenyl[58, 59] (i.e. the archetypal unsubstituted species); tolyl (all three ring-substituted methylphenyl, *o*-[47, 60], *m*-[60] and *p*-[60, 61]), *p*-anisyl (*p*-methoxyphenyl)[62] and *p*-ethoxyphenyl[63], halophenyl[47] (both *p*-chloro and *p*-bromo), *p*-xylyl (2,5-dimethylphenyl)[60, 64, 65], mesityl (2,4,6-trimethylphenyl)[48, 66], *p*-sulfamoylphenyl[67] and 1-naphthyl[68, 69]. These studies resulted in arylpolonium species mostly of the generic types $ArPoX_3$, Ar_2Po, Ar_2PoX_2 and Ar_3PoX where some or all of these are found for a given choice of Ar and X. ArPoX, Ar_2PoO and Ar_4Po derivatives have also been observed; compounds with hexavalent and hexacoordinated polonium such as Ar_4PoX_2, Ar_5PoX and/or Ar_6Po remain unknown.

B. Fluorides and Iodides

Organopolonium species corresponding to the above chlorides and bromides where X = F and I are generally absent. We recall the well-known comparative hyperactivity and inertness of the corresponding diatomic halogens F_2 and I_2, respectively; simple fluorination and iodination with the respective diatomic halogen is rarely observed. That organobismuth fluorides and iodides, in fact, can be obtained from exchange reactions involving other halides only in principle ameliorates the problem because of comparative lack of study of these last organometallic halides. The paucity of references offering comparative data on diverse polonium halides still remains. Examples of organobismuth fluorides and the corresponding polonium fluoride include those of the *p*-xylyl and isomeric tolyl species[65]. Halogen exchange reactions with already formed organopolonium halides[70] plausibly provide an alternative synthetic route to polonium fluorides and iodides but this approach has rarely been studied. An example[59, 71] is the reaction of triphenylpolonium chloride with KI to form Ph_3PoI by simple halogen exchange.

C. Other Aryl Polonium Species

For all four of the lighter chalcogens (O, S, Se, Te), the literature gives us ample examples of 'onium' ion salts with the generic cation, R_3Ch^+ (R both 'aryl' and 'alkyl', Ch = chalcogen), and for tellurium, there are even well characterized[71, 72] 'per-onium salts' such as $Ph_5Te^+X^-$ where $X = ClO_4$ and $[3,5\text{-}(CF_3)_2C_6H_3]_4B$ (the uncomplexed cation Me_5Te^+ has been observed[72] in the gas phase as a fragment ion in the mass spectrum of Me_6Te). It is perhaps poignant that the sole element in the periodic table with 'onium' as part of its name seems to lack definitive examples of 'onium' and 'per-onium' species. There is one possible contender for a study involving Ph_3Po^+. This is the 1:1 complex of Ph_3PoCl (with isoelectronic Te carrier) with $HgCl_2$ in which a $[HgCl_3]^-$ salt may plausibly be invoked because the product was chromatographically immobile[59]. Alternatively, a nonstoichiometric mixed salt, $[(Ph_3Po)_x(Ph_3Te)_{2-x}{\cdot}HgCl_4]$, is also consistent with the data; salts of both types of chloromercurates are known for pure triphenyltellurium species[73].

As said above, polonium atoms as synthesized by a nuclear reaction are generally 'hot'. It was thus proposed that so-produced sufficiently energetic atomic Po would interact/react with fullerenes[74]. As experimentally reported by the same authors[75], targets for neutron irradiation composed of C_{60} and As_2S_3, and of C_{60} and Sb_2O_3 upon neutron irradiation resulted in products identified as endohedral and/or heterofullerene C_{60} compounds with Se and Te, respectively. Soon thereafter a study was reported by them[76] on a bismuth containing target and formation of an endohedral $Po@C_{60}$ compound was described. Group 15 to group 16 nuclear interconversion (transmutation) and *in situ* chemical trapping seems to be a powerful synthetic protocol.

We close this section by noting two synthetic approaches that work well for organotellurium derivatives but very poorly for the desired polonium species. The first is reaction of diphenyl mercury with the elemental chalcogen[77]. The lack of success was ascribed to weak C–Po bonds in the resultant diphenyl polonium. We anticipate the mercury chalcogenide to be the accompanying product rather than elemental mercury and now note the comparative instability predicted for solid HgPo compared to HgTe[78]. The second and likewise incompletely described synthesis[76] involves reaction of the chalcogen tetrachloride with anisole. Ascribed again to the weakness of C–Po bonds compared to C–Te, we wonder about the relative electrophilicity of the activated chalcogen cations, $TeCl_3^+$ and $PoCl_3^+$, that are plausibly the reactive species in this case.

IV. POLONIUM COMPOUNDS OF OTHER TYPES

Polonium has long been known to form[79, 80] volatile compounds with diverse complexing and chelating agents such as 8-hydroxyquinoline; thiourea and its *N*,*N*′-diphenyl derivative, and thiosemicarbazide and its N^1-phenyl derivative; diphenylcarbazone (PhNHNHC(O)N=NPh), its sulfur counterpart (also known as dithizone), and the 'saturated' diphenylcarbazide (PhNHNHC(O)NHNHPh). Bis(dithiocarbamates) have also been popular[78, 79, 81]. All of these reagents form related species (of diverse volatility) with numerous metals and metalloids and so their complexing reactivity with polonium is entirely plausible. It is these ligands' nitrogen, oxygen or sulfur atoms that are responsible for the binding. As such, unless there is a carbon–polonium bond in the unreacted starting material, the final products are interesting but not relevant to the current chapter. Tellurium again provides precedent, e.g. the formation of bis (8-oxoquinolinato)dimethyl tellurium[82]. The structure of this complex has been crystallographically determined as well as investigated by variable temperature, multinuclear NMR. Were there only this level of such data for the corresponding polonium species, or for that matter, any polonium-containing species?

Polonium, again like many other metals and metalloids, forms complexes with β-diketones[83–86] such as acetylacetone and 1-(2-thienyl)-4,4,4-trifluoro-1,3-butanedione. It was suggested therein that these are Po^{IV} species by comparison with other tetravalent metal derivatives, although concomitant (but otherwise unprecedented) Po^{III} was also proposed[86]. Once again, we have evidence of existence—and even in this case relative stabilities of diverse polonium complexes with inadequate documentation. Oxygen coordination appears the most plausible, but as both Te^{II} and Te^{IV} have been shown to also form carbon-bonded β-diketonates[87–89] this suggests more investigations need be made on these last organopolonium compounds to ascertain their structure, and even their identity. And, for that matter, are likewise needed for any and all other organopolonium species in this chapter. We close this chapter with the observation that ketones, esters and ethers solubilize both Po^{II} and Po^{IV} [90]. Is the polonium acting like a Lewis acid, a Brønsted acid, or dare we suggest, a substituent, i.e. there has been the formation of C−Po bonds and so, another example of alkyl polonium compounds? We also note the inadequately understood suggestion of the reversible formation of Po^{VI} in the presence of methyl isobutyl ketone[91]. Let us now close this section, and indeed this chapter on the chemistry of polonium, and *a fortiori* its organic chemistry, with an aphorism we so often find appropriate: there is more than one thinks and less than one needs.

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Organoselenium and organotellurium compounds: Toxicology and pharmacology

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0567

I. INTRODUCTION

In the last three decades, interest in the field of synthesis and reactivity of organoselenium and organotellurium compounds has increased, particularly in view of the observations that they can exhibit important biological activities[1]. In effect, the demonstration that selenium was an integral part of the antioxidant enzyme glutathione peroxidase[2] invariably as a selenocysteine residue advanced the physiological significance of the selenol/selenolate group in cell biology. Consequently, the area of synthesis and reactivity of organoselenium and organotellurium compounds as important intermediates in organic synthesis gained a new dimension, i.e. their potential capacity to mimic the biological chemistry of selenium. For the case of selenium compounds, literature data accumulated in the last 3–4 decades clearly indicated that part of the pharmacological effects of different classes of organoselenium compounds, namely ebselen and diselenides, are related to their transformation to selenol intermediates (for recent reviews see Nogueira, Zeni and Rocha[3a], Nogueira and Rocha[3b] and references therein). Of particular therapeutic significance, the clinical trials demonstrating that ebselen had borderline protection against neuropathological conditions associated with brain ischemia in human patients[4] strongly reinforced the importance of further studying the pharmacology and toxicology of organoselenium and organotellurium compounds. For the case of tellurium compounds, there are only limited data about their pharmacological effects. Furthermore, the existence of tellurol/tellurate under a physiologically relevant environment is improbable, and although several organotellurium compounds can mimic the activity of glutathione peroxidase[5], the mechanism is supposed to be quite distinct from the native enzyme. Another point that must be cited here is the fact that tellurium is a non-essential element, consequently its use as a pharmacological agent has become more complicated. Perhaps this can explain the scarcity of *in vivo* studies about the potential use of organotellurium compounds as pharmacological agents, when compared to organoselenium compounds.

In this chapter, we shall cover a wide range of toxicological and pharmacological effects in which organoselenium and organotellurium compounds are involved, but the effects of inorganic compounds will not be discussed here. Since it is not possible to cite all of the findings that have taken place, we apologize to those whose work has been omitted.

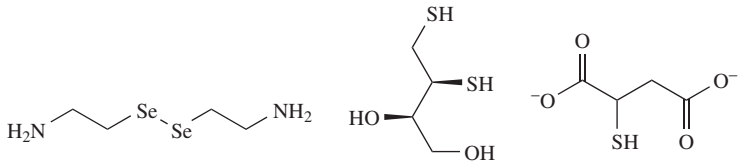
II. TOXICOLOGY

A. The Molecular Toxicology of Organoselenium Compounds

Our knowledge about the molecular toxicity of organoselenium compounds is still incipient. Much of our current knowledge of organoselenium toxicity arose from experience with inorganic selenium. In effect, the toxicity of inorganic selenium compounds seems to be related to the oxidation of thiols of biological importance[6] and part of the toxicity of Se(IV) can be related to the generation of reactive oxygen species (superoxide anion) formed during the catalytic oxidation of thiols[7].

According to Seko and collaborators[7a, b] and to Spallholz and collaborators[7c, d] the selenium toxicity will be manifested acutely or chronically when oxidative damage exceeds antioxidant defenses (for details about the interaction of Se(IV) with thiols of biological significance, see Nogueira, Zeni and Rocha[3a], Nogueira and Rocha[3b] and references therein).

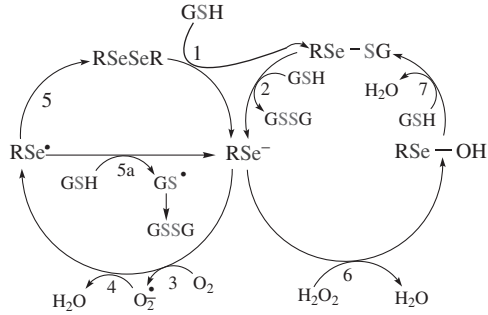
Similarly to Se(IV), organoselenium compounds can also oxidize different thiol groups. The thiol oxidase activity of diorganoyl diselenides and organoselenols can explain at least in part their toxicity[8]. For instance, the classical study of Chaudière and coworkers illustrated the ease of one-electron transfers from RSe^- to a variety of reducible substrates in which selenocystamine **1** efficiently catalyzes oxygen reduction in the presence of excess thiol groups from dithiothreitol **2**, reduced glutathione (GSH) and mercaptosuccinate **3** (Chart 1)[8a].



(**1**) (**2**) (**3**)

CHART 1

Selenocystamine **1** can catalyze the oxidation of molar excess of GSH to glutathione disulfide, at neutral pH and ambient oxygen pressure PO_2, which was dependent on the heterolytic reduction of the diselenide bond. This results in the formation of two selenolate equivalents (RSe^-) (Scheme 1; 1), via the transient formation of a selenyl sulfide intermediate (RSe-SG) (Scheme 1; 2). At ambient PO_2, the kinetics and stoichiometry of GSSG production as well as that of GSH and oxygen consumptions demonstrated that RSe^- performed a three-step reduction of oxygen to water. The first step was a one-electron transfer from RSe^- to dioxygen, yielding superoxide and the putative selenyl radical $RSe^{\cdot}$ (Scheme 1; 3), which decayed very rapidly to RSe−SeR (Scheme 1; 5). Some of the selenyl radicals would be reversibly trapped by excess GSH to yield the glutathione radical $GS^{\cdot}$ (Scheme 1; 5a), which would decay to GSSG.

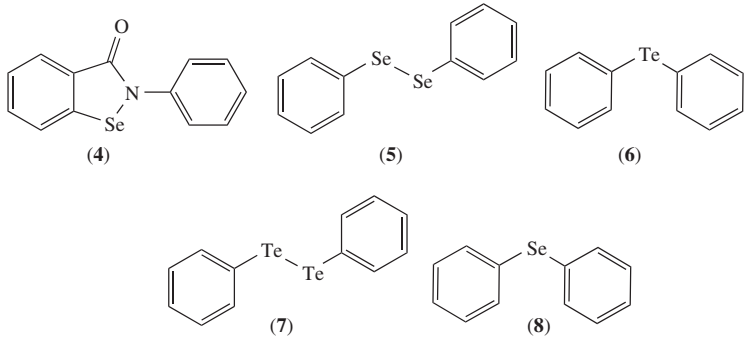


SCHEME 1

In the second step, RSe^- reduced the superoxide radical anion to hydrogen peroxide through a much faster one-electron transfer (Scheme 1; 4), which is also associated with the decay of $RSe^{\cdot}$ to RSe−SeR. The third step was a two-electron transfer from a RSe^- to hydrogen peroxide, again much faster than oxygen reduction, which resulted in the production of RSe−SG (Scheme 1; 6), presumably via a selenenic acid intermediate (RSeOH) which was trapped by excess GSH (Scheme 1; 7).

In short, the series of reactions depicted in Scheme 1 indicate two opposing pathways of thiol oxidation by diselenides, i.e. a potentially toxic and pro-oxidant pathway (which consumes thiol and forms superoxide anion and hydrogen peroxide) and a potentially pharmacological or therapeutic pathway (which consumes thiols but decomposes the potentially toxic hydrogen peroxide). However, the existence of the pathway which forms reactive oxygen species under physiological conditions has not been clearly established. For instance, we have observed that the oxidation of dithiothreitol and the inhibition of δ-aminolevulinate dehydratase (δ-ALA-D) (a thiol-containing enzyme) was not modified by the addition of catalase and superoxide dismutase or both[9]. It is possible that the oxidation of thiol by organoselenium compounds can occur via a simple exchange reaction without significant formation of reactive oxygen species.

The interaction of diselenides with high-molecular-weight thiols, particularly with the enzyme δ-ALA-D, will be discussed with more details in the Section II.C, but here we must emphasize that the toxicity of diselenides can be related to their ability to catalytically oxidize both low- and high-molecular-weight thiols. However, our understanding about the interaction of different organoselenium compounds with specific high-molecular-weight thiol-containing proteins is still very limited. In order to establish a mechanistic link between ebselen **4** and diphenyl diselenide **5** (Chart 2 below) pharmacology/toxicity and mitochondrial dysfunction, the effects of these organoselenium compounds on liver mitochondrial swelling were investigated. From this study emerges the idea that ebselen and diphenyl diselenide induce mitochondrial dysfunction, which was associated with mitochondrial thiol groups oxidation. The inability of cyclosporine A to reverse mitochondrial effects induced by ebselen **4** and diphenyl diselenide **5** suggests that the redox-regulated mitochondrial permeability transition (MPT) pore was mechanistically regulated in a manner that is distinct from the classical MPT pore[10].



(**4**) (**5**) (**6**) (**7**) (**8**)

CHART 2

The *in vivo* toxicity of organoselenium compounds was previously reviewed by Nogueira, Zeni and Rocha[3a] and Nogueira and Rocha[3b], consequently we will not refer to these studies here. However, we must emphasize that systematic studies about the toxicity of organoselenium compounds are relatively limited and have been conducted by empirical approaches.

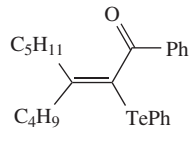
B. The Molecular Toxicology of Organotellurium Compounds

Despite its widespread use in industry and synthetic chemistry, descriptions of human intoxication with tellurium are rare[11]. Regarding organotellurium compounds, data on their toxicity are still scarce in the literature. Here we will give more details about organotellurium compounds toxicity, because the toxicology of organotellurium compounds is scarcely reviewed[3a]. Although some authors have described that organotellurium compounds are less toxic than their selenium analogues[12], consistent data have indicated that organotellurium compounds are more toxic than organoselenium compounds[13]. From experiments using erythrocytes as a model of cell injury it was further demonstrated that organotellurides **6** and **7** (Chart 2) are toxic whereas the selenium analogues (**5** and **8**) (Chart 2) are not. It is important to emphasize that organoselenium compounds were not hemolytic to erythrocytes even when tested at high concentrations[14]. A relationship between the oxidation of intracellular thiols and subsequent generation of free radicals with the hemolytic activity of chalcogens has been evidenced[15].

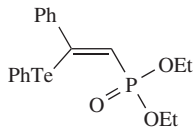
In contrast to its selenium analogue, diphenyl ditelluride **7** has been reported as a highly toxic compound in rats and mice[3a].

Additionally, an acute subcutaneous exposure to diphenyl ditelluride **7** induced oxidative damage and an adaptive response of non-enzymatic and enzymatic antioxidants in pulmonary tissue of rats[16]. The potential toxicity of repeated administration of **7** in rats was also reported. Diphenyl ditelluride **7** induced hematological disorders, as indicated by the increase in total leukocyte counts, and hepatic and renal toxicity. A decrease in plasma triglyceride and cholesterol levels was also demonstrated[17].

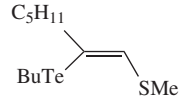
The potential toxicity of the α,β-unsaturated ketone, (phenyltelluro)oct-2-en-1-one **9** (Chart 3), was shown *in vitro* and *in vivo*. *In vitro*, compound **9** induced oxidative stress in the cerebral cortex of rats and serum of human[18]. A single acute intraperitoneal administration of **9** in rats induced cerebral oxidative stress[19].



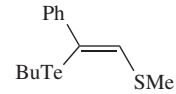
(**9**)



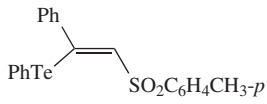
(**10**)



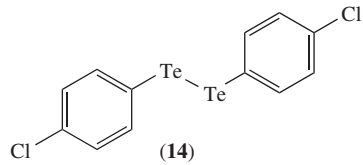
(**11**)



(**12**)



(**13**)



(**14**)

CHART 3

Since the toxicity of organochalcogens is closely related to the chemical structure, the dose and the way of administration among other factors[20], organotellurium compounds relatively free of toxic effects have appeared in the literature. In this way, diethyl 2-phenyl-2-phenyltelluro vinylphosphonate **10** (Chart 3) has been reported as a low toxic agent for mice. It is important to emphasize that the chemical structure of **10** is very different from those of ditellurides and tellurides reported in the literature. The main reason for many different effects found *in vivo* for **10** when compared to diphenyl ditelluride **7** is the weak

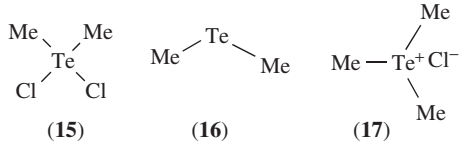
Te−Te bond when compared to the Te−C bond, which makes diphenyl ditelluride a more reactive compound[21].

Much evidence has indicated that the antioxidant, 1-butyltellurenyl-2-methylthioheptene **11** (Chart 3), is also a low toxic vinylic telluride compound for rodents. Although no overt signs of toxicity have been demonstrated, **11** caused the reduction of the body weight of treated animals, and all animals injected with 100 and 200 μmol kg^{-1} died after 72 h of oral administration. Regarding the chemical structures, **11** shares chemical characteristics with diethyl 2-phenyl-2-tellurophenyl vinylphosphonate **10**; **11** contains an organosulfur group instead of an organophosphorus group and has a butyl group directly bonded to the tellurium atom instead of a phenyl group, which probably modifies the reactivity of the metabolite[22].

A series of experiments screening for acute toxicity of vinylic tellurides **12** and **13** (Chart 3) was performed in rats. The oral administration of compounds **12** and **13** caused a decrease in body weight gain and food intake in rats. Accordingly, a loss of body weight in rats administered with a very small dose of diphenyl ditelluride **7** has been reported[23]. Vinylic telluride **12** neither affected rat exploratory behavior nor the motor system, while **13** increased the freezing time. The findings indicated that compound **13** was more toxic than compound **12**. Compared with diphenyl ditelluride **7**, **12** presented a value for LD_{50} about 30-fold higher than that for **7**[13f, 24].

The hypothesis that the chlorines introduced into the diaryl ditelluride molecule, to form bis(*p*-chlorophenyl) ditelluride **14** (Chart 3) alters its toxicity was investigated. The data demonstrated that the chlorines introduced into the diaryl ditelluride molecule did not alter acute oral toxicity in rats. The body weight loss and the manifested signs of toxicity were similar in animals exposed to compounds **7** and **14**, suggesting no difference in general toxicity among these compounds[25].

Inorganic and organic tellurium compounds are highly toxic to the central nervous system of rodents[26]. Inorganic tellurium(IV) is metabolized by a route similar to that of selenium[1m], but in contrast to selenium, the tellurium methylated products **15**–**17** (Chart 4) are considered more toxic for mammals[27]. Histological data from our laboratory have shown that mice exposed (s.c.) to diphenyl ditelluride **7** for one day (0.5 mmol kg^{-1}) or 14 days (2.5, 10 and 18.5 μmol kg^{-1}) presented accentuated vacuolization of cellular bodies in the brain[26c].



(**15**) (**16**) (**17**)

CHART 4

In an attempt to better understand the toxicology of organotellurium compounds, we studied the effect of **7** on the glutamatergic system[13b].

As shown in Table 1, **7** and its analogue, diphenyl diselenide **5**, caused a significant inhibition in [^{3}H]glutamate binding in human platelets, suggesting that platelets are as sensitive as brain synaptosomes[13h].

Accordingly, the inhibitory effect of diphenyl ditelluride **7** on [^{3}H]glutamate uptake in human platelets was also reported[13h]. Moreover, the inhibitory effect of **7** on glutamate uptake and release by synaptosomes of rats was demonstrated to be age- and concentration-dependent[28].

TABLE 1. Inhibitory effect of diphenyl ditelluride and its selenium analogue on [^{3}H]glutamate binding *in vitro*

	Diphenyl diselenide[a] 100 μM	Diphenyl ditelluride[a] 100 μM
Synaptosome	50	70
Platelets	30	50

[a]Data represent % binding inhibition in relation to control value (100%).

Since the slices preserve the neuron–glial interactions, the involvement of the glutamatergic system in the neurotoxicity of **7** was further confirmed in slices of cerebral cortex of rats. At 100 μM, **7** inhibited the [^{3}H]glutamate uptake in cortical slices of rats. Reduced glutathione and dithiothreitol prevented the inhibition of glutamate uptake induced by **7**[29].

In an attempt to better understand the mechanisms behind the neurotoxic effects of **7**[30], this organotellurium compound was investigated in the phosphorylation of cytoskeletal proteins. At low concentrations **7** induced hyperphosphorylation of the high-salt Triton insoluble neurofilament subunits (NF-M and NF-L), glial fibrillary acidic protein (GFAP) and vimentin, without altering the immunocontent of these proteins[31]. To further confirm this effect on cytoskeletal proteins, a single subcutaneous exposure of **7** to rats was carried out. Animals exposed to **7** presented loss of body weight and cortical hyperphosphorylation of neurofilament subunits NF-M and NF-L, GFAP and Vim. The hyperphosphorylation of neurofilaments was accompanied by increased immunocontent of these proteins. The authors demonstrated that cortical cytoskeleton is more susceptible to **7** than hippocampal cytoskeleton. Consequently, it was concluded that cytoskeletal dysfunction in cortical and hippocampal cells could be involved in the neurotoxicity induced by acute exposure to **7**[32].

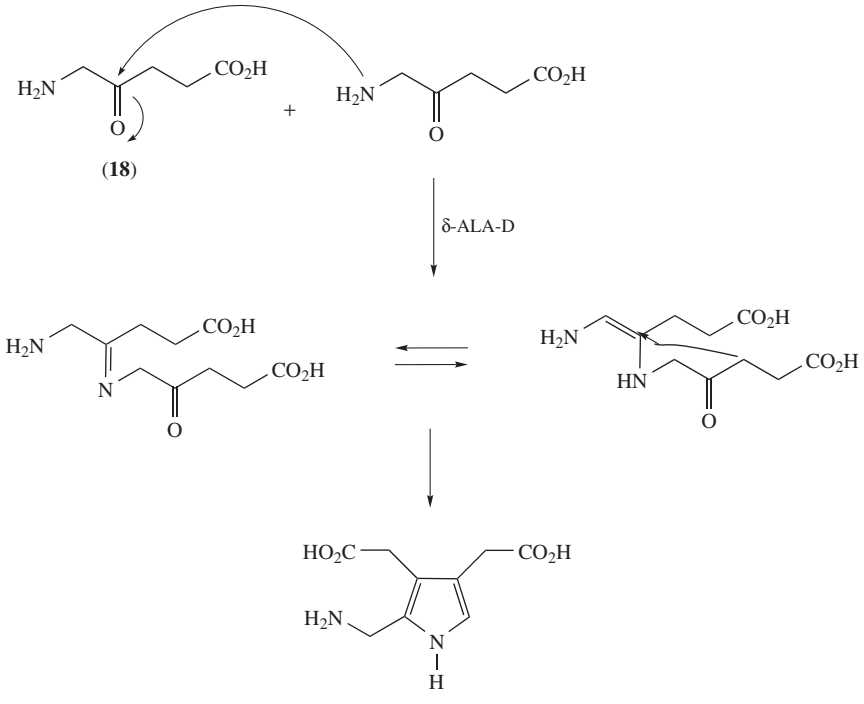
Diphenyl ditelluride has been also reported as a potent teratogen in rats[23] but not in mice, suggesting that the teratogenic effect is dependent on the species[33].

Since diphenyl ditelluride **7** was teratogenic to rats, we wonder if this organotellurium compound could be toxic to the offspring. Thus, the effects of low level of **7** during the first 14 days of lactational period on later offspring behavior were investigated. This study revealed that exposure to small doses of **7** results in disinhibitory behavioral tendencies of offspring determined in the elevated plus-maze. Moreover, neither significant specific overt signs of maternal intoxication nor lethality following administration of **7** during the suckling period was found[34]. In an extension of this study, using the same experimental protocol, **7** exposure to mothers was investigated on the cerebral oxidative status and short-term memory of their offspring. It was concluded that exposure to **7**, via maternal milk, caused oxidative stress in cerebral structures and cognitive impairment of young rats[35].

The effect of diphenyl ditelluride **7** on male reproductive parameters has been demonstrated. When **7** was administered either intraperitoneally (acute treatment) or subcutaneously (subchronic treatment) to adult male rats, it did not cause reproductive toxicity[36]. Moreover, subchronic exposure of male rats to small doses of **7** had no adverse effects on reproductive or pharmacological parameters in their progeny[37].

C. Interaction of Organoselenium and Organotellurium Compounds with δ-Aminolevulinate Dehydratase (δ-ALA-D)

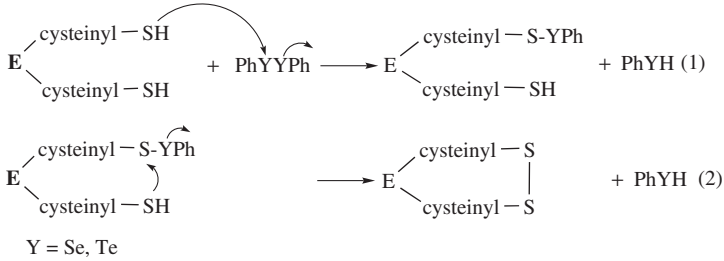
Reduced cysteinyl residues from proteins can be oxidized by organoselenium and organotellurium compounds, which can inhibit enzyme catalytic activity. For instance, δ-aminolevulinate dehydratase or porphibilinogen synthase (δ-ALA-D) is a sulfhydryl-containing enzyme that is extremely sensitive to oxidizing agents[9, 38]. δ-ALA-D catalyzes



SCHEME 2

the asymmetric condensation of two molecules of 5-aminolevulinic acids **18** to form porphibilinogen **19**, an intermediate in tetrapyrrol biosynthesis (Scheme 2)[39].

We have proposed the mechanism of δ-ALA-D inhibition by diphenyl diselenide **5** shown in Scheme 3[40]. The first step in Scheme 3 (equation 1) involves the reaction of enzyme (E) with diphenyl diselenide **5** forming an unstable intermediate of the type E-Cys-S-SePh and selenophenol. Then, the other cysteinyl residue in close spatial



SCHEME 3

proximity to the more reactive residue attacks the sulfur–selenium bond of the intermediate, resulting in inactivating δ-ALA-D, and generates a second molecule of selenophenol (equation 2). Accordingly, we have observed that dithiols (dithiothreitol, dimercaptosulfonate) were more efficiently oxidized by diorganoyl diselenide and diorganoyl ditelluride[26c, 41] than monothiols (cysteine or GSH). The selenophenol molecules formed after reaction with the thiol group are oxidized back to diphenyl diselenide by atmospheric O_2. The oxidation of selenophenol by oxygen explains the protection of δ-ALA-D against diphenyl diselenide inhibition in an anaerobic atmosphere[9].

We believe that diphenyl ditelluride follows a similar mechanism (Scheme 3) to inhibit δ-ALA-D activity.

δ-ALA-D from human erythrocytes is also a target for organoselenium and organotellurium compounds. In effect, diphenyl diselenide **5**, ebselen **4** and diphenyl ditelluride **7** inhibit δ-ALA-D from human erythrocytes, and dithiothreitol reactivates and protects blood human δ-ALA-D from the inhibitory effects of chalcogenides[42]. Based on these results, we presuppose that thiol-containing enzymes (such as δ-ALA-D) can participate in exchange reactions between thiol groups and diorganoyl diselenides. The selenol formed in the thiol-diselenide-selenol-disulfide exchange reaction can be oxidized to diselenide by O_2 more rapidly than the thiol, and consequently, the final products of this type of exchange reaction are expected to be disulfide and diphenyl diselenide forms. This exchange reaction, catalyzed or not, can have a profound influence on the toxicity of diorganoyl chalcogenides, particularly for selenium- and tellurium-containing compounds.

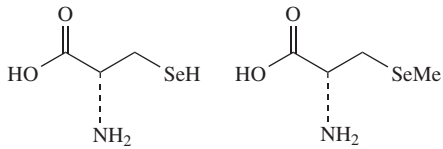
The experimental data about the inhibition of δ-ALA-D by diphenyl diselenide and diphenyl ditelluride indicate that proteins containing cysteinyl residues in close spatial proximity in their three-dimensional structures can react more promptly with this class of organic molecules. Consequently, the cellular toxicity of these compounds may be related, at least in part, to the oxidation of vicinal sulfhydryl groups of specific dithiol target proteins.

III. PHARMACOLOGY

A. Biochemical Pharmacology of Organoselenium Compounds

The association between selenium and liver pathology dates from the initial observations of Schwarz and Foltz that selenium, the essential part of the active organic Factor 3, could prevent liver necrosis in rats fed a selenium-deficient torula yeast-based diet[43]. This observation led rapidly to the recognition that a number of previously unexplained deficiency diseases in various species of animals were selenium-responsive and a new chapter in the selenium story began[44].

Organoselenium compounds such as selenocystine and a variety of diorgano diselenides can react with different types of synthetic and endogenous mono- and dithiols, including cysteine, dithiothreitol, reduced glutathione and proteins containing single or vicinal thiols



(**20**) (**21**)

CHART 5

(for instance, δ-ALA-D), to produce selenocysteine **20** (Chart 5), selenols, and disulfides[45]. Firstly, the reduction of diorganoyl diselenides to selenol derivatives by reaction with thiols was considered to be of physiological significance[8c] and it was hypothesized that selenoamino acids, particularly methylselenocysteine **21** (Chart 5), could catalytically act as biological antioxidants[45a].

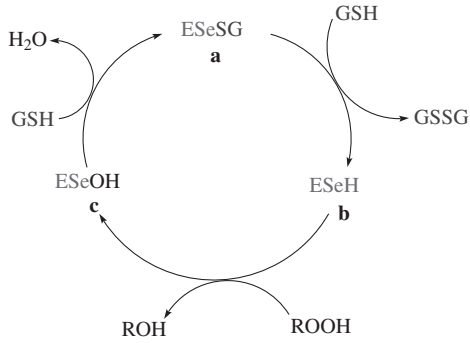
However, it is now clear that selenium plays a biological function as a component of the active center of the selenoproteins, including the enzymes thioredoxin reductase, glutathione and phospholipid glutathione peroxidases[2a, 46]. In fact, all mammalian selenoproteins contain selenium in the chemical form of selenocysteine, an analogue of serine and cysteine[47].

The glutathione peroxidase isoforms catalyze the decomposition of a variety of hydroperoxides (ROOH and H_2O_2), using GSH as a reducing agent (Scheme 4), and they have a fundamental role as a modulator of redox balance in mammalian cells.

$$ROOH + 2\,GSH \longrightarrow ROH + GSSG + H_2O_2$$

SCHEME 4

Glutathione peroxidase catalyzes the reduction of H_2O_2 by GSH, following a ping-pong mechanism. The selenol **b** group from a selenocysteine residue (Scheme 5) is then oxidized by peroxides generating selenenic acid **c**. GSH then reacts with the selenenic acid **c**, resulting in the corresponding water and selenenyl sulfide **a**. Sequentially, a second molecule of GSH (Scheme 5) attacks the sulfur of the —Se-S- bond, producing disulfide and regenerating the selenol **b** (Scheme 6)[48].



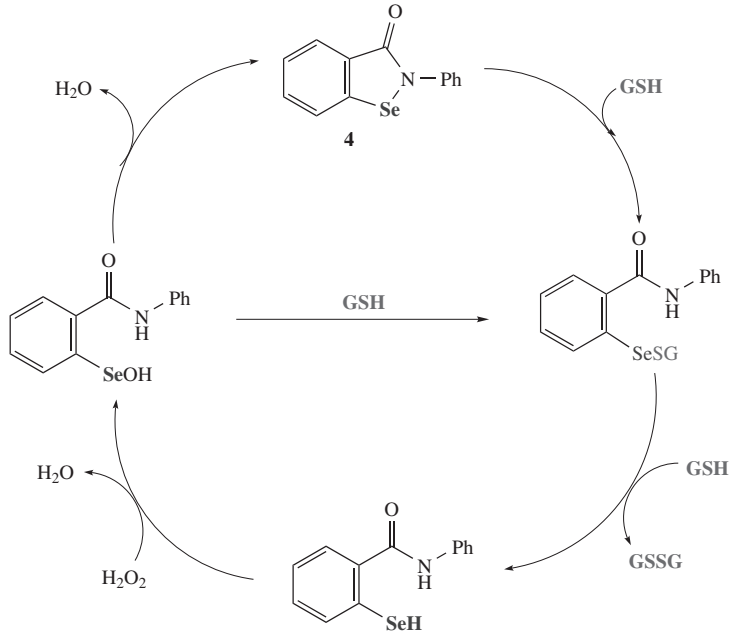
SCHEME 5

Since glutathione peroxidase isoforms constitute a potent cellular defense system against oxidative stress, there is an endeavor in the scientific community to develop compounds that could mimic the glutathione peroxidase activity. In effect, semisynthetic enzymes, obtained by enzyme engineering, have been proposed as a mimic of glutathione peroxidase[49]. However, in view of the drawbacks of using high-molecular proteins as therapeutic agents, several research groups have developed a number of small molecules, including various substituted diselenides, N−Se heterocycles and other types of selenium compounds with glutathione peroxidase-like activity[50]. Here it is important to highlight that simple aryl and alkyl diselenides can be *in vitro* good mimetics of glutathione peroxidase activity, which emphasizes the importance of this class of molecules as potential pharmacological and therapeutic agents.

1. Glutathione peroxidase-like activity

Ebselen **4** was the first compound suggested for hydroperoxide-inactivating therapy in the presence of glutathione[8e, f, 51].

Consequently, the mechanism of hydroperoxides decomposition by ebselen and thiols has been widely investigated[52]. The mechanism of peroxide decomposition by ebselen seems to be kinetically identical to that of the glutathione peroxidase, i.e. it follows a ter uni ping-pong mechanism (Scheme 6)[53].

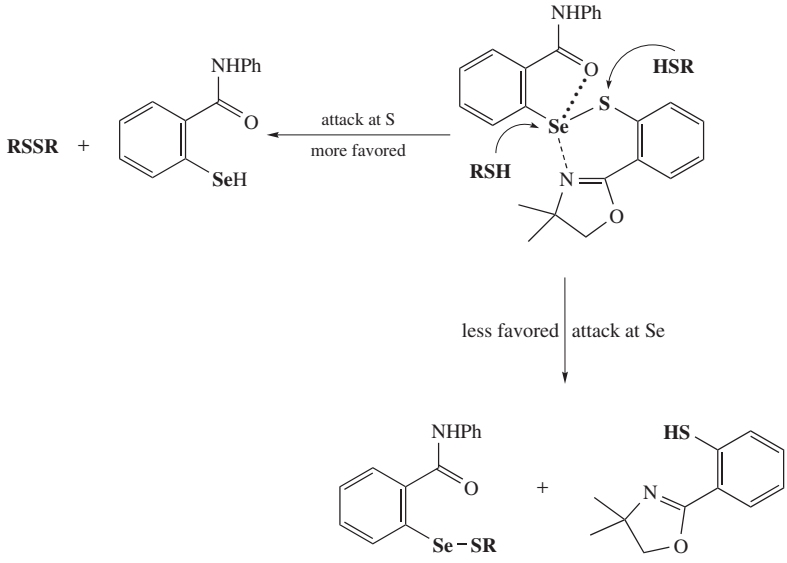


SCHEME 6

As depicted in Scheme 6, ebselen reacts with the thiols (e.g. GSH), yielding a selenenyl sulfide intermediate. The selenenyl sulfide reacts with another GSH molecule to yield a selenol. Finally, the selenol reacts with H_2O_2 or organic hydroperoxide to form H_2O or the respective alcohol (ROH) and ebselen selenenic acid intermediate, which spontaneously produces another molecule of H_2O and regenerates ebselen. However, it is difficult to accept that the seleninic acid intermediate of ebselen could spontaneously regenerate ebselen. In fact, in the presence of an excess of reduced GSH (i.e. at the physiological molar concentrations of GSH), it is more plausible to suppose that, in analogy with the catalytic cycle of the native seleno-glutathione peroxidase, the selenenic acid intermediate reacts successively with two thiol equivalents to regenerate the selenol intermediate of ebselen.

On the other hand, strong evidence has been accumulated that ebselen, irrespective of the reaction pathway, is a relatively inefficient catalyst in the reduction of hydroperoxides with aryl and benzylic thiols[54]. In fact, Back and Moussa[54b] have reported that alkylselenenyl sulfides undergo a deactivation pathway that competes with the main catalytic cycle explaining the reduction in the catalyst property of ebselen.

Based on the fact that glutathione peroxidase-like activity of ebselen depends on the reduction of the selenenic acid to selenol by thiols, the effect of the nature of the thiols on the GPx-like activity of ebselen was investigated. This was the first experimental evidence that any substituent that is capable of enhancing the nucleophilic attack of thiol at sulfur in the selenenyl sulfide intermediate would enhance the antioxidant potency of ebselen and possibly of other organoselenium compounds. It was demonstrated that the use of thiol having an intramolecular coordinating group would enhance the biological activity of ebselen. According to Scheme 7, S−N interactions modulate the attack of an incoming thiol at the sulfur atom in ebselen selenenyl sulfide[55].



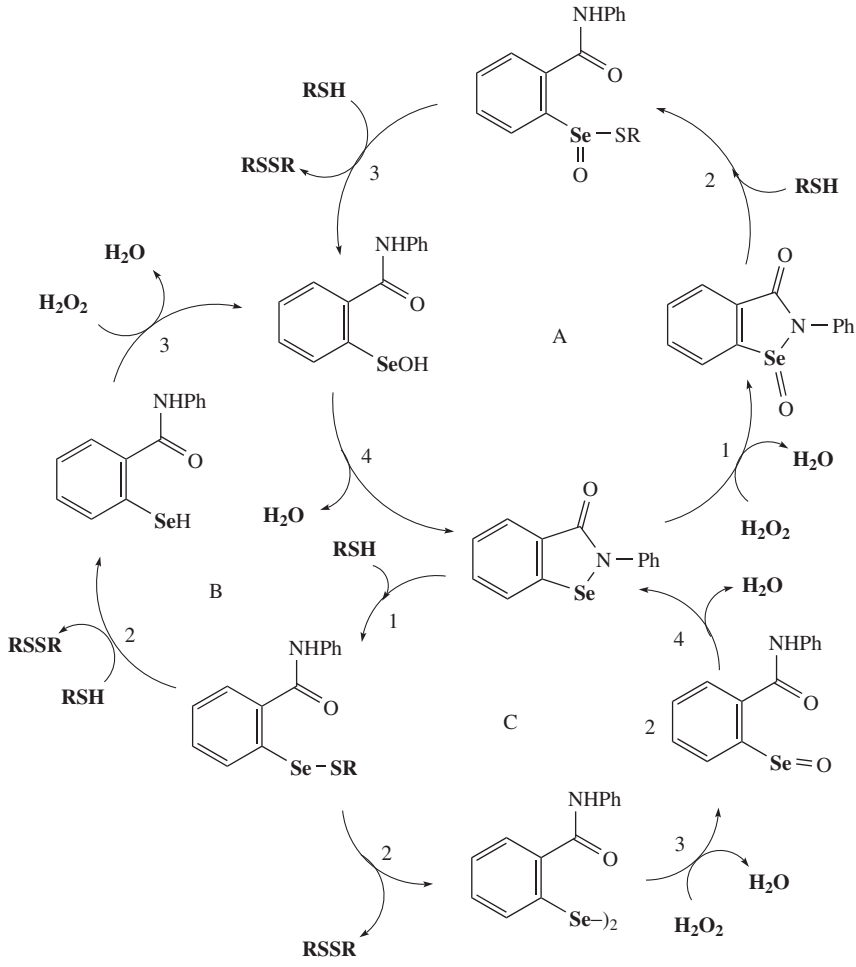
SCHEME 7

In an extension of this research, Bhabak and Mugesh[56] further revealed that the nature of the peroxide has little effect on the catalytic efficiencies, while the nature of thiols shows a dramatic effect on the catalytic activity of ebselen and its analogues.

The influence of electronic and steric effects on the GPx-like activity of ebselen has been also reported. The incorporation of a substituent ortho to the selenium atom sterically hinders attack of a nucleophile at selenium and promotes production of selenol, the GPx-active form, and thus the GPx-like activity is greatly enhanced[57].

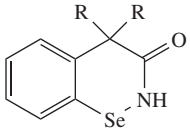
In 2008, a revised mechanism for the GPx-like activity of ebselen emerged in the literature. Considering the complications associated with the catalytic mechanism of ebselen and that none of the intermediates other than the selenenyl sulfides have been confirmed, the mechanism depicted in Scheme 8 was proposed by Sarma and Mugesh[58]. This study shows the first structural evidence that the seleninic acid, which was never proposed as an intermediate in the catalytic mechanism of ebselen, is the only stable and isolable product in the reaction of ebselen with peroxides. In the presence of excess thiol, under physiologically relevant conditions, the Se−N bond in ebselen is readily cleaved by the thiol to produce the corresponding selenenyl sulfide. The authors also proposed that the disproportionation of the selenenyl sulfide to produce the corresponding diselenide (Scheme

8, cycle C, step 2) is more important than the generation of selenol (Scheme 8, cycle A, step 2). Finally, the authors suggest that the regeneration of ebselen by cyclization of the selenenic acid under a variety of conditions protects the selenium moiety from irreversible inactivation.

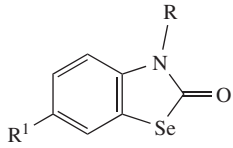


SCHEME 8

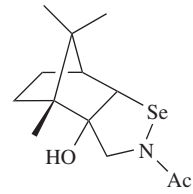
Based on the recognized glutathione peroxidase-like activity of ebselen, the 1990s were characterized by an explosion in information concerning the simple synthetic organoselenium compounds that could imitate glutathione peroxidase, such as benzoselenazinones **22a**–**d**[59], benzoselenazolinones **23a**–**g**[60], camphor-derived selenenamide **24**[61], 2-phenylselenenylnaphthol **25**[62], α-selenylketones **26a**–**g**[63] and oxygen-containing diselenides **27**–**31** (Chart 6)[8g]. Importantly, data from these researches led to compounds with thiol peroxidase-like activity higher than that of the original ebselen **4**.



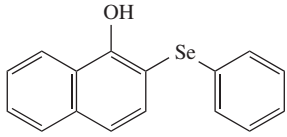
(**22a**) R = H
(**22b**) R = CH_3
(**22c**) R = $CH_2C_6H_5$
(**22d**) R = C_6H_5



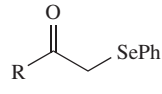
(**23a**) R = H; R^1 = $COCH_3$
(**23b**) R = H; R^1 = $COCH_2CH_2CH_3$
(**23c**) R = H; R^1 = COC_6H_5
(**23d**) R = H; R^1 = CH_2CH_3
(**23e**) R = CH_3; R^1 = $COCH_3$
(**23f**) R = CH_3; R^1 = $COCH_2CH_2CH_3$
(**23g**) R = CH_3; R^1 = COC_6H_5



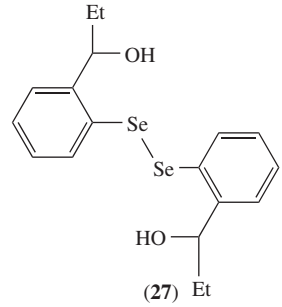
(**24**)



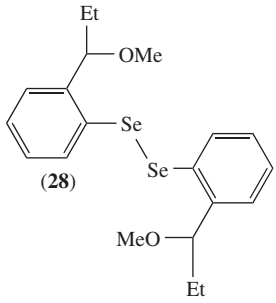
(**25**)



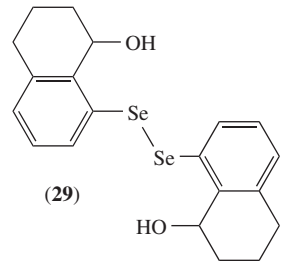
(**26a**) R = C_6H_5
(**26b**) R = *p*-$NO_2C_6H_4$
(**26c**) R = *p*-$MeOC_6H_4$
(**26d**) R = 2-thienyl
(**26e**) R = 2-naphthyl
(**26f**) R = Me
(**26g**) R = *t*-Bu



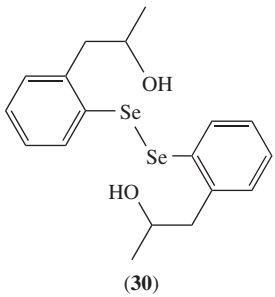
(**27**)



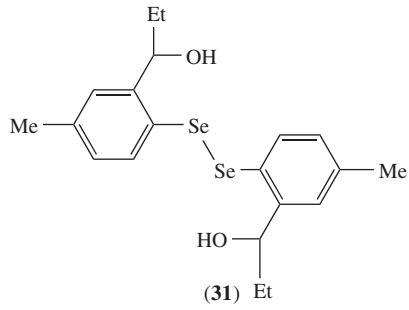
(**28**)



(**29**)



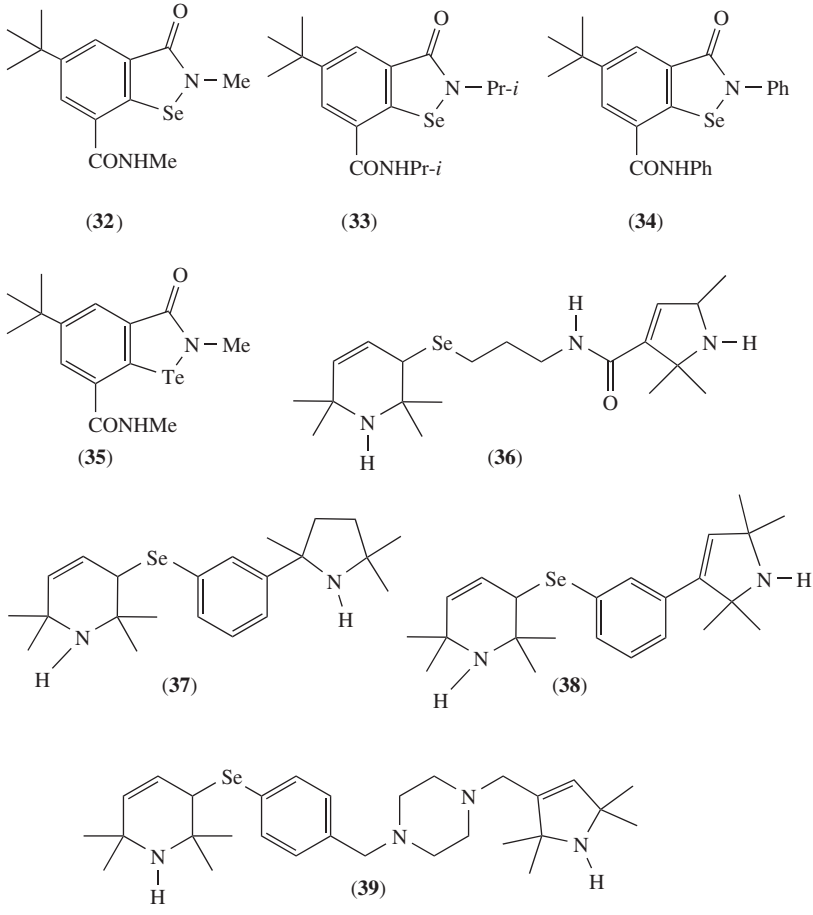
(**30**)



(**31**)

CHART 6

During this decade a number of attempts were also made to design and synthesize ebselen-related GPx mimics based on substituent effects or isosteric replacements; most of them met with limited success. Thus benzisochalcogenazolones **32** and **33** (Chart 7), organoselenium compounds that have intramolecular interactions as Se−O, enhanced the catalytic capacity of ebselen. However, **34** showed lower activity which could be attributed to its poor solubility. Following the rule that reactivity toward hydroperoxides increases as one descends the chalcogen group, benzisotellurazolone **35** was 1.5 times more active than the selenium analogue **32** (Chart 7)[64]. Working with benzisoselenazolones Kalai and coworkers reported that the synergist effect of selenium and pyrroline substituents greatly enhances the GPx-like activity of these compounds. A series of closely related benzisoselenazolones have been studied and compounds **36**–**42** (Chart 7) were more potent than ebselen. Of note, compounds **43**, **44** and **45** (Chart 7) which lack selenium in the benzene anellated five-membered ring and **46** nitroxide precursor exhibited GPx-like activity. However, they are about tenfold less active than isoselenazolone derivatives[65].



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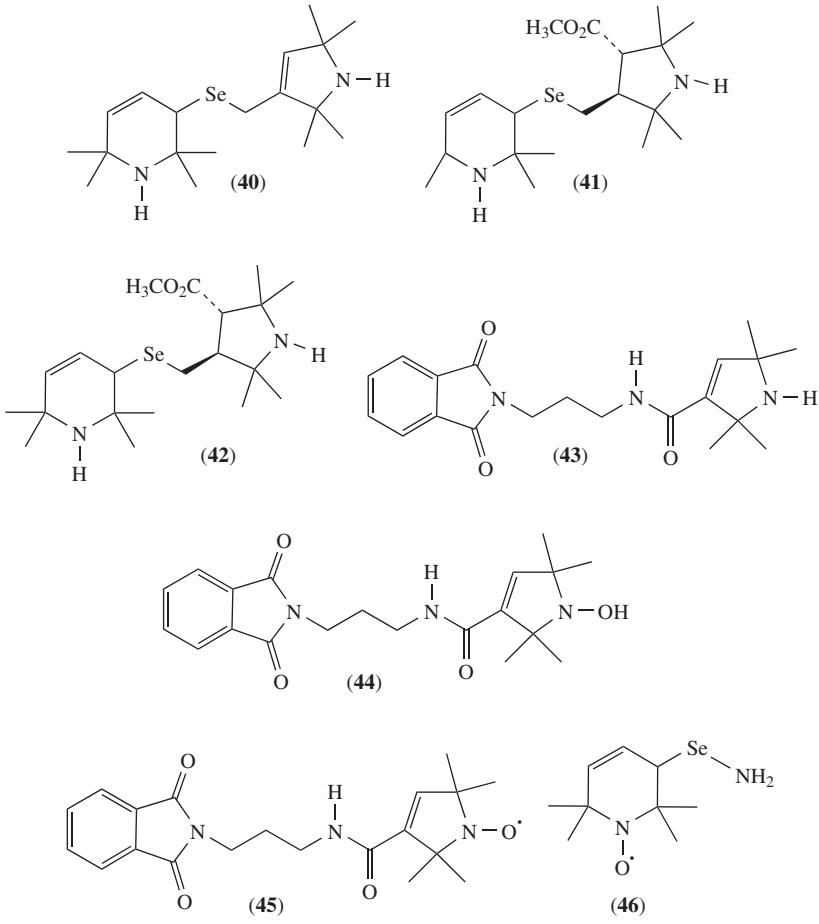


CHART 7

The organochalcogens with an *o*-hydroxy function have been tested as GPx-mimetic in view of better solubility in water for conducting the bioassay. Diselenide **47** and cyclic seleninate ester **48** are more efficient catalysts in comparison to ebselen and have comparable activity to that of aliphatic seleninate ester **49**. Allyl selenide **50** and selenide **51** have a poor GPx-like activity. Compound **52**, a spirocyclic containing selenium in oxidation state IV, was less active than the seleninate ester **48** (Chart 8)[66].

The effects of substituents were investigated in a series of aromatic cyclic seleninate esters and spirodioxyselenuranes as a part of an effort to improve their GPx-like activities. Aromatic cyclic seleninate esters **48** and **53**–**58** (Chart 8) showed GPx-like activity lower than ebselen. Conversely, spirodioxyselenuranes **52**, **62** and **63** (Chart 8) were superior to ebselen. Moreover, the authors demonstrated a clear correlation between GPx-like activity and electron-donating/withdrawing nature of the substituents in both the cyclic seleninates and spirodioxyselenuranes. Thus, while electron-withdrawing substituents such as the halogens in **53**–**55** and **59**–**61** (Chart 8) suppressed the catalytic

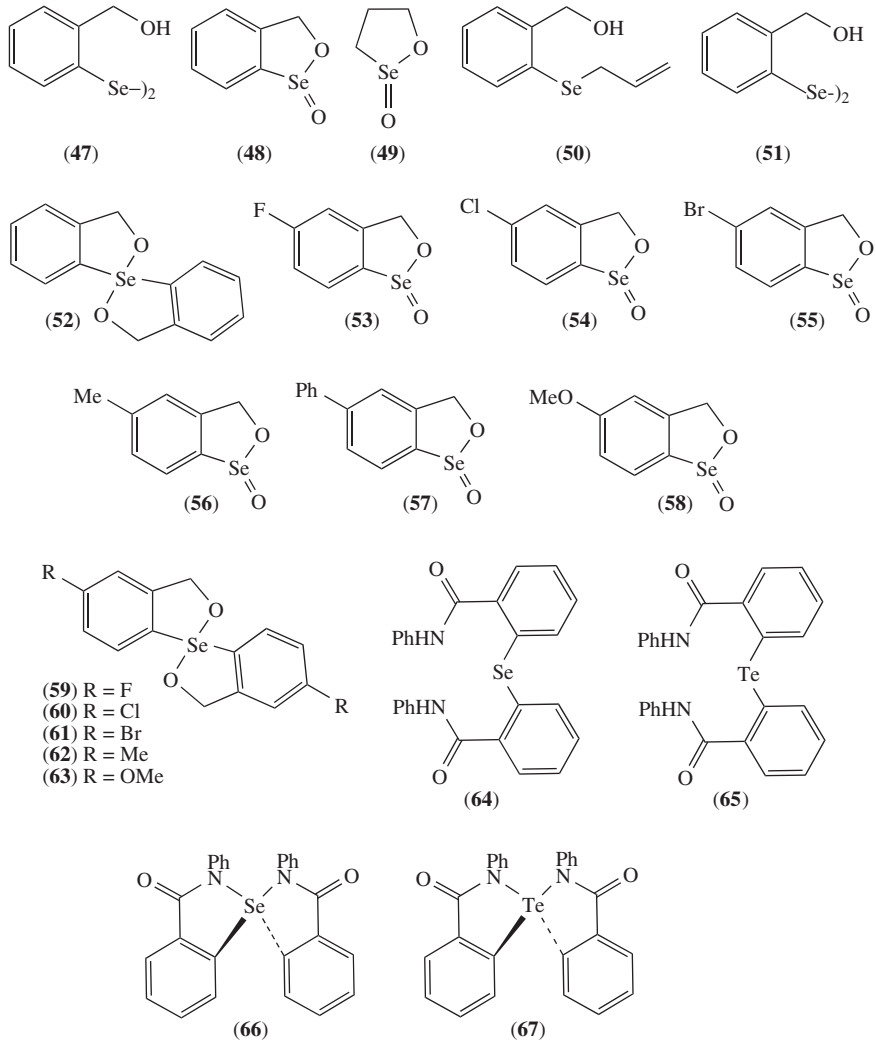
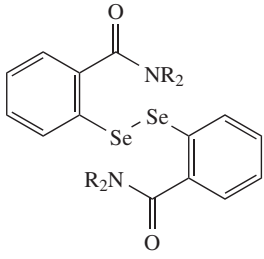


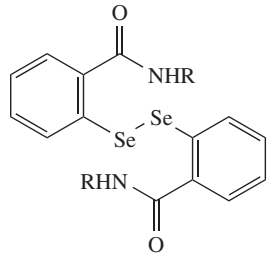
CHART 8

activity, the strongly electron-donating methoxy groups in **58** and **63** enhanced it considerably[67]. The catalytic efficiency of stable spirodiazaselenuranes and their tellurane analogues was recently reported by Sarma and coworkers. Compounds **64**–**67** (Chart 8) were evaluated for their ability to catalyze at least 50% conversion of the thiol (BnSH) to disulfide (BnSSBn) in the presence of *t*-BuOOH, a method for determining the GPx-like activity. The activity of selenide **64** is almost identical to that of ebselen, while the tellurium analogue **65** exhibited very high catalytic activity. The authors explain this catalytic behavior by the involvement of an efficient redox cycle between the telluride and telluroxide. In fact, at low thiol concentrations, the telluroxide undergoes a reversible spirocyclization, which may protect the tellurium moiety from overoxidation[68].

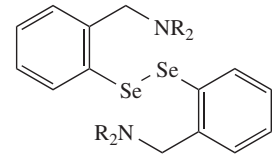
In addition, Bhabak and Mugesh[69] have investigated the GPx-like activity of tertiary- and secondary-amide-substituted diaryl diselenides. Thus the tertiary-amide-substituted diselenides **68**–**70** showed higher activity (6–7 times) than the corresponding secondary-amine-based compounds **71**–**73** (Chart 9). The authors also demonstrated that different catalytic mechanisms may account for the lower GPx-mimetic activity of the amine-based compounds **68**–**73** as compared to that of the *t*-amide-substituted diselenides **74**–**76** (Chart 9)[70].



(**68**) R = Me
(**69**) R = Et
(**70**) R = *n*-Pr



(**71**) R = Me
(**72**) R = Et
(**73**) R = *n*-Pr



(**74**) R = Me
(**75**) R = Et
(**76**) R = *n*-Pr

CHART 9

In a recent published study, the GPx-like activity of a series of *s*-amine-substituted diselenides was reported. The *s*-amine-based compounds **77**–**80** (Chart 10) were better GPx-mimetic catalysts than the *t*-amino-substituted diselenides **74**–**76**. *N*-Methyl derivative **77** was two times more active than the *N*,*N*-dimethyl derivative **74**. *N*-Alkyl-based compounds **77**–**80** were significantly more active than the corresponding *N*,*N*-dialkyl derivatives **75** and **76**. The replacement of the *t*-amino groups in *N*,*N*-dialkylbenzylamine-based diselenides by *s*-amine moieties increased the GPx-like activity, for generating the catalytically active selenols. The absence of thiol-exchange reactions in the selenenyl sulfides may account for the highest catalytic activity of *s*-amine-based diselenides[71].

Based on an understanding of the structure of the enzyme GPx, its mode of molecular recognition and catalysis, Luo and collaborators[72] have developed some GPx mimics in which the β-cyclodextrin cavity provided a hydrophobic environment for substrate binding. Because of the role of the hydrophobic cavity of β-cyclodextrin in binding substrate, diseleno-bis(β-cyclodextrin) **81** (Chart 10) was 4.3 times more efficient as GPx-mimetic than ebselen. In an extension of their research dicyclohexylamine-diselenide-bis(β-cyclodextrin) **82** (Chart 10) was synthesized based on the idea that the cyclohexylamine group incorporated in the proximity of the selenium atom and the β-cyclodextrin cavity provided a hydrophobic environment for substrate binding. Thus **82** exhibited better GPx-like activity than **81** and ebselen **4**. A ping-pong mechanism was observed in steady-state kinetic studies on reactions catalyzed by **82**[73].

Recently, we have screened a series of chiral amino acid derivatives containing selenium as GPx-mimetic compounds. Thereupon, diselenides **83** and **84** (Chart 10), with a long chain length derived from L-phenylalanine, exhibited GPx-like activity higher than diphenyl diselenide. Conversely, compound **85** was a poor catalyst (Chart 10)[74].

Redox chemistry of selenides and selenoxides has attracted increasing interest in relation to their biochemical applications; therefore, catalytic activities of *trans*-3,4-dihydroxyselenolanes, water-soluble cyclic selenide, were investigated. On one hand, the

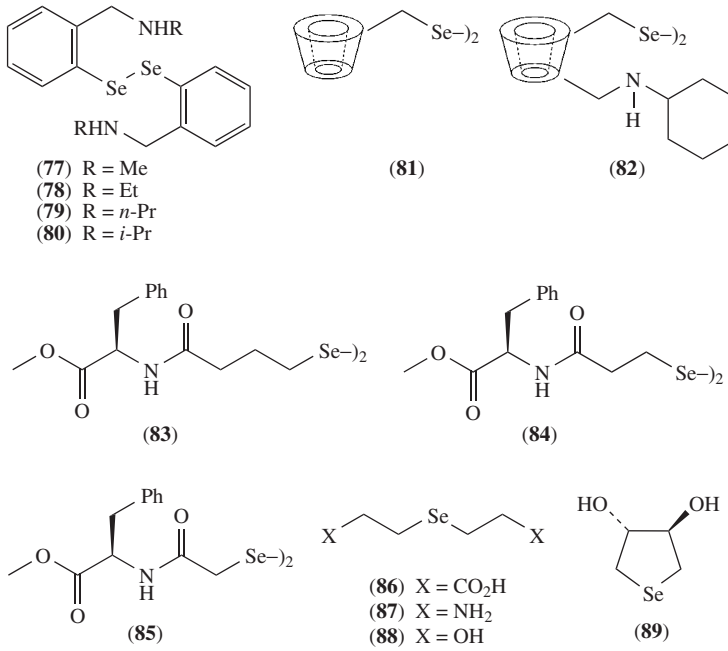


CHART 10

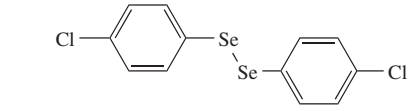
highest GPx-mimetic activity of **86** was explained by the ionization of the carboxylic groups in the buffer solution to COO^-, the negative charge of which should inductively increase the oxidizability of the selenium atom. On the other hand, the lowest activity of **87** would be due to the ionization of the amino groups to NH_3^+, which decreases the oxidizability of the selenium atom. Water-soluble cyclic selenide **89** exhibited higher GPx-like catalytic activity than linear analogue **88** (Chart 10)[75].

Further, a previous study from our laboratory indicated that bis(*p*-chlorophenyl) diselenide **90**, diphenyl diselenide **5** and dimethyl diselenide **91** were more catalytic than ebselen **4**. Diaryl diselenide substituted with *p*,*p*′-methyl groups **92** showed GPx-like activity similar to that of ebselen **4**. The diselenides bis(*p*-aminophenyl) diselenide **93** and dibutyl diselenide **94** had poor GPx-like activity, while bis(*p*-methoxylphenyl) diselenide **95** and dipropyl diselenide **96** had no catalytic activity (Chart 11)[8h, 76].

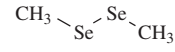
Additionally, we have demonstrated that dicholesteroyl diselenide **97** (Chart 11), a bulky diselenide, markedly decreased GPx-like activity if compared to diphenyl diselenide **5**[41].

After a series of oxidation and [2,3] sigmatropic rearrangement steps *in situ*, allyl 3-hydroxypropyl selenide **98** generated the corresponding cyclic seleninate **99**, which has higher GPx-mimetic activity than ebselen. Results from Back's group reflect that O−Se compounds can be even more effective catalysts than the more widely studied N−Se analogues[54a, b]. The exceptional GPx-mimetic activity of di(3-hydroxypropyl) selenide **100** was also reported by Back and collaborators (Chart 12)[77].

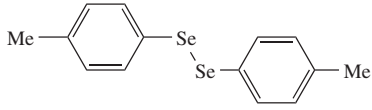
Of particular importance, the mechanism for peroxidase catalytic activity of **100** is distinct from that employed by GPx enzyme and by many of its small-molecule mimics and involves a spirodioxaselenanonane **101**, as an intermediate (Scheme 9)[77].



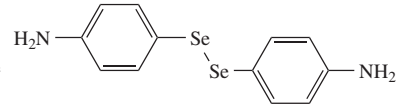
(**90**)



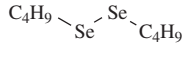
(**91**)



(**92**)



(**93**)



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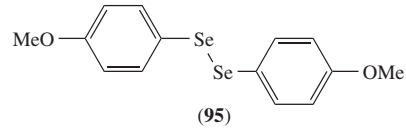
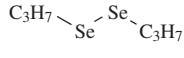
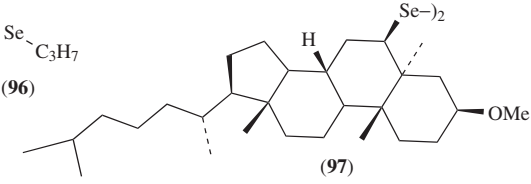


(**95**)

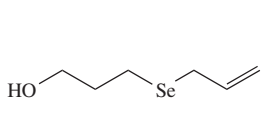


(**96**)

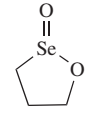


(**97**)

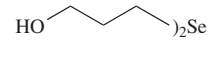
CHART 11



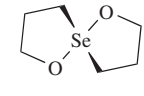
(**98**)



(**99**)

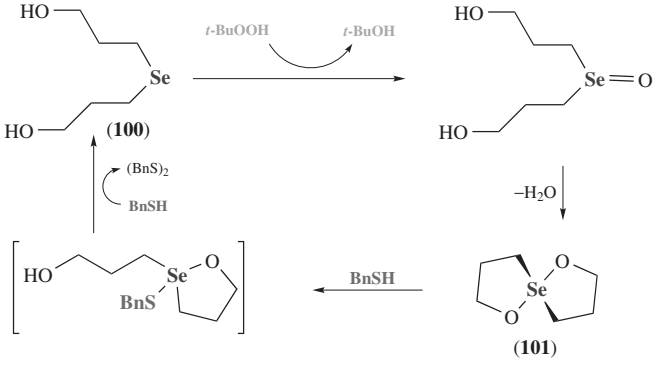


(**100**)



(**101**)

CHART 12



SCHEME 9

2. Antioxidant activity

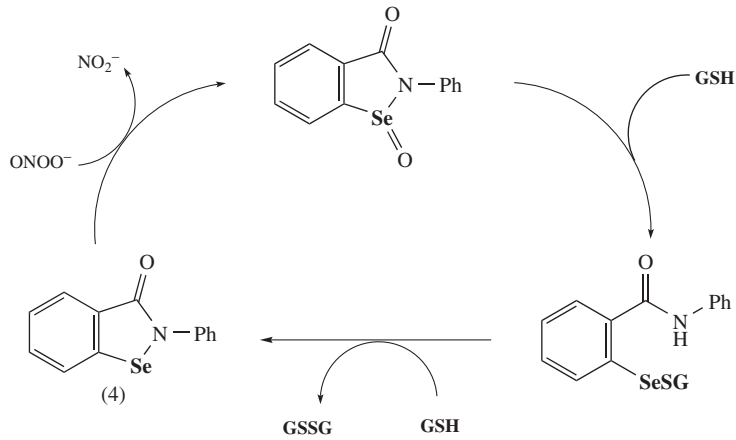
Oxygen-derived species are well known to be cytotoxic and have been implicated in the etiology of a wide array of human diseases. Organoselenium compounds, capable of propagating the redox cycle of selenium, with the property of imitating the redox physiological chemistry of selenol/selenolate groups, might supplement natural cellular defenses against the oxidizing agents[78]. In this way, several reports have appeared describing the antioxidant activity of ebselen[79] and other organoselenium compounds[80] in different experimental models associated with oxidative stress.

One of the constraints in the development of selenium compounds as antioxidants is their stability and poor water solubility. For a selenium compound to act as an antioxidant, it must show nucleophilicity necessary for glutathione peroxidase-like activity, free radical-scavenging capability and low toxicity. It has been recognized that organoselenium compounds react very efficiently with hydroperoxides. In addition, there is an increasing amount of evidence showing that ebselen and other organoselenium compounds can also serve to protect against peroxynitrite, a reactive toxic radical and a potent inflammatory mediator[81].

In fact, peroxynitrite ($ONOO^-$) is a strong oxidizing and nitrating agent that is produced by the diffusion-limited reaction of nitric oxide and superoxide anion. Its synthesis may be beneficial in inflammatory response in terms of an oxidative destruction of intruding microorganisms. However, elevated concentrations of peroxynitrite can cause excessive oxidation and the destruction of host cellular constituents.

Of particular therapeutic significance, ebselen can react with peroxynitrite efficiently, exhibiting one of the highest second-order rate constants for a low-molecular-weight compound[81c].

As depicted in Scheme 10, ebselen **4** catalytically reduces peroxynitrite to nitrite in the first step, yielding its selenoxide, 2-phenyl-1,2–benzisoselenazol-3(2*H*)-one-1-oxide, as the sole selenium-containing product at 1:1 stoichiometry[81d]. The selenoxide is than reduced back to ebselen in two consecutive one-electron reduction steps via the selenodisulfide, utilizing reducing equivalents from glutathione thiol groups. The analogy to the glutathione peroxidase catalytic cycle is obvious. Here it must be emphasized that the selenol group of GPx can also react with peroxynitrite[82], which implicates that a number of

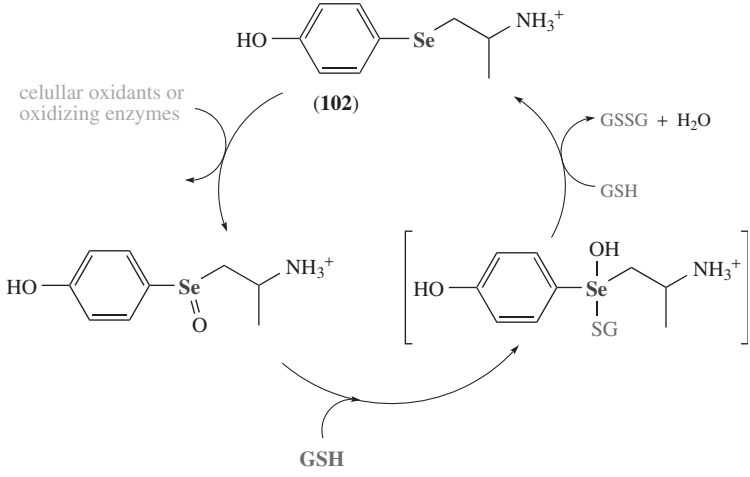


SCHEME 10

different selenol-containing molecules can be potential peroxynitrite scavengers. Further, the mammalian selenoprotein thioredoxin reductase can also reduce ebselen selenoxide at the expense of NADPH[83].

Data from our laboratory have demonstrated that diphenyl diselenide **5**, bis(*p*-chlorophenyl) diselenide **90** and ebselen **4** are able to inhibit lipid peroxidation-induced by sodium nitroprusside, a substance usually used as an NO generator[79d]. The potency of ebselen was higher than that of diselenides, which may indicate that part of their antioxidant activity is related to a direct interaction with NOO^- formed from NO.

In this context, 4-hydroxyphenyl 2-ammonioprop-1-yl selenide **102** protected plasmid DNA from peroxynitrite-mediated damage by scavenging this powerful cellular oxidant. The protective effect of **102** was potentiated by glutathione-mediated redox cycling of selenium forming 4-hydroxyphenyl 2-ammonioprop-1-yl selenoxide as the sole selenium-containing product (Scheme 11)[84].

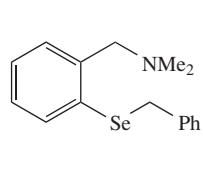


SCHEME 11

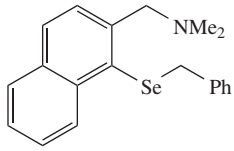
Saluk-Juszczak and collaborators[85] have compared the *in vitro* effect of bis(4-aminophenyl) diselenide **93** with ebselen **4** on the level of carbonyl group formation, tyrosine nitration and lipid peroxidation induced by peroxynitrite in plasma. The authors found that **93** and ebselen **4** have very similar protective effects against peroxynitrite-induced oxidative/nitrative damage to human plasma proteins and lipids.

The protection against peroxynitrite-mediated nitration reaction by diorganoselenides and sulfides has been investigated by Singh and coworkers. The data presented by the authors clearly demonstrated that selenides, having basic amino groups with weak intramolecular Se–N–C_{sp^3} interaction **103**–**105**, were more active than the selenides having imino groups with strong Se-N-C_{sp^2} interaction **106**–**109** (Chart 13) against peroxynitrite-mediated nitration reactions. The selenoxides of diorganoselenides, which can be reduced back to selenides, showed better protective action in the peroxynitrite assay. Intramolecularly coordinated diaryl selenoxides **110**–**112**, ferrocenyl selenides **113**–**116** and aryl benzyl selenoxides **117**–**123** (Chart 13), lacking a β-hydrogen, did not undergo any selenoxide elimination reaction[86].

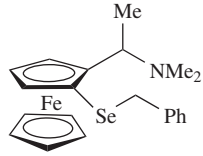
A number of studies emphasize that organoselenium compounds can effectively scavenge and eliminate reactive oxygen species. In this context, the scavenging effects



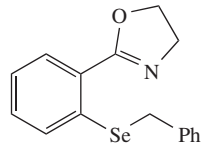
(**103**)



(**104**)



(**105**)



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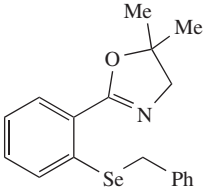
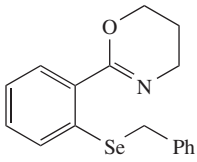
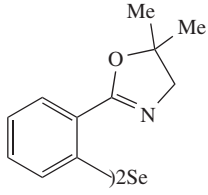


(**107**)



(**108**)



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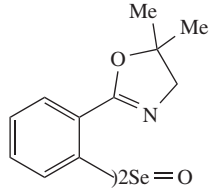
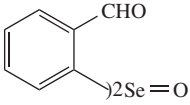


(**110**)



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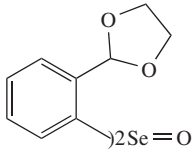

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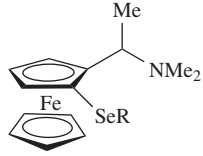
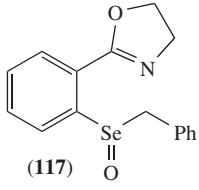
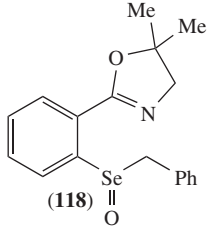


(**113**) R = Ph
(**114**) R = 2-MeC$_6$H$_4$
(**115**) R = 2,5-Me$_2$-4-*t*-BuC$_6$H$_2$
(**116**) R = Me



(**117**)



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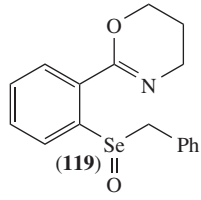
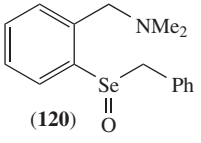
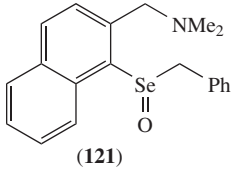


(**119**)



(**120**)



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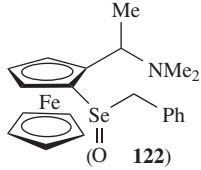

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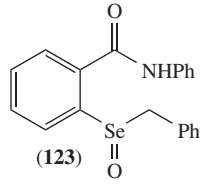


(**123**)

CHART 13

of tertiary selenoamide compounds for superoxide radicals were evaluated. Among the compounds tested, **124**–**126** (Chart 14) were the most potent scavengers of superoxide radicals *in vitro*[87].

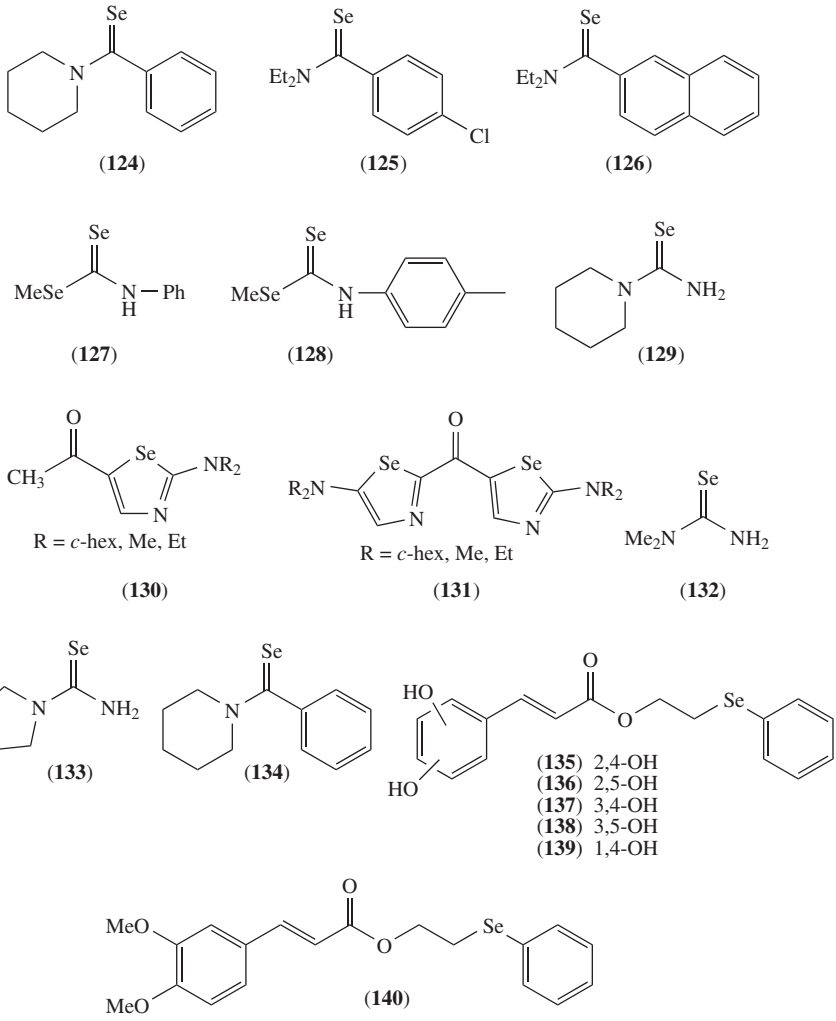


CHART 14

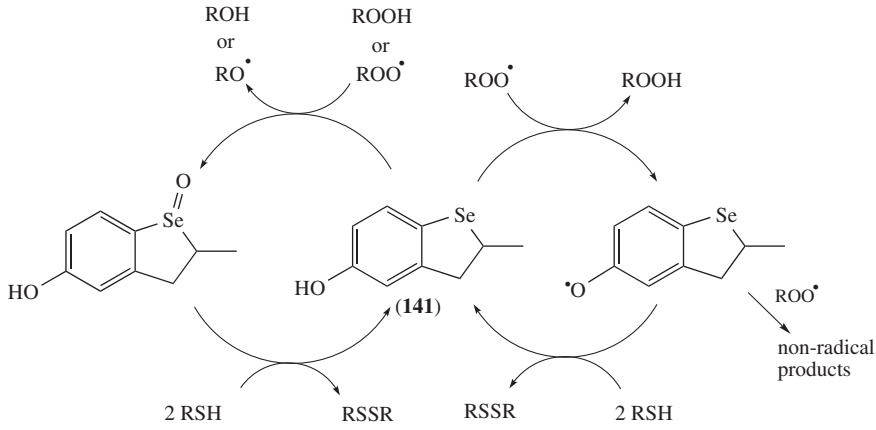
In addition, selenocarbamates and selenoureas were reported as superoxide anion scavenger compounds. In these *in vitro* studies Se-methyl-*N*-phenylselenocarbamate **127**, Se-methyl-*N*-(4-methylphenyl) selenocarbamate **128** and 1-selenocarbamoylpiperidine **129** had the most effective activity as scavengers of superoxide radicals[88]. The superoxide anion-scavenging activity of 2-amino-5-acyl-1,3-selenazoles **130** and bis(2-amino-5-selenazoyl)ketones **131** was also demonstrated (Chart 14)[89]. A subsequent work by

Koketsu and collaborators[90] reported the antioxidant activity of these organoselenium compounds in polymorphonuclear leukocytes (PMNs). As a result, *N*,*N*-dimethylselenourea **132**, 1-selenocarbamoylpyrrolidine **133**, *N*-(phenylselenocarbonyl)piperidine **134** (Chart 14) and *N*,*N*-diethyl-4-chloro selenobenzamide **125** effectively scavenged superoxide radical O^{2-} from PMNs.

In addition, the antioxidant efficiency of diseleno-bis(β-cyclodextrin) **81** was superior to ebselen **4** for scavenging hydrogen peroxide. **81** inhibited the increase of p53 expression level and the decrease of expression of Bcl-2 induced by ultraviolet (UVB) radiation. **81** was non-toxic for NIH3T3 cells[91].

The antioxidant capacity of a series of selenium-containing polyphenolic acid esters was investigated. It has been demonstrated that the substitution of dihydroxy group by methoxy group decreased dramatically the 1,1-diphenyl-2-picrylhydrazyl (DPPH)-scavenging activity. Thus the potency for quenching DPPH followed the order **139** > **137** > **138** > **135** > **140** (Chart 14). Moreover, the DPPH scavenger activity of **136** and **139** were similar. Therefore, compounds **136**, **139** and **137** were investigated in 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced lipid peroxidation and scavenging of peroxynitrite radical. The results pointed out that **136**, **139** and **137** showed antioxidative activity comparable to the caffeic acid[92].

In searching for simple synthetic chain-breaking antioxidants, Engman and collaborators revealed 2-methyl-2,3-dihydrobenzo[*b*]selenophene-5-ol **141** as an antioxidant; **141** was regenerated by water-soluble *N*-acetylcysteine in a two-phase model system for lipid peroxidation. The catalytic chain-breaking mechanism of **141**, shown in Scheme 12, involves an electron transfer from thiol to phenoxyl radical followed by proton transfer and dimerisation of the thiyl radicals[93]. Since this study was performed in a lipid phase, the authors planned a new work in which the antioxidant activity of **141** was performed in aqueous environment. Compound **141** was more potent in scavenging 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid diammonium salt) ABTS-radicals than trolox and ascorbic acid. In addition, low toxicity in five human cell-lines was reported for **141**[94].



SCHEME 12

Four new synthesized seleno-organic analogues of ebselen **4**, 2-(5-chloro-2-pyridyl)-7-azabenzisoselenazol-3(2*H*)-one **142**, 2-phenyl-7-azabenzisoselenazol-3(2*H*)-one **143**, 2-(pyridyl)-7-azabenzisoselenazol-3(2*H*)-one **144** and 7-azabenzisoselenazol-3(2*H*)-one

145 (Chart 15), and bis(*p*-aminophenyl) diselenide **93** were screened for antioxidant activity on oxidative changes in human blood platelets. Among these compounds only **93** prevented the generation of oxidized low-molecular-weight thiols (glutathione, cysteine, cysteinylglycine) in platelets. Compound **93** was more efficient than ebselen **4** against lipid peroxidation in platelets[95].

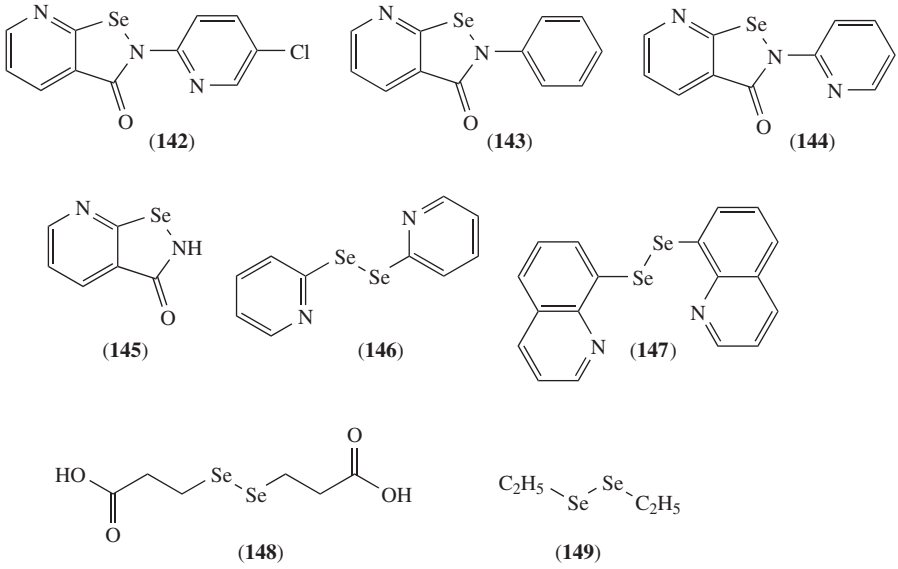


CHART 15

In attempt to test the hypothesis that simple agents that combine redox, catalytic and metal binding sites might act as multifunctional antioxidants, Collins and colleagues[96] have prepared dichalcogen derivatives of pyridine, aniline and quinoline. Thus all dichalcogens and their reduced analogues were redox active, but only the selenium compounds had GPx-like activity. Pyridine derivatives caused the largest shift in the Cu^{2+} reduction potential while aniline showed the smallest shift. The shift of the copper potential implies a lesser reduction of Cu^{+} ion, which could be beneficial since Cu^{+} is acting as an electron donor in the Fenton reaction. Compounds **146** and **93** reduced the loss of cell viability induced by ultraviolet (UVA) irradiation. In contrast, quinoline derivative **147** (Chart 15) showed a slightly protective effect against UVA irradiation.

A simple, stable and water-soluble diselenide derivative of selenocystine, 3,3′-diselenodipropionic acid **148** (Chart 15), was examined for *in vitro* antioxidant activity and cytotoxicity. Compound **148** is comparable to ebselen **4** in protecting red blood cells from hemolysis and is an excellent scavenger of peroxyl radicals. It shows GPx-like activity with higher substrate specificity toward peroxides than thiols. However, the catalytic activity of ebselen **4** is much higher than that of **148**. The cytotoxicity of **148** was studied in lymphocytes and EL4 tumor cells and the results showed that **148** is non-toxic to these cells at the concentrations employed[97].

The antioxidant activity of simple diaryl diselenides *in vitro* was demonstrated by us in 2004[80d]. This study demonstrates that diaryl diselenides, such as diphenyl diselenide **5** and bis(*p*-chlorophenyl) diselenide **90**, and dialkyl diselenides, such as diethyl diselenide **149** (Chart 15), dipropyl diselenide **96** and dibutyl diselenide **94**, were the most potent

antioxidants in brain homogenate of mouse *in vitro*[80d]. After the publication of this article a number of studies from our research group appeared in the literature demonstrating the *in vivo* antioxidant effect of diphenyl diselenide **5** in different models of oxidative stress in brain, kidney, liver of rodents and platelets of humans[98].

It is not clear whether altered physiological pH alters the antioxidant potential of **5**. Consequently, the effect of pH on the GPx mimic and other possible antioxidant mechanisms of **5** *in vitro* was investigated. On the one hand, **5** did not exhibit either free radical scavenging ability or Fe^{2+} chelating effect. However, it exhibited increasing ability to reduce Fe^{3+} with increasing pH. On the other hand, the GPx mimic of **5** was maximal at physiological pH and totally abolished in the acidic medium. Furthermore, irrespective of the pH of the medium, **5** significantly inhibited both deoxyribose degradation under hydrogen peroxide and Fe^{2+} assault and lipid peroxidation induced by either Fe^{2+} or sodium nitroprusside, suggesting that the antioxidant mechanism of **5** in the acidic medium may not be related to its generally accepted GPx-mimetic activity[99]. In this context, the antioxidative property of diaryl diselenides substituted with electron-withdrawing and electron-donating groups has been demonstrated. All diselenides **90**, **95** and **150** (Chart 16) tested were found to be protective against oxidative damage caused by sodium nitroprusside in brains of mice[100].

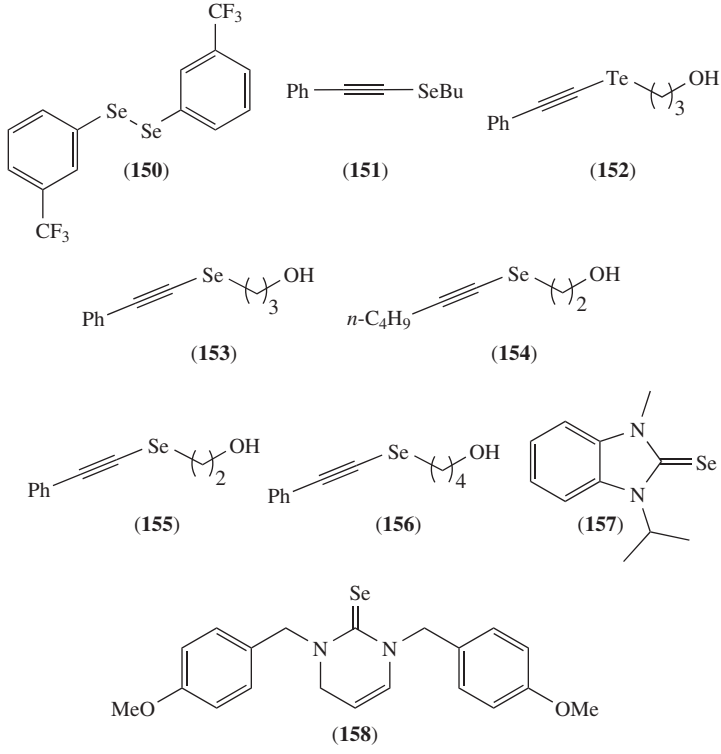


CHART 16

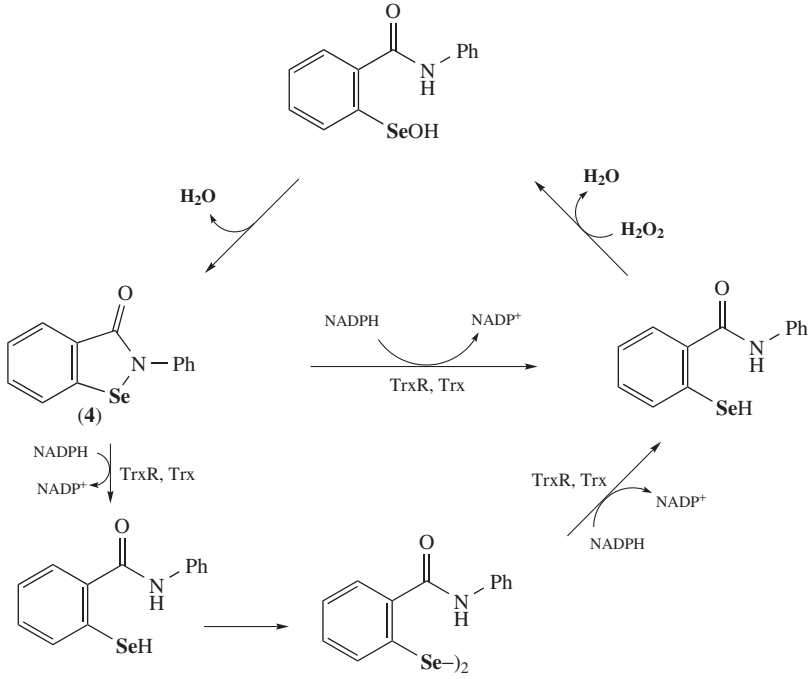
Furthermore, a series of alkynylselenoalcohols were screened for *in vitro* antioxidant activity. The results revealed that the antioxidant activity depends on their chemical

structures. Compounds **151** and **152** presented better antioxidant profiles than **153** (Chart 16) against lipid and protein oxidation. Compound **154** did not modify the effect of compound **155** (Chart 16) on lipid peroxidation. Compounds **151** and **152** showed DPPH radical-scavenging activity. Compounds **152**, **153** and **156** (Chart 16) inhibited isocitrate-mediated oxidation of Fe^{2+}. The modifications in the molecular structure of compound **153**, such as the absence of hydroxyl group and the presence of the tellurium atom, improved its overall antioxidant effect[101].

Talas and collaborators have reported the antioxidant effect of 1-*i*-propyl-3-methylbenzimidazole-2-selenone **157** and 1,3-di-*p*-methoxybenzylpyrimidine-2-selenone **158** (Chart 16) against 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced oxidative stress in lungs, kidney, heart, brain and erythrocytes of rats[102].

3. Thioredoxin reductase- and dehydroascorbate reductase-like activities

An increasing amount of evidence indicates that the antioxidant and anti-inflammatory effects of ebselen are, to a large extent, due to the reactions with the thioredoxin system. As demonstrated in Scheme 13, ebselen **4** is a highly efficient peroxiredoxin mimic catalyzing the hydroperoxide reduction by the mammalian thioredoxin (Trx) system. Ebselen can be rapidly reduced by both TrxR in the presence of NADPH or by reduced Trx to form the ebselen selenol, reacting with hydroperoxide yielding a selenenic acid derivative. Ebselen selenol can also suffer a rapid oxidation to form the ebselen diselenide that acts as a substrate for the mammalian TrxR, forming the active selenol as a final product[103].



SCHEME 13

The thioredoxin system comprises NADPH, thioredoxin (Trx) and thioredoxin reductase (TrxR). Thioredoxin reductase is a dimeric FAD-containing selenoenzyme that catalyzes the NADPH-dependent reduction of the active-site disulfide in oxidized thioredoxin to give a dithiol in reduced thioredoxin ($Trx(SH)_2$)[47c].

The mammalian thioredoxin system is a dehydroascorbic acid (DHA) reductase recycling ascorbic acid essential for cell functions[104]. In this way, Zhao and Holmgren[105] have reported the same phenomenon by ebselen and ebselen diselenide. In this report the authors demonstrated that in the presence of ebselen, ebselen selenol is rapidly formed by the mammalian TrxR and Trx and reduces dehydroascorbic acid more efficently due to the higher nucleophilicity and better leaving character of the arylselenolate moiety (Scheme 14).

Additionally, ebselen **4**, in the presence of physiological concentrations of glutathione, has been described as possessing dehydroascorbate reductase and thioltransferase (TTase)-like activities[106].

Mammalian thioredoxin reductases are particularly interesting because they are large selenoproteins and their structures show a close homology to glutathione reductase. Besides, thioredoxin reductases have wide substrate specificity[107], reducing not only different thioredoxins but also sodium selenite[108], selenodiglutathione **159**[109], selenocystine[110], selenenyl iodides **160**–**162**[111] and ebselen **4**[103a, b, 112]. (Chart 17).

Holmgren and coworkers have demonstrated that α-tocopherol-quinone can be reduced by ebselen **4**, in the presence of TrxR and NADPH. Therefore, ebselen acts as a tocopherol-quinone reductase mimic via TrxR by the mechanism depicted in Scheme 15. Ebselen forms ebselen selenol which partly dissociates in pH 7.5 forming the selenolate anion. The higher nucleophilicity and better leaving character of the selenolate anion makes effective attack on tocopherol-quinone and produces tocopherolhydroquinone, regenerating ebselen. The authors proposed that the ability of ebselen to reduce α-tocopherol-quinone via the thioredoxin system could be another mechanism that explains the effects of ebselen as an antioxidant *in vivo*[113].

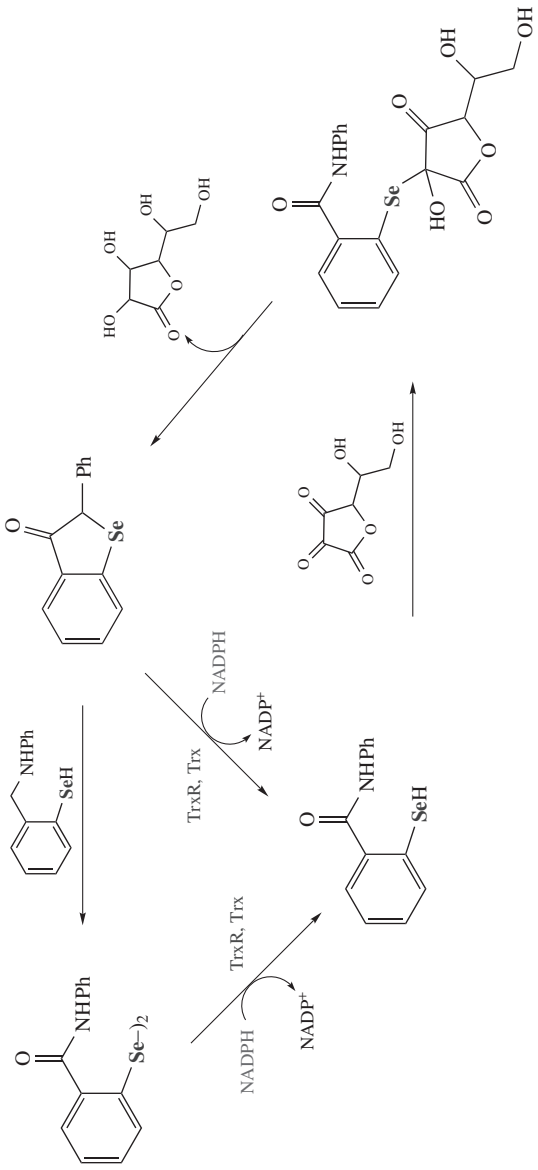
Thiredoxin reductase can reduce the selenenyl sulfide complex of serum albumin-ebselen and release free ebselen as demonstrated by Arteel and collaborators[83].

The fact that ebselen **4** is a good substrate for TrxR[112a] motivated us to test the hypothesis whether diphenyl diselenide **5** and its analogous bis(*m*-trifluoromethylphenyl) diselenide **150**, bis(*p*-methoxyphenyl) diselenide **95**, bis(*p*-carboxyphenyl) diselenide **163**, bis(*p*-chlorophenyl) diselenide **90** and bis(2,4,6-trimethylphenyl) diselenide **164** could be substrates for rat hepatic TrxR. As a result, **5**, **150**, **95** and **90** (Chart 18) stimulated NADPH oxidation in the presence of TrxR, indicating that they are good substrates for hepatic mammalian TrxR[114].

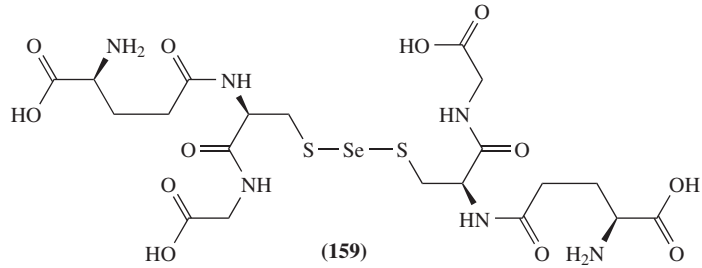
Although data regarding the dehydroascorbate reductase activity of simple diorganoyl diselenides and selenides are yet scarce in the literature, the DHA reductase-like activity of diphenyl diselenide **5** was reported. Thereupon we have proposed the mechanism, shown in Scheme 16, to explain the DHA reductase-like activity of **5**. In this proposed mechanism, **5** is reduced by reduced glutathione (GSH) to phenylselenol, giving the oxidized form glutathione disulfide, GSSG. Phenylselenol reacts with DHA to form phenylselenohemiketal, which reacts with another molecule of GSH to release ascorbic acid and the intermediate, phenyl selenoglutathione sulfide. This compound then reacts with another GSH to regenerate **5** and GSSG. Based on the reaction stoichiometry and the detection of **5** after DHA reductase-like assay, we suggest that this is a catalytic cycle[115].

4. Thioltransferase-like activity

From model studies, using bovine serum albumin, Nomura and coworkers reported that ebselen **4** rapidly binds to albumin *in vitro*[116]. In addition, the Nikawa group reported


NHPh
Se–)2
NADPH
NADP+
TrxR, Trx
NHPh
SeH
TrxR, Trx
NADPH
NADP+
Ph
Se
NHPh
SeH
NHPh
Se
HO
OH
OH
OH
OH
OH

SCHEME 14



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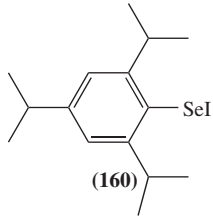

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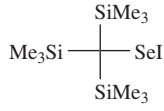

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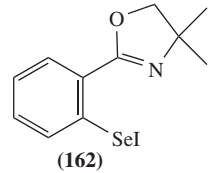
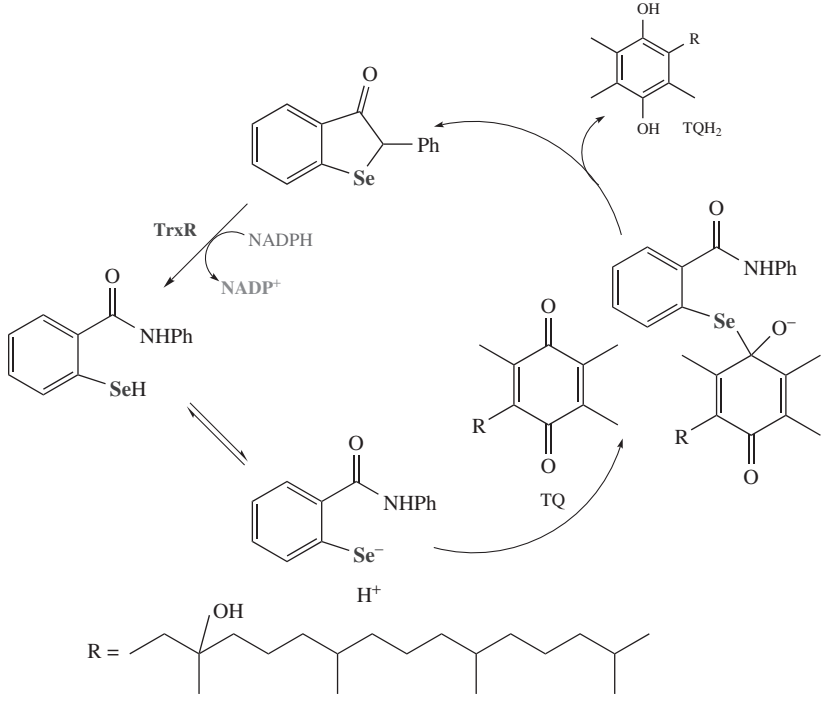


(162)

CHART 17



SCHEME 15

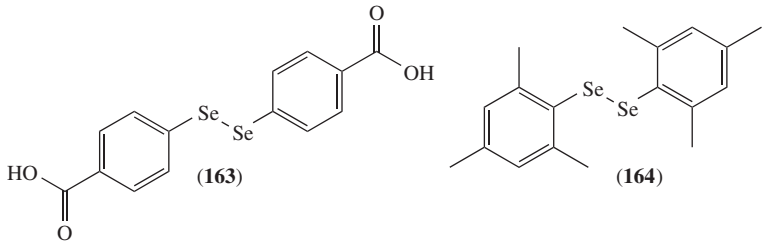
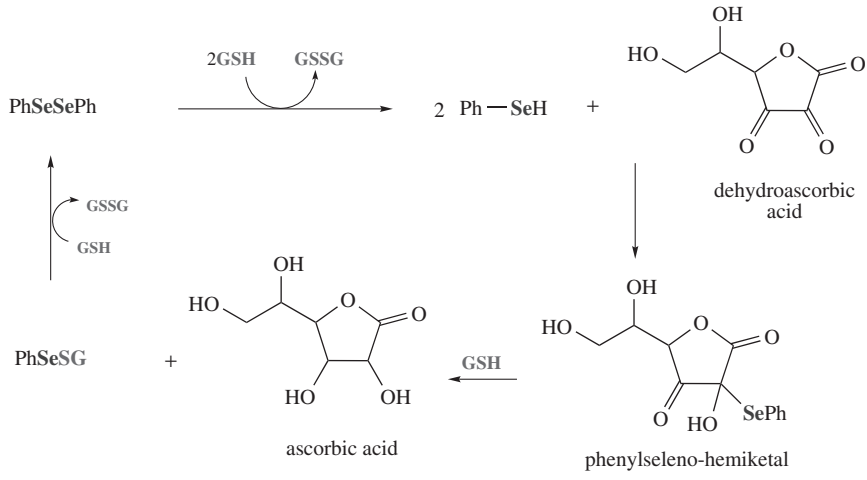


CHART 18



SCHEME 16

that ebselen interacts with glutathione S-transferase and papain by forming seleno-sulfide bonds[117]. In a related study, the same group suggests that ebselen is transferred from an albumin complex to rat liver cytosolic glutathione S-transferase by their sulfhydryl groups and concludes that this transfer may be necessary for uptake and distribution of ebselen in the cell[118]. Therefore, the multiple enzyme-like activities of ebselen, such as its GPx, TTase and DHA reductase, may contribute to ebselen's well-documented efficacy as a potent anti-inflammatory and antioxidative agent.

In this context, the thiol transferase-like activity (glutathione-S-transferase) of diphenyl diselenide **5** was demonstrated to be dependent on the presence of GSH. The reaction rate was essentially proportional to the concentration of **5**[115].

5. Anti-inflammatory and antinociceptive activities

The role of reactive oxygen species in tissue injury and particularly in inflammatory disorders has been the subject of intensive investigation[119]. Consequently, intensive research has been conducted to develop new drugs with low toxicity, which could potentially

scavenge reactive oxygen species. Of particular importance for the field of organoselenium compounds, ebselen **4** and other mimetics of GPx have been shown to be efficient anti-inflammatory agents in a wide range of *in vitro* and *in vivo* models of inflammation[120].

The anti-inflammatory effects of ebselen can be partially mediated by its selenol intermediate (formed after interaction of ebselen with GSH) via modulation of the peroxide tonus or via inhibition of the pro-inflammatory enzymes, 5- and 15-lipoxygenases, even in the absence of GSH[121].

The inhibitory effect of ebselen on nucleotide hydrolysis was first reported by the Sarkis group. Data presented by the authors showed that ebselen inhibited ATP and ADP hydrolysis in platelets of rats. The inhibition of nucleotide hydrolysis may represent an important approach for the use of ebselen as an anti-inflammatory agent[122].

The combination of ebselen and ethylhydroxyethyl cellulose on the acute phase responses and the severity of multiple organ dysfunction associated with acute pancreatitis was investigated. In this study, enteral nutrition supplemented with ebselen and ethylhydroxyethyl cellulose significantly prevented pancreatitis-induced multiple organ injury, IL-6 production and ICAM-1 expression in rats. Thus the combination of ebselen and ethylhydroxyethyl cellulose may be a new potential treatment of acute severe pancreatitis[123]. Recently, the anti-inflammatory activity of ebelsen has been attributed to be responsible for the improvement of lung function in transplanted rats[124].

Our group has also investigated the anti-inflammatory and antinociceptive activities of simple diaryl diselenides *in vivo*, thereupon concluding that diphenyl diselenide **5** displayed the most promising profile in carragenin-induced paw edema. In fact, bis(*p*-methoxyphenyl) diselenide **95** and bis(*p*-chlorophenyl) diselenide **90** were less efficient in inhibiting carragenin-induced edema than diphenyl diselenide. As well, bis(*p*-methylphenyl) diselenide **92** was the weakest inhibitor of paw edema. Besides, **5** was demonstrated to be an antinociceptive compound, due to its effective action on different experimental models of pain. Interestingly, the antinociceptive and anti-inflammatory potency of **5** was higher than ebselen[125].

Since oral administration of drugs has some advantages including greater ease and convenience, **5** was screened for antinociceptive action after oral administration to mice. It was as effective at a subcutaneous[125] as at an oral route in different chemical and thermal models of nociception in mice[126]. In an attempt to better understand the mechanisms by which **5** elicits its antinociceptive action, we have carried out pharmacological studies and demonstrated that **5** acts through multiple targets rather than a single one[127].

In order to test the hypothesis that the substitution of an H at the aryl group of diaryl diselenides by an electron-withdrawing group would affect the expected effect, the effects of bis(*p*-methoxyphenyl) diselenide **95** on chemical models of nociception in mice were investigated. Contrary to our hypothesis, the introduction of an electron-donating substituent in the aromatic ring of diselenide did not alter the pharmacological action of bis(*p*-methoxyphenyl) diselenide **95** when compared with **5**[128]. Additionally, we showed that multiple mechanisms are likely to be involved in the antinociceptive action of **95**[129].

The anti-inflammatory activity of diaryl diselenides has been also reported by other research groups. Shen and collaborators demonstrated that bis(2-hydroxyphenyl) diselenide **165**, bis(3-hydroxyphenyl) diselenide **166**, bis(4-hydroxyphenyl) diselenide **167**, bis(2-pyridyl) diselenide **168** (Chart 19) and diphenyl diselenide **5** significantly inhibited nitric oxide production in lipopolysaccharide-activated macrophage cells. **166** was the most potent inhibitor against lipopolysaccharide-induced nitric oxide, prostaglandin (PGE2), tumor necrosis factor-α (TNF-α) and interleukins (IL-1β and IL-6) production. Thus, **166** acts at the transcriptional level by blocking nuclear factor (NF-$_K$B) activation in RAW 264.7 macrophages[130].

The anti-inflammatory activity of 2-alkylselenyl benzoic acid derivatives and *p*-alkylselenobenzamides on granuloma induced by subcutaneous implantation of cotton

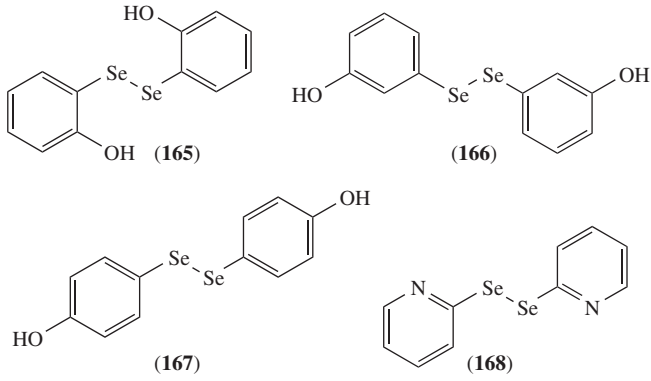


CHART 19

pellets in rats was reported. After a screening in the molecular docking analysis aiming to examine the interactions between selenium derivatives and the cyclooxygenase enzyme (COX-2), compounds **169**–**174** (Chart 20) were selected as the most suitable candidates to be evaluated in the granuloma bioassay. Thus it was found that 2-alkylselenyl benzoic acid derivatives **169**–**171** decreased the inflammatory process, while selected alkylselenobenzamides **172**–**174** did not have an anti-inflammatory effect[131].

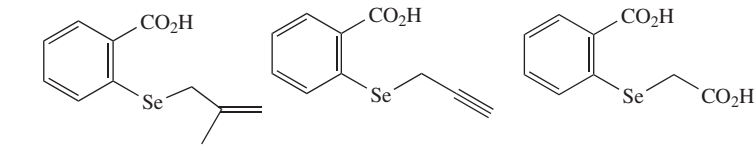
Heterocyclic pyridazines have attracted a lot of attention in view of the large variety of pharmacological activities. In this context, new series of selenolo[2,3*c*]pyridazine and pyrimido [4′,5′:4,5] selenolo[2,3*c*]pyridazine derivatives were evaluated as anti-inflammatory and antinociceptive compounds. Compounds **175**–**181** (Chart 20) were effective in inhibiting carragenin-induced paw edema in rats. The most active anti-inflammatory compounds **171** and **178**–**180** were tested for further antinociceptive action in the hot-plate test. The presence of amide group in position 2 of **180** reduced the antinociceptive activity as compared to the ketone **177**, the cyano **178** and the ester **179**[132].

In an extension of his study Abdel-Hafez reported anti-inflammatory and antinociceptive activities of selenolo[2,3*b*]quinolines and pyrimido[4′,5′:4,5] selenolo[2,3*b*] quinolines. Compounds **182**–**185** (Chart 21) were the most active in carragenin-induced paw edema in rats. It is important to point out that the conversion of **186** to **182** increased the anti-inflammatory activity. In general, the presence of the selenium atom in cyclic structures, e.g. **183**–**185**, increased the anti-inflammatory activity when compared to the open structure, e.g. **187** (Chart 21). Compounds **184** and **185** were also the most effective in the hot-plate test[133].

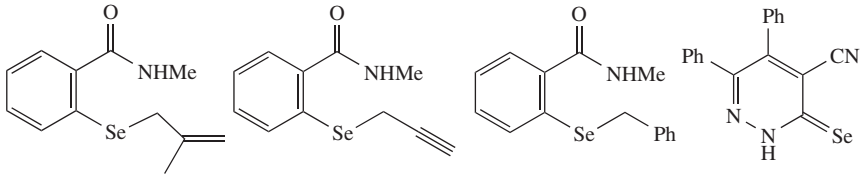
In addition, 3-alkynyl selenophene **188** (Chart 22) was proved to be an antinociceptive and antihyperalgesic agent in chemical and thermal models of pain in mice[134].

Bis selenide alkene derivatives **189a** and **189b** (Chart 22) were demonstrated to be effective in different models of pain without altering motor performance in mice[135]. By extending this study, we demonstrated that compounds **189a** and **189b** inhibited neurogenic and inflammatory pain in mice[136].

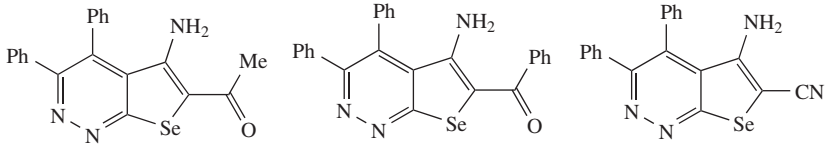
The antinociceptive activity of alkynylselenoalcohols has been reported. Compound **190** produced a significant inhibition of the acetic acid-induced abdominal constriction in mice, while **191** (Chart 22) did not cause significant inhibition of the nociceptive response. From this study, a structure–activity relationship can be distinguished, since the elongation of the carbon chain between Se and OH group in **191** completely abolished the antinociceptive activity of compound **190**[137].



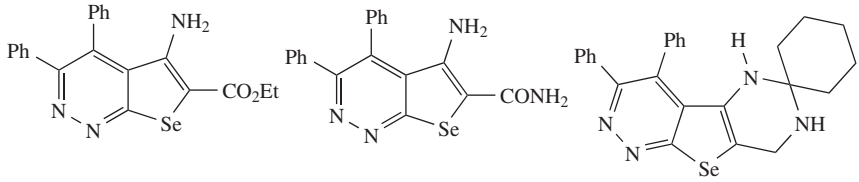
(**169**) (**170**) (**171**)



(**172**) (**173**) (**174**) (**175**)



(**176**) (**177**) (**178**)



(**179**) (**180**) (**181**)

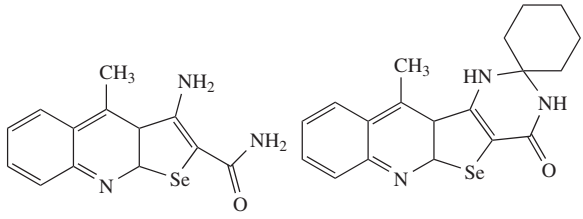
CHART 20

6. Antidepressant-like and anxiolytic activities

An important set of evidence has indicated that a low selenium status is associated with depressed mood, anxiety and cognitive decline[138]. Therefore, selenium supplementation could be associated with an improvement in mood and depression status[139].

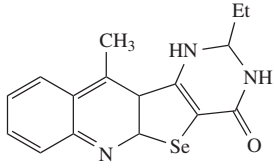
In this context, ebselen **4** was investigated as a possible antidepressant agent in two predictive tests for antidepressant activity in rodents: the forced swimming test (FST) and tail suspension test (TST). Ebselen ($10\,mg\,kg^{-1}$, s.c.) decreased the immobility time in the FST but did not produce any effect in the TST[140].

The antidepressant-like activity of bis selenide **189b** was recently revealed by using the mouse FST and TST. At $0.5–5\,mg\,kg^{-1}$ (p.o.) it reduced the immobility time in both tests[141]. In addition, we investigated if the chronic constriction injury (CCI) model of neuropathic pain causes depression-like behavior in animals and whether this behavior could be reversed by antidepressant drugs. Depressive behavior in CCI mice in the FST

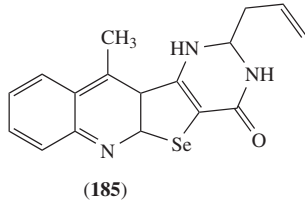


(**182**)

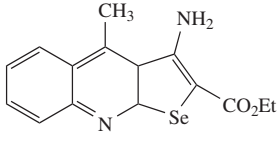
(**183**)



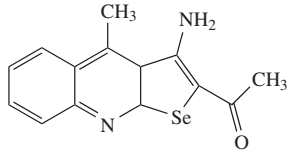
(**184**)



(**185**)

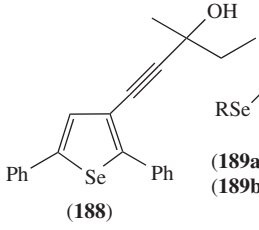


(**186**)

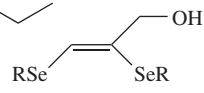


(**187**)

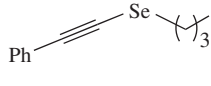
CHART 21



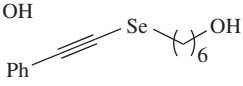
(**188**)



(**189a**) R = 2,4,6-$Me_3C_6H_2$
(**189b**) R = 4-ClC_6H_4



(**190**)



(**191**)

CHART 22

was reversed by **189b** and amitriptyline but not by the conventional antidepressants, fluoxetine and buproprion. Compound **189b** was more potent than the other drugs tested for antidepressant-like and antiallodynic effects in mice[142].

Diphenyl diselenide **5** at the dose range of 0.1–30 mg kg^{-1} (p.o) was reported as an antidepressant-like agent in the mouse FST[143] and TST[144]. Additionally, the antidepressant-like effect of repeated administration of **5** in rats exposed to the organophosphorus pesticide malathion was reported by us. Treatment with **5** (50 mg kg^{-1}, p.o) ameliorated the performance of rats in the FST, without altering the locomotor activity in the open-field test. Na^+, K^+ATPase activity is, at least in part, involved in the antidepressant-like effect of **5**[145].

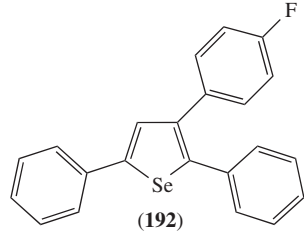
Diphenyl diselenide has been also proposed to have anxiolytic action in different animal models. In fact, **5** showed anxiolytic action in the elevated plus-maze, light-dark box and open-field tests. In rats, **5** (16 mg kg^{-1}, i.p.) increased the time spent and the entries in the open arms in the elevated plus-maze as well as decreased the number of fecal boli in the open field arena, with the absence of undesirable effects, such as alterations in locomotor activity or memory[146].

Moreover, administration of **5** (50–100 mg kg^{-1}, p.o) to mice increased the time spent and the entries in the open arms in the elevated plus-maze and increased the time spent in the illuminated side in the light-dark box[144a].

In parallel with these *in vivo* studies, we investigated the effect of diphenyl diselenide **5** and its disubstituted analogues on [^{3}H] serotonin uptake in rat synaptosomes. The results demonstrated that disubstituted diaryl diselenides **95** and **150** (1–100 μM) altered the monoaminergic system by inhibiting [^{3}H] serotonin uptake[147].

Motivated by the results on serotonin uptake *in vitro*, we provided pharmacological and neurochemical evidence for the anxiolytic effect of bis(*m*-trifluoromethylphenyl) diselenide **150** in mice. Administration of **150** (100 mg kg^{-1}, p.o) to mice produced a significant anxiolytic effect in two well-consolidated anxiety models, the elevated plus-maze and the light-dark choice test, without modifying the locomotor and exploratory activities. This study indicated that **150** is a selective inhibitor of monoamino oxidase A (MAO -A) activity in cerebral cortex of mice[148].

Recently, the potential antidepressant property of 3-(4-fluorophenyl)-2,5-diphenylselenophene **192** (Chart 23) was investigated. Selenophene **192** significantly reduced the immobility time during the FST and TST, without accompanying changes in ambulation when assessed in the open-field test. Pharmacological and neurochemical evidence indicates that the antidepressant-like effect of **192** seems most likely to be mediated through an interaction with the serotonergic system, particularly by 5-HT reuptake inhibition[149].



(**192**)

CHART 23

7. Hepatoprotective activity

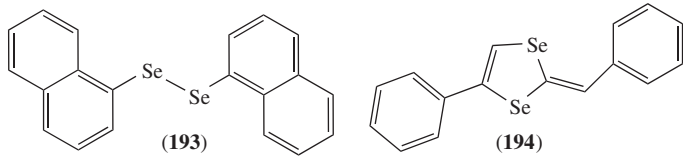
Ebselen **4** has been reported to inhibit both *in vitro* and *in vivo* hepatotoxicity induced by different agents, including galactosamine/endotoxin[150], paracetamol[151], CCl_4[152], *Propionibacterium acnes*[153], alcohol[154], ethanol-induced hepatic vasoconstriction[155], ischemia-reperfusion injury[156] and by lipopolysaccharide[157].

In addition, diphenyl diselenide **5** was investigated and proved to be effective against liver damage induced by 2-nitropropane[158], cadmium[159] and acetominophen[160]. Conversely, repeated administration of **5** potentiated hepatotoxicity induced by CCl_4 in rats. It has been accepted that inhibitors of CYP 450s can impair the bioactivation of CCl_4 into their respective reactive species and thus provide protection against the hepatocellular damage[161]. Thus pharmacological evidence supports the hypothesis that **5**

activates CCl_4 biotransformation by inducing hepatic CYPs, potentiating CCl_4-induced hepatic damage[162].

In an attempt to better understand the influence of functional groups in the aryl group of diaryl diselenide, the effect of bis(*m*-trifluoromethylphenyl) diselenide **150**, using 2-nitropropane-induced hepatic damage, has been studied. Thus it was found that **150** protected against hepatotoxicity induced by 2-nitropropane, suggesting that the introduction of the CF_3 group on the aryl group of diaryl diselenide does not alter its protective effect against liver damage[163]. Additionally, the effect of the methoxy group in the hepatoprotective effect of diaryl diselenide was investigated. Bis(*p*-methoxyphenyl) diselenide **95** was effective in attenuating liver failure induced by lipopolysaccharide and D-galactosamine in mice[164].

In this context, bis(1-naphthyl) diselenide **193** (Chart 24) was demonstrated to be hepatoprotective against 2-nitropropane-induced damage. Thus, the introduction of a naphthyl group at the selenium atom generating binaphthyl diselenide confers a very similar hepatoprotective action to this molecule as compared with **5**[165]. Using the same experimental model of liver damage, a five-membered ring containing two selenium atoms, namely (*E*)-2-benzylidene-4-phenyl-1,3-diselenole **194** (Chart 24), was reported to be a hepatoprotective agent in rats[166].



(**193**) (**194**)

CHART 24

The 3-alkynylselenophene **188** has been proved to be effective against different models of hepatic damage in rats. In fact, the hepatoprotective action of compound **188** on lipopolysaccharide and D-galactosamine, CCl_4 and 2-nitropropane induced acute liver injury in rats was reported[167].

Motivated by the ability of diseleno-bis(β-cyclodextrin) **81** in mimicking GPx activity and its water solubility[91], Lin and coworkers have demonstrated that **81** inhibits inflammation and apoptosis after ischemia/reperfusion of rat liver[168]. The authors consider **81** as a very promising candidate to prevent oxidative tissue damage encountered in the course of various surgical treatments.

8. Gastroprotective activity

Ebselen **4** has been effective in preventing ulceration induced by aspirin, diclofenac[169], HCl and acidified ethanol[170], 48/80 compound[171], ethanol[172] and water-immersion restraint stress[173]. Similarly, diphenyl diselenide **5** prevented and reversed ethanol and indomethacin-induced ulcers as well as inhibited gastric acid secretion in pylorus-ligated rats[174]. The anti-ulcerogenic effects of ebselen[175] and **5** can be related to inactivation of the sulfhydryl-containing enzyme H^+, K^+ ATPase.

9. Renoprotective activity

Ebselen **4** has been shown to be protective against ischemic acute renal failure injury, improving renal function due to suppression of peroxynitrite production or its scavenging

activity, consequently preventing lipid peroxidation and oxidative DNA damage[176]. The scavenging peroxynitrite activity of ebselen has been implicated in the amelioration of microvasculopathy and angiogenesis of nephropathy in Zucker diabetic fat rats[177].

The nephrotoxicity of cisplatin, a highly effective antineoplastic DNA alkylating agent, has been well documented. Thus ebselen alone or combined with allopurinol has been reported to significantly reduce cisplatin-associated nephorotoxicity[178].

Despite beneficial effects of gentamicin, a widely used amino glycoside antibiotic, it has considerable nephrotoxic effects. In this context, ebselen protected against gentamicin-induced oxidative and nitrosative renal damage[179].

Recently, our research group has reported that diphenyl diselenide **5** and bis(1-naphthyl) diselenide **193** were effective in protecting against acute renal failure induced by glycerol[180].

10. Cardioprotective activity

It is well known that extreme dietary selenium deficiencies lead to endemic Keshan and Kashin-Beck disease. As well, an inverse correlation exists between the appearance of some cardiopathies and low selenium levels in the blood[181]. Therefore, selenium status has been associated with cardiovascular disorders. Hypercholesterolemia has been also associated to selenium deficiency[182], which leads to an increased activity of 3-hydroxy-3-methylglutaryl-CoA reductase, the rate-controlling enzyme in the cholesterol biosynthesis, that in turn resulted in increased endogenous cholesterol synthesis[183].

In this context, organoselenium compounds have been investigated in different models of cardiovascular damage. Ebselen **4** was evaluated in daunorubicin-induced cardiomyopathy in rats and proved to be effective. In fact the results obtained by Saad and collaborators clearly demonstrated that ebselen normalized serum cardiac enzymes creatine kinase, lactate dehydrogenase and glutathione peroxidase[184].

Considering that atherosclerosis affects the vascular wall and leads to coronary artery diseases, and that lipoprotein oxidation is a key early stage in the development of atherosclerosis, the potential beneficial effect of diphenyl diselenide **5** in protecting low-density lipoprotein (LDL) oxidation *in vitro* was investigated. The results point out that **5** inhibited lipid peroxidation and prevented the oxidation of protein moieties in human isolated LDL *in vitro*. The thiol-peroxidase activity was demonstrated to be involved in **5** antioxidant effect[185]. Since hyperlipidaemia is one of the major risk factors for atherosclerosis, the hypolipidaemic potential of **5** was examined in cholesterol-fed rabbits. As a result, supplementation with 10 ppm **5** reduced approximately twofold total cholesterol levels as compared to cholesterol-fed rabbits[186]. Data from the Triton WR-1339 model of hyperlipidaemia further support the hypolipidaemic potential of **5**[187].

In addition, results from Ali's group revealed that ebselen attenuates H_2O_2-induced endothelial cell death through the inhibition of signaling pathways mediated by p38 MAP kinase, caspase-3 and cytochrome c release, suggesting ebselen as a potential drug for treatment of atherosclerosis[188].

Ebselen reduces nitration and restores voltage-gated potassium channel function in small coronary arteries of diabetic rats. Therefore, ebselen may be beneficial for the therapeutic treatment of vascular complications[189].

Compounds **157** and **158** were evaluated for their antihypertensive and therapeutic properties by adrenomedullin peptide hormone levels, tyrosine hydroxylase activity and RNA total levels in rat heart tissue. **157** and **158** elevated adrenomedullin levels and tyrosine hydroxylase activity and total RNA levels reduced by DMBA in the heart of rats, suggesting that these organoselenium compounds might play an important role in suppression of oxidative stress, homeostasis of blood pressure and cardiovascular function[190].

11. Insulin-mimetic activity

Selenium mainly in the selenate form has been reported to mediate a number of insulin-like actions. A very comprehensive review by Stapleton covered some of the findings that support selenate as an effective insulin-mimetic and potential antidiabetic agent[191]. However, current knowledge concerning the hypoglycemic action of selenium compounds is limited to inorganic derivatives.

Regarding organoselenium compounds, few studies on insulin-like activity have appeared in the literature in recent years. Thus chronic treatment with **5**, but not ebselen **4**, caused a significant reduction in blood glucose levels, glycated proteins and some parameters of oxidative stress of streptozotocin-treated rats[192]. Moreover, **5** supplementation contributed to the prevention of diabetic complications associated to oxidative stress[193].

Selenium in the diet exists mainly as selenoamino acids, therefore hypoglycemic properties of methylselenocysteine **21** in alloxan diabetic rats were investigated. The result is that **21** normalized blood glucose concentration and renal function in diabetic rats[194].

12. Neuroprotective activity

With regard to neuroprotection, ebselen **4** has been suggested to protect against brain damage from different models of permanent focal ischemia[195], transient focal ischemia[196] and hypoxia/ischemia-induced neuronal damage[197]. It was also reported that ebselen ameliorated cerebral vasospasm in a canine two-hemorrhage model[198], inhibited cerebral vasospasm after subarachnoid hemorrhage in rats and primates[199], protected against cerebral ischemia and accelerated the recovery during reperfusion[200]. Moreover, long-term administration of ebselen was effective against cerebral injury in stroke-prone spontaneously hypertensive rats. The inhibition of inducible nitric oxide synthase (iNOS) protein expression is involved in ebselen neuroprotective effect[201].

Oxidative DNA damage has been proposed to be a major contributor to focal cerebral ischemic injury. Therefore, the possible role of oxidative damage in the degeneration of the thalamic ventroposterior nucleus after focal cerebral cortical infarction in hypertensive rats was investigated. The data showed that ebselen attenuated oxidative DNA damage, enhanced its repair activity and protected the thalamus against the secondary damage[202].

Additionally, Arakawa and collaborators demonstrated that pretreatment with a low concentration of *N*-acetylcysteine potentiates the neuroprotective effect of ebselen against hydroxynonenal-induced neurotoxicity in cerebellar granule neurons. These data further suggest that ebselen exerts a neuroprotective effect under conditions of increased glutathione production, a consequence of *N*-acetylcysteine pretreatment[203].

Ebselen has been also suggested to protect the brain against oxygen and glucose deprivation, an *in vitro* ischemic model[204]. As ischemic insults decrease cellular glutathione levels Shi and coworkers[205] have investigated the role of glutathione in ebselen-induced cell death under ischemia. Thus the study provides persuasive evidence that depletion of cellular glutathione plays an important role in ebselen increased C6 glioma cell damage under ischemic condition.

Moreover, the capacity of ebselen to protect astrocytes against degeneration caused by an *in vitro* model of ischemia and simultaneous depletion of glutathione was investigated. In this study, toxicity of simulated ischemia was attenuated in a concentration-dependent manner by ebselen[206]. Pawlas and Malecki demonstrated that ebselen normalized neuronal viability and increased glutathione levels in normoxia and ischemia[207].

The mechanism behind neuroprotective effect of ebselen against ischemic damage in the hippocampal CA1 region was disclosed. Thus the authors reported a set of evidence demonstrating that GABA shunt enzymes are involved in the neuroprotective

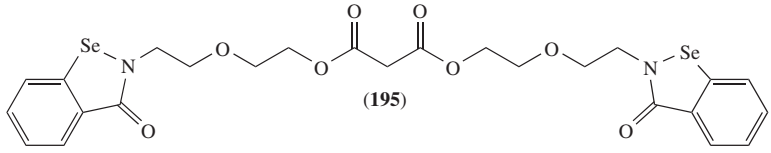
effect of ebselen. Treatment with ebselen increased the expression of glutamic acid decarboxylase (GAD), GABA transaminase (GABA-T) and succinic semialdehyde dehydrogenase (SSADH) in the hippocampal CA1 region[208].

Although Salom and collaborators reported that ebselen did not provide neuroprotection to rats subjected to severe focal ischemia[209], data from clinical trials have consistently demonstrated that ebselen reduced brain damage in patients with delayed neurological deficits after aneurismal subarachnoid hemorrhage[4a] and improved the outcome of acute ischemic stroke, suggesting that ebselen may be a promising neuroprotective agent[4b].

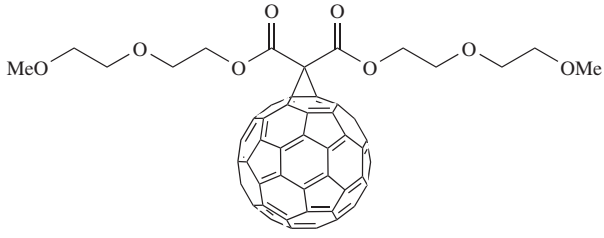
Data from our research group have clearly indicated that ebselen protects neuronal cells from injury induced by glutamate by blocking lipid peroxidation and inhibiting the synaptosomal release of glutamate[13c, 210]. However, ebselen displayed a dual effect on vesicular glutamate uptake. In fact, low concentrations of ebselen increased, while high concentrations inhibited, the vesicular glutamate uptake[211].

The mechanisms underlying the neuroprotective actions of ebselen have been explored. In this way, data from Zhang's group demonstrated that the neuroprotective effects of ebselen are associated with the regulation of Bcl-2 and Bax proteins but are unrelated to glutamate-mediated elevation of intracellular calcium[212].

Consistent with these findings, studies *in vivo* have found that ebselen has neuroprotective effects against spinal cord injury in rats. Ebselen has neuroprotective and restoring effects on secondary pathochemical events after spinal cord injury, suggesting that ebselen treatment might have potential benefit in spinal cord tissue damage on clinical grounds[213]. In view of the well-reported antioxidative and neuroprotective properties of ebselen, the hypothesis tested by Liu and coworkers[214] is that the covalent attachment of the biologically active ebselen moiety to C_{60}-fullerene may lead to the formation of a new C_{60}-based ebselen derivative (Chart 25). The results showed that the antioxidative and protective activities of **196** against H_2O_2-mediated neuronal injury were significantly higher than those of C_{60}-derivative **196**, ebselen derivative **195** and the equimolar mixture of **196** and **195**.



(**195**)



(**196**)

CHART 25

Even though ebselen is a redox regulator, neuronal differentiation induced by ebselen has been attributed to activation of the classical Ras/MAPK (mitogen-activated protein kinase) cascade rather than to regulation of the redox state[215].

To test the hypothesis that a scavenging peroxynitrite attenuates noise-induced excitotoxicity, ebselen was investigated in Guinea pigs. Thus Yamasoba and coworkers[216] demonstrated that ebselen prevented noise-induced excitotoxicity and temporary threshold shift, suggesting its potential clinical use to prevent or treat noise-induced hearing loss in humans.

The idea that immobilization stress induces cell death through production of reactive oxygen species was further proved by the use of the antioxidant agent ebselen. By mechanisms mediated by NADPH oxidase, interleukin-1β (IL-1β) or cyclooxygenase 2 (COX-2), ebselen inhibited the mouse cerebral cortex cell death induced by immobilization stress[217].

Despite the well-documented neuroprorective effect of ebselen in different experimental *in vitro* and *in vivo* conditions, this organoselenium compound does not appear to exhibit neuroprotective effects against dopaminergic toxicity induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the nigrostriatal tract of mice[218]. In addition to neuroprotective effect against superoxide dismutase 1 (SOD1) related familial motor neuron degeneration[219], alcohol-induced rat hippocampal stress[220] and demyelination lesion caused by ethidium bromide[221], ebselen has been also described by others and us to produce an antioxidant effect at multiple steps in different experimental models of neurotoxicity[79d, 80b, 210, 222].

In this context, neuroprotective effects of other glutathione peroxidase mimetics have appeared in the literature in the past years[223]. Based on the idea that ebselen **4** has not only antioxidant activity but also the ability to modulate intracellular signaling, the effect of three different selenazoles, 5-chloroacetyl-2-piperidino-1,3-selenazole **197**, 5-chloroacetyl-2-morpholino-1,3-selenazole **198** and 5-chloroacetyl-2-dimethylamino-1,3-selenazole **199** (Chart 26), were investigated in Ras/mitogen-activated protein kinase (MAPK) cascade. The results demonstrated that all selenazoles tested stimulated the phosphorylation of Akt and MAP kinase, suppressed serum-deprivation-induced apoptosis and facilitated the neuronal differentiation of cultured cells of the PC12 pheochromocytoma cell line. Therefore, these selenazoles are promising candidates as neuroprotective and neurotrophic agents[224]. By testing the same selenazoles Nam and coworkers reported that **197** and **198** inhibited lipopolysaccharide-induced nitric oxide release from microglial cells, by reducing production of nitric oxide, tumor necrosis factor (TNF)-α and prostaglandin E2 and suppressing factor-$_K$B and Akt[225].

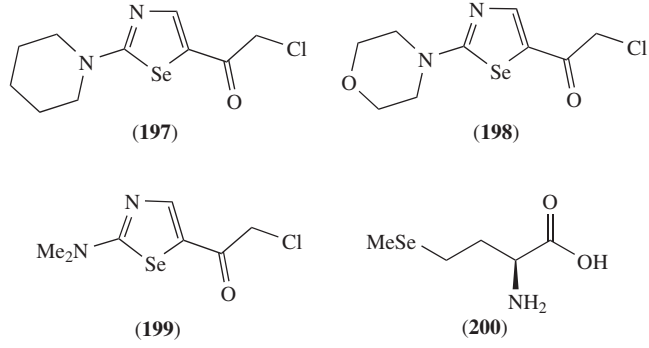


CHART 26

Selenomethionine **200** (Chart 26), the major component of dietary selenium, was investigated against β-amyloid and Fe^{2+}/H_2O_2-mediated neuron death. Pretreatment of primary

cortical neurons with selenomethionine decreased free radical production by β-amyloid and Fe^{2+}/H_2O_2 and increased glutathione peroxidase activity, suggesting its potential use as a therapeutic agent in neurodegenerative diseases[226].

Diphenyl diselenide **5** has been demonstrated as a neuroprotector agent in a classical model of *in vitro* ischemia[227]. Interestingly, ebselen and **5** blocked the increase in inducible nitric oxide synthase (iNOS) overexpression caused by glucose and oxygen deprivation in rat brain slices. Although there is a scarcity of studies on the molecular mechanisms behind neuroprotective action of **5**, a decrease in lipid peroxidation and inhibition of H_2O_2-induced MAPKs phosphorylation (ERK-1/2 activation) have been demonstrated[228]. The prevention of ecto-enzymes modulation, essential for the maintenance of purinergic/glutamatergic signaling interaction, has been also reported as a mechanism by which **5** protects against glutamate toxicity[229].

Considering that hyperphosphorylation of cytoskeletal proteins is associated with neuronal dysfunction and neurodegeneration, **5** and ebselen were able to prevent methylmercury- and diphenyl ditelluride-induced hyperphosphorylation of the high-salt Triton insoluble neurofilament subunits (NF-M and NF-L), glial fibrillary acidic protein (GFAP) and vimentin in cerebral cortex of young rats[31, 230].

Tardive dyskinesia, a serious neurological syndrome characterized by involuntary orofacial movements, is most frequently found in older patients using typical antipsychotic agents. We have investigated the effect of organoselenium compounds in dyskinesia induced by antipsychotics in rats. Thus **5** showed modest protective effects on reserpine-induced orofacial dyskinesia in old rats[231], while it decreased the prevalence of vacuous chewing movements induced by fluphenazine[232]. In addition, both **5** and ebselen attenuated dyskinesia induced by haloperidol[233]. The results reported by Burger and coworkers further support the idea that ebselen decreases orofacial dyskinesia caused by acute administration of reserpine[234].

It has been documented that low selenium concentrations in the eldery were significantly associated with senility and cognitive decline[235]. Accordingly, **5** has been demonstrated to be an inductor of facilitation of long-term object recognition memory and of acquisition and retention of spatial memory in rats[236]. Moreover, bis(*p*-methoxyphenyl) diselenide **95** was able to reverse the learning and memory impairments induced by intracerebroventricular injection of streptozotocin, a model of sporadic dementia of Alzheimer's type, in mice. The impairment of learning and memory was accompanied by increasing activity of cerebral acetylcholinesterase and **95** normalized the enzyme activity[237].

In a model of apomorphine-induced stereotypy in mice, bis(*m*-trifluoromethylphenyl) diselenide **150** attenuated behavioral features associated with a mouse model of psychosis. Of particular importance is the authors observation that at the highest dose used ($25\,\mu mol\,kg^{-1}$), **150** did not affect open-field behavior, habituation or aversively motivated memory[238].

Additionally, **150** has been reported as an anticonvulsant agent against pentylenetetrazole-induced seizures in mice. The detailed mechanism behind the anticonvulsant action remains incompletely understood; however, it appears to involve the reduction of GABA levels in the synaptic cleft by inhibiting GABA uptake[239].

The anticonvulsant action of other organoselenium compound, namely 3-alkynyl selenophene **188**, has been evaluated. As a result, **188** protected against seizures induced by pilocarpine in 21-day-old rats. In this study an antioxidant action of **188** in pilocarpine model was also demonstrated[240].

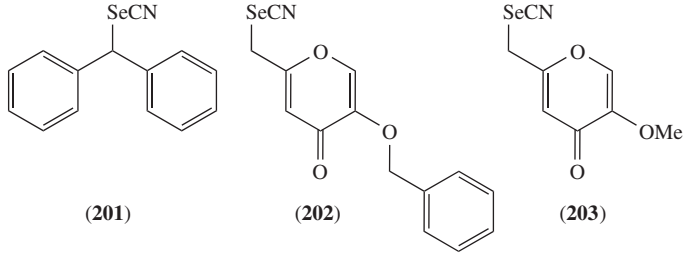
13. Chemopreventive activity

The epidemiological points of evidence indicating that selenium can protect human cancinogenesis[241] have been recently questioned[241w]. Indeed, it has been suggested that

overexposure to dietary selenium can increase the incidence of some types of cancer, which contrast with experimental models demonstrating that synthetic organoselenium compounds are chemopreventive agents in laboratory animals[242].

Benzyl selenocyanate and derivatives have been found to be effective as chemopreventive agents against different types of cancer[243]. Based on mechanistic and metabolic studies[244], the structure of benzyl selenocyanate[245] was modified to develop a more effective and less toxic[246] chemopreventive agent. As a consequence, *p*-phenylenebis(methylene) selenocyanate arose as a compound less toxic than benzyl selenocyanate[247]. No attempt is made here to thoroughly discuss the chemopreventive effects of *p*-phenylenebis(methylene) selenocyanate, as these have been adequately reviewed elsewhere[3a, 248].

Additionally, diphenylmethyl selenocyanate **201** was evaluated for its ability to act as a chemoprotective agent against 7,12-dimethylbenz[*a*]anthracene (DMBA)–croton oil two-stage mouse skin carcinogenesis model. The chemopreventive effect of **201** was related to the modulation of phase II detoxifying enzyme activity and inhibition of membrane lipid peroxidation in the target organ skin. Therefore, a non-toxic dose of **201** had maximum effect regarding the decrease in incidence and multiplicity of skin papilloma, inhibited cell proliferation and induction of caspase-3-mediated apoptosis[249]. Diphenylmethyl selenocyanate **201** (Chart 27) was able to reduce the cellular toxicity of cyclophosphamide and improves its tumor efficacy in mice bearing Ehrlich ascites carcinoma[250].



(**201**) (**202**) (**203**)

CHART 27

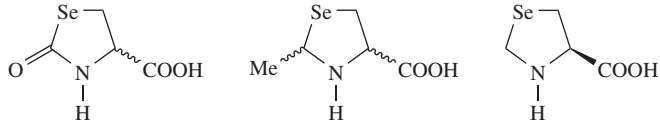
Since suforaphane, the major metabolite of broccoli responsible for its anti-cancer properties, is one of the most potent Nrf2 inducers known, the authors investigated if the substitution of sulfur with selenium in the isothiocyanate functional group of suforaphane would result in an isoselenocyanate compound with enhanced nuclear factor-erythroid 2-related factor 2 (Nrf2) induction capability. As a result, suforaphane isoselenocyanate activated an antioxidant response element (ARE)-luciferase reporter in HepG2 cells more potently than suforaphane. It was also found that suforaphane isoselenocyanate induced GSH biosynthetic enzymes including the rate-limiting glutamate cysteine ligase (GCL), as well as other Phase II detoxification enzymes results from SFN-mediated induction of Nrf2/ARE signaling pathway[251].

Derivatives and analogues of kojic acid, 5-hydroxy-2-hydroxymethyl-4-pyranone, are distinguished by increased biological activities than the maternal compound alone, especially those with antiproliferative properties in neoplastic cells. This idea motivated the search for novel selenocyanatomethyl derivatives of kojic acid as potential antiproliferative and cytotoxic agents. 5-Benzyloxy-2-selenocyanatomethyl **202** and 5-methoxy pyranone derivatives **203** (Chart 27) inhibited the growth of either human skin carcinoma A431 or human breast carcinoma MCF7 cells in a time- and dose-dependent manner. The **202**

derivative of kojic acid was more effective in inhibiting cell growth than **203**. The data on lactate dehydrogenase assay demonstrated an exaggerated cytotoxic effect of **202**. The results reported by Fickova and collaborators further suggest that the substitution of sulfur for selenium did not affect considerably the antineoplastic activity of both 5-benzyloxy kojic acid derivatives[252].

Naturally-occurring selenium-containing amino acids, such as methylselenocysteine **21** and selenocysteine **20**, have been extensively studied as chemopreventive agents[253].

In addition, promising results were observed with the novel selenazolidines **204**–**206** (Chart 28), prodrugs of selenocysteine **20**, as potential selenium delivery agents for cancer chemoprevention[254].



(**204a**) L
(**204b**) D

(**205a**) L
(**205b**) D

(**206**) L

CHART 28

Selenocystine and selenodiglutathione have also been reported to inhibit phorbol ester-induced transformation of epidermal cells[255]. A mechanistic study of *in vitro* anticancer activity of selenocystine revealed that reactive oxygen species play a key role in the signaling pathway of selenocystine-mediated apoptosis in susceptible cancer cells[256].

3,3′-Diselenodipropionic acid **148**, a derivative of selenocystine, was reported to be protective against whole-body exposure to γ-radiation in mice. The mechanisms of action involve the maintenance of antioxidant enzymes, prophylactic action through the attenuation of the DNA damage and inhibition of apoptosis[257].

The study elegantly performed by Spallholz and coworkers investigated organic selenoamino acids, selenomethionine **200** and methylselenocysteine **21** for their toxicity and mutagenicity as well as potential detrimental effects on DNA yeast *Saccharomyces cerevisiae*. The results demonstrated that sodium selenite, but not selenomethionine **200** and methylselenocysteine **21**, is toxic and may be mutagenic in yeasts[258]. Compound **21** holds effective potential as a chemopreventive agent against tumorogenesis *in vivo*[259] and *in vitro*[260]. In this context, Cao and collaborators reported that the combination of **21** and the chemotherapy drug irinotecan significantly increased the cure rates of human head and neck xenografts and protected animals from irinotecan-induced death[261].

The selenium supplementation in human trials has revealed that L-selenomethionine **200** reduced the incidence of colon, lung, and prostate cancer by nearly 50%[262]. Accordingly, supplementation with only **200** is the focus of the present ongoing National Cancer Institute (NCI) sponsored SELECT Trial for the prevention of prostate cancer in men over 50 years of age (http://www.crab.org/select/).

Methylselenol **207** (Chart 29) from selenium metabolism is postulated to be, and most experimental evidence now indicates that it is, the selenium metabolite responsible for the dietary chemoprevention of cancers. The study of Spallholz further confirmed that methylselenol, a metabolite of methioninase catalysis of selenomethionine, generates superoxide in the presence of glutathione. Further, **21** *in vivo* is very likely carcinostatic in a similar manner to **200** by generating **207** from other enzymatic activity, i.e. β-lyase or amino acid oxidases. Redox cycling, oxidative stress-induced apoptosis by

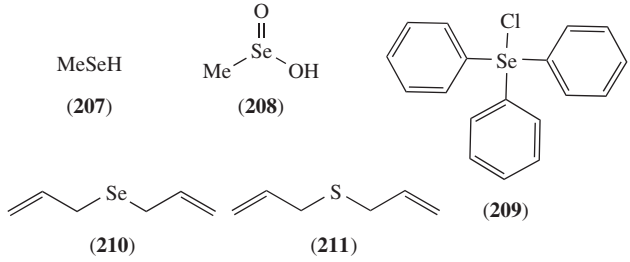


CHART 29

methyl and other selenides appear to account for the carcinostatic attributes of selenium supplementation to animals and humans[263].

Methylselenocysteine **21** and methylseleninic acid **208** (Chart 29) are believed to be the direct precursors of methylselenol **207**, possibly the key metabolite responsible for selenium's anticancer activity[264]. Accordingly, **208** has been reported to protect against prostate cancer by inhibiting cell proliferation, by modulating the expression of androgen receptor and androgen receptor-regulated genes and by inducing carcinogen defenses[265].

In addition, the synergistic effect of **208** on growth-inhibitory action and resistance of tamoxifen in breast cancer cells has been reported. The growth inhibition synergy and reversal of tamoxifen resistance occurs via the increase in G1 arrest cell cycle by tamoxifen, allowing more cells to enter the intrinsic apoptotic pathway elicited by **208**[266].

The protective effect of selenomethionine against ionizing radiation has been reported[267] and was related to the activation of tumor suppressor p53 via the modulation of redox status[268]. Selenomethionine at a select dose range has been proved to elicit protective effect against toxicity caused by antineoplastic drugs, cyclophosphamide and irinotecan[269].

In an attempt to design new organoselenium compounds for chemoprevention, triphenylselenonium chloride **209** (Chart 29) and diphenylselenide **8** have been found to have a number of desirable attributes for cancer chemoprevention[270].

Moreover, studies performed by El-Bayoumy and coworkers demonstrated that diallyl selenide **210** was 300 times more active than diallyl sulfide **211** (Chart 29) in inhibiting mammary cancer in rats[271].

Consistent with the idea of developing new organoselenium compounds with chemopreventive activity, Wu and collaborators studied 1,3-selenazine derivatives **212** and **213** (Chart 30). The results show that **212** and **213** inhibit human gastric adenocarcinoma cells by the induction of apoptosis[272].

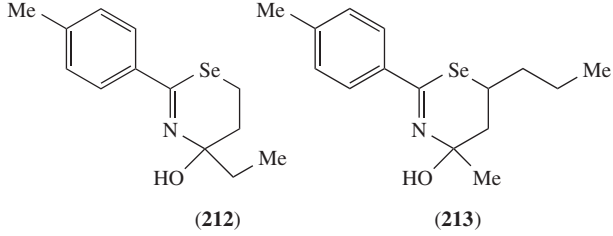
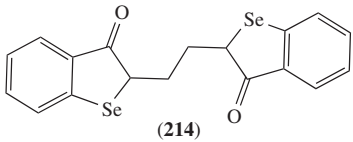


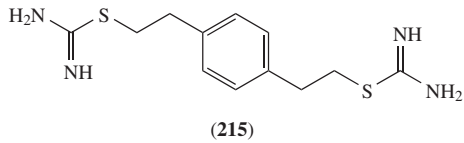
CHART 30

In parallel to a number of pharmacological properties described, ebselen **4** has been studied as an antitumor agent[273]. In addition, ebselen has been shown to inhibit apoptosis[274] and necrosis[275].

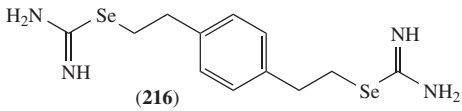
2,2′-dibenzo[*b*]selenophen-(2*H*)-one ethane **214** (Chart 31) was reported as a potent antitumor drug against a variety of human cancer cells, including lung, gastric, hepatic, cervix and blood. The therapeutic action of **214** is probably related to TrxR inactivation and alterations in Bcl-2, Bax and caspase-3 expressions[276]. In addition, **214** was able to induce a cell growth inhibition and elicites typical apoptotic morphologic changes in Tca8113 tongue cancer cells *in vitro* and *in vivo*[277].



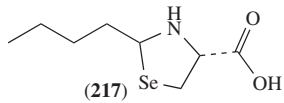
(**214**)



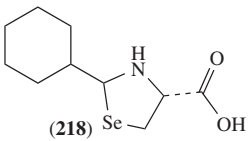
(**215**)



(**216**)



(**217**)



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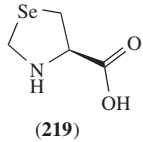

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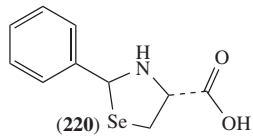
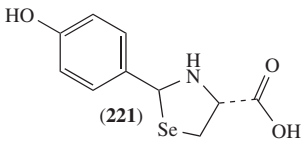
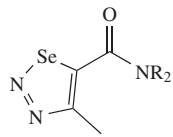


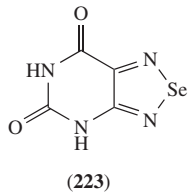
(**220**)



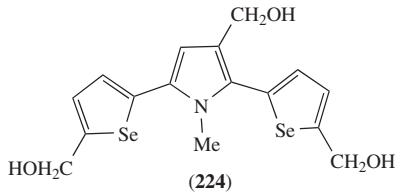
(**221**)



(**222a**) R = Me
(**222b**) R = *i*-Pr



(**223**)



(**224**)

CHART 31

A recent report has demonstrated that the combination therapy of **214** and cisplatin offers a synergistic antitumor effect on A549-grafted nude mouse model. Compared to

single drug administration (cisplatin or **214**), the combination therapy showed significantly reduced tumor size and no obvious renal and hepatic toxic damage. Overall, these results are encouraging and will stimulate further investigation into the potential clinical utility of **214** and cisplatin combined chemotherapy[278].

S,S-1,4-phenylenebis(1,2-ethanediyl)bisisothiourea **215** (Chart 31), an iNOS-selective inhibitor, has limited effect on colon cancer and requires high concentration for its inhibitory effects[279]. Based on the evidence that sulfur substitution by selenium of established cancer chemopreventive agents resulted in more effective chemopreventive analogues[248], a more potent compound was planned and synthesized by replacing sulfur with selenium in thiourea **215**. Se,Se'-1,4-phenylenebis(1,2-ethandiyl)bisisoselenourea **216** (Chart 31) kills melanoma cells which were more sensitive to the compound than normal cells. Compared with **215**, **216** is a more potent agent with negligible associated toxicity[280]. El-Bayoumy's group was also able to demonstrate that **216** altered molecular targets that are involved in the development of human lung cancer and colon cancer cells[281].

The chemopreventive potential of **157** and **158** was investigated in the well-established DMBA-treated rat model, and they were found to prevent oxidative and mammary duct damage caused by DMBA[282].

By using short-term assays for screening newly synthesized compounds, Franklin and coworkers have examined the effect of selenazolidines on the levels of the transcription products (mRNAs) of the genes of the murine hepatic protective enzymes. Although all of selenazolidines are L-selenocysteine prodrugs, only the derivative without a substitution at the 2-position failed to significantly increase any mRNAs of the chemoprotective enzymes[283].

Selenazolidines with alkyl (butyl and cyclohexyl) and aryl (phenyl and 2′-hydroxyphenyl) substituents at the 2-position were evaluated for chemopreventive activity against 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumors. The major effect of selenazolidines at a single dietary level was a reduction in the number of tumors per animal rather than a decrease in the number of animals bearing tumors. Selenazolidine derivatives **217** and **218** reduced the number of lung tumors to a similar extent as **219**, while **220** caused a greater reduction. The reduction in the tumor number by **220** was similar to that elicited by selenocystine. Among the five selenazolidines tested, only **221** (Chart 31) failed to reduce the numbers of tumors[284].

The synthesis and antitumor activity of a series of 4-methyl-1,2,3-selenadiazole-5-carboxylic acid amides **222** (Chart 31) on human fibrosarcoma HT-1080, mouse hepatoma MG-22A and mouse fibroblasts 3T3 cell lines were reported. From this study an antitumor action and cytotoxicity correlation were distinguished[285]. Based upon 1,2,5-selenadiazolo-[3,4-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione **223** (Chart 31) selective cytotoxicity toward cancer cells, the underlying molecular mechanisms triggered by **223** for antiproliferative and apoptotic cell death were investigated. **223**, a selenadiazole derivative, was an antiproliferative agent against MCF-7, HepG2 and A375 cells, by the induction of mitochondria-mediated apoptosis. The activation of extrinsic and intrinsic apoptotic pathways was demonstrated as well as an overproduction of reactive oxygen species and depletion of mitochondrial membrane potential. Despite its high potency against cancer cells, **223** displays non-toxic activity against normal cells[286].

The applicability of selenophene compounds as pharmacotherapeutic agents has some limitations in view of their poor solubility and stability, similar to the terthiophene. To improve solubility and stability, *N*-methylpyrroles with one or more hydroxymethyl groups were systematically introduced to the original selenophene compounds and one of these novel compounds, 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-*N*-methylpyrrole **224** (Chart 31), showed potent antitumor activity with better solubility and stability. Moreover, **224** had highly antiproliferative activity against various human solid cancer cells, with IC_{50} value in the nanomolar range. Not only the induction of reactive

oxygen species but also the formation of Se-DNA adducts contribute to **224**-induced DNA damage, which leads to the activation of ataxia telangiectasia-mutated nuclear protein kinase activation, and p53-dependent and -independent apoptosis pathways[287]. Moreover, data reported by the same research group provided a strong support for the induction of mitochondria-mediated apoptosis by **224**[288].

A balance between therapeutic activity and toxic effects of a compound is an important parameter when evaluating its usefulness as a pharmacological agent. In this way, the cytotoxicity of organoselenium compounds could be employed in antiproliferative therapy.

The antimutagenic properties of selenazolidine-4-(*R*)-carboxamide and 2-substituted derivatives **222** (Chart 31), as a prelude to *in vivo* chemopreventive investigation, were explored. All the selenazolidines significantly reduced mutagenicity induced by benzo[*a*]pyrene and acridine orange, independent of requiring oxidative bioactivation or not[289].

Experimental evidence indicates that diphenyl diselenide **5** has genotoxic potential, since it induces frameshift mutations in both *Salmonella typhimurium* and haploid yeast, as well as increases crossing over and gene conversion frequencies in diploid strains of *Saccharomyces cerevisiae*[290]. In a model of yeast mutant strains defective in antioxidant defenses, **5** had pro-oxidant activity by depleting free glutathione, probably via a direct coupling of the drug to the sulfhydryl group of the cysteine residue in glutathione and thus sensitizing the cell to reactive oxygen species[291]. Moreover, cytotoxic, genotoxic and mutagenic effects of **5** were reported. From this study it is possible to conclude that the cellular effects of **5** are dependent on the concentration. On one hand, the cytotoxicity of **5** was demonstrated by the reduction of lung fibroblast cell (V79) viability and was related to its ability to deplete glutathione, which leads to a pro-oxidant cellular status and genotoxicity. On the other hand, at low micromolar concentrations, **5** was non-cytotoxic and had antioxidant effect[292].

Different from the data reported for **5**, Henriques and coworkers demonstrated that ebselen was capable of protecting against hydrogen peroxide-induced cytotoxicity and DNA damage and mutation in *Saccharomyces cerevisiae* as well as in V79 cultured cells. Therefore, ebselen has been reported to be neither cytotoxic nor mutagenic in *Saccharomyces cerevisiae*[293].

Based on pro-oxidant and mutagenic properties of **5** in different cells, the threshold dose at which the molecule presents genotoxic effects was investigated in mice. From this study emerged evidence that **5** induces DNA damage in brain, kidney, liver and testes of mice. The systemic genotoxicity was clearly dependent on the dose (ranging from 75 to 200 $\mu mol\,kg^{-1}$, intraperitoneal). There was also evidence of a correlation between the pro-oxidant, characterized by the decreased levels of glutathione, and genotoxic effects, demonstrated by an increase in lipid peroxidation and DNA damage[294].

The antigenotoxic and antimutagenic effects of **5** on Chinese hamster V79 cell line have been evaluated. The experimental data revealed **5** as a potential chemopreventive agent using several mutagens. At low concentrations **5** was capable of protecting against methyl methanesulfonate, UVC radiation and hydrogen peroxide-induced cytotoxicity, DNA damage and clastogenesis in V79 cells by increasing glutathione peroxidase activity. As a result, **5** was demonstrated to be a potent antigenotoxic agent against reactive oxygen species-induced DNA lesions[295].

The hypothesis that structural modifications in the aryl group of diaryl diselenide could achieve greater chemopreventive efficacy with minimal toxic side effects stimulated the investigation of antimutagenic potential of diaryl diselenide derivatives. Therefore, a series of experiments was planned to investigate the genotoxic, mutagenic and protective effects of bis(*m*-trifluoromethylphenyl) diselenide **150**. Similar to **5**, **150**, at high concentrations, was a weak cytotoxic agent and had genotoxic effects on V79 cells[296].

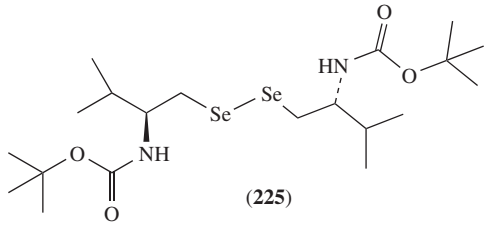
Additionally, other symmetrical diselenide derivatives, namely bis(*p*-chlorophenyl) diselenide **90**, bis(*p*-methylphenyl) diselenide **92** and bis(*p*-methoxyphenyl) diselenide **95**, were screened for cytotoxicity and mutagenicity, using the yeast *Saccharomyces cerevisiae* as a model organism. In contrast to **90** and **92**, **95** was highly cytotoxic. From the accumulated data it must be concluded that the introduction of a methoxyl group in the aromatic ring of a diaryl diselenide increases cytotoxic and genotoxicity of **5**, since **95** is a powerful mutagen, in contrast to **5**. Moreover, the introduction of the methyl group increases the cytotoxicity of the compound without affecting mutagenicity. At low concentrations, **95** was even more cytotoxic and mutagenic than diphenyl ditelluride, an analogous of **5**[297].

Using *in vivo* experiments, the chemopreventive effect of dietary diphenyl diselenide **5** was evaluated in *N*-nitroso-*N*-methylurea (NMU)-induced mammary carcinogenesis in rats. Supplementation with **5** promoted pronounced increase in the latency to the onset of tumor development and reduction in the incidence and frequency of tumors. Diphenyl diselenide was also effective in restoring the antioxidant defenses altered by a carcinogen. The results indicated that **5** presents a protective effect against the tumor development, even when supplemented at a relatively low concentration (1 ppm)[298].

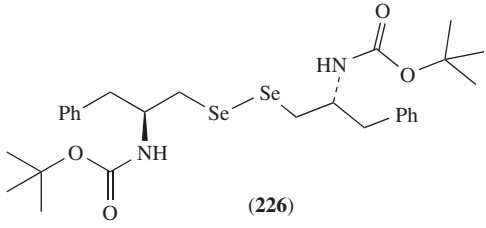
In an extension of our study we were interested to know whether a new class of amino acid derivatives could have similar cytotoxic and genotoxic properties to that of simple diaryl diselenides in human leukocytes cells. The exposure of leukocytes to [bis(*S*)-*t*-butyl-3-methylbutan-2-yl carbamate] diselenide **225**, [bis(*S*)-*t*-butyl-3-phenyl propan-2-yl carbamate] diselenide **226**, [bis(*S*)-2-amino-3-methylpropanyl carbamate] diselenide **227**, [bis(*S*)-2-amino-3-phenylpropanyl carbamate] diselenide **228** (Chart 32), bis(*m*-trifluoromethylphenyl) diselenide **150**, bis(*p*-methoxyphenyl) diselenide **95**, bis(*p*-chlorophenyl) diselenide **90** and bis(2,4,6-trimethylphenyl) diselenide **164** induced a significant increase in damage index. All organoselenium compounds tested were genotoxic and cytotoxic to human leukocytes cells, by inducing loss of cell viability and DNA damage, but the amino acid derivatives **225**–**228** were more genotoxic than diaryl diselenides **90**, **95**, **150** and **164**[299].

Moreover, diphenyl selenide **8**, diphenyl diselenide **5** and [bis(*S*)-2-amino-3-methylpropanyl carbamate] diselenide **227** as well as their organotellurium analogous diphenyl telluride **6**, diphenyl ditelluride **7**, butyl(styryl)telluride **229** and 2-(butyltellurium) thiophene **230** (Chart 32) produced a decrease on osmotic stability of human erythrocytes *in vitro*. The hemolytic effect was strictly related to the presence of Se and Te atoms in their moieties, since the organic structure without these elements did not alter the effect. Indeed, **8** and **229**, which had the greatest hemolytic effect were genotoxic to leukocytes cells. Therefore, the hemolytic and genotoxic effects were related to orgachalcogen thiol oxidase activity and a preferential interaction with sulfhydryl groups critical to enzymes[300].

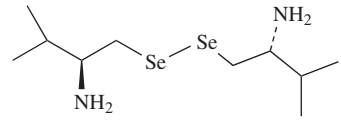
Induction of Phase II enzymes has emerged as an effective strategy for cancer chemoprevention. Thus Xiao and Parkin[301] reported that among twenty-seven selenium and sixteen structurally related organosulfur compounds tested, the most potent were dimethyl diselenide **91**, 2,5-diphenylselenophene **231**, dibenzyl diselenide **232**, methylseleninic acid **208**, diphenyl diselenide **5**, benzeneseleninic acid **233**, benzene selenol **234**, triphenylselenonium chloride **209** and ebselen **4**, increasing quinone reductase and glutathione S transferase activities in murine hepatoma (Hepa IcIc7) cells, at low micromolar concentrations. The concentration-dependence of quinone reductase induction and cell growth inhibition were linearly correlated among the group of organoselenium compounds **4**, **5**, **91**, **208** and **232**–**234** (Chart 32) with putative selenol-generating potential, implying that both responses of Hepa IcIc 7 cells were based on these selenol metabolites.



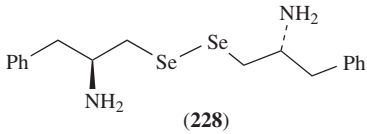
(**225**)



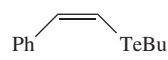
(**226**)



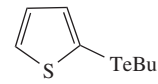
(**227**)



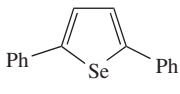
(**228**)



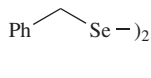
(**229**)



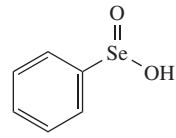
(**230**)



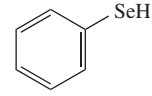
(**231**)



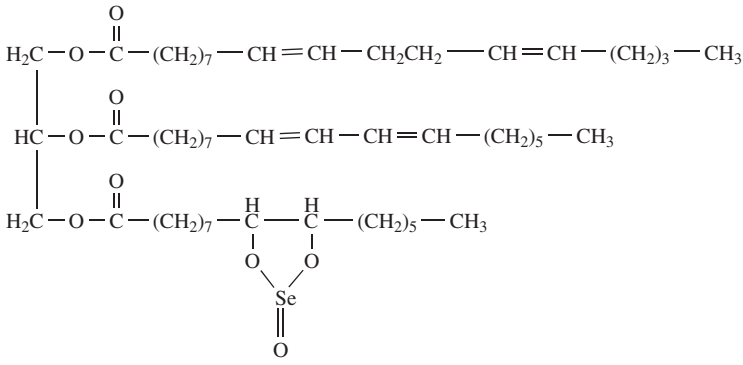
(**232**)



(**233**)



(**234**)



(**235**)

CHART 32

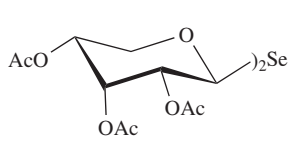
Selol **235** (Chart 32), a selenite-triglyceride containing selenium (+4), has been reported as a compound able to inhibit cell proliferation and to induce apoptosis on leukemia HL-60 cells and multidrug-resistant[302a]. In this context, Rahden-Staron and collaborators[302b] demonstrated that selol exhibited chemopreventive and anticancer activities. They were able to show that selol did not induce mutagenesis in any of the strains, in either the presence or absence of metabolic activation.

14. Miscellaneous

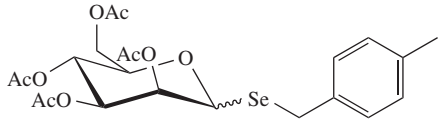
Esophageal burns due to accidental ingestion of corrosive substances are the most common cause of esophageal stricture development in childhood. Ebselen **4** treatment prevented stenosis and strictures in the esophagus of NAOH-treated rats. Thus the results of this study suggest a possible new use for ebselen in the treatment of corrosive esophageal burns[303].

Only a few studies have shown that ebselen and its sulfur analogue exhibit inhibitory actions toward selected strains of bacteria and fungi, but the underlying mechanisms remain unclear[304]. In this context Chan and collaborators demonstrated that the fungicidal action of ebselen is due to interference with the proton-translocating function and inhibition of ATPase activity of the plasma membrane H^+-ATPase[305].

Melanins are the skin pigments in humans and they play a major role in photoprotection. Therefore, the depigmenting potency of selenium-containing carbohydrates has been investigated based upon the direct inhibition of mushroom tyrosinase. Among eleven selenoglycosides tested, **236** and **237** (Chart 33) had inhibitory effects on mushroom tyrosinase. **237** showed concentration-dependent cytotoxicity in a study of melanin synthesis inhibition by melan-a cells[306].



(**236**)



(**237**)

CHART 33

B. Biochemical Pharmacology of Organotellurium Compounds

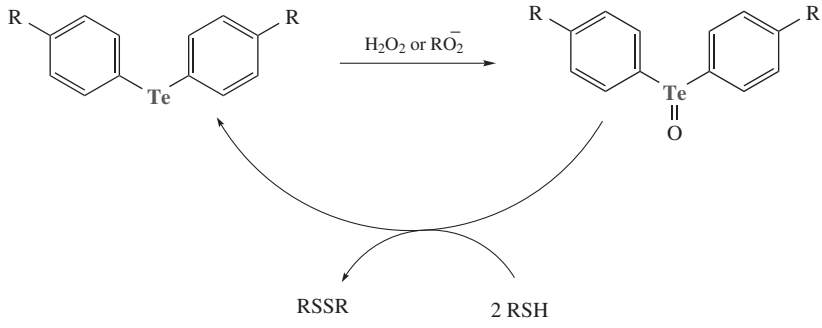
1. Glutathione peroxidase-like activity

Although the tellurium atom is generally regarded as a toxic metalloid, its role in biological systems has been demonstrated[307]. Concerning organotellurium compounds, little is known about their biological and pharmacological effects.

Organotellurium compounds can be oxidized from the divalent to the tetravalent state, which makes tellurides attractive as potential scavengers of reactive oxidizing agents such as hydrogen peroxide, hypochlorite and peroxyl radicals. In effect, diaryl tellurides can exhibit potent glutathione peroxidase-like activity[308].

Based on mechanistic studies, diaryl tellurides were seen to exert an antioxidative effect by deactivating both peroxides and peroxyl radicals with the formation of telluroxides (Scheme 17)[5a, 309].

The potential glutathione peroxidase mimetic activity of cyclic tellurinate ester **238** and spirodioxytellurane **239** (Chart 34) was demonstrated by Back and colleagues[310]. **238**



SCHEME 17

and **239** were proved to be superior catalysts to their selenium analogues, resulting in fast reaction rates. The authors also showed that thiolysis, rather than oxidation of the catalyst, provides entry into the catalytic cycle. However, it is also possible that the corresponding tellurenyl sulfide was produced during the catalytic cycle of **238** but that, in contrast to its selenenyl sulfide counterpart **240** (Chart 34), it served as an efficient catalyst for the reduction of hydroperoxide.

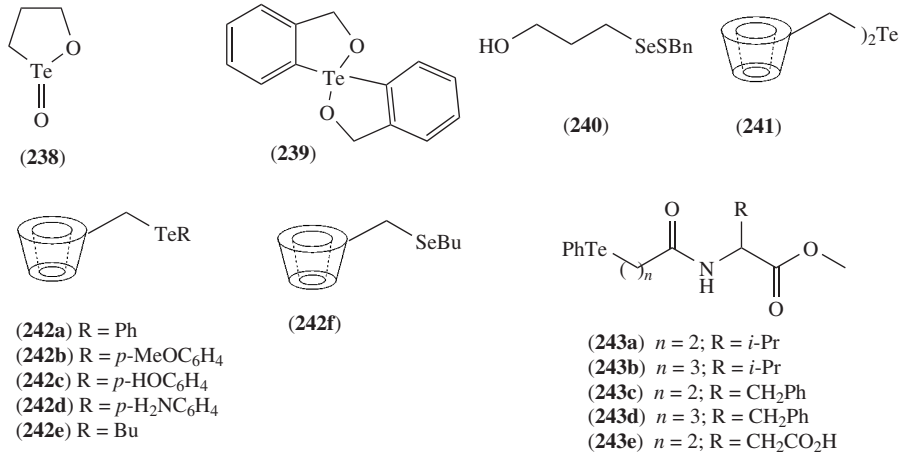


CHART 34

In addition, a cyclodextrinyl ditelluride **241** compound has been noted as an excellent glutathione peroxidase-mimic, demonstrated by its highly catalytic efficiency[311], which was very similar to that of natural glutathione peroxidase[312], Compounds **242** (Chart 34) reduced H_2O_2, *t*-BuOOH and CuOOH by an arylthiol effectively and the thiol peroxidase activity was almost 10^5 times higher than that of diphenyl diselenide. The large difference in the activities of **241** with arylthiol was ascribed to the role of the binding ability as compared with thiol GSH[313].

Cyclodextrin-derived diorganyl tellurides **242** were investigated and proved to be glutathione peroxidase-like and inhibitors of thioredoxin reductase and cancer cell growth. Among organotelluriums **242a–e**, the cyclodextrin **242e**, a butyltelluro substituted molecule, was the best glutathione-peroxidase mimetic, further supporting the idea that compounds carrying alkyltelluro moieties are better catalysts than those carrying aryltelluro groups. The catalytic efficiency of organotelluriums with hydrogen peroxide and *t*-butyl hydroperoxide as substrates followed the order: **242d** > **242c** = **242b** > **242a**. By contrast, the phenylseleno derivative **242f** of β-cyclodextrin was devoid of catalytic activity. With the catalysts **242a**, **242b** and **242e**, cumene hydroperoxide was reduced 10–12 times faster than hydrogen peroxide, suggesting their specificity for reduction of cumene hydroperoxide[314].

The semisynthetic GPx mimic, tellurosubtilisin, catalyzes the reduction of hydroperoxide by an aryl thiol with high catalytic efficiency, but it exhibits kinetic properties substantially different from those of selenosubtilisin[315]. In this context, other complex organotellurium compounds with glutathione peroxidase-like activity were reported, such as dendrimeric organotellurides[5b].

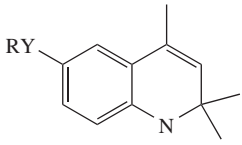
The hypothesis that the variation of amino acid residues and the chain length between the chalcogen atom and the amino acid moiety increases the glutathione peroxidase catalytic activity of telluroamino acid derivatives was tested. Compounds **243a** and **243b** (Chart 34), derived from L-valine, and **243c**, derived from L-phenylalanine showed similar catalytic activity, but **243d**, derived from L-phenylalanine, was less effective in the reduction of H_2O_2 (Chart 34). Regarding the variation of amino acid moiety, to enhance the ability of telluroamino acid derivatives to mimic the glutathione peroxidase enzyme, it was demonstrated that **243e** derived from L-aspartic acid was the best catalyst. Thus it was clearly shown that the T_{50} time required to reduce the concentration of the PhSH to a half is strongly influenced by both the amino acid residue and the steric effects. The changing of electronic environment at the tellurium atom did not produce a pronounced change in the glutathione peroxidase activity of the compounds[5c].

