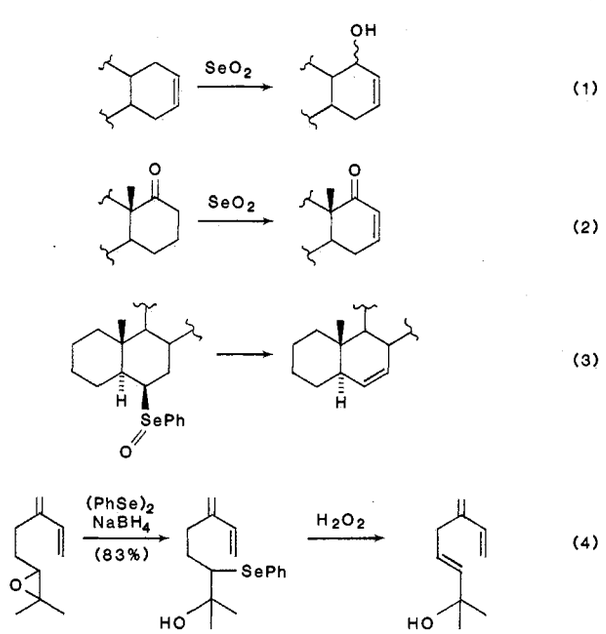
Selenium in Organic Synthesis

DENNIS LIOTTA AND ROBERT MONAHAN III

The introduction, manipulation, and ultimate removal of selenium-containing functional groups allow a variety of synthetically useful processes to be accomplished in high overall yields under mild conditions. In particular, transformations such as allylic oxidations, nucleophile-induced cleavage reactions, regiospecific alkylations, and olefin cofunctionalizations can be readily achieved by taking advantage of selenium's unique properties.

BEFORE 1970, SELENIUM DIOXIDE, A VERSATILE OXIDANT for ketones, alkenes, and other compounds, was the only selenium reagent in common use by organic chemists (Eqs. 1 and 2) (*1*). However, in that year Jones, Mundy, and Whitehouse (*2*) observed that certain steroidal selenoxides rapidly decompose at room temperature to produce the corresponding olefins (Eq. 3; Ph stands for a phenyl group). Three years later a general method for the conversion of epoxides to allylic alcohols that utilizes a selenium nucleophile, sodium phenylselenide, was reported by Sharpless and Lauer (Eq. 4) (*3*). Shortly thereafter many useful chemical reactions that make use of electrophilic selenium reagents were reported.

During this period interest in selenium chemistry was also spurred by developments in related fields. For example, chemists who were working on the design of organic metals recognized that increasing interstack molecular interactions might effectively suppress undesired metal-insulator transitions. Such interactions were reduced by replacing the sulfur atoms in a given organic metal with larger, but electronically similar, selenium atoms (for example, by replacing tetrathiafulvalene with tetraselenafulvalene (*4*). At about the same time, biochemists demonstrated that proteins containing selenium are essential components of a number of bacterial and mammalian enzyme systems (*5*). In fact, the period between 1973 and 1975 represents a turning point in the field of selenium chemistry. During this time the chemists' perception of selenium compounds as useful and interesting materials gradually began to replace their previously held view that such compounds were esoteric substances of limited importance.

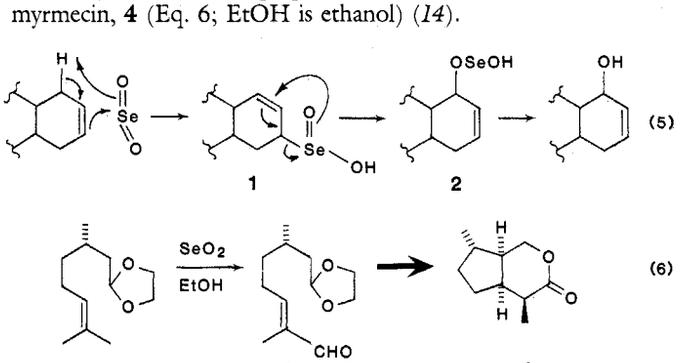


Dennis Liotta is an associate professor of chemistry and Robert Monahan III is a graduate student at Emory University, Atlanta, GA 30322.

