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N-PHENYLSELENOPHTHALIMIDE (NPSP)

A VALUABLE SELENENYLATING AGENT

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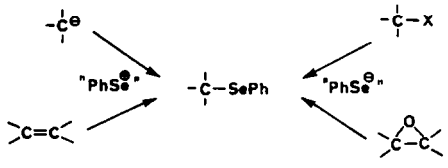
Abstract—The phenylseleno group (PhSe) has evolved in recent years as a very useful and versatile functionality. Its facile introduction into organic molecules and its subsequent oxidative or reductive removal, has allowed many important synthetic transformations.[1-7] Due to the fact that, similarly to halogens, it can exist either as an electrophilic species ($PhSe^+$) or as a nucleophilic one ($PhSe^-$), this group can be introduced either via nucleophilic substrates (e.g. carbanions, olefins), or via electrophilic ones (e.g. epoxides, halides), as illustrated in Scheme 1. Another valuable aspect of the phenylseleno group is that it can be readily oxidized to the corresponding selenoxide (PhSe(O)—), which undergoes β-hydrogen abstraction and *syn*-elimination to form olefins, under relatively mild conditions (Scheme 2(a)). Furthermore, this group can be substituted with hydrogen, upon the action of an appropriate reducing agent (Scheme 2(b)).

The great synthetic utility of the phenylseleno group is apparent from its extensive utilization in numerous natural products syntheses,[1] as well as many other synthetic studies.[2-7]

REAGENTS FOR THE INTRODUCTION OF THE PhSe GROUP

The most common sources of the PhSe group are: phenylselenenyl chloride (PhSeCl), phenylselenenyl bromide (PhSeBr), diphenyl diselenide (PhSeSePh) and phenylselenocyanate (PhSeCN). These reagents are used directly, as carriers of the electrophilic phenylseleno species ($PhSe^+$), or they are combined with other reagents, to generate *in situ* new electrophilic or nucelophilic selenenylating agents. Despite their effectiveness and versatility, however, these organoselenium reagents are often undesirable and inconvenient to use. Their main drawbacks arise from their rather limited stability, the release of malodorous and highly toxic vapors, and the formation of various reactive by-products, during certain reactions (e.g. HCl from PhSeCl).

In search of a better selenenylating agent, we recently[8,9] examined the properties of two novel carriers of the phenylseleno group, namely N-phenylselenophthalimide (1, NPSP) and N-phenylselenosuccinimide (2, NPSS). These compounds were expected to be quite stable when pure, but reactive in the proper environment, as deduced from other similarly structured reagents (e.g. N-bromosuccinimide (NBS), N-phenylthiophthalimide). Indeed, NPSP, a previously unknown compound, but readily obtainable from potassium phthalimide and phenylselenenyl chloride (Scheme 3(a)), was found to be an odorless and colorless crystalline solid, stable indefinitely when stored under argon at 25°. Also, NPSS, a compound orginally reported by Sharpless and co-workers[10] and prepared from N-chlorosuccinimide and phenyl allyl selenide



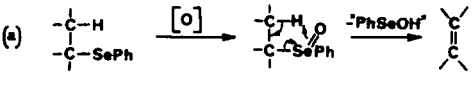
Scheme 1. Introduction of phenylseleno group.

(Scheme 3(b)), was found to be relatively stable at −20° under argon, but decomposed slowly in air, at 25°. The chemistry of NPSP and NPSS, turned out to be quite similar and in some respects different from the chemistry of other selenenylating agents. Between the two, however, NPSP is clearly the reagent of choice, due to its easier preparation and higher stability. As a result of its unique physical and chemical properties, NPSP has now become a valuable selenenylating agent, and is also commercially available.[11]

The chemistry of NPSP is the subject of this article, which gives a full account of the results obtained in our laboratories, including some new findings.

A. *Reactions with olefinic substrates*

One of the most important properties of NPSP is its facile reaction with olefins to give various addition products, bearing the PhSe group. We have found that such transformations proceed with higher conversions and better yields, when they are performed under



Scheme 2. (a) Oxidative and (b) reductive removal of the phenylseleno group.

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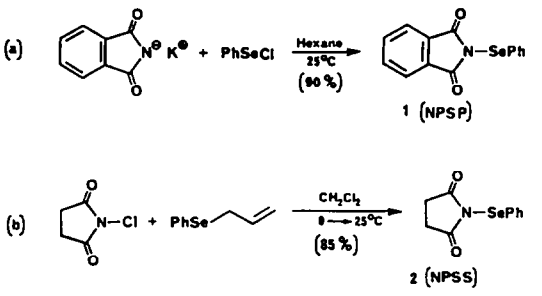
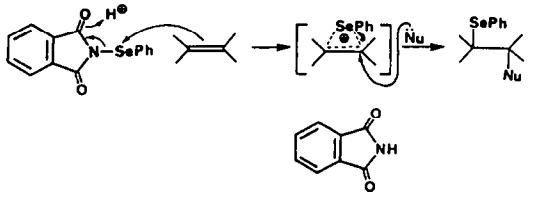


