derivative almost certainly arises from the hydrolysis of a fluorodiazomethane precursor complex, these two compounds can condense in a "tail-chasing" type of reaction to yield the final dinuclear product (Scheme XVI). Clear precedent for this latter condensation is found in the reaction of Me_2NCHO with $[Me_2N{=}CHCl]^+$, which gives the symmetrical, delocalized tetramethyl formamidinium ion by decarbonylation and loss of HCl.[36]

Conclusion

The organic chemistry of dinitrogen, in its molybdenum and tungsten complexes is clearly rich and varied. Sometimes it may resemble classical organonitrogen chemistry, as in the condensation of hydrazido(2–) complexes with carbonyl compounds, or in the facile dinitrophenylation of a diazenido(1–) (HN_2–) ligand. More often, however, the presence of the metal atom, with its ability to serve as an electron sink or as a center for redox processes, can generate novel mechanistic pathways, and as shown in this Account, the outcome of any new reaction is far from predictable. Nevertheless, once a mechanism has been identified, it often proves quite general and allows further extension of this fascinating and potentially valuable area of chemical synthesis.

I wish to thank Imperial Chemical Industries PLC for the opportunity to work in this field of chemistry, and in particular I am grateful to Drs. E. P. Goodings and W. Hewertson who initiated the project and to Dr. R. A. Head who has advised throughout. Much of the work described in this Account was carried out in collaboration with workers outside ICI, and I am grateful to Dr. K. Henrick, Dr. D. J. Williams, and the late Professor T. J. King for crystallographic studies and to Professor J. Chatt and Dr. G. J. Leigh for advice and encouragement. A joint research project with Drs. A. E. Crease and S. A. Taylor at Trent Polytechnic was supported by a grant from the Science and Engineering Research Council.

(36) W. Kantlehner and P. Speh, *Chem. Ber.*, **104**, 3714 (1971).

New Organoselenium Methodology

DENNIS LIOTTA

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received January 15, 1982 (Revised Manuscript Received July 22, 1983)

Although the field of organoselenium chemistry dates back to the 19th century, it did not become a part of the mainstream of organic chemistry until the early 1970s. The apparent turning point came when Sharpless reported a mild method for the conversion of epoxides into allylic alcohols, which made use of the "first" organoselenium reagent, phenyl selenide anion.[1] Within months of this report, Reich disclosed his findings on reactions of various electrophilic selenium species.[2] What followed over the next 10 years was a worldwide explosion of interest in the development and use of new organoselenium methodology. In that period of time over 1000 publications utilizing some type of organoselenium methodology appeared in print.[3] In this Account some of the newer aspects of this renaissance in organoselenium chemistry are discussed.

What factors are responsible for the intense activity in this field? While there are a plethora of reasons that have contributed to the widespread interest, several factors clearly stand out as important. First, organoselenium anions are potent nucleophiles that exhibit a strong preference for reaction with soft acids.[4] On the other hand, when organoselenium species contain reasonable leaving groups (e.g., Cl, Br, O_2CCF_3, etc.), they can serve as extremely reactive, soft electrophiles.[5] Thus, in general, organoselenium moieties can be introduced into a variety of substrates in either a nucleophilic or an electrophilic sense. Moreover, these processes can almost always be accomplished in high yields and under very mild conditions.

Second, once selenium is incorporated into a substrate, a number of options become available for subsequent functional group manipulations. For example, since an arylseleno moiety is a relatively poor leaving group (its nucleofugality is comparable to phenoxide),[6]

Dennis Liotta was born in Brooklyn, NY, in 1949. He received his B.A. and Ph.D. degrees at the City University of New York (Queens College), where he worked with Robert Engel. After 2 years postdoctoral work with Leo A. Paquette at the Ohio State University, he joined the Emory University faculty, where he is now Associate Professor of Chemistry. He is the recipient of both an Alfred P. Sloan and a Camille and Henry Dreyfus Teacher–Scholar Fellowship. He has served as co-chairman of the NSF-sponsored Workshop on Reactive Intermediates from 1981 to 1983 and is currently one of the co-chairman of the Gulf Coast Chemistry Conference. Besides organoselenium chemistry, he is interested in synthetic methodology, total synthesis, photoelectron spectroscopy, and the application of molecular orbital concepts in understanding chemical reactivity. His older brother, Charles, is also a chemist and teaches at Georgia Institute of Technology.

(1) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. Note, however, that a selenium reagent that has been in common use since 1932 is a selenium dioxide. See: (b) Riley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875. (c) Rabjohn, N. *Org. React.* **1949**, *5*, 331. (d) For the first reported selenoxide elimination, see: Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc. D* **1970**, 36.

(2) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

(3) For some excellent reviews on organoselenium chemistry through 1977, see: (a) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (c) Reich, H. J. In "Oxidation in Organic Chemistry"; Trahanovsky, W., Ed.; Academic Press: New York, 1978; Part C, 1.

(4) (a) Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605. (b) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4369. (d) Scarborough, R.; Smith, A. B. *Tetrahedron Lett.* **1977**, 4361. (e) Gunther, W. H. *J. Org. Chem.* **1966**, *31*, 1201. (f) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319. (g) Barth, H.; Gosselck, J. *Z. Naturforsch.* **1961**, *166*, 280. (h) Liotta, D.; Paty, P. B.; Johnston, J.; Zima, G. *Tetrahedron Lett.* **1979**, 5091.