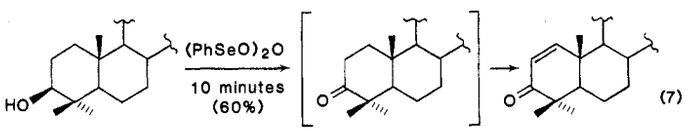
Selenium can be introduced into a variety of substrates, typically as an arylselenenyl group, as either a nucleophile or an electrophile (*6–8*). Once incorporated, it can be used immediately for a desired conversion or, since it is relatively stable, retained and manipulated at a later stage. Although organoselenium groups undergo many chemical reactions, the most widely used has been the selenoxide *syn*-elimination reaction. It has been amply demonstrated that eliminations of selenoxides represent the mildest general olefin-forming reaction known (*9*). The introduction, manipulation, and subsequent removal of selenium-containing species represents a general and useful approach to functional group manipulation.

Selenium(IV) Oxidations

The mechanism of selenium dioxide–mediated allylic oxidation has been thoroughly studied (*10–12*). In nonpolar solvents it is thought that this reaction occurs by an initial ene reaction of SeO_2 with the alkene to form a seleninic acid, **1** (Eq. 5). This intermediate then undergoes a [2,3]sigmatropic rearrangement to form a selenenate, **2**, which readily cleaves to form the corresponding allylic alcohol. This oxygenation has been extensively applied in natural products synthesis (*13*). For example, this reagent was effectively utilized in the preparation of **3**, a precursor to isoirridomyrmecin, **4** (Eq. 6; EtOH is ethanol) (*14*).



Benzeneseleninic anhydride [$(PhSeO)_2O$] has proven to be an especially versatile reagent for the introduction of unsaturation in carbonyl compounds (Eq. 7) (*15–20*). It is also effective for the α-hydroxylation of ketones (Eq. 8) and phenols and the γ-hydroxylation of enones. Alcohols (*21*), hydrazones (*22*), lactams (*23*), and amines (*24*) can be oxidized with $(PhSeO)_2O$, and it also removes thioketals without disturbing oxygen ketals (Eq. 9) (*25*).



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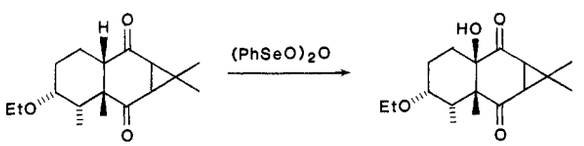

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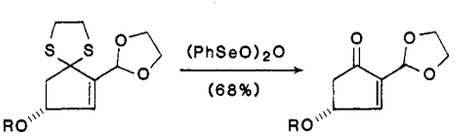

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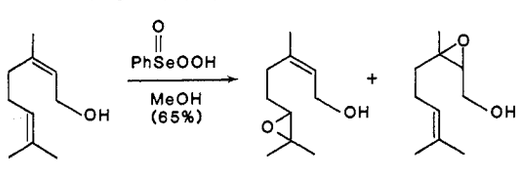
Another selenium(IV) compound, diphenylselenium bis(trifluoroacetate) [$Ph_2Se(O_2CCF_3)_2$], is effective for converting amines to the corresponding imines (*26*). Benzeneperoxyseleninic acid [PhSe(O)OOH], prepared by oxidation of diphenyldiselenide with hydrogen peroxide, has been used for the epoxidation of olefins (Eq. 10; MeOH is methanol) (*27*) and the conversion of ketones to esters and lactones (Eq. 11) (*28*).