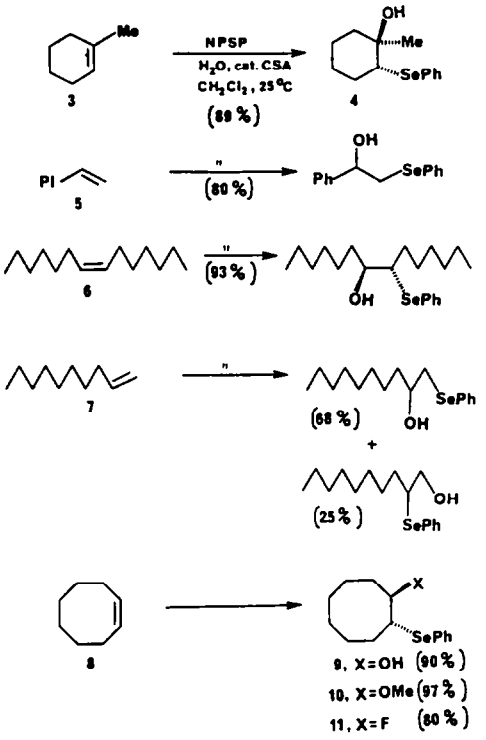
Scheme 3. Preparation of: (a) N-phenylselenophthalimide (NPSP)[9] and (b) N-phenylselenosuccinimide (NPSS).[10]

mildly acidic conditions. In practice, this is achieved by adding to the reaction mixture, catalytic amounts of an acid, such as *p*-toluenesulfonic acid (TsOH), camphorsulfonic acid (CSA) or pyridinium-*p*-toluenesulfonate (PPTS). The beneficial role of the acid catalyst presumably relies on facilitating the electrophilic attack from the olefin to NPSP, as illustrated in Scheme 4. This process, presumably results in the initial formation of a selenonium intermediate, which is followed by intermolecular or intramolecular capture of this species by a nucleophile (Nu), as shown in Scheme 4. The lack of any interference from the rather inert and non-nucleophilic phthalimide residue of NPSP, allows the formation of various types of products in this operation, which depends mainly on the nature and origin of the participating nucleophile (Nu). The following are among the possibilities we have examined:

1. *Hydroxyselenation of olefins.* Addition of the elements of "PhSe—OH" to olefins, has been previously achieved by several methods, including: the use of *in situ* prepared $PhSeOCOCF_3$[12] or PhSeOAc[13] followed by hydrolysis, the use of "PhSeOH" generated *in situ* from $PhSeO_2H$ and PhSeSePh[14] or H_3PO_2,[15] the use of PhSeCN and water in the presence of a copper catalyst,[16] and the reaction with PhSeCl in an aqueous medium.[17] The same transformation, however, was found to proceed in high yields by using NPSP and 2–3 equiv of water in the presence of an acid catalyst (TsOH, CSA or PPTS), in methylene chloride at 25°. The remarkable regioselectivity of this reaction is illustrated in the conversion of **3** to **4**. Olefins **5–8** react similarly. As it is evident from these results, the reaction follows Markovnikov's rule, i.e. it gives preferentially the *trans*-addition product having the PhSe group on the less-substituted carbon. Further elaboration of the *β*-hydroxyselenides obtained in this reaction, leads to the formation of various selenium-free products, such as allylic alcohols, olefins, epoxides, etc. This methodology has already been applied in total synthesis.[18]



Scheme 4. Mechanism of the acid-catalyzed reaction of NPSP with olefins.

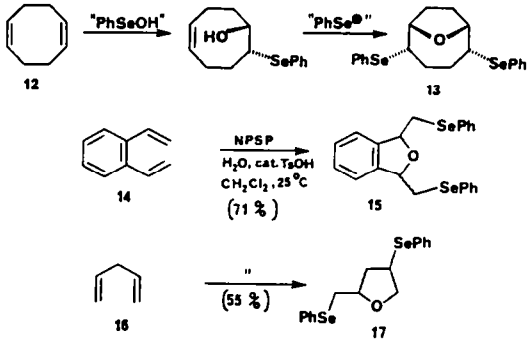


2. *Alkoxyselenation of olefins.* Reactions of an olefin with PhSeCl or PhSeBr, in the presence of an alcohol, gives *β*-alkoxyselenides, which can then be converted to allylic ethers via oxidative elimination of the PhSe group.[19] This is a very useful synthetic transformation, that has been utilized in several occasions.[20] Another method for the addition of the elements of "PhSe—OR" to olefins involves the use of PhSeCN and a copper catalyst, in an alcohol solution.[21] NPSP, however, was found to be an excellent alternative for this reaction. Thus, treatment of **8** with NPSP (1.1 equiv), methanol (3 equiv) and catalytic amounts of CSA in methylene chloride, gave after stirring for 20 hr at 25°, a 97% yield of *β*-methoxy selenide **10**. An application of this reaction was recently reported by Smith *et al.*[22]

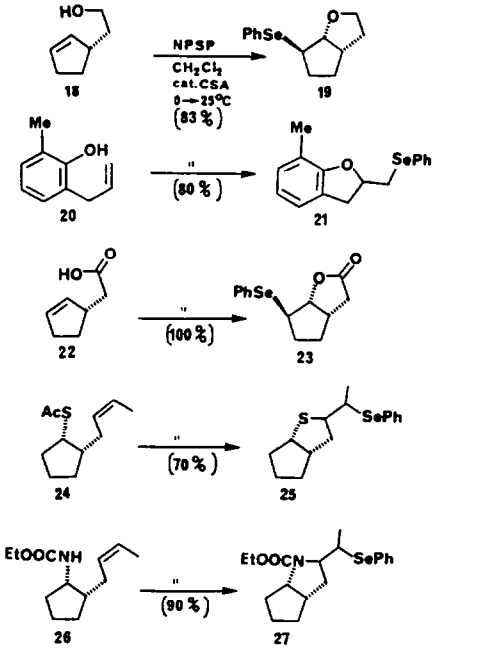
3. *Fluoroselenation of olefins.* In contrast to PhSeCl and PhSeBr, which are readily and commercially available, and to PhSeI, which can be formed *in situ* from PhSeSePh and iodine,[23] the fluoro derivative (PhSeF) is not known. Nevertheless, we have found that the combination of NPSP and HF · pyr complex, can be used to obtain the expected addition product of "PhSeF" to olefins. Thus, cyclooctene (**8**) gave the labile *β*-fluoro-selenide **11** in 80% yield.

