(25), bound covalently or by physical forces to the enzyme system, is then converted into uro'gen-III (1) by an intramolecular rearrangement which directly affects only ring D and the two carbons which become C-15 and C-20. The nature of the intermediate between the bilane and uro'gen-III remains to be established, and this leads to the concluding section.

Prospect. In the presence of deaminase alone, and also nonenzymically, the cyclization of bilane (**25**) occurs at C-19 to produce **26**, leading to uro'gen-I (**11**). We suggest that in the presence of cosynthetase cyclization occurs at C-16 rather than at C-19 (Scheme XIII). The postulated attack at C-16 would produce the spiro intermediate **27**; the labeling arising from **25b** and **25c** is shown. Fragmentation and cyclization again as illustrated would generate uro'gen-III.[46] The spiro system is related to that proposed by Mathewson and Corwin[47] in 1961, and its intermediacy is consistent with all the work summarized above. Notice that both **26** and **27** contain a new sp^3 center, and they differ less in shape than may appear from a planar diagram.

How does cosynthetase divert the unrearranged bilane to exclusive type-III formation when in its absence type I is exclusively formed? We consider here two possibilities. One is that cosynthetase alters the conformation of the deaminase–bilane complex to direct cyclization of **25** at C-16. There are indications[48,49] that deaminase associates with cosynthetase, and it has been suggested[33b,50] that cosynthetase acts as a "specifier protein" in the way lactoalbumin works during the biosynthesis of lactose. The other possibility is that the bilane (**25**) is the *product* from deaminase but is then the *substrate* for cosynthetase which brings about ring closure with rearrangement to produce uro'gen-III specifically.

Work is in hand on these aspects and on the problem of the structure of the intermediate[51] between the bilane and uro'gen-III. It will be good to have the answers to the few remaining questions.

We are glad to have this opportunity to record our debt and thanks to our young colleagues whose courage in this demanding field and experimental skills made the work posible. Their names are given in the literature references. We are also grateful for financial support from the Nuffield Foundation, Science Research Council, and Roche Products.

(46) The alternative, and equivalent, fragmentation from ring A would simply regenerate an equivalent of the unrearranged bilane ready for re-formation of the spiro system **27**.

(47) J. H. Mathewson and A. H. Corwin, *J. Am. Chem. Soc.*, **83**, 135 (1961).

(48) R. B. Frydman and G. Feinstein, *Biochim. Biophys. Acta*, **350**, 358 (1974).

(49) M. Higuchi and L. Bogorad, *Ann. N.Y. Acad. Sci.*, **244**, 401 (1975).

(50) B. Middleton, Cambridge, quoted by A. R. Battersby and E. McDonald in ref 2, p 96.

(51) The only alternative to the spiro intermediate involves fission of the C-15/C-16 bond of bilane (**25**) while it is bound to the enzyme, followed by inversion of ring D with strictly no exchange with the medium of the now separated pyrrole fragment. We find this possibility less attractive.

Functional Group Manipulation Using Organoselenium Reagents

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The use of second, third, and fourth row elements in organic synthesis received its major modern impetus from the discovery of the Wittig olefin synthesis. Since then many applications of silicon, tin, phosphorus, sulfur, selenium, and other metalloids in organic synthesis have been proposed, and a significant number of these procedures are finding their place in routine organic synthesis.

In this Account some recent developments in the chemistry of organoselenium compounds which have synthetic potential are described, with particular emphasis on the exploitation of chemical properties of selenium which differ from those of sulfur. In addition to work at Wisconsin, research groups headed by Sharpless, Seebach, Grieco, Krief, Nicolaou, and others have been active in this area.[1]

The utility of selenium and sulfur is derived from the great ease with which a wide variety of organoselenium and organosulfur compounds can be prepared, as well as the facility of transformations of these compounds to effect useful functional group interconversion. Both nucleophilic and electrophilic reagents are readily available for the introduction of selenium. The large stabilization of carbanions provided by sulfur and selenium substituents (at least 10–15 pK_a units for PhS and PhSe, more for sulfoxides, selenoxides, and sulfones[2]) has resulted in their use as activating groups for a variety of carbon–carbon bond-forming procedures involving organometallic reagents.

The chemistry of sulfur and selenium is very closely related. The greater expense of selenium and the hazard resulting from its toxicity[3] are justifiable only

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(1) For a comprehensive account of synthetic organoselenium chemistry, see H. J. Reich in "Oxidation in Organic Chemistry, Part C", W. Trahanovsky, Ed., Academic Press, New York, 1978, p 1.

(2) F. G. Bordwell et al., *J. Org. Chem.*, **42**, 326 (1977).

(3) See K. Schwartz and K. D. Pathak, *Chem. Ser.*, **8A**, 85 (1975), and D. V. Frost and D. Ingvoldstad, *ibid.*, **8A**, 96 (1975), for reviews on the beneficial and harmful effects of dietary selenium.