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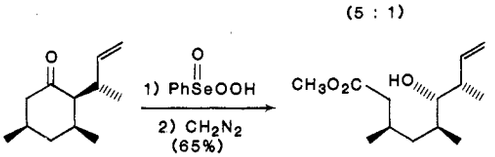

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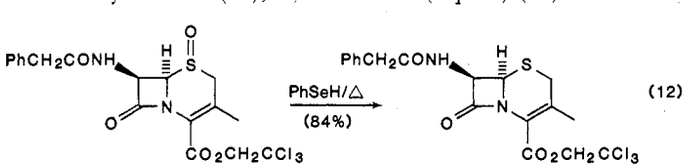
Benzeneselenol Reductions

Benzeneselenol can act as a reducing agent for a variety of functional groups including hydrazones (*29*), azo compounds (*30*), nitro compounds (*31*), α,β-unsaturated carbonyl compounds (*29*), iodomethyl ketones (*32*), and sulfoxides (Eq. 12) (*33*).



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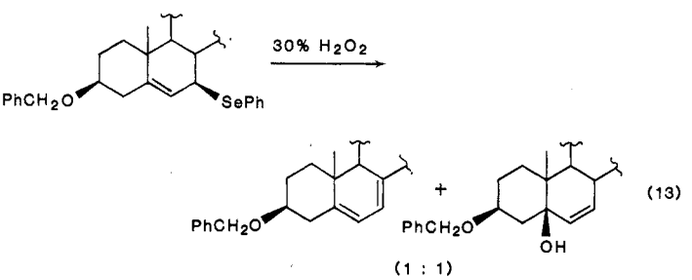
Nucleophilic Selenium

According to the theory of hard and soft acids and bases (*34*), organoselenium anions (RSe^-) are quite soft; that is, they possess low ionization potentials (*35*), and their highest occupied molecular orbitals are polarizable. Thus, selenide anions are predicted to be powerful nucleophiles. They are sufficiently nucleophilic to react with secondary alkyl halides and produce good yields of alkyl aryl selenides (*36*). By contrast, the reaction of carbon nucleophiles with secondary alkyl halides is, typically, an unreliable process.

Arylselenide anions produce aryl allyl selenides when treated with allylic halides. Oxidation produces an allylic selenoxide that can undergo either *syn*-elimination to produce dienes or [2,3]sigmatropic rearrangement to form (after hydrolysis) allylic alcohols (Eq. 13) (*37*). For most systems the latter process is dominant and, as such, represents an alternative to the epoxide-opening oxidative elimination route to allylic alcohols.



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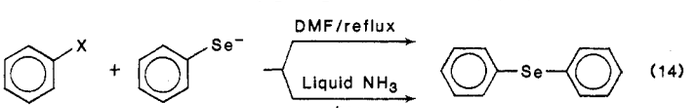
The reaction of arylselenide anion with aryl halides can, depending on the reaction conditions, take two distinct mechanistic pathways: $S_{RN}1$ (photostimulated nucleophilic substitution) (*38*) or nucleophilic addition-elimination (Eq. 14; DMF is dimethylformamide) (*39*). Similarly, unactivated vinyl halides, when treated with arylselenide anion, yield vinyl aryl selenides stereospecifically (Eq. 15; HMPA is hexamethylphosphoric triamide) (*40*).



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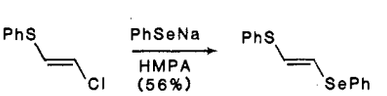

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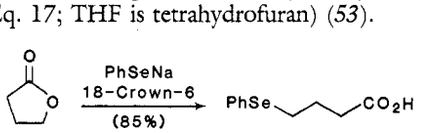
Benzeneselenol and arylselenide anions will add in conjugate fashion to acetylenic and olefinic carbonyl compounds (*41, 42*).