4. *Conversion of diolefins to cyclic ethers.* The reaction of "PhSeOH" with substrates having two strategically located olefinic bonds, was earlier found[24] to produce cyclic ethers bearing two PhSe groups. Similar findings were subsequently reported by Uemura.[25] As illustrated with the conversion of **12** to **13**, such transformations proceed via addition of 1 equiv of "PhSeOH" across one olefinic bond, followed by subsequent Se-induced cyclization involving the newly introduced OH group and the second olefinic bond.

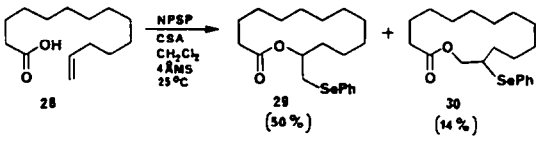
The NPSP–H_2O–acid catalyst system employed in these reactions was anticipated to be as effective as other sources of "PhSeOH", provided that the amounts of H_2O used, were reduced. Indeed, **12** could be converted to **13** in 97% yield, upon treatment with 1.25 equiv of NPSP, 0.75 equiv of H_2O and catalytic amounts of TsOH, in CH_2Cl_2 at 25°. Under similar conditions, **14** gave **15** in 71% yield, while **16** gave **17** in 55% yield.



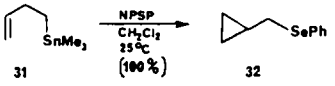
5. Cyclization of unsaturated substrates containing internal nucleophiles. Earlier work in these and other laboratories has demonstrated the power and potential of organoselenium-induced cyclizations.[26] Thus, treatment of unsaturated alcohols,[27] carboxylic acids,[28] thio-compounds[29] or urethanes[30] with phenylselenenyl chloride or bromide, leads, respectively to cyclic ethers, lactones, cyclic thioethers and cyclic amines. As it turned out, in certain cases, NPSP is a superior reagent for these cyclizations, presumably, due to the lack of any reactivity by the phthalimide residue of NPSP. Representative examples with various types of substrates (**18, 20, 22, 24, 26**) are shown below. In all cases, the use of an acid catalyst enhances the yields substantially. The NPSP-mediated cyclizations were recently utilized by other workers for the synthesis of butanolides,[31] cyclic vinyl ethers,[32] spiroketals,[33] carbohydrates[34] and cyclic amines.[35]



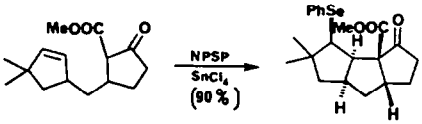
6. Formation of macrolides. Particularly noteworthy is the ability of NPSP to mediate the macrolactonization of long-chain unsaturated acids, forming macrolides in good yields. Thus, treatment of **28** with NPSP (10 equiv), CSA (1.0 equiv) and 4 Å MS as water scavenger, in CH_2Cl_2 at 25°, gave **29** in 50% yield, accompanied by its regioisomer **30** in 14% yield. In a similar fashion the corresponding 16-membered lactone was prepared in 54% yield. These macrocyclizations, however, are not observed with PhSeCl, PhSeBr or PhSeOH, which add readily across the double bond.



7. Carbocyclizations. We have observed an interesting carbocyclization mediated by NPSP, namely the conversion of the unsaturated organotin derivative **31** to cyclopropane **32**. Furthermore, it was recently shown by Ley and co-workers[32,36] that NPSP is an



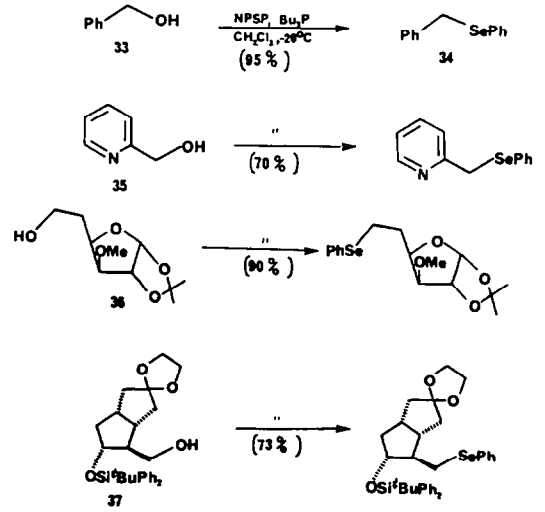
excellent reagent for the formation of carbocyclic rings from appropriately substituted unsaturated precursors. An illustrative example, taken from the application of this methodology to the synthesis of hirsutene,[36] is shown in Scheme 5.



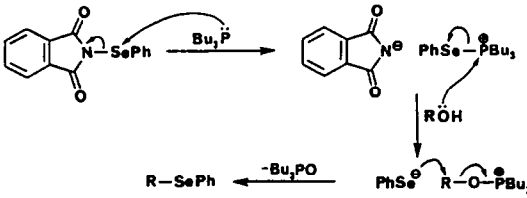
Scheme 5. An NPSP-mediated carbocyclization.