(5) (a) Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, 4977. (b) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100. (c) Reich, H. J. *J. Org. Chem.* **1974**, *34*, 428. (d) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *34*, 429. (e) Ryu, I.; Murai, S.; Nirva, I.; Sonoda, N. *Synthesis* **1977**, 874.

0001-4842/84/0117-0028$01.50/0

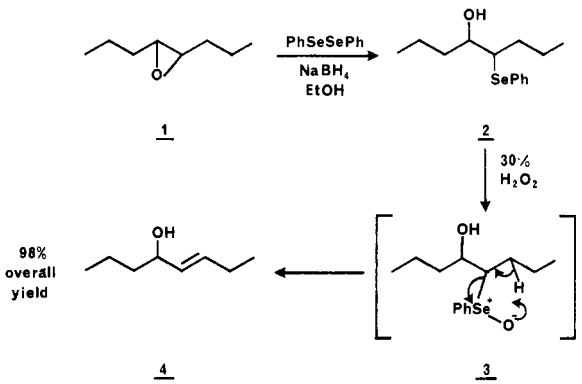
one can effect a variety of synthetic transformations at remote sites in a molecule without disturbing the selenium. Additional synthetic flexibility is derived from the fact that arylseleno groups can stabilize both adjacent positive and adjacent negative charges.[7]

Third and most important, although most Se(II) species are quite stable toward β-elimination, their corresponding selenoxides undergo facile syn eliminations, at or below room temperature.[8] In fact, β-eliminations of selenoxides represent the mildest, general olefin-forming reaction known. In addition to these oxidative eliminations, one can also remove organoselenium groups via a number of reductive elimination processes. Thus, in general, organoselenium species can be efficiently introduced, manipulated, and removed in a variety of ways under mild conditions.

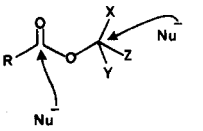
Nucleophilic Selenium

Organoselenium compounds possess many unique and desirable qualities. According to hard–soft acid–base theory (HSABT), selenium anions are quite soft, i.e., they possess low ionization potentials[9] and their highest occupied molecular orbitals (HOMO) are very polarizable. Thus, it is not surprising that anions such as phenylselenide are powerful nucleophiles that react rapidly with many substrates.

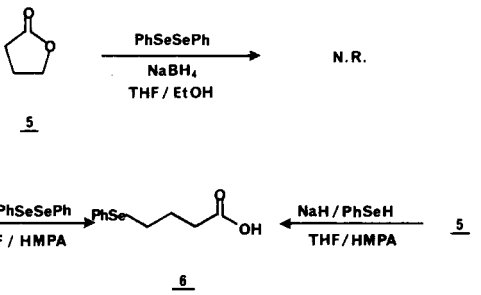
As noted previously, it was Sharpless who first showcased some of the unique properties of nucleophilic selenium, by using selenide anions in general epoxide/allylic alcohol interconversion.[1] His process involves two distinct steps: (a) nucleophilic opening of an epoxide with phenyl selenide anion and (b) regiospecific oxidative elimination of the phenylseleno group to produce an allylic alcohol. The generation of phenyl selenide anion was conveniently accomplished by reduction of diphenyl diselenide with sodium borohydride in ethanol.



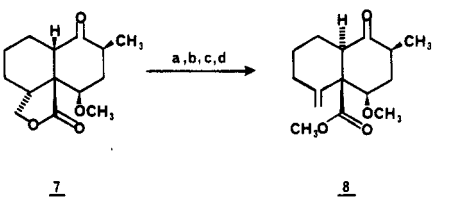
Our interest in phenyl selenide anion began with the notion that, because it is such a potent nucleophile, it might prove to be an effective reagent for the S_N2 cleavage of esters and lactones. This idea is reinforced by hard–soft acid–base theory, in that soft nucleophiles such as phenyl selenide anion are predicted to show a preference for attack at the carbinol carbon of an ester (soft–soft interaction) rather than at its carbonyl carbon (soft–hard interaction).



It was thus surprising to us that even after prolonged exposure to phenyl selenide anion (PHSeSePh, $NaBH_4$), a number of esters and lactones were recovered unchanged. This apparent anomaly was later resolved by demonstrating that phenyl selenide anion, generated by sodium borohydride reduction of diphenyl diselenide, actually exists as a borane complex.[4b] When the anion is generated by other means and properly solubilized, the S_N2 cleavage of esters and lactones proceeds smoothly and in high yield (vide infra).[4a-d]



On the basis of our results, some interesting generalizations can be made. First, phenyl selenide anion is an effective reagent for S_N2 cleavage of methyl, primary alkyl, and some secondary alkyl esters. These results are quite different than the previously reported S_N2-type ester cleavage processes that are typically successful only with methyl esters.[10] Second, the reagent exhibits a high degree of selectivity, both with respect to the steric bulk of the ester around the carbinol carbon (e.g., methyl esters are selectively cleaved in the presence of ethyl esters) and with respect to the other functional groups that may be present in a given substrate (ethers and amides are completely inert to phenyl selenide ion). For example, **7** is converted to **8** in 73% overall yield with use of this methodology.[11]

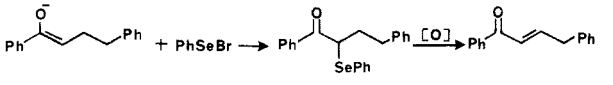


Third, the nucleophilicity of this reagent can be dramatically attenuated by varying the counterion and/or the degree of solvation of the anion. On the basis of our results, the following reactivity gradient has been proposed for phenyl selenide anion: NaSePh/18-crown-6/THF > NaSePh/HMPA/THF > LiSePh/HMPA/THF > LiSePh/THF or ether > PhSeSePh/NaBH4/THF/EtOH. Overall, it is our belief that phenyl selenide anion is the most effective reagent yet reported for carrying out S_N2-type ester cleavage reactions.[12]