Organoselenium anions are effective reagents for the S_N2-type (carbinol carbon-oxygen) cleavage of methyl, primary alkyl, and some secondary alkyl esters (Eq. 16) (*42–49*). By contrast, alternative reagents are generally useful only with methyl esters (*50–52*). This observation suggests that organoselenium anions should be classified as "super" nucleophiles. These reagents also exhibit a high degree of selectivity with respect to the degree of substitution of the ester at the carbinol carbon; under appropriate conditions methyl esters can be selectively cleaved in the presence of ethyl esters. Additionally, ketones, ethers, and amides are inert to sodium phenylselenide under ester cleavage conditions. For example, **5** was converted to **6** in 73 percent overall yield by the sequence shown below (Eq. 17; THF is tetrahydrofuran) (*53*).



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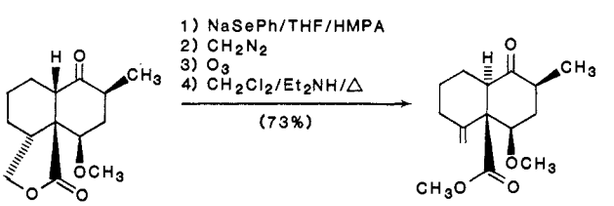
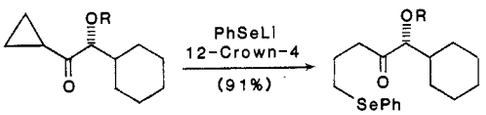


(17)

5 **6**

Sodium and lithium phenylselenide cleave mono-activated cyclopropanes in low to moderate yield (Eq. 18) (*54*). In the case of the lactone **7**, no cyclopropyl cleavage was observed. The acid was obtained in 81 percent yield (Eq. 19) (*55*). Quaternary ammonium salts can be demethylated with sodium phenylselenide (*56*). The reaction is faster and cleaner than the analogous demethylation with thiophenoxide anion.



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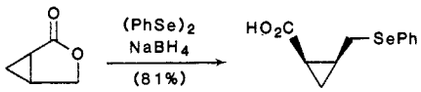

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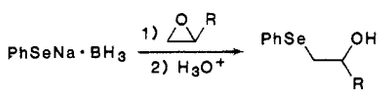
The nucleophilicity of selenide anion is heavily dependent on both the nature of the counterion and the degree of solvation of the anion. For example, the highly ionic sodium phenylselenide is more reactive than the lithium analog (*57*). Phenylselenide anion is most reactive in polar aprotic solvents such as hexamethylphosphoric triamide and dimethylformamide. Crown ethers also increase the reactivity of the anion by coordinating with the metal ion (*58*).

The method of generating these reagents can effect their potency as nucleophiles. The typical procedure for generating sodium phenylselenide ($PhSeSePh/NaBH_4/EtOH$) produces a reagent that can open epoxides in refluxing ethanol (Eq. 20) but that will not cleave esters under the same conditions. Presumably complexation of the anion with borane decreases its nucleophilicity. A suitable reagent for the latter conversion may be prepared by sodium metal or sodium hydride reduction of diphenyldiselenide in tetrahydrofuran (Eqs. 21 and 22) (*59*).



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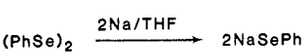

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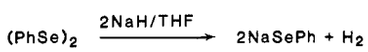

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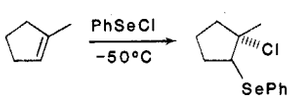
Electrophilic Selenium

The addition of electrophilic selenium reagents to carbon-carbon multiple bonds allows for a number of interesting synthetic transformations. Phenylselenenyl chloride, PhSeCl, adds to variously substituted olefins regioselectively (by Markovnikov addition) to produce β-chloroselenides (Eq. 23) (*60–65*). $PhSeO_2Ph$ (*66*), $PhSeOSnBu_3$ (*67*), PhSeOSePh (*68*), and PhSeBr [with DMSO and $AgPF_6$ (*69*)] have also been added successfully across double bonds.