B. *Reactions with alcohols*

The direct formation of selenides from alcohols, by using phenyl- or *o*-nitrophenyl-selenocyanate (ArSeCN) and tri-n-butylphosphine (Bu_3P), introduced by Grieco *et al.*,[37] has been recognized as a very useful synthetic method.[38] This transformation allows



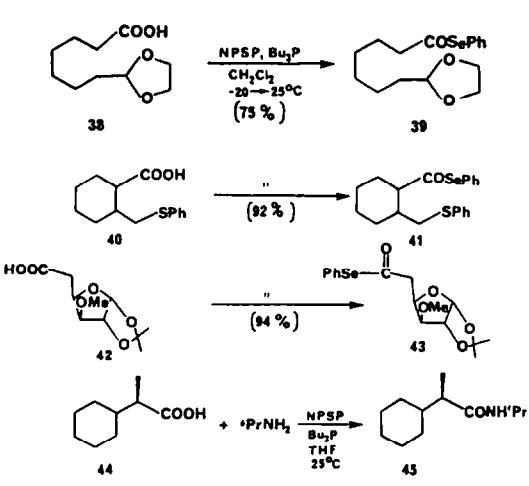
the formation of an olefinic bond or a saturated carbon, at the site of the alcohol, under relatively mild conditions. In collaboration with Professor Grieco, we have employed the NPSP–Bu_3P system in this reaction, with excellent results.[39] Thus, benzyl alcohol (**33**) was converted to **34** in 95% yield, upon treatment with NPSP and Bu_3P in CH_2Cl_2 (or THF) at $-20°$. Similar reactions with **35–37** gave the expected phenyl selenides in high yields. A major advantage of the NPSP–Bu_3P system is the availability, stability and convenient handling of NPSP as opposed to PhSeCN, which is hard to prepare, strongly malodorous and quite unstable. The NPSP–Bu_3P method was recently applied by Ley *et al.*[40] in an approach to clerodane diterpenes. A rationalization of this transformation, similar to that proposed by Grieco *et al.*[37] for the ArSeCN–Bu_3P system is shown in Scheme 6. Presumably, the phosphine mediates both the generation of a nucleophilic phenylseleno-species ($PhSe^-$) and the conversion of the OH to a good leaving group.



Scheme 6. Presumed mechanism of the conversion of alcohols to selenides with NPSP–Bu_3P.

C. *Reactions with carboxylic acids*

Application of the NPSP–Bu_3P system to carboxylic acids, gives selenol esters in good to excellent yields.[39] Representative examples are the conversions of **38** to **39** (75% yield), of **40** to **41** (92% yield) and of **42** to **43** (94% yield). Similar results were previously observed by Grieco *et al.* with the ArSeCN–Bu_3P system.[41] The selenol esters obtained from these reactions are potentially useful intermediates for the formation of various derivatives including esters, amides and lactones. In fact, when the reaction is performed in the presence of an amine, carboxylic acids are directly converted to the corresponding amides[39] (e.g. **44** → **45**).



CONCLUSION

N-Phenylselenophthalimide (NPSP) was developed to be a valuable reagent for the introduction of the PhSe group to various substrates. This odorless and stable reagent is a good alternative to other PhSe—carriers in many reactions, such as the hydroxyselenation and alkoxyselenation of olefins, the conversion of diolefins to cyclic ethers, various selenium-induced cyclizations, the conversion of alcohols to phenylselenides and the conversion of carboxylic acids to selenol esters. Furthermore, this reagent is unique in effecting the fluoroselenation of olefins, the macrolactonization of unsaturated carboxylic acids, as well as various selenium-induced carbocyclizations. It is therefore, expected to find wide application in organic synthesis.

EXPERIMENTAL

General. All reactions were carried out under an argon atmosphere, using freshly distilled solvents under anhydrous conditons unless otherwise stated. Methylene chloride, hexane and toluene were distilled from calcium hydride, while benzene and tetrahydrofuran were distilled from sodium-benzophenone, in a N_2 atmosphere. Reaction temps were measured externally.

Analytical TLC, for monitoring reactions and measuring R_f values, was carried out on 0.25 mm E. Merck precoated silica gel plates (60F-254), using UV light and/or 7% polyphosphomolybdic acid in ethanol followed by heating on a hot plate, as visualizing agents. Preparative TLC was performed on 0.25 or 0.5 mm × 20 cm × 20 cm E. Merck precoated silica gel plates (60F-254). Preparative flash chromatography was performed using E. Merck 230–400 mesh silica gel.

M.ps were recorded on a Thomas–Hoover Unimelt apparatus and are uncorrected.

^{1}H-NMR spectra were recorded on a Bruker 250 or 360 MHz spectrometer, using $CDCl_3$ as solvent, unless otherwise indicated. Chemical shifts are reported in ppm from Me_4Si (δ values). The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublets of triplets; tt, triplet of triplets; m, multiplet; b, broad. Coupling constants (J) are reported in Hz. IR spectra were obtained with a Perkin–Elmer Model 237 spectrophotometer, either as neat liquid films or in solutions in CCl_4 or $CHCl_3$. Peaks are reported as ν_{max} in cm^{-1}. Only the strongest and/or structurally most significant peaks are given, using the following abbreviations: vs, very strong; s, strong; m, medium; w, weak; b, broad. Mass spectra were provided by the Mass Spectrometry Center of the Department of Chemistry, University of Pennsylvania, and are reported as *m/e*, with the relative intensity as a percentage of the base peak. Only the strongest and/or most significant peaks are reported. Exact masses, determined by high resolution MS and microanalyses, performed by the Galbraith Laboratories, Knoxville, Tennessee, were within acceptable limits.

Preparation of N-*phenylselenophthalimide* (NPSP, **1**)

In a 250 ml RB 3-necked flask equipped with an argon inlet, were placed potassium phthalimide (3.00 g, 16.2 mmol) and phenylselenenyl chloride (3.72 g, 19.0 mmol). The flask was connected to a vacuum line and after several evacuations and purges with argon, dry and degassed hexane (15 ml) was added. The mixture was vigorously stirred at 25° for 2 hr (all PhSeCl dissolves). Dry CH_2Cl_2 (100 ml) was then added and the pale red solution was filtered to remove solid materials. The solution was concentrated on a rotary evaporator to *ca* 20 ml and was diluted with dry hexane (80 ml). The resulting ppt was collected by filtration and washed thoroughly with dry

hexane. Obtained was 87% yield (4.22 g) of NPSP (**1**) as pale yellow crystals. This product was sufficiently pure for use. An analytical sample was obtained by recrystallization from CH_2Cl_2–ether (or hexane) as colorless crystals.