2. Antioxidant activity

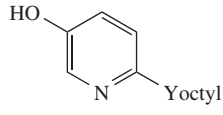
The most thoughtfully reported pharmacological action of organotellurium compounds is related to their capacity of inhibiting peroxidation in chemical and biological systems, which can be ascribed to either chain-breaking and/or peroxide-decomposing effects[316]. Furthermore, organotellurium compounds can protect against the pro-oxidant effects of peroxynitrite. Thus, it has been suggested that organotellurium compounds can catalytically scavenge $ONOO^-$ in the presence of GSH[317].

Kumar and collaborators[318] have synthesized ethoxyquin antioxidants **244b–d** (Chart 35) carrying ethylthio, ethylseleno and ethyltelluro groups in the 6-position and investigated their antioxidant potential in comparison with that of the corresponding phenylthio **244e**, phenylseleno **244f** and phenyltelluro **244g** derivatives (Chart 35). They found that **244a** and its organotellurium analogue **244d** were as efficient quenchers of peroxyl radicals as α-tocopherol, the ethyl derivatives **244b** and **244c** showed lower quenching capacity and the phenyl derivatives **244e–g** were the worst. The tellurium analogues **244d** and **244g** were able to catalyze the reduction of hydrogen peroxide in the presence of thiophenol.

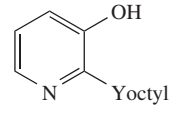
In addition, 3-pyridinols **245a–c** (Chart 35) substituted in the 6-position with octyltelluro, octylseleno and octylthio groups and the corresponding 2-substituted derivatives **246a–c** (Chart 35) were synthesized and assayed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a water/chlorobenzene two-phase system. Compounds **245a** and **246a** did not inhibit peroxidation in the absence of *N*-acetylcysteine. The selenium



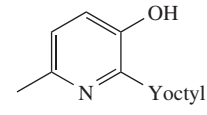
(**244a**) YR = OEt
(**244b**) YR = SEt
(**244c**) YR = SeEt
(**244d**) YR = TeEt
(**244e**) YR = SPh
(**244f**) YR = SePH
(**244g**) YR = TePh



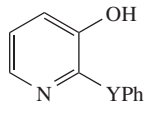
(**245a**) Y = S
(**245b**) Y = Se
(**245c**) Y = Te



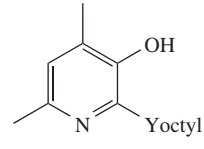
(**246a**) Y = S
(**246b**) Y = Se
(**246c**) Y = Te



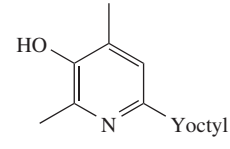
(**247a**) Y = S
(**247b**) Y = Se
(**247c**) Y = Te



(**248a**) Y = S
(**248b**) Y = Se
(**248c**) Y = Te



(**249a**) Y = S
(**249b**) Y = Se
(**249c**) Y = Te



(**250a**) Y = S
(**250b**) Y = Se
(**250c**) Y = Te

CHART 35

245b, **246b** and sulfur derivatives **245a** and **246a** were poorer quenchers of peroxyl radicals than the tellurium derivatives **245c** and **246c**. The addition of thiol to the aqueous phase caused an increase in the antioxidant activity. With the intention to improve the chain-breaking capacity of antioxidants, a methyl group was introduced in the pyridinol ring. Compounds **247a–c** (Chart 35) were investigated together with the corresponding phenyltelluro, seleno and thiol derivatives **248a–c** (Chart 35). Pyridinol **247a** inhibited peroxidation as efficiently as α-tocopherol in the presence of the thiol regenerating agent, but the phenyltelluro derivative **248c** performed poorer than **247a**. Among the pyridinols **249a–c** and **250a–c** (Chart 35) bearing *o*- or *p*-organochalcogen substituents, compound **249c**, bearing an *o*-alkyltelluro group, showed improved antioxidant characteristics. The authors clearly demonstrated that 3-pyridinols substituted with organyltelluro groups act as catalysts not only for the reduction of peroxyl radicals, but also for decomposition of hydroperoxides in the presence of stoichiometric amounts of thiol reducing agents[319].

Engman and collaborators have designed a series of *o*- and *p*-sulfur, selenium and tellurium phenol derivatives. They conclude that *p*-substituents reduced the O–H bond dissociation enthalpy, while the effect of *o*-substituents was slight[320].

Vinylic tellurides have been explored as potential antioxidant agents *in vitro*. Thus, 1-butyltellurenyl-2-methylthioheptene **11** and diethyl 2-phenyl-2-tellurophenyl vinylphosphonate **10** have potent antioxidant activity *in vitro*, reducing lipid peroxidation induced by iron[22, 321]. Moreover, **10** was able to reduce lipid peroxidation caused by quinolinic acid and sodium nitroprusside without affecting mitochondrial viability and glutamate system in cerebral tissue[322].

The *in vitro* antioxidant activity of the vinylic telluride derivatives, *Z*-2-(methylthio)-1-(butyltelluro)-1-phenylethene **12**, *Z*-1-(4-methylphenylsulfonyl)-2-(phenyltelluro)-2-phenylethene **13**, *Z*-2-(butyltelluro)-1-(benzylthio)-1-heptene **251** and *Z*-2-(phenylthio)-1-(butyltelluro)-1-phenylethene **252** (Chart 36), has been reported. The maximal inhibitory effect of these derivatives on lipid peroxidation was in the following order: **12** = **252** > **251** > **13**[24].

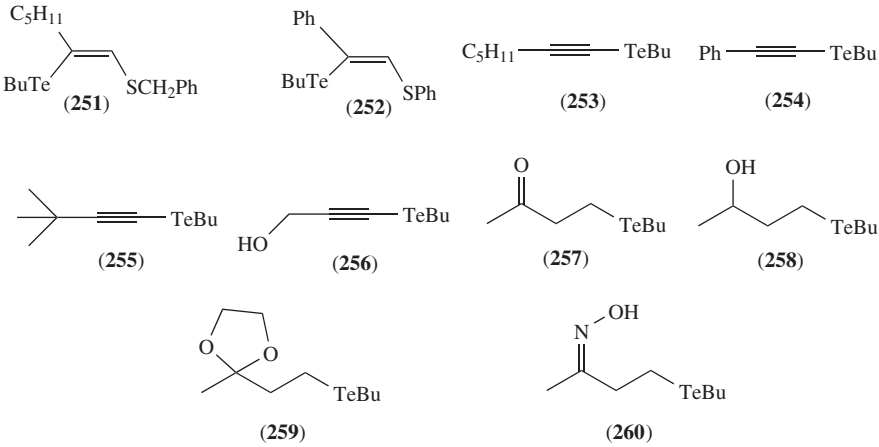


CHART 36

From experiments with telluroacetylenes **253**–**256** (Chart 36) emerged the evidence that these are efficient antioxidants *in vitro*. At low μmolar range they reduced cerebral lipid peroxidation and protein carbonyl. They were also scavengers of DPPH radical. Telluroacetylene **254** was proved to be antioxidant against oxidative stress induced by sodium nitroprusside in the brain of rat[323].

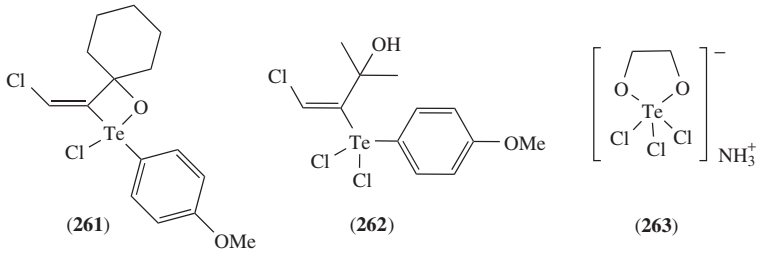
Alkyl-organotellurides **257**–**260** (Chart 36) were screened using lipid peroxidation and protein carbonylation assays. They were more effective in reducing lipid peroxidation induced by Fe^{2+}/EDTA than trolox. All alkyl organotellurides tested reduced protein carbonylation at low μmolar concentrations[324].

Diphenyl ditelluride **7** has been reported as an effective antioxidant against lipid peroxidation induced by various pro-oxidants[80b, 325]. Furthermore, **7** significantly reduced in a concentration-dependent manner lipid peroxidation at different pH (5.4–6.8) values in brain and kidney homogenates. From these studies emerged *in vitro* evidence for acidosis induced oxidative stress and antioxidant effect of **7** not only at physiological pH, but also at a range of acidic values[326]. Moreover, introduction of the chloro functional group into diaryl ditelluride molecule generates bis(*p*-chlorophenyl) ditelluride **14**, an antioxidant compound able to reduce lipid peroxidation and protein carbonyl as well as to scavenge ABTS and DPPH radicals in a very similar way to **7**[25].

The effects of organotelluranes **261** and **262** (Chart 37) on the mitochondrial function were reported. The antioxidant property of **261** and **262** was demonstrated to be dependent on the concentration of the drugs. Thus, at the nanomolar concentration range, **261** and **262** exhibited antioxidant activity with protective effect against lipid oxidation and matrix oxidative stress. They also induced the formation of a transition pore in mitochondrial inner membrane in the absence of oxidative stress. The induction of transition pore was explained by the formation of organotellurium IV species from the interaction of organotelluranes with membrane proteins[327].

3. Neuroprotective activity

Ammonium trichloro(dioxoethylene-*O*,*O*'-)tellurate (AS101 **263**) (Chart 37), the most studied synthetic tellurium compound from the standpoint of its biological activity, has



(**261**) (**262**) (**263**)

CHART 37

been reported as able to protect ischemic stroke in mice. The protective effects of AS101 demonstrated by the improvement of functional outcome and reduction of brain damage in a mouse model of focal ischemic stroke have been related to its inhibitory action in apoptotic and inflammatory caspase activities, and also in protein tyrosine nitration[328]. The effects of AS101 are attributed to the peculiar chemistry of tellurium(IV)-thiol which confers to this compound the property of interacting with cysteine residues on inflammatory and apoptotic caspases, resulting in their inactivation. In this context, AS101 protects dopaminergic neurons in 6-OH dopamine and MPTP models of Parkinson disease. Multiple functional activities have been attributed to the AS101 neuroprotective action, AS101 activates Ras by interacting with its residues of cysteine, which activates ERK and Bcl2 expression. AS101 inhibits the activity of caspases 1 and 3, which prevents apoptosis and reduces the production of the proinflammatory cytokine IL-1β. AS101 also inhibits IL-10, up-regulating GDNF and the antiapoptotic protein Bcl-2 and activating Akt and mitogen-activated protein kinases[329].

Despite the well-documented pharmacological effects of AS101, little or nothing is known regarding the neuroprotective effects of organotellurium compounds. In this way, the antiepileptogenic action of **261** has been reported. The intraperitoneal injection of **261** prior to pilocarpine suppressed the behavioral and electroencephalographic seizure occurrence in rats. The ability to inhibit caspase activity was related to **261** neuroprotective action. In fact, this study clearly showed that **261** is a potent caspase inhibitor, more potent than AS101 **263**[330].

Manganese (Mn) is selectively deposited in striatum, causing oxidative stress, glutamate homeostasis deregulation and mitochondrial impairment. These alterations culminate in behavioral changes (motor impairment). The neuroprotective effect of diethyl 2-phenyl-2-tellurophenyl vinylphosphonate **10** against Mn-induced neurotoxicity in a rat model of physiologically relevant chronic low-dose drinking water exposure was demonstrated. The antioxidant activity and the effect on striatal Mn transport have been related to the **10** neuroprotective action against Mn-induced neurotoxicity[331].

4. Chemopreventive activity

Organotellurium compounds are good candidates as anticarcinogenic agents, either via induction of apoptosis or via inhibition of enzymes involved in cancer development, including thioredoxin reductase[332] and cathepsins[333].

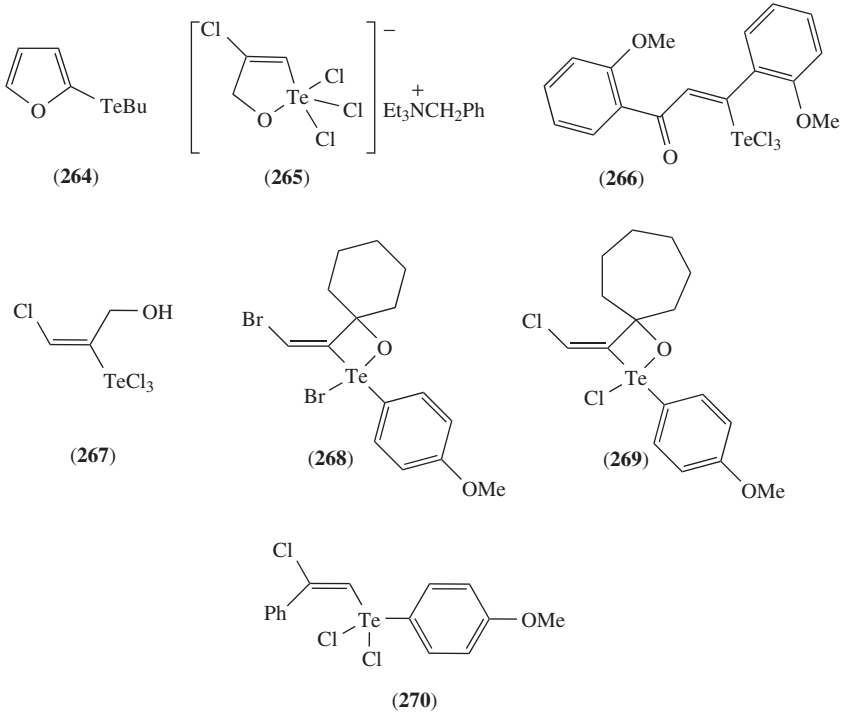
The relatively non-toxic compound AS101 **263** was demonstrated for the first time to present immunomodulating properties and, when administered to mice, mediated antitumor effects[334].

Sredni, Albeck and collaborators[335] have shown that AS101 interaction with a cysteine residue in the active site of proteins explains most of its protective activities. In this

context, the synergism between thiols and AS101 in its antitumoral activity on Jurkat cells was reported. In this study, the addition of thiols that do not contain a free carboxylate (e.g. 2-mercaptoethanol or cysteamine) synergistically increased apoptosis, which was accompanied by an increase of reactive oxygen species, a decrease of the mitochondrial membrane potential and an increase of the percentage of cells that express caspase-9 and caspase-3. Thus the antitumoral effect of AS101 was increased by neutral and positively charged thiols, by increasing its uptake into cells[336], which is in accordance with previous studies demonstrating that organotellurium compounds can be cytotoxic and induce apoptotic cell death[337].

Shrunken cells are used as a measure of cytotoxicity because they occur before some characteristic changes in apoptosis, such as cytochrome C release from mitochondria, caspase activation and DNA fragmentation[338]. Diphenyl ditelluride **7** at submicromolar concentrations increased the populations of shrunken cells, in rat thymocytes and hypodiploidal cells. The authors suggest that diphenyl ditelluride **7** activated caspases in rat thymocytes, resulting in the induction of apoptosis[339].

Hemolytic and genotoxic effects of organotellurium compounds were investigated in human blood cells. Diphenyl telluride **6**, diphenyl ditelluride **7**, butyl(styryl)telluride **229** and 2-(butyltellurium)furan **264** (Chart 38) were hemolytic at high concentrations. The exposure of erythrocytes to **229**, which had greater hemolytic effect, significantly inhibited Na^+/K^+ ATPase activity of erythrocyte ghosts. At the higher concentrations, **229** was genotoxic and cytotoxic to human leukocytes cells. The hemolytic and genotoxic effects of **229** in human blood cells were related to the thiol oxidase activity[340].



(**264**) (**265**) (**266**)

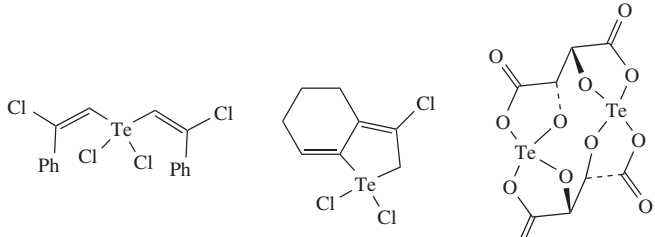
(**267**) (**268**) (**269**)

(**270**)

CHART 38

Lysosomal cysteine proteases, especially cathepsin B, can participate in tumor invasion by degradation of extracellular matrix components[341]. Searching for new chemotherapeutic agents, organotelluranes **265**–**270** (Chart 38) were planned and screened as protease inhibitors. All compounds **265**–**270** tested exhibited high specific second-order constant for cathepsin B inactivation. The best inhibitor was compound **266**, showing a second-order rate constant about 100-fold higher than AS101[333a].

Organotelluranes were reported to be irreversible inhibitors of cysteine cathepsins. The development of selective inhibitors of cathepsins B, L, S and K was obtained by changing the organic groups attached to the tellurium atom. The bis-vinylic organotellurane **271** (Chart 39) was the most efficient compound to inhibit cathepsin B, while **268**, a bromotelluroxetane, was the most promising inhibitor of cathepsin L. Interestingly, the chlorotelluroxetane **261** was a weaker inhibitor of cathepsin L than **268**. Organotelluranes **266**, **268** and **272** (Chart 39) were inhibitors of cathepsin S. **268** was the most efficient while **266** and **272** had a similar inhibitory effect on cathepsin S[333b].



(**271**) (**272**) (**273**)

CHART 39

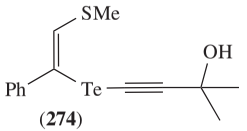
Accordingly, RT-04 **262** induces apoptosis in human leukemia HL-60 cells, which could be partially mediated by the Bcl-2 expression down-regulation. The chemopreventive effect of **262** is also related to the induction of DNA fragmentation and caspase-3, -6 and -9 activations[342].

A novel organotellurium compound, octa-*O*-bis-(*R*,*R*)-tartarate ditellurane **273** (Chart 39), has been reported as selective to cysteine protease inhibition. Compound **273** was selective inhibitor of papain and cathepsin B, but inert toward serine, metallo and aspartic proteases. In comparison to AS101 **263**, **273** delivers two tellurium atoms per molecule, is more stable in aqueous solutions and the solubility in water is very similar[343].

5. Miscellaneous

AS101 **263** has been reported as an anti-inflammatory and anti-apoptotic compound against fulminant hepatic failure. AS101 inhibited TNFα or anti-FAS-induced apoptotic processes in hepatocytes *in vitro* and reduced necrosis and apoptosis in a lipopolysaccharide model of hepatic failure[344].

NFkB is one of the most ubiquitous transcription factors and functions as a central player in the chronic inflammatory diseases development[345]. Since NFkB may be regulated by thiol modifications and AS101 has important roles in thiol redox biological activity, the anti-inflammatory properties of AS101 with respect to modulation of inflammatory cytokines in activated macrophages via targeting the NFkB complex was explored. AS101 inhibits NFkB activities and thereby acts as an anti-inflammatory agent in NFkB target genes such as iNOS and NO formation as well as IL-6 production[346].



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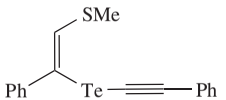

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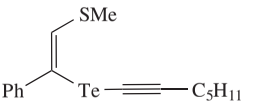

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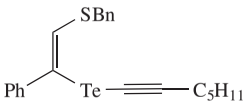

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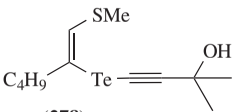

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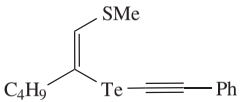

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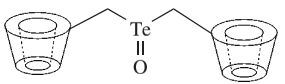

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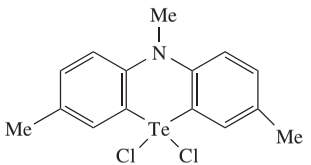

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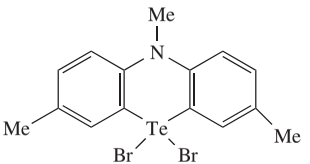

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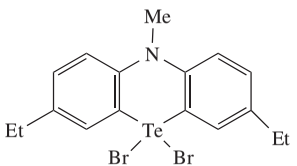

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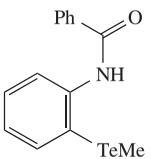
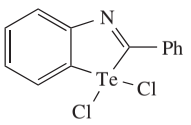


(**284**)



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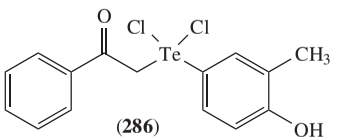
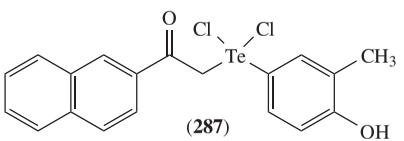
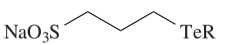


(**286**)



(**287**)



(**288a**) R = *n*-Bu
(**288b**) R = *p*-$MeOC_6H_4$
(**288c**) R = *p*-$H_2NC_6H_4$
(**288d**) R = C_6H_5

CHART 40

The immunomodulator AS101 has been shown to have beneficial effects due to the direct inhibition of the anti-inflammatory cytokine IL-10[347]. The immunomodulatory property was found to be crucial for the pharmacological activities of AS101 in parasite and viral infected mice models, in autoimmune diseases, in septic mice and human papilloma virus[348].

Moreover, AS101 provides protection against chemotherapy-induced fertility and sperm DNA damage, suggesting its use as an alternative method of fertility preservation[349].

Alkynyl vinyl tellurides, compounds **274**–**276** and **277**–**279** (Chart 40), were screened for their antidepressant-like activity. All alkynyl vinyl tellurides tested had a significant antidepressant-like action in the tail suspension test. Alkynyl vinyl telluride **279** showed the best antidepressant-like action since at $1\,mg\,kg^{-1}$ it attained 50% of the effect. The antidepressant-like effect of **279** was similar to that of paroxetine, a well-known antidepressant, in the tail suspension test[350].

Hydrolases are ubiquitous and essential for living organisms because the hydrolytic cleavage of ester bonds is involved in metabolic and signaling biochemical pathways[351]. In this context, the hydrolytic capacity of telluroxy-bis(6-deoxy-β-cyclodextrin) **280** was demonstrated by the hydrolysis of carbonate bonds from 4,4′- dinitrophenyl carbonate. As a result, the hydrolase mimetic activity of **280** has been reported[352].

The antiparasitic activity of organotellurium compounds **281**–**285** (Chart 40) was investigated and compared to mebedazole. Compound **283** was devoid of anthelmintic activity, whereas **281** and **282** were less effective compared to that of mebedazole; **285** showed anthelmintic activity similar to mebedazole[353].

Leishmaniasis is a parasitic disease that is endemic in developing countries. Organotellurane **265** was reported to be effective against the flagellate and non-flagellate parasitic forms and in *Leishmania amazonensis*-infected BALB/c mice[354].

Unsymmetrical diorganyltellurium(IV) dichlorides were screened for antibacterial activity. From the experimental data it was possible to conclude that phenacyl (3-methyl-4-hydroxyphenyl) tellurium(IV) dichloride **286** and naphthacyl (3-methyl-4-hydroxyphenyl) tellurium(IV) dichloride **287** (Chart 40) showed significant activity against both gram-positive and gram-negative strains[355].

Cyclodextrin **242** and sulfonic acid-derived **288a**–**d** organotelluriums (Chart 40), known to inhibit mammalian TrxR, were investigated for their efficacy against P. falciparum TrxR and Trichomonas vaginalis TrxR. All organotelluriums tested were inhibitors of the parasite TrxRs, with the results clearly showing some selectivity between the two enzyme types[356].

Klebsiella pneumoniae is one of the most common gram-negative pathogens that can cause pneumonia, urinary tract infections and sepsis. AS101 was effective in inhibiting bacterial growth. The inhibition of growth was in a concentration-dependent manner and dependent on the combination of AS101 with β-mercaptoethanol or cysteamine[357].

IV. CONCLUSION

The data presented in this chapter clearly indicate the potential pharmacological and therapeutic use of organoselenium and organotellurium compounds. Indeed, these classes of molecules exhibit a variety of interesting biological effects, namely antioxidant properties, which can account for their *in vitro* and *in vivo* beneficial effects in a wide range of models of different human pathologies. Here we can cite the *in vivo* hepatoprotective, renoprotective, gastroprotective, chemopreventive and neuroprotective effects of different organoselenium compounds and the immunomodulatory and neuroprotective effects of a few organotellurium compounds. One noteworthy aspect to be cited here is the quite distinct chemical nature of these compounds; however, they can be active *in vitro* and *in vivo* via the formation of analogous reactive metabolites. For instance, ebselen and

diphenyl diselenide can exert part of their antioxidant and bioprotective effects via their metabolism to selenol intermediates. In this case, ebselen and diphenyl diselenide will be 'imitating the natural biological chemistry' of selenoenzymes and possibly of non-enzymatic selenoproteins. In the case of selenides and tellurides, the antioxidant and bioprotective effects can be exerted, at least in part, by their metabolism to the respective selenoxides or telluroxides, i.e. the reversible redox transition from state (II) to state (IV) valency could account for their biological effects. However, the metabolism of organoselenium and organotellurium compounds to metabolites that were not yet identified is also plausible. In short, we can say that the 'medicinal chemistry' of organoselenium and organotellurium compounds is still incipient from both a chemical and biological point of view. In effect, our knowledge in this exciting field is deficient regarding the chemical and biological effects that the introduction of selenium and tellurium atoms causes in different organic moieties. We know that the introduction of these atoms confers impressive biological effects on relative inert organic moieties; however, at the moment, we cannot predict with accuracy the type of 'chemical behavior' that will be imposed by introducing the selenium or tellurium atom into organic substrates. From the toxicological and pharmacological point of view, our knowledge is much more embryonic than that of chemical effects. One plausible reason for this is that the knowledge in organoselenium (organotellurium) pharmacology and toxicology has been assembled, but not in the chemical field. Consequently, we can conclude that the future of 'medicinal chemistry' of organoselenium and organotellurium compounds will depend on the rational development of new molecules, which can be guided by our state of the art obtained empirically using both chemical and biological approaches with the compounds reviewed in the past and in this chapter. Importantly, the structure–activity relationship for a given class of organoselenium or organotellurium compounds should enter in 'a hypothetical' hierarchical model for screening molecules with high probability of exhibiting low toxicity and high pharmacological activity in mammals. For instance, the screening model could start with computational analysis, antioxidant effect in pure chemical systems and in simple biological systems, and *in vivo* toxicity test in simple organism (invertebrates) and in vertebrates. Furthermore, the computational analysis will also be useful for the identification of the molecular biological targets of organoselenium and organotellurium compounds. Here we have an additional complicating factor in the 'medicinal chemistry' of these compounds: they apparently act at multiple targets and, consequently, the future of their therapeutic chemistry will depend on the synthesis of new molecules that could target more specifically few enzymes, proteins or other informational biomolecules (i.e. RNA molecules and DNA specific sequences).

V. ACKNOWLEDGMENTS

The authors wish to sincerely thank their coworkers listed in the references for their dedicated collaboration and devotion. Financial support by UFSM, CAPES, CNPq and FAPERGS is acknowledged. The authors are also thankful to the FINEP research grant 'Rede Instituto Brasileiro de Neurociência (IBN-Net)' # 01.06.0842-00, INCT for Excitotoxicity and Neuroprotection-CNPq and FAPERGS/CNPq (PRONEX) research grant # 10/0005-1.

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Vinyl selenides

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0568

I. INTRODUCTION

Organoselenium chemistry has become an important tool in organic chemistry for the preparation of several synthons as reactive intermediates in organic synthesis and for an ever-increasing number of technical applications. Over the last decade, the importance of selenium atom in organic chemistry has greatly increased, in part due to the development of new methods for the synthesis of optically active selenoxides, enantio- and diastereoselective selenoxide *syn* eliminations and [2,3]-sigmatropic rearrangements.

The prime aim of this chapter is to summarize the main reactions of interest to the synthetic chemist for the preparation of vinyl selenides. Wherever feasible, this chapter covers only literature published during the last ten years; for earlier publications it may be advisable to refer also to previously published reviews[1] and books[2]. An excellent review dealing with the synthesis of vinyl selenides was recently described and we are greatly indebted to the authors for allowing us its use as a source for this chapter[1k].

Vinyl selenides have been recognized as important synthetic intermediates in many applications[3]. These compounds are well suited as precursors to a variety of compounds with geometrically defined double bonds, which can also undergo Se–Li exchange, cycloaddition and cross-coupling reactions, Nazarov cyclizations, selenoxide eliminations and deselenylation in which the double-bond geometry is frequently retained.

The main synthetic pathways to synthesize vinyl selenides described in this chapter are based on the use of: (a) alkynes and alkynyl selenides, (b) alkenes and allenes, and (c) carbonyl compounds. Some applications of this class of compounds in organic synthesis will also be outlined when appropriate. Finally, some aspects of the physical properties and characterization of vinyl selenides will be briefly discussed.

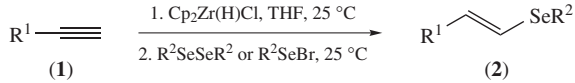
II. GENERAL SYNTHETIC PATHWAYS TO VINYL SELENIDES

A. Synthesis of Vinyl Selenides from Alkynes and Alkynyl Selenides

1. Methods based on the hydrozirconation reaction

The hydrozirconation of alkynes became a useful method for the regio- and stereoselective synthesis of a variety of functionalized alkenes[4a]. A wide range of zirconium-mediated transformations and the relative ease of preparation of alkenyl-chlorozirconocenes contribute to the broad appeal of this chemistry. In addition, the hydrozirconation of alkynes is often performed at room temperature and does not require special glassware or glove-box techniques[4b].

Functionalized vinyl selenides can be easily prepared from the hydrozirconation of the corresponding alkynes **1**, by using the Schwartz reagent, $Cp_2Zr(H)Cl$, followed by the capture of the alkenyl zirconium intermediate with diaryl diselenides[5], or arylselenyl bromides[6], to yield the corresponding *E*-vinyl selenides **2** in good yields (Scheme 1).

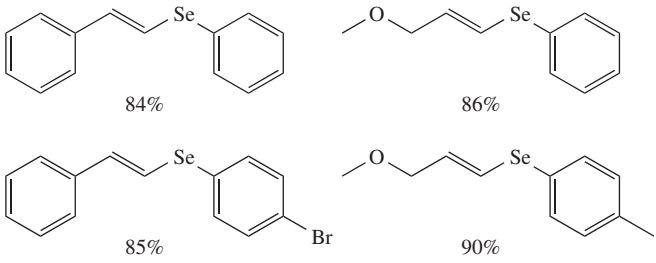


(**1**) (**2**)

R^1 = aryl, alkenyl, alkyl
R^2 = aryl

E
64–89%

Products of selected examples:

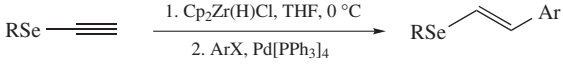


SCHEME 1

The diphenyl diselenide and phenylselenenyl bromide are commercially available. The desired arylselenenyl bromide can be conveniently prepared in solution as needed. Care must be taken to avoid an excess of bromine and to ensure thorough mixing of the solution during the reaction with the appropriate diaryl diselenide to prevent the formation of undesirable $ArSeBr_3$.

An extension of the method, which avoids the use of diaryl diselenides or arylselenyl bromides, was based on the insertion of elemental selenium into the alkenyl zirconium intermediate, followed by the treatment of the intermediate with alkyl halides[7] or diaryliodonium salts[8] gave the respective *E*-alkylvinyl selenides and *E*-arylvinyl selenides in moderate to good yields.

The hydrozirconation of terminal alkynyl selenides **3** using the Schwartz reagent, followed by a cross-coupling with aryl halides promoted by Pd[0] gave exclusively the corresponding *E*-vinyl selenides **4** in good to moderate yields[9] (Scheme 2).



(**3**) (**4**)

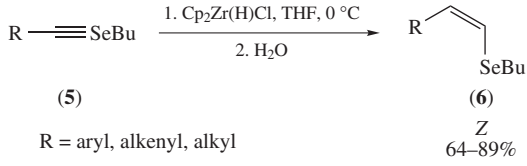
E

R = Bu, *p*-Tol, 4-BrC_6H_4
X = Br, I

43–85%

SCHEME 2

When internal alkynyl selenides **5** were submitted to the hydrozirconation conditions using two equivalents of Schwartz reagent, the *Z*-isomer **6** was obtained in a very stereoselective way and in good yields[10] (Scheme 3).



(**5**)

R = aryl, alkenyl, alkyl

(**6**)

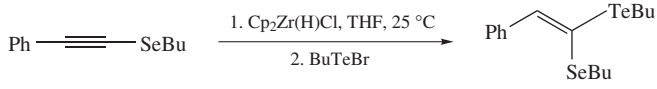
Z

64–89%

SCHEME 3

The hydrozirconation of alkynyl selenides using 2.0 equivalents of $Cp_2Zr(H)C1$ was very stereoselective, although the regiochemistry in this reaction was highly dependent on the structure of the employed substrate.

The scope of the reaction was extended to the synthesis of selenotelluroketene acetals **8**, whose regio- and stereoselectivity depends on the structure of the starting alkynyl selenide **7** (Scheme 4).



(**7**)

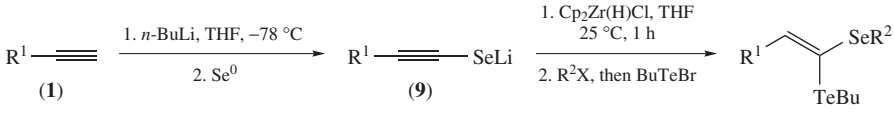
(**8**)

Z

63%

SCHEME 4

Later, a more regioselective method for the synthesis of **10**, based on the hydrozirconation of lithium alkynyl selenolates[11] **9**, was described by the same group (Scheme 5).



(**1**)

(**9**)

R^1 = alkyl, aryl

R^2 = alkyl

(**10**)

Z

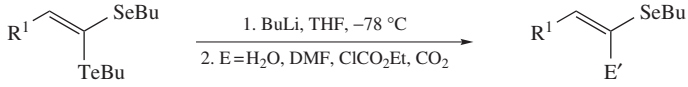
71–82%

SCHEME 5

The synthetic utility of the selenotelluroketals, **10** was demonstrated by a tellurium/metal exchange reaction followed by the capture with several electrophiles, to yield the corresponding functionalized vinyl selenides **11** in good yields (Scheme 6).

The same method was also applied in the synthesis of *Z*-selenothioketene acetals[12] and iodides[13], which were later converted into the corresponding *Z*-enynes in a cross-coupling reaction with terminal alkynes.

Similar results were observed in the hydrozirconation of alkynyl selenides **12**[14]. The capture of the vinyl zirconium intermediate with a variety of electrophiles (E) gave the

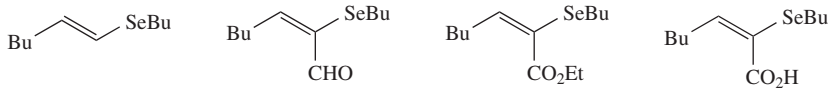


(**10**) R^1 = Bu

(**11**)

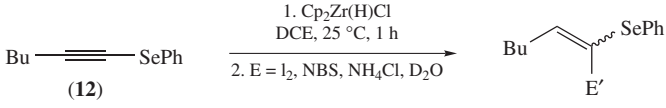
E′= H, CHO, CO_2Et, CO_2H

Products of selected examples:



91% 70% 65% 70%

SCHEME 6



(**12**)

E′ = I, Br, H, D

(**13**)

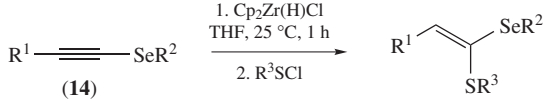
E/Z

62–71%

SCHEME 7

corresponding functionalized vinyl selenides **13** in good yields, but low stereoselectivities were observed in some cases (Scheme 7).

Selenothioketals **15** were also prepared from **14**, where the α-zirconated intermediate was trapped with alkyl- and benzylthio chlorides to yield the corresponding products in good yields[15] (Scheme 8).



(**14**)

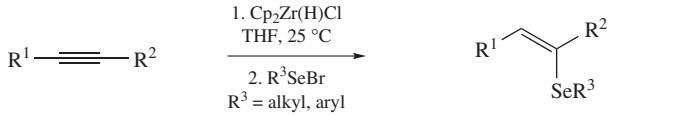
R^1 = alkyl, aryl
R^2 = alkyl
R^3 = alkyl, aryl, benzyl

(**15**)

69–82%

SCHEME 8

The hydrozirconation of 1-silyl- **16**[16] and 1-stannyl alkynes **17**[17] followed by the addition of phenylselenyl bromide gave the corresponding products **18** and **19** in moderate to good yields (Scheme 9).



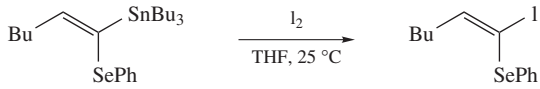
(**16**) R^2 = TMS
(**17**) R^2 = $SnBu_3$

R^1 = aryl, alkyl

(**18**) R^2 = TMS (80–87%)
(**19**) R^2 = $SnBu_3$ (36–65%)

SCHEME 9

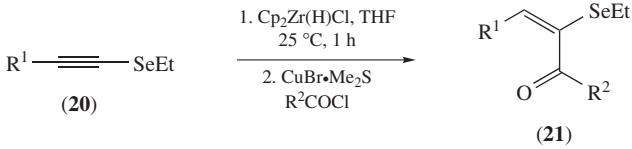
Later, Dabdoub and Baroni observed that the yield of the ketene stannyl(seleno) acetals can be improved by the addition of phenylselenyl bromide at lower temperatures[18] and an insight regarding the different reactivity of the tin and selenium moieties was provided by performing the halogenolysis with iodine (Scheme 10).



95%

SCHEME 10

The hydrozirconation of 1-alkynyl selenides **20** followed by the addition of acyl chlorides gave the corresponding α-seleno functionalized α,β-unsaturated ketones **21** in good yields[19] (Scheme 11).



(**20**)

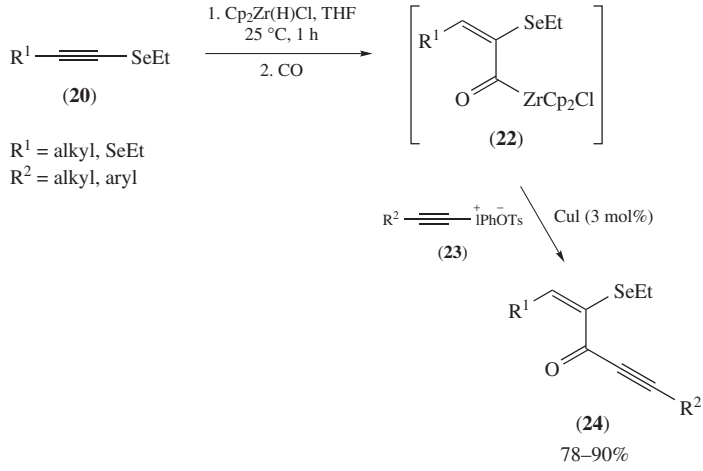
(**21**)

R^1 = alkyl, SeEt
R^2 = alkyl, aryl

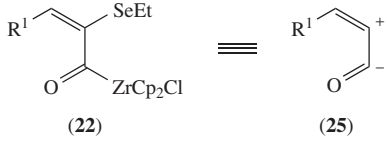
SCHEME 11

The use of the same reaction conditions followed by treatment of the vinyl zirconium intermediate with carbon monoxide gave intermediate **22**[20], and sequential coupling with alkynyl iodonium tosylates **23** gave the corresponding ketones **24** in good yields (Scheme 12).

Since the EtSe- and the zirconocene functions exert an opposing polarization on the double bond, intermediate **22** represents the synthetic equivalent of the cation–anion synthon **25** (Scheme 13).



SCHEME 12

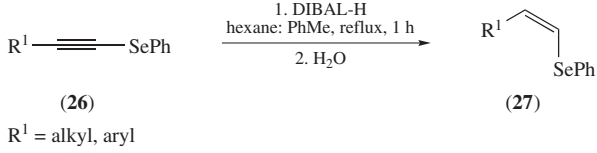


SCHEME 13

2. Methods based on the hydroalumination reaction

The addition of Al−H bonds to the triple bonds of unsaturated organic compounds (hydroalumination) is a very powerful method for the synthesis of vinyl selenides. The reaction is very stereoselective due to a *cis* arrangement of the hydrogen and aluminum atoms in most secondary products containing a triple bond. That particular configuration may be representative for the first step of all addition reactions involving dialkylaluminum hydrides by the reasonable assumption that they proceed by a concerted addition process including a heterocyclic transition state[21].

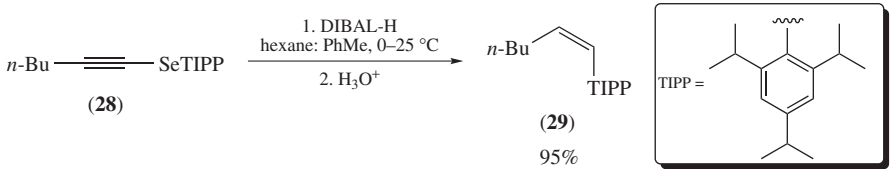
The addition of DIBAL-H to alkynyl selenides **26** is a very selective method to prepare the corresponding *Z*-vinyl selenides **27** in good yields (Scheme 14)[22].



SCHEME 14

When the appropriate electrophile was used, the corresponding functionalized vinyl selenides were also obtained in good yields. The drawback of the reaction is the low tolerance of DIBAL-H to oxygenated functional groups as well as the competitive $C_{sp}-Se$ bond cleavage to yield PhSeSePh as a side product.

An alternative to circumvent this problem was based on the use of a more hindered alkynyl selenide **28** as the starting material. The intermediate vinylalane was quenched with aqueous HCl to give the *Z*-vinyl selenide **29** in 95% yield[23] (Scheme 15).



SCHEME 15

The use of other electrophiles, such as iodine, gave the corresponding halogenated products **30** also in good yields (Chart 1). However, the method failed when the starting selenoalkyne derived from phenylacetylene was used.

3. Methods based on the hydrostannation reaction

The hydrostannation of alkynyl selenides **14**, using tributyltin hydride catalyzed by Pd(0), gave the corresponding α-selenostannanes **30** in good yields[24] (Scheme 16).

Subsequent treatment of **30** with iodine gave the α-iodovinyl selenides in yields ranging from 80–92%.

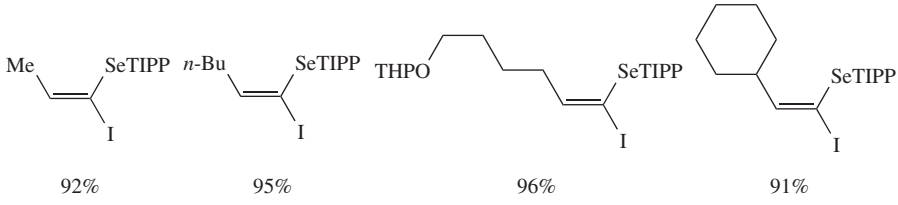
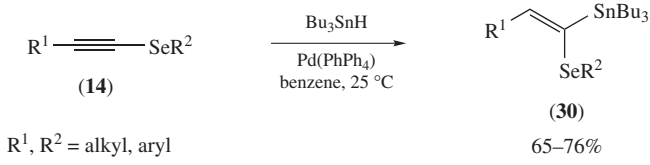


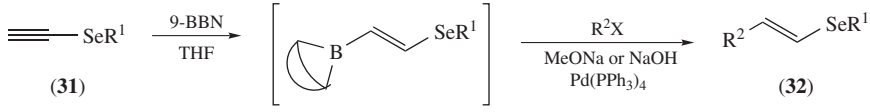
CHART 1



SCHEME 16

4. Methods based on the hydroboration reaction

E-vinyl selenides **32** can also be obtained in good yields from the hydroboration of the corresponding selenoalkynes **31**, using the commercial available 9-BBN followed by the Suzuki coupling with aryl, allyl and alkyl halides using $Pd(PPh_3)_4$ as a catalyst and sodium methoxide or hydroxide as a base (Scheme 17)[25].



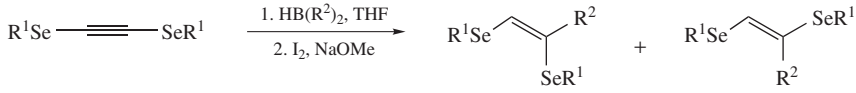
(**31**) (**32**)

R^1 = alkyl, aryl
R^2 = alkyl, allyl, aryl, benzyl

80–91%

SCHEME 17

The vinyl selenides **32** were obtained in good yields and in a stereoselective way. 1,2-Dialkylseleno alkynes **33** can also be submitted to the hydroboration conditions using other commercially available boranes[26]. Subsequent iodination reaction under basic conditions gave the corresponding *Z*-vinyl selenides **34**, along with a minor amount of the *E*-isomer **35**, in good yields (Scheme 18).



(**33**) (**34**) (**35**)

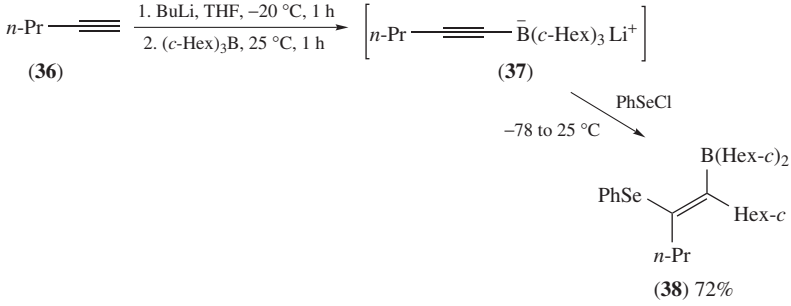
R^1, R^2 = alkyl, aryl

77–90%
Z:E = 93:7 to 97:3

SCHEME 18

The addition of PhSeCl to 1-alkynyl boron intermediate **37**, prepared *in situ* from alkyne **36**, gave the corresponding *Z*-phenylseleno alkenylborane **38** in 72% yield (Scheme 19).

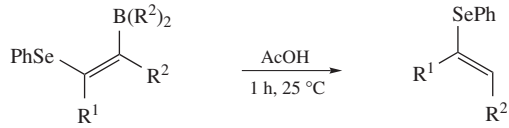
The obtained boranes e.g., **39** can be further submitted to a protodeboration reaction using AcOH to yield the corresponding vinyl selenides **40** in good yields and selectivities (Scheme 20)[27].



(**36**) (**37**)

(**38**) 72%

SCHEME 19



(**39**)

R^1, R^2 = alkyl

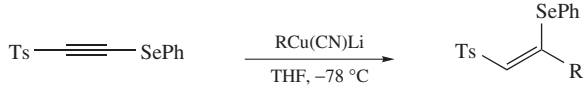
(**40**)

65–81%

SCHEME 20

5. Methods based on the use of organocopper reagents

Back and coworkers[28] described the stereo- and regioselective addition of lower order cyanocuprates to the β-position of tosyl-functionalized alkynyl selenides **41** to give the corresponding adducts **42** in good yields (Scheme 21).



(**41**)

R = Me, Bu, Ph

(**42**)

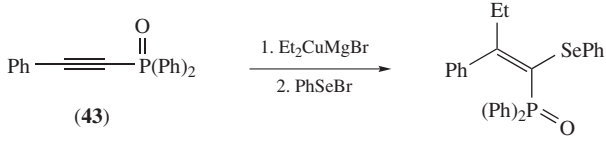
Z

72–78%

SCHEME 21

The reactions of **41** with hard and soft heteroatom nucleophiles gave different types of products. The additions of hard nucleophiles (amines, alkoxides) produce the corresponding anti-Michael (nucleophile at C_β regioisomers as the major or sole products. However, the reactions of **41** with soft nucleophiles (thiolates and selenolates) are more complex, yielding the rearranged adducts and Michael adducts as the major and minor products, respectively. The regioselectivity in the addition of cuprates to alkynyl selenides was also described by other groups[29].

The carbocupration of alkynes containing a phosphine oxide **43** as a functional group with organocopper(I) reagents gave the corresponding vinyl copper species which was trapped with phenylselenyl bromide to yield the corresponding α-phenylseleno vinylphosphine oxide **44** in good yield (Scheme 22)[30].



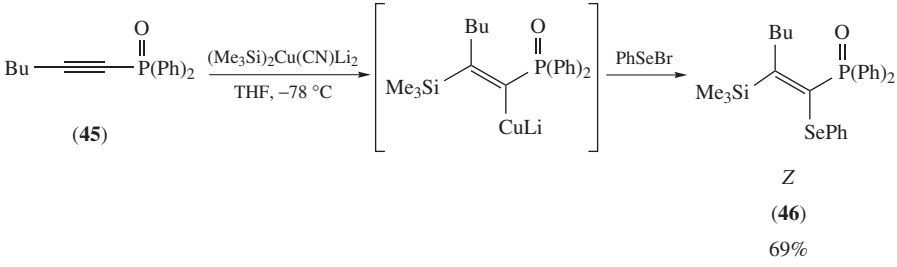
(**43**)

(**44**)

81%

SCHEME 22

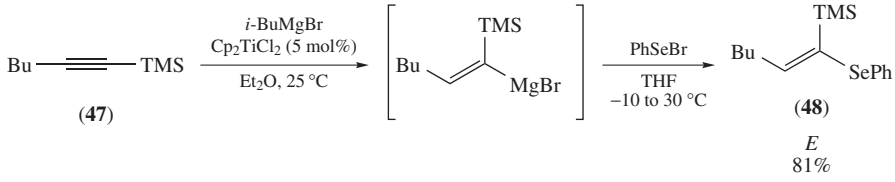
In a similar way, when organosilylcopper(I) reagent were added to **45**, followed by the addition of the phenylselenyl bromide and several other electrophiles, the respective functionalized *Z*-1-phenylseleno vinylphosphine oxide **46** was obtained in good yield[31] (Scheme 23).



SCHEME 23

6. Methods based on the use of organomagnesium reagents

E-Vinyl selenides **48** can be stereoselectively synthesized by the hydromagnesiation of 1-trimethylsilylalkynes **47**, catalyzed by Cp_2TiCl_2[32]. The obtained *Z*-vinyl Grignard intermediate was trapped with arylselenyl halides to give the products in good yields (Scheme 24). Subsequent treatment of the obtained *E*-vinyl selenides **48** with HI gave the corresponding silyl free alkenes in 74–83% yield.



SCHEME 24

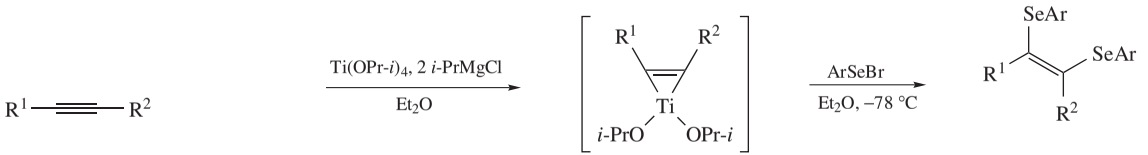
7. Methods based on the use of organotitanium reagents

An approach based on the use of alkynyl–titanium complexes, prepared from the corresponding functionalized alkynes **49** and arylselenyl bromides[33], was used for the preparation of functionalized vinyl bis-arylselenides **50**. The corresponding products were obtained in a stereoselective way and in good yields (Scheme 25).

8. Methods based on the addition of electrophilic selenium species

The reaction of alkynyl bromides **51** with phenylselenyl bromide using $ZnBr_2$ as catalyst gave exclusively the *Z*-isomer of the dibromovinyl selenide **52**, in moderate to good yields (Scheme 26)[34].

The stereospecificity of the addition was established to be *trans* and the presence of $ZnBr_2$ was found to be essential for the reaction. The use of other Lewis acid such as $ZnCl_2$ and $HgBr_2$ gave the corresponding products in lower yields.



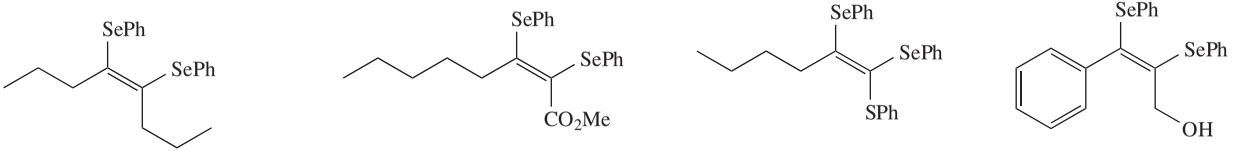
(**49**)

R^1= alkyl, aryl
R^2 = alkyl, CO_2R, SR, CH_2OH
Ar = Ph, 4-ClC_6H_4

(**50**)

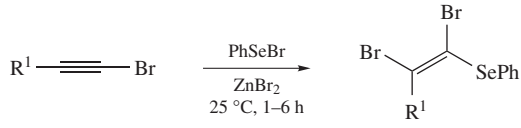
54–70%

Products of selected examples:



63% 70% 60% 62%

SCHEME 25

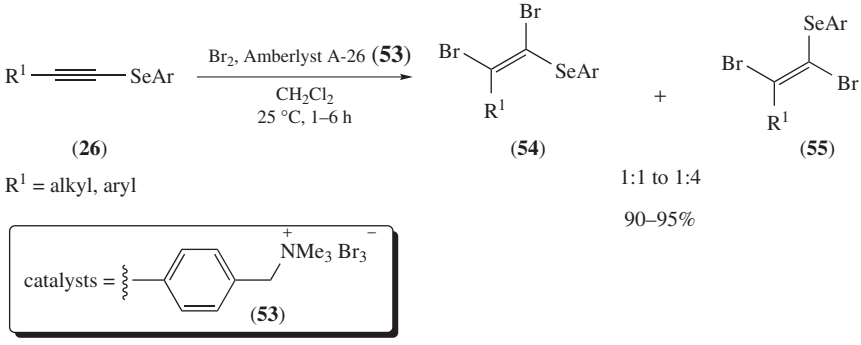


(**51**) (**52**)

R^1 = alkyl, aryl 48–64%

SCHEME 26

In a similar way, alkynyl selenides **26** can be brominated using Amberlyst A-26 in the perbromide form **53** to give a mixture of the corresponding *E*- and *Z*-vinyl selenides **54** and **55** in excellent yields with only moderate selectivities (Scheme 27).



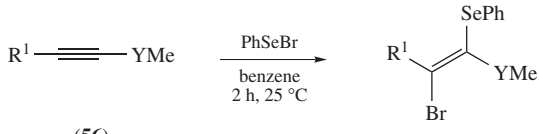
(**26**) (**54**) 1:1 to 1:4 (**55**)

R^1 = alkyl, aryl 90–95%

(**53**)

SCHEME 27

The stereoselective addition of phenylselenenyl bromide to alkynyl sulfides and selenides **56** was used to prepare several β-bromovinylchalcogenoketene acetals **57**[35]. In all cases, good yields were observed (Scheme 28).



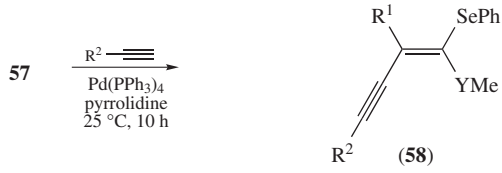
(**56**) (**57**)

Y = S, Se 70–83%

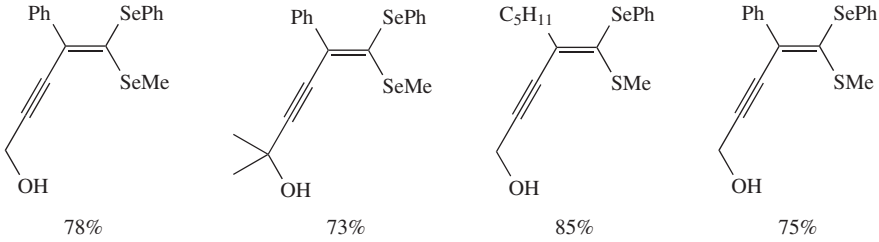
R^1 = alkyl, aryl

SCHEME 28

The obtained compounds were later submitted to a Sonogashira-type cross-coupling reaction to yield the corresponding chalcogenoenynes **58** in 62–85% yields (Scheme 29).



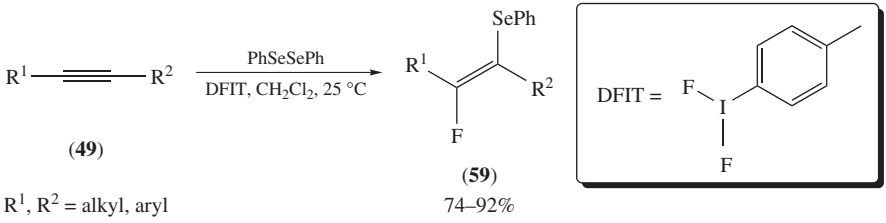
Products of selected examples:



SCHEME 29

The use of PhSeF equivalents for the synthesis of selenium/fluorine functionalized alkenes from internal alkynes **49** can be achieved by the use of PhSeSePh/DFIT (Scheme 30)[36].

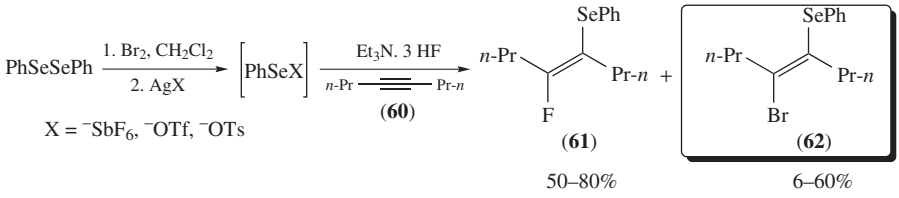
For all studied examples, the *E*-isomer **59** was obtained exclusively in excellent yields. The method, however, did not work for terminal alkynes where phenylselenoalkynes, the product of the substitution of terminal hydrogen by the PhSe group, were obtained.



SCHEME 30

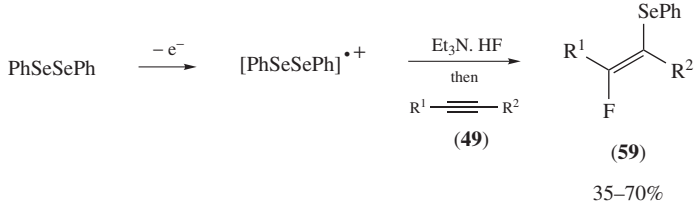
The use of novel PhSeF equivalents in the fluoroselenylation of internal alkynes **60** gave the corresponding vinyl selenides **61** and **62** in reasonable to good yields (25–71%) (Scheme 31)[37].

The seleno electrophiles are generated by bromination of PhSeSePh with Br_2 followed by a subsequent reaction of the obtained PhSeBr with the silver salts $Ag^+SbF_6^-$, Ag^+TfO^-, $Ag^+BF_4^-$ or Ag^+TsO^-. The drawback of the reaction is that in almost all experiments compound **62** was detected as a byproduct, probably due to the low solubility of the silver salts in the reaction solvent.



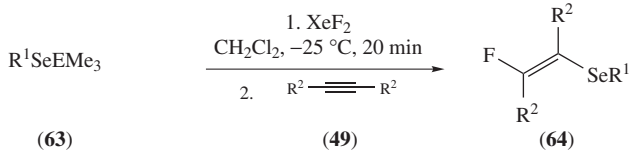
SCHEME 31

The generation of PhSeF by the electrochemical oxidation of PhSeSePh followed by the addition of an internal alkyne **49** gave the corresponding *E*-fluoroalkenes **59** in moderate to good yields (Scheme 32)[38].



SCHEME 32

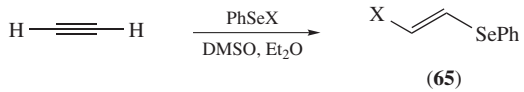
RSeF species can also be efficiently generated *in situ* by the cleavage of selenides of the type $RSeEMe_3$ (**63**), where E = Si, Ge, Sn, Pb, with xenon difluoride[39]. The reaction with XeF_2 was fast and the addition step was done in a one-pot procedure to yield in a very selective way the corresponding *E*-vinyl selenides **64** in moderate to good yields (Scheme 33).



SCHEME 33

Better results were observed with $RSeSiMe_3$, while $RSeSnMe_3$ derivatives exhibit lower reactivity.

A simple method for the addition of alkylselenenyl chlorides or bromides to acetylene to yield the corresponding *E*-vinyl selenides **65** was described by Potapov and coworkers (Scheme 34)[40].



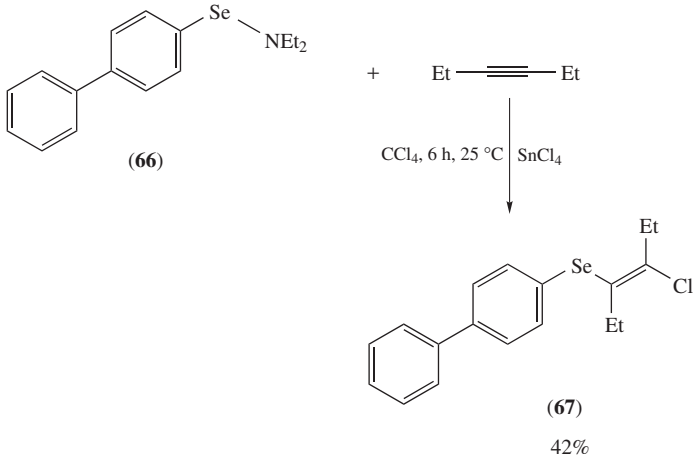
(**65**)

X = Cl, 92%
X = Br, 88%

SCHEME 34

However, when phenylacetylene was used as the alkyne source a mixture of *E*- and *Z*-vinyl selenides was obtained[41].

More recently, the use of a biphenylselenamide **66**, and $SnCl_4$ as a replacement of PhSeCl[42] was described. The effective electrophilic species of selenium was generated *in situ*, via chlorination of **66**. Further reaction with the alkyne gave the corresponding vinyl selenide **67** in modest yield (Scheme 35).



(**66**)

(**67**)

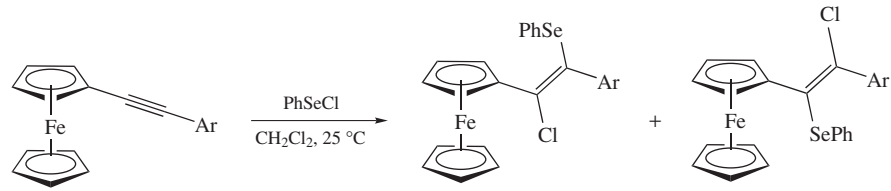
42%

SCHEME 35

In the same work, some examples of vinyl sulfides were also synthesized using the sulfur-analogue, biphenylsulfenamide.

The regioselective addition of PhSeCl to ferrocenylalkynes **68** in dichloromethane at room temperature gave a regioisomeric mixture of vinyl selenides **69** and **70**, rich in the *E* isomer in 40–83% yield (Scheme 36)[43].

Using a semiempirical calculation, the authors suggested that the preferential formation of the major adduct is probably due to a favorable iron–selenium interaction. Standard spectroscopic methods (^1H and ^{13}C NMR spectroscopy) proved ineffective in providing information on the phenylselenylation adducts, but the regiochemistry of the reaction could be determined by ^{77}Se NMR spectroscopy.



(**68**) (**69**) (**70**)

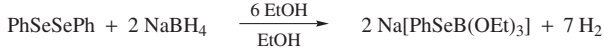
Ar = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4
p-FC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$

40–83%
63:37 to 100:0

SCHEME 36

9. Methods based on the addition of nucleophilic selenium species

The hydroselenation of alkynes is a common method to prepare the corresponding vinyl selenides. The reaction of diphenyl diselenide with sodium borohydride was first described by Sharpless and Lauer and it was used for the synthesis of allylic alcohols[44]. Later, Miyashita and coworkers determined that the structure of the nucleophilic selenium species obtained using this method is a boron complex **71**, which is slightly less nucleophilic than the selenolate anion (Scheme 37)[45].



(**71**)

SCHEME 37

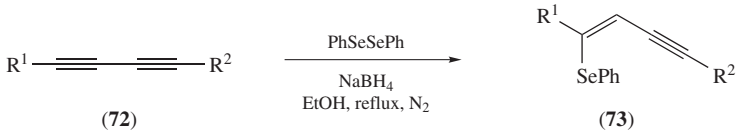
Since then, several other methods using the RSeSeR/$NaBH_4$ system appeared in the literature, where the main modification from the original method involved the use of more functionalized alkynes. The simplified 'RSeNa' notation is generally used for almost all of the methods involving the *in situ* generation of nucleophilic selenium species.

Diynes **72** can be hydroselenated using PhSeSePh/$NaBH_4$ in EtOH[46]. The reaction is regio-, stereo- and chemoselective for the formation of the *Z*-phenylseleno enynes **73** in good yields (Scheme 38).

The authors also observed that the terminal triple bond of 1,3-diacetylenes was more reactive than alkyl- and aryl-substituted ones, while the propargylic triple bond (alcohol derivative) presents an intermediate reactivity toward the hydroselenation.

The hydroselenation of electron-deficient enyne sulfones **74** was studied by Yoshimatsu and Hasegawa[47]. The authors generated the nucleophilic selenium species using sodium borohydride and EtOH or THF as the reaction solvent. In all cases, a high selectivity for the *anti* addition product at the δ-position **75** was observed (Scheme 39).

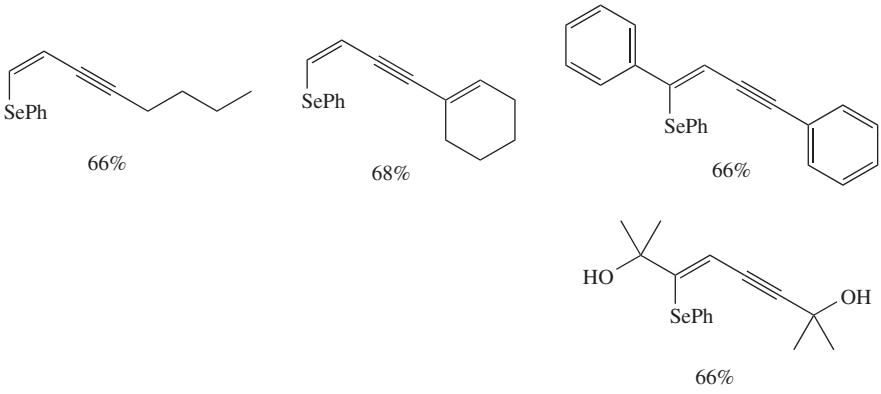
Braga and coworkers[48] described the nucleophilic addition of selenium species to alkynylphosphonates **76**, to yield the corresponding vinyl phosphonates **77** in moderate to good yields (Scheme 40).



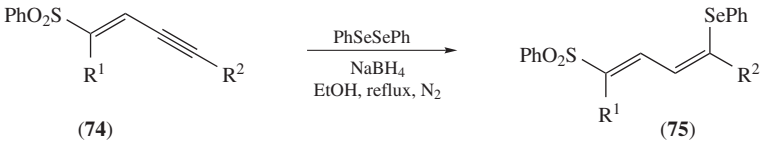
(**72**) (**73**)

R^1, R^2 = H, alkyl, aryl 54–75%

Products of selected examples:



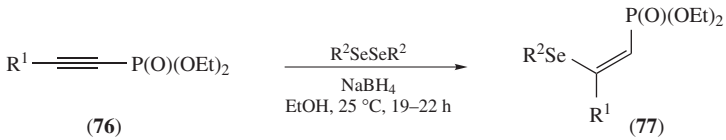
SCHEME 38



(**74**) (**75**)

R^1, R^2 = alkyl, aryl 11–96%

SCHEME 39



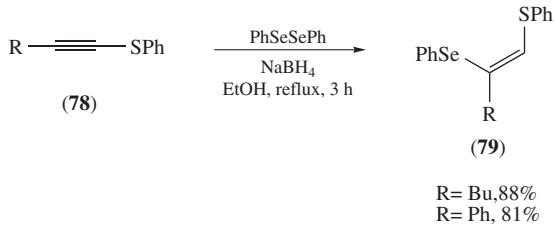
(**76**) (**77**)

R^1, R^2 = alkyl, aryl 26–70%

SCHEME 40

The reaction was performed by addition of alkynylphosphonates to a solution of the nucleophilic selenium species at room temperature. When diphenyl diselenide was used as a starting material, the corresponding *Z*-isomers were obtained in modest yields (26–40%), while for dibutyl diselenide, a mixture of *E*- and *Z*-isomers were obtained in good yields (68–70%).

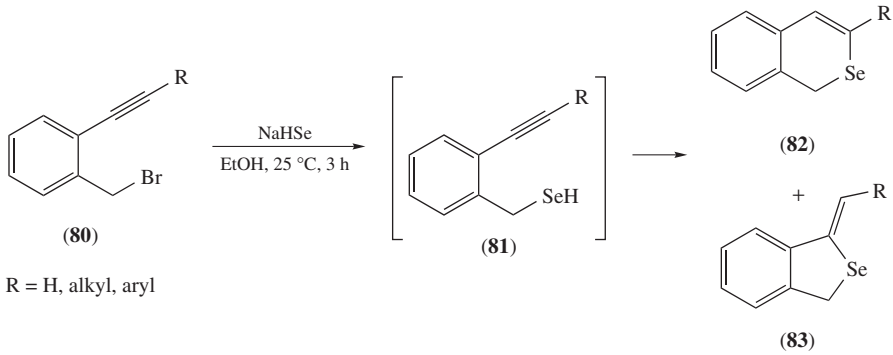
The hydroselenation of (phenylthio)acetylene **78** to prepare selectively the corresponding addition products **79** with *Z*-geometry was described by Dabdoub and coworkers (Scheme 41)[49].



SCHEME 41

The authors observed that the PhS group acts as a directing and activating group for the nucleophilic addition of the nucleophilic selenium species. In the same article, the authors prepared the tellurium derivative using PhTeNa and BuTeNa as the nucleophilic species.

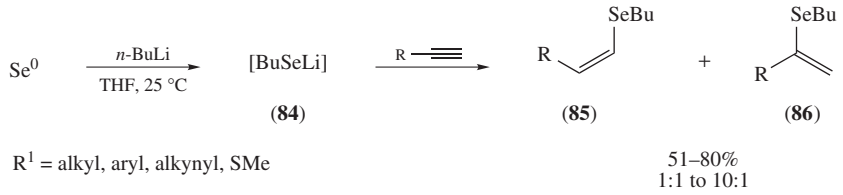
o-Alkynylbenzyl selenols **81**, obtained from the reaction of *o*-alkynylbenzyl bromides **80** and NaHSe, were easily cyclized to give a mixture of the respective cyclic compounds **82** and **83** in 56–81% yields (Scheme 42)[50].



SCHEME 42

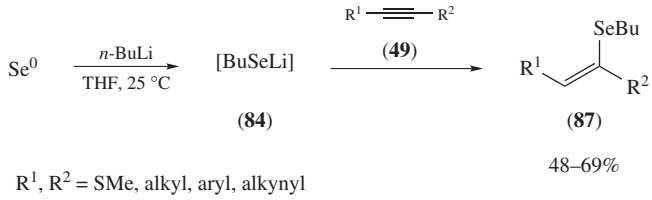
When R = H, the corresponding *o*-ethynylbenzylselenol was regioselectively cyclized to the corresponding isoselenochromene **82** in 56% yield. On the other hand, when R = Ph, only the benzylidene-2-selenaindane **83** was obtained in 66% yield via a *5-exo-dig* reaction. The *iso*-selenochromenes were later converted into the corresponding selenonium salts or 5*H*-2,3-benzodiazepines in mild conditions and in moderate yields.

The use of nucleophilic selenium species **84** obtained *in situ* from elemental selenium and *n*-BuLi in THF at room temperature constitutes an important improvement in the hydroselenation reaction while it avoids the preparation of diselenides or the use of selenophenol. Using this approach, the hydroselenation of terminal alkynes was described, and the corresponding vinyl selenides **85** and **86** were obtained in excellent yields (Scheme 43)[51].

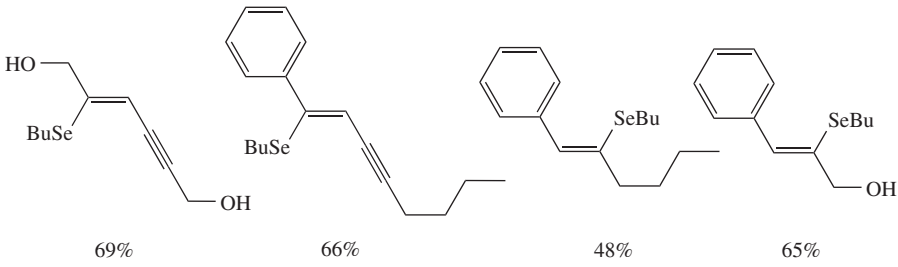


SCHEME 43

Except for the hydroselenation of phenylacetylene, which gave exclusively the *Z*-isomer, in all cases a mixture of *Z*- and geminal vinyl selenides was obtained. When internal alkynes were used, the reaction showed high stereoselectivity for the synthesis of *Z*-vinyl selenides **87** (Scheme 44).

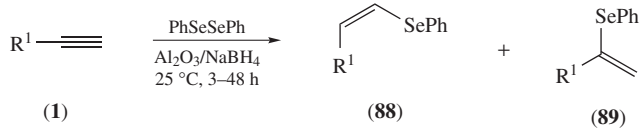


Products of selected examples:



SCHEME 44

The hydroselenation of terminal alkynes **1** using PhSeSePh and sodium borohydride supported on alumina under solvent-free conditions at room temperature gave a regioisomeric mixture of adducts **88** and **89** in good yields with a ratio dependent on the structure of the alkyne (Scheme 45)[52].



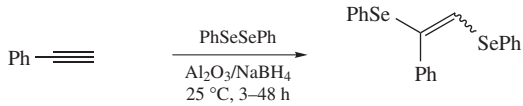
(**1**) (**88**) (**89**)

$R^1 = (CH_3)_2C(OH), HOCH_2$

62–83%
70:30 to 93:7

SCHEME 45

Interestingly, when phenylacetylene was used as the alkyne source, the corresponding 1,2-bis(organylseleno)alkene **90** with preferential *E* stereochemistry was obtained in good yield after three hours at room temperature (Scheme 46).

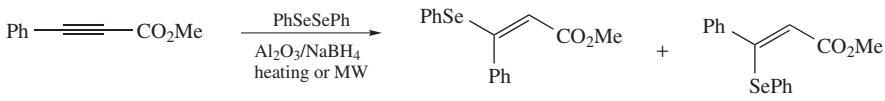


(**90**)

72%
E:*Z* = 74:26

SCHEME 46

The reaction time was drastically reduced when microwave radiation was employed as a nonclassical energy source, and the vinyl selenides with preferential *Z* configuration were obtained in shorter reaction times. When Michael acceptors such as alkynyl ketones, nitriles and esters **91** were used, the desired vinyl selenides **92** and **93** were obtained in yields ranging from 69 to 83%, and preferentially with *Z* configuration (Scheme 47)[53].

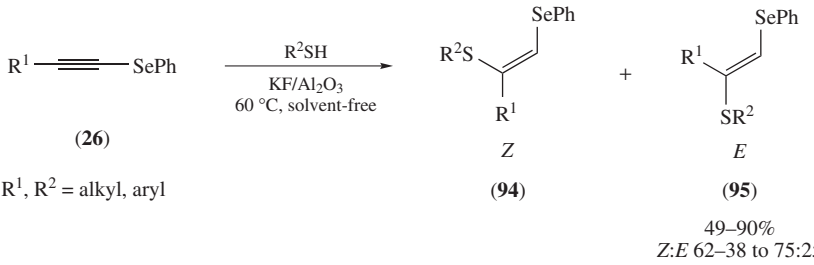


(**91**) (**92**) (**93**)

	Time (min.)	Yield (%)	**92:93**
25 °C	360	83	79.21
MW (662 W)	3	82	85.15
65 °C	30	69	73.27

SCHEME 47

More recently, the same authors described an efficient protocol for the hydrothiolation of phenylselenoalkynes **26** using KF/Al_2O_3 under solvent-free conditions[54]. The method gave the corresponding *Z*-vinyl selenides **94** as the major isomer, together with the isomer **95**, in moderate to good yields (Scheme 48).



(**26**)

R^1, R^2 = alkyl, aryl

Z

(**94**)

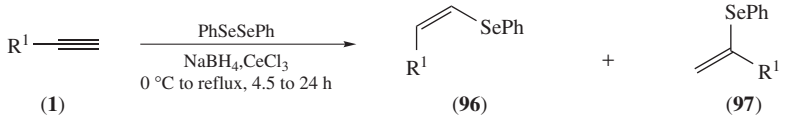
(**95**)

49–90%
Z:*E* 62–38 to 75:25

SCHEME 48

The presence of the phenylseleno group in the alkyne also directed the regiochemistry of the thiol addition. The catalytic system was reused up to 4 times without previous treatment.

Functionalized vinyl selenides **96** and **97** can also be synthesized from the corresponding alkynes **1** by means of a cerium trichloride mediated reaction (Scheme 49)[55].



(**1**)

(**96**)

(**97**)

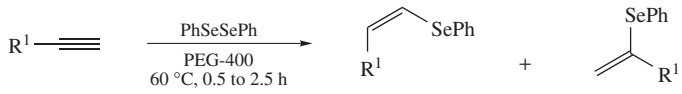
R^1 = $(CH_3)_2C(OH)$, $HOCH_2$, Ph, Bn_2NCH_2

69–96%
63:37 to 98:2

SCHEME 49

The authors suggested an association between the organochalcogen group and cerium trichloride, and that a cerium–selenium complex might be involved in the control of the regio- and stereoselectivity of the reaction. The vinyl selenide ratios obtained were markedly dependent on the substitution pattern of the alkyne, but very high regio- and stereoselectivities were observed.

PEG-400 was successfully used as recyclable solvent for the synthesis of several vinyl selenides **96** and **97** in good yields and with high selectivity by the hydroselenation of terminal alkynes **1** (Scheme 50)[56].



(**1**)

(**96**)

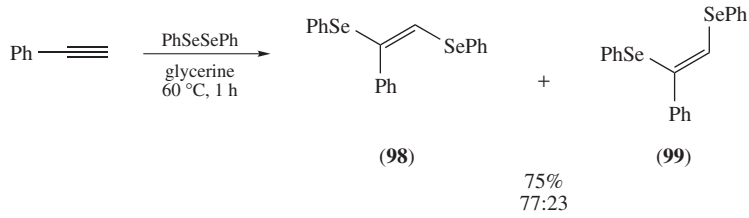
(**97**)

R = $HOCH_2$, Ph, HOCH(Me)(Et)

65–95%
100:0 to 79:21

SCHEME 50

The products were preferentially obtained with *Z* configuration and the solvent system could be reused up to 4 times without previous treatment with comparable yields and selectivities when compared to the standard hydroselenation protocol. Interestingly, when phenylacetylene was used as the alkyne source and glycerin was used as solvent, the formation of a mixture of *E*- and *Z*-1,2-bis(phenylseleno) styrenes **98** and **99** was observed (Scheme 51).



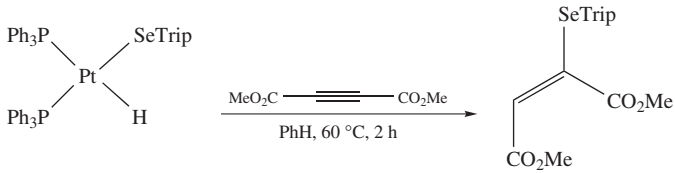
(**98**) (**99**)

75%
77:23

SCHEME 51

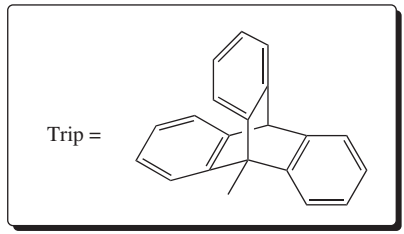
The hydroselenation of dimethyl acetylenedicarboxylate using [PtH(SeTrip)(phosphine)$_2$] (Trip = 9-triptycyl) complex **100** gave preferentially the corresponding *syn* addition products **101** with a selectivity dependent on the phosphane σ-donor ligand (Scheme 52)[57]. The reaction of [PtH(SeTrip)(PPh$_3$)$_2$] with dimethyl acetylenedicarboxylate gave the corresponding *syn* adducts. However, when [PtH(SeTrip)(dppe)], which has a stronger phosphane σ-donor ligand, was used, both *syn* and *anti* adducts were observed.

The use of bis(phenylseleno)iodoindium(III) **102**, obtained from the reaction of diphenyl diselenide and indium(I) iodide, for the selective formation of the vinylic selenides **103** was described by Peppe and coworkers (Scheme 53)[58].

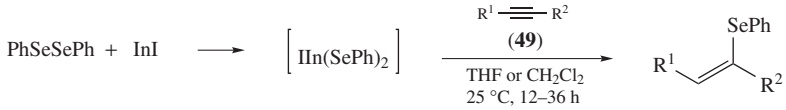


(**100**) (**101**)

E
24%

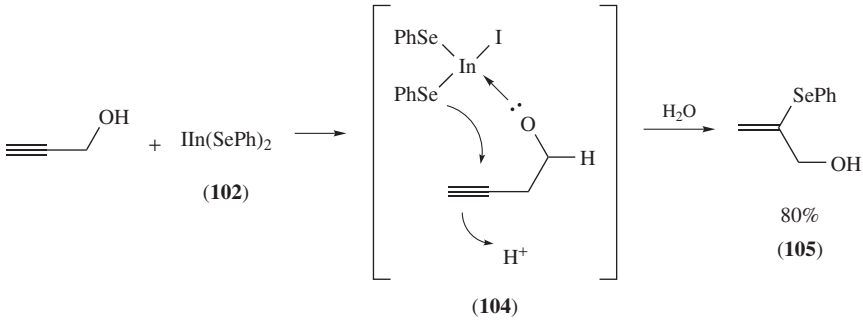


SCHEME 52



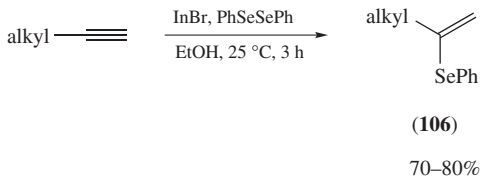
SCHEME 53

This protocol gave yields comparable to the methods based on the use of the stench, toxic and air-sensitive selenols. The adduct **104** obtained from coordination of the alkyne to **102** is the key intermediate in the process to give the Markovnikov adduct **105** (Scheme 54).



SCHEME 54

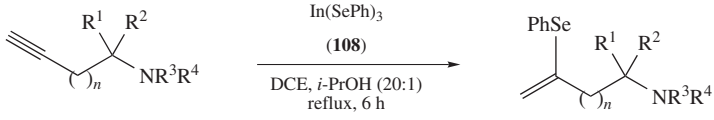
The scope of the reaction was later expanded for the reaction of bis(phenylseleno) bromoindium(III) obtained from the reaction of indium(I) bromide and diphenyl diselenide with terminal alkynes[59]. The authors observed the formation of the Markovnikov adducts **106** in good yields (Scheme 55).



SCHEME 55

When phenylacetylene was used in the reaction, a mixture of *E*- and *Z*-1,2-bis(phenylseleno)styrenes was obtained in a 9:1 *E*:*Z* ratio, indicating that a radical mechanism involving PhSeH, generated *in situ*, is probably involved.

Terminal aminoalkynes **107** can be regioselectively hydroselenated using indium(III) phenylselenolate **108**[60]. The corresponding allylic amines **109** were obtained in moderate to good yields (Scheme 56).



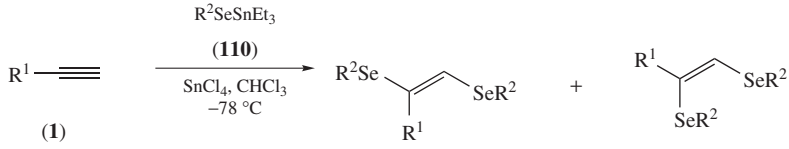
(**107**) (**109**)

R^1, R^2, R^3, R^4 = H, alkyl, aryl
n = 1, 2, 3

17–89%

SCHEME 56

The addition of organylselenostannanes **110** to terminal alkynes **1** in the synthesis of vinyl selenides was first described by Martynov and coworkers[61]. The corresponding products **111** and **112** were obtained in modest yields as a mixture of *E*- and *Z*-isomers (Scheme 57).



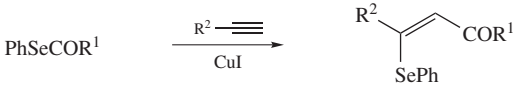
(**1**) (**111**) (**112**)

R^1, R^2 = alkyl, aryl

12–59%

SCHEME 57

The selenocarbonylation of alkynes using selenoesters **113** with a catalytic amount of Cu(I) is an efficient method to prepare the corresponding β-(arylseleno)-α,β-unsaturated ketones **114** in good yields (Scheme 58)[62].



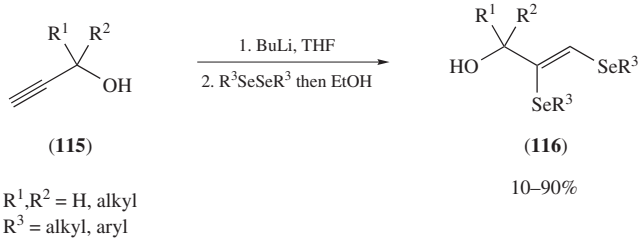
(**113**) (**114**)

R^1 = aryl
R^2 = Ph, $MeOCH_2$, $PhCO_2CH_2$

77–94%

SCHEME 58

Several terminal alkynes such as propargyl ether, alkyl and arylacetylenes can be used in the reaction.



(**115**) (**116**)

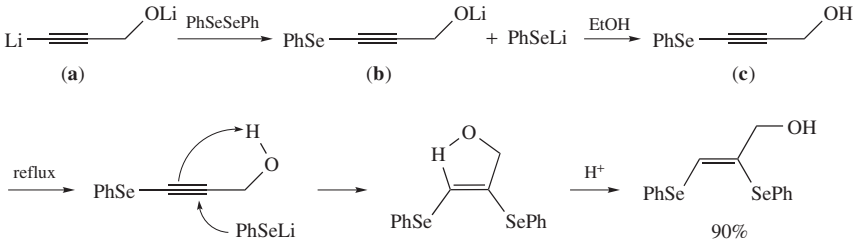
10–90%

R^1,R^2 = H, alkyl
R^3 = alkyl, aryl

SCHEME 59

The reaction of diorganoyl diselenides with substituted propargyl alcohols **115** under catalyst-free conditions, using a one-pot procedure, gave stereoselectively the corresponding bi(chalcogeno)alkenes **116** (Scheme 59)[63].

The method avoids the preparation of alkynyl chalcogenides, and the selectivity was governed by the effective participation of the hydroxyl group when propargyl alcohols were used as the substrate. A plausible mechanism for the formation of a vinylic selenide starting from propargyl alcohol is shown in Scheme 60.



SCHEME 60

The removal of acid hydrogens with *n*-BuLi from propargyl alcohol gave the lithium intermediate (**a**), and the reaction with dichalcogenide gave (**b**). Subsequent protonation of the intermediate (**b**) by the addition of EtOH gave the acetylenic chalcogenide (**c**). The addition of the chalcogenate anion onto the triple bond of the acetylenic chalcogenide, with concomitant trapping with a proton from the hydroxyl group, gave the desired vinyl selenide.

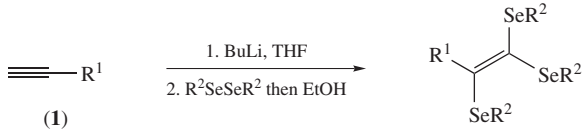
Conversely, alkynes **1** without a more acidic hydrogen gave exclusively the corresponding tri(chalcogeno)alkenes **117** (Scheme 61).

The method was successfully extended to diorganyl sulfides, but failed with the tellurium analogues.

$RhH(PPh_3)_4$ and dppf can be used for the regio- and stereoselective addition of diaryl disulfides and diaryl diselenides to terminal alkynes. The corresponding *Z*-alkenes **118** were obtained in low to good yields (Scheme 62)[64].

The selenothiolation of acetylene can be also attempted using base-catalyzed conditions ($KOH/DMSO/H_2O$) to yield the corresponding *Z*-isomer[65].

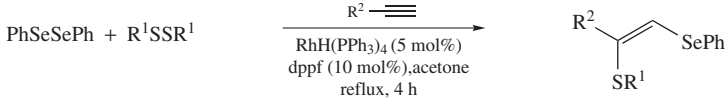
When sulfenamides **119**, terminal aliphatic alkynes **1**, carbon monoxide and diphenyl diselenide were in contact in benzene at 80 °C, in the presence of 3% $Pd(PPh_3)_4$, the corresponding *Z*-3-phenylselenoacrylamides **120** were obtained with high regio- and stereospecificity for the *Z*-isomer (Scheme 63)[66].



(**1**) (**117**)

R^1= alkyl, Ph, CH_2OEt, CH_2NEt_2 45–87%
R^2 = alkyl, aryl

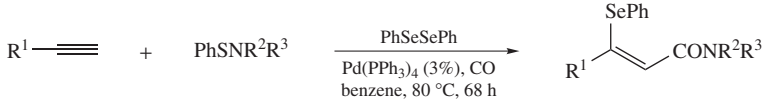
SCHEME 61



(**118**)

R^1= aryl
R^2 = H, alkyl, $HO(CH_2)_2$, $AcO(CH_2)_2$, $TBDMSOCH_2CH_2$ 11–79%

SCHEME 62

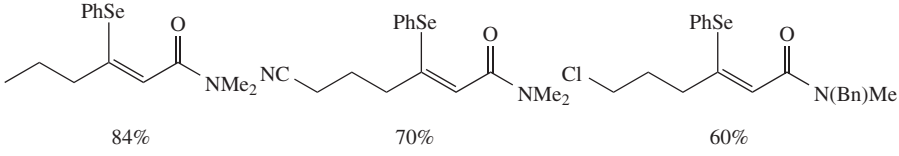


(**1**) (**119**) (**120**)

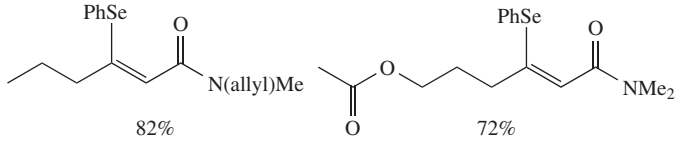
60–85%

R^1= alkyl
R^2, R^3 = alkyl, $(CH_2)_3CN$, $(CH_2)_3Cl$, C_6H_{13}

Products of selected examples:



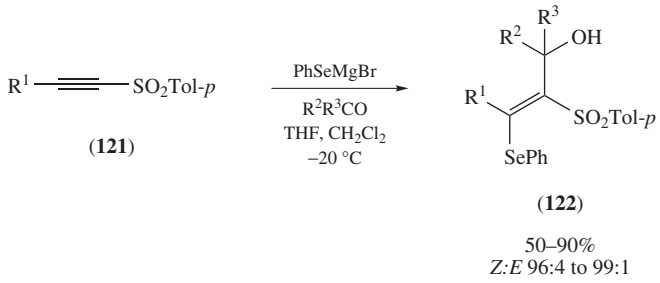
84% 70% 60%



82% 72%

SCHEME 63

Several substituted *p*-tolylsulfonyl alkenyl selenides were synthesized by Huang and Xie[67] by the reaction of acetylenic sulfones **121**, phenylselenomagnesium bromide, and aldehydes and ketones at −20 °C; the Michael-aldol tandem adducts **122** were obtained regioselectively (Scheme 64).



(**121**)

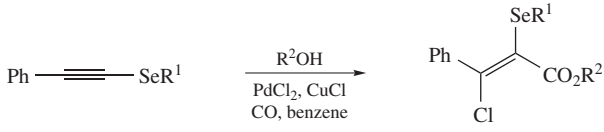
(**122**)

50–90%
Z:*E* 96:4 to 99:1

SCHEME 64

10. Miscellaneous

The reaction of alkynyl selenides **123** containing a phenyl group with carbon monoxide catalyzed by $PdCl_2$ and CuCl in the presence of an alcohol gave stereoselectively the corresponding *E*-acrylates **124** in good yields (Scheme 65)[68].



(**123**)

R^1= aryl, alkyl
R^2 = alkyl

(**124**)

45–93%
E:*Z* = 98:2 to 74:16

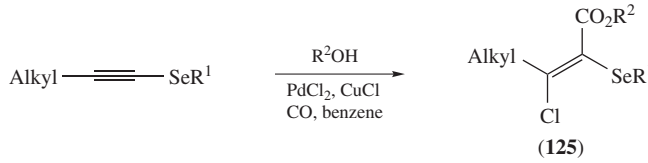
SCHEME 65

Interestingly, when an alkyl group was present, the stereochemistry of the obtained products was directly opposite, yielding the corresponding *Z*-acrylates **125** in 67–86% yield (Scheme 66).

When a heteroatom was present in the selenides the chlorocarbonylation adducts were not formed, possibly due to the coordination of the heteroatom with the catalyst. Two mechanisms were suggested for the reaction, one based on the alkoxycarbonyl palladation chlorination mechanism[69] and the other based on the chloropalladation carbonylation mechanism[70].

Tiecco and coworkers[71] described the stereoselective addition of anhydrous *p*-toluenesulfonic acid to alkynyl phenylselenides **126** to yield the corresponding *p*-toluenesulfonates **127** in 56–80% yields (Scheme 67).

Only the *Z*-isomer was observed and the functionalized selenides were then converted into the corresponding α-phenylseleno γ- and δ-lactones **128** in good yields (Scheme 68).

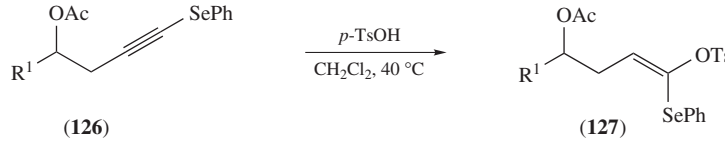


(**125**)

R^1= aryl, alkyl
R^2 = alkyl

67–86%
E:*Z* =100:0 to 80:20

SCHEME 66



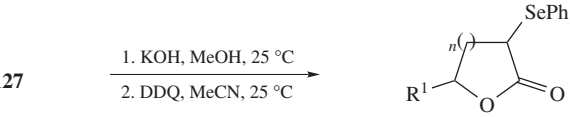
(**126**)

R^1 = alkyl, aryl

(**127**)

Z
56–80%

SCHEME 67

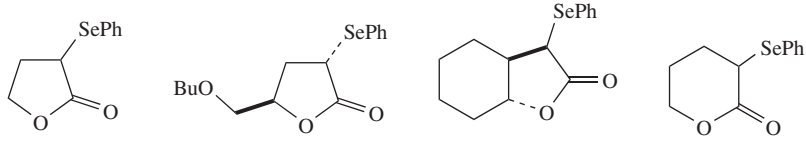


n = 0, 1

(**128**)

40–76%

Products of selected examples:

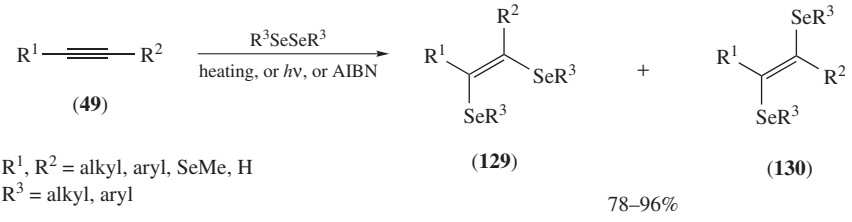


67% 76% 73% 52%

SCHEME 68

The thermal addition of diselenides to nonactived alkynes gave a mixture of *Z*- and *E*-1,2-bis(alkylseleno)ethenes **129** and **130** in good yields (Scheme 69)[72].

When a mixture of a dialkyl diselenide and phenylacetylene was heated at 140 °C in a sealed tube, the *E*-isomers were obtained preferentially. The authors claim that this method is complementary to the results obtained with the palladium catalyzed addition, where the *Z*-isomer was obtained as the major product[72b]. The same group realized a



(**49**)

R^1, R^2 = alkyl, aryl, SeMe, H
R^3 = alkyl, aryl

(**129**)

(**130**)

78–96%

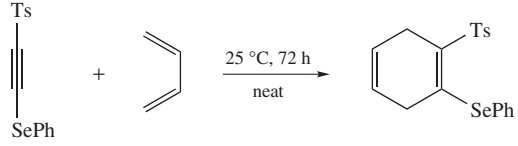
SCHEME 69

detailed study of the thermal, photoinitiated and AIBN-induced reactions of diorganyl diselenides to alkynes, and found that the reactivity order for diselenides in the reaction is dominated by steric effects according to the order:

$$\text{PhSeSePh} \cong \text{MeSeSeMe} \geq \text{EtSeSeEt} > i\text{-PrSeSePr-}i \gg t\text{-BuSeSeBu-}t$$

The authors also claim that internal alkynes are less reactive than terminal alkynes using the reaction conditions[71]. The use of more reactive alkynes such as trimethylsilylacetylene gave the *Z*-isomer as the major product in 70% yield and in a *Z*:*E* ratio of 95:5 at 150 °C.

Compound **41** was used in the Diels–Alder reaction with a variety of symmetrical and unsymmetrical dienes to yield the corresponding vinyl selenides as the cycloaddition products **131** (Scheme 70)[73].



(**41**)

(**131**)

81%

SCHEME 70

For unsymmetrical dienes with an electron-withdrawing group, an anomalous regiochemistry was observed, with the formation of the respective 1,3-adducts.

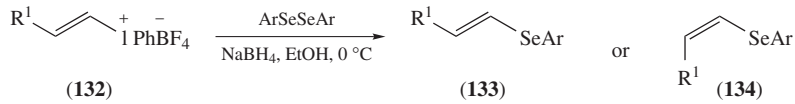
B. Synthesis of Vinyl Selenides from Alkenes and Allenes

1. Methods based on the use of nucleophilic selenium species

The reaction of *E*-vinylphenyliodonium salts **132** with nucleophilic selenium generated from ArSeSeAr with $NaBH_4$/EtOH gave the respective vinyl selenides **133** and **134** in good yields (Scheme 71)[74].

Interestingly, when R = Ph, the products were obtained with retention of the configuration of the double bond. On the other hand, when R = butyl, an inversion of the configuration of the starting alkene was observed.

Tiecco and coworkers described the synthesis of vinyl selenides by the nucleophilic vinylic substitution of vinyl halides with nucleophilic selenium species[75]. Vinyl selenides



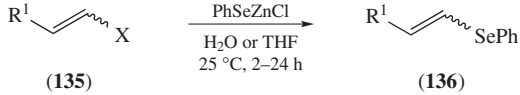
(**132**) (**133**) (**134**)

Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, Bn
R^1 = Ph, Bu

51–65%

SCHEME 71

136 can also be obtained through nucleophilic substitution of the corresponding halides **135** by the use of PhSeZnCl in THF as well as 'on water' conditions[76]. The reaction is stereospecific with retention of the alkene geometry (Scheme 72).



(**135**) (**136**)

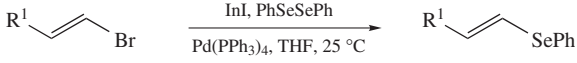
R^1= aryl, COAr

40–85%

SCHEME 72

The only exception was observed when a β-chloro-α,β-unsaturated ketone was used, which gave the *Z*-isomer starting from either the *E*- or *Z*-isomer.

The use of indium(I) iodide for the synthesis of vinyl selenides was first described by Peppe and coworkers[77]. An extension of the method was used for the preparation of *E*-vinyl selenides **138** from the corresponding vinyl bromides **137**[78]. The substitution reaction was catalyzed by Pd(0) and was stereoselective for *E*-vinyl bromides, while the *Z*-vinyl bromides gave a mixture of *Z*- and *E*-vinyl selenides (Scheme 73).



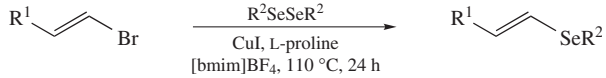
(**137**) (**138**)

E
70–90%

SCHEME 73

The use of a recyclable catalyst based on CuI/proline for the substitution reaction of *E*-vinyl bromides **137** with diorganoyl diselenides in [bmim]BF_4 gave the corresponding *E*-vinyl selenides **2** stereoselectively (Scheme 74)[79].

When R^1 = alkyl, a slight amount of the *Z*-isomer was observed and the authors reused the catalyst up to four times without significant losses in the yield and selectivity. Later, the same group described the use of [bmim]Gly for the synthesis of *Z*-vinyl selenides from PhSeSePh and *Z*-vinyl bromides catalyzed by CuI/Zn[80]. The desired compounds were obtained in good yields and catalysts immobilized in [bmim]Gly could be reused up to four cycles.

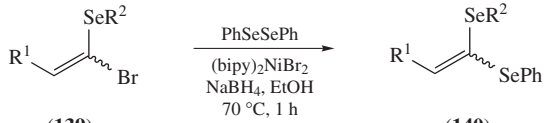


(**137**) (**2**)

65–91%

R^1, R^2 = alkyl, aryl

SCHEME 74



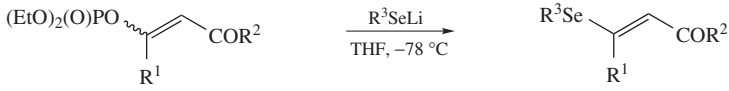
(**139**) (**140**)

R^1, R^2 = alkyl, aryl 70–95%

SCHEME 75

The substitution of bromine or iodine in 1-chalcogeno-1-haloalkenes **139**[81] by the phenylselenolate anion catalyzed by $(bipy)_2NiBr_2$ was described by Stefani and coworkers[82] for the synthesis of several selenoketene acetals **140** (Scheme 75).

The reaction of enol phosphates **141** of β-dicarbonyl compounds with lithium organoselenolates gave the corresponding α,β-unsaturated carbonyl compounds **142** in good yields (Scheme 76)[83].



(**141**) (**142**)

68–90%

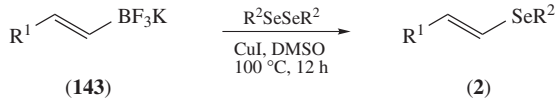
SCHEME 76

When the reaction was performed at $-78\,^{\circ}C$, only the Z-isomer was observed, even starting from a Z/E mixture of the enol phosphates.

More robust boron compounds were also used to prepare selectively E-vinyl selenides[84]. Potassium E-vinyl trifluoroborates **143** react with aromatic and aliphatic diselenides using CuI as catalyst to give the desired products **2** in 44–98% yields (Scheme 77).

The hydroselenation of allenyl phosphine oxides[85] **144** and allenyl sulfoxides[86] **145** using nucleophilic species of selenium generated *in situ* from $NaBH_4/R^4SeSeR^4$/EtOH system gave the corresponding addition products **146** and **147** exclusively at the β-position (Scheme 78).

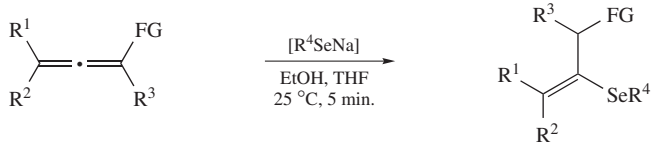
The selectivity was attributed to the mechanism of the reaction, which involves the conjugated addition of R^4SeNa to the functionalized allenyl moiety at the β-position giving a stabilized carbanion. The procedure was also successfully extended to the tellurium and sulfur analogues.



(**143**) (**2**)

R^1, R^2 = alkyl, aryl 44–98%

SCHEME 77

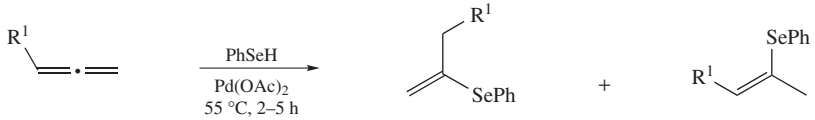


(**144**) FG = $P(O)(Ph)_2$
(**145**) FG = S(O)Ph

(**146**) FG = $P(O)(Ph)_2$ (80–92%)
(**147**) FG = S(O)Ph (80–83%)

SCHEME 78

Deactivated allenes **148** can also be submitted to hydroselenation using $Pd(OAc)_2$ as catalyst to yield the internal and terminal adducts **149** and **150** in 36–74% yields (Scheme 79)[87].



(**148**) (**149**) (**150**)

R^1 = alkyl, aryl internal addition terminal addition

36 to 74%
44:56 to 75:25

SCHEME 79

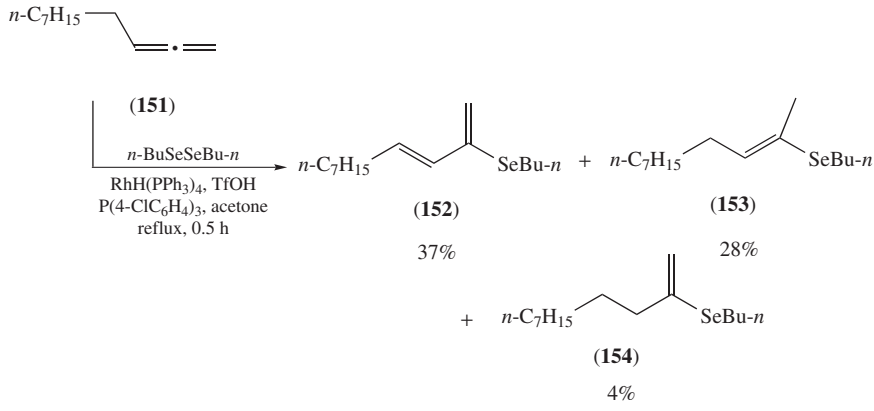
When a low-valent palladium or platinum catalyst was employed in place of $Pd(OAc)_2$ under the same conditions, the vinylic selenide **149** was obtained preferentially.

The reaction of dibutyl diselenide with the allene **151** using a rhodium complex and TfOH gave a mixture of alkenes (**152–154**) in moderate yield (Scheme 80)[88].

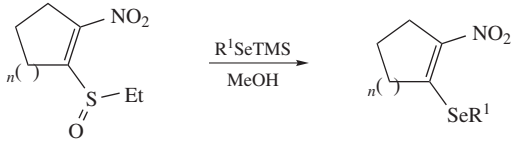
Only alkyl diselenides gave satisfactory results, while PhSeSePh gave only 18% yield of the respective vinyl selenides. The authors attributed this result to the deactivation of the catalyst by PhSeSePh.

Abe and coworkers[89] described the nucleophilic addition/elimination of phenylselenol and methylselenol, generated *in situ* from the respective trimethylsilyl selenides in methanol, to β-sulfinyl-α,β-unsaturated cyclic nitroalkenes **155** to give selenides **156** in good yields (57–97%) (Scheme 81).

When an alicyclic sulfoxide was used in the reaction, a mixture of stereoisomers was obtained in 71% yield and in a 9:1 ratio.



SCHEME 80



(**155**)

n = 1, 2
R^1= Ph, Me

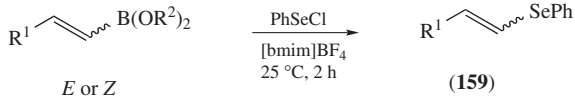
(**156**)

57–97%

SCHEME 81

2. Methods based on the use of electrophilic selenium species

The reaction of vinyl boronic acids **157** and esters **158** with phenylselenyl chloride in ionic liquid can be used to synthesize the corresponding vinyl selenides **159** in good yields with retained geometry of the double bond of the starting material (Scheme 82)[90].



E or *Z*

(**157**) R^2 = H
(**158**) R^2 = Me, *i*-Pr

R^1 = alkyl, aryl

(**159**)

E or *Z*

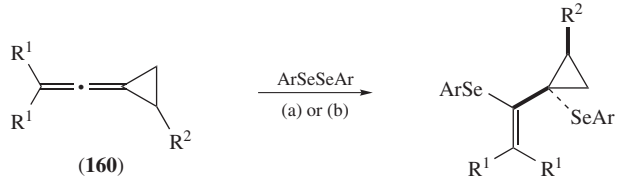
44–98%

SCHEME 82

Good yields were observed when vinyl boronic acids **157** were used and the solvent could be recycled without significant loss in yields. Pinacolate esters are also reactive, but

catechol esters are not suitable substrates due to the electrophilic substitution reactions of the phenyl selenium cation on the catechol moiety.

The reaction of vinylidenecyclopropanes **160** containing electron-withdrawing or electron-donating groups with diaryl diselenides gave the corresponding addition adducts **161** in moderate to good yields (Scheme 83)[91].



(**160**)

(**161**)

53–92%

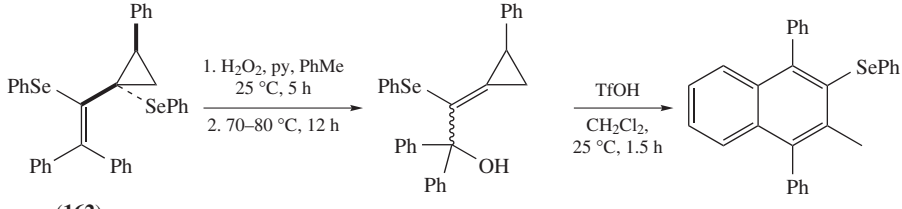
(a) AIBN, benzene, reflux
(b) BAIB, THF, reflux

R^1 = Ph, Tol, 4-FC_6H_4, 4-ClC_6H_4
R^2 = Ph, Tol, 4-ClC_6H_4, 4-$MeOC_6H_4$
Ar = Ph, Tol, 4-$MeOC_6H_4$

SCHEME 83

The reaction can be promoted by the use of AIBN[91] as a radical initiator or by BAIB[92] probably through a selenonium cation.

The further transformation of the addition product **162** by treatment with hydrogen peroxide in the presence of pyridine gave the corresponding methylenecyclopropane **163** in moderate yields as a mixture of E/Z isomers, which was later converted into the corresponding naphthalene derivative **164** (Scheme 84).



(**162**)

(**163**)

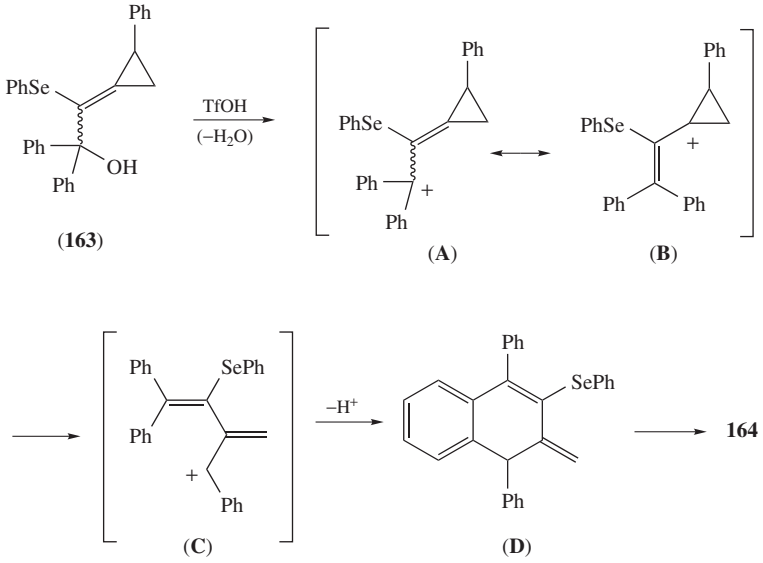
55%
E/Z 7:1

(**164**)

94%

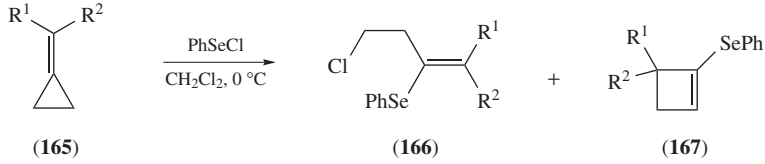
SCHEME 84

A plausible reaction mechanism is shown in Scheme 85. Upon treatment of **163** with TfOH, a resonatively stabilized carbenium ion [**A** ↔ **B**] is formed. It then undergoes ring-opening reaction via **C** to afford aryl 1,3-dienyl intermediate **D**, from which the corresponding naphthalene derivative **164** is ultimately produced via an aromatization process.



(**163**) (**A**) (**B**) (**C**) (**D**)

SCHEME 85



(**165**) (**166**) (**167**)

R^1, R^2 = aryl

75–88%
53:47 to 0:100

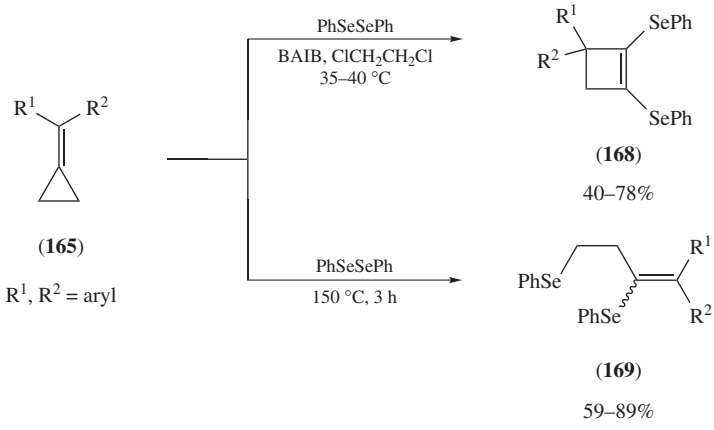
SCHEME 86

Methylenecyclopropanes **165** can also react with phenylselenenyl chloride at 0 °C in dichloromethane giving the vinyl selenide **166** along with the cyclobutenyl derivative **167** in good overall yields (Scheme 86)[93].

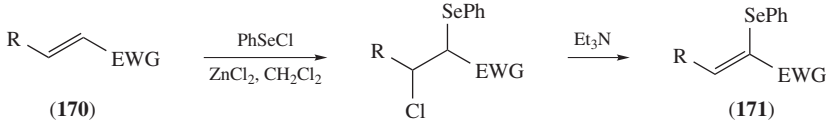
When diphenyl diselenide was used under heating, the respective ring-opened vinyl selenides **169** were obtained in good yields (59–89%) as a mixture of stereoisomers[94]. However, when *gem*-aryl disubstituted methylenecyclopropanes **165** were reacted with diaryl diselenides in the presence of BAIB, the corresponding cyclobutenes **168** were obtained in good yields (Scheme 87)[95].

The use of $ZnCl_2$ to promote the chloroselenation/dehydrochlorination of α,β-unsaturated compounds **170** was first described by Berlin and Engman[96]. The method gave preferentially the *E*-alkenes **171** and is suitable both for terminal and internal electron-deficient alkenes (Scheme 88).

The method was applied in the synthesis of several pyrrolidines. Thus, conjugate addition of allylamine to vinylic selenide **172** gave a diastereomeric mixture of Michael



SCHEME 87



EWG = CO_2Me, $CONH_2$, COMe, CHO, CN, SO_2Ph
R = H, CO_2Me, Me, *n*-pentyl

53–90%

SCHEME 88

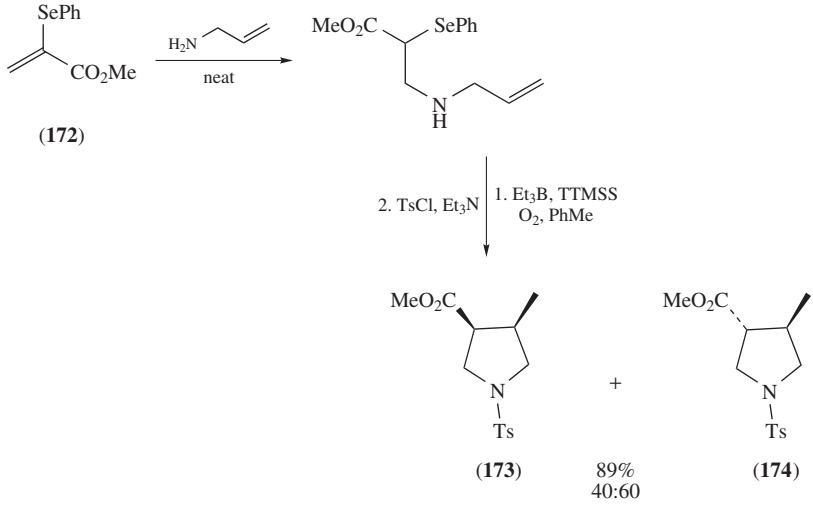
adducts, which were submitted to a reductive radical cyclization with triethylborane initiation and tris(trimethylsilyl)silane (TTMSS) serving as the hydrogen atom donor to yield the corresponding *N*-tosyl-3,4-disubstituted pyrrolidines **173** and **174** in good yields in a 40:60 ratio (Scheme 89).

3. Methods based on the use of radical selenium species

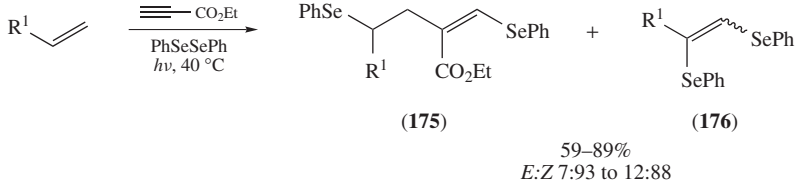
The reaction of activated alkynes, alkenes and PhSeSePh under visible-light irradiation gave a mixture of vinyl selenides **175** and **176** (Scheme 90)[97].

The difficulty in realizing a three-component coupling between alkyne, alkene and a radical precursor (X-Y) is shown on Scheme 91: (i) the addition step of heteroatom-centered radical ($Y^{\bullet}$) to an alkyne (or alkene) is a reversible process, and the concentration of the vinylic radical (**177**) is generally very low; (ii) in the case of the lower carbon-radical capturing ability of radical precursor (X−Y), polymerization may occur in preference to the desired three-component reaction preventing the formation of the alkyl radical **178**; (iii) in the case of the higher carbon-radical capturing ability of X−Y, the vinylic radical (**177**) may be quenched to give the vicinal addition product of alkyne (Scheme 91).

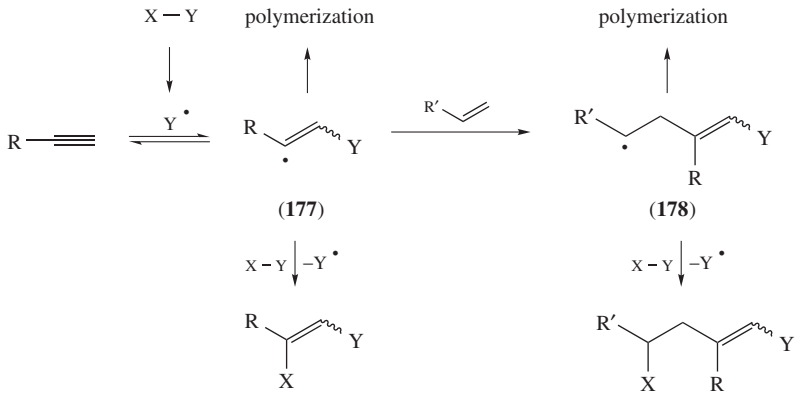
When an alkene containing a cyclopropyl group **179** was used in the three-component coupling reaction, the fast rearrangement process of cyclopropylcarbinyl radical intermediate gave only the corresponding ring-opened products **180** in good yield (Scheme 92)[98].



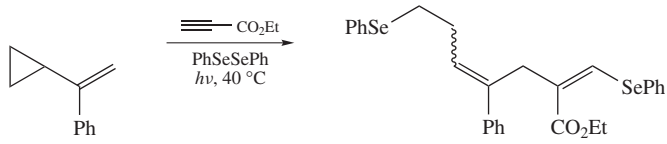
SCHEME 89



SCHEME 90



SCHEME 91



(**179**) (**180**)

72%
E/*Z* = 82:18

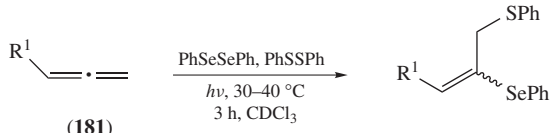
SCHEME 92

The absorption maximum of organic dichalcogenides such as diphenyl disulfides, diselenides and ditellurides lies in the ultraviolet, near-UV and visible regions, respectively[99]. Accordingly, upon irradiation with the corresponding lights, homolysis of dichalcogenides takes place to generate the chalcogen-centered radicals as labile species (Scheme 93).

	λ_{max} (nm)	ε_{max}
S	250	5×10^2
Se	330	1×10^3
Te	406	8×10^2

SCHEME 93

Compared to oxygen-centered radicals, chalcogen-centered radicals such as $PhS^{\bullet}$, $PhSe^{\bullet}$ and $PhTe^{\bullet}$ are generally less reactive, and the relative reactivities between the chalcogen-centered radicals decrease with increasing molecular weight ($PhS^{\bullet} > PhSe^{\bullet} > PhTe^{\bullet}$). The use of PhSeSePh/PhSSPh system in the photoinduced addition to allenes **181** gave the desired vinyl selenides **182** in good yields (Scheme 94)[100].

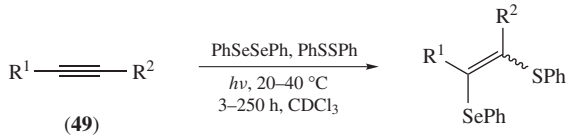


(**181**) (**182**)

70–99%
E:*Z* 22:78 to 40:60

SCHEME 94

The authors observed that the selenium radical preferentially attacks at the allene, which was later converted into the thioselenation product via displacement of the terminal phenylseleno group. An extension of the method using alkynes was described by the same authors, when the stereochemistry of the products depended on the alkyne[101]. When phenylacetylene was used, the corresponding *E*-vinyl selenide was obtained exclusively,



(**49**)

(**183**)

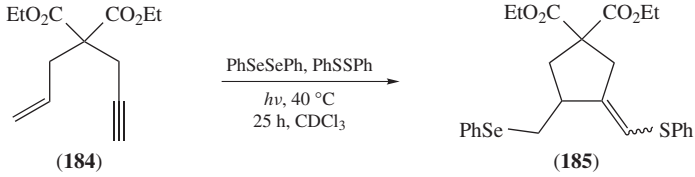
R^1, R^2 = alkyl, aryl, alkenyl

31–96%
E:*Z* 100:0 to 58:42

SCHEME 95

however, when other terminal and internal alkynes were used, prolonged irradiation times were necessary and the formation of the *Z*-isomer **183** was observed (Scheme 95).

The $(PhS)_2-(PhSe)_2$ binary system was also applied in the thioselenation reaction of enynes via 5-*exo-trig* radical cyclization. The photoirradiated reaction of **184** with $(PhS)_2$ and $(PhSe)_2$ gave regioselectively in good yield the corresponding five-membered ring product **185** bearing phenylthio and phenylseleno groups at both terminal positions (Scheme 96).



(**184**)

(**185**)

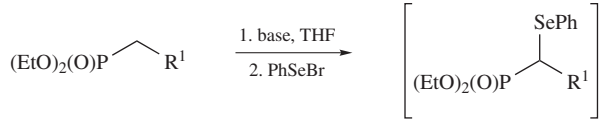
61%
E:*Z* 72:28

SCHEME 96

C. Synthesis of Vinyl Selenides from Carbonyl Compounds

1. Methods based on Horner-type olefination

The use of the Horner olefination for the preparation of vinyl selenides is a known procedure and the subject of an early review article[102]. Thus, the reaction of commercial available phosphonates **186** and **187** with a base followed by the addition of phenylselenyl halides gave *in situ* the derivatives **188**[103] and **189**[104] (Scheme 97).

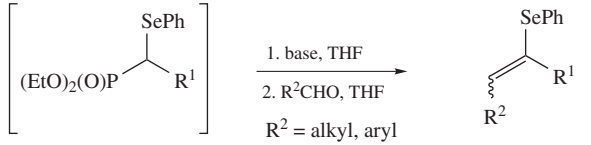


(**186**) R^1 = CN
(**187**) R^1 = CO_2Et

(**188**) R^1 = CN
(**189**) R^1 = CO_2Et

SCHEME 97

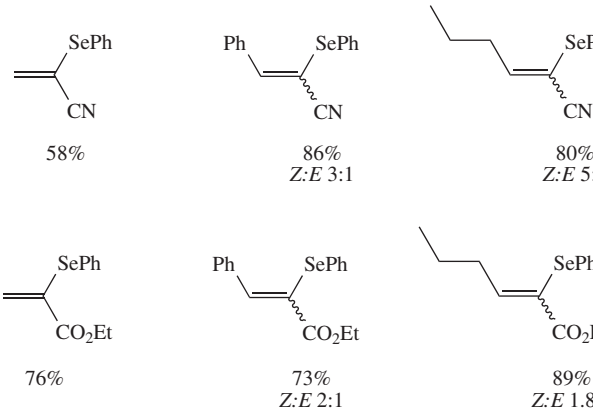
Further reaction of **188** or **189** with aromatic and aliphatic aldehydes under basic conditions gave the corresponding functionalized vinyl selenides **190** and **191** in good yields, with the stereochemistry of the products being dependent on the type of phosphonate used (Scheme 98).



(**188**) R^1 = CN
(**189**) R^1 = CO_2Et

(**190**) R^1 = CN
(**191**) R^1 = CO_2Et

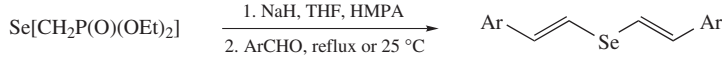
Products of selected examples:



SCHEME 98

More recently, the same group described an extension of the method using another phosphonate, where R^1 = Ph[105]. Selenium lithium exchange by the reaction with *n*-BuLi gave the vinyl lithium species, which were captured with several electrophiles, like aldehydes and DMF, to yield exclusively the *Z* allyl alcohols, and *E*-*α*-phenyl-*α*,*β*-unsaturated aldehydes, in good yields.

Similarly, the selenium bis(phosphonate) **192** was employed in the synthesis of the *E*,*E*-divinyl selenides **193** via reaction with aromatic aldehydes using sodium hydride as a base (Scheme 99)[106].

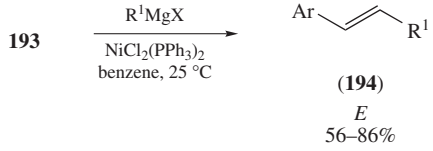


(**192**)

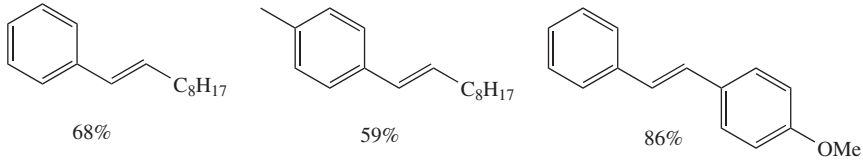
(**193**)
E
51–87%

SCHEME 99

The method was highly regioselective, yielding the corresponding *E*,*E*-divinyl selenides **193** which were later converted to the corresponding *E*-alkenes **194** by a nickel-catalyzed cross-coupling reaction with Grignard reagents (Scheme 100). An extension of the method by using of phosphine oxides in the synthesis of *E*,*E*-divinyl selenides in good yields was described later[107].



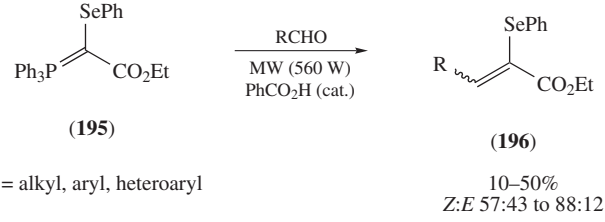
Products of selected examples:



SCHEME 100

2. Methods based on Wittig-type olefination

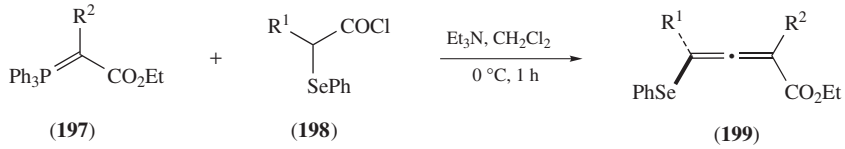
The use of the Wittig reaction for the stereoselective synthesis of functionalized vinyl selenides **196** using stabilized phosphoranes **195** was described by Silveira and coworkers (Scheme 101)[104].



SCHEME 101

The products were obtained in low yield, with the *Z*-isomer being the major product. The authors claim that the method is an alternative for the Horner reaction previously described.

Similarly, the reaction of stabilized phosphoranes **197** with derivative **198** gave the corresponding allenes **199** in good yields and under mild conditions (Scheme 102)[108].

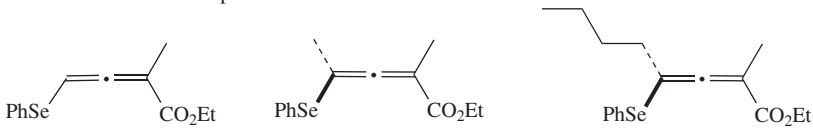


(**197**) (**198**) (**199**)

68–98%

R^1, R^2 = H, alkyl

Products of selected examples:



78% 97% 68%

SCHEME 102

3. Methods based on Knoevenagel-type reaction

An efficient method for the synthesis of vinyl selenides based on the Knoevenagel-type reaction was described by Perin and coworkers[109]. The reaction between the phenylseleno nitrile **200** or ester **201**, prepared from the reaction of the corresponding halides with PhSeSePh and sodium borohydride, with the appropriate aldehyde under solid supported catalysis (KF/Al_2O_3) and solvent-free conditions gave the vinyl selenides **202** and **203** in moderate yields and stereoselectivities (Scheme 103).

4. Methods based on aldol-type reaction

The aldol-type condensation of compound **204** with aldehydes followed by the alkylation with methyl iodide gave preferentially the *Z*-isomer **205** in moderate to good yields (Scheme 104)[110].

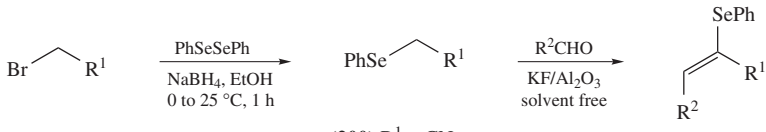
III. PROPERTIES OF VINYL SELENIDES

A. Solubility

Vinyl selenides generally show high solubility in nonpolar solvents like dichloromethane, ether and hydrocarbons. Some are soluble in polar solvents like methanol, acetonitrile, acetone, DMF and DMSO.

B. Stability

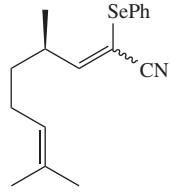
Vinyl selenides show variable stability toward air and water, and their purification is straightforward by distillation or chromatographic techniques. Moreover, they can be stored at low temperatures without any observed decomposition.



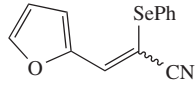
(**200**) R^1 = CN
(**201**) R^1 = CO_2Et

(**202**) R^1 = CN, 40-80%
(**203**) R^1 = CO_2Et, 39–40%

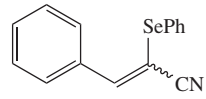
Products of selected examples:



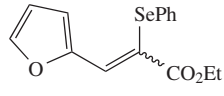
42%
Z/*E* 60:40



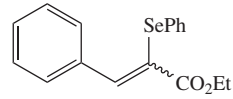
80%
Z/*E* 85:15



71%
Z/*E* 71:29

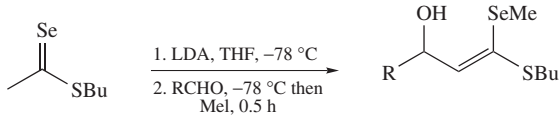


40%
Z/*E* 63:37



39%
Z/*E* 55:45

SCHEME 103



(**204**)

(**205**)

53–79%
E:Z 12:88 to 3:97

SCHEME 104

The stability of vinyl selenides toward acids revealed some interesting features[111]. Phenyl vinyl selenides can be hydrolyzed with a reversible protonation step, providing sufficiently stable intermediate carbenium ions. The presence of a methyl group or even of a *p*-nitrophenyl group at the α-position of the vinyl moiety appears to stabilize the carbenium ion enough to allow the observation of some reversibility. The stabilization of carbenium ions by α-alkyl- and/or α-arylseleno groups shows that α-(methylseleno)styrene hydrolyzes 15.4 times faster than α-(phenylseleno)styrene. In addition, 2-(phenylseleno)propene hydrolyzes 4.3 times faster than does α-(phenylseleno)styrene.

The electrochemical behavior of some substituted vinyl selenides has also been studied[112]. When the chlorovinyl selenides are oxidized by electrochemical methods, the double bond bearing chlorine atoms is conserved, and oxidation affects only the selenium atom.

IV. CHARACTERIZATION OF VINYL SELENIDES

The purity of vinyl selenides can be easily checked by gas chromatography, mass spectrometry, ^{1}H, ^{13}C and ^{77}Se NMR spectra. Despite the interest in vinyl selenides, very few reports are devoted to the investigation of mass spectral fragmentation of this class of compounds. However, mass spectrometric studies of some organoselenium compounds were undertaken[113]. In addition, exact mass measurements were obtained for a variety of vinyl selenides.

While selenium has six natural isotopes: ^{74}Se (0.87%), ^{76}Se (9.02%), ^{77}Se (7.58%), ^{78}Se (23.52%), ^{80}Se (49.82%) and ^{82}Se (9.19%), ^{77}Se is the only NMR active nucleus. The ^{77}Se nucleus has no quadrupolar moment, with a nuclear spin quantum number $I = {}^{1}/_{2}$, making high-resolution NMR spectroscopy possible[114]. The sensitivity of this nucleus is three times higher than that of ^{13}C, and selenium is very sensitive to its electronic environment and possesses a large chemical shift range (approximately 3400 ppm), with narrow lines normally 51 Hz, which result in well-resolved lines and coupling patterns even when mixtures of several configurational isomers are studied.

Diphenyl diselenide is a common reference used in ^{77}Se NMR spectroscopy, with a ^{77}Se chemical shift of $\delta = 463$. This compound is commercially available, is a stable solid and can be handled conveniently, avoiding the use of more volatile and malodorous selenium compounds.

Apart from cases where the presence of a vinylic proton–proton coupling constant can reveal the stereochemistry, a general method for differentiation between isomeric alkenes substituted with two or more organoselenium groups was described by Johannsen and coworkers[115]. The method was based on the homonuclear ^{77}Se coupling which gives rise to a satellite pattern at the foot of each ^{77}Se line: 77–117 Hz coupling constants were found for *cis* $^{3}J_{Se-Se}$, 19–55 Hz for *gem* $^{2}J_{Se-Se}$ and 2–12 Hz for *trans* $^{3}J_{Se-Se}$. Furthermore, the authors described an extended set of assigned J_{Se-H} coupling constants. These provide a basis for using $^{1}H-^{77}Se$ coupling constants to determine the stereochemistry of selenium-substituted alkenes including those with only one selenium group attached.

Later, Campos and Stefani[116] proposed the use of the γ-*cis* effect as a reliable criterion for the assignment of vinyl selenide stereo- and regiochemistry. The authors proposed that the *Z*-vinyl selenides present ^{77}Se absorptions shielded in regard to *E*-isomers (due to the γ-*cis* effect).

V. CONCLUSION

We have attempted to demonstrate in this chapter the development in the past 10 years of different methodologies for the syntheses of vinyl selenides. Although the application of this class of compounds in the synthesis of more complex molecules is still discreet when compared with other vinyl counterparts such as stannanes and boranes, the synthetic utility of vinyl selenides suggests further studies and will yield additional opportunities for synthetic chemists. In addition, the recent studies about the pharmacological properties, as well as the toxicity of some selenides, make these compounds promising biological agents in view of their unique properties.

VI. ACKNOWLEDGMENTS

We wish to thank our colleagues, cited in the references, for their contributions to many of the studies presented in this chapter. We are grateful to CAPES (SAUX), CNPq (INCT-INAMI and INCT-catálise) and FAPERGS (PRONEX-10/0005-1) for financial support of our research. We also thank CNPq for our fellowships.

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   (e) L.-B. Han and M. Tanaka, *Chem. Commun*., 395 (1999).
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Vinylic tellurides

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0569

I. INTRODUCTION

Since the discovery of the first organotellurium compound, reported more than 150 years ago with the synthesis of diethyl telluride by Wöhler in 1840[1], they have been increasingly applied to the synthesis of essentially all types of organic compounds. There have also been numerous attempts to utilize the potential of these compounds for the chemistry to natural products and bioorganic synthesis. There are several features which make reactions involving organotellurium compounds and reagents particularly useful and versatile

among many transformations used for organic synthesis[2]. Most importantly, organotellurium compounds offer an abundance of possibilities of carbon–carbon bond formation. The importance of the carbon–carbon bond formation in organic synthesis needs no explanation. Tolerance of these compounds to many functional groups such as carbonyl and hydroxyl groups is the second important feature. Many different classes of organotellurium compounds have been prepared and studied to date, and vinylic tellurides are among the most useful and the most promising in view of their usefulness in organic synthesis. In addition to their utility in the field of organic chemistry, the toxicological and pharmacological aspects of organotellurium compounds have also been reviewed[3].

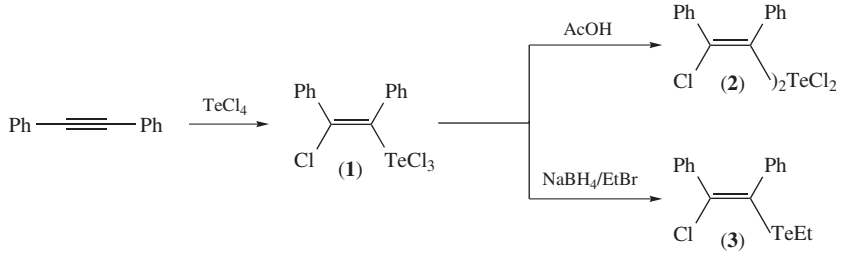
Due to the growing importance and utility of vinylic tellurides in the field of organic synthesis and the many new remarkable findings and applications which have been published in the last years[4], the purpose of this chapter is to critically and comprehensively review the several methods described for the preparation of vinylic tellurides. Furthermore, this chapter will also discuss the vinylic telluride reactivity toward several different reaction conditions and the applicability of such transformations in organic synthesis. Finally, the use of vinylic tellurides in the synthesis of biologically active compounds will be covered.

II. PREPARATION OF VINYLIC TELLURIDES

A. Preparation of Vinylic Tellurides by Electrophilic Tellurium Species

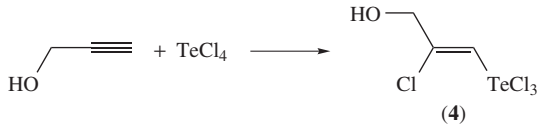
1. Addition of tellurium tetrahalides to alkynes

The electrophilic addition of tellurium tetrahalides to alkynes is one of the most traditional methods to prepare vinylic tellurides. It was first developed by Petragnani and Campos in the early 1960s[5a]. The authors described the preparation of β-chlorovinyl tellurium trichloride **1** by the addition of tellurium tetrachloride to diphenylacetylene. Further treatment of the vinyl tellurium trihalide with AcOH or $NaBH_4$/EtBr leads to bis(β-chlorovinyl) tellurium dichloride **2** and to vinylic telluride **3**, respectively (Scheme 1)[5b].



SCHEME 1

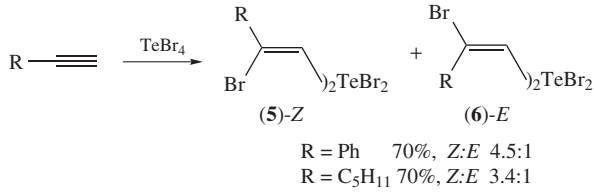
Propargyl alcohol was successfully employed in such a reaction and furnished β-hydroxymethyl-β-chlorovinyl tellurium trichloride **4** in good yield (Scheme 2). The presence of the hydroxyl group in the starting alkyne has an important influence on the reaction of these compounds with tellurium tetrahalides. When hydroxyalkynes were used, cyclic oxychlorides were formed through an *anti* addition, probably involving a telluronium ion giving the *E* isomer. In this case an isomerization is taking place and the *E* isomer was



SCHEME 2

completely transformed into the *Z* isomer after 2 h. A second isomer presenting the *Z* stereochemistry was formed through the four-center mechanism[6].

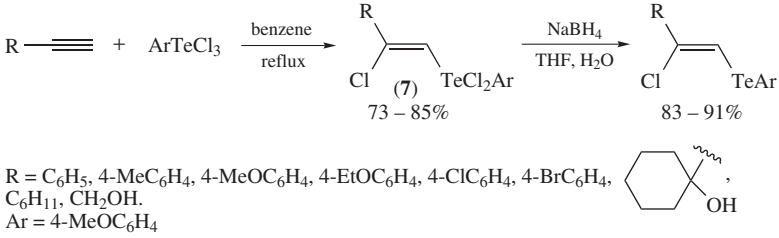
Similarly, tellurium tetrabromide has been employed in this reaction, leading directly to the corresponding bis(β-bromovinyl) tellurium dibromides **5** and **6** in good yields (Scheme 3)[7]. Mixtures of *Z* and *E* isomers were formed, and in all cases studied the *Z* isomer was formed as the major product.



SCHEME 3

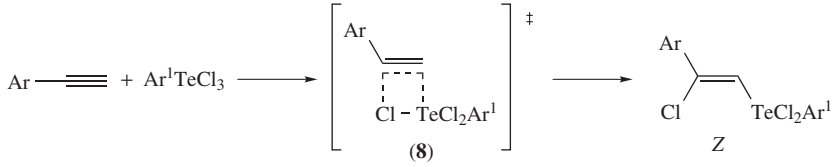
2. Addition of organotellurium halides to alkynes

Organotellurium halides behave similarly to tellurium tetrahalides, acting as an electrophilic source of tellurium. In light of this, *p*-methoxyphenyltellurium trichloride has been added to terminal alkynes to give 1-chloro-1-organyl-2-[dichloro(*p*-methoxyphenyl)telluro]ethenes **7** of a *Z* configuration, which can be reduced to the corresponding vinylic tellurides by $NaBH_4$ in THF and H_2O (Scheme 4)[8].



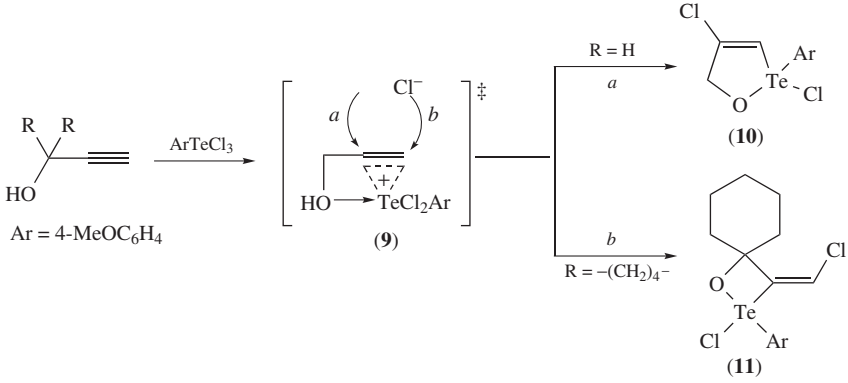
SCHEME 4

The reaction proceeds with high regio- and stereoselectivity, and the structure of the compounds is confirmed by their ^{13}C shifts and X-ray structures. A mechanistic rationale is proposed by the authors explaining the *Z*-stereochemistry obtained as a result of a four-centered cyclic transition state **8** (Scheme 5).



SCHEME 5

Further studies on the addition of *p*-methoxyphenyltellurium trichloride to 3-hydroxyalkynes were later reported[9]. The influence of the hydroxyl group in the regio- and stereochemistry has been examined. X-ray crystallography of the reaction product of propargyl alcohols with *p*-methoxyphenyl telluride revealed that cyclic oxytellurides **10** and **11** were obtained instead of the desired acyclic tellurides. Different from simple alkynes, propargyl alkynes gave the products through an *anti* addition pathway, via the formation of a telluronium ion **9**, coordinated with the hydroxyl group. Opening of the telluronium ion can proceed by paths *a* and *b*. Path *a* is favored over *b* when the propargylic position is unencumbered, leading to a five-membered oxytelluride ring. On the other hand, with hindered propargylic alcohols, path *b* is favored and a four-membered oxytelluride ring is formed (Scheme 6).

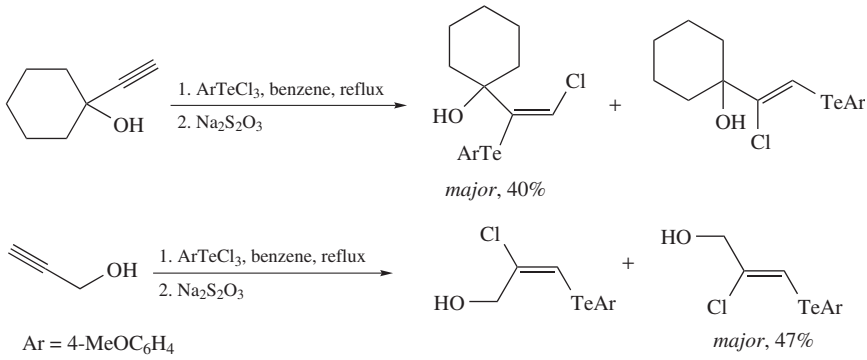


SCHEME 6

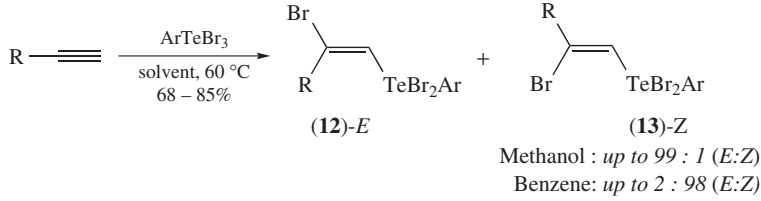
When propargyl alcohols are subjected to electrophilic tellurium addition with *p*-methoxyphenyltellurium trichloride plus sodium thiosulfate, the β-chlorovinylic tellurides were isolated in good yields instead of the oxychlorides (Scheme 7). This is explained by the direct reduction of the oxychlorides to the corresponding vinyl tellurides.

The analogous aryltellurium tribromides can be employed in a similar manner as their parent trichlorides. Huang and Wang have described the stereoselective synthesis of **12**-(*Z*)- and **13**-(*E*)-β-bromovinyl tellurides by the addition of aryltellurium tribromides to terminal alkynes (Scheme 8)[10].

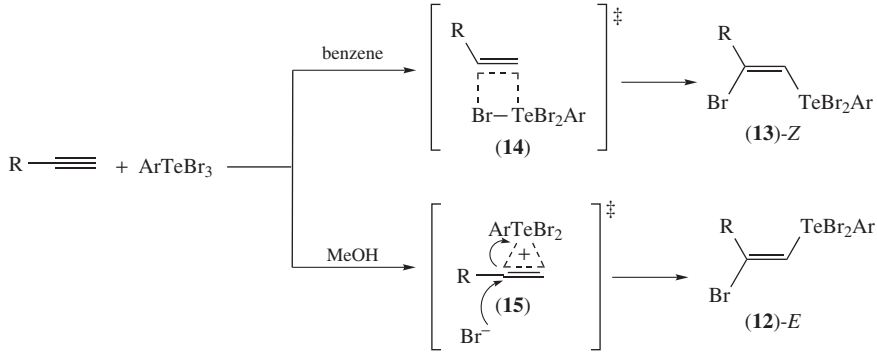
The reaction is highly regioselective, but the stereoselectivity is dependent on the polarity of the solvent. In methanol, tellurium ions **15** can be formed due to the more polar environment, predominantly giving the *anti* products **12**. On the other hand, when non-polar benzene was used, the reaction proceeded through a four-membered transition state **14**, which led almost exclusively to the *Z* isomers **13** (Scheme 9).



SCHEME 7

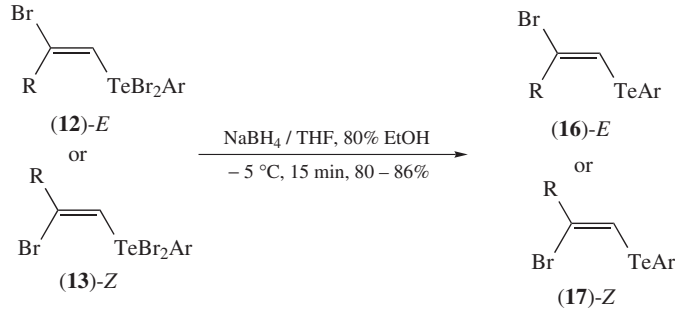


SCHEME 8



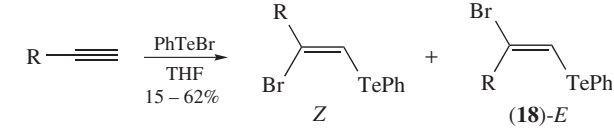
SCHEME 9

The dibromides **12** and **13** described in Scheme 10 can be further reduced to the corresponding vinylic tellurides **16** and **17** by debromination, leading to trisubstituted alkenes. This was achieved by the treatment of the *Z*- or *E*-β-bromovinyl aryltellurium dibromides with sodium borohydride, furnishing the desired compounds in good yields (Scheme 10).



SCHEME 10

Organotellurenyl bromides have been used to prepare vinylic tellurides[11]. The reaction between alkynes and organotellurenyl bromide (prepared *in situ* from the reaction between diphenyl ditelluride and bromine) affords the vinylic tellurides, without the need of a reduction step for tellurium dihalides, which are obtained by the previously discussed method. However, the selectivity is lower when compared to the addition of organotellurium trihalides, and the best result in terms of stereoselectivity is a 4.5 to 1 ratio, in favor of the *E* isomer **18** (Scheme 11). Interestingly, when propargyl alcohol was used, the opposite regioisomer was obtained with tellurium being attached to the internal carbon of the alkyne.



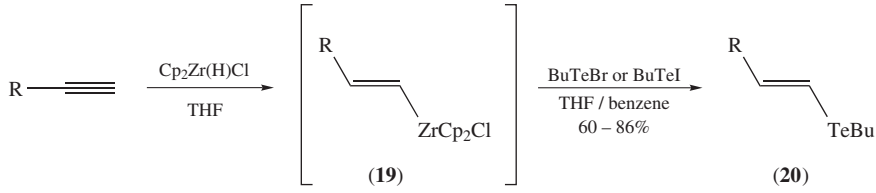
R = H, Ph, C_5H_{11}, CH_2OH *Z:E* ratios up to 1 : 4.5

SCHEME 11

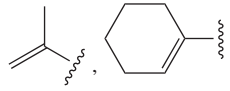
3. Preparation of vinylic tellurides by metal/tellurium exchange reaction

a. Zirconium/tellurium exchange reaction. The hydrozirconation of alkynes is a powerful approach to the preparation of several functionalized alkenes with high regio- and stereoselectivity[12]. Conversely, the preparation of *E*-vinylic tellurides has been much less studied in comparison to that of the *Z* isomers. Thus, the well-known potential of the hydrozirconation reaction to stereoselectively produce *E*-organometallics has attracted the attention of many researchers. The vinylic zirconium intermediates can further undergo a zirconium/tellurium exchange reaction with an electrophilic tellurium source, such as organotellurenyl halides, to furnish *E*-vinylic tellurides.

Two groups have independently reported the zirconium/tellurium exchange reaction for the preparation of *E*-vinylic tellurides[13]. The reaction is performed by the treatment of an alkyne with Schwartz's reagent, $Cp_2Zr(H)Cl$, where the vinyl zirconocene chloride **19** intermediate undergoes an exchange reaction with butyltellurenyl halide to exclusively give *E*-vinylic tellurides **20** in high yields (Scheme 12).

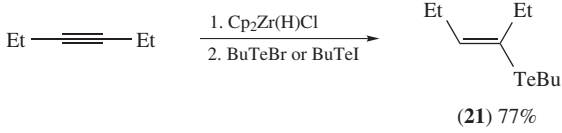


R = Ph, C_6H_{13}, C_4H_9, C_3H_7, C_2H_5, CH_3OCH_2, $THPOCH_2$, $PhCH_2O(CH_2)_3$, $HO(CH_2)_3$,



SCHEME 12

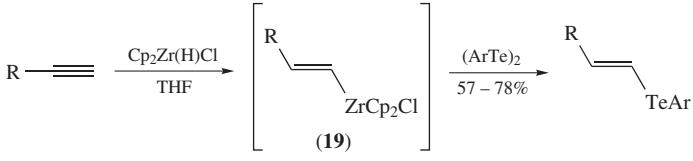
For the most part, terminal alkynes have been employed in this reaction, but internal alkynes can also be used. For instance, hex-3-yne was successfully employed in the sequential hydrozirconation/tellurium exchange reaction and afforded the corresponding vinylic telluride **21** in 77% yield (Scheme 13).



(**21**) 77%

SCHEME 13

A variation of the procedure described above employing diaryl ditellurides as the electrophilic tellurium source was published by Huang and Liang[14]. The advantage of this procedure is that it avoids the previous preparation of tellurenyl halides. On the other hand, half of the aryltellurium starting material is lost in the reaction (Scheme 14).



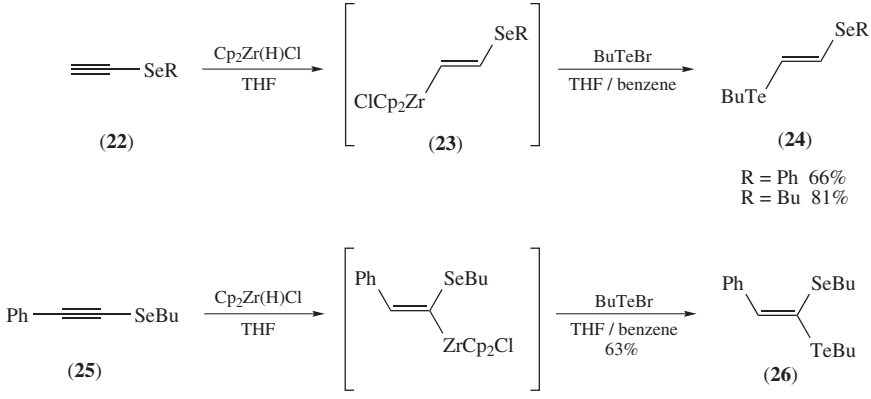
R = C_4H_9, C_5H_{11}, CH_3OCH_2, $CH_3CH_2OCH_2$; Ar = Ph, 4-$MeOC_6H_4$

SCHEME 14

Special interest has been devoted to the preparation of mixed chalcogen-containing alkenes, and further studies on the sequential hydrozirconation/tellurium exchange reaction directed to the synthesis of functionalized vinylic tellurides have been carried out. This methodology was applied from simple aryl and alkyl substituted alkynes to

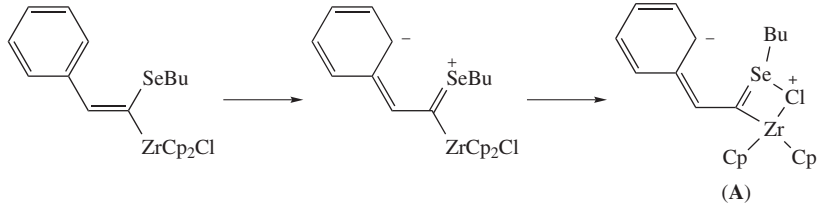
terminal and internal alkynyl selenides and the regioselectivity of this process was also studied in detail[15].

In addition, terminal selenoalkyne **22** was treated with Schwartz's reagent to afford the vinyl zirconate intermediate **23**, which was trapped with butyltellurenyl bromide, leading to the *E*-vinylic telluride **24** as the sole product in good yields. The reaction was performed with two different starting selenides and the best results were achieved when R was the butyl group (Scheme 15). When an internal selenoalkyne **25** bearing an aromatic phenyl group was used, the regiochemistry observed was completely different from that of terminal selenoalkyne, affording only the ketene telluro(seleno) acetal **26**, which demonstrates that the reaction proceeds through a different pathway (Scheme 15).



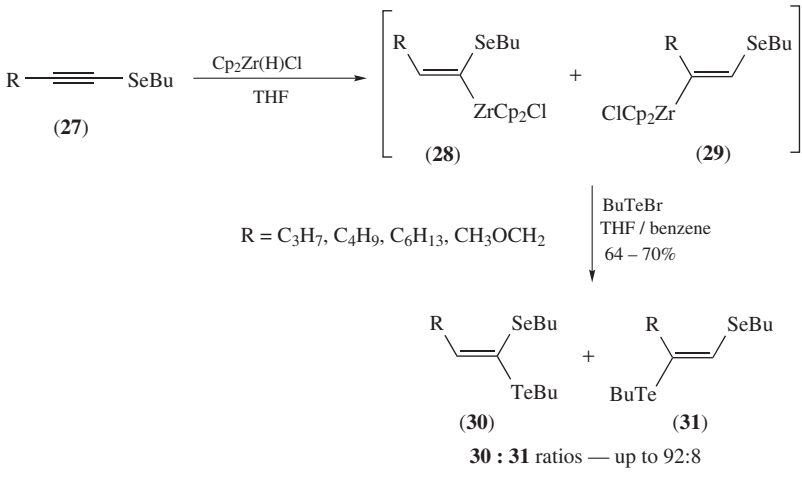
SCHEME 15

The authors suggest that an interaction between the chloro atom in product **A** formed from the Schwartz's reagent and the organoselenium moiety is responsible for the change in the regioselectivity of the reaction (Scheme 16).



SCHEME 16

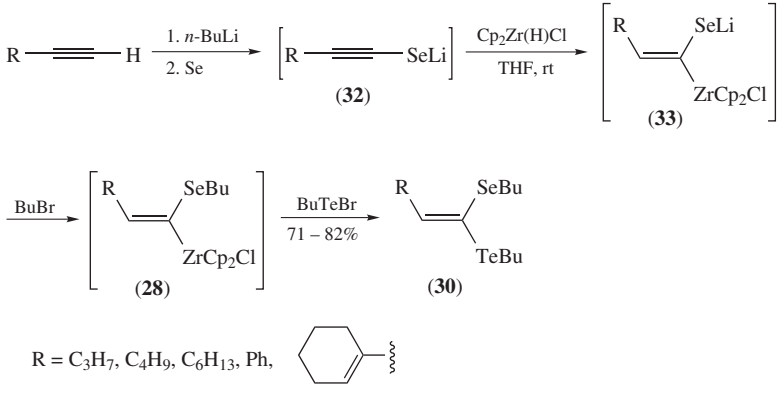
However, when selenoalkynes **27** bearing an alkyl group were submitted to the hydrozirconation reaction, a mixture of the regioisomers, α- and β-zirconated vinylselenides **28** and **29**, was obtained, which can be observed through the ratios of the products formed after trapping with BuTeBr. Different ratios of the regioisomeric products were obtained, as deduced from the ratios of products **30** and **31** formed, and the major isomer was always the α-substituted product **30**. This indicates that the organoselenium moiety is partially



SCHEME 17

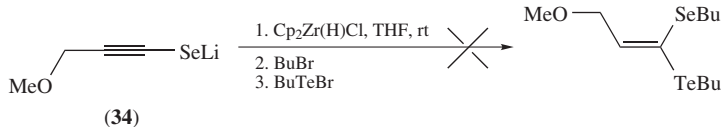
responsible for zirconium's preference to attach to the α-position, although the formation of the cyclic intermediate proposed in Scheme 17 is less favored when compared to the alkyl substituted selenoalkyne (Scheme 17).

These problems of regioselectivity depicted in Scheme 18 were creatively circumvented in an additional study by the same authors, where they described the preparation of ketene telluro(seleno) acetal with total regio- and stereocontrol[16]. The strategy adopted in this work was the *in situ* generation of alkynylselenolate salts **32** instead of alkynylselenides. In this reaction, the hydrozirconation of both alkyl and aryl substituted lithium alkynylselenolate, followed by trapping with butyl bromide, exclusively furnished the α-zirconated vinyl selenide intermediates **33**, which, upon the Zr/Te exchange reaction with BuTeBr, led to the formation of the desired ketene telluro(seleno) acetals **30** in good yields as



SCHEME 18

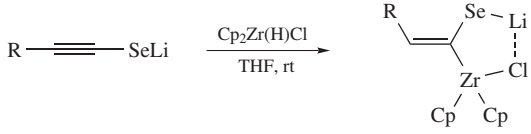
a sole product (Scheme 18). Interestingly, when the propargyl ether **34** derivative was employed as a starting material, no product was obtained (Scheme 19).



(**34**)

SCHEME 19

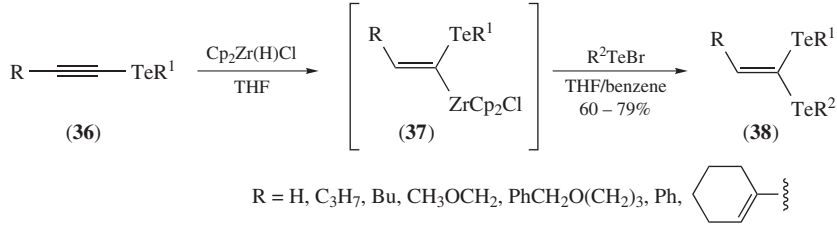
A plausible mechanism to explain the exclusive formation of the α-zirconated vinyl selenolate intermediate is the formation of a five-membered cyclic intermediate **35** (Scheme 20), which is by far more efficient than the four-membered intermediate (Scheme 16) previously proposed for the alkynyl selenides.



(**35**)

SCHEME 20

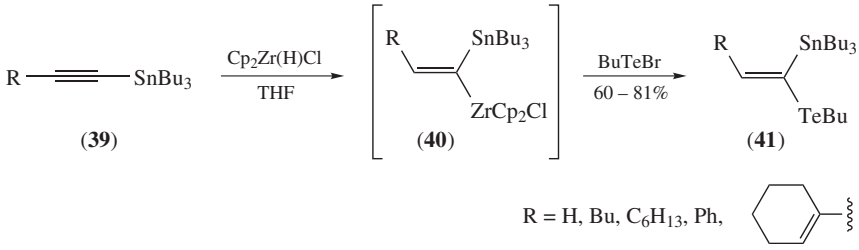
Telluroalkynes **36** have been evaluated under these reaction conditions and have proven to be suitable substrates for the sequential hydrozirconation/tellurium exchange reaction leading to the ketene telluro acetals **38**[15, 17]. The only product obtained by the hydrozirconation of telluroalkynes was the α-zirconated intermediate **37**, regardless of the nature of the substituents in the starting material (Scheme 21). All ketene telluro acetals **38** were obtained in good yields and no cleavage of the $C_{sp}-Te$ bond was observed under this condition.



(**36**) (**37**) (**38**)

SCHEME 21

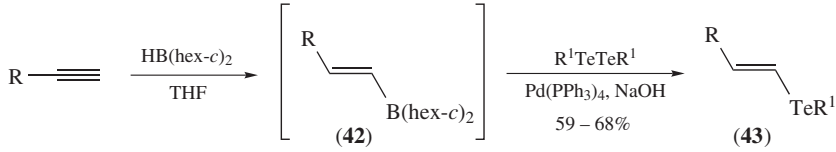
The hydrozirconation of trialkylstannyl acetylenes **39** has attracted attention due to the high regio- and stereoselectivity observed in the preparation of *Z*-vinylic stannanes[18]. Therefore, the hydrozirconation/telluration conditions were applied to stannylalkynes in an attempt to prepare ketene stannyl(telluro) ether **41** (Scheme 22)[19]. The reaction was shown to be 100% stereoselective and the functionalized vinylic tellurides **41** were obtained in good to excellent yields. The reaction is completely regioselective, affording only the α-zirconated intermediate **40**, probably due to a complexation similar to that found in the selenium and tellurium analogues.



(**39**) (**40**) (**41**)

SCHEME 22

b. Boron/tellurium exchange reaction. Organoboranes offer a wealth of transformations involving the C−B bond. In general, the $C_{sp^2}-B$ undergoes reactions under mild conditions, such as Suzuki cross-coupling[20] or transmetallations to organozinc[21] or organocopper reagents[22]. Diorganoyl ditellurides can be applied as coupling partners with alkenyl boranes, in the presence of a palladium catalyst in a C−heteroatom coupling reaction. Thus, vinylic tellurides of an *E*-configuration **43** were prepared by this methodology, via a dicyclohexyl alkenyl borane intermediate **42** in the presence of a catalytic amount of $Pd(PPh_3)_4$ and a diorganoditelluride (Scheme 23)[23]. Only *E*-isomers were obtained, indicating that the boron−tellurium exchange is stereoselective, with retention of the vinyl borane intermediate configuration.



(**42**) (**43**)

R = Ph, CH_3OCH_2, $CH_3CH_2OCH_2$; R^1 = Ph, Bu, 4-MeC_6H_4

SCHEME 23

The authors propose a catalytic cycle for the Pd catalyzed boron−tellurium exchange, where an oxidative addition of ditelluride to Pd(0) affords palladium(II) intermediate **A**, which is converted by transmetallation to intermediate **B**, followed by the reductive elimination to give the product, which in turn regenerates Pd(0) to the catalytic cycle (Figure 1). It is valid to comment that the reaction does not occur in the absence of the palladium catalyst.

Further methodologies for the chemistry involving boron and tellurium species lie in the tellurium electrophile induced rearrangement of 1-alkynyl trialkyl borate salt **44**[24]. One reaction can be carried out by the deprotonation of a terminal alkyne with BuLi and further trapping with a trialkylborane, furnishing the alkynyl trialkylborate salt **44** intermediate, which reacts with tellurenyl halide to afford vinyl telluride **45** in good yields. Another approach consists of the addition of acetic acid at the end of the reaction, in order to promote a protodeborylation, which yields vinylic telluride **46** (Scheme 24).

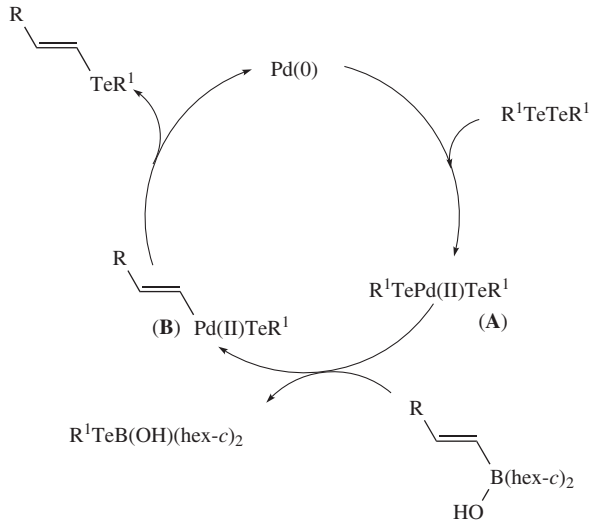
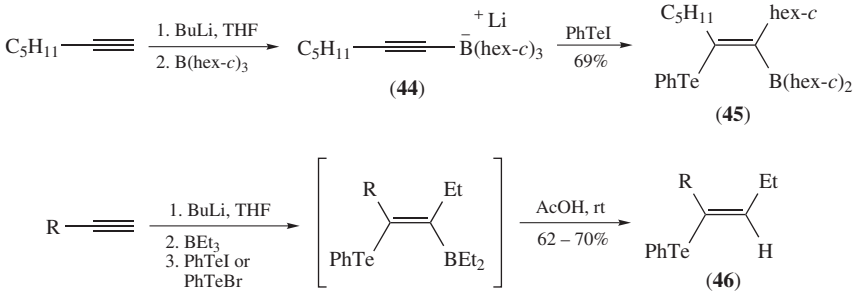
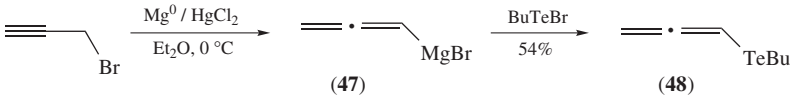


FIGURE 1



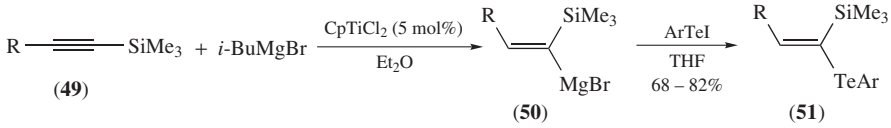
SCHEME 24

c. Magnesium/tellurium exchange reaction. There are only a few reports dealing with the magnesium–tellurium exchange for the preparation of vinylic tellurides. In 1996, it was applied to the preparation of telluro allenes **48**[25]. The reaction consists of the generation of allenyl magnesium bromide **47** from propargyl bromide with $Mg/HgCl_2$ in diethyl ether. The reaction of the Grignard reagent with butyltellurenyl bromide furnished the butyltelluro allene **48** in 54% yield after purification (Scheme 25).



SCHEME 25

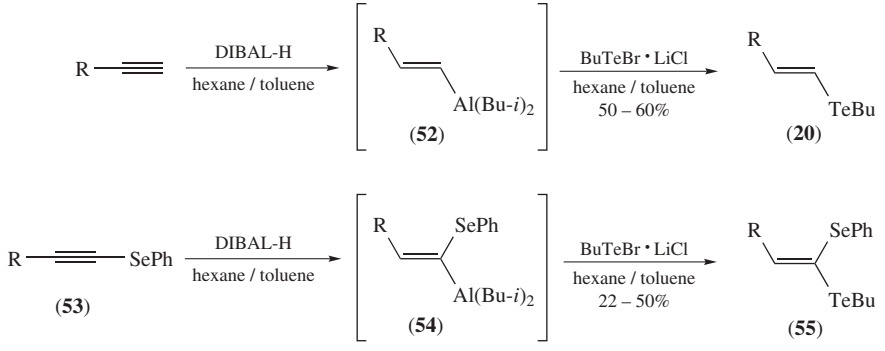
In addition to this work, a recent paper concerning a hydromagnesiation of alkynyl silanes **49** has been published, in which vinyl magnesium reagent intermediates **50** were trapped by tellurium electrophilic reagents[26]. The reaction was performed using alkynyl silanes as starting materials which were hydromagnesiated with *i*-BuMgBr in the presence of a catalytic amount of Cp_2TiCl_2. The magnesium was attached exclusively to the same carbon as the silicon atom. The vinyl Grignard reagent **50** underwent the magnesium–tellurium exchange reaction with a complete retention of the double bond geometry, to afford the *E*-α-aryltellurenyl vinylsilanes **51** in good yields (Scheme 26).



R = C_4H_9, C_5H_{11}, C_6H_{13}, $PhCH_2$; Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4

SCHEME 26

d. Aluminum/tellurium exchange reaction. Vinyl alane **52** intermediates are produced by the hydroalumination of alkynes with DIBAL-H and react with tellurenyl halides to produce *E*-vinylic tellurides **20**[27]. The aluminum–tellurium exchange reaction occurs with total retention of the vinyl organometallic intermediate configuration to exclusively afford the *E*-vinylic telluride **20**. The best results were obtained when the reaction was carried out in the presence of LiCl (Scheme 27). Moreover, the hydroalumination of alkynyl selenides **53** has been reported. The reaction produces the mixed ketene telluro(seleno) acetals **55** after the exchange of the vinyl alane intermediate **54** with butyltellurenyl bromide in the presence of lithium chloride (Scheme 27)[28].

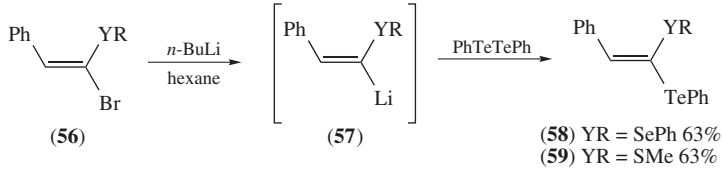


R = Ph, $C_{10}H_{21}$, C_6H_{13}, C_4H_9, C_3H_7,

SCHEME 27

e. Lithium/tellurium exchange reaction. Our group reported the lithium–tellurium exchange via generation of the reactive lithium species by treatment of α-bromo vinylchalcogenides **56** with butyllithium in hexane[29]. The functionalized vinyl lithium

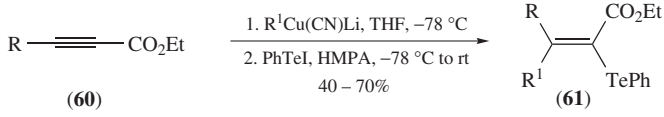
intermediates **57** readily react with diphenyl ditelluride to afford the vinylic tellurides **58** and **59** in good yields. It is noteworthy that no isomerization of the vinyl lithium was observed under the conditions employed, and the reaction proceeded with retention (Scheme 28).



(**56**) (**57**) (**58**) YR = SePh 63%
(**59**) YR = SMe 63%

SCHEME 28

f. Copper/tellurium exchange reaction. A copper–tellurium exchange was successfully applied in the synthesis of vinylic tellurides via carbocupration reaction of alkynes containing electron-withdrawing groups in conjugation. The carbocupration reaction of alkynes is of high synthetic interest since it allows the preparation of functionalized vinyl copper intermediates by a Michael-type addition. These intermediates can be further trapped by convenient electrophiles to give tri- or tetrasubstituted olefins. One approach to the synthesis of α-phenyltelluro-α,β-unsaturated esters **61** was described by Silveira and coworkers. The authors described the reaction of substituted ethyl propiolates **60** with organocuprates to generate the vinyl copper species that reacts with the tellurenyl iodide to afford the vinylic tellurides **61** in good yields (Scheme 29)[30]. When R = Ph, a higher temperature is needed for the completion of the reaction. However, the increase in the temperature leads to a mixture of *E* and *Z* isomers. When another R, such as an H or an alkyl substituent, is present, only one isomer is obtained.

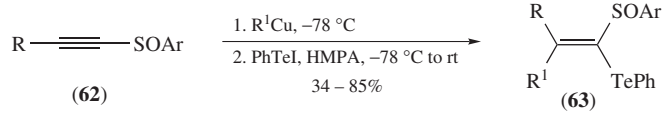


(**60**) (**61**)

R = H, Ph, C_5H_{11}; R^1 = *n*-Bu, *s*-Bu, Me

SCHEME 29

The carbocupration of acetylenic sulfoxides **62** has been accomplished, where a monocopper reagent added regio- and stereoselectively in a Michael-type reaction in a syn fashion to give vinyl copper intermediates. These were efficiently trapped with PhTeI affording the α-phenyltellurovinyl sulfoxides **63** in good to excellent yields. When allyl copper reagents were employed, however, lower yields were obtained (Scheme 30)[31].



(**62**) (**63**)

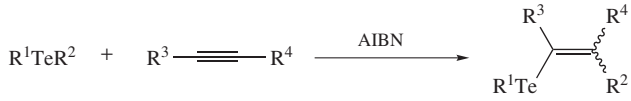
R = C_4H_9 C_5H_{11}; R^1 = Et, Ph, allyl; Ar = *p*-Tol

SCHEME 30

B. Preparation of Vinylic Tellurides by Free Radical Processes

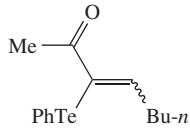
1. Carbotelluration of alkynes

The carbotelluration of alkynes was described by Sonoda and coworkers[32]. Diorganyl tellurides add to alkynes regioselectively to afford alkenyl tellurides, as shown in Scheme 31. Primary, secondary and tertiary alkyls and benzyl-substituted tellurides are suitable substrates for this carbotelluration, and good yields of the trisubstituted vinylic tellurides can be obtained in moderate E:Z ratios.