(6) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.
(7) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Daucher, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Metthews, W. S. *J. Org. Chem.* **1977**, *42*, 326.
(8) (a) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697. (b) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc. D* **1970**, 86.
(9) Baker, A. D.; Armen, G. H.; Guang-di, Y.; Liotta, D.; Flannagan, N.; Barnum, C.; Saindane, M.; Zima, G.; Grossman, J. *J. Org. Chem.* **1981**, *46*, 4127.
(10) The S_N2-type cleavage of esters is the subject of a recent review; see: McMurry, J. *Org. React.* **1977**, *24*, 187.
(11) Goldsmith, D. J., Emory University, personal communication.

Electrophilic Selenium

Unsaturated Carbonyl Compounds. HSABT predicts that electrophilic selenium species should be soft acids that react readily with nucleophiles possessing low ionization potentials and low charge densities. Thus, electrophilic selenium reagents, such as phenylselenenyl chloride and phenylselenenyl bromide, undergo facile reaction with the enol form of ketones,[13] ketone enolate anions,[14] enol acetates,[5b,c] and silyl enol ethers[5e] at the softer carbon center. The resulting α-phenylselenated ketones are then easily transformed to their corresponding enones via the now standard oxidative elimination sequence. Many other enolate anions (e.g., esters,[14] nitriles,[15] lactones,[16] and others,[17]) have been phenylselenated in a similar fashion. Utilization of this methodology allows for the introduction of unsaturation into a wide spectrum of carbonyl derivatives in yields that are generally higher than any other available methods (e.g., the conversion of **9** to **11**).

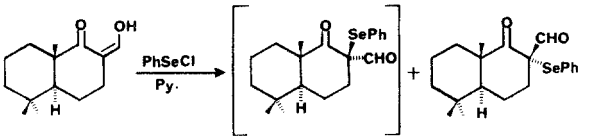


9 10 11

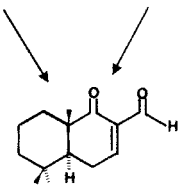
In fact, under certain circumstances carbonyl derivatives can be selenated under effectively neutral reaction conditions. For example, we have shown that β-dicarbonyl compounds that possess a significant degree of enol character react rapidly and essentially quantitatively with 1:1 phenylselenyl chloride/pyridine to produce the corresponding selenated derivatives.[18] Oxidative elimination then yields the corresponding unsaturated derivatives. The synthetic utility of this method was nicely demonstrated by Goldsmith in his synthesis of the insect antifeedant, warburganal (vide infra).[19]

In this regard we have also demonstrated that certain selenated carbonyl derivatives that possess sterically hindered phenylselenyl groups (e.g., **13**) undergo a trans-diaxial, nonoxidative elimination.[18] A similar observation has been made by Schlessinger in his synthesis of eriolanin.[20]

One of the most useful reagents for introducing unsaturation α,β to carbonyl groups is benzeneseleninic anhydride. This reagent, which has been extensively studied by Barton[21] and others,[22] allows for the direct

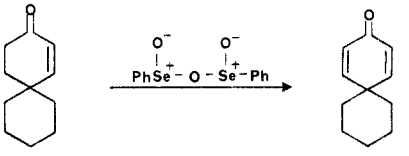


12 13 14

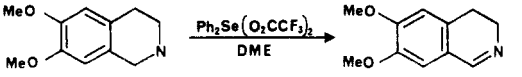


15

introduction of selenium moieties in the selenoxide oxidation state (vide infra). The reagent[23] is also useful for the oxidation of other functional groups, including alcohols,[24] phenols,[25] hydrazones,[26] lactams,[27] and amines.[28] Another selenium(IV) electrophile, diphenylselenium bis(trifluoroacetate), has been reported by Marino to be very effective at the conversion of amines to their corresponding imines.[29]



16 17



18 19

Perhaps the major drawback to these procedures is the high cost associated with the various PhSeX reagents (X = Cl, Br, SePh). These often prove to be prohibitively expensive to use in moderate- or large-scale reactions. As a way around this problem, we developed an alternative procedure for effecting the selenation of ketone (or ester) enolates that can be accomplished in yields comparable to enolate/PhSeX reactions but at a greatly reduced cost.[30,31] The key

(12) For comparison purposes, see ref 10. Also see: (a) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459. (b) Kelly, T. R.; Dali, H. M.; Tsang, W. *Tetrahedon Lett.* **1977**, 3859.

(13) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

(14) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(15) (a) Brattesani, D. N.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, 2279. (b) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2166.

(16) (a) Grieco, P. A.; Nishizawa, M. *J. Chem. Soc., Chem. Commun.* **1974**, 2279. (b) Grieco, P. A.; Nyashita, M. *J. Org. Chem.* **1974**, *39*, 120. (c) Yamakawa, K.; Tominga, T.; Nishitani, K. *Tetrahedron Lett.* **1975**, 4137. (d) Grieco, P. A.; Pognowski, C. S.; Burke, S. *J. Org. Chem.* **1974**, *40*, 542.

(17) For summary of some other anions that have been selenated, see ref 3b.

(18) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S. *J. Org. Chem.* **1981**, *46*, 2920.