Compound **1**: colorless crystals; m.p. 171–175° (dec); IR ($CHCl_3$, ν_{max}, cm^{-1}): 3010(w), 1780(m), 1730(s), 1620(w), 1480 (m), 1472 (m), 1440 (m), 1350 (m), 1280 (s), 1175 (m), 1060 (s), 1040 (w), 1000 (w), 860 (m); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 7.20–7.00 (m, aromatic); mass spectrum *m/e* (rel. intensity): 303.0 (M^+, ^{80}Se, 32.7), 299.0 (8.1), 158.0 (12.0), 157.0 ($Ph^{80}Se$, 13.6), 156.0 (11.3), 155.0 (10.0), 147.0 (base peak, M^+ – PhSe), 130.1 (10.0), 104.0 (33.0), 103.0 (28.1), 78.0 (27.8), 77.0 (25.1), 76.0 (98.1). Exact mass *m/e*: calc for $C_{14}H_9NO_2{}^{80}Se$: 302.9798. Found: 302.9798. (Found: C, 55.41; H, 2.88; N, 4.51; Se, 25.83. Calc for $C_{14}H_9NO_2Se$: C, 55.64; H, 3.00; N, 4.64; Se, 26.13%.)

Hydroxyselenation of olefins

Preparation of 1-methyl-2-phenylselenyl)cyclohexan-1-ol (**4**): A soln of 1-methyl cyclohexene (50 mg, 0.51 mmol) in CH_2Cl_2 (2.2 ml) was treated with water (28 mg, 1.56 mmol), NPSP (200 mg, 0.66 mmol) and camphorsulfonic acid (12 mg, 0.05 mmol). The reaction was sealed under an argon atmosphere and stirred for 20 hr at 25°. Petroleum ether was then added and the mixture was directly flash chromatographed (silica, petroleum ether and ether) to give 89% yield (123 mg) of **4**. Similar results were obtained by using *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate as the acid catalyst.

Compound **4**: oil; R_f = 0.16 (silica, CH_2Cl_2); IR (neat, ν_{max}, cm^{-1}): 3300 (m, OH), 3050 (w, ArC—H), 2950 (s), 2870 (m), 1570 (m), 1474 (s), 1430 (s), 1370 (m), 1320 (m), 1200 (m), 1125 (s), 1030 (m), 970 (m), 925 (m); ^{1}H-NMR (360 MHz, $CDCl_3$, δ): 1.30 (s, 3H, C$\underline{H}_3$), 1.19–1.58 (m, 3H, C$\underline{H}_2$), 1.72 (m, 3H, C$\underline{H}_2$), 1.90 (d, J = 10.0 Hz, 1H, C$\underline{H}$H), 2.18 (bd, J = 10 Hz, 1H, C$\underline{H}$H), 2.60 (s, 1H, O$\underline{H}$), 3.20 (dd, J = 10.0, 2.0 Hz, 1H, C$\underline{H}$SePh), 7.25 (m, 3H, aromatic), 7.58 (m, 2H, aromatic); mass spectrum *m/e* (rel. intensity): 270.2 (M^+, ^{80}Se, 19.0), 268.2 (M^+, ^{78}Se, 9.0), 159.0 (34.9), 156.0 (18.0), 113.1 (73.4), 95.1 (base peak); exact mass *m/e*: calc for $C_{13}H_{18}{}^{80}OSe$: 270.0523, found: 270.0517.

Alkoxyselenation of olefins

Preparation of 1-methoxy-2-phenylselenylcyclooctane (**10**): To a soln of **8** (55 mg, 0.50 mmol) in dry CH_2Cl_2 (2 ml), were added anhyd MeOH (60 μl, 48 mg, 1.50 mmol), camphorsulfonic acid (12 mg, 0.05 mmol) and NPSP (166 mg, 0.55 mmol). The mixture was stirred under argon for 20 hr and then it was directly flash chromatographed (silica, 10% ether in petroleum ether) to give 97% yield (144 mg) of **10**.

Compound **10**: colorless oil; R_f = 0.43 (silica, 10% ether in petroleum ether); IR (neat, ν_{max}, cm^{-1}): 3080 and 3070 (m, aromatic H), 2930 (s), 2860 (s), 2830 (s), 1585 (s), 1480 (s), 1470 (s), 1440 (s), 1100 (s), 1030 (s), 740 (s), 700 (s); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 2.03–1.36 (m, 12H, C$\underline{H}_2$), 3.31 (s, 3H, OC$\underline{H}_3$), 3.55 (dt, J = 9.4 and 2.5 Hz, 1H, C$\underline{H}$OMe), 3.40 (dt, J = 6.4 and 2.0 Hz, 1H, C$\underline{H}$SePh), 7.25 (m, 3H, aromatic), 7.58 (m, 2H, aromatic); mass spectrum *m/e* (rel. intensity): 298.1 (M^+, ^{80}Se, 13), 296.1 (M^+, ^{78}Se, 7), 141.0 (33), 109.0 (base peak), 71.0 (34), 67.0 (85); exact mass *m/e*: calc for $C_{15}H_{22}O^{80}Se$: 298.0836, found: 298.0822.