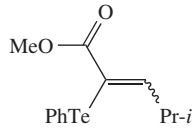


tellurides: PhTeBu-*n*, PhTePr-*i*, *n*-BuTeBu-*t*, *n*-BuTeCH$_2$Ph

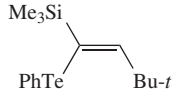
selected examples:



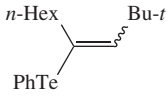
73%, *E:Z* : 20/80



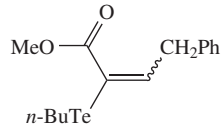
93%, *E:Z* : 29/71



77%



42%, *E:Z* : 80/20



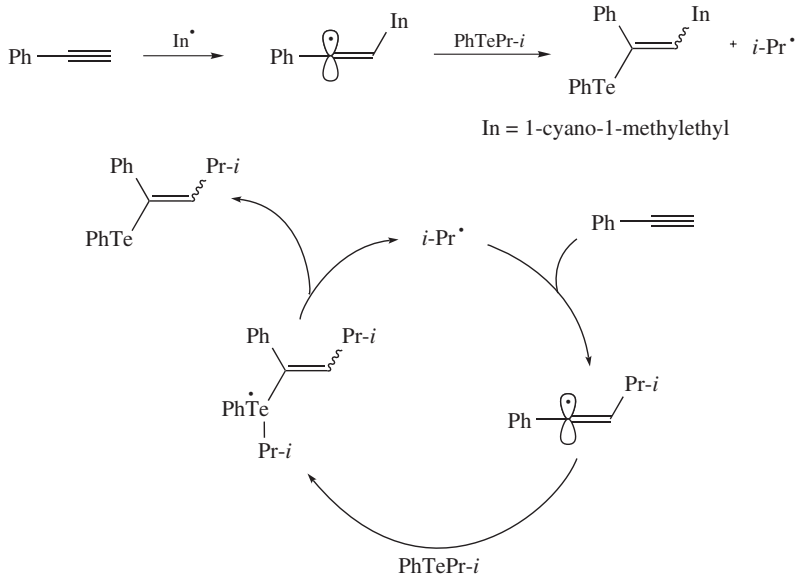
91%, *E:Z* : 56/44

SCHEME 31

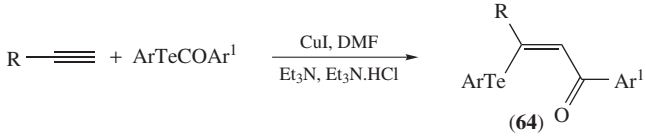
The mechanism of the reaction is believed to be a radical chain reaction initiated by the addition of 1-cyano-1-methylethyl radical (In$^{\bullet}$) to phenylacetylene, leading to the formation of as here *i*-Pr$^{\bullet}$, which then reacts with phenylacetylene to afford a vinylic radical. This species undergoes a reaction with diorganyl telluride, leading to the formation of vinylic telluride and regenerates *i*-Pr$^{\bullet}$ (Scheme 32).

2. Telluroacylation of alkynes

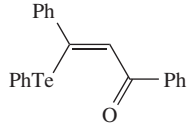
The telluroacylative addition of telluro-carbonyl compounds to alkynes has been described. The reaction proceeds with the simultaneous introduction of the aryltellurenyl and acyl groups to the organic molecule[33]. The reaction was performed in anhydrous dimethylformamide in the presence of cuprous iodide and triethylamine, and, after exposure to air, the vinylic tellurides **64** were isolated in good yields (Scheme 33). It is noteworthy that the reaction was highly stereoselective, and only Z-adducts were isolated. Their configuration was confirmed based on differential NOE experiments.



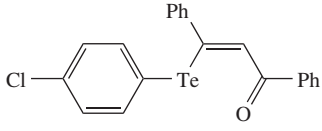
SCHEME 32



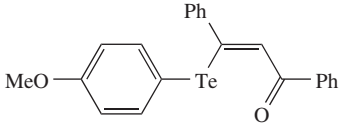
selected examples of **64**:



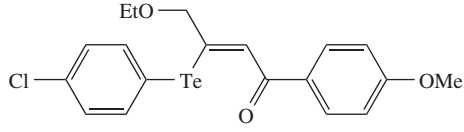
81%



88%



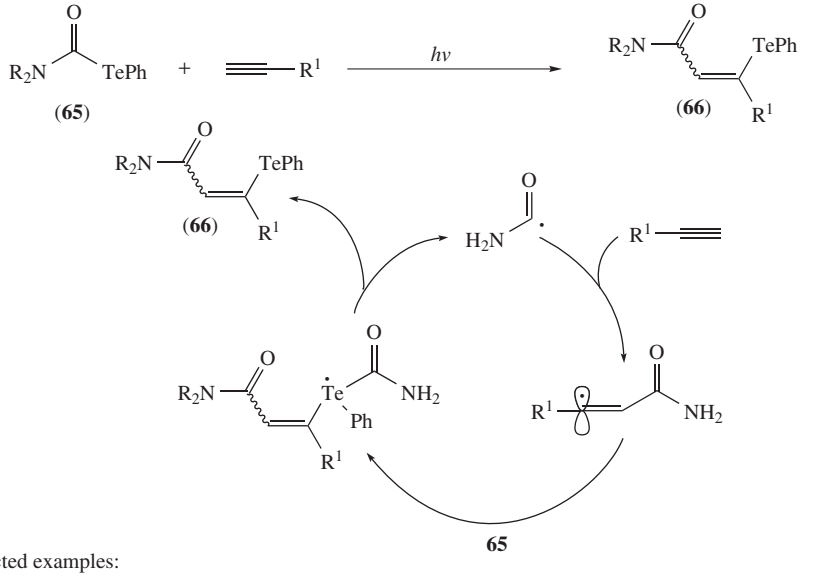
75%



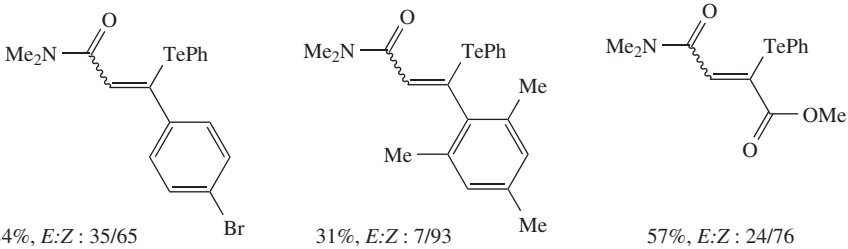
64%

SCHEME 33

Carbamotelluroates **65** have been reported to add to acetylenes under irradiation of a visible light to form β-telluroacrylamides **66** in a regioselective manner[34]. The reaction proceeds via a radical chain mechanism comprising two processes: (i) the addition of carbamoyl radicals at the terminal carbon of the triple bond, giving vinylic radicals, and (ii) the S_N2 reaction on the Te atom caused by the attack of vinyl radicals on **65** (Scheme 34). The reaction typically occurs in good yields and with E:Z ratios of up to 7:93.



selected examples:

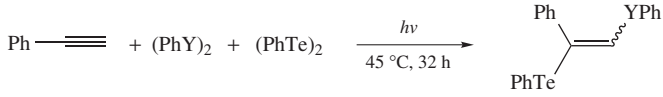


84%, *E:Z* : 35/65 31%, *E:Z* : 7/93 57%, *E:Z* : 24/76

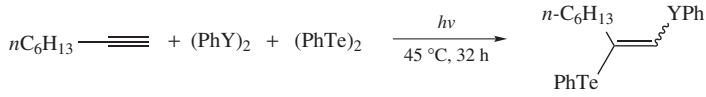
SCHEME 34

3. Thio- and selenotelluration of alkynes

The thio- and selenotelluration of alkynes using a $(PhS)_2$ or $(PhSe)_2/(PhTe)_2$ binary system were reported by Ogawa and coworkers[35]. The reaction occurs with a visible light irradiation using equimolar amounts of diphenyl disulfide or diphenyl diselenide and diphenyl ditelluride, giving the thio- and selenotelluration products in high yields and very high E:Z ratios for aromatic alkynes. Alkylalkynes gave much poorer yields and selectivity for the thiotelluration system (Scheme 35).



Y = S, 80% *E:Z* : 100:0
Y = Se, 95% *E:Z* : 90:10

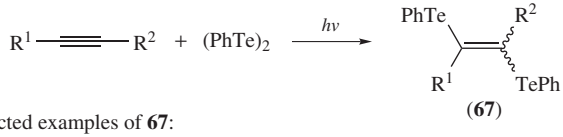


Y = S, 60% *E:Z* : 55:45
Y = Se, 29% *E:Z* : 100:0

SCHEME 35

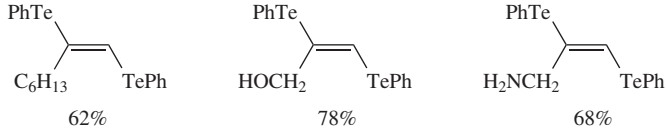
4. Bistelluration of alkynes

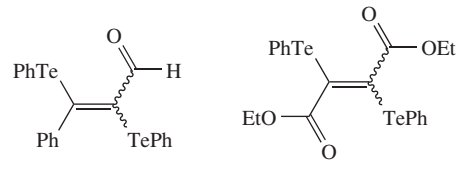
A method involving the photo-induced addition of diphenyl ditelluride to alkynes has also been developed, leading to the formation of bis(phenyltelluro) alkenes **67**[36]. The reaction was performed under a visible light irradiation (>400 nm), and a series of vicinal ditelluroalkenes **67** were produced in high yields and in good to excellent diasteroselectivities, with preferential formation of the *E*-isomer (Scheme 36).



(**67**)

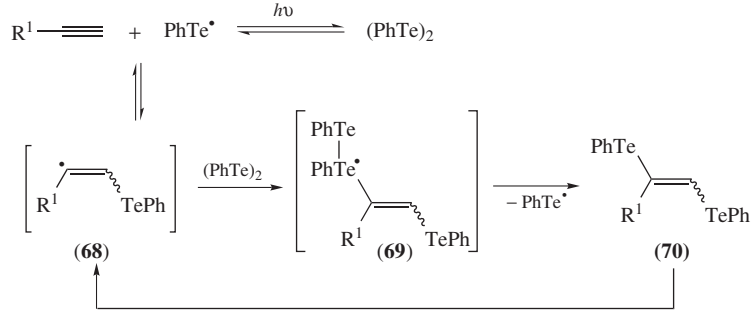
selected examples of **67**:





SCHEME 36

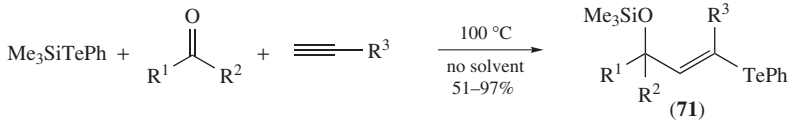
The authors provided a mechanistic proposal which includes the addition of the phenyltelluro radical (PhTe•) to acetylenes to form the alkenyl radical intermediate **68** and the subsequent S_N2 reaction of **69** with $(PhTe)_2$, leading to 1,2-bis(phenyltelluro)alkenes **70** with a regeneration of PhTe (Scheme 37).



SCHEME 37

5. Addition of trimethylsilyl phenyl telluride to alkynes

A three-component reaction of trimethylsilyl phenyl telluride, carbonyl compounds and an alkyne was reported by Yamago and coworkers[37]. The reaction occurs at 100 °C without solvent. This reaction is applicable to a variety of carbonyl compounds and alkynes and seems to be useful for the diversity oriented synthesis of silyl ethers (Scheme 38). Aromatic ketones and aldehydes are the most suitable substrates, since shorter reaction times are required and the product **71** is obtained in high yields. The reaction is *E* stereoselective and *E*:*Z* ratios up to 96:4 are obtained.



R^1, R^2 = Ph, *p*-$MeOC_6H_4$, *p*-$Me_2NC_6H_4$, *i*-Pr, H; R^1R^2 = -$(CH_2)_3$-
R^3 = Ph, *p*-$EtO_2CC_6H_4$, *p*-BrC_6H_4, 3-pyridyl, 1-cyclohexenyl, CO_2Et

E:*Z* ratios 67:33 to 96:4

SCHEME 38

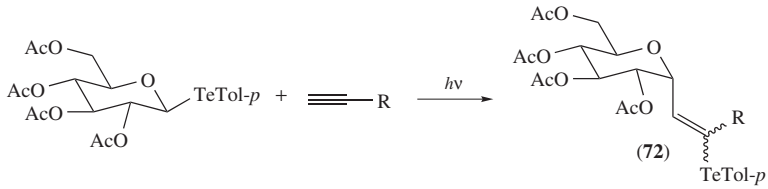
6. Radical addition of telluroglycosides to alkynes

A very interesting paper on the preparation of a vinylic telluride with a glucosyl moiety has been published[38]. The reaction is applicable to a variety of aryl and heteroaryl alkynes in high yields, and it proceeds under neutral conditions, allowing the use of acid- and base-labile groups. Alkylalkynes gave low yields of the product **72** and internal alkynes did not react under the described conditions. In all cases the α-isomers were preferentially obtained over the β-isomers (Scheme 39).

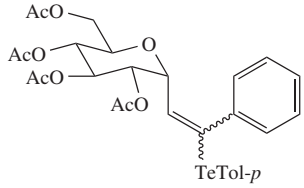
C. Preparation of Vinylic Tellurides by Wittig and Wittig–Horner Reactions

1. Vinylic tellurides by Wittig reactions

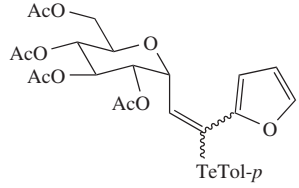
The preparation of vinylic tellurides by the Wittig reaction[39] was accomplished by Silveira and coworkers in the 1990s[40]. Two different methods were developed; the first



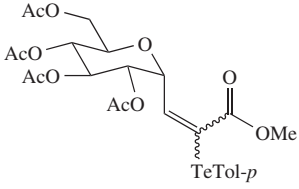
selected examples of **72**:



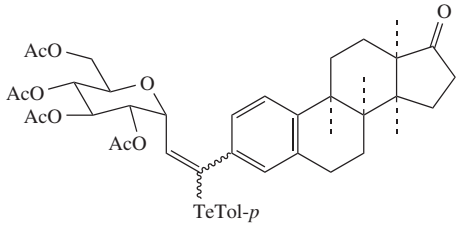
93%
a(*E*:*Z*):b : 75(61:39):25



48%
a(*E*:*Z*):b : 79(67/33):21



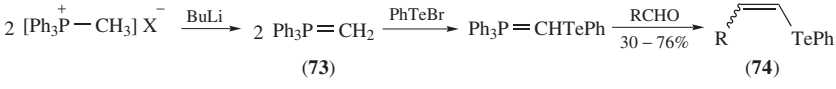
38%
a(*E*:*Z*):b : 69(49/51):31



41%
a(*E*:*Z*):b : 41(63/37):24

SCHEME 39

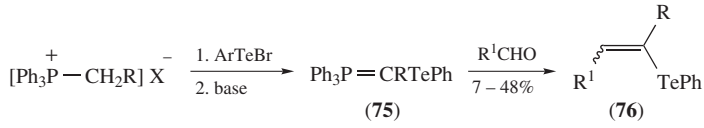
consists of the transylidation reaction between alkylidenetriphenylphosphorane **73** and phenyltellurenyl bromide. The subsequent reaction with aldehydes furnishes vinylic tellurides **74** in moderate to good yields in *E*:*Z* ratios of up to 1:8 (Scheme 40).



R = Ph, 2-furyl, 4-$NO_2C_6H_4$, 4-ClC_6H_4

SCHEME 40

The second method consists of the generation of tellurophosphoranes by the reaction of equimolar amounts of aryltellurenyl bromides, phosphonium salts and base. The reaction of tellurophosphoranes **75** with aldehydes gives vinylic tellurides **76** in moderate yields and good selectivity (up to 13:1) in favor of the *Z*-isomer (Scheme 41).

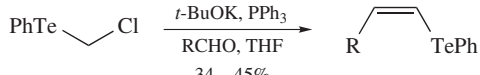


(**75**) (**76**)

R = H, Me; R^1 = Ph, 2-furyl, 4-$NO_2C_6H_4$, 4-ClC_6H_4

SCHEME 41

Vinylic tellurides **78** have been prepared by a one-pot procedure, exclusively in the *Z*-configuration, via addition of *t*-BuOK to a solution of chloromethyl phenyl telluride **77** and triphenylphosphine in THF, followed by addition of an aldehyde (Scheme 42)[41].

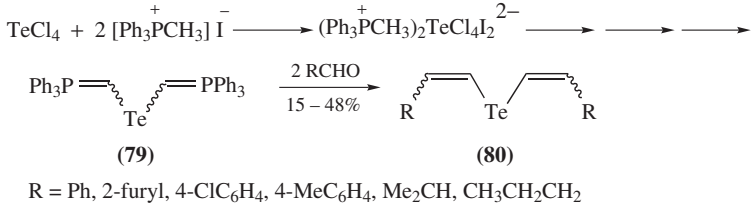


(**77**) (**78**)

R = Ph, 2-furyl, 4-$NO_2C_6H_4$, 4-MeC_6H_4

SCHEME 42

The same group has reported the preparation of symmetrical divinyl tellurides **80** by the reaction of intermediate **79** with aldehydes to generate bis-vinylic tellurides in a mixture of isomers in moderate yields (Scheme 43)[42].



(**79**) (**80**)

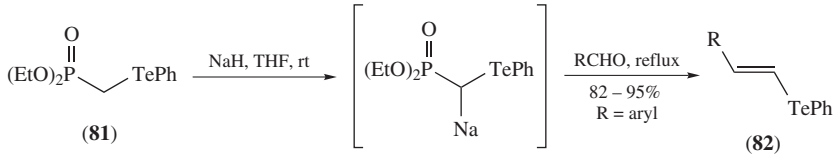
R = Ph, 2-furyl, 4-ClC_6H_4, 4-MeC_6H_4, Me_2CH, $CH_3CH_2CH_2$

SCHEME 43

2. Vinylic tellurides by Wittig–Horner reaction

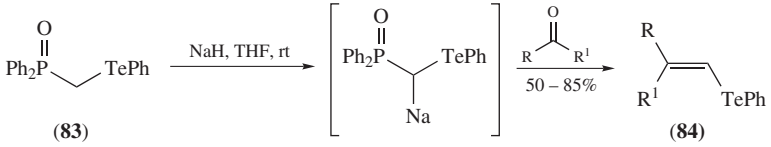
The preparation of *E*-vinylic tellurides by a Wittig–Horner reaction was accomplished by the deprotonation of 1-(phenyltelluro)methyl phosphonate **81** by sodium hydride, followed by the addition of aromatic aldehydes to afford the corresponding vinylic tellurides **82** in high yields exclusively with an *E*-configuration (Scheme 44)[43].

Phenyltelluroalkylphosphine oxide **83** has been applied in the preparation of vinylic tellurides through a reaction with aldehydes or ketones. When aromatic aldehydes were employed, the formation of the *E*-isomer was favored in a ratio of up to 15.6:1. However, with aliphatic aldehydes, the favored product was the *Z*-isomer, though in lower diastereoselectivities. The reaction with ketones worked well, furnishing trisubstituted vinylic tellurides **84** in good yields (Scheme 45)[44].



(**81**) (**82**)

SCHEME 44

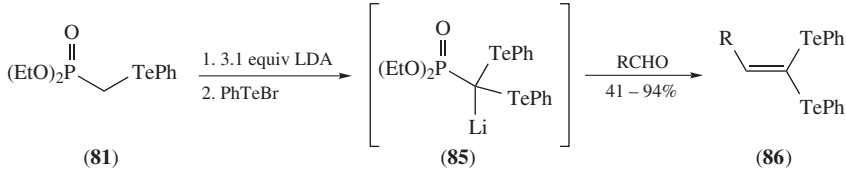


(**83**) (**84**)

R, R^1 = H, alkyl, aryl

SCHEME 45

The preparation of ketene telluroacetals **86** by the reaction of diethyl alkylphosphonates with LDA and the subsequent addition of phenyl tellurenyl bromide was described by Silveira and coworkers. The resulting intermediate **85** was treated with carbonyl compounds to furnish products **86** in good yields (Scheme 46)[45].



(**81**) (**85**) (**86**)

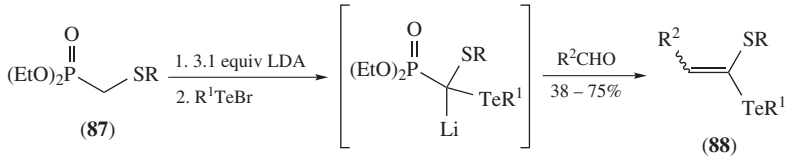
R = Ph, 2-furyl, 4-$NO_2C_6H_4$, Me_2CH, $CH_3CH_2CH_2$, $H_2C{=}CH$

SCHEME 46

The reaction of thiomethyl phosphonates **87** with aryl or butyl tellurenyl halides, under basic conditions, provides moderate to good yields of ketene thio(telluro) acetals **88**. Both aromatic and aliphatic aldehydes gave a mixture of *Z* and *E* isomers (Scheme 47)[46].

Phenyltelluro acrylonitriles **90** have been synthesized by an analogous reaction to that described in Scheme 47. Cyanomethyl phosphonate **89** was treated with LDA whose intermediate reacted with PhTeBr affording an α-phenyltelluro(cyano) phosphonate intermediate **91**, which reacted with aldehydes to give acrylonitriles, typically, in good yields and in *Z*:*E* ratios ranging from 4.5:1 to 5.6:1. Lower yields were obtained when formaldehyde (R = H) was employed (Scheme 48)[47].

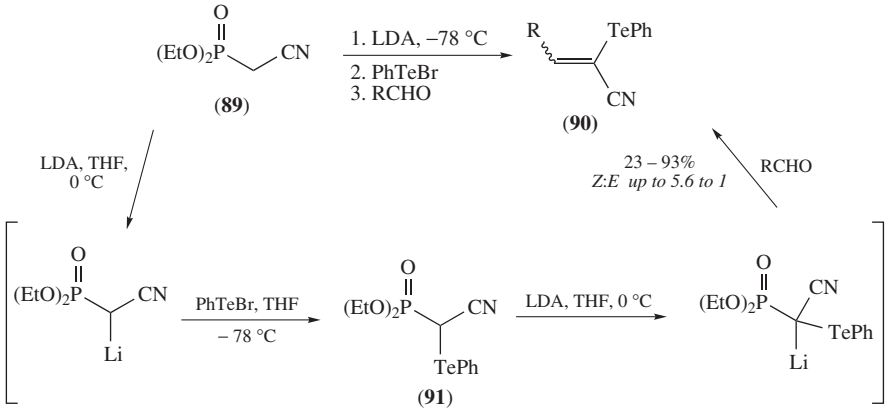
Symmetrical and unsymmetrical divinylic tellurides **94** and **96**, with preferential *E*-stereochemistry, were prepared by Horner–Wittig-type reaction of bis[(diphenylphosphinoyl)methyl] tellurides **93** with appropriate carbonyl compound (Scheme 49)[48]. By this methodology the telluride **93** was prepared in 71% yield via treatment of tosylate **92** with sodium telluride in DMF. Thus, treatment of **93** with an excess amount of



(**87**) (**88**)

R = Me, Ph; R^1 = Ph, Bu; R^2 = Ph, 2-furyl, 4-MeC_6H_4, 4-ClC_6H_4, Me_2CH, $CH_3CH_2CH_2$, H

SCHEME 47



(**89**) (**90**) (**91**)

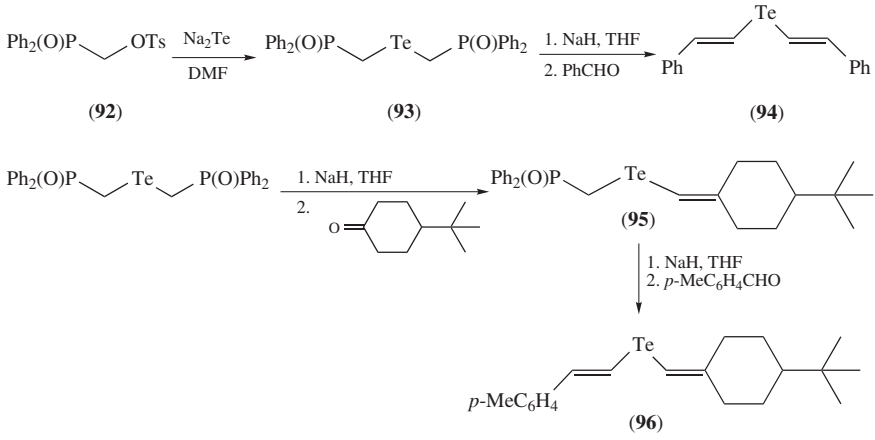
SCHEME 48

base (NaH) and 3 equivalents. of benzaldehyde furnished the corresponding bis(styryl) telluride **94** in 78% yield. The reaction of **93** with 4-*t*-butylcyclohexanone, which is less reactive in Wittig-type reactions, can selectively perform the reaction at one side of the substrate and vinylic telluride **95** was prepared. Telluride **95** was isolated and purified and subsequently reacted with *p*-tolyl aldehyde to give **96**, which allows easy entry to unsymmetrical divinylic telluride (Scheme 49).

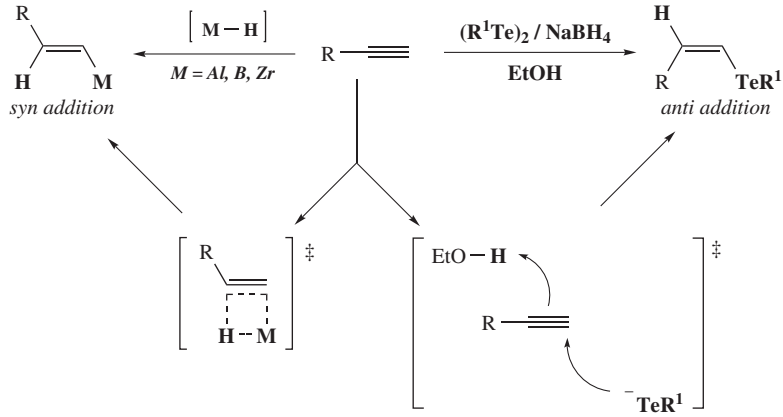
D. Preparation of Vinylic Tellurides by Nucleophilic Tellurium Species

1. Hydrotelluration of alkynes

The hydrometallation of alkynes, such as hydroalumination[49], hydroboration[50] and hydrozirconation[12, 51], is a common method for the preparation of functionalized alkenes. Usually, the hydrometallation of an alkyne affords the *E*-alkene, by a *syn* addition of the hydrogen and the metal to the triple bond in a four-membered transition state (Scheme 50). On the other hand, the hydrotelluration of alkynes is the most important and widely employed method for the preparation of vinylic tellurides[52]. It differs from the other hydrometallation reactions, since it proceeds in an *anti* fashion, as a result of an addition of an organotellurolate anion to the alkyne. This *anti* addition leads to the *Z*-vinylic telluride, which is stereochemically stable, since no isomerization to the *E*-isomer has been reported to date. This characteristic makes the hydrotelluration reaction unique and



SCHEME 49

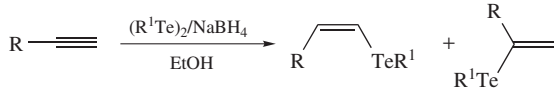


SCHEME 50

a very important method for the generation of *Z*-alkenes, which are not easily accessible by other methodologies, starting from alkynes (Scheme 50).

The nucleophilic organotellurium species are most commonly generated *in situ* by the reduction of the corresponding diorganoditellurides with sodium borohydride in ethanol as solvent. Diorganoditellurides are used as precursors of tellurium anions due to the instability of the organotellurols, which cannot be isolated in the same way as the related selenols and thiols. The reduction of the diorganoditelluride can easily be visualized, since the initial dark red color of the solution disappears with the addition of sodium borohydride and a gas evolution is observed, resulting in a colorless solution at the end of the reduction. The exact structure of the species formed has yet to be determined. In view of the protic nature of the solvent, an equilibrium between the ionic species and the solvent can occur, suggesting that the most probable hydrotelluration agent is $(R^1Te)_2/NaBH_4$.

The addition of the nucleophilic tellurium agent across the alkyne triple bond can give two regioisomeric products, and the regioselectivity of the reaction is dependent on the nature of alkyne (Scheme 51)[52].



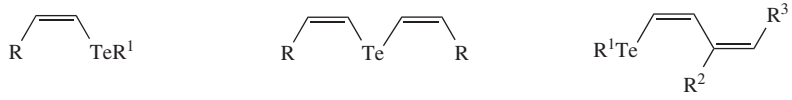
SCHEME 51

Although the first example of a reaction of a nucleophilic tellurium species with a terminal alkyne was reported in 1966[53], this reaction has received little attention in the subsequent years, and only isolated examples were reported until the middle 1980s when Comasseto and coworkers described a systematic study of the synthesis of vinylic tellurides, divinyl tellurides and 1-(organyltelluro)-1,3-butadiene (Figure 2)[54].

Since this pioneering work, several different alkynes with different steric and electronic properties were subjected to hydrotelluration conditions, giving numerous different types of vinylic tellurides. Our aim here is to describe them, based on the structure of the starting alkyne, to discuss the differences in the reactivity of the substrates employed and to comment on the regiochemistry and yields of the reactions.

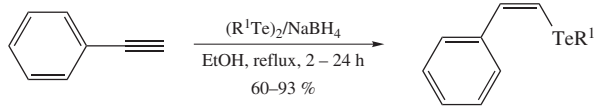
a. Hydrotelluration of alkynes via $(RTe)_2/NaBH_4$.

i. Hydrotelluration of aryl and alkyl alkynes. Arylalkynes are excellent substrates for the preparation of vinylic tellurides. For example, phenylacetylene is hydrotellurated in very high yields in short reaction times, and it tolerates a variety of organotellurides containing different R^1 groups, such as butyl, phenyl, 4-methoxyphenyl, 2-thienyl and vinyl (Scheme 52). The authors reported that alkynes bearing the aliphatic butyl group gave higher yields than an unsaturated group. In all cases, the reaction led exclusively to the 1,2-addition product **97** with *Z*-stereochemistry[54, 55].



vinylic telluride ***divinyl telluride*** ***1-(organotelluro)-1,3-butadiene***

FIGURE 2

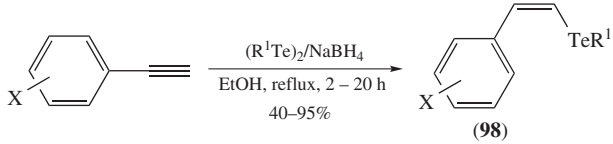


(**97**)

R_1 = Bu, Ph, 4-$MeOC_6H_4$, 2-Thi, $CH{=}CH_2$, $C(CH_3){=}CH_2$

SCHEME 52

Substituted arylalkynes are suitable substrates for the preparation of *Z*-vinylic tellurides. The reaction is tolerant of several different functional groups in the alkyne, such as halogens (Cl, Br), alkyl, methoxy groups and even more sensitive substituents, for example, carboxylic acids and esters (Scheme 53)[54, 56]. In general, the electronic nature of the substituents at the aromatic ring does not have a significant influence on the yield of the reaction. Usually, the yields are high for both electron-donating and electron-withdrawing groups. Steric effects do not seem to exert a great influence, since similar yields are obtained with alkynes with substituents at all three possible positions on the aromatic ring. A decrease in the yield of the vinylic telluride **98** is observed when a free carboxylic acid[56] or a nitro[56b] group is present in the starting alkyne.

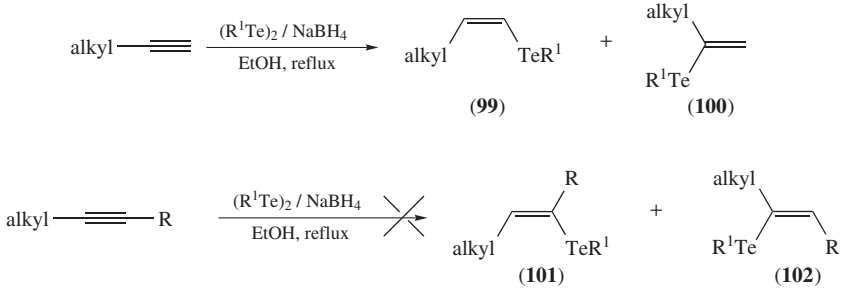


(**98**)

X = Br, Cl, MeO, Me, NO_2, CO_2H, CO_2Et; R^1 = Me, Ph, $CH{=}CH_2$, $C(CH_3){=}CH_2$

SCHEME 53

Conversely, alkyl substituted alkynes display regioselectivity problems, as they give rise to two different regioisomeric vinylic tellurides, **99** and **100**. The 1,2-addition products predominate, whereas a lower amount (11–28%) of the 1,1-disubstituted product is formed. Vinylic tellurides **101** and **102** are not formed, since internal disubstituted alkylalkynes are not hydrotellurated (Scheme 54)[2d].



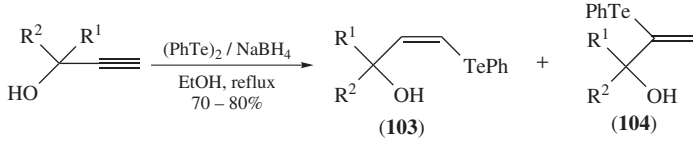
(**99**) (**100**)

(**101**) (**102**)

SCHEME 54

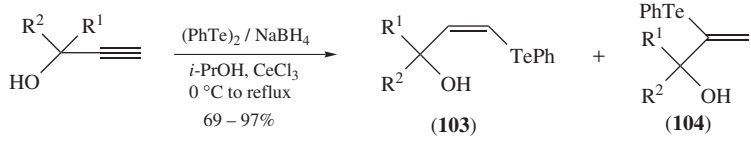
ii. Hydrotelluration of hydroxy- and aminoalkynes. Hydroxyalkynes are remarkable substrates for the hydrotelluration reaction, in that they furnish allylic alcohols, which are very important intermediates in organic synthesis. They can be further converted to a wide range of functional groups. Thus, the synthesis of allylic alcohols that contain stereodefined geometry of the double bond is of general interest in organic chemistry. Therefore, propargylic alcohols of different substitution patterns were subjected to hydrotelluration conditions and furnished the desired vinylic tellurides containing an allylic alcohol moiety (Scheme 55)[56]. The yields were typically good and the regioselectivity of the reaction always favored product **103**. However, both regioisomeric tellurides **103** and **104** were

easily separated by column chromatography. On the contrary, regioisomers **104** were found to be the major products when hydroxyalkynes were used as substrate in the hydrotelluration reactions employing Ce(III) chloride as catalyst (Scheme 56)[57]. These results, unlike those from previous work, strongly suggest that the Ce(III)-mediated addition of ditellurides across the triple bond follows an *anti*-pathway, with effective participation by the propargylic hydroxyl group as the source of the vinylic hydrogen.



103 : **104** ratio: 95–80 : 5–20; R^1 and R^2 = H, Me, *i*-Bu, *c*-Hex

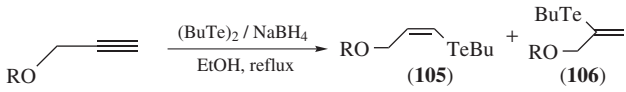
SCHEME 55



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

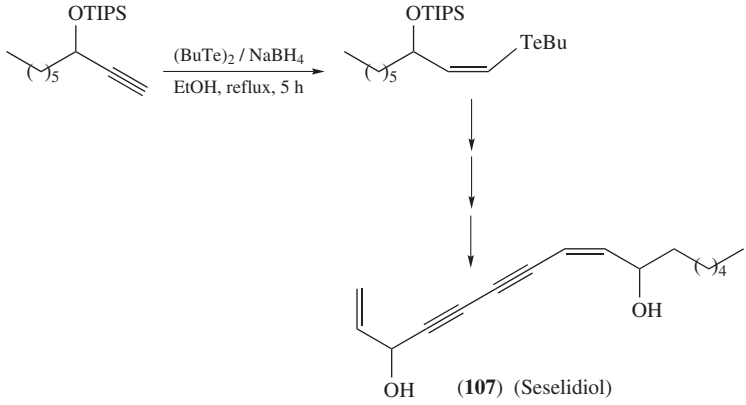
SCHEME 56

The influence of protecting groups in the synthesis of regio- and stereodefined vinyl tellurides, derived from the reaction of BuTeNa and propargyl alcohols, was recently described[58]. The protected propargyl alcohols were then subjected to hydrotelluration conditions to yield the corresponding regioisomeric vinyl tellurides **105** and **106** (Scheme 57). The influence of the protective group is remarkable. When bulky groups such as TBS and TIPS were used, better regioselectivities were observed. The THP and MEM ethers gave lower regioselectivities when compared with the silyl groups (Scheme 57). The influence of the temperature on the reaction was also studied. When the hydrotelluration reaction was performed at 0 °C, the formation of the vinyl tellurides **105** and **106** was not observed for all substrates. This might be due to the lower reactivity of the species involved at this temperature. When the reaction was performed at 25 °C, under controlled conditions, the observed regioselectivities were lower if compared with the results obtained under reflux conditions. The two regioisomers **105** and **106** were obtained under different conditions, with vinyl telluride **105** predominating at higher temperature. This fact should indicate that the telluride **105** might be the thermodynamic product and hence vinyl telluride **106** would be the product of kinetic control, since it should be formed faster at lower temperatures. This methodology was then applied for the diastereoselective synthesis of the double bond present in (±)-Seselidiol **107** (Scheme 58), a natural product isolated in 0.0085% yield from the roots of *Seseli mairei* Wolff (Umbelliferae) and used as herbal remedies for human inflammation, swelling, rheumatism, pain and common cold in folk Chinese medicine[59]. It also showed significant cytotoxicity in KB, P-388 and L-1210 tumor cells (ED50 $<10\,\mu g\ mL^{-1}$)[60].



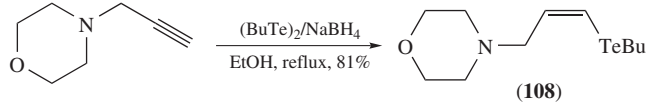
R = TBS, TIPS, TBPS, MEM, THP

SCHEME 57



SCHEME 58

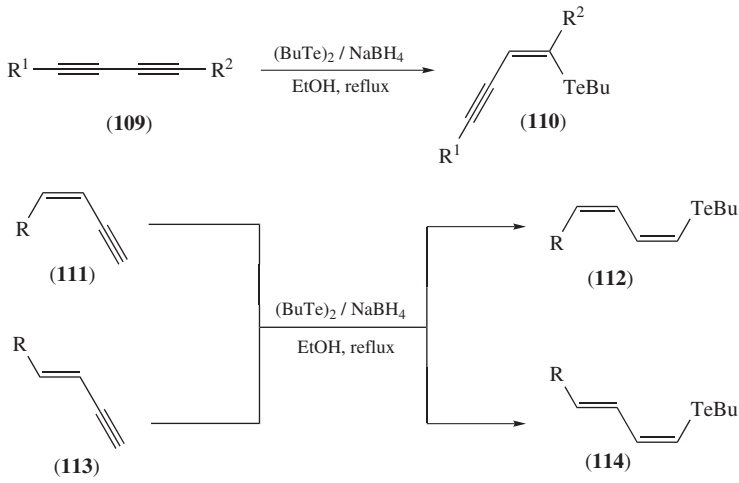
Similar to propargylic alcohols, propargylic amines can be hydrotellurated giving rise to allylic amines. For example, a morpholine-derived propargylic amine was hydrotellurated with $(BuTe)_2/NaBH_4$, furnishing the *Z*-vinylic telluride **108**, which is an allylic morpholine, in 77% yield as a single isomer (Scheme 59)[54a].



SCHEME 59

iii. Hydrotelluration of enynes and diynes. Diynes **109** and enynes **111** and **113** can also be used as substrates for the hydrotelluration reaction (Scheme 60). These are very attractive precursors, since the products will be conjugated dienes **112** and **114** or enynes **110**, which can be further converted to highly unsaturated compounds with defined stereochemistry. In addition to their great utility in organic synthesis, enynes and diynes occur in numerous natural products[61].

One very relevant characteristic of this type of product is the possibility of obtaining stereodefined conjugated dienes in high yields with the *Z*,*Z* and *E*,*Z* combinations. This represents a very important feature of the present methodology, because such conjugated systems are not easily obtained through other routes[62].



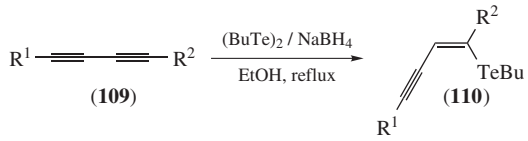
SCHEME 60

Regarding the preparation of vinylic tellurides containing a triple bond, the reaction is usually very fast with symmetrical 1,3-diynes of different types. For instance, alkynes with substituents, such as propargyl alcohol, methyl, hydrogen and aromatic rings, successfully react with the tellurium nucleophile, leading to the corresponding enynes functionalized with the organotellurium group in good to excellent yields. When the diyne carries aromatic substituents with an electron-donating group, the yield of the reaction is slightly lower than with the parent phenyl substituent (compare entries 4 and 5, Table 1).

Extending the above-mentioned studies, a remarkable paper has been published by Dabdoub and Dabdoub, in which they describe the chemoselective triple bond reduction of unsymmetrical butadiynes by treatment with the $(BuTe)_2/NaBH_4$ hydrotelluration system[63]. With the monosubstituted butadiynes, the reaction takes place exclusively at the terminal triple bond, leading to the *Z*-butyltelluro enynes in a very fast reaction and in good yields (Table 1, entries 7 and 8). The terminal triple bond is more reactive than the internal one, due to steric hindrance of the phenyl group, which hampers the attack of the telluride anion on the other triple bond. Further evidence of the influence that steric effects have on this system is the fact that when unsymmetrical disubstituted diynes are employed, for example, when the terminal hydrogen is replaced by a larger methyl group (Table 1, entry 9), the reaction is slower, taking 2 h for its completion. However, tellurium addition takes place exclusively at the methyl substituted triple bond. A further explanation is given by the authors, who suggest that electronic effects are operating in the hydrotelluration of unsymmetrical diynes. The incipient negative charge, which is formed in the transition state at the adjacent carbon, is better stabilized by the phenylethynyl moiety (Figure 3, structure **C**) than by the ethynyl or propynyl groups (Figure 3, structure **D**).

In the case of propargylic substituents at one of the triple bonds, the reaction is faster than that with triple bonds bearing aryl or alkyl substituents. This fact is probably due to the formation of cyclic five-membered transition states of type **E** and **F** (Figure 3), which are trapped by hydrogen intramolecularly, rather than by hydrogen from the solvent. The more hindered the propargylic alcohol, the more difficult is the ring formation, explaining the longer reaction times when the two propargylic hydrogens are replaced by two methyl groups (Table 1, entries 10–12). In a single case (Table 1, entry 13), a mixture

TABLE 1. Hydrotelluration of diynes



(**109**) (**110**)

Entry	R^1	R^2	Time (h)	Yield (%)
1	H	H	0.25	93
2	CH_2OH	CH_2OH	0.25	71
3	Me	Me	2.5	81
4	Ph	Ph	2.5	83
5	4-MeC_6H_4	4-MeC_6H_4	3	73
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	3	68
7	Ph	H	0.16	75
8	C_6H_{13}	H	0.28	79
9	Ph	Me	2	80
10	Ph	CH_2OH	0.25	76
11	Ph	Me_2COH	1	82
12	C_6H_{13}	CH_2OH	0.58	89
13[a]	Me_2COH	H	0.16	70

[a] A 88:12 mixture of regioisomers was obtained, favoring the 1,2-disubstituted product.

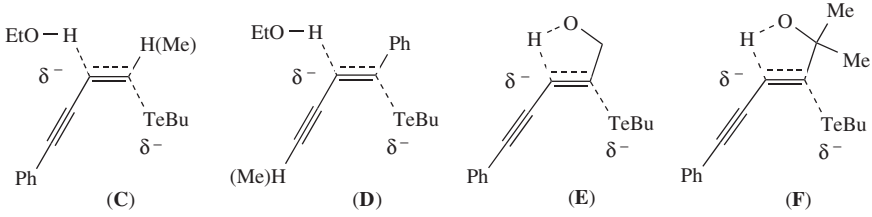


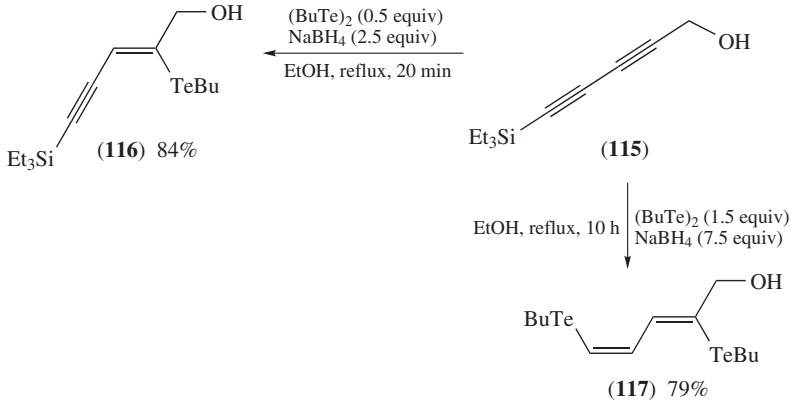
FIGURE 3

of regioisomers is obtained, where the attack of tellurium is favored at the terminal triple bond rather than at the propargylic position, resulting in an 88:12 regioisomeric mixture (Table 1, entry 13). On the basis of these data, the authors suggest the following order of reactivity for the butyltellurolate anion:

terminal > propargylic > alkyl > aryl

Another example of 1,3-diyne hydrotelluration was reported by Marino and Nguyen[64]. Unsymmetrical diyne alcohol **115** was selectively functionalized at the propargylic carbon–carbon triple bond (Scheme 61).

After several optimization studies, it was found that the stoichiometry as well as the reaction time were crucial for the outcome of the reaction. Thus, when 0.5 equivalent of dibutyl ditelluride was employed, and the reaction was stopped after 20 minutes at reflux, vinylic telluride **116** was obtained in high yield. However, when excess amounts of $(BuTe)_2$ and $NaBH_4$ were used with longer reaction times, the ditellurated product **117** was predominantly formed.

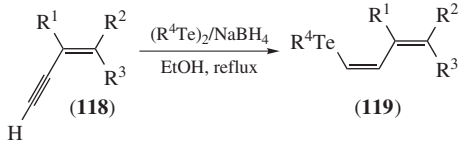


SCHEME 61

Moreover, tellurium containing dienes are obtained by the hydrotelluration of enynes **118**[54b, 62a, b]. The reaction takes place stereoselectively at the triple bond, yielding the corresponding tellurobutadienes **119** with the new double bond formed exclusively with *Z* stereochemistry (Table 2).

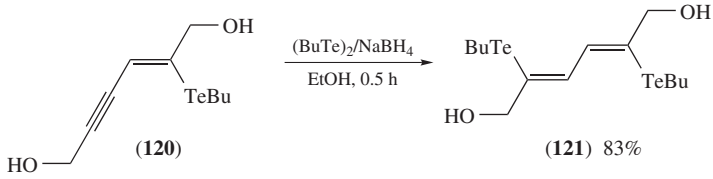
Only enynes bearing terminal alkynes are reactive at the hydrotelluration conditions. Enynes with disubstituted triple bonds fail to react under the given conditions. An exception is when the enyne **120** containing a propargyl alcohol is employed. In this case, the

TABLE 2. Hydrotelluration of enynes



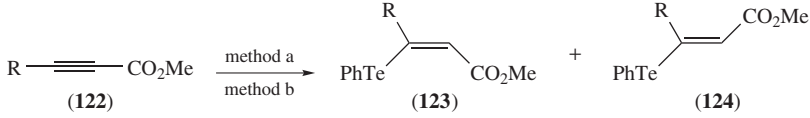
Entry	R^1		R^2	R^3	R^4	Time (h)	Yield (%)
1	H		H	OMe	Bu	28	50
2	Me		H	CH_2OH	Bu	2	69
3	H		H	TeBu	Bu	2	70
4		*c*-$(CH_2)_4$		H	Bu	12	89
5	Me		H	CH_2OH	C_2H_5	5	80
6	Me		H	CH_2OH	4-$MeOC_6H_4$	5	70
7	Me		H	CH_2OH	4-$MeOC_6H_4$	5	91
8	Me		CH_2OH	H	C_2H_5	5	65
9	Me		CH_2OH	H	2-MeC_6H_4	5	75
10		*c*-$(CH_2)_4$		H	C_2H_5	5	60
11		*c*-$(CH_2)_4$		H	4-$MeOC_6H_4$	5	53
12	Me		CH_2OTHP	H	Bu	4	83
13	H		CH_2OTHP	H	Bu	5	89
14	Me		H	H	Bu	5	75

hydroxyl group at the propargyl position activates the butyltellurolate attack at the triple bond and affords the tellurobutadiene **121** in 83% yield (Scheme 62).



SCHEME 62

A simple, clean and efficient solvent-free protocol was developed for hydrochalcogenation of alkynes containing an ester Michael acceptor **122** with phenyl tellurolate anion generated *in situ* from the respective diphenyl ditelluride, using alumina-supported sodium borohydride (Scheme 63)[65]. This method was general and furnished the respective β-phenyltelluro-α,β-unsaturated esters **123** and **124** in good yields and higher *Z* (**123**) selectivity, compared with those that used organic solvent and inert atmosphere. In addition, the use of microwave (MW) irradiation facilitated the procedure and accelerated the reaction.

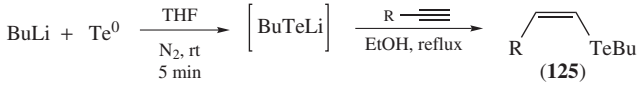


method a — $Al_2O_3/NaBH_4$, rt, 5h : R = Ph — 73% 98:2 (*Z*:*E*)
10h : R = C_5H_{11} — 50% 90:10 (*Z*:*E*)

method b — $Al_2O_3/NaBH_4$, MW, 3 min. : R = Ph — 73% 98:2 (*Z*:*E*)
10 min. : R = C_5H_{11} — 52% 83:17 (*Z*:*E*)

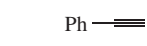
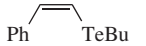
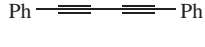
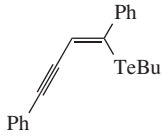
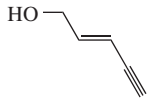
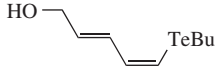
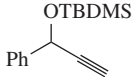
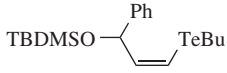
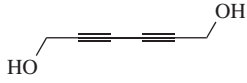
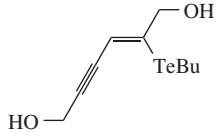
SCHEME 63

b. Hydrotelluration of alkynes via BuLi/Te^0. One of the major drawbacks of the hydrotelluration reaction is the use of dibutyl ditelluride as the precursor of the butyltellurolate anion, since it is not commercially available. To circumvent this problem, an improved procedure to generate the butyltellurolate anion was published in 2000[66]. It consists of the reaction between butyllithium and elemental tellurium in THF at room temperature, which gives lithium butyltellurolate, by the consumption of gray tellurium to form a pale yellow solution. To this solution, a solution of the alkyne in dry deoxygenated ethanol is added and refluxed (Scheme 64). The *Z*-vinylic tellurides **125** obtained by this method are obtained in similar yields to those observed by using the dibutyl ditelluride/$NaBH_4$ method. In addition, an intramolecular version of this hydrotelluration has been employed to prepare tellurium containing heterocycles from terminal or internal alkynes. These studies indicated that this hydrotelluration affords both exo-*dig* and endo-*dig* cyclization products in moderate to good yields (Table 3)[67].

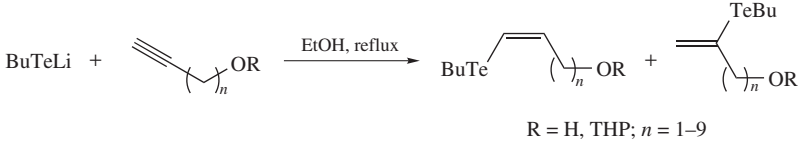


SCHEME 64

TABLE 3. Hydrotelluration of alkynes using the BuTeLi method

Entry	Alkyne	Product	Time (h)	Yield (%)
1			4	88
2			8	75
3			6	77
4			8	72
5			7	80

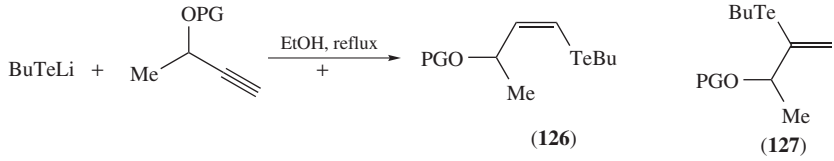
i. Hydrotelluration of hydroxyalkynes. This method has been employed in regioselectivity studies on the hydrotelluration of hydroxyalkynes of both short and long chains (Scheme 65)[68].



SCHEME 65

The best results in terms of regioselectivity were achieved when propargylic alcohol was hydrotellurated. The ratio of both products was 8:1, in favor of the 1,1-disubstituted vinylic telluride. In the case of a protected propargyl alcohol, this regioselectivity is lost, and the major product is the 1,2-disubstituted vinylic telluride, although with low selectivity (ratio 1.7:1). For the other hydroxyalkynes studied, the regioselectivity of the reaction is low, usually from 1.4:1 to 1.9:1, in favor of the 1,2-disubstituted product.

In order to circumvent this problem, a study of the effect of protection of the hydroxyl group of propargyl alcohols with different commonly used protecting group (PG) was described (Scheme 66)[69].



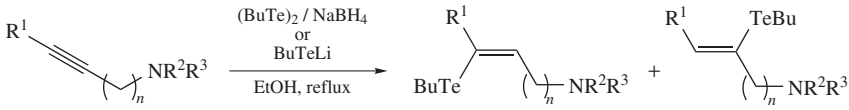
(**126**) (**127**)

		126 : 127
PG =	H	3 : 1
	THP	6 : 1
	Trityl	15 : 1
	TBS	>99 : 1

SCHEME 66

It was found that the steric demand of protecting groups was decisive for the outcome of the reaction and the best choice was protection by TBS, which virtually furnishes only product **126**, instead of the 1,1-disubstituted **127**.

ii. Hydrotelluration of aminoalkynes. We have described a comparative study on the hydrotelluration of aminoalkynes, using two different methods for the generation of tellurium nucleophile[70]. In this article, the hydrotelluration of several differently substituted aminoalkynes and with different chain lengths were tested (Scheme 67).



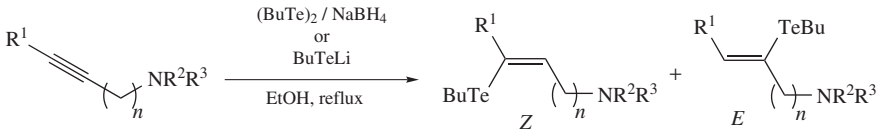
SCHEME 67

Previous to this article, only isolated examples of the hydrotelluration of amino-substituted alkynes had been published and information about the reaction of this class of alkynes with tellurium nucleophiles was lacking[54a, 55a].

The reactions were performed using procedures for the generation of both nucleophilic tellurium species, BuTeTeBu/$NaBH_4$ and BuLi/Te^0. The authors observed an *E* and *Z* mixture of stereoisomers (Table 4) and no significant difference in yields and regioselectivity was obtained.

The best results of regioselectivity were obtained with trisubstituted amines. The pyrrolidine, piperidine and morpholine derivatives gave product in yields ranging from 57 to 71% (Table 4, entries 4–6). Interestingly, when an internal aminoalkyne, with one of the termini of the alkyne moiety, is substituted with a SMe group (Table 4, entry 7), complete reversal of the regiochemistry was observed. This fact is probably due to the high ability of the sulfur atom to stabilize a neighboring negative charge. In contrast, when selenium or alkyl analogues were treated under the same conditions, no reaction was observed. In

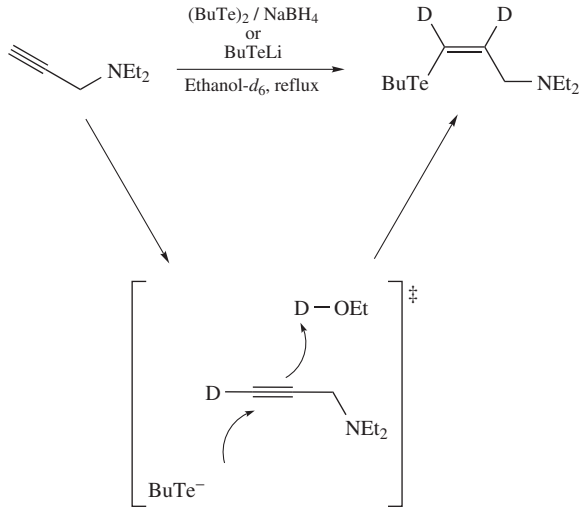
TABLE 4. Hydrotelluration of aminoalkynes



Entry	R^1	R^2		R^3	n	Yield (%)	Ratio *Z*:*E*
1	H	Et		Et	1	60	1:0
2	H	H		H	1	50	2:1
3	H	H		Me	1	60	3:1
4	H		*c*-$(CH_2)_4$		1	67	1:0
5	H		*c*-$(CH_2)_5$		1	57	1:0
6	H		*c*-$(CH_2)_2O(CH_2)_2$		1	71	1:0
7	MeS	Et		Et	1	50	0:1
8	H	H		H	5	35	1.4:1
9	H	Et		Et	5	55	1.6:1

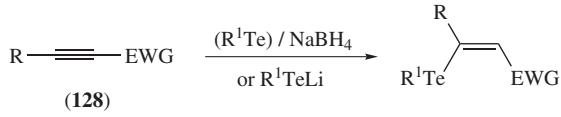
the hydrotelluration of primary, secondary and long chain aminoalkynes, a loss in the regioselectivity was detected.

To elucidate the mechanism of the reaction an additional experiment, in which deuterated ethanol was employed, was carried out in order to determine if the hydrogen, added to the triple bond, comes from the solvent or from water. As observed by ^1H and ^{13}C NMR, the product was a dideuterated alkene, and its formation is explained by a H–D exchange of the acetylenic hydrogen, following the hydrotelluration and capture of deuterium from the solvent (Scheme 68).



SCHEME 68

c. Hydrotelluration of alkynes bearing an electron-withdrawing group. The hydrotelluration of alkynes bearing electron-withdrawing groups **128** is an attractive variant of the hydrotelluration reactions. This methodology is discussed below and organized according to the nature of the EWG group present in the precursor alkyne (Scheme 69).

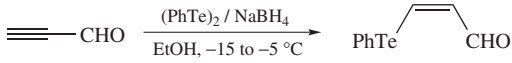


(**128**)

EWG = aldehyde, ketone, ester, phosphonate, phosphine oxide, sulfone, sulfoxide, sulfide

SCHEME 69

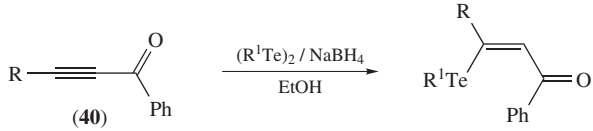
i. Hydrotelluration of alkynes bearing aldehyde and ketone groups. The hydrotelluration of propargyl aldehydes and ketones is scarcely studied. To the best of our knowledge there are only a few reports dealing with the hydrotelluration of propargyl aldeydes and ketones[71, 72]. One of the examples is the preparation of β-phenyltelluroacrolein **129** by treating propargyl aldehyde with phenyltellurolate anion to yield the **129** in 80% yield (Scheme 70)[71].



(**129**) 80%

SCHEME 70

The addition of tellurolates to alkynyl ketones proceeds in a manner similar to that of aldehydes. Good yields of **130** are obtained with alkyl or aryl substituents, and lower yields are achieved when the substituent is a carboxyl group (Scheme 71)[72].

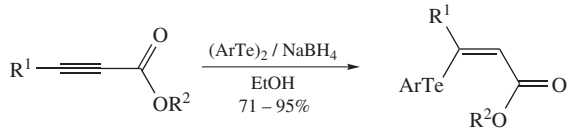


(**40**) (**130**)

R = CO_2H, R^1 = 2,4-$(MeO)_2C_6H_3$, 21%
R = Bu, R^1 = 4-$MeOC_6H_4$, 68%
R = Ph, R^1 = Ph, 86%

SCHEME 71

ii. Hydrotelluration of alkynes bearing ester groups. Acetylenic esters are suitable substrates for the preparation of vinylic tellurides **131**. They underwent a smooth addition of the tellurolate anion to furnish the tellurium-containing acrylates in good to excellent yields (Scheme 72)[72, 73]. Regarding the electronic and steric nature of the substituent at the aryltellurolates, it seems that the electronic effects of the substituents on the aromatic ring do not significantly affect the time and yield of the reaction.

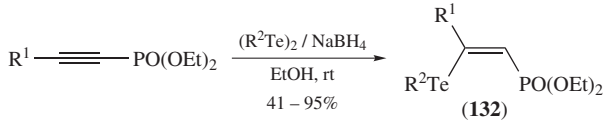


(**131**)

R^1 = H, Ph, Me, 1-cyclohexanol; R^2 = H, Me, Ph, *i*-Pr, COCH=C(TePh)(Ph); Ar = Ph, 4-$MeCOC_6H_4$, 2,4-$(MeO)C_6H_3$ 2-MeC_6H_4, 3,5-$(MeO)C_6H_3$, 3-FC_6H_4, 3-$MeOC_6H_4$, 3-MeC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4

SCHEME 72

iii. Hydrotelluration of alkynes bearing phosphonate and phosphine oxide groups. The phosphonate group is well known to be a good Michael acceptor[74]. Thus, the hydrotelluration of alkynyl phosphonates proceeds in a Michael-type addition giving the β-organyltelluro vinyl phosphonates **132** in good yields with complete stereoselectivity in favor of the *Z* diastereoisomer[75]. The reaction has been performed at room temperature and dibutyl and diaryl ditellurides have been used as the nucleophilic organyltellurium source. The reaction was also carried out with terminal and internal alkynyl phosphonates, and good results were obtained in both cases. Lower yields were achieved when the R^1 substituent at the β-position was 1-cyclohexenyl, probably due to the steric effect (Scheme 73).



(**132**)

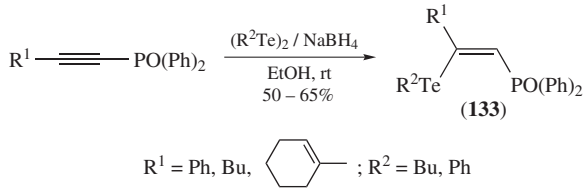
R^1 = H, Ph, Bu, C_5H_{11},  ; R^2 = Bu, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4

SCHEME 73

With regard to the substitution pattern at the ditelluride, little influence in the yield has been observed. For example, the results obtained in the hydrotelluration of the same substrate, with the following three different tellurolate precursors each with substituents of different electronic properties, $(p\text{-}RC_6H_4Te)_2$, R = H, Me, Cl, showed no significant difference in the yields of the corresponding products. The yields were 59, 63 and 61%, respectively[75c].

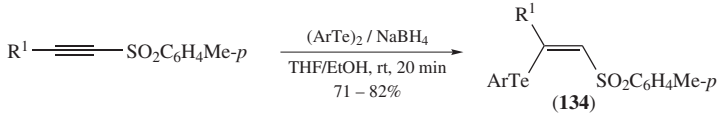
We have successfully described the reaction between the nucleophilic tellurium species and 1-alkynylphosphine oxides[76]. The phosphine oxide group behaves similarly to the phosphonates acting as a Michael acceptor, in that it reacts with the organotellurolate to give the corresponding β-organyltellurovinyl phosphine oxide **133** in moderate yields (Scheme 74).

When R^2 = Ph, all products were obtained with a *Z* geometry of the double bond. However, when the organic group attached to tellurium was a butyl group, the unexpected formation of a smaller amount of *E*-β-organyltellurovinylphosphine oxide was observed.

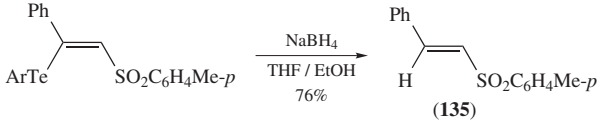


SCHEME 74

iv. Hydrotelluration of alkynes bearing sulfone and sulfoxide groups. β-Sulfonyl vinyltellurides **134** with *Z*-stereochemistry can be obtained by hydrotelluration of 1-alkynyl sulfones[75c]. The addition of aryltellurolate to the alkyne occurred smoothly in a mixture of THF and EtOH as solvent. The reaction was very fast, being completed in 20 minutes and furnishing the *Z*-2-aryltelluro-1-alkenyl sulfones in good yields (Scheme 75). No isomeric products were obtained, as determined by ^{1}H NMR. Interestingly, when the reaction was conducted for longer periods of time, the product was converted to the *E*-vinyl sulfone **135**, free of tellurium.

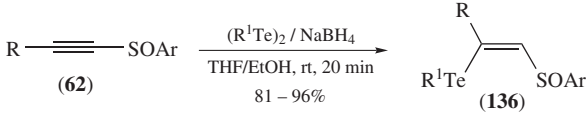


R^1 = Ph, H, C_6H_{13}; Ar = Ph, 4-FC_6H_4



SCHEME 75

The same reactivity pattern was observed for alkynyl sulfoxides[77]. The hydrotelluration reaction led to β-organotellurovinyl sulfoxides **136** in good yields with very short reaction times (Scheme 76).

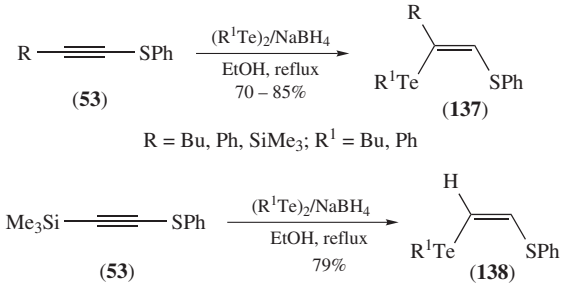


R = H, C_4H_9, C_5H_{11}; R^1 = Ph, Bu; Ar = Ph, *p*-Tol

SCHEME 76

v. Hydrotelluration of alkynes bearing a sulfide group. Although the sulfide group is not exactly an electron-withdrawing group, alkynyl sulfides **53** react with organotellurium nucleophiles in a similar manner as do alkynyl esters, phosphonates and sulfones. This is explained by the ability of the sulfur atom to stabilize an adjacent negative charge,

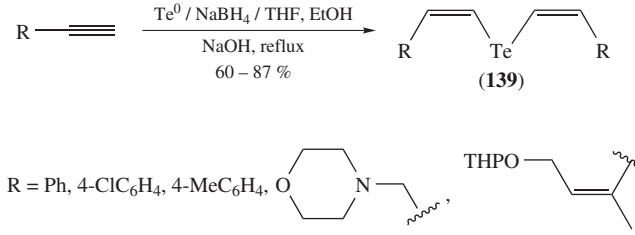
allowing alkynyl sulfides to react in a Michael-type addition of the organotellurolate anion to yield the trisubstituted alkenes **137** in good yields (Scheme 77)[78]. An attractive result was obtained when the $SiMe_3$ group was attached at the triple bond, giving the desilylated product **138** instead of the trisubstituted olefin.



SCHEME 77

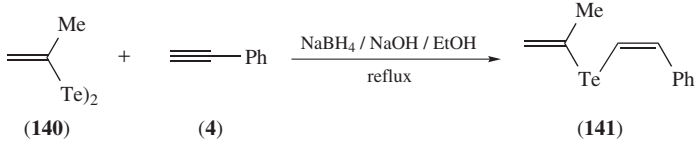
2. Preparation of bis-vinylic tellurides

Bis-vinylic tellurides **139** constitute a very attractive class of tellurium compounds in which the tellurium atom is attached to two alkene moieties. Such compounds were obtained in good yields by the reaction of Na_2Te (generated by the reduction of Te^0 with $NaBH_4$) with 2 equivalents of a terminal alkyne. The reaction was performed with several different alkynes (Scheme 78)[54b, 55a].



SCHEME 78

Unsymmetrical bis-vinylic tellurides **141** can also be prepared. The reaction between divinyltelluride **140** and sodium borohydride and the subsequent hydrotelluration of phenylacetylene **4** leads to unsymmetrical bis-vinylic telluride **141** in good yields (Scheme 79). The presence of sodium hydroxide is crucial for the reaction since it converts tellurols to tellurolate anions, avoiding side reactions at the alkene moiety.

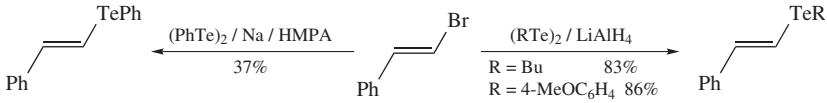


SCHEME 79

3. Preparation of vinylic tellurides via vinylic substitution reactions

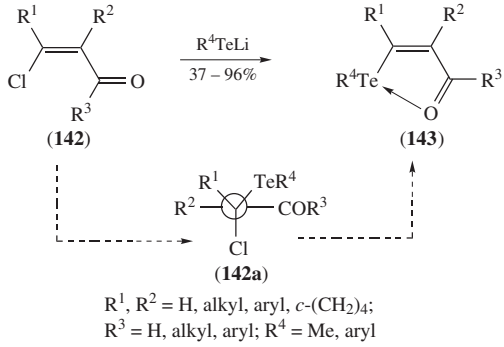
The vinylic substitution reactions by the lithium butyltellurolate anion are a useful alternative which agreeably complements the hydrotelluration of alkynes in the synthesis of vinylic tellurides. This methodology allows the preparation of tri- and tetrasubstituted vinylic tellurides which are otherwise more difficult to prepare. Another advantage of this reaction is the availability of the starting materials, since β-dicarbonyl compounds are used as precursors for the vinylic substrate (Figure 4).

The first report on a vinylic substitution promoted by a tellurium anion was reported by Comasseto and coworkers[54a], in which they describe the reaction of E-β-bromostyrene with the tellurium anion generated by the reduction of dibutyl ditelluride with lithium aluminum hydride. Subsequently, Ohe, Uemura and coworkers published an analogous reaction with ditelluride to tellurolate (Scheme 80)[79].



SCHEME 80

The reaction remained unexplored until the end of the 1990s when Minkin and coworkers published a systematic study on the preparation of functionalized vinylic tellurides by the substitution of activated vinylic halides **142**[77]. The reaction is tolerant to both aldehydes and ketones and furnishes selectively vinylic tellurides **143** in moderate to good yields (Scheme 81). The stereospecific character of the reaction could involve the two-step



SCHEME 81

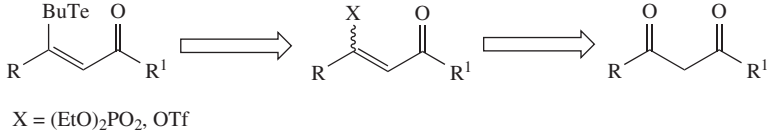
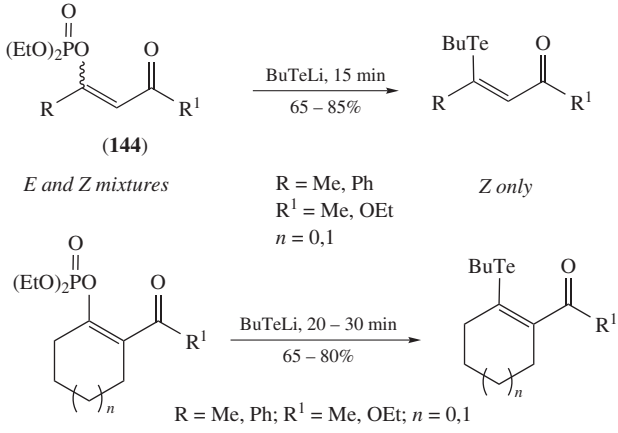


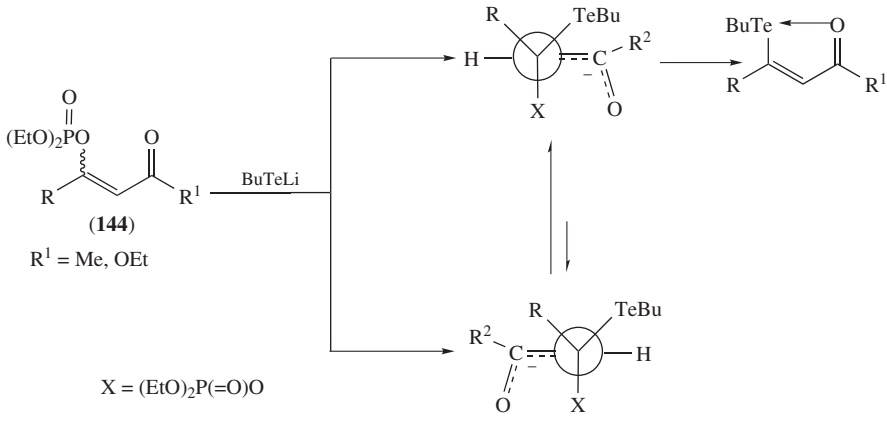
FIGURE 4

mechanism of nucleophilic vinylic addition–elimination. First the tellurolate anions add on the carbon–carbon double bond to give preferentially the conformer **142a**. Second, the elimination of chloride anions from **142a** gives the vinylic tellurides **143**. Both conformer **142a** and product **143** are highly stabilized by the intramolecular O–Te coordination.

In an extension of their previous studies, Comasseto and coworkers disclosed, in 1999, an approach for vinylic substitution by lithium butyltellurolate. This approach consists of the reaction of enol phosphates **144** instead of vinyl halides[80]. The advantages of this method are the easy availability of β-dicarbonyl compounds, which are the precursors for the enol phosphates, and the possibility to obtain a single isomer of vinylic telluride starting from a mixture of *E* and *Z* isomers of the enol phosphate (Scheme 82). The reaction is believed to proceed by an addition–elimination mechanism, since a tellurium–oxygen interaction is observed by X-ray, Raman and IR analyses (Scheme 83)[81].



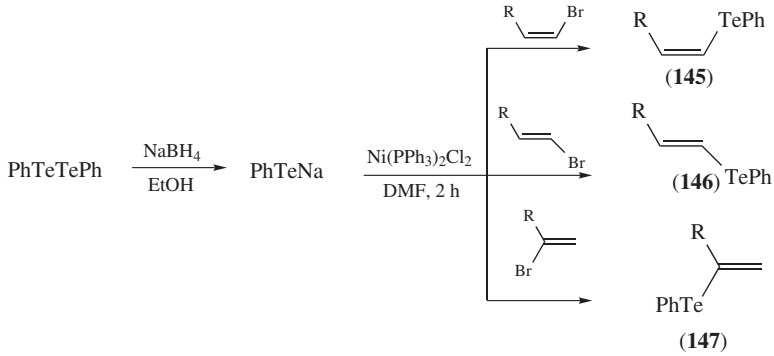
SCHEME 82



SCHEME 83

Additional studies on the reaction revealed that the organic moiety attached to tellurium can be varied, thus several different organolithium reagents can be used to generate lithium tellurolate, showing that the reaction is general for a variety of organyltellurolates[82]. Furthermore, the nature of the leaving group was examined. Performing the reaction of lithium butyltellurolate with enol phosphate, tosylate, triflate and acetate afforded the desired product in similar yields and within the same reaction times. In all cases, only *Z*-vinylic tellurides were obtained.

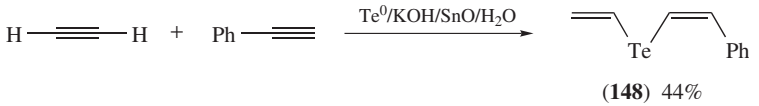
In 2008, Silveira and coworkers reported a novel carbon–tellurium bond formation reaction via $Ni(PPh_3)_2Cl_2$-catalyzed tellurolate substitution of vinyl halides (Scheme 84)[83]. The reaction was carried out by cleaving the ditellurides using $NaBH_4$ in ethanol, followed by addition of DMF (the removal of ethanol was not necessary), the vinylic halide and the catalyst (5 mol%). After that, the reaction mixture was heated at 110 °C for 2 h. The generality and synthetic usefulness of this method has been demonstrated in the efficient synthesis of the *E*-, *Z*- and *gem*-vinylic tellurides **145**–**147**, in all cases, as a single isomer.



SCHEME 84

4. Preparation of vinylic tellurides from elemental tellurium with the KOH/SnO/H_2O system

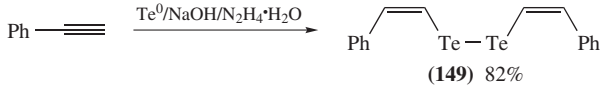
Elemental tellurium is useful for the preparation of unsymmetrical divinyl tellurides by reaction with the KOH/SnO/H_2O system[84]. The reaction is conducted in the presence of both acetylene precursors in a one-pot procedure and in a single step. For instance, when Te, acetylene and phenylacetylene react under these conditions, *Z*-styryl vinyl telluride **148** is synthesized in a moderate yield (Scheme 85).



SCHEME 85

5. Preparation of vinylic tellurides from elemental tellurium, alkynes and NaOH/$N_2H_4 \cdot H_2O$ system

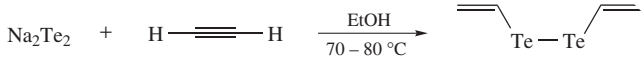
The reduction of elemental tellurium with hydrazine under basic conditions conveniently generates metal ditelluride[84]. The reaction whith Na_2Te_2, prepared under these conditions, and phenylacetylene leads to the preparation of *Z*,*Z*-distyryl ditellurides **149** in 82% yield (Scheme 86).



(149) 82%

SCHEME 86

Accordingly, this procedure can be applied for the preparation of divinyl ditelluride **150**, although in low yields, due to the instability of the product. It is worth noting that ethanol is added to the reaction mixture, which is heated at 70–80 °C (Scheme 87).



(150) 24%

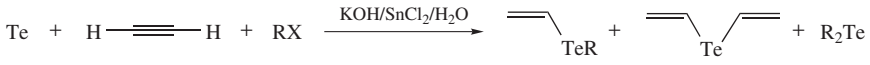
SCHEME 87

6. Preparation of vinylic tellurides from elemental tellurium, alkynes and alkyl halides

A convenient method for the preparation of vinylic tellurides by the direct reaction between elemental tellurium, acetylene and alkyl halides has been described. The reaction is performed in the presence of the strongly basic and strongly reducing system $KOH/SnCl_2/H_2O$, according to equation 1[85].

$$Te^0 + 6\,KOH + SnCl_2 \longrightarrow K_2Te + 2\,KCl + K_2SnO_3 + 3\,H_2O \qquad (1)$$

The authors affirm that the nucleophilic tellurium species generated reacts initially with the acetylene to give a vinyl tellurium anion, which further reacts with the alkyl halide to afford the alkylvinyl tellurides **151**. When alkyl iodides were employed, the yields of the alkylvinyl telluride decreased at the expense of the dialkyl telluride which was the major product observed. The major drawback of this methodology is the formation of a considerable amount of divinyltelluride **152** and dialkyltellurides **153** as by-products (Scheme 88).



(151) 20 – 70% **(152)** **(153)**

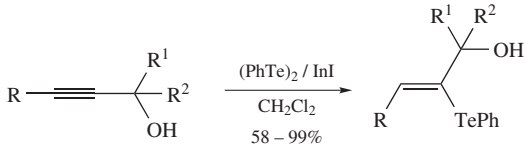
R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu, X = Cl, Br, I

SCHEME 88

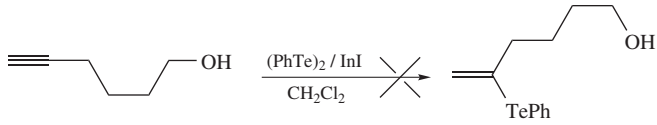
E. Miscellaneous

1. Preparation of vinylic tellurides via indium tellurolate

We have described a rigorous chemo-, regio- and stereoselective protocol for the hydrotelluration of several propargyl alcohol derivatives using an indium(III) tellurolate[86]. The tellurium nucleophile is readily generated by the reaction of In(I) iodide with $(PhTe)_2$ in dichloromethane through an oxidative insertion of indium monoiodide to the Te−Te bond. The reaction of the indium tellurolate, generated *in situ*, with a range of propargyl alcohols furnishes Markovnikov adducts in good to excellent yields (Scheme 89). The reaction is efficient for a series of substituted substrates at R, R^1 and R^2 positions. However, when longer-chain alcohols were employed, no product was obtained (Scheme 89).



R = H, Bu, SePh, BuC≡C; R^1 = H, Et, Ph, Me; R^2 = H, Me, Et



SCHEME 89

We believe that the reaction occurs through the coordination of the propargyl alcohol hydroxyl group with indium tellurolate, indicating that this could be the key to the high chemo-, regio- and stereoselectivity obtained in the addition of a tellurium moiety to an alkyne. This observation can be used to explain why longer-chain alcohols did not react under these conditions (Figure 5).

2. Vinylic tellurides from acetylenic tellurides

Acetylenic tellurides **154** are suitable substrates for the preparation of vinylic tellurides. Several different reducing agents were tested to reduce alkyne to alkene, leading to vinylic tellurides. However, many reagents, such as $LiAlH_4$ and hydrazine, fail to be successful in

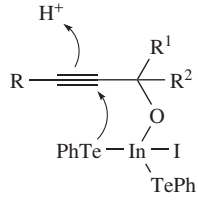
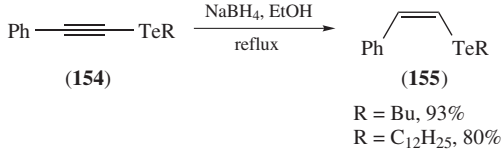


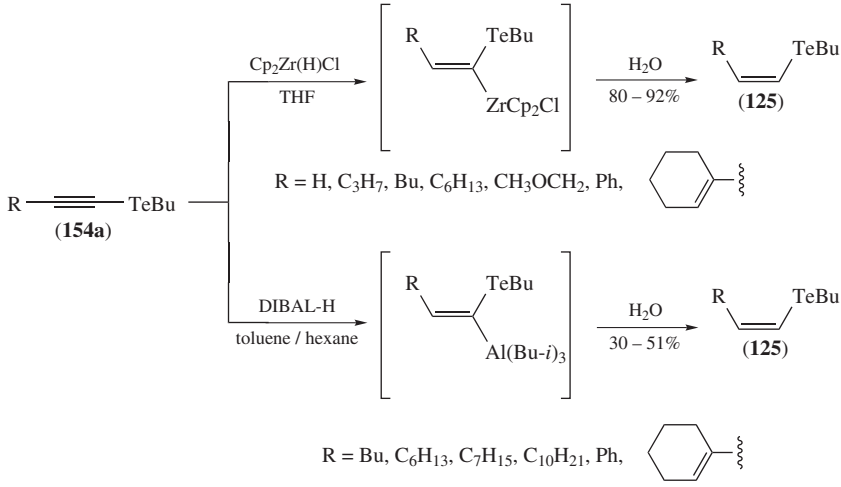
FIGURE 5

this transformation, since only terminal alkynes and the corresponding ditellurides were obtained. The first successful method reported was the reduction of alkynyl tellurides **154** with sodium borohydride in ethanol, under reflux[87]. The reaction is believed to form acetylide and tellurolate anions by the cleavage of the $C_{sp}-Te$ bond. Next, the tellurolate attacks the triple bond in a hydrotelluration reaction to generate vinylic tellurides **155** in good yields (Scheme 90).



SCHEME 90

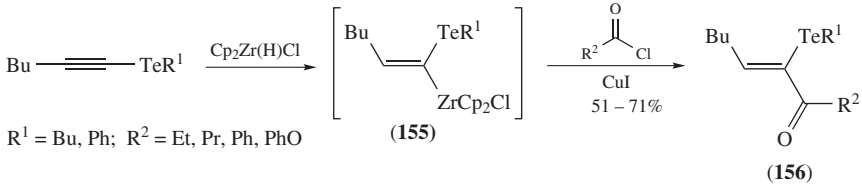
Another approach to the reduction of acetylenic tellurides **154a** to vinylic tellurides **125** is a hydrometallation reaction followed by acidic quenching. The most commonly used metals are aluminum[27] and zirconium[15], due to their ability to reduce the triple bond without cleaving the very labile $C_{sp}-Te$ bond. Comparatively, hydrozirconation offers advantages over hydroalumination reactions, mainly because it is performed at room temperature and higher yields are significantly obtained. On the other hand, the use of DIBAL-H as a reducing agent results in a partial removal of the organotellurium moiety from the acetylenic tellurides **154a**, explaining the lower yields of vinylic tellurides **125** (Scheme 91).



SCHEME 91

In another example of hydrozirconation of acetylenic tellurides, the vinylzirconium intermediates **155** are trapped with acyl chlorides to give a range of *Z*-α-organotelluro-α,β-unsaturated carbonyl compounds **156** (Scheme 92)[88]. Regio- and stereocontrol of the

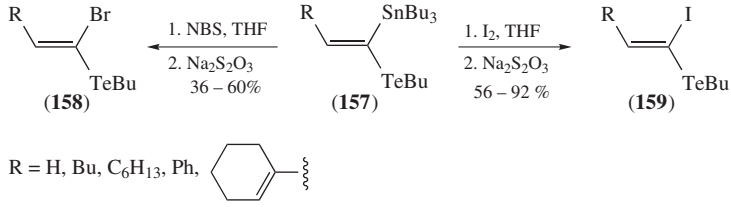
reaction is well defined and only the *Z*-products are obtained. The reaction is assumed to pass though a Zr–Cu transmetallation with retention of the configuration at carbon[89]. Besides CuI, other copper salts, such as CuBr, CuCN and $CuBr.SMe_2$, gave similar results.



SCHEME 92

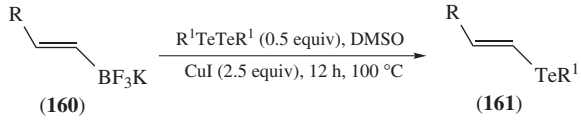
3. Preparation of α-halo vinylic tellurides from ketene stannyl(telluro) ether

Halogen functionalized vinylic tellurides have a great potential for organic synthesis. Their preparation has been described to occur through a Sn–halogen exchange reaction in mixed ketene stannyl(telluro) ether **157**[19]. The reaction was carried out under mild conditions and the iodo derivatives were obtained upon treatment of the starting material **157** with 2.15 equivalents of iodine in THF (Scheme 93). Other solvents and different amounts of iodine resulted either in lower yields or partial isomerization of the double bond. Similarly, brominolysis was performed with NBS in THF; however, a mixture of products was obtained when Br_2 was used instead of NBS. Total retention of the double bond configuration was observed here, although the brominated products **158** were obtained in lower yields when compared to iodinolysis product **159** (Scheme 93).



SCHEME 93

Braga and coworkers reported an efficient synthesis of *E*- vinyl tellurides **161** from potassium vinyltrifluoroborates **160** using copper(I) iodide as a catalyst (Scheme 94)[90]. The reaction of diphenyl ditelluride with potassium (*E*)-styryltrifluoroborate in the presence of 5 mol% of CuI in DMSO gave (*E*)-phenyl styryl telluride in 78% yield. The scope of the reaction was examined using various substituted organotrifluoroborate salts and diorganyl ditelluride; the yields of the products were not as high upon reaction of potassium (*E*)-styryltrifluoroborate with diaryl ditellurides in the presence of 5 mol% of catalyst. In order to improve the product yields, the amount of catalyst was varied, but no change in product yields was observed for 2.5–10 mol% of the catalyst. However, the change of CuI to $CuCl_2$ gave slightly better results. Among the solvents examined, only DMF gave somewhat near the performance of DMSO. No reaction occurred in CH_2Cl_2, even though a long reaction time was used (24 h).



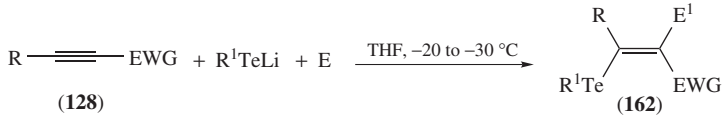
(**160**) (**161**)

R = C_6H_5, *p*-BrC_6H_4, *p*-MeC_6H_4, *n*-C_5H_{11}; R^1 = C_6H_5, *p*-ClC_6H_4, *p*-MeC_6H_4, *o*-MeC_6H_4, *o*-ClC_6H_4, *n*-C_4H_9

SCHEME 94

4. Preparation of vinylic tellurides via electrotelluration reactions

An approach to the synthesis of vinylic tellurides has been described by Marino and Nguyen[91]. This reaction involves the addition of a lithium tellurolate anion to alkynes **128** containing an electron-withdrawing group, followed by the trapping of the incipient vinyl anion with electrophiles E. Examples of eight different such reactions are shown in Table 5. This method leads to tri- and tetrasubstituted alkenes **162** bearing an organotellurium group (Scheme 95).



(**128**) (**162**)

EWG = esters, sulfones, sulfoxides; R^1 = Bu, Ph; E = $R^1R^2C{=}O$, Me_3SiCl; E^1 = $R^1R^2C(OH)$, Me_3Si.

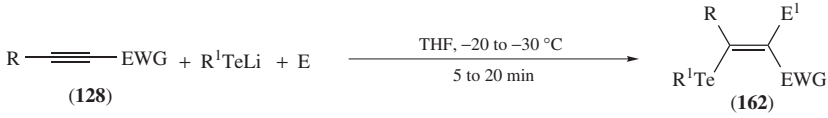
SCHEME 95

Initial tests of this reaction were performed with non-activated alkynes, and no trapping of benzaldehyde was achieved. Attention was turned to the more activated alkynes, such as alkynyl esters, sulfones and sulfoxides.

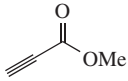
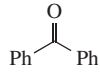
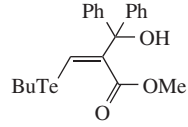
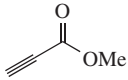
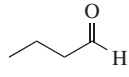
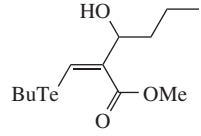
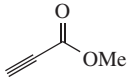
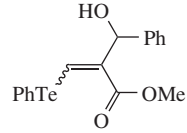
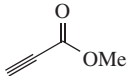
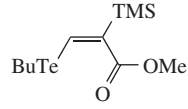
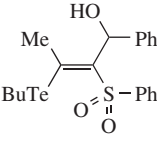
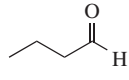
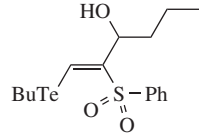
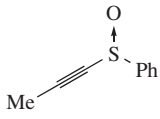
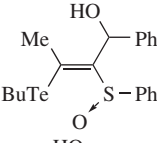
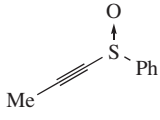
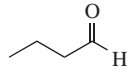
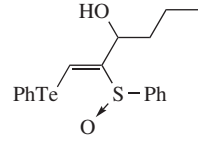
Several variations in the organic group attached to tellurium as well as the electrophile are tolerated. The authors observed that the aldehydes are very good electrophiles giving the products in very short reaction times (Table 5). Trimethylsilyl chloride was also employed as electrophile, which gave the vinylic tellurides, without any O-silylation product formation (Table 5, entry 4). The authors also described that the phenyl tellurolate is less reactive than the butyl tellurolate, allowing a *cis*/*trans* equilibration of the vinyl anion (Table 5, entry 3). Except for this case, all other examples with esters, sulfones and sulfoxides afforded the *Z*-vinylic telluride in good yields.

Upon the success of this first attempt at the electrotelluration reaction, the intramolecular version of this method was studied. The reaction is analogous to the intramolecular Baylis–Hillman reaction[92], with the advantage that the tellurium nucleophile is incorporated into the product after ring formation, and the product can then be further transformed into other functional groups. The reactions were performed mainly with lithium phenyltellurolate due to the fact that its products demonstrated higher stability than those of lithium butyltellurolate. The intramolecular electrotelluration was completed very quickly and the cyclized products were obtained in moderate to good yields (Table 6). Seven- and eight-membered rings were obtained in lower yields because the proton trapping of the vinyl anion intermediate was competitive with the intramolecular cyclization (Table 6, entries 5 and 6).

TABLE 5. Electrotelluration reaction

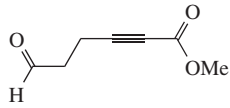
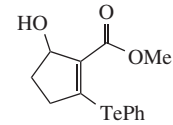
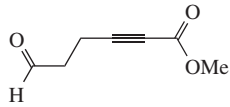
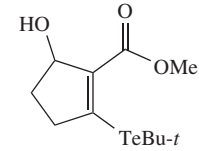
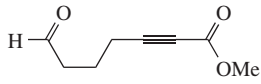
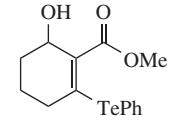
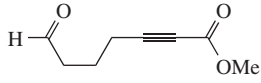
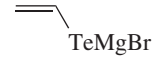
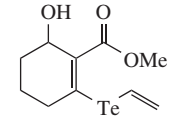
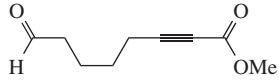
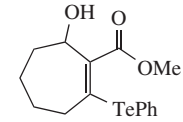
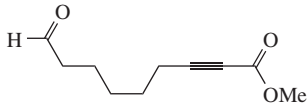
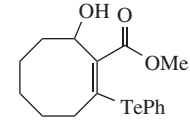


(**128**) (**162**)

Entry	Alkyne	Nucleophile	Electrophile (E)	Product	Yield (%)
1		BuTeLi			43
2		BuTeLi			46
3[a]		PhTeLi			84
4		BuTeLi	TMSCl		45
5		BuTeLi			69
6		BuTeLi			60
7		BuTeLi			65
8		PhTeLi			78

[a]A 1:13 ratio of *E*:*Z* isomers was obtained.

TABLE 6. Intramolecular electrotelluration

Entry	Alkyne	Nucleophile	Product	Yield (%)
1		PhTeLi		72
2		*t*-BuTeLi		51
3		PhTeLi		80
4				74
5		PhTeLi		41
6		PhTeLi		48

III. REACTIVITY OF VINYLIC TELLURIDES

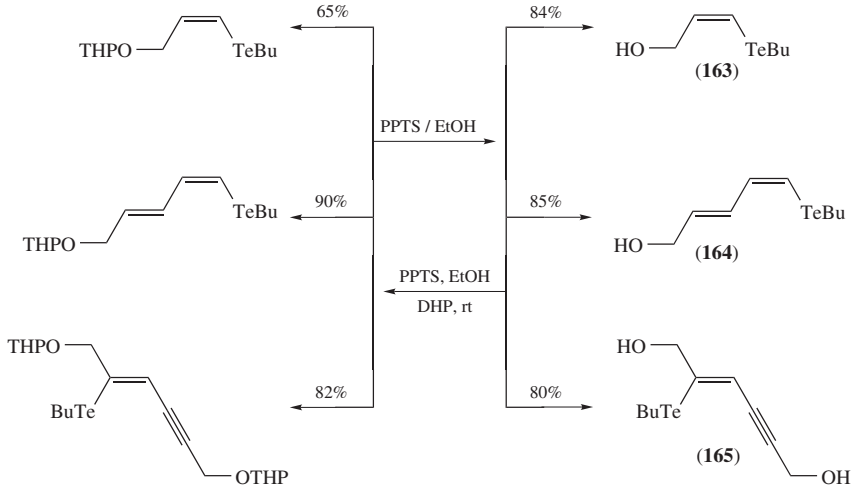
A. Stability of the Carbon–Tellurium Bond in Vinylic Tellurides

A significant paper was published by Rahmeier and Comasseto in 1997 that dealt with the stability of the carbon–tellurium bond in vinylic tellurides toward several different reagents frequently used in organic chemistry laboratories worldwide[93].

The authors studied both transmetallation reactions, which we will discuss in detail in the upcoming section, and the behavior of vinylic tellurides under several different conditions, such as the presence of acids, bases and oxidizing and reducing agents.

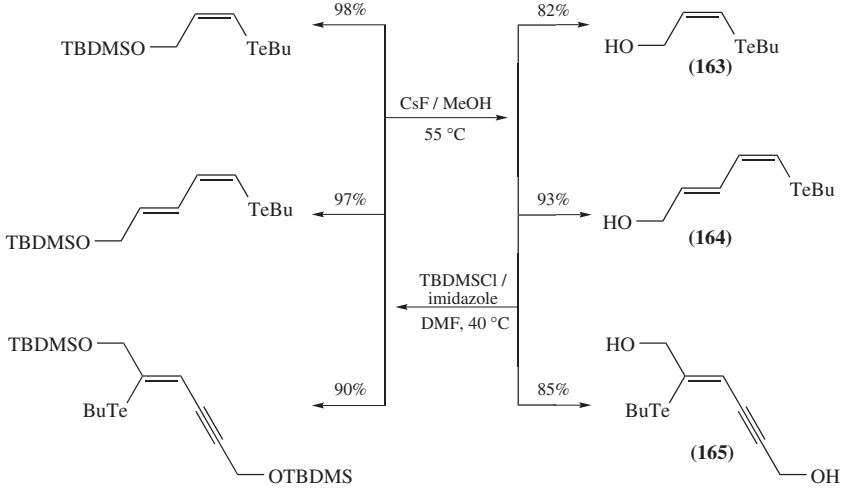
First, the stability of the C−Te bond was studied under protection/deprotection conditions. Hence, three different vinylic tellurides, **163, 164** and **165**, containing a free hydroxyl group were protected as their THP ether under acid catalysis of PPTS (Scheme 96). The hydrolysis of the THP ether regenerated the vinylic tellurides with free hydroxyl groups and was performed under acidic conditions with PPTS/EtOH at 50 °C (Scheme 96). In the protection or deprotection reaction, neither removal of the

tellurium group nor isomerization of the double bond was observed. When the reaction temperature was higher than 55 °C, dibutyl ditelluride was formed as a by-product.



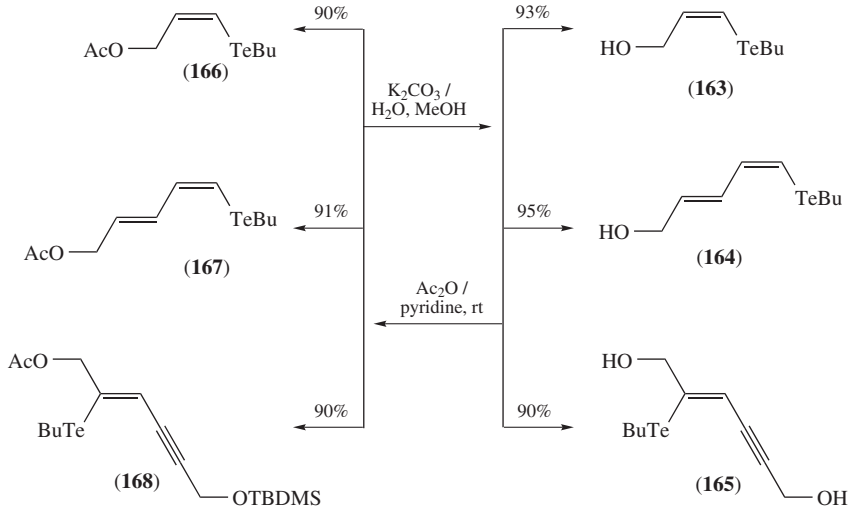
SCHEME 96

When TBDMS was used as a protecting group, under a basic catalysis of imidazole, high yields were obtained. Conversely, the deprotection of the corresponding tellurides with free OH groups was easily achieved by treatment with cesium fluoride in MeOH at 55 °C (Scheme 97). The C−Te bond has also proven to be stable under these reaction conditions.



SCHEME 97

Acetylation of vinylic tellurides was performed with acetic anhydride in pyridine giving the acetylated products, **166, 167** and **168**, in high yields. The corresponding hydrolysis of the acetylated products was performed under basic conditions, regenerating the vinylic tellurides in excellent yields (Scheme 98).



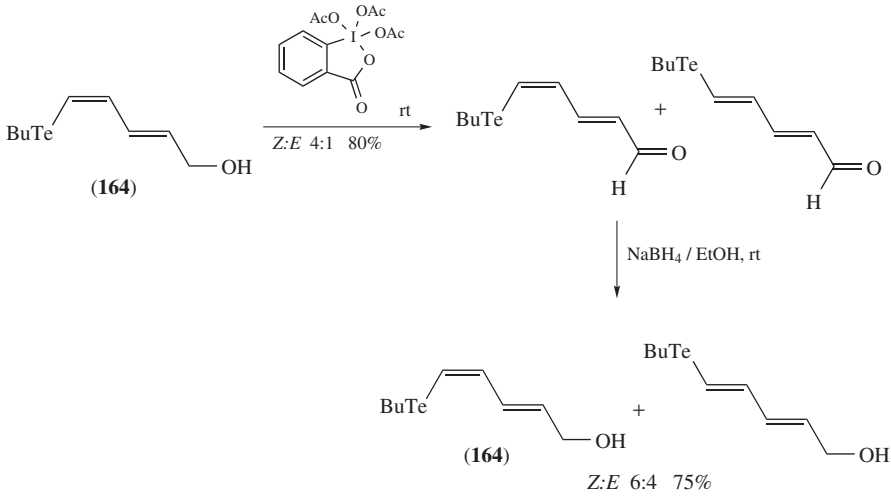
SCHEME 98

The studies have been further extended toward oxidizing and reducing conditions. In fact, it has been observed that telluride **164** was oxidized to the corresponding unsaturated aldehyde in 80% yield by treatment with Dess–Martin periodinane. However, the isomerization of the telluride carbon–carbon double bond took place and a 4:1 *Z*:*E* mixture was isolated. The reduction of this mixture with $NaBH_4$ resulted in vinylic telluride with a *Z*:*E* ratio of 6:4 (Scheme 99). On the other hand, the β-butyltellanyl-enones **169** were chemoselectively reduced with $NaBH_4$/MeOH, $NaBH_4/CeCl_3 \cdot 7H_2O$/MeOH and DIBAL-H systems to the corresponding allylic alcohols **170** with total retention of the *Z* stereochemistry (Scheme 100)[94].

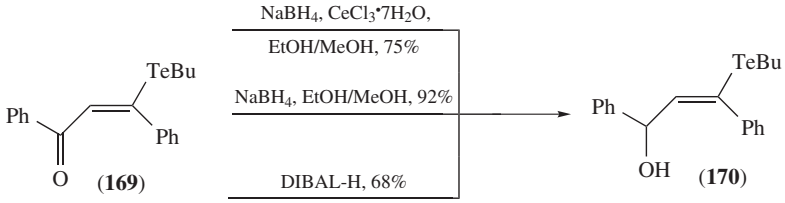
The hydrolysis of vinylic telluride **171** under several different conditions resulted in the formation of unsaturated aldehyde in good yield. However, under all conditions employed, isomerization of the double bond was observed. The highest *Z*:*E* ratio (8 to 1) was obtained when SiO_2 in hexane was employed (Scheme 101).

B. Transmetallation Reactions

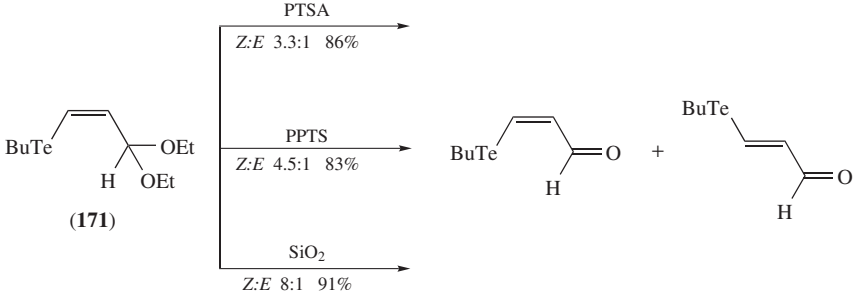
One of the most powerful applications of vinylic tellurides is the ability to undergo tellurium–metal exchange reactions with several different commonly used, commercially available or easily prepared organometallic reagents. This tellurium–metal exchange reaction proceeds very easily, giving vinyl organometallics, which are very useful intermediates from the synthetic point of view. In addition to the ease of the exchange reaction, one unique feature of vinylic tellurides is that they give Z-vinyl organometallics by a simple hydrotelluration–transmetallation sequence (Figure 6).



SCHEME 99



SCHEME 100



SCHEME 101

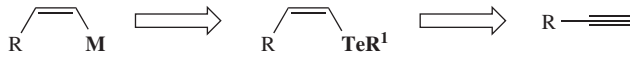


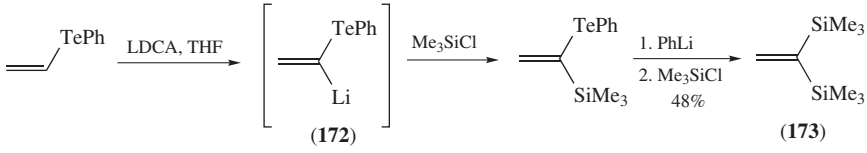
FIGURE 6

In this section we will discuss the nuances of the tellurium–metal exchange reactions, emphasizing their scope and generality for useful transformations in organic synthesis.

1. Tellurium/lithium exchange reactions

The tellurium–lithium exchange is a very attractive transformation of vinylic tellurides, since it affords the corresponding vinyl lithium species, which react with a wide range of electrophiles, providing functionalized alkenes with a complete retention of the stereochemistry of the starting telluride.

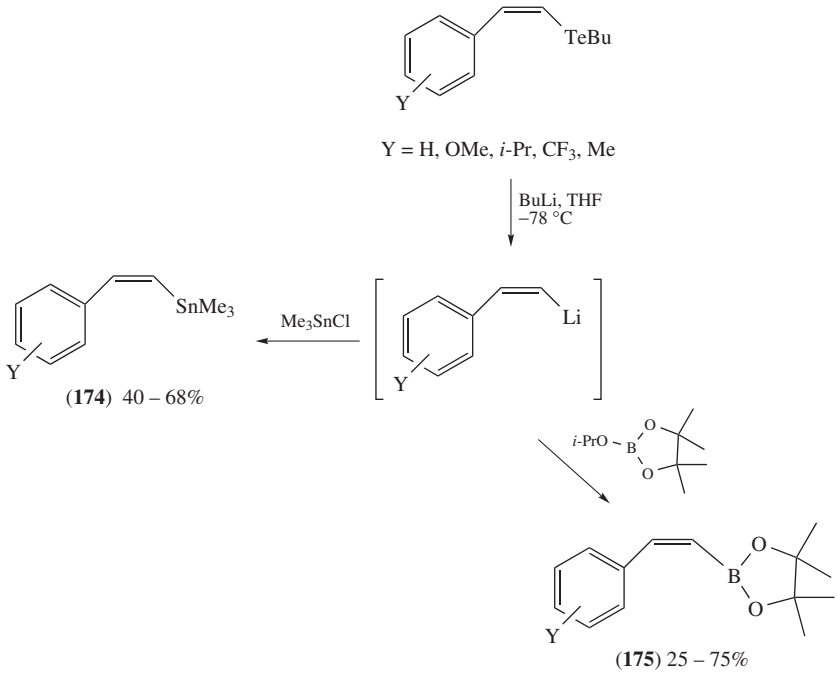
A significant study on the tellurium–lithium exchange was carried out by Kauffmann[95], in an extension of a previous finding of Seebach and Beck[96], in which organic tellurides were transformed into their lithium analogues by treatment with an organolithium reagent. The reaction of lithium intermediates **172** with trimethylsilyl chloride afforded the silylated product **173** in 48% yield (Scheme 102). In a closely related investigation, the *Z*-vinyl tellurides were transmetallated with *n*-butyllithium to the corresponding *Z*-vinyl lithium, which were subsequently quenched with trimethyltin chloride or isopropoxypinacolborate affording the *Z*-vinylstannanes **174** in 40–68% yields or Z-vinylborates **175** in 25–75% yields without any isomerization of the double bond (Scheme 103)[97].



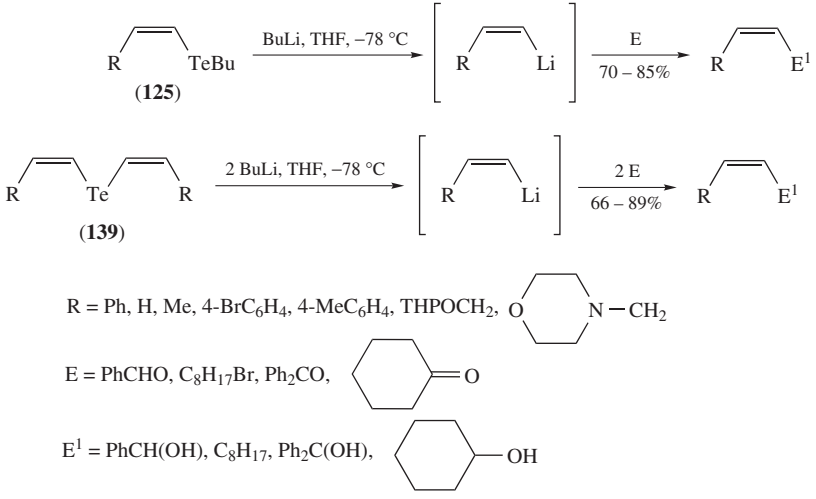
SCHEME 102

A few years later, Comasseto and coworkers studied in detail the transmetallation of *Z*-vinylic **125** and *Z*,*Z*-bis-vinylic tellurides **139** with BuLi[98]. The reaction of the vinyllithium intermediates with several electrophiles, such as aldehydes, ketones and alkyl bromides, was accomplished in good yields, leading to functionalized *Z*-alkenes with a complete retention of the original double bond geometry (Scheme 104). Moreover, when *Z*,*Z*-bis-vinylic tellurides **139** were employed, two equivalents of vinyllithium were formed. The authors observed that when an aryl group instead of a butyl group was attached to the tellurium atom, a complex mixture of products was obtained. This can be explained by the fact that BuLi can attack two sites (the C_{vinyl}–Te and C_{aryl}–Te bonds), giving a mixture of lithium intermediates and, consequently, affording a mixture of products (Figure 7).

After these findings, many other classes of vinylic tellurides have been used to generate vinyllithium intermediates with a defined double bond geometry. Conjugated vinylic tellurides, such as those containing an enyne moiety **110**, were successfully transmetallated with BuLi, yielding enynes free of tellurium **176**[62a]. The reaction occurred with total retention of the double bond geometry, even when the temperature was raised from −78 °C to room temperature. This is noteworthy since the halogen–lithium exchange in



SCHEME 103



SCHEME 104

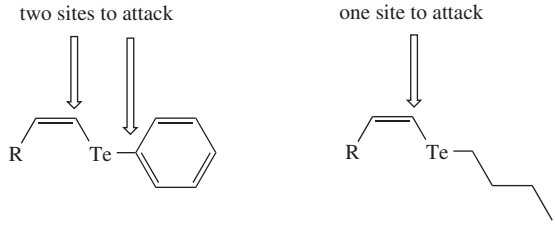
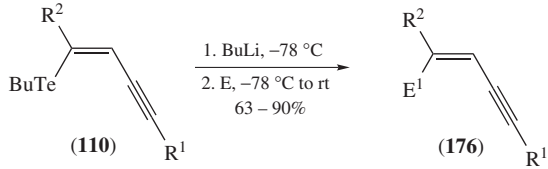


FIGURE 7

conjugated systems, such as enynyl bromides and butadienyl bromides, occurs with a loss of the configuration of the double bond (Scheme 105)[99]. The enynyllithium intermediates obtained by this method successfully react with benzaldehyde, dimethyl sulfate and water in high yields and very short reaction times (*ca* 30 min).

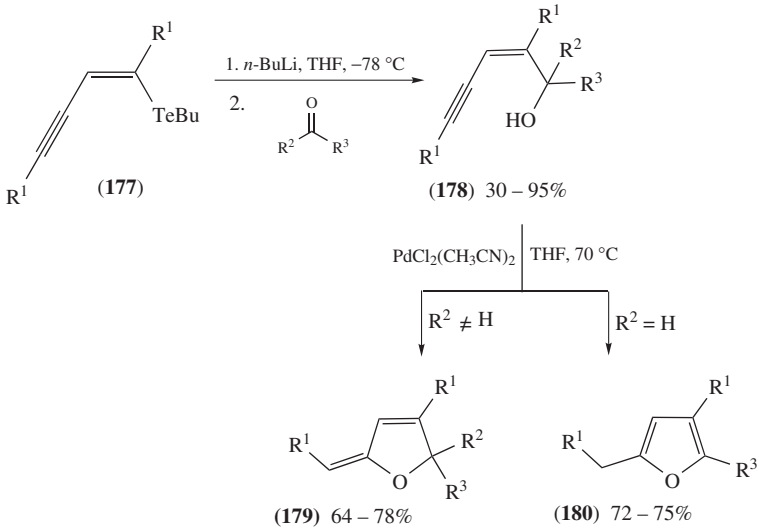


R^1, R^2 = Ph, 4-MeC_6H_4, Me; E = H_2O, Me_2SO_4, PhCHO;
E^1 = H, Me, PhCH(OH)

SCHEME 105

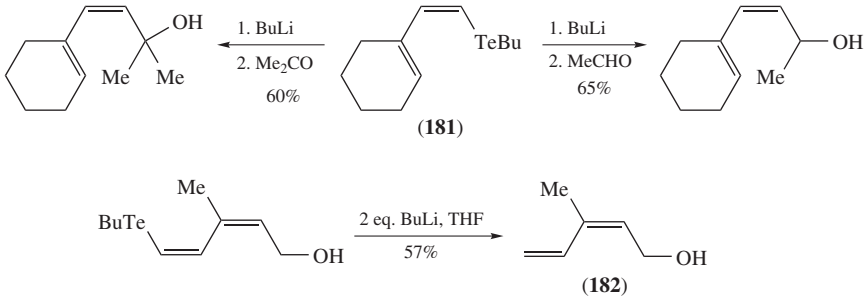
Very recently we described an effective application of this Te/Li exchange reaction in the synthesis of dihydrofurans **179** and furans **180**[100]. In this study, we prepared various *Z*-enynols **178** via reaction of the tellurium–lithium exchange of **177** and the reaction of enynyllithium intermediates with aldehydes and ketones. A variety of aryl and alkyl groups directly bonded to the carbonyl group were successfully used as electrophiles. The enynols **178**, bearing a hydroxyl group, underwent highly selective intramolecular cyclizations when treated with palladium salt, affording 2,5-dihydrofurans **179** or furans **180**. The results demonstrated that the selectivity in the cyclization was significantly influenced by the presence of a substituent in the allylic position. *Z*-Enynols having a hydrogen at the allylic position gave 2,5-dihydrofurans **179** while *Z*-enynols without hydrogen in this position gave furan derivatives **180** (Scheme 106).

The conjugated diene system bearing a tellurium group deserves particular attention in the transmetallation reactions, since it is an important structural feature of many natural products, such as insect pheromones[101]. This system is a highly valuable intermediate in organic synthesis, especially as a substrate for the Diels–Alder reaction[102]. The stereodefined functionalized dienes can be prepared by means of a Te–Li exchange of 1-butyltelluro-1,3-butadiene **181**[62b]. The transmetallation occurs smoothly at low temperatures and the trapping of lithium intermediates by electrophiles, such as acetone and acetaldehyde, gives *Z*-allylic alcohols in good yields (Scheme 107). The reaction with water as a proton source readily furnishes the product free of the tellurium group **182** in moderate yield (Scheme 107).



$R^1 = C_6H_5$, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, C_6H_{13}; R^2 = H, Me, Et; R^3 = Ar, Me, Et, *i*-Pr

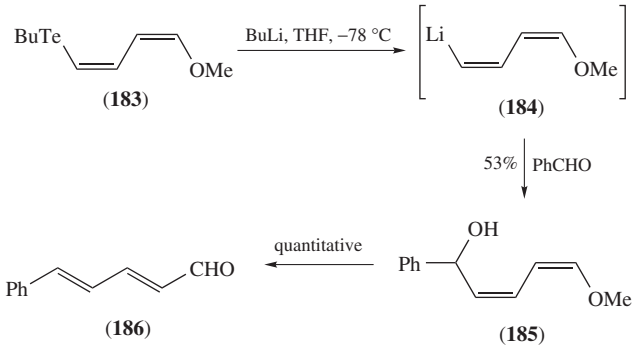
SCHEME 106



SCHEME 107

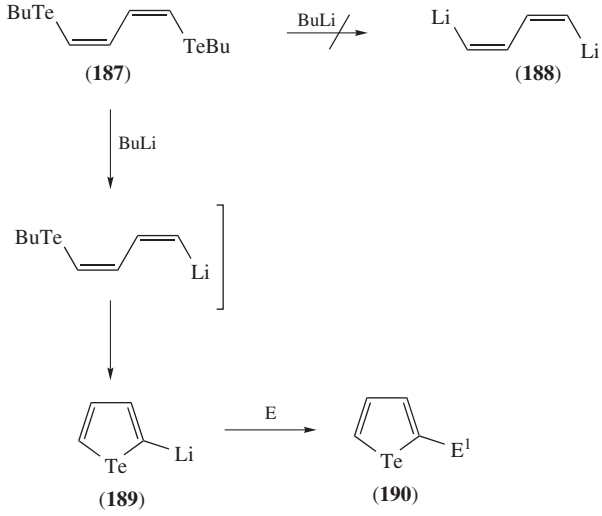
The reaction of (1*Z*, 3*Z*)-1-butyltelluro-4-methoxy-1,3-butadiene **183** with BuLi at −78 °C generates the vinyllithium intermediate **184**, which reacts with benzaldehyde to afford allylic alcohol **185** in 53% yield. The product is spontaneously and quantitatively converted into the 5-phenylpentadienal **186** with an *E*-configuration of the two double bonds (Scheme 108).

Furthermore, the reaction of butyllithium with 1,4-bis(butyltelluro)-1,3-butadiene **187** did not afford the 1,4-dilithium species **188** as expected, rather, a ring closure to form substituted tellurophene **189** was observed[62b]. After the first tellurium–lithium exchange occurs, and before the second exchange takes place, the tellurium atom is intramolecularly attacked by the vinyl anion, and the aromatic heterocycle is formed. A second equivalent of butyllithium is assumed to deprotonate the α-position of tellurophene. This fact is



SCHEME 108

supported by the addition of benzaldehyde to the reaction mixture, affording 2-substituted tellurophene **190** in 60% yield (Scheme 109).

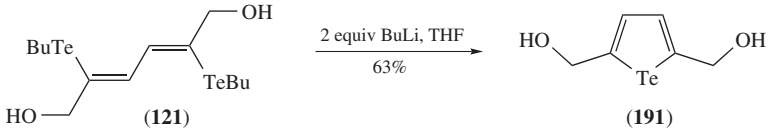


E = H_2O, PhCHO, MeCHO; E^1 = H, PhCH(OH), MeCH(OH)

SCHEME 109

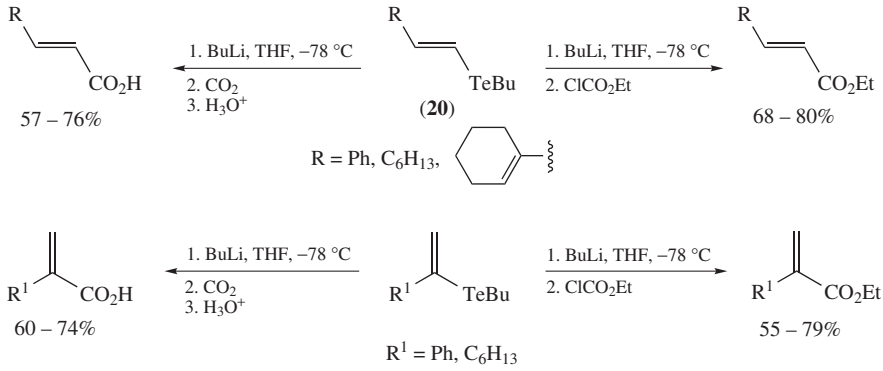
In addition, 2,5-disubstituted tellurophene **191** was prepared by the reaction of bis(butyltelluro)-1,3-butadiene **121** with butyllithium in THF in 63% yield (Scheme 110).

The *E*-isomers of vinylic tellurides **20** undergo a tellurium–lithium exchange in the same manner as the *Z*-isomers. The synthetic potential of such a reaction was tested in the preparation of α,β-unsaturated acids and esters, which were accomplished in good yields by successive transmetallations and trapping of the incipient vinyl anion. Carboxylic acids were obtained by capture of the anion with CO_2 and acidic quenching in



SCHEME 110

yields ranging from 55 to 79%. The parent esters were achieved in comparable yields (60–80%) by a similar protocol, just by changing the trapping agent to ethyl chloroformate (Scheme 111)[13b].

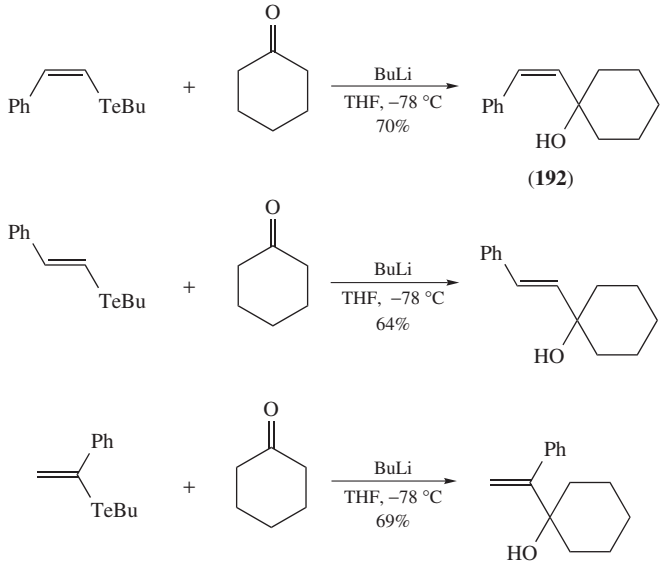


SCHEME 111

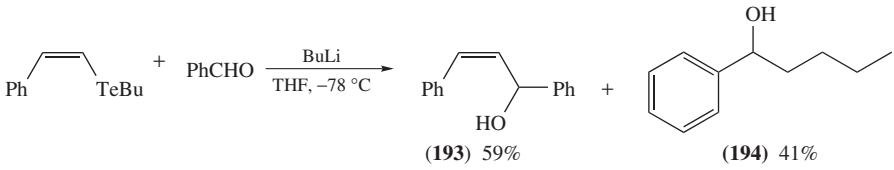
A very remarkable report on the reactivity of vinylic tellurides toward butyllithium describes the intermolecular competition between the tellurium–lithium exchange and the direct addition of the organolithium reagent to carbonyl compounds[103]. For this purpose, 1 equivalent of BuLi was added at −78 °C to a solution of equal amounts of vinylic telluride and the carbonyl compound in THF. This study showed a remarkable reactivity profile for vinylic tellurides in comparison to carbonyl compounds and was useful to predict the reactivity of such systems in an intramolecular version of this reaction. The results of these experiments showed that when the carbonyl compound was a ketone, the reaction of *n*-BuLi took place exclusively at the vinylic telluride, giving the corresponding vinyl lithium intermediate, which further reacted with cyclohexanone to afford allylic alcohol **192** in good isolated yields. The three different isomeric tellurides showed the same behavior and furnished the product in similar yields (Scheme 112).

The same authors observed that when benzaldehyde is employed instead of cyclohexanone, a competition between transmetallation and addition reactions is observed, since the products **193** and **194** were isolated. However, even when the more reactive aldehyde was used, the Te–Li exchange and further attack of the vinylic intermediate on benzaldehyde was the predominant pathway, since the major product was the allylic alcohol (Scheme 113).

On the other hand, when ketene telluroacetal **195** was treated under same reaction conditions described in Scheme 94, the Te–Li exchange occurred exclusively at one of the butyltelluro moieties. The reaction of the vinyl anion intermediate with carbonyl



SCHEME 112

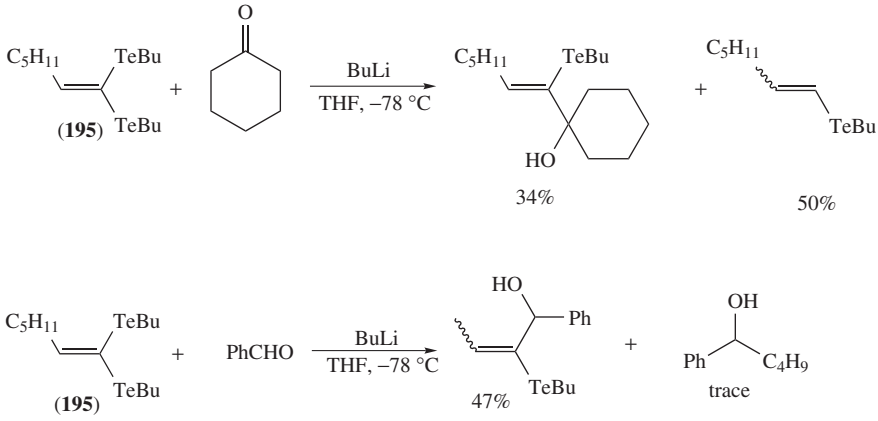


SCHEME 113

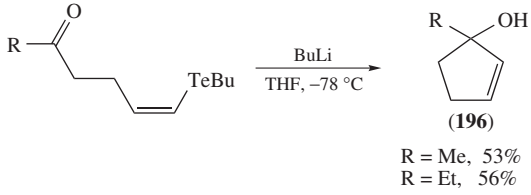
compounds takes place, but the products are isolated in low yields. This is probably due to the lower reactivity of the vinyl anion, as it is partially stabilized by the adjacent tellurium atom (Scheme 114)[103].

Taking advantage of the higher reactivity of the C−Te bond in the presence of a carbonyl functional group, an intramolecular reaction was performed and the cyclopentenols **196** were obtained in moderate yields (Scheme 115)[103]. On the other hand, the presence of a γ-hydroxyl group in the structure of *Z*-hydroxy vinylic telluride **197** produced, by reaction with 2 equivalents of *n*-butyllithium, the *Z* chiral-1,4-C,O-dianions **198**, which on reaction with carbon dioxide gave the corresponding butenolide **199** in 96% *e.e* and 51% yield (Scheme 116)[104].

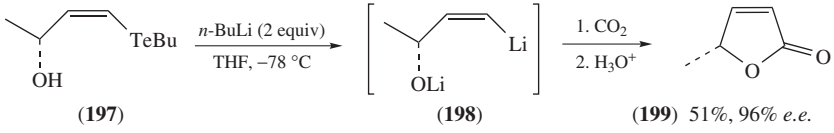
Reactions of ketene telluro(seleno) acetal **200** and telluro(thio) acetals with *n*-BuLi showed a regioselective removal of the organotellurium moiety and formation of functionalized α-chalcogenide vinyllithium **201**. The posterior reaction of **201** with several different electrophiles, such as water, DMF, ethyl chloroformate, carbon dioxide and aldehydes, afforded, respectively, the vinylic selenides, unsaturated aldehyde, ester, acid and allylic alcohol in good yields with total retention of the double bond geometry



SCHEME 114



SCHEME 115



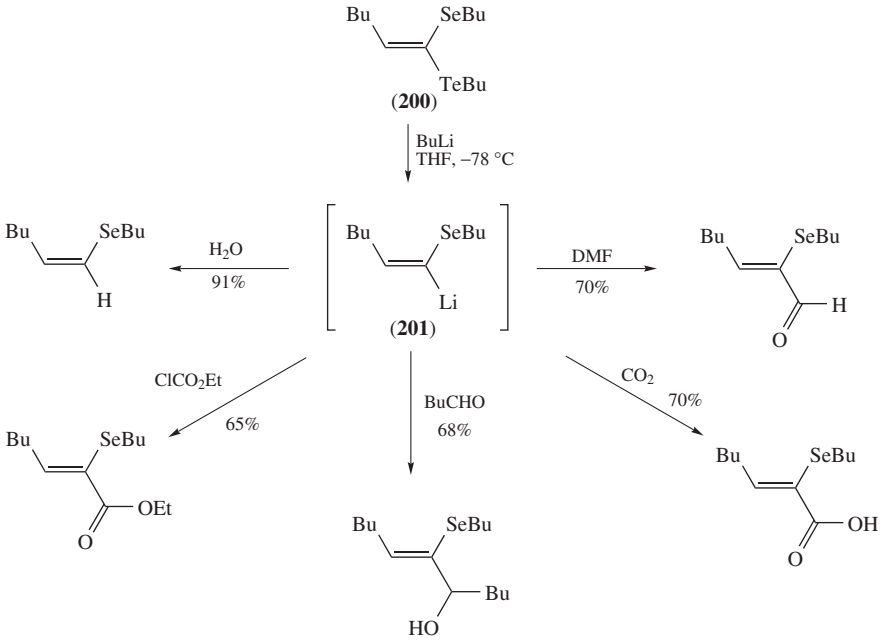
SCHEME 116

(Scheme 117)[16]. It is important to note that the Te–Li exchange occurs much faster than the Se–Li exchange[105].

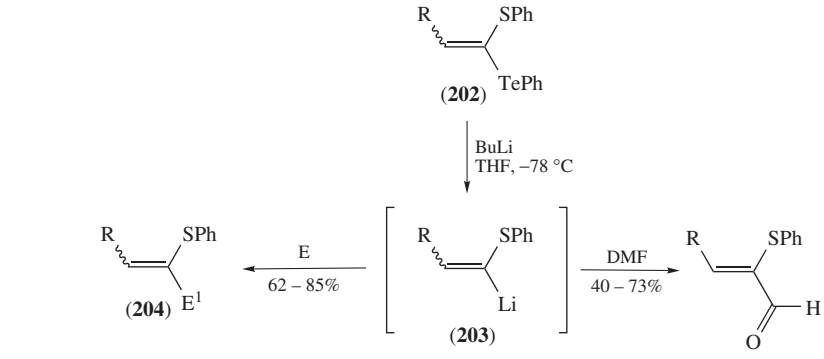
Similarly, ketene telluro(thio)acetals **202** undergo the tellurium–lithium exchange, leading to the α-thiovinyllithium intermediates **203**, which react with water, benzaldehyde and methyl iodide to give the functionalized vinylic sulfides **204** in good yields[46]. The reaction with DMF as the electrophile surprisingly affords almost only one isomer of the product, even if a mixture of *Z* and *E* isomers of the starting material is used (Scheme 118).

2. Tellurium/copper exchange reactions

The tellurium–copper exchange is probably the most important and promising of the tellurium exchange reactions, since it affords vinyl copper reagents of a *Z* configuration,



SCHEME 117



R = Ph, 4-ClC_6H_4, Pr; E = PhCHO, H_2O, MeI; E^1 = PhCH(OH), H, Me

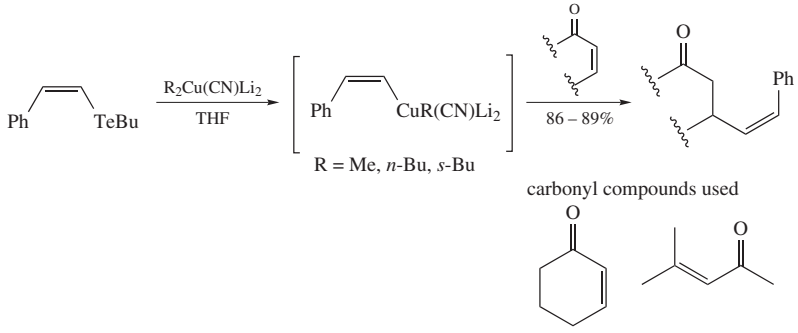
SCHEME 118

which can react with a variety of electrophiles and with complete retention of the double bond geometry.

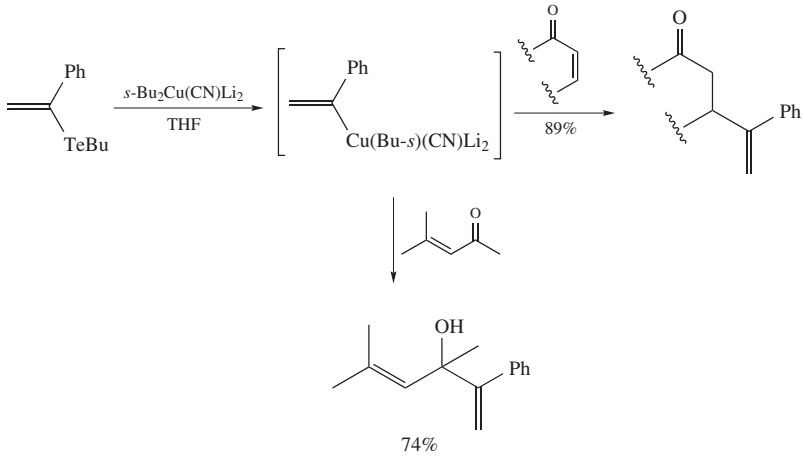
The landmark paper on the tellurium–copper exchange was published by Comasseto and Berriel in 1990, and opened outstanding branches in the field of organotellurium chemistry[106]. The discovery of this methodology to generate *Z*-vinyl copper reagents by

a simple hydrotelluration–tellurium exchange sequence has allowed the exploration of several features of tellurium chemistry that had not been envisaged before.

These reactive alkenyl copper reagents have been successfully employed in conjugate additions to enones, leading to functionalized carbonyl compounds in high yields. The reaction is performed by adding vinylic telluride to the higher order cyanocuprate at room temperature. The ligand exchange reaction between vinylic telluride and the higher order cuprate occurs, followed by the addition of enone to the mixture at $-78\,^{\circ}C$. The nature of the R groups at the cuprate is important for the outcome of the reaction. No significant difference in the generation of the mixed cuprate was observed when an Me or *n*-Bu group was used, but sometimes competition between the vinyl and butyl transfers can be observed (Scheme 119). However, when more crowded *s*-Bu or sterically hindered enones were employed, the 1,2-addition reaction took place instead of the 1,4-addition (Scheme 120). It is important to point out that if a phenyl, instead of a butyl group, is linked to tellurium at the vinylic telluride, a change in the selectivity of the transfer reaction of the phenyl group over the vinyl is observed.

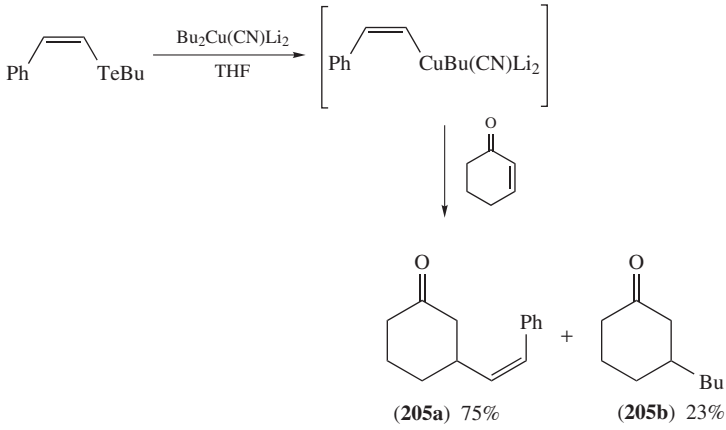


SCHEME 119



SCHEME 120

Later studies by the same group have revealed that the reaction has been carried out with a wide range of enones using several different vinylic tellurides as precursors for the mixed cuprates.[55a, 107] Detailed examination of the reaction conditions indicated that the butyl group was not the best residual ligand of the cuprate, since it led to a mixture of vinyl and butyl transfer products **205a** and **205b** (Scheme 121). The better results were achieved when the cuprate was formed from methyl, 2-thienyl (2-Thi) or imidazoyl (Imid) cuprates, all of which exclusively gave the vinyl transfer product **205a**. The cuprates most used were $Me_2Cu(CN)Li_2$ and $Bu(2\text{-Thi})Cu(CN)Li_2$.



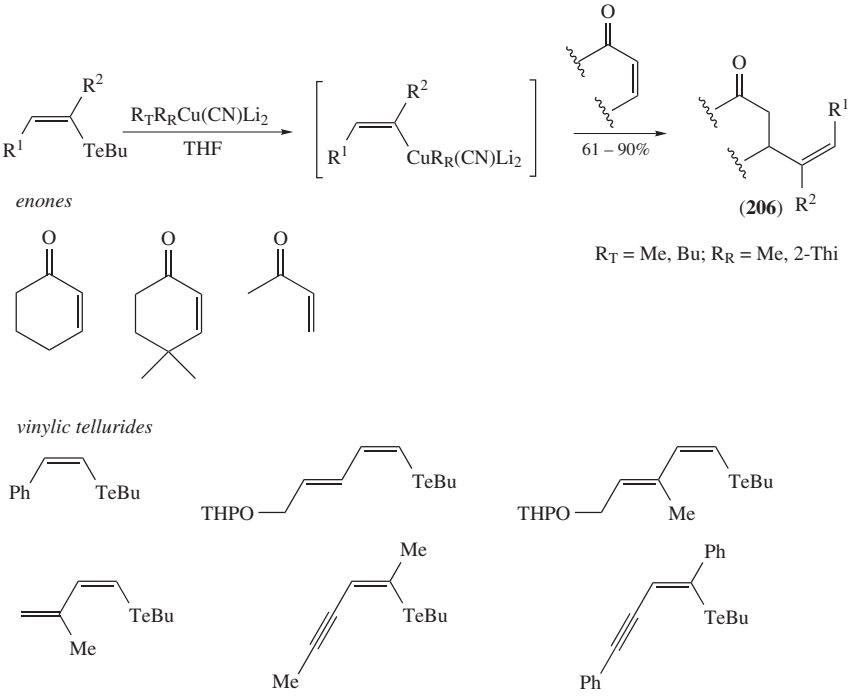
SCHEME 121

Three different enones were employed in this study, namely cyclohexenone, 4,4-dimethylcyclohexenone and methyl vinyl ketone. A range of vinylic tellurides was employed, and all of them were successfully transmetallated to the mixed higher order vinyl cyano cuprates, exclusively giving the alkenyl 1,4-addition products **206**. Several useful products have been achieved by this methodology, since stereochemically defined vinylic tellurides bearing diene or enyne moieties undergo the tellurium–copper exchange smoothly, and are then transferred to the enones in good yields (Scheme 122). It is also noteworthy that no isomerization of the double bonds is observed. There is no great influence if the R_R group is changed from 2-Thi to Me[55a, 107].

Moreover, bis-vinylic tellurides **139** are suitable substrates for the generation of the mixed cuprates with the advantage that 1 equivalent of the bis-vinylic telluride can generate 2 equivalents of the higher order vinyl cuprate. The reaction proceeds in similar yields when compared to butyl vinyl tellurides and the vinyl moiety is transferred exclusively, with complete retention of the stereochemistry of the starting telluride (Scheme 123)[55a, 107].

The authors observed that hindered enones fail to react under the reaction conditions described in Scheme 123. To overcome this problem, changes in the reaction conditions were studied in order to make it possible to transfer vinyl copper reagents to more encumbered substrates. An efficient solution to this problem was to add $BF_3 \cdot Et_2O$ to the reaction mixture, giving the 1,4-addition product in good yields with both THF and ether as solvents (Scheme 124)[108].

Additional studies on this reaction toward highly unsaturated systems explored the conjugate addition of an organocuprate followed by O-functionalization, leading to enol silanes, triflates and phosphates[109].



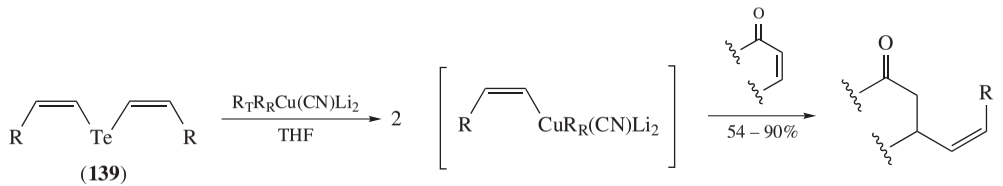
SCHEME 122

Several different vinylic tellurides of a *Z*-configuration, such as those containing diene and enyne moieties and bis-vinylic tellurides, were employed in this reaction. The intermediate enolate was trapped with chlorotrimethylsilane, diethyl chlorophosphate and *N*-phenyltrifluoromethanesulfonamide to generate the enol silanes, phosphates and triflates, respectively (Scheme 125).

Highly unsaturated systems were assembled by this strategy, as depicted in Figure 8. The possibility of further extension of the chain with selective cross-coupling reactions at the OX group, leading to even more complex unsaturated conjugated systems, was devised. Similarly, a Negishi-type cross-coupling reaction catalyzed by Pd(0) was performed with *Z*-vinylzinc chloride **209**, generated by the transmetallation of vinylic telluride **208** with BuLi, followed by the treatment of the vinyllithium intermediate with zinc chloride. The reaction proceeded smoothly to afford the TMS fuctionalized dienyne **210** in 80% yield. In addition, a Sonogashira reaction between propargyl alcohol and enol triflate **207** catalyzed by $Pd(PPh_3)_4$ was performed, giving the cross-coupled product **211** in high yield (Scheme 126).

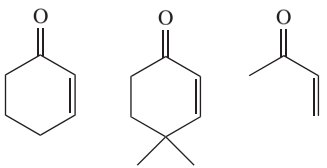
Besides α,β-unsaturated ketones, another class of electrophiles that have been used in reactions with the vinyl copper species generated by the tellurium–copper exchange reaction are epoxides[55a,110].

Epoxide opening proceeds through an S_N2 mechanism and, in the particular case of a reaction with vinyl cuprates, homoallylic alcohols are formed as the major products. The importance of this transformation is highlighted by the fact that homoallylic alcohols are key intermediates in several total syntheses[111].

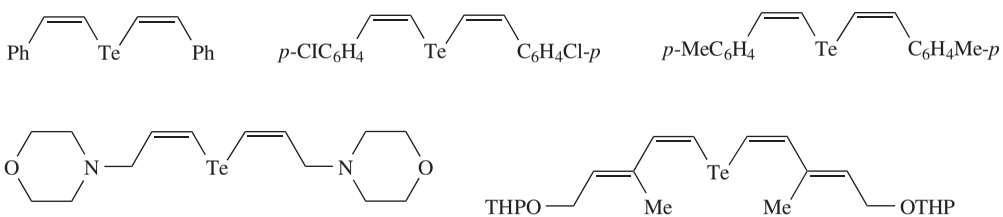


R_T = Me, Bu; R_R = Me, 2-Thi

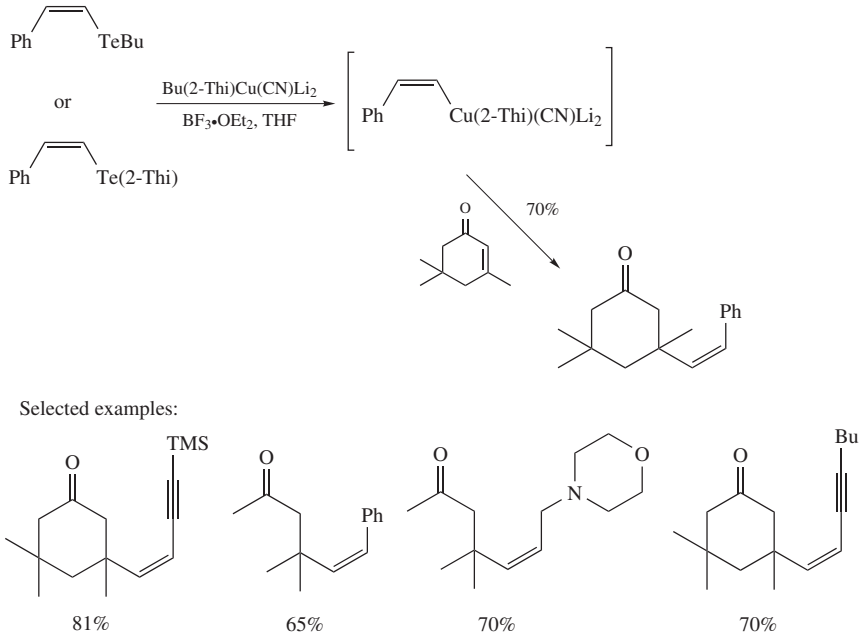
enones



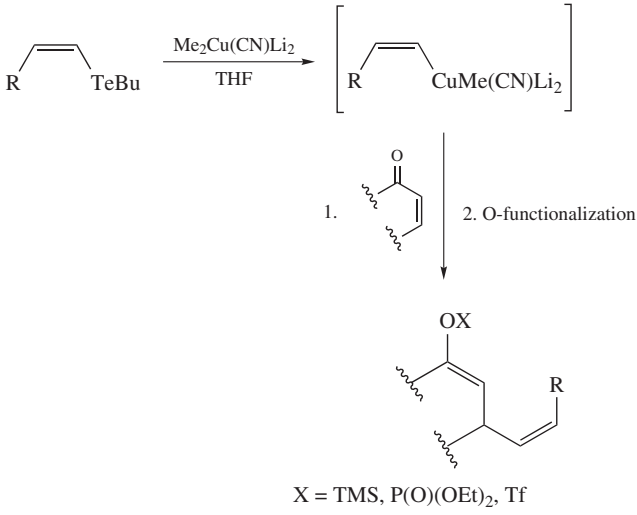
vinylic tellurides



SCHEME 123



SCHEME 124



X = TMS, $P(O)(OEt)_2$, Tf

SCHEME 125

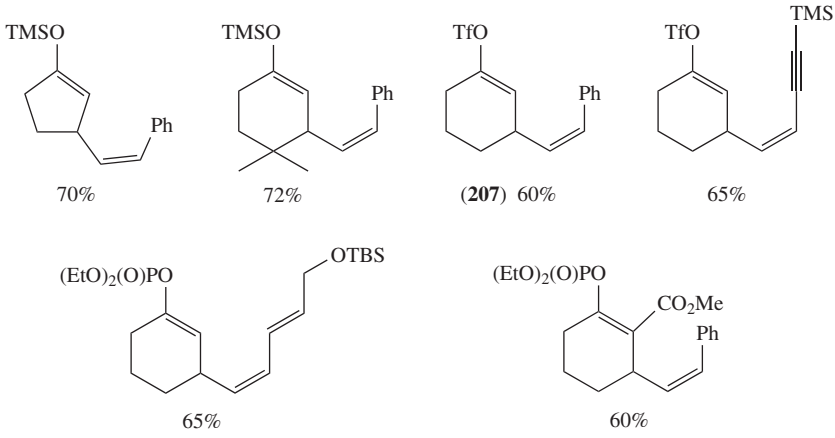
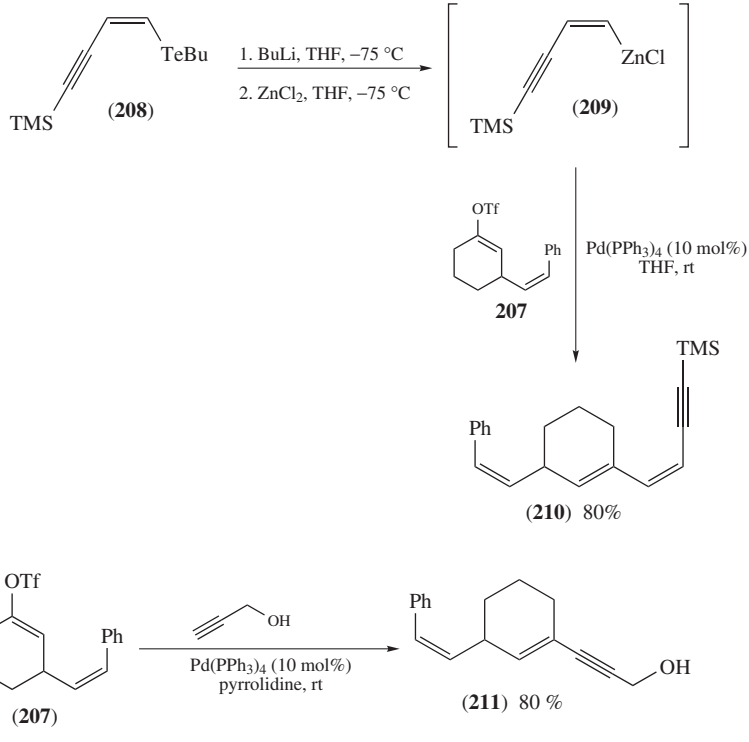


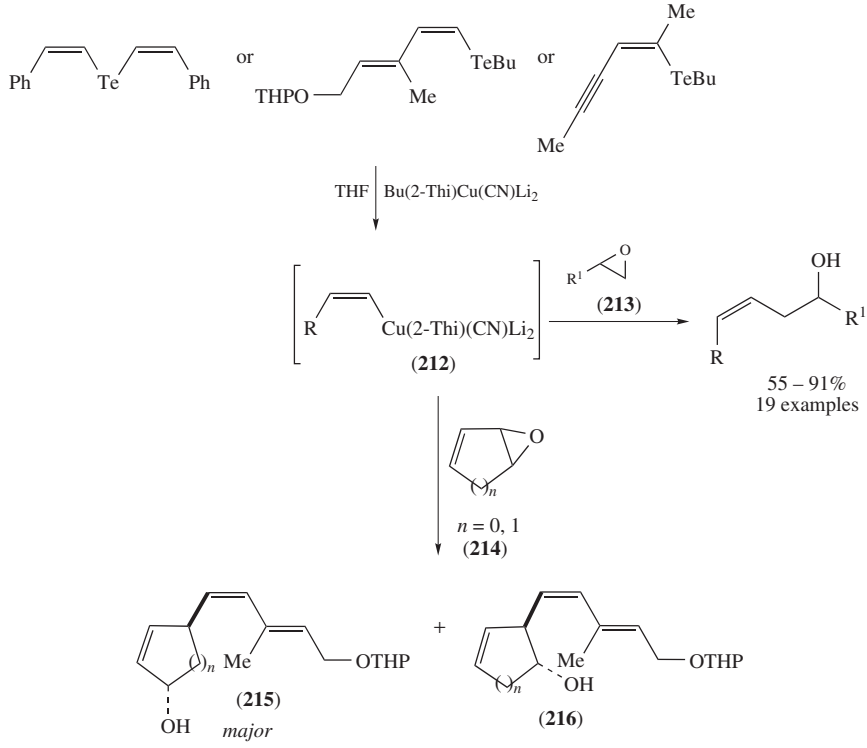
FIGURE 8



SCHEME 126

The higher order vinylic cuprates **212** which were employed in the epoxide openings were generated in the same manner as for the addition to enones. Hence, dilithio-2-thienyl(butyl)(cyano)cuprate was chosen for the transmetallation reaction, since both $Me_2Cu(CN)Li_2$ and $Bu_2Cu(CN)Li_2$ demonstrated transfer competition between alkyl and vinyl groups.

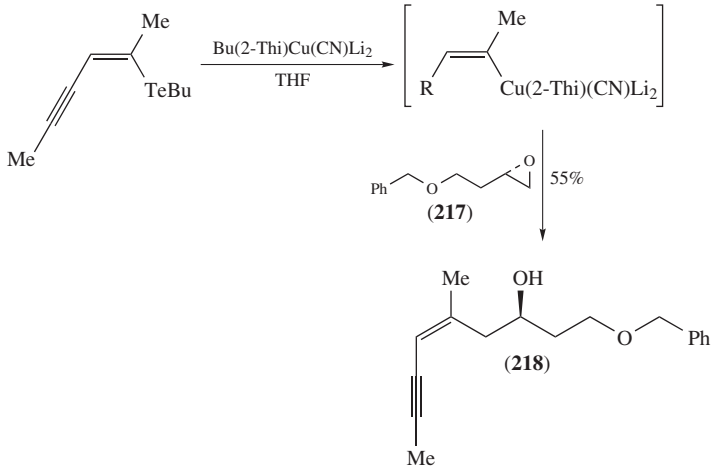
Several different epoxides were opened under these conditions. Usually, monosubstituted epoxides **213** gave the product of attack at the less-substituted position in good yields. Disubstituted epoxides failed to react, even if a Lewis acid was introduced to the reaction medium. It is remarkable to note that cyclic vinyl epoxides **214**, such as cyclopentadiene and 1,3-cyclohexadiene monoxides, yielded preferentially the 1,4-addition **215** over the 1,2-addition **216** product, although in moderate regioselectivities (Scheme 127). Again a remarkable feature of the reaction is the complete retention of the stereochemistry of vinylic telluride during the vinyl transfer process.



SCHEME 127

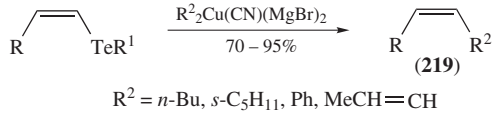
Chiral epoxides, such as **217**, were employed in such transformations since the chiral homoallylic alcohol **218** was isolated without any loss of its optical purity, as determined by ^{19}F NMR spectroscopy of its Mosher's ester (Scheme 128).

A dramatic change in the reactivity pattern is observed when the counterion of a higher order cyanocuprate is changed from the usual lithium to magnesium bromide[112]. The presence of the MgBr counterion favors the coupling reaction instead of the transmetallation



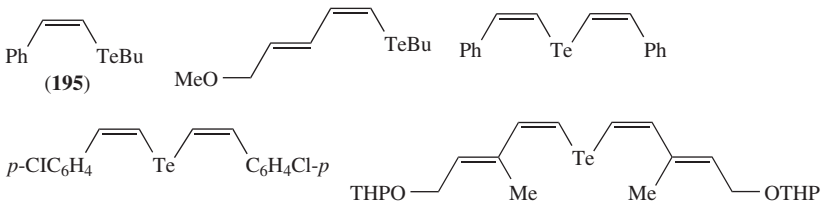
SCHEME 128

reaction, affording the product **219** in good yields (Scheme 129). The reaction failed to furnish the product with a vinylic telluride containing an enyne moiety, which exclusively gave the transmetallation product.



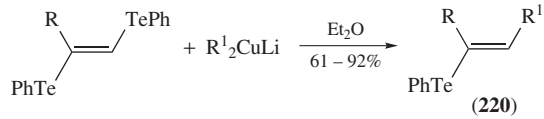
R^2 = *n*-Bu, *s*-C_5H_{11}, Ph, MeCH=CH

vinylic tellurides



SCHEME 129

In contrast to the transmetallation reactions, which occur when a vinylic telluride reacts with a dilithio higher order organocuprate, the reaction of vinylic tellurides with lower order organocuprates furnished the coupling product instead. The coupling reaction proceeds stereoselectively with retention of the configuration of the starting telluride, and only the terminal TePh group undergoes a substitution reaction with the organocuprate[113]. Several different cuprates were successfully employed in this process and the products **220** were isolated in high yields (Scheme 130). The reaction is assumed to proceed through



R = Ph, C_6H_{13}, EtO_2C; R^1 = Me, Bu, Ph

SCHEME 130

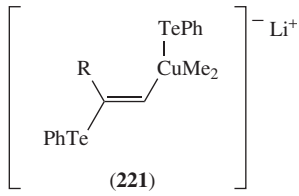
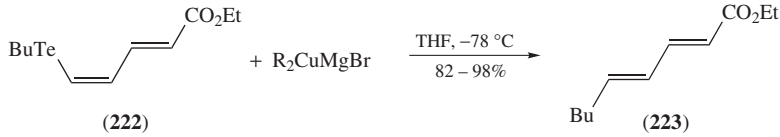


FIGURE 9

an oxidative addition resulting in a Cu(III) intermediate **221**, which suffers reductive elimination to afford the coupled product (Figure 9).

Another report on the coupling reaction with lower order cuprates concerns the substitution reaction of a butyltelluro group to **222** by several different copper reagents and was described[114]. The reaction was highly selective, and when cuprates of type $R_2CuMgBr$ were used, the substitution of the organotellurium group was accomplished with an almost exclusive preference of the 1,4- over the 1,6-addition to the unsaturated ester. The reaction proceeded with a complete inversion of the configuration of the double bond where the tellurium atom is attached, giving in all cases the products as a $2E, 4E$ isomer in a ratio of >98:<2 (Scheme 131). The authors assume that the telluride was first attacked by the organocopper reagent to form an 'ate complex', followed by a 1,6-additon elimination reaction, furnishing the thermodynamically more stable product **223**, through a substitution reaction to give the detellurated product.

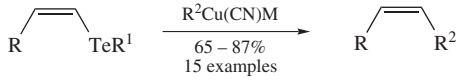


R = C_6H_{13}, $C_{10}H_{21}$, Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *E*-PhCH=CH

SCHEME 131

Lower order cyano cuprates were employed to effect such a transformation[115]. Several vinylic tellurides were employed in these studies, such as those containing aryl, ester and morpholine groups. Bis-vinylic and β-chlorovinylic tellurides can also be employed in the coupling reactions. The influence of the counterion at the cuprate was also examined, showing that both Li and MgBr performed well. In the case of β-chlorovinylic tellurides the reaction occurs selectively at the organotellurium group without affecting the chlorine

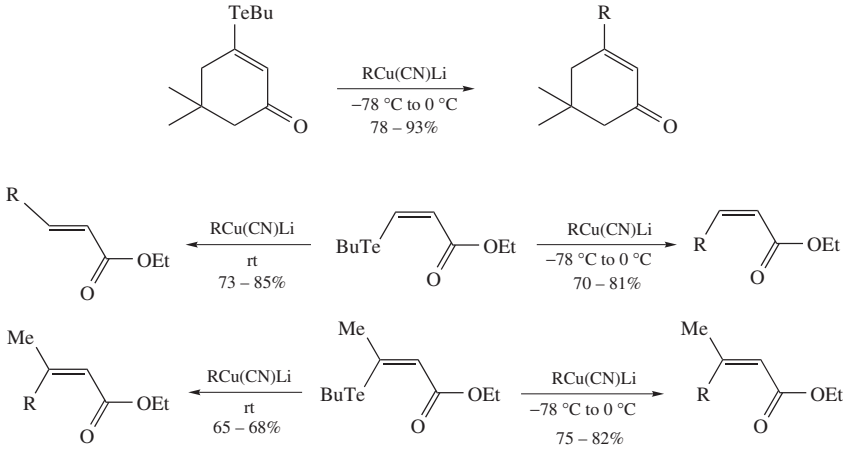
atom. The advantage of using cyanocuprates over dialkylcuprates is that only one equivalent of the lithium or Grignard reagent is required for the formation of the copper reagent (Scheme 132).



M = Li, MgBr;
R^2 = Me, *n*-Bu, *t*-Bu, *s*-C_5H_{11}, Ph, MeCH═CH

SCHEME 132

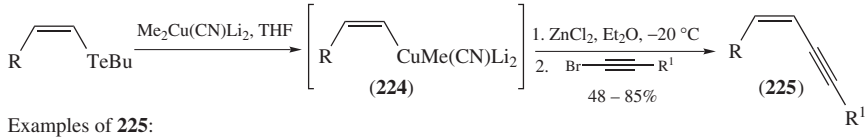
Another application of the coupling reaction of vinylic tellurides with lower order cyano cuprates is the reaction with functionalized tellurides to obtain detellurated products[116]. When the reaction was performed at room temperature, inversion of the double bond configuration or, in some cases, a mixture of isomers was obtained. However, when the temperature was lowered, the reaction took place with complete retention of the double bond geometry (Scheme 133). The results in the preparation of such systems gave higher diastereoselective results than the direct substitution reaction between cuprates and β-keto enol phosphates.



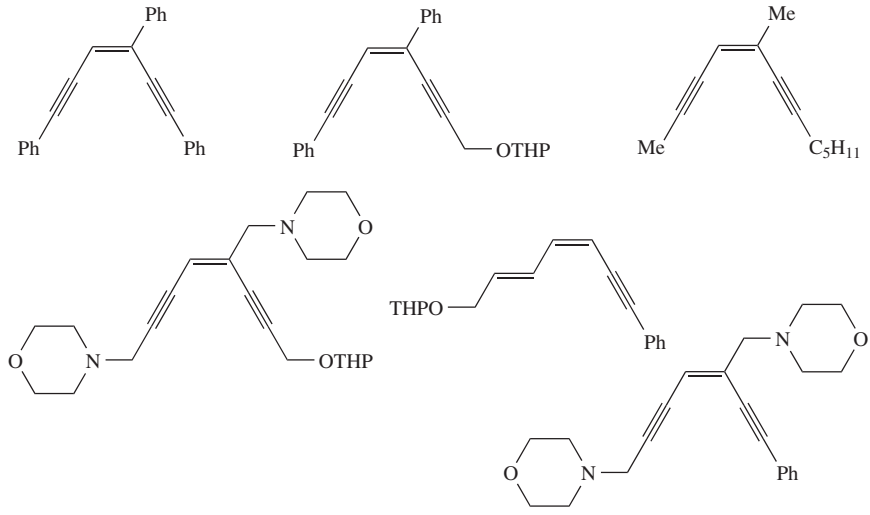
R = *n*-Bu, *s*-Bu, *t*-Bu

SCHEME 133

The synthesis of enynes and enediynes was achieved by taking advantage of the tellurium/copper exchange[117]. The reaction was performed by an initial transmetallation of a vinylic telluride with a higher order cyano cuprate, resulting in vinylic cuprates **224**. These intermediates were transmetallated to the vinylic zinc chlorides, which were coupled with several bromoalkynes, resulting in the enynes and enediynes **225** in good yields (Scheme 134).



Examples of **225**:



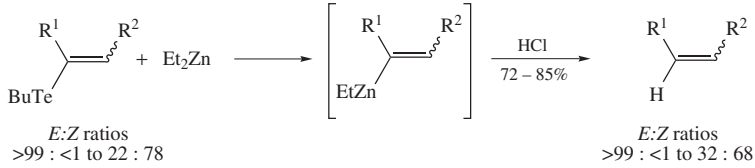
SCHEME 134

3. Tellurium/zinc exchange reactions

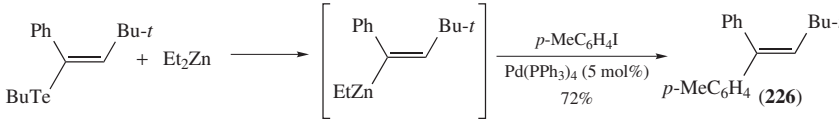
The tellurium/zinc exchange reaction was reported by Terão, Kambe and Sonoda, who have demonstrated that vinylic tellurides can undergo a transmetallation reaction when treated with diethylzinc in THF[118]. When the reaction was carried out in $MeCCl_3$ as solvent, a dramatic decrease in the yield was observed, suggesting that the exchange reaction is accelerated by coordinating solvents. Different mixtures of *E* and *Z* isomers of the starting tellurides were used in the reaction. The stereochemistry displayed a fairly good retention of configuration during the reaction outcome, and the yields were from moderate to good. An advanced application of this tellurium/zinc exchange consists of a further cross-coupling reaction catalyzed by palladium with *p*-iodotoluene. The cross-coupling product **226** was isolated in 72% yield as a single isomer (Scheme 135).

4. Tellurium/aluminum exchange reactions

Vinyl aluminum reagents can be prepared by tellurium/aluminum exchange[119]. The exchange reaction is carried out by treating the vinylic tellurides with an excess of triethylaluminum. The reaction proceeds efficiently with complete retention of the double bond geometry, in polar and non-coordination solvents such as $MeCCl_3$, $CHCl_3$ or CH_2Cl_2. Coordinating or apolar solvents dramatically reduce the product formation, suggesting that the coordination of aluminum to tellurium is essential for the exchange reaction. A synthetic application of this methodology was carried out using the copper-catalyzed

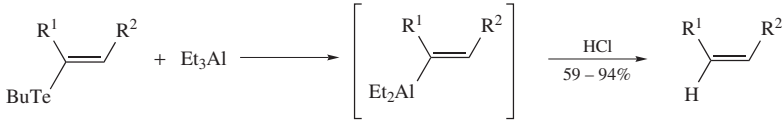


R^1, R^2 = Ph, *t*-Bu, *s*-Bu, *i*-Pr, TMS, CO_2Et

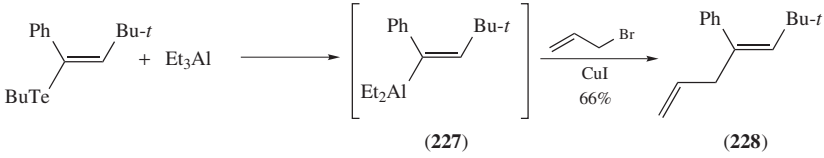


SCHEME 135

coupling of the vinylaluminum reagent **227** with allyl bromide, to give **228** in 66% yield, as a sole isomer (Scheme 136).



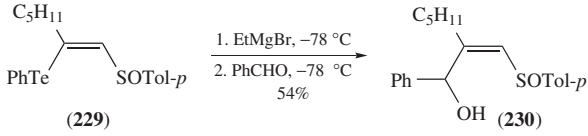
R^1, R^2 = Ph, 4-ClC_6H_4, *t*-Bu, *s*-Bu, *n*-Bu, *i*-Pr, TMS



SCHEME 136

5. Tellurium/magnesium exchange reactions

Only one example of a tellurium/magnesium exchange had been reported in the literature by Xu, Huang and Ni. The authors described the reaction of a vinylic telluride containing a sulfoxide substituent **229**, which undergoes a tellurium/magnesium exchange reaction at low temperatures by treatment with EtMgBr. The vinyl magnesium intermediate was trapped with benzaldehyde to afford allylic alcohol **230** in 54% yield (Scheme 137)[31].



SCHEME 137

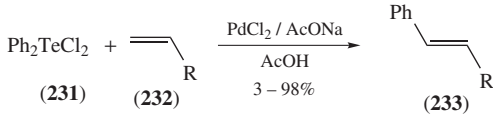
C. Cross-coupling Reactions of Vinylic Tellurides

1. Palladium-catalyzed cross-coupling reactions

An application of vinylic tellurides employing palladium-catalyzed cross-coupling[120] has been described[121] in which they behave as aryl or vinyl carbocation equivalents. They react in a manner similar to vinylic halides or triflates in the Sonogashira[122], Heck[123], Suzuki[124] and Stille[125] cross-coupling reactions with palladium as the catalyst[126]. Therefore, there are some advantages of using vinylic tellurides, such as easy access, by stereoselective reactions, to either (*Z*)- or (*E*)-vinylic tellurides, no isomerization of the double bond and the enhanced stability of these compounds. In addition, the use of vinylic tellurides in cross-coupling reactions tolerates many sensitive functional groups and mild reaction conditions. Conversely, in the last decade there have been developments in Pd-catalyzed coupling systems for Heck, Suzuki, Stille, Sonogashira and other reactions, as a consequence of the great interest in finding coupling substrates that are both more economical and more readily accessible.

a. Reactions of vinylic tellurides with alkenes–Heck-type reactions.

i. Carbodetelluration of aryltellurium(IV) compounds. The history of the use of vinylic tellurides in palladium-catalyzed reactions began with the carbodetelluration of aryltellurium(IV) compounds[127]. The authors found that the reaction between diphenyltellurium(IV) dichloride **231** and styrene (**232**, R = Ph), catalyzed by palladium(II) chloride, using sodium acetate as base and in acetic acid at reflux afforded *E*-stilbene (**233**, R = Ph) in 54% yield. This reaction was very sensitive to the nature of the catalyst. Similar reactions with palladium black, palladium(II) acetate and ruthenium(III) or ruthenium(II) chloride gave unsatisfactory yields of the desired product **233**. The reaction was extended to other olefins **232**, and the olefins **233** were obtained in variable yields (3–98%), (Scheme 138). The stereochemistry of the olefins **233** was *trans* except for those derived from acrylonitrile, which were obtained as a 74:26 *cis:trans* mixture.

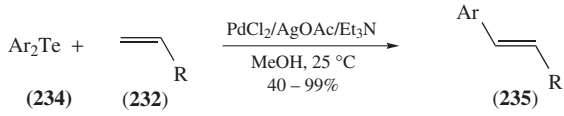


R = Ph, CO_2Me, CN, $H_2C{=}C(CN)Me$, COMe

SCHEME 138

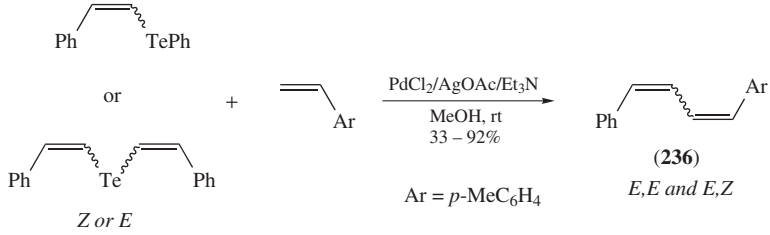
ii. Cross-coupling reactions of the vinyl tellurides with alkenes. It has been reported that the cross-coupling reaction of diaryl tellurides **234** with alkenes **232** in methanol at 25 °C, in the presence of a Pd^{II} catalyst, using Et_3N as base and an appropriate oxidant, such as AgOAc, afforded the corresponding aryl-substituted *Z*-alkenes **235** in good yields (Scheme 139)[128]. The experimental results indicated that no catalytic activity was observed using other solvents, such as tetrahydrofuran, benzene or acetic acid. The coupling reaction was also unsuccessful using oxidants such as ammonium hexanitratocerate, $CuCl_2$ and $K_2S_2O_8$.

This method has been extended to several vinylic tellurides, (*Z*,*Z*)- and (*E*,*E*)-bisvinylic tellurides, with *p*-methylstyrene. This cross-coupling reaction afforded the corresponding diaryl-1,3-butadienes **236** in yields higher than 33% (Scheme 140). The entire process was highly stereoselective and no *E*,*Z*-isomerization was observed during the reaction.



Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-BrC_6H_4
R = Ph, CO_2Me, CO_2Et, CN, CHO, CH_2OAc, COMe

SCHEME 139

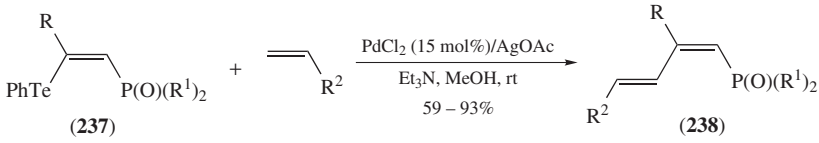


SCHEME 140

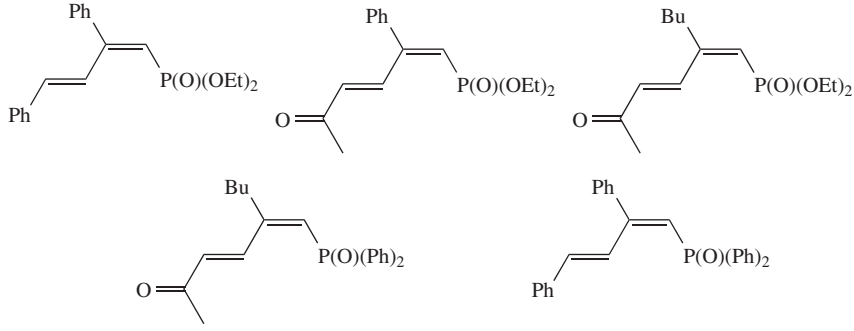
We have disclosed a regio- and stereospecific synthesis of phoshono-(1*Z*, 3*E*)-dienyl compounds **238** from β-phenyltelluro-vinylphosphonates and -vinylphosphine oxides **237** in a Heck-type reaction[129]. Several different reaction conditions were evaluated in this reaction, such as solvent, base and the nature of the reoxidant employed. We have found that the best results were obtained using methanol as solvent, triethylamine as base and silver acetate as the reoxidant agent. The presence of the latter is of crucial importance, since it allows us to employ the palladium salt in catalytic amounts. The reaction has proven to be efficient for vinyl phosphonates, phosphine oxides, styrenes and methyl vinyl ketones. The regio- and stereochemistry of all dienes obtained were readily established by ^1H NMR spectroscopy, and the stereochemistry of the newly formed double bond was *E* in all cases. There was no evidence of the presence of the *Z* isomer probing the highly stereoselective character of the coupling reaction. Moreover, the reaction proceeds with retention of the stereochemistry of the original double bond of the starting telluride (Scheme 141).

Telluronium salts **239** have been employed as suitable substrates for the Heck-type reaction with alkenes[130]. The major advantage in the employment of this class of tellurium compounds is their high stability in comparison to tellurides. $Pd(OAc)_2$, $PdCl_2$ and $PdCl_2(PPh_3)_2$ have been evaluated as the palladium source, and it was found that $PdCl_2$ was the best choice in association with silver acetate as reoxidant and acetonitrile as solvent. Good yields of the products were obtained and either electron-donating or electron-withdrawing groups can be present in the telluronium salt. The alkene reactant can also be varied, giving good results with substituents, such as aldehydes, ketones, esters and nitriles (Scheme 142).

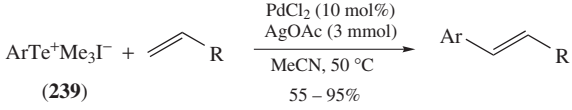
iii. Homocoupling reactions of vinylic tellurides. The reaction of vinylic tellurides **240** and **241** in the presence of catalytic amounts of $Pd(OAc)_2$ afforded the isomeric homocoupling products 1,4-diphenyl-1,3-butadienes (*E*,*E*; *E*,*Z*; and *Z*,*Z*) **236** in good to moderate yields. The presence of a reoxidant was critical for the success of the coupling, and the reaction rate was greatly enhanced by the addition of AgOAc as the reoxidant. The nature



Examples of **238**:



SCHEME 141

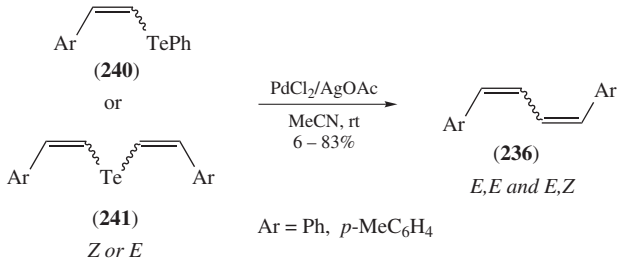


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2-MeC_6H_4, 2-$MeOC_6H_4$;
R = CO_2Bu, CN, CHO, COMe, Ph

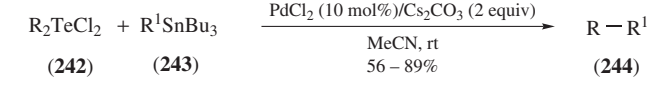
SCHEME 142

of the solvent also proved to be very important to the success of this reaction, and the best results were obtained with methanol and acetonitrile. Benzene and tetrahydrofuran furnished the product in lower yields. Thus, the optimum condition for the coupling in Scheme 143 was found to be the use of $PdCl_2$ (0.05 mmol)/AgOAc (1 mmol), vinylic tellurides (**240**–**241**, 0.5 mmol) and acetonitrile (10 mL) at 25 °C for 20 h[131].

b. Cross-coupling reactions of the organotellurium compounds with organostannanes—Stille-type reactions. Organostannanes have been successfully employed in cross-coupling reactions with diaryl- or divinyl-tellurium dichlorides. The reaction of organotellurium dichlorides **242** with vinylstannane species **243** in the presence of $PdCl_2$ with Cs_2CO_3 as the base and MeCN as the solvent afforded the cross-coupling products **244** in good yields as illustrated in Scheme 144. In this method, the authors tested other catalysts, such as $Pd(PPh_3)_4$, $Pd_2(dba)_3CHCl_3$ and $PdCl_2(PPh_3)_2$. The best results were obtained with $PdCl_2$ as catalyst. Concerning the bases used, Cs_2CO_3 was more efficient than K_2CO_3, Na_2CO_3 or MeONa[132].



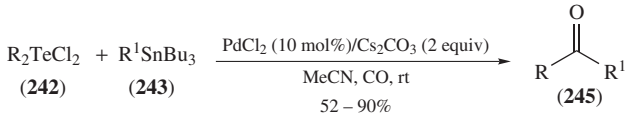
SCHEME 143



R = Ph, *p*-$MeOC_6H_4$, *Z*-PhCH=CH; R^1 = 2-furyl, 2-thienyl, *Z*-PhCH=CH

SCHEME 144

Similarly, the authors promoted detelluric cross-coupling carbonylations of diaryl- or divinyl-tellurium dichlorides **242** through a reaction with vinylstannanes **243**. This cross-coupling reaction can be carried out using catalytic amounts of $PdCl_2$ (10 mol%), CO (1 atm) in MeCN and Cs_2CO_3 as the base, affording ketones **245** in 52–90% yields (Scheme 145)[132].

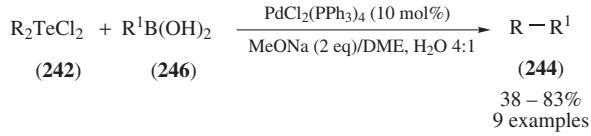


R = Ph, *p*-$MeOC_6H_4$, *Z*-PhCH=CH; R^1 = Ph, 2-furyl, 2-thienyl, *Z*-PhCH=CH, α-styryl, Ph —≡

SCHEME 145

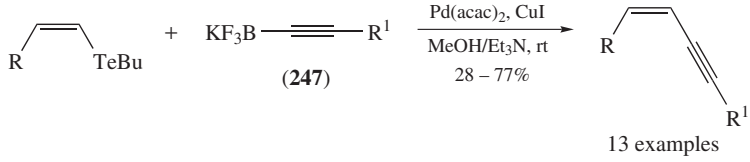
c. Cross-coupling reactions of the organotellurium compounds with organoboranes—Suzuki-type reactions. The Suzuki palladium-catalyzed cross-coupling reaction between arylboronic acids and aryl halides or triflates has proven to be a very popular and versatile method for the formation of carbon–carbon bonds[20]. An investigation of the palladium-catalyzed cross-coupling of diaryl and bis-vinyltellurium dichlorides with organoboronic acids has been reported[133]. As illustrated in Scheme 146, various diaryl or bis(vinyltellurium) dichlorides **242**, R = vinyl, were allowed to react with arylboronic acids **246** in the presence of $PdCl_2(PPh_3)_2$ and NaOMe in DME/H_2O, affording the coupled products **244** in fair to good yields (Scheme 146).