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if there is some qualitative or quantitative chemical difference which allows introduction, modification, or removal of the organoselenium group under conditions not possible with sulfur:

(1) Selenium forms weaker σ bonds than sulfur; hence, many reactions which involve cleavage of C–Se, O–Se, and N–Se bonds are more rapid than cleavage of analogous bonds to sulfur. In this regard, alkyl selenoxides undergo syn elimination about 1000 times as fast as do sulfoxides,[4] [1,3] and [2,3] sigmatropic rearrangements proceed at markedly lower temperatures,[5,6] and episelenides spontaneously lose selenium at room temperature.[7-9]

(2) Selenides and selenolate anions are less basic[10] and more nucleophilic[11,12] than corresponding sulfur compounds. Selenoxides are more polar and more basic than are sulfoxides.[13]

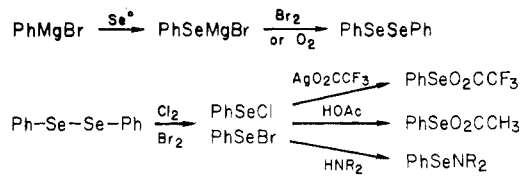
(3) Selenium is oxidized somewhat more easily to Se(IV), but with more difficulty to Se(VI) than the corresponding sulfur oxidations. Thus most oxidizing agents convert selenides to selenoxides, selenols to seleninic acids ($RSeO_2H$), and hydrogen selenide to selenium dioxide, but higher oxidation states (selenone, selenonic acid, selenium trioxide) are difficult to achieve.

(4) Organoselenium compounds are more subject to nucleophilic attack at selenium. Thus α-phenylseleno ketones are easily deselenated in the presence of base,[14] and most organoselenium compounds are attacked at selenium by organolithium reagents.[15,16] This property permits the convenient synthesis of α-lithio selenides by cleavage of selenoacetals and -ketals.[16a-d]

(5) Tetracovalent selenium compounds (selenuranes) are usually more stable and more easily prepared than corresponding sulfur systems.[17]

(6) The stereochemical lability of selenoxides is much greater than that of sulfoxides. Selenoxides are readily racemized in neutral or weakly acidic media.[18] It is this property of facile acid catalyzed nucleophilic exchange at Se(IV), coupled with resistance to further oxidation (3, above) that permits benzeneseleninic acids to serve as catalysts for epoxidation of olefins with hydrogen peroxide ($ArSeO_3H$ is thought to be the active oxidant).[19]

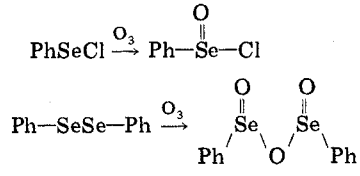
Organoselenium Reagents. Most synthetic transformations using organoselenium reagents have involved use of the arylseleno (usually phenylseleno) group, for which the primary source is a diaryl diselenide or an aryl selenocyanate. Diphenyl diselenide



is readily available by a Grignard synthesis.[14,20] Aryl selenocyanates are usually prepared by the reaction of diazonium salts with KSeCN.[19d,20b]

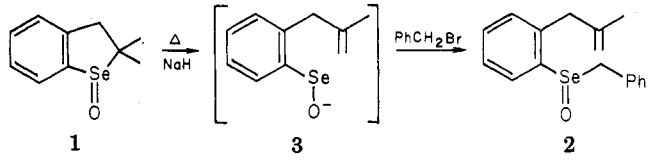
Powerful nucleophiles attack Ph_2Se_2 at selenium, but more efficient sources of electrophilic selenium are the selenenyl halides (PhSeCl, PhSeBr). Both are crystalline, shelf-stable materials which can in turn be converted to other useful reagents: mixed selenenic anhydrides ($PhSeO_2CCF_3$,[21] $PhSeO_2CCH_3$[22]) or selenenamides ($PhSeNR_2$[23]).

Benzeneseleninyl chloride and benzeneseleninic anhydride are used for the electrophilic introduction of the seleninyl group.[14,24] Utilization of a nucleophilic



(1)

seleninyl reagent ($ArSeO^-$, benzeneselenenate anion) has been reported. Decomposition of the selenoxide **1**



1 **3** **2**

in the presence of sodium hydride and benzyl bromide leads to the selenoxide **2**, presumably by Se-alkylation of the intermediate sodium selenenate **3**.[25]

Diphenyl diselenide is reduced to benzeneselenol (PhSeH or $PhSe^-$) by a variety of reducing agents of which $NaBH_4$ in ethanol is the most convenient. Less expensive reductants are available.[26-28] Selenols and

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(5) (a) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **37**, 3973 (1972); (b) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972).