Fluoroselenation of olefins

Preparation of 1-fluoro-2-phenylselenylcyclooctane (**11**): In a plastic (scintillation) vial was placed a soln of **8** (55 mg, 0.50 mmol) and NPSP (226 mg, 0.75 mmol) in dry CH_2Cl_2 (2 ml). The vial was sealed under argon and cooled to 0°. To this soln was added dropwise via a plastic syringe, commercially available (Aldrich) HF·Py (0.1 ml) and the mixture was allowed to warm to 25°. After stirring for 10 min TLC analysis indicated complete conversion. The mixture was then poured into a separatory funnel loaded with ether (50 ml) and 2.5% KOH aq (5 ml). Extraction, washing with water and sat. Na_2CO_3 aq, drying over $MgSO_4$, and evaporation of the solvents gave the crude product, which was purified by flash column chromatography (silica, 3% ether in petroleum ether), affording pure **11** (85 mg, 80%).

Compound **11**: colorless oil; R_f = 0.40 (silica, 3% ether in petroleum ether); IR (neat, ν_{max}, cm^{-1}): 3080 and 3040 (m, aromatic H), 2930 (s), 2860 (s), 1585 (s), 1480 (s), 1470 (s), 1440 (s), 1025 (s), 740 (s), 690 (s), 675 (s, C—F); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 2.1–1.10 (m, 12H, CH_2), 3.55 (m, 1H, C$\underline{H}$SePh), 4.74 (ddt, $J_{H,F}$ = 46.4 Hz, J = 9.3 and 2.6 Hz, 1H, C$\underline{H}$F), 7.25 (m, 3H, aromatic), 7.59 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 286.1 (M^+, ^{80}Se, 16), 284.1 (M^+, ^{78}Se, 8), 244.0 (15), 242 (8), 186.0 (29), 184.0 (29), 184.0 (15), 157.9 (base peak), 155.9 (51), 109.1 (68), 87.0 (54); exact mass *m/e*: calc for $C_{14}H_{19}{}^{80}SeF$: 286.0636, found: 286.0625.

Conversion of diolefins to cyclic ethers

Preparation of **13**: To a stirred soln of **12** (2.8 mg, 0.25 mmol) in CH_2Cl_2 (0.2 ml) were added NPSP (200 mg, 0.66 mmol), water (7 mg, 0.38 mmol) and *p*-toluenesulfonic acid (5 mg, 0.025 mmol). The reaction was sealed under argon and stirred at 25° for 18 hr. Flash chromatography (silica, CH_2Cl_2) of the mixture, yielded 97% (96 mg) of the diseleno ether **13**.

Compound **13**: white solid; m.p. 95.5–96°; R_f = 0.55 (silica, methylene chloride); IR ($CHCl_3$, ν_{max}, cm^{-1}): 3070 (m, aromatic, H), 3020 (s, aromatic, H), 2930 (m), 1580 (m), 1475 (s), 1440 (m), 1360 (w), 1320 (w), 1215 (s), 1040 (m), 900 (m); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 2.08 (m, C$\underline{H}_2$, 8H), 3.67 (m, 2H, C$\underline{H}$SePh), 4.62 (m, 2H, OC$\underline{H}$), 7.28 (m, 6H, aromatic), 7.55 (m, 4H, aromatic); mass spectrum, *m/e* (rel. intensity): 438.1 (M^+, ^{80}Se, ^{80}Se, 11.1), 436.1 (M^+, ^{80}Se, ^{78}Se, 11.1), 281.1 (34.2), 279.1 (16.8), 170.9 (10.6), 156.9 (27.9), 155.0 (14.1), 124.1 (46.8), 105.1 (36.2), 95.1 (base peak). (Found: C, 55.28; H, 5.18. Calc for $C_{20}H_{22}OSe_2$: C, 55.05; H, 5.08%.)

Cyclization of unsaturated alcohols (phenylselenoetherification)

Preparation of 8-exo-(phenylseleno)-2-oxa-bicyclo[3.3.0]octane (**19**): To a soln of **18** (45 mg, 0.40 mmol) in CH_2Cl_2 (2.5 ml) stirred under argon, was added camphorsulfonic acid (9.3 mg, 0.04 mmol). The mixture was cooled to 0° and after adding NPSP (152 mg, 0.50 mmol), it was allowed to reach 25° over a period of 30 min. Direct flash chromatography of the mixture (silica, CH_2Cl_2) gave **19** in 83% yield (89 mg).

Compound **19**: yellow oil; R_f = 0.42 (silica, CH_2Cl_2); IR (neat, ν_{max}, cm^{-1}): 3030 (s), 2929 (s), 2841 (s), 1570 (m), 1471 (m), 1433 (w), 1290 (m), 1212 (w), 1064 (m), 1038 (m), 1022 (m), 998 (m), 917 (w), 898 (w); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 1.33–1.80 (m, 3H), 2.05 (m, 3H), 2.80 (m, 1H), 3.66 (m, 3H, OC$\underline{H}_2$, C$\underline{H}$Se), 4.31 (d, J = 7.0 Hz, 1H, OC$\underline{H}$—), 7.15 (m, 3H, aromatic), 7.33 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 268.0 (M^+, 37.0), 157.0 (PhSe, 17.0), 111.0 (M^+ – PhSe, 38), 110.0 (41.1), 93.0 (94.1), 77.0 (46.2), 55.1 (base peak). (Found: C, 58.47; H, 6.13. Calc for $C_{13}H_{16}OSe$: C, 58.20; H, 5.97%.)

Cyclization of unsaturated carboxylic acids (phenylselenolactonization)

Preparation of bicyclo[3.3.0]-2-oxa-3-keto-8(phenylselenyl)octane (**23**): A soln of **22** (55 mg, 0.44 mmol) in CH_2Cl_2 (3 ml), cooled to 0°, was treated with camphorsulfonic acid (10 mg, 0.40 mmol) and NPSP (173 mg, 0.57 mmol). The mixture was allowed to warm to 25° over 1 hr, at which time TLC indicated completion of the reaction. Flash chromatography of the mixture (silica, CH_2Cl_2) gave 100% (124 mg) yield of **23**.