In addition to the reaction of bis-vinyltellurium dichlorides with organoboronic acids, a protocol for the synthesis of 1,3-enynes via a Suzuki-type reaction of vinyl tellurides with potassium alkynyltrifluoroborate salts **247** was published[134]. $Pd(acac)_2$ furnished better results than other palladium salts, such as $PdCl_2$, $Pd(dba)_3$, $PdCl_2(PhCN)_2$ and

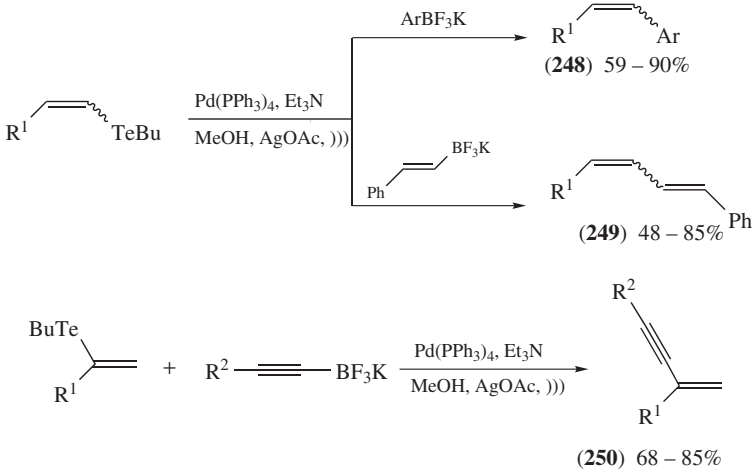


SCHEME 146

[Pd(allyl)Cl_2]. Several bases were also studied and the best yields were achieved with triethylamine, which furnished the product in better yields than cesium carbonate, sodium hydroxide, potassium *tert*-butoxide and potassium carbonate. The reaction tolerates several functional groups, such as hydroxyl, esters, dienes and enynes; however, it fails to promote the coupling product when an amine functionality is present in the vinylic telluride (Scheme 147). In a closely related investigation, the same group reported a microwave-assisted Suzuki-type reaction of vinyl tellurides with potassium aryl[135], vinyl[136] and alkynyl[137] trifluoroborate salts to give the cross-coupled products **248**–**250** in moderate to good yields (Scheme 148).



SCHEME 147

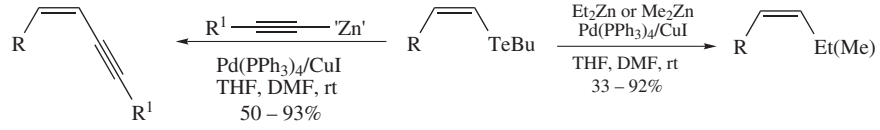


R^1, R^2 = alkyl, aryl, propargyl alcohol; Ar = aryl,2-thienyl, furyl, pyridyl

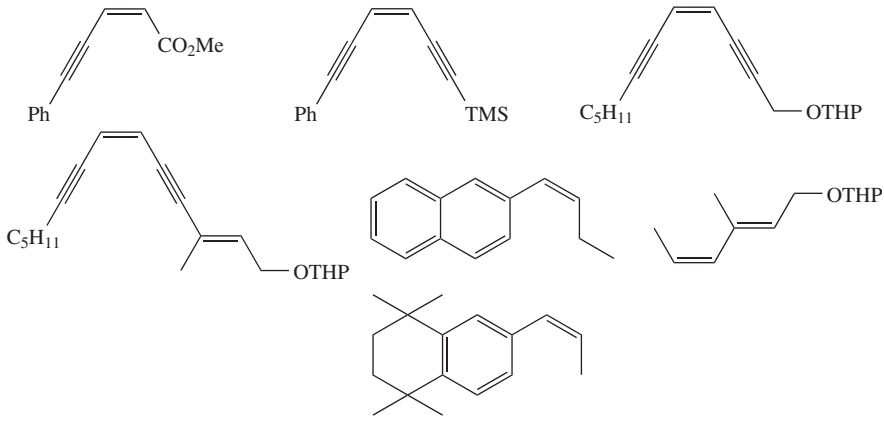
SCHEME 148

d. Cross-coupling reactions of the organotellurium compounds with organozinc reagents—Negishi-type reactions. Cross-coupling reactions of organozinc reagents are a versatile and very useful tool in modern organic synthesis, because of their known ability to tolerate many functional groups[138]. In this context, Dabdoub, Dabdoub and Marino have described efficient routes to promote the palladium-catalyzed coupling of alkylzinc[139] or alkylnylzinc[140] reagents with vinylic tellurides. The reaction is efficiently accomplished in the presence of catalytic amounts of $Pd(PPh_3)_4$ and 1 equivalent of copper iodide. The use of DMF as a co-solvent together with THF has substantially increased the yields of coupled products. In the absence of the palladium catalyst, only the detellurated product was isolated. Copper iodide also plays an important role in the outcome of the process, since the consumption of the starting material was incomplete in its absence.

Polyfunctional unsaturated compounds have been prepared by this methodology, as this function is present at either vinylic telluride or alkynylzinc reagent. Thus, several enediyne structures were prepared in good yields (Scheme 149).



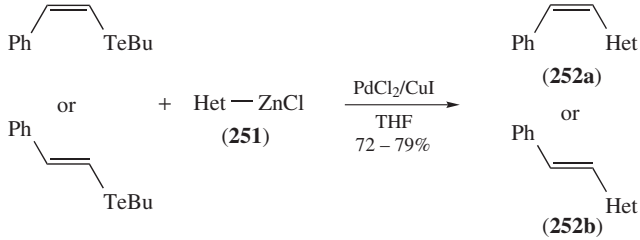
Examples of products:



SCHEME 149

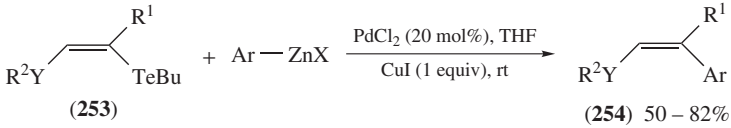
In addition to the achievements described by these authors, our group has concentrated efforts for the development of organozinc-based protocols to promote the cross-coupling of vinylic tellurides[141]. In fact, we have described the coupling of non-functionalized vinylic tellurides of a *Z* or *E* configuration with heteroaromatic zinc reagents **251**, namely 2-furyl, 2-thienyl and 2-pyridylzinc chlorides. Optimized conditions were achieved with *Z*-vinylic telluride and 2-furylzinc chloride, which was prepared *in situ* from 2-furyllithium and zinc chloride, to yield product **252a** or **252b** (Scheme 150). The best reaction conditions employed a catalytic amount of $PdCl_2$ and 1 equivalent of CuI. The reaction has been further extended to the other isomer of vinylic telluride and to different heteroaromatic zinc

reagents, demonstrating that this is an efficient method for the preparation of vinyl heterocycles in good yields (Scheme 150). In addition to non-functionalized vinylic tellurides, we also examined the Negishi cross-coupling reaction of functionalized vinylic tellurides **253** with arylzinc reagents to obtain functionalized alkenes **254** (Scheme 151)[142]. The optimized reactions revealed that the optimum condition was general to a variety of arylzinc halides and functionalized vinylic tellurides, such as β-butyltelluro vinylphosphonates and β-butyltelluro vinylphosphine oxides.



Het = 2-furyl, 2-thienyl, 2-pyridyl

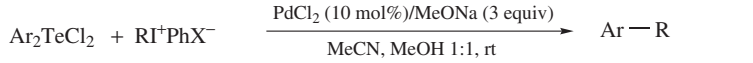
SCHEME 150



R^1, R^2 = alkyl, aryl, benzyl; Ar = aryl, heteroaryl; X = Cl, Br; Y = S, P

SCHEME 151

e. Palladium-catalyzed cross-coupling of organotellurium compounds with hypervalent iodonium salts—Heck-type reactions. Kang and coworkers[143] have shown that diaryltellurium dichlorides **255** can be readily coupled with iodonium salts **256** in the presence of palladium catalysts to give coupled products **257** (Scheme 152). This method gave the best yields when the iodonium salts were allowed to react with diaryltellurium dichlorides in the presence of $PdCl_2$ (10 mol%) and MeONa (3 equivalents), in CH_3CN/MeOH (1:1) at room temperature for 7 h. This protocol gave the products in 70 to 88% yields.

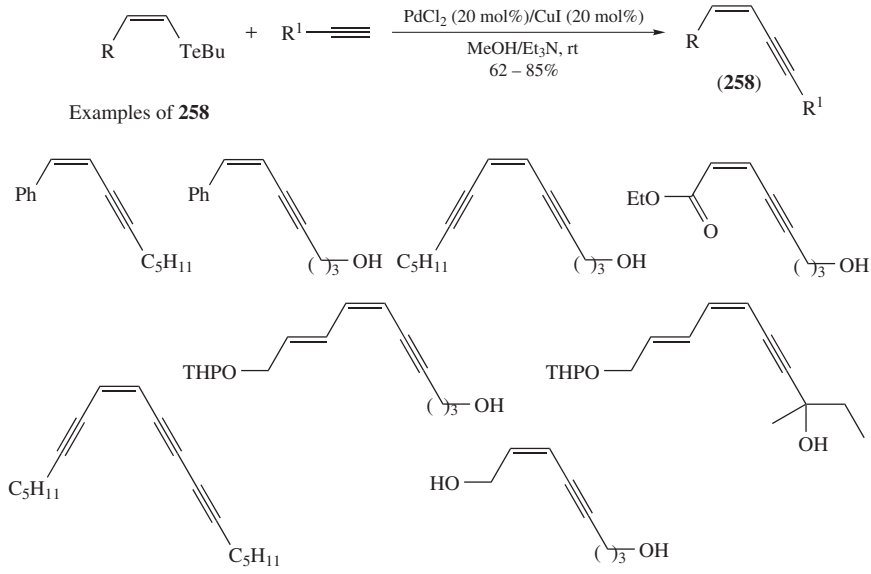


Ar = Ph, *p*-$MeOC_6H_4$; R = *p*-$MeOC_6H_4$, 2-thienyl, *E*-β-styryl;
X = OTs, OTf, BF_4

SCHEME 152

f. Reactions of the vinylic tellurides with alkynes—Sonogashira-type reactions.

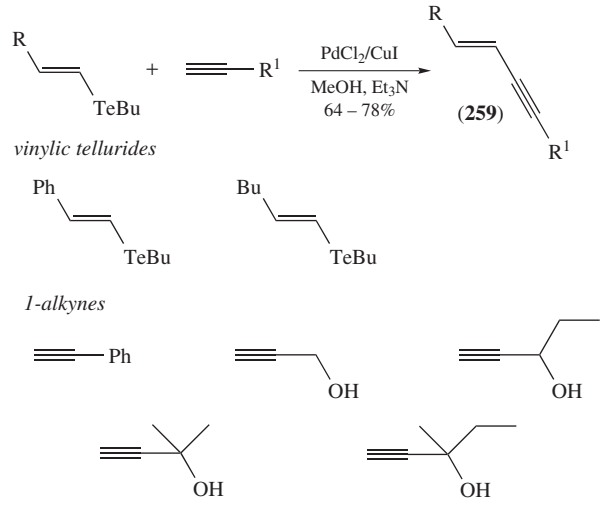
i. Synthesis of enynes and enediyne systems via palladium-catalyzed cross-coupling of vinylic tellurides with 1-alkynes. Calicheamycins, esperamycins and dynemycins are a class of antibiotic molecules that emerged some years ago[144]. Among them are some of the most potent antitumor agents known to date. The synthesis of enynes and enediynes has received special interest during the last 20 years[145], and a variety of methods based on palladium-catalyzed reactions have been developed[146]. The cross-coupling reaction of vinyl bromides, iodides, chlorides and triflates with monosubstituted acetylenes has been achieved in the presence of a Pd^0 or Pd^{II}/CuI catalyst[147]. The reaction has also been performed using bromoalkynes and a vinyl boron[148], copper[149], zinc[150], aluminum[151] or magnesium reagent[152]. The use of vinylic tellurides to obtain enyne and enediyne systems using transmetallation with *n*-BuLi[63] and cyanocuprates[109a] has been previously described. Nonetheless, the cross-coupling of vinylic tellurides with 1-alkynes was unknown. Initially, we described the stereospecific formation of (*Z*)-enynes and (*Z*)-enediynes **258** in a palladium-catalyzed cross-coupling reaction of (*Z*)-vinylic tellurides with 1-alkynes[153]. We found that the optimum conditions for the coupling in Scheme 153 was the use of $PdCl_2$ (20 mol%)/CuI(20 mol%), MeOH (5 mL), (*Z*)-vinylic telluride (1 mmol), the appropriate alkyne (2 mmol) and Et_3N (1 mmol) at 25 °C. By extending the coupling reaction to other alkynes, various *Z*-enynes and *Z*-enediynes **258** were obtained in good yields (Scheme 153). Our approach represented an improvement over previously described methods, in that it avoids both the preparation of vinyl metals and haloalkynes and the protection of functional groups, such as alcohols. Another advantage of this method is the easy access and stability of (*Z*)-vinylic tellurides.



SCHEME 153

In 2004, the scope of the cross-coupling reaction of *Z*-vinylic tellurides with 1-alkynes was extended to *E*-vinylic tellurides[154]. Although several different conditions, including

other palladium catalysts and different solvents and bases, were examined, the $PdCl_2$/CuI system has still proven to be the most effective for the coupling reaction, giving the *E*-enynes **259** in high yields (Scheme 154). Similar to the reaction of the *Z* isomers, no isomerization of the starting double bond was observed during the reaction.

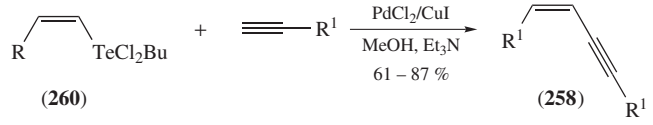


SCHEME 154

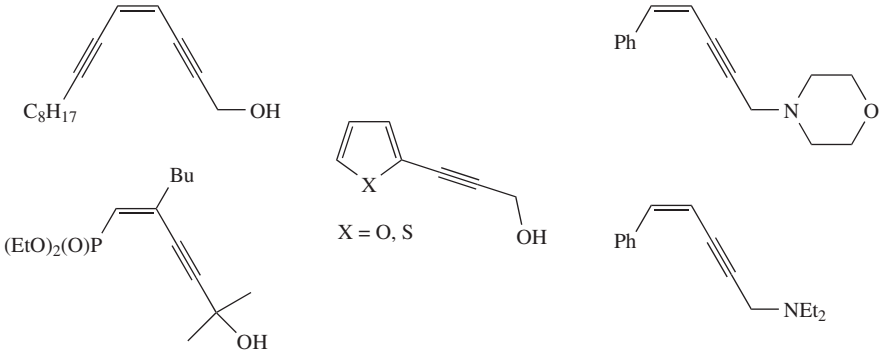
Another alternative to vinylic tellurides as starting materials for the synthesis of enynes **258** is the use of the corresponding organotellurium dichlorides **260**, which are much more stable to air oxidation than their parent vinylic derivatives[155]. Again, the $PdCl_2$/CuI system furnished the best results and the reaction was tolerant to several functional groups, such as amines, phosphonates and hydroxyl, without previous protection (Scheme 155).

ii. Palladium-catalyzed cross-coupling of bis-vinylic tellurides with 1-alkynes. Along with the exploration of the synthetic potential of the Pd-catalyzed cross-coupling reaction with vinylic tellurides, we have also investigated the stereospecific formation of (*Z*)-enyne **258** systems by palladium-catalyzed cross-coupling reactions of (*Z*)-bis-vinylic tellurides **139** with 1-alkynes (Scheme 156)[156]. Initial research efforts were dedicated to the development of a good catalytic system, and the influence of the ligands in the palladium complex were investigated. Thus, (*Z*)-bis-vinylic telluride **139** (1 equivalent) was treated in methanol at room temperature with 2-propyn-1-ol (2 equivalents) in the presence of different catalysts and Et_3N (1 equivalent) as the base (Scheme 156). $Pd(PPh_3)_4$ or $Pd(PPh_3)_4$/CuI did not exhibit catalytic activity in this reaction and Pd(II) catalysts, such as $PdCl_2/PPh_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ and $PdCl_2(PhCN)_2$, gave unsatisfactory yields of the desired enyne **258**. The reaction yields were greatly enhanced by increasing the amount of $PdCl_2$/CuI from 1 to 10%, where the desired enyne **258** was obtained in 85% isolated yield.

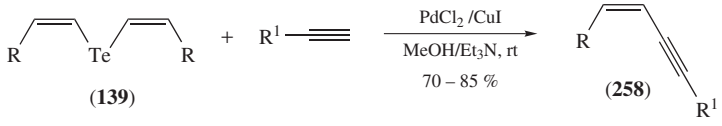
The nature of the amine was critical for the success of the coupling. Using pyrrolidine, piperidine or morpholine (1 equivalent) as base, no reaction was observed. With Et_2NH, *n*-$PrNH_2$ or *n*-$BuNH_2$, moderate yields were observed (15 to 28%). However,

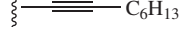


Examples of **258**:



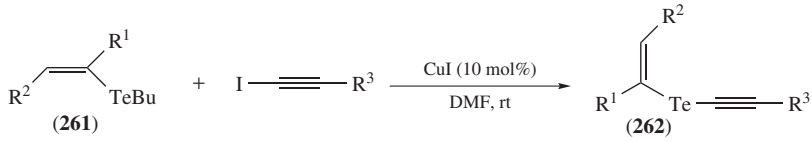
SCHEME 155



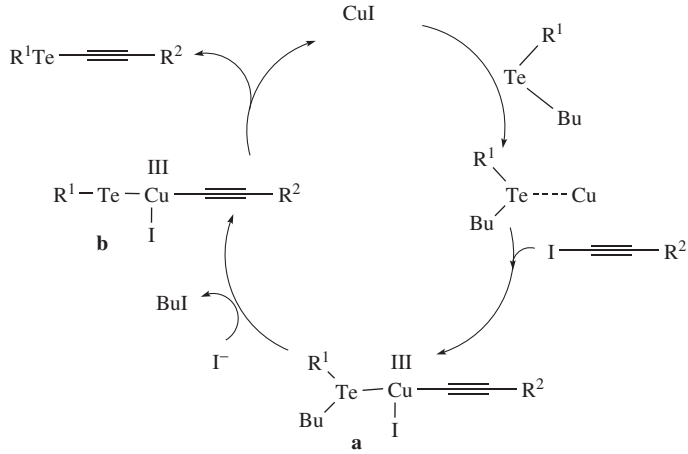
R = Ph, CH_2OH; R^1 = C_5H_{11}, C_7H_{15}, *t*-Bu, TMS, CH_2OH, $(CH_2)_3OH$, C(Me)(Et)OH, 1-cyclohexanol, 

SCHEME 156

with Et_3N, the enyne **258** was obtained in 85% isolated yield and the reaction was completed within 6 h. The stereoisomeric purities of the enynes **258** were similar to that of starting bis-vinylic tellurides **139**, indicating a complete retention of the configuration in this type of reaction. Extending the coupling reaction to other alkynes, various *Z*-enynes **258** were obtained in good yields (Scheme 156). In an extension of these previous studies using vinylic tellurides as substrates in the palladium cross-coupling, we demonstrated, in 2009[157], that organotellurium compounds **261** having a carbon–tellurium single bond are suitable substrates to copper cross-coupling reactions, providing an interesting protocol for the synthesis of alkynyl tellurides **262**. This behavior appears to involve the (a) BuTe complexation with CuI; (b) insertion of CuI into the alkyne, followed by nucleophilic attack of the tellurium atom on copper to give the cationic organo-Cu(III) complex **a**; (c) nucleophilic attack of iodide anion on the butyl group bound to the tellurium atom to give the Cu(III) intermediate **b**; (d) the reductive elimination to give the product and regenerate Cu(I) (Scheme 157).



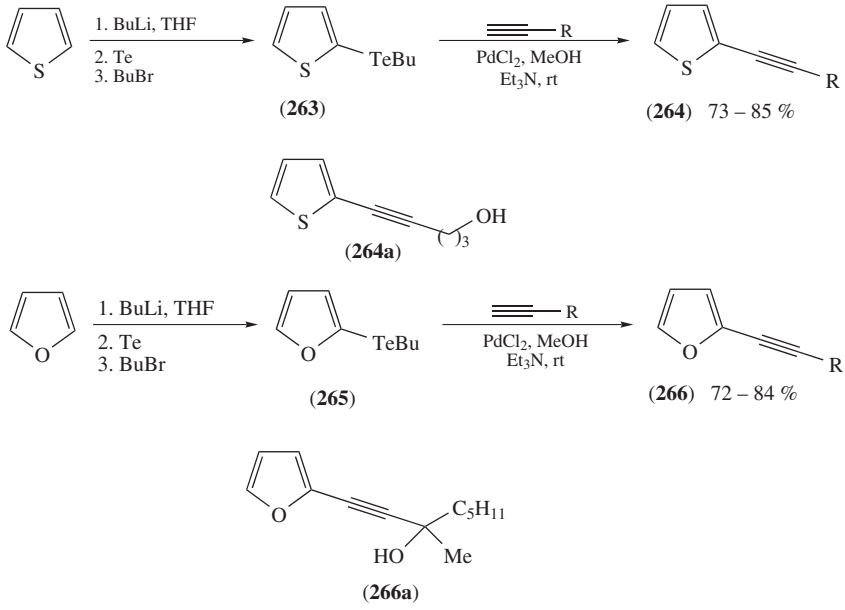
R^1 = H, Ph, C_4H_9, C_6H_{13}; R^2 = SMe, SPh, SBn, Ph, $P(O)(OEt)_2$; R^3 = Ph, C_5H_{11} CH_2O, $C(CH_3)_2OH$



SCHEME 157

iii. Palladium-catalyzed cross-coupling of 2-(butyltelluro)thiophene and 2-(butyltelluro) furan with 1-alkynes. Several thiophene derivatives have been found to show nematocidal[158], insecticidal[159], antibacterial[160], antifungal[161] and antiviral[162] activity. We have investigated the anti-inflammatory activity of acetylenic thiophene derivatives synthesized via a Pd-catalyzed coupling reaction of 2-(butyltelluro)thiophene with 1-alkynes[163]. In this study, our research group evaluated: a) the influence of the nature of the catalyst; b) the effect of the nature of the amine and c) the anti-inflammatory activity of the acetylenic thiophene derivatives prepared. The starting material required for the synthesis, 2-(butyltelluro)thiophene **263** (Scheme 158), was obtained from the metallation of thiophene with *n*-butyllithium[164] followed by the treatment of 2-thienyllithium with elemental tellurium. Subsequent addition of 1-bromobutane gave the 2-(butyltelluro)thiophene **263** in good yield. This compound is stable and can be chromatographed and stored in the dark at room temperature for several days. Treatment of 2-(butyltelluro)thiophene **263** with 1-alkynes in methanol using $PdCl_2$ as the catalyst and triethylamine as the base at room temperature gave the acetylenic thiophenes **264** in 73–85% yield after purification (Scheme 158).

Of the catalysts tested, $Pd(PPh_3)_4$ and $Pd(PPh_3)_4$/CuI did not exhibit catalytic activity in this reaction and a Pd(II) catalyst, such as $PdCl_2/PPh_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ and $PdCl_2(PhCN)_2$, gave unsatisfactory yields of the desired acetylenic thiophenes. However, by using $PdCl_2$ (10 mol%), the acetylenic thiophene was obtained in improved yields. The nature of the amine was also very important, because when the reaction was performed



SCHEME 158

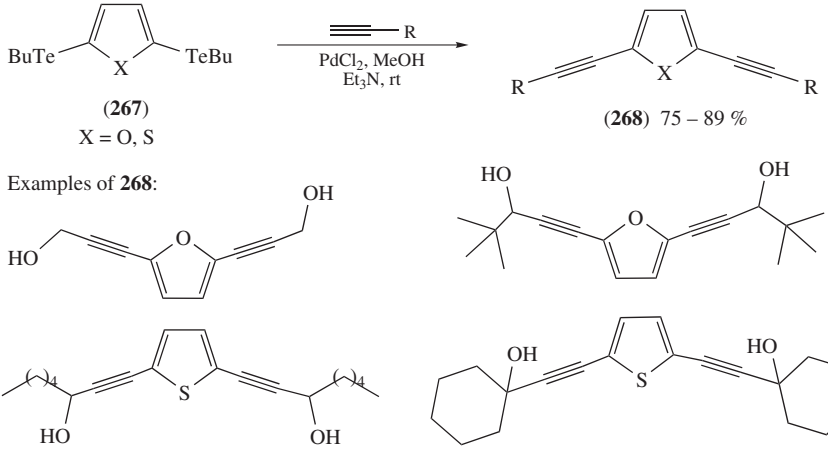
using pyrrolidine, piperidine or morpholine (1 equivalent), no product was obtained. The use of Et_2NH, n-$PrNH_2$ or n-$BuNH_2$ gave the desired products in low yields (5–8%). However, by using Et_3N, the acetylenic thiophene derivatives were obtained in good yields. We also found that the yields of acetylenic thiophenes were markedly decreased using DMF, CH_3CN, THF or CH_2Cl_2, instead of MeOH as the solvent. Thus, the optimum condition for the coupling in Scheme 158 was the use of $PdCl_2$ (10 mol%), MeOH (5 mL), 2-(alkyltelluro)thiophene **263** (1 mmol), the appropriate 1-alkyne (2 mmol) and Et_3N (1 mmol) at 25 °C. Moreover, the coupling reaction was extended to other alkynes. The acetylenic thiophenes obtained are summarized in Scheme 158.

The acetylenic thiophenes **264** obtained were screened for anti-inflammatory activity, using the carrageenin-induced paw edema method[165]. This method is customarily used for the screening of new pharmacologically active compounds. The acetylenic thiophene **264a** ($p<0.05$, 50% of the edema inhibition at a dose of 250 mg kg^{-1}; i.p) demonstrated significant potential to reduce the carrageenin-paw edema when compared to acetylsalicylic acid (100 mg kg^{-1}, i.p).

We also applied the method described above to prepare acetylenic furan derivatives **266** (Scheme 158)[166]. We found that direct coupling of 2-(alkyltelluro)furan **265** with 1-alkynes in the presence of palladium dichloride as the catalyst in methanol and triethylamine affords the desired acetylenic furan derivatives **266** in good yields (72–84%). The obtained acetylenic furans were also screened for anti-inflammatory activity. The acetylenic furan (100 mg kg^{-1}; i.p.) inhibited 40% of the edema ($p<0.05$ by Duncan's multiple range test) induced by carrageenin when compared to control. Compound **266a** (250 mg kg^{-1}; i.p.) inhibited paw edema formation with greater potency than acetylsalicylic acid (100 mg kg^{-1}, i.p.), a classical anti-inflammatory agent. The synthetic methods

described represent a general and efficient protocol for carrying out the synthesis of acetylenic furans and thiophene derivatives with potential biological activities.

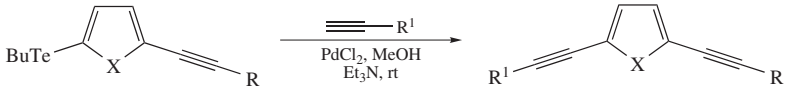
With success in the synthesis and biological evaluation of acetylenic furan and thiophene derivatives, we turned our attention to the preparation of bis-acetylenic heteroaromatic compounds **268**, as an extension of our previous findings. Thus, the reaction of 2,5-bis(butyltelluro)furan[167] and thiophene[168] **267** proceeded under mild conditions of palladium catalysis in the presence of an excess of 4 equivalents of the terminal alkyne to afford the 2,5-bis-acetylenic product **268** in good yields (Scheme 159).



SCHEME 159

In a further attempt, we reduced the amount of the alkyne employed in the cross-coupling reaction to 1 equivalent, and the solvent was changed to THF; thus we were able to isolate the 2-(butyltelluro)-5-(acetylenic) thiophenes and furans **269**, which are suitable candidates for the next cross-coupling reaction, leading to unsymmetrical 2,5-bis(acetylenic) heterocycles **268** in high yields (Scheme 160).

iv. Enynephosphonates via palladium-catalyzed cross-coupling of β-organotelluro vinylphosphonates with alkynes. Unsaturated phosphorus compounds represent an important class of synthetic intermediates. Many of these compounds have attracted attention because of their antibacterial, antiviral, antibiotic, pesticidal, anti-cancer and enzyme inhibitory properties[169]. The synthetic methods for producing the C−P bond have been extensively reviewed[170]. However, so far, only one method of enynephosphonate preparation, which utilizes palladium-mediated cross-coupling reactions of α-iodovinylphophonates with 1-alkynes, has been disclosed[171]. We have shown that β-organochalcogeno vinylphosphonates **270**, prepared by the hydrochalcogenation of 1-alkynylphosphonates, are suitable substrates for the preparation of enynephosphonates **271** via cross-coupling reactions with alkynes[172]. Thus, the optimum condition for the coupling, described in Scheme 161, was found to be the use of $PdCl_2$/CuI (20 mol% each), methanol (10 mL), β-organotelluro vinylphosphonates **270** (1 mmol), the appropriate 1-alkyne (2 mmol) and Et_3N (1 mmol) at room temperature. Using this method, several enynephosphonates **271** were prepared in good yields (Scheme 161). The stereoisomeric

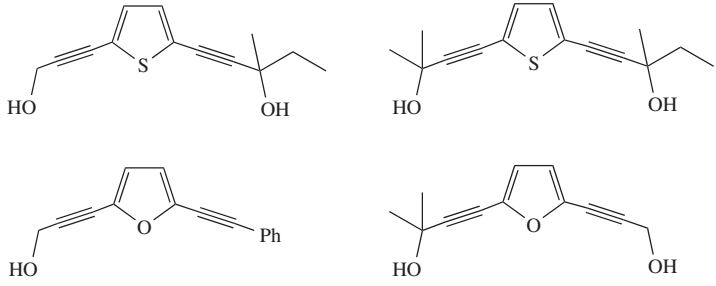


(**269**)

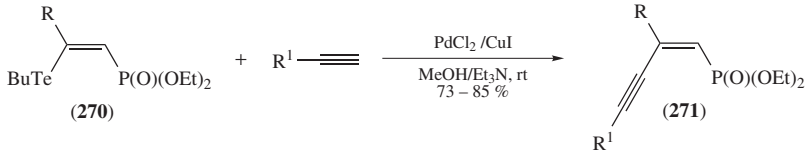
X = O, S

(**268**) 62 – 78 %

Examples of **268**:



SCHEME 160



(**270**)

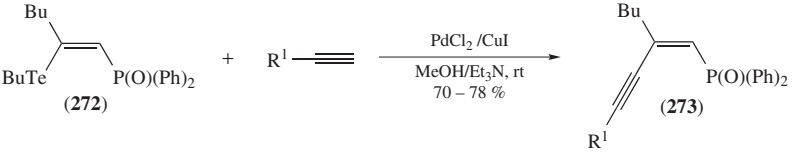
(**271**)

R = Ph, C_5H_{11}, H; R^1 = Ph, C_5H_{11}, CH_2OH, $(CH_2)_3OH$

SCHEME 161

purities of **271** were equal to those of the starting β-organotelluro vinylphosphonates **270**, indicating complete retention of the configuration in this type of reaction.

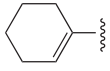
Similar reactions were developed in the preparation of enynephosphine oxides[76]. We found that the coupling reaction of compounds **272** with appropriate alkynes, under the same cross-coupling conditions described before, afforded the β-alkynyl vinylphosphine oxides **273** in 70–78% yields (Scheme 162).



(**272**)

(**273**)

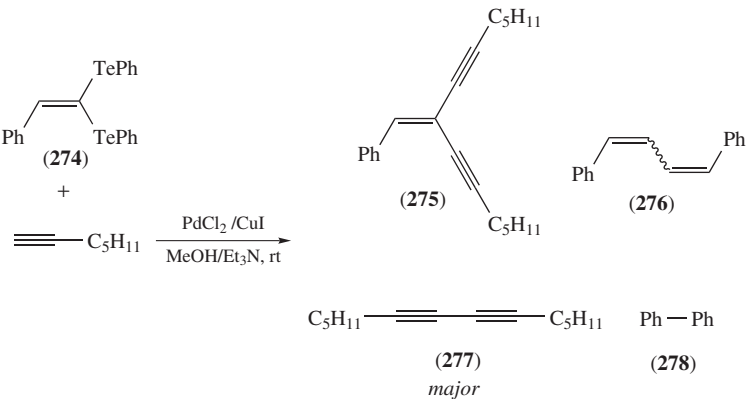
R^1 = Ph, C_4H_9, CH_2OH,



SCHEME 162

v. Synthesis of cross-conjugated geminal enediynes via palladium-catalyzed cross-coupling reaction of ketene butyltelluroacetals. The interest in developing palladium-mediated synthetic methods stimulated us to examine the reactivity of ketene telluroacetals (vinylic 1,1-bis(tellurides)) with terminal alkynes to obtain conjugated and cross-conjugated enediynes via palladium-catalyzed cross-coupling reactions[173].

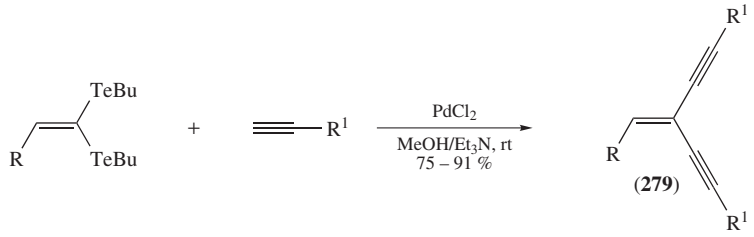
Initially, efforts were focused on the reactivity of ketene phenyltelluroacetal **274** in a cross-coupling reaction with 1-alkynes (Scheme 163). Thus, ketene phenyltelluroacetal **274** (1 equivalent) was treated in methanol at room temperature with 1-heptyne (2 equivalents) in the presence of $PdCl_2$ (20 mol%)/CuI (20 mol%) and using Et_3N (1 equivalent) as base. Under these conditions, the corresponding enediyne **275** was obtained as the minor product, but the major product **277** and a small amount of homocoupling products **276** and **278** were also isolated (Scheme 163).



SCHEME 163

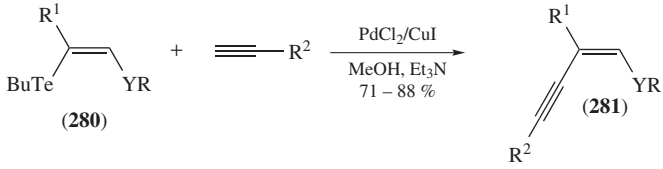
The reaction between ketene phenyltelluroacetal **274** in methanol at room temperature and 1-alkynes in the presence of $PdCl_2$ as catalyst and Et_3N as base in the absence of CuI was investigated. Under these conditions, diyne **277** was not observed. However, the cross-coupling reaction still proceeded unsatisfactorily and **275** was obtained in a mixture with **276** and **278**. After the optimizations reactions, the optimum condition for the coupling was found to be the use of $PdCl_2$ (20 mol%), CuI, MeOH (5 mL), ketene butyltelluroacetals (1 mmol), the appropriate 1-alkyne (4 mmol) and Et_3N (1 mmol) at 25 °C. In the next stage, the generality of the method was explored extending the coupling reaction to other 1-alkynes, obtaining the enediynes **279** in good yields in the absence of by-products (Scheme 164). The reaction conditions tolerate the use of functionalities, such as hydroxyl and labile acetylenic trimethylsilyl groups.

vi. Synthesis of chalcogenoenynes by palladium-catalyzed cross-coupling reactions. The coupling reaction of 1,2-bis(organylchalcogeno)-alkenes **280** with terminal alkynes was accomplished smoothly in the presence of the $PdCl_2$/CuI system to afford the chalcogenoenynes in good yields[174]. The stereochemistry of the products **281** was determined by NOE experiments and complete retention of the configuration of the double bond was observed. The reaction was efficient for a wide range of terminal alkynes and the chalcogenoenynes **281** were obtained in yields ranging from 71 to 88% (Scheme 165).



R = Ph, C_3H_7, C_5H_{11}; R^1 = C_5H_{11}, TMS, CH_2OH, $(CH_2)_3OH$, C(Me)(Et)OH

SCHEME 164



YR = SMe, SeMe; R^1 = Ph, C_5H_{11};
R^2 = CH_2OH, $(CH_2)_3OH$, CMe_2OH, C(Me)(Et)OH

SCHEME 165

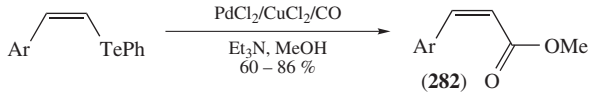
vii. Palladium-catalyzed carbonylation of vinylic tellurides with carbon monoxide. The carbonylation of vinylic tellurides in the presence of a catalytic amount of palladium dichloride and carbon monoxide was described[55b]. The reaction is carried out in methanol as solvent and the corresponding α,β-unsaturated esters **282** are isolated in good yields from a wide range of vinylic tellurides **283** and related species with different substitution patterns at the aromatic ring (Scheme 166). All products **282** were obtained in a *Z*-configuration of the double bond, which accounts for a stereoconservative reaction, as the starting tellurides were also of *Z*-configuration. This chemistry can also be extended to the synthesis of butenolides **284a** by the carbonylation of tellurides containing an internal hydroxyl group **283**. The reaction takes place in low yields of **284b** and **284c** in dichloromethane as solvent (Scheme 166).

2. Mechanistic considerations on palladium-catalyzed cross-coupling reactions

The palladium-catalyzed cross-coupling reaction of vinylic tellurides has become one of the most exciting and promising topics in the field of organic tellurium chemistry and there is still much to be discovered and understood about the subject, especially concerning the generality of substrates and their behavior toward different reaction conditions[109].

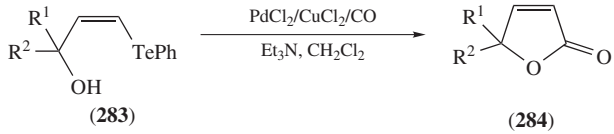
Regarding the mechanism of the reaction, some attempts have been made to clarify what occurs when an organic telluride reacts in the presence of a palladium salt. The first mechanistic proposal for this reaction was made by Uemura and coworkers for their palladium-catalyzed Heck-type reaction of organic tellurides with alkenes[128, 131].

They initially proposed that a complex between organic telluride **B** and palladium(II) **A** is formed at the initial stage, and it can exist in either a monomeric **C** or dimeric



(**282**)

Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$



(**283**) (**284**)

23% 21%

(**284b**) (**284c**)

SCHEME 166

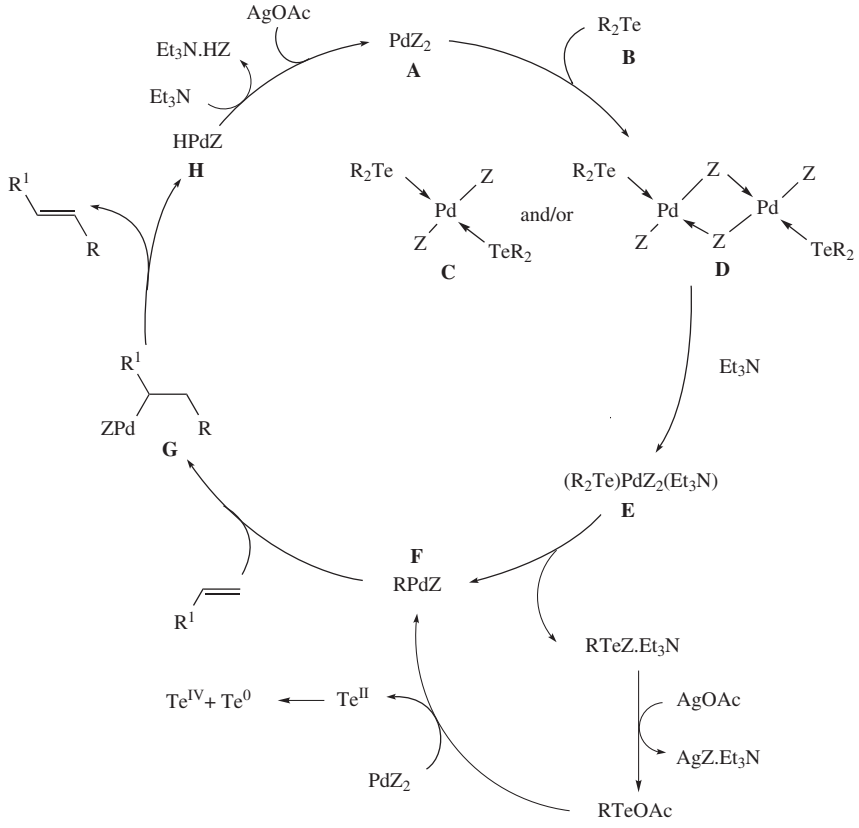
D form. After the formation of this complex, aryl or alkenyltellurium migration occurs to give species **E** which gives aryl or alkenyl-palladium species **F**, which reacts with alkenes to give arylalkenes of alkenylalkenes via an unstable σ-organopalladium complex **G**. The species produced, RTeOAc, may react with PdZ_2 to give an organopalladium species, RPdZ, and an inorganic Te(II) species; the latter disproportionates to Te^0 and an inorganic Te(IV) species. Both Et_3N and AgOAc played an important role for this catalytic coupling reaction. Et_3N may act in the formation of a new monomeric species from **C** and/or **D**. It also may be responsible for the capture of HZ from HPdZ **H**, assisting in the rapid formation of palladium(0). Silver acetate works as the oxidant of Pd(0) to Pd(II) species, forming the active catalytic species required (Scheme 167).

An elegant study described by Comasseto, Eberlin and coworkers evaluated the mechanistic details of the coupling of vinylic tellurides with alkynes promoted by palladium dichloride[175]. In order to determine the advanced intermediates of the reaction, the authors used mass spectrometry techniques.

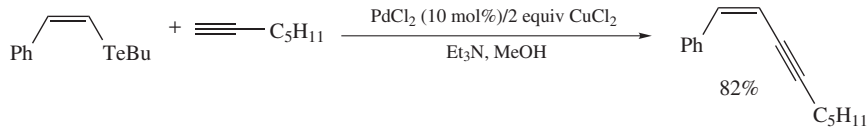
First, they developed a protocol for the cross-coupling reaction, which employed 10 mol% of $PdCl_2$ and 2 equivalents of $CuCl_2$ as a reoxidizing agent in the presence of Et_3N and MeOH as solvent (Scheme 168).

In a second stage, they investigated the coupling reaction using mass spectrometry. Electrospray ionization (ESI-MS) and tandem electrospray ionization (ESI-MS/MS)[176] were the techniques of choice for these studies, since they were applied to transfer the Pd- and Te-containing cationic intermediates, which are directly involved in the reaction, from the reaction medium to the gas phase for ESI-MS and ESI-MS/MS measurements[177].

Among the several data that could be obtained by mass spectrometry, the most relevant for the proposal of a catalytic cycle were those shown in Scheme 169, indicating which are Te- and Pd-containing cationic complexes with m/z 717, m/z 627 and m/z 499. The authors have inferred that the detection of species m/z 717 and m/z 499, in their cationic forms, by ESI suggests a solution equilibrium between them in the palladium insertion process. BuTeCl acts as a ligand that stabilizes the m/z 717 species, which is formed by the coordination of two styryl butyltellurides with $PdCl_2$, followed by transmetallation.

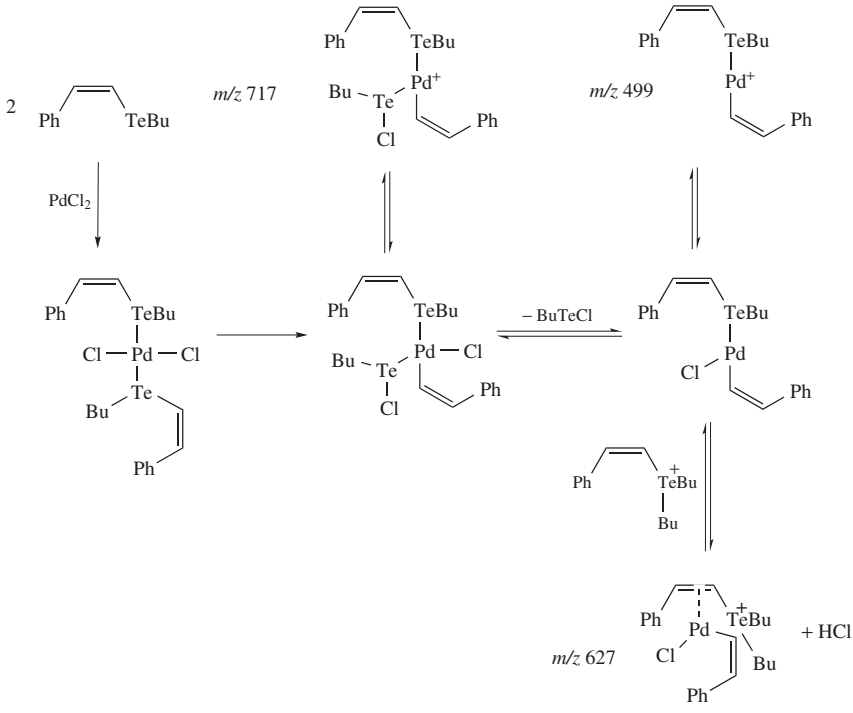


SCHEME 167



SCHEME 168

An expanded catalytic cycle, depicted in Scheme 170, is proposed by the authors based on mass spectrometry measurements. The key aspects of this proposal involve the formation of the Te- and Pd-containing complexes **K** and **L**, starting from vinylic telluride **I** and palladium intermediate **J**, which suffer a posterior insertion of the Pd atom into the $C_{sp^2}-Te$ bond to afford intermediate **M**, which upon transmetallation leads to the alkyne complex **N**. Reductive elimination delivers the enyne product and Pd(0), which is reoxidized to the active Pd(II) by reaction with $CuCl_2$, and then returns to the catalytic cycle (Scheme 170).



SCHEME 169

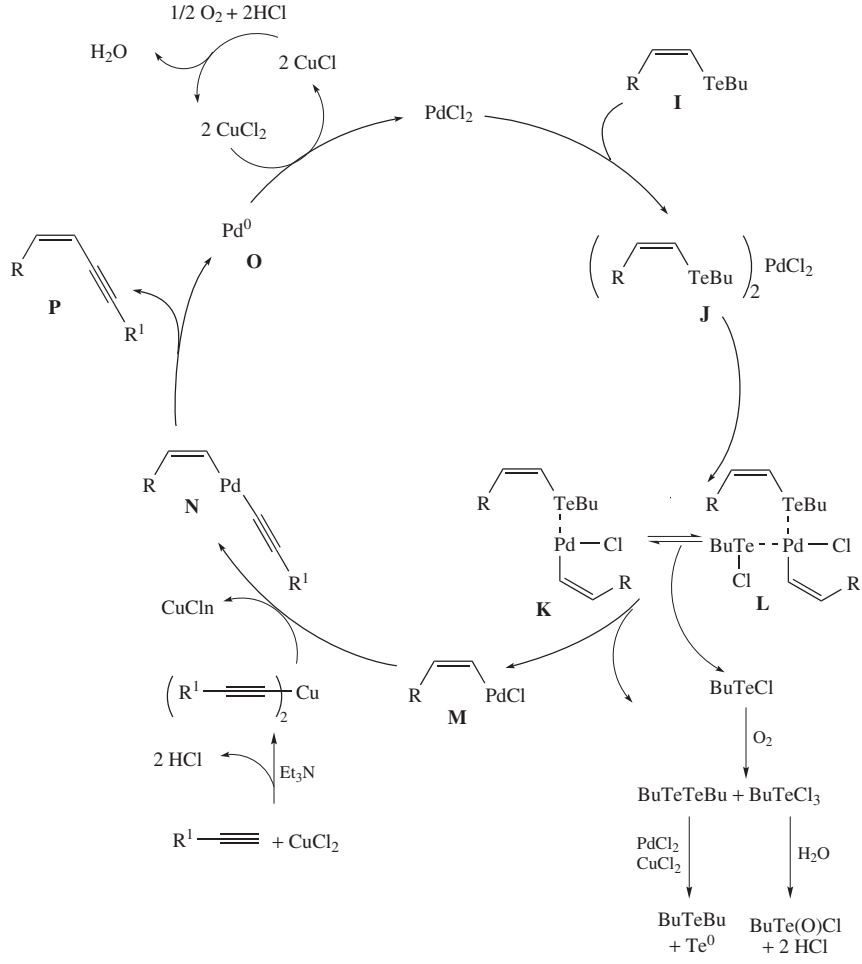
3. Nickel-catalyzed cross-coupling reactions

Nickel complexes are effective in catalyzing coupling reactions of vinylic tellurides. The first report on this subject was described by Uemura and Fukuzawa in 1982[55b]. They described the cross-coupling reaction of a vinylic telluride with excess of a Grignard reagent catalyzed by $NiCl_2(PPh_3)_2$ in THF (Scheme 171). When the reaction was performed at room temperature, lower yields and a Z:E ratio of 90:10 in favor of the Z isomer were obtained. A temperature increase to reflux temperature resulted in improved yields and an almost exclusive formation of the Z isomer. When the nickel catalyst was changed to $NiCl_2$(dppp), poor Z:E selectivities were achieved, while alkyl Grignard reagents gave much lower yields of the corresponding alkenes.

Another extension of this method was described for the preparation of unsaturated hydrocarbon **286** with loss of the tellurium group moiety[178]. The tellurobutadiene **285** reacted with PhMgBr in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ in THF with retention of the configuration of both double bonds (Scheme 172).

Trisubstituted olefin **288** was also prepared by a cross-coupling reaction of vinylic telluride **287** with PhMgBr, mediated by a nickel complex in good yield with excellent regio- and stereocontrol (Scheme 173)[179].

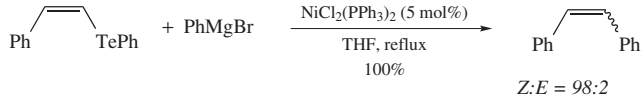
We have described a general approach to the preparation of Z and E enynes, through a nickel-catalyzed cross-coupling reaction of (Z,Z)- and (E,E)-bis-vinylic chalcogenides **80** with 1-alkynes[180]. By this method, the transfer of both vinyl groups linked to the tellurium atom was accomplished, which constitutes an attractive feature of the process. Initial efforts have employed $Ni(PPh_3)_2Cl_2$ as catalyst; however, the enynes **289** were obtained



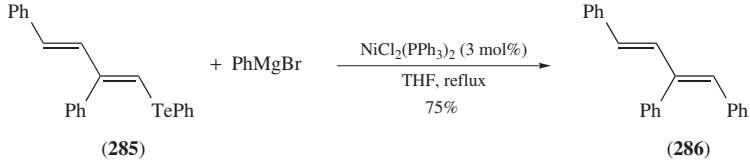
SCHEME 170

in low yields. When Ni(dppe)Cl_2 was used in the presence of CuI, an improvement was achieved and the desired products **289** were obtained in high isolated yields. The influence of the solvent was also evaluated, but we did not observe any further improvement by using THF, DMF, MeCN, CH_2Cl_2, benzene, MeOH or mixtures of them. Thus, the best conditions were established to be Ni(dppe)Cl_2 (5 mol%), CuI (5 mol%) and pyrrolidine as the solvent at room temperature. The reaction has been successfully applied to both (*Z*,*Z*)- and (*E*,*E*)-isomers and extended to telluride **290** containing free hydroxyl groups (Scheme 174).

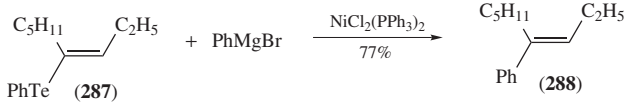
Noteworthy is the efficiency of the coupling reaction, since this is one of the first examples of cross-coupling reactions involving terminal alkynes in the presence of a nickel catalyst. Other advantages of this nickel-based system include air stability, low cost and ease of preparation of the catalyst, all of which are important considering the scale-up of a reaction.



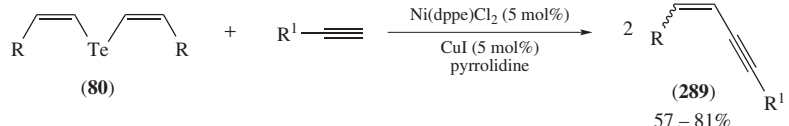
SCHEME 171



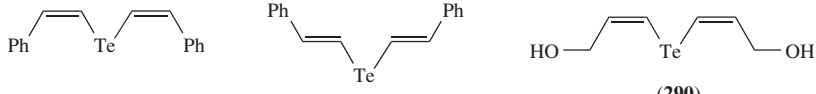
SCHEME 172



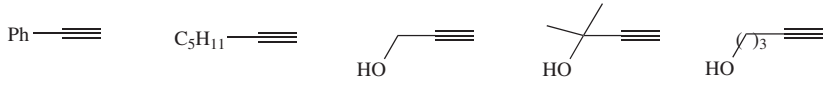
SCHEME 173



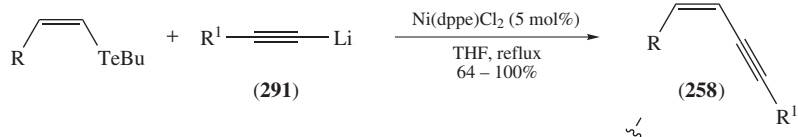
bis-vinylic tellurides

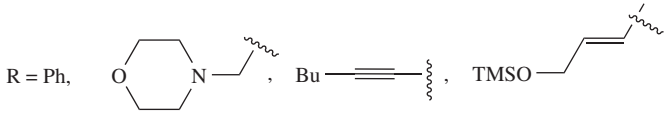


1-alkynes



SCHEME 174



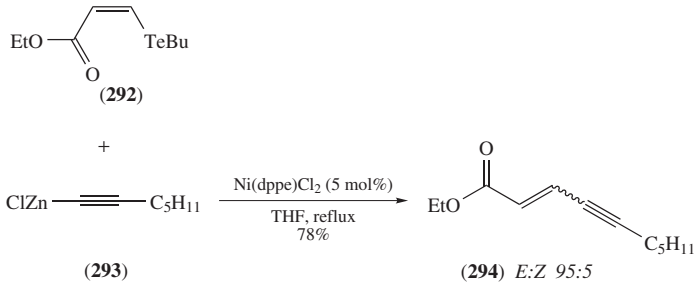


R^1 = Ph, C_5H_{11}, TMS, CH_2=CCH_3

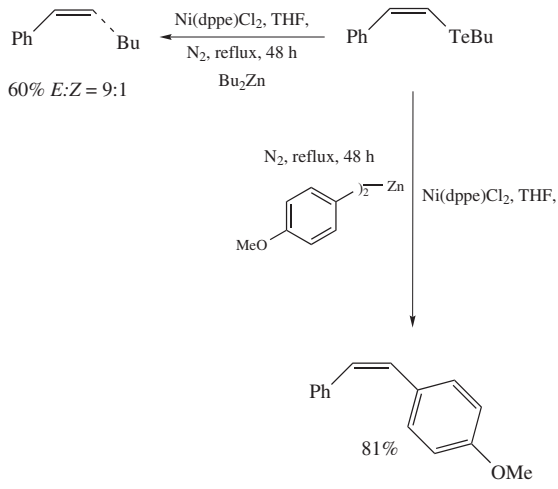
SCHEME 175

Another remarkable fact is that, if the reaction is performed with pure (*Z*,*Z*)- and (*E*,*E*)-isomers, pure *Z*- or *E*-enynes are isolated in all cases.

A variation of the above methodology was developed and consists of the synthesis of enynes **258** by the coupling of vinylic tellurides with an excess of the alkynyllithium salt **291**, in the presence of $Ni(dppe)_2Cl_2$ (5 mol%) and in the absence of CuI[181]. The reaction was carried out in THF at reflux, giving the products in high yields with retention of the double bond configuration (Scheme 175). However, when the telluride functionalized with an ester group **292** was submitted to the reaction conditions, addition of the alkynoate to the reactive ester group occurred. To circumvent this problem, transmetallation to the less reactive alkynylzinc chloride **293** was performed to give the desired product **294** in 78% yield, preferentially in the *E*-configuration (Scheme 176). The authors observed that the reduction of the catalyst and the alkynoate amounts resulted in a drop of the yield. When a telluride containing a TBS protected alcohol was employed, the reaction failed to give the expected products. The same strategy was also applied by the authors to the coupling of vinylic tellurides with sp^2 and sp^3 hybridized organometallic compounds (Scheme 177)[182].



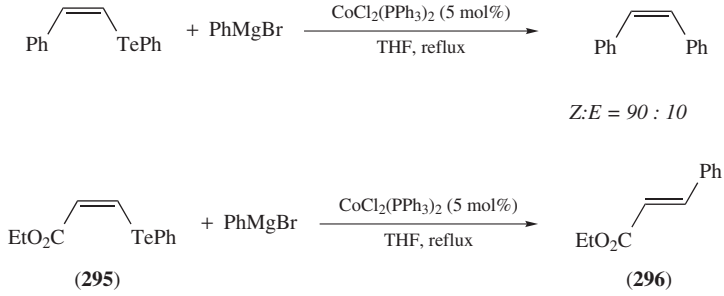
SCHEME 176



SCHEME 177

4. Cobalt-catalyzed cross-coupling reactions

Cobalt(II) has appeared as a catalyst for the cross-coupling of vinylic tellurides with Grignard reagents[183]. The reaction works for PhMgBr; however, the yields were greatly decreased for aliphatic Grignard reagents, due to a sluggish reaction (Scheme 178). The *Z*-isomer is obtained preferentially in a 90:10 *Z*:*E* ratio.



SCHEME 178

A completely different result was obtained when telluride **295** was used. Though it started from the *Z*-vinylic telluride, the isolated product **296** was the *E*-isomer, with no traces of the formation of the *Z*-isomer.

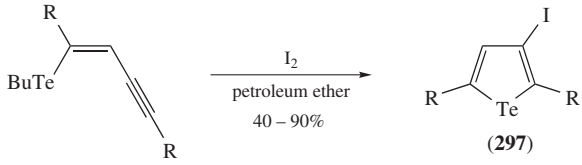
D. Miscellaneous

1. Cyclization of telluroenynes

Chalcogenophene heterocycles (S, Se, Te) and their derivatives have numerous uses in the fields of biochemistry, physical organic chemistry, materials chemistry and organic synthesis. For example, selenophene oligomers are compounds of current interest because many of them show photoenhanced biological activities[184] and crystalline polymerizations[185]. Thus, a wide variety of oligomers and related chalcogen compounds, including mixed thiophene-pyrrole oligomers, have been synthesized mainly with the expectation of obtaining excellent precursor compounds for molecular devices and electroconductive polymers[186]. The electrophilic cyclization of alkynes bearing an organotellurium moiety is a powerful approach to the preparation of several functionalized tellurophenes with high regioselectivity, particularly when one considers that there are many ways to transform selectively the resulting halogen and tellurium functionalities into a great number of interesting substituted heterocycles.

a. Iodo-cyclization of butyltelluroenynes. Tellurobutenynes are one of the most important classes of vinylic tellurides. By studying the chemistry and application of this class of compounds, Dabdoub and coworkers have discovered that they undergo cleavage of the $Te-C_{sp^3}$ bond by reaction with iodine, to produce 3-iodo tellurophenes **297** as main products[187]. The reaction is applicable to a series of tellurobutenynes and the corresponding 3-iodotellurophenes **297** are isolated in good to excellent yields (Scheme 179).

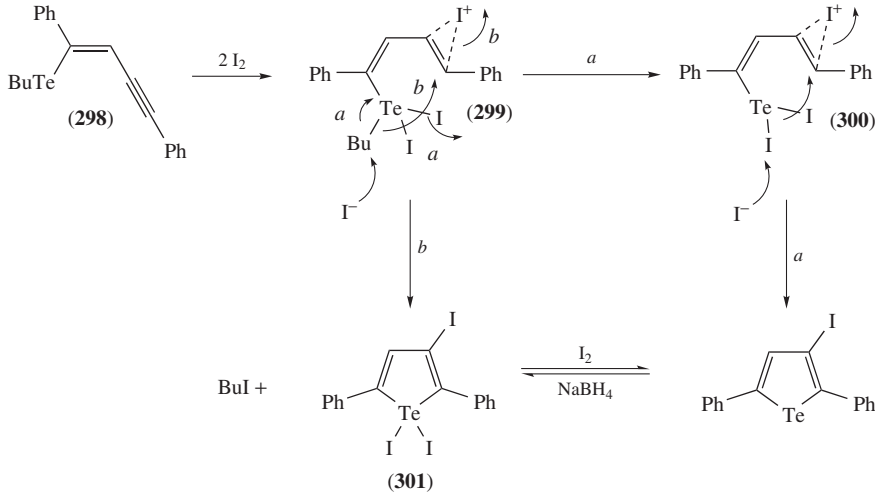
A mechanistic proposal has been provided by the authors, which consists of an initial reaction of butyltelluroenyne **298** with iodine to generate the iodonium intermediate **299**.



R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, Me, H

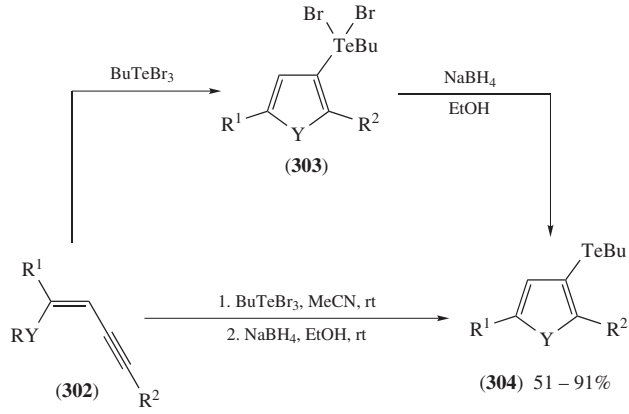
SCHEME 179

The reaction with iodide gives iodobutane and tellurenyl iodide **300**, which undergoes attack by an iodide ion at the iodine atom, followed by ring closure through opening of the iodonium ion (pathway *a*, Scheme 180). In another possibility, a direct ring closure can give the tellurophene **301** and iodobutane (pathway *b*, Scheme 180).



SCHEME 180

b. Tellurium-cyclization of butyltelluroenynes. We reported the use of butyltellurium tribromide ($BuTeBr_3$), as an electrophilic agent, in the electrophilic cyclization reaction of butyltelluroenynes[188]. We found that the reaction of (*Z*)-butyltelluroenynes **302** with $BuTeBr_3$ in CH_3CN at room temperature yielded 3-[dibromo(butyl)tellanyl]tellurophene **303** in 76% isolated yield (Scheme 181). The treatment of compound **303** with $NaBH_4$ in EtOH gave the desired 3-(butyltellanyl)tellurophene **304** (Y=Te) as the product in quantitative yield (Scheme 181). Since the product **304** was obtained in two-step processes, we tried to use a one-pot reaction to prepare the same product. In this way, (*Z*)-butyltelluroenynes **302** were treated with $BuTeBr_3$ in CH_3CN at room temperature for 24 hours, and after that a solution of $NaBH_4$ and EtOH was added and the product was obtained in an acceptable yield (Scheme 181). The methodology was extended to a series of (*Z*)-butyltelluroenynes giving the 3-(butyltellanyl)tellurophene derivatives

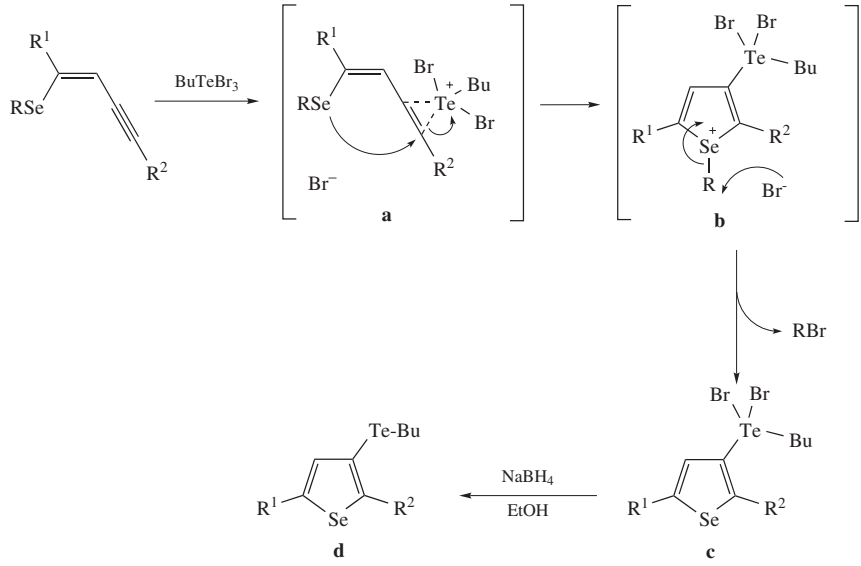


Y = Se, Te; R = alkyl; R^1, R^2 = H, alkyl, aryl

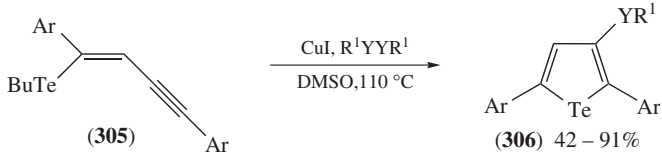
SCHEME 181

in good yields. We believe that the mechanism of this tellurium cyclization reaction involves the following: (i) coordination of the carbon–carbon triple bond to the $BuTeBr_3$ to generate a telluronium intermediate **a**, (ii) *anti* attack of the selenium atom on the activated telluronium intermediate to produce the salt **b**, and (iii) facile removal of the alkyl group by the bromide ion present in the reaction mixture to generate the corresponding 3-dibromo(butyl)tellanyl]selenophene **c** and one molecule of RBr. The reduction of **c** with $NaBH_4$ in EtOH gave the corresponding 3-(butyltellanyl)tellurophenes **d** as the product (Scheme 182).

c. Copper iodide-catalyzed cyclization of butyltelluroenynes. In 2008, we described a simple and efficient copper-catalyzed cyclization of telluroenynes **305** and established a new route to obtain 3-substituted tellurophenes **306** in good yields (Scheme 183)[189]. The best results were obtained using telluroenyne (0.5 mmol), diorganyl dichalcogenide (1.1 equivalent), CuI (10 mol%) in DMSO (3 mL) at 110 °C for 10 h. Since the accomplishment of this reaction is probably dependent on the nature of the group directly linked to the chalcogen atom, we explored this influence using different aryl and alkyl groups, and the results revealed that the reaction with telluroenynes having an alkyl group bonded at the tellurium atom gave the tellurophene derivatives in good yields, although the yields were lower for telluroenynes with a methyl or ethyl group. Nonetheless, performing the reaction with telluroenyne having an aryl group bonded at the tellurium atom, the desired product was not observed, even under long reaction time. These results demonstrated that the efficiency of the chalcogenophene formation significantly depended on the steric effects and that this cyclization reaction occurred only with chalcogenenynes having a $Y-C_{sp^3}$ bond (Scheme 184). Our working mechanism for the copper-catalyzed conversion of chalcogenoenynes to chalcogenophenes was based on experimental data obtained: (1) in all cases, we isolated the BuYAr as by-product; (2) the reaction did not work with Cu(0) catalyst; (3) no product was obtained when a sp^2 carbon was bonded to the tellurium atom; and (4) no product was obtained in the absence of both copper salt and dichalcogenides. Then it could involve (a) CuI inserts into the Y–Y bond to give a Cu(III)-tetracoordinated square-planar selenolate **a**[190], (b) alkyne coordination to the metal center to give the cationic organo-Cu(III) complex **b**, (c) *anti*-attack of the chalcogen atom on the activated

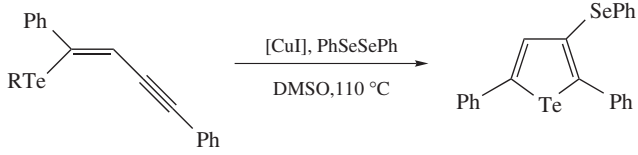


SCHEME 182



R^1 = C_6H_5, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, *m*-$CF_3C_6H_4$, *o*-MeC_6H_4, *n*-Bu; Y = Se, Te

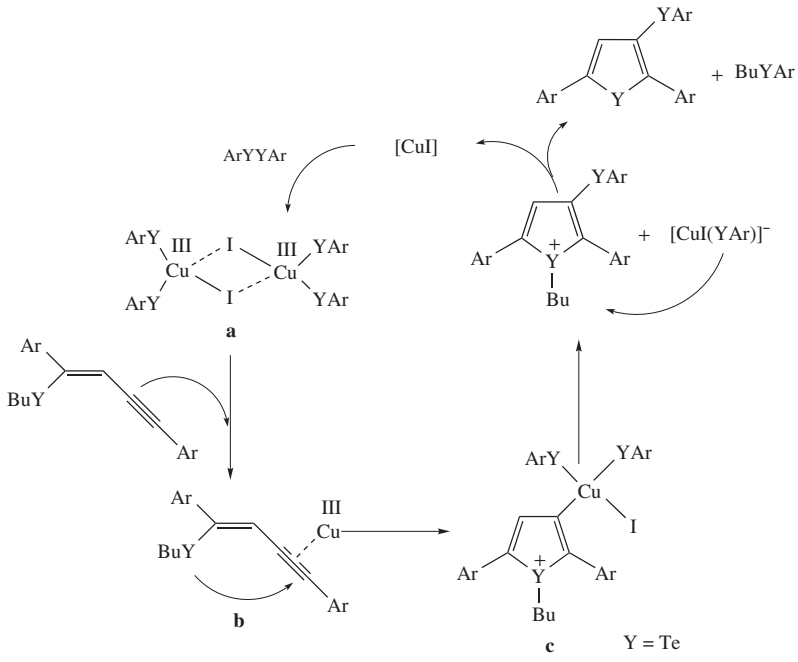
SCHEME 183



R = *n*-Bu = 79%
R = Et = 44%
R = Me = 47%
R = Ph = no reaction

SCHEME 184

triple bond to produce the chalcogen salt **c**, (d) the Cu(I) anionic complex formations [CuI(YAr)]-, and (e) nucleophilic attack of selenolate anion on the alkyl group bonded to the chalcogen atom (Scheme 185).



SCHEME 185

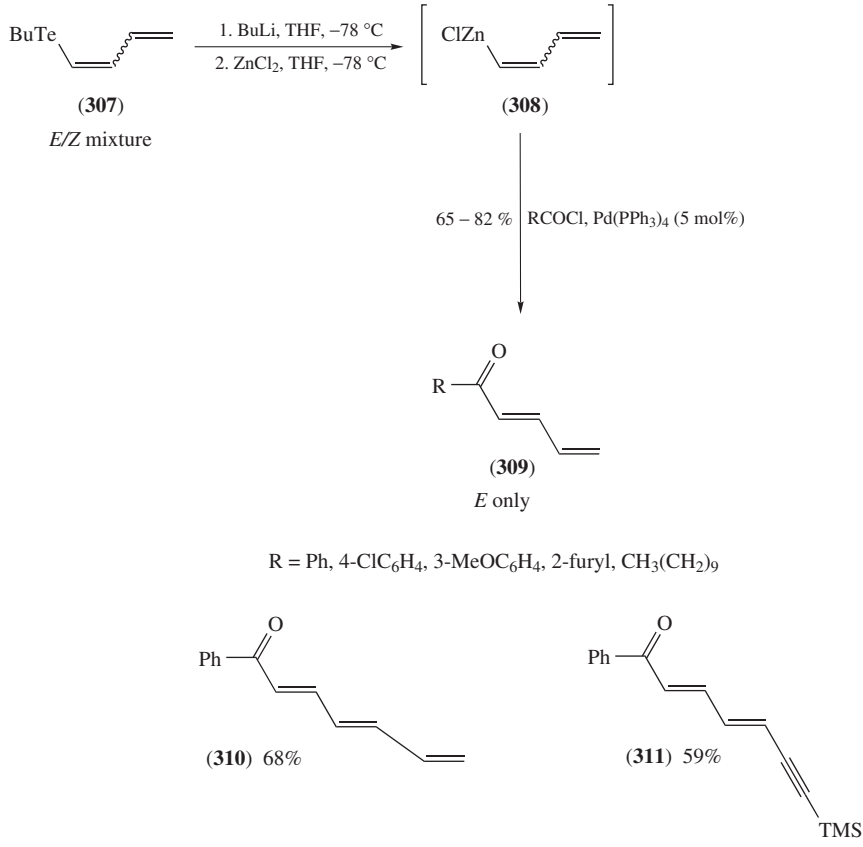
2. Stereoselective preparation of conjugated polyenic ketones

A sequential transmetallation/cross-coupling reaction of vinylic tellurides, which aims to prepare conjugated polyenic ketones, has appeared in the literature[191]. The reaction consists of the treatment of a vinylic telluride **307** with BuLi, followed by the transmetallation of the vinyllithium intermediate to a vinylzinc reagent **308**, which is coupled with acyl chlorides to afford the conjugated polyenic ketones **309** with high stereoselectivity. Important to note is the fact that *E*:*Z* mixtures of the vinylic telluride can be employed in the reaction, and the product **309** is always isolated as the *E*-isomer with no trace of the *Z*-isomer (Scheme 186).

The best catalyst for this transformation was found to be $Pd(PPh_3)_4$, although $Pd(PPh_3)_2Cl_2/i\text{-}Bu_2AlH$ (1:2) can also be used. This procedure allows the synthesis of other highly unsaturated conjugated systems, such as trienone **310** and dienynone **311**, with high stereoselectivity (Scheme 186).

3. Internal acetylenes from vinylic tellurides

Vinylic tellurides, having no β-hydrogen on a sp^3 carbon, were quicky transformed into internal alkynes **312** when treated with aqueous sodium hypochlorite solution. Similar



SCHEME 186

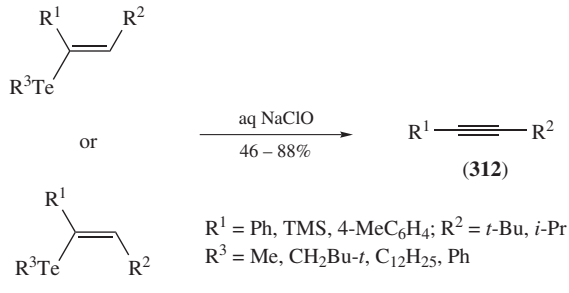
results have been achieved when the oxidizing agent was changed to H_2O_2 or *t*-BuOOH. The internal acetylenes **312** were obtained in good isolated yields (Scheme 187)[192].

IV. APPLICATIONS TO THE SYNTHESIS OF NATURAL PRODUCTS

A. Synthesis of Montiporic Acids A and B

Two new polyacetylenic acids, namely Montiporic Acids A and B, were isolated by Fusetani and coworkers[193] from the eggs of scleractinian hard coral *Montipora digitata*, a hermaphroditic coral. The bioassays of these acids show that both exhibited antibacterial activity against *Escherichia coli* and cytotoxicity against P-388 murine leukemia cells (IC_{50} values of 5.0 and 12.0 $\mu g\,mL^{-1}$).

The total synthesis of both acids was accomplished in 1999, using vinylic telluride chemistry[194]. Montiporic Acid B **313** has a terminal double bond, which has been proven to be the major challenge in the synthesis of the compound. After several attempts to convert a terminal alkyne to the desired alkene, the reduction by means of a hydrotelluration reaction followed by a detelluration reaction through a Te/Li exchange proved to be a



SCHEME 187

successful means of overcoming this difficulty. The hydrotelluration was performed under $(BuTe)_2/NaBH_4$ conditions and furnished two regioisomeric vinylic tellurides, **314** and **315**, in an 8:1 ratio in favor of the 1,2-*Z*-product **314**. This mixture was then treated with *n*-BuLi in THF, to give the intermediate vinyl lithium, which is protonated by quenching with NH_4Cl to furnish the desired alkene **316** in 97% yield (Scheme 188). It is important to point out that this approach gave better results than the common Lindlar reduction.

B. Synthesis of Polyacetylenic Acids Isolated from *Heisteria acuminata*

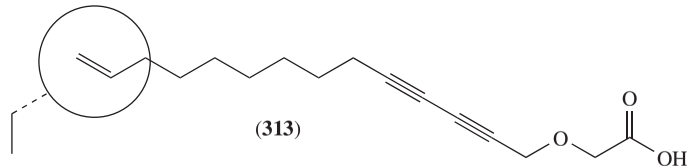
The non-cyclic polyacetylenic acids **317** and **318** (Scheme 189) were isolated from the bark of *Heisteria acuminate* by bioassay-guided fractionation[195]. These compounds were found to have potent anti-inflammatory activity by the inhibition of cyclooxygenase (COX) and 5-lipoxygenase (5-LO)[196]. Polyacetylenes have been previously reported in the literature as potent inhibitors of the arachidonic acid metabolism[197]. Therefore, it may be inferred that these compounds are, at least in part, responsible for the anti-inflammatory activity of *Heisteria acuminate* bark preparations used in folk medicine.

Their unusual structure, attractive biological activities and scarce natural availability prompted us to synthesize them[198]. The retrosynthesis of both acids shows that the key *Z*-enediyne skeleton of the structure could be constructed by a palladium-catalyzed cross-coupling reaction of a *Z*-vinylic telluride **319** with the appropriate diyne alcohol **320** (Scheme 189).

Thus, the synthesis of vinylic telluride **319** was accomplished by the hydrotelluration of a terminal alkyne **321** through a reaction with BuTeLi, generated *in situ*, to afford the vinylic telluride **319** in a 6:1 mixture of regioisomers, in favor of the *Z*-1,2-vinylic telluride. Both isomers were easily separated by column chromatography, and the major product was obtained in 48% yield. The tellurides were then coupled with the appropriate alkynes **320** under $PdCl_2$/CuI conditions to exclusively afford enediyne alcohol **322** with the desired *Z* configuration (Scheme 190).

C. Synthesis of Polyacetylenic Acids Isolated from *Nanodea Mucosa*

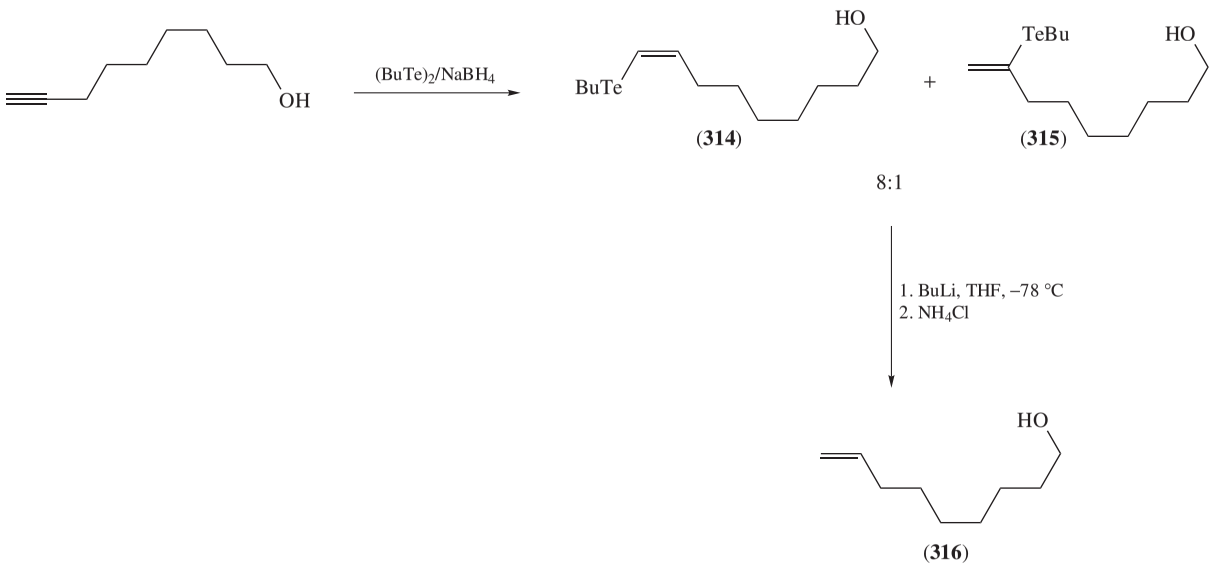
Two linear polyacetylenic acids [(13*E*)-octadec-13-en-11-ynoic acid] **323** and (13*E*)-heptadec-12-en-10-ynoic acid **324** (Figure 10) were isolated from the aerial parts of *Nanodea muscosa*, a small herb found in extreme southern regions of South America[199]. The authors also elucidated the structure of compounds **323** and **324** by spectroscopic



(**313**)

Reduction of a triple bond by means of hydrotelluration/detelluration

Montiporic Acid B

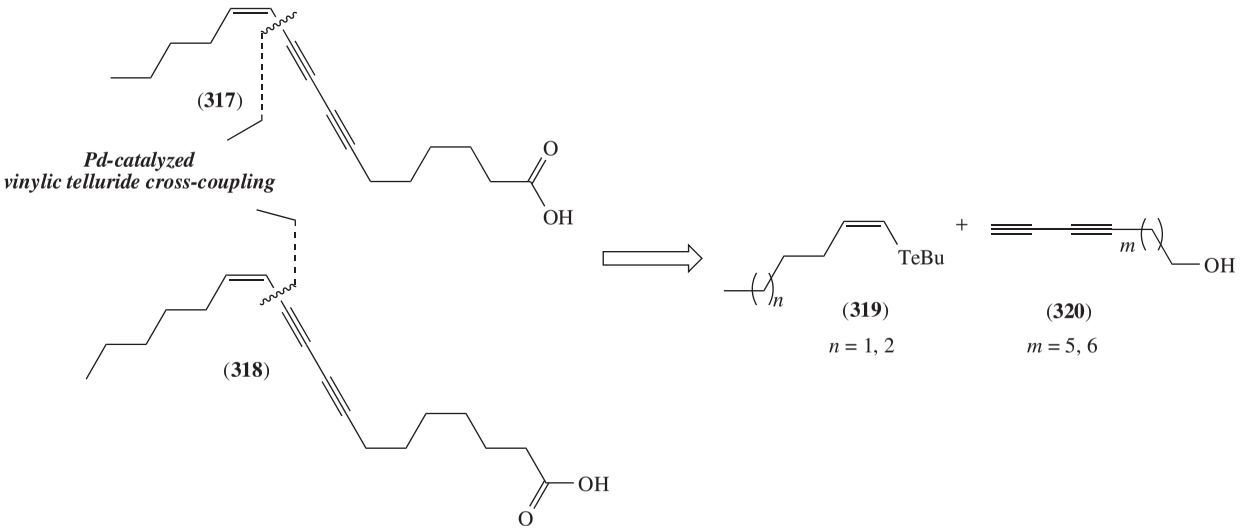


(**314**) + (**315**)

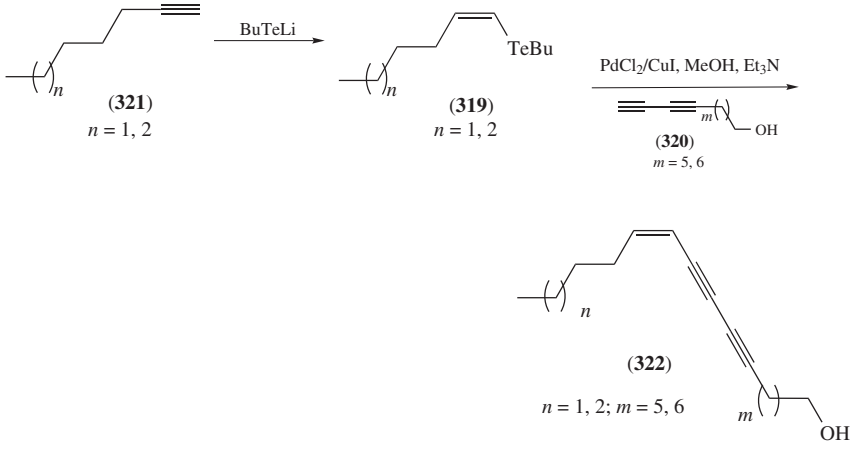
8:1

(**316**)

SCHEME 188


(317)
Pd-catalyzed
vinylic telluride cross-coupling
O
OH
(318)
OH
O
TeBu
n
(319)
n = 1, 2
+
m
OH
(320)
m = 5, 6

SCHEME 189



SCHEME 190

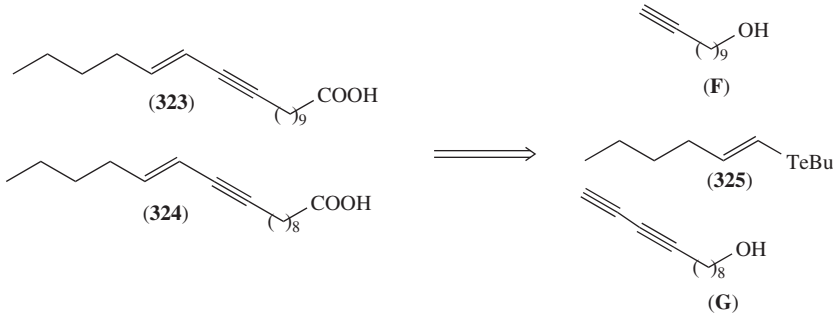
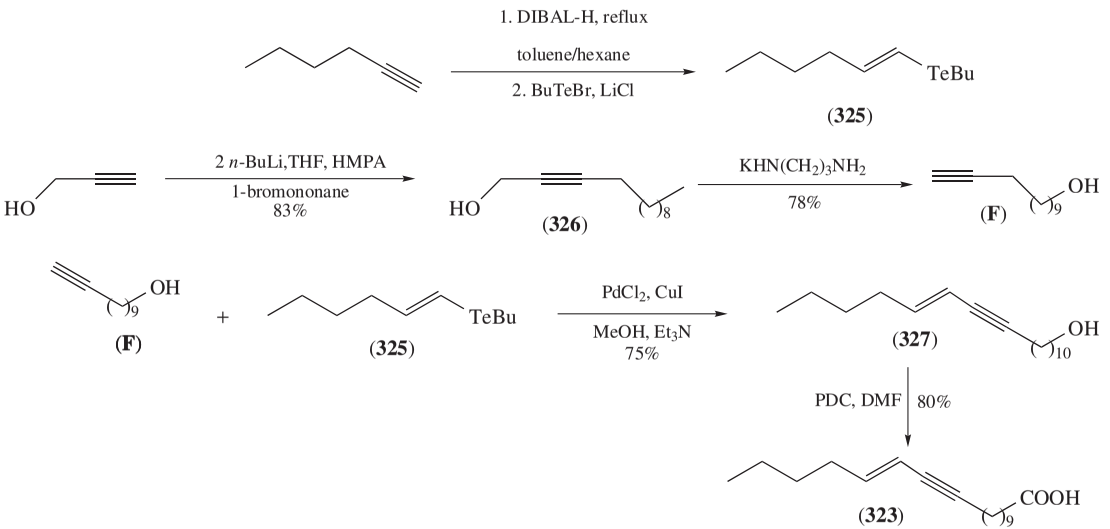


FIGURE 10

methods and assigned their absolute stereochemistry. The challenge of this synthesis, reported by our group[200], was to build the requisite *E*-stereochemistry of the double bond (Figure 10). It could be easily achieved using one of the most important behaviors of the vinylic tellurides; their high stereospecific synthesis and reactivity.

The retrosynthetic analysis of compounds **323** and **324** afforded three basic fragments: (*E*)-vinylic telluride **325**, alkyne **F** and 1,3-alkadiyne system **G**. Both polyacetylenic acids **323** and **324** could be derived from the (*E*)-vinylic telluride **325**, a key intermediate to this synthesis (Scheme 191). Firstly, the synthesis of the (*E*)-vinylic telluride **325** was carried out by the hydroalumination of 1-hexyne followed by the reaction with BuTeBr/LiCl in 52% yield (Scheme 191)[27]. Polyacetylenic acid **323** was synthesized following the sequence shown in Scheme 191. The synthesis of alkyne **F** began by the treatment of propargylic alcohol with 2 equivalents of *n*-BuLi in HMPA/THF[11] to generate the corresponding dianion, which was subsequently quenched with 1-bromononane to afford alcohol **326** in 83% yield. This compound was subjected to prototropic migration of triple bond with potassium 3-aminopropanamide (KAPA)[201] to afford the desired


1. DIBAL-H, reflux
toluene/hexane
2. BuTeBr, LiCl
TeBu
(325)
HO
2 n-BuLi,THF, HMPA
1-bromononane
83%
HO
(326)
KHN(CH2)3NH2
78%
OH
(F)
OH
(F)
+
TeBu
(325)
PdCl2, CuI
MeOH, Et3N
75%
(327)
OH
PDC, DMF
80%
COOH
(323)

SCHEME 191

terminal acetylenic alcohol **F** in 78% yield. The cross-coupling reaction of **F** with the (*E*)-vinylic telluride **325** using $PdCl_2$/CuI in methanol[154] afforded **327** in 75% yield, with the desired *E* geometry of the double bond. Next, the oxidation of **327** using PDC in DMF[202] gave polyacetylenic acid **323** in 80% yield. The overall yield of total synthesis was 38%. Polyacetylenic acid **324** was synthesized according to Scheme 191. The synthesis of fragment **G** started with the alkylation of the dilithium derivative of propargylic alcohol with 1-bromoheptane[203], yielding the alkynyl alcohol in 80% yield. This compound was subjected to prototropic migration of triple bond with KAPA to afford terminal acetylenic alcohol **328** in 76% yield. Subsequent coupling reaction of acetylenic alcohol **328** with alkynyl iodide **329** using CuI and pyrrolidine[204] yielded diyne **330** in 85%. Treatment of compound **330** with NaOH in toluene under reflux[205] afforded 1,3-alkadiyne system **G** in 71% yield. This terminal diyne was coupled to the (*E*)-vinylic telluride **325** using $PdCl_2$/CuI in methanol, under reflux, giving the enediyne system **331** in 74% yield. The oxidation with PDC in DMF provided the corresponding polyacetylenic acid **324** (78%). The overall yield of this total synthesis was 21% (Scheme 192).

D. Synthesis of 1-(*Z*)-Atractylodinol

The total synthesis of 1-(*Z*)-atractylodinol **332** was achieved using a newly developed telluride synthon and revealed a novel application for the Negishi-type coupling reaction employing vinyl tellurides[206]. 1-(*Z*)-Atractylodinol **332** is a natural product isolated from the dried rhizomes of *Atractylodes lancea* De Candolle (Chinese: Cangzhu) widely used in China and Japan against rheumatic diseases, digestive disorders, night blindness and influenza (Figure 11)[207–211]. The retrosynthetic approach for 1-(*Z*)-atractylodinol **332** is outlined in Figure 11. The vinyl telluride **334**, that was required for assembling the *Z*-double bond, was prepared in 83% yield via a stereoselective hydrotelluration of 1,3-butadiyne **333**. The protection of the terminal alkyne as its trimethylsilyl derivative **335** followed by a cross-coupling reaction with an excess of 2-furylzinc chloride (3 equivalents) gave **336** in a 78% yield (Scheme 193). Treating **336** with sodium carbonate in methanol followed by Cadiot–Chodkiewicz coupling reaction with **337** gave the desired 1-(*Z*)-atractylodinol **333** in 24% yield. The poor yield obtained for 1-(*Z*)-atractylodinol **333** is probably due to its extreme instability and rapid polymerization to a pale orange solid. This behavior was observed before, and the authors attributed this instability to the furan moiety, which promotes polymerization due to its susceptibility for addition reactions (Scheme 194).

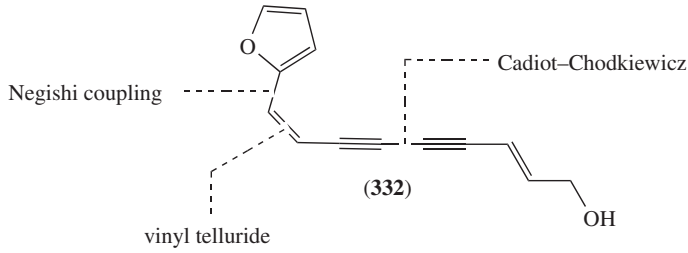
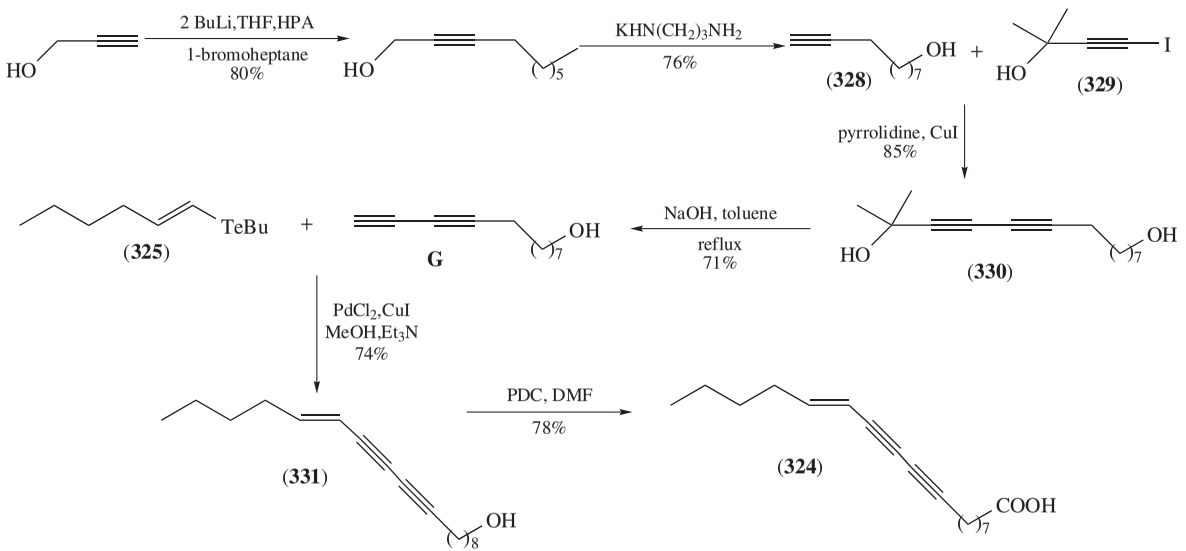
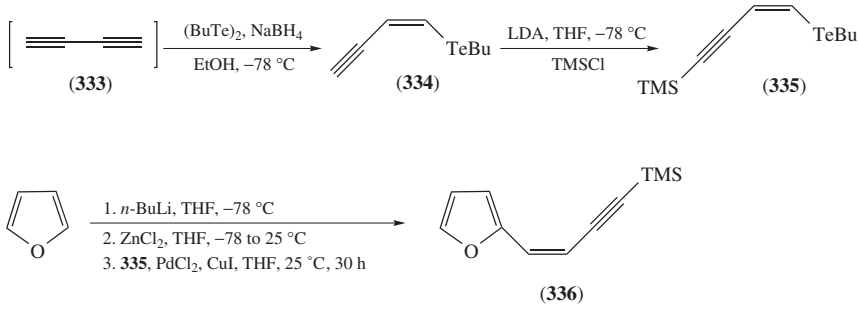


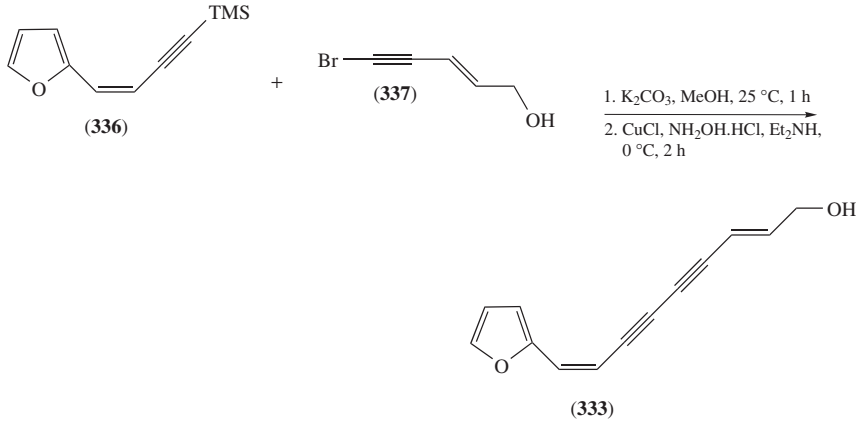
FIGURE 11


2 BuLi,THF,HPA
1-bromoheptane
80%
KHN(CH2)3NH2
76%
(328)
(329)
pyrrolidine, CuI
85%
(330)
NaOH, toluene
reflux
71%
(325)
G
PdCl2,CuI
MeOH,Et3N
74%
PDC, DMF
78%
(331)
(324)

SCHEME 192



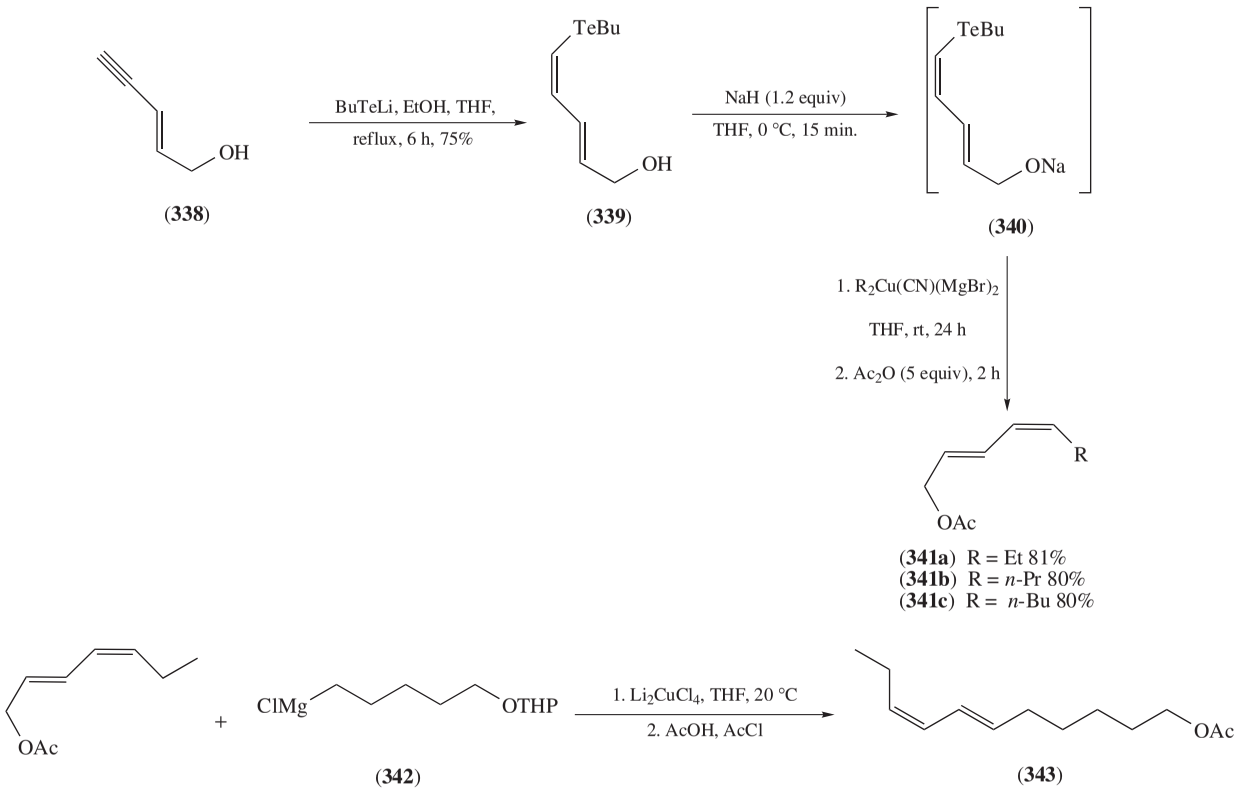
SCHEME 193



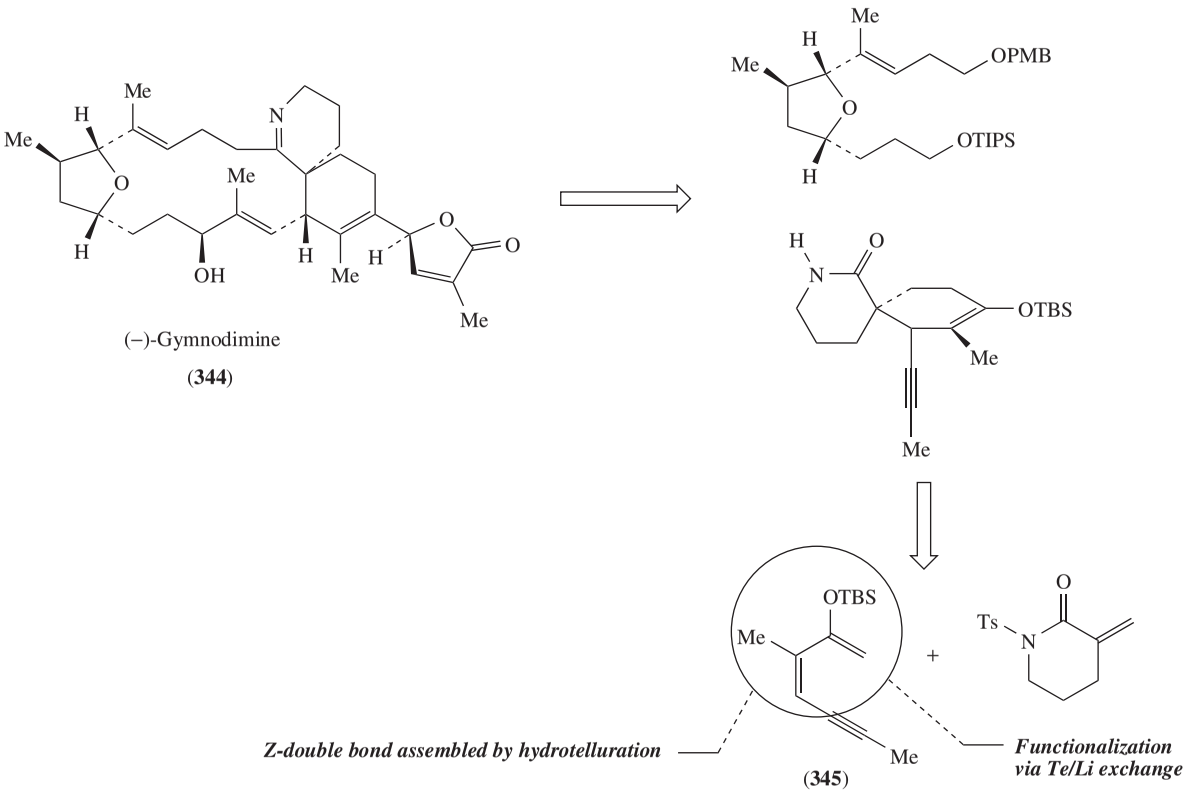
SCHEME 194

E. Synthesis of Insect Pheromones

The acetates **341a–c** constitute precursors of the insect sex pheromones of, respectively, *Lobesia botrana*[212], *Bombyx mori*[213] and *Malacososma disstria*[214]. Their synthesis were described by Comasseto and coworkers in 2006 (Scheme 195)[215]. Their synthesis employed a strategy that elaborated the tellurodiene **339**, a common precursor for this class of compounds. The tellurodiene **339** was prepared by reaction of **338** with lithium butyltellurolate, prepared *in situ* from insertion of elemental tellurium into *n*-butyllithium in THF, in the presence of ethanol[66]. The tellurodiene **339** was transformed into the corresponding alcoholate **340** by reaction with sodium hydride in THF at 0 °C. This solution was then transferred via canula to a solution of a previously prepared magnesium alkylcyanocuprate in THF at room temperature. The reaction of this cuprate with an excess of acetic anhydride at room temperature gave the (*Z*,*E*)-dienic acetates **341a–c** in good yields (Scheme 195). The treatment of **341a–c** with the appropriate Grignard reagent **342** in the presence of dilithium tetrachlorocuprate, followed by deprotection and acetylation, gave the sex pheromone of *Lobesia botrana* **343** (Scheme 195).


OH
(338)
BuTeLi, EtOH, THF,
reflux, 6 h, 75%
TeBu
OH
(339)
NaH (1.2 equiv)
THF, 0 °C, 15 min.
TeBu
ONa
(340)
1. R2Cu(CN)(MgBr)2
THF, rt, 24 h
2. Ac2O (5 equiv), 2 h
R
OAc
(341a) R = Et 81%
(341b) R = n-Pr 80%
(341c) R = n-Bu 80%
OAc
+
ClMg
OTHP
(342)
1. Li2CuCl4, THF, 20 °C
2. AcOH, AcCl
OAc
(343)

SCHEME 195

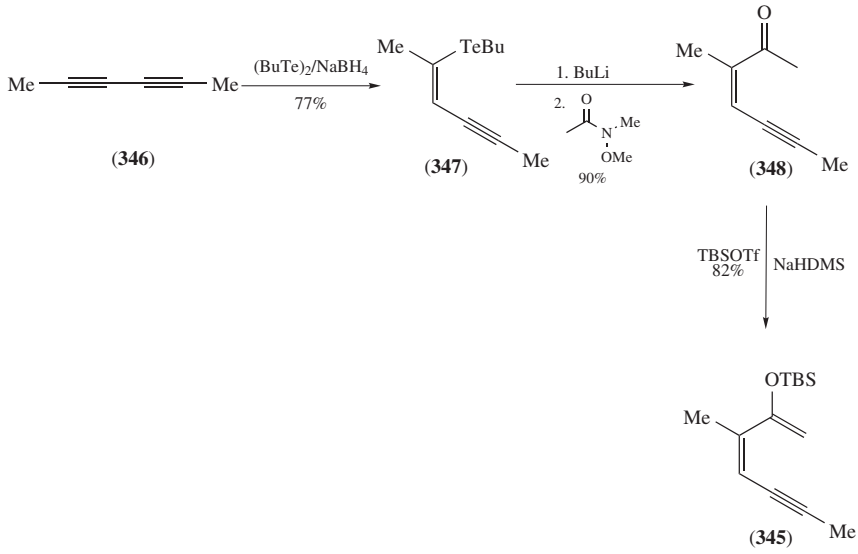

(–)-Gymnodimine
(344)
OPMB
OTIPS
OTBS
Me
Ts
Z-double bond assembled by hydrotelluration
Functionalization via Te/Li exchange
(345)

SCHEME 196

F. Studies Toward the Synthesis of (–)-Gymnodimine

Gymnodimine **344** is a member of a class of isolated marine toxins that possess unusual spirocyclic imines within macrocycles that also contain an ether or polyether subunit[216]. The relative or absolute stereochemistry of gymnodimine was determined by X-ray analyses[217]. An approach toward the total synthesis of (−)-gymnodimine **344** was described by Romo and coworkers, in which they envisioned the use of a Diels–Alder strategy to access the spirocyclic moiety of the molecule as a key step of the synthesis (for retrosynthesis see Scheme 196)[218].

The required diene **345** for the Diels–Alder reaction was prepared by taking advantage of the unique features of tellurium chemistry. A hydrotelluration of propyne dimer **346** furnished a vinylic telluride **347** with a *Z*-configuration of the double bond. The posterior Te/Li exchange reaction followed by the capture of the vinyl anion by the Weinreb amide gave the corresponding ketone **348**, which upon treatment with base and *tert*-butyldimethylsilyl triflate, under carefully controlled conditions, furnished enol ether **345** without isomerization. It is noteworthy that the tellurium/lithium exchange proceeded with complete retention of the geometry of the double bond. In this study, it is relevant that the diene was prepared on a large scale (*ca* 5 g) (Scheme 197).



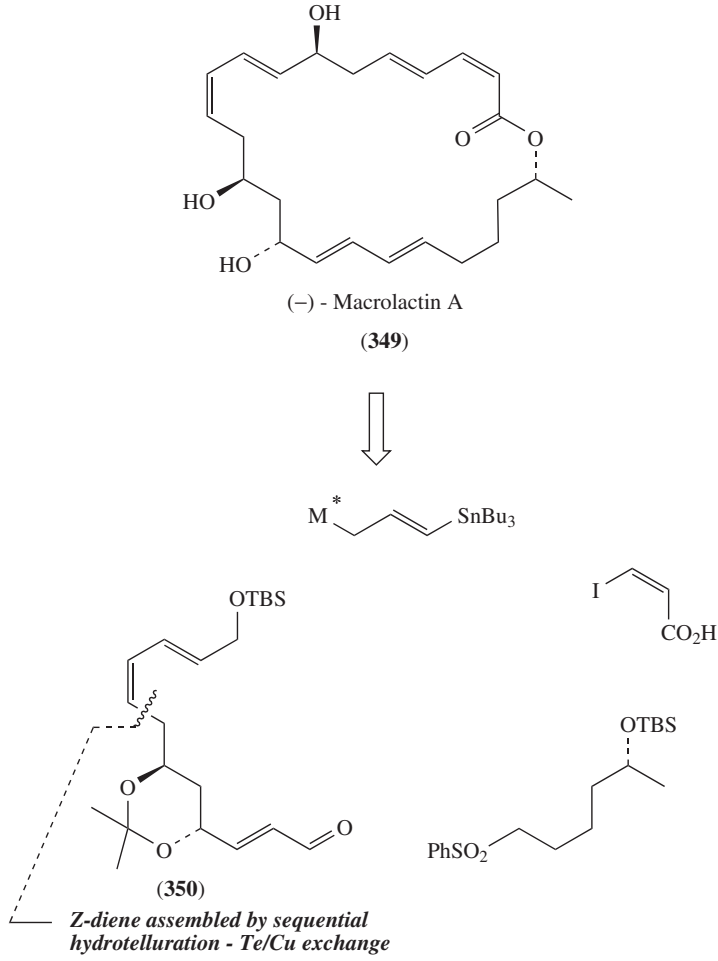
SCHEME 197

G. Synthesis of (–)-Macrolactin A

The macrolactins are a class of secondary metabolites isolated from a deep-sea bacterium[219]. Macrolactin A **349** exhibits a broad spectrum of activity with significant antiviral and cancer cell cytotoxic properties, including the inhibition of B16-F10 murine melanoma cell replication with an *in vitro* IC_{50} value of $3.5\,\mu g\,mL^{-1}$. It also has implications for controlling human HIV replication and for inhibiting *Herpes simplex* types I and II. Stereochemical assignments for Macrolactin A were made through the comparison of spectral

data with those already established for Macrolactins B and F[220] and the first total synthesis developed by Smith and Ott[221].

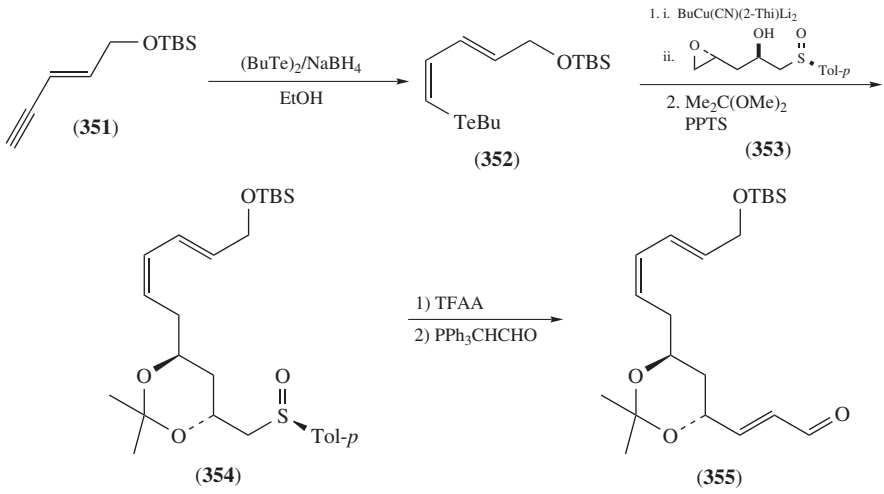
In another total synthesis, developed by Marino, Comasseto and coworkers, the retrosynthetic analysis of the molecule involved the construction of a key fragment containing a diene moiety using tellurium chemistry (Scheme 198)[222].



SCHEME 198

Initially, the *Z*-diene **350** moiety was assembled by a hydrotelluration reaction of terminal enyne **351** via $(BuTe)_2/NaBH_4$ in ethanol, which exclusively afforded *Z*-vinylic telluride **352** in 92% yield. Further transmetallation with a higher order cyano cuprate resulted in *Z*-vinylic cuprate which reacted with chiral epoxides **353** to furnish 1,3-anti diol, which is protected as its acetonide derivative **354**. Later, a Pummerer reaction at a sulfoxide group delivered the corresponding aldehyde. Wittig homologation resulted in

the desired diene fragment **355** as a single stereoisomer (Scheme 199). It is noteworthy that both hydrotelluration and the Te/Cu exchange occurred with complete control of the stereochemistry, and without formation of the *E*-diastereoisomer of the double bond.



SCHEME 199

V. CONCLUSIONS

Over the last decade, the importance of vinylic tellurides in organic synthesis has grown dramatically. In this chapter, we have presented numerous synthetic routes and applications of vinylic tellurides. The reactions discussed herein demonstrated the high synthetic potential of vinylic tellurides as useful precursors in organic synthesis. As mentioned in this chapter, most of the reactions were carried out under mild conditions at room temperature. On the other hand, the use of tellurium chemistry for synthetic organic chemists or as a tool in organic synthesis has been hampered due to a bad reputation related to the bad smell, toxicity or instability of these compounds. In fact, these comments are true for a particular group of organotellurium compounds, but it is not a rule for all tellurium compounds. In our lab, we have used many different classes of organotellurium compounds and observed that tellurides or ditellurides bearing an alkyl group, with a low molecular weight, have a bad smell. However, when these alkyl groups present any additional substituent, the corresponding tellurides or ditellurides are practically odorless. Other tellurium compounds, such as organotellurium trihalides, diaryl tellurides and ditellurides, are solids, very stable (can be stored in the lab, in a simple flask, for a long time) and completely odorless. In addition, the vinylic tellurides, one of the most used classes of organotellurium compounds, contain either an aromatic or an aliphatic with saturated or unsaturated chains, all of which are odorless compounds and can be easily prepared, purified and stored as a common chemical used in the lab. At this time the bad reputation related to these compounds is over. Hence, the vinylic tellurides are very powerful and useful substrates and we have no doubt that many further applications will appear in the future, mainly in electrophilic cyclizations or palladium cross-coupling reactions, as well as studies in the toxicological and pharmacological aspects.

VI. ACKNOWLEDGMENTS

We are pleased to thank our collaborators (students and coworkers) whose names appear in the references, for their dedicated and devoted contributions to our own work described herein. We are also grateful to CAPES (SAUX), CNPq (INCT-INAMI and INCT-catalise) and FAPERGS (PRONEX-10/0005-1) for financial support of our research. G. Z. and P. H. M. thank CNPq for fellowships.

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Electrochemistry of organic selenium and tellurium compounds

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I. INTRODUCTION

Electrochemical investigations of organic selenium and tellurium compounds have not been reviewed so extensively as applications of these compounds in organic synthesis. In monographic chapters dealing with electrochemistry of organoelemental

PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0571

and organometallic compounds only a few examples of such studies were mentioned[1]. More information was given in a Russian monograph[2], which however is not available in English. A comprehensive review on the oxidation and reduction processes of the title compounds, including many results of electrochemical investigations, was published recently by Detty and Logan[3]. However, electrode syntheses of organoselenium and organotellurium compounds were not discussed there. On the other hand, because of great interest in organoselenium reagents in organic synthesis a wide array of electrochemical methods were developed to be applied for their preparation as intermediates or starting reactants for further processes. These applications were often stimulated by unique properties of organoselenium and tellurium compounds: the selenium or tellurium fragments can be easily introduced into organic systems and, after appropriate transformations, selenium and tellurium atoms can be easily removed. Moreover, for both, the introduction and removal of chalcogen groups, electrochemical methods can be used. Synthetic applications of the title compounds, important in organic chemistry but also in the field of organic metals, liquid crystals and biologically and pharmacologically active compounds, are considered to be more interesting for readers of this Chapter and thus will be discussed in more detail.

Section II of this Chapter presents a review of investigations on the synthesis of organoselenium and tellurium compounds and their functionalization. In this Section are described: the electrode synthesis including the processes which use directly the elemental selenium and tellurium (Section II.A) as well as anodic reactions based mainly on the generation of arylselenium or tellurium cations (Section II.B) and the cathodic reduction, in particular based on the generation of organoselenium or tellurium anions (Section II.D). The preparation of new organic selenium or tellurium compounds by anodic functionalization of already available chalcogen compounds is given in Section II.C. A brief review on the electrochemical synthesis in which organic selenium compounds play only the role of intermediates or catalysts is given in Section III.

The successive sections present the discussion on electrochemical behavior of the title compounds: the anodic behavior is presented in Section IV, and the cathodic reduction in Section V. The anodic oxidation was more extensively investigated and thus the results presented in Section IV are divided into separate parts, each of them concerned with a different class of selenium and/or tellurium compounds.

In this Chapter the following common abbreviations are used, beside those used in this book: TEAP, tetraethylammonium perchlorate; TBAP, tetrabutylammonium perchlorate; LiICA, lithium *N*-isopropylcyclohexylamide; CV, cyclic voltammetry; $E_{1/2}$, half-wave potential; E_p, cathodic or anodic peak potential; $E_{p/2}$, half-peak potential; GC electrode, glassy carbon electrode; RDE, rotating disc electrode; F, Faraday constant; EWG, electron-withdrawing group; and M, mole dm^{-3}.

The quoted potentials are given against the same reference electrodes as those originally used in the measurements, i.e. mainly versus an aqueous saturated calomel electrode (SCE) or versus the Ag/Ag^+ couple in acetonitrile.

II. ELECTROCHEMICAL SYNTHESIS AND FUNCTIONALIZATION OF ORGANIC SELENIUM AND TELLURIUM COMPOUNDS

A. Direct Synthesis from Elemental Selenium and Tellurium

Elemental selenium and tellurium can be used directly for the electrode synthesis of their organic compounds. The reduction at a graphite cathode of a suspension of selenium in aqueous solutions containing sodium sulfate and saturated with acrylonitrile results in $Se(CH_2CH_2CN)_2$ (**1**) with 23% yield[4,5]. The proposed reaction mechanism involves the formation of hydrogen selenide as the intermediate according to equations 1a and 1b. The

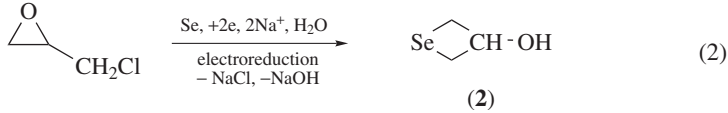
tellurium analog $Te(CH_2CH_2CN)_2$ can be synthesized using a tellurium cathode in similar conditions[4,5].

$$Se + 2H_2O + 2e \rightarrow H_2Se + 2OH^- \quad (1a)$$

$$H_2Se + 2CH_2{=}CHCN \rightarrow Se(CH_2CH_2CN)_2 \quad (1b)$$

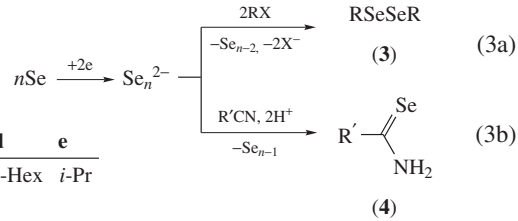
(1)

The electroreduction at a graphite cathode of epichlorohydrin in aqueous solutions of NaCl in the presence of a powder of metallic selenium[6] gives **2**, according to equation 2, with the current efficiency of 50%. The possible use of Se and Te as sacrificial electrodes in the electrochemical formation of their organic compounds was mentioned in patents[7]; however, no evidence that the desired reactions occur were given there. Twenty years had elapsed before this idea was realized after successful preparation of a selenium electrode by fusing a 3:1 mixture of Se and graphite on a platinum net[8–10]. It was found that the application of cathodic potentials to such an electrode in aprotic solvents results in the formation of polyselenide ions, Se_n^{2-}, which can react with organic halides[8,9] and nitriles[10] giving diselenides **3** (equation 3a) and amidoselenides **4** (equation 3b). The typical electrolysis of RX was performed in DMF using a cell with a diaphragm and some examples of the yields of the products and potentials applied are given in Table 1. Ditellurides RTeTeR (**5**) were prepared[11,12] (Table 1) using a similar cathode with tellurium fused upon platinum but with small modifications of the procedure. Namely, after electrochemical generation of polytelluride ions in anaerobic conditions, mainly of Te_4^{2-}, the electrolyte was cooled to 5–10 °C and then organic halide was added. The electroreduction in the presence of MeI resulted in the formation of trimethyltelluronium iodide Me_3TeI (80%)[12]. The unsymmetrical telluride *c*-HexTeTeMe was obtained in 60% yield by the consecutive addition of *c*-HexCl to a cooled (5 °C) electrolyte, followed by MeI after 48 hours at room temperature. Moreover, using α,ω-dihalides XRX (**6**), cyclic compounds **7** with two tellurium atoms in the ring were prepared according to reaction 4. However, **8** with only one Te atom in the ring was obtained[12], but not isolated, from $Br(CH_2)_4Br$.



(2)

(2)



3	**a**	**b**	**c**	**d**	**e**
R	2-$O_2NC_6H_4$	4-NCC_6H_4	Bn	*c*-Hex	*i*-Pr

(4)

In general, the above-mentioned method has a mechanism corresponding to the S_N2 substitution. However, later Degrand and coworkers[13–15] elaborated a method based on the radical nucleophilic substitution, the $S_{RN}1$ mechanism. Sacrificial selenium and tellurium electrodes were used in this method and the best results were found for tea bag-type cathodes, prepared from pieces of graphite cloth in the form of a double jacket containing Se pearls or Te pellets[13]. The electrochemically induced $S_{RN}1$ substitution, described by overall reaction 5a, was carried out in MeCN containing 0.1 M Bu_4NPF_6 and using

TABLE 1. Yields of diselenides $(RSe)_2$ and ditellurides $(RTe)_2$ synthesized by the electrolysis of RX using selenium[8,9] or tellurium[11,12] electrodes, respectively[a]

R	$(RSe)_2$	$-E^b$ (V)	Yield (%)	$(RTe)_2$	Yield (%)
Bn	**3c**	1.25	96	**5a**	50
2-$NO_2C_6H_4$	**3a**	0.95	92		-
n-Hex		-	-	**5f**	68
c-Hex	**3d**	1.2	70	**5g**	66
n-Pr		-	-	**5d**	57
i-Pr	**3e**	1.25	90	**5e**	73
$PhCOCH_2$		1.8	74[c]		-
Me		-	-	**5b**	32
Et		-	-	**5c**	74
$C_{10}H_{21}$		-	-	**5h**	80
n-$PrMe_2SiCH_2$		-	-	**5i**	55
$PhMe_2SiCH_2$		-	-	**5j**	60

[a]Electrolysis in DMF containing 0.1 M $NaClO_4$. X = Br with the exception of **3a, 3c** and **5i** where X = Cl and **5b** where X = I.
[b]Cathodic potential vs. SCE applied to the Se electrode[8]. The potential applied to the tellurium electrode was always -1.4 V vs. SCE[11,12].
[c]Obtained[8] by the addition of RX to a solution of Se_n^{2-} ions after cooling to 0 °C.

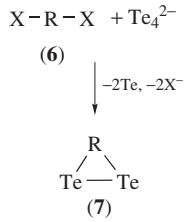
at first a three-compartment cell equipped with membranes[13,14]. Later on, a more convenient undivided cell with a magnesium anode was proposed[15] and reasonable yields were obtained if fluoride salt, e.g. $Et_4NF{\cdot}2H_2O$, was added before electrolysis in order to obtain **10c**–**10f** or after the first step for the preparation of ArEPh. The total process includes cathodic dissolution of chalcogen electrode (Se, Te and also a sulfur-graphite electrode[16]) in reaction 5b and the reduction of ArX (**9**) yielding aryl radical in reaction 5c. The following reaction of nucleophiles with aryl radicals according to equation 5d is the key step, which is favored by nitrile or carbonyl substituents in the radical. The last reaction 5d is much faster in MeCN than in DMSO[17]. Further possible steps, including side reactions with a solvent, are shown in Scheme 1. For example, the electroreduction of 4-bromobenzophenone at Se cathode resulted[13] in the formation of diselenide **10a** with 40% yield, diarylselenide ArSeAr (Ar = $PhCOC_6H_4$; 20%) and benzophenone (6%) were formed probably in reaction 5f with the solvent. On the other hand, the yields of **10j** and **10k** were 54% and 70%, respectively[14] if selenium was reduced before the reduction of ArX. A similar $S_{RN}1$ mechanism induced by the cathodic reduction of **10** was also reported by Degrand and coworkers, as will be discussed in Section II.C.

5	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
R	Bn	Me	Et	*n*-Pr	*i*-Pr	*n*-Hex	*c*-Hex	$C_{10}H_{21}$	*n*-$PrSiMe_2CH_2$

RTe—TeR (**5**)

(**8**)

6, 7	**a**	**b**	**c**	**d**
R	$(CH_2)_3$	$(CH_2)_5$	$(CH_2)_6$	$(CH_2)_2O(CH_2)_2$
Yield (%)	20	26	30	70



(4)

$$2\,ArX + E_2^{2-} \xrightarrow[S_{RN}1]{-2X^-} ArEEAr \qquad (5a)$$

(**9**) (**10**) E = S, Se, Te

10	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
E	Se	Te	Se	Te	Se	Te	Se	Te	Se	Se	Se
Ar	4-$PhCOC_6H_4$	4-$PhCOC_6H_4$	4-NCC_6H_4	4-NCC_6H_4	1-Naph	1-Naph	Ph	Ph	4-ClC_6H_4	9-anthryl	2-quinolyl

$$2E \xrightarrow{2e} E_2^{2-} \qquad (5b)$$

$$ArX \underset{}{\overset{e}{\rightleftharpoons}} [ArX]^{-\bullet} \xrightarrow{-X-} Ar^{\bullet} \qquad (5c)$$

$$Ar^{\bullet} + E_2^{2-} \rightleftharpoons (ArE_2^-)^{-\bullet} \qquad (5d)$$

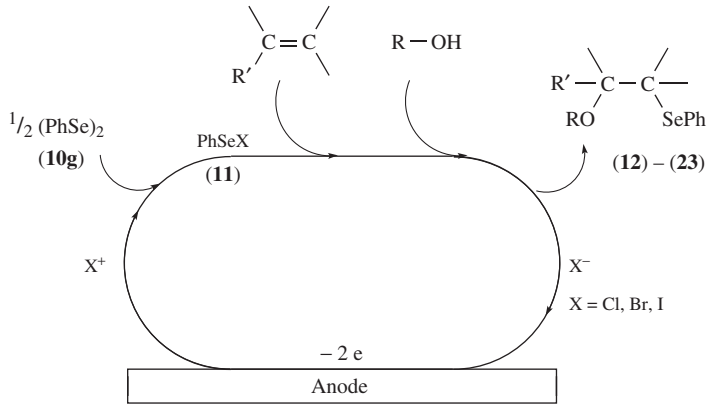
$$(ArE_2^-)^{-\bullet} + ArX \xrightarrow{-X-} ArE_2^- + Ar^{\bullet} \longrightarrow (ArEEAr)^{-\bullet} \xrightarrow{ArX} ArEEAr + [ArX]^{-\bullet} \qquad (5e)$$

$$Ar^{\bullet} + CH_3CN \longrightarrow ArH + {}^{\bullet}CH_2CN \qquad (5f)$$

SCHEME 1

B. Synthesis by Anodic Reactions

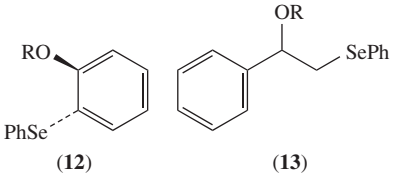
Most electrochemical reactions leading to the synthesis of new organoselenium and tellurium compounds were based on the anodic oxidation of diphenyl diselenide (**10g**), which then forms an electrophilic phenylselenenylating reagents. The introduction of the phenylseleno group into unsaturated compounds and its removal are easy and thus this functionality is important in organic synthesis. Torii and coworkers described convenient electrochemical methods for oxyselenenylation of olefins[18–21] (Scheme 2) and for the formation of α-phenylselenenyl carbonyl compounds[22] (Scheme 3). In both methods **10g** was used directly without the necessity for formation of the activated reagents PhSeX, X = Cl, Br, OH, CN, NR_2, etc. However, in fact the reaction is promoted by anodic oxidation of a catalytic amount of halide ions[18–20, 22], as is shown in Schemes 2 and 3, with the formation *in situ* of a halonium ion X^+ (or bromine Br_2[18,22]) which reacts with **10g** giving phenylselenenyl halide (**11**). The electrolysis was performed in an undivided cell at room temperature in protic media with small amounts of sulfuric acid in order to suppress oxidation of the solvent (and to help the enolization of some ketones[22]) using a platinum foil as the anode. A number of methoxy, acetoxy and hydroxyselenides **12**–**23** were obtained[18] using MeOH, AcOH and aqueous acetonitrile, respectively, as solvents. Electrolytic oxyselenenylation was performed with high yields of the isolated products and high regioselectivities (namely, the high Markovnikov to anti-Markovnikov isomer ratio)[18]. The yields of oxyselenides were high for chloride as well as bromide and iodide ions (e.g. for electrolysis of cyclohexene in MeOH the yields were equal to 95%, 96% and 97%, respectively), but the current efficiency was poor for the latter ions[18].



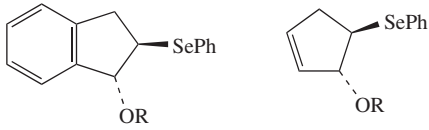
SCHEME 2

The electrochemical oxyselenenylation of olefins without halide ions as mediators but with the generation of phenylselenenyl reagents PhSeOMe or PhSeOH during the electrolysis of **10g** in MeOH or MeCN–H_2O, respectively, was also reported[21]; more details will be mentioned in Section III.

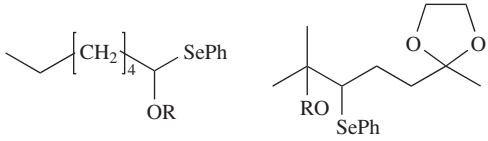
For α-phenylselenenylation of carbonyl compounds (Scheme 3) in MeOH, AcOH or MeCN, the presence of magnesium ion was necessary (probably to promote enolization) in order to obtain final selenides **24**–**31** with a good yield[22]. For example, for α-phenylselenoketones **24**–**27**, obtained from cycloalkanones by electrolysis at platinum electrodes in AcOH, the isolated yield based on **10g** was in the range of 84%–97%, much higher than for other, non-electrochemical methods. Selenenylation of active methine compounds giving **28** and **29** was obtained[22] by the addition of triethylamine.



(**12**) (**13**)

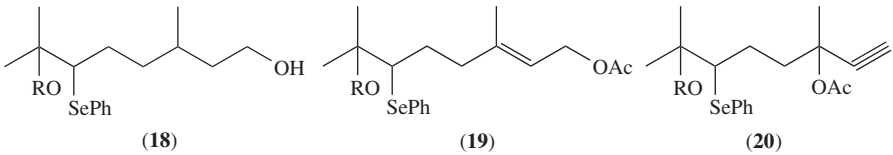


(**14**) (**15**)

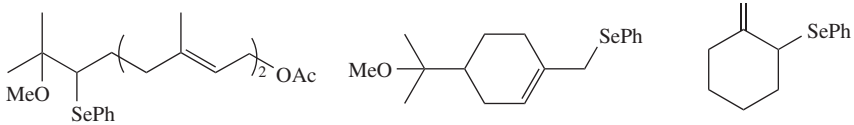


(**16**) (**17**)

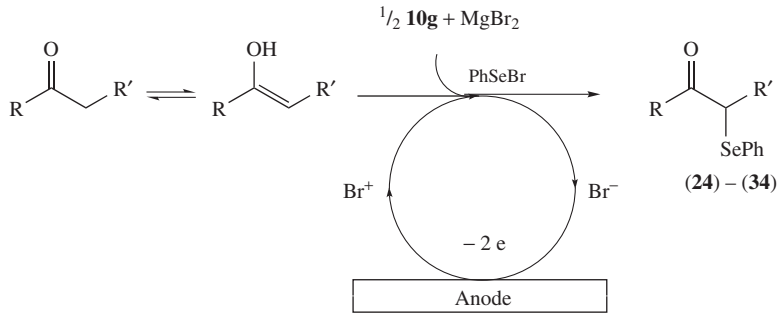
Compound	R	Yield (%)	Markovnikow isomer (%)
12a	Me	96	-
12b	Ac	98	-
12c	H	96	-
13a	Me	91	100
13b	Ac	96	100
13c	H	92	100
14a	Me	91	98
14b	H	91	100
15	Me	89	99.6
16a	Me	92	83
16b	H	94	86
17	Me	80	100
18a	Me	90	99.5
18b	H	91	98
19a	Me	83	100
19b	H	80	98
20a	Me	91	99
20b	H	93	99
21	-	56	98
22	-	63	100
23	-	95	100



(**18**) (**19**) (**20**)

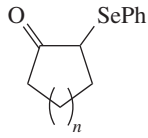


(**21**) (**22**) (**23**)

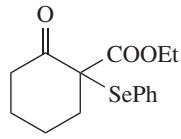


(**24**) – (**34**)

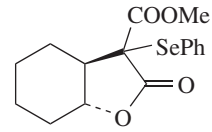
SCHEME 3



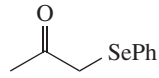
(**24**) $n = 1$
(**25**) $n = 2$
(**26**) $n = 3$
(**27**) $n = 8$



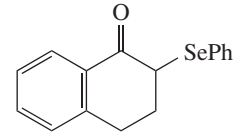
(**28**)



(**29**)

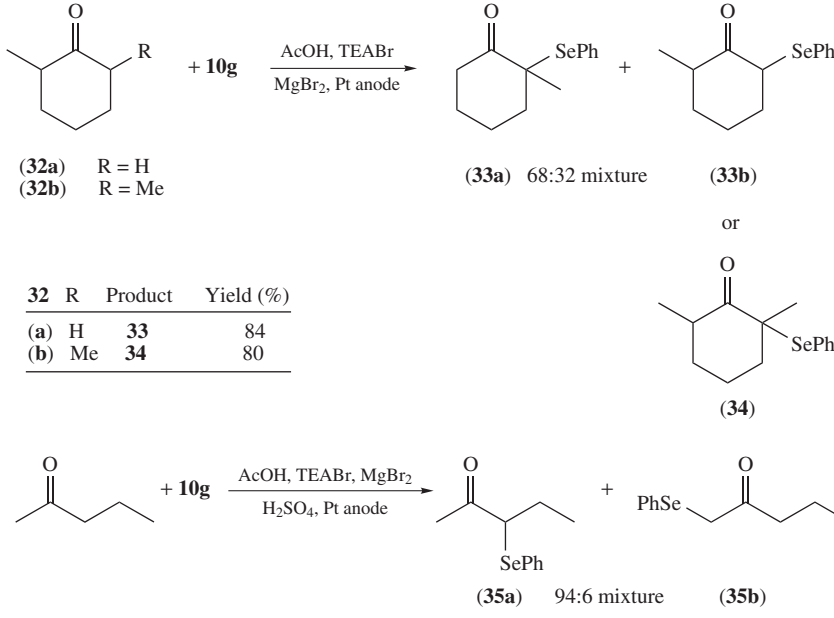


(**30**)



(**31**)

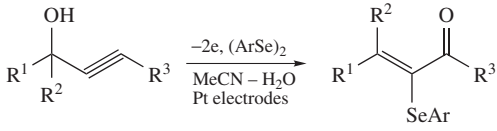
However, the effectiveness of the synthesis depended remarkably on the nature of the halide ion. For example, the electrolysis of cyclohexanone in the presence of Br^-, Cl^- and I^- ions afforded **25** with the yield of 96%, 70% and 9%, respectively[22]. On the other hand, α-phenylselenenylation of tetralone producing **31** (with the isolated yield 71%) was performed in methanol containing $MgSO_4$ (and sulfuric acid), because in the presence of $MgBr_2$ (as in Scheme 3) the reaction results in α-bromoketone as the main product. Other results[22] including syntheses of **33** or **34** from **32** and of the mixture of **35a** and **35b** are shown in Scheme 4.



32	R	Product	Yield (%)
(**a**)	H	**33**	84
(**b**)	Me	**34**	80

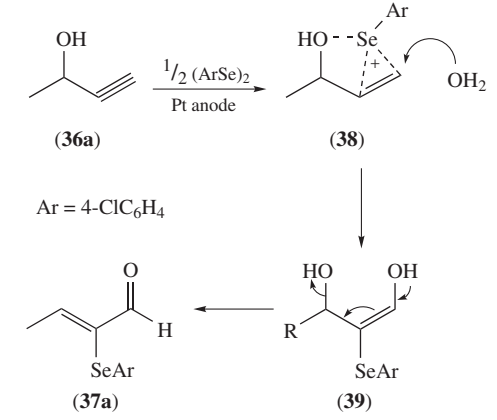
SCHEME 4

Electrochemical hydroselenenylation of 3-hydroxyalkynes (**36**) with the formation of α-arylseleno-α,β-unsaturated aldehydes or ketones (**37**) was realized[23] by electrolysis in the presence of **10g** or *p*-chlorodiphenyl diselenide (**10i**) and sulfuric acid in MeCN–H_2O mixture at 65 °C in an undivided cell. In contrast to unsuccessful chemical reactions using phenylselenenic acid, the proposed method avoids the undesirable disproportionation of this acid which is gradually generated by the control of a current. Higher yields of **37** were obtained with **10i** than with **10g** due to the presence of an electron-withdrawing substituent. The regioselectivity with an anti-Markovnikov product **37** is controlled by the hydroxyl group as is shown in Scheme 5 for **36a**: the hydrolysis of cation **38** from the less hindered side gives enol **39**, which yields the final product **37a** after dehydration. The change of the hydroxyl group to acetoxyl or methoxyl decreases the reactivity and the regioselectivity, and the alkyne without any of these groups gives the Markovnikov product with a low yield[23].



(**36**) (**37**)

36, 37	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R^1	Me	Et	Pen	Ph	Et	Et	Me	Me
R^2	H	H	H	H	H	H	Me	Me
R^3	H	H	H	H	Ph	Bu	H	Ph
Yield (%)	87	81	81	74	90	94	62	65



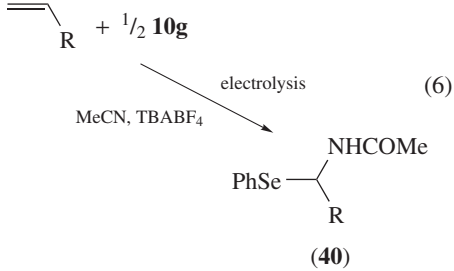
(**36a**) (**38**) (**37a**) (**39**)

SCHEME 5

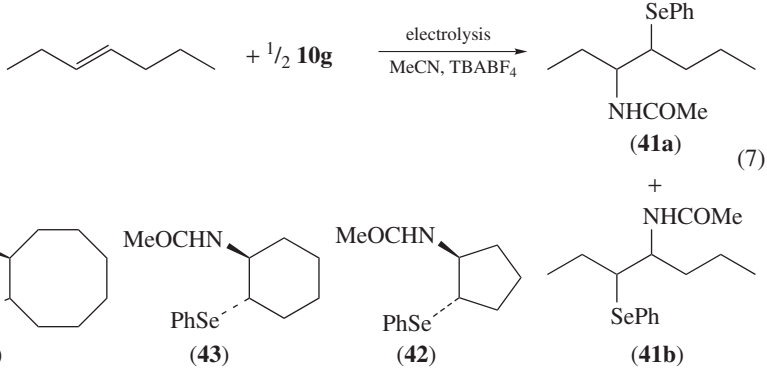
Anodic acetamidoselenation of alkenes by electrolysis of **10g** with alkene in acetonitrile containing Bu_4NBF_4 as a supporting electrolyte and using a platinum anode at the potential 1.3 V vs. Ag/Ag^+ (a little higher than $E_{p/2} = 0.96$ V for the oxidation of **10g** alone) results[24] in direct addition of geminal selenium and nitrogen substituents with a good yield. For terminal alkenes (from hexene-1 to dodecene-1) high regioselectivity of products **40**

obtained in reaction 6 was reported[24] whereas for heptene-3 the ratio of isomers **41a** to **41b** obtained in reaction 7 was 50:50 and the overall yield was 70%. Acetamidoselenation of cyclopentene, cyclohexene and cyclooctene gives products **42**, **43** and **44** with 66%, 77% and 41% yields, respectively, and all of them have the substituents preferentially in the *trans* position[24].

40:	**a**	**b**	**c**	**d**
R	C_4H_9	C_6H_{13}	C_8H_{17}	$C_{10}H_{21}$
Yield (%)	64	62	99	91



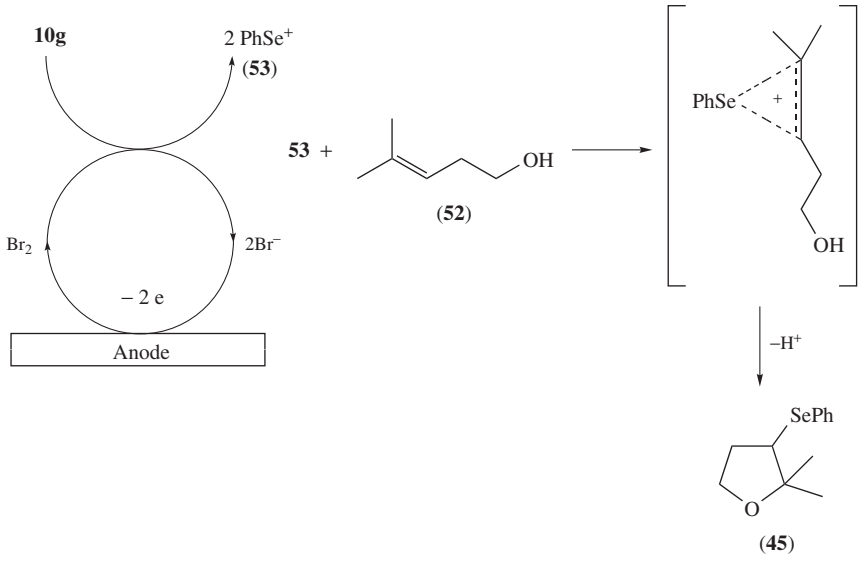
(**40**) (6)



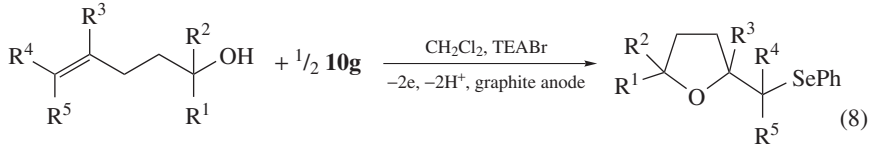
(7)

Electrochemical selenocyclofunctionalization was proposed[25–27] as a convenient tool for the synthesis of natural compounds containing tetrahydrofuran and tetrahydropyran rings from unsaturated hydroxyl compounds. With this purpose in mind a one-step intramolecular cyclization of unsaturated alkenols to cyclic β-phenylselenoethers, termed electro-oxidative phenylselenoetherification, was elaborated[25, 27], as well as the phenylselenolactonization of unsaturated carboxylic acids[26, 27]. In both cases the electrolysis of the hydroxyl compound and **10g** was performed at a constant current using an undivided cell with a graphite stick anode and a copper foil cathode. For the formation of cyclic β-phenylselenoethers **45–51**, methylene chloride containing Et_4NBr[25, 27] was used as the electrolyte (at a low temperature of -10 to $-5\,^{\circ}C$) or methanol containing $CaCl_2$[27] (at 15 to 20 °C) and the electrode reactions were completed after 2 $F\,mol^{-1}$. For the formation of cyclic β-phenylselenolactones the electrolysis up to 6 $F\,mol^{-1}$ was applied[26, 27] in methanol solutions containing NH_4Br. The suggested mechanism[27] is illustrated in Scheme 6, which shows as an example the formation of the five-membered cyclic ether 2,2-dimethyl-3-(phenylseleno)tetrahydrofuran (**45**) (in 72% yield) from the terminally

dialkylated Δ^3-alkenol, 4-methyl-3-penten-1-ol (**52**), the simplest alkenol reacting under these conditions; 3-buten-1-ol did not cyclize under these conditions[25, 27]. The reaction starts with the formation of the reactive intermediate $PhSe^+$ ion (**53**) by the indirect anodic oxidation of **10g** with halide ions as mediators. The formation of cyclic phenylselenoethers **46, 47** and **48** at a graphite anode is illustrated by equations 8, 9 and 10, respectively. It was found that the cyclization of Δ^4-alkenols with a terminally dimethyl substituted double bond occurs for primary alcohols according to the Markovnikov rule with the formation of six-membered rings of **48**, but for tertiary alcohol the stereochemical control in agreement with the anti-Markovnikov rule leads to the formation of a five-membered cycle of **46d**. On the other hand, both regioisomers **49a** and **49b** are formed (1:1, 52% yield) in the reaction 11 for the secondary alcohol where steric and electronic factors did not favor any of the two trigonal carbon atoms[27]. Stereochemistries of **46b, 47b** and **48b** were not determined.



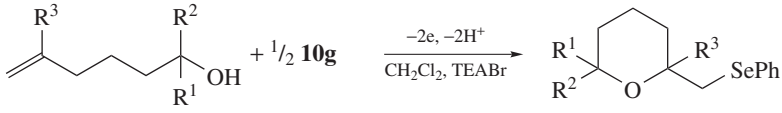
SCHEME 6



(8)

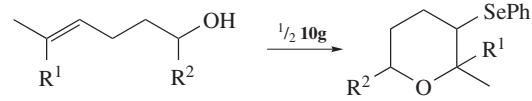
46	R^1	R^2	R^3	R^4	R^5	Yield (%)
(**a**)	H	H	H	H	H	80
(**b**)	Me	H	H	H	H	61
(**c**)	H	H	Me	H	H	79
(**d**)	Me	Me	H	Me	Me	50

47	R^1	R^2	R^3	Yield (%)
(**a**)	H	H	H	75
(**b**)	H	Me	Me	75
(**c**)	Me	Me	Me	76

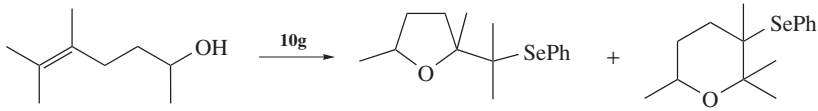


(**47**) (9)

48	R^1	R^2	Yield (%)
(**a**)	Me	H	61
(**b**)	Me	Me	67

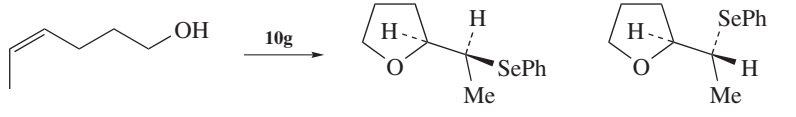


(**48**) (10)

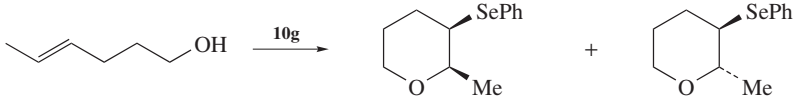


(**49a**) (**49b**) (11)

Reactions 12a and 12b illustrate the electrolysis of the two isomers (*Z*)-4-hexen-1-ol (**54a**) and (*E*)-4-hexen-1-ol (**54b**), respectively, with a terminally monosubstituted double bond[27]. The reaction of **54a** is regioselective and affords only five-membered cyclic ethers. However, with Et_4NBr as the mediator in the CH_2Cl_2 solution only *threo*-phenylselenoether **50a** is formed with the 86% yield, whereas with $CaCl_2$ in methanol a 50:50 mixture of *threo*-phenylselenoether (**50a**) and *erythro*-phenylselenoether (**50b**) were formed with 82% yield. On the other hand, the *E*-isomer **54b** gives only six-membered cyclic ethers and the ratio of the *cis*-isomer **51a** to the *trans*-isomer **51b** is 70:30 with Et_4NBr as the mediator (77% yield) and 33:67 with $CaCl_2$ as the mediator (80% yield).



(**54a**) (**50a**) (**50b**) (12a)

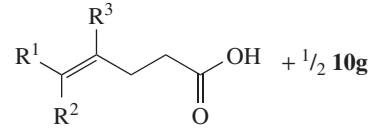


(**54b**) (**51a**) (**51b**) (12b)

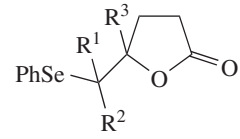
In a similar electrolysis of solutions containing **10g** and unsaturated carboxylic acids the cyclic phenylselenolactones are formed with good yields[26, 27]: γ-lactones from 4-enoic acids (substituents at the double bond had no effect on their regioselectivity) and

δ-lactones from terminally unsubstituted 5-enoic acids. Namely, **55** are formed from 4-pentenoic acid and its methyl-substituted derivatives according to equation 13, **56a** from 5-hexenoic acid, **56b** (only one isomer either *cis*- or *trans*- as shown by the ^{1}H NMR spectrum) from 4-*tert*-butyl-5-hexenoic acid, **57** with unknown stereochemistry from 3-cyclohexenecarboxylic acid (**58**) according to equation 14, and **59** (73% yield) with *cis*-configuration (proved by the ^{1}H NMR spectrum) from 2-cyclohexene-1-acetic acid. On the other hand, no cyclization product was obtained for 3-butenoic and 6-heptenoic acids.

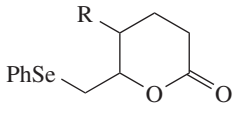
55	R^1	R^2	R^3	Yield (%)
(**a**)	H	H	H	71
(**b**)	H	H	Me	69
(**c**)	Me	Me	H	62
(**d**)	H	Me	H	76



graphite anode | $MeOH, NH_4Br$ (13)

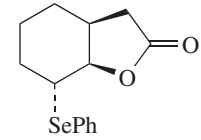


(**55**)

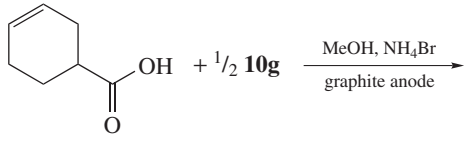


(**56**)

56	R
(**a**)	H
(**b**)	*t*-Bu



(**59**)

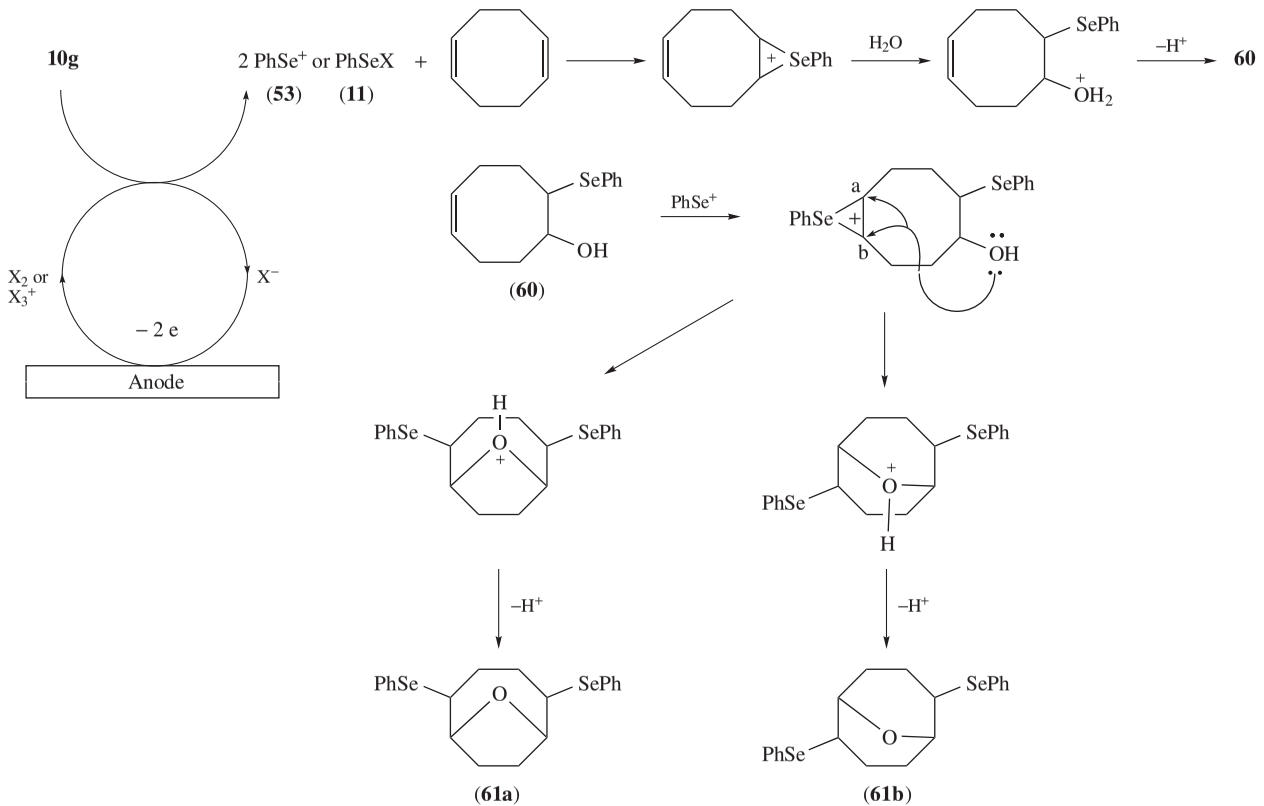


(14)

(**58**) (**57**)

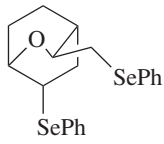
Cyclic acetals of the glucoside-type derivatives were obtained[28] as well in the electrochemical phenylselenoetherification by electrolysis of Δ^4-unsaturated carbonyl compounds, namely enals and enones, with **10g** in saturated solutions of KBr in MeOH using a graphite anode and a Cu cathode.

Cyclic β-phenylselenoethers were synthetized[29] by the electrode oxyphenylselenation of dienes during electrolysis of a diene and **10g** in 10:1 solution of acetic acid/water containing Et_4NBr or Et_4NCl. The electrolysis at a constant current applied to platinum electrodes was continued up to 4 F mol^{-1}. The suggested mechanism[29], shown in Scheme 7 for the oxyphenylselenation of 1,5-cyclooctadiene, is similar to that discussed previously.

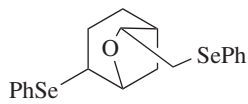

10g
2 PhSe+ or PhSeX
(53) (11)
+
SePh
H2O
SePh
OH2
–H+
60
X2 or X3+
X–
– 2 e
Anode
SePh
OH
(60)
PhSe+
a
b
PhSe
SePh
OH
H
O
PhSe
SePh
–H+
(61a)
(61b)

SCHEME 7

It starts with indirect oxidation of **10g** by elemental halogen (or halonium ions) formed at an anode to phenylselenyl cation **53** or phenylselenyl halide **11**, which react with one of the double bonds of the diene yielding an episelenonium ion. The last ion attacks the nucleophilic water molecule giving phenylselenoalcohol **60** with one double bond, which is the subject of a similar addition of the second phenylselenyl group with the formation of final products: 2,5-bis(phenylseleno)-9-oxabicyclo[4.2.1]nonane (**61a**) and 2,6-bis(phenylseleno)-9-oxabicyclo[3.3.1]nonane (**61b**). Both products were identified by IR and NMR spectroscopy. The isolated yields (based on **10g**) of **61a** and **61b** are 67% and 7%, respectively, for the reaction at ambient temperature but 77% and 8%, respectively, under reflux[29]. Similar electrolysis of 4-vinylcyclohexene affords a mixture of **62a** and **62b** with yields at ambient temperature of 13% and 2%, respectively, but under reflux of 46% and 8%, respectively. For open-chain dienes the cyclic β-diphenylselenoethers **63a** and **63b** were obtained with good yields (73% and 69%, respectively, for the reaction under reflux) from 1,5-hexadiene and 1,6-heptadiene, respectively, according to reaction 15. A small amount of **64** (8% under reflux) was also obtained from 1,5-hexadiene. However, the electrolysis of 1,7-octadiene gives **63c** with very low yields (12% under reflux), as expected for the remote double bonds[29]. It can be added that MNDO-PM3 molecular orbital calculations were used to study the mechanism of phenylselenoetherification of Δ^4-alkenols and the results obtained[30] revealed that the reactions should be highly regio- and stereospecific.

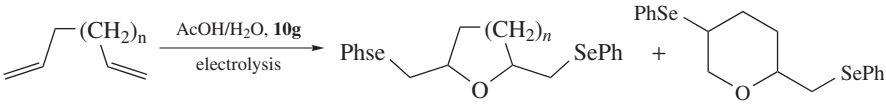


(**62a**)



(**62b**)

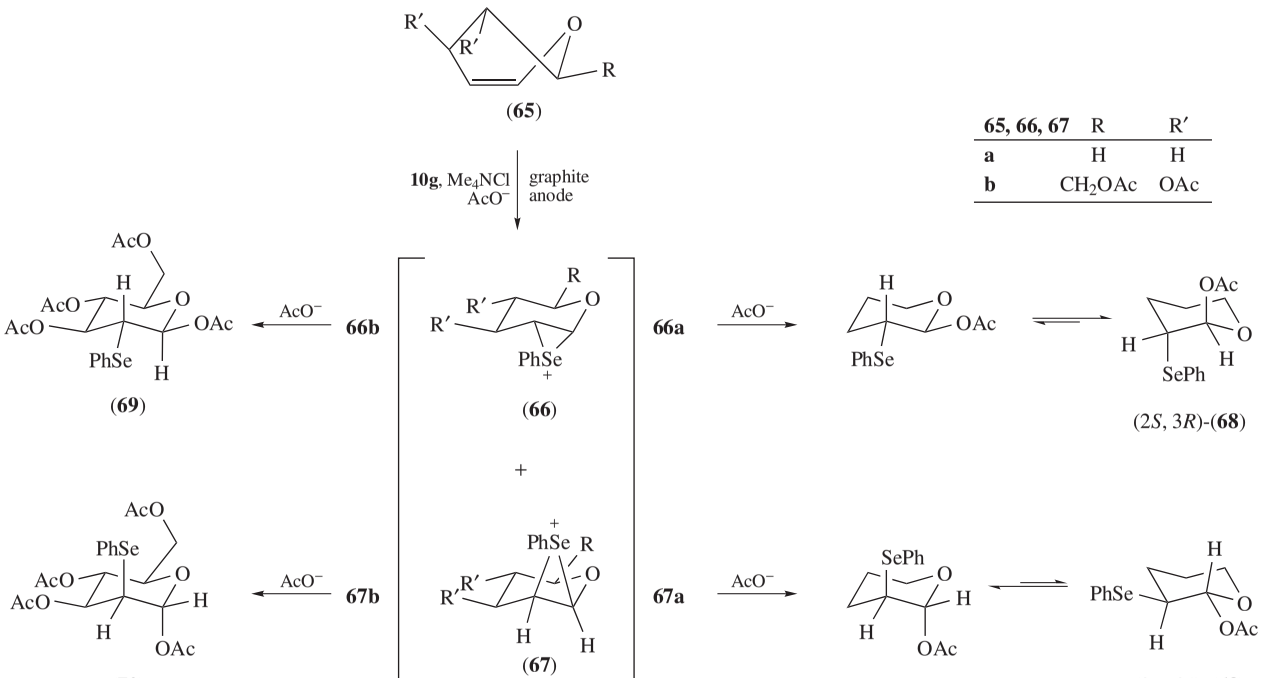
(15)



(**63a**) $n = 1$
(**63b**) $n = 2$
(**63c**) $n = 3$

(**64**)

Taking into account the synthetic usefulness of saccharides containing the phenylselenyl group, which can be removed by reduction or oxidation yielding 2-deoxysugars or unsaturated sugars, respectively, the electrochemical acetoxyphenylselenation of 3,4-dihydro-2*H*-pyran (**65a**), as a model compound, and of D-3,4,6-tri-*O*-acetylglucal (**65b**) was investigated[25]. The electrolysis of **65** and **10g** was performed at constant current in a solution containing Me_4NCl in glacial acetic acid using an undivided cell with a graphite anode and an aluminum cathode at room temperature. As in previous literature reports[18, 19, 22] it was assumed[31] that phenylselenyl chloride, formed indirectly at the anode, attacks the double bond of **65a** from both sterically identical sides giving equal amounts of two α-phenylselenyl cations **66a** and **67a**, as is shown[31] in Scheme 8. The further nucleophilic attack of acetate ions results in the final racemic product (identified by high resolution MS, IR and NMR spectra) *trans*-DL-2-acetoxy-3-phenylselenyltetrahydropyran: (2*S*,3*R*)-**68** and (2*R*,3*S*)-**68** with 13.5% yield each. On the other hand, the reaction of **65b**, containing three chiral carbon atoms, with a phenylselenyl cation follows Markovnikov's



65, 66, 67	R	R′
a	H	H
b	CH_2OAc	OAc

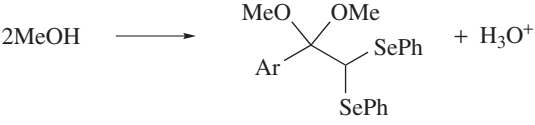
SCHEME 8

rule with the formation of intermediate cations **66b** and **67b**, but the nucleophilic attack on them proceeds as an *anti*-addition and only two diastereomeric products were formed with 87% overall yield: β-D-2-phenylselenyl-1,3,4,6-tetra-*O*-acetylglucopyranose (**69**) and α-D-2-phenylselenyl-1,3,4,6-tetra-*O*-acetylmannopyranose (**70**) with a ratio of 60:40, respectively. Structures of **69** and **70** were confirmed[31] by X-ray crystal analysis.

It is interesting to note that diphenyl diselenide (**10g**) can be directly oxidized in MeOH solutions containing $LiClO_4$ or Et_4NBF_4 at a platinum electrode ($E_p = 1.26$ V vs. Ag/AgCl for the CV method at a scan rate 0.1 V s^{-1})[32] and the cation formed, $PhSe^+$ (**53**), reacts with aryl methyl ketones (which have much higher oxidation potentials under these conditions) causing the methoxyselenylation and giving finally **71b** in reactions 16a and 16b. The formation of intermediates $ArC(O)CH_2SePh$ (**71a**) was supported by GC/MS analysis. Further reaction includes methoxydeselenenylation giving α-keto acetals, as will be discussed in Section III. Anodic synthesis of trialkylselenonium salts was also reported[33].

(16a)

Ar = 1-Naph, 2-Naph, Ph, 4-HOC_6H_4, 4-$MeOC_6H_4$ (**71a**)

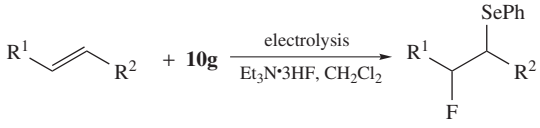


(16b)

(**71b**)

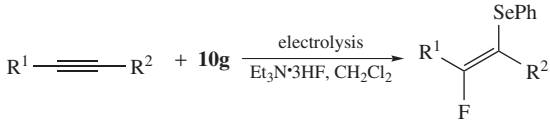
Fluoro-selenenylation of alkenes and alkynes by the electro-oxidation of **10g** in the $Et_3N{\cdot}3HF{-}CH_2Cl_2$ system at 0 °C using a divided cell with sintered glass filter and platinum electrodes was reported[34, 35]. It was suggested that the anodic oxidation of **10g** to a radical cation, followed by bond cleavage and the reaction with fluoride ion from the electrolyte, generates [PhSeF], which reacts with olefins. The electrolysis of **10g** and alkene or alkyne at constant current with the consumption of 4 F mol^{-1} resulted in the formation of fluoroselenides **72** and **73**, respectively. Some examples[34] are shown in Scheme 9, where the yields given for **72** were obtained from ^{19}F NMR, whereas the isolated yields based on **10g** were given for **73**. The *trans*-isomer was the major product in the case of **73** as well as of **72** obtained from cycloalkenes (from cyclopentene to cyclododecene); **72a** and **72b** are regioisomers with 2-F:1-F ratios of 95:5 and 94:6, respectively. Further oxidation of alkenes under the same conditions, up to 6 F mol^{-1}, resulted in the formation of allylic fluorides, as will be discussed in Section III.

However, that last mentioned method could not be used to perform the fluoro-selenenylation of electron-deficient olefins. Thus, other conditions of electrolysis were proposed recently[36], namely the use of the electrolytic solution of $Et_3N{\bullet}5HF/CH_3NO_2$ (2/8) in an undivided cell with platinum electrodes at room temperature. The main idea was that the electrochemically generated [PhSeF] equivalent is more stable in $Et_3N{\bullet}5HF$ due to higher nucleophilicity of fluoride ions. It can be added that the electrochemical formation of [PhSeF] postulated earlier[34] could not be detected[36]. However, recently aryl selenenyl fluorides substituted in the *ortho* position of the benzene ring, which are more stable owing to electronic and steric protection, were detected[37] by low-temperature ^{19}F and ^{77}Se NMR spectroscopy. Indeed, **74** or **75** were obtained[36] from α,β-unsaturated



(**72**)

72	R^1	R^2	Yield (%)
(**a**)	H	Bu	63
(**b**)	H	Hex	65



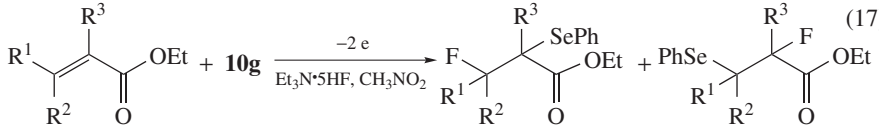
(**73**)

73	R^1	R^2	Yield (%)
(**a**)	Pen	Pen	70
(**b**)	Ph	Bu	51
(**c**)	Ph	Me	35

SCHEME 9

esters (**76**) according to reaction 17 with good yields. For example, the yields determined by ^{19}F NMR were equal to 73% and 18% for **74a** and **75a**, 99% for **74c**, 90% for **74d** but 73% and 26% for **75b** and **74b**, respectively[36]. The formation of either **74** or **75** depends on the relative stability of cations **77** and **78**, formed[36] by attacks on different positions of the cycle giving selenenylation in the α- or β-position of the ester group, respectively. The overall mechanism proposed[36] is shown in Scheme 10. Namely, **77a** is more stable than **78a** due to the electron-withdrawing properties of the ester group, whereas the effect of the electron-donating methyl group in **76b** stabilizes **78b** more than **77b**.

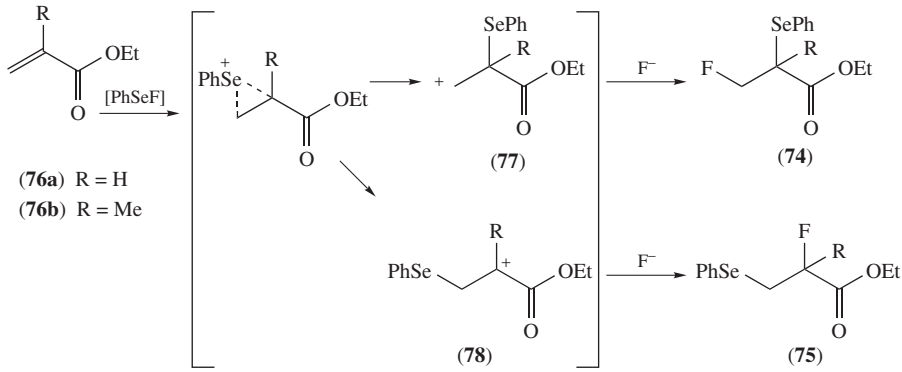
74, 75, 76	**a**	**b**	**c**	**d**
R^1	H	H	Me	Me
R^2	H	H	H	Me
R^3	H	Me	H	H



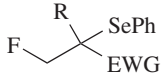
(**76**) (**74**) (**75**)

On the other hand, the change of the ester group in **76a** to a stronger EWG, like diethyl phosphonate and methylsulfonyl groups, decreases the yields of products **79a** and **79b** to 59% and 19%, respectively (based on ^{19}F NMR), whereas for the strongest cyano group the expected product **79c** was not found[36].

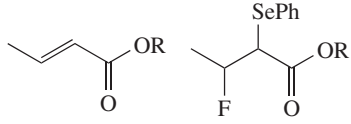
Fluoro-selenenylation of various crotonates (**80**), even substituted by bulky groups, under the same conditions[36] produces **81** with high yields. However, much lower yields (based on ^{19}F NMR) were reported[36] for other α,β-unsaturated carbonyl compounds: 71%, 50% and 8% for **82a, 82b** and **82c**, obtained from methacrylic acid, methacrylic amide and methacrolein, respectively, as well as 59% and 21% for **83a** and **83b**, obtained from crotonic acid and methyl vinyl ketone, respectively. The electrolysis of amides having oxazolidinone moiety (**84**) resulted in α-selenenylation with respect to the carbonyl group, as is shown in reaction 18 giving the diastereomeric mixtures of **85** (1.5:1 and 1.3:1 for **85a** and **85b**, respectively, as determined by ^{19}F NMR), but practically no β-selenenylation takes place[36].



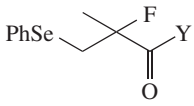
SCHEME 10



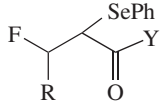
(**79a**) R = H, EWG = $P(O)(OEt)_2$
(**79b**) R = H, EWG = SO_2Me
(**79c**) R = Me, EWG = CN



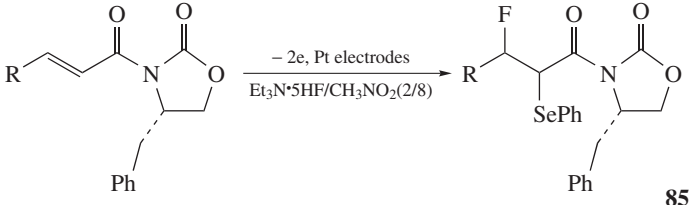
80, **81**:	**a**	**b**	**c**	**d**
R	Me	Et	*i*-Pr	4-$MeOC_6H_4CH_2$
Yield (%)	96	99	92	99



(**82a**) Y = OH
(**82b**) Y = NH_2
(**82c**) Y = H



(**83a**) R = Me, Y = OH
(**83b**) R = H, Y = Me



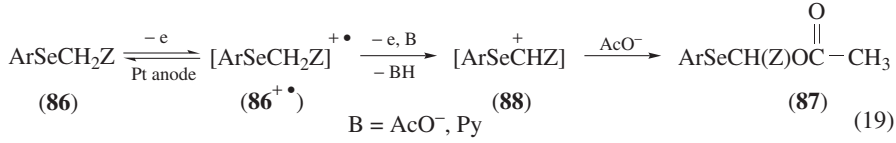
(18)

85	**a**	**b**
R	H	Me
Yield (%)	57	90

C. Anodic Functionalization

Organic selenium compounds, in particular those with the phenylseleno group, were widely used to carry out electrochemical functionalization of organic molecules. This process usually occurs at the organic saturated radical and does not affect the phenylseleno group.

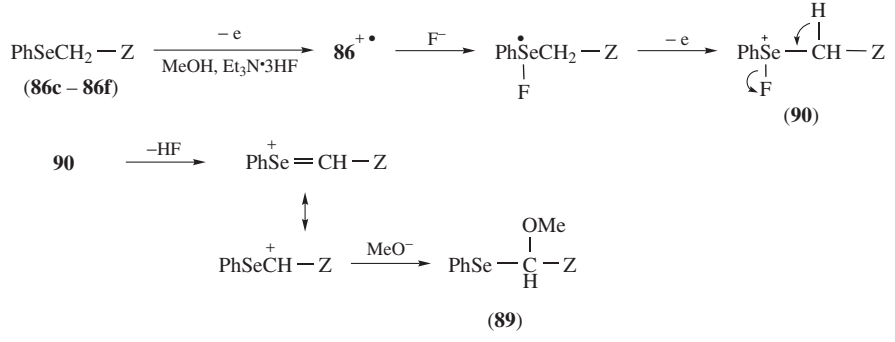
Regioselective anodic acetoxylation of alkylphenyl selenides **86a–86f** using platinum electrodes in AcONa/AcOH medium[38] was possible only for selenides bearing EWG, in particular perfluoroalkyl groups. Namely, only traces of **87a** and **87b** were obtained, but 67%, 61% and 69% of **87c, 87d** and **87e**, respectively[38]. However, the restriction above was surmounted[39] by the change of electrolyte. Understanding that deprotonation of the radical cation $\mathbf{86}^{+\bullet}$ at the β-position with the formation of the cation **88** is a fundamental step in the overall reaction 19, the use of absolute MeOH as sufficiently polar but non-acid solvent was proposed[39] and molten anhydrous sodium acetate because the AcO^- ions can act as nucleophiles as well as bases trapping the protons to be eliminated. In the media above the electrolysis in a divided cell with a platinum anode and a nickel cathode resulted in the formation of **87a** (87%), and **87b** (56%; Na_3PO_4 was additionally added), as well as **87g** (63%) and **87h** (92%).



(19)

86, 87	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
Ar	Ph	Ph	Ph	Ph	Ph	Ph	*p*-MeC_6H_4	*p*-$NO_2C_6H_4$
Z	H	Me	CF_3	C_2F_5	C_3F_7	CN	H	H

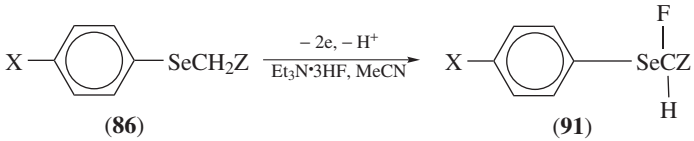
Anodic nucleophilic substitution of 1,1-dihydro-perfluoroalkyl or cyanomethyl selenides (**86c–86f**) was successfully carried out in the presence of fluoride ions (Scheme 11)[40]. It was found that products **89** of α-methoxylation were obtained in good yields if $Et_3N{\cdot}3HF$ was used as the supporting electrolyte in MeOH. The reaction proceded via the intermediate cation **90**. Only small amounts of **10g**, the main product of electrolysis performed in the absence of fluoride ions, were obtained under the proposed conditions and only traces of α-fluorinated phenylselenides **91** (X = H) (equation 20). The last result is clear taking into account that fluoride ions are much weaker nucleophiles than methoxide ions. The highest yields of 75% and 74% were found for the methoxylation of **86d** and **86e**, respectively. However, no products were found for **86a**.



SCHEME 11

On the other hand, α-fluorinated selenides can be interesting as potential versatile building blocks. Anodic regioselective monofluorination at position α to the selenium atom for organoselenium compounds **86f, 86i–86l** bearing EWG substituents was described[41]. The anodic reaction 20 was performed at platinum electrodes at constant potentials using an undivided cell. Good yields of α-fluorinated products **91** were obtained with the exception of **86k** and **86l**. In the last case **10g** was the main product (suggesting a cathodic regeneration of **86l** from its radical cation) unless a divided cell with an anion-exchange membrane was used, giving then **91l** in 60% yield[41]. Introduction of a second EWG substituent reduces the yield of fluorinated products **92**. Moreover, further anodic fluorination of **91i** in CH_2Cl_2 solution of $Et_3N{\cdot}3HF$ resulted[42] in the formation of the corresponding α,α-difluoro-α-(phenylseleno)acetate (**92c**).

The α-fluorination of analogous telluride compounds was unsuccessful. Instead of that, anodic fluorination under galvanostatic conditions in a divided cell results in selective difluorination of the tellurium atom[43], as is shown in reaction 21. The presence of EWG was not necessary, as illustrated by products **94c** and **94d** from **93**.