(19) Goldsmith, D. G.; Kezar, H. S. *Tetrahedron Lett.* **1980**, 3543.

(20) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724.

(21) (a) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130. (b) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2209.

(22) (a) Yamakawa, K.; Satoh, T.; Ohba, Sakaguchi, R. *Chem. Lett.* **1979**, 763. (b) Yamakawa, U.; Satoh, t.; Ohba, N.; Sakaguchi, R.; Takita, S.; Tamura, N. *Tetrahedron* **1981**, *37*, 473.

(23) For a convenient method of generating this reagent in situ, see: Barton, D. H. R.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Commun.* **1981**, 1044.

(24) Barton, D. H. R.; Brewster, A. G.; Hui, R. A. H. F.; Lester, D. J.; Ley, S. V.; Back, T. G. *J. Chem. Soc., Chem. Commun.* **1978**, 952.

(25) Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Read, C. M.; Rosenfeld, M. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1473.

(26) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1212.

(27) Back, T. G. *J. Chem. Soc., Chem. Commun.* **1978**, 278.

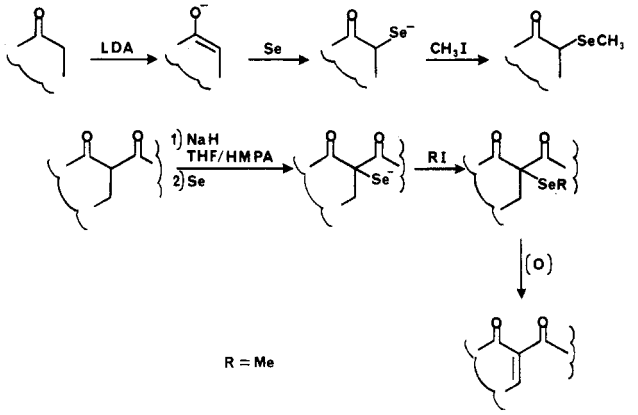
(28) Czarney, M. R. *J. Chem. Soc., Chem. Commun.* **1976**, 81.

(29) Marino, J. P.; Larsen, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 4642.

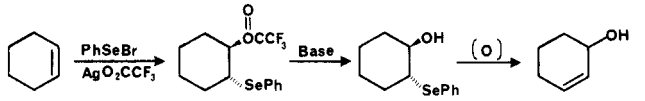
(30) Liotta, D.; Zima, G.; Barnum, C.; Saindane, M. *Tetrahedron Lett.* **1980**, 3643.

(31) Liotta, D.; Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett.* **1981**, 3043.

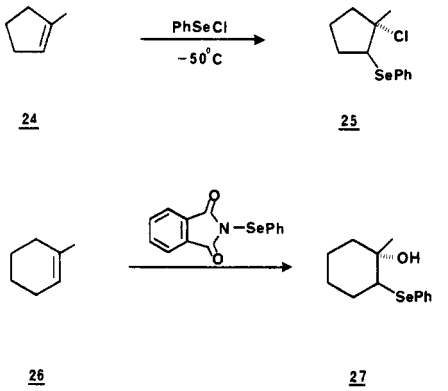
feature of this procedure involves the reaction of an enolate with selenium metal to form a selenolate (selenide) ion (the enolate–selenolate transformation). The resulting selenolate can then be directly alkylated to give the corresponding α-alkylselenenyl derivative. These α-alkylselenenyl ketones and esters are generally well-behaved compounds that can be efficiently converted to their corresponding enones and enoates via the same type of oxidative elimination procedures commonly employed for their α-phenylselenenyl counterparts. Since selenium metal is 5–10 times less expensive than phenylsenenyl chloride, these selenium metal reactions represent the method of choice for large-scale laboratory synthesis.



Additions to Double Bonds. The addition of electrophilic selenium reagents to carbon–carbon double and triple bonds affords the possibility of a number of interesting synthetic transformations. For example, Clive[32] and, very soon thereafter, Reich[5c] and Sharpless,[5d] reported sequences for the conversion of simple olefins to allylic alcohols that utilize the addition of various selenium electrophiles to simple olefins. Unfortunately, with unsymmetrical olefins these additions proceeded with poor regioselectivity and are thus of limited synthetic utility.



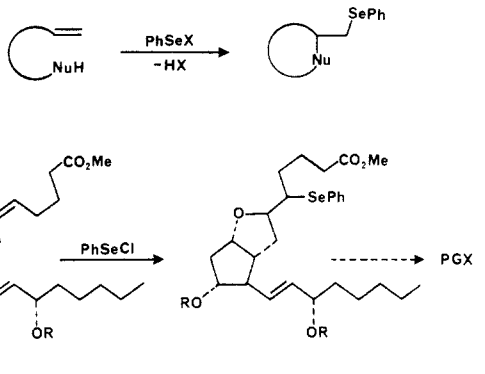
We were able to show that phenylselenenyl chloride adds to variously substituted olefins in high yield with high regioselectivity (Markovnikov additions).[5a] Complementary studies on terminal olefins had also been previously reported by Raucher[33] and by Schmid and Garrat.[34] Furthermore, although heavily substituted phenylselenenyl chloride/olefin adducts are oftentimes unstable at room temperature, regiospecific adduct formation can be achieved if the addition and subsequent synthetic manipulations (e.g., oxidative elimination, dehydrohalogenation, etc.) are carried out at temperatures below −50 °C. Subsequent to our work, Nicolaou demonstrated that the combination of *N*-phenylselenophthalimide, 2–3 equiv of water, and a catalyst results in the regiospecific phenylselenohydroxylation of olefins.[35]