Compound **23**: yellow oil: R_f = 0.37 (silica, CH_2Cl_2); IR (neat, ν_{max}, cm^{-1}): 3057 (m), 2985 (s), 1770 (s, C=O), 1563 (m), 1471 (m), 1429 (m), 1312 (m), 1295 (m), 1163 (m), 1002 (m), 971 (w), 951 (m), 876 (m), 738 (m), 690 (w); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 1.50 (m, 1H), 1.77 (m, 1H), 2.20 (m, 3H), 2.72 (dd, J = 17.0, 10.0 Hz), 3.00 (m, 1H), 3.85 (m, 1H, C$\underline{H}$Se), 4.84 (d, J = 7.0 Hz, 1H, C$\underline{H}$O), 7.30 (m, 3H, aromatic), 7.55 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 282.0 (M^+, ^{80}Se, 73.0), 158.0 (PhSeH, base peak), 125.0 (M^+ – PhSe, 25), 107.0 (38.0). (Found: C, 55.54; H, 5.21, Se, 28.58. Calc for $C_{13}H_{14}O_2Se$: C, 55.32; H, 5.00; Se, 28.34%.)

Cyclization of unsaturated thioacetates (phenylselenothioetherification)

Preparation of 3 - [(1' - *phenylseleno)ethyl*] - 2 - *thia* - *bicyclo*[3.3.0]*octane* (**25**): To a soln of **24** (147 mg, 0.80 mmol) in CH_2Cl_2 (2 ml), stirred at 0° under argon, were added camphorsulfonic acid (19.0 mg, 0.08 mmol) and NPSP (314 mg, 1.04 mmol). After stirring for 10 hr, followed by TLC, the mixture was directly flash chromatographed (silica, CH_2Cl_2) to give 70% yield (158 mg) of **25**.

Compound **25**: yellow oil, $R_f = 0.37$ (silica, methylene chloride); IR (neat, ν_{max}, cm^{-1}): 3057 (w), 2985 (s), 1770 (s, C=O), 1563 (m), 1471 (m), 1429 (m), 1312 (m), 1295–1163 (m), 1002 (m), 971 (m), 876 (m), 738 (m); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 1.50 (m, 1H), 1.77 (m, 1H), 2.20 (m, 3H), 2.72 (dd, J = 17.0, 10.0 Hz), 3.00 (m, 1H), 3.85 (m, 1H, CHSe), 4.85 (d, J = 7.0 Hz, 1H, CHO), 7.30 (m, 3H, aromatic), 7.55 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 282.1 (M^+, ^{80}Se, 73.0), 280.0 (M^+, ^{78}Se, 36.0), 158.0 (PhSeH, base peak), 125.0 (M^+ – PhSe, 25.0). (Found: C, 57.61; H, 6.44; S, 10.39. Calc for $C_{15}H_{20}SSe$: C, 57.68; H, 6.46; S, 10.25%.)

Cyclization of unsaturated urethanes

Preparation of **27**: To a soln of **26** (70 mg, 0.33 mmol) in CH_2Cl_2 (0.83 ml), stirred under argon at 0°, were added camphorsulfonic acid (7.7 mg, 0.03 mmol) and NPSP (130 mg, 0.43 mmol). Stirring was continued for 8 hr, while the reaction was monitored by TLC. Direct flash chromatography (silica, CH_2Cl_2) yielded 90% (109 mg) of **27**.

Compound **27**: oil; $R_f = 0.22$ (silica, methylene chloride); IR (neat, ν_{max}, cm^{-1}): 3055 (w), 2960 (s), 2870 (m), 1705 (C=O, s), 1580 (m), 1480 (m), 1410 (m), 1380 (s), 1310 (s), 1275 (s), 1230 (m), 1140 (s), 1095 (m), 1070 (m), 1035 (m), 740 (m); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 1.24 (d, J = 7.0 Hz, 3H, CH_3CH), 1.26 (t, J = 6.6 Hz, 3H, CH_3CH_2), 1.20–2.15 (m, 8H, CH_2), 2.45 (m, 1H, CH), 2.87 (m, 1H, CHSe), 3.46 (1H, NCH), 7.26 (m, 3H, aromatic), 7.58 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 367.1 (M^+, ^{80}Se, 10.6), 365.1 (M^+, ^{78}Se, 5.2), 352.1 (4.7), 350.1 (2.3), 210.1 (M^+ – PhSe, base peak), 182.1 (56.9), 138.1 (23.3), 95.1 (16.7), 93.1 (12.0); exact mass *m/e*: calc for $C_{28}H_{25}{}^{80}SeNO_2$: 367.1051, found: 367.1034.

Formation of macrolides

Preparation of 14-(*phenylselenomethyl*)-*tetradecanolide* (**29**): A soln of **28** (84 mg, 0.37 mmol) in CH_2Cl_2 (37 ml), stirred under argon at 25° was treated with camphorsulfonic acid (173 mg, 0.74 mmol) and NPSP (1117 mg, 3.70 mmol). After 48 hr of stirring at 25°, the mixture was directly flash chromatographed (silica, benzene) to give 50% yield (70 mg) of **29** and 14% yield (20 mg) of **30**.