(**86**) (**91**) (20)

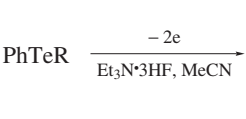
PhSeCFRCO$_2$Et

(**92**)

86, 91	**f**	**i**	**j**	**k**	**l**
X	H	H	Cl	MeO	H
Z	CN	CO_2Et	CO_2Et	CO_2Et	$CONH_2$
Yield(%)	71	70	81	51	60

92	**a**	**b**	**c**
R	Cl	CO_2Et	F
Yield(%)	65	55	84

93, 94	**a**	**b**	**c**	**d**
R	CH_2CF_3	CHF_2	Me	Ph
Yield(%)	86	86	81	77



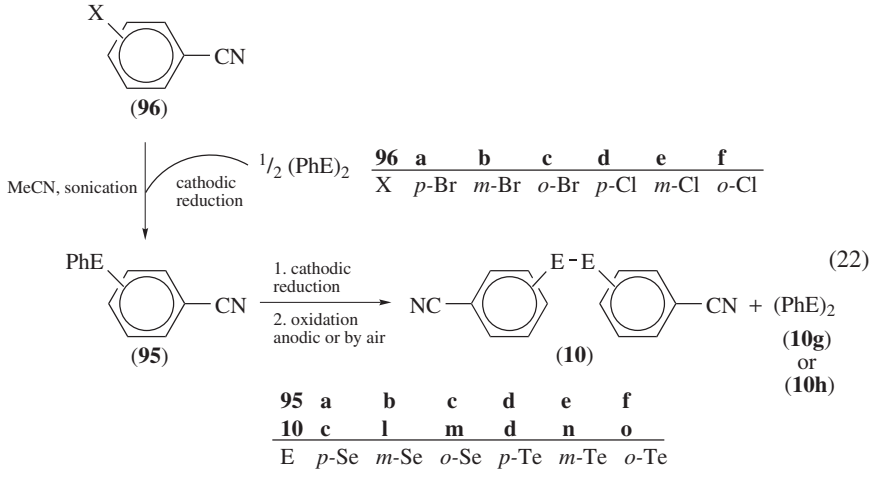
(**93**) (**94**) (21)

D. Cathodic Syntheses

Synthetic applications discussed so far were based on anodic oxidation of organoselenium and organotellurium compounds. However, the cathodic reduction processes were also useful. In particular, the electrochemical reduction of diaryl diselenides or ditellurides (first of all **10g** and **10h**) produce *in situ* arene selenolate or tellurate anions[17, 44–50] which can undergo further reactions, e.g. with aromatic radicals formed in electroreduction of their halides. The electrochemical methods proposed are useful in particular for aryl halides which are either unactivated and therefore not convenient for classic chemical reactions, or which cannot be converted into Grignard or lithium reagents due to substitution by unsaturated groups, like carbonyl or cyano groups. Thus, the most widely investigated was the synthesis of phenylchalcogenobenzonitriles **95** formed in the reaction with halogenated benzonitriles **96** after an electrochemical induction. Moreover, products **95** undergo a two-electron reduction with C–E bond

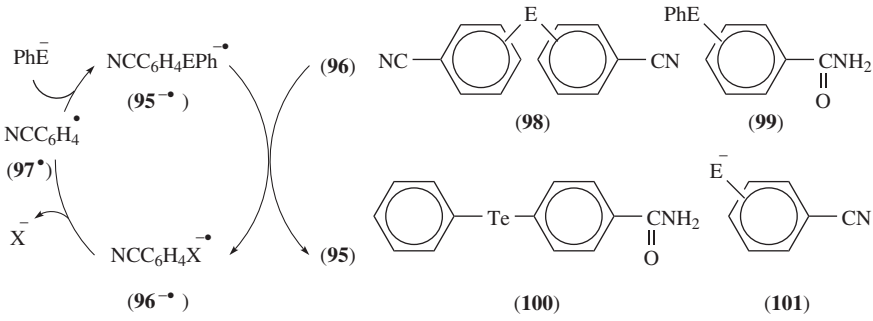
cleavage, which occurs preferentially on the side of the unsubstituted phenyl group. Thus, during further oxidation, either anodic or by air, dicyanodiphenyl dichalcogenides **10c, 10d, 10l–10o** were formed. The overall process is shown in reaction 22[44–46, 48–49].

For the synthesis of **95**, the $PhSe^-$ or $PhTe^-$ ions were generated at a graphite cloth cathode in MeCN with 0.1 M Bu_4NPF_6 using H-type cell with three compartments separated by ion-exchange membranes to avoid anodic migration of the generated anions[45, 46]. After the complete large-scale electrolysis (with a sonication) of **10g** or **10h**, in the second step **96** was added and reduced at a proper potential. Then aryl radicals, formed in that reductive C–X bond cleavage, couple with PhE^- ions giving $\mathbf{95}^{-\bullet}$ radical anions, which exchange an electron with **96** yielding the final product **95** and $\mathbf{96}^{-\bullet}$ which begins the next cycle. Thus, the role of the electrochemical process is only an induction of the reaction and consequently, the consumption of electrons is very low, typically 0.1 to 0.25[46]. The whole chain reaction, shown in Scheme 12, corresponds to aromatic nucleophilic substitution according to the $S_{RN}1$ mechanism. The yields of **95** obtained under optimal conditions are given in Table 2. In order to obtain higher yields the concurrent side reactions have to be eliminated, first of all the cathodic reduction of aryl radicals $\mathbf{97}^{\bullet}$. This was realized using **96** with X = Cl, because then the bond cleavage is slower than for compounds with X = Br which form radicals $\mathbf{97}^{\bullet}$ closer to the electrode (cf. data in Table 2). The reduction of **10g** or **10h** mediated by a redox catalyst is also helpful[46] because it allows one to use lower reduction potentials. Side products **98–100** were isolated[46] in low yields (usually lower than 10% for **98** and **99**, but 20–30% for **100**) which indicated a rapid decomposition of $\mathbf{95}^{\bullet}$ radical leaving the phenyl radical and cyanobenzenechalcogenate anions $NCC_6H_4E^-$ (**101**).



(22)

Further synthesis of cyano-substituted **10** from isolated **95**, according to equation 22, is attractive because the final products are not available by the classic Grignard method. The cathodic one-electron reduction of **95** (carried out mainly in DMF with 0.1 M Bu_4NPF_6 at a graphite electrode[48, 49]) gives radical anions $\mathbf{95}^{-\bullet}$, which decompose forming small amounts of PhE^- anions and **101** in the main path (about 85% in the presence of acids such as fluorene, phenol or Bu_4NSO_4H). By-products **99** were formed in the absence of added acid. The anodic oxidation of **101** (or the oxidation by air in alkaline aqueous solutions) results in the formation of final products **10** with the best isolated yields given in Table 2.



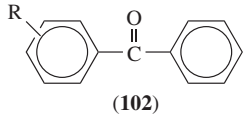
SCHEME 12

TABLE 2. Electrochemical synthesis of phenylchalcogenobenzonitriles $PhEC_6H_4CN$ (**95**) and dicyanodiphenyl dichalcogenides $(NCC_6H_4E)_2$ (**10**) from ArX (**96**) according to reaction 22

E	**95**	X	Yield (%)	Ref.	X	Yield (%)	Ref.	**10**	Yield (%)	Ref.
p-Se	**a**	*p*-Br	58 (57)[a]	45	*p*-Cl	70	46	**c**	75[c]	48
p-Te	**d**	*p*-Br	- (42)[a]	44	*p*-Cl	53	46	**d**	63[d]	49
m-Se	**b**	*m*-Br	42	45	*m*-Cl	68[b]	46	**l**	70[e]	48
m-Te	**e**	*m*-Br	-		*m*-Cl	48[b]	46	**n**	62[d]	49
o-Se	**c**	*o*-Br	36	45	*o*-Cl	48 (61)[b]	46	**m**	59[f]	48
o-Te	**f**	*o*-Br	-		*o*-Cl	20 (39)[b]	46	**o**	*ca* 70[d]	49

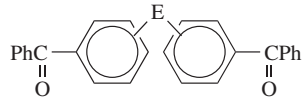
[a] Partial reduction consuming 0.2 electron mol^{-1} as described in Reference 44.
[b] Mediated by the redox catalyst 1,2-di(4-pyridyl)ethylene.
[c] Hg electrode, oxidation by air.
[d] Anodic oxidation at 0 V vs. SCE in the presence of fluorene.
[e] Solvent: MeCN, added acid: phenol.
[f] Solvent: MeCN, added acid: Bu_4NSO_4H.

Electrochemical synthesis of (phenylchalcogeno)benzophenones **102** was achieved[47] in the same process based on the $S_{RN}1$ mechanism as shown in Scheme 12 for **95**. The electrochemical generation of PhE^- ions from **10g** or **10h** was performed in MeCN solutions at a graphite cathode using 0.1 equivalent of azobenzene as the redox catalyst and a sonication. A weak acid, fluorene or malononitrile, was added to avoid the formation of $^-CH_2CN$ ions from solvent molecules and their further reactions. High isolated yields of **102** were obtained with the exception of **102c** and **102d** for which a competitive formation of **103a** and **103b**, respectively, occurs[47].

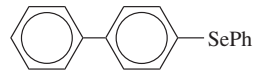


(**102**)

102	**a**	**b**	**c**	**d**	**e**
R	*p*-SePh	*m*-SePh	*p*-TePh	*m*-TePh	*o*-TePh
Yield (%)	86	62	45	48	75



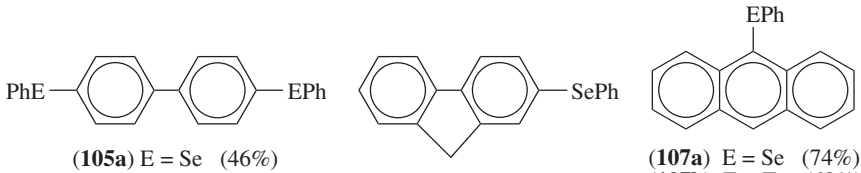
(**103a**) E = *p*-Te (36%)
(**103b**) E = *m*-Te (31%)



(**104**) (65%)

The same method of electrochemically induced $S_{RN}1$ substitution in MeCN, using appropriate bromoarenes and mainly 2,3-dimethylquinoxaline as the redox mediator, was successfully applied[50] for the synthesis of phenylchalcogeno substituted arenes **104**–**107**. Although the yields of some of these products were not high, it is interesting to note that, for example, the photochemically induced synthesis of **105a** in liquid ammonia failed at all.

It was also proved[17] that MeCN is a better solvent for the synthesis above than DMSO because of a much higher ratio of k_c/k_H in MeCN (k_c and k_H are the rate constants for competitive reactions of the aryl radical, e.g. 9-anthryl, with $PhSe^-$ and its hydrogen abstraction from the solvent molecule, respectively).

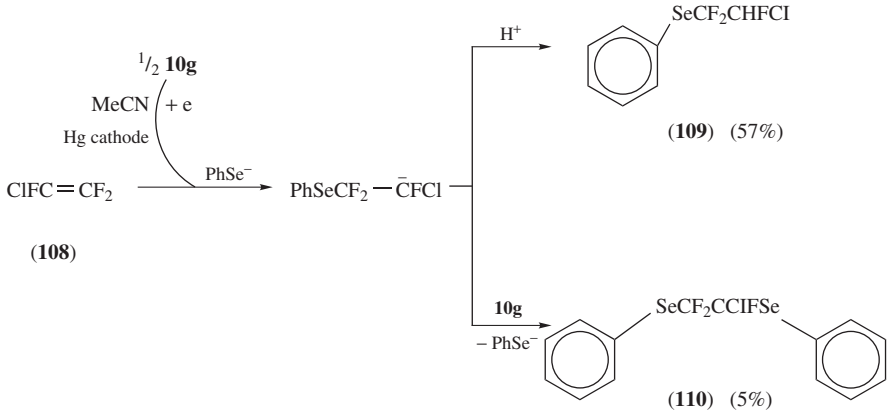


(**105a**) E = Se (46%)
(**105b**) E = Te (16%)

(**106**) (53%)

(**107a**) E = Se (74%)
(**107b**) E = Te (68%)

The reductive addition of $PhSe^-$ anions, generated in anhydrous MeCN from **10g** at a mercury cathode, to chlorotrifluoroethene (**108**) resulted (Scheme 13)[51] in the formation of 2-chloro-1,1,2-trifluoroethyl phenyl selenide (**109**) as the main product and 1,2-bis(phenylselenyl)-2-chloro-1,1,2-trifluoroethane (**110**). However, no addition product was found after electrolysis of **10g** in the presence of CFCl=CFCl, indicating that there is no formation of $PhSe^{\bullet}$ radical, contrary to the behavior of the sulfur analog. Direct nucleophilic additions of the electrochemically generated phenylselenyl anion to α,β-unsaturated carbonyl compounds were also reported[52].



(**108**)

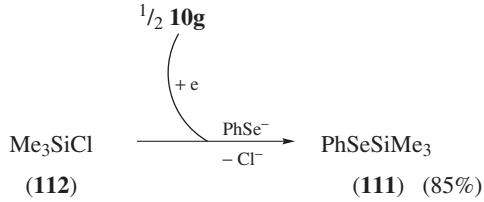
(**109**) (57%)

(**110**) (5%)

SCHEME 13

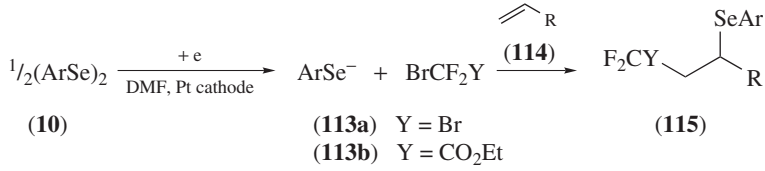
Silylselenides, i.e. organic selenides with the trimethylsilyl group attached to the selenium atom, very useful as soft silylating agents and protectors of carbonyl groups, are quite unstable and easily hydrolyze in the presence of moisture. Thus, convenient methods for their electrochemical generation and further *in situ* use were proposed[53]. For the formation of trimethylsilyl phenylselenide (**111**) the cathodic pre-electrolysis of chlorotrimethylsilane (**112**) at a titanium electrode in anhydrous MeCN containing Et_4NBr

was performed until the hydrogen evolution stopped and, next, the reduction of added **10g** was continued. The generated $PhSe^-$ ions substitute Cl atoms in **112** with the formation of **111** according to equation 23[53]. The rate constant for this S_N2 reaction is 9.3 times higher than for the analogous reaction of PhS^- ions with **112**.



(23)

The electrochemical synthesis of difluoromethylene compounds based on the reduction at a platinum electrode of dibromodifluoromethane (**113a**) or ethyl bromodifluoroacetate (**113b**) with olefin (**114**) and **10g** in DMF solutions was proposed[54]. Intermediate products **115** of the bromodifluoromethyl-selenylation were formed according to equation 24[35, 54]. Similar reactions of C_4F_9I, instead of **113**, with **114** or cyclopentene gave seleneny-lated products with yields ranging from 71 to 77%. In order to obtain difluoromethylene compounds subsequent non-electrochemical oxidative deselenation of **115** was used[35, 54].



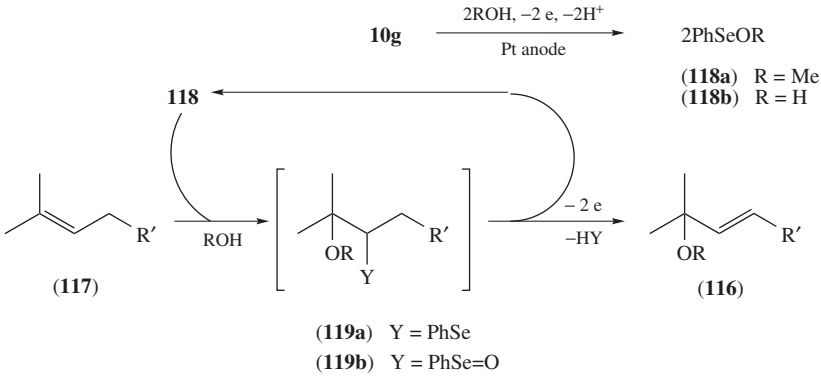
(24)

115	**a**	**b**	**c**	**d**
Y	Br	Br	CO_2Et	CO_2Et
R	*i*-PrO	Pen	*i*-PrO	Pen
Yield(%)	45	57	80	58

III. ORGANIC SELENIUM COMPOUNDS AS INTERMEDIATES IN ELECTROCHEMICAL SYNTHESIS

In a number of electro-organic syntheses, the anodic oxidation of diphenyl diselenide (**10g**) used for selenenylation could be continued in order to perform deselenenylation of the initially formed selenides and recyclization of the phenylselenenyl reagent. Such processes, formally beyond the scope of this Chapter, are very interesting from the synthetic point of view and thus some examples will be briefly mentioned in this Section, including only reactions in which the formation of organic selenium compounds as intermediate were proposed.

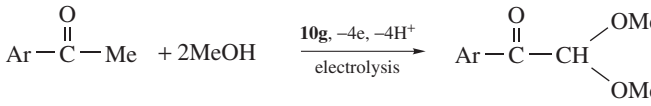
Torii and coworkers elaborated[19, 21] the electrochemical one-step method (Scheme 14) for the preparation of allylic derivatives **116** from isoprenoids **117** using a catalytic amount of **10g**. Electrolysis at platinum electrodes in an undivided cell of **10g, 116** and $MgSO_4$ in MeOH or $MeCN–H_2O$ generate phenylselenenyl reagent PhSeOMe (**118a**) or PhSeOH (**118b**), respectively[21]. It reacts regioselectively with olefins producing oxyselenide **119a**, which is subsequently oxidized at an anode to the corresponding selenoxide **119b** yielding



SCHEME 14

the final product after instantaneous *syn*-elimination. The regeneration *in situ* of **118** was proved and it was found that the presence of salts, such as $MgSO_4$, favors the recycle.

Electrosynthesis of α-keto acetals from aryl methyl ketones, which cannot be oxidized directly, occurs in the presence of catalytic amounts of **10g** in MeOH solutions[32], according to the overall reaction 25. The reaction starts with the anodic generation of $PhSe^+$ cation (**53**) which forms $ArC(O)CH_2SePh$ (**71a**) in reaction 16a and di(phenylselenium) compound **71b** in reaction 16b. It is followed by deselenenylation including the bond cleavage reaction 26 with the formation of the leaving anion $PhSe^-$, which in turn reacts with the cation **53** regenerating **10g**.



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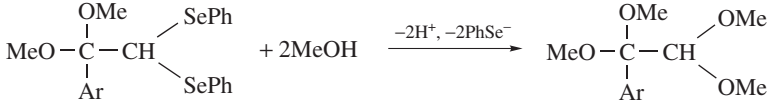
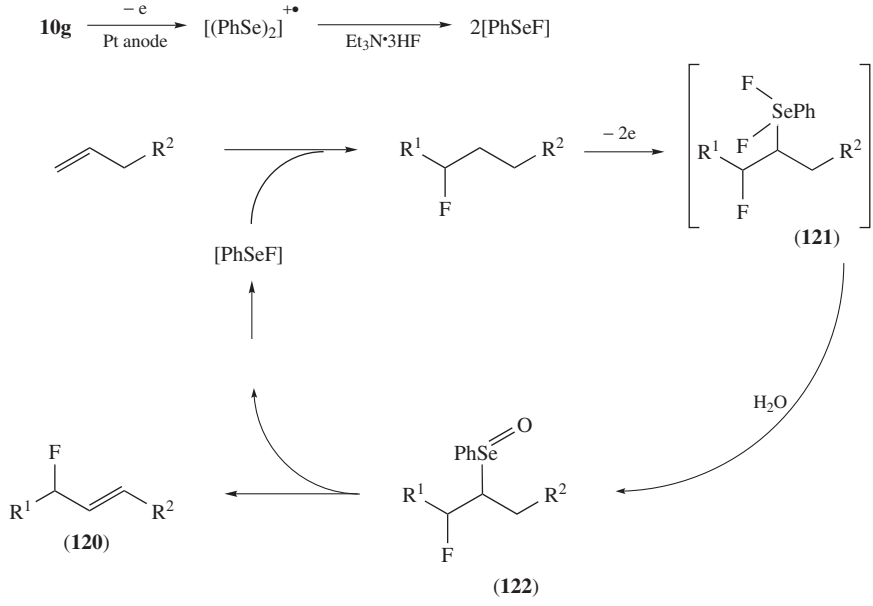


(26)

(**71b**)

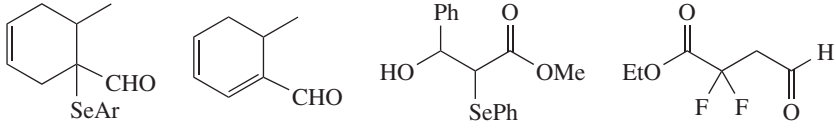
Electrochemical selenenylation–deselenenylation with the recycle use of the selenating reagent (Scheme 15) was proposed[34] for the transformation of alkenes to allylic fluorides (**120**). The electrolysis of **10g** and an alkene in $Et_3N{\bullet}3HF–CH_2Cl_2$ at platinum electrodes gives [PhSeF] after 4 F mol^{-1} (Scheme 9). However, the allylic fluoride is formed when the electrolysis is continued until **10g** is consumed (6 F mol^{-1}). According to Scheme 15, the formation of **121** was suggested[34], which undergoes hydrolysis to selenoxide **122** giving the final product after elimination of phenylselenenic acid PhSeOH which regenerates [PhSeF].

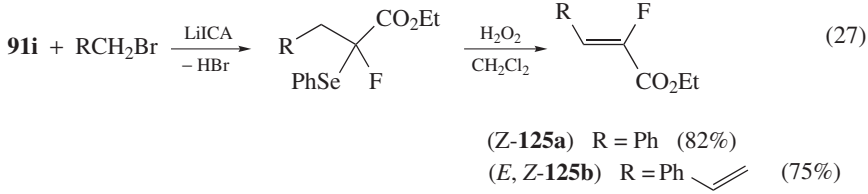
Electrochemical generation of α-arylseleno-α,β-unsaturated aldehyde **37a** (Scheme 5) was used[23] to afford **123** in the Diels–Alder reaction with butadiene and, after deselenenylation, cyclic dienal **124** was obtained. α-Monofluoroselenide **91i** generated in



SCHEME 15

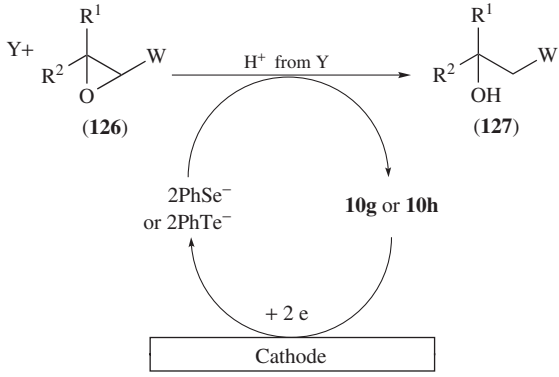
anodic reaction 20 was successfully transformed[41] by benzylation followed by oxidative deselenenylation, described by equation 27, to stereoselective esters **125**. They were useful for the preparation of monofluorinated insect sex pheromones retinoides as well as pyrethdroides[41].





On the other hand, the reductive ring-opening of α,β-epoxy ketones (**126a**) with the formation of the corresponding aldols (**127a**) or α,β-epoxy esters (**126b**) and nitriles (**126c**) with their conversion to the corresponding β-hydroxy compounds **127b** and **127c**, respectively, was described[55]. It was based on their electrolysis at a platinum cathode in the presence of **10g**, or **10h** in MeOH solutions containing $NaClO_4$. Apparently, in these

reactions phenylchalcogen compounds served only as mediators between reactants and an electrode in their indirect reduction[55] in the overall process (Scheme 16). However, it was shown[55] that during electroreduction at room temperature the organoselenium compounds are formed. For example, the electrolysis of 60 mol% of phenylglycidic ester **126b** with **10g** resulted in the formation of α-(phenylseleno)-β-hydroxy ester **128** in 68% yield. On the other hand, similar electrolysis at 50°C with only catalytic amounts of **10g** gave the desired product **127b** in 75% yield. Moreover, it was proved[53] that the electrolysis of **128** at 50°C afforded **127b** in 93% yield.

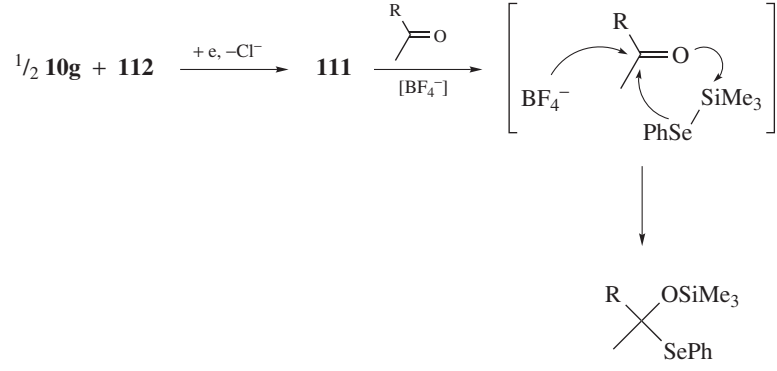


126	a	b	c
W	COR	COOMe	CN
Y	$CH_2(CO_2Et)_2$	HOAc	HOAc

SCHEME 16

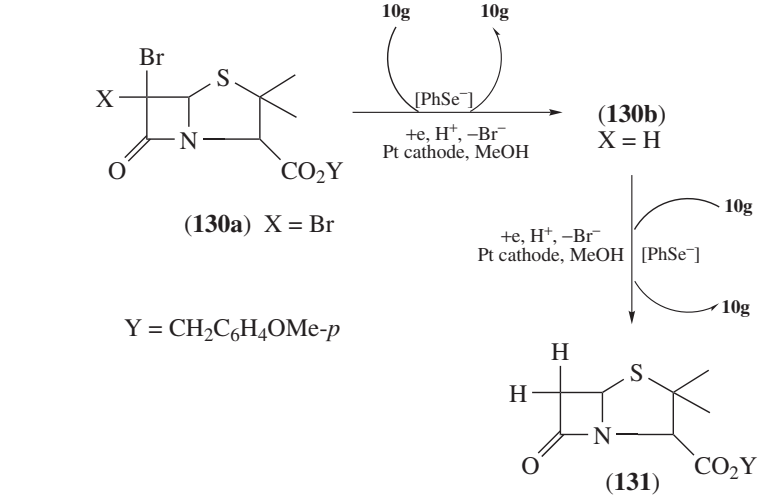
Another application of $PhSe^-$ anions generated at a cathode is the electrolysis of ethyl bromodifluoroacetate (**113b**) and vinyl isopropyl ether which produced organoselenium intermediate compound **115c** according to equation 24[35, 54]. After an oxidative deselenation of **115c** in aqueous MeCN, difluoromethylene ester **129** useful for synthetic applications is formed[35].

Silylselenide **111** electrogenerated[53] in reaction 23 was further used for a one-pot functionalization of carbonyl compounds leading to selenoketals and acetals through reaction 28 as the key step.

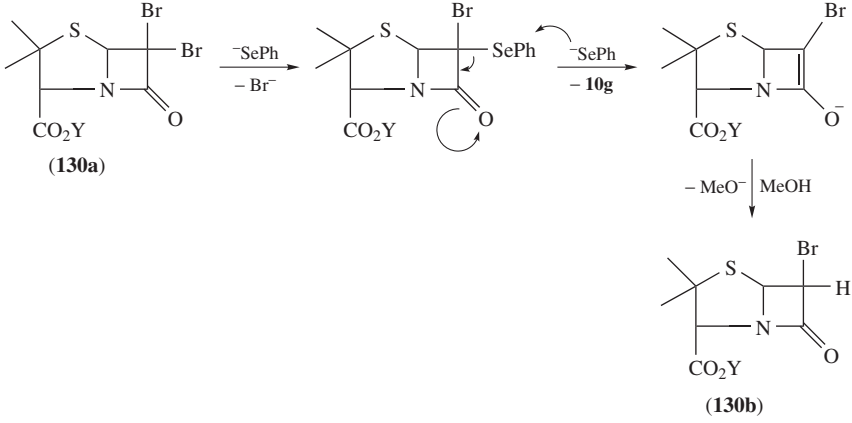


(28)

Indirect electroreduction of α,α-dibromolactams, using **10 g** or **10 h** as recyclable mediators, leads[56] to the preparation of complete dehalogenated β-lactams useful in the β-lactamase inhibitor synthesis. For example, the electrolysis of 6, 6-dibromopenicillanate (**130 a**) in MeOH containing 0.2 M $NaClO_4$ at platinum electrodes in a divided cell in the presence of **10 g** results in the formation of **131**, as shown in reaction 29. The detailed experimental results indicated[56] that the debromination occurs stepwise with the formation of monobromide **130 b** first (Scheme 17), and then the desired product **131**. The yields of **131** were equal to 91–92% or 90–91% using **10 g** or **10 h**, respectively (i.e. much higher than those obtained by chemical methods) and practically did not depend on the presence of added AcOH.



(29)

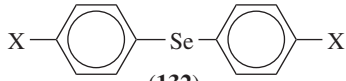


SCHEME 17

IV. ANODIC OXIDATION OF ORGANIC SELENIUM AND TELLURIUM COMPOUNDS

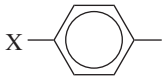
A. Diaryl, Dialkyl and Alkylarylselenides and Tellurides

Investigations of anodic reactions of organoselenium and organotellurium compounds were focused mainly on the oxidation of disubstituted selenides and tellurides having chalcogen heteroatoms on the second oxidation state, in particular, substituted diphenyl selenides (**132**), diphenyl tellurides (**133**) and phenylmethyl compounds. Electrochemical oxidation starts as usual from one-electron exchange with the formation of a radical cation followed by its chemical reactions, which give final products with chalcogen atoms on the fourth oxidation state. Thus, irreversible CV peaks were usually recorded, even if the first electron transfer is reversible, and peak potentials reported in the literature usually have no strictly thermodynamic meaning. Oxidation potentials for an extended series of **132** and **133** were reported by Engman and coworkers[57]. They were recently reviewed[3] and thus will not be repeated here. Mechanisms of electrode reactions will be rather reviewed in this Section.



(**132**)

132, 133	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
X	H	NO_2	OMe	CO_2H	Cl	F	Me	NHAc	NH_2

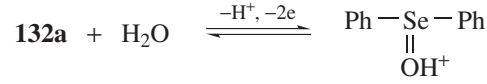


(**133**)

132, 133	**j**	**k**	**l**	**m**	**n**	**o**	**p**
X	NMe_2	CF_3	CO_2Me	Br	Ph	OH	NHPh

Anodic oxidation of diphenylselenide (**132a**) in MeCN at a platinum electrode was first investigated by Seeber and coworkers[58] using different electrochemical techniques, IR and ^{1}H NMR spectroscopy. Three consecutive anodic peaks were observed without cathodic responses. The first one, investigated in detail, was not diffusional. Two further peaks were considerably smaller. Electrochemical characteristics of the first step indicated ECE mechanism with a proton loss from a radical cation suggested as the slow chemical step. However, the apparent number of electrons slightly lower than 2 indicated some competition pathways. It can be added that one two-electron peak or wave was also usually observed in later works[59, 60] but the use of **132a** freshly distilled over Cu dust revealed[60] splitting into two waves. A strong acid along with a weak acid were determined in solutions after electrolysis[58]. Moreover, NMR spectra revealed the absence of aliphatic protons and the presence of the $>S{=}O$ group, which have to be protonated by residual water molecules giving the overall reaction 30. In the mechanism proposed[58] coupling reactions leading to the formation of **134a** or **134b** were considered as being responsible for the second and the third oxidation peaks, but it was not proved sufficiently. Later, Ryan and coworkers considered[59] **134b** as the main product for the CV oxidation in rigorously dried MeCN. It was produced in a coupling between a radical cation and a parent molecule with the formation of a new C−Se bond. On the other hand, diphenyl selenoxide (**135a**) was the main product of the oxidation in the presence of water[58, 59]. In particular, **135a** and **135b** were identified[59] by ^{1}H and ^{13}C NMR spectra after an exhaustive coulometry of **132a** and **132g**. However, the oxidation peak of **135**, which is anodicaly electroactive, was not

observed in CV experiments because of its protonation (cf. the product of reaction 30) and the formation of selenoxide hydrate, as verified by isolation of the dimethoxy derivative[59].



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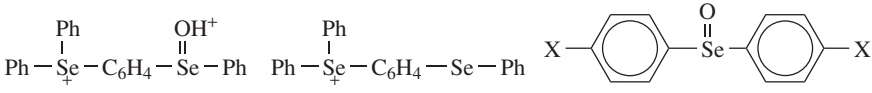
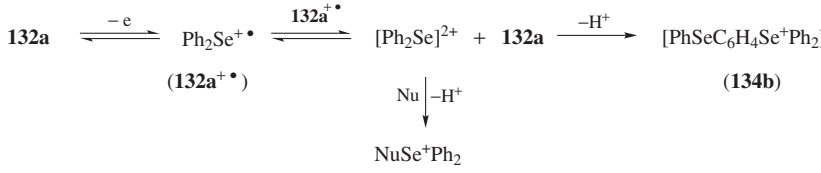


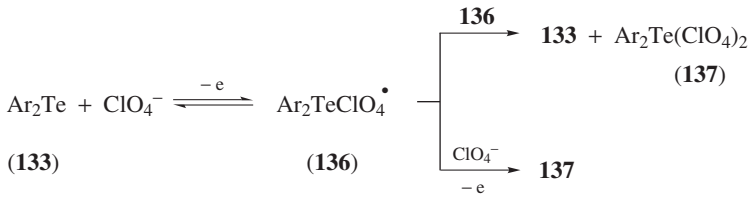
(**134a**) (**134b**) (**135a**) X = H (**135b**) X = Me

The nature of chemical reactions of radical cations **132**$^{+\bullet}$ formed from **132** in the first anodic step was definitively explained by Jouikov and coworkers[60]. They investigated the oxidation of **132a** in MeCN using the commutated voltammetry at a platinum RDE electrode in order to investigate back reactions of generated short-living intermediates. The formation of radical cations **132a**$^{+\bullet}$ in the reversible first step and the following, potential-determining, second-order reaction were proved by the characteristic dependence of $E_{1/2}$ on the angular velocity of the rotating electrode, ω, with the slope equal to $\Delta E_{1/2}/\Delta \log \omega = 23 \pm 3$ mV. Moreover, this following reaction was not identified as dimerization, which was suggested earlier[58, 59], but as the orbital-controlled disproportionation, giving the dication **132**$^{2+}$ with a positive charge localized on the selenium atom. Dications **132**$^{2+}$ are more reactive than radical cations **132a**$^{+\bullet}$. They react with a starting reactant or a nucleophile and the same reaction pathway is valid[60] in the presence and in the absence of nucleophiles (like water, benzene, toluene or pyridine) as is shown in Scheme 18. The electrolysis of **132a** with excess of benzene (3:1) in MeCN containing 0.01 M $NaClO_4$ in a divided cell resulted in triphenylselenonium salt $[Ph_3Se]^+ClO_4^-$ with 86% yield and a small amount of **135a** (Scheme 18). A similar salt was obtained using toluene. The rate constants for the reaction of **132a**$^{2+}$ with toluene and pyridine were determined to be 18.9 and $6.35 \cdot 10^3$ l mol^{-1} s^{-1}, respectively.



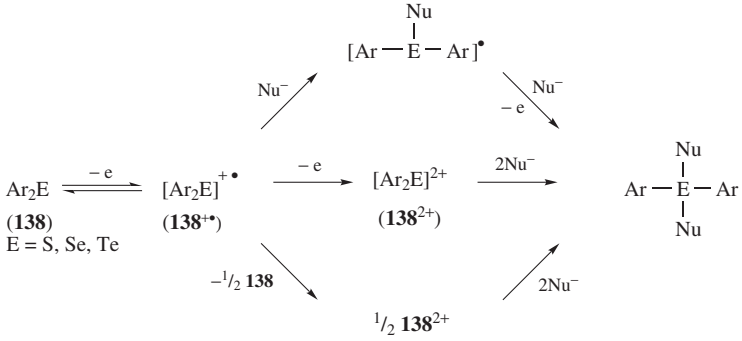
SCHEME 18

On the other hand, the oxidation of the corresponding telluride **133a, 133b, 133c** and difuryltelluride, $(C_4H_3O)_2Te$, at a platinum electrode in CH_2Cl_2 containing 0.1 M TBAP showed[61, 62] only one anodic peak. This diffusional peak corresponds to a two-electron process in which perchlorate ions from the supporting electrolyte participate giving intermediate radical **136** and finally **137**. Moreover, a broad ESR signal was found[62] during the oxidation of **133a**, supporting the mechanism proposed[62] shown in reactions 31.



(31)

In a more general mechanism for diarylchalcogenides (**138**), proposed[57] on the basis of earlier studies on diaryl sulfides[63], electrochemical oxidation is a two-electron and is usually an irreversible process resulting in the successive formation of the radical cation (**138**$^{+\bullet}$) and dication (**138**$^{2+}$). The last one can be formed in the anodic oxidation of **138**$^{+\bullet}$ radical ions or in their disproportionation. Both intermediates, **138**$^{+\bullet}$ and **138**$^{2+}$, are next attacked by any nucleophile present in solutions (Scheme 19). No reversibility of the first step was shown[57] in the original Scheme; however, the formation of radical cations was reported as electrochemically reversible for both aryltellurides[62, 64] and arylselenides[60, 64].

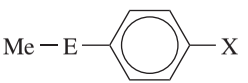


SCHEME 19

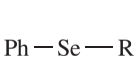
The anodic reactivity of alkylseleno derivatives was not intensively investigated. Nevertheless, peak potentials for the anodic oxidation of dimethylselenide MeSeMe and a series of diselenoethers $MeSe(CH_2)_nSeMe$ (with n changing from 1 to 5) as well as similar dithioethers and selenothioethers were measured[65] in MeCN solutions containing 0.1 M TEAP. They were recently reviewed[3]. One two-electron, irreversible CV peak corresponding probably to the formation of dications was observed. It was commonly accepted that the first electron transfer to MeSeMe and to MeTeMe results in the formation of the corresponding radical cations. The same radical cations were generated by γ-irradiation and were observed by ESR technique in a solid matrix at 77 K. They interact with the parent molecules forming dimers with Se−Se or Te−Te bonds and these intramolecular interactions and bonding in dimers were extensively discussed by Detty and Logan[3].

The anodic oxidation of alkylaryl chalcogenides, in particular substituted arylmethyl chalcogenides **139** or **140**, attracted a great deal of attention. Their oxidation proceeds with the reversible formation of radical cations which undergo the following reactions giving oxides in the presence of residual water, in a similar manner as diaryl analogs **132** in equation 30. For example, the oxidation of benzyl phenyl selenide **140i** at a platinum electrode in MeCN containing 0.1 M $NaClO_4$ gave[66] in reaction 32 benzyl phenyl selenoxide,

139	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**r**	**s**
E	S	S	S	S	S	Se	Se	Se	Se	Se	Te	Te	Te	Te	Te	Se	Se	Se	Se
X	CF_3	H	Me	OMe	NMe_2	CF_3	H	Me	OMe	NMe_2	CF_3	H	Me	OMe	NMe_2	NH_2	Cl	Br	NO_2

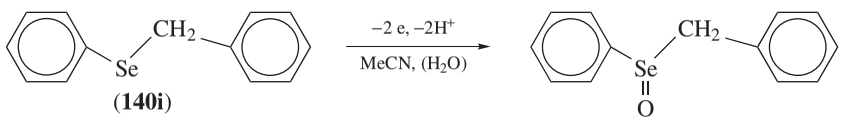


(**139**)



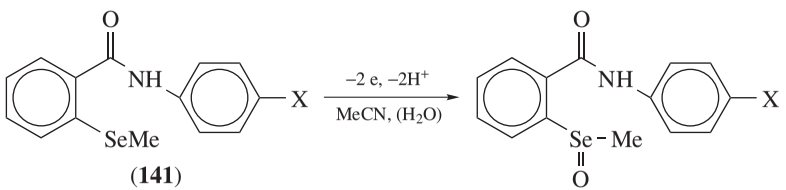
(**140**)

140	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R	Et	Pr	*i*-Pr	*i*-Bu	*t*-Bu	Pen	*i*-Pen	Hex
$(ArSe)_2$ Yield (%)	47	68	83	88	97	70	78	71



(32)

141	**a**	**b**	**c**	**d**	**e**	**f**	**g**
X	H	OMe	F	Cl	CF_3	CN	NO_2

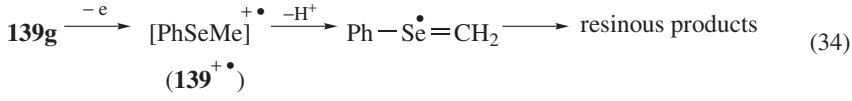


(33)

which underwent further transformations to the final product diphenyl diselenide **10g**, benzaldehyde and *N*-benzylacetamide formed in a reaction with the solvent molecule. Similarly, the oxidation of 2-(methylseleno)benzanilide and its 4-phenyl substituted derivatives **141** under the same conditions resulted[67] in the formation of the respective selenoxides as is shown in reaction 33.

On the other hand, in aprotic solvents and in the absence of any good nucleophiles the loss of an α-proton to the chalcogen atom or the carbon–chalcogen bond cleavage can occur[68–73]. For the oxidation of **139g–139i** and **139p–139s** in MeCN at a platinum electrode, the ECE mechanism was proposed[68] with a first-order reaction (probably deprotonation or dealkylation) as the chemical step. The proton loss as the potential-determining step was found for the oxidation of **139g** which produces final resinous products[3, 71, 72] as shown in equation 34. It was suggested[39] that these products resulted in the polymerization of cationic intermediates formed after the deprotonation of **139**$^{+\bullet}$ radical cation. However, the addition of a strong proton donor, like CF_3COOH, suppresses the elimination of an acidic methyl proton and then the radical cation formed in the first reversible electron transfer follows a slower second-order reaction, showing two one-electron anodic waves[74].

For other alkylphenyl selenides **140** investigated using RDE the single, diffusional, two-electron anodic wave corresponded to the ECE mechanism (Scheme 20)[72]. The radical cation (**140**$^{+\bullet}$), formed in the reversible step, underwent heterolytic fragmentation, which is the potential and the current determining reaction, and resulted in the formation of $PhSe^{\bullet}$ radical. The homolytic fission to $PhSe^+$ (**53**) and alkyl radical does not take place. This was proved by large-scale electrolysis of **140b**, which did not produce a dimer as expected under experimental conditions for $n\text{-Pr}^{\bullet}$ radicals. The second electron transfer gives $PhSe^+$ (**53**), which produces the final product **10g** in reactions that could not be identified electrochemically[72]. The yields of **10** increase with the size of the alkyl group from 5–10% for Me in the case of **139g** to 47% for Et and 97% for the most stable leaving group *t*-Bu radical[39]. However, the process above is complicated by adsorption of organoselenium compounds on the surface of metallic electrodes. The effect of that adsorption on the shift of oxidation potentials was examined[70]. The same center, namely the selenium atom, is mainly responsible for both the ability of oxidation and the adsorption. In order to eliminate the adsorption effect, the oxidation potentials of **140** were determined[72] using a GC RDE electrode.



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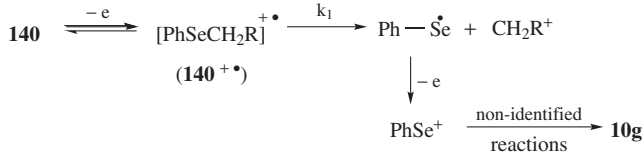
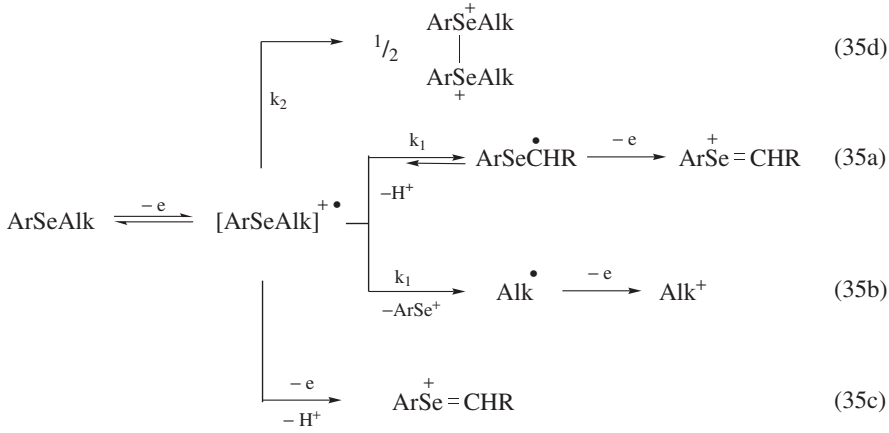


SCHEME 20

As was discussed above, radical cations formed in the first oxidation step from diaryl selenides fade out in a second-order potential-determining reaction, whereas those formed

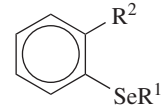
from alkylaryl selenides fade out in first-order reactions. Looking for factors governing this different behavior Jouikov and Ivkov investigated[75] in MeCN containing 0.1 M Et_4NBF_4 a series of selenides with substituents which lower the charge density at the selenium atom and with substituents which change steric effects. As usual, for ArSeAlk compounds with electron donor substituents (**139g**, **139h**, **139i**, **142a** and **143**) only one diffusional wave was observed which corresponded to the exchange of two electrons ($n = 2$). The potential-determining step was the first-order reaction, as revealed from the slope $\Delta E_{1/2}/\Delta \log(\omega) = 30$ mV/decade. The products obtained in the large-scale electrolysis of **139g**–**139i**, **142a** and **143a** indicated that this reaction is the deprotonation according to equation 35a. However, it was the dealkylation for the *t*-Bu derivatives **143b** and **143c** according to equation 35b, as was reported earlier[39] for **143b**. For *o*-methyl derivatives **142a** and **143a** the ECE mechanism was also found[75] with the first-order chemical step, but a little higher $E_{1/2}$ potentials were observed. This was explained by inductive and hyperconjugation effects of the methyl group resulting in a higher localization of the positive charge on the Se atom.

On the other hand, for compounds with carbonyl groups **142b**–**142d**, **140j**, **140l** and **140m** two oxidation waves were found of which the second one corresponded to further anodic oxidation of the radical cation according to reaction 35c. However, the first wave with the slope of 60 mV was the one-electron process described by the EC mechanism, i.e. the reversible electron transfer followed by the second-order reaction, as revealed from the values $\Delta E_{1/2}/\Delta \log(\omega) = 20$ mV/decade. Then, the process is described by equation 35d. Such a change from the first-order to the second-order kinetics was explained[75] by stabilization of the reaction center, the Se atom, by the anchimeric assistance of the carbonyl group which can approach the positively charged selenium atom resulting in $> Se^+ \cdots O =$ interactions. In particular, these interactions are possible in cation radicals when Se and O atoms are separated by 4 or 5 bonds allowing the formation of an unlocked 5- or 6-membered cycle like structures **142b**$^{+\bullet}$ and **142d**$^{+\bullet}$. A dimerization of radical cations of **139g** was suggested, but a disproportionation as the second-order chemical step could not be excluded[75]. On the other hand, in ethyl ether of 2-phenylselenoacetic acid **140k** the approach of the oxygen atom of the carbonyl group to the selenium atom is restricted and thus the oxidation according to the ECE mechanism with the first-order reaction ($\Delta E_{1/2}/\Delta \log(\omega) = 30$ mV/decade, $n = 2$) was established[75].

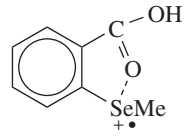


(**140i**) R = Ph
(**140j**) R = CH_2CO_2H
(**140k**) R = CO_2Et

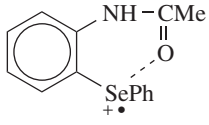
(**140l**) R = *n*-Bu
(**140m**) R = Pen



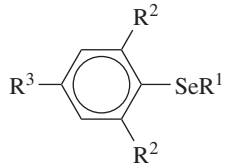
(**142a**) $R^1 = R^2 = Me$,
(**142b**) $R^1 = Me$, $R^2 = CO_2H$
(**142c**) $R^1 = Me$, $R^2 = CO_2Me$
(**142d**) $R^1 = Ph$, $R^2 = NHCOMe$



(**142b**$^{+\bullet}$)



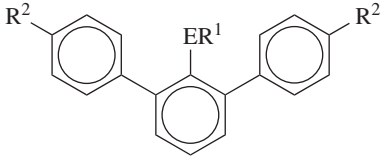
(**142d**$^{+\bullet}$)



(**143**)

143	**a**	**b**	**c**
R^1	Me	*t*-Bu	*t*-Bu
R^2	Me	H	H
R^3	Me	H	Me

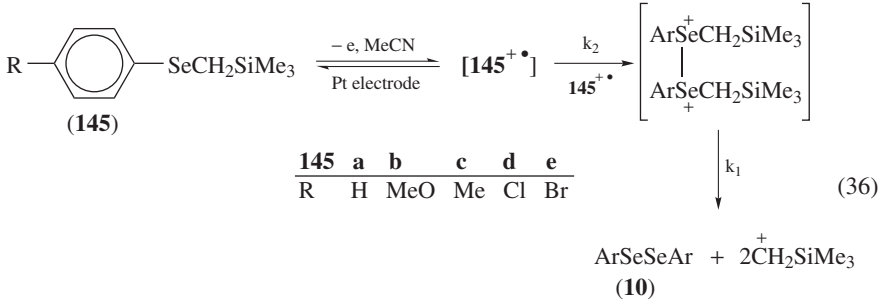
Peak potentials E_p for the first irreversible oxidation step of *m*-terphenyl chalcogenoethers **144** were measured[76] at a platinum electrode in MeCN solutions and compared with the values for sulfur analogs. The potentials obtained for seleno or sulfur compounds were substantially less positive than expected. For example, the bulky 2,6-diaryl groups in methylseleno compounds **144a–144c** favor the perpendicular conformer for which lone-pair electrons on the selenium atom do not overlap with the π-system of the benzene ring attached to it. This should result in more positive oxidation potentials than for selenoanisole ($E_p = 0.965$ V vs. Ag/Ag^+), whereas the E_p value is the same for **144a** and even less ($E_p = 0.86$ V) for **144b** and **144c**. The through-space interaction between the selenium *p*-orbital lone-pair and 2,6-aromatic π-systems was proposed[76] to explain the results obtained, and the same effect was reported for analogous thioethers but not for tellurium compounds.



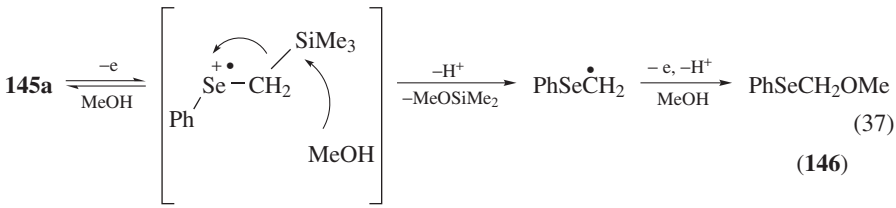
(**144**)

144	**a**	**b**	**c**	**d**	**e**	**f**	**g**
E	Se	Se	Se	Se	Se	Te	Te
R^1	Me	Me	Me	Ph	Ph	Ph	Ph
R^2	*o*-OMe	*p*-OMe	1-Naph	*o*-OMe	*p*-OMe	*o*-OMe	1-Naph

The oxidation of aryl(trimethylsilylmethyl)selenides **145** at a platinum RDE in MeCN containing 0.1 M TEAP reveals[77] two waves. The first one is diffusional and corresponds to the one-electron transfer. The second one was not well reproducible and could not be attributed to further oxidation of radical cations. For the first step the slopes of plots of half-wave potentials against the reactant concentration and against the angular velocity of a rotating electrode were equal to 20 mV/decade. This indicates the second-order chemical reaction of radical cations formed in the first step. This behavior, characteristic of diarylselenides rather than arylalkylselenides as discussed above, is caused by stabilization of radical cations by the Me_3Si group in the β-position to the Se atom. This second-order reaction was identified as the dimerization in agreement with the results of large-scale electrolysis of **145a** which gave **10g** as the major product. Thus, the overall mechanism[77] proposed by equation 36 includes the formation of diselenonium dications which decompose to the final product. On the other hand, in the presence of oxygen-containing nucleophiles, for example, if the electrolysis was performed in methanol, the competitive pathway was observed with a C−Si bond cleavage followed by the addition of a nucleophile to the cationic fragment[77]. Thus, the electrolysis of **145a** in MeOH containing 0.1 M $LiClO_4$ in a divided cell resulted[77] in the formation of methoxylated product **146** (15%) in reaction 37, in addition to a small amount of **10g**, similarly as it was found for aryl(trimethylsilylmethyl) sulfides.

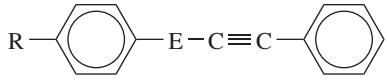


(36)



(37)

The ECE mechanism was proposed[78] for the anodic oxidation of arylethynylselenides and tellurides **147** in MeCN containing 0.08 M TEAP using an oxidized platinum RDE. A two-electron wave was observed at a lower angular velocity of the electrode ω, but a one-electron wave was observed at higher ω, indicating the formation of unstable radical cations in the first step. It was confirmed[78] for **147a** and **147f** by commutated polarographic curves. The following chemical reaction corresponded to the second-order kinetics, as revealed by the derivative $\Delta E_{1/2}/\Delta \log \omega = 20 \pm 5$ mV/decade[78]. The last result is obvious taking into account that the first-order deprotonation reaction can be excluded for these molecules having no acidic α-protons. As usual, the $E_{1/2}$ potentials for tellurides are lower than for the corresponding selenides.



(**147**)

147	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
E	Se	Se	Se	Se	Se	Te	Te	Te
R	MeO	Me	H	Cl	Br	Me	H	Cl

B. Diaryl and Dialkyl Diselenides

The anodic oxidation of diphenyl diselenide **10g** was widely used in electrochemical synthetic reactions as was already reviewed in Sections II.B and III. The formation of radical cation **10g**$^{+\bullet}$ in the first step (heterogeneous or mediated by a catalyst, like halonium ions) and next the Se−Se bond cleavage were postulated by some authors. It resulted in the formation of phenylselenenyl halide (**11**) [18–20], phenylselenenyl cation (**53**)[27, 29, 32] or, in the presence of water, phenylselenic acid (PhSeOH)[21], but details were not investigated. In this Section extended investigations of the oxidation mechanism will be reviewed.

In anhydrous MeCN, **10g** exhibited[79] two irreversible anodic CV peaks. The first one corresponded to the two-electron step at a lower sweep rate, but to the one-electron process at higher scan rates. The mechanism proposed[79], shown in reaction 38, involves the formation of radical cation (**10g**$^{+\bullet}$), the bond cleavage yielding cation **53** and radical PhSe$^{\bullet}$, and finally the electron exchange between PhSe$^{\bullet}$ and the radical cation in the disproportionation reaction. Thus, the whole oxidation process corresponds to the so-called DISP1 mechanism. However, a similar ECE mechanism with the electrode oxidation of PhSe$^{\bullet}$ to **53** was suggested[80] for the same process. Finally, **53** may react with the solvent molecule in reaction 39[79]. The formation of **53** was confirmed by its reaction with the added excess of cyclohexene which resulted in the formation of mainly 2-acetamido-1-phenylselenocyclohexane. Similar acetamidoselenation of alkenes in MeCN solutions was reported earlier[24, 80]. Moreover, the rate constant of the decay of **53** in MeCN solutions containing cyclohexene equal to 4.9 s^{-1} was measured[80] using modulated specular reflectance spectroscopy. Further oxidations of intermediates in reaction 38 are accelerated by the presence of water[79] giving $n = 6$ electrons in the overall reaction 40.

$$\underset{(\mathbf{10g})}{Ph_2Se_2} \overset{-e}{\rightleftharpoons} \underset{(\mathbf{10g}^{+\bullet})}{[Ph_2Se_2]^{+\bullet}} \longrightarrow \underset{(\mathbf{53})}{PhSe^{+}} + PhSe^{\bullet} \xrightarrow[\mathbf{10g}^{+\bullet}]{} \mathbf{53} + \mathbf{10g} \qquad (38)$$

$$\mathbf{53} + MeCN + H_2O \longrightarrow PhSeNHCOMe + H^{+} \qquad (39)$$

$$\mathbf{10g} \xrightarrow{4H_2O,\ -6\ e} 2\ PhSeO_2H + 6\ H^{+} \qquad (40)$$

The oxidation of diaryl diselenides Ar_2Se_2 **10p** (Ar = $MeOC_6H_4$) and **10r** (Ar = $EtOC_6H_4$) at a platinum anode in MeCN containing 0.1 M Bu_4NBF_4 revealed[81] a single anodic peak and reduction peaks after reversing the potential scan. It was suggested that the first reduction peak corresponds to the reduction of selenium deposited on the electrode. The overall oxidation reaction 41 was proposed[81].

On the other hand, the oxidation of **10h** at a platinum anode in CH_2Cl_2 containing 0.1 M TBAP yielded in the overall reaction 42 triperchlorate salt as was identified by its cathodic wave, whereas the oxidation of difuryl ditelluride $(C_4H_3O)_2Te_2$ (**10s**) yielded in reaction

43 difuryltelluride perchlorate and metallic tellurium which precipitates in the solution[82].

$$\mathrm{Ar_2Se_2} \xrightarrow[\text{Pt anode}]{2\mathrm{BF_4^-},\ -2e} \mathrm{Ar_2Se(BF_4)_2} + \mathrm{Se} \qquad (41)$$

(**10p**) Ar = $MeOC_6H_4$
(**10r**) Ar = $EtOC_6H_4$

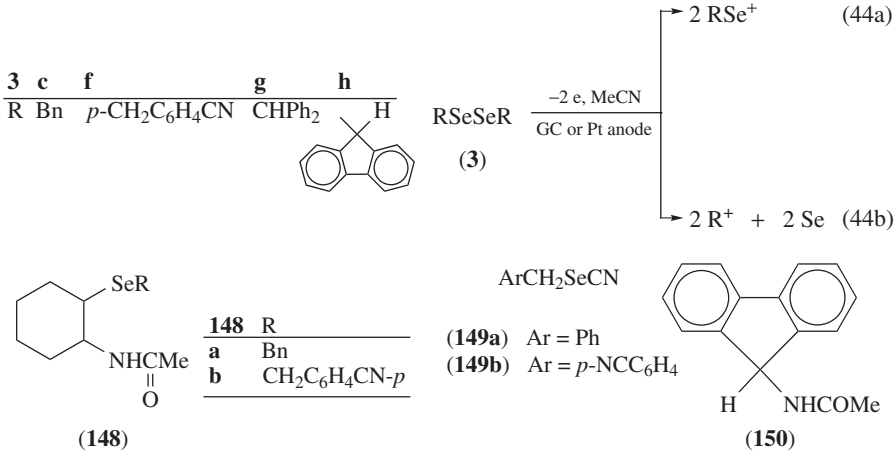
$$\mathrm{PhTeTePh} \xrightarrow[\mathrm{CH_2Cl_2,\ TBAP}]{6\mathrm{ClO_4^-},\ -6e} 2\ \mathrm{PhTe(ClO_4)_3} \qquad (42)$$

(**10h**)

$$(\mathrm{C_4H_3O})\mathrm{TeTe}(\mathrm{OC_4H_3}) \xrightarrow[\mathrm{CH_2Cl_2,\ TBAP}]{2\mathrm{ClO_4^-},\ -2\ e} (\mathrm{C_4H_3O})_2\mathrm{Te(ClO_4)_2} + \mathrm{Te} \qquad (43)$$

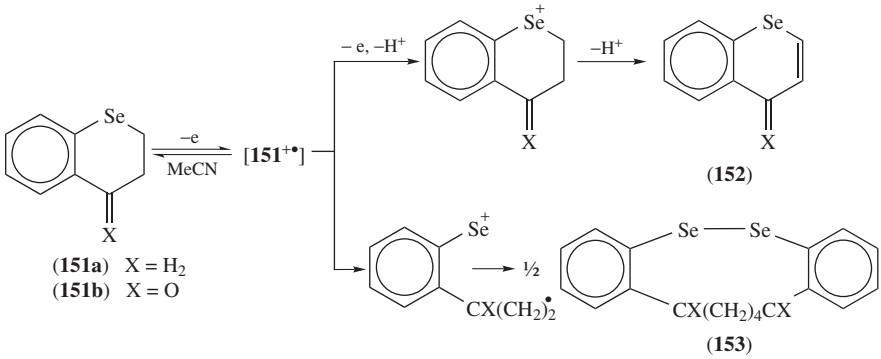
(**10s**)

The anodic oxidation of dialkyl diselenides **3** at GC or Pt anodes in MeCN can follow the same mechanism as diaryl dielenides with the Se−Se bond cleavage and the formation of RSe^+ cations[83], as is shown in reaction 44a. This behavior was proved[83] for **3c** and **3f** where, after passing a charge of 2 F per mol of **3** during the preparative electrolyses, acetamides **148a** and **148b** or selenocyanates **149a** and **149b** were isolated if the process was performed in the excess of cyclohexene or KCN, respectively. On the other hand, the cleavage of C−Se bonds according to reaction 44b was found for **3g** where red selenium was deposited on a platinum anode surface, and for **3h** where the preparative electrolysis in the presence of cyclohexene resulted[83] in the formation of fluorenone, fluorenol and *N*-fluorenyl acetamide **150**. In the presence of residual water the overall oxidation process of **3c** and **3f** led to the formation of the corresponding seleninic acids[83], similarly as it was reported[79] for **10g**. It was not possible to prove that the RSe^+ cations generated at an anode can be then reduced and the origin of a small cathodic peak observed on CV curves of **3c** remained unclear[83].



C. Heterocyclic Selenides and Tellurides

The anodic oxidation of cyclic alkylphenylselenides **151** in MeCN containing TEAP using an oxidized platinum RDE showed[69] one anodic wave, diffusional and less than a two-electron one. The commutative curves confirmed the formation of radical cations $\mathbf{151}^{+\bullet}$ which were, however, less stable than for acyclic alkylphenylselenides. The slope $\Delta E_{1/2}/\Delta \log \omega = 30\,\text{mV/decade}$ indicated the decay of $\mathbf{151}^{+\bullet}$ in a first-order chemical reaction. Moreover, the preparative electrolysis resulted in the formation of two main products **152** and **153**. Thus, in the mechanism (Scheme 21) either deprotonation of radical cation $\mathbf{151}^{+\bullet}$ giving finally **152** or the (C_{sp}^3)−Se bond cleavage followed by the dimerization to **153** was proposed[69] as the following chemical step. The competition between both routes depends on the protons' mobility at the α-carbon atom near the selenium atom.

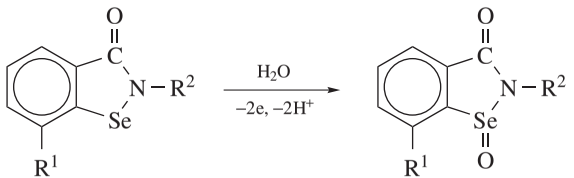


SCHEME 21

A series of *N*-alkyl- and *N*-aryl-1,2-benzisoselenazol-3(2*H*)-one **154** and 7-substituted analogs **155** were electrochemically oxidized at platinum electrodes (stationary and RDE) in formally 'dry' MeCN and in the presence of water and acids[84, 85]. These compounds looked attractive because **154g**, called ebselen, has biological activity against hydroperoxide-dependent inflammatory pathological conditions. Two irreversible, diffusional oxidation waves (or peaks) were observed at relatively high potentials. The preparative electrolysis at the potential of the first step after passing the charge of $2\,\text{F mol}^{-1}$ gave the corresponding selenoxides as the products of the overall reaction 45. Remarkable substituent effects on oxidation potentials were found, but no direct relations to biological activity were observed[85]. On the other hand, for 4,7-diisopropyl-1,2,3-benzotrichalcogenoles **156** the CV curves recorded at a GC electrode in MeCN containing 0.1 M TBAP showed a reversible anodic one-electron step, but the mechanism was not investigated[86]. The peak potentials given here (expressed vs. Ag/Ag^+ reference) are mainly governed by the atom present at the 2-position in the chalcogen ring.

The anodic oxidation of benzo(*b*)selenophene (**157a**) and dibenzo(*b*, *d*)selenophene (**158**) in MeCN resulted[87] in the formation of proper selenoxides in reaction 46; **159** was obtained in the preparative electrolysis and identified by the cathodic reduction at +0.20 V vs. Ag/Ag^+ in MeCN containing 0.1 M $NaClO_4$. The reduction regenerates **158** if protons are available in the solution. Anodic potentials for the oxidation in MeCN of **157b** and **157c** were reported[88].

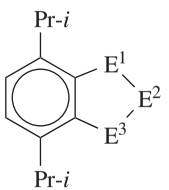
155	**a**	**b**	**c**	**d**	**e**
R^1	H	OMe	Cl	F	NO_2



(45)

(**154**) $R^1 = H$
(**155**) $R^2 = Ph$

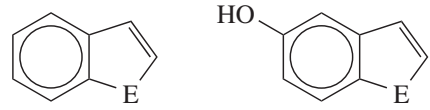
154	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**
R^2	Me	Et	Bu	Hex	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	Ph	*p*-FC_6H_4	*p*-ClC_6H_4	*p*-$EtCO_2C_6H_4$	*p*-NCC_6H_4	*p*-$O_2NC_6H_4$



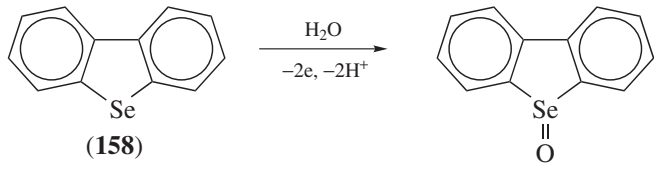
(**156**)

156	**a**	**b**	**c**	**d**
E^1	S	S	S	Se
E^2	Se	S	Se	S
E^3	S	Se	Se	Se
E_p (V)	0.64	0.75	0.63	0.71

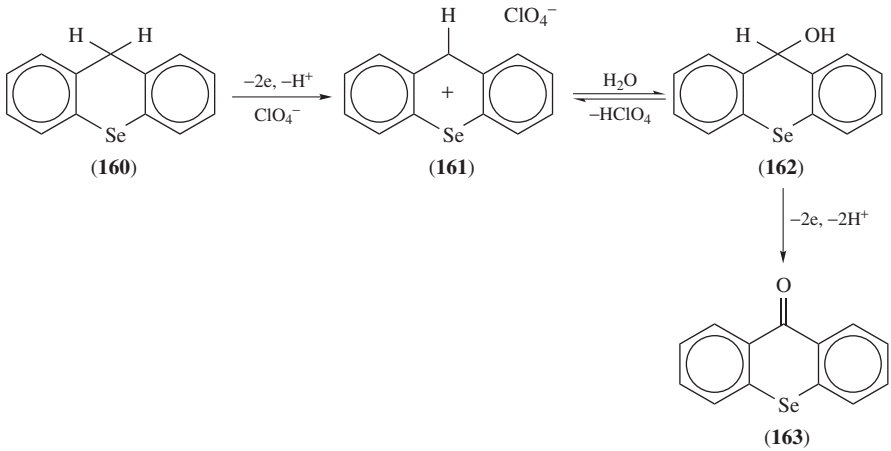
The anodic behavior of selenoxanthene **160** in MeCN containing 0.1 M $LiClO_4$ at a GC or a platinum RDE and at a stationary Pt electrode was examined[89] by various techniques. The two-electron oxidation (Scheme 22) yielded the selenoxanthylium cation **161**, which was isolated quantitatively as a perchlorate salt and identified by the UV spectrum and the melting point. The formation of **161** changes the colorless electrolyte solution to deep red purple. In solutions after the electrolysis, selenoxanthene-9-ol **162** was detected by TLC. Its formation required residual water present in MeCN. **162** can be further oxidized at an electrode to selenoxanthone **163** (Scheme 22) or **163** is formed in the disproportionation of **162**. On the other hand, for anodic oxidation of **160** in a 3% mixture of water and MeCN a new anodic peak was observed in CV curves, but only for slow sweep rates 5 and 10 mV s^{-1}. This peak was attributed to the oxidation of **163** to the corresponding selenoxide. Further electroreduction of **161** was also reported[89].



(**157a**) E = Se (**157b**) E = Se
(**157c**) E = Te



(**158**) (**159**) (46)

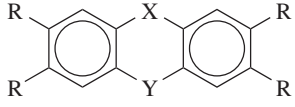


(**160**) (**161**) (**162**) (**163**)

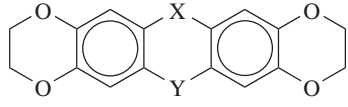
SCHEME 22

Half-wave potentials for the oxidation of a series of dibenzo[1,4]dichalcogenines **164** and **165** were determined[90] and some of them were correlated with their antioxidant capacity in biological systems[91]. Quasi-reversible CV peaks were observed[92] for the one-electron oxidation to radical cations of most compounds **164** and **165** in CH_2Cl_2 or MeCN and sometimes also for the second electron transfer. The presence of methoxy groups in **164** and **165** caused a remarkable stability of **164**$^{+\bullet}$ and **165**$^{+\bullet}$ radical cations. Thus, crystalline salts of radical cations of 1:1 stoichiometry were prepared[90] for **165b**$^{+\bullet}$ ClO_4^-, **165b**$^{+\bullet}$ AsF_6^- and **165c**$^{+\bullet}$ ClO_4^- but, for example, for **165a**$^{+\bullet}$ AsF_6^- the stoichiometry was 4:3. Later, the electrode mechanism of similar cyclic compounds selenanthrene[92] **166a** and thioselenanthrene[93] **166b** was examined in detail using different electrochemical methods. The CV oxidation of **166a** in MeCN solutions containing 0.1 M Bu_4NBF_4 showed[92] two anodic peaks at 1.26 and 1.86 V vs. SCE, respectively. The electrolysis at the first potential changed the colorless solution to deep blue-black (characteristic of the radical cation) and again to colorless after passing 2 F mol^{-1}. The final product of the overall reaction 47 was identified as selenanthrene-5-oxide **167a**. The electrolysis at the potential of the second peak resulted in the formation of 5,10-dioxide **168a**, which can be reduced back to **166a**, as is shown in reaction 48. The CV curves for the first electron transfer were fully reversible at a scan rate $\upsilon = 10$ V s^{-1}, and a peak width $E_p - E_{p/2} = 46 \pm 1$ mV and a peak potential shift $\Delta E_p/\Delta \log \upsilon = 31.6 \pm 6$ mV/decade were found[92]. The results above were indicative of the ECE or DISP1 mechanism shown by reactions 47a and 47b, respectively. The apparent first-order rate constant for the rate-determining chemical reaction between **166a**$^{+\bullet}$ and residual water was measured to be $k_1 = 10.5$ s^{-1}. This means that the half-life time of **166a**$^{+\bullet}$ is about 66 ms.

On the other hand, for the first oxidation step of **166b** the CV peak width $E_p - E_{p/2} = 38.1 \pm 2$ mV was indicative[93] of the DISP2 mechanism. It corresponds to reaction 47b with the slowest disproportionation reaction, described by the k_2 rate constant. The formation of selenoxide as the final product was confirmed by TLC and ^{77}Se NMR. The half-life time of **166b**$^{+\bullet}$ was about 78 ms. The change of mechanism from DISP1 for **166a** to DISP2 for **166b** was ascribed to the enhancement of the rate constant for the hydroxylation of **166b**$^{+\bullet}$ in undried MeCN. For **166d** and **166e** only anodic peak potentials were reported[94].

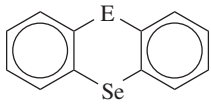


(**164**) R = OMe X,Y = O,S,Se,Te

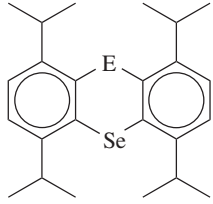


(**165**) X,Y = O,S,Se,Te

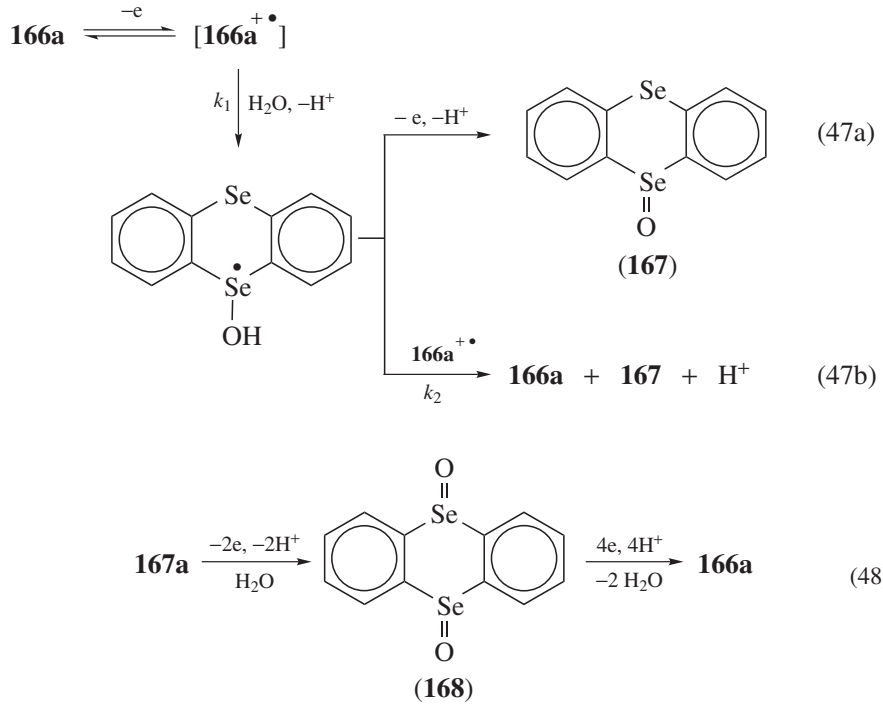
165	**a**	**b**	**c**
X	O	S	Se
Y	Te	Se	Se



(**166a**) E = Se
(**166b**) E = S
(**166c**) E = O



(**166d**) E = Se
(**166e**) E = S



The CV peak potentials for the anodic oxidation in MeCN of a series of dichalcogena cyclic compounds are given in Table 3. They were used to estimate the stability of radical cations and dications formed in electrode processes as well as to indicate transannular interactions between chalcogen atoms in cyclic compounds. The CV curves for the oxidation of **169** and **170a** showed[95, 96] one reversible peak at much lower potentials than were observed for analogous compounds **171, 172** and **170b**, which in turn showed irreversible peaks (Table 3). Potential lowering was explained by a greater stability of cationic products of the oxidation caused by *peri*-Se−Se interactions. The electrochemical mechanism was not investigated, but chemical oxidation of **170a** using concentrated H_2SO_4 gave an ESR signal of the selenide cation radical and, after the addition of water with ice, the formation of mono-selenoxide. It was suggested that the radical cations disproportionate forming dications which react with water giving selenoxide[95]. Cationic products of the oxidation of **173a** were more stable than those of **173b** (Table 3) due to stabilization by

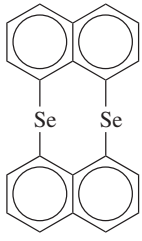
TABLE 3. Peak potentials for the oxidation at GC electrodes of cyclic chalcogena compounds

Reactant	**169**	**170a**	**170b**	**171**	**172**	**173a**	**173b**	**173c**	**174c**
E_p/(V)[a]	0.33	0.48	0.70	0.77	0.82	1.05	0.75	0.41	−0.02
Ref.	95	95	96	95	95	97	97	98	99

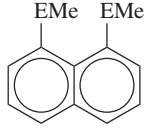
[a]Measured vs. Ag/0.01 M $AgNO_3$ in MeCN containing 0.1 M $NaClO_4$ at $\upsilon = 0.3$ V s^{-1}.

transannular Se–S interaction[97]. A similar Te–S interaction was suggested[98] for **173c**. The easiest oxidation occurs[99] for **174c**.

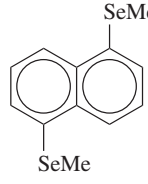
Recently, a more detailed mechanism of anodic reactions for a series of dichalcogenamesocycles were reported[100]. For 1,5-diselenocane (1,5-diselenacyclooctane) **174a** and 1,5-ditellurocane (1,5-ditelluracyclooctane) **174c**, a two-electron reversible process shown in equation 49 was observed in the CV curves. It corresponds to two successive electron transfers with the formation of radical cations and dications, respectively, but they occur with the 'inverted potentials', i.e. the removal of the second electron is easier than the removal of the first one. It gives a positive potential difference $E^{\circ}_1 - E^{\circ}_2 = 44\,\text{mV}$ and 36 mV for **174a** and **174c**, respectively, as proved by a simulation of the CV curves at different scan rates. The stability of the dications decreases in the order $\mathbf{174a}^{2+} > \mathbf{174c}^{2+} > \mathbf{174e}^{2+}$. On the other hand, the electro-oxidation of 1,5-selenathiocane **174b** and 1,5-tellurathiocane **174d** showed two irreversible one-electron peaks. The first one corresponds to the formation of radical cations followed by the rapid formation of dimer dications $[\mathbf{174}]_2^{2+}$ as is shown in Scheme 23. The second oxidation peak corresponds to their further oxidation. The mechanism proposed[100] was proved by a simulation of voltammograms. Moreover, X-ray structures of crystalline dimer salts $[(\mathbf{174b})_2]^{2+}[HOB(C_6F_5)_3]_2^-$ and $[\mathbf{174d}]^{2+}$ $[CF_3SO_3]_2^-$ were reported. The oxygen-bridged dimer **175** was obtained by the chemical oxidation of **174d** using $NOBF_4$. Similar compounds **176** containing silicon or tin atoms in the ring instead of carbon atoms showed[100] irreversible oxidation peaks (one for **176a** and analogous thio compounds, but two for **176b**) or reversible ones for **176c** and **176d**. This change in behavior was ascribed to differences in transannular bond strengths. It was concluded[100] that the preferred oxidation pathway with the formation of more stable products follows the strongest dicationic bond: $Te^+-Te^+ > Se^+-Se^+ > S^+-S^+$, $Te^+-Te^+ > Te^+-Se^+$ and $Se^+-Se^+ > Se^+-S^+$.



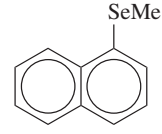
(**169**)



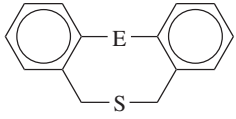
(**170a**) E = Se
(**170b**) E = S



(**171**)

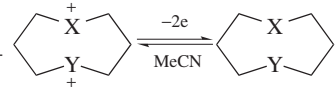


(**172**)



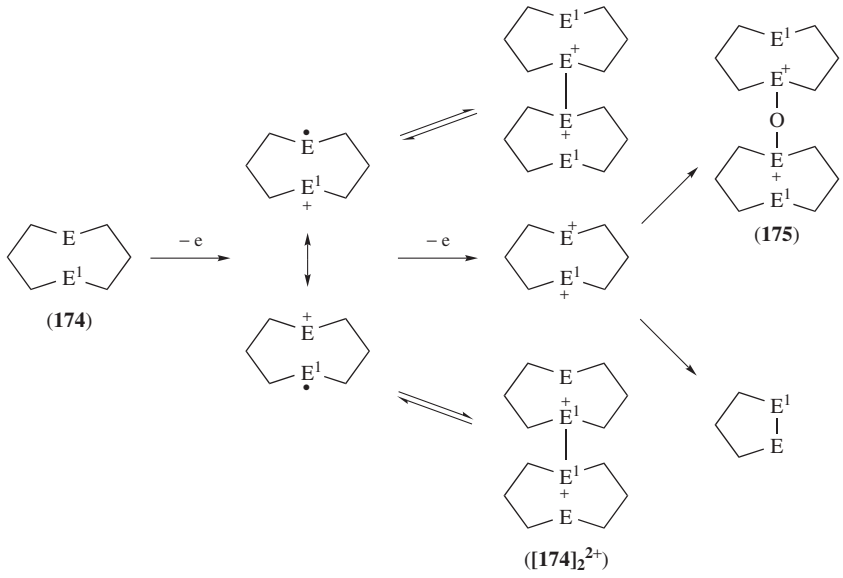
(**173a**) E = Se
(**173b**) E = Se
(**173c**) E = Te

174	**a**	**b**	**c**	**d**	**e**
X	Se	S	Te	S	S
Y	Se	Se	Te	Te	S

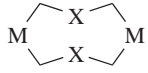


(49)

(**174a**$^{2+}$) X = Y = Se (**174**)
(**174c**$^{2+}$) X = Y = Te



SCHEME 23



(**176**)

176	**a**	**b**	**c**	**d**
X	Se	Se	Te	Te
M	$SiMe_2$	$SnMe_2$	$SiMe_2$	$Si(SiMe_3)_2$

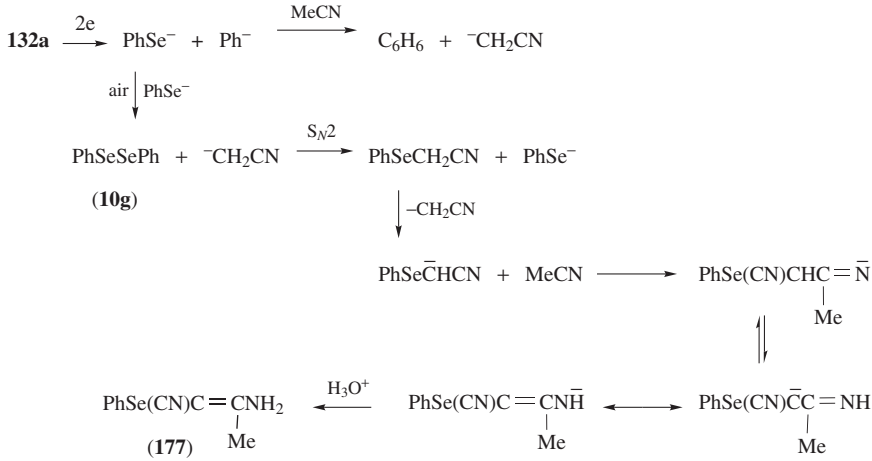
D. Other Organoselenium and Organotellurium Compounds

The electrochemical oxidation of triphenyltellurium chloride Ph_3TeCl in CH_2Cl_2 containing 0.1 M TBAP at a platinum RDE showed[101] the anodic wave at the potential $E_{1/2} = 1.23$ V vs. SCE. The mechanism suggested involved bond cleavage with the formation of $Ph_2TeCl^{\bullet}$ radicals and their dimerization to the final ditelluride $Ph_2(Cl)TeTePh_2(Cl)$, which can be reduced in a cathodic scan. The anodic oxidation of $Me_2NPhTeCl_3$ was also reported[61]. However, for organotellurium chlorides the cathodic reduction is more characteristic. The anodic oxidation of ferrocene derivatives containing selenium and tellurium atoms was investigated[102–104] but the electrode processes did not involve chalcogen groups. Oxidation and reduction potentials of a few 21-telluraporphyrins, candidates as catalysts for the activation of H_2O_2, were reported[105] as well.

V. REDUCTION MECHANISMS OF ORGANIC SELENIUM AND TELLURIUM COMPOUNDS

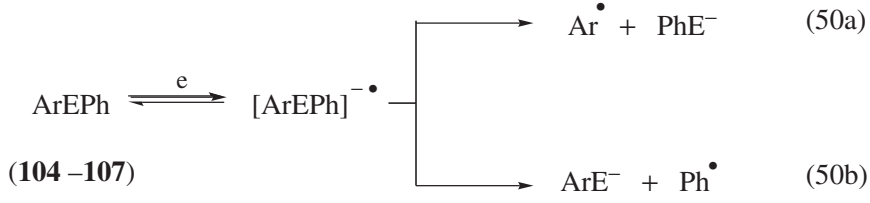
In a number of papers, reduction potentials of the title compounds were reported but the electrode mechanism was not investigated. However, cathodic reactions of organic selenides and tellurides as well as diselenides and ditellurides were investigated in detail, as will be reviewed below.

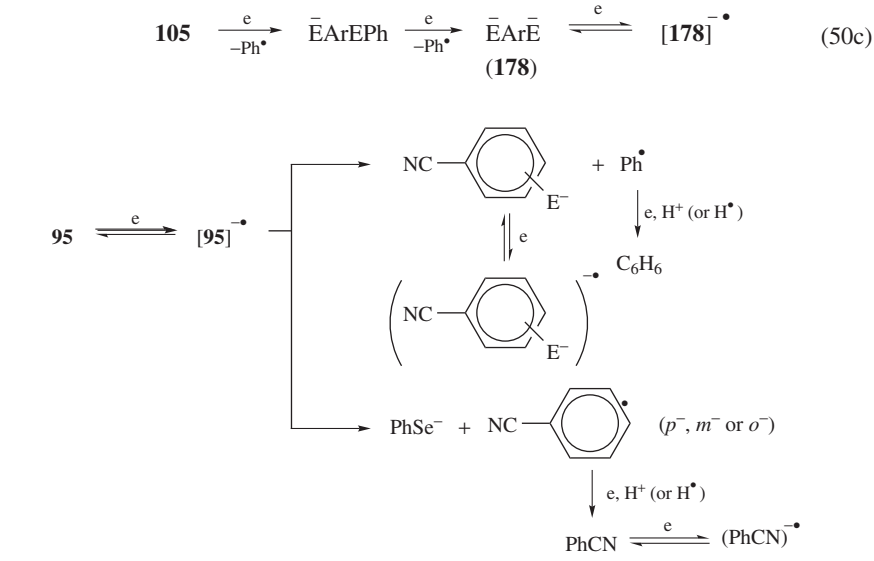
The electroreduction of aromatic selenides is not easy. The two-electron irreversible reduction wave of diphenyl selenide **132a** at a GC RDE in MeCN containing 0.1 M Bu_4NPF_6 was observed[106] only at $E_{1/2} = -2.54$ V vs. SCE. A large-scale electrolysis of **132a** was accompanied by an increase of the anodic wave of $PhSe^-$ anions formed in the bond cleavage. The Ph^- ions which were also obtained in this cleavage were protonated by solvent molecules with the formation of benzene and $^-CH_2CN$ ions (Scheme 24)[106]. The $PhSe^-$ anions were oxidized by air yielding PhSeSePh (**10g**), which underwent the reaction with $^-CH_2CN$ ions giving the final product 1-phenylseleno-1-cyano-2-aminopropene (**177**). The effect of residual water on the yields of products were discussed[106].



SCHEME 24

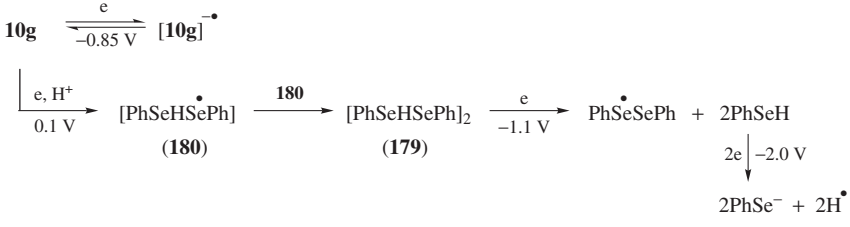
The electroreduction of isomeric *o*-, *m*- and *p*-(phenylseleno)benzonitriles[48] and (phenyltelluro)benzonitriles[49] (**95**) at Hg, Pt and GC electrodes followed the reversible formation of radical anions which next decomposed by the C–Se or C–Te bond cleavage (Scheme 25). In DMF, two clear CV peaks were observed corresponding to the formation of the respective radical anions and a small reversible peak between them which corresponds to the reduction of PhCN. Di(cyanophenyl)dichalcogenides **10** were the main products of interest[48, 49] in the preparative electrolysis of **95** as was discussed in Section II.D. For the reduction of a number of arylphenyl chalcogenides **104**–**107** in DMF at GC electrodes[50] the products were aryl anions ArE^- (Ar = 4-biphenyl or 2-fluorenyl for the reduction of **104** or **106**, respectively) formed in reaction 50b and aryl dianions $^-EArE^-$ (**178**), with Ar = 4, 4′-biphenyl, for the reduction of **105** in schematic reaction 50c as well as benzene. However, anthracene and PhE^- anions were formed[50] in the schematic reaction 50a as products for the reduction of **107**.





SCHEME 25

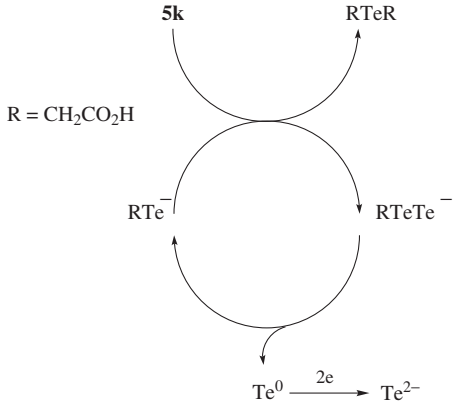
The two-electron reduction of diaryl diselenides and diaryl ditellurides with C−Se or C−Te bond cleavage, respectively, and the formation of selenolate $ArSe^-$ or tellurate $ArTe^-$ anions[17,44–50] was already mentioned in Section II.D. Electrode reactions were performed mainly in MeCN solutions, but also in DMA where the formation of polyselenide ions was studied[107,108]. The first attempts at a polarographic reduction of **10g** indicated[109–111] that it reacts with the mercury electrode prior to the electron transfer and, in the preparative electrolysis, PhSeHg and PhSeH were formed. However, the use of a GC electrode allowed the authors to obtain the reversible one-electron CV reduction peak at −0.85 V vs. SCE in MeCN containing 0.1 M TEAP[111]. After an initial positive scan an additional reduction peak was observed at −1.1 V corresponding to the one-electron transfer to dimer **179**. The same peak was observed if the reduction occurred in the presence of protons. Thus, the first peak which appears at +0.1 V was ascribed[112] to the formation of radicals (**180**) undergoing further dimerization (Scheme 26). Catalytic properties of **10g** for the reduction of protons and the oxidation of water were also reported[109]. However, later Ludvík and Nygård discussed[113] the results and found a two-electron reduction



SCHEME 26

of **10g** as well as the absence of radical intermediate $ArSe^{\bullet}$ during this process at different solid electrodes (no EPR signal, no electrochemiluminescence and no chemical reactions characteristic of such radicals were observed). Thus, the authors suggested[113] three different electroreduction pathways.

On the other hand, at mercury electrodes the reduction mechanism of aromatic diselenides and ditellurides in aprotic solutions[114] and organic ditellurides in protic media[115] is accompanied by the formation of mercury-containing complexes, as was investigated in detail by Ludvík and Nygård[113–116]. The reduction of **10g, 10p, 10h** and **10r** in DMF showed two diffusion-controlled polarographic waves (or two reversible pairs of CV peaks) and the current of the second step was always two times higher than for the first one[114]. Coulometric measurements confirmed that the total number of electrons is equal to two. Moreover, the first peak was not observed if platinum or gold electrodes were used. Furthermore, $Hg(PhSe)_2$ (**181g**) was isolated as the product of the spontaneous reaction between **10g** and mercury in de-aerated DMF. Thus, the mechanism proposed[114], shown in reaction 51, involves the reduction of **181** in the first electrode step and further reduction of the triangular complex ion **182** at more negative potentials. In general, in protic media (aqueous or aqueous/ethanolic) the surface pre-reaction 52a leads to the formation of mercury chalcogenide compounds **183** which are strongly adsorbed[113, 115]. They are reduced in a one-electron reaction 52b. Then, the reduction of aliphatic and aromatic diselenides and aromatic ditellurides proceeds as a mercury-assisted Se−Se or Te−Te bond cleavage. Contrary to this, for aliphatic bis(carboxymethyl)ditelluride **5k** a strong catalytic evolution of free tellurium Te^0 formed in the C−Te bond cleavage was observed[115] and explained by a S_N2 mechanism (Scheme 27). The two-electron reduction of elemental



SCHEME 27

$$\underset{(\mathbf{10})}{ArEEAr} + Hg \longrightarrow \underset{(\mathbf{181})}{Hg(ArE)_2} \xrightarrow[-Hg]{2e} 2(ArE)^- \xrightarrow{2\,\mathbf{181}} \underset{(\mathbf{182})}{2Hg(ArE)_3^-} \xrightarrow[-2Hg]{4e} 6ArE^- \qquad (51)$$

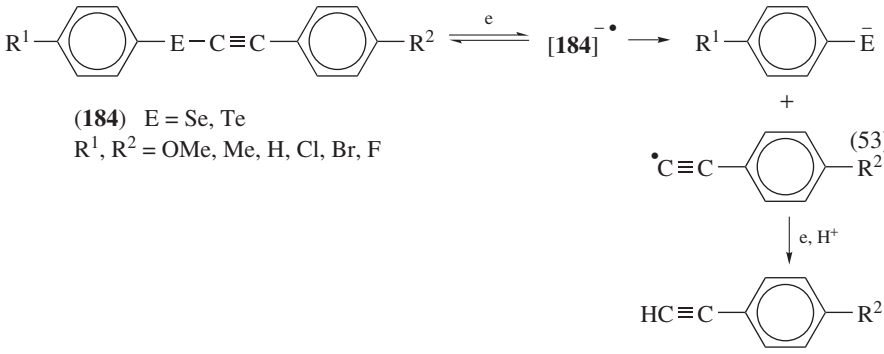
10, 181	**g**	**p**	**h**	**r**
E	Se	Se	Te	Te
Ar	Ph	*p*-BrC_6H_4	Ph	*p*-MeC_6H_4

tellurium was responsible for the maxima observed in polarographic and CV curves[115]. Other details including a catalytic hydrogen evolution during the reduction of **10h** in acidic solutions due to a strong reductive ability of $PhTe^-$ anions were also discussed[115].

$$\mathrm{REER} + \mathrm{Hg} \longrightarrow [\mathrm{REHgER}]_{ads} \xrightarrow{\mathrm{Hg}} 2[\mathrm{REHg}]_{ads} \qquad (52a)$$

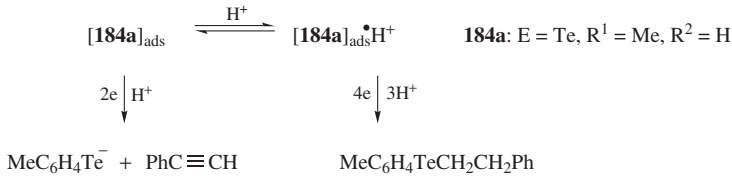
(**3**) E = Se, R = Alk, Ar (**183**)
(**5**) E = Te, R = Ar

$$\mathbf{183} \xrightarrow[-\mathrm{Hg}]{\mathrm{e},\ \mathrm{H^+}} \mathrm{HER} \qquad (52b)$$

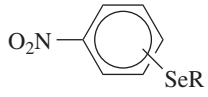


(**184**) E = Se, Te
R^1, R^2 = OMe, Me, H, Cl, Br, F

The electroreduction of arylethynylchalcogenides (**184**) in aprotic media[117–119] proceeds with the formation of radical anions in the first step followed by a carbon–chalcogen bond cleavage. At a mercury electrode a two-electron overall wave was observed according to reaction 53. However, in the presence of proton donors (like benzoic acid) the reduction of **184a** (E = Te, R^1 = Me, R^2 = H) includes surface protonation of adsorbed reactant and its radical anions, and the overall four-electron process leads to hydrogenation of the triple bond with the formation of saturated alkylaryltelluride (Scheme 28)[119]. The reversible formation of a radical anion during the reduction of **184b** (E = Se, $R^1 = NO_2$, R^2 = H) in DMF was proved by an ESR spectrum[120]. The first electron transfer to selenium *o*-, *m*- and *p*-derivatives of nitrobenzene **185** in DMF was also reversible, but further reactions were not investigated[121].



SCHEME 28



R = HC=CH2
H2CCH=CH2
HC=CHCl

(**185**)

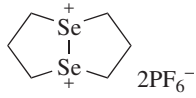
Aryltellurium trichlorides $ArTeCl_3$ were reduced in CH_2Cl_2 in a one-electron process to radicals (**186**) that dimerized to ditellurides, which can further disproportionate to tellurides, for example in reaction 54[61]. However, during the reduction of $PhTeCl_3$ the metallic tellurium was deposited on the platinum electrode[61]. A similar processes were found for the reduction of diarylselenium dichlorides (**187**) in MeCN at a platinum electrode[81]: diaryl diselenide was the main product according to reaction 55 but selenium was also deposited. Reduction potentials for a series of 12-Te-5 pertelluranes and oxidation potentials of the corresponding oxatellurolylium halides obtained from CV measurements in CH_2Cl_2 were reported[122] and recently discussed[3]. Finally, it can be mentioned that the unexpected reversible one-electron reduction of diselenide dication salt 1,5-diselenoniabicyclo[3.3.0]octane bis(hexafluorophosphate) (**188**) in MeCN was observed[123] at an extremely low potential of 0.11 V vs. Ag/Ag^+.

$$ArTeCl_3 \xrightarrow[-Cl^-]{e} ArTeCl_2^{\bullet} \xrightarrow{\mathbf{186}} Cl_2(Ar)TeTeCl_2(Ar) \longrightarrow Ar_2Te + TeCl_4 \quad (54)$$

(**186**)

$$Ar_2SeCl_2 \xrightarrow[-Cl^-]{e} Ar_2SeCl^{\bullet} \xrightarrow[-Cl^-]{\mathbf{187},\ e} Ar_2Se(Cl)Se(Cl)Ar_2 \xrightarrow[-2Cl^-]{2e} Ar_2SeSeAr_2 \quad (55)$$

(**187**) Ar = *p*-$MeOC_6H_4$
p-$EtOC_6H_4$



(**188**)

VI. ADDITIONAL REMARKS

In this Chapter our attention was mainly focused on electrochemical synthesis and on the mechanisms of electrode reactions, in particular the anodic oxidation of organic selenium and tellurium compounds which was more intensively investigated than cathodic processes. However, it should be added that oxidation potentials for a series of compounds were also widely used to discuss the electron-donating properties of chalcogen atoms and stereoelectronic effects which affect the stability of neutral molecules, as well as cationic and radical intermediates formed in anodic reactions. For mechanistic studies substituent effects on the oxidation potentials were investigated by many authors using the Hammett equation or similar relationships. These problems were taken into account by Detty and Logan in their recent review[3] and so they were not included in this Chapter, despite the fact that some earlier Russian papers were not discussed there. However, let us mention here that the Hammett equation was successfully used to elucidate substituent effects on the oxidation potentials of substituted diphenyl selenides **130** and tellurides

131 and substituted phenylmethyl compounds **138**[57, 68], methylphenylselenides oxidized in the presence of CF_3COOH[74], aryl(trimethylsilylmethyl)selenides **145**[73, 77], substituted 1,2-benzisoselenazol-3(2*H*)ones **154** and **155**[84, 85] as well as on the reduction potentials of aryltellurium trichlorides[61] and nitrophenylseleno derivatives **184** ($R^1 = NO_2$, $R^2 = H$, E = S, Se, C)[121] and **185**[121]. On the other hand, a dual-parameter relationship with Taft inductive constants and steric constants was successfully applied to anodic potentials for the oxidation of a series of alkylphenylselenides[72].

Finally, it can be added that structural effects on oxidation potentials were also elucidated using molecular orbital calculations. For recent examples, quantum-chemical calculations of different possible conformations of cyclic dichalcogen compounds[100] and of frontier orbitals energies in arylselenides[73] were helpful in explaining their electrochemical behavior. However, that promising approach is beyond the scope of this Chapter.

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Stereoselective reactions of organoselenium reagents including catalysis

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0573

I. INTRODUCTION

The first organoselenium compound was already synthesized in 1836, but the development of organoselenium chemistry was slow until the late 1960s[1]. Organoselenium chemistry received much more attention of organic chemists after the discovery of the selenoxide elimination in the early 1970s[2]. Many different organoselenium reagents have been introduced since that time and chemo-, regio- stereoselective as well as stereospecific reactions in various synthetic transformations such as selenenylations, selenocyclizations, selenoxide eliminations and 2,3-sigmatropic rearrangements have been described[3]. Recently, organoselenium reagents have received particular attention due to their use in asymmetric catalysis[4]. Organoselenium chemistry has now become a well-established field of organic chemistry and few books[5], book chapters[6] and review articles have appeared to describe the different aspects of organoselenium reagents[3, 4, 7]. This chapter highlights the developments of stereoselective reactions of organoselenium reagents including catalytic reactions.

II. ELECTROPHILIC REAGENTS

Early on in organoselenium chemistry it was discovered that electrophilic selenium compounds can undergo stereospecific addition reactions with alkenes[3, 7b]. After that discovery the reaction has been developed as an important tool of organic chemistry[3]. Diselenides are versatile precursors for the synthesis of various selenium-based electrophiles and they can be converted easily into corresponding selenenyl halides or other selenenyl cations with non-halogen counterions[5b].

A. Type of Chiral Diselenides

1. Binaphthyl-based chiral diselenides

Tomoda and coworkers reported the synthesis of new chiral binaphthyl diselenides **1** in 1988 and used these as optically active selenium reagents in stereoselective electrophilic selenenylation reactions. The synthesis of novel chiral binaphthyl diselenides **1a–c** (Figure 1) was achieved by a two-step synthesis from chiral binaphthylamines in about 30% overall yield[8].

2. [2.2]Paracyclophane-based chiral diselenides

Around the same time, Reich and Yelm developed the synthesis of [2.2]paracyclophane-based diselenides **2** (Figure 2) from racemic 2-bromoparacyclophane in 21% overall yield[9].

3. C_2-Symmetrical diselenides

The above findings encouraged some other research groups to synthesize different types of optically active diselenides. Déziel and his group reported the synthesis of a different class of chiral diselenides having C_2 symmetry (**3** and **4**, Figure 3) from 2-bromoisophthalic acid in overall good yields[10].

4. Ferrocenyl-based chiral diselenides

Uemura and colleagues[11] reported the first synthesis of ferrocenyl-based chiral diselenides **5** by single-step synthesis from chiral ferrocenyl compounds in 80% yield and

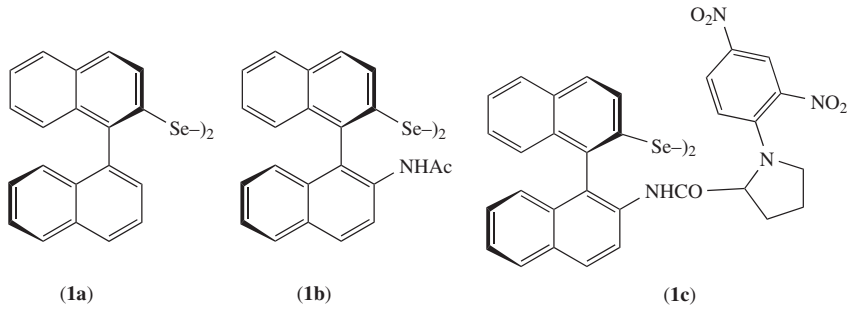


FIGURE 1. Structures of binaphthyl-based chiral diselenides **1a–1c**

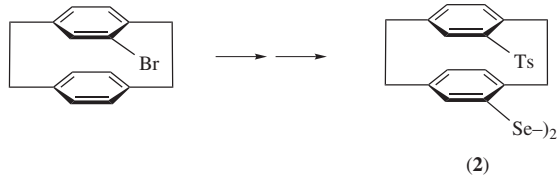
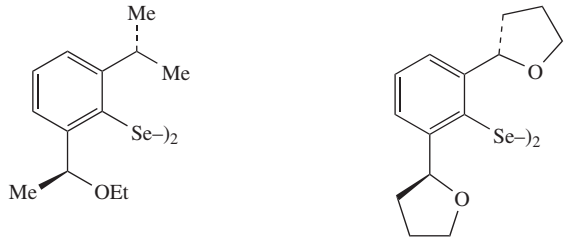
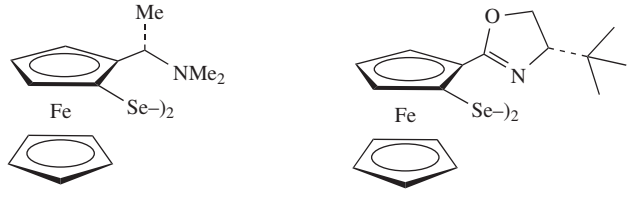


FIGURE 2. Structure of [2.2]paracyclophane-based diselenide **2**



(**3**) (**4**)

FIGURE 3. Structures of chiral diselenides **3** and **4** having C_2 symmetry



(**5**) (**6**)

FIGURE 4. Structures of ferrocenyl-based chiral diselenides **5** and **6**

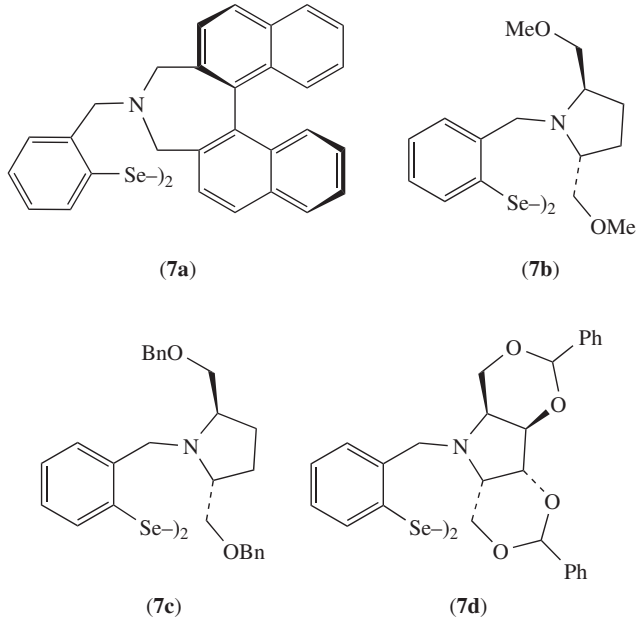
used these successfully in stereoselective selenenylation reactions. The synthesis of ferrocenyl diselenide **6** (Figure 4) was achieved in 69% yield by a directed *ortho*-lithiation of (*S*)-2-ferrocenyl-4-*tert*-butyloxazoline followed by addition of selenium powder and air oxidation[12].

5. Chiral diselenides containing cyclic amines

Tomoda and his research group synthesized new chiral diselenides **7a**–**d** (Figure 5) containing cyclic amines as chiral moieties and employed these in stereoselective selenenylation reactions. The synthesis of these chiral diselenides has been achieved from bis[2-(chloromethyl)phenyl]diselenide using bis chiral cyclic amines in 48–89% yields[13]. These diselenides have a nitrogen atom at the position segregated by four bonds from the selenium atom. There is a possibility of strong Se---N interactions which are necessary for a transfer of the chirality in asymmetric selenenylation reactions[13a].

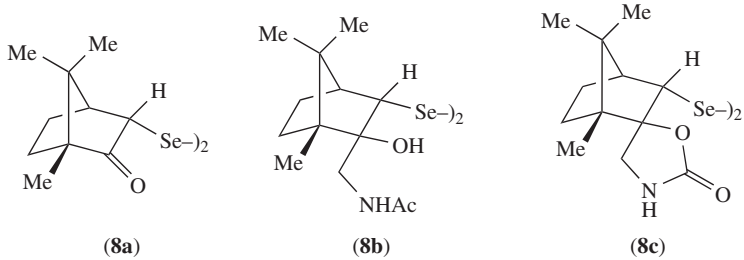
6. Camphor-based chiral diselenides

Camphor-based chiral diselenides have been developed by Back and then successfully used in selenenylation reactions. Camphor-based chiral diselenides **8a** have been synthesized by *ortho*-lithiation of commercially available chiral camphor followed by addition of selenium powder and air oxidation. The synthesis of other camphor-based chiral diselenides **8b**–**8e** (Figure 6) has been achieved by functionalizing the carbonyl moiety of diselenide **8a**[14]. Other research groups have also used camphor-based chiral diselenides successfully in stereoselective selenenylations of alkenes[14h,i].

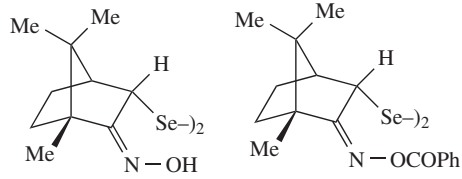


(**7a**) (**7b**) (**7c**) (**7d**)

FIGURE 5. Structures of cyclic amine based chiral diselenides **7a**–**d**



(**8a**) (**8b**) (**8c**)



(**8d**) (**8e**)

FIGURE 6. Structures of camphor-based chiral diselenides **8a**–**8e**

7. Nitrogen-, oxygen- and sulfur-containing chiral diselenides

The success of the above mentioned diselenides led to the design and synthesis of more simple chiral diselenides having a heteroatom at the position segregated by four bonds from the selenium atom. Wirth and others have developed the synthesis of some nitrogen- and oxygen-containing chiral diselenides **9a**–**9d** and **10a**–**10c** (Figure 7) by a one-step synthesis from sometimes commercially available chiral precursors in 60–80% yields[15]. Tiecco and his research group reported the sulfur-containing chiral diselenides **11a** and **11b** (Figure 7) to explore the role of Se---S interactions in asymmetric selenenylation reactions[16]. Some other selenium-stabilized diselenides have also been synthesized and used in stereoselective selenenylation reactions[17].

8. Optically active terpene-based chiral diselenides

In 2006, Scianowski and his research group introduced novel chiral dialkyl diselenides and used these in asymmetric selenenylation reactions. The chiral diselenides **12a**–**12c** (Figure 8) based on menthol were synthesized by tosylation of commercially available optically pure menthol followed by the treatment with sodium diselenide in good to moderate yields[18]. Later on, the same research group reported also the synthesis of

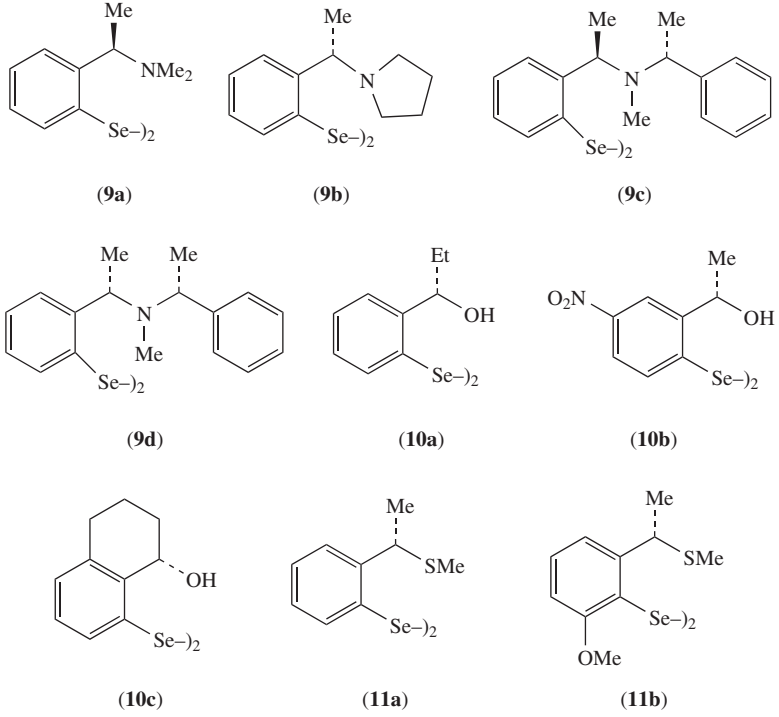


FIGURE 7. Structures of nitrogen-, oxygen and sulfur-containing diselenides **9a**–**9d**, **10a**–**10c** and **11a** and **11b**

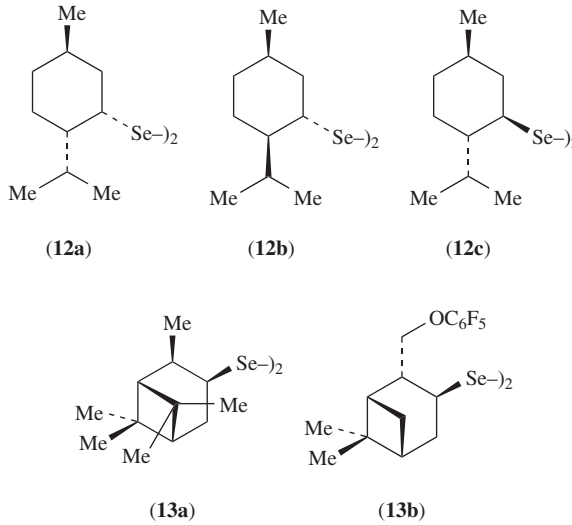


FIGURE 8. Structures of terpene-based chiral diselenides **12a**–**12c**, **13a** and **13b**

terpene-based optically active diselenides **13a** and **13b** (Figure 8) from commercially available chiral terpene alcohols functionalized at position C-10[19].

9. Sulfone- and sulfoxide-containing chiral diselenides

Recently, Wirth and coworkers reported novel sulfone- and sulfoxide-containing chiral diselenides. The synthesis of these chiral diselenides **14a** and **14b** (Figure 9) was achieved by *ortho*-lithiation of (*S*)-*tert*-butyl phenyl sulfoxide followed by the treatment with selenium to afford the diselenide in 39% yield after oxidative workup. Another chiral diselenide **14c** (Figure 9) was also synthesized by using the commercially available (−)-(1*R*)-menthyl (*S*)-*p*-toluenesulfinate in 6% overall yield[20].

Diselenides can be easily converted into their corresponding selenium electrophiles containing different counterions such as halides, triflates etc. Selenium electrophiles are quite powerful reagents and undergo addition reactions with symmetrical and unsymmetrical alkenes[3]. These addition reactions usually consist of two steps involving the formation of

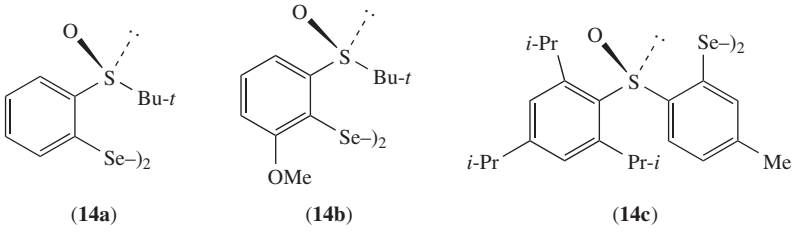
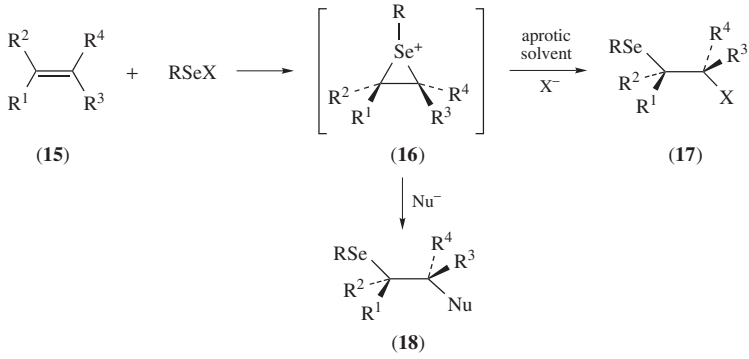


FIGURE 9. Structures of novel sulfone and sulfoxide-based chiral diselenides **14a**–**14c**

seleniranium ion intermediate **16** from **15** and RSeX followed by the attack of nucleophile X^-. Internal and external nucleophiles can be used in these addition reactions. External nucleophiles lead to the formation of addition products **18** while internal nucleophiles generate the selenocyclized compounds. These reactions exhibit *anti*-stereoselectivity with the nucleophile attacking usually at the more substituted carbon atom in case of unsymmetrical alkenes[21]. These reactions are effected by the counterions of selenium electrophiles, as in the absence of protic solvents these counterions can react as nucleophile and undergo the addition reaction to form products **17** with seleniranium ion intermediates (Scheme 1)[3c].



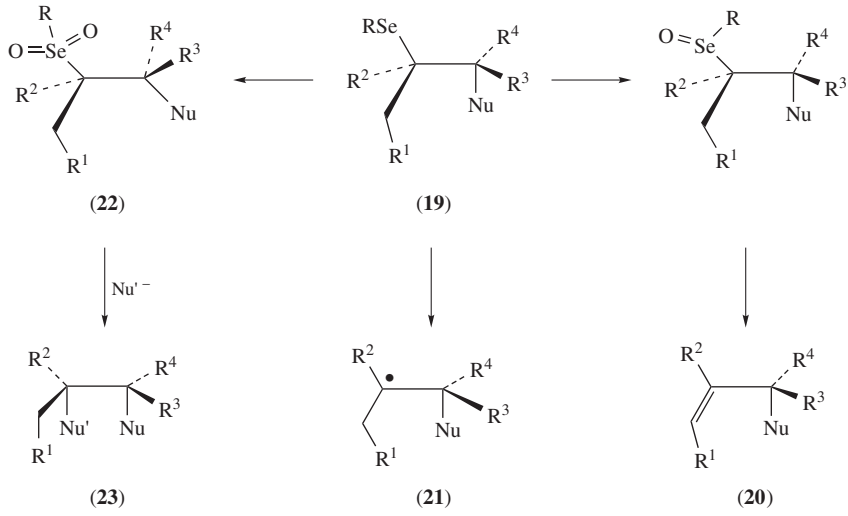
SCHEME 1

Addition products of type **19** are important scaffolds in synthetic organic chemistry because they can be converted into several valuable synthetic intermediates. Compounds **19** can be transformed into their corresponding unsaturated compounds **20** by oxidation, followed by a selenoxide elimination. These products can also be used for the generation of radicals **21** through a homolytic cleavage of the carbon—selenium bond. Furthermore, the addition products can be oxidized into the corresponding selenones **22**, which can act as a leaving group in a nucleophilic substitution reaction to generate products **23** (Scheme 2).

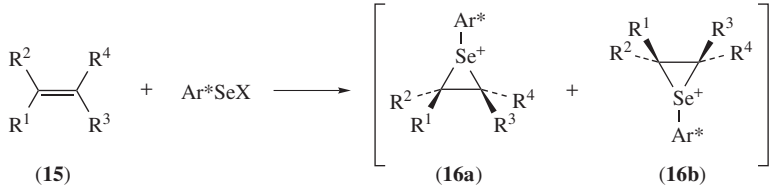
B. Stereoselective Selenenylation Using Chiral Selenium Electrophiles

Chiral diselenides can be converted into their corresponding selenenyl halides or other selenenyl compounds with non-halogen counterions[5b]. Several research groups have employed the selenenylation reaction in stereoselective synthesis. The addition product **19** has sp^3 carbon atoms, which are generated during selenenylation reaction from the alkene. The new chiral centers can be generated by the selenenylation reactions. The asymmetric version of selenenylation reaction of alkenes can be developed either by using chiral seleneium electrophile or by using chiral olefins or by the reaction with optically active nucleophiles (Scheme 3).

As already shown in Scheme 1, the selenenylation of alkenes proceeds via the generation of seleniranium ion intermediates of type **16a** and **16b** resulting in an *anti*-addition of the moieties RSe and nucleophile. The formation of the seleniranium ions is reversible, but at low temperatures the reaction is under kinetic control. The mechanistic course of these selenenylation reactions with chiral selenium electrophiles has already been investigated in detail[22, 23]. The presence of a chiral selenium electrophile can result in a differentiation between the two faces of unsymmetrically substituted alkenes. The attack on the



SCHEME 2



SCHEME 3

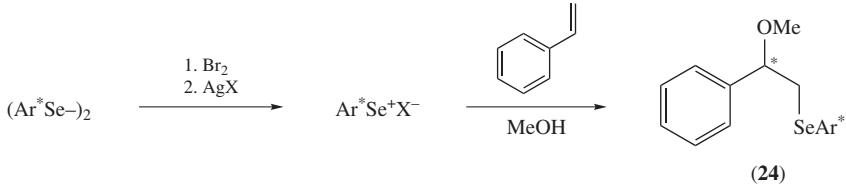
alkene double bond from either the *Re*- or the *Si*-face is different from the steric and electronic point of view, and the resulting seleniranium ions **16a** and **16b** are diastereomers (Scheme 3) while in case of symmetrical (*Z*)-alkenes, the seleniranium ions are identical and the stereoselectivity is determined by the nucleophilic attack in the product-forming step[8a, 14c]. The first chiral version of selenenylation reactions was reported in 1985 using chiral selenenamides as selenium nucleophiles[24]. The first example of a stereoselective selenenylation of alkenes was reported by Tomoda and coworkers in 1988 using binaphthyl-based chiral selenium electrophiles[8a]. Several stereoselective selenenylation reactions of alkenes have been reported with different oxygen-, nitrogen- and carbon-containing nucleophiles using various chiral selenium electrophiles in the past few decades[3].

1. Oxygen nucleophiles

a. Stereoselective methoxyselenenylations. Although stereoselective selenenylation of alkenes with chiral selenium electrophiles are reported with oxygen, nitrogen and carbon nucleophiles, mostly oxygen nucelophiles such as OH, OR, OCOR have been employed.

Tomoda and colleagues have reported the stereoselective methoxyselenenylation of different symmetrical and unsymmetrical alkenes using optically active selenobinaphthyls generated *in situ* from the corresponding diselenides **1** and **7**[8]. To avoid the nucleophilic attack of bromide counterions in the selenenylation reactions, the nucleophilic bromide anion has been replaced by a less nucleophilic counterion such as SbF_6^-, PF_6^-, BF_4^- or OTf^- by using the appropriate silver salts. The stereoselective methoxyselenenylation using styrene is shown in Scheme 4. Almost all the synthesized chiral diselenides have been employed in this reaction. Therefore, the yields and *d.r.* ratios of product **24** obtained by the different research groups can be compared and they are summarized in Table 1.

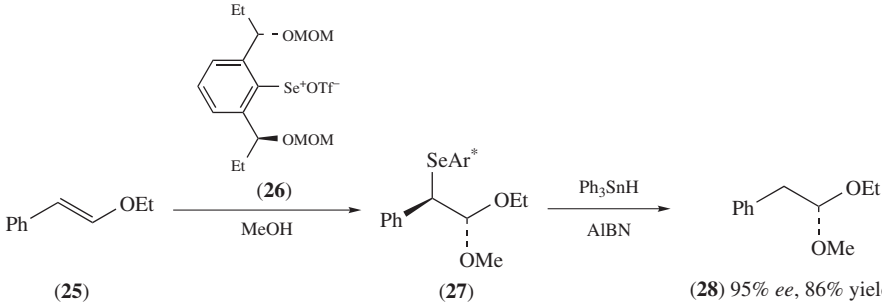
Uehlin and Wirth have developed the synthesis of polymer-bound chiral selenium electrophiles **26** and their application in asymmetric selenenylation reactions of various alkenes with good selectivities[25]. Recently, the diastereoselective synthesis of chiral acetals **28** has been developed by asymmetric methoxyselenenylation of (*E*)-β-ethoxystyrene **25** using the chiral selenium electrophile **26** generating the product **28** via **27** with 95% enantiomeric excess (Scheme 5)[26]. Tiecco and his colleagues have reported the kinetic resolution promoted by sulfur containing chiral selenium electrophiles with high selectivities[27]. Recently, the same research group developed the enantioselective methoxyselenenylation of α,β-unsaturated aldehydes using chiral diselenides of type **11a**[27c].



SCHEME 4

TABLE 1. Stereoselective methoxyselenenylation of styrene

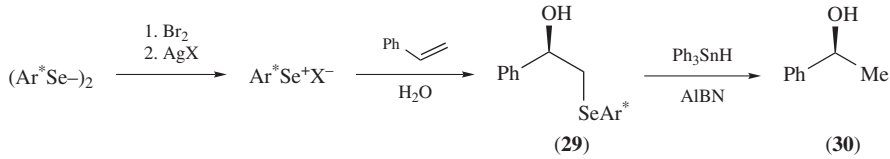
Chiral diselenide	Counterion X	Reaction conditions	**24** Yield (%)	**24** *d.r.*	Reference
1a	Br	MeOH, 25 °C	49	74.5:25.5	8f
3	OTf	Ether, −78 °C	88	88.5:11.5	10c
4	OTf	Ether, −78 °C	94	86.5:13.5	10a
5	Br	CH_2Cl_2, 25 °C	21	98.5:1.5	11e
7d	PF_6	CH_2Cl_2/MeOH, −78 °C	79	71:29	13a
8d	OTf	CH_2Cl_2/MeOH, −78 °C	52	96:4	14b
9c	OTf	MeOH, −78 °C	40	97:3	15i
9c	OSO_3H	MeOH, 25 °C	70	95:5	15i
9d	OSO_3H	MeOH, 25 °C	70	81:19	15i
10a	OTf	MeOH, −114 °C	46	96:4	15f
10b	OTf	MeOH, −114 °C	37	97.5:2.5	15f
10c	OTf	MeOH, −100 °C	28	96.5:3.5	15f
11b	OTf	CH_2Cl_2/MeOH, −78 °C	80	96:4	16a
11b	OSO_3H	MeOH, −30 °C	72	98:2	16b
12a	OTf	MeOH, −78 °C	86	70:30	18b
12a	OTf	MeOH, −78 °C	57	82:18	18a
13b	OTf	MeOH, −78 °C	56	86:14	19c



SCHEME 5

b. Hydroxyselenenylation. Some research groups have investigated the stereoselective hydroxyselenenylation of alkenes using chiral selenium electrophiles. The addition products in hydroxyselenenylation reactions have been obtained with high selectivities. Different research groups have achieved the hydroxyselenenylation reactions using various chiral diselenides using styrene as representative compound (Scheme 6). Selectivities of such addition products **29**, leading to alcohols **30**, are summarized in Table 2.

c. Factors influencing the selectivity in selenenylation reactions. Several research groups have achieved methoxyselenenylation reactions of alkenes by using chiral selenides (Ar*SeX) containing different scaffolds, so it is difficult to set a general structure-relationship with the selectivity. The factors which are influencing and explaining the selectivities in methoxyselenenylation reactions are as follows:



SCHEME 6

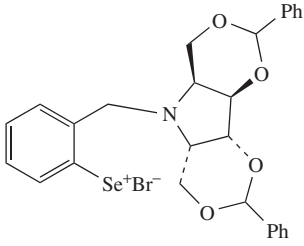
TABLE 2. Stereoselective hydroxyselenenylation of styrene

Chiral diselenide	Counterion X	Conditions	**29** Yield (%)	**29** *d.r.*	Reference
9c	OTf	THF/H_2O, −78 °C	40	98:2	15i
9c	OSO_3H	THF/H_2O, 25 °C	70	95:5	15i
9d	OSO_3H	THF/H_2O, 25 °C	72	80:20	15i
11a	OTf	THF/H_2O, −78 °C	75	95:5	16a
9b	OTf	$MeCN/H_2O$, −78 °C	65	98:2	16b
8a	OSO_3H	$MeCN/H_2O$, −70 °C	68	65:35	14h

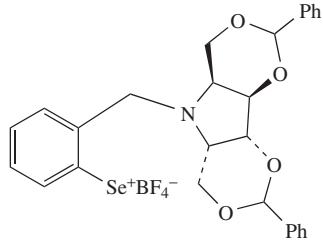
i. Nature of the counterion. The nucleophilicity of the counterion of the selenium electrophile affects the selectivity of selenenylation reactions[3d]. Tomoda and coworkers converted chiral diselenide **7d** into the corresponding electrophiles **30a–30c** with various counterions of different nucleophilicity and employed them in selenenylation reactions. The highest selectivity was observed with counterions having lowest nucleophilicity (Figure 10)[13a–c]. Similar observations were also reported by other research groups[28].

ii. Selenium–heteroatom non-bonding interactions. Non-bonding interactions between selenium and a heteroatom in selenium electrophiles play a vital role in the asymmetric methoxyselenenylation of alkenes. The non-bonding interactions of heteroatoms such as nitrogen, oxygen and sulfur with the selenium cation led to the formation of a fixed conformation in the electrophilic reagent. On addition of the alkene, the chirality is transferred to the newly formed asymmetric centers. Selenium electrophiles **31**, **32** and **33** have been used as chiral inducer in asymmetric methoxyselenenylation of styrene and the highest selectivity was observed with chiral diselenide **33** (Figure 11)[15c,f, 16].

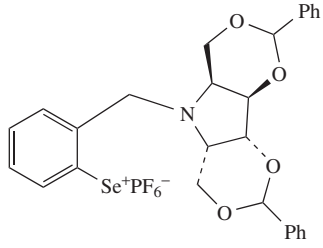
iii. Size of the alkyl group attached to the heteroatom. In selenium electrophiles of type **34–36** containing alkyl groups attached to oxygen atom, the size of the alkyl substituent plays an important role in the selectivity. For selenium electrophiles **34–36**, the ability of the oxygen to coordinate with Se was found to be influenced by the size of the alkyl substituent. The larger the substituent, the weaker is the Se· · ·O coordination and the smaller is the inducing effect on the newly formed stereocenter. Therefore, the highest diastereoselectivity on addition to styrene was observed using selenium electrophile **34** (Figure 12)[15a,f].



(**30a**) 52% *de*

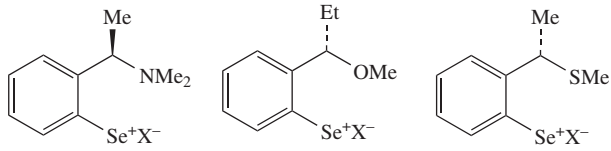


(**30b**) 90% *de*



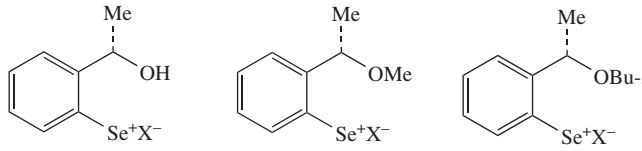
(**30c**) 97% *de*

FIGURE 10. Chiral electrophiles **30a–c** with different counterions



(**31**) 69% *de* (**32**) 61% *de* (**33**) 95% *de*

FIGURE 11. Chiral electrophiles **31**–**33** with different heteroatoms

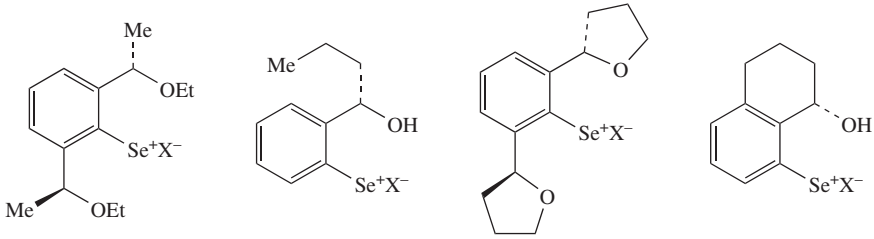


(**34**) 83% *de* (**35**) 74% *de* (**36**) 36% *de*

FIGURE 12. Chiral electrophiles **34**–**36** with different substituents on oxygen

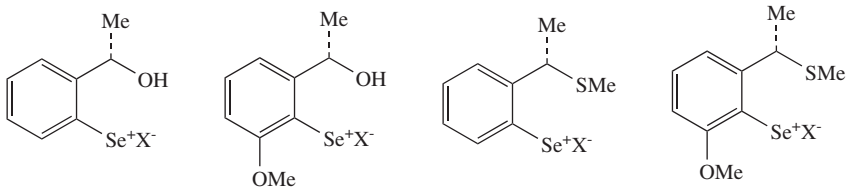
iv. Conformational flexibility of the chiral moiety. It has been found that selenium electrophiles with reduced conformational flexibility in the chiral moiety are more efficient chiral inducers in asymmetric methoxyselenenylation of olefins. The conformational flexibility of the chiral moiety in electrophiles **39** and **40** is reduced and a higher selectivity was observed in comparison to the selenium electrophiles **37** and **38** in methoxyselenenylation of styrene (Figure 13)[10, 15f].

v. Electronic effect of the methoxy group in ortho-position to selenium. It has been observed that the electronic properties of selenium cations also play an important role in the selectivity of these reactions. The methoxyselenenylation of styrene was obtained in higher selectivity with methoxy-substituted chiral electrophiles **41**[29] and **42**[16b] at the *ortho*-position of the selenium cation in comparison to the unsubstituted chiral electrophiles **35**[15f] and **33**[16a] (Figure 14).



(**37**) 1:8 *d.r.* (**38**) 1:14 *d.r.* (**39**) 1:30 *d.r.* (**40**) 1:28 *d.r.*

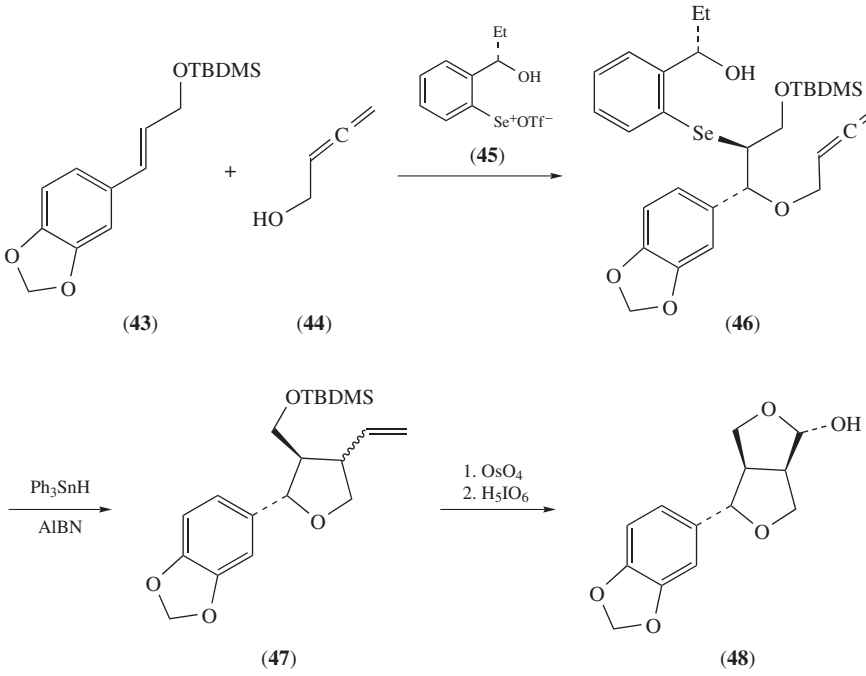
FIGURE 13. Chiral electrophiles **37**–**40** with different conformational flexibility



(**35**) 11:1 *d.r.* (**41**) 50:1 *d.r.* (**33**) 95:5 *d.r.* (**42**) 98:2 *d.r.*

FIGURE 14. Chiral electrophiles with different substituents

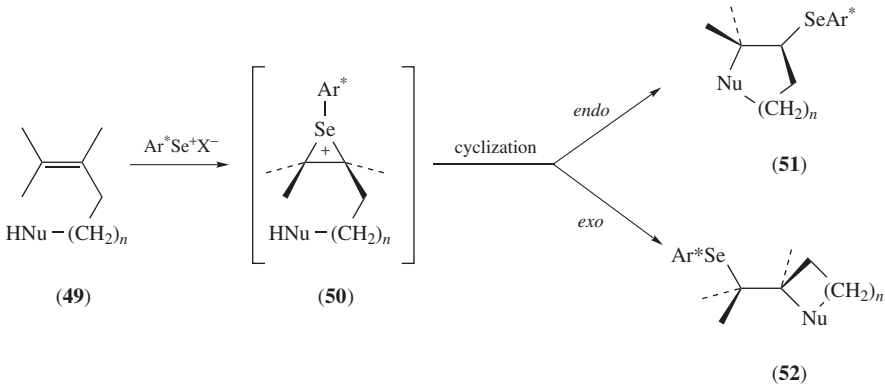
d. Oxyselenenylation in the synthesis of (+)-Samin. Chiral selenium electrophiles inducing stereoselective addition reactions to double bonds have been also employed in the synthesis of naturally occurring tetrahydrofuran derivatives. Wirth and coworkers group developed the synthesis of chiral furofuran lignans in 1996 as depicted in Scheme 7. The stereoselective selenenylation of the functionalized alkene **43** with chiral selenium electrophile **45** generated from diselenide **10a** and an allenylic alcohol **44** as an external nucleophile led to addition products of type **46** in good yields and diastereoselectivities. The addition product **46** was further transformed into the cyclized product **47** via a 5-*exo-trig* radical cyclization using AIBN/Ph_3SnH. The cyclized product **47** was converted into (+)-Samin **48** by oxidative cleavage of the alkene moiety followed by the deprotection



SCHEME 7

of the hydroxyl group[30]. These scaffolds can be used as important synthetic precursors for the synthesis of other biologically important lignans[31].

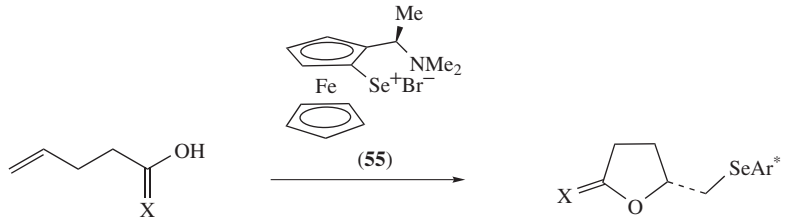
e. Asymmetric selenocyclization with oxygen nucleophiles. Asymmetric oxyselenocyclization is a versatile approach for the synthesis of various biologically active synthetic and naturally occurring oxygen heterocycles[3, 71]. The use of chiral organoselenium electrophiles as reagents for ring formation is an attractive approach, particularly when combined with further manipulation of the selenium functionality. The reaction generally involves the intramolecular trapping of the selenium species by suitable nucleophile to yield different products[32]. The first step in selenocyclizations of alkenes type **49** is the formation of the seleniranium intermediates **50**. These seleniranium intermediates are then opened by an intramolecular nucleophilic attack of the nucleophile resulting in an *anti* addition of the selenium moiety. Depending on ring-size and reaction conditions, the seleniranium intermediates **50** can undergo either *endo*-cyclization to products **51** or *exo*-cyclizations yielding other heterocyclic derivatives such as compounds of type **52** (Scheme 8). The selenium moiety in the products **51** and **52** can be used in further reactions, making this a very versatile approach in the synthesis of heterocyclic compounds having various ring-sizes[3].



SCHEME 8. Possible *endo*- and *exo*-cyclization pathways of seleniranium intermediates **50**

Selenocyclizations were reported for the first time by Campos and Petragnani in 1960 using a carboxylic acid group as the internal nucleophile; however, the reaction conditions were harsh and the reaction failed to find general application[33a]. Subsequently, chiral ferrocene-based selenium electrophiles **55** have been employed in stereoselective selenocyclizations of unsaturated carboxylic acids **53** and alcohols **54** by Uemura and coworkers. The cyclized products **56** and **57** were obtained in good to moderate yields with high diastereoselectivities (Scheme 9)[11d].

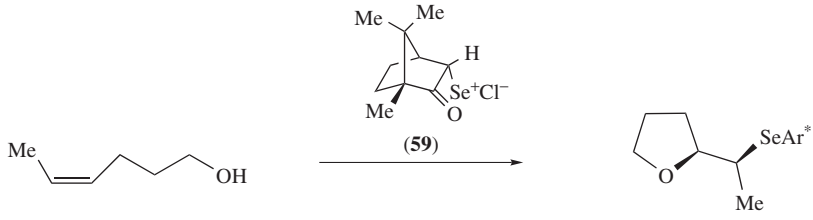
Back and his research group reported highly diastereoselective selenofunctionalizations of alkenols of type **58** and alkenoic acid **61** using camphor cored chiral selenenyl chlorides **59** and **62**, respectively, as chirality inducer[14a,c,e]. The cyclized products of type **60** and **63** were obtained with 95:5 and 67:33 *d.r.*, respectively (Scheme 10)[14e]. Selenocyclization reactions proceeded efficiently with high selectivities using the corresponding selenenyl chlorides unlike asymmetric oxyselenenylation reactions[14c]. Different kinds of



(**53**) X = O
(**54**) X = H

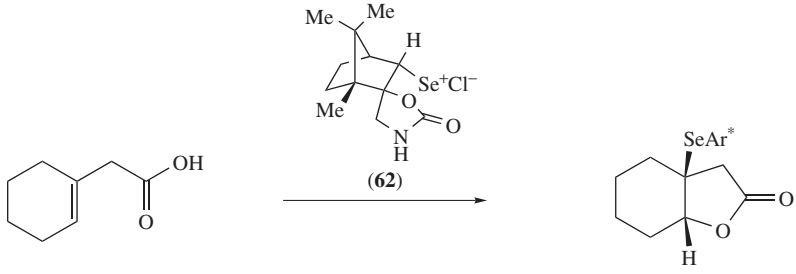
(**56**) X = O; >95% *de*, 84% yield
(**57**) X = H_2; 76% *de*, 29% yield

SCHEME 9



(**58**)

(**60**) 95:5 *d.r.*, 80% yield



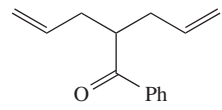
(**61**)

(**63**) 67:33 *d.r.*, 66% yield

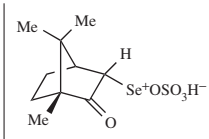
SCHEME 10

unsymmetrical alkenes have been employed, but higher diastereoselectivity are obtained with monosubstituted and 1,2-disubstituted alkenes.

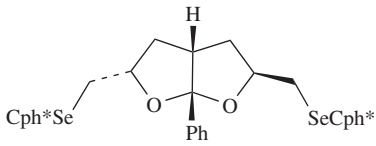
The chiral camphor-based diselenide **8a** has been converted to the corresponding camphorselenenyl sulfate **65** by *in situ* oxidation with ammonium persulfate in the presence of a stoichiometric amount of trifluoromethanesulfonic acid[32]. Recently, Tiecco and his colleagues reported the synthesis of enantiomerically pure trisubstituted perhydrofuro[2,3-*b*]furans **67a–d** via **66a–d** by double selenocyclization of bisalkenylketones **64** using chiral camphorselenenyl sulfates **65** followed by deselenenylation with triphenyltin hydride and AIBN (Scheme 11)[33b]. The same research group has also reported the synthesis of enantiomerically pure 1,6-dioxaspiro[4.4]nonane derivatives (spiroacetals) by selenocyclization of 1-hydroxyoct-7-en-4-one using chiral selenium electrophile



(**64**)

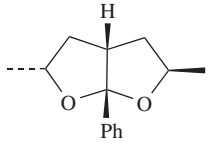


(**65**) = Cph*SeOSO$_3$H

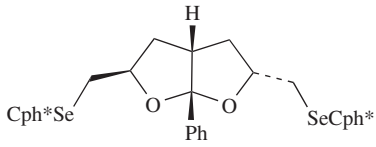


(**66a**) (2*S*, 5*S*), 21%

AIBN, Ph_3SnH

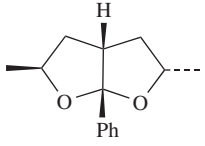


(**67a**) (2*R*, 5*R*), 89%

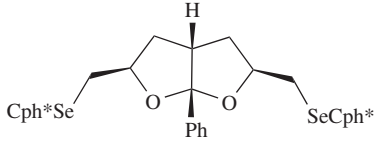


(**66b**) (2*R*, 5*R*), 25%

AIBN, Ph_3SnH

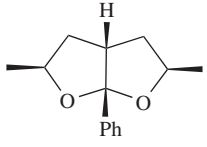


(**67b**) (2*S*, 5*S*), 70%

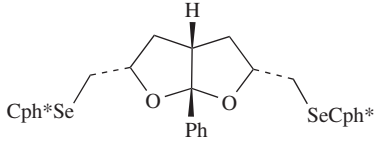


(**66c**) (2*S*, 5*R*), 26%

AIBN, Ph_3SnH

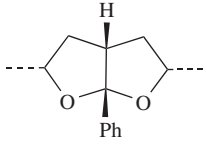


(**67c**) (2*R*, 2*S*), 99%



(**66d**) (2*R*, 5*S*), 8%

AIBN, Ph_3SnH

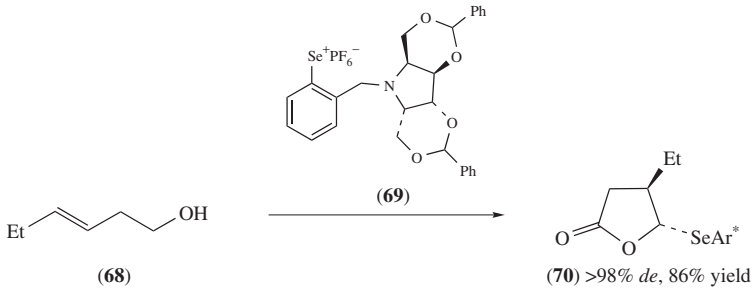


(**67d**) (2*R*, 2*S*), 70%

SCHEME 11

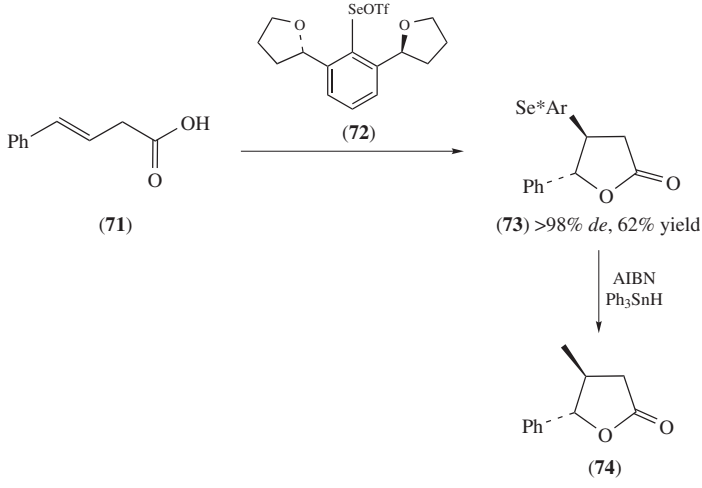
65[33c]. The bistetrahydrofuranyl scaffolds have been reported as potent non-peptidyl HIV protease inhibitors[34]. This approach can be applied to the cyclization of other bisalkenylketones, thus leading to a variety of perhydrofuro[2,3-*b*]furan scaffolds. Moreover, the presence of the organoselenium moiety allows the introduction of new functionalities in these compounds.

Tomoda and coworkers reported the synthesis of chiral cyclic lactones and ethers with excellent selectivities by the cyclization of different di- and trisustituted alkenes of type **68** containing oxygen nucleophiles using selenium electrophile **69** with a chiral tertiary amino group. The cyclic products **70** were obtained in poor selectivities in case of mono-substituted alkenes (Scheme 12)[13a].



SCHEME 12

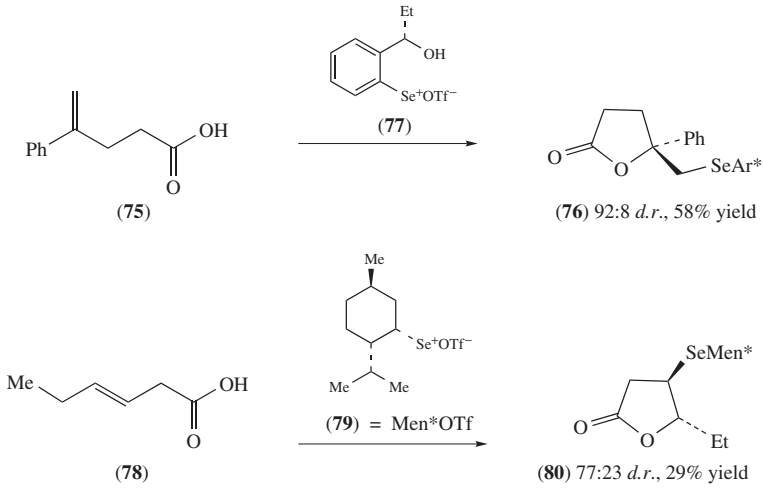
Déziel and coworkers have used C_2-symmetrical chiral selenium electrophile **72** in asymmetric selenofunctionalizations of **71**. Chiral selenium electrophile **72** has selenium and oxygen atoms in close proximity, allowing a Se· · ·O intramolecular interaction. The cyclized product **73** was obtained with more than 98% diastereomeric excess (Scheme 13).



SCHEME 13

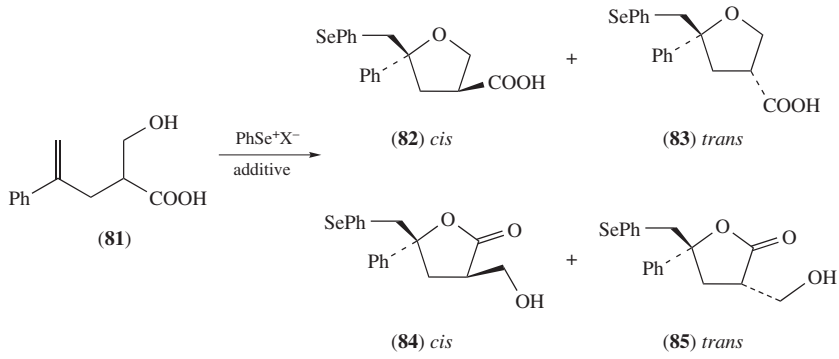
The absolute stereochemistry of lactone **73** was assessed by removal of the chiral organoselenium moiety and comparison of the optical rotation of the resulting lactone **74** with the literature value[10c]. It was also demonstrated that the element of C_2 symmetry is a key feature for obtaining high facial selectivity in these cyclization reactions[10c, 35].

Wirth and coworkers developed some highly stereoselective selenocyclizations (d.r. up to 92:8, product **76**) of unsaturated carboxylic acids of type **75** using selenium electrophiles such as **77** (Scheme 14). Polymer-bound chiral selenium electrophilic reagents have also been employed in stereoselective selenocyclization reactions[25]. The asymmetric selenocyclizations of γ-alkenyl oximes have been investigated by using sulfur-containing arylselenenylbromides obtained from diselenides of type **11**[36]. Recently, some enantiomerically pure selenenyl triflates **79** have been used in the asymmetric selenocyclization reaction of **78** and the product **80** was obtained in up to 77:23 diastereomeric ratio (Scheme 14)[19b].



SCHEME 14

Several observations on the effect of counterions in selenenylation reactions have already been reported, but they do not yet allow a conclusive picture. Several research groups found that the structure of the selenium electrophile, its counterion, solvents and external additives coordinating to the electrophilic species are influencing the course of selenocyclization reactions[37, 71]. This has recently been demonstrated by the selective cyclization of substrate **81**, which contains a hydroxy and a carboxylic acid functionality as internal nucleophiles. 5-*exo*-Cyclizations of alkene **81** can, depending on the cyclizing nucleophile, lead to two different heterocycles: tetrahydrofurans **82/83** or lactones **84/85**. Different interactions with selenium electrophiles can be used to influence the cyclization of **80** either towards tetrahydrofurans **82/83** or towards lactones **84/85**[38]. For example, phenylselenenyl triflate (X = OTf) with 10 equivalents of acetic acid leads exclusively to the formation of tetrahydrofurans **82/83**, whereas with phenylselenenyl hexafluorophosphate (X = PF_6) and 10 equivalents of methanol as external additive only lactones **84/85** are formed (Scheme 15). Enantiomerically pure selenium electrophiles have also been used in this cyclization reaction and selectivities were found similar to the one reported in earlier schemes.



(**81**)

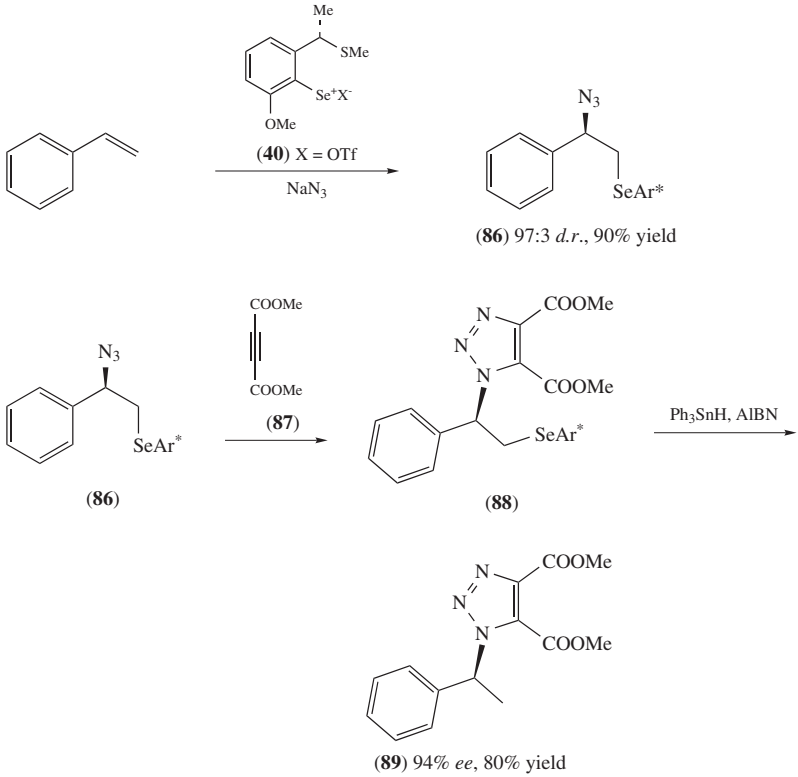
(**82**) *cis*

(**83**) *trans*

(**84**) *cis*

(**85**) *trans*

SCHEME 15



(**86**) 97:3 *d.r.*, 90% yield

(**86**)

(**87**)

(**88**)

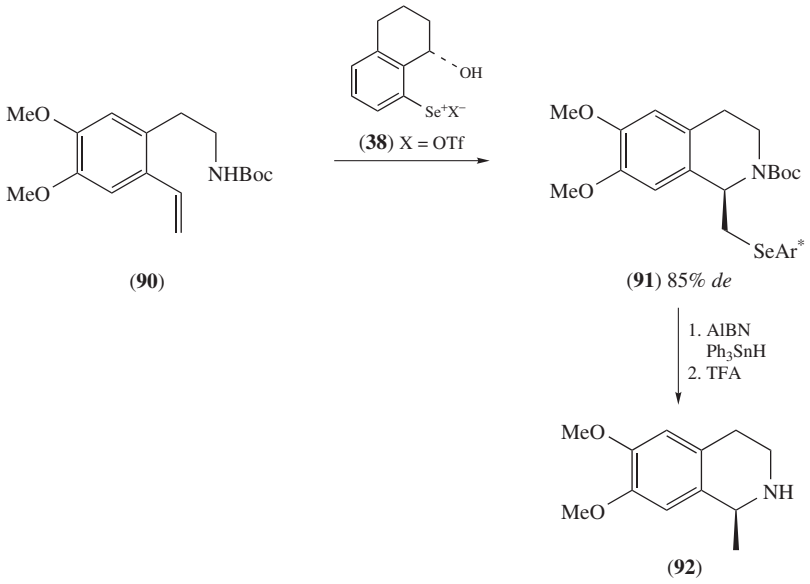
(**89**) 94% *ee*, 80% yield

SCHEME 16

2. Nitrogen nucleophiles

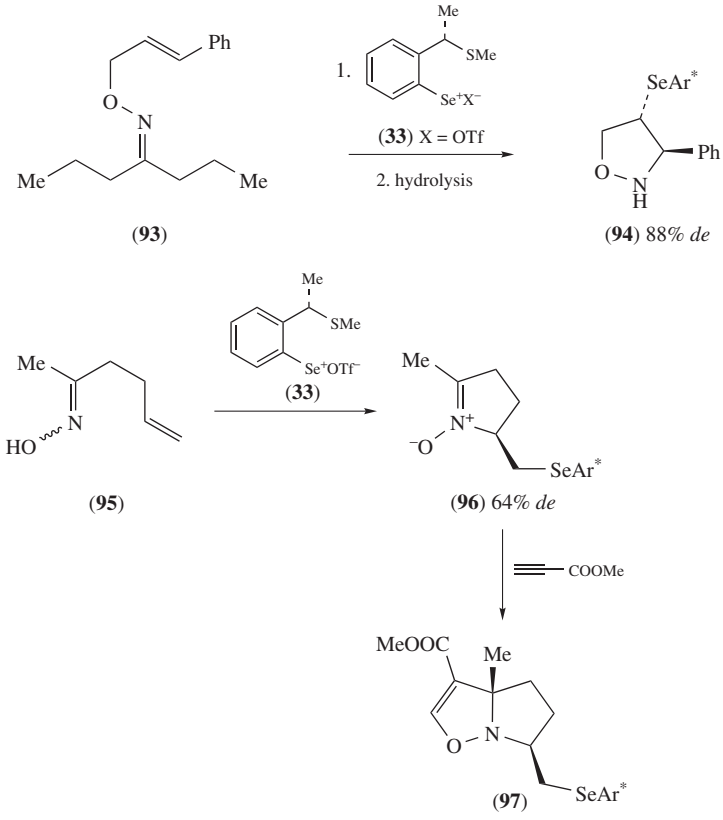
a. Stereoselective azidoselenenylations. The selenenylation reactions of alkenes with chiral and achiral selenium electrophiles using nitrogen nucleophiles have attracted the attention of several chemists in past decades. Different nitrogen nucleophiles such as nitriles, carbamates and tosylamides have been reported as external nucleophiles in these reactions[39]. Azidoselenenylation reactions have also been developed in which the azide ion serves as nitrogen nucleophile[40, 41]. Recently, Tiecco and researchers developed an azidoselenenylation of styrene using chiral electrophiles **40** and azide ions as external nucleophiles and the addition product **86** was obtained in diastereomeric ratio of 97:3. These chiral azidoselenides **86** can be employed as precursors for the synthesis of chiral nitrogen heterocyclic compounds **89** via **88** using dimethyl but-2-ynedioate **87**, as shown in Scheme 16[42]. The same research group has also reported the enantioselective synthesis of β-azidoselenides starting from natural terpenes using the same class of chiral selenium electrophiles[43].

b. Stereoselective aminoselenocyclizations with nitrogen nucleophiles. Nitrogen nucleophiles have been used in the stereoselective selenocyclization reactions. Aminoselenocyclization reactions are a versatile approach in heterocyclic chemistry because of its application in the synthesis of a wide range of nitrogen heterocycles, including natural products. Both chiral and racemic selenium electrophiles have been employed in these reactions. An aminoselenocyclization was used as the key reaction for the synthesis of isoquinoline alkaloids. Salsolidine **92** (Scheme 17) was synthesized by cyclization of the styrene derivative **90** to **91** using chiral selenium electrophile **38** followed by deselenylation[29, 44].



SCHEME 17

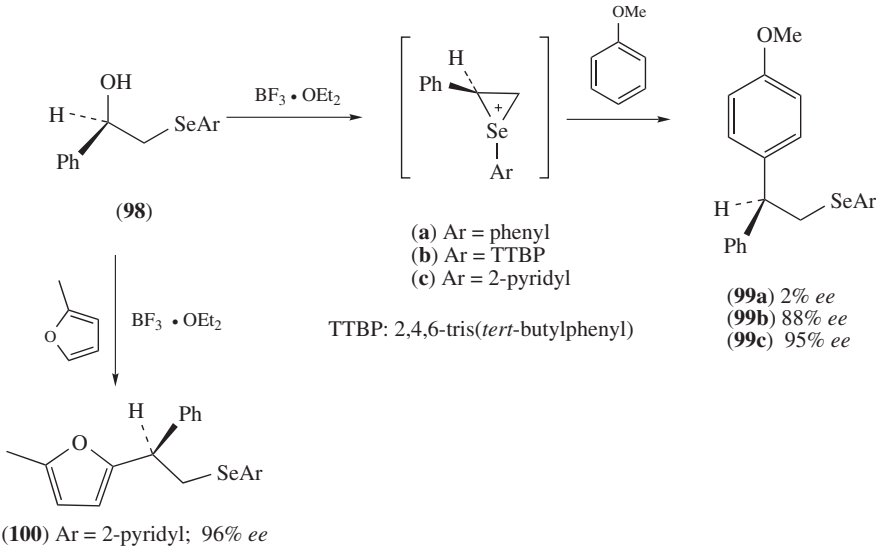
O-Allyl oximes such as **93** can be cyclized into enantiomerically enriched isoxazolidines **94** with up to 88% *de*, which are isolated after hydrolysis, using chiral selenium electrophiles **33** obtained from diselenide **11a** (Scheme 18)[45, 46]. Important cyclic nitrones **96** have been synthesized by aminoselenocyclization of oximes **95** using chiral selenium electrophiles with up to 64% diastereomeric excess. Furthermore, compound **96** can be transformed into the bicyclic compound **97** by using a dipolar cycloaddition with methyl propiolate (Scheme 18)[36].



SCHEME 18

3. Carbon nucleophiles

a. Stereoselective carboselenenylation reactions. Carbon nucleophiles have been used in selenocyclization reactions although carboselenenylation reactions are not as much investigated as oxyselenenylations. Carboselenenylation reactions are an important synthetic tool for asymmetric carbon–carbon bond formation reactions in organic chemistry. Toshimitsu and coworkers have investigated the reaction of chiral seleniranium ions with aromatic compounds acting as carbon nucleophiles. By the reaction of a chiral alcohol bearing a phenylseleno group on the adjacent carbon atom **98a** with anisole in the presence



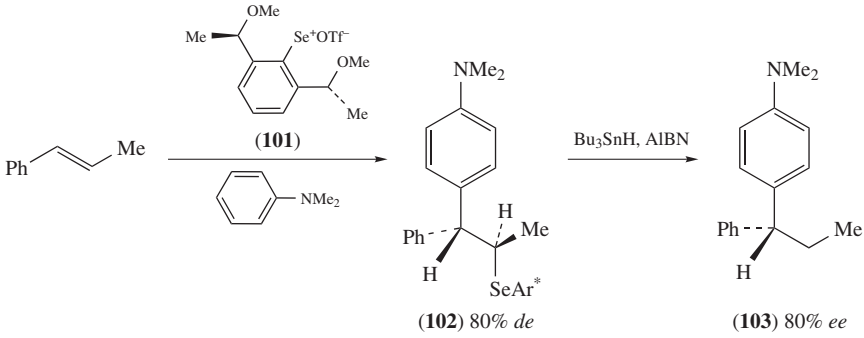
SCHEME 19

of trifluoroborane–diethyl ether (Scheme 19), the substitution of a hydroxyl group at the aromatic carbon proceeded to afford **99a** in high yield. In order to obtain high stereoselectivities in the addition reactions, aryl moieties such as 2,4,6-tris(*tert*-butylphenyl) (**98b**) and 2-pyridyl (**98c**) were employed and the addition products **99b** and **99c** obtained with 88% and 95% enantiomeric excess, respectively. Their use is essential to prevent racemization during the reaction. The stereospecificity of these reactions has also been found to depend to a large extent on the aromatic nucleophiles involved. Furan derivatives have also been used as nucleophiles in this reaction instead of anisole, and the carboselenenylated product **100** was obtained with 96% enantiomeric excess as shown in Scheme 19[47].

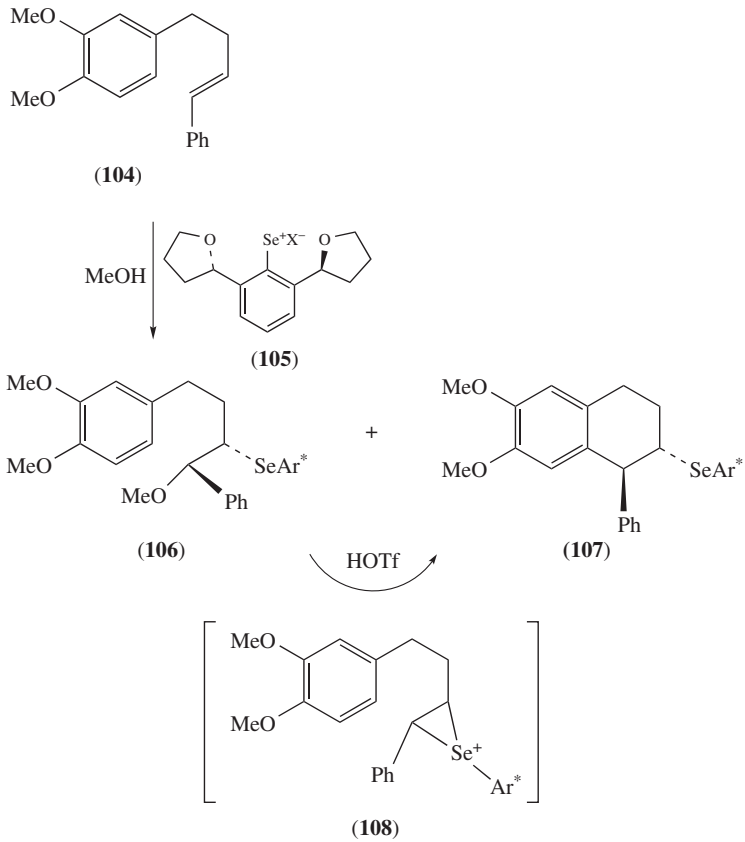
The same research group also reported the first example of a diastereoselective carboselenenylation reaction using β-methylstyrene and aniline derivatives using an optically active electrophilic selenium reagent **101** as chiral inducing agent. The addition product **102** was obtained with 80% diastereomeric excess. Further, the addition product **102** can be deselenenylated into **103** with 80% *de* using tributyltin hydride and azobisisobutyronitrile. The presence of 4 Å molecular sieves is essential to obtain these products in high yields (Scheme 20)[48].

This reaction is a convenient method for the synthesis of chiral hydrocarbons that bear an aryl moiety at the stereogenic carbon atom and can be considered as a new kind of asymmetric Friedel–Crafts alkylation reaction of aromatic compounds with alkenes.

b. Selenocyclizations with carbon nucleophiles. Selenocyclization reactions of olefins using carbon nucleophiles was introduced in 1980s[49a,b]. In the early days, β-dicarbonyl compounds were cyclized to various functionalized cyclic products by using carboselenocyclization reactions[49c,d]. In 1998, Déziel and coworkers[49e] developed the synthesis of tetrahydronaphthalene scaffolds **107** by cyclizations of alkenes of type **104** using chiral selenium electrophile **105**. Initially, the product of a methoxyselenenylation **106** was obtained with 98% *de* in a 1:1 ratio with the cyclized product **107**. Further treatment of



SCHEME 20



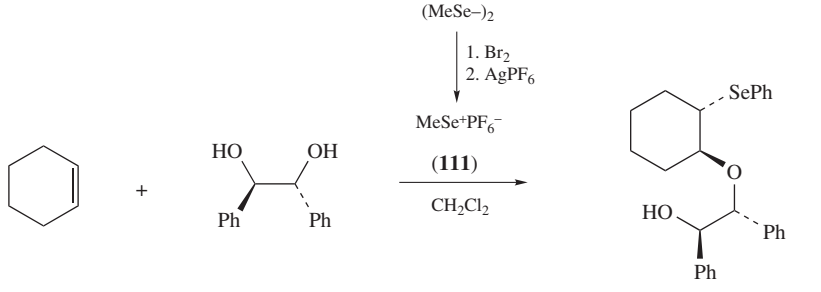
SCHEME 21

106 with triflic acid resulted in a complete conversion to **107** via the formation of the seleniranium intermediate **108**, as shown in Scheme 21.

It is also noted that a small amount of methanol is essential to achieve high selectivities; however, there is a competing reaction between formation of the methoxylated and the cyclized product. The cyclization product **107** was obtained in low yields and low diastereoselectivities without using methanol. β-Methoxyselenides have been identified as versatile precursors of seleniranium ions when treated with strong acids.

4. Asymmetric selenenylation and achiral selenium electrophiles

Some research groups have developed asymmetric selenenylation reactions of alkenes using achiral selenium electrophiles with good selectivities. The oxyselenenylation of cyclohexene **109** has been reported employing chiral (*R*,*R*)-hydrobenzoin **110** and the methylselenenyl electrophile **111**. The addition products **112** were obtained in reasonable yields in a 85:15 diastereomeric ratio. Other achiral selenium electrophiles have also been investigated but low diastereoselectivities were observed. The addition products were obtained with almost the same diastereoselectivities using other methylselenium electrophiles with different counteranions (Scheme 22)[50].

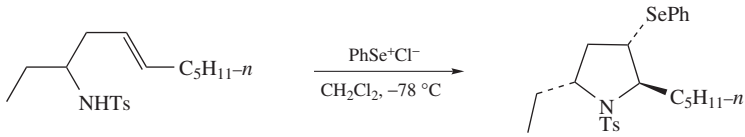


(**109**) (**110**) (**112**) 85:15 *d.r.*, 58% yield

SCHEME 22

Asymmetric selenocyclizations of alkenes by achiral selenium electrophilic reagents using internal nucleophiles are more common in the literature than selenenylation reactions. In 1995, Lipshutz and Gross[51] investigated that cyclization of chiral homoallylic alcohols using arylselenium halides such as 2,4,6-tri(isopropylphenyl)selenium bromide (TIPPSe-Br) and phenyl selenenyl chloride has yielded substituted tetrahydrofuran derivatives with good selectivities. The stereoselective synthesis of hydroxy-substituted γ- and δ-lactones and 1,4-dioxanes has also been developed without using chiral selenium electrophiles[37b, 52]. Recently, diastereoselective synthesis of enantiopure morpholines has been reported by oxyselenocyclization of chiral 3-allyl-2-hydroxymethyl-substituted perhydro-1,3-benzoxazine derivatives using phenyl selenenyl chloride[53]. Also recently, Denmark and Edwards reported the mechanistic aspects of selenolactonization reactions with selenenyl halides in detail[54].

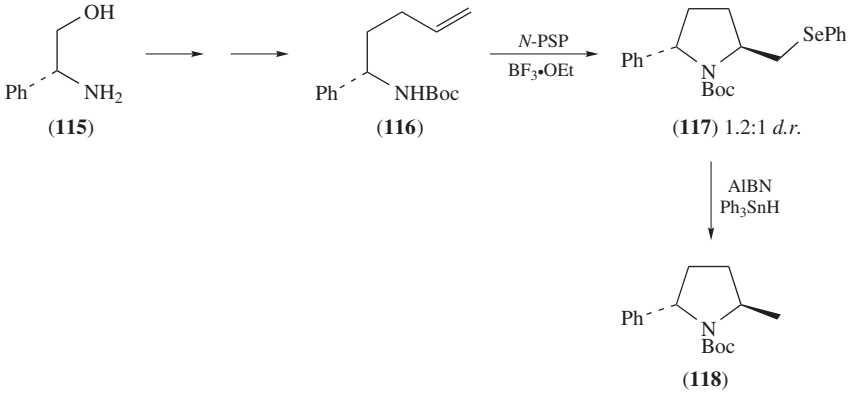
Selenocyclization of homoallylic sulfonamides such as **113** using phenyl selenenyl halides lead exclusively to β-selenyl pyrrolidines **114** by a 5-*endo*-*trig* pathway, but with considerable variations in the stereochemical outcome, depending upon the substituents and the reaction conditions employed (Scheme 23). Subsequent oxidative eliminations



(**113**) (**114**)

SCHEME 23

lead smoothly to 3-pyrrolines and polyhydroxylated pyrrolidines[55]. The synthesis of enantiomerically enriched selenenylated pyrrolidines **117** has been achieved by substrate-controlled cyclization of *N*-Boc-protected *δ*-alkenylamines **116** formed in turn from **115** using *N*-(phenylseleno)phthalimide (*N*-PSP). Furthermore, the selenenylated pyrrolidines **117** can be converted into enantiomerically pure functionalized pyrrolidines **118** by deselenenylation, as shown in Scheme 24[56].



(**115**) (**116**) (**117**) 1.2:1 *d.r.* (**118**)

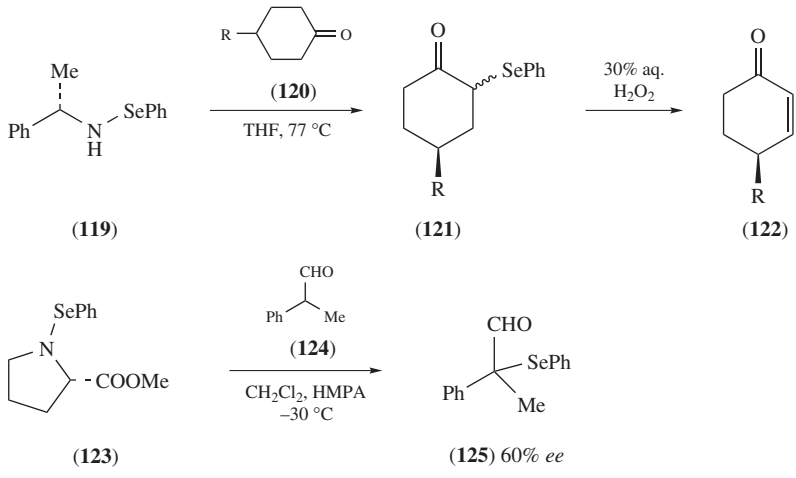
SCHEME 24

Recently, the highly diastereoselective synthesis of substituted pyrrolidines has beeen revealed in the literature by selenocyclization of chiral alkylidene-cored optically active *N*-(alkenylidene)alkylamines using different achiral arylselenenyl bromides, followed by subsequent reduction[57].

5. Stereoselective α-selenenylation of carbonyl compounds

Selenium electrophiles have been used in the *α*-selenenylation of carbonyl compounds. *α*-Selenenylation of carbonyl compounds has been proven to be an important tool in synthetic and natural product chemistry. *α*-Selenoaldehydes and ketones can undergo useful reactions such seleno-Pummerer reactions[58], selenoxide eliminations[59] and [2,3]-sigmatropic rearrangements[60] to produce various synthetically important compounds.

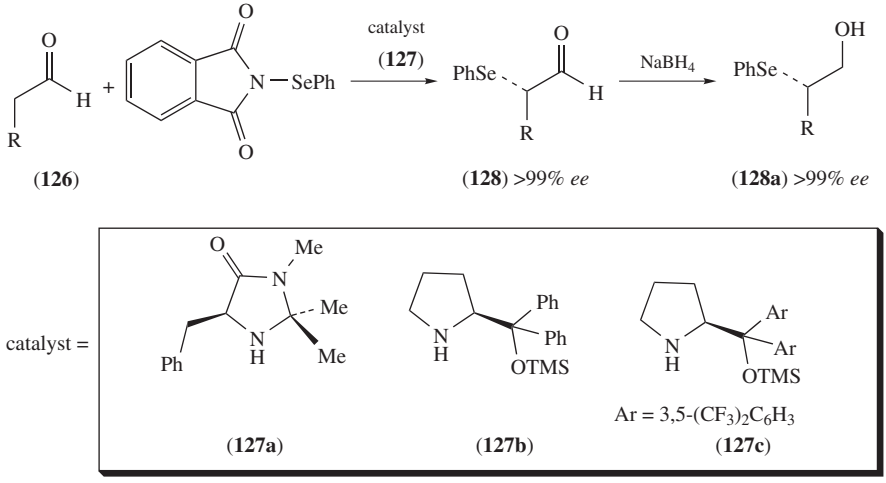
Stereoselective *α*-selenenylations of carbonyl compounds have been introduced successfully in the recent past. Stereoselective *α*-selenenylation of cyclohexanones **120** was achieved using chiral selenamides **119**. Using a selenoxide elimination, the *α*-selenoketone



SCHEME 25

121 was converted into cyclohexenone derivative **122** with 26% *de*[24]. The stereoselective α-selenenylation of aldehydes **124** has been reported by using chiral selenium electrophiles of type **123** resulting in products **125** with up to 60% enantiomeric excess (Scheme 25)[61].

Wang and coworkers recently reported a catalytic protocol for the α-selenenylation of aldehydes using a chiral cyclic amine as catalyst. Attempts were also made to develop a stereoselective reaction but almost racemic products were formed. However, three asymmetric examples were achieved with aldehydes using (*S*)-pyrrolidine tosylsulfonamide as

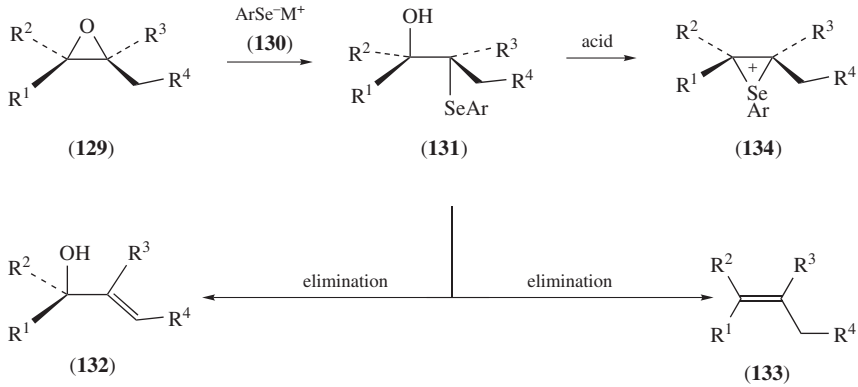


SCHEME 26

the catalyst. The corresponding products were isolated with poor enantiomeric selectivities[62]. Recently, highly enantioselective (>99% *ee*) α-selenenylation of aldehydes **126** were achieved by using chiral 4-imidazolidinones of type **127a**, diarylprolinol silyl ethers **127b** and **127c** as catalyst and *N*-(phenylseleno)phthalimide as selenium electrophile. The α-selenoaldehydes **128** were then transformed into corresponding β-selenoalcohols **128a** with more than 99% enentiomeric excess on reduction using sodium borohydride as reducing agent (Scheme 26)[63a,b]. Marini and his colleagues have reported enantioselective organocatalytic Michael addition of α-substituted cyanoacetates to α,β-unsaturated selenones with 99% enantiomeric excess[63c]. Highly diastereoselective synthesis of β-hydroxyselenides can be obtained by the reduction of chiral (ferrocenylseleno)methyl aryl ketones using DIBAL[63d].