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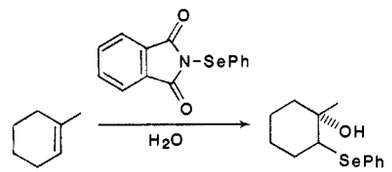
Highly substituted adducts of phenylselenenyl chloride and alkenes are often unstable at room temperature, but they can serve as useful intermediates if the subsequent synthetic manipulations, such as oxidative elimination or dehydrohalogenation, are carried out at temperatures below −50°C. It has been demonstrated that the combination of *N*-phenylselenophthalimide, two or three equivalents of water, and a catalyst results in the regiospecific phenylselenohydroxylation of olefins (Eq. 24) (*70*).

Addition of PhSeCl to allylic alcohols generally occurs with high regio- and stereoselectivity. For example, cyclohexenol (**8**, R = H) reacts with PhSeCl to produce only one of the four possible isomers.



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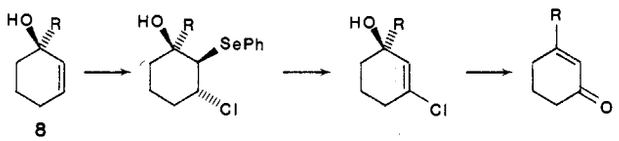
This regioselective addition to allylic alcohols has been used as the key step in a generalized 1,3-enone transposition sequence (Eq. 25) (*71–76*).



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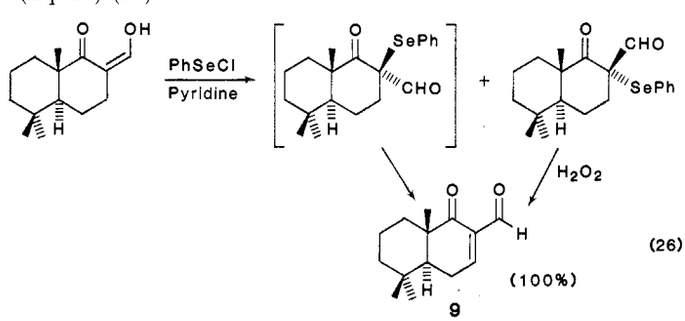
Electrophilic selenium species are soft acids that react with nucleophiles possessing low ionization potentials and low charge densities (*77*). Because of this property, phenylselenenyl chloride and phenylselenenyl bromide undergo facile reaction with ketones (*78*), ketone enolate anions (*79*), ester enolate anions (*80*), nitrile anions (*80, 81*),lactone enolate anions (*82–85*), enol acetates (*86, 87*), and silyl enol ethers (*88*) at the softest carbon center. The resulting α-phenylselenenyl carbonyl compounds can be transformed to the corresponding unsaturated derivatives by oxidative elimination. This method allows for the introduction of unsaturation into a number of carbonyl compounds in yields that are generally higher than those of other available methods.

β-Dicarbonyl compounds react directly and produce, essentially quantitatively, the enedione when treated with a one-to-one mixture of phenylselenenyl chloride and pyridine. This olefination was employed in the synthesis of the insect antifeedant warburganal, **9** (Eq. 26) (*89*).



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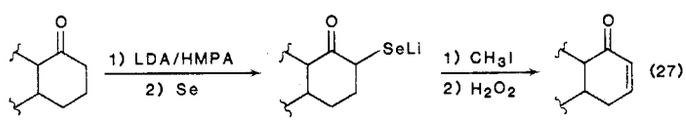
A major drawback to these olefinations is the high cost of the various PhSeX reagents (X = Cl, Br, and SePh). They are oftentimes prohibitively expensive for use in moderate or large-scale reactions. To circumvent this problem, alternative procedures (*90, 91*) were developed for effecting the selenation of carbonyl compounds with PhSeX reagents in yields comparable to that of the previously described reaction of enolates. The key features of these procedures is the reaction of an enolate with elemental selenium to form a selenolate (selenide) anion (Eq. 27; LDA is lithiumdiisopropylamide). The resulting selenolate is alkylated to give the α-alkylselenenyl derivative that can be converted to the unsaturated carbonyl compound by the usual oxidative elimination procedures.