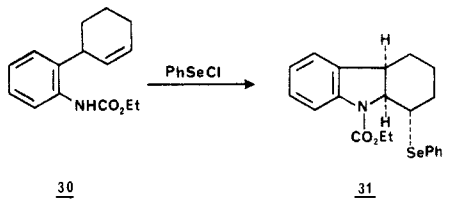
The selenium-induced cofunctionalization of double bonds containing internal nucleophiles has also been extensively studied,[36] most notably by Nicolaou[37b,c] and by Clive.[37d] Use of this methodology permits easy access to a wide variety of synthetically useful oxygen[38a] and nitrogen heterocycles.[38c] For example, Nicolaou has prepared prostacyclin analogues with use of an intramolecular phenylselenoetherification reaction.[38b,g] Recently, Ley and co-workers have reported some interesting selenium-mediated carbocyclization reactions involving alkenyl-substituted β-keto esters.[38d-f] In addition to these intramolecular cofunctionalizations, a number of PhSeX reagents have been successfully added across double bonds. These include, inter alia, $PhSeSO_2Ph$,[39a] $PhSeOSnBu_3$,[39b] PhSeOSePh,[39c] and $PhSeBr/Me_2SO/AgPF_6$.[39d]

In the course of our studies with various electrophilic selenium reagents, we observed that additions of PhSeCl to allylic alcohols generally proceed with high regio- and stereoselectivity. For example, cyclohexenol (**35**, R = R′ = H) reacts with PhSeCl to produce only one of the four possible regio- and stereoisomers.[40] This is important because additions of this type could, in principle, be used as the key step in the 1,3-enone transposition sequence shown below. In order to test this hypothesis, we undertook two separate but eventually convergent studies. These were (a) to probe the origins of the regio- and stereoselectivity of these addition reactions and (b) to demonstrate the generality and synthetic viability of the proposed transposition sequence.[41]

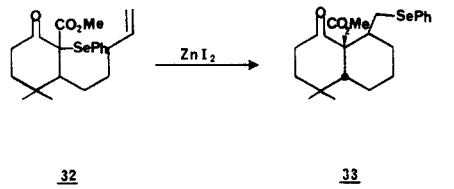
(32) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695.
(33) (a) Raucher, S. *J. Org. Chem.* **1977**, *42*, 2950. (b) Raucher, S. *Tetrahedron Lett.* **1977** 3909. (c) Raucher, S.; Hansen, M. R.; Colter, M. A. *J. Org. Chem.* **1978**, *43*, 4885.
(34) (a) Garrat, D. G.; Schmid, G. H. *Can. J. Chem.* **1974**, *52*, 3599. (b) Garrat, D. G.; Schmid, G. H. *J. Org. Chem.* **1977**, *42*, 1776.
(35) Nicoloau, K. B.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
(36) For an informative review on organoselenium-induced cyclizations, see: Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097.
(37) (a) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, 4801. (b) Scarborough, R. M.; Smith, A. B.; Barnett, W. F.; Nicoloau, K. C. *J. Org. Chem.* **1979**, *44*, 1743. (c) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.*, **1979**, *101*, 3884. (d) Clive, D. L.; Chittatu, G. *J. Chem. Soc., Chem. Commun.* **1977**, 484. (e) See ref 5a.
(38) See also: (a) Nicolaou, K. C.; Lysenko, Z. *Tetrahedron Lett.* **1977**, 1257. (b) Nicolaou, K. C.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1977**, 331. (c) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120. (d) Jackson, W.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173. (e) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Ibid.* **1980**, 1028. (f) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, 2601. (g) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3486. (h) Webb, R. B.; Danishefsky, S. *Tetrahedron Lett.* **1983**, 1357.
(39) (a) Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, 2215. (b) Kuwajima, I.; Shimizu, M. *Ibid.* **1978**, 1277. (c) Shimizu, M.; Takeda, R.; Kuwajima, I. *Ibid.* **1979**, 419. (d) Raucher, S. *Ibid.* **1978**, 2261.
(40) Liotta, D.; Zima, G. *J. Org. Chem.* **1980**, *45*, 2551.