III. NUCLEOPHILIC REAGENTS

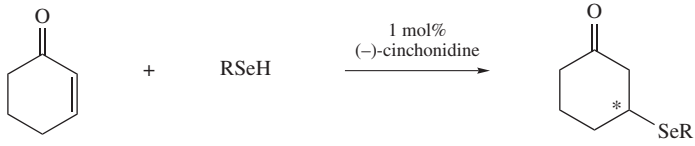
The chemistry of nucleophilic selenium reagents was discovered by Sharpless in 1973[64]. He investigated the synthesis of phenyl selenolate and its utility as nucleophile in the ring opening of epoxides. Since that time, various nucleophilic reagents have been widely applied in synthetic organic chemistry. The synthesis of diverse selenium nucleophiles can be achieved by easily accessible precursors, such as by reduction of either elemental selenium, diselenides or selenocyanates or by insertion of selenium into organometallic reagents[65]. Selenolates are highly reactive but soft nucleophiles that can lead to the formation of various target compounds. The ring opening of epoxides **129** with selenium nucleophile **130** leads to the formation of β-hydroxyselenides **131**. Elimination from selenoxides **131** affords allylic alcohols **132** with high selectivities[64]. Furthermore, the β-hydroxyselenides **131** can lead to the corresponding alkenes of type **133** by eliminations with retention of configuration (Scheme 27)[66].



SCHEME 27

The hydroxy group of β-hydroxyselenides **131** can be activated using acids to form the corresponding seleniranium ions **134**[67a], although seleniranium ions are produced more commonly by the reaction of alkenes with selenium electrophiles as described earlier. Finally, these seleniranium ion intermediates can be opened inter- or intramolecularly to yield further functionalized compounds, for example the stereoselective synthesis of functionalized tetrahydrofurans through acid-catalyzed ring closure of selenyl diols[67b].

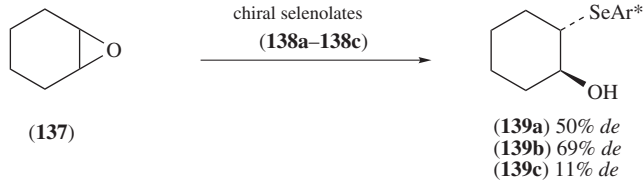
The chemistry of nucleophilic selenium reagents in terms of asymmetric synthesis was initiated with the addition of selenols **135** to α,β-unsaturated carbonyl compounds using chinchona alkaloids as a catalyst. The selenenylated products of type **136** were obtained in up to 43% *ee* (Scheme 28)[68].



(**135**) (**136**) 43% *ee*

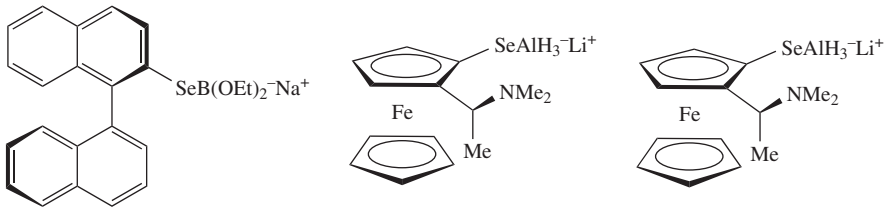
SCHEME 28

The chiral selenium reagents as nucleophiles were used for the first time in the nucleophilic ring-opening of epoxides. The chiral selenolates of type **138a**–**138c** have been used in stereoselective nucleophilic ring opening of *meso*-epoxides **137** and ring-opened products **139a**–**139c** were obtained in up to 69% diastereomeric excess (Scheme 29)[69].



(**137**)

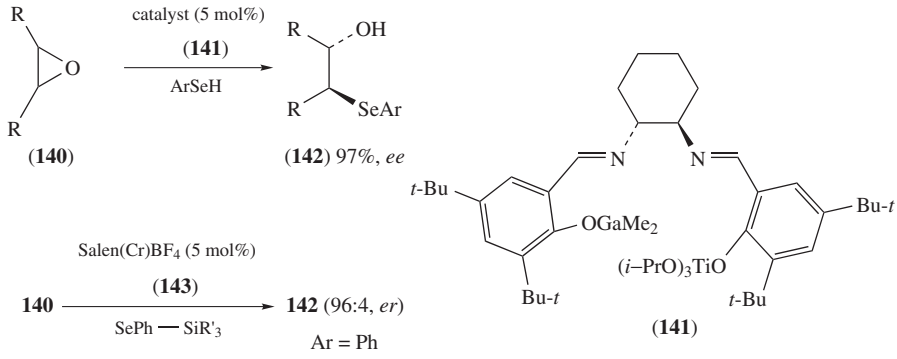
(**139a**) 50% *de*
(**139b**) 69% *de*
(**139c**) 11% *de*



(**138a**) (**138b**) (**138c**)

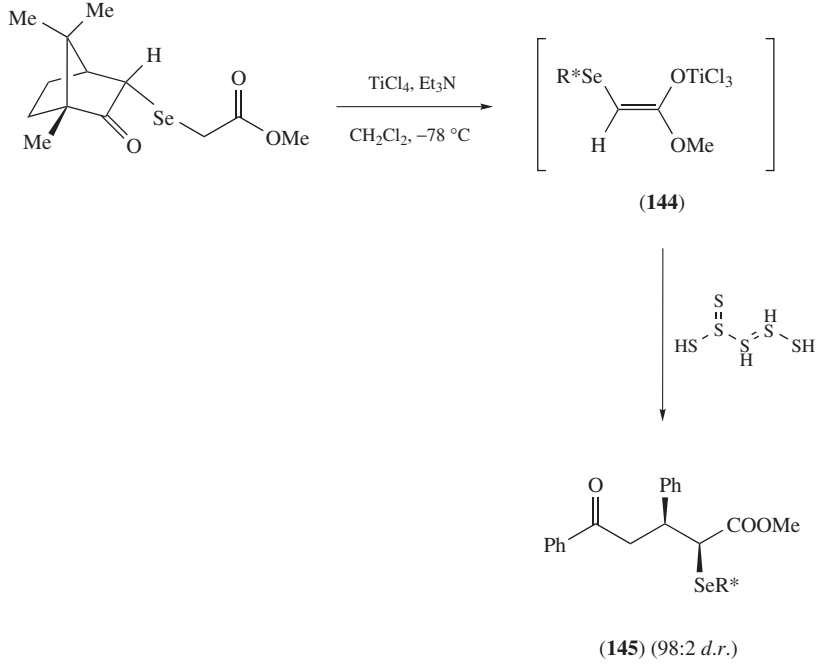
SCHEME 29

Recently, some other asymmetric ring openings of *meso*-epoxides with selenium nucleophiles have been reported. Zhu and coworkers have developed new enantioselective ring-opening of *meso*-epoxides **140** with aryl selenols using the chiral Ti-Ga-salen heterobimetallic catalyst **141** leading to products with up to 97% enantiomeric excess (Scheme 30)[70a]. The enantioselective synthesis of β-hydroxyselenides **142** has been achieved by the enantioselective ring-opening of *meso*-epoxides **140** with (phenylseleno)silanes using a salen(Cr)complex[70b] **143** as catalyst (Scheme 30)[70c,d]. Recently, stereoselective synthesis of selenosteroids have been reported using asymmetric epoxidation of commercially available cholesterol, followed by stereoselective epoxide ring opening employing selenium nucleophiles[70e].



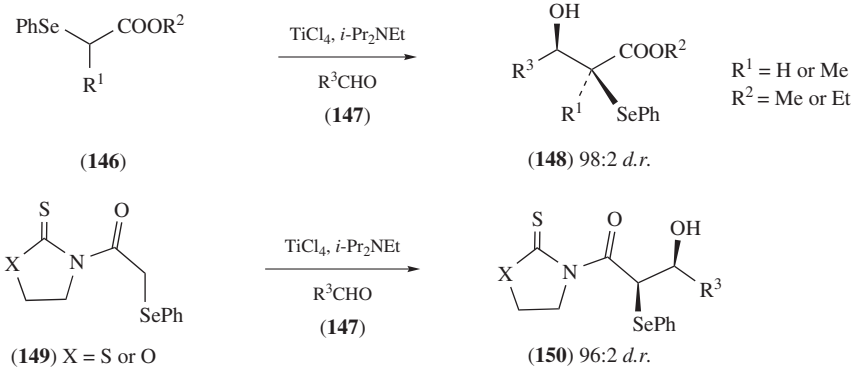
SCHEME 30

α-Selenoenolates **144** containing a chiral auxiliary linked to the selenium atom can be efficiently employed as Michael donors for stereoselective synthesis of enantiomerically pure δ-oxo-α-seleno esters **145**. The Lewis acids, necessary to activate the starting enones towards addition, greatly influence the reactivity as well as the stereochemical outcome of these reactions (Scheme 31). It has been found that the chiral selenium-containing group can transfer the chirality to the 1,4-addition products affording δ-oxo-α-seleno esters **145** with high levels of diastereoselectivity and facial selectivity[71].



SCHEME 31

During recent progress of organoselenium reagents in stereoselective reactions, selenium-based nucleophiles have been employed in stereoselective aldol condensations. The first stereoselective aldol condensation using a selenium nucleophile was reported by Toru and coworkers in 2001[72]. They have developed $TiCl_4$-mediated diastereoselective aldol condensation of α-seleno esters **146** with aromatic aldehydes **147**. The chiral β-selenoalcohols **148** were obtained in good yields as aldol products in up to 98:2 diastereomaric ratios (Scheme 32)[72].



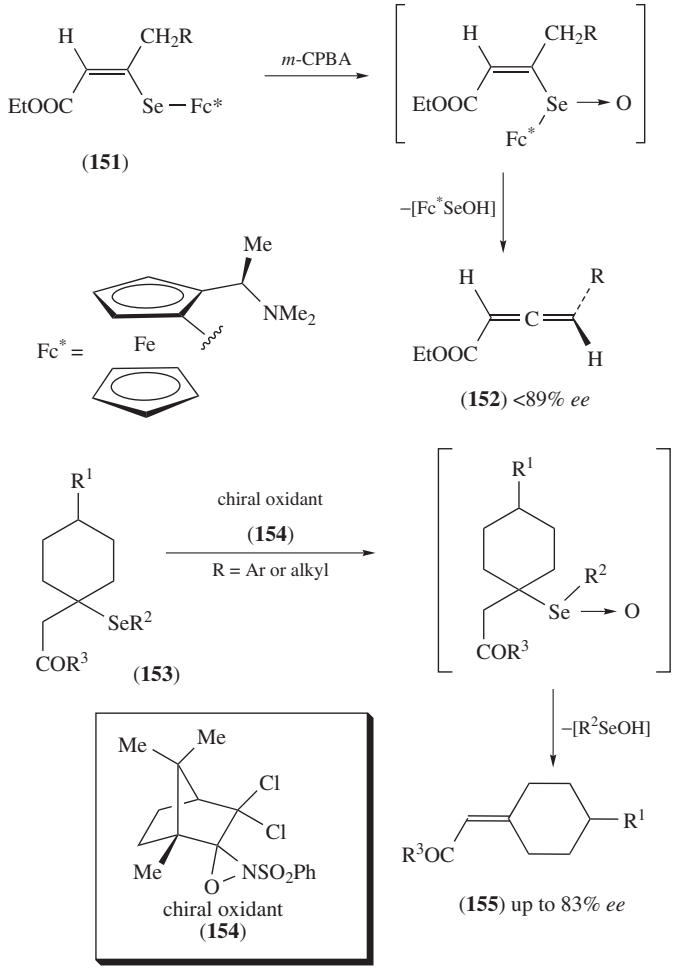
SCHEME 32

Tiecco and coworkers developed highly diastereoselective aldol condensation of chiral titanium enolates derived from (*R*)-camphorselenoacetone in the presence of aldehydes[73]. Recently, diastereoselective aldolizations of *N*-phenylselenylacetyl derivatives **149** with aldehydes **147** have been reported to give products **150** in high selectivities (Scheme 32)[74]. Stereoselective Mannich-type reactions of chlorotitanium α-phenylseleno ester enolates with aromatic aldimines have been developed successfully with excellent selectivity[75].

IV. STEREOSELECTIVE SELENOXIDE ELIMINATIONS

Selenoxide elimination of various selenium-containing scaffolds is an important approach in synthetic organic chemistry, although this reaction has failed to receive the main attention of several organic chemists. Selenides obtained from the selenenylation of alkenes can be oxidized into corresponding selenoxides, which can undergo subsequent *syn*-elimination and yield the corresponding alkenes. Chiral selenoxides can be obtained either by enantioselective oxidation[76] or by diastereoselective oxidation[77] of selenides bearing a chiral moiety. It had been shown that the formation of an achiral hydrate accounts for the fast racemization of selenoxides in the presence of acid and water. Bulky substituents can prevent racemization[78] but, in the presence of a β-hydrogen atom, the subsequent selenoxide elimination leads to more stable products.

In 1992, the first stereoselective selenoxide elimination was reported by Uemura and coworkers with good to moderate selectivities[79]. The same research group reported highly enantioselective synthesis of chiral allenecarboxylic esters **152** (up to 89% enatiomeric excess) by ferrocenyl-substituted vinyl selenides **151** using an oxidation–elimination sequence (Scheme 33)[11c,e]. Enantioselective synthesis of alkyl and aryl cyclohexylidenemethyl ketones **155** has been achieved by selenoxide elimination of selenoxide of type **153** using selective oxidations by chiral oxidants of type **154**, as shown in Scheme 33[80].



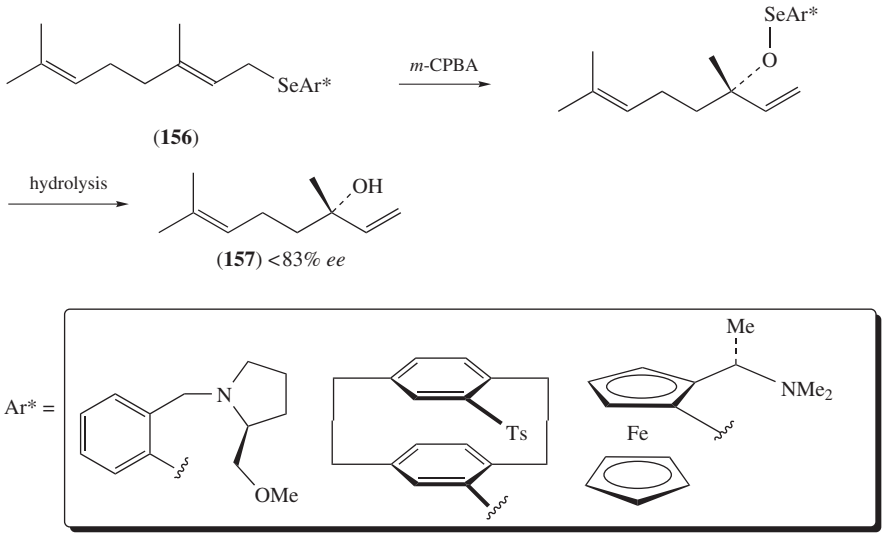
SCHEME 33

V. STEREOSELECTIVE [2,3]-SIGMATROPIC REARRANGEMENTS

The [2,3]-sigmatropic rearrangement via allylic selenoxides is the tailor-made approach for the synthesis of allylic alcohols[3a,d, 7a]. This rearrangement involves an oxygen transfer from selenium to carbon followed by hydrolysis of the allylic selenolates into allylic alcohols[7a]. The mechanistic studies indicated that these rearrangements proceed predominantly via an *endo* transition state[77].

The literature revealed that the rearrangement of the allylic selenoxides proceeds much faster than that of the corresponding sulfoxides[81]. Like the selenoxide eliminations, the stereoselectivity in these rearrangements can again be introduced either by enantioselective oxidation of the prochiral selenides or by diastereoselective oxidation of allylic selenides having a chiral moiety[76, 77]. Davis and Reddy reported the efficient synthesis

of allylic alcohol derivatives by oxidation of cinnamyl selenoxides using Davis oxidants followed by 2,3-sigmatrotropic rearrangement with moderate selectivities[76]. Uemura and coworkers reported the synthesis of the same allyl alcohol derivatives with a similar strategy using Sharpless oxidants and found improved enantiomeric excesses of up to 92%[82]. The several examples for stereoselective synthesis of allylic alcohols by diastereoselective oxidation of optically active allyl selenides followed by sigmatropic rearrangement has also been revealed in the literature. The stereoselective synthesis of (*S*)-linalool **157** has been achieved from optically active selenides **156** by oxidation and rearrangement and hydrolysis in up to 83% enantiomeric excess (Scheme 34)[11c, 79, 83].



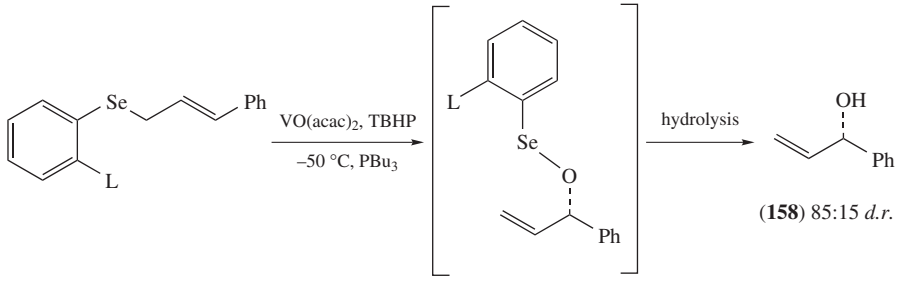
SCHEME 34

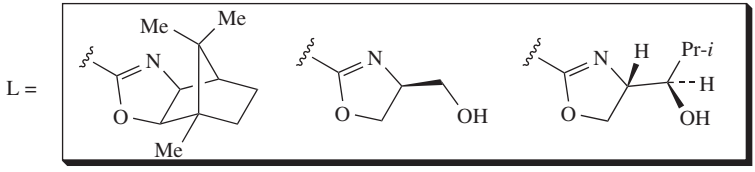
Carter and coworkers reported the stereoselective synthesis of chiral allyl alcohol **158** by vanadium-catalyzed, ligand-based selenide oxidation and [2,3]-sigmatropic rearrangement and hydrolysis *in situ* using either cumene hydroperoxide (CHP) or *tert*-butyl hydroperoxide (TBHP) as oxidant (Scheme 35). Camphor, serine and threonine-based oxazoles have been used as ligands, but the best selectivity was obtained with threonine-based oxazoles[84].

Recently, Hess and Posner developed the enantioselective synthesis of α-hydroxy-(*E*)-β,γ-unsaturated esters **161** with up to 97% enantiomeric excess. The synthesis of α-hydroxy-(*E*)-β,γ-unsaturated esters involves the oxidation of allylic selenide **159** and spontaneous [2,3]-sigmatropic rearrangement of intermediate **160** (Scheme 36)[85].

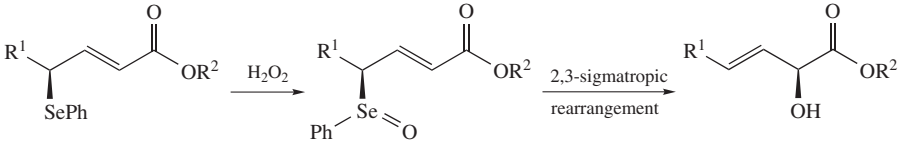
The same research group has applied this approach to the total synthesis of (+)-symbioramide **164**. An important intermediate **163** has been synthesized by the oxidation and spontaneous 2,3-sigmatropic rearrangement followed by the reduction of **162** in 28% overall yield with 95% enatiomeric excess (Scheme 37). By using the same approach, they have reported the synthesis of important building blocks **166**, which is useful for the synthesis of new vitamin D side-chain analogues from **165**[86].

The enantioselective synthesis of γ-hydroxy-α,β-unsaturated sulfones and esters of type **169** via epoxide intermediates **168** has been reported through the reaction of chiral





SCHEME 35

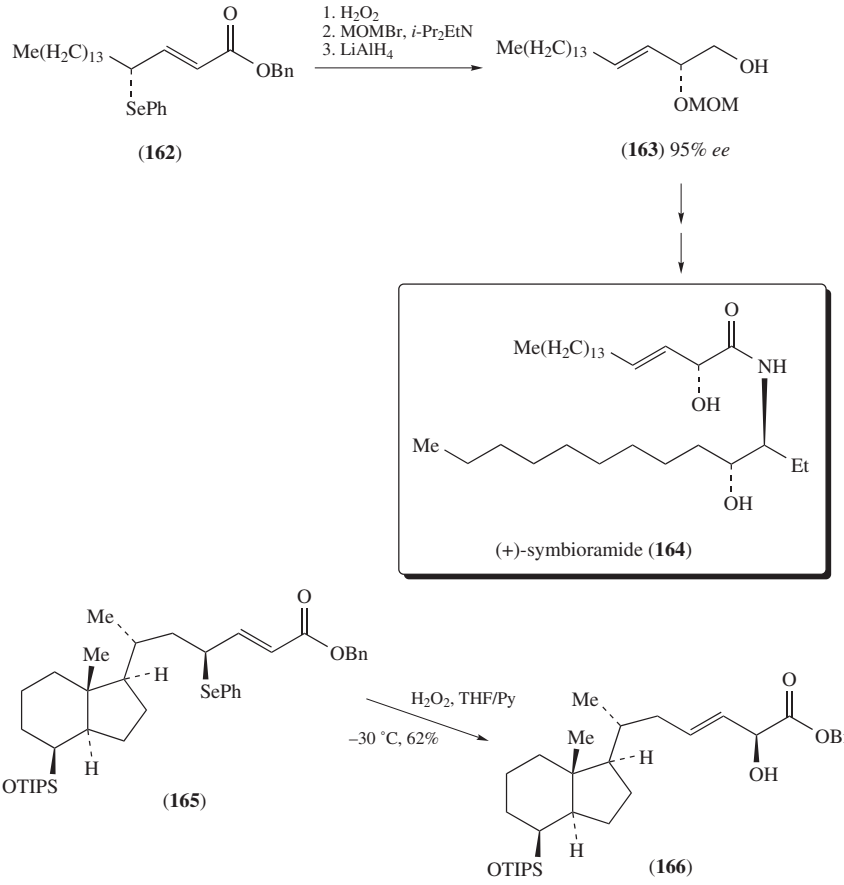


SCHEME 36

γ-selenyl-β-hydroxy sulfones and esters **167** with stabilized carbanions and followed by a one-pot selenide oxidation and an *in situ* epoxide formation and ring-opening. The allylic products **169** were obtained with up to 95% enantiomeric excess (Scheme 38)[87]. This approach has been employed in the synthesis of the natural product (+)-α-conhydrine **172** starting from γ-selenyl-β-hydroxy sulfones and esters **170** via formation of a γ-hydroxy ether-α,β-unsaturated ester of type **171** (Scheme 38)[87].

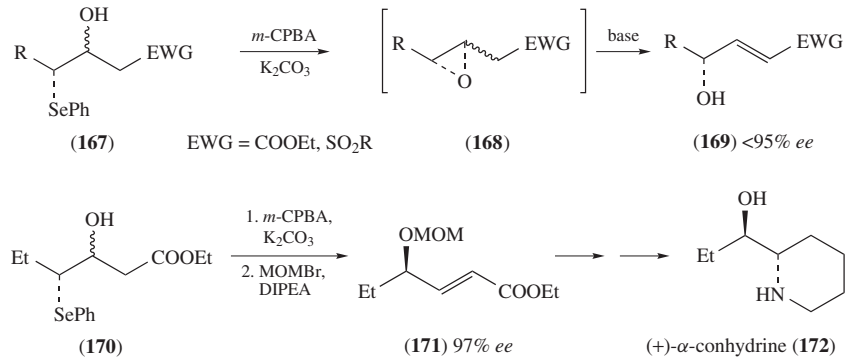
Like selenoxides, selenimides (nitrogen analogues of selenoxides) have been also reported to perform similar [2,3]-sigmatropic transformations. Uemura and coworkers have developed the enantioselective synthesis of allylic amines **175** by asymmetric imidation of cinnamyl selenides **173** using chiral catalyst **174**, followed by 2,3-sigmatropic rearrangement. The products were obtained with up to 30% enantiomeric excess (Scheme 39)[88]. Stereoselective synthesis of chiral allylic selenimides has been achieved by stereoselective 2,3-sigmatropic rearrangement with selectivities up to 93% *ee*[89].

The chemistry of selenonium ylides has been known for a long time, but the chiral version was introduced only recently. The stereoselective synthesis of chiral selenonium ylides **176** was reported by the nucleophilic substitution reaction of a chloroselenurane with active methylene compounds as a carbon nucleophile[90]. The first example of stereoselective 2,3-sigmatropic rearrangement of selenonium ylide was reported by Uemura and coworkers, but the products were obtained with low selectivity[91a]. Koizumi and coworkers



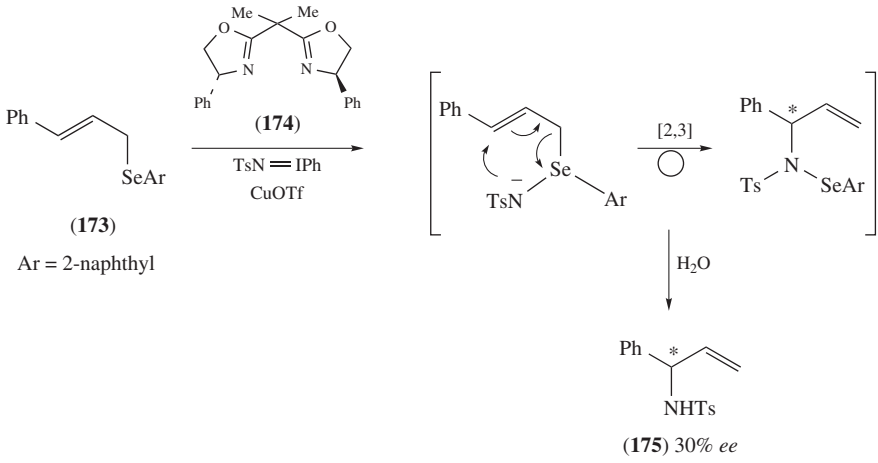
(**162**) (**163**) 95% *ee* (**165**) (**166**)

SCHEME 37

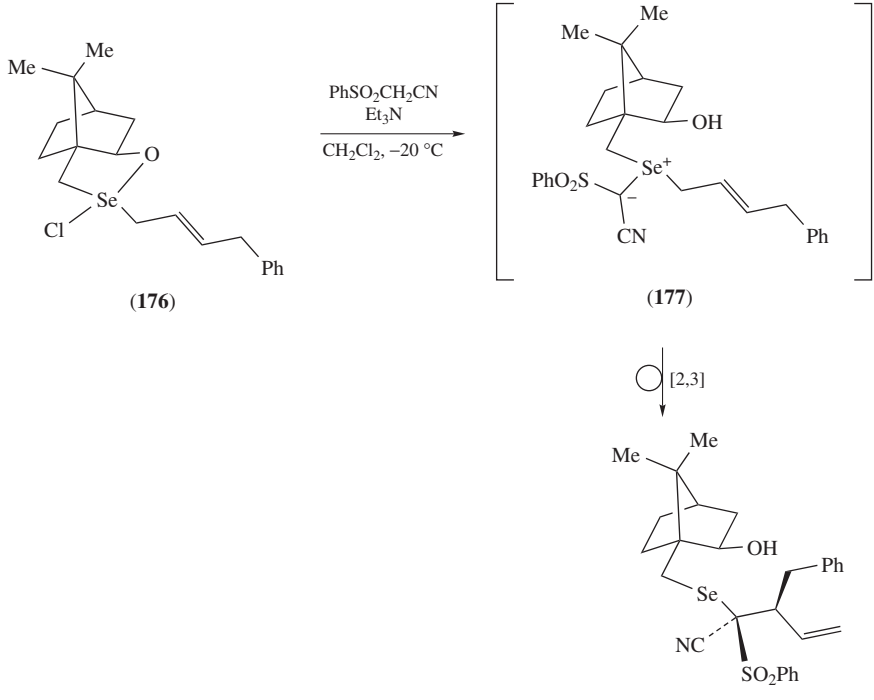


(**167**) EWG = COOEt, SO_2R (**168**) (**169**) <95% *ee* (**170**) (**171**) 97% *ee* (+)-α-conhydrine (**172**)

SCHEME 38



SCHEME 39

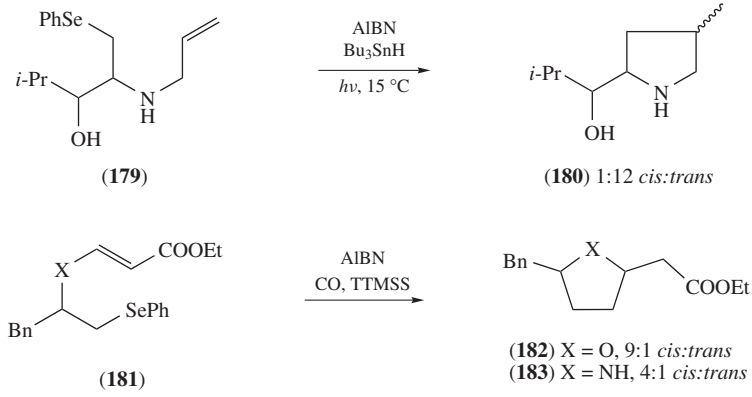


SCHEME 40

developed the synthesis of selenonium ylides **177** by the reaction of allylic chloroselenuranes **176** with (phenylsulfonyl)acetonitrile; the selenonium ylides **177** then undergo an *in situ* [2,3]-sigmatropic rearrangement into homoallylselenides **178** in 88% diastereomeric excess (Scheme 40)[91b].

VI. STEREOSELECTIVE RADICAL REACTIONS

Only few reports are available in the literature on related stereoselective radical reactions. Besev and Engman reported on the 5-*exo*-cyclization of readily available organoselenium precursors of 3-aza-5-hexenyl radicals **179** to substituted pyrrolidines **180** with more than 90% selectivity (Scheme 41)[92]. The same research group has extended this approach and developed the stereoselective synthesis of tetrahydrofurans **182** and pyrrolidines **183** from **181** by radical carbonylation/reductive cyclization processes using tris(trimethylsilyl) silane (TTMSS) as a radical initiator[93].



(**179**)

(**180**) 1:12 *cis:trans*

(**181**)

(**182**) X = O, 9:1 *cis:trans*
(**183**) X = NH, 4:1 *cis:trans*

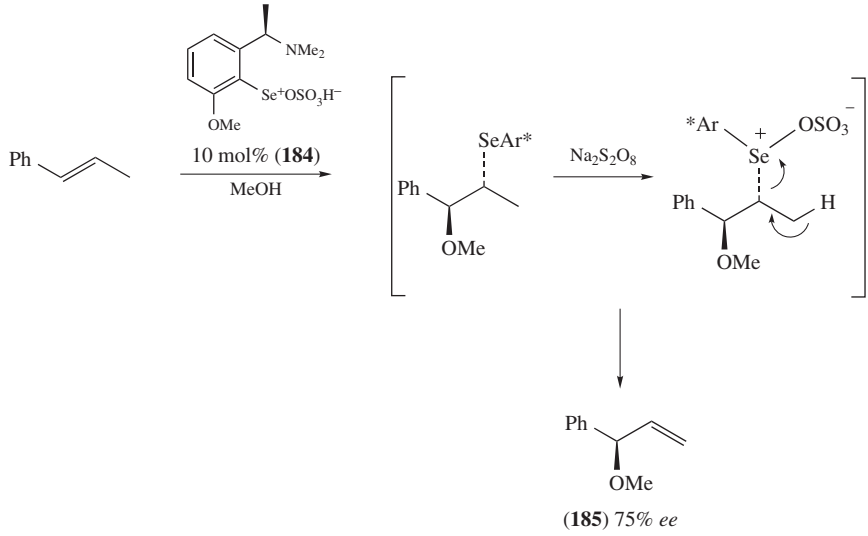
SCHEME 41

VII. STEREOSELECTIVE CATALYTIC REACTIONS

Selenium-containing compounds have been employed as catalyst or ligand in various organic transformations. Uemura and coworkers investigated the utility of chiral selenium-based ligands in asymmetric catalysis[94]. After these initial reports, selenium-based chiral ligands have been used with great success in a wide range of stereoselective catalytic methodologies.

A. Stereoselective Catalytic Selenenylation–Elimination Reactions

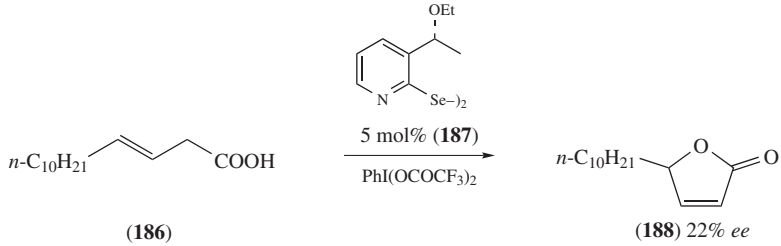
Chiral selenium reagents have been used as catalyst in stereoselective selenenylation–elimination reactions. These catalytic reactions provide double bond transpositioned allylic ethers or allylic alcohols from the corresponding alkenes. In these catalytic reactions, different oxidants have been used in stoichiometric amounts to activate the chiral selenium electrophiles. Wirth and coworkers developed a sequence of methoxyselenylation and oxidative β-hydride elimination of alkenes **185** using only catalytic amounts of chiral



SCHEME 42

reagents **184** (Scheme 42). The reaction products were obtained in low yields and up to 75% enantiomeric excess[95].

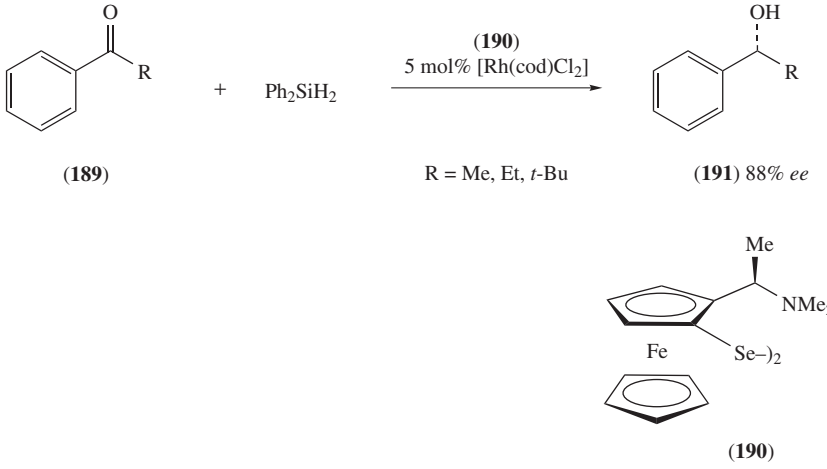
Furthermore, Wirth and coworkers developed the catalytic cyclization of β,γ-unsaturated carboxylic acids **186** to butenolides **188** using catalytic amounts of diphenyl diselenide and [bis(trifluoroacetoxy)iodo]benzene as stoichiometric oxidant. The efforts were also made towards the stereoselective synthesis of butenolide **188** using 5 mol% of chiral diselenide **187**. The chiral butenolide **188** was obtained in low yields and poor selectivity with maximum enantiomeric excess of 22% (Scheme 43)[96].



SCHEME 43

B. Selenium-based Chiral Ligands in Stereoselective Hydrosilylation of Ketones

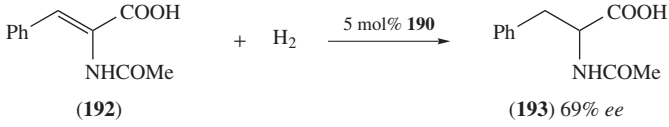
Some diselenides have been identified as promising ligands in transition metal-catalyzed asymmetric hydrosilylation or transfer hydrogenations of ketones. The rhodium(I)-catalyzed stereoselective hydrosilylation of alkyl aryl ketones **189** is



SCHEME 44

successful using diferrocenyl diselenide **190** as chiral ligand. The chiral alcohols **191** were obtained in up to 88% enantiomeric excess (Scheme 44)[97]. Ruthenium(II)-catalyzed stereoselective transfer-hydrogenation of ketones has been also investigated by using the same diselenide **190** as chiral ligand. However, the stereoselectivities obtained are low in most of the examples reported (up to 48% *ee*)[12, 98].

Rhodium(I)-catalyzed stereoselective hydrogenation of enamides **192** also proceeds smoothly using the same chiral ligand **190** to give the corresponding amides **193** with up to 69% enantiomeric excess (Scheme 45)[97].

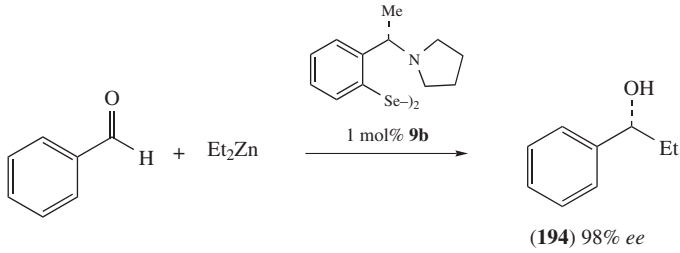


SCHEME 45

C. Stereoselective Addition of Diorganozinc Reagents to Aldehydes

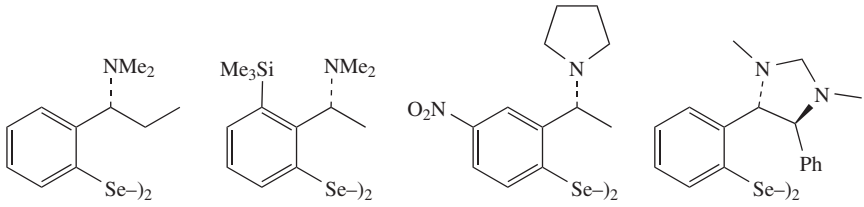
1. Diethylzinc addition

The stereoselective addition of diethylzinc to aldehydes in the presence of chiral catalysts is a widely used test reaction in asymmetric catalysis[99]. It has become an important tool for the synthesis of chiral secondary alcohols and a number of catalysts have been employed successfully in this reaction[100]. Wirth developed the first selenium-catalyzed stereoselective addition reaction of diethylzinc to aldehydes in 1995. He catalyzed the stereoselective addition of diethylzinc to aldehydes by chiral diselenides of type **9b** (1 mol%). The chiral secondary alcohols **194** were obtained in very high yields in up to 98% enantiomeric excess (Scheme 46)[15d,h, 101]. Both aromatic and aliphatic aldehydes can be employed in this reaction, but aromatic aldehydes showed higher selectivity than the aliphatic ones.



(**194**) 98% *ee*

SCHEME 46

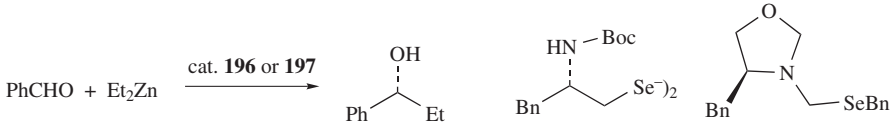


(**195a**) (**195b**) (**195c**) (**195d**)

FIGURE 15. Diselenides used as catalysts for diethylzinc addition

Some other diselenides **195a**–**195d** based on the same framework with different substituents have been synthesized by the same group and were evaluated in the same stereoselective addition of diethylzinc addition to benzaldehyde (Figure 15). The presence of an electron-withdrawing functionality in diselenide **195c** decreases both yield and selectivity. The other catalyst **195d** containing an additional stereogenic center in the five-membered ring is more efficient in the addition reaction and the product was obtained with 97% enantiomeric excess[101].

Braga and coworkers reported the synthesis of some aliphatic diselenides **196**[102] and selenides with oxazolidine moieties **197**[103] and employed these as chiral catalysts (0.5 mol%) in the stereoselective addition of diethylzinc to benzaldehyde. The chiral selenium diselenides **196** were found to be more efficient catalysts than the selenides **197**. The addition products **194** were obtained up to 99% enentiomeric excess; however, the selenide-containing oxazolidines **197** showed maximum 95% enantiomeric excess in product **194** (Scheme 47)[102c].



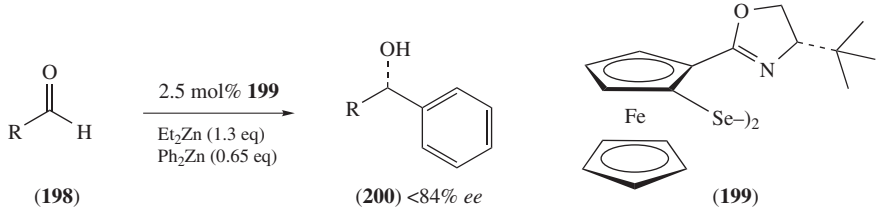
(**194**) 99% *ee* with **196**
95% *ee* with **197**

(**196**) (**197**)

SCHEME 47

2. Diphenylzinc addition

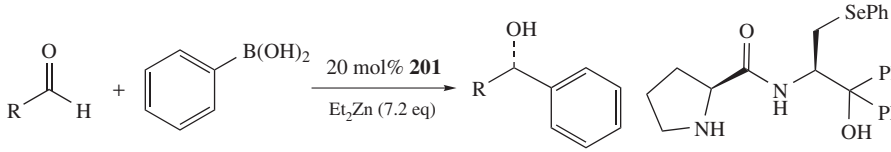
The enantioselective arylation of aldehydes can be achieved by the addition of diarylzinc to aldehydes using selenium-based chiral catalysts. Bolm and coworkers synthesized chiral oxazolinyl-substituted ferrocenyl diselenide **199** and employed it as catalyst (2.5 mol%) in the asymmetric arylation of aldehydes **198** using a zinc reagent prepared by the mixture of diphenylzinc and diethylzinc in a 1:2 ratio. The arylated chiral secondary alcohols **200** were obtained in up to 84% enantiomeric excess (Scheme 48)[12].



(**198**) (**200**) <84% *ee* (**199**)

SCHEME 48

Recently, a new class of selenium-based reagents has been developed as chiral catalysts of type **201**, which have been used in the enantioselective arylation of aromatic aldehydes using arylboronic acids with up to 91% enantiomeric excess (Scheme 49)[104]. Various aromatic aldehydes having different functionalities in the aromatic ring can be used in this reaction.



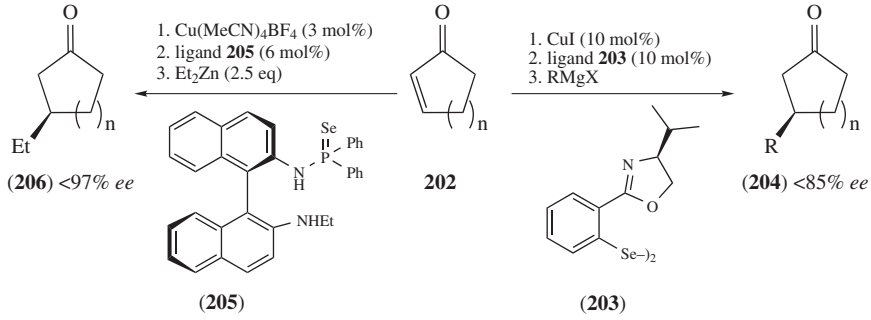
(**198**) (**200**) <91% *ee* (**201**)

SCHEME 49

3. Enantioselective conjugate addition of organometallic reagents to enones

The conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is an important synthetic tool for the construction of carbon–carbon bonds. Braga and coworkers developed the stereoselective conjugate addition of Grignard reagents to enones **202** using a combination of an oxazolidine ligand **203** and copper(I) as catalyst (10 mol%). The addition products **204** were obtained in good yields in up to 85% enantiomeric excess (Scheme 50)[105].

Recently, Zhang and coworkers developed a new copper(I)-based catalyst with an axially chiral binaphthyl selenophosphoramide ligand **205** and employed this catalyst in the enantioselective conjugate addition of diethylzinc to enones **202**. The Michael adducts-type compounds **206** were obtained in high yields with excellent enantiomeric excess for both cyclic and acyclic enones (Scheme 50)[106].



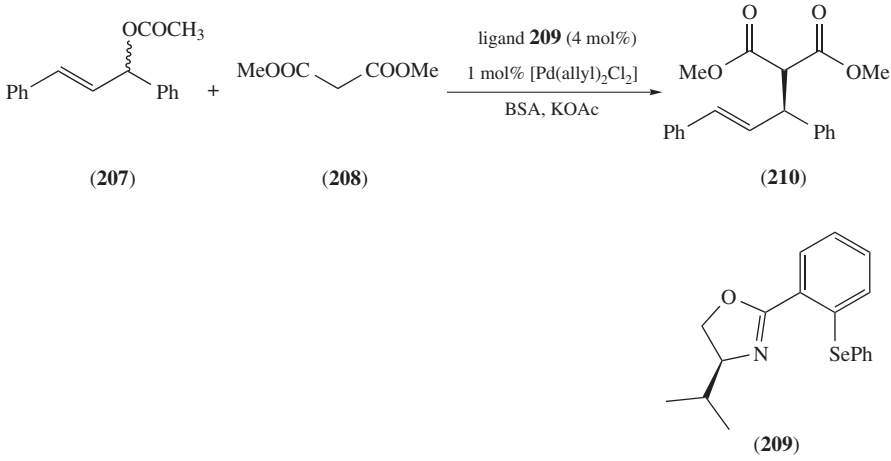
SCHEME 50

D. Palladium-catalyzed Asymmetric Allylic Alkylation

Enantioselective palladium-catalyzed allylic alkylation is one of the most valuable tools for stereoselective carbon–carbon bond-forming reactions[107]. Structurally diverse chiral selenium reagents have been investigated as promising ligands in palladium-catalyzed asymmetric allylic substitution reactions[108].

Helmchen and coworkers reported the first palladium-catalyzed asymmetric allylic substitution of (*E*)-1,3-diphenylallyl acetate **207** with dimethyl malonate **208** using chiral oxazolidine containing selenide **209** (4 mol%) as a chiral ligand with 95% enantiomeric excess (Scheme 51)[108]. After the discovery of the utility of selenium reagents as chiral ligand in palladium-catalyzed allylic substitution reactions, different classes of chiral selenium compounds have been developed as new chiral ligands.

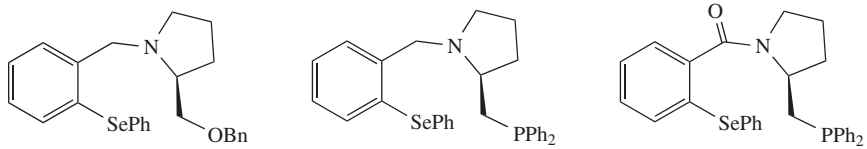
Hiroi and coworkers synthesized the (*S*)-proline-derived enantiopure selenium-based chiral ligands **211a**–**211d** and used them in the palladium-catalyzed asymmetric allylic



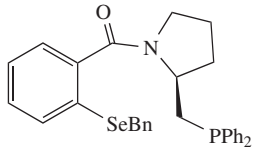
SCHEME 51

alkylation shown in Scheme 51, leading to the product **210** with 36–85% enantiomeric excess; the values are shown in Figure 16 after the compound numbers[109].

The chiral ferrocenyl-oxazoline containing selenides **212a**–**212d** were synthesized as novel chiral ligands and successfully employed in palladium-catalyzed asymmetric allylic substitution reactions. Although the product **210** was obtained in poor to moderate yields, the enantioselectivities (up to 99% *ee*) were excellent (Figure 17)[110].

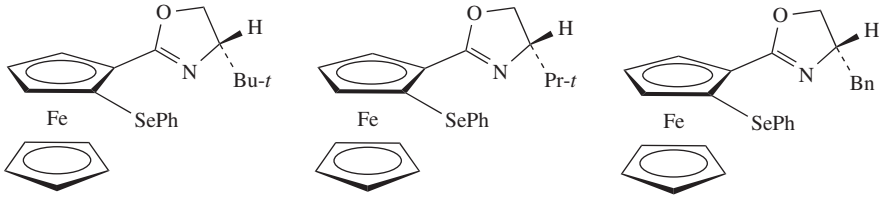


(**211a**) 36% *ee* (**211b**) 85% *ee* (**211c**) 74% *ee*

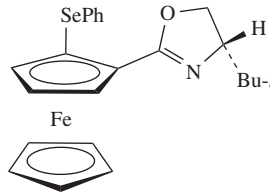


(**211d**) 86% *ee*

FIGURE 16. Structures of various selenides (**211a**–**211d**) employed as chiral ligands

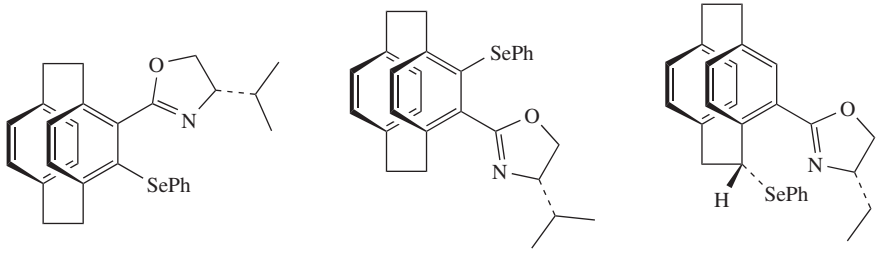


(**212a**) 99% *ee* (**212b**) 90% *ee* (**212c**) 92% *ee*



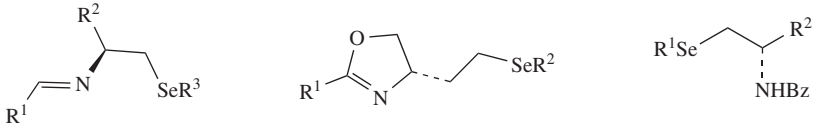
(**212d**) 92% *ee*

FIGURE 17. Chiral ferrocenyl-oxazoline containing selenides **212a**–**212d** for the asymmetric palladium-catalyzed allylic substitution



(**213a**) 57% *ee* (**213b**) 73% *ee* (**213c**) 93% *ee*

FIGURE 18. Chiral *N,Se*-ligands **213a**–**213c** based on the [2.2]paracyclophane structure



(**214**) 97% *ee* (**215**) 91% *ee* (**216**) 98% *ee*

FIGURE 19. Seleno imines **214**, oxazoline-based selenides **215** and β-seleno amides **216** as chiral selenium-containing ligands

The same research group developed the synthesis of chiral *N,Se*-ligands **213a**–**213c** based on the [2.2]paracyclophane structure and have applied these ligands in palladium-catalyzed asymmetric allylic substitutions (Scheme 51). The reaction products **210** were obtained in excellent yields with a maximum enantiomeric excess of 93% using **213c** as chiral ligand (Figure 18)[111]. Recently, some new chiral organoselenides, containing cinchona alkaloid moieties[112a] and *N*-trifluoroacyl β-chalcogeno amides[112b], have been successfully employed in enantioselective carbon–carbon bond-forming alkylations[112].

Braga and coworkers have developed various classes of selenium-based chiral ligands such as seleno imine derivatives **214**[113], oxazoline-based selenides **215**[103] and β-seleno amides **216** (Figure 19)[102]. All chiral selenium ligands have been used in stereoselective palladium-catalyzed asymmetric allylations. The chiral β-seleno amides were found to be the most efficient ligands in term of yields and selectivity.

Various chiral β-selenium, sulfur- and tellurium amides have been synthesized by ring-opening reaction of 2-oxazolines. Furthermore, all the compounds were evaluated as chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with malonates. The corresponding alkylated products were achieved with up to 98% *ee* using chiral β-selenium amides as ligand. It has also been demonstrated that selenium has higher ability to complex with palladium compared to other chalcogens, and selenium analogues have shown slightly better performance than sulfur and tellurium analogues[114].

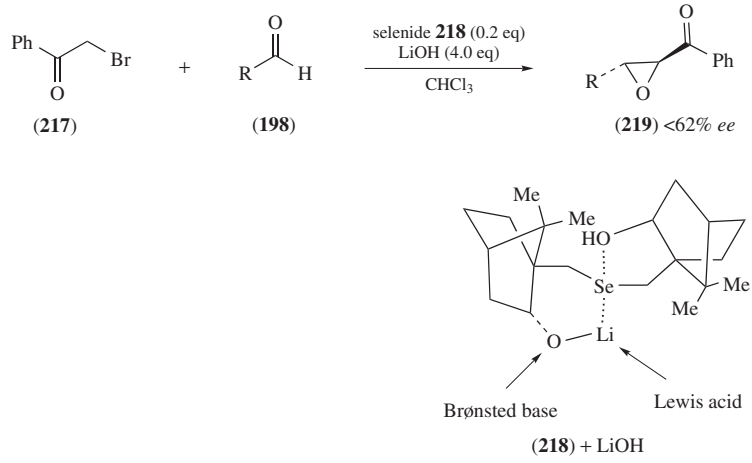
E. Asymmetric Dihydroxylation of Alkenes

Selenium-catalyzed stereoselective dihydroxylation of alkenes has been achieved recently using hydrogen peroxide as an oxidant. The chiral diols were obtained in good

yields with high diastereoselectivity, but the reactions were found to be extremely slow[115]. Seoane and colleagues have reported the selenium-catalyzed stereoselective synthesis of iodohydrins in good yields with up to 97% diastereomeric excesses[116].

F. Stereoselective Darzens Reactions

Recently, selenium-mediated stereoselective Darzens reactions have been reported. Watanabe and colleagues have developed an enantioselective synthesis of chiral epoxides **219** by a Darzens reaction of phenacyl bromide **217** with aldehydes **198** using a novel Lewis acid/Brønsted base catalyst **218** formed by the C_2-symmetric chiral selenide bearing isoborneol skeletons. The chiral epoxides **219** were obtained in good yields with up to 62% enantiomeric excess. Both aromatic and aliphatic aldehydes can be employed in this reaction, but the enantioselectivity was extremely poor with aliphatic aldehydes (Scheme 52)[117].

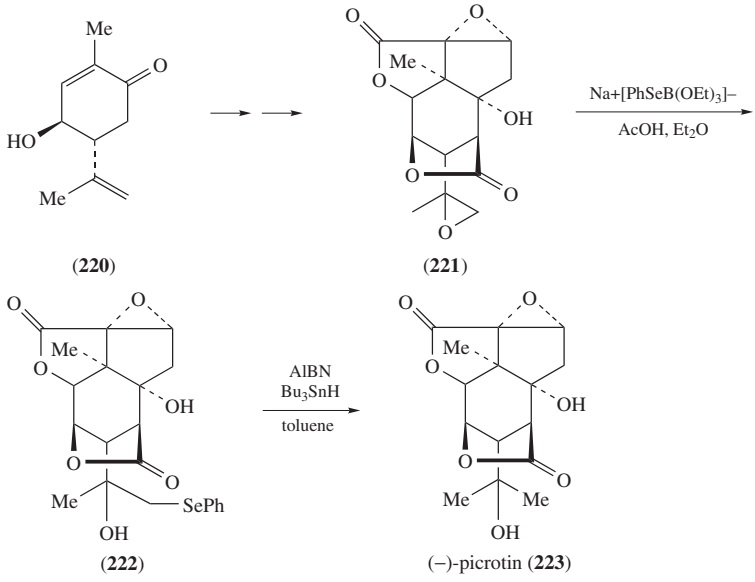


SCHEME 52

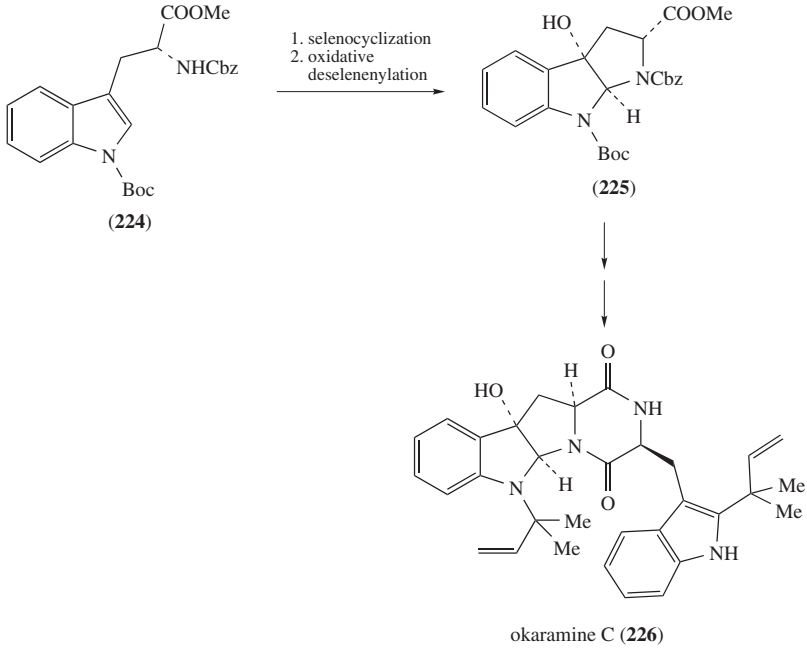
VIII. APPLICATION OF ORGANOSELENIUM REAGENTS IN NATURAL PRODUCT SYNTHESIS

As outlined in the earlier sections of this chapter, organoselenium reagents can perform various asymmetric reactions such as stereoselective selenenylations, selenocyclizations, asymmetric catalysis, selenoxide eliminations and stereoselective 2,3-sigmatropic rearrangements etc. Some of these have been employed in the total synthesis of several naturally occurring compounds such as leucascandrolide A[118], phytuberin[119], salinosporamide A[120], chloptosin[121], solandelactone E[122] and diterpene-based natural products[123]. The diastereoselective reduction of epoxides and a subsequent deselenenylation have been used in the total synthesis of (−)-picrotin **223** using 5-β-hydroxycarvone **220** as precursor molecule via **221** and **222** (Scheme 53)[124].

Recently, Ley and coworkers have employed asymmetric selenocyclization-oxidative–deselenenylation sequence during the total synthesis of natural product (+)-okaramine C **226** from precursor **224** via **225** (Scheme 54)[125].



SCHEME 53



SCHEME 54

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Biological and biochemical aspects of tellurium derivatives

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0574

I. BACKGROUND AND PURPOSE

Unlike its chalcogen relatives sulfur and selenium, tellurium does not hold a biological niche. It is not an essential trace element like selenium. It is not an integral part of any natural protein or enzyme in prokaryotes or in eukaryotes. Tellurium ends up in biological systems due to its presence in the environment. Trace amounts of tellurium have been found in human blood and urine[1] and tellurium is the fourth most abundant trace element found in human blood[2]. Plants that accumulate selenium are also able to accumulate tellurium up to a concentration of about 1 ppm[3]. The amino acids *L*-tellurocysteine (*L*-**TeCys**) and *L*-telluromethionine (*L*-**TeMet**) have been found in bacteria[4, 5], yeast[6] and fungi[7] as a result of mis-incorporation of tellurium rather than sulfur or selenium (Chart 1).

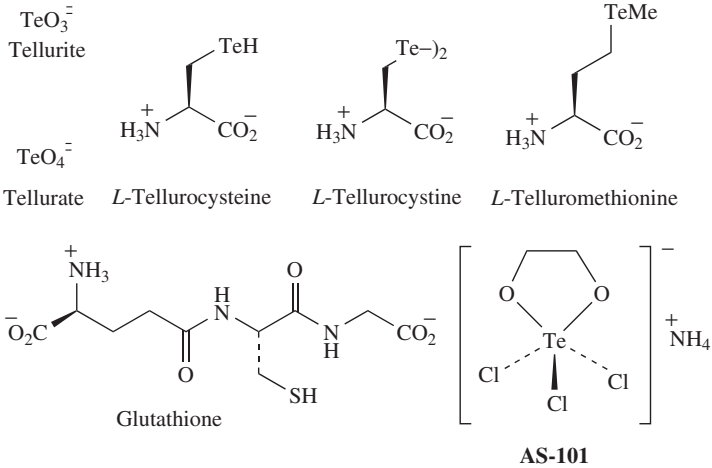


CHART 1

The biology and biochemistry of tellurium have been reviewed in two recent manuscripts[8, 9]. The most recent of these describes tellurium as a forgotten element and that the chemistry of tellurium compounds represents an emerging area even with respect to biology and biochemistry[8].

As this chapter describes, the biology and biochemistry of tellurium-containing compounds are often driven by tellurium replacing sulfur or selenium in a biologically relevant molecule or by interactions of tellurium-containing compounds with the thiol groups of cysteine or homocysteine residues. The biological and biochemical effects of low-molecular-weight organotellurium compounds interacting with biopolymers (proteins, RNA, DNA) have been actively investigated in three major areas: (1) as mimics and inhibitors of enzymatic systems that utilize peroxides and other oxidizing oxygen species, (2) as stimulators and inhibitors of the ATP binding cassette (ABC) transporters, and (3) as photosensitizers for the photodynamic therapy of cancer and/or the photodynamic inactivation of viruses and bacteria. Both inorganic and organic compounds of tellurium have been evaluated as anti-microbial compounds in the dark, as well.

There is considerable overlap of desirable physical and photophysical properties of tellurium and tellurium compounds with respect to the various uses of individual tellurium compounds. The biochemically and biologically interesting compounds take advantage of the ease of oxidation of the tellurium atom, the accelerated intersystem crossing of singlet excited states to the triplet state in tellurium-containing chromophores, and the reduced ability of the tellurium atom to accept hydrogen bonds[9–11].

II. BIOLOGICAL AND BIOCHEMICAL STUDIES OF INORGANIC TELLURIUM COMPOUNDS

A. Biosequestration and Bioincorporation of Tellurium

Certain organisms have the ability to accumulate or concentrate tellurium in their cells/tissues, which makes these organisms viable candidates for remediation of soil/water that is contaminated with unacceptable levels of tellurium[11–13]. The tellurium can be removed from soil/water by biosequestration, bioreduction and/or biomethylation. The preferred method of uptake is through the roots and sequestered tellurium does not involve biochemical reduction. In other organisms, tellurite/tellurate can be reduced to tellurium metal, which is less toxic than the oxidized forms. The crystalline metal is precipitated within the cell. Subsequent methylation converts tellurite/tellurate to dimethyltelluride, which is volatile and thus removed from soil/water. Methylation reactions are likely to occur at the H_2Te/Te^{2-} oxidation state following reduction of tellurite/tellurate.

1. Bioreduction of telluium compounds

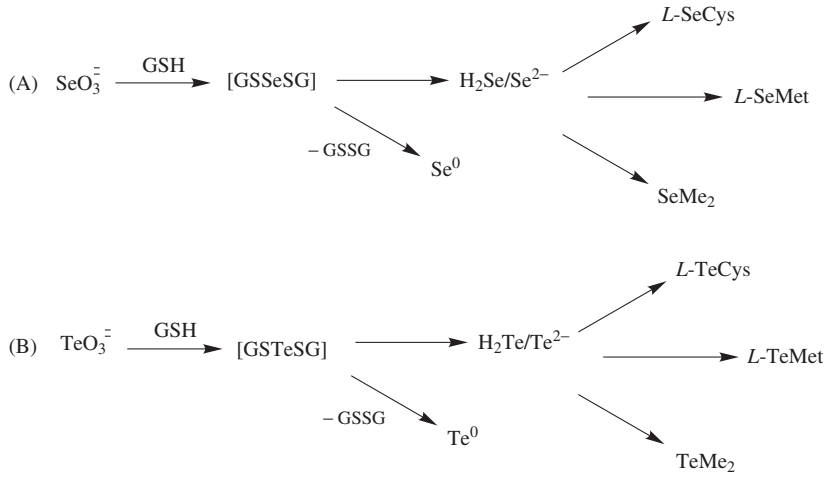
The bacterial reduction of tellurite/tellurate to tellurium metal has been used to prepare nanoparticles of tellurium of very uniform size. The bacteria *Bacillus selenitireducens, Sulfurospirillum barnesii* and *Bacillus beveridgei* sp. nov., which are all isolated from deep-ocean, hydrothermal vents[14–16], utilize tellurite and tellurate (Chart 1) as electron acceptors to produce nanoparticles of metallic tellurium. *Bacillus selenitireducens* produces 10-nm × 200-nm nanorods while *Sulfurospirillum barnesii* produces irregular nanospheres less than 50 nm in diameter[14].

In the absence of a source of sulfur, selenium as well as tellurium can be incorporated as part of the biochemistry of certain organisms. In fungi grown in the presence of sodium tellurite, tellurium is metabolized to give the amino acids *L*-tellurocysteine, *L*-tellurocystine and *L*-telluromethionine as well as some tellurium-containing proteins[17]. The protein analogues containing the heavy metal tellurium are suitable for X-ray diffraction studies that

can give higher resolution than the natural proteins without the heavy atom[18] and several derivatives with telluromethionine have been examined[4, 5].

2. Reduction of higher oxidation states of tellurium

The chemistry of higher oxidation states of tellurium is similar but not identical to the chemistry of corresponding sulfur and selenium compounds. The higher oxidation states of tellurium (+4 and +6 oxidation states) are more stable than corresponding sulfur and selenium oxidation states. Tellurite is not as easily oxidized to tellurate (+0.07 V) as sulfite is to sulfate (−0.94 V) in alkaline solution[8]. The metabolic reduction of tellurite is thought to be similar to the metabolic reduction of selenite as illustrated in Scheme 1[8]. The tripeptide glutathione (**GSH**, Chart 1) functions as a biological reducing agent to give **GSSeSG** as an intermediate as shown in path A of Scheme 1. Reductive elimination of glutathione disulfide (**GSSG**) produces selenium metal (Se^0) while further reduction of **GSSeSG** produces H_2Se/Se^{2-}. Methylation of H_2Se/Se^{2-} produces volatile dimethylselenide (Me_2Se) while biochemical utilization of H_2Se/Se^{2-} leads to the production of selenocysteine (*L*-**SeCys**) and selenomethionine (*L*-**SeMet**). It is plausible that tellurite is reduced in a similar manner producing **GSTeSG** as an intermediate as shown in path B of Scheme 1. As noted in the paragraphs below, the interaction of the tellurium atom in various oxidation states with thiol groups as ligands appears to drive much of the biochemistry associated with tellurium-containing compounds.



SCHEME 1 Possible routes for the biological reduction of (A) selenite and (B) tellurite

B. Toxicity of Inorganic Tellurium Compounds

Tellurium has a 'toxic' reputation perhaps due to the unpleasant garlic odor associated with individuals exposed to tellurium compounds. The garlic odor is from the formation of dimethyltelluride. While tellurium compounds were thought to be less toxic than selenium compounds, more recent studies suggest that some tellurium compounds may be more toxic than their selenium counterparts[19]. In the bacterium *Pseudomonas fluorescens*, elemental tellurium is less toxic than tellurate, which is about 10-fold less

toxic than tellurite[20, 21]. While it is dependent upon the specific structure, organotellurium compounds, in general, are less toxic than inorganic tellurium compounds[22]. Certain bacteria and fungi are capable of reducing tellurite to produce tellurium metal and dimethyltelluride, which is volatile and excreted through breath, perspiration and urine[17]. The precise mechanism of tellurium toxicity in bacteria is not known, but the toxicity of tellurite may be due to its strong oxidizing properties and the production of reactive oxygen species[23]. The production of reactive oxygen species from **GSSeSG** has been demonstrated[24] and similar species would be expected from **GSTeSG**.

C. Inorganic Complexes AS-101 and SAS

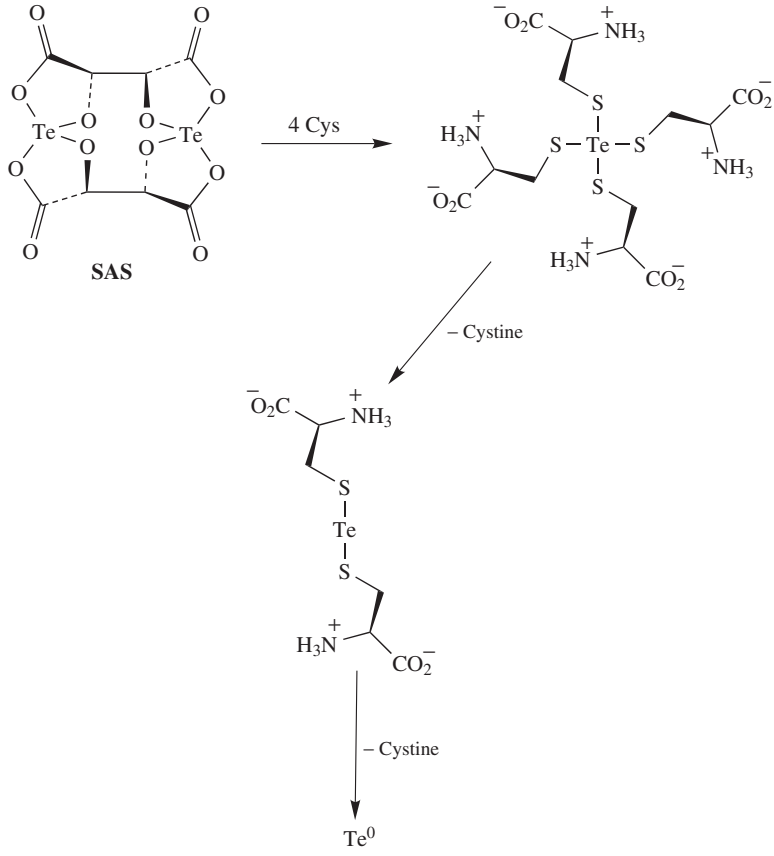
The toxicity of tellurium has been harnessed in two different ways. Inorganic tellurium complexes have been used as anti-microbial agents in one application and as media supplements to select for tellurium-resistant bacteria in another. Tellurite has been used as an anti-bacterial agent since the 1930s[25] and has even been used to treat syphilis and leprosy[26]. The inorganic tellurium complex **AS-101** (Chart 1) was shown to be an anti-microbial agent in both lag and log phases for the treatment of extended spectrum β-lactamase (ESBL)-producing strains of *Klebsiella pneumoniae*[27]. Complex **AS-101** was tested against eleven strains and the average minimum inhibitory concentration to give 50% reduction in bacterial growth (MIC_{50}) was $9-18\,\mu g\,ml^{-1}$.

Inorganic tellurium complexes have also been evaluated in several other applications. Tellurite was proposed as an anti-sickling agent in the treatment of sickle cell anemia[28]. The inorganic complex **AS-101** (Chart 1) was proposed as an immune-modulating drug for the treatment of AIDS[29]. **AS-101** has been examined in several other applications including inhibition of caspase-1[30], protection against homocysteine-promoted apoptosis[31], enhancement of neuron survival in an animal stroke model[32] and protection and restoration of dopaminergic neurons in an animal model for Parkinson's disease[33]. The interaction of the Te(IV) of **AS-101** with the thiol groups of cysteine and homocysteine amino acid residues is thought to be responsible for the activity of **AS-101**[34].

The tartarate complex **SAS** is similar to **AS-101** in that an inorganic tellurium(IV) center is at the core of the molecule[35]. As shown in Scheme 2, **SAS** reacts with the amino acid cysteine to give a sulfur-coordinated tellurium(IV). Sequential reductive elimination of a total of two cystine reduces tellurium(IV) to tellurium metal. **SAS** displayed time- and concentration-dependent inhibition of the cysteine proteases papain and cathepsin B. The kinetic parameters for the inhibition process were: $K_i = 2.5\,\mu M$, $k_i = 5.7 \times 10^{-4}\,s^{-1}$ and $k_i/K_i = 225\,l\,mol^{-1}\,s^{-1}$ for papain inactivation and $K_i = 0.13\,\mu M$, $k_i = 7.8 \times 10^{-4}\,s^{-1}$ and $k_i/K_i = 5900\,l\,mol^{-1}\,s^{-1}$ for cathepsin B inactivation. The stronger interaction of **SAS** for cathepsin B appears to be a consequence of the binding affinity of **SAS** for the enzyme rather than differences in k_i, which are very similar for the two enzymes. Compounds like **SAS** and **AS-101** most likely inactivate cysteine proteases through oxidation of catalytic cysteines at the active site. In contrast, **SAS** does not inhibit serine, metallo and aspartic proteases where interaction is non-specific[34].

D. Tellurite-resistant Bacteria

Tellurite can also be used as an additive for growth media to select for bacteria that are resistant to tellurite[36–43]. This technique has been recently reviewed[44]. Perhaps the most 'famous' of the tellurite-resistant bacteria to be isolated by this technique is the pathogenic *E. coli* O157:H7—the 'hamburger disease' bacterium[45, 46]. This strain is highly tolerant to tellurite and other metalloids and reduces telluride to the metal giving colonies of the bacterium a black appearance. Tellurite selection[47] was also used to select the Shiga-toxin



SCHEME 2 Interactions of **SAS** with cysteine residues to give sequential two-electron reductions of tellurium(IV) to tellurium metal and oxidation of cysteine residues to cystine residues

producing bacterium *E. coli* (STEC) 026[48]. Tellurite resistance is not a necessary condition for production of the Shiga toxin as shown by a study comparing *E. coli* O46 and O15:H7 strains[49].

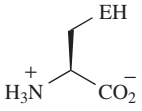
E. Tellurite Inhibition of Squalene Monooxygenase

Demyelination of peripheral nerves has been observed in rats and mice that have ingested tellurite due to inhibition of squalene monooxygenase. This enzyme converts squalene to squalene-2,3-epoxide as part of the biosynthesis of cholesterol, which is a significant component of myelin[50, 51]. Squalene monooxygenase contains two cysteine residues at the active site and the thiol groups of these two residues interact with tellurite[52, 53]. These Cys-490 and Cys-557 residues reside in a hydrophobic pocket[53] and interact more strongly with organotelluride compounds than with tellurite[54].

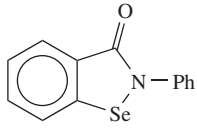
III. TELLURIUM AND GLUTATHIONE PEROXIDASES AND THIOREDOXIN REDUCTASES

The development of medically relevant antioxidants to combat oxidative stress has been an active area of research with inorganic chalcogen compounds and organochalcogen compounds, especially with compounds that act to catalyze the reduction of oxidizing species. Increasing intracellular concentrations of oxidizing species contributes to the pathology of various diseases via the oxidation of membranes, proteins and DNA[55]. Oxidative damage may ultimately lead to cell death.

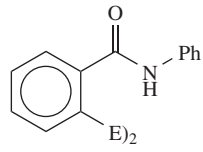
In mammals, the glutathione peroxidases (**Gpx**s)[56–60] and thioredoxin reductases (**TrxR**s)[61, 62], which act in combination with the small-protein thioredoxins (**Trx**s), are among the key enzymes for destroying oxidizing species and for reducing certain products of oxidative damage. The activity of the **Gpx** enzymes is dependent upon the selenium-containing amino acid *L*-selenocysteine (*L*-**SeCys**, Chart 2), which is oxidized and reduced in catalytic cycles. Glutathione (**GSH**, Chart 1) is used as the reducing substrate with the **Gpx** enzymes and the cartoon of Figure 1A illustrates the mechanism of action[63]. A peroxide produced by an undesired oxidation oxidizes the selenol of **Gpx** to the selenenic acid, which then reacts with **GSH** to produce water and the selenosulfide. The selenosulfide intermediate in the enzymatic process then reacts with a second molecule of glutathione to produce **GSSG**[64].



L-cysteine (***L*-Cys**), E = S
L-selenocysteine (***L*-SeCys**), E = Se
L-tellurocysteine (***L*-TeCys**), E = Te



Ebselen



(**EbSe-**)$_2$, E = Se
(**EbTe-**)$_2$, E = Te

CHART 2

The flavoprotein **TrxR**s also contain *L*-selenocysteine and are responsible for the reversible-dependent reduction of cysteine residues in **Trx**[61, 62]. There are two mammalian **Trx**s, each with the conserved redox catalytic sequence Trp–Cys–Gly–Pro–Cys[65–68]. Human **Trx-1** is found in the cytoplasm and nucleus of cells[65, 66] while **Trx-2** is found in the mitochondria[67, 68], where it protects against oxidative damage[69].

A. Tellurocysteine-containing Protein Gpx Mimics

The recent literature has provided an excellent example for comparing the role of tellurocysteine and selenocysteine at a catalytic center of a **Gpx** mimic[70]. Significant structural similarity was found between the **GSH**-binding-domain folds in glutathione *S*-transferase (**GST**) and **Gpx** as well as a similar orientation of the catalytic site in both proteins[71]. A serine residue (Ser-9) was replaced with *L*-**SeCys** in **GST** from *Lucilia cuprina* to give **SeGST**, which was a **Gpx** mimic with high activity with **GSH** as the reducing agent[72, 73]. In contrast, wild-type **GST** showed no **Gpx**-like activity[70]. Values for **Gpx**-like activity and kinetic parameters associated with **GSH** and peroxide are compiled in Table 1.

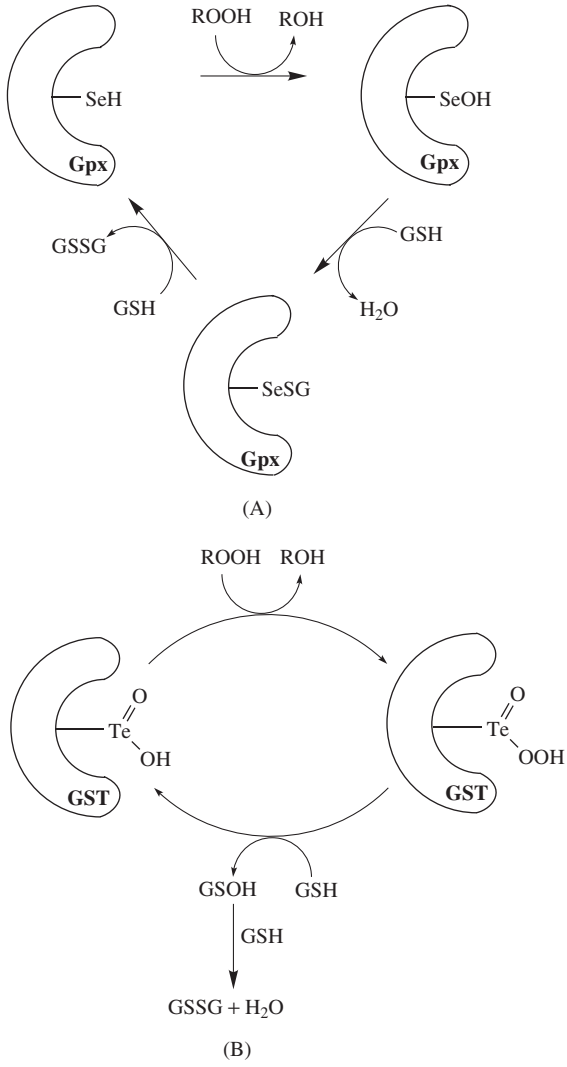


FIGURE 1 General mechanism (A) at the *L*-selenocysteine residue for glutathione peroxidase reduction of a peroxide in the presence of glutathione (**GSH**) and (B) at the oxidized *L*-tellurocysteine residue of telluroglutathione *S*-transferase or tellurosubtilisin

L-Tellurocysteine was introduced to **GST** using methods similar to those used for the introduction of *L*-**SeCys**[70]. *L*-Tellurocysteine is more readily oxidized than *L*-**SeCys** (-0.85 V and -0.64 V vs. Ag/AgCl, respectively)[70], which should facilitate biological redox processes. As shown in Table 1, the **Gpx**-like activity of **TeGST** was greater than that of **SeGST** and was comparable to native **Gpx** (rabbit liver)[74, 75] in activity. The dissociation constants for **GSH** from either **GST** or **TeGST** were identical (*ca* 100 μM),

TABLE 1. **Gpx** activity and reduction of hydrogen peroxide in the presence of **GST**, **Gpx**, **SeGST** and **TeGST** as enzymatic catalysts and comparison to ebselen (**Eb**), ditelluride **8-Te** and diselenide **9-Se**

Enzyme	**Gpx** Activity (U mol^{-1})	Reference	k_{max}/K_{GSH} ($l\ mol^{-1}\ s^{-1}$)	$k_{max}/K H_2O_2$ ($l\ mol^{-1}\ s^{-1}$)	Reference
GST	0	70	–	–	–
native **Gpx**	5780	74	9.33×10^5	9.63×10^6	75
SeGST	2960	73	1.60×10^5	1.63×10^5	73
TeGST	3870	70	2.43×10^5	1.29×10^6	70
Eb	0.99	101	–	–	–
8-Te	–	–	1.05×10^3	1.33×10^3	96
9-Se	–	–	6.45×10^0	2.55×10^2	95

which suggests that substitution of *L*-**TeCys** for serine did not change the binding of **GSH** at the active site and that the increased **Gpx**-like activity is due to the new tellurium center from the *L*-**TeCys**[70].

Subtilisin is also a serine-containing enzyme that has been modified to introduce cysteine[76, 77], selenocysteine[78] and tellurocysteine[79] via nucleophile displacement at the carbon of the serine hydroxymethyl group. The resulting Se-subtilisin and Te-subtilisin also display thiolperoxidase activity, but arylthiols are better substrates than **GSH** due to the hydrophobic pocket where the Ser-221 is located. The thiolperoxidase activity of Te-subtilisin is greatly reduced relative to either native **Gpx** or **TeGST**. However, both Te-subtilisin and **TeGST** share one structural characteristic: the tellurium atom appears to be in the tellurinic acid ($RTeO_2H$) oxidation state and not in the tellurol (RTeH) oxidation state. How then do **TeGST** and Te-subtilisin show thiolperoxidase-like activity?

If the tellurol functionality were important mechanistically, then the pathway shown in Figure 1A could be operative with 'Te' replacing 'Se' as the critical atom at the catalytic site. However, in analogy with well-established catalytic chemistry of seleninic acids with peroxides[80–83], the tellurinic acid residue could also act as the catalytic center as shown in Figure 1B. The formation of a pertellurinic acid intermediate would be followed by reaction of **GSH** with the pertellurinic acid to regenerate the tellurinic acid catalyst and the thienyl oxidation state in **GSOH**. Evidence for the formation of **GSOH**-like intermediates has been provided by stopped-flow spectroscopy[84].

B. Low-molecular-weight Organotellurium Mimics of Gpx and TrxR

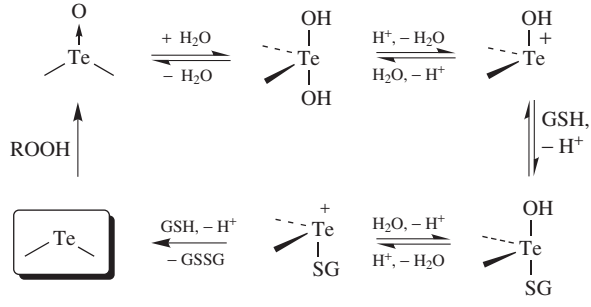
Many low-molecular-weight (<500 Daltons) organoselenium and organotellurium compounds have been evaluated as mimics of **Gpx** and this area through the year 2000 has been reviewed[64]. Ideally, these low-molecular-weight molecules would intercept the peroxy species formed by unwanted oxidation and reduce the peroxy functionality to hydroxyl functionality before events leading to cellular death occurred. Mechanistically, the organoselenides/selenols/diselenides and diorgano ditellurides are similar to **Gpx** in that an RSeOH, $RSeO_3H$ or $RTeO_3H$ intermediate is formed upon reaction with the peroxide, and these intermediates then react with a thiol to complete the catalytic cycle. While these molecules may be efficient scavengers of peroxides as model systems in solution, they lack binding sites for **GSH** as found in the **Gpx**s. Consequently, when **GSH** is the biologically available reducing agent, most of the organselenium and organotellurium **Gpx**-mimics are poor antioxidants.

1. Ebselen-related compounds

One exception is the organoselenium compound Ebselen (**Eb**, Chart 2), which has been evaluated clinically for the treatment of stroke (cerebral ischaemia)[85]. The ability of **Eb** and the related compounds ebselen diselenide (**EbSe**$_2$) and ebselen ditelluride (**EbTe**$_2$, Chart 2) to act as catalysts for the reduction of oxidized species in biological systems has been evaluated[86]. While **Eb** and **EbTe**$_2$ were similar in their ability to inhibit horseradish peroxidase activity by scavenging the oxidant, **Eb** showed much greater **Gpx** activity than **EbTe**$_2$ and **Eb** showed much greater inhibition of γ-radiation-induced lipid peroxidation than either **EbTe**$_2$ or **EbSe**$_2$. While the mechanism of action of each of these compounds is not known, oxidation of the chalcogen atom is thought to be involved.

2. Diorganotellurides

Diorganotellurides have also been evaluated as **Gpx** mimics and early solution studies were with model systems and were not with biological targets. Engman and coworkers were the first to examine the thiolperoxidase-like activity of diorganotellurides[87–89] while Detty and coworkers were the first to examine the mechanism of action with **GSH** by spectroscopic means[90]. The mechanism of **Gpx**-like activity with diorganotellurides is summarized in Scheme 3. The first step is oxidation of the organotelluride to the telluroxide. Unlike corresponding sulfoxide and selenoxide compounds, telluroxides prefer to add water to give the dihydroxytelluranes [$R_2Te(OH)_2$]. The dihydroxytellurane exchanges ligands through telluronium intermediates to give a series of **GSH**-containing intermediates. The key step is the reductive elimination of **GSSG** from the telluronium center. Again, a direct interaction of a sulfur ligand with the tellurium atom is involved. Evidence in support of the thiotelluronium intermediate of Scheme 3 came from stopped-flow studies examining the effects of thiol concentrations on rates of reductive elimination to give disulfides[84].



SCHEME 3 Mechanism for the **Gpx**-like behavior of diorganotellurides

The dihydroxytellurane intermediates are viable intermediates for *in vitro* and *in vivo* studies. The telluropyrylium dye **1** (Chart 3) has been used as a photosensitizer in photodynamic therapy and dihydroxytellurane **2** (Chart 3) has been observed in cells with a lifetime sufficiently long for other biochemical studies[91,92]. The diaryltellurides **3**–**5** (Chart 3) have shown **Gpx**-like activity in cultured lung fibroblasts inhibiting *tert*-butyl hydroperoxide-induced cell death by $\geq$ 50% at concentrations less than 2 μM[93]. Oxidation of the telluride to the dihydroxytellurane is a likely mechanistic path for the biological activity of these compounds. Compound **6** (Chart 3) mimicked the ability of **Eb** to limit

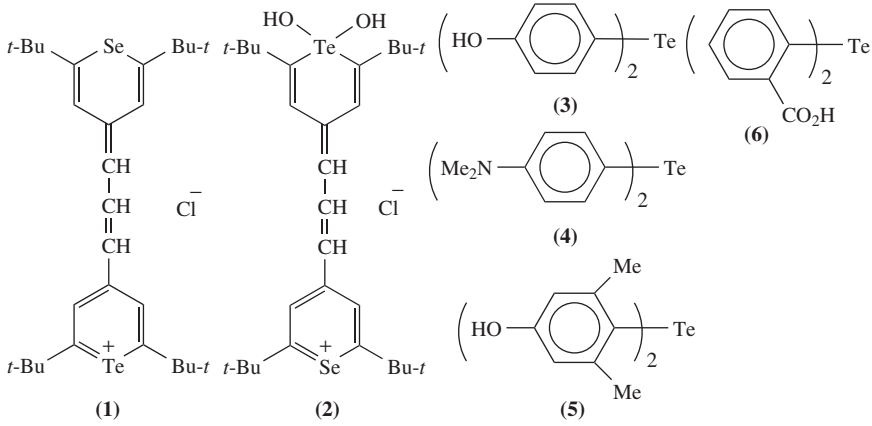


CHART 3

the effects of stroke-induced ischaemia. It reduced ischaemia/reperfusion-induced vascular permeability at concentrations $\leq 0.1\,\mu M$ in a hamster cheek-pouch model[93]. Compound **6** also protected Caco-2 cells against leukocyte-mediated damage at concentrations of $0.1\,\mu M$[93].

3. Polymeric/immobilized diorganotellurides

Several interesting organotellurium systems have been developed in recent years that have used the **Gpx**-like activity of the organotelluride. An acrylate polymer based on the tellurium-containing diacrylate monomer **7** (Chart 4) has **Gpx**-like activity that varies with the polymer molecular weight[94]. The porosity of the system is thought to control the rate of approach of reagents to the catalytic tellurium centers.

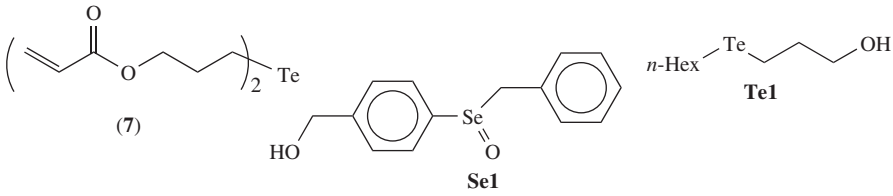
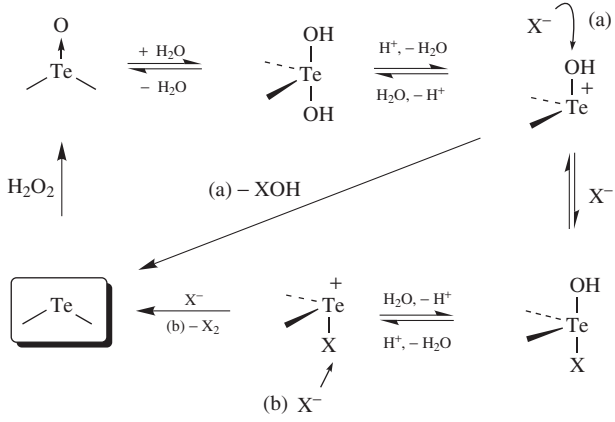


CHART 4

The **Gpx**-like activity of organotellurides has also been used to minimize the settlement of fouling organisms on surfaces exposed to a marine environment[95]. The organotellurides are attached covalently to a xerogel matrix coated as a thin film onto glass, fiberglass, aluminum or wood surfaces.

As shown in Scheme 4, $R_2Te(OH)_2$ intermediates can exchange halide ligands through telluronium intermediates to form hypohalous acids [path (a) of Scheme 4] or elemental halogen [path (b) of Scheme 4] via reductive elimination induced by nucleophilic attack of halide ion[96, 97]. The positive halogen species (halogen/hypohalous acid) are biocidal in a marine environment[98]. Organotelluride catalysts have been used for the oxidation



SCHEME 4 Mechanism for haloperoxidase-like behavior of diorganotellurides in the presence of hydrogen peroxide and halide ions

of chloride[96], bromide[96] and iodide[97] with hydrogen peroxide. This behavior mimics the activity of the haloperoxidase enzymes[96, 97].

Seawater contains hydrogen peroxide from decomposition of organic matter and, in coastal areas, from rainwater and runoffs[99–102]. Concentrations vary from 0.2 to 50 μM near the surface of these waters. Some bacterial biofilms also produce hydrogen peroxide on submerged surfaces and concentrations near the biofilm-covered surface can be as high as 50 μM[103, 104]. Seawater contains 0.5 M chloride, 10^{-3} M bromide and 10^{-6} M iodide, and these reagents combined with ambient peroxide can produce an oxidizing surface that can actively or passively discourage settlement of fouling organisms.

Organotellurides and organoselenoxides have been covalently incorporated into xerogel films through hydroxyl functionality. The selenoxide **Se1** and the telluride **Te1** (Chart 4) were incorporated at 5 mol% into sols containing equimolar quantities of 3-aminopropyltriethoxysilane (APTES) and tetraethoxysilane (TEOS), which were then coated onto glass[95]. The resulting xerogel surfaces were immersed in artificial seawater (ASW)[95], ASW with 10^{-4} M added hydrogen peroxide (ASW + H_2O_2)[95] or natural seawater (NSW) collected from the Pacific coast near San Luis Obispo, California, USA[105]. Cypris larvae of the barnacle *Balanus amphitrite* were added to the surfaces and the number that settled after 48 h of immersion were counted. Results are shown in Figure 2. The data are normalized to a glass control in ASW. Xerogel surfaces included a catalyst-free surface (Xerogel) and surfaces containing 5 mol% **Se1** (**Se1** in Figure 2) or **Te1** (**Te1** in Figure 2).

The data in Figure 2 show that settlement on neither the glass control nor the catalyst-free xerogel was impacted by the presence or absence of hydrogen peroxide[95, 105]. The **Se1** coating gave reduced settlement relative to the glass and xerogel controls in all three aqueous environments. The **Te1**-containing xerogel was comparable to glass and xerogel controls in ASW, but gave significantly ($p < 0.05$) reduced settlement of cyprids in ASW + H_2O_2 and NSW, which presumably contained some peroxide. Settlement of larvae of the tubeworm *Hydroides elegans* and settlement of sporelings of the macrofouling alga *Ulva linza* were significantly ($p < 0.05$) reduced on the **Te1**-containing xerogel in the presence of 5 and 100 μM peroxide, respectively, relative to glass controls with and without added peroxide[95].

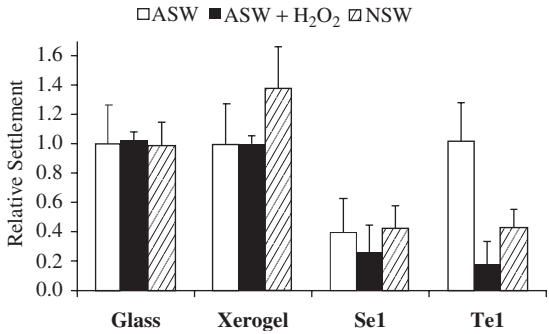


FIGURE 2 Relative settlement of barnacle cyprids (*Balanus Amphitrite*) on a glass control and on a xerogel prepared from a sol of 1:1 3-aminopropyltriethoxysilane/tetraethoxysilane (molar ratio) as a blank (Xerogel) or containing 5 mol% **Se1** (**Se1**) or **Te1** (**Te1**). Surfaces were immersed in artificial seawater (ASW, white bars), ASW with 1×10^{-4} M hydrogen peroxide (ASW + H_2O_2, black bars) and natural seawater (NSW, striped bars), and *ca* 50 barnacle cyprids were added and settlement was determined after 48 h. Settlement on the glass control in ASW was assigned a relative settlement of 1.0. Error bars represent the standard error from the mean

Leachates from the various surfaces were not detrimental to brine shrimp larvae, which was consistent with no appreciable concentrations of toxic chemicals leaving the coatings[95]. Consequently, the catalyst-containing surfaces must present a hostile environment for the settlement cues of barnacle cyprids, tubeworm larvae and algal zoospores.

4. Cyclodextrin-derived tellurides and ditellurides

Several cyclodextrin-derived ditelluride **8-Te**, diselenide **9-Se**, ditelluride **9-Te**, biscyclodextrin-derived telluride **10-Te**, selenide **11-Se** and tellurides **12-Te**–**15-Te** (Chart 5) have been explored as **Gpx**-mimics by the groups of Luo[106–110] and Engman[111]. The ability of these molecules to reduce hydrogen peroxide, *tert*-butyl hydroperoxide and

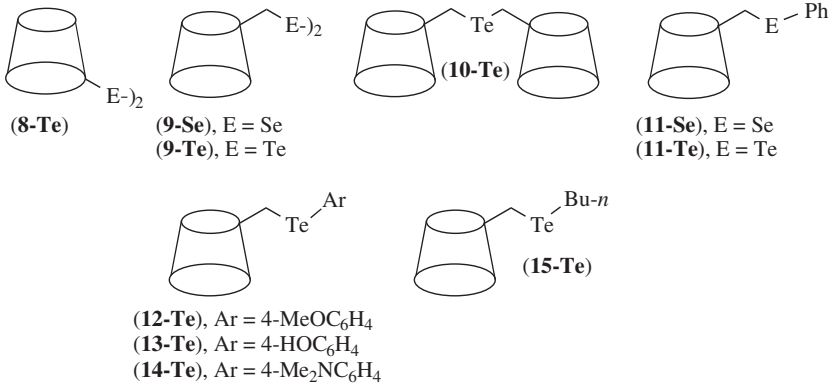


CHART 5

TABLE 2. Relative hydroperoxide decomposing capacity of cyclodextrin-derived organochalcogen compounds[a]

	Relative Activity			
Catalyst	H_2O_2	*t*-BuOOH	CuOOH	Reference
8-Te	1[a]	2	10	99
9-Te	1[a]	7.5	31	99
10-Te	1[a]	251	543	99
	2.9[b]	43	55	100
11-Se	1[b]	1.2	1	100
11-Te	1[a]	3	18	99
	1.7[b]	5.6	21	100
15-Te	5.2[b]	37	64	100

[a]Relative to hydrogen peroxide decomposition having a relative rate of 1 for each compound.
[b]Relative to hydrogen peroxide decomposition equal to 1 for the phenylseleno derivative **11-Se**.

cumene hydroperoxide (CuOOH) is summarized in Table 2. Organotellurium derivatives are more active than organoselenium derivatives (comparing **11-Se** and **11-Te**). The cyclodextrin-derived organotellurium derivatives show a preference for reducing the more hydrophobic oxidizing agents *tert*-BuOOH and CuOOH suggesting that the cyclodextrin acts as a hydrophobic pocket to interact with the oxidant. The alkyltelluro derivative **15-Te** displays greater catalytic activity than aryltelluro derivatives **11-Te**–**14-Te** and, within the aryltelluro derivatives, electron-donating substituents that increase electron density at tellurium (compounds **12-Te**–**14-Te**) give increased catalytic activity relative to the phenyl substituent (compound **11-Te**)[111].

As points of reference, native **Gpx**, **SeGST** and **TeGST** are 3000 to 5000 times more active than **Eb** with respect to **Gpx** activity[112] and are 100 to 10,000 times more active than cyclodextrin ditelluride **8-Te** (Table 1)[70]. The small molecule derivatives do not have a distinct **GSH** binding site, which may impact their reactivity.

The thioredoxin reductase **Trx-1** is a target for drug development for the treatment of cancer. The enzyme is overexpressed in several human primary cancers including gastric cancer, colon cancer, pancreatic cancer, liver cancer and prostate cancer[65, 113–116]. In immunodeficient mice, transfection of cancer cells with a redox inactive mutant **Trx-1** does not transform cells but instead inhibits cell growth, potentiates apoptosis and blocks tumor formation[117]. A highly significant correlation has been found for increased **Trx-1** expression and decreased apoptosis[65] and decreased patient survival has also been correlated with increased **Trx-1** expression[118].

C. Thioredoxin Reductase Inhibitors

Organotellurium compounds have been shown to be inhibitors of the **TrxR/Trx** redox couple both in the isolated enzyme and in cancer cells that overexpress the thioredoxin reductase[111, 119, 120]. Selected data are summarized in Table 3 for the compounds shown in Chart 6 and show that the best organotellurium compounds examined to date are effective in the low micromolar range. The benzdihydrotellurophene **16-Te** was effective against both the isolated **TrxR/Trx** enzyme pair (IC_{50}5.8 μM) and MCF-7 human breast cancer cells (IC_{50}1.8 μM)[119].

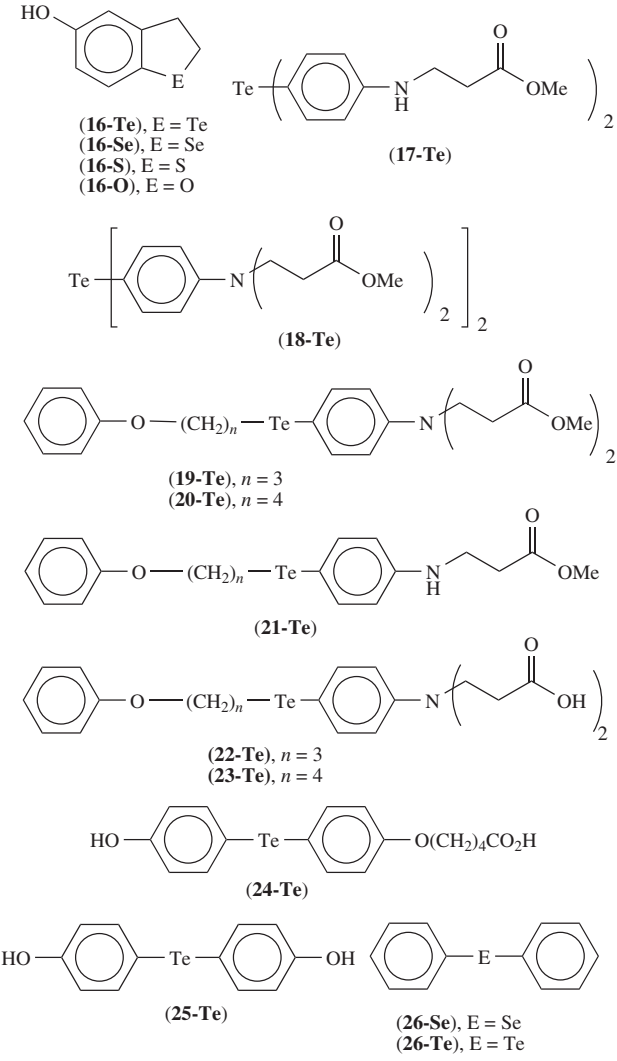


CHART 6

IV. TELLURIUM AND CYSTEINE PROTEASES AND RELATED ENZYMES

Like **AS-101** and **SAS**, low-molecular-weight organotellurium compounds have also shown the ability to inhibit cysteine proteases, especially cathepsin B[121–124]. The aryl ditellurides **27** and **28** (Chart 7) were able to induce apoptosis in human HL-60 cells (promyelocytic leukemia cells) in both a time- and dose-dependent manner.[121] It was speculated that reduction of the ditelluride might involve the generation of reactive oxygen species such as superoxide via electron transfer to give damage to DNA.

TABLE 3. Thioredoxin reductase and MCF-7 breast cancer cell growth inhibiting capacity of organochalcogenide compounds

Compound	IC_{50} (μM)[a]		Reference
	TrxR/Trx	MCF-7	
10-Te	0.5	1.4	100
16-Te	5.8	1.8	108
16-E	>50	–	108
E = O, S, Se			
17-Te	1.6	>50	108
18-Te	2.4	>50	108
19-Te	1.0	41	108
20-Te	2.0	>50	108
21-Te	2.0	>50	108
22-Te	1.0	41	108
23-Te	1.0	>50	108
24-Te	21	–	100
25-Te	4.0	1.6	100
26-Se	18	10	100
26-Te	7.6	10	100

[a]Concentration to give 50% reduction of enzyme activity or cell growth.

The pertelluranes **RT-03**, **RT-04** and **29-Te**–**35-Te** (Chart 7) also displayed the ability to inhibit cathepsin B in both a time- and dose-dependent manner[122]. The second-order inactivation constants are compiled in Table 4 and these compounds were found to be more potent than **AS-101** and other inorganic tellurium compounds[124]. The inactivation involved the catalytic cysteine thiol of the enzyme and the enzymatic activity could be recovered by the addition of reducing agents such as dithiothreitol. These results are consistent with formation of tellurium(IV) intermediates with cysteine thiol ligands that perhaps undergo reductive elimination to form an inactivating disulfide bridge in the enzyme[125]. Addition of a reducing agent such as dithiothreitol would reduce the disulfide bridge and restore enzymatic activity. These compounds were also able to induce apoptosis in HL-60 cells (promyelocytic leukemia cells)[126].

More detailed work on the mechanism of action of these compounds came from studies of the antioxidant behavior of the pertelluranes and the interaction of these compounds with thiols in studies of the mitochondrial permeability transition[125]. Figure 3 shows disulfide bridge formation and oligomerization of the membrane proteins through formation of **RSTeSR** intermediates, which are quite similar to **GSTeSG** above (Section I). At concentrations of 15–30 μM, **RT-03** and **RT-04** depleted reduced mitochondrial thiol groups, which is again consistent with interaction of the cysteine thiol groups with tellurium(IV) and the number of disulfide bridges increased. This 'damage' to the membrane proteins led to opening of the mitochondrial permeability transition pore. The structural damage was prevented/reversed by the addition of reducing agents such as dithiothreitol, which would allow cleavage of disulfide bridges or prevent their formation. Consistent with the **Gpx**-like activity of organotellurium compounds, the pertelluranes **RT-03** and **RT-04** protected against oxidative stress and peroxidation of mitochondrial membranes at low-micromolar, high-nanomolar concentrations[125].

The caspaces also have key thiol residues in their active sites and, like **AS-101**[30], the pertelluranes inhibit the caspaces. The pertelluranes prevented the development of epilepsy, in which caspaces are thought to be involved, in a mouse model and the organic pertelluranes are more effective than **AS-101**[12, 127].

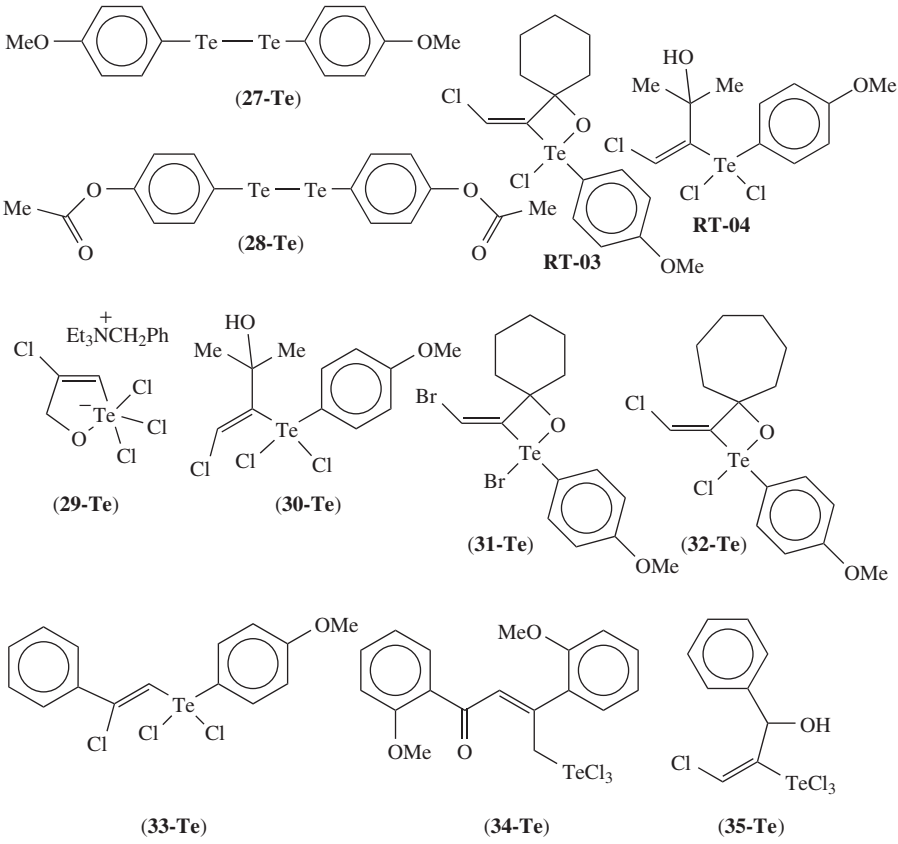


CHART 7

TABLE 4. Second-order inactivation constants for inhibition of capthesin B with pertellurane compounds **RT-03**, **RT-04** and **30-Te**–**35-Te**[a]

Compound	k_i (l mol^{-1} s^{-1})
RT-03	3.6×10^4
RT-04	1.1×10^4
29-Te	6.0×10^3
30-Te	7.9×10^3
31-Te	7.7×10^3
32-Te	1.6×10^4
33-Te	7.9×10^3
34-Te	1.5×10^4
35-Te	1.2×10^4

[a] Values of k_i are taken from Reference 111.

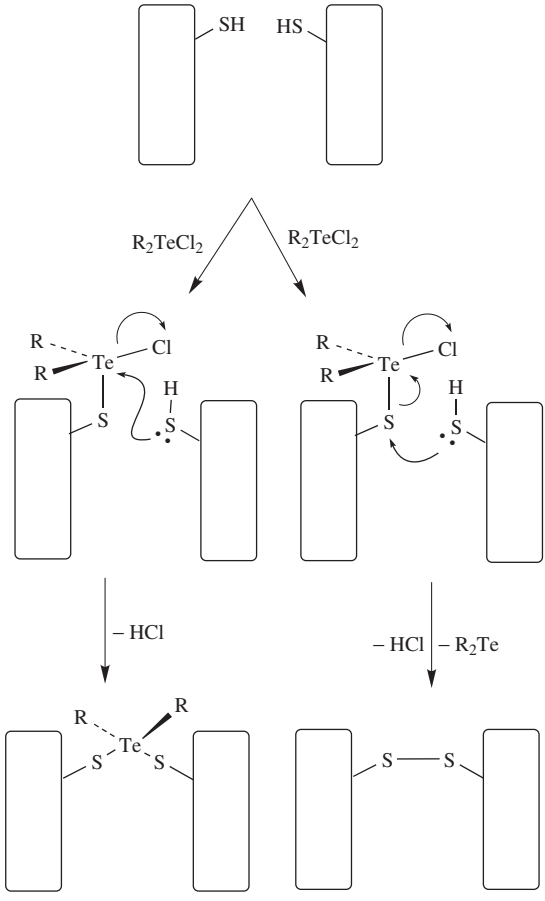


FIGURE 3 A mechanism for disulfide bridge formation and oligomerization of mitochondrial membrane proteins using protein thiol residues and organo pertelluranes

V. P-GLYCOPROTEIN INTERACTIONS WITH ORGANOTELLURIUM COMPOUNDS

A. Drug Resistance and Drug Transport with P-glycoprotein

Unfortunately, the treatment of cancer with chemotherapeutic agents (low-molecular-weight organic molecules) is often thwarted by the appearance of multidrug resistance (MDR) in the transformed cells. P-glycoprotein (**P-gp**, also known as MDR1 or ABCB1)[128–130] was the first efflux protein identified and associated with multidrug resistance in cancer chemotherapy. The drug efflux pumps are collectively members of the adenosine triphophate (ATP)-binding cassette (ABC) superfamily. Verapamil (**VER**) was the first small molecule identified as an inhibitor of **P-gp**[131] and subsequent work has sought to develop clinically useful MDR reversal agents[132–135]. However, the binding site of small molecules to **P-gp** is not easily defined because it is recognized

that both competitive and non-competitive interactions exist within the drug pocket[136, 137] as well as allosteric interactions from outside the drug pocket[138, 139]. Two well-defined, non-overlapping sites on **P-gp** are called the 'H' and 'R' sites for binding by Hoechst 33 342 and rhodamine 123, respectively[140, 141].

Rhodamine dyes have been used to assay **P-gp**-mediated transport. Efflux of rhodamine 123 from cells was used to define **P-gp** transport substrates/antagonists in a cross-correlation of drug-resistance patterns in the NCI 60 set of cells with the NCI Drug Screen Database of compounds[142, 143]. Tombline, Detty and coworkers examined a small library of chalcogenorhodamines and chalcogenorosamines to find that small structural changes impacted both the rate of transport of the dyes in drug-resistant cells, the affinity of the dyes for the protein and the ability of the chalcogenorhodamines/rosamines to stimulate or inhibit ATPase activity[144, 145]. Both chalcogenorhodamine/rosamine dyes[146] and chalcogenopyrylium dyes[147] were found to inhibit ATP hydrolysis and to inhibit the **P-gp** efflux pump. As described below, the nature of the chalcogen atom in the xanthylium or pyrylium core had its greatest impact on the transport of the dye through drug-resistant cells.

B. Protein Structure and Conformational Changes

P-gp consists of two nucleotide binding domains (**NBD**s) in the cytoplasm of the cell connected to two transmembrane domains (**TMD**s) buried in the cell membrane. Drug efflux is driven by conformational changes driven by ATP hydrolysis. A recent X-ray structure of **P-gp**[148] at 3.8 Å resolution shows inward-facing **TMD**s in the absence of nucleotide. A drug enters the internal drug-binding pocket through an open portal from the inner leaflet of the cell membrane and is bound to the **TMD**s in the inward-facing conformation. Upon binding and hydrolysis of ATP, the inward-facing conformer shifts to an outward-facing conformer[149, 150], with rotation of the **TMD**s to prevent sterically re-entry of the drug to the inner leaflet. The drug is directed back to the extracellular aqueous environment from the outward-facing conformation.

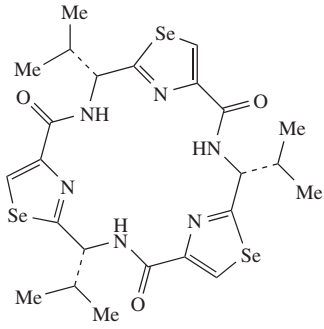
The acquisition of the structure of **P-gp** was aided by binding of two selenium-containing inhibitors of **P-gp**–**QZ59-RRR** and **QZ59-SSS** (Chart 8)—to crystals of the protein[148]. Other heavy-atom analogues of small molecule inhibitors of **P-gp** are being incorporated into **P-gp** in order to achieve a higher-resolution crystal structure. One such molecule is the tellurium analogue of rhodamine II (**TeRh II**, Chart 8), which has given excellent crystals of **P-gp** as shown in Figure 4[151].

In the cellular system, ATP is thought to hydrolyze sequentially in the **NBD**s to drive the conformational flexing between inward- and outward-facing forms. The ATP hydrolysis occurs at one **NBD** where adenosine diphosphate (ADP) and inorganic phosphate are released. This is known as the occluded state and drives the conformational change from inward-facing to outward-facing **P-gp** and the release of the drug back into the aqueous environment (Figure 5)[152, 153]. Tombline, Detty and coworkers found that chalcogenorhodamine/rosamine dyes have the ability to promote ATP occlusion, inhibit **VER**-dependent ATPase activity competitively and be transported in cells without significant rates of ATP hydrolysis[145].

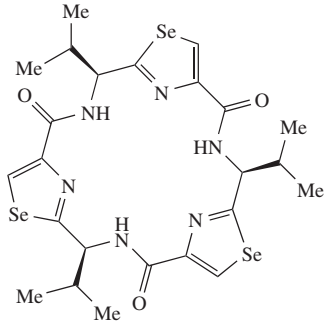
C. Tellurium-containing Inhibitors

1. Tellurorosamines and tellurorhodamines

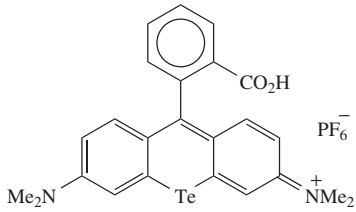
The chalcogenorosamine and rhodamine structures of Chart 9 represent a subset of the structures examined in the various studies with mouse Cys-less **P-gp** (mouse MDR3 CL, ABCB1) and human **P-gp**-His_{10}[144–146]. Table 5 summarizes values of V_{max} (maximal



QZ59-RRR



QZ59-SSS



TeRh II

CHART 8

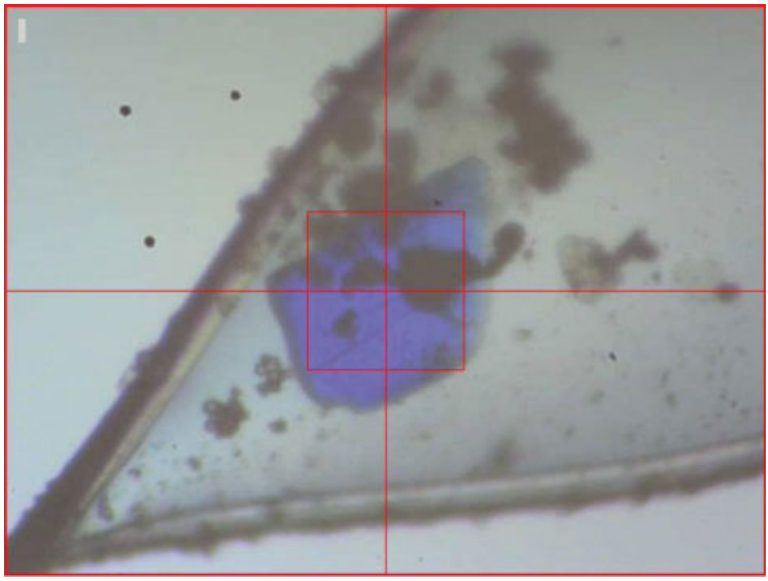


FIGURE 4 Mouse MDR3 CL **P-gp** co-crystallized with tellurorhodamine II (**TeRh II**). Image courtesy of Geoffrey Chang, The Scripps Research Institute

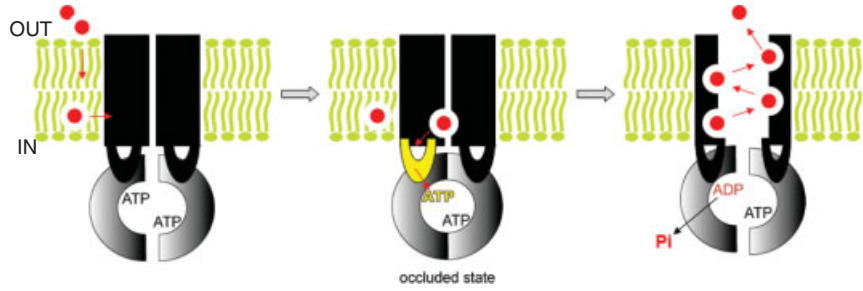
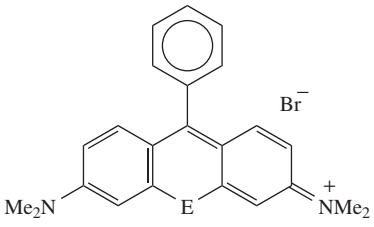


FIGURE 5 ATP hydrolysis from the occluded state where a 'drug' is in the binding pocket induces a conformational change from inward-facing to outward-facing transmembrane domains. The rotation of the transmembrane domains to the outward-facing conformation forcibly rehydrates the drug outside the cytoplasm. Figure courtesy of Gregory Tombline, University of Rochester Medical School

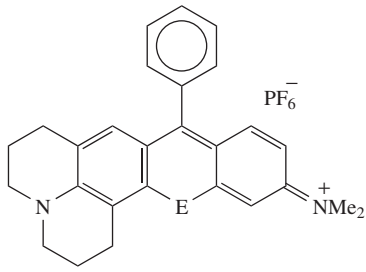
TABLE 5. Stimulation of mouse MDR3 Cys-less (CL) **P-gp** and human P-gp-His_{10} ATPase activity by the chalcogenorosamine and chalcogenorhodamine dyes of Chart 9 and chalcogenopyrylium dyes of Chart 10

	Mouse MDR3 CL			Human P-gp-His_{10}			
Compound	V_{max}[a] (fold)	K_M[b](μM)	IC_{50}[c](μM)	V_{max}[a] (fold)	K_M[b](μM)	IC_{50}[c](μM)	Reference
VER	11	10		18			146
TMR	3.7	77					146
TMR-S	3.5	98		7.7	8.5		146
TMR-Se	4.0	840		7.2	9.1		146
TMR-Te				8.4	8.3		146
36-S	1.0	210	15	2.2	1.3		146
36-Se	2.1	100	0.28	<1.5	ND[d]	2.3	146
36-Te				3.0	4.4		146
37-S	1.9	172		2.7	140		146
37-Se	<1.0	ND[d]	>120	2.8	89		146
37-Te				1.8	9.6		146
38-S	<1.0	ND[d]	4.6	9.0	0.36	7.9	146
38-Se				5.0	0.35	9.0	146
38-Te				7.1	0.41	5.3	146
39-S				3.1	0.087	0.67	146
41-S	3.5		0.88				147
42-S	2.2		5.3				147
43-S	<1.0		71				147
43-Te	1.0		1.2				147
44-Te	2.2		7.9				147

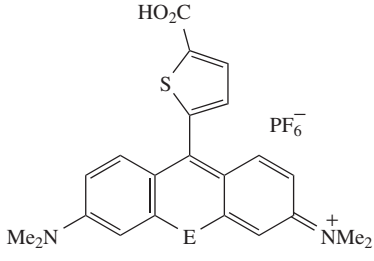
[a] V_{max} is the ratio of the maximum stimulation in the presence of compound relative to that in the absence of compound (the basal activity).
[b] K_M is the apparent Michaelis–Menten constant or the concentration of compound required for half maximal stimulation of ATPase activity.
[c] IC_{50} is the concentration of compound required for 50% inhibition of **VER**-stimulated (200 μM in mouse MDR3 CL P-gp and 400 μM in human P-gp-His_{10}) ATPase activity.
[d] ND, not determined because of low stimulation of ATPase activity.



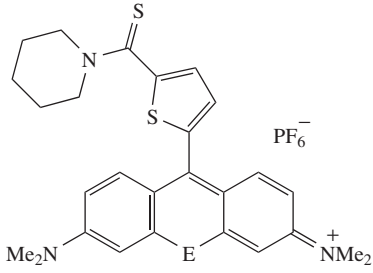
TMR, E = O
TMR-S, E = S
TMR-Se, E = Se
TMR-Te, E = Te



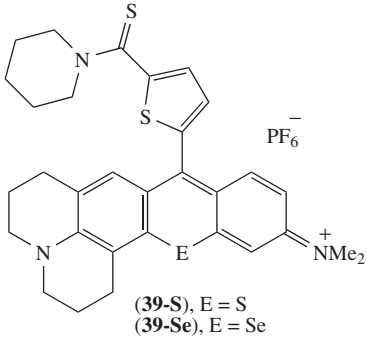
(**36-S**), E = S
(**36-Se**), E = Se
(**36-Te**), E = Te



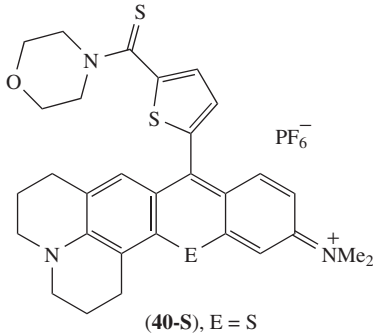
(**37-S**), E = S
(**37-Se**), E = Se
(**37-Te**), E = Te



(**38-S**), E = S
(**38-Se**), E = Se
(**38-Te**), E = Te



(**39-S**), E = S
(**39-Se**), E = Se
(**39-Te**), E = Te



(**40-S**), E = S
(**40-Se**), E = Se

CHART 9

ATPase activity) from chalcogenorosamine- and rhodamine-induced ATPase stimulation of **P-gp** by the dyes in Chart 9. The values of V_{max} are expressed in terms of 'fold-stimulation', which is a factor of stimulation relative to basal ATPase activity. Values of the apparent Michaelis–Menten constant, K_M, for half-maximal stimulation of ATPase activity and values of IC_{50} for 50% inhibition of **VER**-induced stimulation of ATPase activity are also compiled in Table 5. In human **P-gp**-His_{10}, the chalcogen atom has little impact on values of V_{max} and for the series **TMR-E**, **36-E**, **37-E** and **38-E** average

values (with standard deviation) of V_{max} are 7.8 ± 0.6, 2.2 ± 0.8, 2.4 ± 0.6 and 7.0 ± 2.0 fold-stimulation, respectively, as calculated from the data of Table 5. Values of K_M showed more variability. While values of K_M were comparable for the **TMR-E** and **38-E** series (8.6 ± 0.4 and $0.37 \pm 0.03\,\mu M$, respectively, with standard deviation), K_M for **37-Te** ($9.6\,\mu M$) was an order of magnitude smaller than K_M for **37-S** and **37-Se** (140 and $89\,\mu M$, respectively). Values of IC_{50} were measured for the ability of the rhodamines/rosamines to inhibit **VER**-induced stimulation of ATPase activity in isolated protein. In the **38-E** series, values of IC_{50} were around an order of magnitude greater than values of K_M, and the value of IC_{50} for the tellurium analogue was the lowest of the three dyes in the series.

The transport of several of the rhodamine/rosamine dyes of Chart 9 through monolayers of MDCKII-MDR1 cells was examined[146] and values in the absorptive (P_{AB}) and secretory (P_{BA}) directions are compiled in Table 6. Passive transport ($P_{Passive}$) of the dyes in these cells was determined by exposing the MDCKII-MDR1 cells first to a known, potent inhibitor of **P-gp**, and then averaging transport in both absorptive and secretory directions[146]. From the data in Table 6, the slowest active transport in the secretory direction (P_{BA}) was observed with tellurorhodamine derivative **38-Te** ($P_{BA} = 22\,nm\,s^{-1}$), which is perhaps indicative of a slow 'off'-rate for the dye from the protein. The rate of transport of **38-Te** is 40 to 50 times slower than transport of the rosamines **TMR** and **TMR-S** and an order of magnitude slower than the transport of **36-S**, **36-Se** and **37-Se**.

The transport across monolayers of MDCKII-MDR1 cells also can identify whether classes of compounds are transport substrates for the efflux pump[146]. If the ratio $P_{BA/AB}$ (Table 6) is greater than 2–3, the probe molecule is considered to be a substrate for **P-gp**. All of the dyes for which data are shown in Table 5, with the possible exception of **37-Se** ($P_{BA/AB} = 4.4$), would be considered to be transport substrates for **P-gp**. Tellurorhodamine **38-Te** with the slowest rate of transport still is a substrate for **P-gp** with $P_{BA/AB}$ of 24 (Table 6).

TABLE 6. Transport studies of chalcogenorosamine and chalcogenorhodamine dyes of Chart 9 and chalcogenopyrylium dyes of Chart 10 with MDCK-MDR1 cells[a]

Compound	P_{AB} ($nm\,s^{-1}$)	P_{BA} ($nm\,s^{-1}$)	$P_{BA/AB}$	$P_{Passive}$[b] ($nm\,s^{-1}$)	Reference
TMR	3.0	1010	338	17	146
TMR-S	6.0	900	150	34	146
36-S	0.8	310	450	7	146
36-Se	16	250	15	12	146
37-Se	45	200	4.4	22	146
38-S	1.5	80	54	2.8	146
38-Se	1.1	41	37	2.1	146
38-Te	0.9	22	24	2.6	146
39-S	0.8	50	61	1.2	146
41-S	5.3	340	62	3.4	147
41-Se	2.3	290	126	2.8	147
42-S	3.7	170	46	3.1	147
42-Se	3.5	120	34	2.8	147
43-Te	8.5	4.2	0.5	4.8	147

[a] Values of transport in the absorptive (P_{AB}) and secretory (P_{BA}) mode in the absence or presence of inhibitor, the ratio of secretory to absorptive transport ($P_{BA/AB}$) in the absence or presence of inhibitor.

[b] $P_{Passive}$ represents the mean of P_{AB} and P_{BA} in the fully inhibited system.

TABLE 7. IC_{50} for the uptake of calcein AM (**CAM**) in chalcogenorosamine-, chalcogenorhodamine- or chalcogenopyrylium-treated MDCKII-MDR1 cells. **VER** is included as a control compound

Compound	IC_{50} (μM)	Reference
VER	5.1	147
TMR-S	11	146
TMR-Se	11	146
36-S	4.7	146
36-Se	4.9	146
38-S	19	146
38-Se	9	146
38-Te	13	146
39-S	2.1	146
39-Se	5.3	146
39-Te	14	146
40-S	20	146
40-Se	14	146
41-S	7.1	147
41-Se	6.7	147
42-S	14	147
42-Se	20	147
43-Te	5.4	147

The key question is whether the reduced transport indicates inhibition of active efflux of small molecules from MDCKII-MDR1 cells. Cell cultures were treated with various concentrations of the dyes of Chart 9 and calcein AM, which is hydrolyzed in the cytoplasm to a fluorescent molecule. Values of IC_{50} for these compounds are compiled in Table 7[146]. The **38-E** series of dyes had the lowest values of P_{BA} in the secretory direction and also had the relatively low values of IC_{50} in Table 7. The tellurorhodamine dyes **38-Te** and **39-Te** were comparable to one another with respect to promoting calcein AM uptake ($IC_{50} = 13$ and 14 μM, respectively).

2. Telluropyrylium compounds

Chalcogenopyrylium dyes were also found to inhibit ATP hydrolysis and to inhibit the **P-gp** efflux pump by Tombline, Detty and coworkers[147]. The chalcogenopyrylium dyes of Chart 10 are a subset of all the structures examined and data in Tables 5–7 illustrate the performance of these dyes in comparison to the chalcogenorhodamines and chalcogenorosamines. As shown in Table 5, several of the chalcogenopyrylium dyes including telluropyrylium dyes **43-Te** and **44-Te** gave very little stimulation of ATPase activity ($V_{max} \leq 2.2$-fold stimulation) yet inhibited **VER**-induced ATPase activity at low μM concentrations (IC_{50} of 1.2 μM for **43-Te**). Dyes **41-S**, **41-Se** and **43-Te** also gave low μM values of IC_{50} for the uptake of calcein AM in multidrug-resistant MDCKII-MDR1 cells (7.1, 6.7 and 5.4 μM, respectively, Table 7). Telluropyrylium dye **43-Te** also inhibited vinblastine transport in MDCKII-MDR1 cells with an IC_{50} of 9 μM[147].

The most interesting feature of the chalcogenopyrylium dyes was the rate of transport for telluropyrylium dye **43-Te**. Transport in the secretory direction was much smaller than observed for other chalcogenorhodamine/rosamine dyes and chalcogenopyrylium

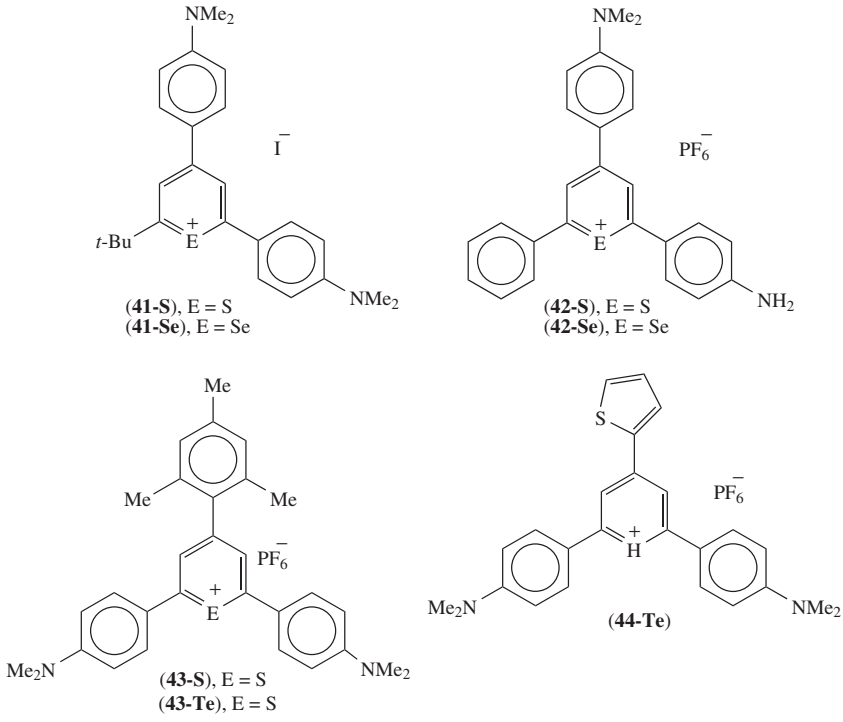


CHART 10

dyes ($P_{BA} = 2.4\,nm\,s^{-1}$)[147]. Furthermore, the ratio $P_{BA/AB}$ was only 0.5 indicating that **43-Te** was not a transport substrate for **P-gp**. These data suggest that telluropyrylium dye **43-Te** may bind to an allosteric site of **P-gp** to inhibit ATP hydrolysis and efflux pump activity.

VI. ORGANOTELLURIUM COMPOUNDS IN PHOTODYNAMIC THERAPY

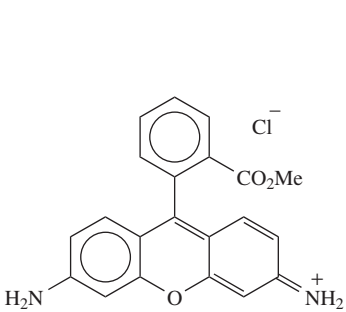
Organotellurium compounds have found significant utility as photosensitizers in the photodynamic therapy (PDT) of cancer and as photosensitizers for the photodynamic inactivation of viruses and bacteria[10]. Photodynamic therapy involves the delivery of a photosensitizer to the biological target—membrane, biopolymer (protein, DNA, RNA), neovasculature, organelle—followed by delivery of light of wavelengths absorbed by the photosensitizer. The excited photosensitizer then produces a localized cytotoxic reagent (singlet oxygen, superoxide, radical species) that then kills the desired cell or organism. Efficacy is determined by the selectivity for the biological target and the quantum yield for the cytotoxic event.

A. Mitochondrial Localization

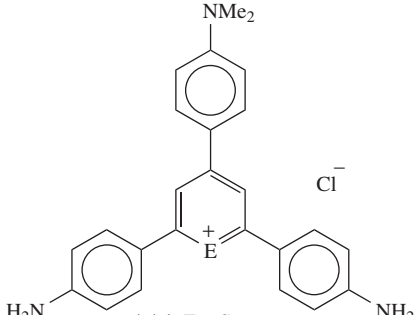
Most organotellurium compounds examined in the role of a photosensitizer have been cationic dyes and their biology is driven by sites of localization in the cell.

The telluropyrylium photosensitizer **1** (Chart 3) displayed efficacy upon irradiation of dye-treated cultured cells[91, 92, 154] as well as in animal models upon interlesional injection of **1**[155]. The mitochondria appeared to be the organelle targeted by the cationic photosensitizer as evidenced by electron micrographs and epifluorescence microscopy studies of U251MG cells treated with telluropyrylium dye **1**[91]. The general uptake of cationic small molecules into the mitochondria has been the object of numerous studies.

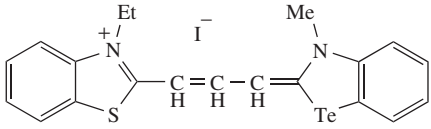
The pioneering work of Chen and coworkers demonstrated that cationic dyes such as rhodamine 123 (**Rh-123**, Chart 11) are localized in the mitochondria of cells[156]. Chen and coworkers also demonstrated that **Rh-123** accumulates selectively in the mitochondria of certain cancer cells relative to other cells[157] and is selectively toxic to certain cancer cell lines leading to prolonged survival upon administration of **Rh-123** to tumor-bearing animals[158]. The thiopyrylium compound **AA1** (Chart 11) shares structural similarity to **Rh-123** in that both molecules have two amino groups positioned for cyanine-like resonance. The amino substituents of both molecules delocalize the positive charge and both molecules target the mitochondria of cancer cells[159]. The dye **AA1** was also found to inhibit mitochondrial ATPase activity, to inhibit growth of the human colon carcinoma cell line CX-1 *in vitro* and to prolong the life of tumor-bearing animals treated with **AA1**[159]. Neither **Rh-123** nor **AA1** displayed increased toxicity due to a phototoxic component upon exposure of dye-treated cells to light[158, 159].



Rh-123



AA1, E = S
AA1-Se, E = Se
AA1-Te, E = Te



(**45-Te**)

CHART 11

B. Tellurium-containing Mitochondrial Agents and Photosensitizers

The tellurocarbocyanine dye **45-Te** (Chart 11) has the extended cyanine resonance of the two ring nitrogen atoms and these two nitrogen atoms delocalize the positive charge[160]. Dye **45-Te** targeted mitochondria, showed selective uptake into cancer cell lines relative to normal epithelial cells and prolonged the lifetime of tumor-bearing animals given **45-Te**[160].

The heavy chalcogen atoms selenium and tellurium in photosensitizers promote intersystem crossing from the singlet excited state to the triplet excited state, which can then interact with ground state oxygen to produce singlet oxygen[10]. In the absence of the heavy-atom effect, quantum yields for singlet oxygen can be negligible and no phototoxicity is observed upon treatment with dyes such as **Rh-123** and **AA1**. Dye **1** (Chart 3) has a quantum yield of 9% for the generation of singlet oxygen[91], but was too lipophilic to distribute to the tumor *in vivo*[155]. Heavy-atom analogues of known mitochondrial agents should be good potential photosensitizers for PDT. Unlike dye **1**, tellurocarbocyanine dye **45-Te** was able to reach the tumor following tail-vein injection. Unfortunately, irradiation did not give improved survival in treated animals.

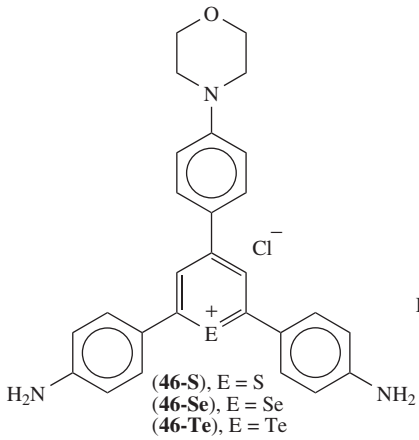
Heavier chalcogen analogues of the rhodamines and rosamines (**TMR-S** and **TMR-Se**, Chart 9)[161] and heavier chalcogen analogues of **AA1** (**AA1-Se** and **AA1-Te**, Chart 11)[162–164] were prepared and their cellular distribution was examined. The selenium and tellurium analogues were found to target the mitochondria. However, **AA1**, **AA1-Se** and **AA1-Te** were found to have high dark toxicity against Colo 26 cells with LD_{50}s of 0.1 μM, 1.4 μM and 0.5 μM, respectively (Table 8)[162]. Irradiation of **AA1-Se**-treated Colo 26 cells gave an EC_{50} 0.37 μM, which is indicative of added phototoxicity from irradiation of **AA1-Se** in the cell.

Several additional series of dyes were examined (Chart 12) with slight modifications of the **AA1** structure in order to find a photosensitizer with more selective phototoxicity[162]. Values of LD_{50} (lethal dose for 50% cell kill) for survival of Colo 26 cells are compiled in Table 8. Replacing the 4-dimethylaminophenyl group of the **AA1** series of dyes with a 4-*N*-morpholinophenyl group in the **46-E** series of dyes gave a 3- to 8-fold reduction in dark toxicity. The LD_{50} for the dark toxicity of **46-Se** was 3.8 μM while EC_{50} (effective concentration for 50% cell kill with light) for phototoxicity was 1.2 μM—a 3-fold selectivity for increased phototoxicity. The heavy-chalcogen-containing dyes **47-Se** and **47-Te** (EC_{50}s of 0.9 and 0.07 μM, respectively) were more toxic than their corresponding **AA1** and **46-E** analogues.

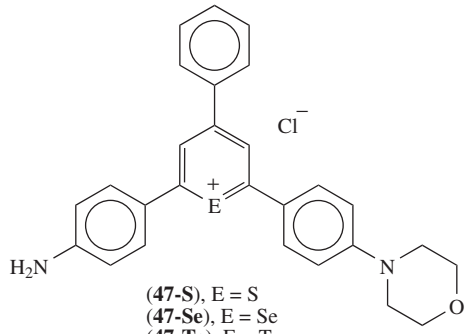
TABLE 8. Values of the concentration of chalcogenopyrylium dye of Charts 11 and 12 to give 50% cell kill in the dark (LD_{50}) or 50% cell kill (EC_{50}) upon exposure to 15 J cm^{-2} of 360–800-nm light[a]

Compound	LD_{50} (μM)	EC_{50} (μM)
AA1	0.1	–
AA1-Se	1.4	0.37
AA1-Te	0.5	–
46-S	0.8	–
46-Se	3.8	1.2
46-Te	1.4	–
47-S	1.8	–
47-Se	0.9	–
47-Te	0.07	–
48-S	66	2.0
48-Se	6.9	1.9
48-Te	0.8	0.6
49-S	0.9	–
49-Se	1.5	0.07
49-Te	0.5	–

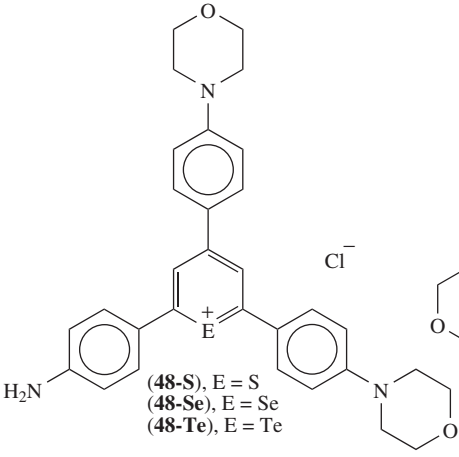
[a]Data taken from Reference 162.



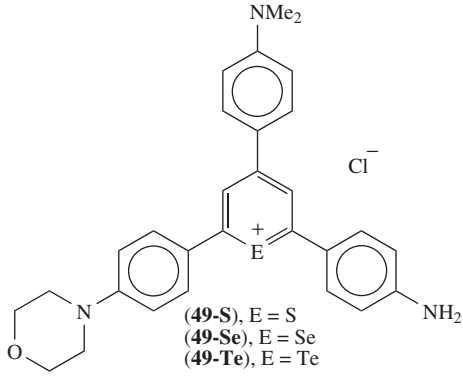
(**46-S**), E = S
(**46-Se**), E = Se
(**46-Te**), E = Te



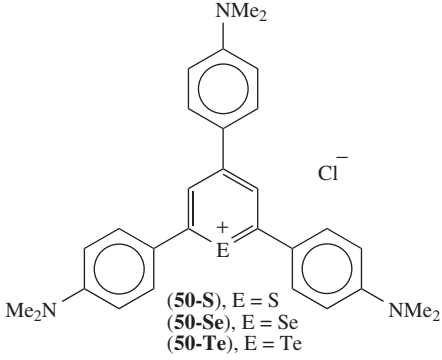
(**47-S**), E = S
(**47-Se**), E = Se
(**47-Te**), E = Te



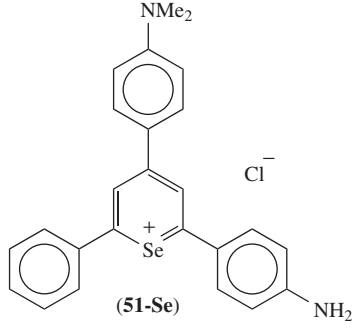
(**48-S**), E = S
(**48-Se**), E = Se
(**48-Te**), E = Te



(**49-S**), E = S
(**49-Se**), E = Se
(**49-Te**), E = Te



(**50-S**), E = S
(**50-Se**), E = Se
(**50-Te**), E = Te



(**51-Se**)

CHART 12

The **48-S** and **48-Se** dyes with two 4-*N*-morpholinophenyl groups were the least toxic of any of the compounds of Chart 12 with LD_{50}s of 66 and 6.9 μM, respectively[162]. Irradiation of dye-treated cells gave EC_{50}s of 2.0 and 1.9 μM for **48-S** and **48-Se**, respectively. While **48-Se** was 3- to 4-fold more selective for phototoxicity, the thiopyrylium dye **48-S** was 33-fold more selective for phototoxicity. Unfortunately, the tellurium analogue **48-Te** showed comparable dark and phototoxicity ($LD_{50} = 0.8\,\mu M$, $EC_{50} = 0.6\,\mu M$).

Removing a morpholino group gave increased dark toxicity. Series **49-E** with one 4-dimethylaminophenyl substituent and one 4-*N*-morpholinophenyl substituent was comparable to the **AA1** series with respect to toxicity[162]. However, **49-Se** with an LD_{50} of 1.5 μM gave an EC_{50} of 0.07 μM upon irradiation of dye-treated cells with $15\,J\,cm^{-2}$ of filtered 360–800-nm light, which represents a 22-fold selectivity for phototoxicity with **49-Se**.

One thing that stands out in the data of Table 8 is the increased dark toxicity of the tellurium analogues relative to the corresponding selenium analogues[162]. Several of the tellurium analogues of Chart 12 may be shown to be worthy candidates for evaluation as chemotherapeutic agents in the absence of light in future studies.

The toxicity/phototoxicity of the telluropyrylium dyes may be related to mitochondrial localization and inhibition of mitochondrial function. Mitochondria were isolated from R3230AC rat mammary adenocarcinoma cells that had been exposed to 10 μM **48-Te** for 24 h[162]. (The R3230AC cells were more tolerant of the chalcogenopyrylium dyes than the Colo 26 cells.) Mitochondrial suspensions from **48-Te**-treated cells that had been irradiated with $1.8\,J\,cm^{-2}$ of filtered 360–750-nm light displayed 14% of the mitochondrial cytochrome *c* oxidase activity of cells (1) treated with dye only and no light, (2) treated with light only, or (3) kept in the dark without dye or light exposure—all of which had essentially identical activity as controls. These results are consistent with uptake of **48-Te** into the cell and localization in the mitochondria with mitrochondrial damage occurring upon irradiation.

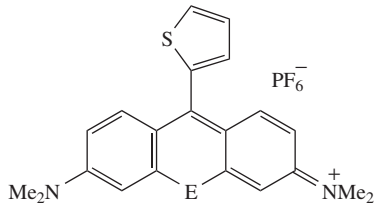
A typical dose of photosensitizer in PDT is $5\,mg\,kg^{-1}$ of body weight[10]. In spite of their toxicity toward cells in culture, several chalcogenopyrylium dyes show acceptable toxicity *in vivo*. Dyes **50-E** (Chart 12) were administered via tail-vein injection to groups of rats at $10\,mg\,kg^{-1}$ (20, 19 and $17\,\mu mol\,kg^{-1}$, respectively, for **50-S**, **50-Se** and **50-Te**) and no toxicity or adverse effects were observed[165].

The **AA1**-related dye **51-Se** (Chart 12) showed no toxicity at doses as high as 29 mg ($62\,\mu mol)kg^{-1}$ and prolonged survival was noted in tumor-bearing Fisher rats administered $10\,mg\,kg^{-1}$ of **51-Se** and $720\,J\,cm^{-2}$ of filtered 579–750-nm light[166]. Six hours following administration of **51-Se**, concentrations of **51-Se** greater than $1\,nmol\,g^{-1}$ of tissue were found in the tumor, heart, speen, liver and kidney with a tumor concentration of $4.0\,nmol\,g^{-1}$ of tissue. After 24 h, the concentration of **51-Se** in tumor was $5.1\,nmol\,g^{-1}$ of tissue and concentrations in all other tissues examined were $\leq 0.1\,nmol\,g^{-1}$ of tissue.

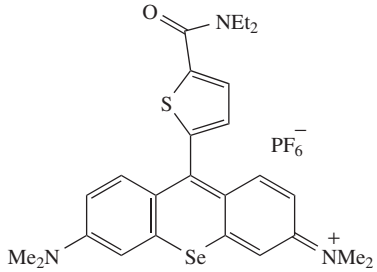
VII. INTERACTIONS OF ORGANOTELLURIUM COMPOUNDS WITH DNA

A. Tellurorosamine–DNA Complexes

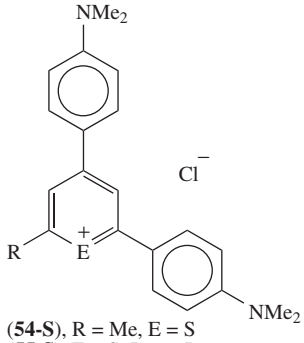
One question regarding the targeting of the mitochondria concerns the specific site(s) of binding in the mitochondria and whether mitochondrial DNA might in fact be a target[167]. That chalcogenorosamine and rhodamine dyes could bind to DNA was demonstrated through binding studies with isothermal titration calorimetry (ITC) using calf-thymus DNA (ctDNA) as well as CG-rich ($[poly(dCdG)]_2$) and AT-rich ($[poly(dAdT)]_2$) DNA to probe binding modes[167]. DNA binding constants (K_b) determined by this method are compiled in Table 9 for the **TMR-E** dyes (Chart 8), their 2-thienyl analogues **52-E** and



(**52-O**), E = O
(**52-S**), E = S
(**52-Se**), E = Se
(**52-Te**), E = Te



(**53-Se**)



(**54-S**), R = Me, E = S
(**55-S**), E = S, R = *n*-Pr
(**56-S**), E = S, R = *t*-Bu
(**56-Se**), E = Se, R = *t*-Bu
(**56-Te**), E = Te, R = *t*-Bu

CHART 13

thienyl rhodamine derivative **53-Se** (Chart 13). Within the **TMR** series and the **52-E** series, the oxygen-, sulfur- and tellurium-containing analogues had comparable values of K_b for binding to ctDNA (*ca* $5–6 \times 10^6 M^{-1}$ for the **TMR** series and *ca* $2 \times 10^6 M^{-1}$ for the **52-E** series) while the selenium-containing analogues in each series bound 2 to 3 times more tightly to ctDNA ($K_b = 1.0 \times 10^7 M^{-1}$ for **TMR-Se** and $K_b = 4.7 \times 10^6 M^{-1}$ for **52-Se**) than did the other chalcogen analogues. The poorer overlap of selenium 4p orbitals with carbon 2p orbitals in the π-framework of the **TMR-Se** and **52-Se** is thought to delocalize more charge to the ring nitrogen atoms leading to increased binding to ctDNA. Since tellurium is more electropositive than selenium, the carbon π-framework of **TMR-Te** and **52-Te** would have increased electron density relative to the selenium analogues and, consequently, decreased binding to ctDNA[167]. The tellurium atom also has a much larger covalent radius than the other chalcogen atoms and the central ring of the chalcogenoxanthylium core is distorted [168], which might also contribute to decreased interactions with ctDNA.

Binding of this same series of dyes to $[poly(dCdG)]_2$ and $[poly(dAdT)]_2$ was indicative of multiple binding modes for the chalcogenorosamines/rhodamines with DNA. Minor groove binders to DNA generally show a strong preference for AT-rich sequences rather than GC-rich sequences[169]. Compound **53-Se** showed a high affinity for ctDNA and a high affinity for $[poly(dAdT)]_2$, which is consistent with **53-Se** being a minor groove

binder. In contrast, binding of **53-Se** to $[poly(dCdG)]_2$ was much weaker with an ITC signal essentially identical to background phosphate. The **52-S** and **52-Se** dyes displayed a preference for CG-rich sequences, which is consistent with intercalation as a preferred binding mode[170] although the **TMR-E** dyes and the **53-E** dyes showed comparable binding to both $[poly(dCdG)]_2$ and $[poly(dAdT)]_2$, indicating the presence of multiple binding modes. Studies with a topoisomerase I assay also were consistent with these modes of binding for the various dyes[167].

B. Telluropyrylium–DNA Complexes

The binding of a series of chalcogenopyrylium dyes to ctDNA was also examined by ITC and values of K_b for dyes **54-S**–**56-S**[171], **56-Se**[171] and **56-Te**[172] (Chart 13) are compiled in Table 9. Values of K_b for these dyes are 10-fold smaller than K_b for the chalcogenorosamine and rhodamine dyes of Table 9. Values of K_b were comparable for the sulfur, selenium and tellurium analogues of **56-E**, suggesting that conformational flexibility in the chalcogenopyrylium dyes can overcome differences introduced by the various chalcogen atoms.

The binding modes of **54-S**, **55-S**, **56-S** and **56-Se** were examined via several techniques including competition dialysis experiments with $[poly(dCdG)]_2$ and $[poly(dAdT)]_2$, ethidium bromide displacement studies and circular dichroism (CD) studies[171]. Results with **54-S** and **55-S** were consistent with intercalation as a preferred binding mode: no strong preference for binding to CG-rich sequences relative to AT-rich sequences, ethidium bromide displacement and concentration-dependent CD intensities with no change in curve shape. Binding of **56-S** and **56-Se** to DNA suggested mixed binding. Competition dialysis experiments showed a 10-fold preference for binding to $[poly(dAdT)]_2$ relative to $[poly(dCdG)]_2$, which suggests binding to the minor groove. However, ethidium bromide displacement and CD studies suggested that there was an intercalative binding component, as well.

TABLE 9. DNA binding affinity data (K_b) as determined by ITC for the **TMR-E** dyes of Chart 9 and the chalcogenorhodamine, chalcogenorosamine and chalcogenopyrylium dyes of Charts 11 and 13

Compound	K_b (ctDNA) (10^6 M^{-1})	K_b (AT) (10^6 M^{-1})	K_b (GC) (10^6 M^{-1})	Reference
TMR-S	5.2	2.2	1.3	167
TMR-Se	10.3	2.8	0.9	167
TMR-Te	6.4	–	–	167
52-O	2.1	2.2	2.1	167
52-S	1.6	1.5	2.7	167
52-Se	4.7	1.6	3.7	167
52-Te	2.1	–	–	167
53-Se	12.4	2.3	*ca* 0	167
54-S	0.17	–	–	171
55-S	0.24	–	–	171
56-S	0.42	–	–	171
56-Se	0.35	–	–	171
56-Te	0.31	–	–	172

VIII. ANTI-MICROBIAL ACTIVITY OF ORGANOTELLURIUM COMPOUNDS

A. Photodynamic Inactivation of Viruses and Bacteria in Blood

One utility for photosensitizers that bind selectively to either DNA or RNA is for photodynamic inactivation of blood-borne viral or bacterial pathogens[10]. In this technique, blood samples treated with photosensitizer are passed through a light source that emits at wavelengths where the photosensitizer absorbs. The photochemical production of a cytotoxic agent then kills virus or bacterium. Effectiveness of photosensitizers is described in terms of the 'log's of inactivation'—the orders-of-magnitude reduction ($\log_{10}$) of viral or bacterial growth. Mature red blood cells lack genomic material and the DNA/RNA of viruses and bacteria become highly specific targets.

1. Telluropyrylium compounds

Dye **54-S** (Chart 13) stains DNA specifically in organisms[173] and dyes **54-S**–**56-S** and **56-Se**, upon binding to DNA, have shown increased fluorescence yields and increased quantum yields for the generation of singlet oxygen. In the absence of strong binding to DNA, energy is lost from the excited photosensitizer through internal conversion via bond rotation in the flexible chalcogenopyrylium dye. This energy-loss pathway diminishes the lifetime of the excited singlet state, reducing fluorescence yields and intersystem crossing to the triplet state[174]. Binding to a biopolymer such as DNA can be a selectivity-determining event by 'switching on' the ability of the photosensitizer to generate a cytotoxic agent or event. Groove binding or intercalation takes away rotational degrees of freedom from the chalcogenopyrylium dyes increasing the relative yields of fluorescence and intersystem crossing relative to internal conversion. The selenopyrylium dye **56-Se** shows potent antiviral activity and gave nearly $8\log_{10}$ inactivation of pseudorabies virus (PRV) at a concentration of 6 μM while the thiopyrylium analogue **56-S** gave $<4\log_{10}$ of inactivation at the same concentration with irradiation of 1.1 J cm^{-2} from 660–680-nm light from an LED source[174].

Dye **50-Te** (Chart 12) and dyes **57-Te**–**61-Te** (Chart 14) were evaluated for their ability to inactivate vesicular stomatitis virus (VSV), a model single-stranded RNA virus. Of these 6 telluropyrylium dyes, 3 (**57-Te**, **58-Te** and **60-Te**) displayed adequate extracellular virucidal activity with $>6\log_{10}$ inactivation of VSV at concentrations of 5–10 μM with irradiation of 1.1 J cm^{-2} from 660–680-nm light from an LED source[10].

2. Tellurorosamines

The selenorosamines **TMR-Se** (Chart 9) and **52-Se** (Chart 13) were found to be effective photosensitizers for the photodynamic inactivation of extracellular VSV and PRV and intracellular VSV in red blood cells[175]. Red blood cells treated with 10 μM **TMR-Se** or 10 μM **52-Se** and 2.5–5 J cm^{-2} of 400–750-nm white light gave *ca* $8\log_{10}$ inactivation of either extracellular VSV or PRV. Under these same conditions, *ca* $4\log_{10}$ inactivation of intracellular VSV was observed with **TMR-Se** and *ca* $3\log_{10}$ inactivation of intracellular VSV was observed with **52-Se**. The corresponding tellurium analogues (**TMR-Te** and **52-Te**) were much less effective with *ca* $4–5\log_{10}$ inactivation of extracellular VSV.

Both **TMR-Se** and **52-Se** gave some photodynamic inactivation of both gram-positive (*Staphylococcus aureus* and *Staphylococcus epidermis*) and gram-negative (*Pseudomonas fluorescens* and *Yersinis enterocolica*) bacteria[175]. Both **TMR-Se** and **52-Se** gave $\geq 2.5\log_{10}$ inactivation of *S. aureus*, $>8\log_{10}$ inactivation of *S. epidermidis* and $\geq 4\log_{10}$ inactivation of *Y. enterocolitica*. Both **TMR-Se** and **52-Se** were ineffective ($\leq 0.4\log_{10}$ inactivation) against *P. fluorescens*. The tellurorosamines **TMR-Te** and

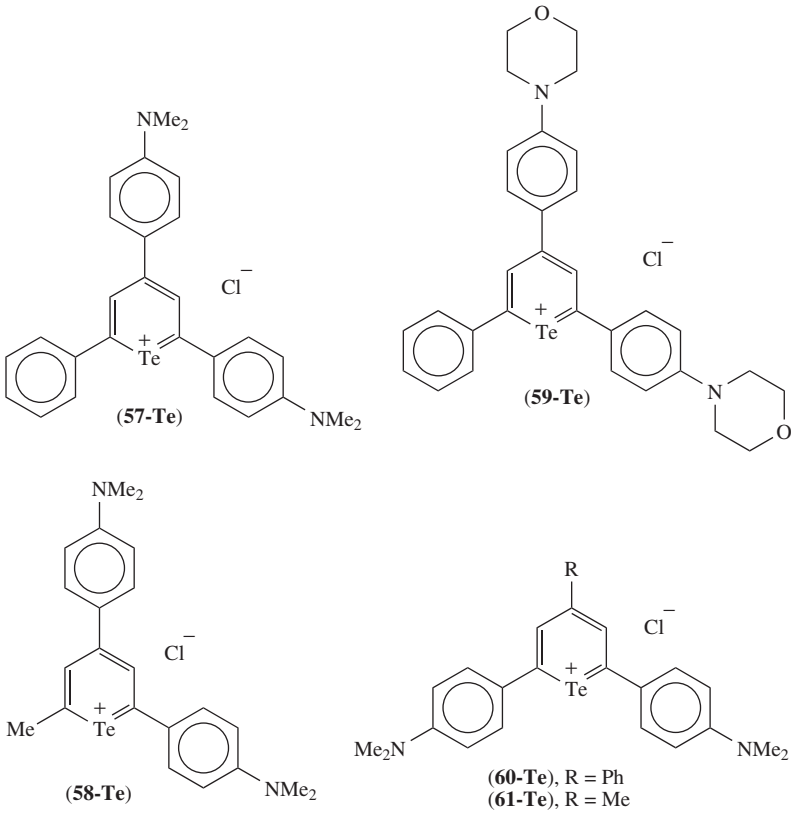


CHART 14

52-Te gave *ca* $4\log_{10}$ inactivation of *S. epidermidis* and were ineffective against the other gram-positive and gram-negative bacteria.

3. Organotellurium compounds and hemolysis

In spite of their photodynamic virucidal activity, chalcogenorhodamine/rosamine dyes and chalcogenopyrylium dyes cause damage to dye-treated red blood cells through hemolysis[10, 175, 176]. The thiopyrylium dye **54-S** is a promising photosensitizer for the photodynamic inactivation of pathogens in blood; several additives to combat radical intermediates and oxidizing agents must be added to achieve acceptable levels of hemolysis[177].

Organochalcogenides that mimic **Gpx**s can contribute to the problem of hemolysis through the formation of radical intermediates. Human erythrocytes incubated with diphenyl ditelluride (**62**, Chart 15) or with di-(1-naphthyl) ditelluride (**63**, Chart 15) showed increased hemolysis relative to controls[178]. Of the seven compounds tested, di-(1-naphthyl) ditelluride induced the most hemolysis. The addition of **GSH** and glucose increased the amount of hemolysis, which suggests oxidation of **GSH** may form radicals that damage the red blood cell.

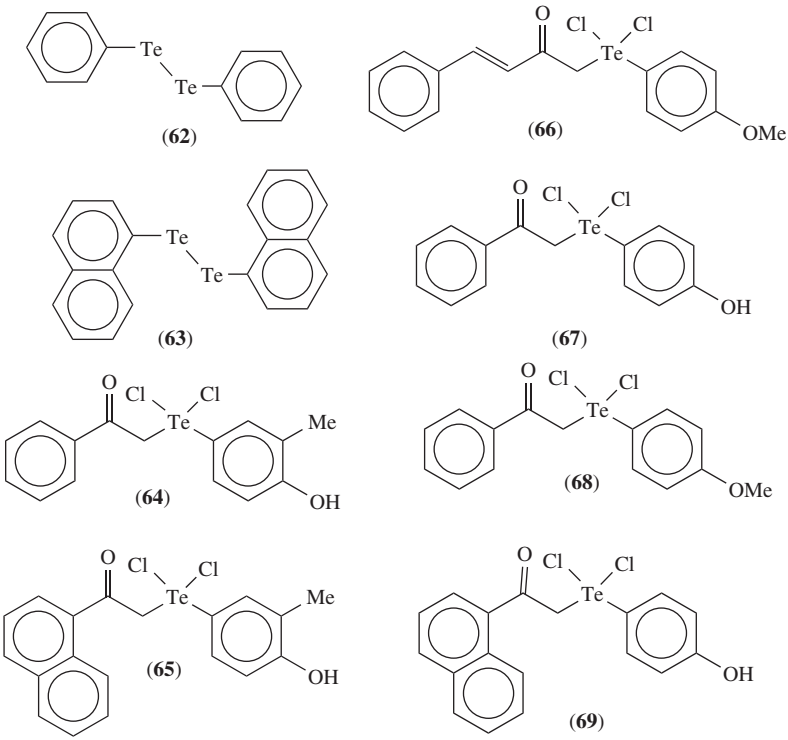


CHART 15

B. Organotellurium Compounds as Antibiotics

Six unsymmetrical diorganyltellurium(IV) dichlorides **64**–**69** (Chart 15) were tested for their antibacterial activity against gram-positive (*Bacillus subtilis* and *S. aureus*) and gram-negative (*Escherichia coli, Pseudomonas aeruginosa* and *Salmonella* sp.) bacteria[179]. All six compounds demonstrated good activity against gram-negative strains. Phenacyl (3-methyl-4-hydroxyphenyl) tellurium(IV) dichloride (**64**) and 1-naphthacyl (3-methyl-4-hydroxyphenyl) tellurium(IV) dichloride (**65**) were active against both gram-positive and gram-negative strains. Compound **64** exhibited maximum activity against gram-positive bacteria, while **65** showed comparable activity toward all strains examined. Styrylacyl (*p*-methoxyphenyl) tellurium(IV) dichloride (**66**) showed maximum activity against the three gram-negative bacteria.

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Organoselenium and organotellurium oxidation and reduction

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0578

I. INTRODUCTION

To most chemists, selenium and tellurium are not among the popular elements of the periodic table. Selenium compounds have a reputation of being malodorous, toxic and sometimes unstable, readily producing elementary red amorphous selenium. Until the early 1970s only selenium(IV) oxide (for instance, in allylic oxidations) and elemental selenium (as dehydrogenating agent) have been applied for synthetic purposes. Four decades after the pioneering use of tellurium compounds in organic synthesis the rising interest was directed toward this field of chemistry. Following the discovery of a broad spectrum of selenium compounds and several tellurium compounds of practical importance as reagents, catalysts and intermediates, they began to play an important role in synthetic organic chemistry, judging from the numerous original papers, books and review articles that have appeared over the years[1–20].

The biochemistry and pharmacology of selenium compounds, and occasionally their tellurium counterparts, are subjects of intense current interest, especially from the point of view of public health. During the last few years, a tremendous effort has been directed toward the synthesis of stable organoselenium and tellurium compounds that could be used

as antioxidants, enzyme modulators, antivirals, antimicrobials, antihypertensive agents and cytokine inducers. The postulated mechanisms of their biological action, particularly their enzyme-like activity, involve selenium and tellurium oxidation–reduction. Their possible applications as therapeutic agents in treatment of several diseases and their toxicology has been revealed in numerous papers and recently discussed in reviews[19–25].

Selenium and sulfur have similar radii (0.109 and 0.122 nm, respetively), shorter than tellurium (0.142 nm). Electronegativity decreases in the order S(2.5)>Se(2.4)>Te(2.1) (in the Pauling scale). Despite the similarities between sulfur-containing molecules and their selenium congeners, there are several unique features of organoselenium compounds. The properties of sulfur and tellurium compounds differ significantly. The selenium and tellurium compounds can be used as nucleophiles, electrophiles as well as radicals in different types of reactions, and many of them can also act as oxidants and reductants. This review is devoted to oxidative and reductive properties of selenium and tellurium compounds as reagents or intermediates, formed in the course of reaction between inorganic and organic selenium or tellurium molecules and organic species. Coverage of the literature up to early 2010 is provided.

II. SELENIUM(IV) OXIDE AND OXYGENATED ORGANOSELENIUM COMPOUNDS

A. Selenium(IV) Oxide and Related Compounds as Oxygen Donors

1. General comments

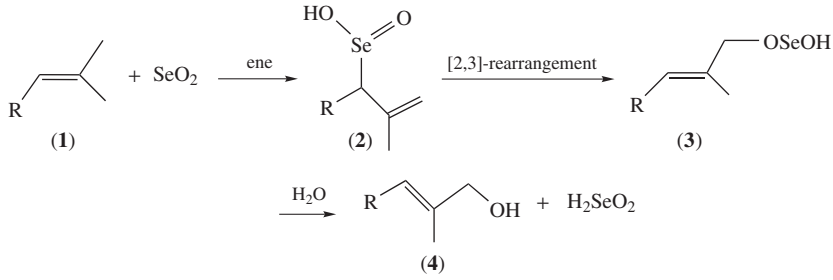
Selenium(IV) oxide (SeO_2), commonly named selenium dioxide, is one of the most frequently used selenium compounds. It is easily prepared by burning of selenium in air or by oxidation with nitric acid or hydrogen peroxide. The most convenient preparation is perhaps by the dehydration of selenic(IV) acid. It is readily reduced to the element by hydrazine. In the reaction of selenium(IV) oxydifluoride with SeO_2, diselenium pentoxide (Se_2O_5) is formed[26]. Dissolution of SeO_2 in selenium oxydichloride gives the trimer $[Se(O)O]_3$[27]. The first publication on the use of selenium(IV) oxide in oxidation reactions appeared in 1932[28] and since then it has been applied as a versatile reagent for the synthesis of various types of organic compounds[29].

SeO_2 is a white solid, which is soluble in water, methanol, ethanol, dioxane, acetone and acetic acid. In water or water-containing solvents it exists as selenic(IV) acid (selenous acid, $(HO)_2SeO$). In alcohols, selenic(IV) esters are formed *in situ*, e.g. dimethyl selenate(IV) is postulated as intermediate for the reactions carried in methanol[30]. Although this ester was never isolated, the stable diethyl analogue was successfully used for oxidation of some organophosphorus compounds and phenacyl halides[31]. Relatively cheap and easily available selenium(IV) oxide is applied as a stoichiometric oxidant or as a catalyst involved in transfer of oxygen from primary oxidants, such as hydrogen peroxide[32, 33] or *t*-butyl hydroperoxide[34], to organic substrate.

Selenium(IV) oxide has an electrophilic center localized on the selenium atom and nucleophilic centers on the oxygen atoms, and can interact with nucleophilic and electrophilic centers of organic molecules. It can perform several common types of oxidations, such as conversion of methylarenes to aldehydes, alcohols to aldehydes and ketones, dehydrogenation of ketones to enones, conversion of ketones into esters, regiocontrolled allylic oxidation of alkenes to allylic alcohols, selective oxidation of benzaldehydes to benzoic acids and other oxidations. Due to its toxicity when taken orally, intense local irritation of skin and eyes, and the sometimes malodorous volatile selenium-containing by-products formed, SeO_2 is used in modern synthesis only when it competes favorably with other methods, provides unique reactivity or when used in catalytic amounts[1, 2, 32, 34].

2. Oxidation with selenium(IV) oxide, selenic(IV) acid and derivatives

a. Allylic hydroxylation. Selenium(IV) oxide mediates the unique allylic oxidation of alkenes **1** with usual retention of the double bond position. The mechanism of this reaction remained unclear until Sharpless and Lauer in 1972[35] explained the selective oxidation as the result of a two-step process: an ene reaction followed by sigmatropic [2,3]-rearrangement of intermediate seleninic acid **2** that give selenic(II) acid ester **3**, while the double bond returns to its original location. In the last step the ester is hydrolyzed into the allylic alcohol **4** (Scheme 1)[35–37]. It was postulated that in the presence of hydroxylated solvent, e.g. water, alcohol or carboxylic acid, the active oxidant can be selenic(IV) acid or its alkyl ester. In order to avoid selenic(IV) acid, hydroxylation of alkenes containing acid-labile groups (e.g. acetals) is run in pyridine[38].

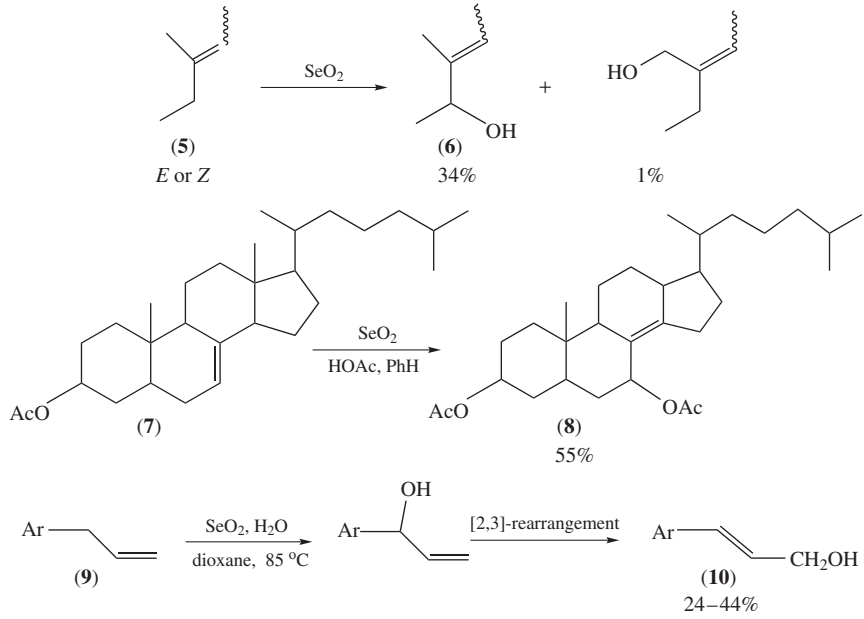


SCHEME 1. Mechanism of selenium(IV) oxide α-hydroxyalkylation of alkenes

More recently, the mechanism of the allylic hydroxylation of alkenes with SeO_2 was explored by a combination of experimental and theoretical studies[39–41]. A comparison of the observed ^{13}C and ^{2}H kinetic isotope effects with the predicted values shows that the observed isotope effects are consistent with an initial concerted ene step reaction mediated by SeO_2. However, this comparison does not rule out the involvement of a selenic(IV) ester in the ene reaction or a stepwise reaction involving reversible electrophilic addition of $HSeO_2^+$ followed by rate-limiting proton abstraction. B3LYP calculations strongly favor SeO_2 over a selenic(IV) ester as the active oxidant, with a predicted barrier of 21–24 kcal mol^{-1} lower for the reaction of 2-methyl-3-butene with SeO_2 than that for reaction with H_2SeO_3. The possibility of a selenic(IV) ester as the active oxidant is also disfavored by the observation of oxidations in non-hydrolytic solvents. A concerted ene reaction with SeO_2 as the active oxidant appears to be the major mechanistic pathway in these reactions.

Selenium(IV) oxide allylic hydroxylation is highly regiospecific and occurs at the α position to the more substituted carbon of the double bond with a reactivity order $CH_2 > CH_3 > CH$. This is demonstrated by the oxidation of the allylic methylene group of 3-methyl-3-butene (**5**), in preference to the methyl position which gives alcohol **6** as the main product (Scheme 2)[42].

When the double bond is inside a ring, oxidation occurs in the ring when possible, and in α-position to the more substituted end of the double bond[43]. For example, oxidation of Δ^7-chonestenyl acetate (**7**), in acetic acid–benzene at 0–5 °C, occurs at C(14) and is followed by allylic rearrangement to give the acetate **8** (Scheme 2)[44]. Several multistep syntheses of 6-hydrocorticosteroids, 6-β-hydroxy derivatives of progesterone and testosterone, other steroids, glycospirostanes, the optically pure cyclohexenone core



SCHEME 2. Regioselectivity of selenium(IV) oxide α-hydroxylation of alkenes and cycloalkenes

of scyphostatin and hydroxytaxadienes involving allylic hydroxylation by selenium(IV) oxide were reported[45–52].

The SeO_2 oxidation of a terminal double bond affords a primary alcohol by allylic migration of the double bond. An example is the oxidation of 3-arylpropenes **9** in dioxane–water followed by isomerization to the primary allylic alcohols **10** (Scheme 2)[53].

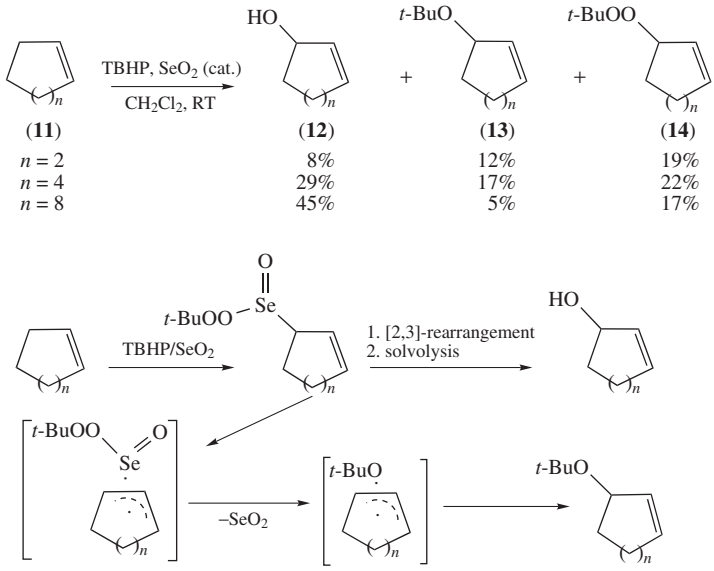
It is generally believed that SeO_2-catalyzed allylic oxidation of alkenes involves initial ene reaction of SeO_2 followed by sigmatropic [2,3]-rearrangement. The resulting selenic(II) acid H_2SeO_2 arriving from hydrolysis of selenic(II) ester **3** can be easily oxidized to H_2SeO_3 and returned to a reaction cycle. Hence, the selenium(IV) oxide promotes allylic oxidation with *t*-butyl hydroperoxide (TBHP) (or with other hydroperoxides). Practically useful processes using a stoichiometric or catalytic amount of SeO_2 and TBHP as a reoxidant were elaborated[1,34].

The TBHP/SeO_2 system is more convenient to use than SeO_2 alone, particularly when it is used in catalytic amounts. Reaction conditions are much milder and, as a result, yields are higher with less oxidation, dehydration, rearrangement of by-products and the problem of the removal of colloidal selenium is circumvented. Like Se(IV) oxide alone, the reagent TBHP/SeO_2 oxidizes alkenes, cycloalkenes and alkynes in the allylic position. Hydroxylation of cycloalkenes carrying alkyl substituents at the allylic position takes place preferentially on the ring α-carbon atom. In different alkenes, the order of susceptibility of α-carbon atoms toward hydroxylation is the same as for SeO_2 oxidation alone. Oxidation of terminal alkenes results in C=C bond migration and primary allyl alcohol formation[54]. Terminal and non-terminal vinyl fluorides have been hydroxylated regioselectively in the allylic position adjacent to the fluorine bearing carbon[55].

TBHP/SeO_2 was used in the allylic hydroxylation of isolated double bonds in straight-chain hydrocarbons, e.g. mono-unsaturated fatty acids, esters and alcohols. Either allylic

position was hydroxylated or both positions reacted to give dihydroxy isomers. Yields of monohydroxy compounds in which the OH group was between the double bond and C(1) were usually higher than those in which the OH group was between the double bond and the methyl terminus[56–60]. When an α-methylene group is oxidized, the reaction proceeds under mild reaction conditions[61–63].

The TBHP/SeO_2 oxidation of some simple cycloalkenes **11** produced, in addition to the expected allylic alcohols **12**, allylic *t*-butyl ethers **13** and *t*-butyl peroxides **14**. For cyclohexene, the major products were ether **13** ($n = 2$) and peroxide **14** ($n = 2$). As the ring size increased, the yields of alcohols increased and those of ethers and peroxides decreased. When the oxidation was carried out in the presence of hydroquinone the peroxides **14** were not observed, although the yields of alcohols and ethers remained unaffected. Consequently, a free-radical pathway has been proposed (Scheme 3)[62].