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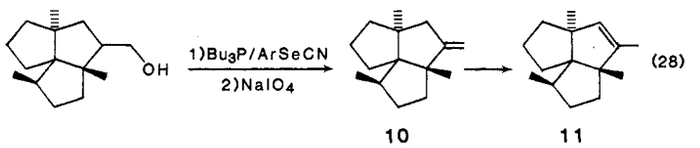
An especially useful selenide-forming method, developed by Grieco *et al.* (*92–94*) has found wide application in natural products synthesis for the preparation of terminal olefins. Reaction of an alcohol with tri(*n*-butyl)phosphine, 2-nitrophenylselenocyanate, and pyridine produces the corresponding selenide in high yield. The active electrophilic species is thought to be $PhSePBu_3^+CN^-$. Nitrophenylselenides are especially attractive since they undergo oxidative elimination at temperatures well below zero. This conversion was used in the preparation of the exocyclic olefin **10**, an intermediate in the synthesis of isocomene, **11** (Eq. 28; Bu stands for a butyl group, and Ar stands for an aryl group) (*95*).



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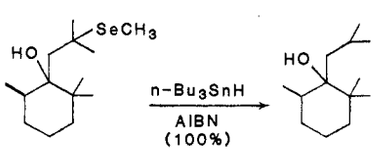
Radical Reactions

Organoselenium compounds undergo a number of synthetically useful radical reactions. Chief among these is the reductive cleavage of carbon-selenium bonds by tributyltin hydride in the presence of a radical initiator, such as azoisobutyronitrile (Eq. 29; AIBN is azoisobutyrlnitrile) (*96*). This allows the selenium moiety to be used (for example, to stabilize a carbanion or open an epoxide) and subsequently removed under effectively neutral conditions. A related carbon-carbon bond-forming process, reductive allylation, can be induced by irradiation or a free-radical initiator (Eq. 30) (*97*).



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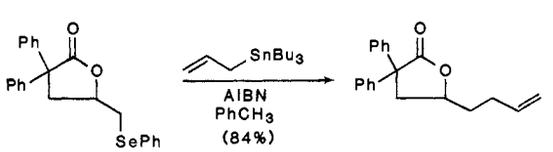

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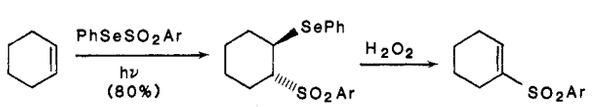
Alkenes can be converted to synthetically useful vinyl sulfonates in high yield by photochemically induced selenosulfonation, followed by oxidative elimination (Eq. 31) (*98*).



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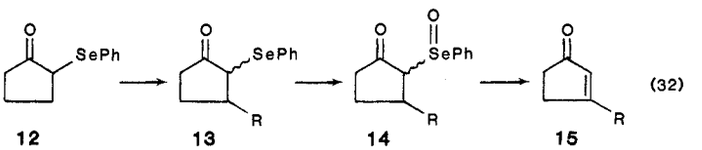
2-Phenylselenenylenones

Recently a number of general methods for converting simple enones into 2-phenylselenenylenones have been reported (*99–102*). These 2-phenylselenenylenones have proved to be versatile synthetic intermediates. Simple procedures for converting compounds such as **12** into a variety of new ketones and enones in high overall yields have been developed (*103*). For example, oxidative elimination of either the *cis* or *trans* isomer of **13** leads to the 3-alkylcycloalkenone **15** in excellent yield, which implies that epimerization at the α-carbon of the intermediate selenoxide **14** occurs prior to elimination (Eq. 32) (*103, 104*). Therefore, both epimers can be simultaneously converted to product without additional synthetic manipulation. Similar protocols have been developed for the efficient conversion of mixtures of **16** and **17** to either the endocyclic enone **18** or the exocyclic enone **19** (Eq. 33) (*105–107*).