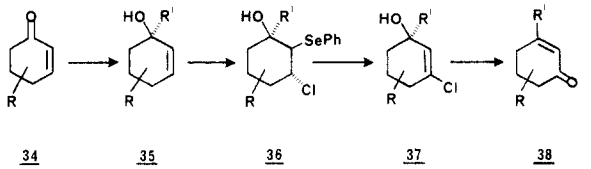
28 29



30 31



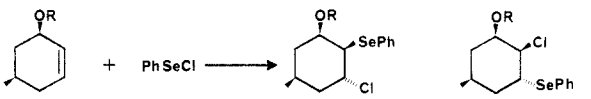
32 33



34 35 36 37 38

R = H or alkyl; R' = H or alkyl

39 40

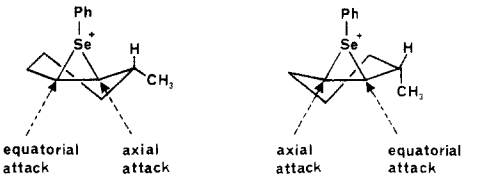


41 a. R = H
b. R = Ac

42 a. R = H
b. R = Ac

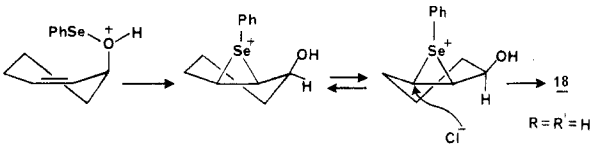
43 a. R = H
b. R = Ac

With regard to (a), we have examined the additions of PhSeCl to over 30 allylic systems. Some of the more important conclusions that were reached can be summarized with use of examples shown above. For example, the additions of PhSeCl to **39** results in a total reversal of observed regioselectivity relative to the addition of PhSeCl to **35**. The simplest rationale for this is that PhSeCl initially reacts with **39** on its less hindered face to yield selenonium ion **44**. Intermediate **44** is then attacked by chloride ion in an axial fashion to yield **40**.[42] Since **44** is presumably in equilibrium with its less stable conformer **45**, some of the products derived from chloride attack on it might also be expected to form. However, these are not observed, presumably because axial attack by chloride ion on **45** is hindered by the axial methyl substitutent.



44 45

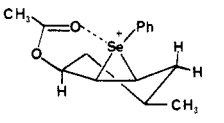
The regio- and stereoselectivity observed in the reaction of **35** and PhSeCl can also be readily understood with use of this model, if one assumes an initial coordination of PhSeCl with the electron-rich hydroxyl group, followed by an intramolecular "delivery" of the electrophilic selenium species to the double bond (**46** → **47** ⇄ **48**). Ring flip of **47** to its conformationally more stable form **48**, followed by axial attack of the chloride ion would then yield **36**.



46 47 48

In **41** the hydroxyl and methyl groups are cis. Therefore, when the hydroxyl group is pseudoaxial, the methyl must also necessarily be pseudoaxial. This arrangement results in relatively severe 1,3-diaxial interactions, not only between the methyl and hydroxyl groups but also between these groups and the incoming selenium electrophile. Consistent with this rationale, the additions of PhSeCl to **41a** produces a 7:3 mixture of **42a** and **43a**, respectively.

Since the inability of a pseudoequatorial hydroxyl group to direct an incoming selenium electrophile syn to itself places severe limitations on the synthetic utility of this process, we focused our attention on reactions involving allylic acetates. In principle, these species could induce syn selenonium ion formation via carbonyl oxygen, followed by a subsequent intramolecular delivery to the double bond to form intermediate **49**. Axial attack by chloride ion would then produce **42b**. In fact, addition of PhSeCl to **41b** results in the formation of **42b** as the only observable product.[43]



49

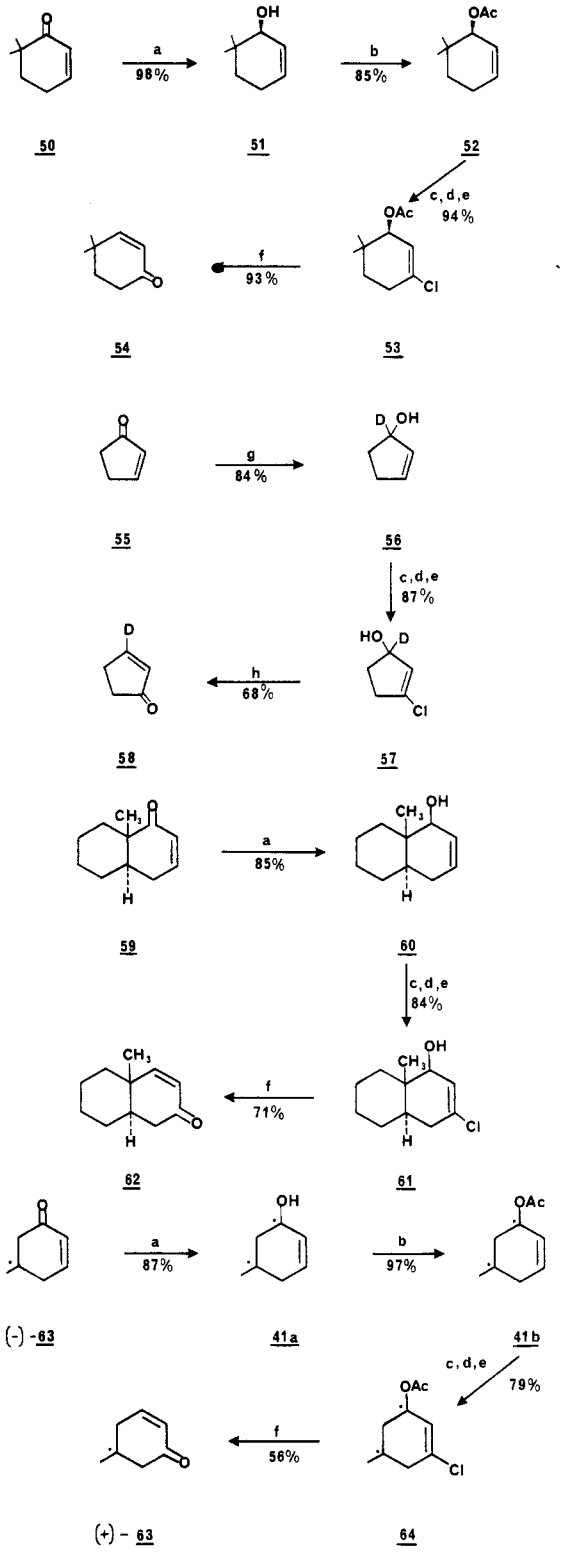
The regio- and stereospecificity of phenylselenyl chloride additions to allylic alcohols would be of little

(41) Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258.