(6) (a) H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); (b) H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **99**, 263 (1977).

(7) T. H. Chan and J. R. Finkenbine, *Tetrahedron Lett.*, 2091 (1974).

(8) D. L. J. Clive and C. V. Denyer, *J. Chem. Soc., Chem. Commun.*, 253 (1973).

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(16) (a) D. Seebach and N. Peleties, *Chem. Ber.*, **105**, 511 (1972); (b) D. Seebach and A. K. Beck, *Angew. Chem., Int. Ed. Engl.*, **13**, 806 (1974); (c) W. Dumont, P. Bayet, and A. Krief, *ibid.*, **13**, 804 (1974); (d) D. Seebach, N. Meyer, and A. K. Beck, *Justus Liebigs Ann. Chem.*, **846** (1977); (e) H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **97**, 3250 (1975); (f) R. H. Mitchell, *J. Chem. Soc., Chem. Commun.*, 990 (1975); (g) B.-T. Grobel and D. Seebach, *Chem. Ber.*, **110**, 867 (1977).

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(19) (a) P. A. Grieco, Y. Yokoyama, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **42**, 2034 (1977); (b) H. J. Reich, F. Chow, and S. L. Peake, *Synthesis*, 299 (1978); (c) T. Kametani, H. Nemoto, and K. Fukumoto, *Heterocycles*, **6**, 1365 (1977); (d) T. Hori and K. B. Sharpless, *J. Org. Chem.*, **43**, 1689 (1978).

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(21) (a) H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974); (b) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 695 (1973); (c) D. L. J. Clive, *ibid.*, 100 (1974).

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(23) (a) H. J. Reich and J. M. Renga, *J. Org. Chem.*, **40**, 3313 (1975); (b) H. J. Reich, J. M. Renga, and J. E. Trend, *Tetrahedron Lett.*, 2217 (1976).

(24) (a) M. R. Czarny, *J. Chem. Soc., Chem. Commun.*, 81 (1976); (b) M. R. Czarny, *Synth. Commun.*, **6**, 285 (1976).

(25) H. J. Reich and J. E. Trend, *J. Org. Chem.*, **41**, 2503 (1976).

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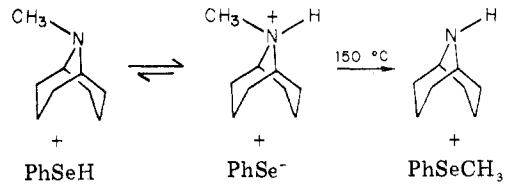
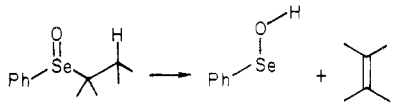
(27) W. G. Salmond, M. A. Barta, A. M. Cain, and M. C. Sobala, *Tetrahedron Lett.*, 1683 (1977).

selenolate anions are usually prepared and used in situ because of their odor and sensitivity to air oxidation. PhSeNa is a powerful nucleophile[11] for S_N2 displacements and Michael additions. It has been recommended for nucleophilic cleavage of quaternary ammonium salts,[29] lactones,[30] and methyl esters.[31] Amines can be dealkylated using PhSeH, since essentially

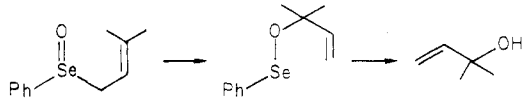


complete conversion to ammonium salt occurs.[32] Other procedures for the dealkylation of tertiary amines are available, but these are not applicable to secondary and primary amines. Benzenethiol does not protonate or dealkylate amines.

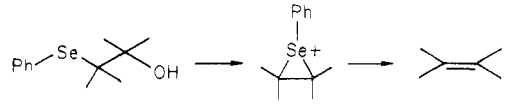
Reactions of Organoselenium Compounds. Three synthetically useful reactions of organoselenium compounds which lead to selenium-free products will be illustrated in the following sections: (1) the selenoxide syn elimination leading to olefins;



(2) the [2,3] sigmatropic rearrangement of allyl, propargyl, and allenyl selenoxides to form allyl alcohols, enones, and propargyl alcohols;



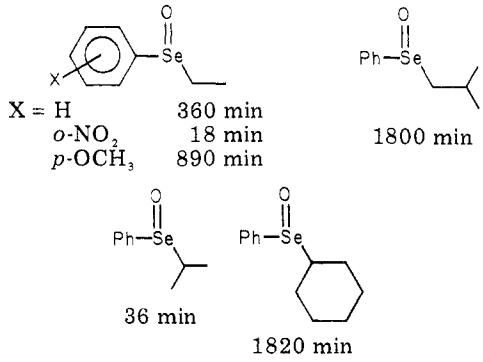
and (3) the "reductive elimination" of β-hydroxy selenides to form olefins.