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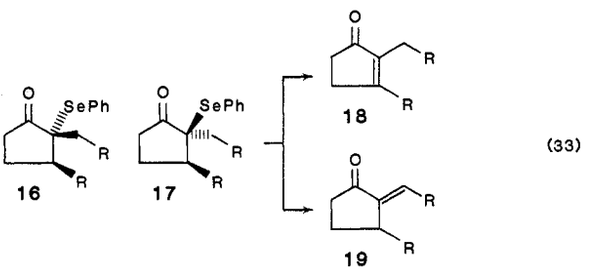

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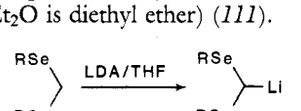
Selenium Stabilized Carbanions

The hydrogen atoms on a carbon atom adjacent to selenium are 10 to 15 pK_a units more acidic than their hydrocarbon counterparts (*108*). This extra stabilization provided by selenium permits the generation of novel carbon nuclephiles. After reaction, the arylselenenyl group can be reductively removed or oxidatively eliminated.

Three general methods exist for the generation of selenium stabilized carbanions: (i) metalation of selenides, selenoxides, and selenones (Eq. 34) (*109*), (ii) lithium-selenium exchange reactions of selenoketals and selenoacetals (Eq. 35) (*110*), and (iii) conjugate addition of nucleophiles to vinyl selenides, selenoxides, and selenones (Eq. 36; Et_2O is diethyl ether) (*111*).



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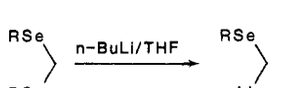

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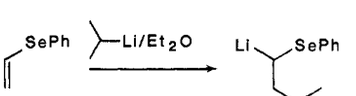

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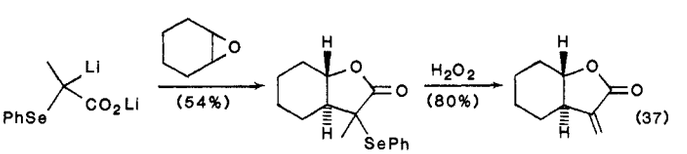
Numerous synthetic applications of selenium-stabilized carbanions can be found in the recent chemical literature (*112–115*). Shown below is a general α-methylene lactone synthesis (Eq. 37) (*116*).

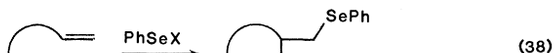


(37)

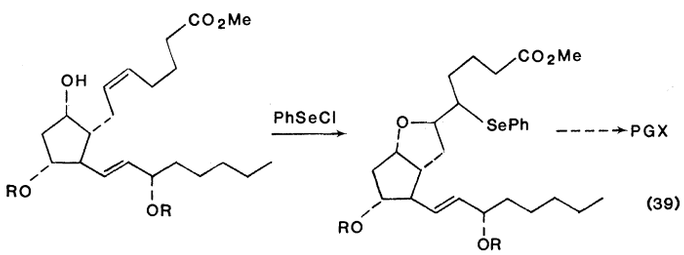
Cyclizations

The selenium-induced cofunctionalization of the double bonds of systems containing internal nucleophiles has been widely studied (Eq. 38; Nu stands for a nucleophilic group) (*117–120*). Use of this method provides easy access to a wide variety of synthetically useful oxygen (*121*) and nitrogen (*122*) heterocycles. For example, the

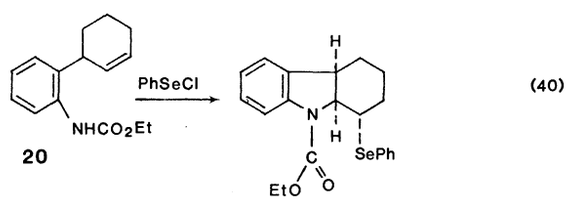
intramolecular phenylselenoetherification reaction, developed by Nicolaou and his co-workers (*123, 124*), has been used in the preparation of prostacyclin analogs (Eq. 39; PGX is prostaglandin PGX). A similar cyclization has been reported with the carbamate **20** (Eq. 40; Et stands for an ethyl group) (*125*). Lactones have also been prepared by this type of reaction (*126*).