(42) Axial attack is kinetically favored in six-membered rings because it involves a chairlike transition state. Equatorial attack in six-membered rings involves a boatlike transition state and is generally a slower process.

(43) In acyclic systems a higher degree of regioselectivity can usually be attained by using allylic acetates in place of allylic alcohols.

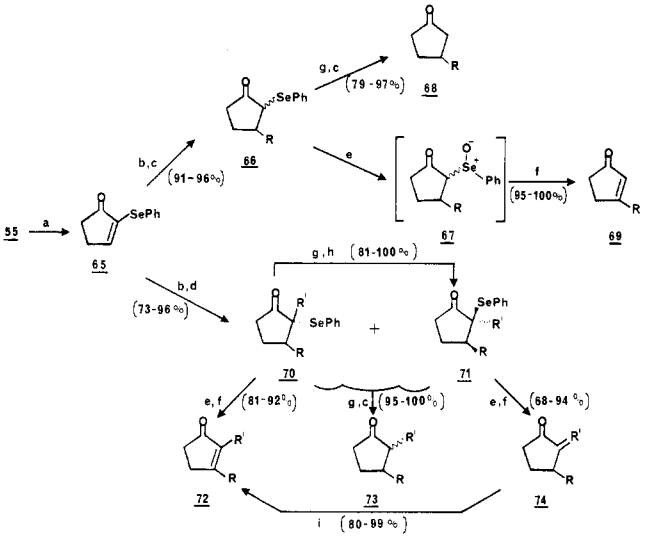
Scheme I



interest unless one could further elaborate the phenylseleno adducts in a constructive fashion. We have exploited the regiospecificity of these additions to allylic alcohols by using them as the key step in the generalized 1,3-enone transposition sequence shown in the conversion of **34** to **38**.[40,41,44]

(44) For examples of 1,3-enone transpositions, as well as 1,3-alkylative enone transpositions, see: (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Wharton, P. S. *Ibid.* **1961**, *26*, 4781. (c) Trost, B. M.; Shanton, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 4018. (d) Trost, B. M.; Hiroi, K.; Holy, N. *Ibid.* **1975**, *97*, 5873.

Scheme II



Allylic alcohols of type **35** are generated from the corresponding enone either reductively ($LiAlH_4$) or alkylatively (M^+R). If electronic and steric parameters are correct (vide supra), **36** is produced by the addition of PhSeCl.[45] Since selenoxide eliminations are strongly favored to proceed away from an oxygen substituent,[1a] oxidative elimination of **36** to chloroallylic alcohols like **37** occurs regiospecifically. Hydrolysis of these masked enones completes the transformation to yield transposed species **38**. As discussed earlier, since phenylselenenyl chloride additions to allylic systems generally produce adducts that possess the desired regiochemistry (e.g., **35**), this transposition sequence is applicable to a variety of structurally diverse enones in overall yields of approximate 40–70%. Some specific examples are shown in Scheme I.

2-Phenylselenenyl Enones

Recently, we reported a general method for converting simple enones into 2-phenylselenenyl enones (illustrated below for the conversion of **55** to **65**). These phenylselenenyl enones proved to be excellent Michael acceptors and, as such, enabled us to develop simple procedures for converting compounds such as **65** into a variety of new ketones and enones in high overall yields.[47] A generalized illustration of the various transformations that can be accomplished with use of the methodology is given in Scheme II.

While many of the attractive features of this methodology are self-evident (e.g., excellent yields, high regioselectivity, etc.), some others are more subtle and thus require some comment. First, oxidative elimination of either the cis or trans isomer of **66** leads to the corresponding 3-alkylcyclopentenone in excellent yield. Since it is well-established that selenoxide elimination occurs in a syn fashion,[48] epimerization at the α-carbon of the intermediate β-keto selenoxide **67** (R = n-Bu)

(45) The regio- and stereochemistries of these addition reactions are easily verified by NMR.

(46) (a) Zima, G.; Liotta, D. *Synth. Commun.* **1979**, *9*, 697. (b) Buckley, D. J.; Kulowit, S.; McKervey, A. *J. Chem. Soc., Chem. Commun.* **1980**, 506. (c) Shumizer, M.; Takeda, R.; Kuwajima, I. *Tetrahedron Lett.* **1979**, 3461. (d) For a method for converting enoates to their corresponding phenylselenenyl enoates, see: Hase, T. A.; Kukkola, P. *Synth. Commun.* **1980**, *10*, 451.

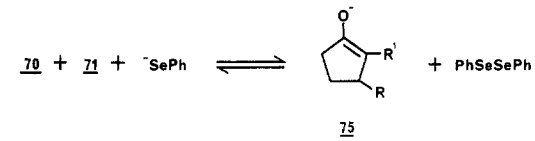
(47) Zima, G.; Barnum, C.; Liotta, D. *J. Org. Chem.* **1980**, *45*, 2737.

(48) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979.

must be occurring under the reaction conditions prior to elimination.[47,49] This is significant since both epimers can be simultaneously converted to product without any additional synthetic manipulations.