Compound **29**: oil; $R_f = 0.46$ (silica, benzene); IR (neat, ν_{max}, cm^{-1}): 3050 (w), 2920 (s), 2850 (m), 1725 (s, C=O), 1205 (m), 1170 (m), 1140 (m), 1100 (m), 1020 (m), 730 (m); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 1.20–1.80 (m, 20H, CH_2), 2.28 (m, 2H, CH_2C=O), 3.08 (m, 2H, CH_2Se), 5.10 (m, 1H, CHO), 7.26 (m, 3H, aromatic), 7.52 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 382.0 (M^+, ^{80}Se, 25.9), 380.1 (M^+, ^{78}Se, 13.3), 225.3 (M^+ – PhSe, 25.5), 158.0 (PhSeH, 20.4), 157.0 (PhSe, 16.6), 156.0 (PhSeH, 10.7), 155.0 (PhSe, 12.1), 123.1 (10.0), 117.1 (10.0), 116.1 (14.6), 111.1 (10.4), 109.1 (16.9), 97.1 (30.7), 95.1 (25.2), 55.1 (base peak); exact mass *m/e*: calc for $C_{20}H_{30}O_2Se$: 382.1411, found: 382.1428.

Compound **30**: oil; $R_f = 0.44$ (silica, benzene); IR (neat, ν_{max}, cm^{-1}): 3060 (w), 2920 (s), 2850 (m), 1730 (s, C=O), 1575 (m), 1470 (m), 1455 (m), 1435 (m), 1370 (m), 1340 (m), 1240 (m), 1160 (m), 1015 (m), 960 (m), 730 (m); ^{1}H-NMR (250 MHz, $CDCl_3$, δ): 1.20–1.80 (m, 20H, CH_2), 2.32 (t, J = 6.0 Hz, 2H, CH_2C=O), 3.36 (m, 1H, CHSe), 4.19 (dd, J = 12.5, 10.0 Hz, 1H, CH_aH_bO), 4.34 (dd, J = 4.0, 12.5 Hz, 1H, CH_aH_bO), 7.32 (m, 3H, aromatic), 7.60 (m, 2H, aromatic); mass spectrum, *m/e* (rel. intensity): 382.0 (M^+, ^{80}Se, 26.0), 380.1 (M^+, ^{78}Se, 13.5), 225.3 (M^+ – PhSe, 25.5), 158.0 (PhSeH, 20.5), 157.0 (PhSe, 16.7), 156.0 (PhSeH, 10.7), 155 (PhSe, 12.1), 123.1 (10.0), 117.1 (10.0), 116.1 (14.6), 111.1 (10.4), 109.1 (16.9), 97.1 (30.6), 95.1 (25.2), 55.1 (base peak); exact mass *m/e*: calc for $C_{20}H_{30}O_2Se$: 382.1411, found: 382.1402.

Conversion of alcohols to alkyl phenyl selenides

Preparation of α-(phenylseleno)-toluene (**34**): To a stirred soln of **33** (100 mg, 0.93 mmol) in dry CH_2Cl_2 (2.3 ml), cooled at –20° under argon, was syringed in tri-n-butylphosphine (0.47 ml, 1.88 mmol). This was followed by addition of NPSP (423 mg, 1.40 mmol) and stirring for about 1 hr, at which time TLC indicated completion of the reaction. The mixture was then diluted with CH_2Cl_2 (100 ml), washed with water (3 × 30 ml), 10% K_2CO_3 aq (2 × 30 ml) and brine (30 ml), and dried over $MgSO_4$. Filtration and evaporation of the solvent, gave a residue which was flash chromatographed (silica, petroleum ether) to give 95% yield (219 mg) of **34**.

Compound **34**: $R_f = 0.09$ (silica, petroleum ether); IR (CCl_4, ν_{max}, cm^{-1}): 3030 (m), 3020 (m), 1600 (w), 1575 (m), 1490 (s), 1475 (s), 1450 (m), 1430 (s), 1175 (m), 1070 (m), 1060 (m), 1020 (m), 995 (w); ^{1}H-NMR (60 MHz, $CDCl_3$, δ): 4.15 (s, 2H, CH_2Se), 7.20–7.70 (m, 10H, aromatic); mass spectrum, *m/e* (rel. intensity): 248.2 (M^+, ^{80}Se, 40.2), 246.1 (M^+, ^{78}Se, 20.3), 158.1 (18.9), 157.1 (PhSe, 30.1), 155.1 (17.8), 92.1 (60.1), 91.1 (base peak).

Conversion of carboxylic acids to selenol esters

Preparation of (*phenylselenyl*)-8-[2'-3' *dioxolane*]*octanoate* (**39**): This procedure is similar to the preparation of **34**. Obtained was a 75% yield of **39** from **38**.

Compound **39**: low melting solid: $R_f = 0.17$ (silica, CH_2Cl_2); IR (CCl_4, ν_{max}, cm^{-1}): 3075 (m), 2950 (s), 2780 (w), 1725 (s, C=O), 1580 (m), 1475 (s), 1460 (m), 1440 (s), 1405 (m), 1370 (m), 1150 (s), 1030 (s); ^{1}H-NMR (60 MHz, $CDCl_3$, δ): 1.00–2.00 (m, 12H, CH_2), 2.70 (t, 7Hz, 2H, CH_2C=O), 3.82 (m, 4H, OCH_2CH_2O), 4.85 (t, J = 3.0 Hz, 1H, CHO_2), 7.50 (m, 5H, aromatic); mass spectrum, *m/e* (rel. intensity): 356.1 (M^+, ^{80}Se, 0.1), 200.1 (M^+ + 1 – PhSe, 26.8), 199.1 (M^+ – PhSe, 85.2), 157.1 ($Ph^{80}Se$, 26.6), 155.1 ($Ph^{78}Se$, 25.2), 109.2 (69.8), 73.1 (base peak); exact mass *m/e*: calc for $C_{17}H_{24}O_3{}^{80}Se$: 356.0890, found: 356.0812.

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