(38)

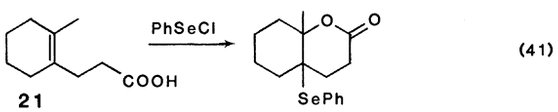


(39)



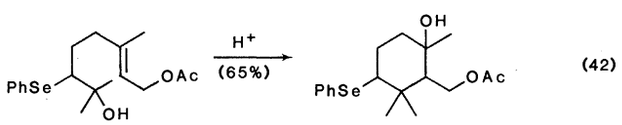
(40)

Although γ-lactones are more stable and form faster than δ-lactones, the phenylselenolactonization of **21** produces none of the former compound (Eq. 41) (*60*). The preference for Markovinkov addition is the overriding factor in predicting product distribution from this reaction.



(41)

Cyclization of β-hydroxyselenides has been used in the biomimetic synthesis of safranal from geranyl acetate (Eq. 42; Ac stands for an acetate group) (*127, 128*).



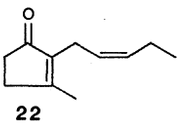
(42)

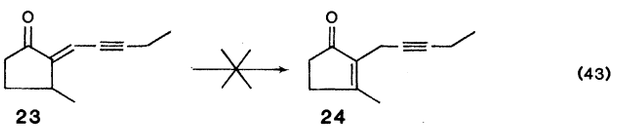
Recently some interesting selenium-mediated carbocyclization reactions involving alkenyl-substituted β-ketoesters were reported (*129–132*).

Phenylselenenyl Rearrangements

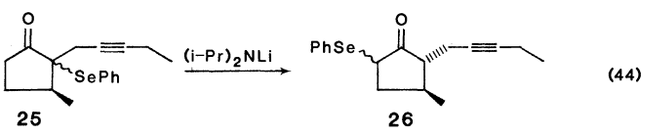
Initial attempts to prepare *cis*-jasmone, **22**, were unsuccessful because it was not possible to isomerize **23** to dehydrojasmone, **24** (Eq. 43) (*133*). However, *cis*-jasmone was finally prepared using an alternative strategy that employed the base-induced [1,3]selenium shift for the conversion of **25** to **26** (Eq. 44; *i*-Pr stands for an isopropyl group).

Mechanistically, this reaction consists of a series of intermolecular phenylselenenyl and proton exchanges for which the driving force is the production of increasingly stable enolate ions. This [1,3]selenium shift reaction allows compounds such as **16**, **17**, and **26** to be regiospecifically alkylated in the α′-position (*134*). Compound **27** has been isomerized to **28** and, since the phenylselenenyl group stabilizes an adjacent negative charge, **28** can be regiospecifically alkylated at C-2 (Eq. 45) instead of at the usually preferred C-4 of the unsubstituted ketone.

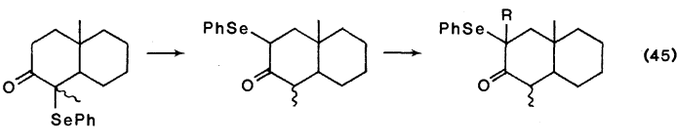




(43)



(44)



(45)

Conclusion

In this article, we have described a number of synthetically useful processes that can be accomplished in high overall yield and under very mild conditions. We have focused on some selective aspects of organoselenium methodology that provide significant advantages over existing methodologies and that depend on the unique properties of selenium.

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