Second, we have been able to selectively convert mixtures of **70** and **71** to either the endocyclic enone **72** or the exocyclic enone **74**, irrespective of the relative amounts of the two isomers present. Exclusive formation of **72** is achieved via a standard oxidative elimination of the mixture of **70** and **71** that produces a mixture of enones **72** and **74**. This mixture can then be completely converted to **72** by exposure to acid.[50]

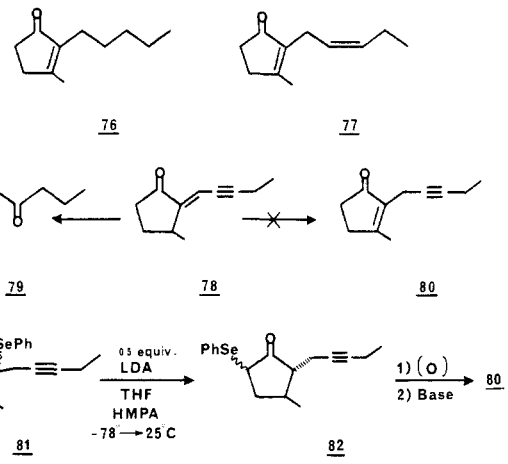
Our approach to the production of **74** involves isomerizing the mixture of **70** and **71** entirely to **71**, prior to the oxidation/elimination process. We envisioned effecting the isomerization in a relatively straightforward, two-step process: first, a nucleophilic cleavage of the carbon–selenium bond, followed by a reselenation of the resulting enolate. Since in the selenation transition state, the carbon–selenium separation is probably quite large, we reasoned that alkyl–alkyl repulsions would be most important in determining the stereochemistry of the product, thereby favoring the formation of the trans isomer **71**.



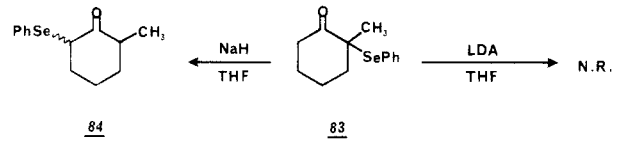
In practice, the nucleophilic cleavage of the carbon–selenium bonds of **70** and **71** is readily accomplished by exposing a mixture of these compounds to lithium phenyl selenide in THF at −78 °C.[14,47] The resulting enolate **75** can then be directly selenated with either PhSeCl or CH_3I. The latter reagent presumably reacts preferentially with the potent nucleophile $PhSe^-$, thereby shifting the equilibrium back to the leeft. The use of this method results in the formation of mixtures of **70** and **71** in which **71** is by far the major component. In fact, in most of the cases reported, the epimerized mixtures contain only trace amounts of **70**. Once isomerized, these mixtures can then be oxidized and eliminated under standard conditions to give excellent overall yields of **74**.

By using the methodology illustrated in Scheme II, we were able to complete a synthesis of the perfume component, dihydrojasmone (**76**), in 67% overall yield.[51] By contrast, all our attempts to prepare *cis*-jasmone (**77**) by this approach were thwarted because of our inability to isomerize **78** to dehydrojasmone (**80**). However, we were ultimately able to prepare *cis*-jasmone in 76% overall yield by using the synthetic sequence shown below.

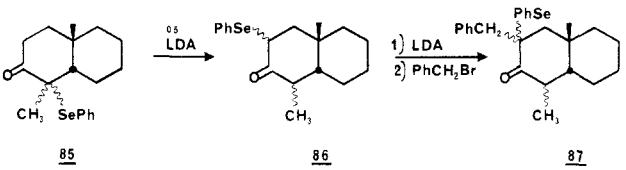
The novel feature of this sequence is the base-induced 1,3 selenium shift used in the conversion of **81** to **82**. This reaction involves a series of intermolecular phenylseleno and proton exchange processes whose driving force is the production of increasingly more stable



enolate ions. Steric interactions between properly placed alkyl groups and the phenylselenenyl group accelerate the exchange process. In cases in which there is relatively little steric repulsion (e.g., **83** → **84**), the reaction fails when lithium diisopropylamide is used as the base. In these cases we have found sodium hydride is an effective substitute, presumably because of the higher reactivity of sodium enolate vs. lithium enolates.[52]



In general terms, this formal 1,3 selenium shift methodology further extends the versatility of species, such as **70** and **71**, to be regiospecifically functionalized in the α'-position.[53] For example, **85** is readily isomerized to **86**. Since the phenylseleno group stabilizes an adjacent negative charge, **86** can be regiospecifically alkylated at C2 instead of the usually preferred position C4.



Conclusion

In this Account, we have described a number of synthetically useful processes, all of which can be accomplished in high overall yields and usually under very mild conditions. Our review of the newer aspects of organoselenium chemistry is by no means exhaustive; instead, we have focused on some selective aspects of organoselenium methodology that we feel provide significant advantages over existing methodology and that depend heavily for their success on one or more of the unique properties of selenium.

It is a pleasure to acknowledge the significant contributions of my co-workers, whose names are given in the references. Our studies have been generously supported by the National Institutes of Health, Research Corp., the Petroleum Research Fund, administered by the American Chemical Society, the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.

(49) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133.

(50) (a) Caton, M. P. L.; Coffee, E. C. J.; Watkins, G. L. *Tetrahedron Lett.* **1972**, 773. (b) Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248. (c) Wakamatsu, T.; Hahimoto, K.; Ogura, M.; Ban, Y. *Synth. Commun.* **1978**, *8*, 319.

(51) (a) Liotta, D.; Barnum, C. S.; Saindane, M. *J. Org. Chem.* **1981**, *46*, 4301. (b) For a comprehensive review of all the syntheses of jasmonoids, prior to 1974, see: Ho, T. *Synth. Commun.* **1974**, *4*, 265.

(52) D. Liotta, unpublished results.

(53) Liotta, D.; Saindane, M.; Brothers, D. *J. Org. Chem.* **1982**, *47*, 1598.