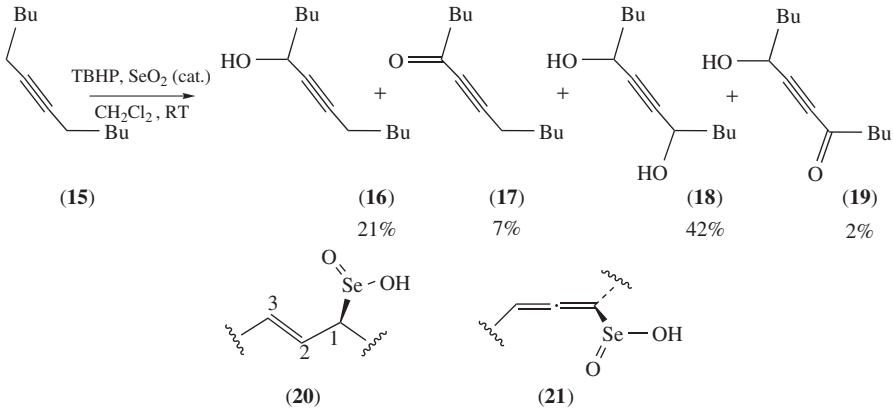


SCHEME 3. TBHP/SeO_2 oxidation of some cycloalkenes

Another mechanism, involving a carbocation intermediate, can be also envisaged to explain the isolation of isomeric allylic esters, resulting from SeO_2/TBHP oxidation of pinene derivatives[1, 62].

Selenium(IV) oxide associated with *N*-methylmorpholine *N*-oxide was applied as very efficient hydroxylating agent for monocyclic unsaturated terpenoids. An advantage of this feature is high conversion of the substrate (67–100%) and stereospecific functionalization[64].

Unlike alkenes, alkynes show a strong tendency to α,α'-dihydroxylation upon reaction with TBHP/SeO_2. The oxidation of different acetylenes allowed assignment of the reactivity sequence $CH_2{=}CH > CH_3$. Alkynes bearing one methylene and one methine substituent afforded the enynone as the major product. When internal alkynes such as **15** were treated with TBHP/SeO_2, in addition to the expected products **16** and **17** a substantial amount of dioxygenated products **18** and **19** was also found (Scheme 4). In considering

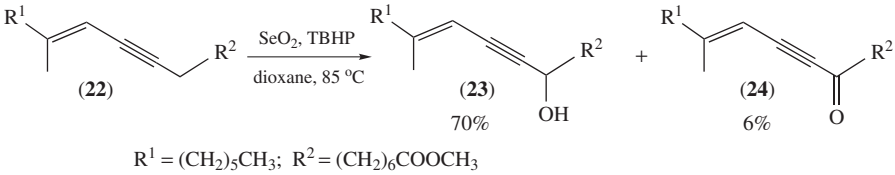


SCHEME 4. Oxidation of alkyne with TBHP/SeO_2

stereochemical aspects, it is worth pointing out an interesting difference between SeO_2 oxidations of alkenes and alkynes. In the case of alkenes, the allylic selenic acid intermediate **20** can in principle give rise to allylic alcohol by a [2,3]-sigmatropic shift to either face of the olefinic bond. This is a consequence of free rotation about C(1) to C(2) bond in **20**. However, in the case of alkynes, the putative allenic seleninic intermediate **21**, arising from an ene reaction of SeO_2 with the alkyne, has a fixed geometry and only one [2,3]-transition state is feasible. Thus in the case of acetylenes, the stereochemistry of the oxidation product should be determined only by the stereochemistry of the initial ene reaction, which produces the allenic seleninic acid **21**[61].

Hydroxylation of methylene groups adjacent to an acetylenic bond was achieved when the acetylenic fatty ester substrates were reacted with a stoichiometric amount of TBHP and SeO_2 in aqueous dioxane. Some of the hydroxy groups in these derivatives were also oxidized to the corresponding oxo functions. However, in the case of an enyne system, the hydroxylation reaction was regiospecific with hydroxylation taking place at the methylene carbon atom adjacent to the acetylenic bond only.

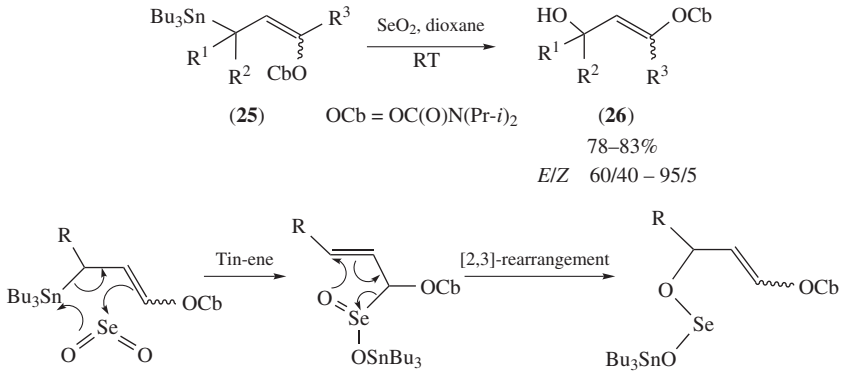
Thus, selenium(IV) oxide α-hydroxylation of methyl santalbate (**22**) gave exclusively methyl 8-hydroxyoctadec-11*E*-en-9-ynoate (**23**) in 70% yield and 6% of the corresponding oxo derivative **24** (Scheme 5)[59].



SCHEME 5. Selenium(IV) oxide oxidation of enyne system

The hydroxyl group can be introduced in an α-position to the C=C bond by selenium(IV) oxide oxidation of easily available 3-tributylstannyl-1-alkenyl carbamates **25**. The corresponding allylic alcohols **26** are produced in high yields and under mild

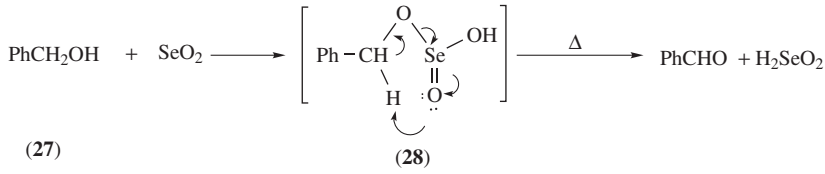
conditions. A plausible mechanistic pathway for the reaction could involve a sequential process, analogous to the one described in the classical SeO_2 reaction mechanism with two consecutive pericyclic reactions. The first step could be a selenoxide tin–ene reaction followed by subsequent sigmatropic [2,3]-rearrangement as depicted in Scheme 6.



SCHEME 6. Oxidation of 3-tributylstannyl-1-alkenyl carbamates with SeO_2

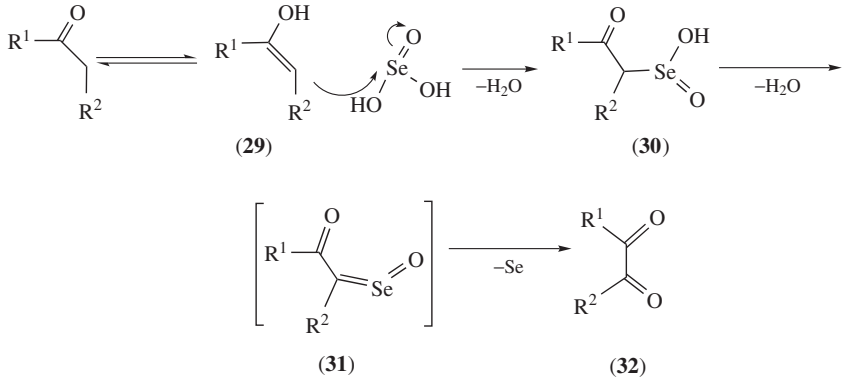
The higher electropositivity of Sn compared with H can account for the milder reaction conditions required to initiate the ene reaction, by comparison with the classical allylic oxidation reactions. Moreover, the weaker C–Sn than C–H bond can also facilitate the initiation of the reaction. The high stereoconvergence observed for the allylic double bond can be due to the steric preferences in the sigmatropic [2,3]-migration[65].

b. α-Oxygenation of alkenes and enolizable ketones. Selenium(IV) oxide can introduce carbonyl functionality at activated positions and can also affect highly activated saturated sites[1, 32, 34]. In some cases, allylic and propargylic alcohols have been accompanied by the other higher oxidized product aldehydes or ketones[59, 61, 62, 66]. When an alkene is oxidized by excess SeO_2 under more severe conditions, the final product is an α,β-unsaturated aldehyde or ketone[67–69]. Silica gel supported SeO_2 with TBHP was used for oxidation of primary allyl alcohols into α,β-unsaturated aldehydes. The reaction carried out under mild conditions is selective and secondary allyl or benzyl alcohols and saturated alkanols remain unreactive[70]. It is possible that initially formed allyl alcohol is subsequently oxidized according to a mechanism similar to that proposed for aromatic alcohols **27** (Scheme 7), where the reaction proceeds via the intermediate selenic(IV) ester **28**, which spontaneously decomposes to a carbonyl compound[71].



SCHEME 7. Oxidation of benzyl alcohol with selenium(IV) oxide

The mechanism for oxidation of active methylene groups in enolizable carbonyl compounds is based on the assumption that the key intermediate in this sequence is the β-ketoseleninic acid **30**, formed by electrophilic attack of selenic(IV) acid on the enol **29**. Pummerer-like decomposition of **31** yields the α-diketone **32** (Scheme 8)[1, 72].



SCHEME 8. The mechanism of oxidation of active methylene group in an enolizable carbonyl compound with selenic(IV) acid

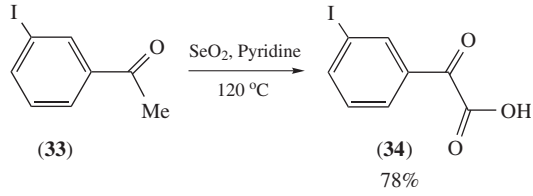
Oxidation of an activated methyl or methylene group with SeO_2 is a general convenient method to introduce a carbonyl group into the α-position of alkenes or enolizable carbonyl compounds[1, 32, 34]. Examples are phenylglyoxal, isolated in 72% yield from α-oxidation of acetophenone[73], and 2-indolylglyoxal, obtained from 2-acetylindole in 94% yield[74]. A methyl group in 6-methyluracil was readily oxidized to a formyl group and 2,4-dioxo-1*H*-pyrimidine-6-carbaldehyde (orotaldehyde) was produced in 58% yield[75]. Different phenyl and alkyl glyoxal monohydrates were obtained by selenium(IV) oxide oxidation of the corresponding acetophenones and alkyl methyl ketones[76]. Treatment of pentane-2,4-dione with SeO_2 in dioxane under reflux resulted in pentane-2,3,4-trione[77].

Oxidation of the allylic methyl group to a formyl group followed by $NaBH_4$ reduction of an aldehyde group was a crucial step for synthesis of the group named bakkanes, the sesquiterpenoids possessing a *cis*-hydrindane skeleton[78]. Camphor-derived dicarbonyl compounds and 3-oxocamphorsulfonylimine were synthesized in 60–92% yield, from the corresponding ketones or sulfonylimine, by microwave-assisted oxidation with SeO_2[79]. Similar oxidation of 1,2-diarylethanones gave corresponding diones[80]. Compared to the classical reaction conditions, the reaction was completed in a much shorter time, and removal of the selenium precipitate from the reaction mixture is easier.

A series of biologically active α-ketocarboxylic acids was synthesized by heating aryl methyl ketones with selenium(IV) oxide in pyridine[81–83]. For instance, *m*-iodoacetophenone (**33**) was efficiently oxidized to the α-ketoacid **34** (Scheme 9)[82].

A novel one-pot synthesis of aryl α-ketoesters involves oxidation of aryl ketones using selenium(IV) oxide and followed esterification accompanied by ketalization and hydrolysis[84]. Competitive coupling of α-methylene carbons was observed when ferrocenyl ketones $FcCH_2COR$ were oxidized with SeO_2. The major products were 1,4-butanediones RCOCH(Fc)–CH(Fc)COR instead of the expected diketones FcCOCOR[85].

The TBHP/SeO_2 has been also used to convert alkenes to their corresponding α,β-unsaturated ketones[86] or aldehydes[87–89] under standard conditions and extended reaction

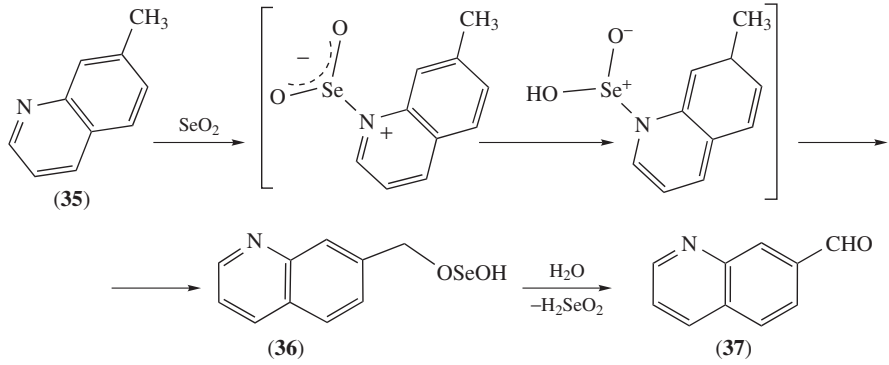


(**33**) (**34**) 78%

SCHEME 9. Selenium(IV) oxide oxidation of an aryl methyl ketone to α-ketocarboxylic acid

periods or by using silica gel-supported SeO_2[87]. The same reagent was found to be highly selective for the oxidation of allylic methyl groups to *trans*-α,β-unsaturated aldehydes under microwave irradiation[90]. The TBHP/SeO_2 reagent was applied for the synthesis of 1,2,3-triones from 1,3-diketones[91]. The urea-hydrogen peroxide, in the presence of catalytic quantities of SeO_2 under microwave irradiation, has successfully led to allylic oxidation of alkenes while keeping intact the other chemical functionalities[92].

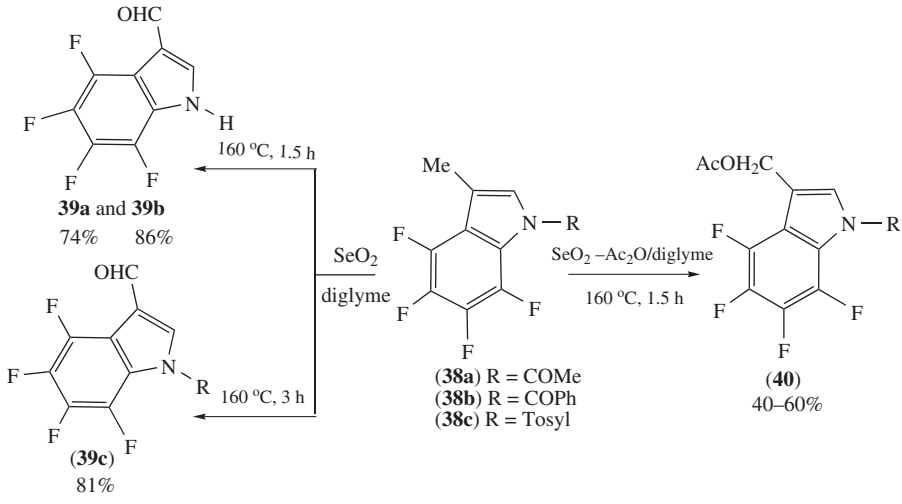
c. Oxidation of the methyl group in arenes and heteroarenes. The well-known selenium(IV) oxide oxidation of methylpyridines, methylquinolines, methylphenanthrolines, methylpterines and related heterocycles by heating with selenium(IV) oxide in dioxane is a good way for synthesis of the corresponding aldehydes[93–102]. The 2-methyl group is more susceptible toward oxidation than 4-methyl group, e.g. in the 2,4-dimethylquinoline or its oxide, the 2-methyl group was oxidized preferentially[103]. The relative ease of over-oxidation to carboxylic acid is the most serious disadvantage of the reagent. The reaction can be reasonably interpreted by analogy with ketone oxidation as illustrated by the conversion of 7-methylquinoline (**35**) to the corresponding aldehyde **37** via selenic(II) ester **36** (Scheme 10)[104]. The oxidation can be stopped at the first stage in the presence of acetic anhydride. The intermediate selenic(II) ester is re-estrified and the acetate derived from the primary alcohol is formed.



(**35**) (**36**) (**37**)

SCHEME 10. Selenium(IV) oxide oxidation of the methyl group in 7-methylquinoline

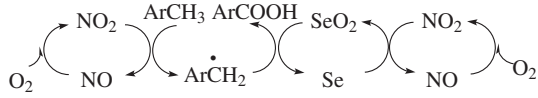
One example is the selective oxidation of 3-methyl-4,5,6,7-tetrafluoroindoles **38a–c** to the aldehydes **39a–c** or acetates **40** (Scheme 11)[105].



SCHEME 11. Selenium(IV) oxide oxidation of the methyl group in 3-methyl-4,5,6,7-tetrafluoroindoles

A subsequent oxidization of the formyl group to carboxylic group, which underwent spontaneous decarboxylation, was applied for selective elimination of the methyl substituent from azaheterocyclic compounds such as 2,4-dimethylselenazole[106], 2-methyl-3-nitropyridine *N*-oxides[107] or 7-methylxantopterin[108].

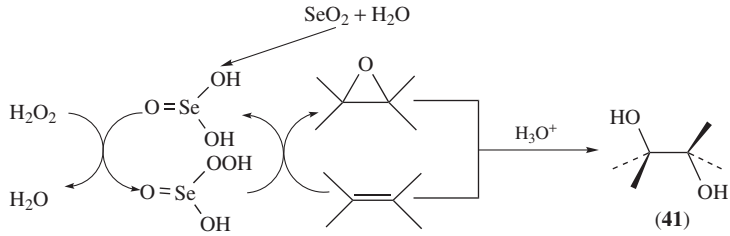
Oxidation of toluenes to benzaldehydes was improved by the formation of active oxidant obtained by treatment of SeO_2 with TBHP, prior to addition to the substrate. However, the oxidation of toluenes to benzaldehydes, in the presence of other oxidizable groups, is most often troublesome. The TBHP/SeO_2 reagent allowed the oxidation of activated methyl groups of *N*-heterocyclic compounds under milder conditions than SeO_2 alone without the formation of the over-oxidized carboxylic acids[109]. On the other hand, the oxidation of benzylic groups to the corresponding carboxylic acid functionality is mediated by a combination of selenium(IV) oxide (or elemental selenium) and nitrogen oxides while the stoichiometric oxidant is dioxygen. 2-Methylnaphthalene, after 4 h at 160 °C was completely reacted, forming 2-naphthalenecarboxylic acid in 80% yield. Under the same reaction conditions 4-pyridinecarboxylic acid was obtained from 4-methylpyridine in 94% yield. The proposed mechanism is summarized in Scheme 12. Nitric oxide (NO) is oxidized rapidly and spontaneously to nitrogen dioxide (NO_2). The latter has two functions. First, it abstracts one of the benzylic hydrogens from the substrate to form the benzyl radical, nitric oxide and water. Second, it oxidizes selenium to SeO_2 (or H_2SeO_3 formed in the presence of water), which then selectively oxidizes the benzyl radical to the corresponding aldehyde and finally to acid[110].



SCHEME 12. The mechanism of nitrogen oxides/SeO_2 benzylic oxidations

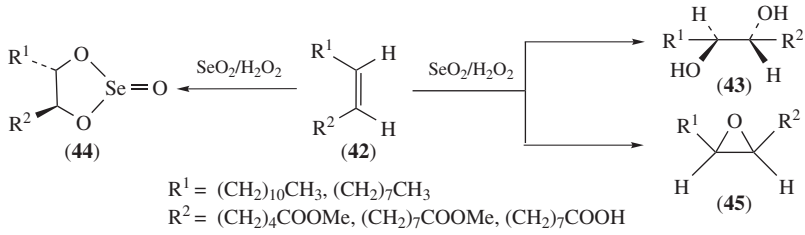
d. 1,2-Dihydroxylation of alkenes. A number of alkenes were *trans*-dihydroxylated with 30% aqueous hydrogen peroxide in the presence of 20 mol% of SeO_2 at room temperature. The isolated yield of the diols were in the range 55–88%. Cyclic, acyclic, terminal and internal alkenes were smoothly converted to their corresponding diols and no α-hydroxylation or α-oxygenation to aldehydes or ketones was observed. It was found that aliphatic alkenes exhibited better results than their aromatic analogues, and the sterically hindered double bonds exhibited poor yield compared with less hindered ones. When arylidenemalononitriles were used as substrates, they produced the corresponding carbonyls due to the presence of the two electron-withdrawing groups on one terminal of the olefins. It was proposed that in the presence of water, selenium(IV) oxide forms selenic(IV) acid which is oxidized to the peroxy acid with hydrogen peroxide.

The peroxyselenic(IV) acid is responsible for the epoxidation of alkenes, which in the presence of water and selenic(IV) acid forms the corresponding diols **41** (Scheme 13)[111]. A novel SeO_2-mediated dihydroperoxidation of 3-aryl-1,4,5,6-tetrahydropyridine was also examined[112].



SCHEME 13. Hydrogen peroxide *trans*-dihydroxylation of alkenes catalyzed by SeO_2

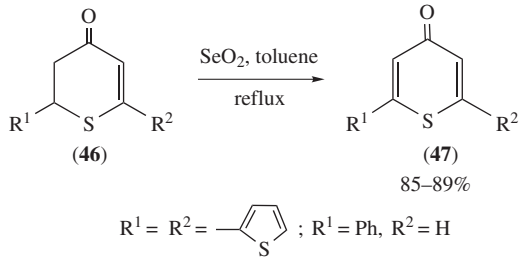
Long-chain alkenes and unsaturated acid esters **42** oxidized with H_2O_2/SeO_2 at ambient temperature gave, depending on the reaction time, vicinal diols **43**, selenite esters **44** and epoxides **45**. Methyl oleate gave after 4 h the epoxide **45**, while after prolonged time (24 h) the ester **44**, accompanied with diol **43**, was the major product (Scheme 14). This supported the hypothesis that the sequence of product formation is epoxides → selenite esters → vicinal diols[113].



SCHEME 14. Reaction of the C=C bond in long-chain alkenes with H_2O_2/SeO_2

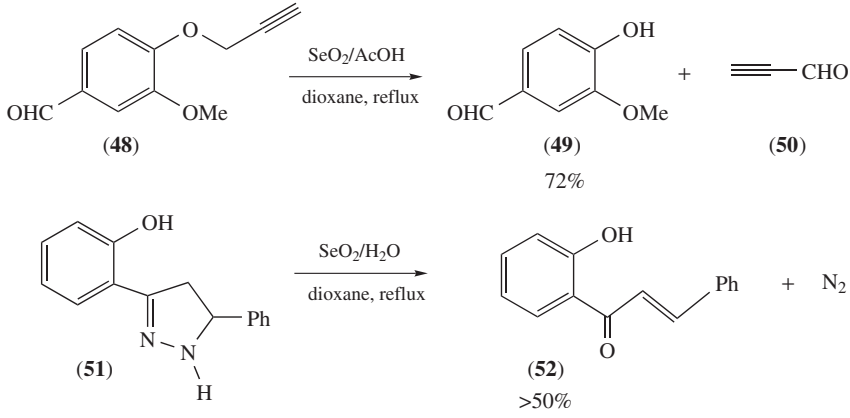
e. Dehydrogenation and oxidative C–O and C–C bond cleavage. The elimination reaction, including dehydrogenation, is favored when a strong conjugated system can be formed, and is often applied for aromatization of unsaturated carbocyclic and heterocyclic

systems. For this purpose selenium(IV) oxide is a good reagent. An example is dehydrogenation of dihydro-4*H*-thiopyran-4-ones **46** to resonance-stabilized 4*H*-thiopyran-4-ones **47** (Scheme 15)[114, 115]. 1,4-Dihydropyridines were aromatized in a similar way, using stoichiometric SeO_2 at ambient temperature, in 87–98% yields[116]. Most recently, aromatization of Hantzch 1,4-dihydropyridines to the corresponding pyridines was carried out in heterogeneous conditions in 75–92% yields using silica-supported P_2O_5 and SeO_2 as the reagent in dichloromethane at 40 °C[117]. Microwave-assisted dehydrogenation of dihydropyridazinones with SeO_2 in solid state results in aromatization of the heterocyclic ring[118]. Selenium(IV) oxide activated by trimethylsilyl polyphosphate in carbon tetrachloride effectively aromatizes substituted cyclohexenes and cyclohexadienes under mild reaction conditions[119].



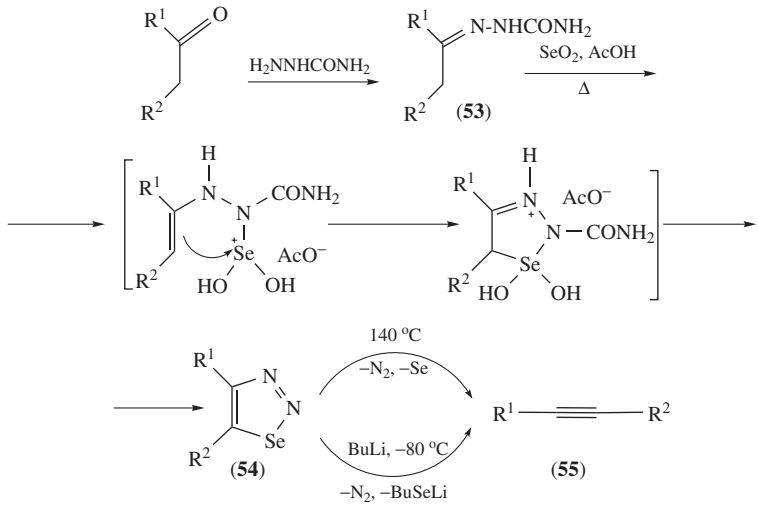
SCHEME 15. Selenium(IV) oxide dehydrogenation of dihydro-4*H*-thiopyran-4-ones

Attack of selenium(IV) oxide at activated positions can lead to oxidative bond cleavage when appropriate leaving groups are present. Aryl propargyl ethers **48** undergo oxidation at the α-alkynyl position to afford a phenolic species **49** and propargyl aldehyde (**50**). The analogous aryl allyl ether fragmentations occur in somewhat lower yields[32, 120]. (Hydroxyaryl)pyrazolines **51** have been oxidized with nitrogen extrusion to afford 2′-hydroxychalcone **52** (Scheme 16)[32, 121].



SCHEME 16. Selenium(IV) oxide C−O and C−C bond cleavage

f. Oxidative ring closure and ring transformations. Selenium(IV) oxide reacts with semicarbazones of aldehydes or ketones **53** including cyclic ketones with two geminal α-hydrogen atoms under heating in acetic acid or dioxane. The oxidative ring closure take place and 4-substituted, 4,5-disubstituted, as well as carbocyclic and heterocyclic fused 1,2,3-selenadiazoles **54** are produced[122, 123] (Scheme 17).

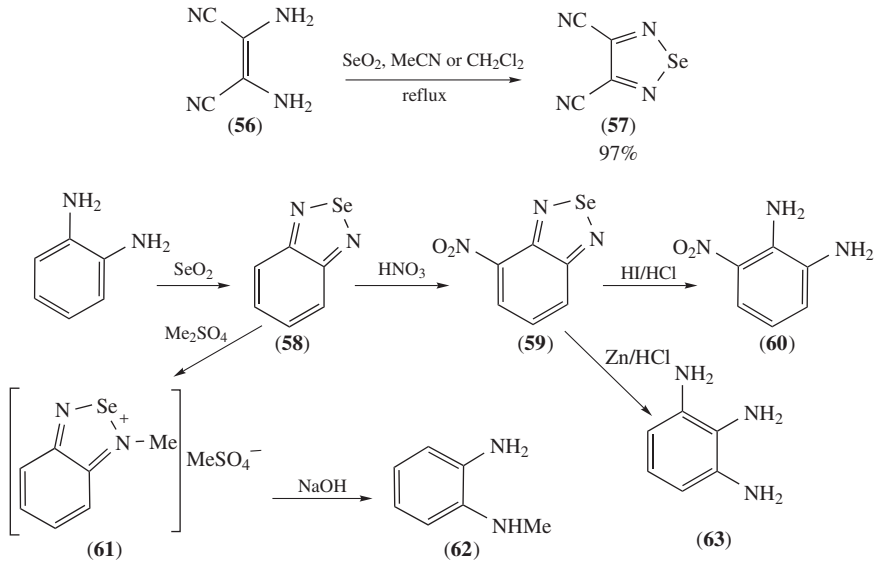


SCHEME 17. Selenium(IV) oxide oxidative cyclization of semicarbazones followed by ring decomposition of the formed 1,2,3-selenadiazoles

The reaction is the most general way for synthesis of these heterocycles, and has a practical value because 1,2,3-selenadiazoles are utilized as useful synthetic intermediates through a variety of thermal and photochemical decomposition reactions with the loss of nitrogen and/or selenium. For example, the thermolysis of **54** or their decomposition with butyllithium gave the alkynes **55**. In this manner cycloalkynes were obtained by thermolysis of 1,2,3-selenadiazoles fused to carbocyclic rings[124]. More recently, ethoxycarbonyl hydrazones and tosylhydrazones were also used for the reaction with SeO_2 in acetic acid and in this manner some 1,2,3-selenadiazoles were prepared for evaluation as microbials[125, 126]. A number of works on the synthesis and use of 1,2,3-selenadiazoles has been presented in reviews[127–131] and more recently published original papers[132–137].

Most ring syntheses of 1,2,5-selenadiazoles and their fused systems such as 2,1,3-benzoseladiazoles involve the reaction of 1,2-diamines with selenium(IV) oxide or selenium oxychloride[128, 130, 138, 139]. For example, reaction of diaminomaleodinitrile (**56**) with SeO_2 in acetonitrile or CH_2Cl_2 gave almost quantitatively 3,4-dicyano-1,2,5-selenadiazole (**57**) (Scheme 18)[140, 141].

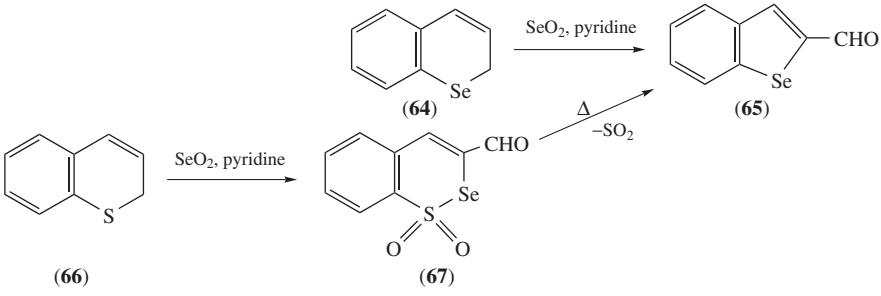
In a similar way, 1,2-phenylenediamine and different ring-substituted derivatives were cyclized to 2,1,3-benzoselenadiazoles in good to excellent yield[142–144]. Some of them, such as unsubstituted benzoselenadiazole (**58**), are valuable synthetic intermediates used for preparation of *N*-methyl-1,2-phenylenediamine (**62**) by deselenenylation of 2,1,3-benzoselenadiazolonium *N*-methyl salt (**61**) and 3-nitro-1,2-phenylenediamines (**60**) or 1,2,3-triaminobenzene (**63**) by deselenenylation of 4-nitro-2,1,3-benzoselenadiazole (**59**) (Scheme 18)[131, 145].



SCHEME 18. Selenium(IV) oxide cyclization of 1,2-diamine into 1,2,5-selenadiazole and conversion of 2,1,3-benzoselenadiazole into substituted phenylenediamines

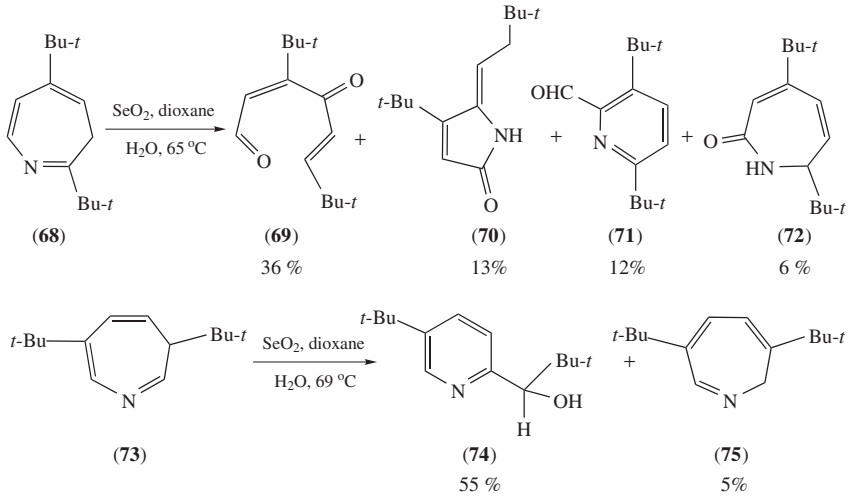
5-Amino-3-methyluracils treated with SeO_2 in dioxane at 110 °C produced isoselenazolo[4,3-d]pyrimidines[146]. Under the action of selenium(IV) oxide and hydrogen bromide 3-phenylpropiolamides were transformed into the corresponding 3-bromobenzo[*b*]selenophenes[147]. A single-pot novel synthesis of various substituted 4-hydroxyimidazoles by SO_2-mediated oxidation of 1-aryl-2-phenyl(thiomethyl)secondary amino-4-*N*,*N*-dimethylamino-4-methyl-1,3-diazabuta-1,3-dienes has been reported recently[148].

Selenium(IV) oxide affects the oxidative ring contraction of six-membered selenaheterocyclic ring to a five-membered ring. Thus, oxidation of selenachromene (**64**) leads to the benzo[*b*]selenophene-2-carboxaldehyde (**65**) while the corresponding oxidation of thiochromene (**66**) provides the selenosulfone **67**, which is degraded thermally to the same aldehyde **65** (Scheme 19)[149–151].



SCHEME 19. Oxidative ring contraction of selenachromene and thiochromene with SeO_2

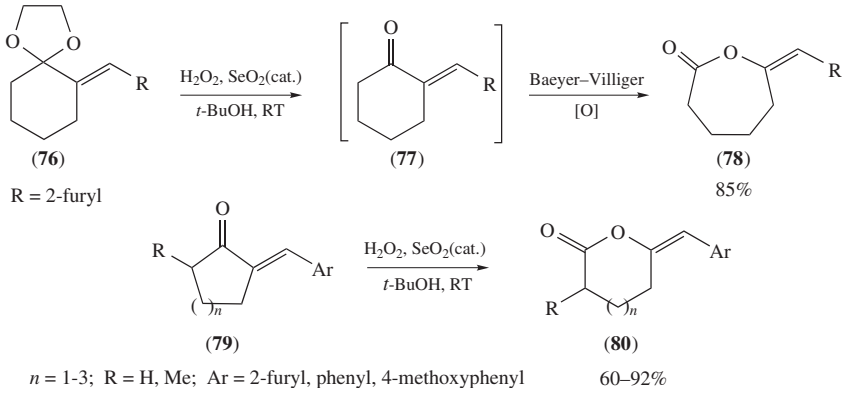
The reaction of 2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline with SeO_2 in AcOH/H_2O resulted in ring transformation to give the 1,4-dihydro-4-oxopyridazino[3,4-*b*] quinoxaline[152] while the result of oxidation of dialkyl-3*H*-azepines **68** and **73** depends on the position of alkyl groups and different products **69**–**72** and **74**, **75** respectively are formed (Scheme 20). In the case of **68** electrophilic attack on the 4,6-diene of 3*H*-azepine ring gave the intermediate 4,7-diol, which is converted to the final product **69** via an oxepine structure followed by elimination of NH_3. The initial step of the other transformations is electrophilic attack of selenic(IV) acid on the nitrogen atom and N–Se bond formation, followed by ring hydroxylation and then contraction to a pyridine or pyrrole ring[153].



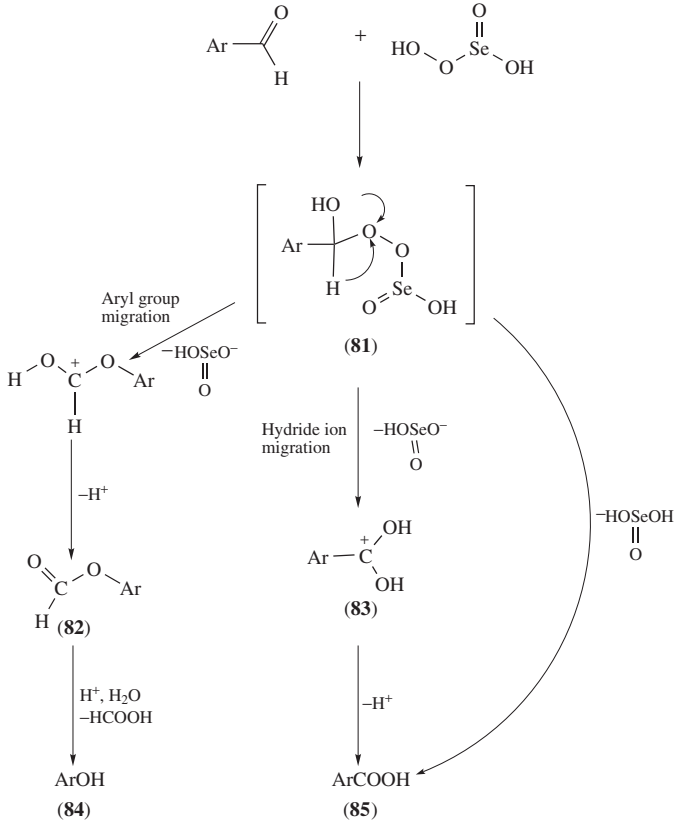
SCHEME 20. Selenium(IV) oxide oxidations of dialkyl-3*H*-azepines

Ring transformations using SeO_2 in catalytic amounts in conjunction with stoichiometric quantities of H_2O_2 include the ring contraction of cycloalkanones to norcycloalkane carboxylic acids[154, 155], and related rearrangements in acyclic ketones[154–158] as well as 3-ketosteroids[159, 160]. Moreover, it was observed that ketal **76** was rapidly converted, in high yield, into the *ε*-enol lactone **78**. A simple explanation for the formation of **78** involves acid-catalyzed hydrolysis of the ketal protecting group, followed by a Baeyer–Villiger-type oxidation of intermediate ketone **77**. The reaction extended to other 2-alkylidenecycloalkanones **79** yielded corresponding lactones **80**[161] (Scheme 21).

g. Miscellaneous transformations. The Baeyer–Villiger reaction using H_2O_2/SeO_2 for various benzaldehydes possessing hydroxy or methoxy substituents mainly in *ortho* and *para* position, and/or a furan ring afforded phenols rapidly in good yield or mixtures of the phenols and carboxylic acids. On the other hand, *meta*-substituted benzaldehydes or benzaldehydes carrying less effective electron-donating groups, electron-deficient heteroaromatic and aliphatic aldehydes were oxidized to the corresponding carboxylic acids[161–163]. This behavior can be explained by the mechanism presented in Scheme 22. The initial step of the reaction is addition of peroxyselenic(IV) acid to the aldehyde carbonyl group. Selenic(IV) acid is eliminated from adduct **81** and the overall process



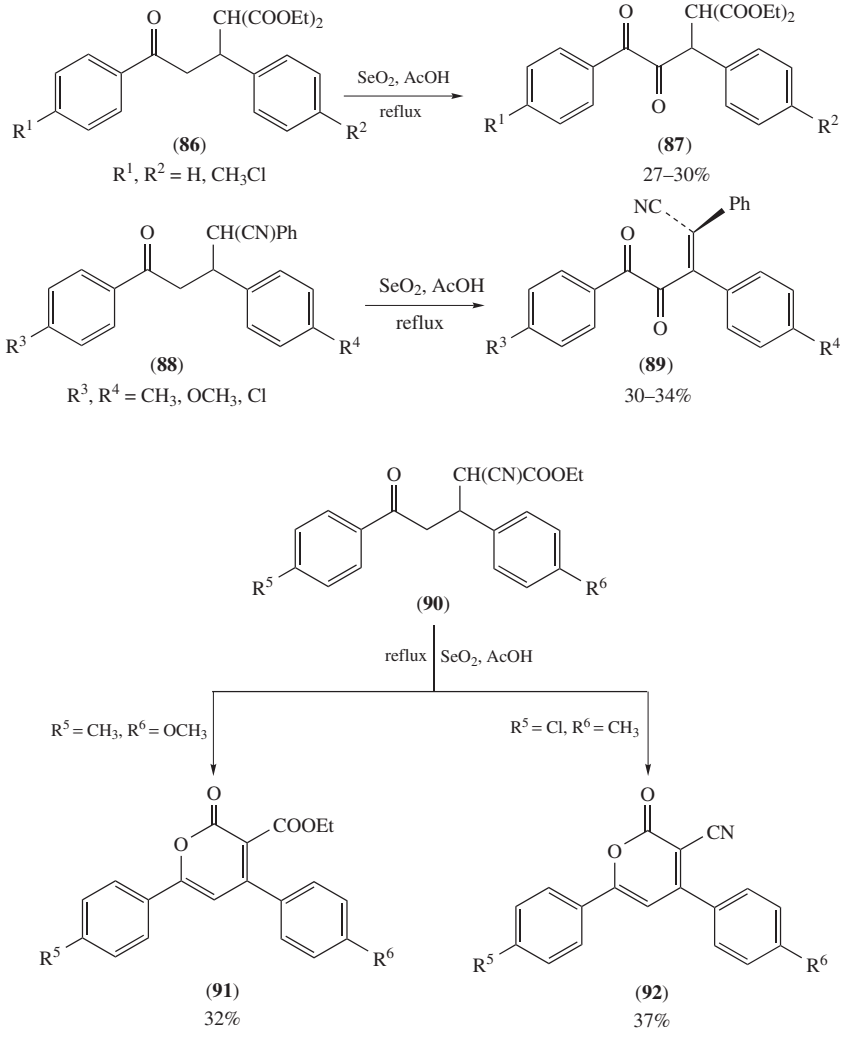
SCHEME 21. Lactonization of cycloalkanones with H_2O_2/SeO_2



SCHEME 22. Hydrogen peroxide oxidation of aromatic aldehydes catalyzed by SeO_2

can be characterized as an addition–elimination. When the aromatic ring is substituted with an electron-donating group, aryl migration to the electrophilic oxygen atom takes place, giving a carbocation from which a proton is abstracted and the formed formate **82** hydrolyzes to phenol **84**. The alternative pathway involves intramolecular hydride ion migration, and then elimination of a selenic(IV) anion. Subsequent deprotonation of the intermediate cation **83** affords the acid **85**. A competitive route to acid **85** is a direct elimination of selenic(IV) acid from adduct **81**[163].

With more complex molecules selenium(IV) oxide reacts in a different way, as in the case of the 3-substituted 1,3-diphenylpropan-1-ones **86**, **88** and **90** (Scheme 23).

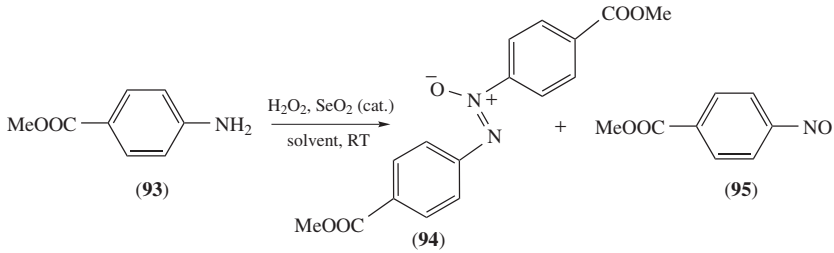


SCHEME 23. Selenium(IV) dioxide oxidation of 1,3-diphenylpropan-1-ones

The reaction depends mainly on the nature of the substituent present on the β-carbon atom, leading to different products **87**, **89**, **91** and **92** (by α-oxidation, dehydrogenation, enolization and cyclization)[164].

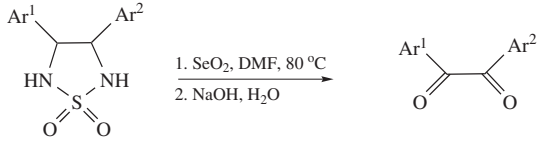
Selenium(IV) oxide in acetic anhydride has been used as oxidative coupling reagent for synthesis of 1,1′-diphosphaindigo derivatives from 1-ethoxy-1-oxophosphindolin-3-one[165].

The oxidation of aryl hydrazines by selenium(IV) oxide in acidic media provides a method for the preparation of diazonium salt[166]. *S*-Oxidation of sulfides in aqueous medium leads to sulfoxides[167] while *N*-oxidation of secondary amines with H_2O_2/SeO_2 is a convenient way of synthesizing nitrones[168–170]. Differently ring-substituted anilines were oxidized to nitroso compounds or azoxybenzenes using hydrogen peroxide and various catalysts, including selenium(IV) oxide. As has been shown for methyl 4-aminobenzoate (**93**), the result depends strongly on the solvent. Treatment of **93** with H_2O_2/SeO_2 in methanol at room temperature furnishes exclusively the azoxybenzene **94**. By conducting the oxidation with H_2O_2/SeO_2 in aprotic, non-polar dichloromethane, the nitrosoarene **95** was a major product (Scheme 24)[171].



SCHEME 24. Hydrogen peroxide oxidation of methyl 4-aminobenzoate catalyzed by selenium(IV) oxide

The C−N bond in some endocyclic sulfonamides can be split off and converted into a carbonyl group by oxidation with SeO_2 followed by hydrolysis. The treatment of 3,4-diaryl-1,2,5-thiazolidine 1,1-dioxides **96** with selenium(IV) oxide generates the unstable thiadiazole 1,1-dioxides, which are subsequently hydrolyzed to the corresponding diaryl 1,2-diketones **97**. Symmetrical and unsymmetrical diketones are readily prepared by this method[172] (Scheme 25).



Ar^1, Ar^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, 2-piperonyl

SCHEME 25. Conversion of 3,4-diaryl-1,2,5-thiazolidine 1,1-dioxides to diaryl 1,2-diketones

B. Organoselenium Oxidants and Oxygen-transfer Agents

1. Selenoxides

a. General comments. Organic selenoxides of general formula $R^1-Se(O)-R^2$ contain a seleninyl group (Se=O). They are colorless or white, odorless solids easily dissolved in many organic solvents: Selenoxides have a trigonal–pyramidal structure analogous to their sulfur analogues. The Se–C bond length in dimethyl selenoxide is 0.192 nm. The Se–O distance is 0.170 nm (compared with 0.153 nm in DMSO), consistent with a highly polar σ-bond. Selenoxides have a more polar and weaker Se–O bond than the S–O bond in the corresponding sulfoxides; the dissociation enthalpies are about 10 kcal mol^{-1} smaller. The significantly shorter hydrogen bond measured in the solid state for SeO···HX interactions (0.178 nm) in comparison with SO···HX (0.185 nm), where HX = HF, H_2O, 2-FC_6H_4OH, shows that selenoxides are better hydrogen bond acceptors than sulfoxides[173–176]. It facilitates the formation of adducts such as hydrates and hydrochlorides. Dimethyl, diethyl, diaryl, aryl methyl and vinylic selenoxides as well as selenoxides having no hydrogen on the β-carbon are relatively stable compounds. They can be isolated, stored and used as reagents or substrates while the selenoxides in which the β-carbon bears a hydrogen atom spontaneously undergo *syn*-elimination. Since the early 1970s it became obvious that the *syn*-elimination is a powerful method for generation of carbon–carbon double bonds and systematic investigation has been summarized in reviews[1–12].

The alkyl selenides are generally oxidized to selenoxides at a lower potential than the aryl selenides. This trend is different from that of the sulfur analogues, where aryl sulfides are easier to oxidize than their alkyl counterparts[177].

Selenoxides are readily reduced into selenides by reducing agents such as phosphorus iodides (P_2I_4 or PI_3)[178], phosphorus pentasulfide[179] and with triaryl phosphates[180]. Various alkyl, aryl and benzyl selenoxides (also sulfoxides, telluroxides, sulfones, selenones and tellurones) can be deoxygenated to the corresponding sulfides, selenides and tellurides in nearly quantitative yields using Mg–MeOH at ambient temperature[181]. Upon UV-irradiation, diphenyl and dibenzyl selenoxides underwent deoxygenation and α-cleavage competitively to give selenides, and diselenides[182]. The chemistry of selenoxides is of particular interest owing to their ability to stabilize adjacent anionic centers and synthetic usefulness[1–12, 17].

b. Formation of selenoxides. Selenoxides are easy to obtain by oxidation of selenides, which can be generated by nucleophilic, electrophilic or radical reactions[183]. It has been shown by experiments and by *ab initio* calculations that electron-withdrawing substituents stabilize selenides toward oxidation, whereas electron-donating substituents accelerate the oxidation process to selenoxides[184]. They are final products or when oxidant is used in excess, particularly in the presence of catalyst, their subsequent oxidation to selenones occurs (see Section II.B.2). Nevertheless, over-oxidation of selenoxides to selenones is seldom a complication, in contrast to sulfur analogues where competing sulfone formation is more difficult to avoid.

The preparation of optically active selenoxides is essential for asymmetric reactions. The difficulty of preparing optically enriched selenoxides is their configurational lability and they can racemize quickly in the presence of water and/or acid as they form achiral hydrates as intermediates[185]. Non-racemic selenoxides can be obtained in different ways by oxidation in a diastereselective fashion by using a selenide bearing a chiral substituent or in an enantioselective way by using a chiral oxidant. An alternative way is racemic resolution of enantiomers by their complexation with optically active binaphthol[186].

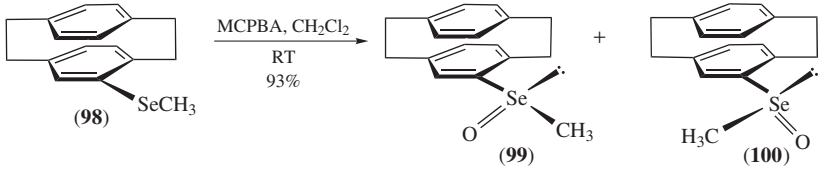
The facile oxidation of selenides can be achieved using different oxidizing agents; 30% hydrogen peroxide is commonly used as oxidant, particularly for unsaturated selenides

and in the presence of groups such as sulfides, amines, sulfoxides, tertiary alcohols, esters, lactones, nitriles and carboxylic acids. Generally the oxidant is used in excess, in THF at a temperature below 0 °C. For example, oxidation of dimethyl selenide with hydrogen peroxide at −15 °C gave dimethyl selenoxide in 91% yield[187]. When selenoxides having a hydrogen atom on the β-carbon are oxidized, it can be followed by a spontaneous *syn*-elimination reaction that can occur even at room temperature and usually the reaction is faster in aprotic solvents[1, 188–193].

t-Butyl hydroperoxide was used as a gentle oxidant in place of hydrogen peroxide. Its use permits one to avoid epoxidation and Baeyer–Villiger oxidation of keto group-containing selenides[194]. The Sharpless oxidant, a combination of *t*-butyl hydroperoxide and titanium(IV) alkoxide, afforded the selenoxides but stereoselectivity was lower than expected[195, 196].

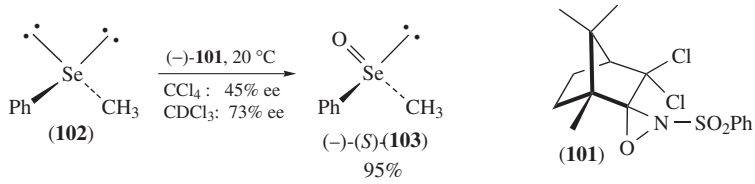
Sodium metaperiodate[197–199], ozone[192, 200, 201], 3-aryl-2-benzenesulfonyloxaziridines[202], thorium(III) nitrate[203], *t*-butyl hypochlorite[204], (dichloroiodo)benzene[198] and nitrogen oxides[205] were also used for conversion of selenides into selenoxides.

m-Chloroperoxybenzoic acid (MCPBA) and sometimes peroxyacetic acid were employed, at low temperature (−78 °C) in THF or dichloromethane, for synthesis of thermally unstable selenoxides. The presence of a double bond, a triple bond and an amino group is tolerated[197, 200, 206–210]. When chiral selenides derived from [2,2]paracyclophane systems were oxidized with this reagent, the chiral aryl substituent provided for asymmetric induction to a new selenoxide chiral center. Thus 4-methylseleno[2,2]paracyclophane (**98**) gave a mixture of enantiomeric selenoxides **99** and **100** (Scheme 26). Additional experiments show their 1:1 kinetic ratio and a 30:1 thermodynamic ratio at equilibrium[211].



SCHEME 26. Oxidation of 4-methylseleno[2,2]paracyclophane

(−)-α,α-Dichlorocamphorsulfonyloxaziridine (Davis reagent) (**101**) was successfully applied for stereoselective oxidation. Oxidation of methyl phenyl selenide (**102**) in $CDCl_3$ at 20 °C affords 95% yield of (−)-(*S*)-selenoxide (**103**) in 73% ee. Oxidation at −60 °C improves the ee to 83%. Higher ee values were observed in $CDCl_3$ compared to CCl_4 (Scheme 27)[212].

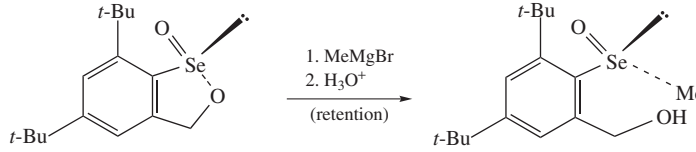


SCHEME 27. Enantioselective oxidation of methyl phenyl selenide with Davis reagent

The first synthesis and characterization of unstable monocyclic selenophene 1-oxide has been achieved by oxidation of sterically hindered selenophene with dimethyldioxirane at low temperature[213]. Oxidation of tetraarylselenophenes (2,4-dimethyl-3,4-diphenylselenophene, 2,4-dimethyl-di-*t*-butylselenophene and benzo[*b*]selenophene) with an excess of 2,2-dimethyldioxirane leads to 1,1-dioxides, whereas oxidation of 1-benzoselenophene with MCPBA results in its 1-oxide[214]. Oxidation of the selenium in the non-aromatic heterocyclic moiety of benzisoselenazol-3(2*H*)-ones is referred to in Section II.B.4.

A number of alkyl phenyl selenides were oxidized to the corresponding selenoxides in excellent yields and under mild reaction conditions, by the 2-nitrobenzenesulfonyl peroxy intermediates generated *in situ* from the reaction of 2-nitrobenzenesulfonyl chloride with potassium superoxide at −15 °C in dry acetonitrile[215]. Diphenyl selenide as well as phenyl benzyl and phenyl methyl selenides were oxidized to the corresponding selenoxides in methanol/water, in the presence of K_2CO_3, using singlet oxygen[216].

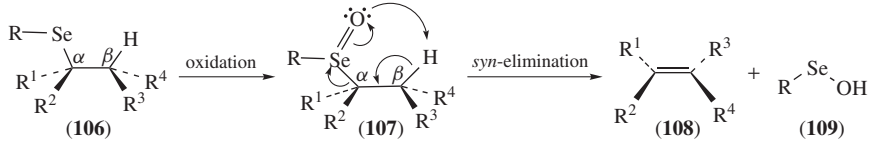
Indirect preparation of selenoxides is achieved by hydrolysis of dihalodiarylselenium[217,218] or by treatment of selenides with *N*-bromo- or *N*-chlorosuccinimide followed by hydrolysis of the intermediate adduct[204,219]. Kamigata and coworkers reported the synthesis and isolation of cyclic optically active seleninate esters such as **104**, and their transformation into chiral selenoxides **105** by treatment with Grignard reagent (Scheme 28). Pure individual enantiomers were obtained in high ee, but in very low preparative yield[220]. In further studies, they showed the stabilizing effect of intramolecular Lewis bases toward racemization of optically active selenoxides[221].



(*R*)-(−)-(**104**) (*R*)-(+)-(**105**)
6% ee 97%

SCHEME 28. Transformation of seleninate ester into chiral selenoxide

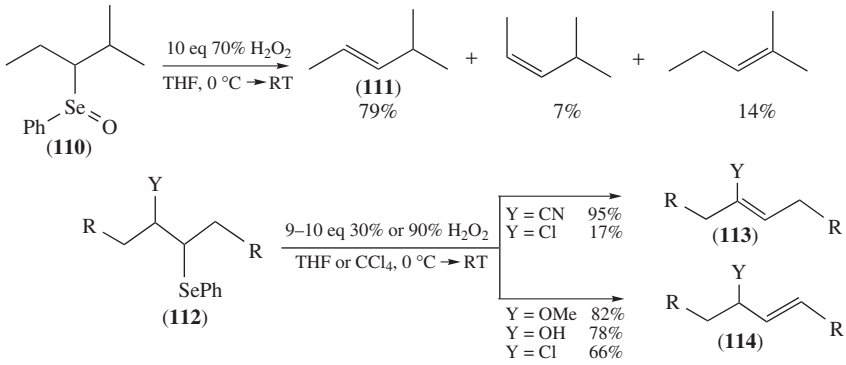
c. syn-Elimination and [2,3]-rearrangement. The selenoxide *syn*-elimination constitutes one of the most expedient methods for introducing a carbon–carbon double bond into a saturated substrate and numerous examples have appeared in the past 35 years[1,2,5–7,11,222]. The selenides **106** having a hydrogen atom on the β-carbon, prepared by substitution reaction, epoxide opening, ester or lactone hydrolysis, or enolate or nitronate selenenylation, are oxidized and formed *in situ* selenoxides **107**, which undergo subsequent *syn*-elimination. The process usually takes place under very mild conditions at or below room temperature to yield alkene **108** and selenenic acid **109** as by-product (Scheme 29). The strong polarization of the Se–O bond and the high basicity of the oxygen atom, as



SCHEME 29. *syn*-Elimination of selenoxides

well as cleavage of a relatively weak C−Se bond, contribute to the driving force of the reaction. In comparison to the corresponding sulfur compounds, the activation energy of *syn*-elimination is much lower.

Selenoxide eliminations usually favor formation of the less substituted olefin in the absence of heteroatom substituents or delocalizing groups as shown for the reaction of selenoxide **110**, where *trans*-4-methyl-2-pentene (**111**) is a main product (Scheme 30)[189]. Elimination generally proceeds away from β-oxygen substituents (e.g. hydroxyl, ether, acetoxy), strongly favoring allylic over vinylic products, whereas the effects of the nitrogen substituents are more variable and depend on the character of the nitrogen-containing functional group. The regioselectivity observed for the elimination, i.e. the formation of a vinylic product **113** from β-cyanoselenide **112** (Y = CN) and a mixture containing mainly allylic compounds **114** from the β-chloroselenide **112** (Y = Cl), agrees well with the theoretical calculations (Scheme 30)[223].

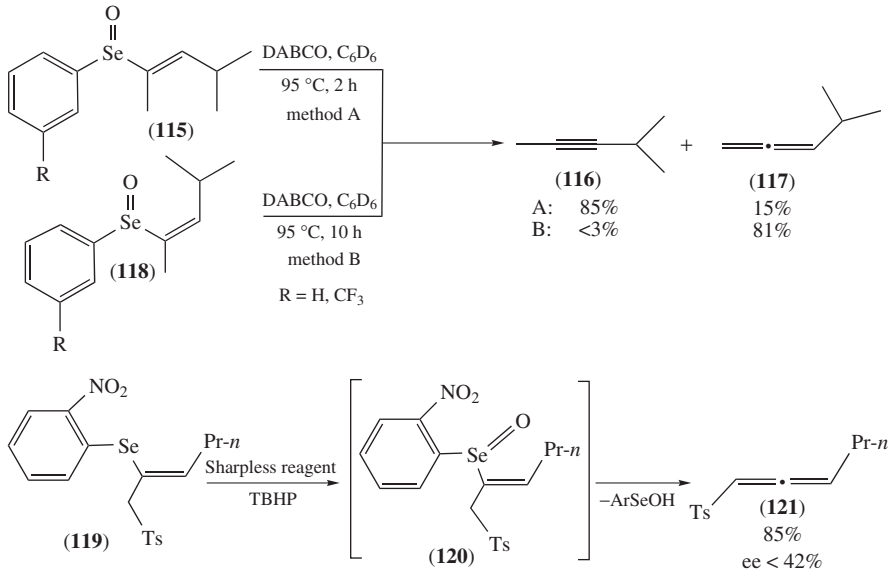


SCHEME 30. Regioselectivity of *syn*-elimination

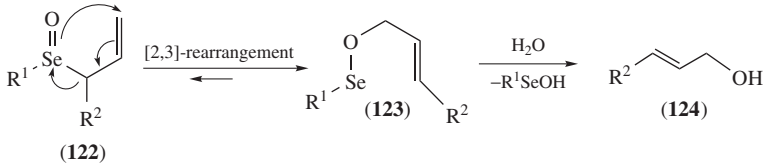
In contrast to the numerous reports of alkene preparation via selenoxide, there are relatively few examples leading to allenes or alkynes. Vinyl selenoxides **115**, that have both a *cis* hydrogen and an allylic hydrogen available for elimination, afford chiefly the corresponding alkyne **116** via hydrogen abstraction from the *cis* position, while the allene **117** is a minor product. In the compound **118** when no *cis* hydrogen is available, elimination toward the allylic position produces the corresponding allene **117** almost exclusively. The reaction is facilitated by substituents that render the eliminated hydrogen atom more acidic[222, 224] (Scheme 31).

This reaction can also be performed in a stereoselective way to generate optically active allenes. Compounds like **119** can be oxidized stereoselectively either by the method of Sharpless[196, 215, 225, 226] or by the Davis reagent[202, 227]. The subsequent elimination via selenoxide **120** gave the chiral allenic compound **121** in moderate enantiomeric excess (Scheme 31).

The elimination of selenenic acid from allylic selenoxides **122** does not lead to a conjugated diene, but a typical sigmatropic [2,3]-rearrangement involves transfer of oxygen from the selenium atom to the carbon atom to produce allylic selenenate **123**, which readily hydrolyzed to the corresponding allylic alcohol **124** (Scheme 32)[1, 2, 5, 7, 11]. In comparison with allylic sulfoxides, the advantage of the allylic selenoxides is that the activation energy for the rearrangement is much lower and the reaction proceeds smoothly even at low temperature[228].



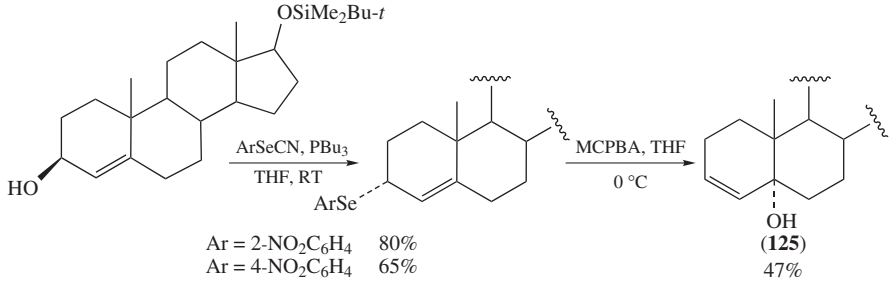
SCHEME 31. Elimination of selenoxides to alkynes and/or allenes



SCHEME 32. Sigmatropic [2,3]-rearrangement of allylic selenoxides

Oxidation of allylic selenides usually provides good yields of the corresponding primary, secondary and tertiary allylic alcohols via allylic selenoxides, followed by hydrolysis of the intermediate selenates. In these reactions, hydrogen peroxide or MCPBA, in solvents such as THF, methanol or dichloromethane, are the most common oxidants used for the oxidation of selenides to selenoxides. Functional groups that are generally compatible with the sigmatropic [2,3]-rearrangement include esters, amides, cyanides, ethers, ketones, aldehydes, alcohols, alkenes and alkynes. No special precautions are usually needed, but the addition of bases such as pyridine or triethylamine to the reaction is normally effective at improving the yields of the allylic alcohols. The double bond formed after sigmatropic [2,3]-rearrangement shows a strong preference for the *E* configuration in the case of 1,2-disubstituted alkenes. Density-functional theory was used to model the *endo* and *exo* transition states for sigmatropic [2,3]-rearrangement of allylic arylselenoxides. The *endo* transition state is generally preferred for selenoxides if there is no substitution at the 2-position of the allyl group. Based upon the relative energies of the *endo* and *exo* transition states, the enantioselectivity of rearrangements is expected to be greatest for molecules with substitutions at the 1- or (*E*)-3-position of the allyl group[229].

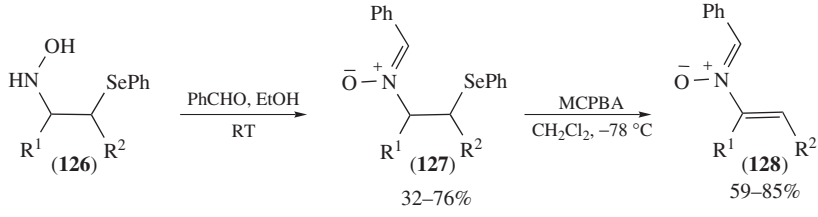
Sigmatropic [2,3]-rearrangement of selenoxides has been broadly exploited in synthesis of natural products and bioorganic chemistry[1, 2, 5, 7, 11]. Some examples are: the conversion of A-type prostaglandin to J-type[230], enantioselective total synthesis of the marine oxylipin solandelactone E[231], synthesis of steroidal alcohols **125** (presented in Scheme 33)[232] and intrastrand cross-linking of DNA[233].



SCHEME 33. Applications of sigmatropic [2,3]-rearrangement of selenoxides for synthesis of steroidal alcohols

Oxidative rearrangement of the allylic selenides in the presence of various nucleophilic amines provided synthetic access to a variety of allylic amine derivatives. Several D-α-amino acids and racemic β,γ-unsaturated α-amino acids were prepared in this manner[234].

The sigmatropic [2,3]-rearrangement of selenoxides tolerates a variety of functional groups. Enantioselective synthesis of chiral allylic alcohols is possible when the selenoxide is produced using a chiral oxidizing agent or a chiral auxiliary group including those that stabilize the selenoxide against racemization[211, 221, 235, 236]. Conjugated dienes have only been isolated in a few cases with modest yields, but this transformation requires the formation of strong conjugated system and steric constraints in the selenolate ester, and the sulfoxide route is more appropriate for the preparation of dienes[228, 237]. A general synthesis of *N*-vinyl nitrones **128**, a new type of heterodienes, has also been achieved using the selenoxide elimination strategy starting from easy-to-prepare β-hydroxylamines **126** via nitrones **127** (Scheme 34)[238].

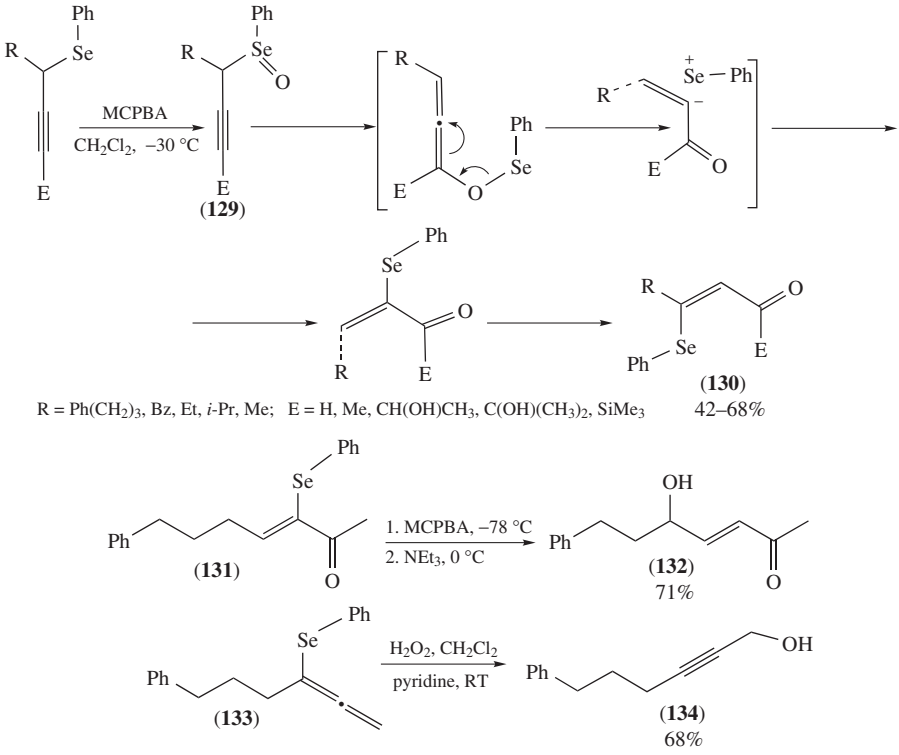


R^1, R^2 = H, Me, COOMe, Ph, $(H_2C)_4O$, *o*-$MeC_6H_4(CH_2)_2CH{=}CH_2$

SCHEME 34. Synthesis of *N*-vinyl nitrones

Propargylic selenoxides **129** and allenic selenoxides **133** also undergo the sigmatropic [2,3]-rearrangement. The first provides a route to the synthesis of α-arylselenoenones **130** which can be converted into γ-hydroxyenones, e.g. **131** into **132**, and the second allows the

preparation of α-unsubstituted propargylic alcohols[1, 209, 239, 240]. Oxidation–elimination of 3-(phenylseleno)-6-phenyl-1,2-hexadiene (**133**) to 6-phenyl-2-hexynol (**134**) is an example (Scheme 35)[239].



SCHEME 35. Sigmatropic [2,3]-rearrangement of propargylic and allenic selenoxides

Oxidation of an optically active allylic selenide, derived from L-proline with MCPBA, afforded the corresponding chiral allylic alcohol via asymmetric [2,3]-rearrangement with enantioselectivity up to 66% ee[241].

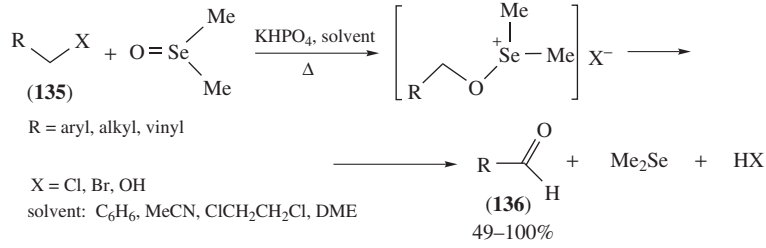
d. Selenoxides as oxidizing agents. Synthetic applications of selenoxides as reagents or oxygen-transfer catalysts are less common than the use of selenium(IV) oxide and are limited to only a few cases. The selenoxides, particularly diphenyl, bis(*p*-methoxyphenyl) and dimethyl, are known as mild reagents for oxidation of various organic compounds such as alkenes, thiols, sulfides, phosphines, hydrazides, amines, catechols, benzyl alcohols and halomethylarenes[1, 17, 18, 242–251]. Although their properties are generally similar to those of analogous sulfoxides, the selenoxides are more reactive because the Se–O bond is weaker than the S–O bond and its cleavage proceeds more smoothly.

Diphenyl selenoxide (or its precursor diphenyldichloroselenuran ($PhSeCl_2Ph$) has been employed for oxidation of hydrazides into 1,2-diacetylhydrazides and aromatic amines into azo compounds[242–244]. Oxidation of tertiary amines into *N*-oxides as well

as conversion of thiones, and thio- and selenophosphorus compounds with both of these reagents, can also be accomplished in this way[245–248]. Diphenyl selenoxide treated with trifluoroacetic anhydride in dry ethylene glycol dimethyl ether (DME) produces diphenylselenium bis(trifluoroacetate), a hygroscopic solid, which can be isolated in an inert atmosphere or generated *in situ* without isolation. It serves as a mild two-electron oxidant for phenols, catechols, amines and amino acids[252].

Di(*p*-methoxyphenyl) selenoxide was used for the oxidation of aromatic alcohols in combination with catalytic amounts of selenium(IV) oxide or elemental selenium[251]. For hydroxylation of the alkenes with diphenyl selenoxide, osmium(VIII) oxide was employed as the catalyst. In this case the oxyanion $OsO_4(OH)_2^{2-}$, formed *in situ* by oxidation of OsO_4 with diphenyl selenoxide in aqueous medium, is an active intermediate[250].

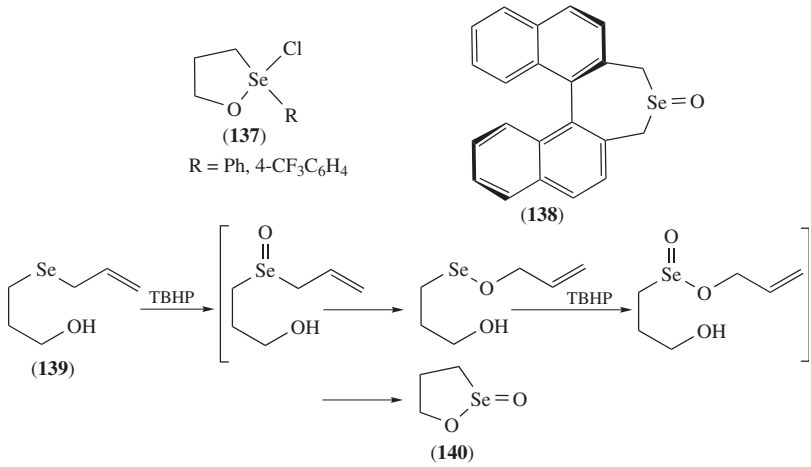
The dimethyl selenoxide, easy to prepare from dimethyl selenide, is a more reactive stronger base and softer nucleophile than dimethyl sulfoxide. It was found to be an excellent oxidizing agent which converts trivalent phosphorus compounds, thio- and selenophosphoryl compounds, and thiocarbonyl compounds into their phosphoryl or carbonyl analogues under very mild conditions. For this reason it is the reagent of choice for selective modification of thiocarbonyl compounds such as thiouracils and the corresponding thionucleosides and thionucleotides[247]. By employing dimethyl selenoxide, different aromatic, aliphatic and α,β-unsaturated aldehydes **136** were efficiently obtained from halomethyl or hydroxymethylarenes and saturated aliphatic or allyl alcohols (**135**). It was postulated that the first step of the reaction is nucleophilic attack of the oxygen atom on the electrophilic carbon of the halide, as shown in Scheme 36, or electrophilic attack of selenium on the oxygen atom of the alcohol. Finally, cleavage of the Se−O bond takes place and the products are formed in very high yields[253].



SCHEME 36. Oxidation of the halomethyl or hydroxymethyl group to the formyl group with dimethyl selenoxide

Other oxidants based on selenoxides are their adducts with sulfonic acids. An adduct formed from dimenthyl selenoxide and 2,2,2-trifluoroethanesulfonic acid or chlorooxaselenuranes, such as **137**, can be used for oxidation of sulfides into sulfoxides[254–256]. The chiral selenoxide **138** (Scheme 37) in the presence of 2,2,2-trifluoroethanesulfonic acid was found to oxidize dialkyl sulfides to the corresponding sulfoxides in good yield and with clean regeneration of selenide, although the expected stereoselectivity was low[257, 258].

Selenoxides and selenides have been used as catalysts in both H_2O_2/R_2SeO or H_2O_2/R_2Se systems, since the selenoxides are generated *in situ* from selenides and returned to the reaction cycle. 2-Carboxyphenyl phenyl selenide was successfully used as catalyst for oxidation of sulfides into sulfoxides and/or sulfones[259]. 3,5-Di(trifluoromethyl)phenyl benzyl selenoxide is an efficient catalyst for the epoxidation of various olefinic substrates and the Baeyer–Villiger oxidation of aldehydes and



SCHEME 37. Oxidative selenium reagents: chlorooxaselenurane **137**, chiral selenoxide **138** and seleninate ester **140**

ketones with hydrogen peroxide[260]. Another oxygen-transfer, easy-to-regenerate, catalyst 2,4-bis(perfluorooctyl)phenyl butyl selenide was used for epoxidation of alkenes by 60% hydrogen peroxide in fluorinated solvents. Oxidation of aldehydes and ketones under mono-, bi- or triphasic conditions with 3,5-bis(perfluorooctyl)phenyl butyl selenide gave the carboxylic acids or carboxyesters, respectively. The active intermediates were the corresponding bis(perfluorooctyl)benzeneseleninic acids[261, 262].

Epoxidation in combination with a subsequent ring-opening reaction leading to dihydroxylated products was developed recently. The alkene is epoxidized by peroxyselenic(IV) acid generated *in situ* by oxidation of diphenyl diselenide with hydrogen peroxide and the epoxide is opened by an S_N2-type reaction. The stereocontrol in these reactions depends on the steric and electronic properties of the substrate[263].

Allyl selenides are good catalysts for the oxidation of benzyl thioalcohol with TBHP. 3-Hydroxypropyl allyl selenide (**139**) proved to be exceptional in this reaction. It was found that this selenide is a procatalyst which undergoes a series of rapid oxidation and sigmatropic [2,3]-rearrangement steps to form a cyclic seleninate ester **140**, the true catalyst for hydroperoxide oxidation (Scheme 37)[264]. Ester **140** exibits also glutathione peroxidase mimic activity as catalyst for hydroperoxide oxidation[265].

Dendrimeric polyphenyl selenide can catalyze the oxidation of bromide with hydrogen peroxide for subsequent reaction with alkenes[266]. A dendrimer with twelve PhSe groups showed an autocatalytic effect which resulted in turnover numbers of above $6 \bullet 10^4$. The reaction is initiated by the bromonium cation generated in the uncatalyzed background reaction[267]. The impressive catalyst for the brominations of arenes and for bromolactonization is the easily recoverable (4-hydroxymethyl) phenyl selenoxide. The catalyst is easily separated from the reaction mixture by filtration and the recovered catalyst can be reused without loss of activity[268].

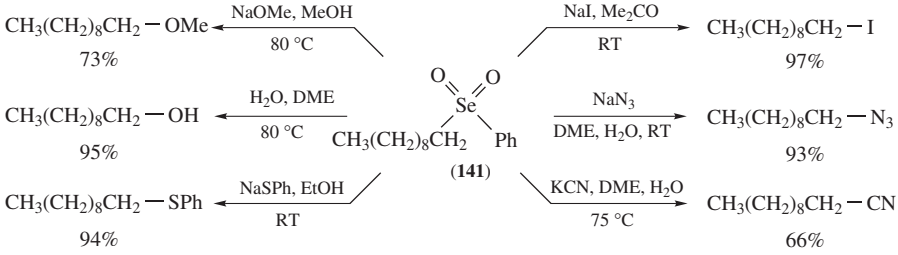
2. Selenones

Selenones $R^1-Se(O_2)-R^2$ contain a selenonyl group (SeO_2), and are counterparts of their well-known analogue sulfur sulfones[1, 258, 269]. Some selenones are stable compounds

and their structure was completely elucidated by X-ray diffraction techniques as for ethyl phenyl selenone[270]. The lower alkyl phenyl selenones are quite water soluble and at temperatures around 100 °C decompose, through an unknown mechanism.

Selenones are easily available by oxidation of selenides or selenoxides but the reactivity of most selenoxides prevent access to the corresponding selenones. The earlier literature has reported synthesis of diaryl, aryl, methyl and dimethyl selenones by oxidation of stable selenoxides using potassium permanganate[271], ozone[272] or MCPBA[273]. The direct oxidation of selenides by iodosylbenzene[274], hydrogen peroxide[275], potassium permanganate[276] and oxone[277] has also been described. Aqueous sodium hypochlorite and a peroxo complex of molybdenum $[MoO(O_2)_2(H_2O)(hmpa)]$ are useful reagents for rapid oxidation of a variety of selenides and selenoxides to the corresponding selenones at ambient temperature in 69–91% yield[278, 279].

Despite the fact that a number of selenones including diaryl, dialkyl, alkyl aryl, vinyl and cyclopropyl derivatives have been reported, their practical use as compared with selenoxides or sulfones is still limited[1, 258]. None of them was used as an oxidizing reagent. However, the excellent leaving group properties of the benzeneselenonyl group ($PhSeO_2$) have been synthetically useful for intermolecular nucleophilic substitution. The illustrative examples where the benzeneselenonyl group in decyl phenyl selenone (**141**) is substituted with different nucleophiles are given in Scheme 38. Competitive experiments using dodecyl selenone and dodecyl halide revealed that the benzeneselenyl moiety is a better leaving group than bromide or iodide ion[280].

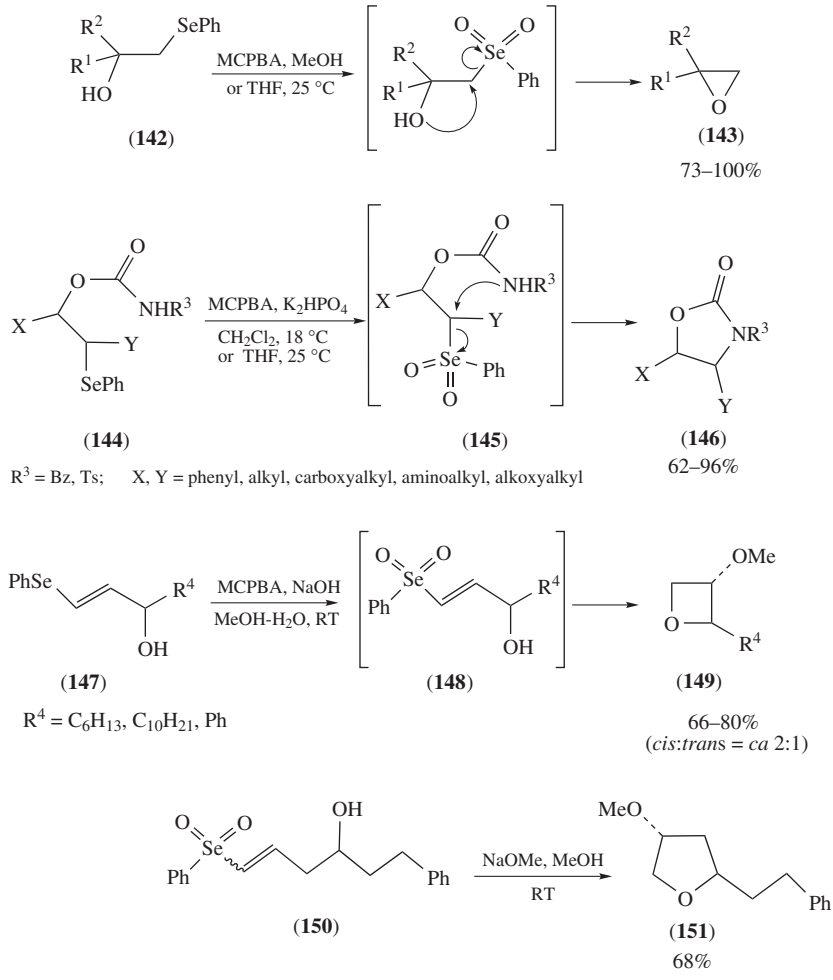


SCHEME 38. Nucleophilic substitution of decyl phenyl selenone

When selenides are employed as starting materials, it is not always necessary to isolate the selenones in order to obtain the corresponding substitution products. Alkyl phenyl selenides treated with excess MCPBA in methanol gave alkyl methyl ethers in high yields via the corresponding selenones as intermediates[281–283]. The substitution of the $PhSeO_2$ group by methanol has been shown to occur with inversion of configuration[258]. In a similar manner, long-chain dodecyl formate was obtained from dodecyl phenyl selenoxide or telluride[284] and nucleophilic displacement of the benzeneselenyl group with NaOH was utilized for synthesis of piperidine-derived alcohol[285].

For selenones having suitable nucleophile in the same molecule, the substitution occurs intramolecularly and it is a convenient way for synthesis of oxygen and nitrogen heterocycles[1, 258, 286–294]. Thus, the treatment of β-hydroxyalkyl phenyl selenides, such as **142**, with excess MCPBA affords the corresponding oxiranes **143** (Scheme 39)[286].

Intramolecular nucleophilic substitution of the $PhSeO_2$ group by the nitrogen atom of *N*-tosyl or *N*-benzylcarbamate nucleophile in selenones **145** generated *in situ* from selenides **144** is a key step of stereospecific synthesis of various 5- and 4,5-substituted-1,3-oxazolidin-2-ones **146**[289].



SCHEME 39. Nucleophilic intramolecular substitution of the $PhSeO_2$ group in selenones

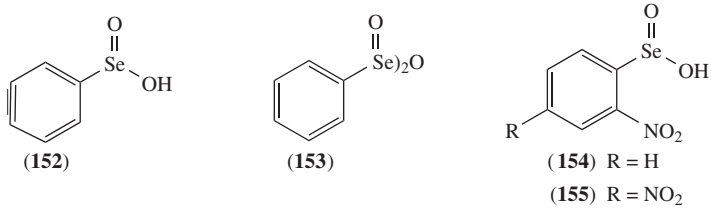
An electron-withdrawing arylselenonyl group in vinylic selenones can activate the carbon–carbon double bond toward nucleophilic addition. Several synthetically useful reactions, based on the fact that the selenonyl moiety is an excellent leaving group, have been elaborated. It made the phenyl vinyl selenide **147**, via vinylic selenone **148**, a valuable building block for synthesis of oxetanes **149**; likewise, selenone **150** is used for synthesis of tetrahydrofuran derivative **151**, as shown in Scheme 39[258, 290, 295].

3. Seleninic acids, peroxyseleninic acids, their precursors and derivatives

The seleninic acids are amphoteric and their acidity is comparable to that of the carboxylic acids ($PhSeO_2H$, $pK_a = 4.8$). A strong hydrogen bonding accounts for the

solubility in water and in the solid state. In contrast with the analogous sulfinic acids, they are moderately strong oxidizing agents; they are readily reduced with hypophosphorus acid, hydrazine and hydroxylamine hydrochloride. Thiophenol and selenophenol reduce the seleninic acids to the corresponding selenenic anhydrides, and alkanethiols give selenols[1].

In the 1970s and 1980s Barton, Ley and Back recognized the synthetic utility of benzeneseleninic acid (BSA) (**152**) and anhydride **153** as oxidants, or catalysts of hydrogen peroxide oxidation[1, 2, 4, 7–9, 13, 17, 296, 297]. A couple of years later, 2-nitro- and 2,4-dinitrobenzeneseleninic acid (**154** and **155**) were also successfully employed as catalysts for hydrogen peroxide oxidation of various organic compounds (Scheme 40).



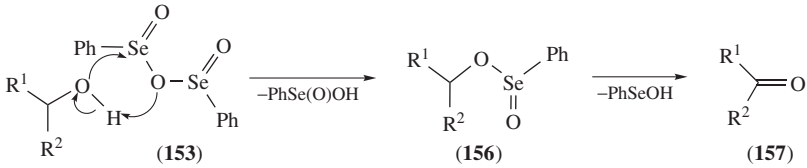
(**152**) (**153**) (**154**) R = H (**155**) R = NO_2

SCHEME 40. Areneseleninic acids and anhydride

These acids and anhydride **153** are easily prepared by oxidation of the corresponding diselenide with ozone, *tert*-butyl hydroperoxide, hydrogen peroxide, or by other, less frequently used, methods. The areneseleninic acids are stable compounds and can be stored for a long time without decomposition whereas alkaneseleninic acids easily decompose. Various optically active areneseleninic acids were obtained as solutions by optical resolution on a chiral column using medium-pressure liquid chromatography. Optically active seleninic acids with a low activity were more stable against racemization than those with high activity. The areneseleninic acids having bulky substituents in the *ortho* position were found to be effective for retarding the racemization proceeding via seleninate anion with the extrusion of a proton under dilute conditions[298, 299]. Each optical isomer of methaneseleninic acid was isolated as chiral crystals[300].

Commercially available anhydride **153** easily hydrolyzes into acid **152** upon exposure to moisture. All these compounds show some similarity to selenium(IV) oxide in their behavior, but often react more cleanly making isolation of the products less troublesome. Moreover, the formation of evil-smelling by-products is minimized and formation of red selenium is generally avoided.

The reaction of phenols with benzeneseleninic acid (**152**) gives 2-phenylseleno and 2,6-bis(phenylseleno)-1,4-benzoquinone via the corresponding 2- and 2,6-selenenylated phenols; initiating ene-reactions were suggested for both the *o*-selenenylation and the *p*-oxidation sequence and provide a useful route to 1,4-quinones[301, 302]. The use of anhydride **153** affords chiefly the corresponding 1,2-quinones[301] and the reaction was employed in the synthesis of alkaloids carbazoquinocins[303]. When the reaction is carried out in the presence of hexamethyldisilazane, a reactive intermediate, namely oligomeric $(RSeN)_4$, is formed and oxidized a phenol to selenoiminoquinones. The reduction gives *ortho*-hydroxyanilines or their derivatives, and is a useful, general way of synthesizing these important compounds[304–306]. Alkyl groups in alkyl arenes and alkyl heteroarenes are oxidized by anhydride **153** into carbonyl groups[307]. Aromatic and aliphatic alcohols give aldehydes or ketones **157** via postulated ester **156**, according to the mechanism presented in Scheme 41[308–310].

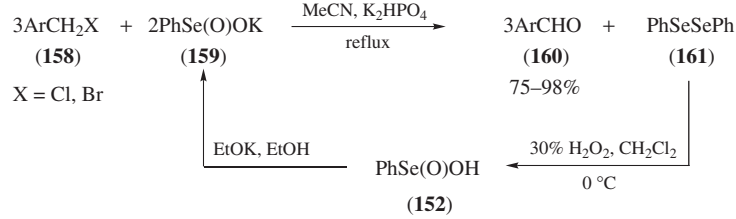


SCHEME 41. Oxidation of alcohol with benzeneseleninic anhydride

The acid **152**, and more often anhydride **153**, was employed for oxidation of sulfides, thioketones and thioacetals, and for oxidation of nitrogen compounds such as hydrazines, hydrazides, amines, imines, hydroxylamines and enamides. Oxidation of indolines afforded the corresponding indoles, and applications of this method include key steps in the synthesis of the ergot alkaloids[4, 311]. Pentafluorobenzeneseleninic acid and 2-(*N*-oxide)pyridineseleninic anhydride have been proposed as reagents for oxyfunctionalization of the allylic position in alkenes and oxidation of the hydroxymethyl group into the formyl group[312].

A variety of dehydrogenations of carbonyl compounds into the corresponding α,β-unsaturated derivatives with anhydride **153** has been reported. This reagent is particularly effective for dehydrogenation of biologically important cholestenones[308, 313, 314] and for α,β-dehydrogenation of lactones and lactams oxidized in some cases to imides[309, 311, 315]. When iodylbenzene ($PhIO_2$) or 3-iodylbenzoic acid is a stoichiometric oxidant, anhydride **153** or its precursor, diphenyl diselenide, can be employed in a catalytic amount[316].

Potassium benzeneseleninate (**159**), a stable nonhygroscopic solid, has been employed for the oxidation of halomethylarenes **158** into aldehydes **160** (Scheme 42). Diphenyl diselenide (**161**) resulting from this reaction can be quantitatively converted into salt **159** and reused[253]. A broad spectrum of substituted aromatic aldehydes, precursors of oxiranylquinones, expected to be bioactivated alkylation agents, was obtained in this way[317].



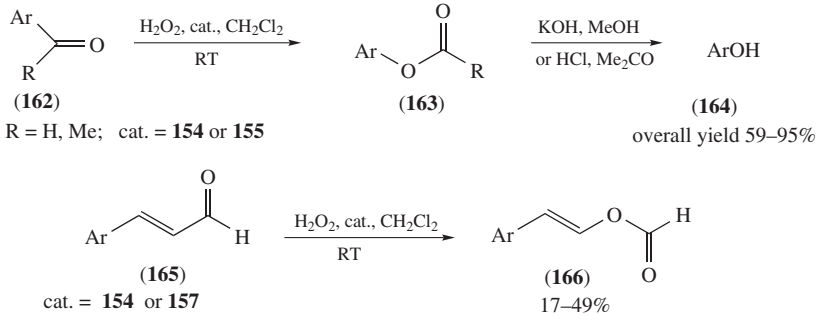
SCHEME 42. Oxidation of halomethylarenes with potassium benzeneseleninate

In the last two decades different, easily accessible seleninic acids, or more frequently their precursors diselenides (RSeSeR), and also the selenides and selenoxides have been used as catalysts for the oxidation of different organic compounds with hydrogen peroxide, TBHP and other oxygen donors[2, 8, 9, 17, 18, 318].

Peroxybenzeneseleninic acid, generated from diphenyl diselenide and hydrogen peroxide, was applied for the oxidation of primary aromatic amines to aromatic nitroso compounds, which can be used in a one-pot hetero Diels–Alder reaction with conjugated dienes to form oxazines as well as for preparation of azoxyarenes[319, 320].

2-Nitro- and 2,4-dinitrobenzeneseleninic acids (**154** and **155**) and related diselenides have been applied as catalysts for hydrogen peroxide and TBHP oxidation of different

groups of organic compounds[321–327]. Oxidation of aldehydes and aryl methyl ketones **162** (R = Me) into phenol formates or acetates **163**, which in a one-pot procedure are subsequently hydrolyzed to phenols **164**, is a useful way of synthesizing phenols with electron-donating substituents or polycondensed ring systems[324]. In a similar reaction, α,β-unsaturated aldehydes **165** give vinyl formates **166**, accompanied by the products of their subsequent transformations (Scheme 43)[325]. Recently, Ichikawa and coworkers described bis(2-phenyltrifluoromethanesulfonate) diselenide (2-$TfOC_6H_4Se)_2$ as a catalyst for the Baeyer–Villiger oxidation. Reaction with hydrogen peroxide generates the peracid, which reacts with cyclic ketones to yield the corresponding lactones in high yields[326].

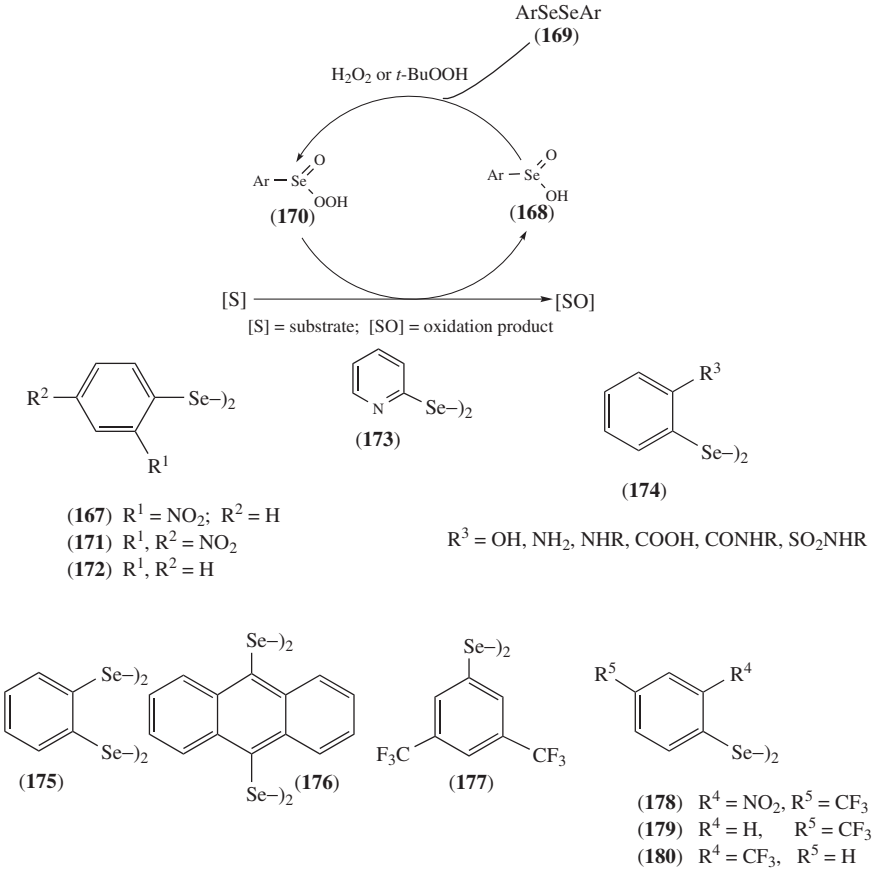


SCHEME 43. Hydrogen peroxide oxidation of aldehydes and ketones catalyzed by seleninic acid or diselenide

Epoxidation of styrene and its analogues with hydrogen peroxide catalyzed by acid **154** also has synthetic value[323]. The same reagent can be used for practical conversion of *N*,*N*-dimethylhydrazones into nitriles[327] while aldoximes in the presence of primary or secondary alcohols produce carboxyesters[328]. By means of the treatment of mercurated polystyrene with selenium(IV) oxide, a stable polymeric seleninic acid was generated. This material was used for catalytic processes with H_2O_2 and TBHP. A triphasic system of the polymer (in catalytic amounts), aqueous hydrogen peroxide, and dichloromethane was shown to be an effective medium for the conversion of alkenes into *trans* diols and ketones into esters. A biphasic system of the polymer and TBHP in refluxing chloroform affects the selective oxidation of benzylic alcohols to the carbonyl species. In a similar catalytic system hydroxyaromatic compounds can be converted into quinones. Conversion of 1,5-dihydroxynaphthalene into juglone can be realized in 70% yield[329].

An easily accessible perfluorooctaneseleninic acid ($C_8F_{17}Se(O)OH$) was employed as the catalyst in allylic oxidation leading to α,β-unsaturated carbonyl compounds whereas the stoichiometric oxidant was iodylbenzene[330]. The same oxidation system was used for the efficient oxidation of alkyl aryl ketones to ketoacids and even benzylic methylene groups can be oxidized to the corresponding ketones[331].

The proposed mechanism of the oxidation of organic substrate in the presence of areneseleninic acid **168** or its precursor, the diaryl diselenide **169**, is presented in Scheme 44. Both of them are oxidized *in situ* with hydrogen peroxide or TBHP into areneperoxyseleninic acid **170**, the active oxygen donor. Benzeneperoxyseleninic acid and its 2-nitro- and 2,4-dinitro analogues were obtained by hydrogen peroxide oxidation of the corresponding diaryl diselenides and fully characterized. Oxidation of carbonyl compounds with 2-nitroperoxybenzeneseleninic acid, used in a stoichiometric amount, gave similar



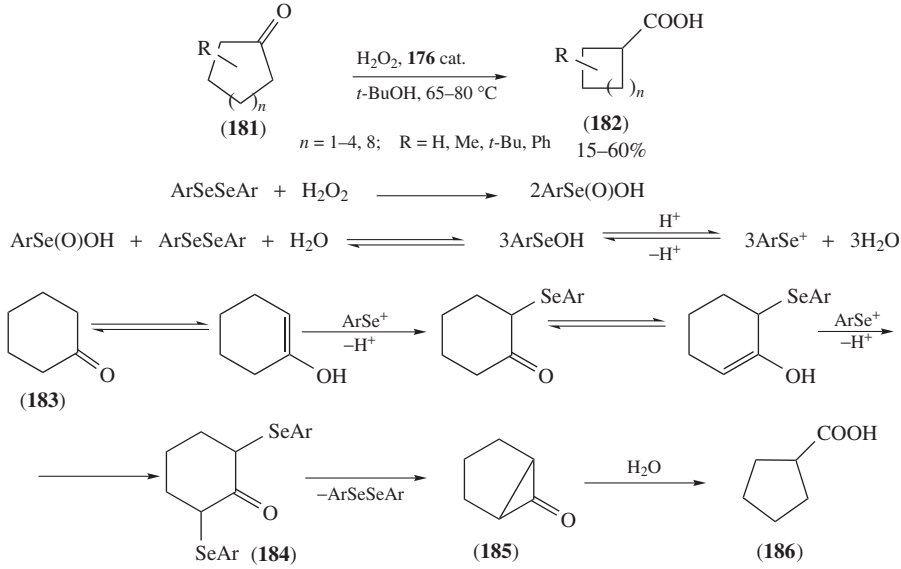
SCHEME 44. The mechanism of hydroperoxide oxidation of organic substrate catalyzed by diaryl diselenide or areneselenenic acid

results to these (presented in Scheme 43), when its precursors, the acid **154** or the related diselenide **167**, were used as catalysts[332].

Diselenides used more recently as catalysts for oxidation of different groups of organic substrates are presented in Scheme 44. They are easily available in the reaction of alkyl, aryl and heteroaryl halides with dilithium diselenide formed *in situ* from elemental lithium and selenium in aprotic media[333–335]. Apart from diselenides **167**, **171** and **172**, other compounds of this class, such as **173**–**180**, are also synthetically valuable oxidation catalysts.

It has been observed that the effectiveness of selenium catalysts strongly depends on the substrate used. While *ortho*-substituted diphenyl diselenides are the best catalysts for hydrogen peroxide oxidation of sulfides into sulfoxides and ketazines into their parent ketones[336,337], the poly(bis-1,2-phenylene) diselenide (**175**) was selected for preparative oxidation of various aromatic aldazines, aldoximes and conversion of tosylhydrazones into arenecarboxylic acids[338].

In the presence of poly(bis-9,10-anthracenylene) diselenide (**176**) a broad spectrum of aliphatic, unsaturated and aromatic nitriles was obtained, in excellent preparative yields, by oxidation of the corresponding *N*,*N*-dimethylhydrazones[339]. It was the catalyst of choice for oxidation of cycloalkanones **181** to cycloalkanecarboxylic acids **182**[340]. The results of more detailed studies on the chemo- and stereoselectivity of this reaction support the mechanism presented for cyclohexanone (**183**) in Scheme 45.

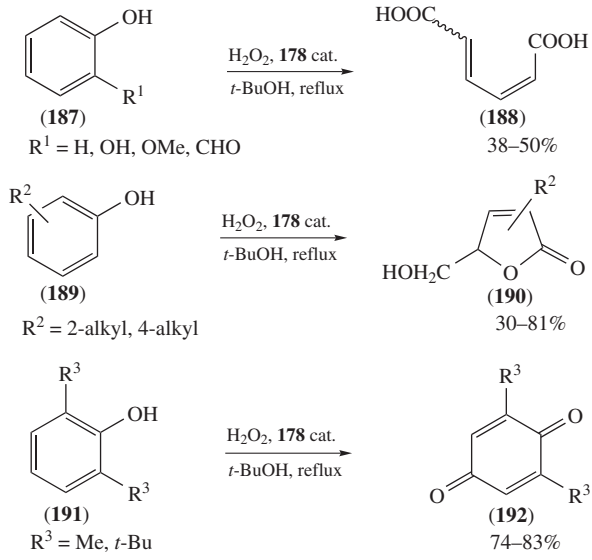


SCHEME 45. Oxidative conversion of cycloalkanones into cycloalkanecarboxylic acids catalyzed by poly(bis-9,10-anthracenylene) diselenide

Most probably, the reaction involves addition of two bulky arylselenium cations in both α-positions of the ketone, elimination of diaryl diselenide from adduct **184** and finally the Favorski-like rearrangement of intermediate **185** to the acid **186**[18].

Although preparative yields of the cycloalkanecarboxylic acids did not exceed 60%, they were substantially higher than those obtained when selenium(IV) oxide was the catalyst. Since the cycloalkanones are cheap and easily available substrates, the elaborated method is suitable for the synthesis of acids **182**, particularly those having five-, six- and seven-membered rings. Thus the H_2O_2/**176** system can be regarded as a potential reagent for obtaining bicyclo[4.3.0]nonanes, intermediates in the total synthesis of homocarbaprostacyclins[341].

The bis[(2-nitro-4-trifluoromethylphenyl)] diselenide (**178**) was found as an efficient catalyst for hydrogen peroxide oxidative degradation of the electron-rich benzene ring in phenol or its substituted derivatives **187**, **189** and **191**. Depending on the substrate used muconic acid (**188**), muconolactones **190** or 1,4-benzoquinones **192** were produced in satisfactory to good yields. Similar ring-degradation took place when substituted naphthalenes were oxidized. Cinnamic acid or benzofuran derivatives were the final products[334, 335] (Scheme 46).

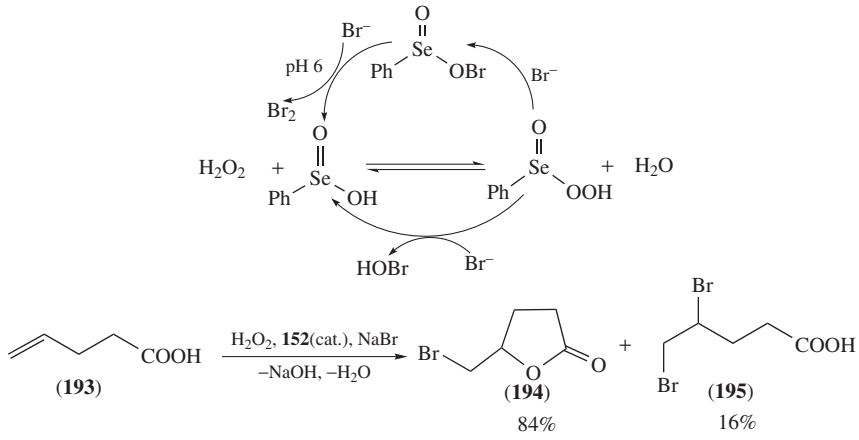


SCHEME 46. Oxidation of the benzene ring of phenols with H_2O_2/bis[(2-nitro-4-trifluoromethyl)-phenyl] diselenide

Recently, it was reported that bis[3,5-di(trifluoromethyl)phenyl] diselenide (**177**) has been significantly more active than other previously described selenium catalysts for epoxidation and Baeyer–Villiger oxidation of carbonyl compounds with hydrogen peroxide[342, 343]. The active intermediates, with an electrophilic center localized on the selenium atom, are generated from diselenides using oxidants such as ammonium peroxysulfate $(NH_4)_2S_2O_8$[344, 345], the sodium salt of chloramine-T ($4\text{-}ClC_6H_4SO_2NClNa$)[346] and iodylbenzene[347]. In the first reaction, applied for conversion of α,β-unsaturated carboxyesters, amides and nitriles into allyl ethers, the anion $PhSeOSO_3^-$ is an active selenium intermediate. The reaction is stereospecific when the catalyst diphenyl diselenide is replaced by dicamphoryl diselenide[245]. *N*-(Arylseleno)-4-chlorobenzenosulfonamide $4\text{-}(ArSeNHSO_2)C_6H_4Cl$, formed in the second reaction, oxidizes secondary alcohols into ketones[346]. 2,2′-Dipyridyl diselenide (**173**) promotes iodylbenzene oxidation of allylic carbons and dehydrogenation of cycloalkanones into enones and dienones[313, 347]. When diphenyl diselenide and benzenesulfonic acid are treated with hydrogen peroxide, dihydroxyphenylselenonium benzenesulfonate $PhSe(OH)_2{}^+PhSO_3^-$ (or tosylate) is formed. These salts are active intermediates or can be isolated and used as stoichiometric reagents for oxidation of arenes into quinones[348–350].

Areneseleninic acids (and selenoxides) can be used as catalysts for the oxidation of bromide with hydrogen peroxide to hypobromite and bromine in a two-phase reaction mixture[351, 352]. Among various areneseleninic acids tested as catalysts, the most effective were benzeneseleninic acid (**152**) and 4-methoxybenzeneseleninic acid.

Generated *in situ* Br_2 and NaOBr bring on the cyclization of γ,δ-unsaturated acids such as, for example, 4-pentenoic acid (**193**) or related unsaturated alcohols, which give the lactone **194** accompanied by a small amount of dibromo acid **195**. Similarly, the electrophilic bromination of activated aromatic rings can be performed in high yield (Scheme 47)[351, 352].



SCHEME 47. Bromolactonization of an γ,δ-unsaturated acid via benzeneseleninic acid catalyzed oxidation of NaBr with H_2O_2

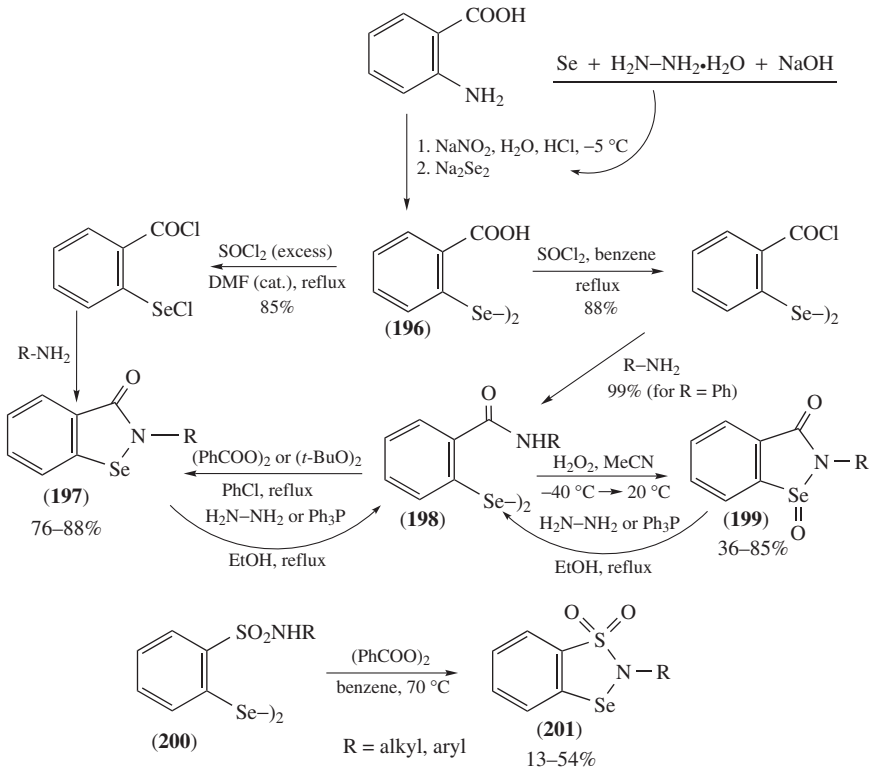
4. Selenenamides and seleninamides

When bis[(2-carbamoyl)phenyl] diselenides **198** is treated with *t*-butyl or benzoyl peroxide, it undergo oxidative cyclization to endocyclic selenenamides (benzisoselenazol-3(2*H*)-ones) **197** whereas use of hydrogen peroxide results in endocyclic seleninamides (benzisoselenazol-3(2*H*)-one 1-oxides) **199**[25, 353] (Scheme 48). Similar oxidative cyclization of bis[(2-sulfamoyl)phenyl] diselenides **200** with benzoyl peroxide gave 1,3,2-thiaselenazole 1,1-oxides **201**[354, 355] (Scheme 48).

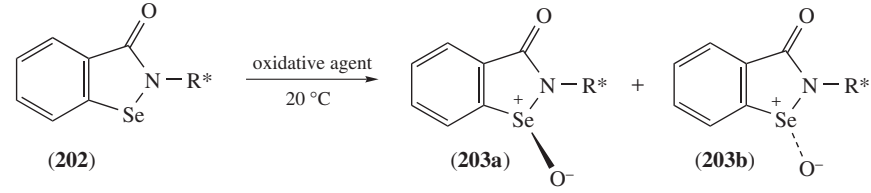
Both **198** and **197** can be obtained simply from anthranilic acid via bis(2-carboxyphenyl) diselenide (**196**) and the corresponding amines. The method has a more general value because, by using various amines and other compounds with primary amino groups, different benzisoselenazol-3(2*H*)-ones and 2-substituted diphenyl diselenides can be obtained in high yields[355]. When the cyclic compounds **197** or **199** react with reducing agents such as hydrazine or triphenylphosphine, the Se−N bond is cleaved to give diselenides **198**.

Optically active seleninamides having bulky subtituents were prepared by oxidation of selenenamides with H_2O_2 or ozone followed by chromatographic resolution on a chiral column. The pure enantiomers were found to racemize in solution via dihydroxyselenuranes formed by reaction with water[25, 356]. Oxidation of the benzisoselenazol-3(2*H*)-ones **202** 2-substituted with a chiral group derived from L-phenylalanine with MCPBA generates a new stereogenic center at the selenium atom. The mixture of diastereoisomeric seleninamides **203a** and **203b** was recrystallized to give the individual diastereoisomers which were resistant to racemization (Scheme 49)[25, 357, 358].

The most common compound of the cyclic selenenamides class is 2-phenylbenzisoselenazol-3(2*H*)-one, named ebselen (**197**, R = Ph). It acts against oxidative stress in a similar way to the common selenoenzyme glutathione peroxidase (GSH-Px)[359, 360]. Also, other 2-substituted-1,2-benzisoselenazol-3(2*H*)-ones **197** and their open-chain analogues, among them bis[(2-carbamoylphenyl)phenyl] diselenide (**198**, R = Ph), are able to deactivate active oxygen species present in the living cell, such as peroxides, hydroperoxides, hydroxyl radical and superoxide anion. The recently reported salicylglycine seleninic acid anhydride exhibits catalytic activity fourfold higher than that of ebselen and it inhibits

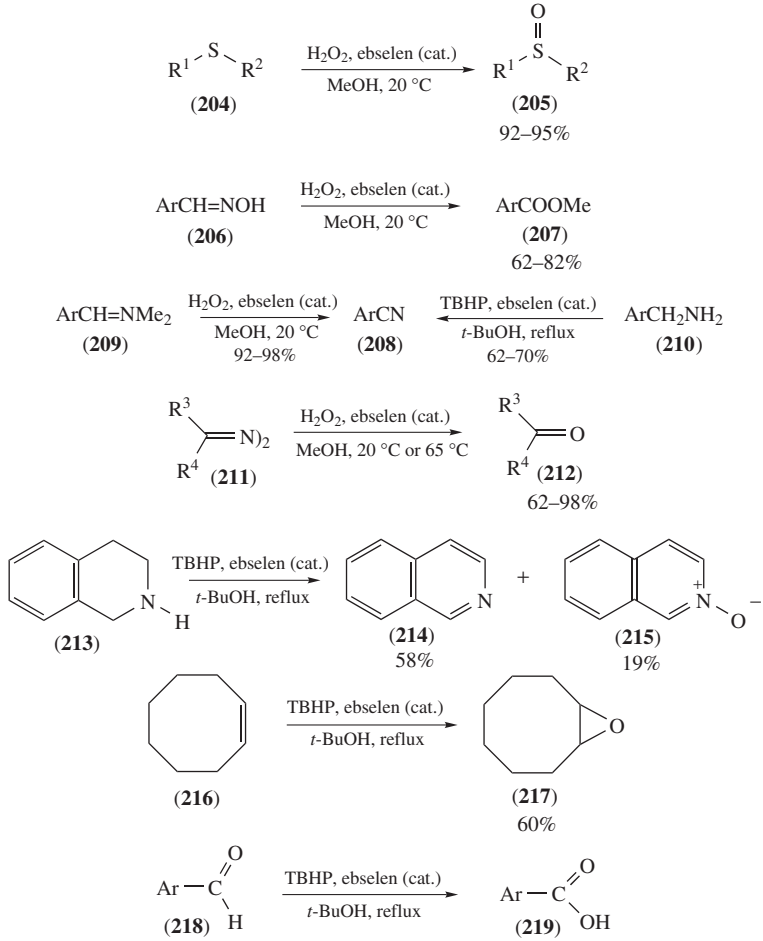


SCHEME 48. Oxidative cyclization of bis[(2-carbamoyl)phenyl] diselenides and 1,3,2-thiaselenazole 1,1-oxides



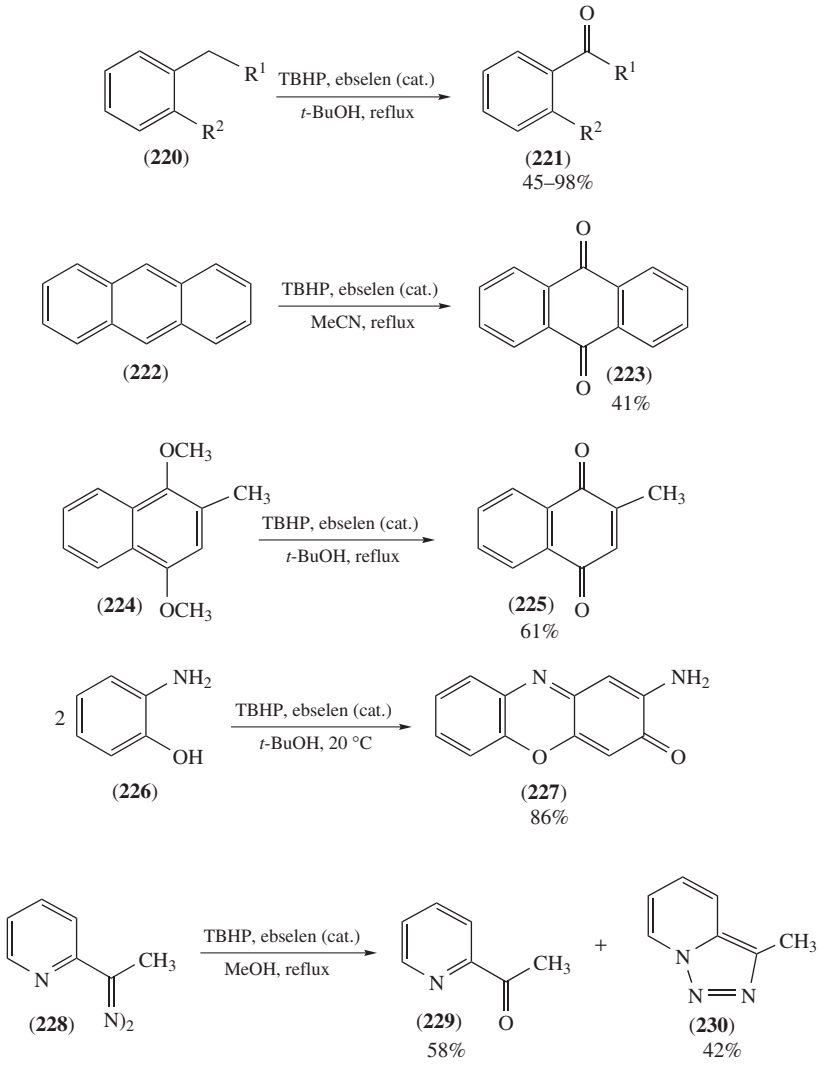
SCHEME 49. Stereoselective oxidation of cyclic selenenamides to seleninamides

lipoxygenases at lower micromolar concentration[361]. The mode of the biological action of compounds **197** and **198** has been postulated to be similar to that observed for GSH-Px, and results in dehydrogenation of thiols into disulfides while hydrogen peroxide is reduced to water[362–365]. Surprisingly, it has been found that ebselen (**197**, R = Ph) and the related diselenide **198** (R = Ph) did not promote hydrogen peroxide oxidation of thiols such as *N*-acetylcysteine, butanethiol and octanethiol[366]. Other works provided evidence that ebselen, related selenenamides and diselenides could catalyze the hydroperoxide oxidation of various organic compounds other than thiols (Scheme 50)[17–19,25,334,367]. Catalyst **197** was used in 5 mol%, and diselenide **198** in 2.5 mol% while the stoichiometric oxidant was 30% hydrogen peroxide or 80% TBHP. The reactions of ionic character are presented in Scheme 50.



SCHEME 50. Oxidations of ionic character catalyzed by ebselen

The sulfides **204** are exclusively oxidized into sulfoxides **205**[336]. Aromatic aldoximes **206** oxidized in methanol gave aromatic methyl esters **207**[328]. Nitriles **208** are produced from *N*,*N*-dimethylhydrazones **209** by oxidation with hydrogen peroxide[327, 336] or from benzylamines **210** oxidized with TBHP[368]. Hydrogen peroxide oxidation of ketazines **211** give the parent ketones **212**[336]. 1,2,3,4-Tetrahydroisoquinoline (**213**) is dehydrogenated to isoquinoline (**214**), which undergoes subsequent oxidation into the *N*-oxide **215**[369]. Cyclooctene (**216**) treated with TBHP gives epoxide **217** accompanied by trace amounts of 3-hydroxycyclooctene resulting from α-hydroxylation[370], while oxidation catalyzed by



SCHEME 51. Ebselen catalyzed oxidations with a free-radical character

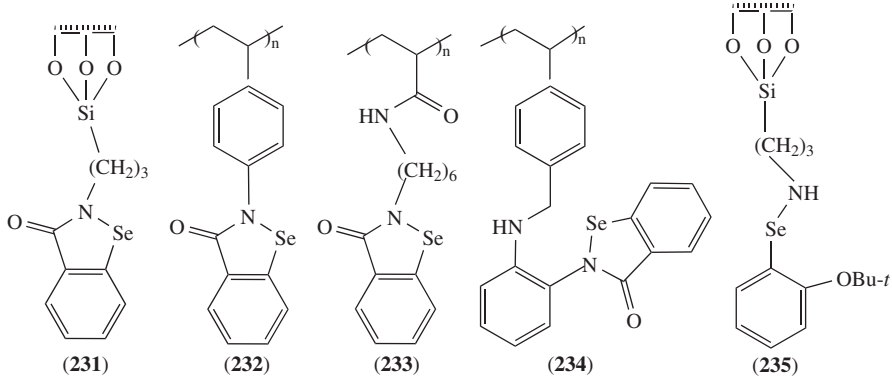
selenium(IV) oxide affords 3-hydroxycyclooctene as a major product and epoxidation is not observed[62]. Oxidation of aromatic aldehydes having electron-donating substituents **218** with TBHP in the presence of ebselen led almost exclusively to the acids **19**, thus avoiding the Baeyer–Villiger rearrangement[371] contrary to (mentioned earlier in Section II.A.2.g) oxidation with hydrogen peroxide in the presence of selenium(IV) oxide, where mixtures of arenecarboxylic acids and phenols, or even phenols as the sole products, were produced[163].

Despite the ionic reactions presented above, some other reactions can proceed via a free-radical mechanism. Catalyzed by ebselen, TBHP oxidation of alkylarenes **220** to alkyl aryl ketones **221**[368], anthracene (**222**) to anthraquinone (**223**)[372], 1,4-dimethoxyarenes to 1,4-quinones (e.g. 2-methyl-1,4-dimethoxynaphthalene (**224**) to menaquinone (**225**)[373]) and oxidative coupling of 2-aminophenols (e.g. **226** to phenoxazinones **227**[374]) gave results similar to those with the one-electron oxidants Ce(IV), Ag(II) or Mn(III) (Scheme 51).

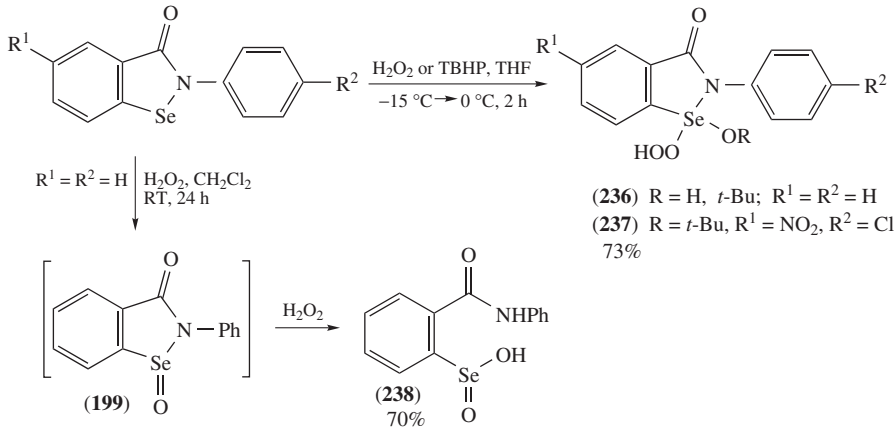
Moreover, oxidation of ketazine derived from 2-acetylpyridine (**228**) gave a mixture of ketone **229** and condensed triazole **230**[368]. The same result was found when cerium ammonium nitrate was used as the reagent. This suggests that the reaction proceeds via cation-radicals. Both of the postulated mechanisms, ionic and free-radical, were discussed in more detail in a review article[19].

A few benzisoselenazol-3(2*H*)-ones **231**–**234** and open-chain selenenamide **235** were covalently immobilized on the solid support, either silica or polymer (Scheme 52)[372, 375, 376]. They exhibited appreciable catalytic activity similar to the activity of ebselen. The most prospective oxygen-transfer recoverable catalyst is benzisoselenazolone covalently bound to a silica support **231** named HALICAT. It has been applied to hydrogen peroxide oxidation of sulfides and TBHP oxidation of the aromatic aldehydes to acids and alkylarenes to alkyl aryl ketones[375].

Catalytic acivity of ebselen for hydroperoxide oxidation of different groups of organic compounds raised a question about the role of the oxidant and catalyst in this reaction, the more so because similar activity of its 1-oxide (**199**) and related open-chain diselenides was observed[360, 374, 377]. It was shown that ebselen treated with a large excess of hydrogen peroxide, under cooling, yielded an unstable crystalline compound, i.e. the hydroperoxyselenurane **236**. A more stable and fully characterized analogue **237** was obtained under similar conditions by oxidation of the corresponding benzisoselenazol-3(2*H*)-one with hydrogen peroxide or with TBHP (Scheme 53). It seems possible that treatment of



SCHEME 52. Benzisoselenazol-3(2*H*)-ones and selenenamide covalently immobilized on solid supports



SCHEME 53. Oxidation of benzisoselenazol-3(2*H*)-ones with hydroperoxides

organic substrates in the presence of ebselen, but also of its 1-oxide or related diselenide, with a large amount (100-fold molar excess) of hydroperoxide results in the formation of hydroperoxyselenurane **236** being the active oxygen donor involved in oxidation of the organic substrate[371, 372]. On the other hand, it has been shown that the GPx-like catalytic mechanism of ebselen is different for the antioxidant and anti-inflammatory activities and involves reversible cyclization of the selenenic acid (RSeOH) to ebselen. The long time reaction of ebselen with hydrogen peroxide (10-fold molar excess) produces exclusively the corresponding seleninic acid **238**, being a crucial intermediate involved in the postulated oxidation mechanism[364].

III. HYDROGEN SELENIDE AND RELATED ORGANOSELENIUM COMPOUNDS

A. Hydrogen Selenide and its Salts

1. General comments

Hydrogen selenide, H_2Se (mp $-65.73\,^{\circ}C$, bp $-41.25\,^{\circ}C$ under atmospheric pressure), is one of the simplest inorganic derivatives of selenium[378]. It is a malodorous, highly toxic gas poorly water-soluble ($0.084\,mol\,cm^{-3}$ at 1 atm) and well soluble in CS_2 and phosgene. Hydrogen selenide in aqueous solution displays acidic features ($pK_{a1} = 3.89$, $pK_{a2} = 11$ at $25\,^{\circ}C$). In general, two main synthetic strategies that allow to obtain this compound have been elaborated: direct reaction of selenium and hydrogen in a sealed tube or over pumice stone at *ca* $440\,^{\circ}C$ and decomposition of iron, magnesium or aluminum selenides in water. Due to the fact that hydrogen selenide presents a lower stability as compared to hydrogen sulfide, it can be oxidized directly with oxygen in the presence of light[379] whereas heating with oxygen enables one to achieve either SeO_2 or SeO_3[378].

Owing to its acidic properties hydrogen selenide is able to form such salts as selenides $M^{(I)}{}_2Se$ and hydrogen selenides $M^{(I)}HSe$ ($M^{(I)}$–metal). Furthermore, both hydrogen selenide and its alkali salts, as well as hydrogen selenides such as NaHSe or LiHSe, are strong reducing agents successfully applied for reduction of many functional groups:

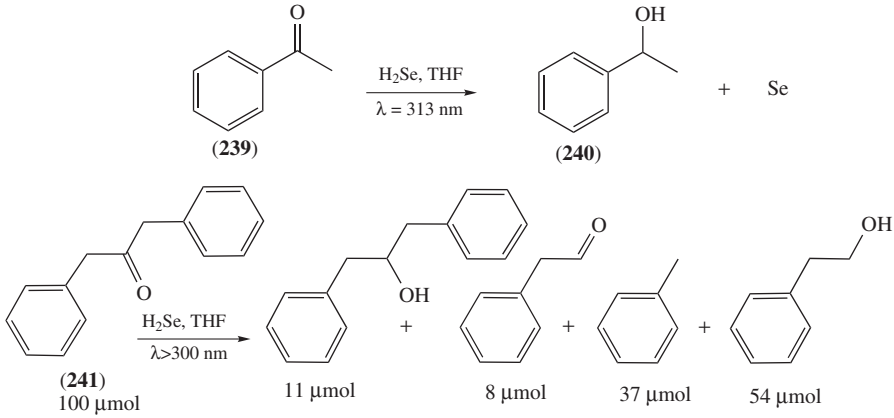
carbonyl, nitro, sulfoxide and carbon–carbon double bond[380–383]. Sodium hydrogen selenide can be generated *in situ* from elemental selenium and sodium borohydride in ethanolic solution[384].

Sodium selenide is a valuable reagent for iodine, bromine and chlorine elimination[385, 386]. Similar reaction takes place with chalcone dibromides and dibenzalacetone dibromide as substrates.

2. Reduction with hydrogen selenide

a. Reduction of carbonyl compounds. The reaction between hydrogen selenide and a carbonyl compound in the presence of tertiary amines produces symmetric dialkyl diselenides[387]. The reduction of 1,2-diketones with H_2Se gave α-hydroxy ketones. The base and the solvent have an important influence on the synthetic procedure. It has been elucidated that the higher yield was obtained when pyridine or DBU and dimethyformamide were applied[388, 389].

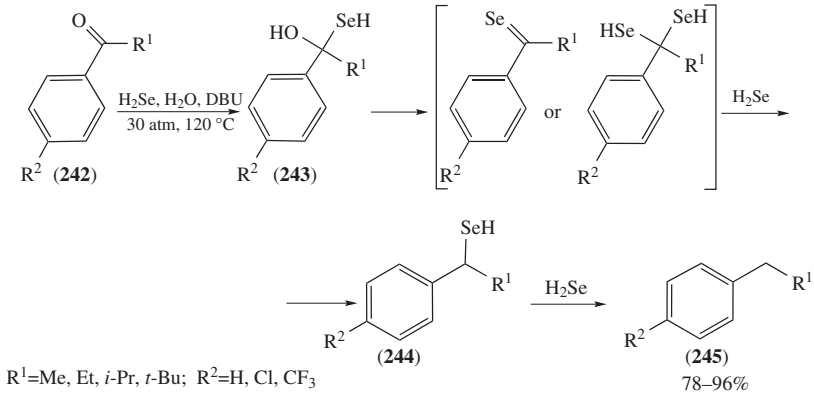
Kambe and coworkers found that UV irradiation of the reaction mixture of acetophenone (**239**) and H_2Se by use of a high-pressure mercury lamp leads to selenium formation and the alcohol **240** is a sole product obtained in high yield. Carbonyl compounds, having alkylaryl moiety, e.g. dibenzyl ketone (**241**), react with hydrogen selenide violently, giving a mixture of different products[390, 391] (Scheme 54).



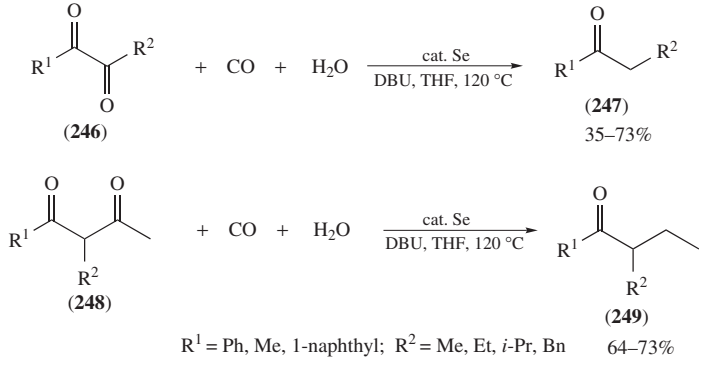
SCHEME 54. Hydrogen selenide reduction of ketones under UV irradiation

In the presence of base some carbonyl groups can be reduced to a methylene group. It can be assumed that the reaction begins by a nucleophilic attack of H_2Se on the carbonyl carbon atom of substrate **242**. The newly formed adduct **243** can be further reduced to selenole **244**, via unstable intermediates such as selenone or selenoketal, and finally reduced to the alkyl arene **245** (Scheme 55)[392, 393].

Diketones are reduced selectively to monoketones with water gas in the presence of selenium, particularly when the α-substituent is an aryl group (Scheme 56). The reducing agent is *in situ* formed hydrogen selenide and the selenium resulting from these reductions is reduced further in the medium, so that catalytic amounts of elemental selenium can be used. This methodology opens a convenient access to several monoketones **247** and **249** achieved from appropriate 1,2-diketones **246** and 1,3-diketones **248**[389].



SCHEME 55. Reduction of the carbonyl group in alkyl aryl ketones to a methylene group



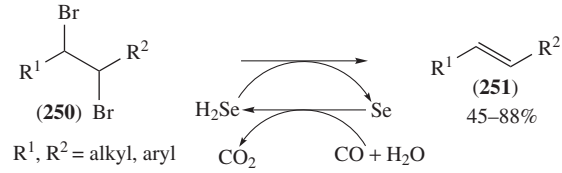
SCHEME 56. Selective reduction of carbonyl groups in diketones

b. Reduction of nitrogen and sulfur compounds. Dehalogenation. Hydrogen selenide, generated *in situ* by heating of water gas with selenium, is able to reduce nitrobenzene to aniline in 86% yield. This process employs only a catalytic amount of selenium and different nitrobenzenes were reduced to aromatic amines in this manner[394]. Furthermore, the process carried out in the presence of a tertiary amine has been successfully applied for reduction of sulfoxides to sulfides[395] and for synthesis of alkenes **251** from vicinal dihaloalkanes **250** (Scheme 57)[396]. Treatment of α-haloketones with a mixture of CO/H_2O and selenium results in dehalogenation and provides an efficient way for high-yield preparation of ketones[396].

B. Selenols and Related Compounds

1. General comments

Organoselenium compounds derived from hydrogen selenide having an alkyl or aryl group instead of a hydrogen atom exhibit strong reducing properties, comparable to the



SCHEME 57. Reductive dehalogenation of vicinal dibromoalkanes

parent H_2Se. They can be easily prepared from metalorganics by treatment with selenium or by alkylation of hydrogen selenide. Selenols (RSeH) are relatively strong acids (for PhSeH, $pKa = 5.9$)[397–400]. Therefore, the conjugated base is smoothly generated under alkaline conditions. Even though the RSe^- anion is a weak base, it possesses strong nucleophilic properties due to high polarizability of the selenium atom[399]. Hence, it reacts with electrophiles according to an S_N2 mechanism that gives a selenide with inversion of configuration. Additionally, selenoboranes reveal similar features[401]. Selenols and their salts selenolates find wide application, since like H_2Se they are able to reduce many functional groups but their use is preferred over use of hydrogen selenide. For example, vicinal dihaloalkanes can be transformed into alkenes and α-haloketones into ketones, whereas nitro compounds would be converted into other nitrogen derivatives.

2. Reduction of nitrogen, sulfur and halogen compounds

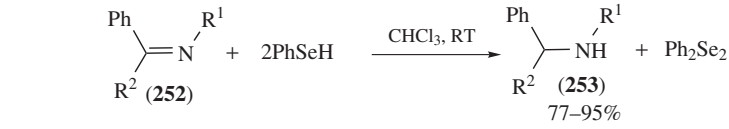
Efficient reduction of nitrobenzene to aniline by benzeneselenol (selenophenol) in the presence of diazabicyclo[2.2.2]octane (DABCO) was first reported in 1979. Addition of amine was necessary to liberate the strongly nucleophilic benzeneselenolane anion which reacts with the nitro compound[402]. The yield of this process was almost quantitative. Excess of benzeneselenol provided no isolated intermediates, while an equimolar amount of reductant allowed one to stop the reaction at the azoxy compound or the hydroxylamine formation stage.

Application of benzeneselenol facilitates preparation of secondary amines **253** by reduction of Schiff bases **252**, while reductive amination of carbonyl compounds **254** via alkylation of the intermediate secondary amine **255** leads to tertiary amines **256** (Scheme 58)[403].

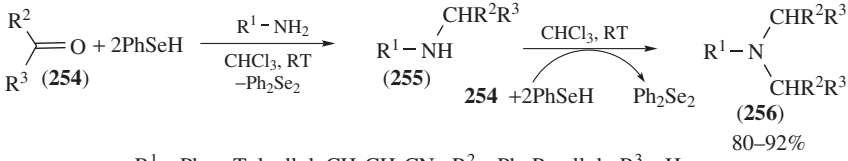
Esters of boric acid and selenols such as tri(phenylseleno)- and tri(methylseleno)boranes found application for deoxygenation of *N*-oxides, e.g. **257** to the parent amines **258** (Scheme 59)[401]. The same esters as well as silylated benzoselenols were used for deoxygenation of sulfoxides **259** to sulfides **260**, selenoxides to selenides and telluroxides to tellurides[401, 404, 405]. This reaction has been commercially utilized in the drug industry for cephalosporin synthesis[406]. Selenolate anion, of a strong nucleophilic character, easily reacts with various halogenated compounds. These reactions are very important for synthesis of alkenes by dehalogenation of vicinal dihaloalkanes with sodium methaneselenolate or benzeneselenolate[407].

3. Reduction of conjugated alkenes, alcohols and epoxides

Hydroselenenylation appears to be a preferable synthetic approach for the conversion of α,β-unsaturated carbonyl compounds **261** into the β-seleno derivatives **262**. The crucial step is addition of the nuleophilic alkyl selenol generated *in situ* from lithioorganics to the carbon–carbon double bond of the substrate (Scheme 60). A similar reaction proceeds with α,β-unsaturated nitro compounds or esters[408].

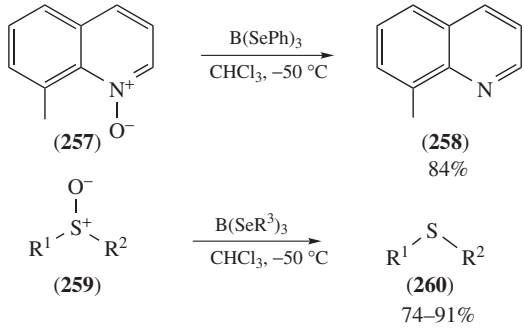


R^1 = *p*-Tol, Pr, allyl, CH_2CH_2CN; R^2 = H, Ph



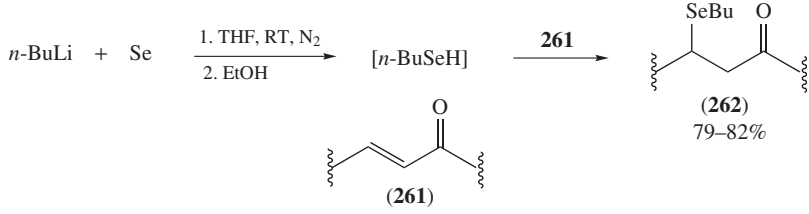
R^1 = Ph, *p*-Tol, allyl, CH_2CH_2CN; R^2 = Ph, Pr, allyl; R^3 = H

SCHEME 58. Reduction of Schiff bases and reductive amination of carbonyl compounds with selenophenol



R^1, R^2 = Bn, Ph, *t*-Bu; R^3 = Me, Ph

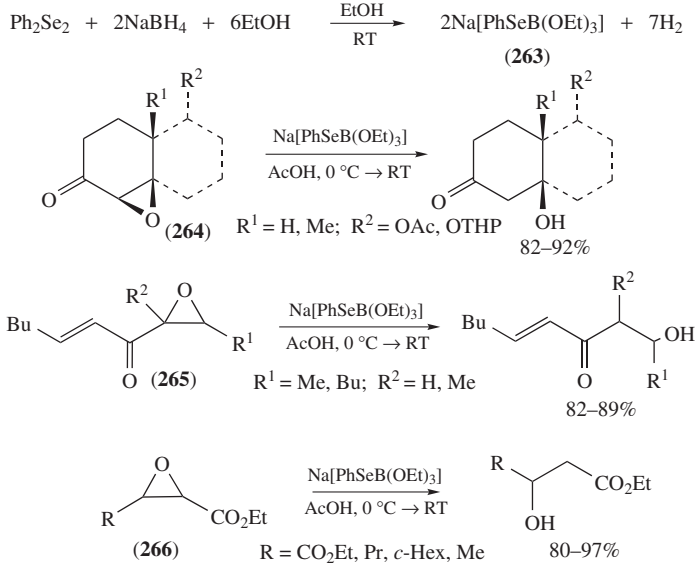
SCHEME 59. Deoxygenation of *N*-oxides and sulfoxides with selenoboranes



SCHEME 60. Hydroselenylation of α,β-unsaturated carbonyl compounds

Under photochemical conditions or in air, an unstable α-selenoketone is formed and it can be deselenenylated to the desired ketone by treatment with an additional equivalent of benzeneselenol[409, 410].

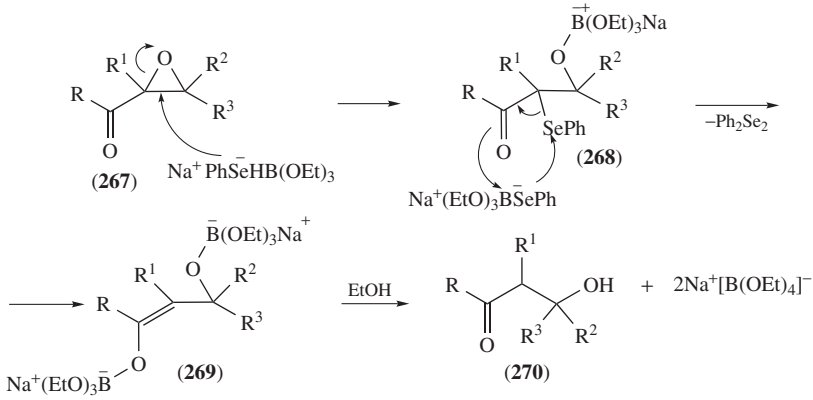
The soft nucleophilicity of organoselenium reagents has been utilized for reduction of a wide variety of substrates, such as α,β-epoxy ketones, α,β-epoxy enones, glycidic esters, α,β-epoxylactones, α,β-epoxylactams and their congeners, to their corresponding β-hydroxy compounds[411]. The proper reducing agent—sodium phenylseleno(triethyl)borate complex Na[PhSeB(OEt)$_3$] (**263**)—is readily achieved by treatment of diphenyl diselenide with $NaBH_4$ in ethanol. The required benzeneselenol is generated *in situ* from borate complex due to acetic acid presence. Although the reduction mechanism is complex, it has been deduced that the process involves selenenylation and deselenenylation as the major steps. Due to the specific properties of the borane complex, high regioselectivity under mild reaction conditions could be obtained. Examples of reductive ring opening in epoxides **264**–**266** are presented in Scheme 61.



SCHEME 61. Reductive epoxide ring opening with sodium phenylseleno(triethyl)borate complex

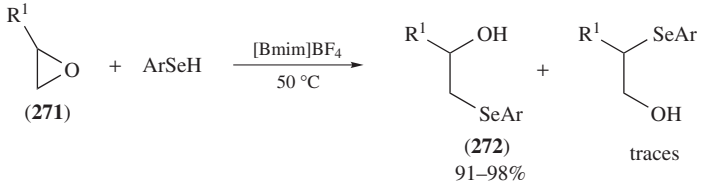
According to the proposed mechanism (Scheme 62), the attack of the selenium nucleophile on the carbon atom in an epoxide ring of substrate **267** occurs in the first step and α-phenylseleno ketone **268** is formed. Subsequently, the ketone **268** reacts with a second molecule of sodium phenylseleno(triethyl)borate complex and the formed enolate **269** gives the β-hydroxy ketone **270**[411].

β-Hydroxy selenides **272** represent important intermediates in organic synthesis, especially applicable to the preparation of different medicinal and natural products via oxidation and selenoxide elimination (see Section II.B.1.c). A convenient method for their synthesis is based on a ring opening reaction of 1,2-epoxides **271** with arylselenols in an ionic liquid (e.g. 1-butyl-3-methylimidazolium tetrafluoroborate [Bmim]BF_4). Interaction of the acidic hydrogen at C(2) position with the epoxide oxygen makes the C−O

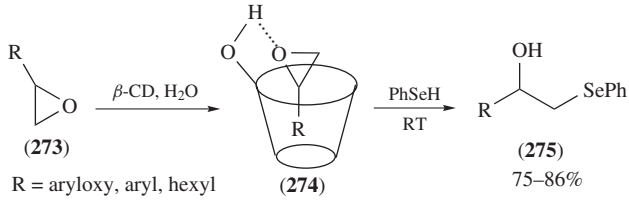


SCHEME 62. Mechanism of reductive oxirane ring opening with sodium phenylseleno(triethyl)-borate complex

bond weaker and triggers nucleophilic attack of selenolate anion on the carbon atom to afford the desired product. Consequently, the β-hydroxy selenides are formed with high regioselectivities and in yields up to 98% (Scheme 63)[412].



R^1 = Ph, 2-$MeC_6H_4OCH_2$, $CH_2{=}CH(CH_2)_6$, CH_2Cl; Ar = Ph, 1-naphthyl



SCHEME 63. Synthesis of β-hydroxy selenides

Another efficient method for preparation of β-hydroxy selenides **275** is based on regioselective ring opening of epoxides **273** by treatment with selenophenol in water in the presence of β-cyclodextrine as catalyst via the supramolecular complex **274** (Scheme 63)[413]. The advantages of this procedure are a one-pot process, 'green' solvent (water) and possibility of cyclodextrine recovery and reuse.

An alcohol can be easily converted into selenide, either by treatment of its tosylate or mesylate derivatives with selenolates, or by direct coupling with selenols in the presence

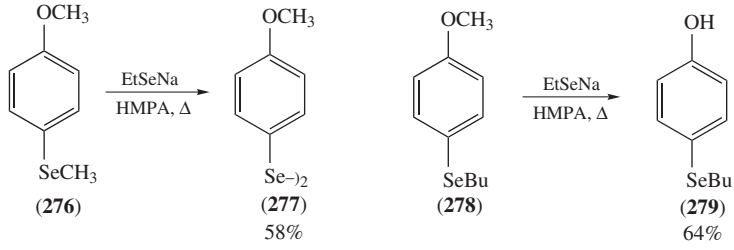
of sulfuric(VI) acid or zinc chloride[414]. Deselenenylation of these selenides to the corresponding alkanes occurs under mild conditions when Raney nickel[415–417], nickel boride[418], lithium triethylborohydride[419] and Li/$EtNH_2$[420] are applied.

4. Reduction of esters, ethers and carbonyl compounds, and dealkylation of tertiary amines

Deoxygenation of carbonyl compounds to hydrocarbons can be carried out using reductive deselenenylation of selenoacetals derived from aldehydes and ketones[421]. This approach would be a facile alternative to the Wolf–Kishner and Clemmensen reductions[422, 423]. Benzeneselenol was reported as an efficient reagent for reduction of the carbonyl moiety in the presence of oxygen[410].

Phenyl and alkyl esters of alkanecarboxylic acids are easily cleaved to the parent carboxylic acids in 75–99% yield by treatment with PhSeNa or PhSeLi in HMPA/THF. Under the same reaction conditions *N*-alkyl arylamines were obtained from *N*-alkyl *N*-aryl carbamates[424]. Moreover, selenolates manage to open the lactone ring without interaction with other functional groups[425].

Particularly convenient reagents for demethylation of aromatic methyl ethers and sulfides are $Ph_2Se_2/NaBH_4$ and RSeH/HMPA systems. Selective demethylation of only one of several existing methoxy groups in a molecule found practical application in synthesis of apocodeine from the dimethoxy derivative or of others alkaloids. Sodium methane- and ethaneselenolate were successfully used for *S*-demethylation of thioethers. Benzene derivatives having both methoxy and selenomethyl groups **276** do not undergo *O*-demethylation because the Me–Se bond is cleaved preferentially and diselenide **277** is formed. Nevertheless, in the presence of other selenoalkyl groups as in compound **278**, *O*-demethylation occurs and phenol **279** is formed (Scheme 64)[426, 427].

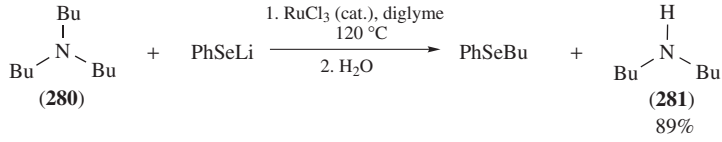


SCHEME 64. Se-Demethylation versus *O*-demethylation

Benzeneselenol, in contrast to thiophenol, is a sufficiently strong acid to protonate tertiary amines, e.g. **280**. During this process, the liberated benzenoselenolate anion reacts with one of the amine substituents to give the secondary amine **281** in poor yield, which is substantially improved when a ruthenium salt is a catalyst (Scheme 65)[428, 429].

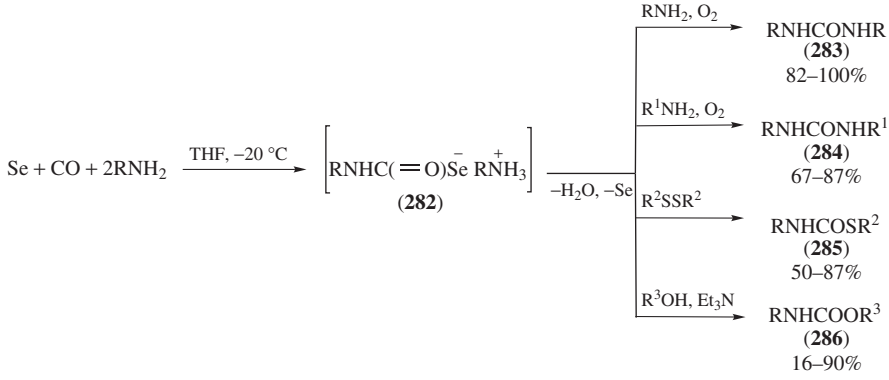
C. Carbonyl Selenide

Elemental selenium reacts smoothly with carbon monoxide to give carbonyl selenide COSe. If the reaction is performed in any solvent in the presence of amine, the ammonium selenocarbamate (**282**) is formed. Treatment of **282** with another equivalent of



SCHEME 65. Dealkylation of tertiary amine

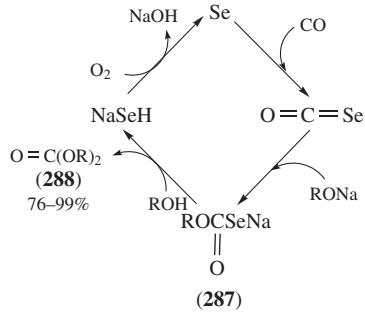
amine yields the symmetrically substituted urea derivatives **283**[430–434]. Unsymmetrical urea **284** is formed when in the second reaction step a different amine is added. When a disulfide is a nucleophilic reagent, thiocarbamates **285** are formed as the major products. Ammonium selenocarbamate can be converted in a facile way into carbamate **286** by treatment with alcohol in the presence of triethylamine (Scheme 66)[435]. Kondo and coworkers successfully employed selenocarbamates for synthesis of semicarbazides and their derivatives[433].



SCHEME 66. Reactions of ammonium selenocarbamate with N, S and O nucleophiles

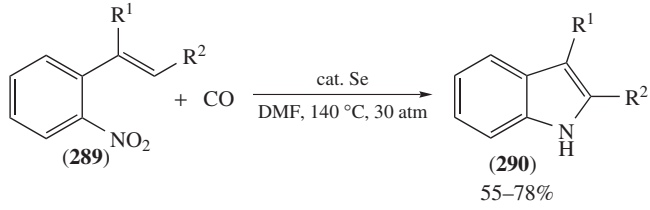
When sodium *O*-alkylselenocarbamate (**287**) was obtained in the reaction of carbonyl selenide with sodium alkoxide treated with alcohol, it gave dialkyl carbonates **288**, whereas in the case of phenols the process completely failed. The yield of products depends strongly on the alcohol used. The highest yields were achieved for primary alcohols. The process is catalyzed by small amounts of elemental selenium. It could be explained by the fact that sodium hydrogen selenide, as a by-product, is oxidized to selenium, followed by subsequent reduction by carbon monooxide to carbonyl selenide (Scheme 67)[436–438].

Different *N*- and *O*-heterocycles were obtained using carbonyl selenide or selenocarbamate as the reagent. An example is the synthesis of imidazoles from selenocarbamates and diamines[433]. In other types of reactions a catalytic system CO/Se was empolyed. The synthetic routes appeared convenient and suitable enough to allow synthesizing a series of heterocycles from compounds carrying two nucleophilic centers (alcohols, phenols, thiols, amines). The process was carried out at a temperature up to 60 °C and at both CO and CO_2 overpressure (3 atm). Catalytic amounts of selenium and triethylamine were also required[439, 440]. Following this procedure several 2- and 3-substituted indoles



SCHEME 67. The selenium-catalyzed production of dialkyl carbonates

290 were obtained from 2-nitrostyrenes **289** and carbon monoxide in the presence of a catalytic amount of elemental selenium with a CO/Se system (Scheme 68)[441]. The selenium-assisted formation of *C*-carbonylated products has been reported as a useful method leading to coumarine derivatives[442].



R^1 = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, H, Me; R^2 = H, Me

SCHEME 68. Reductive cyclization of 2-nitrostyrenes to indoles with CO/Se

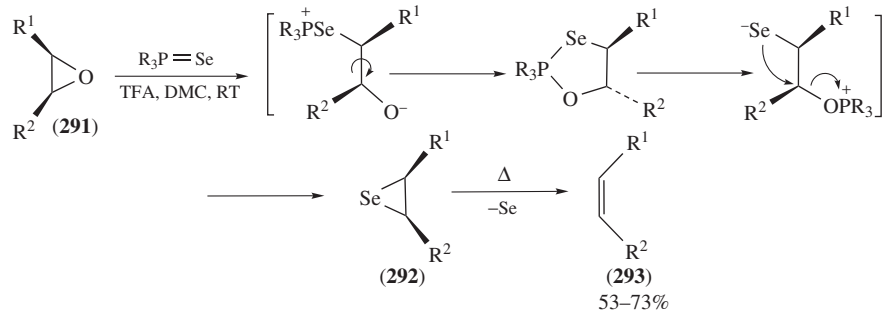
D. Triphenyl- and Trialkylphosphine Selenides and Selenoamides

About 40 years ago Clive and Denyer reported that the triphenylphosphine selenide $R_2P{=}Se$ in the presence of trifluoroacetic acid deoxygenated epoxides **291** stereospecifically to give the appropriate alkenes **293** in moderate to high yield. The episelenide **292**, deselenenylated under heating, was postulated intermediate (Scheme 69)[443].

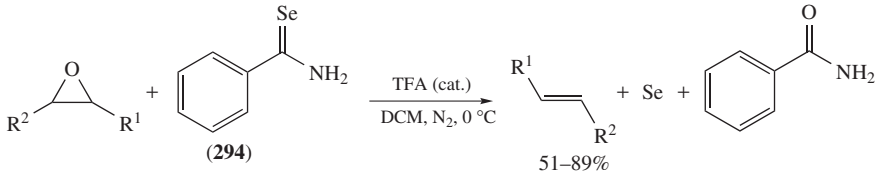
Further studies on epoxide deoxygenation showed that 3-methyl-2-selenoxobenzothiazole in the presence of a stoichiometric amount of trifluoroacetic acid gave similar results as $Ph_3P{=}Se$. The reaction is similar to the well-known desulfurization of episulfides[444].

Benzeneselenocarboxamide (**294**) and other selenocarboxamides have been found as efficient reagents for conversion of epoxides into alkenes under mild conditions and in high yields when only 0.03 equivalents of TFA (relative to epoxide) was used (Scheme 70). This approach permits one to avoid stoichiometric amounts of TFA, which have negative influence on some functional groups present in the molecule. These efficient, easy-to-prepare reagents can be successfully used to obtain mono-, di- and tri-substituted alkenes with high stereospecificity[445].

The selenocyanate anion (derived from potassium selenocyanate) allows one to convert epoxides into alkenes under slightly alkaline conditions. The best results were obtained

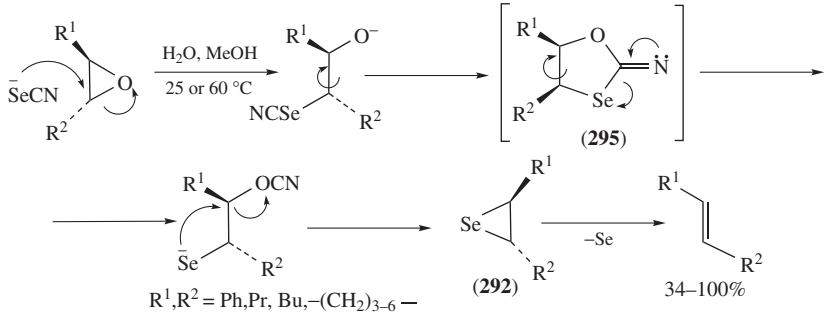


SCHEME 69. Deoxygenation of epoxides with triphenylphosphine selenide



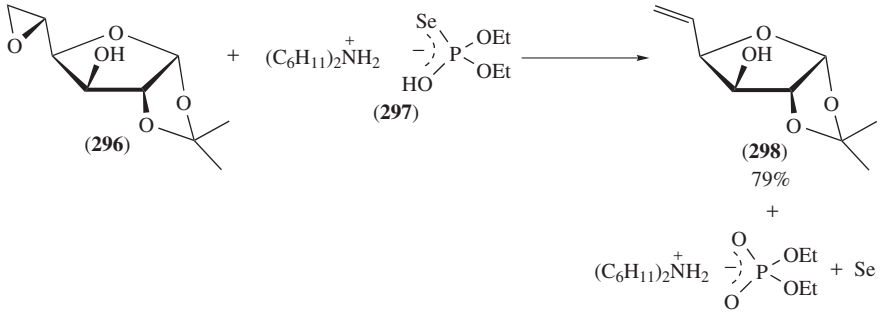
SCHEME 70. Deoxygenation of epoxides with benzeneselenocarboxamide

for straight-chain epoxy derivatives. On the other hand, if the epoxy group is condensed with other rings, the substrates show remarkable diversity in reactivity. The plausible mechanism involves intermediates such as oxaselenaheterocyclic compound **295** and the earlier-mentioned episelenide **292** (Scheme 71)[446, 447].



SCHEME 71. Deoxygenation of epoxides with potassium selenocyanate

The selenium-containing derivatives of phosphoric(V) acid, such as trialkylammonium *O*,*O*-dilakyl phosphoroselenolate (**297**), were the reagents of choice for the transformation of sugar epoxides **296** into unsaturated sugars **298** (Scheme 72).



SCHEME 72. Deoxygenation of sugar epoxides with trialkylammonium *O*,*O*-dialkyl phosphoroselenolate

Deoxygenation could be performed with unprotected OH groups and no polymerization or degradation was observed. Phosphoroselenoic acid salts were prepared *in situ* from *O*,*O*-dialkylphosphites and elemental selenium in the presence of secondary or tertiary amines[448].

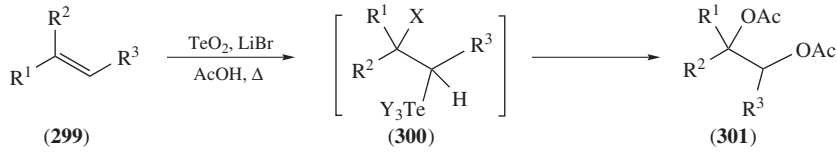
IV. TELLURIUM(IV) OXIDE AND OXYGENATED ORGANOTELLURIUM COMPOUNDS

A. Tellurium(IV) Oxide and Related Compounds

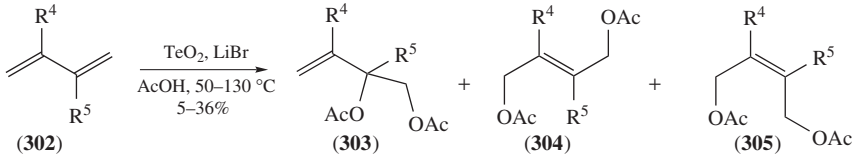
The use of TeO_2 as an oxidant in organic synthesis was tentatively explored as early as the 1940s[12, 449–451]. The results, however, were not especially encouraging due to the very low solubility of tellurium(IV) oxide in water and almost all organic solvents. Interest was therefore focused on the catalytic activity of TeO_2 in high-temperature vapor-phase oxidations. The Te-containing oxide catalysts have been used for oxidation, aminooxidation and oxidative dehydrogenation, e.g. the gas-phase oxidation of propylene to acrolein[452]. Catalytic systems containing TeO_2 and acetic acid or sulfolane have attracted considerable attention[453–455]. Ethylene, for example, was catalytically converted to ethylene glycol in 95% yield. Alkyl-substituted aromatic compounds could be oxidized by a similar procedure to benzyl acetates[456]. It was found that benzene, toluene, xylenes and mesitylene were acetoxylated to benzyl acetates, in low to moderate yield, by the action of TeO_2 in acetic acid containing LiBr at 120 °C or at higher temperatures. Diarylmethane derivatives were also formed. In contrast, Te(VI) compounds such as $Te(OH)_6$ and TeO_3 mainly effected side-chain acetoxylation[455].

The tellurium(IV) oxide/lithium bromide system in acetic acid was employed to afford the *syn*-diacetoxylation of alkenes. The first step in the tellurium(IV) oxide oxidation of alkenes **299** to diacetoxyalkane **301** is an electophilic *anti* addition giving an intermediate of the type **300** where X, Y is a halogen atom or an oxygen-bearing substituent, followed by an S_N2-type acetolysis leading mainly to a *cis*-adduct (Scheme 73).

In a more detailed investigation focusing on the 1,4-diacetoxylation of conjugated dienes **302** (isoprene, 2,3-dimethylbutadiene, 2,5-dimethylhexadiene, cyclopentadiene, cyclohexa-1,3-diene) with the same oxidizing system, it was ascertained that mixtures of 1,2- and 1,4-diacetoxy adducts **303**, **304** and **305** are formed in yields and proportions depending on the substrate and reaction conditions. A procedure utilizing catalytic TeO_2 was successfully used in the diacetoxylation of 1,3-butadiene by adding a reoxidizing reagent such as hydrogen peroxide or TBHP[457, 458].



R^1, R^2, R^3 = H, alkyl, cycloalkyl, vinyl, Ph, Bz

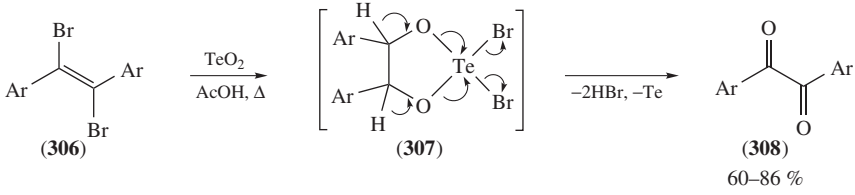


R^4, R^5 = H; R^4 = Me, R^5 = H; R^4, R^5 = Me

SCHEME 73. Diacetoxylation of alkenes and dienes with TeO_2/LiBr/AcOH

Certain aromatic ketones were regenerated in modest yields from the corresponding semicarbazones, azines or hydrazones by treatment with the TeO_2/LiBr/AcOH system. The tellurocyclization of ω-hydroxyalkenes and allylphenols by TeO_2/HCl/MeOH gave bis(2-oxacycloalkyl)tellurium dichlorides[459].

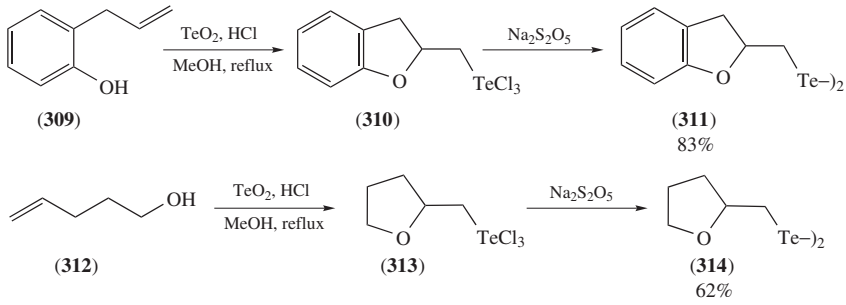
By treatment of dibromostilbenes **306** with TeO_2 in refluxing acetic acid, benzils **308** are formed as the main products. Strongly electron-withdrawing groups such as nitro on the aromatic ring promote acetolysis to the corresponding diacetates. A mechanism involving a cyclic intermediate **307** has been proposed (Scheme 74)[460].



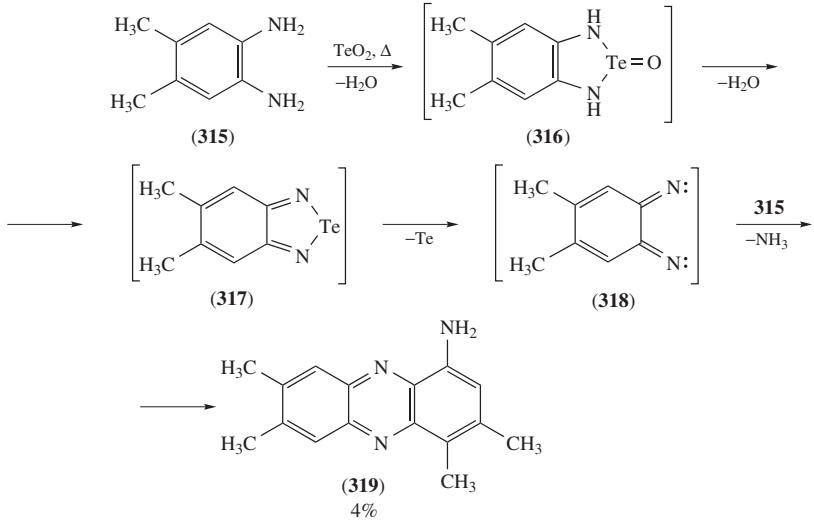
SCHEME 74. Tellurium(IV) oxide oxidation of dibromostilbenes to benzils

The tellurocyclization of allylphenols **309** and ω-hydroxyalkenes **312** by TeO_2/HCl/MeOH gave respectively furan-2-yltellurium trichlorides **310** and **313**, which were reductively converted to the corresponding tellurides **311** and **314** (Scheme 75)[461].

The synthesis of 2,1,3-benzotelluradiazole was attempted by direct heating of 4,5-dimethyl-1,2-phenylenediamine (**315**) with tellurium(IV) oxide. Since the only isolated product was 1-amino-3,4,7,8-tetramethylphenazine (**319**), it was postulated that the reaction proceeds via a telluroxodihydrodiazole intermediate **316**, which lost water to give telluradiazole **317**. Loss of tellurium from **317** gave highly active intermediate **318**, which attacked the second molecule of the diamine **315** yielding the final product **319** (Scheme 76)[462].



SCHEME 75. Tellurocyclization of allylphenols and ω-hydroxyalkenes



SCHEME 76. Oxidative cyclocondensation of 4,5-dimethyl-1,2-phenylenediamine with TeO_2

Despite using tellurium(IV) oxide as a stoichiometric oxidant, it was applied in a small molar ratio as catalyst while H_2O_2 or TBHP were the reoxidants[463]. The TeO_2/H_2O_2 system was used for the selective oxidation of sulfides to the corresponding sulfoxides. Reaction occurs at room temperature and is highly chemoselective. Neither over-oxidation of the formed sulfoxide to sulfone occurs, nor are double bonds or other functional groups such as hydroxyl or carbonyl group affected even in the presence of one equivalent of TeO_2. An initially observed disadvantage of the method, which is a long reaction time, was circumvented by the addition of a small amount of concentrated hydrochloric acid[464].

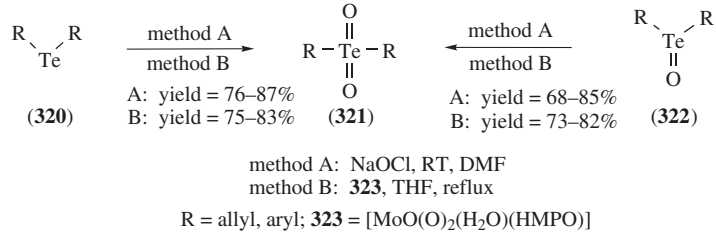
Oxidation of cyclohexanone with TeO_2/H_2O_2 under reflux afforded 1-hydroxy-1′-hydroperoxydicyclohexyl peroxide in 42.7% yield[465] whereas oxidation with SeO_2/H_2O_2 resulted in ring contraction and cyclopentanecarboxylic acid was produced (Section II.A.2.f.). Tellurium(IV) oxide/H_2O_2 was also applied for oxidative conversion of *N*,*N*-dimethylhydrazones derived from aliphatic and heteroaromatic aldehydes into nitriles, although the more efficient catalyst was phosphomolybdic acid[466].

Sodium tellurite (Na_2TeO_2) and sodium tellurate (Na_2TeO_4) have been recognized as a mild and selective oxidizing agent of thiols. Under phase-transfer conditions sodium tellurite oxidizes instantaneously aromatic thiols, and rapidly benzylic thiols, whereas primary thiols are slow, *sec*-thiols are sluggish and *tert*-thiols fail to react. Oxidative cross-coupling of two different thiols lead to unsymmetrical disulfides[467].

B. Organotellurium Oxidants and Oxygen-transfer Agents

1. Telluroxides and tellurones

a. General comments. The chemistry of telluroxides $R^1Te(O)R^2$ has been less extensively explored than that of their selenium counterparts (Section II.B.1) and reports on their properties and use in synthesis are limited to a few examples[2, 12–15]. Furthermore, diaryl and dialkyl tellurones (**321**), the tellurium analogues of the well-known sulfones and selenones (Section II.B.2) until the last decade, were not well-defined compounds and it was doubtful whether a compound corresponding to the formula R_2TeO_2 has ever been obtained in pure form[468, 469]. More recently, the simple and efficient synthesis of tellurones **321** by oxidation of tellurides **320** or telluroxides **322** with sodium hypochlorite or the peroxo complex of molybdenum $[MoO(O)_2(H_2O)(hmpa)]$ (**323**) has been reported (Scheme 77)[278, 279]. No detellurenylation products were obtained in any of these reactions. No dehalogenation was observed in substrates containing halogen on a benzene ring. Oxidation of tellurides to the corresponding tellurones has been observed to proceed via the corresponding telluroxides.

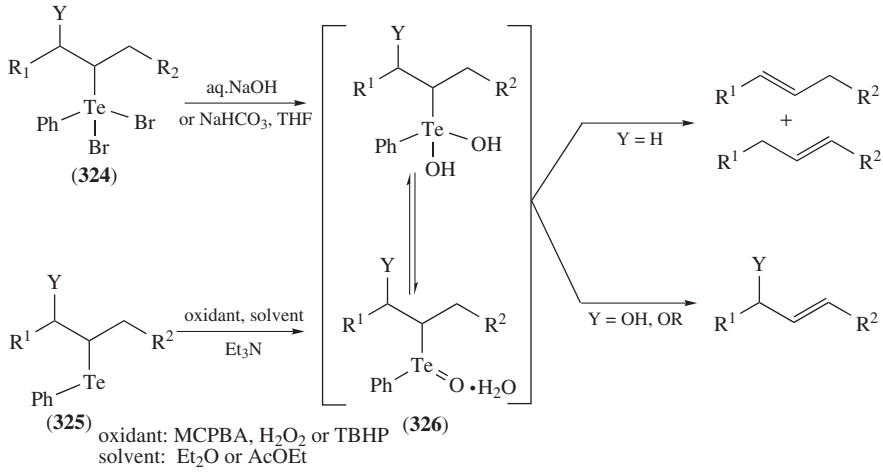


SCHEME 77. Oxidation of tellurides and telluroroxides to tellurones

Optically active telluroxides stabilized by bulky substituents and/or intramolecular coordination with an amino group were isolated from the racemic mixture by liquid chromatography using an optically active column. The configurational lability and mechanism for racemization via achiral hydrate were clarified[470–472].

Various alkyl, aryl and benzyl telluroxides and tellurones can be deoxygenated in nearly quantitative yields using Mg−MeOH at room temperature[181]. Most recently, it has been found that telluroxides exhibit catalytic activity. For instance, 6,6′-telluroxy-bis(6-deoxy-β-cyclodextrin) acts as hydrolase mimic and shows a significant rate acceleration of $1 \bullet 10^5$ for the hydrolysis of 4,4′-dinitrodiphenyl carbonate[473].

b. Telluroxide elimination. Although not so well known as the selenoxide elimination leading to double-bond formation, the corresponding telluroxide elimination has gained more attention in the last years, becoming a well-established method for the synthesis of olefins. It was found that *sec*-alkyl phenyl telluroxides **326**, prepared by treatment



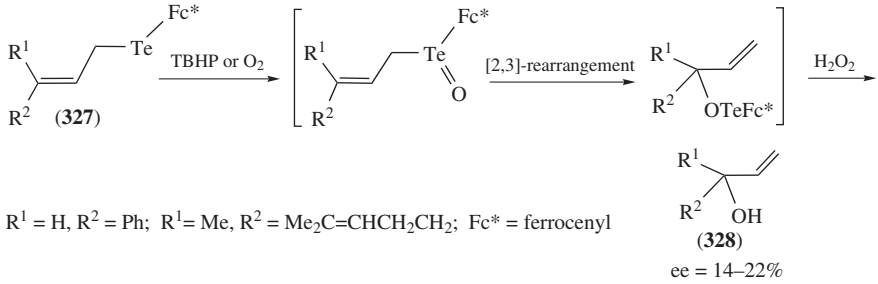
SCHEME 78. Telluroxide elimination

of the corresponding organotellurium dibromides **324** with NaOH or $NaHCO_3$, readily decompose to afford alkenes, allylic alcohols or allylic ethers under mild conditions (Scheme 78)[474]. It was also soon disclosed that similar elimination occurs even by direct oxidation of alkyl phenyl tellurides **325** (or better, alkyl pyridyl tellurides) with such oxidants as MCPBA, H_2O_2 or TBHP, especially in the presence of Et_3N[14, 475–477]. This finding disclosed a new characteristic feature of telluroxides and also showed their utility for alkene and allylic compound syntheses, a reaction which previously appeared to be of little value[478].

Treatment of alkyl phenyl telluroxides, with excess of MCPBA or trifluoroperacetic acid in alcohols, leads to detellurenylation and formation of alkyl ethers. Alkyl phenyl tellurones, obtained by oxidation of telluroxides with $NaIO_4$, give similar results under the same conditions. Ring contraction of 1-tellurium-2-alkoxycyclohexanes has also been accomplished under similar detellurative methoxylation conditions. MCPBA and methanol were found to be the most appropriate oxidant and solvent, respectively, and the fundamental reaction is a substitution of PhTe moiety with a methoxy group instead of β-elimination. Phenyl migration has been reported with structures bearing a phenyl group vicinal to the tellurium moiety. The key intermediate of the reaction is the MCPBA-addition product to an alkyl phenyl tellurone where a PhTe(VI) moiety (similar to PhSe(VI) moiety in selenones (Section II.B.2)) works as a very good leaving group[478].

Allylic telluroxides undergo sigmatropic [2,3]-rearrangements furnishing allylic alcohols after hydrolysis. TBHP or aerial oxidation of allylic chiral ferrocenyl tellurides **327** produces chiral allylic alcohols **328** via rearrangement of the intermediate allylic telluroxides (Scheme 79)[479, 480].

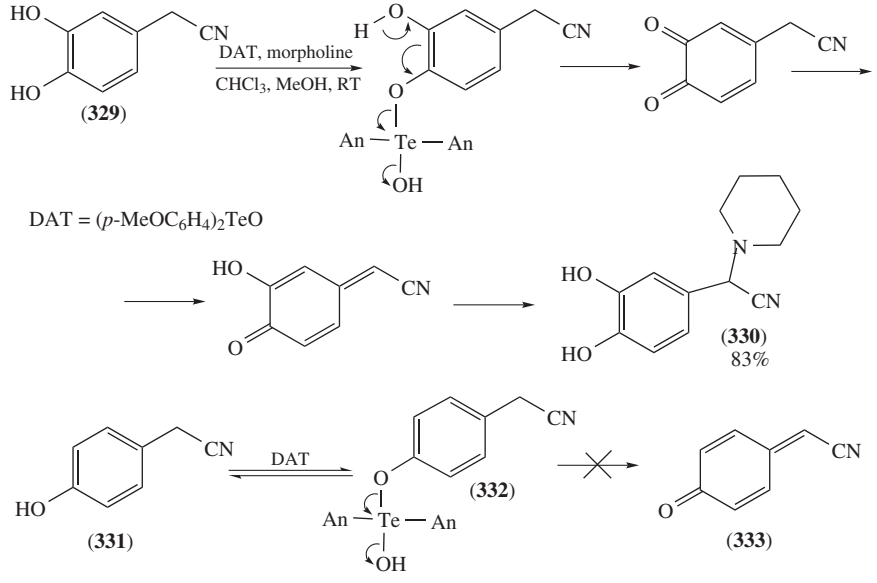
c. Telluroxides as oxidizing agents. Synthetic applications of telluroxides as oxidizing agents are less common than the use of selenoxides or tellurium(IV) oxide and are limited to only bis(4-methoxyphenyl) telluroxide (dianisyltellurium oxide, DAT). This compound is known as a mild and highly selective reagent for the conversion of xanthates, thiocarbonates, thioamides and thiones into their corresponding oxo derivatives and thiols into disulfides in 66–100% yield. The same telluroxide reacting with arylhydrazines gave



SCHEME 79. Sigmatropic [2,3]-rearrangements of allylic telluroxides

the corresponding arene, telluride and nitrogen[481, 482]. More recently, DAT was used for oxidation of a series of catecholic tertiary amines and novel heterocyclic betaines were formed in high yield by cyclization of the intermediate *o*-quinones[483].

Treatment of 4-cyanomethylcatechol (**329**) with DAT in the presence of morpholine gave the 2-aminonitrile **330**. When 4-cyanomethylphenol (**331**) was treated with DAT under identical conditions, with or without the addition of morpholine, quinomethane **333** formation was not observed. However, the ^{1}H NMR spectrum showed that the phenol was in equilibrium with a species whose spectrum is consistent with the structure of the Te(IV) complex **332** (Scheme 80)[484].



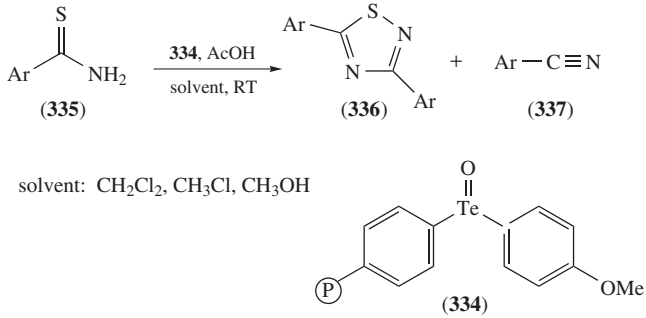
SCHEME 80. Oxidation of 4-cyanomethylcatechol and 4-cyanomethylphenol with dianisyltellurium oxide

Electrochemical oxidation of thioamides was developed using DAT as mediator. In this process a mixture of thioamide, tetrabutylammonium acetate or tosylate and DAT is

submitted to electrolysis. Depending on the supporting electrolyte, applied current density and solvent, different mixtures of nitriles and thiadiazoles were obtained[485].

A polystyrene-bound diaryl telluroxide **334**, prepared from 4-methoxyphenyltellurium cyanate and poly-4-lithiostyrene, exhibits some advantages over the monomeric DAT, such as easier product workup and multiple recycle of the spent reagent. Like its monomeric counterpart this reagent is inert to simple amines, amides, alcohols or phenols, but readily oxidizes thiols to disulfides, phosphine to phosphine oxides, hydroquinones to *p*-quinones and catechols to *o*-quinones in dichloromethane, chloroform or acetic acid at room temperature. Thioketones and *O*-alkyl thioesters are smoothly converted to the corresponding oxo-compounds. Polymeric selenoxides behave similarly, but require longer reaction time and are unreactive with some thioketones or thioesters[486].

The telluroxide **334** reacts with thioamides **335** in acetic acid at room temperature to give 1,2,4-thiadiazoles **336**, while thioureas yield 4,5-dihydrothiazoles. However, when dichloromethane, chloroform or methanol is used as the solvent, dehydrosulfurization occurs and nitriles **337** are formed (Scheme 81)[486].



SCHEME 81. Oxidation of thioamides with polymer-supported diaryl telluroxide

Like dianisyltellurium oxide (DAT), dianisyl tellurone is a relatively mild oxidant, capable of effecting a variety of organic transformations. Thus, benzenethiol was oxidized to diphenyl disulfide, hydroquinone was converted into *p*-benzoquinone and benzylic alcohols were oxidized to the corresponding carbonyl compounds. Benzoin, piperonyl alcohol and veratryl alcohol could be oxidized to benzil, piperonal and veratraldehyde, respectively[468].

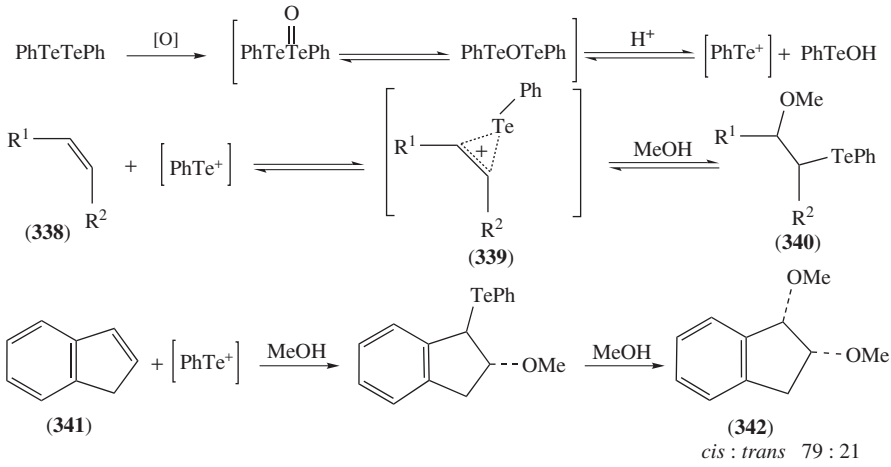
2. Tellurinic acids, tellurinic anhydrides, their precursors and derivatives

Tellurinic acids RTe(O)OH (R = alkyl, aryl), prepared by alkaline hydrolysis of alkyl or aryltellurium trichloride, are amorphous, high melting compounds that are poorly soluble in most organic solvents[487–492]. Optically active tellurinic acid was obtained for the first time by chromatographic resolution of racemic 2,4,6-triisopropylbenzenetellurinic acid[490].

The lack of catalytic activity of soluble tellurinic acids was confirmed by the preparation of phenethyl tellurinic acid and anisyl tellurinic acid. They were found to be inactive under typical epoxidation conditions. Dimethyl ditelluride and diphenyl ditelluride, which may be regarded as precursors for tellurinic acids assuming that H_2O_2 acts upon them as it does upon diselenides, were found to be inactive in this reaction. It was assumed that when tellurinic acids were treated with hydroperoxides, even in aqueus medium, they form

anhydrides instead of peroxytellurinic acids[493]. The exception is cross-linked polystyrene-tellurinic acid used as a catalyst for selective hydrogen peroxide epoxidation of olefins. In the presence of this catalyst, cyclohexene treated with H_2O_2 in *t*-BuOH at 60 °C for 24 h yielded quantitatively the epoxide[494]. Despite lack of success in epoxidation of alkenes catalyzed by ditellurides, diaryl ditellurides have been found to be a thiol peroxidase-like catalyst for hydrogen peroxide oxidation of thiols to the corresponding disulfides[366].

Reaction of aliphatic alkenes with TBHP or H_2O_2 and PhTeTePh in refluxing MeOH, containing sulfuric acid, gave methoxytellurenylation products (e.g. $CH_3(CH_2)_5CH(OMe)CH_2TePh$ from 1-octene). A mechanism has been proposed involving a rapid equilibrium between the starting alkene **338**, an intermediate telluronium compound **339** and the product **340** (Scheme 82).



SCHEME 82. Methoxytelluration of alkenes

Under similar conditions aromatic olefins, such as styrene and 4-methylstyrene, give the dimethoxy adducts as the sole products. α,β-Dimethoxyphenylethane was obtained from styrene in 88% yield. The stereochemistry of the reaction has been established as involving *anti* methoxytellurenylation, followed by methanolysis with inversion of the configuration. The final result, as illustrated for indene (**341**) conversion to compound **342**, is a predominantly *syn* dimethoxylation[495, 496].

Arenetellurinic anhydrides $(ArTeO)_2O$ (where Ar = phenyl, 4-methoxyphenyl, 4-butoxyphenyl, 4-phenoxyphenyl, 2-naphthyl) are easily prepared by alkaline hydrolysis of the aryltellurium trihalides or in a one-pot procedure involving oxidation of diaryl ditellurides with phenyliodine(III) dicarboxylate in a biphasic system[497]. They are mild and selective oxidizing reagents while reduced in turn to the corresponding diaryl ditellurides as the reaction proceeded. Several substrates, such as hydroquinones, thiols, xanthates, thioamides, *S*-alkylthioesters, thioureas and phosphines, were easily oxidized. Other compounds, such as phenols, 2,3-dihydroindole, 2-phthaloylhydrazide and 4-phenyl-3,5-dioxo-1,2,4-triazolidine, were unaffected by tellurinic anhydrides[469, 498–500].

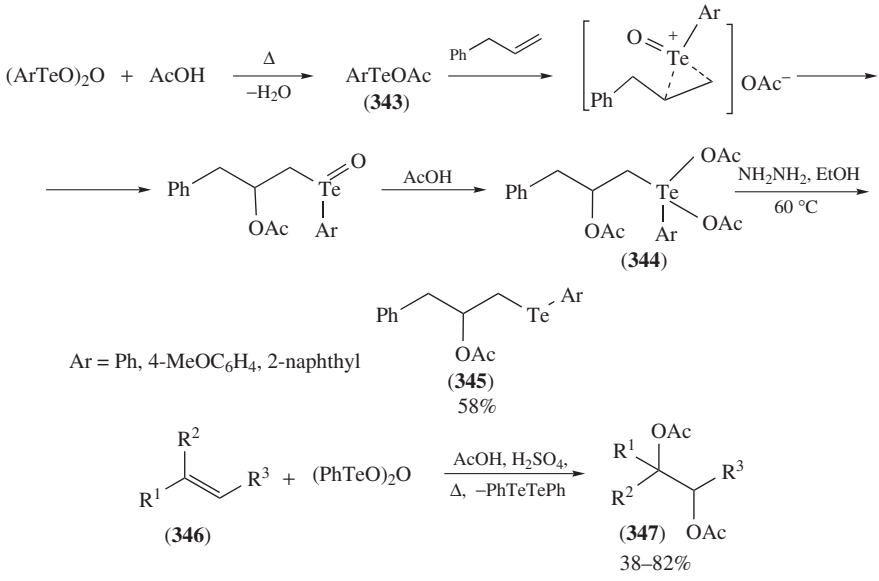
Competitive experiments to assess the relative oxidizing capacity of the tellurinic anhydrides and telluroxide have been performed employing oxidation of 2,5-di-*tert*-butyl-1,4-hydroquinone to 2,5-di-*tert*-butyl-1,4-quinone. The established order of reactivity was: $(2\text{-naphthylTeO})_2O > (4\text{-MeOC}_6H_4)_2TeO > (4\text{-MeOC}_6H_4TeO)_2O > 4\text{-PhOC}_6H_4(TeO)_2O$[500].

Arylmethanols, benzoin, and methyl lactate were oxidized with arenetellurinic anhydrides to arylaldehydes benzyl and methyl 2-oxopropanoate, respectively, in good yields. This illustrates the capacity of tellurinic anhydrides to oxidize alcohols, in analogy with tellurones, but in contrast with diaryl telluroxides, which do not oxidize simple alcohols[14].

Non-terminal acetylenes are inert toward tellurinic anhydrides. However, if the reaction is performed in the presence of catalytic amounts of sulfuric acid, diphenylacetylene is converted into benzyl. Furthemore, it was found that tellurinic anhydrides in refluxing acetic acid catalyze the hydration of terminal acetylenes to ketones[469, 501].

Tellurinic anhydrides react with acetic, trifluoroacetic or with trifluoromethanesulfonic acids under heating to give the mixed anhydrides arenetellurinyl acetate, arenetellurinyl trifluoroacetate or arenetellurinyl trifluoromethanesulfonate, respectively. Benzenetellurinic mixed anhydrides are mild oxidants for various substrates such as thiols, phosphines, acyloines, α-hydroxyesters, catechol, hydroquinone, thionoesters, benzylic alcohols, thioureas and thioamide. The reactions toward the last two substrates are highly chemoselective, depending on both reagent and substrate[469, 500, 502].

Arenetellurinyl acetate **343**, formed *in situ* from arenetellurinic anhydride and acetic acid, was used for the conversion of allylbenzene into 2-acetoalkyl(phenyl)tellurium diacetate **344**, which was isolated in its telluride form **345**[503, 504] (Scheme 83).



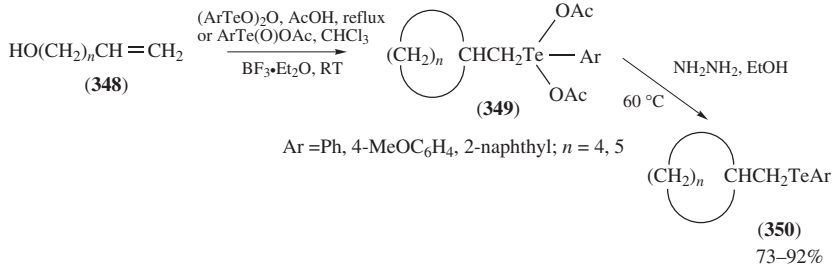
$R^1 = R^2 = H$, $R^3 = Ph$; $R^1 = n\text{-}C_6H_{13}$, $R^2 = R^3 = H$; $R^1 = H$, $R^2 = Me$, $R^3 = n\text{-}C_5H_{11}$; $R^1 = H$, $R^2R^3 = —(CH_2)_4—$

SCHEME 83. Acetoxylation of allylbenzene and alkenes with arenetellurinic anhydrides

This reaction is therefore different from that effected for the alkenes **346**, which when treated in acetic acid with benzenetellurinic anhydride in the presence of a catalytic amount of sulfuric acid gave the diacetoxylated products **347**[505]. Internal alkenes give low yields

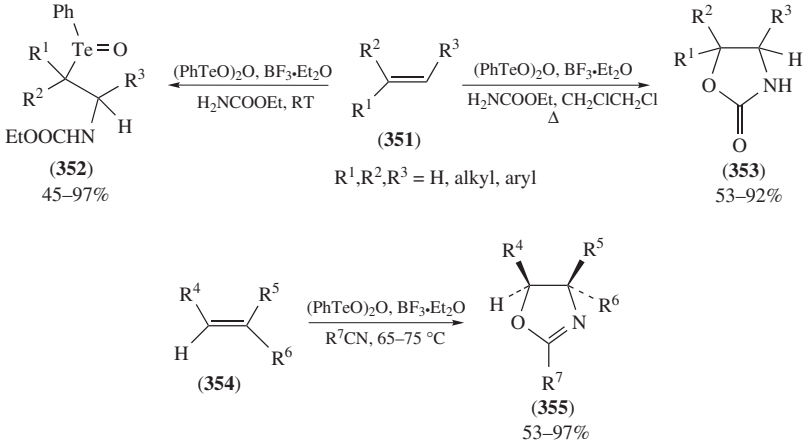
of diacetates. Stereochemically, the inversion of configuration during the two consecutive acetoxylations results in a *syn* addition (Scheme 83).

When an alkene, bearing a hydroxyl group **348** in a suitable γ or δ position, is treated with arenetellurinyl anhydrides, an intramolecular reaction occurs leading to a ring closure, and tellurinated esters, having cycloalkane ring **349**, are produced. The products are isolated as the corresponding tellurides **350** after reduction with hydrazine hydrate (Scheme 84). The tellurides **350** can be converted to the tellurium free ethers by treatment with tributyltin hydride or by other transformations such as reductive detelluration, oxidative elimination, halogenolysis and methanolysis[503, 504].



SCHEME 84. Cyclization of hydroxyalkenes with arenetellurinyl anhydrides

Benzenetellurinyl anhydride adds to alkenes **351** in the presence of ethyl carbamate giving β-(phenyltellurenyl)alkylcarbamates **352**[506]. However, if the reaction is effected in refluxing 1,2-dichloroethane, than 2-oxazolidin-2-ones **353**, an important class of heterocyclic compounds, are formed in high yield[507–509]. This synthetic approach has been further explored leading to the conversion of alkenes **354** into 4,5-dihydrooxazoles **355**



SCHEME 85. Reactions of benzenetellurinyl trifluoroacetate

(Scheme 85). The method is based on the addition of a nitrile acting as a solvent as well as a nucleophile. These reactions are highly regio- and stereoselective[510, 511].

V. HYDROGEN TELLURIDE AND RELATED ORGANOTELLURIUM COMPOUNDS

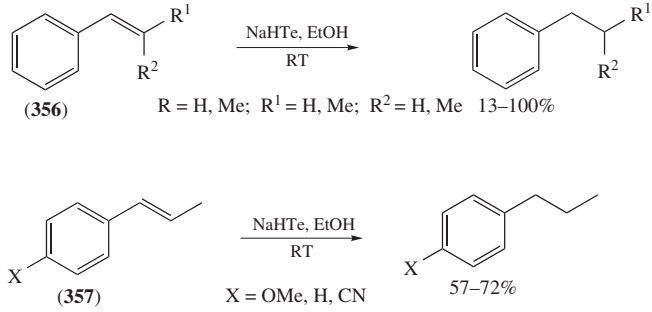
Due to progress of synthetic methodologies, hydrogen telluride finds application as reducing agent for many classes of functional groups and for reductive cleavage of the carbon–heteroatom bond. A number of organic compounds, such as carbonyl compounds, alkenes and alkynes, ketones, epoxides and nitro or bromo derivatives, can be reduced by tellurium species. Among the most commonly used reductants are H_2Te, NaHTe, Na_2Te, PhTeH and PhTeNa. They are advantageous due to mild reaction conditions, desired regioselectivity, opportunity of *in situ* generation of active reactants and possibility of elemental tellurium recovery. The inconveniences in organotellurium chemistry are comparable to those related to organoselenium chemistry and include their odor nature and instability.

A. Hydrogen Telluride, Tellurols and Related Compounds

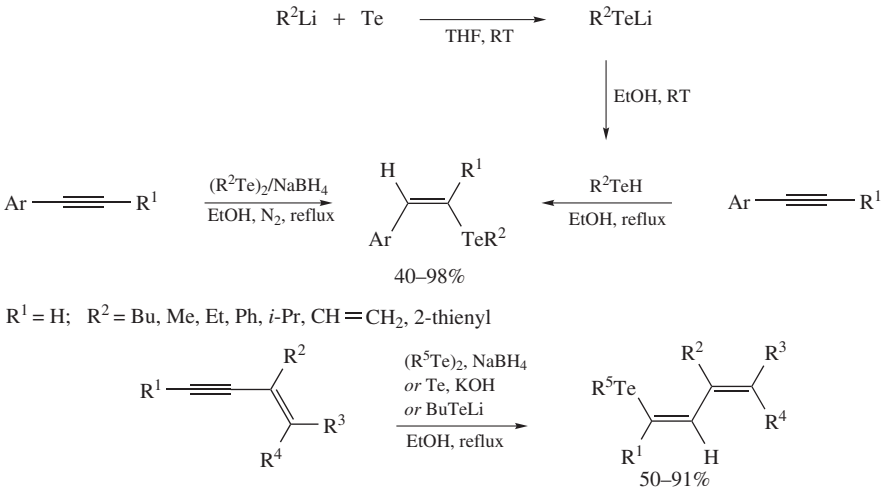
Hydrogen telluride appears as a highly toxic colorless gas (m.p. $-49\,^{\circ}C$, b.p. $-2.2\,^{\circ}C$) poorly soluble in water (0.7 g/100 ml). As a diprotic, weak acid ($pK_a = 2.6$), it forms two types of salts: tellurides $M^{(I)}{}_2Te$ and hydrogen tellurides $Me^{(I)}HTe$[378]. During acidification of tellurides, mainly Al_2Te_3 or Na_2Te, tellurium hydride is liberated.

1. Reduction of alkenes and alkynes

Alkenes and alkynes conjugated to an aryl group can be reduced to the corresponding saturated derivatives by reaction with benzenetellurol, 2-thienyltellurol[512] or sodium hydrogen telluride[513]. In 1990, Barton and coworkers reported that the reaction of sodium hydrogen telluride with a non-electrophilic C=C bond leads to a mixture of reduction and addition products[514]. The best results were obtained when the double bond was conjugated to an aromatic ring. An effect of substituents in the *para* position on the reduction course was not observed. Sodium hydrogen telluride was generally inert toward isolated double bonds, but some styrenes of structures **356** or **357** could be prone to reduction (Scheme 86)[515–517].



SCHEME 86. Reduction of styrenes with NaHTe



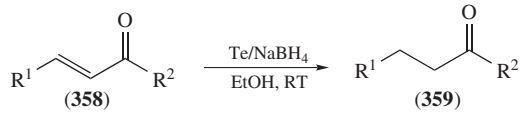
SCHEME 87. Hydrotelluration of alkynes and the coupling of *Z*-vinylic tellurides with other organometallics

Hydrotelluration of alkynes was applied for synthesis of *Z*-vinylorganometallics, constituting valuable intermediates, for construction of C=C bonds in defined configuration[518]. In contrast, the coupling of *Z*-vinylic tellurides with other organometallics such as magnesium and lithium cyanocuprates, mixed cyanocuprates or Gilman cuprates, as well as organozinc compounds, results in a new C−C bond formation in good yield and retention of configuration (Scheme 87)[519–522].

2. Reduction of carbonyl compounds

Reduction of aldehydes and ketones with benzenetellurol or H_2Te leads to primary and secondary alcohols[390, 512, 513, 523]. Hydrogen telluride is usually obtained *in situ* by hydrolysis of Al_2Te_3, while benzenetellurol is prepared by treatment of PhTeLi with trifluoroacetic acid (TFA) or by methanolysis of $PhTeSiMe_3$.

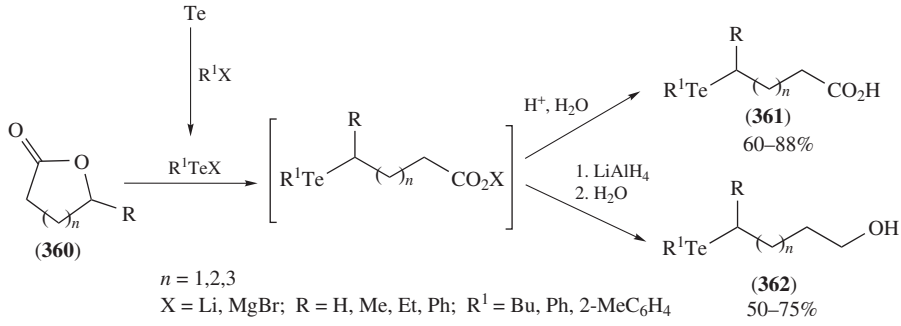
Hydrogen telluride[90] as well as benzenetellurol[512, 513] and sodium hydrogen telluride (prepared from $NaBH_4$ and tellurium powder) were employed as reagents for selective reduction of α,β-unsaturated carbonyl compounds **358** to saturated aldehydes and ketones **359** (Scheme 88)[512, 524, 525]. Another reagent i-$Bu_2Te/TiCl_4$ is an effective reductant for several functional groups such as NO_2, S=O and C=O[526].



SCHEME 88. Selective reduction of α,β-unsaturated carbonyl compounds with $Te/NaBH_4$

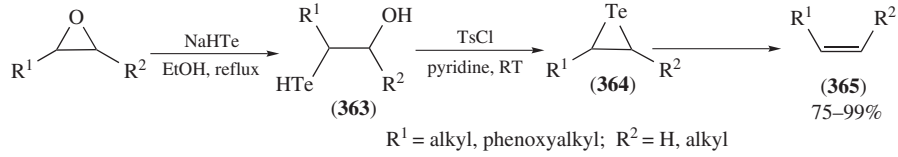
3. Reduction of lactones and epoxides

Lithium and magnesium organotellurolates easily cleave the lactone ring, and from lactones **360** the corresponding tellurocarboxylic acids **361** or hydroxyalkyl tellurides **362** are formed[527]. The aim was achieved in a single operation by using *in situ* generated metal organotellurolates in a reaction obeying the S_N2 mechanism. The direct reduction of organyl telluride carboxylates by LAH appeared to be applicable to hydroxyalkyl tellurides preparation (Scheme 89)[527].



SCHEME 89. Lactone ring cleavage with organotellurolates

O,*O*-Diethyl phosphorotellurolates, easily obtained in the reaction of sodium diethyl phosphite with tellurium, reduce epoxides stereospecifically to the 2-alkenes under mild conditions. The reaction can be applied even for terminal epoxides[528]. When sodium hydrogen telluride is the reagent, the corresponding telluro alkanol **363** appears as intermediate that is converted to epitelluride **364**, which undergoes detelluration to an alkene **365** (Scheme 90)[529].



SCHEME 90. Deoxygenation of epoxides with sodium hydrogen telluride

A chemo- and regioselective method for reduction of cyclic and acyclic α,β-epoxy ketones to β-hydroxy ketones employed NaHTe as the reducing agent. The method required molar excess of the tellurium compound but resulted in good yield (72–96%)[516].

4. Reduction of nitrogen compounds

A mixture of different nitrogen compounds (nitroso, azo, azoxy) is obtained when nitroarenes are treated with arenetellurolate at room temperature[530]. At elevated temperature, the azo compounds are formed as the major products in moderate to excellent yields (43–91%).

Imines and enamines are easily reduced to the corresponding amines by hydrogen telluride under mild conditions[531]. The method developed by Kambe and coworkers enables one to perform the reaction in water, while H_2Te is generated *in situ* from Al_2Te_3. A procedure was successfully introduced for a reductive *N*-alkylation of amines with carbonyl compounds[531, 532].

5. Dehalogenation

Vicinal dibromides undergo *anti*-E2 elimination, giving alkenes by treatment with diaryl tellurides[533], ditellurides[534], sodium hydrogen telluride[535], sodium ditelluride[536], sodium diethyl phosphorotelluride[537], thienyl telluride[538] or $(Ph_3Sn)_2Te$[539]. With these reagents α-halo ketones are reduced to ketones. Moreover, OAc, OMs or SPh can be the leaving groups in the reductive cleavage of the carbon–heteroatom bond[540–543].

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Hypervalent derivatives of selenium and tellurium

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PATAI'S Chemistry of Functional Groups; The Chemistry of Organic Selenium and Tellurium Compounds (2012)
Edited by Zvi Rappoport, Online © 2011 John Wiley & Sons, Ltd; DOI: 10.1002/9780470682531.pat0583

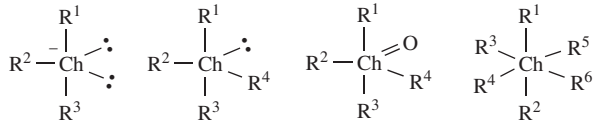
I. INTRODUCTION

Selenium and tellurium form a very large number of inorganic and organic compounds showing different reactivity and structural properties. A very useful criterion to classify all of them, like other heteroatom-containing derivatives, is to consider formal oxidation state and number (n) of ligands bonded to selenium or tellurium. Based on it, the derivatives in which the central chalcogen atom has expanded its valency shell from 8 to 10 or 12 electrons can be considered as hypervalent compounds (the concept of which and the theoretical basis for their occurrence was first proposed by Musher in 1969)[1]. Among them are the following selenium and tellurium derivatives:

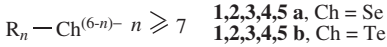
(a) trivalent, tricoordinated negatively charged selenium or tellurium ate-complexes (selenuranide anions or telluranide anions),
(b) tetravalent, tetracoordinated (selenuranes or telluranes),
(c) hexavalent, pentacoordinated (selenurane oxide or tellurane oxides),
(d) hexavalent, hexacoordinated (perselenuranes or pertelluranes),
(e) compounds having the formal oxidation state and numbers of ligands higher than 6.

According to a general systematic scheme proposed by Martin and coworkers[2], selenium or tellurium ate-complexes **1a,b** should be considered as 10-Ch-3 species, selenuranes and telluranes **2a,b** should be included to the family of 10-Ch-4 derivatives, selenurane oxide and tellurane oxides **3a,b** should be considered as 12-Ch-5 species and perselenuranes and pertelluranes **4a,b** should be viewed as 12-Ch-6 derivatives. Compounds having the formal oxidation state and numbers of ligands higher than 6 should form the 2*n*-Ch-*n* ($n > 6$) group **5a,b** (Chart 1).

Having accepted the definition of hypervalent selenium and tellurium compounds as a group of compounds in which a chalcogen atom has expanded its formal valence shell from 8 to 10, another group of hypervalent selenium and tellurium derivatives should also be considered, namely the corresponding ylides. Due to the fact that the most important



(**1a,b**) (**2a,b**) (**3a,b**) (**4a,b**)



1,2,3,4,5 a, Ch = Se
1,2,3,4,5 b, Ch = Te

(**5a,b**)

CHART 1

(**6a,b**) **6,7 a**, Ch = Se **6,7 b**, Ch = Te (**7a,b**)

CHART 2

resonance structures of these compounds **6a,b** ↔ **7a,b** are polarized from chalcogen to carbon, they should be in principle considered as 8-Ch-3 species (Chart 2). Therefore, these two groups of tricoordinated chalcogen derivatives do not meet the condition of hypervalency and their chemistry is discussed in another chapter of this volume[3].

The advances in the chemistry of these derivatives, which emerged after the chapter entitled 'Tetra- and higher-valent (hypervalent) derivatives of selenium and tellurium' was included in the first volume of *The Chemistry of Organic Selenium and Tellurium Compounds*, edited by Patai and Rappoport and published in 1986[4], will be discussed below. It should be noted here that in 1999 another excellent monographic chapter devoted to this topic was included in *Chemistry of Hypervalent Compounds*, edited by Akiba. This chapter, by Furukawa and Sato, presents very comprehensively the structural diversity and reactivity of hypervalent selenium and tellurium compounds[5]. Due to the existence of the chapters mentioned above and the appearance of many other textbook compilations and review papers[6], in which hypervalent selenium and tellurium compounds are also discussed more or less extensively, the present chapter will cover only the advances in most recent years (usually after 1998).

The nature of bonding of hypervalent derivatives, including selenium and tellurium compounds, is presented in detail in a few chapters of *Chemistry of Hypervalent Compounds* edited by Akiba[7, 8a,b]. Therefore, there is no need to repeat such a presentation in the present chapter. It is enough to recall here the commonly accepted view that the structure and reactivity of such derivatives is dominated by the weak three-center–four-electron (3c–4e) bond. Its weakness results from the fact that two of the four electrons that participate in the bonding are in a nonbonding molecular orbital. However, it should be noted here that the nature of chemical bonding in hypervalent molecules of P, As, S, Se, Te, Cl and Br with the ligands F, Cl, O, CH_3 and CH_2 has again been recently studied using the topological analysis of the electron localization function (ELF)[9]. These studies showed that this function partitions the electron density of a molecule into core and valence basins and further classifies valence basins according to the number of core

basins with which they have a contact. The number and geometry of these basins is generally in accord with the VSEPR model. The population of each basin can be obtained by integration, and so the total population of the valence shell of an atom can be obtained as the sum of the populations of all the valence basins which share a boundary with its core basin. It was concluded that 'the bonds in hypervalent molecules are very similar to those in the corresponding nonhypervalent compounds. They are all polar bonds ranging from weakly to strongly polar depending on the electronegativity of the ligands'. Therefore, in the authors' opinion the term 'hypervalent' has little significance except for the indication that an atom in a molecule forms more than four electron pair bonds.

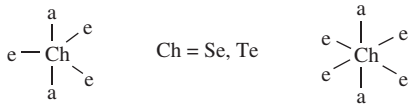
Considering the molecular geometry of hypervalent selenium and tellurium molecules, it should be expected that 10-Ch-4 and 12-Ch-5 derivatives will always form a trigonal bipyramidal structure (TBP geometry in which the 3c–4e bond is apical and the equatorial bonds are formed using the sp^2 orbitals), regardless of the nature of the chalcogen atom and the kind of formal charge located on it (neutral, plus or minus). On the other hand, perselenuranes and pertelluranes (12-Ch-6 species and 12-Ch-5, bearing a free electron pair) will have a square bipyramidal structure (SBP geometry generated by the use of three equivalent 3c–4e bonds) regardless of the nature of the chalcogen atom and the kind of formal charge located on it (neutral, plus or minus) (Chart 3)[8a].

It is commonly accepted that the molecular structure of hypervalent compounds having TBP geometry obeys the Mutterties rule[10], which states that the more electronegative ligands tend to occupy the apical positions whereas the lone electron pair should be located at the equatorial position. Moreover, five- and six-membered rings, which stabilize the hypervalent molecules, span both the axial and equatorial positions[2a]. Very early molecular orbital calculations[11] clearly indicated that the following factors determine the stability of hypervalent compounds:

(a) the smaller the electronegativity of the central heteroatom, the more stable the hypervalent compounds;
(b) more electronegative ligands stabilize the hypervalent bond;
(c) the lone electron pair plays an important role in the formation and stabilization of the hypervalent bond.

In full accord with these calculations, and as predicted by the valence bond treatment of Shaik and coworkers[12], telluranes have been found to be more stable than selenuranes, whereas sulfuranes are least stable.

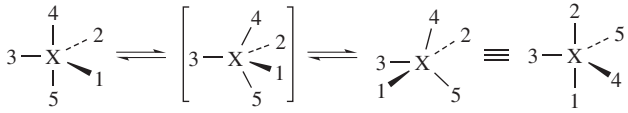
In hypervalent selenium and tellurium molecules which can be described as 10-Ch-4 and 10-Ch-5 species, the apical and equatorial ligands can be interchanged with each other according to the Berry pseudorotation mechanism[13] (Scheme 1) or by a closely related mechanism called the 'turnstile' rotation coined by Ugi and Ramirez[14] (Scheme 2). It is interesting to note that the latter was shown to be a higher energy process in comparison



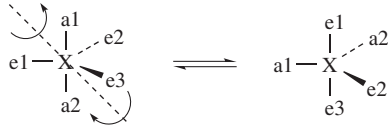
selenuranes or telluranes
(10-Ch-3; 10-Ch-4; 10-Ch-5)
TBP geometry

perselenuranes or pertelluranes
(12-Ch-6)
SBP geometry

CHART 3



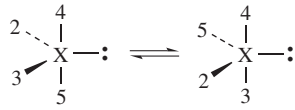
SCHEME 1



SCHEME 2

with the Berry pseudorotation sequence. It should also be indicated that a pseudorotation interconverting one 10-Ch-4 hypervalent structure into another according to the Berry mechanism requires passing through a very unstable chalcogenurane with an apical electron pair, which makes its probability very little[2a]. Its rate decreases going from telluranes to selenuranes. As a consequence of such processes the stereochemical outcome of a nucleophilic substitution of four-valent, tricoordinated chalcogen compounds is complex, in contrast to the S_N2 nucleophilic substitution reaction at carbon. Both retention and inversion can be observed due to the stability of intermediate 10-Ch-5 species, which are prone to undergo fast positional isomerization[8a].

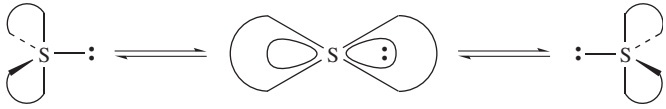
Taking into consideration the theoretical studies on the ligand coupling reaction of tetramethyl sulfurane, Furukawa and coworkers[15] proposed a non-Berry pseudorotation (NBPR) process in which one apical and two equatorial ligands interchange their positions in one step (Scheme 3). Considering the topological properties of TBP structures, the NBPR process is equivalent to two successive BPR interchanges involving the lone electron pair as a pivot for which the theoretical calculations have shown that their barriers are much higher than those of BPR.



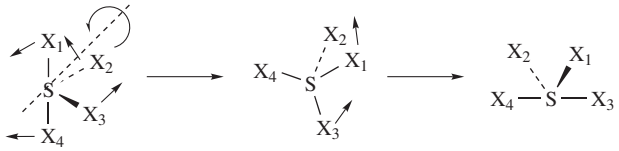
SCHEME 3

Earlier, a mechanism involving a planar transition state, named the cuneal inversion, was proposed for interconverting two-wedge-shaped sulfuranes (Scheme 4)[16]. An alternative for this mechanism was proposed recently by Mauksch and Schleyer (Scheme 5)[17]. It recalls the 'turnstile' rotation process with a transiton state having C_s symmetry.

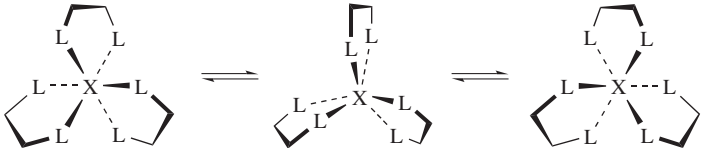
In the hypervalent selenium and tellurium molecules, which can be described as 12-Ch-6 species, the apical and equatorial ligands can be interchanged with each other very slowly according to a nondissociative mechanism (the so-called Balilar twist) (Scheme 6)[8a]. On the other hand, much faster isomerization can be induced by a dissociative mechanism involving a 10-Ch-5 cationic intermediate analogous to the 10-S-5 persulfonium cation **9** generated during the antimony pentafluoride-catalyzed isomerization of the all-*trans* 12-S-6 difluoropersulfurane **8** to its *cis,cis,trans* isomer **10** (Scheme 7)[18].



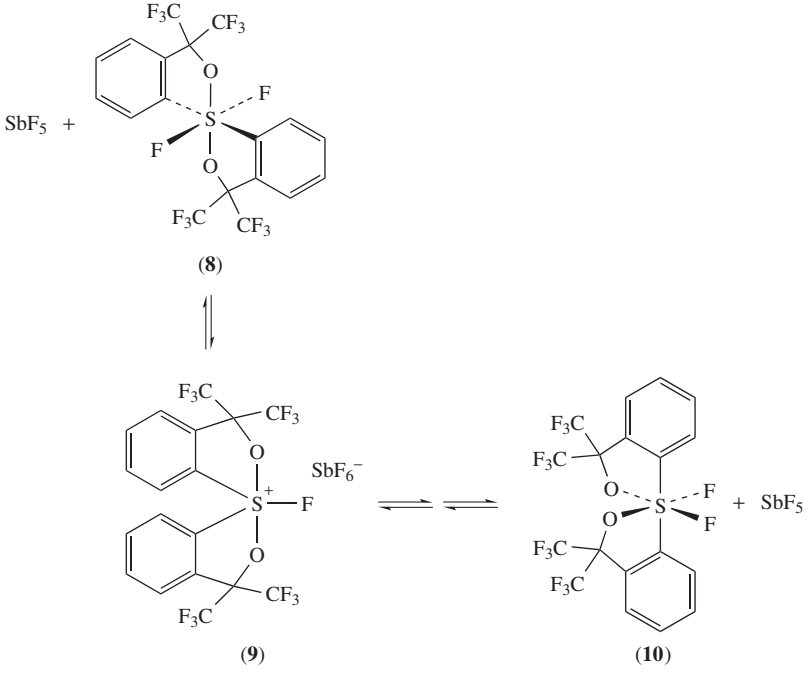
SCHEME 4



SCHEME 5

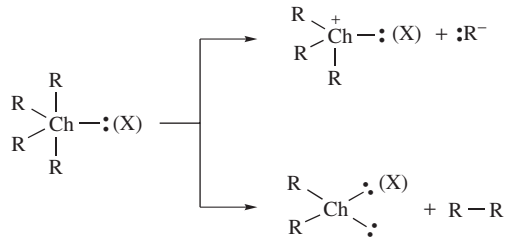


SCHEME 6



SCHEME 7

Considering reactivity of hypervalent derivatives, it should be noted that for hypervalent compounds of 10-Ch-4 or 10-Ch-5 structures the two most common modes constitute the ligand exchange reaction (LER) and the ligand coupling reaction (LCR)[8a]. It results from the fact that the most essential feature of chalcogenuranes as the species having an expanded valence shell is their relatively low stability (decreasing in the order Te, Se, S derivatives) caused by the tendency of the central chalcogen atom to return to the normal valency by extruding either a ligand bearing pair of electrons or a pair of ligands that afford stable compounds having an octet around the chalcogen atom (Scheme 8).



SCHEME 8

II. HYPERVALENT SELENIUM AND TELLURIUM STRUCTURES AS REACTIVE INTERMEDIATES

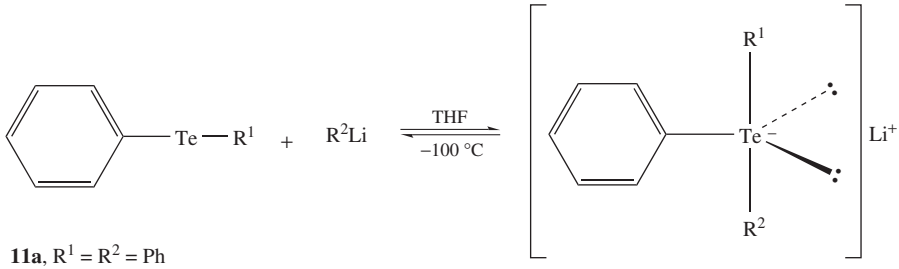
The details of the detection of unstable selenurane and tellurane as reactive intermediates reported in the chemical literature before 1998 are collected in Furukawa and Sato's chapter[5]. They include discussion devoted to the organotellurium–organolithium exchange reactions (Scheme 9) for which an initial formation of 10-Te-3 telluranes **11a–c** was detected via low-temperature NMR spectroscopies (^{1}H, ^{13}C, ^{7}Li and ^{125}Te). These results clearly indicate that the ligands that exhibit higher electronegativity are preferentially located in the apical positions in the considered ate-complexes. It should be noted that using this process new organolithium reagents, which are difficult to prepare by other protocols, can be generated *in situ* and applied in organic synthesis[19].

This chapter presents also the work of Reich and coworkers on the detection of the similar selenium ate-complex **13** (⇌ **14**) in the organoselenium–organolithium exchange reaction between cyclic bromoselenide **12** and *n*-butyllithium (Scheme 10)[20].

Tetraphenylsulfurane **15**[21], teraphenylselenurane **16**[22], 2,2′-biphenylylene-diphenylsulfurane **17**[23] and selenurane **18**[23], generated by adding one or two equivalents of phenyllithium to the corresponding substrate (Scheme 11), can be observed by low-temperature NMR spectroscopies.

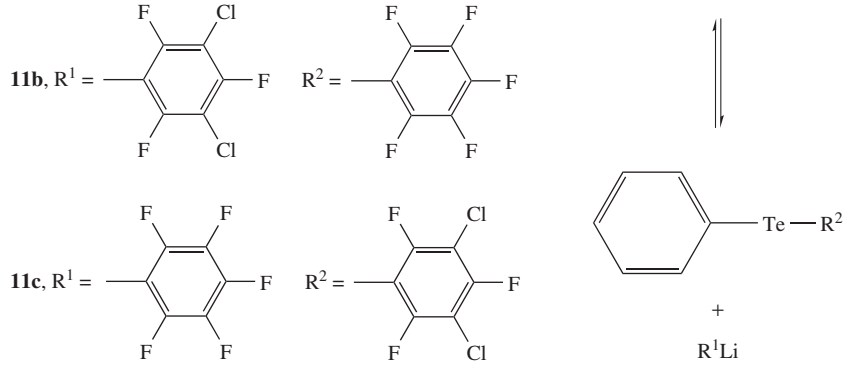
Recently, the formation of 2,2′-biphenylylenedimethylselenurane **21**[24], and -tellurane **22**[24] was observed by the ^{1}H, ^{13}C, ^{77}Se and ^{125}Te NMR spectroscopies at low temperature, in the reactions of 2,2′-biphenylylenedibromotellurane **19** and dibenzoselenophene Se-oxide **20** and with methyllithium. Both compounds were unstable and decomposed at room temperature to give the corresponding dibenzochalcogenophenes **23** quantitatively (Scheme 12).

Tetrabutyltellurane **24a** prepared by the reaction of tellurium tetrachloride with 4 equivalents of *n*-butyllithium in diethyl ether at 0 °C was found to be stable at this temperature in a C_6D_6 solution (as determined by ^{1}H-NMR) within 4 h, but it gradually decomposed at 25 °C and only 30% of tetrabutyltellurane remained after 20 h. It reacts, like other tetraalkyl telluranes, with arylacetylenes **25a–c** to afford *Z*-1,2-disubstituted olefins

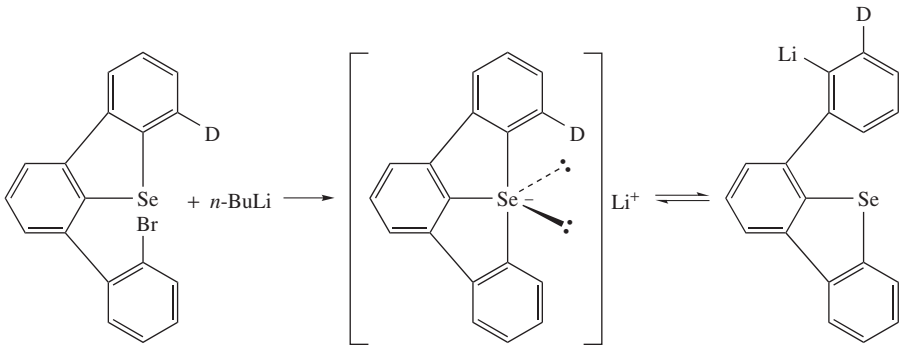


11a, $R^1 = R^2 = Ph$

(**11a–c**)

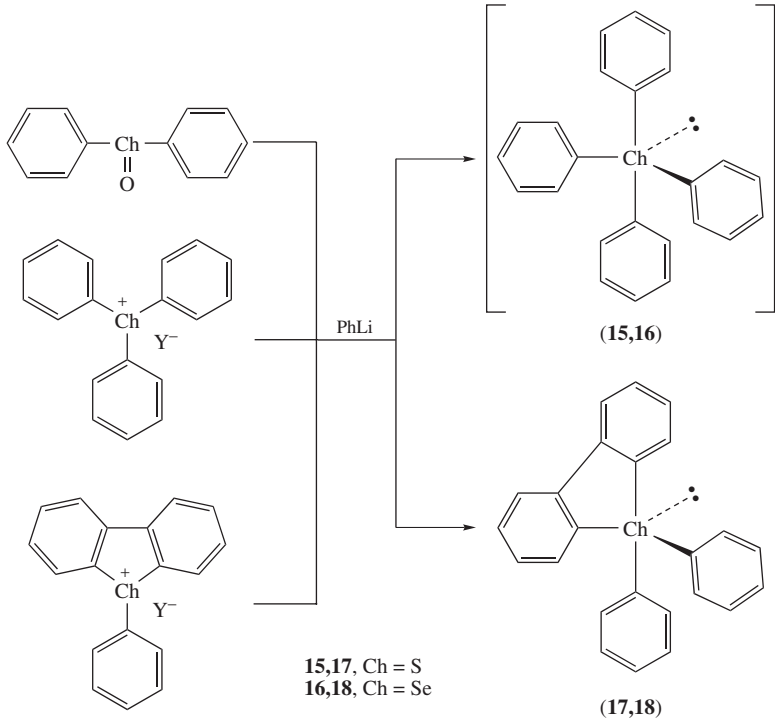


SCHEME 9



(**12**) (**13**) (**14**)

SCHEME 10



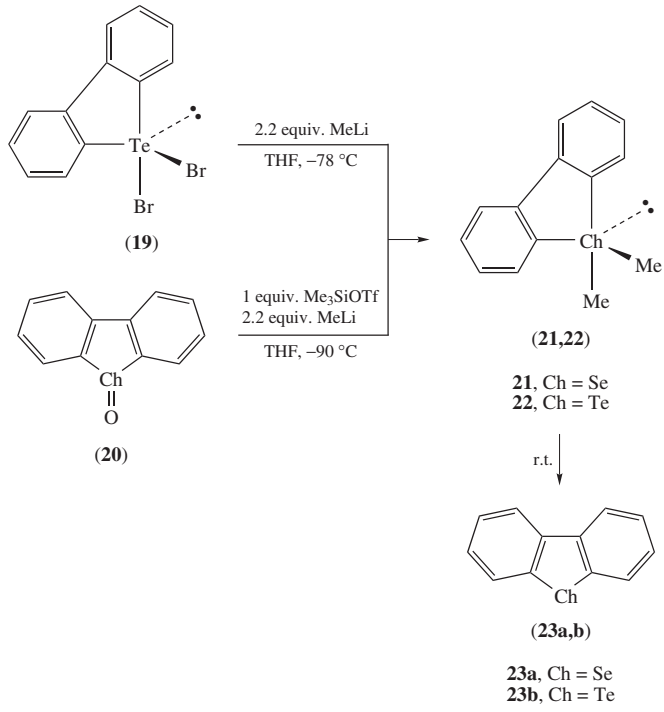
SCHEME 11

26a–c as the major product along with the concomitant formation of dibutyl telluride and but-1-ene, originating from the *n*-butyl substituent of tetrabutyltellurane and playing the role of a hydrogen source. The alkylation was proposed to proceed by the radical addition of tetrabutyltellurane **24a** to arylacetylenes to yield tellurane **27**, which then decomposes to afford olefins **26a–c** via a β-hydrogen transfer from the butyl radical on tellurium to the vinyl carbon (Scheme 13)[25].

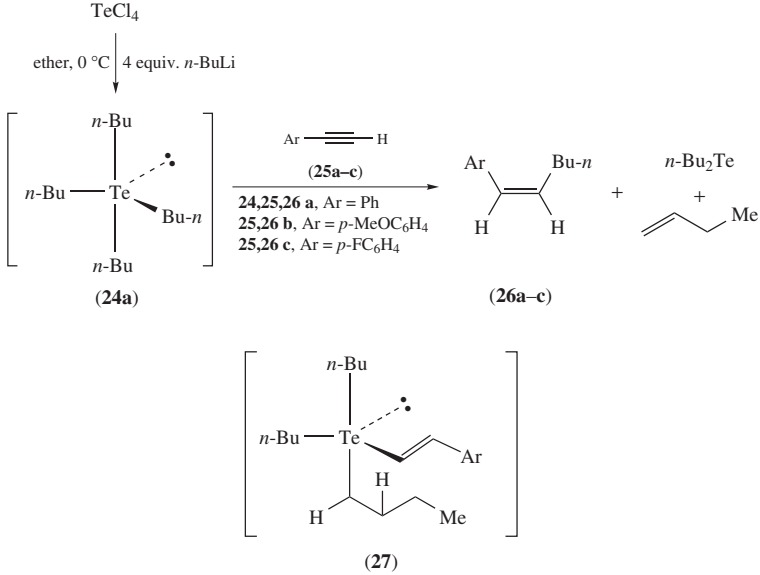
The generation of selenuranes **29a–c** as intermediates was recently suggested for the stereospecific oxidation of hydrazine into *cis*-diimide and the catalytic disproportionation of hydrogen peroxide effected by selenoxides **28a,b** (Scheme 14)[26].

Using density-functional theory (DFT) and solvent-assisted proton exchange, the thiol reduction of methyl- and benzeneseleninic acid **30a,b** into the corresponding selenenic acids **33a–b** has been modeled as distinct two-step pathways with intermediates as either a seleninyl sulfide or a hypervalent selenurane. The DFT results suggest that short-lived selenuranes **31a,b**, formed by addition of thiol to the seleninic acid, undergo rearrangement to the thioseleninates **32a,b**, which are finally converted to the selenenic acids **33a–b** by the second equivalent of thiol (Scheme 15)[27].

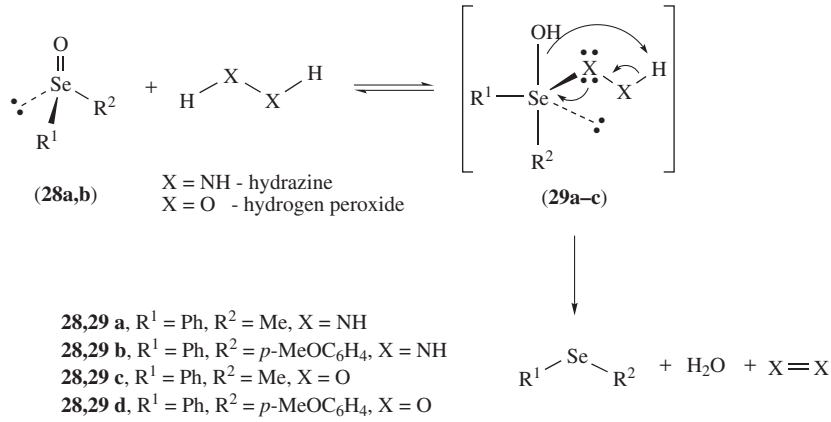
The Se–N selenuranes **36a,b** were detected by ^{1}H and ^{77}Se NMR during the oxidation of selenomethionines **34a,b** into corresponding selenoxides **35a,b** using hydrogen peroxide in aqueous solutions. It was found that the selenoxide **35a** exists in an acid–base equilibrium with the corresponding selenoxide **35a**. It is noteworthy that the theoretically



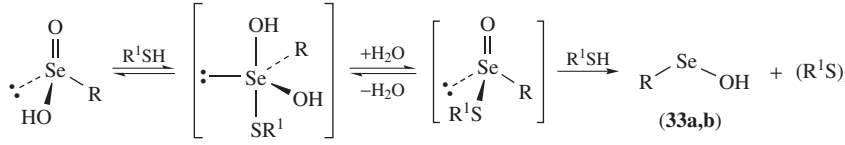
SCHEME 12



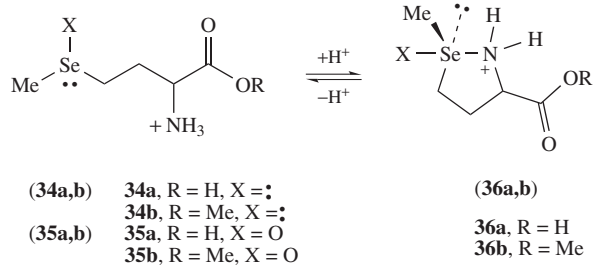
SCHEME 13



SCHEME 14



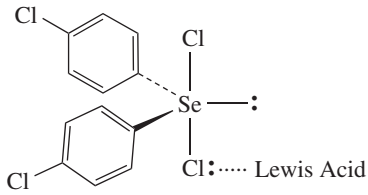
SCHEME 15



SCHEME 16

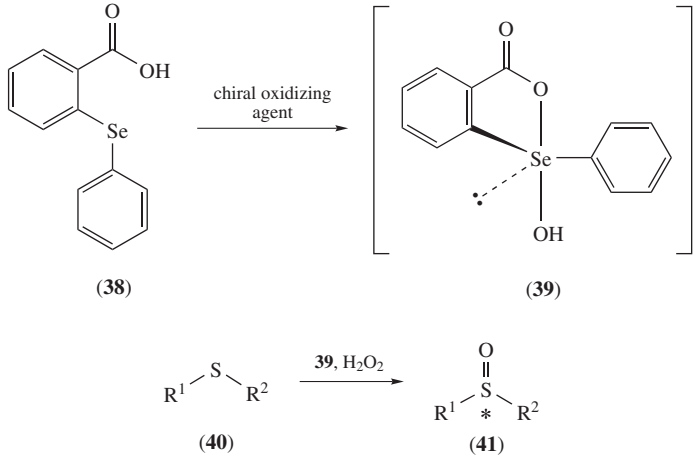
calculated ^{77}Se NMR chemical shifts are in good agreement with experimental results for both **35a** and **36a** (Scheme 16)[28].

The enhanced *para* selectivity observed during the electrophilic chlorination of toluene with bis(4-chlorophenyl) selenide/Lewis acids as catalysts has been ascribed to the intermediacy of a bis(4-chlorophenyl)selenium dichloride/Lewis acid complex **37** (its existence was supported by ^{1}H-NMR studies in acetone) which functions as a sterically hindered source of chlorine which loses chlorine directly from the selenium atom[29].



(**37**)

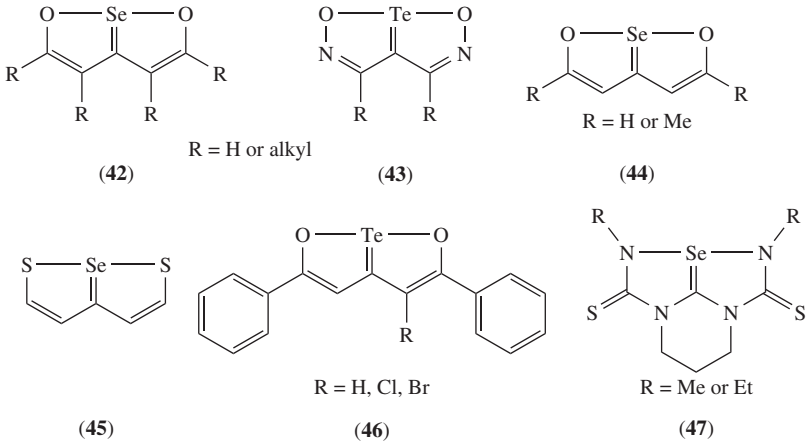
Optically active selenurane **39** generated *in situ* by the asymmetric oxidation of *ortho*-phenylselenylbenzoic acid **38** was used as a chiral catalyst in the hydrogen peroxide oxidation of prochiral sulfides **40**. However, the ee values of the optically active sulfoxides **41** were low (Scheme 17)[30].



SCHEME 17

III. ISOLABLE SELENURANES AND TELLURANES

A rich number of isolable hypervalent selenium and tellurium derivatives have been reported in the chemical literature. The representative reports devoted to the basic synthetic protocols, structural determinations including X-ray crystallographic analysis and NMR studies for selected derivatives which appeared before 1998 have been well documented in the previously mentioned chapters by Bergman and coworkers[4] and Furukawa and Sato[5]. Our presentation will be based, like the latter chapter, on the inclusion of the discussed compounds into particular subsections. This division arises from the commonly accepted Martin's—*N*-Ch-*L* (A_nB_m) coding system, in which N stands for the number of valence electrons associated formally with a central chalcogen atom and L shows the number of ligands (A and B stand for the bonding element)[31].



(**42**) (**43**) (**44**)

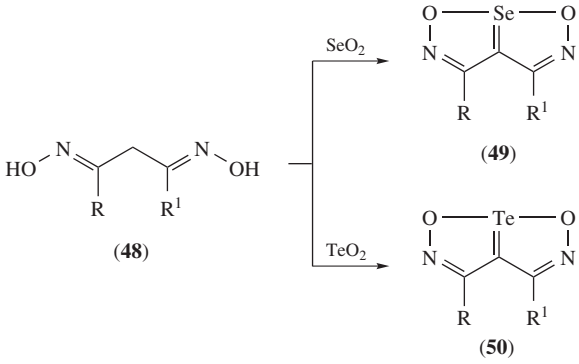
(**45**) (**46**) (**47**)

CHART 4

A. 10-Ch-3 Chalcogenuranes (Ch = Se, Te)

Among the isolable π-hypervalent selenium and tellurium derivatives discussed by Furukawa and Sato[5] there are species **42**[32], **43**[33], **44**[34], **45**[34], **46**[35] and **47**[36], collected in Chart 4.

Synthesis of a series of 1,6-dioxa-6*a*-selena(IV)-2,5-diazapentalenes **49** and their tellurium-containing analogs **50** was based on treating bis-oximes **48** with selenium dioxide or tellurium dioxide (Scheme 18)[37].

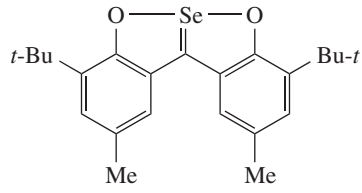


(**48**) (**49**) (**50**)

R = H, Me, CO_2Et
R^1 = H, Ph, 4-MeC_6H_4, 4–ClC_6H_4, Me
RR^1 = $-(CH_2)_3-$, $-(CH_2)_4-$

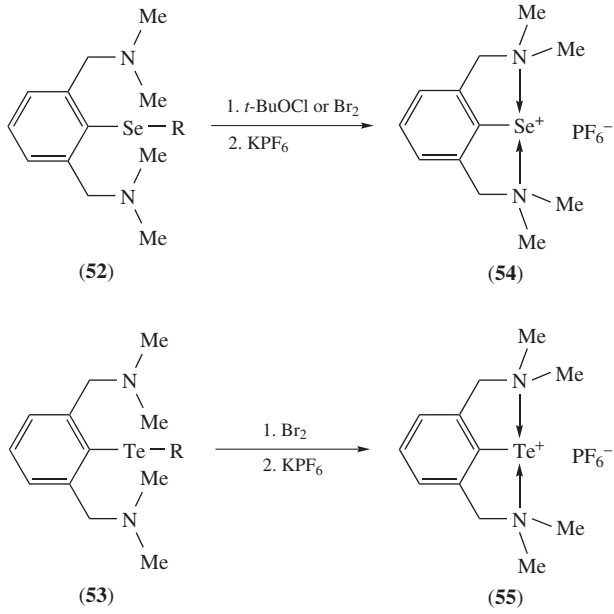
SCHEME 18

Another selenium-containing π-hypervalent selenium derivative **51** was described recently[38].



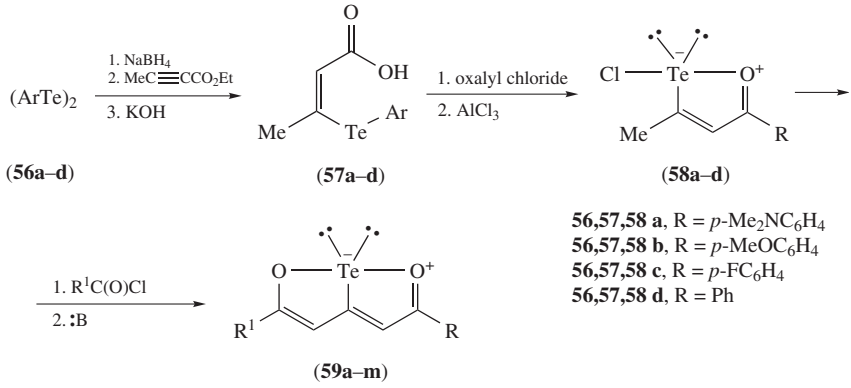
(**51**)

Chalcogenium cations **54** and **55** constitute other examples of hypervalent compounds. The first procedure leading to them, starting from the corresponding divalent precursors **52** and **53**, is shown in Scheme 19[5, 39].



SCHEME 19

The three-center, four-electron bond, typical for hypervalent compounds, with partial covalent bonding between Te or Se and the more electronegative ligand atoms, can also be considered for 1,2-oxatellurolyl-l-ium halides and 1,2-oxaselenolyl-1-ium halides[40a]. The preparation of a series of such 10-Te-3 telluranes, 3-methyl-5-aryl-1,2-oxatellurolyl-1-ium chlorides **58a–d** with donor groups in the *para* position, was achieved by the reaction sequence indicated in Scheme 20. The appropriate diary1 ditelluride **56a–d** was reduced with sodium borohydride in ethanolic tetrahydrofuran, and the formed sodium aryltelluride was added to ethyl propiolate. The resulting (*Z*)-3-aryltellurabutenoate ester was converted to the acid **57a–d** with ethanolic potassium hydroxide. The acids gave the acid chlorides



(**56a–d**) (**57a–d**) (**58a–d**)

56,57,58 a, R = *p*-$Me_2NC_6H_4$
56,57,58 b, R = *p*-$MeOC_6H_4$
56,57,58 c, R = *p*-FC_6H_4
56,57,58 d, R = Ph

(**59a–m**)

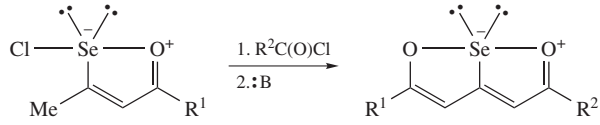
	R	R^1
59a	*p*-$Me_2NC_6H_4$	*p*-$O_2NC_6H_4$
59b	*p*-$Me_2NC_6H_4$	*p*-NCC_6H_4
59c	*p*-$MeOC_6H_4$	*p*-$O_2NC_6H_4$
59d	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$
59e	*p*-$MeOC_6H_4$	Me
59f	*p*-FC_6H_4	Ph
59g	*p*-FC_6H_4	*p*-$O_2NC_6H_4$
59h	*p*-FC_6H_4	*p*-FC_6H_4
59i	*p*-FC_6H_4	*p*-$MeOC_6H_4$
59j	*p*-FC_6H_4	2,4-$(O_2N)_2C_6H_3$
59k	*p*-FC_6H_4	3,5-$(O_2N)_2C_6H_3$
59l	*p*-FC_6H_4	Me
59m	Ph	Ph

SCHEME 20

upon treatment with oxalyl chloride. The acid chlorides were finally converted to the oxatellurolyl-1-ium chlorides **58a–d** with aluminum chloride as catalyst (Scheme 20)[40b]. Their reaction with a series of acyl chlorides (benzoyl chloride, *p*-nitrobenzoyl chloride, *p*-anisoyl chloride, *p*-fluorobenzoyl chloride, *p*-cyanobenzoyl chloride, 2,4-dinitrobenzoyl chloride, 3,5-dinitrobenzoyl chloride, and acetyl chloride) in the presence of an amine gave the corresponding dioxatellurapentalenes **59a–m** (Scheme 20)[40b–d].

These condensation reactions were extended to the preparation of 10-Se-3 selenuranes such as the oxaselenolyl-1-ium chlorides **60a,b**[40d], which upon reaction with *p*-nitrobenzoyl chloride or *p*-anisoyl chloride gave the appropriate dioxaselenapentalenes **61a–c** in modest yield (Scheme 21)[40b].

The spectroscopic properties of the dioxatellurapentalenes show some differences from those of their selenium and sulfur analogues. The ^{1}H NMR spectrum of **59m** shows a sharp singlet at $\delta = 8.15$ ppm for the two ring protons which is at 1 ppm lower field than of the corresponding S and Se analogues[32]. The ^{13}C NMR spectrum of **59m** showed the carbons bearing the heteroatoms to be at low field ($\delta = 181.0$ and 180.5 ppm) while the remaining two ring carbons were at a quite high field ($\delta = 107.7$ ppm). These values suggest that the ring carbons are pentadienyl cation-like in their charge densities[40b]. The IR spectra of all



(**60a,b**) (**61a–c**)

(**60a**) $R^1 = p\text{-}MeOC_6H_4$
(**60b**) $R^1 = p\text{-}FC_6H_4$

(**61a**) $R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}O_2NC_6H_4$
(**61b**) $R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}MeOC_6H_4$
(**61c**) $R^1 = p\text{-}FC_6H_4$, $R^2 = p\text{-}O_2NC_6H_4$

SCHEME 21

the dioxachalcogenapentalenes are similar, with a strong absorption around 1520 cm^{-1}. The UV-Vis absorption spectrum of **59m** displays a long-wavelength maximum at 424 nm ($\log \varepsilon = 4.61$). This value is more than 20 nm bathochromic from the absorption maxima of the S and Se analogues. The incorporation of the dimethylamino substituent into dioxatellurapentalenes **59a** and **59b** gave long-wavelength absorption maxima at 480 and 470 nm, respectively.

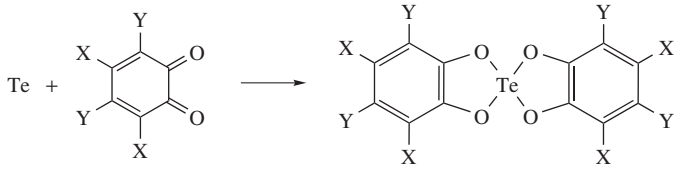
B. 10-Ch-4-Chalcogenuranes (Ch = Se, Te)

This class of chalcogenuranes has been regarded for years as intermediates in many organic reactions involving tetravalent, tricoordinated chalcogenonium compounds. More recently, attention has been slowly shifted to studies on their use as reagents in organic synthesis and to experiments aimed at finding the chalcogenium compounds that mimic the properties of the selenium-containing enzyme (GSH-Px) which plays an important role in the human body through participation in a catalytic redox cycle of reduction of a wide variety of hyperoxides. Simultaneously, it has been found that some selenium and tellurium compounds showed broad biological activity including, for example, good activity to catalyze the reaction of hyperoxide with thiols. The formation of 10-Ch-4 chalcogenuranes has been proposed as the key process in these reactions. Moreover, hydroxyoxatelluranes, $R_2Te(OH)_2$, have also been suggested as important intermediates, in the oxidation of halides to positive halogens with hydrogen peroxide, in biomimetic research of haloperoxidase enzymes. Other research showed that some chalcogenuranes from this group possess different levels of immunomodulating activity and would be a kind of potent immunomodulator with a variety of potential therapeutic applications. The most important findings will be presented briefly below when the chemistry of particular groups of 10-Ch-4 chalcogenuranes (Ch = Se, Te) will be discussed.

1. 10-Ch-4 chalcogenuranes (L4, Ch = Se, Te, L = halogen, OR, etc.)

Besides well-known and stable inorganic selenium and tellurium tetrahalides such as selenium tetrachloride, selenium tetrabromide and tellurium analogues, there are not too many compounds which could be included in this group of hypervalent chalcogenuranes. Earlier reports were devoted to the preparation and basic reactivity of tetraalkoxychalcogenuranes. The first representative of such compounds, tetramethoxy tellurane, was prepared by Meerwein and Bersin as early as 1929[41] and has been presented in the

chapters of Bergman and coworkers[4] and Furukawa and Sato[5]. Both chapters contain also a brief presentation of symmetrical and unsymmetrical chalcogenuranes possessing four σ heteroatom–selenium or heteroatom–tellurium bonds. Most of the presented compounds were prepared by the treatment of tellurium or selenium tetrachlorides with alcohols, amines or thiols in the presence of base[4, 5, 42]. Other reported methods are based on the reaction between tellurium terachloride and sodium alkoxide[43–45] and they are covered very comprehensively by Irgolic in his chapter in the E12b Houben-Weyl volume[46]. Recently, it was found that the oxidation of elemental tellurium by three *ortho*-benzoquinones **62a–c** is a direct route to the corresponding tellurium(IV) catecholates **63a–c** (Scheme 22)[47].

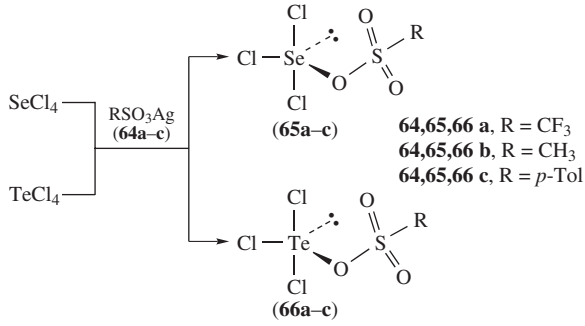


(**62a–c**) **62,63 a**, X = Y = Cl; **62,63 b**, X = Y = Br; **62,63 c**, X = H, Y = *t*-Bu (**63a–c**)

SCHEME 22

The reactions proceed by one-electron transfer, since the presence of the semiquinone radical in the reaction mixture has been demonstrated by ESR spectroscopy. The formed tellurane **63a–c** species resist further oxidation, and also show weak donor and acceptor properties. For example, the *t*-butyl substituted compound **63c** forms a 1:1 complex with 2,2′-bipyridine for which structure $Te[O_2C_6H_2(Bu\text{-}t)_2 2,3,5]_2(bipy)$ (bipy = 2,2′-bipyridine) has been determined by X-ray crystallography[47]. A similar complex was formed with a crown ether during a direct oxidation of elemental tellurium by **62a** in the presence of 18-crown-6[47]. On the other hand, the reaction of **63a** with bismuth trichloride gave a product whose tellurium content and the ^{125}Te and ^{13}C spectra indicated the formation of a 1:1 adduct. This adduct was found to be apparently unstable, since reanalysis after 2 weeks showed that bismuth trichloride had been lost. Hence, tellurane **63a** is apparently only a weak Lewis base[47].

Metathetical reactions between tellurium or selenium tetrachlorides and silver sulfonates **64** in 1:1 stoichiometry yielded 10-Ch-4 chalcogenuranes **65a–c** or **66b,c**. Telluranes **66a,b** were also formed by the solvolysis of tellurium tetrachloride in trifluoromethane- and methanesulfonic acids or their anhydrides. It was found that the further substitution of chlorine by a sulfonate anion in **66a–b** could not be effected even when drastic conditions were used. All sulfonates **65a–c** and **66a–c** were found to be highly sensitive to moisture, and fume in moist air. It is intersesting to note that the selenium compounds are soluble in common organic solvents such as carbon tetrachloride, benzene, methylene chloride, etc. whereas the analogous tellurium compounds dissolve only in polar organic solvents such as nitromethane, acetonitrile, etc. Milimolar solutions of all six compounds in nitromethane or acetonitrile were found to be nonconducting, thus suggesting that the sulfonate group is covalently bonded to the chalcogen atom (Scheme 23)[48]. In the context of the above-mentioned results, an earlier report that selenium tetrachloride did not yield any defined compounds with trifluoromethanesulfonic acid should be mentioned[49].

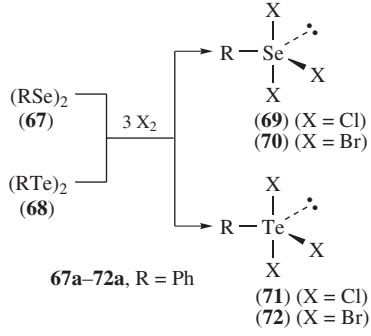


SCHEME 23

2. 10-Ch-4 chalcogenuranes (CL3, Ch = Se, Te, L = halogen, OR, N_3, etc.)

A large number of organic chalcogenium trihalides have been prepared since the first members of this family were unambiguously characterized in the middle of the nineteen twenties[46, 50, 51].

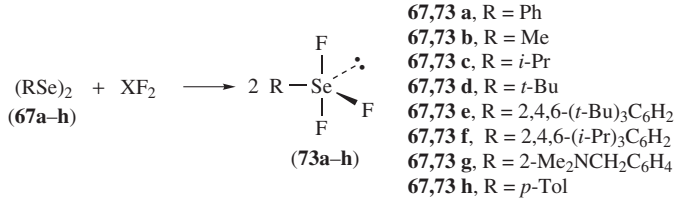
Earlier reports, devoted to their synthesis, structures and reactivity which have since appeared in the literature, are summarized in a review[52] and in a book[53]. The Houben-Weyl volume[46] presented very comprehensively the chemistry of tellurium trihalides. The oldest procedure for the preparation of a few selenium trihalides **69** and **70** and tellurium analogues **71** and **72** is based on treatment of the corresponding diselenides **67** or ditellurides **68** with halogens (Scheme 24)[50, 51, 54]. Recently, phenylselenium trichloride **69a** was synthesized in the reaction of diphenyl disulfide **67a** with three molar equivalents of sulfuryl chloride[54]. A comparison of the solid state structures of this chloroselenurane with the bromo analogue **71a** indicates that the structure of the latter exhibits interesting molecular, charge transfer and ionic bonding aspects[54]. Thus, **69a** exhibits the polymeric chain structure commonly observed for organic chalcogenium trihalides[55–57], while individual $PhSeCl_2$ units are linked by two bridging chlorine atoms. The geometry at selenium is square pyramidal with the phenyl group occupying the apical position. The single crystal X-ray structure of **70a** shows also a square pyramidal geometry for the selenium center. The structure, however, is not isostructural with **71a**, or the analogous tribromide **72a**[58].



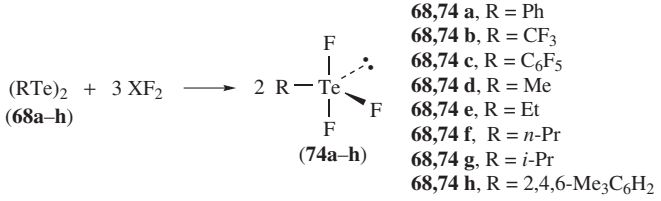
SCHEME 24

Instead of displaying two terminal and two bridging Se−Br bonds, the structure displays an unusual combination of molecular, ionic and CT aspects. The square pyramidal geometry around selenium is more distorted than in trichloroselenurane **69a**, with the phenyl ring again occupying the apical position.

Starting from the diselenides **67a–h** the reaction with 3 equivalents of xenon difluoride furnished the corresponding organoselenium trifluorides **73a–h** (Scheme 25)[59a,b,d]. Interestingly, the chloride ion facilitates this reaction[59b]. This procedure was applied for the generation of very unstable and extremely moisture sensitive alkyl-, aryl- and perfluoroalkyl(aryl)tellurium trifluorides **74a–h** (Scheme 26)[59c, 60].



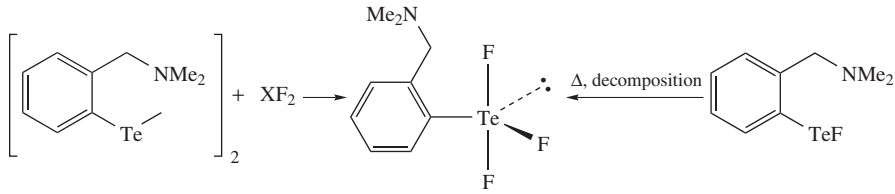
SCHEME 25



SCHEME 26

The prepared selenium trifluorides are much less stable than the trichlorides **69a** and tribromides **70a**, and their decomposition starts at $+4\,^{\circ}C$ within days. All compounds exhibit resonances in the ^{77}Se NMR spectra in the region between $\delta = 1257$ (**73b**) and 996 ppm (**73g**), some of them being extremely broadened. Moreover, in the ^{19}F NMR spectra both resonances for the axial and equatorial fluorine atoms, derived from the expected pseudotrigonal bipyramidal coordination of the selenium atom, could be observed and are between $\delta = -28$ and $+2.8$ ppm (axial) and $\delta = -46$ and -79 ppm (equatorial), respectively. For **73b** ($\delta = -37.8$ ppm) and **73c** ($\delta = -57.7$ ppm), only one broad resonance could be observed in the ^{19}F NMR spectra, due to a fast equatorial–axial fluorine exchange process. **73g** is expected to exhibit a pseudotetragonal bipyramidal coordination of the central atom similar to the tellurium analogue **75** obtained by the fluorination of the ditelluride **68i** with xenon difluoride or by the decomposition the tellurenyl fluoride **76** (Scheme 27)[61].

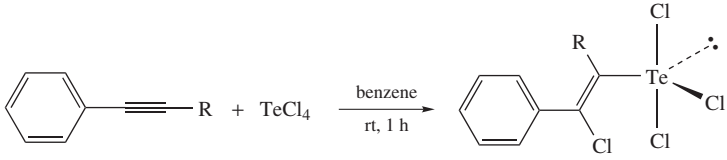
Earlier reports on the formation of trichlorotelluranes in the reaction of tellurium tetrachloride with selected carbonyl compounds, alkenes and acetylenes are discussed in the chapter by Bergman, Engman and Siden[4]. Very recently, the addition reaction of tellurium tetrachloride to alkynes was reinvestigated[62]. It was found that it occurs via two pathways: a concerted *syn* addition leading to *Z*-tri- and tetra-substituted alkenes or by an *anti* addition that yields *E*-alkenes. Thus, when tellurium tetrachloride reacted with



(**68i**) (**75**) (**76**)

SCHEME 27

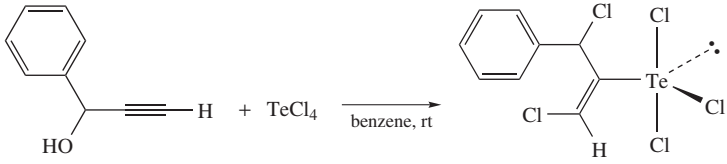
1-phenyl-1-propyne **77a** and diphenylacetylene **77b**, the vinyl tellurium trichlorides **78a,b** were the only isolated products (Scheme 28)[62]. X-ray analysis of **78a** confirmed the regio- and stereochemistry proposed earlier by Uemura and coworkers[63].



(**77a,b**) **77,78 a**, R = Me **77,78 b**, R = Ph (**78a,b**)

SCHEME 28

Similar reaction with 1-phenyl-2-propyn-1-ol **79** carried out in benzene at room temperature for 4 h led to the vinylic tellurium trichloride **80** (Scheme 29)[62]. X-ray analysis confirmed the structure of **80** with an *E* configuration of the double bond and pseudotrigonal bipyramidal arrangement around the Te^{IV} in which a lone pair occupies one of the equatorial positions.

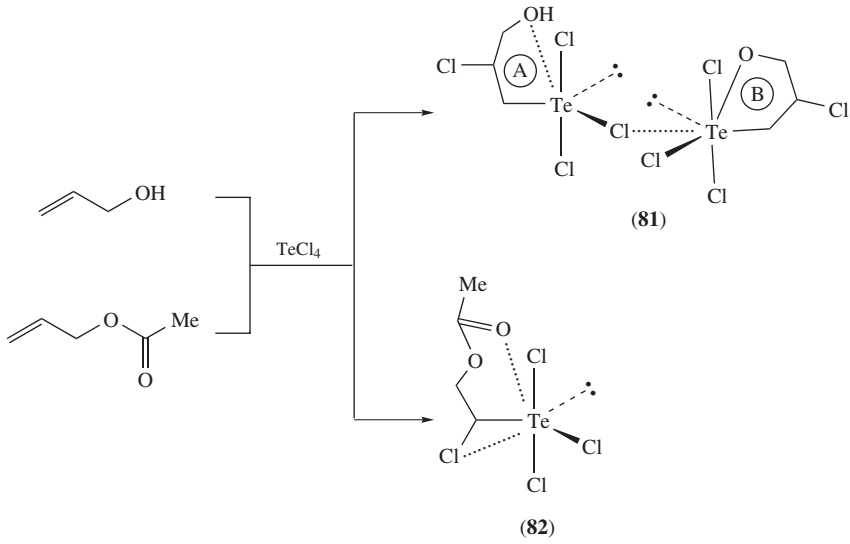


(**79**) (**80**)

SCHEME 29

Earlier, trichlorotelluranes **81** and **82** were isolated in the reaction of tellurium tetrachloride with allyl alcohol or allyl acetate, respectively (Scheme 30)[64].

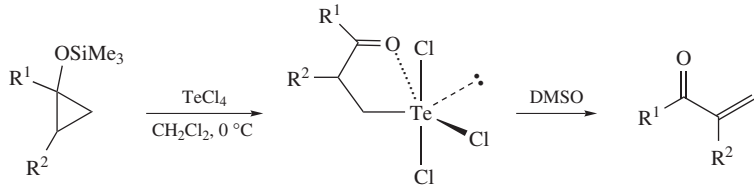
Their molecular and crystal structures were determined by single-crystal X-ray analysis and supported by $^1H-^1H$-NOESY experiments, IR spectroscopy and *ab initio* geometry optimization. These experiments indicated that the tellurane **81** is a composite compound,



SCHEME 30

whose subunits **81A** and **81B** are linked in the solid state via Te···Cl−Te and Te···H−O bridges. Both tellurium atoms participate in similar five-membered rings, having a covalent Te−O bond in one case (**81B**) and a dative Te···O bond in the other (**81A**). Both tellurium atoms have pentacoordinate pseudo-octahedral geometry. On the other hand, in the solid state, single molecules of **82** are linked by weak CHCl···Te contacts, the tellurium atom being hexacoordinate with a distorted-octahedral configuration. Multinuclear NMR spectroscopy and ^{1}H−^{1}H-NOESY experiments indicated that the cyclic structures exist in solution as well. β-Trichlorotelluroketones **84** generated *in situ* from silyloxycyclopropanes **83** and tellurium tetrachloride are another interesting group of trichlorotelluranes. After treatment with dimethyl sulfoxide or some amines, they were converted into the corresponding α-methylene ketones **85** (Scheme 31)[65a]. Two trichlorotelluranes prepared by refluxing tellurium trichloride with 1-phenylprop-2-yn-1-ol or *o*-methoxyacetophenone were specific inhibitors of cysteine protease Cathepsin B[65b].

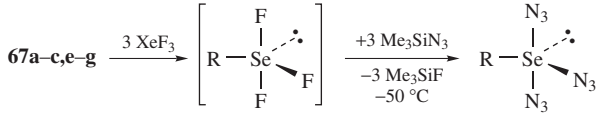
Organoselenium and organotellurium trihalides have also found use in the introduction of selenium into organic molecules. For example, phenylselenyl trichloride **69a** reacts with enolisable aldehydes and ketones to give the corresponding α-phenylselenenyl aldehydes/ketones[66] which on hydrolysis give enones[67]. (2,4-Dinitrophenyl)selenium trichloride and phenylselenyl tribromide **70a** are also known to add across double bonds of cyclic and acyclic olefins to produce unsaturated compounds[68]. A encyclopedic compilation devoted to phenylselenium trichloride **67a** is included in *Encyclopedia of Reagents for Organic Synthesis*[69] and updated in its electronic version (e-EROS). A nucleophilic exchange reaction at selenium or tellurium in alkyl(aryl)fluorochalcogenuranes constitutes a convenient approach to the preparation of other compounds which can be coded as 10-Ch-4 (CL3) derivatives. The reaction of the organoselenium trifluorides **73a–c,e–g** (generated *in situ* according to Scheme 25) with 3 equivalents of Me_3SiN_3 at low temperatures furnished the corresponding organoselenium triazides **86a–c,e–g** (Scheme 32)[59a]. They are unstable even at −50 °C and, when slowly warmed up, decompose immediately to the corresponding diselenide and dinitrogen (Scheme 32). The decomposition products



(**83a–d**) (**84a–d**) (**85a–d**)

	R^1	R^2	**85** yield [%]
83,84,85 a	*t*-Bu	H	78
83,84,85 b	Ph	H	90
83,84,85 c	$-(CH_2)_5-$		83
83,84,85 d	$-(CH_2)_6-$		93

SCHEME 31



(**73a–c, e–g**) (**86a–c, e–g**)

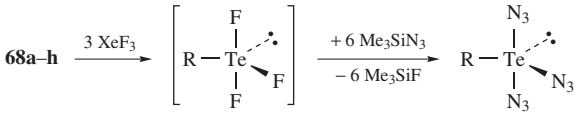
67,73,86 a, R = Ph
67,73,86 b, R = Me
67,73,86 c, R = Et
67,73,86 e, R = *n*-Pr
67,73,86 f, R = *i*-Pr
67,73,86 g, R = 2,4,6-$Me_3C_6H_2$

286 $\longrightarrow$ [2 $RSeN_3$] + 6 N_2 $\longrightarrow$ $(RSe)_2$ + 3 N_2

SCHEME 32

were identified by ^{77}Se NMR spectroscopy which shows the corresponding selenium(II) azide as an intermediate (in one case, with the intermolecular donor-stabilizing substituent 2-$Me_2NCH_2C_6H_4$ present; this intermediate was isolated). From the ^{77}Se NMR spectra of the triazides **86** recorded at $-50\,^{\circ}C$ it is evident that their absorptions, in the range $\delta = 951-884$ ppm, are shifted to a higher field compared to the starting trifluorides.

The corresponding tellurium triazides **87a,d–h** were prepared by a similar exchange reaction between the organotellutium trifluorides **74a–c,e–g** (generated *in situ* according to Scheme 25) with 3 equivalents of trimethylsilyl azide (Scheme 33)[60]. They were isolated as colorless or pale yellow solids, whose solubility in common organic solvents increases with increasing the length of the aliphatic chain. They are much more stable in comparison with the starting trifluorides and the corresponding selenium analogues **86**. However, they hydrolyze in air, and again, moisture promotes decomposition with formation of HN_3, whose presence was supported by ^{14}N NMR spectroscopy. They also explode with a blue flash upon contact with a flame. In general, no shock or impact sensitivity was observed. Interestingly, methyltellurium triazide **87d** is the most nitrogen-rich neutral tellurium compound reported so far, with a nitrogen content of 46.9%[60].



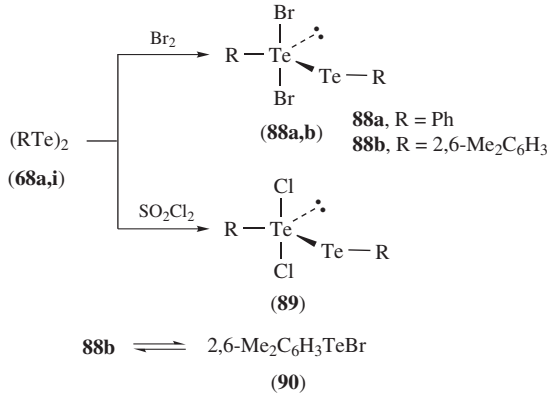
(**74a–h**) (**87a–h**)

68,74,87 a, R = Ph
68,74,87 b, R = CF_3
68,74,87 c, R = C_6F_5
68,74,87 d, R = Me
68,74,87 e, R = Et
68,74,87 f, R = *n*-Pr
68,74,87 g, R = *i*-Pr
68,74,87 h, R = 2,4,6-$Me_3C_6H_2$

SCHEME 33

Among the isolated triazides only **87b, 87c** and **87e** show weakly intense TeC stretching vibrations in the IR and Raman spectra at 559–496 cm^{-1} whereas their ^{125}Te NMR resonances appear at $\delta = 1405–1252$. The phenyl substituents in **87a** and **87h** cause a low-frequency shift relative to alkyl substituents in **87d–g**. All the experimentally determined structures of tellurium triazides (**87b,c** and **87e)** consist of two stereochemically different azide substituents, one at the equatorial position and two at the axial positions. The difference is reflected in the Te–N bond lengths, which are a 2.05 Å for equatorial and *ca* 2.22 Å for axial azide–tellurium bonds. Calculations for tellurium triazide **87b** and the selenium analogue **86b** performed at the B3LYP level showed that both structures are based on a pseudotrigonal bipyramidal arrangement with two azide groups occupying the axial positions and the methyl group, one azide group and the lone pair in the equatorial positions[59a, 60]. Taking into account the fact that the preparation of tellurium trihalides **71** and **72** is based on treatment of the corresponding ditellurides **68** with halogens used in excess (Scheme 24), it should be stressed that the reaction of diphenyl ditelluride **68a** with only one equivalent of bromine provided the mixed-valent phenyltellurenyl bromide **88a** in nearly quantitative yield and the halogenation of the sterically more encumbered ditelluride **68i** with one equivalent of bromine or sulfuryl chloride produced the mixed-valent aryltellurenyl halides **88b** and **89** in almost quantitative yield as blue and green crystalline materials, respectively (Scheme 34)[70].

The molecular structures of **88a,b** and **89** determined by X-ray analysis show a trigonal bipyramidal geometry and a Te–Te bond length of 2.7966(5) for **88a**, 2.759(6) for **88b** and 2.7835(11) for **89**. They are somewhat longer than those of the parent diphenyl ditellurides **68a** (2.712(2))[71] and bis(2,6-dimethyl)phenyl ditelluride **88b** (2.711(1)), whereas the average Te–Cl and Te–Br bond lengths of 2.517(5) Å and 2.695(2) Å compare well with those of diphenyldichloro tellurane, 2.505(3) Å, and diphenyldibromo tellurane, 2.6818(6) Å, respectively[72]. In the crystal lattice, individual molecules of **88a** are associated by intermolecular Te···Br interactions of 3.328(4) Å that may explain the darker color and poorer solubility when compared to **88b** and **89**, which lack similar contacts. The ^{125}Te NMR spectrum of **88a** recorded in toluene-d_8 at −40 °C shows two equally intense broad signals at $\delta = 1291.0$ and 823.7 ppm, which suggests that the molecular structure is retained in solution. However, no spectrum was obtained at room temperature, which points to a dynamic exchange process taking place under these conditions. Moreover, the ^{125}Te NMR spectrum ($CDCl_3$) of **88b** exhibits only one sharp resonance at $\delta = 1683.8$ ppm, which is consistent with an assumption that it undergoes a rapid, reversible rearrangement genarating 2,6-dimethylphenyltellurium bromide **90** upon dissolution (Scheme 34).



SCHEME 34

3. 10-Ch-4 chalcogenuranes (C2L2, Ch = Se, Te, L = halogen, OR, etc.)

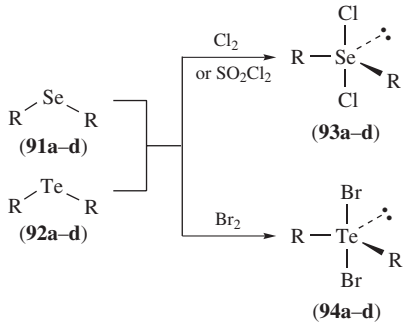
This group of chalcogenuranes constitutes the largest family of hypervalent selenium and tellurium derivatives. In general, compounds having two carbon–chalcogen bonds and two electronegative ligands such as halogen, oxygen and nitrogen are stable enough to be isolated and fully analyzed spectroscopically, including X-ray crystallography. They can be prepared by the following, general approaches:

(a) oxidative halogenation of acyclic and cyclic selenides and tellurides or the corresponding chalcogenide monoxides;
(b) reaction of chalcogenium tetrahalides or trihalides with unsaturated compounds or carbonyl derivatives;
(c) direct insertion of tellurium across a C–halogen bond;
(d) nucleophilic exchange reactions of the halogen-containing dihalochalcogenuranes;
(e) reactions of a suitably projected dianions with negative charges on a carbon and a heteroatom;
(f) Friedel–Crafts-type reactions of aromatic compounds with chalcogenium tetrachlorides.

The chemical literature devoted to the preparation (based in principle on approaches a, d and e), structural determination and basic reactivity of a representative number of chalcogenuranes published before 1998 are discussed comprehensively in the chapter by Furukawa and Sato[5] and by Irgolic[46]. In the present chapter the most recent results, which are related to all the approaches mentioned above, and that have been published after 1998, will be discussed.

The preparation of chalcogenuranes based on the oxidative halogenation of acyclic and cyclic selenides and tellurides with elemental halogens is very convenient from the experimental point of view, since it can be achieved just by mixing the corresponding dicoordinated chalcogenides with a suitable halogen. Thus, chlorination of perfluorinated diphenyl selenide **91a** in liquid chlorine gave very unstable dichloride **93a** which, upon removal of excess chlorine, immediately reforms the selenide **91a** (Scheme 35)[73].

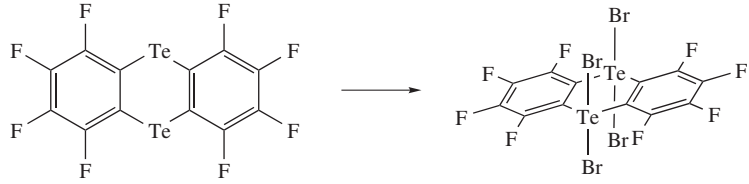
Oxidative bromination of the tellurides **92a–d** with bromine gave isolable diorganotellurium dibromides **94a–d** (Scheme 35).[73,74] A similar reaction of the telluanthrene **95**



91,93 a, R = C_6F_5
91,93 b, R = *p*-$CF_3C_6F_4$
91,93 c, R = 2,6-$F_2C_6H_3$
91,93 d, R = 4′-(*p*-$CF_3C_6F_4O)C_6F_4$

92,94 a, R = C_6F_5
92,94 b, R = $PhC(O)CH_2$
92,94 c, R = *p*-$MeC_6H_4C(O)CH_2$
92,94 d, R = *p*-$MeOC_6H_4C(O)CH_2$

SCHEME 35



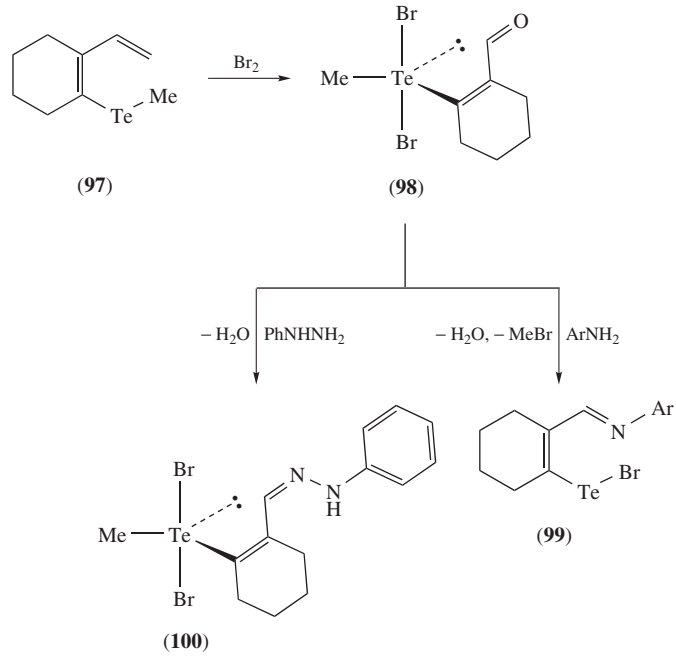
(**95**) (**96**)

SCHEME 36

and the unsaturated telluride **97** afforded the corresponding tetrabromo tellurium derivative **96**[59c] and dibromotellurane **98**[75], respectively (Scheme 36 and 37). The latter dibromide was converted to tellurenyl bromide **99** upon treatment with arylamines or dibromotellurane **100** upon treatment with phenylhydrazine (Scheme 37).

A very large group of diorganodifluoro selenuranes **101a–l** and telluranes **102a–g** were prepared by oxidative fluorination of the selenides **91** or tellurides **92** with xenon difluoride (Scheme 38)[59a, 60, 61, 73].

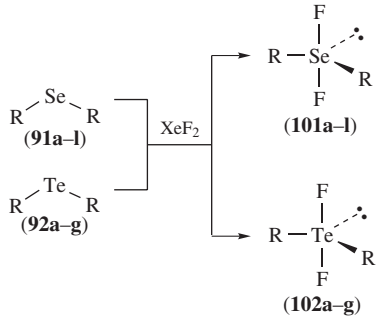
The prepared selenium difluorides were isolated as pale-yellow liquids or colorless solids. They are, like already discussed trifluorides, extremely sensitive toward moisture and are storable at +4 °C [in a perfluoroalkoxy-copolymer (PFA) vessel] over a period of about 2 weeks at maximum. During a longer storage a partial decomposition, leading to various unidentified products, was observed (^{19}F NMR spectroscopy). The resonances of the difluorides **101** in the ^{77}Se-NMR spectra appear as triplets in the range between $\delta = 780$ and 930 ppm, whereas the resonances in the ^{19}F NMR spectra are in the range of $\delta = -110$ to -55 ppm with ^{19}F–^{77}Se coupling constants of 530–660 Hz. Storing a solution of bis(2,4,6-trimethylphenyl)selenium difluoride **101j** in a closed PFA vessel at +4 °C over a period of a few days afforded colorless crystals suitable for X-ray analysis. It shows that in a single crystal (the monoclinic crystal system, space group $C2/c$ with $Z = 8$) the asymmetric unit consists of two molecules, in which the selenium atom is



SCHEME 37

pseudotrigonal bipyramidal coordinated with both fluorine atoms occupying the axial positions and the one electron pair in one equatorial position[59a]. The prepared tellurium difluorides **102** were also isolated at room temperature as colorless liquids or colorless solids **(102b** and **102g)**. The dialkyltellurium difluorides **102b–d** and **102f** showed in the ^{19}F NMR spectra extremely broad resonances (at 25 °C, 800–2200 Hz) for the TeF_2 fluorine atoms, which is due to the restricted rotation of the Te–C bonds, a phenomenom observed earlier for diaryltellurium dihalides[76]. However, for the methyl derivative **102a**, a sharp resonance was observed at 25 °C. Similar to **102a** but in contrast to **102b**, free rotation of the Te–C bonds in the ^{19}F NMR spectra was reported for di(trifluoromethyl) tellurium difluoride[77] and di(pentafluoroethyl)tellurium difluoride[78]. The ^{19}F NMR shifts in difluorides **102b–e** were found to be sensitive to substituents R^1 and R^2 and observed in a relatively wide range between $\delta = -125$ and -153 ppm. The ^{125}Te NMR resonances of **102b–e** were found at $\delta = 1380–1232$ ppm.

Oxidative halogenation was applied also for the synthesis of the chloroselenuranes **105a–c** and telluranes **106a–c** which were prepared by treatment of suitably functionalized ω-hydroxyalkyl selenides **103a–c** and tellurides **104a–c** with *t*-butyl hypochlorite (Scheme 39)[79]. The structure of these compounds was confirmed by spectroscopic techniques and X-ray analysis of chlorophenylselenurane **105a**, which indicated that it has a slightly distorted trigonal bipyramidal geometry around the central selenium atom. Considering the oxidative ability of the prepared chalcogenuranes, it is interesting to note that phenylselenurane **105a** reacted with tellurides **104a** and **104c** in a methylene chloride solution at room temperature giving selenide **103a** and telluranes **106a** and **106c** in quantitative yield (Scheme 39). It was also observed that the oxidation of ethyl selenide

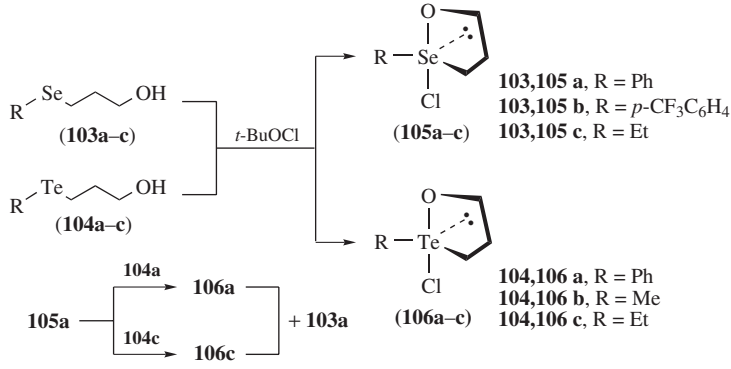


91,101 a, R = C_6F_5
91,101 b, R = *p*-$CF_3C_6F_4$
91,101 c, R = 2,6-$F_2C_6H_3$
91,101 d, R = 4′-(*p*-$CF_3C_6F_4O)C_6F_4$
91,101 e, R = Me
91,101 f, R = Et
91,101 g, R = *i*-Pr
91,101 h, R = *n*-Pr
91,101 i, R = Ph
91,101 j, R = 2,4,6-$Me_3C_6H_2$
91,101 k, R = 2,4,6-(*t*-$Bu)_3C_6H_2$
91,101 l, R = *o*-$(Me_2NCH_2)C_6H_4$

92,102 a, R = C_6F_5
92,102 b, R = Me
92,102 c, R = Et
92,102 d, R = *i*-Pr
92,102 e, R = *n*-Pr
92,102 f, R = *c*-C_6H_{11}
92,102 g, R = *o*-$[Me_2NCH_2]C_6H_4$

SCHEME 38

103c with phenylselenurane **105a** needed a longer time. Ethylselenurane **105c** showed a lower reactivity as compared with phenylselenurane **105a**, and phenyltellurane **106a** was able to oxidize only alkyl selenide **103c**[79].

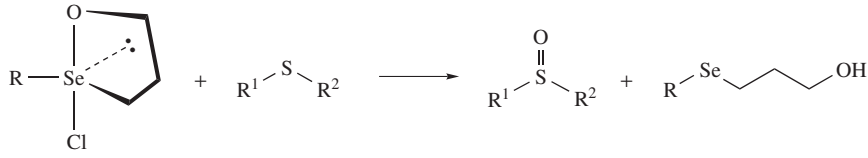


103,105 a, R = Ph
103,105 b, R = *p*-$CF_3C_6H_4$
103,105 c, R = Et

104,106 a, R = Ph
104,106 b, R = Me
104,106 c, R = Et

SCHEME 39

The reaction of chloroselenuranes **105a** and **105c** with sulfides **107** allowed their selective oxidation to the corresponding sulfoxides **108** with the simultaneous formation of selenides **103a,c** under mild conditions (Scheme 40)[79].



(**105a,c**) (**107**) (**108**) (**103a–c**)

	108		
Selenurane	R^1	R^2	Yield%
105a	Me	Me	100
105a	*n*-Bu	*n*-Bu	95
105a	*c*-C_6H_{11}	Me	92
105c	*p*-$MeOC_6H_4$	Et	50

SCHEME 40

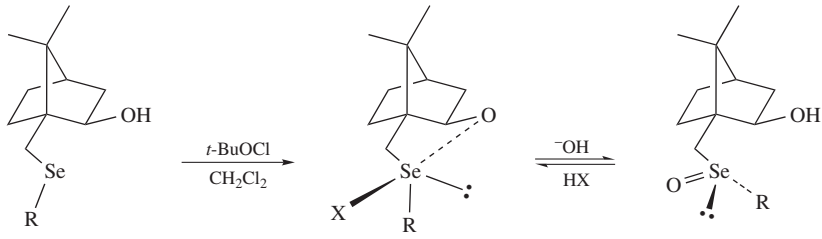
A similar oxidative chlorination of bicyclic hydroxy selenides containing the bornyl moiety **109a–d** with *t*-BuOCl was found to be very rapid (10 min at 0 °C) and to give diasteromeric chloroselenuranes **110a–d** (X = Cl) as single stereoisomers (89–100% yield) (Scheme 41)[80]. Addition of aqueous sodium hydrogen carbonate to a methylene chloride solution of **110a–d** at 0 °C resulted in instantaneous hydrolysis, leading to the selenoxide **115a–d** again as a single diastereomer (90–100% yield). The selenoxide **115a** upon treatment with HCl gave the starting chloroselenurane **110a** as a single diastereomer (100% yield). Bromoselenurane **111** was obtained similarly by treatment of **115a** with HBr (96% yield). A few other diastereomerically pure selenuranes **112–114** were also prepared by the reaction of the selenoxide **115a** with 3,5-dinitrobenzoic acid, *p*-toluenesulfonic acid and trifluoromethanesulfonic acid in the presence of $MgSO_4$ (88–91% yield) (Scheme 41)[80]. Formation of the selenuranes having the opposite absolute configuration at the stereogenic selenium atom might be unfavorable because of steric repulsion between the 7-methyl group of the bornyl moiety and the aryl or methyl group or X.

The structures of the chloroselenurane **110a** and bromoselenurane **111** determined by X-ray analysis showed that both compounds have a trigonal bipyramidal structure. The apical Se–O bond distances [1.838(5) Å and 1.835(6) Å, respectively] are shorter than the sum of van der Waals radii (3.40 Å), indicating transannular bond formation between selenium and oxygen. The ^{77}Se NMR chemical shifts (δ = 890.1 and 890.9 ppm, respectively) of **110a** and **111** are characteristic for the O selenuranes. The formation of selenuranes **112–114** was also evidenced by the ^{77}Se NMR spectra (δ = 885–906 ppm).

The reaction of two equivalents of silyloxycyclopropane **83a** with tellurium tetrachloride gave bis(β-acylethyl)tellurium dichloride **116** (Scheme 42)[65].

Olefins (styrene and cyclohexene) react with phenyltrifluoroselenurane **73a** forming the addition products **117** and **118**, which could not be isolated due to their extreme hydrolytic susceptibility. After treatment with aqueous $NaHCO_3$ or on silica gel during attempted purification they were converted quantitatively into selenoxide **119** or **120**, which are more stable and can be stored in a refrigerator at least for some days. It is interesting to note that selenoxide **120** exists as a mixture of two diastereomers in approximately 2:1 ratio (as shown by ^{1}H and ^{19}F NMR spectroscopy) (Scheme 43)[59d].

The reaction of *p*-substituted benzoylmethyl bromides **121** with tellurium powder which occurs under gentle heating gave the corresponding dibromides **94b–d**. Their nucleophilic

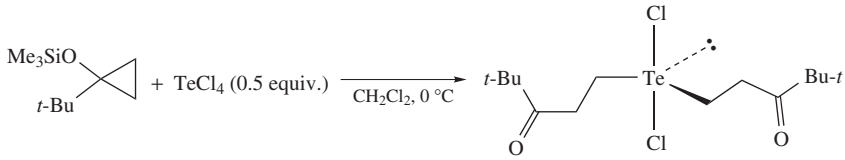


(**109a–d**) **a**, R = Ph; **b**, R = *p*-$MeOC_6H_4$; **c**, R = *p*-$CF_3C_6H_4$; **d**, R = Me

(**110a–d**) (X = Cl); (**111**) (X = Br); (**112**) (X = 3,5-$O_2NC_6H_2CO_2$); (**113**) (X = *p*-$TolSO_3$); (**114**) (X = CF_3SO_3)

(**115a–d**)

SCHEME 41



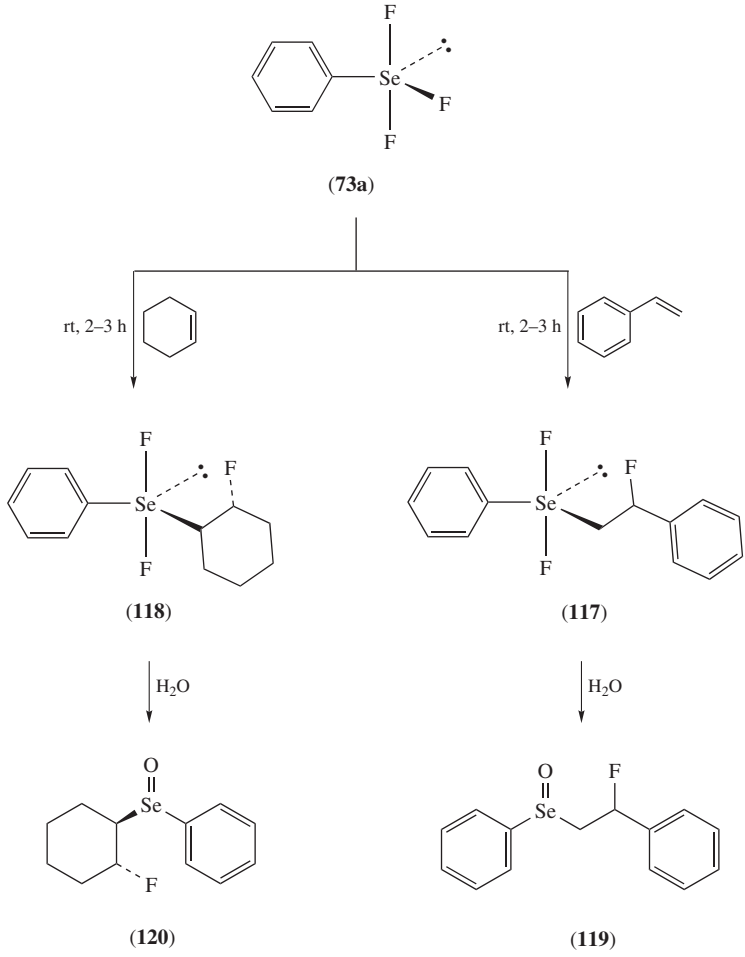
(**83a**) (**116**)

SCHEME 42

exchange reactions with potassium iodide afforded the corresponding diiodoselenuranes **122b–d**, whereas their reduction with sodium thiosulfate in a two-phase system led to ditellurides **92b–d** (Scheme 44)[74].

The nucleophilic exchange of fluorine atoms in difluoroselenuranes **101a–l** or difluorotelluranes **102a–g** with trimethylsilyl azide afforded the corresponding organoselenium diazides **123a–l** or organotellurium analogues **124b–g**, respectively (Scheme 45)[59a, 59c, 60, 61, 81].

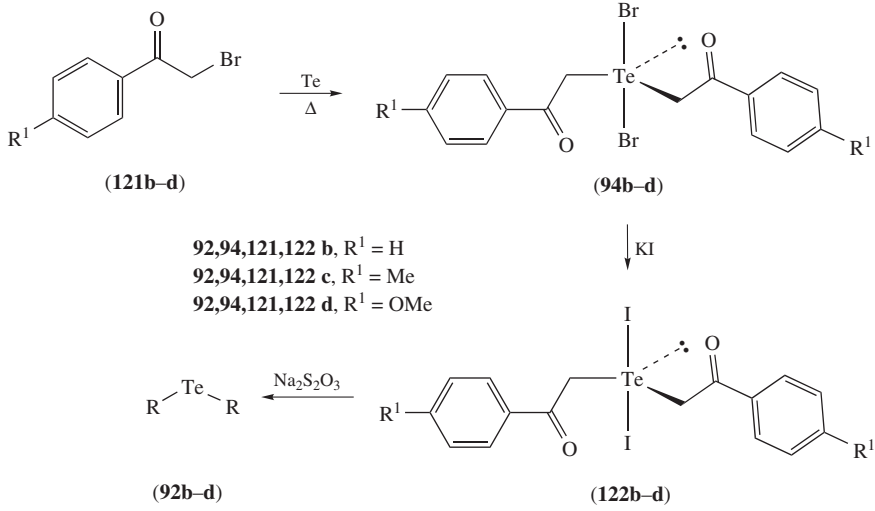
Selenium azides **123** were found to be stable only at temperatures around −50 °C, and according to ^{77}Se NMR spectra they decomposed at increased temperatures under vigorous formation of dinitrogen to the corresponding monoselenides (Scheme 45). The most stable in solution were donor-stabilized selenium diazide **123g** and the methyl **123e**, and phenyl **123i** substituted diazides. In the reaction of difluoride **101e** with trimethylsilyl azide, the resonance of the product diazide was not detected, and only the decomposition product was observed in the ^{77}Se NMR spectrum after a short reaction time at −50 °C. This indicates that in contrast to the organotellurium azides, the organoselenium azides cannot be stabilized by sterically more demanding substituents. In the ^{77}Se NMR spectra, the resonances of the selenium diazides occur in the range between $\delta = 574$ and 816 ppm and, as expected, the values are shifted toward higher field compared to the corresponding difluorides. In the ^{14}N NMR spectra, the resonances for N_β and N_γ can readily be detected, whereas the resonance for N_α is often very broad. The Raman spectrum for **123b** obtained at low temperatures showed antisymmetric stretching vibration medium intense peaks at 2097–2056 cm^{-1}, whereas the Se–N stretching vibration was detected at 403 cm^{-1}



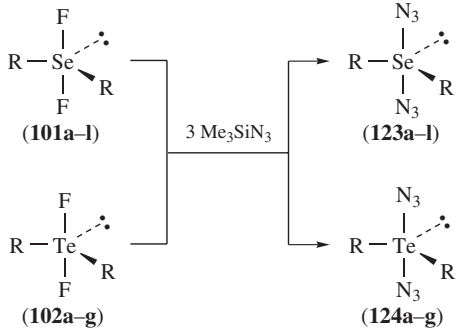
SCHEME 43

and shifted to a higher wavenumber compared to the corresponding tellurium compound (346 cm^{-1}) due to the lighter element selenium. The Se–C stretching vibration (564 cm^{-1}) was also shifted to a higher wavenumber compared to **124b**, $Me_2Te(N_3)_2$ (540 cm^{-1}).

The dialkyltellurium diazides **124b–f** are colorless liquids or solids which explode when heated in a flame, compared with diaryl analogues **124a** and **124g** which are colorless and nonexplosive solids.[81] They are moderately soluble in common organic solvents and hydrolyze slowly in air and moisture, with formation of HN_3. The ^{125}Te resonances of the tellurium diazides **124** at $\delta = 1147–835$ ppm are shifted to lower frequency if compared with the starting difluorides **102**. This is due to the lower electronegativity of the azide group compared to fluorine, which leads to less deshielding of the tellurium nucleus. They show a medium intense Te–C stretching vibration in the 550–492 cm^{-1} region of their Raman spectra. It should be noted that the computed vibrational frequencies are in very



SCHEME 44



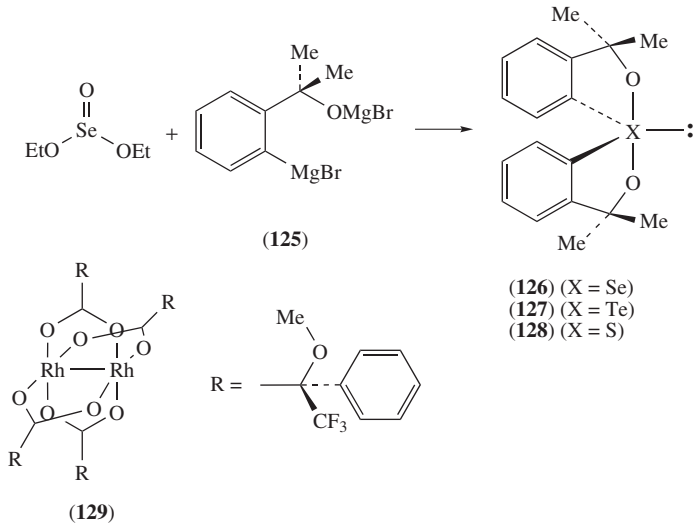
101,123 a, R = C_6F_5
101,123 b, R = *p*-$CF_3C_6F_4$
101,123 c, R = 2,6-$F_2C_6H_3$
101,123 d, R = 4'-(*p*-$CF_3C_6F_4O)C_6F_4$
101,123 e, R = Me
101,123 f, R = Et
101,123 g, R = *i*-Pr
101,123 h, R = *n*-Pr
101,123 i, R = Ph
101,123 j, R = 2,4,6-$Me_3C_6H_2$
101,123 k, R = 2,4,6-(*t*-$Bu)_3C_6H_2$
101,123 l, R = *o*-$(Me_2NCH_2)C_6H_4$

102,124 a, R = C_6F_5
102,124 b, R = Me
102,124 c, R = Et
102,124 d, R = *i*-Pr
102,124 e, R = *n*-Pr
102,124 f, R = *c*-C_6H_{11}
102,124 g, R = *o*-$(Me_2NCH_2)C_6H_4$

SCHEME 45

good agreement with experimental IR and Raman data at all levels of theory applied. Diphenyltellurium diazide **124h** crystallizes in an orthorhombic space group *Pbca* ($Z = 8$), and bis(pentafluorophenyl)tellurium diazide **124a** crystallizes in a monoclinic space group $P21/c$ ($Z = 4$). Both compounds show the expected trigonal bipyramidal structure for a four-coordinated central atom with an additional electron pair in the equatorial position.

Spirochalcogenuranes containing hypervalent selenium and tellurium atoms with trigonal bipyramidal geometry exhibit axial chirality even if both ligand arms are equal. Recently, one example of this type of spiroselenurane, *C*2-symmetric 3,3,3′,3′-tetramethyl-1,1′-spirobi[3*H*,2,1]benzoxaselenole **126**, available earlier in racemic form by a route involving a few steps[82], was synthesized in one step from diethyl selenite and the Grignard reagent **125** derived from *o*-bromocumyl alcohol (Scheme 46)[83].

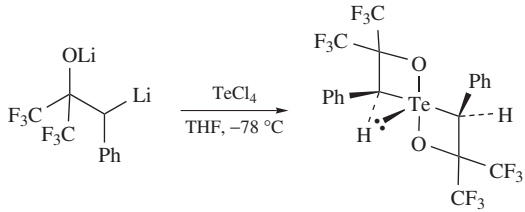


SCHEME 46

The stereogenic character of the selenium atom in this compound is clearly indicated by the presence of the two well-separated methyl singlets in the ^{1}H NMR spectrum at 1.59 and 1.63 ppm and in the ^{13}C NMR spectrum at 32.89 and 33.89 ppm. It was found that the enantiomers of **126** give very well resolved peaks when a solution of the racemate was passed through an analytical chiral column. A semi-preparative separation by repeated injection and collection of the respective fractions from the analytical column gave a sample of each enantiomer, allowing further characterization by means of polarimetry, ^{1}H NMR and CD spectroscopy. The properties of spiroselenurane **126** and its tellurium **127** and sulfur **128** analogues acting as ligands in adducts with a chiral dirhodium tetracarboxylate complex **129** were explored, and the individual adduct species were characterized by low-temperature NMR spectroscopy. The determination of enantiomeric composition of the chiral spirochalcogenuranes was found to be possible

by evaluating NMR signal dispersions both at low and at room or slightly elevated temperatures. The uniformity in the signs of ^{1}H dispersion effects referred to those of the spiroselenurane with known absolute configuration [(*S*)-(−)-**126**] creates a convenient rule for the determination of absolute configuration in the spirochalcogenurane series (Scheme 46)[84]. Moreover, the experimental vibrational circular dichroism (VCD) spectra were obtained for both enantiomers. The theoretical VCD spectra were obtained by means of density functional theoretical calculations with the B3LYP density functional. From a comparison of experimental and theoretical VCD spectra, the absolute configuration of an enantiomer with positive specific rotation in methylene chloride at 589 nm was determined to be *R*. This conclusion was verified by comparing results of experimental optical rotatory dispersion (ORD) and electronic circular dichroism (ECD) with predictions of the same properties using the B3LYP functional[85].

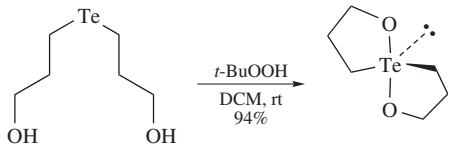
Stereochemically interesting spirotellurane **131** was isolated, as a single *trans,trans* isomer, in the reaction of tellurium tetrachloride with dilithium reagent **130** (Scheme 47)[86].



(**130**) *trans,trans*-(**131**)

SCHEME 47

Dioxatellurane **133**, a strong glutathione peroxidase mimic, was prepared by the reaction of dihydroxy telluride **132** with *t*-butyl hydroperoxide (Scheme 48)[87].

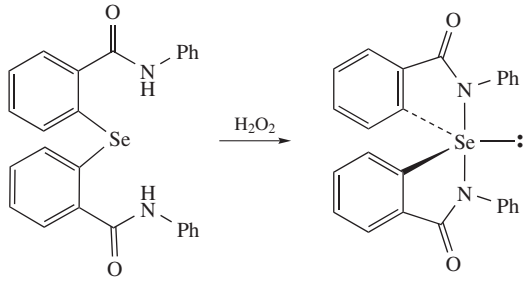


(**132**) (**133**)

SCHEME 48

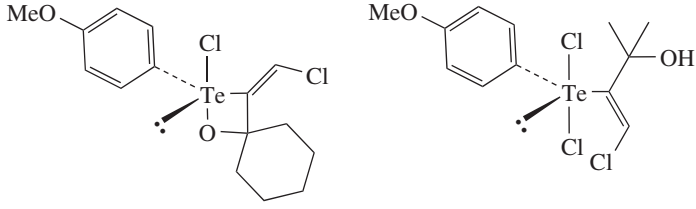
Another glutathione peroxidase mimetic, a very stable diazaselenurane **135**, was obtained by the oxidation of selenide **134** with hydrogen peroxide (Scheme 49)[88]. It is interesting to note that its crystallization is accompanied by a spontaneous optical resolution leading to isolation of optically active samples.

Chlorooxatellurane **136** and dichlorotellurane **137** were found to have very interesting antioxidant and mitochondrial properties[89, 90].



(**134**) (**135**)

SCHEME 49



(**136**) (**137**)

Dichlorotelluraporphyrine **139** was obtained upon treating telluroxide **138** with hydrogen chloride in the two-phase system water/dichloromethane (Scheme 50)[91].

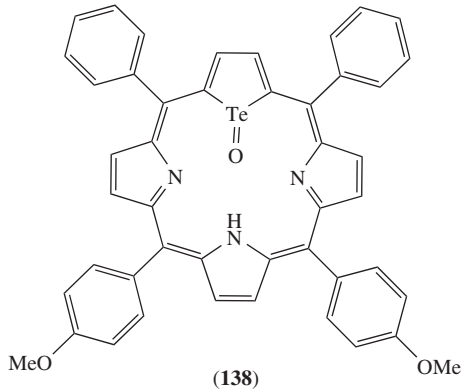
Azodioxotelluranes **141** were isolated by treatment of aminodioles **140** with tetraethoxy or tetraisopropoxy tellurium in an alcohol solution (ethanol or isopropanol) (Scheme 51)[92].

Oligomeric dioxotellurane derivative **144** was isolated in the reaction of ditelluronium salt **142** with di-*p*-tolyltelluroxide **143** (Scheme 52)[93].

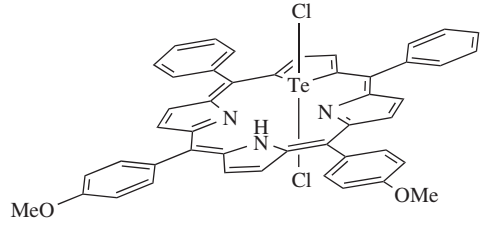
4. 10-Ch-4 chalcogenuranes (C3L, Ch = Se, Te)

Many compounds which belong to this group of formally tetravalent, tetracoordinated chalcogenuranes (especially halogen-containing derivatives) are ionic in character. Therefore they should be considered as the onium salts. The first preparation of triphenylselenonium chloride **145a** was reported as early as 1927[94] and was based on the reaction of selenium dioxide with benzene in the presence of anhydrous aluminum trichloride (Scheme 53)[95]. A few years later the same protocol, slightly modified, was used to obtain the *p*-tolyl analogue **145b** in almost quantitative yield[95].

For triphenylselenium chloride **145a**, where the minimum selenium–chlorine distance is no less than 3.40 Å, the bonding must be ionic[96]. Also trimethylselenium iodide, Me_3SeI, was found by X-ray analysis to have the onium salt character.[97] The interpretation of the infrared spectrum of trimethyselenonium chloride, Me_3SeCl, was also consistent with this conclusion[98]. Futhermore, a few triphenyltelluronium pseudohalides, Ph_3TeX **146** (X = OCN, SCN, N_3, CN), are known[99]. On the other hand, it was concluded, based on molar conductivity measurements, that in triphenyltellurium chloride **146** (X = Cl) the bonding has covalent character[100]. Very recently, it was also found that in tris(perfluorophenyl)tellurium chlorides **147a,b**, isolated unexpectedly in the reaction of

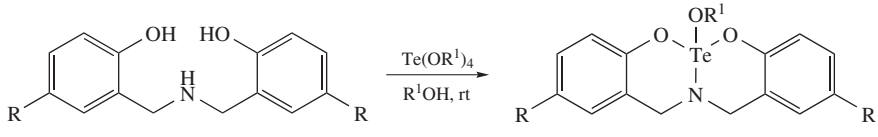


(**138**)



(**139**)

SCHEME 50



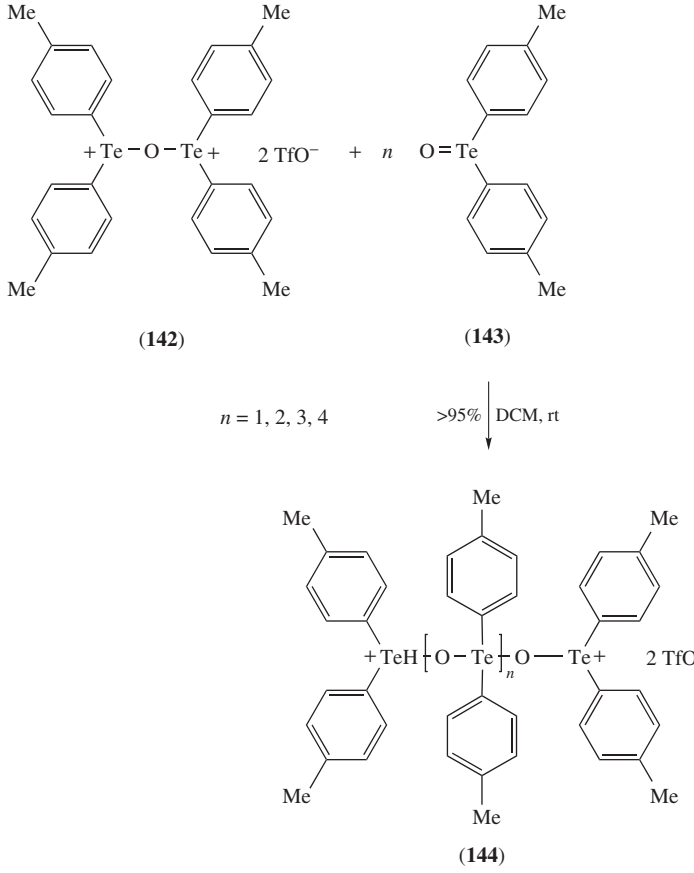
(**140**) (**141**)

R = H, Me, OMe, Cl, Br
R^1 = Et, *i*-Pr

SCHEME 51

pentafluorophenyltellurium dichlorides **102a,e** with silver cyanide in a chloroform solution (Scheme 54)[101], the selenium–chlorine distance is only slightly elongated in comparison with the fully covalent Te–Cl bonds in diaryldichlorotelluranes. It means that for this chlorotellurane a total ionic character should be excluded[101].

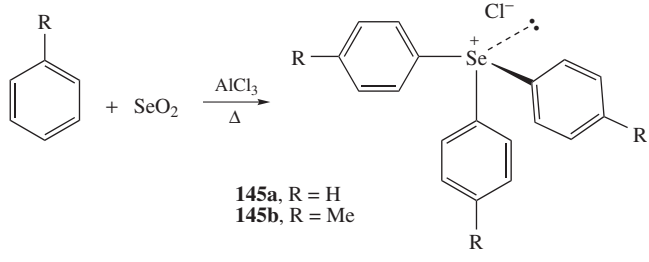
A few other triphenyltelluranes prepared by a nucleophilic substitution reaction of triphenyltelluronium halides with sulfur and oxygen nucleophiles have a typical covalent



(**142**) (**143**)

(**144**)

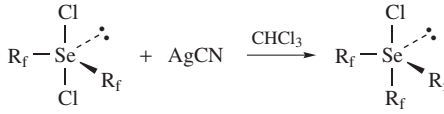
SCHEME 52



145a, R = H
145b, R = Me

(**145a,b**)

SCHEME 53

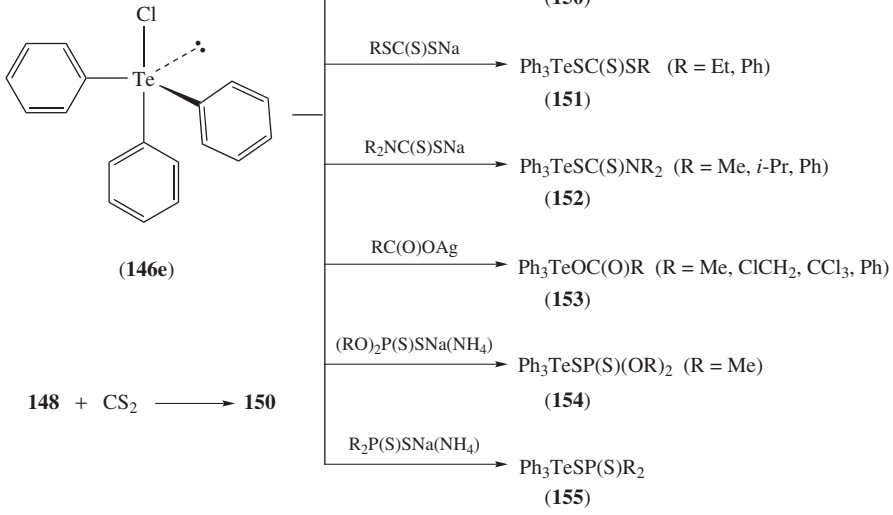


(**102a,e**) (**147a,b**)

101a and **147a**, $R_f = C_6F_5$
101e and **147b**, $R_f = p\text{-}CF_3C_6F_4$

SCHEME 54

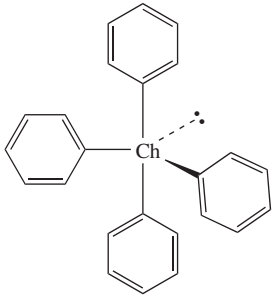
character of the tellurium–heteroatom bond. Thus, triphenyltelluronium alkoxides **148**[102], thioalkoxides **149**[103], xanthates **150**[102] and thioxanthates **151**[102], dithiocarbamate **152**[105], carboxylate **153**[104] and phosphoric analogues **154**[106] and **155**[106] were obtained by treating chlorotellurane **146e** with an appropriate nuleophile (sodium alkoxides, sodium thioalkoxides, sodium xanthate, sodium thioxanthate etc.), respectively (Scheme 55). The xanthates **150** were also prepared from triphenyltelluronium alkoxides **148** and carbon disulfide[102].



SCHEME 55

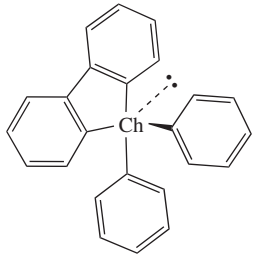
5. 10-Ch-4 chalcogenuranes (C4, Ch = Se, Te)

Aryltellurium compounds having four tellurium carbon bonds have been known since 1952 when Wittig and Fritz succeeded in the synthesis of tetraphenyltellurium **156a**[107]. Another five tetraarylic mono- and bicyclic chalcogenuranes **156b–160** (Chart 5) bearing four carbon ligands, which were prepared before 1998 and discussed by Furukawa and Sato[5], are shown in Chart 5.

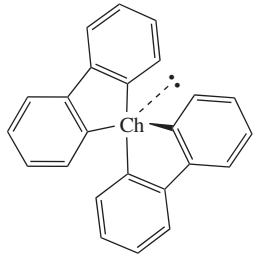


(**156a,b**)

156a, Ch = Te
156b, Ch = Se



(**157**), Ch = Se
(**158**), Ch = Te



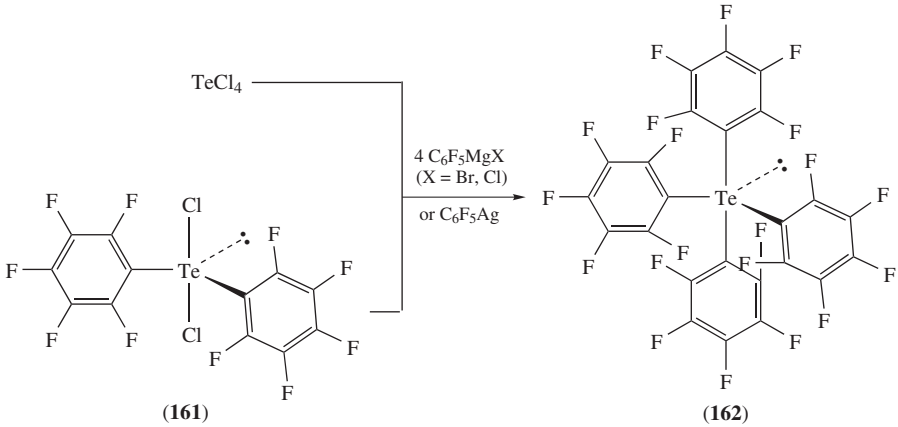
(**159**), Ch = Se
(**160**), Ch = Te

CHART 5

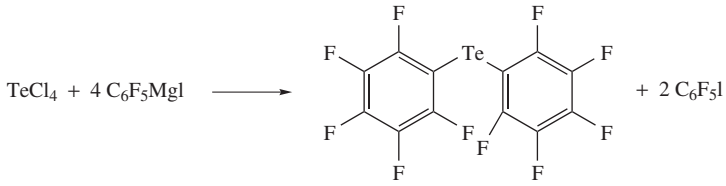
Very recently, perfluorotetraphenyltellurium **162** was prepared in the reactions of tellurium tetrachloride or dipentafluorophenyltellurium dichloride **161** with pentafluorophenylmagnesium bromide (chloride) or pentafluorophenylsilver in moderate to good yield (Scheme 56)[108]. In this context it is interesting to note that the reaction of tellurium tetrachloride with pentafluorophenylmagnesium iodide gave, instead of the expected tellurane **162**, the corresponding perfluorinated diphenyltelluride **92a** (Scheme 56)[108]. Perfluorotetraphenyltellurium **162** was found to crystallize in the monoclinic space group PZ_i/c ($Z = 8$) with two independent molecules per unit cell. In a trigonal bipyramidal structure two perfluorophenyl groups reside in equatorial positions like the lone electron pair, and two occupy axial positions[109].

Interesting reactions of tetrapentafluorophenyltellurium **162** (illustrated in Scheme 57) include as model conversions: a) substitution reactions with Me_3SiX (X = Cl, Br, OSO_2CF_3), with equimolar amounts of bromine, and with silver nitrate; b) oxidation reactions of Cd, Hg; c) hydrolysis[108].

If one considers chalcogenurane cyanides as compounds having a carbon ligand(s), diorganochalcogenium dicyanides and chalcogenium tetracyanides can be included in the family of 10-Ch-4(C4) selenuranes or telluranes, respectively. Two diorganotellurium dicyanides **163a,b** were recently prepared in the reaction of difluorotelluranes **102a** and **102j** with trimethylsilyl cyanide. Interestingly, the same reaction of difluorotellurane **102k** afforded quantitatively, instead of the expected dicyanide **163c**, the corresponding telluride **92k** as the reduction product (Scheme 58)[110].

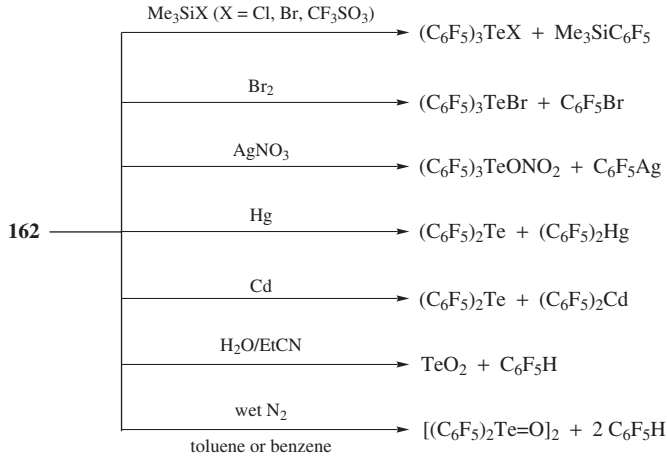


(**161**) (**162**)

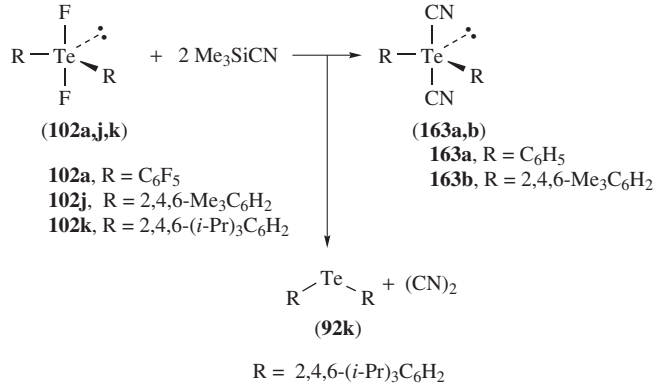


(**92a**)

SCHEME 56



SCHEME 57



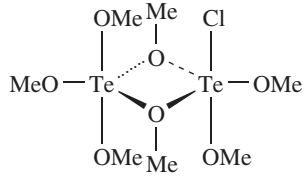
SCHEME 58

IV. ISOLABLE 10-Ch-5 AND 12-Ch-5 SPECIES

Formally, this category of hypervalent selenium and tellurium derivatives comprises noncharged 1:1 complexes of chalcogenuranes with Lewis acids, chalcogenurane oxides and the charged species that are formed upon treatment of chalcogenuranes with nucleophilic reagents. The latter results in the formation of an additional chalcogen–heteroatom bond with simultaneous generation of the negative charge on a chalcogen atom.

A. 10-Ch-5 Chalcogenuranes (Noncharged Complexes of 10-Ch-4 Species)

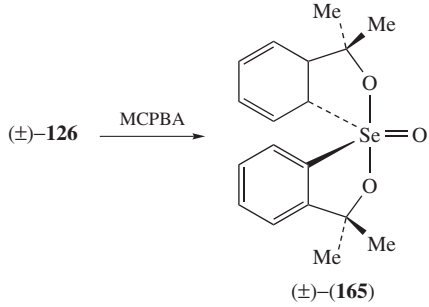
Many molecular and crystal structures of tetravalent, tetracoordinated tellurium compounds exhibiting intramolecular donor–acceptor interactions have so far been reported[111–114]. They can be considered as the simplest model of noncharged 1:1 complexes of chalcogenuranes with Lewis acids. Recently, the solid state structure of the first structurally characterized adduct between different telluranes, namely tetramethoxytellurium and trimethoxychlorotellurim, $Te(OMe)_4ClTe(OMe)_3$ **164**, investigated by single-crystal X-ray diffraction exhibited a very short Te—O···Te bridge between the two Te centers and additional Te···O and Te···Cl contacts between different adduct molecules. The stability of the adduct **164** toward decomposition into tetramethoxytellurium and trimethoxychlorotellurium is attributed to the strengths of the short Te—O···Te bridge between them[115].



(**164**)

B. Stable 12-Ch-5 Chalcogenurane Oxides

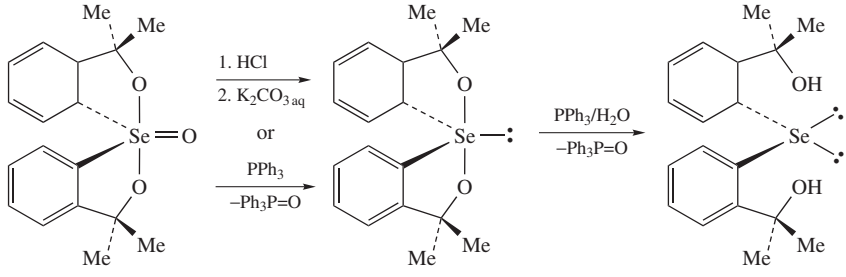
The chemistry of chalcogenurane oxides has not been as extensively studied as the chemistry of tetracoordinated chalcogenuranes. Therefore, in the last few decades only a few papers dealing with this topic have been published. Among them is a report on the first successful isolation of the enantiomers of C2-symmetric 3,3,3′,3′-tetramethyl-1,1′-spirobi[3*H*,2,1]benzoxaselenole oxide **165** via liquid chromatography of the racemate using a chiral stationary phase or by its spontaneous optical resolution, which occurs during the slow evaporation of its acetonitrile solution. Racemic oxide **165** was prepared by oxidation of the parent selenurane **126** with *meta*-chloroperbenzoic acid (Scheme 59)[116]. Its chirality is clearly indicated by the fact that in the ^{1}H NMR spectrum recorded in $CDCl_3$ in the presence of (+)-(*R*)-bi-2-naphthol two singlets for one of the magnetically nonequivalent methyl groups were observed. The presence of two methyl singlets in the ^{13}C NMR spectrum at 30.25 ppm and 31.85 ppm can be taken as additional evidence for the chiral nature of the oxide **165**, which is ultimately confirmed by its ^{77}Se NMR spectrum recorded in the presence of (+)-(*R*)-bi-2-naphthol (6.5 molar excess). In this spectrum two well-separated singlets at 881.64 ppm and 881.86 ppm occur, whereas the oxide alone shows only one singlet at 884.09 ppm.



SCHEME 59

It was found that the enantiomers of **165** gave very well resolved peaks when a solution of the racemate was subjected to chromatography on a Chiralpak AS analytical column using hexane containing 1.0–20% of 2-propanol as a mobile phase. It is of interest to note that there was no resolution when hexane containing 2.5–10% of ethanol was used as a mobile phase and very poor resolutions were observed on a Chiralpak OP analytical column. The reactivity of the selenurane oxide is in sharp contrast to that of its sulfur analogue. For example, it is reduced to the parent selenurane **126** in the presence of HCl and converted into the symmetrical hydroxyalkyl selenide **166** by the action of two equivalents of triphenylphosphine in the presence of water, with simultaneous oxidation of triphenylphosphine to the corresponding oxide (Scheme 60)[116].

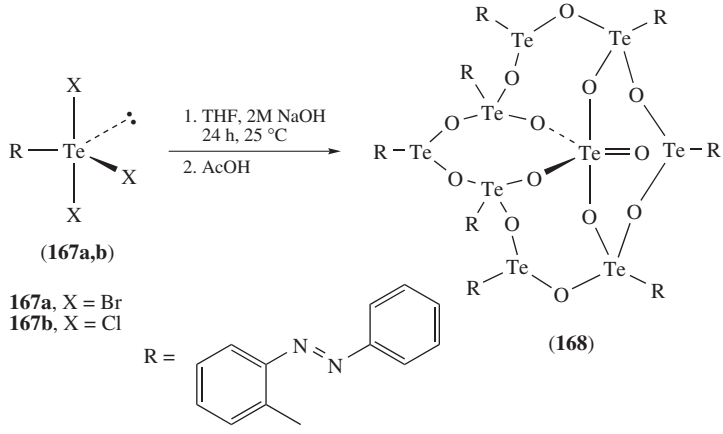
The isolation, in good yield, of the first homometallic, covalent heptanuclear organotellurium oxide cluster, **168**, based on an alkaline hydrolysis of trifluorotelluranes **167a,b** at ambient temperature (Scheme 61) was recently reported[117]. Interestingly, this cluster is a low melting solid which shows good solubility in common organic solvents. The



(**165**) (**126**) (**166**)

SCHEME 60

^{1}H NMR spectrum in CD_3OD showed broad peaks at room temperature which could not be resolved even at −50 °C. Also in the ^{125}Te NMR spectrum only two weak signals at $\delta = 1320$ and 1351 ppm were observed instead of the expected three signals. It was suggested that this may be due to the dynamic behavior of **168** in solution. The X-ray analysis shows that the tellurim oxide **168** has in the solid state the following features: a) a cage consisting of two eight-membered and two six-membered rings, b) the peripheral atoms −Te−O−Te− form a twelve-membered macrocyclic ring where each tellurium is in the +4 oxidation state and bonded to a 2-phenylazophenyl substituent, c) the molecule containing three types of tellurium atoms, i.e. 3-coordinate, 4-coordinate and 5-coordinate.



(**167a,b**)

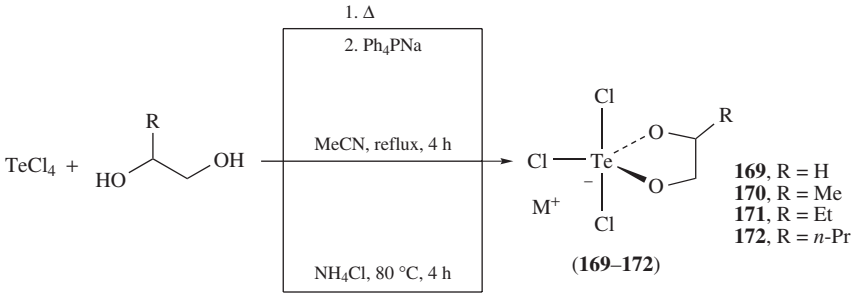
167a, X = Br
167b, X = Cl

(**168**)

SCHEME 61

C. 12-Ch-5 Chalcogenuranes (Negatively Charged on Te)

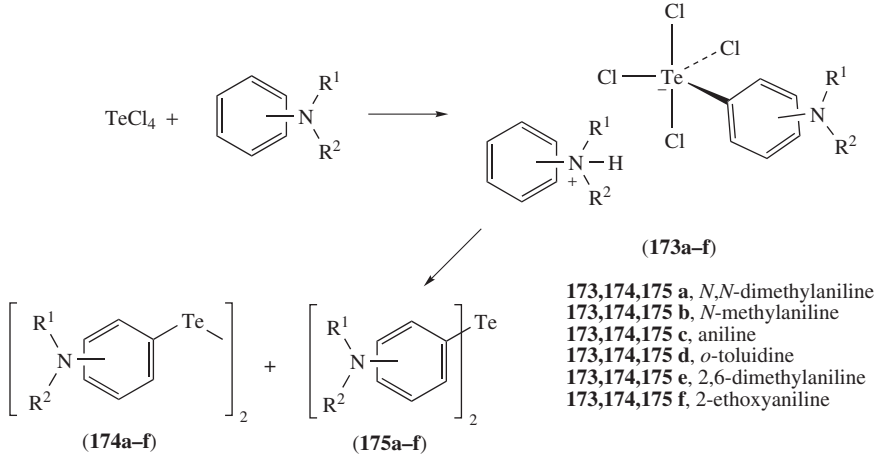
The formation of tetraphosphonium trichloro(1,2-dioxoethane-*O*,*O*′)tellurate **169a** by the reaction of ethylene glycol and tellurium tetrachloride and the subsequent addition of tetraphenylphosphonium ion was reported as early as 1981 (Scheme 62)[118]. Later on, the ammonium salt of this tellurate **169b** was prepared conveniently and directly either by



SCHEME 62

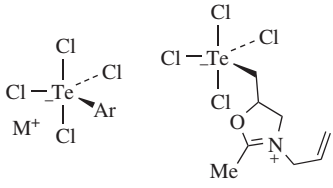
refluxing tellurium tetrachloride with dry ethylene glycol in acetonitrile or by refluxing equimolar amounts of tellurium tetrachloride and ammonium chloride in ethylene glycol (Scheme 62)[119]. The second protocol was extended for the preparation of analogues **170–172** derived from 1-substituted glycols (Scheme 64)[120]. It is interesting to note that ammonium trichloro(1,2-dioxoethane-*O*,*O*′)tellurate **169b** exists in crystalline form mainly as a dimer (uncommonly formed between two anions)[119, 121] and exhibits interesting biological activity including immunomodulatory activity *in vivo* and *in vitro*,[65b, 119, 122], conferring protection against deleterious effects of radio-[123] and chemotherapy[124], synergistic action with Taxol[125] and protease inhibitory activity[126].

It was reported as early as 1929[127] that one molar equivalent of tellurium tetrachloride combined with two equivalents of *N*,*N*-dimethylaniline forms a yellow solid comp1ex. Recently, this finding was confirmed by ^{1}H, ^{13}C, ^{125}Te and ^{14}N NMR studies of properties of a large number of aniline/tellurium tetrachloride complexes[128]. It was concluded that the complexes with *N*- and *o*-substituted anilines have the aryltetrachlorotellurate structure **173a–f**. Their reduction with sodium bisulfite resulted in the formation of mixtures of diaryl tellurides **174a–f** and diaryl ditellurides **175a–f** (Scheme 63)[128]. Earlier



SCHEME 63

phosphonium and tropylium aryltetrahalotellurates **176**[129] and oxazoline derivative **177** (the zwitterionic structure was supported by X-ray analysis) were described (Chart 6)[130].



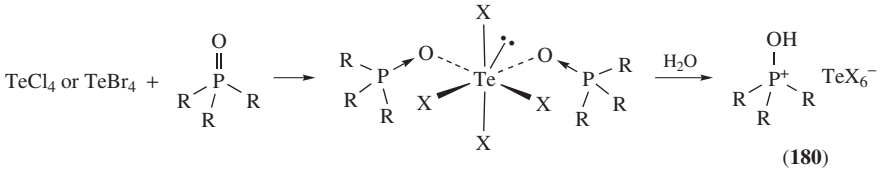
(**176a,b**) (**177**)

176a, M = R_4P
176b, M = tropylium

CHART 6

V. ISOLABLE 10-Ch-6 COMPLEXES OF PERCHALCOGENURANES WITH LEWIS BASES

Formally, this category of hypervalent tetravalent, hexacoordinated selenium and tellurium derivatives comprises no-charge 1:2 complexes of chalcogenuranes with Lewis bases. It is well known that tellurium halides, both tetravalent and divalent, form a significant number of adducts with neutral ligands[131–134]. Moreover, a small number of selenium analogues are also known[135, 136]. Complexes of tetravalent tellurium with neutral oxygen ligands are few, but include *cis*-$[TeCl_4(OPPh_3)_2]$[137–139]. Very recently, the reactions of tellurium tetrachloride or tetrabromide with two molar equivalents of a few phosphine oxides, OPR_3, were found to give very high yields of yellow **178** (Cl) or orange **179** (Br) complexes (Scheme 64). However, attempts to isolate the corresponding adducts of tellurium tetraiodide were unsuccessful[140]. The isolated complexes with tellurium tetrachloride and tetrabromide were stable for extended periods in sealed tubes in the freezer, but slowly darkened at ambient temperatures. In solution, they were hydrolyzed to form (among other products) phosphonium hexahalogenotellurates, $(R_3POH)^+$ TeX_6^- **180**, which were identified by X-ray analysis and/or by the ^{125}Te NMR spectra[141]. The geometry of the *cis*-complex **179a** was reported to be close to octahedral, with only small angular deviations (<5°) between the *cis* ligands from the idealized value (90°) and with the *trans* Br–Te–Br unit bent away [172.88 (4)°] from the neutral ligands. It was suggested that



(**178,179 a**) R = Ph (**178a–c**) (X = Cl)
(**178,179 b**) R = Me (**179a–c**) (X = Br)
(**178,179 c**) R = Et

(**180**)

SCHEME 64

the Te-based lone pair is located on the 5s orbital with the Te−Br, Te−O bonding utilizing Te 5p orbitals and forming 3c−4e bonds[140]. A similar structure was also proposed for complexes of titanium tetrachloride with two equivalents of a few anilines (*m*- and *p*-toluidines, 3,5-dimethyl-, 3-nitro- and 2,4,6-tribromoanilines)[128]. Therefore, in fact these complexes could be considered as 12-Ch-6 perchalcogenurane species, discussed below.

VI. ISOLABLE 12-Ch-6 PERCHALCOGENURANES

Like chalcogenurane oxides, hexacoordinated seleniam and tellurium compounds are quite rare. Moreover, most of the known σ-perchalcogenuranes are those of the tellurium derivatives.

A very rich family of derivatives of telluric acid, $Te(OH)_6$, reported before 1990 is discussed by Irgolic in the Houben-Weyl volume E12b[46b]. Due to the involvement of 12 electrons to bond 6 ligands to the central chalcogen, perchalcogenuranes are considered to have three sets of 3c−4e bonds which are perpendicular to each other. Therefore, they should have an octahedral geometry. Because, according to the expanded Rundle−Musher model[5], the nonbonding orbital splits into bonding and antibonding orbitals, the haxacoordinated chalcogen species are more stable than the corresponding tetravalent, tetracoordinated chalcogenuranes[5].

A. 12-Ch-6 Perchalcogenuranes (CL5, Ch = Se, Te, L = Halogen, etc)

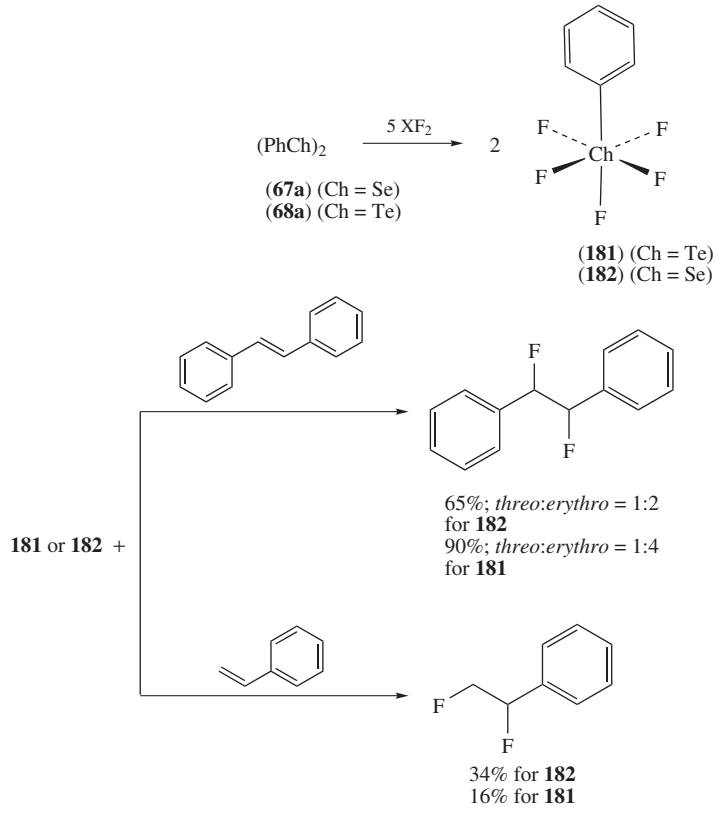
Phenyltelluropentafluoride **181** was described for the first time in 1985[142]. More recently, it was prepared by the room temperature reaction of diphenyl diselenide **67a** with xenon difluoride. The same protocol was applied to obtain phenylselenopentafluoride **182**. Fluorination of diselenide **67a** is slower (3−4 h) than that of ditelluride **68a** (minutes) and is faster in the presence of ammonium chloride (Scheme 65)[59b, 143]. Both pentafluorides react with olefins, affording the corresponding 1,2-difluorides as the main products (Scheme 65)[59d, 143]. Similar fluorination properties were observed for phenyltetrafluorotelluromethoxide **183a**[144], which has been synthesized by the reaction of an equimolar amount of methoxytrimethylsilane with phenyltelluropentafluoride **181** (Scheme 66)[145]. Its reaction with dimethyl (diethyl) amines or their trimethylsilyl derivatives gave the corresponding aminopertelluranes **184** (Scheme 66)[145].

Cis- and *trans*-phenyltellurochlorotetrafluoride **185** was prepared by the oxidative halogenation of diphenyl ditelluride **68a** with xenon difluoride in the presence of ammonium chloride. The corresponding phenyltellurodichlorotrifluoride **186** was detected as a by-product (in the ^{19}F NMR spectrum, an AB_2 spin system was observed). If an excess of xenon difluoride was used, phenyltelluropentafluoride **181** dominated as the reaction product (Scheme 67)[146].

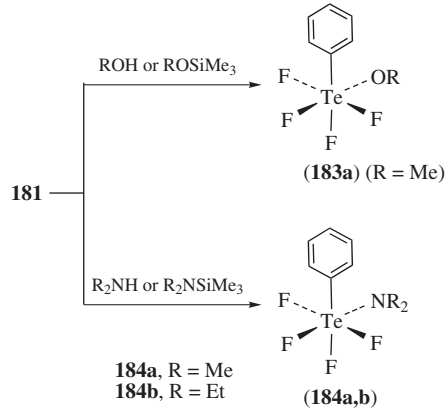
It should be mentioned that phenyltelluropentafluoride **181** was found to behave as a catalyst for the reaction of carbon dioxide with oxiranes (Scheme 68)[147].

B. 12-Ch-6 Perchalcogenuranes (C2L4, Ch = Se, Te, L = Halogen, etc)

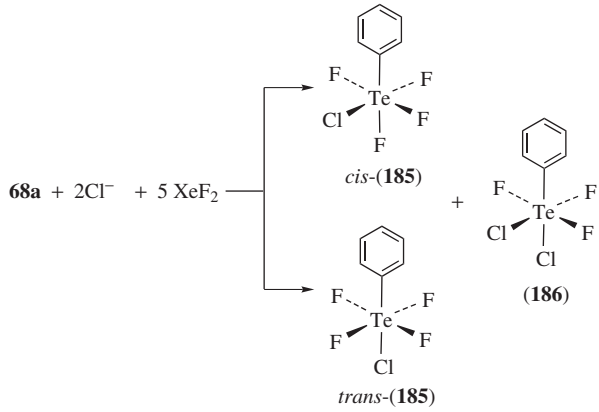
trans-Diphenyltellurotetrafluoride **187** (containing small amounts of *cis* isomer), prepared again by the oxidative halogenation of diphenyl ditelluride **68a** with xenon difluoride, was found to react with alcohols and amines or their trimethylsilyl derivatives to give the appropriate nucleophilic exchange products **188** and **189**. They were characterized by ^{19}F NMR spectroscopy and their isomeric structures were assigned on the basis of their ^{19}F NMR spectra (Scheme 69)[145].



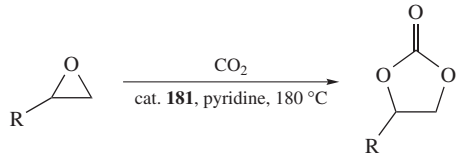
SCHEME 65



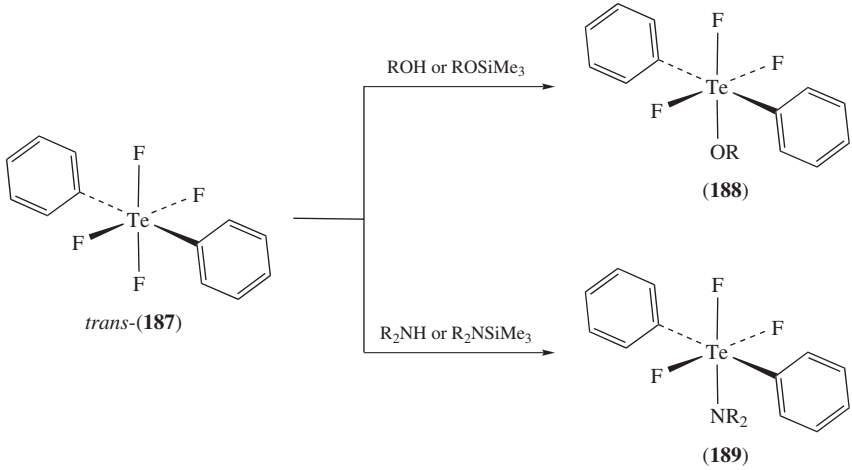
SCHEME 66



SCHEME 67



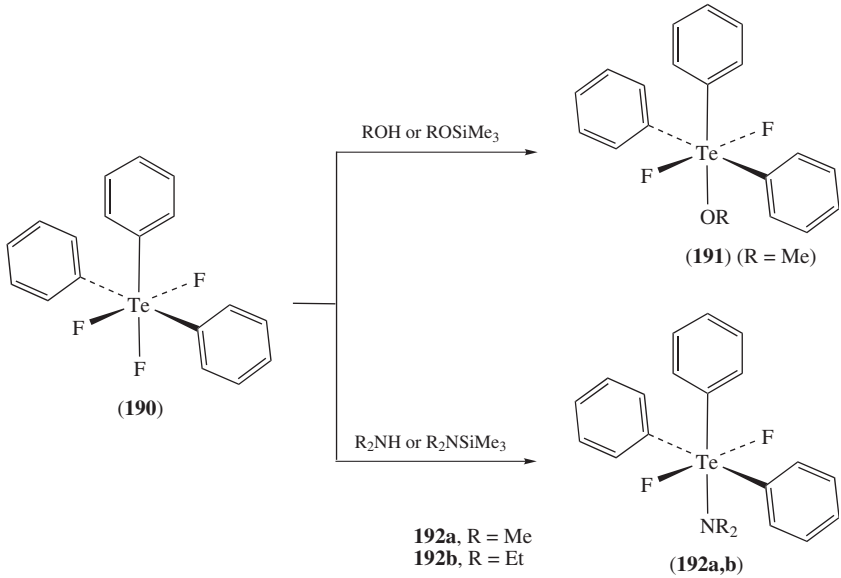
SCHEME 68



SCHEME 69

C. 12-Ch-6 Perchalcogenuranes (C3L3, Ch = Se, Te, L = Halogen, etc)

mer-Triphenyltellurotrifluoride **190**, like the above-presented tetra- and pentafluoropertelluranes, reacts with alcohols and amines or their trimethylsilyl derivatives giving the appropriate nucleophilic exchange products **191** and **192** (Scheme 70)[145].



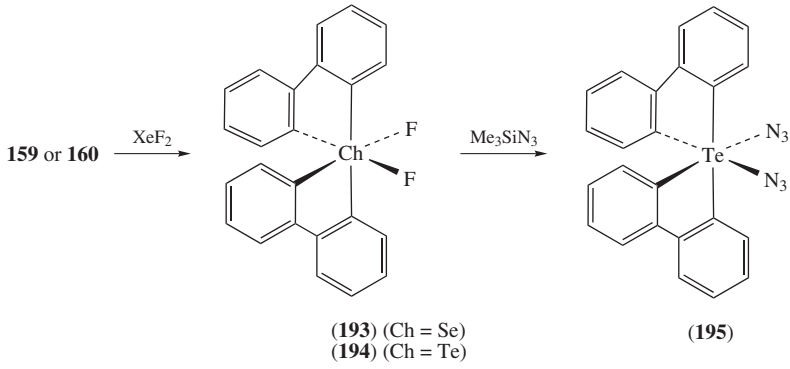
SCHEME 70

D. 12-Ch-6 Perchalcogenuranes (C4L2, Ch = Se, Te, L = Halogen, etc)

The chemistry of this group of hypervalent perchalcogenuranes, including the preparation of difluoro derivatives **193** and **194** (Scheme 71), was presented very comprehensively by Furukawa and Sato in their book chapter[5]. The new details are given in more recent papers[148a,b]. The conversion of pertellurane **194** to the corresponding diazide **195** upon treatment with trimethylsilyl azide was also very recently reported (Scheme 71)[149].

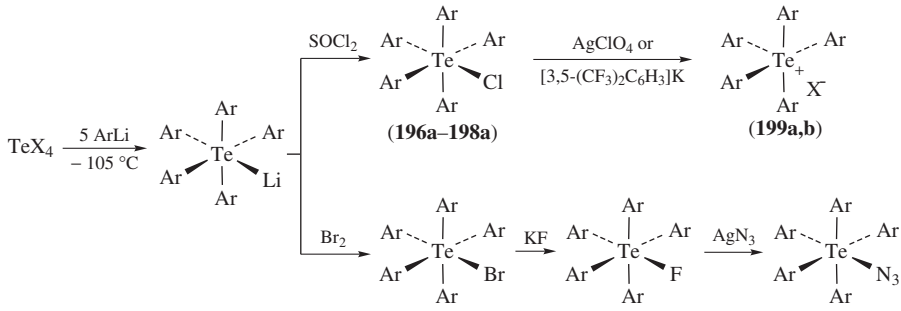
E. 12-Ch-6 Perchalcogenuranes (C5L, Ch = Se, Te, L = Halogen, etc)

The first protocol for the preparation of pentaphenyltellurium monohalides **196a,b** was published only 10 years ago. Both halides are readily obtained by the halogenation of lithium pentaphenyltellurium, which was prepared by reaction of five equivalents of phenyllithium with 1 equivalent of tellurium tetrachloride or tellurium tetrabromide. Sulfuryl chloride or bromine were used as halogenation reagents. A similar procedure was used for the synthesis of two other pentaaryltellurium monohalides, **197** and **198**. The corresponding fluoride **196c** was obtained by treating the bromide **196b** with potassium fluoride (Scheme 72)[150, 151]. All halogens were found to be thermally very stable. Their molecular structures, determined by X-ray crystallographic analysis at $-143\,^{\circ}C$, showed a slightly distorted octahedral geometry around the tellurium. The distortion may be due



SCHEME 71

to the fact that the halogen atoms in **196a–c** are smaller than the phenyl groups. It is also interesting to note that there are no short intermolecular contacts involving the tellurium and halogen; therefore, the halides **196a–c** are monomeric. On the contrary, the corresponding tetravalent, tetracoordinated chalcogenurane compounds exist either as dimers or involve secondary bonding in the solid state[152]. A few years later it was reported that the reaction of the fluoride **196c** with silver azide gave azidopentaphenyltellurium **196d**, which was found to be stable but decomposed slowly in vacuo. Therefore, it could be purified only by crystallization. The molecular structures showed again an octahedrally coordinated tellurium atom (Scheme 72)[149]. The reaction of pentaphenyltellurium chloride **196a**



196, Ar = Ph
197, Ar = *p*-$CF_3C_6H_4$
198, Ar = *p*-BrC_6H_4
199a, Ar = Ph, X = ClO_4
199b, Ar = Ph, X = [3,5-$(CF_3)_2C_6H_3$]

196,197,198 a, X = Cl
196,197,198 b, X = Br
196,197,198 c, X = F
196,197,198 d, X = N_3

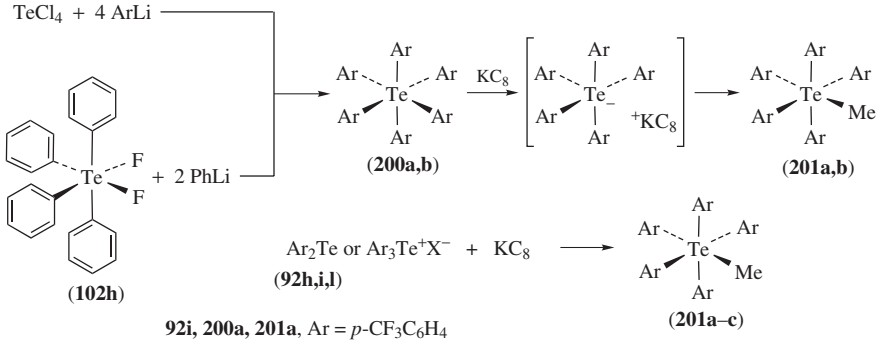
SCHEME 72

with silver perchlorate or silver triflate and tetrakis[3,5-bis(trifluoromethyl)phenyl]borate gave the corresponding salts **199a,b** (Scheme 72)[153]. Both salts were isolated as stable solids. Their X-ray crystallographic analyses revealed square pyramidal geometry around the tellurium atom.

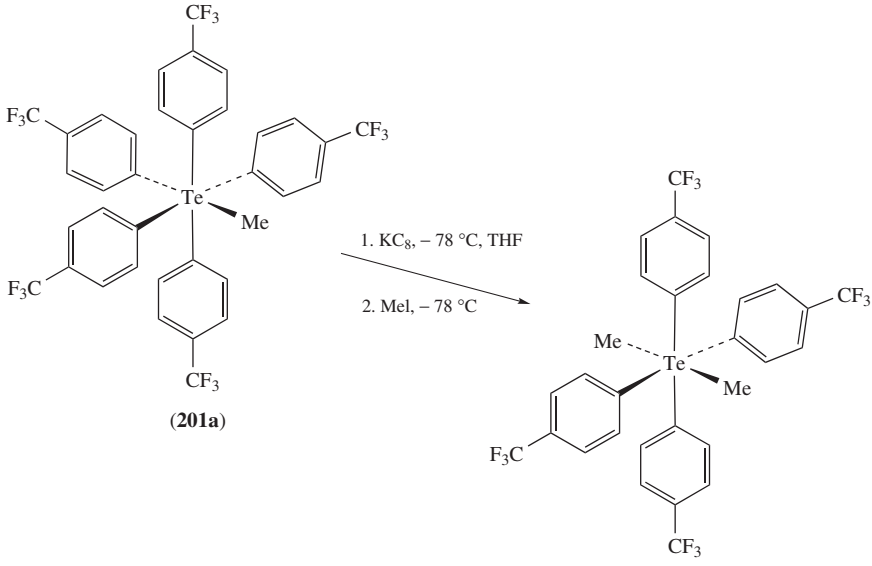
F. 12-Ch-6 Perchalcogenuranes (C6, Ch = Se, Te)

The chemistry of hexavalent perchalcogenuranes bearing six chalcogen–carbon bonds is only 21 years old and limited to tellurium derivatives. The first neutral hexaalkylated compound, hexamethyl tellurium Me_6Te (isolated from the reaction of tetramethyldifluoropertellurane with dimethyl zinc), was structurally characterized only in 1990[154a]. A few years later the first synthesis of hexa(4-trifluoromethylphenyl)tellurium, **200a**, by one-pot reaction of *p*-trifluoromethylphenyllithium, 4-$CF_3C_6H_4Li$, and tellurium tetrachloride was performed[155a,b]. During the subsequent years several new synthetic procedures for novel members of hexavalent organotellurium compounds bearing six Te–C bonds were published by Akiba, Yamamoto and coworkers[150]. Among them are syntheses of hexaphenyltellurium **200b** in the reaction of tetraphenyldifluorotellurium, **102h**, with phenyllithium[155a,b], of pentaphenylmethyltellurium **201a** from $(4\text{-}CF_3C_6H_4)_5Te^-K^+C_8$ by treatment with methyl iodide[155c] and of penta-*p*-tolylmethyltellurium **201c** from di-*p*-tolyltelluride **92l** by treatment with KC_8 followed by reaction with methyl iodide[155d]. These methods are illustrated in Scheme 73.

The selectivity of the Te–C (Te–Ar or Te–CH_3) bond cleavage was checked in heteroleptic hexavalent pertellurane **201a** having five aryl groups and one methyl group (Scheme 74). It was found that its reaction with excess KC_8 carried out at −78 °C in THF, followed by treatment with methyl iodide, gave the dimethyl derivative, *trans*-**202a**, isolated in 14% yield together with **201a** recovered in 75% yield. Its structure was established by NMR spectroscopies and further confirmed by X-ray analysis[150, 155d], which showed that in the solid state *trans*-**202a** had almost perfect octahedral symmetry around the tellurium center. Signals assigned to the *cis* isomer were not observed in the products, and isomerization of *trans*-**202a** to the corresponding *cis*-**202a** did not take place even at 230–250 °C for 1 h in the solid state. Most of *trans*-**202a** was recovered and the decomposition product, bis-*p*-trifluoromethylphenyl telluride, was obtained in small amounts (Scheme 74)[150, 155d].

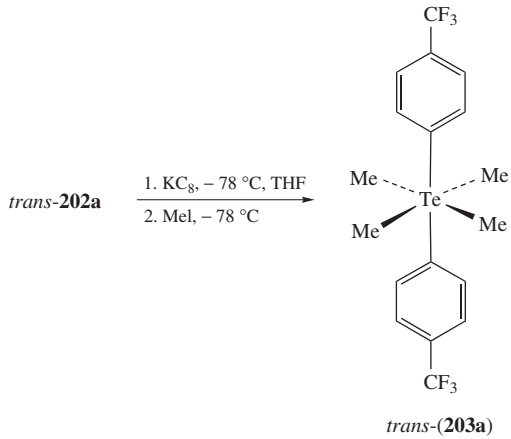


SCHEME 73



SCHEME 74

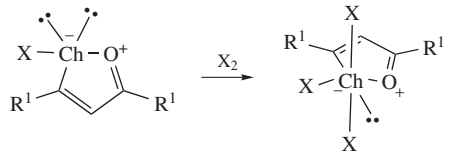
The reductive cleavage of *trans*-**202a** with KC_8 gave tetramethyl pertellurane *trans*-**203a** in 19% yield (Scheme 75)[151, 155d]. Its characterization was based on spectroscopic methods. X-ray analysis confirmed the octahedral structure, which was similar to that of *trans*-**202a**. The two *p*-$CF_3C_6H_4$ groups in *trans*-**203a** were located *trans* to each other[151, 155c].



SCHEME 75

VII. ISOLABLE 12-Ch-5 PERCHALCOGENURANES

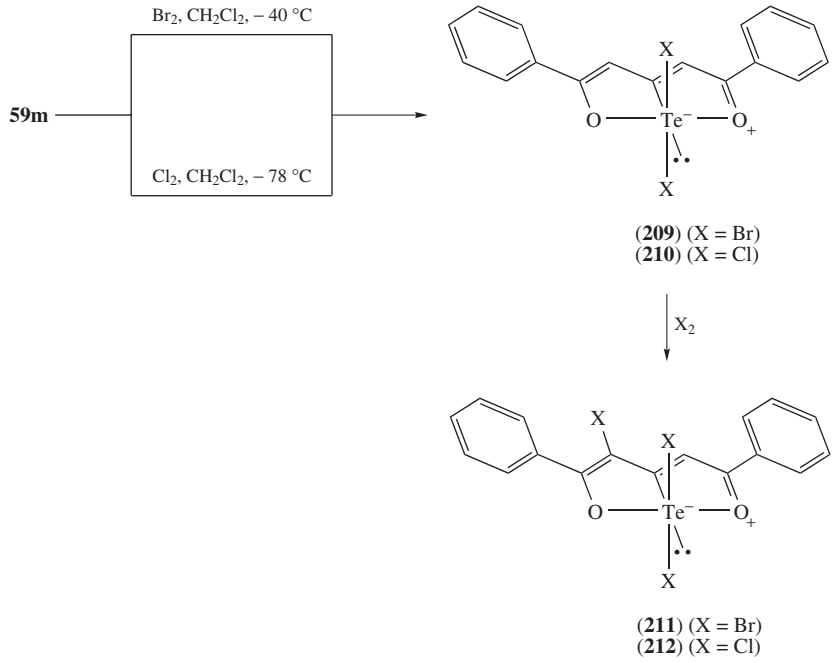
The formal three center, four-electron bond, typical for hypervalent perchalcogenuranes, can also be identified in the product of the oxidative halogen addition to 1,2-oxatellurolyl-l-ium halides and 1,2-oxaselenolyl-1-ium halides. Thus, the addition of chlorine to **204** and bromine to **205** gave the corresponding pertelluranes **206** or **207**, respectively. The similar addition of chlorine to oxaselenolyl-1-ium chloride **60a** afforded perselenurane **208** (Scheme 76)[40a].



(**60a,204,205**) (**206,207,208**)

204,206, Ch = Te, X = Cl, R^1 = H, R^2 = Ph
205,207, Ch = Te, X = Br, R^1 = H, R^2 = Ph
60a,208, Ch = Se, X = Cl, R^1 = Me, R^2 = *p*-$MeOC_6H_4$

SCHEME 76



(**209**) (X = Br)
(**210**) (X = Cl)

(**211**) (X = Br)
(**212**) (X = Cl)

SCHEME 77

The oxidative addition of chlorine or bromine to tellurane **59m** at temperatures below −40 °C gave the corresponding pertelluranes **209** or **210**, respectively. At 0 °C or at a warmer temperature the second equivalent of bromine or chlorine reacted with **209** or **210**, respectively, to give the products of ring halogenation **211** and **212** (Scheme 77)[40c].

VIII. ISOLABLE 2*N*-Ch-*N* CHARGED PERTELLURANES (Ch = Te, *N* > 6)

It has been shown that tellurium can have a maximum coordination number of 8[156]. In recent years, novel hypervalent tellurium compounds with coordination number 7 and 8 have been synthesized. Among them are dialkylthiocarbamate complexes of type TeL_4, where L is a bidentate dialkylthiocarbamate ligand[156], and salts of perfluorinated tellurium anions, TeF_7^- and TeF_8[2, 157, 158].

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