In some situations the carbon–selenium bond can also be advantageously replaced by a C–H,[33] C–Br,[34] or C–Li bond.[16a-d]

The selenoxide syn elimination has received most attention from synthetic chemists because it provides a high-yield procedure for olefin formation near *room temperature* and under essentially neutral conditions. This reaction, first reported by Huguet[35] and Jones, Mundy, and Whitehouse,[4a] was shown to occur with syn stereospecificity by Sharpless, Young, and Lauer.[36] It has two principal advantages over the analogous sulfoxide elimination: first, the reaction occurs at approximately 100 °C lower temperature and second, the oxidation of selenides to selenoxides can be carried out with cheap oxidizing agents (hydrogen peroxide, peracetic acid, or *tert*-butyl hydroperoxide). Oxidation of sulfides cleanly to sulfoxides requires selective and expensive reagents (typically $NaIO_4$) to avoid oxidation to sulfones.

The half-lives for selenoxide syn elimination of several alkyl aryl selenoxides in $CDCl_3$ at 38 °C are given below.[4b] Substituent effects are similar to those



observed for sulfoxide eliminations, including faster rates for compounds forming conjugated olefins (dienes, styrenes, enones) and aryl selenoxides bearing electron-withdrawing substituents.[20b] The *o*-nitrophenyl selenoxides are particularly effective, and considerable use of them in natural product synthesis has been made by Grieco and co-workers.[37]

Several side reactions are known: selenenic acids (PhSeOH) and their disproportionation products react with olefins under acidic conditions to give β-hydroxy selenides;[4b,19d] these conditions may also cause reduction of selenoxides to selenides;[4b,38] Pummerer-like reactions have been observed in some cases.[14,39] *These side reactions can be prevented if the syn elimination is carried out by a brief thermolysis in the presence of an alkylamine.*[4b,16e] Selenoxide syn eliminations, unlike those of sulfoxides, do not seem to be reversible.[4b,25]

Although the selenoxide syn elimination functions well for the introduction of unsaturation in a wide variety of molecules, there are limitations to this technique (described in more detail elsewhere[1]). For example, acetylenes have not been successfully formed by syn elimination, and systems for which heterolysis of the C–Se bond can lead to unusually stable carbonium ions are prone to side reactions.

Dehydrogenation of Carbonyl Compounds. Phenylseleno groups can be easily introduced α to the functionality in ketones, esters, nitriles, lactones, sulfones, and similar species.[14,21a,b,40,41] Oxidation of these

(28) (a) H. J. Reich and S. K. Shah, *J. Org. Chem.*, **42**, 1773 (1977); (b) G. Bergson and A.-L. Delin, *Ark. Kemi*, 18, 441 (1961).
(29) V. Simanek and A. Klasek, *Tetrahedron Lett.*, 3039 (1969).
(30) (a) R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, 4361 (1977); (b) D. Liotta and H. Santiesteban, *ibid.*, 4369 (1977).
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(32) H. J. Reich and M. L. Cohen, unpublished results.
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(35) J. L. Huguet, *Adv. Chem. Ser.*, **No. 76**, 345 (1967).
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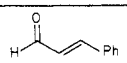
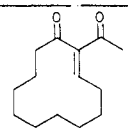
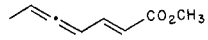
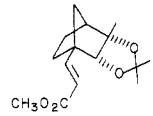
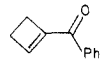
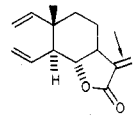
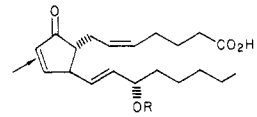
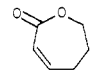
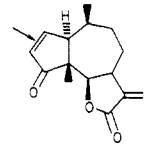
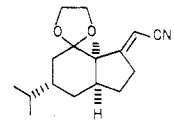
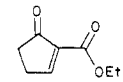
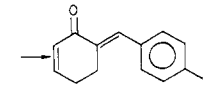
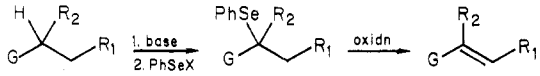
(37) (a) P. A. Grieco, J. J. Reap, and J. A. Noguez, *Synth. Commun.*, **5**, 155 (1975); (b) P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **99**, 5773 (1977).
(38) R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 1396 (1976).
(39) (a) K. B. Sharpless and K. M. Gordon, *J. Am. Chem. Soc.*, **98**, 300 (1976); (b) L. E. Saris and M. P. Cava, *ibid.*, **98**, 867 (1976); B. E. Norcross, J. M. Lansinger, and R. L. Martin, *J. Org. Chem.*, **42**, 369 (1977).
(40) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).

Table I
α,β-Unsaturated Ketones, Aldehydes Esters, and Nitriles Prepared by Selenoxide Syn Elimination

product	yield, %	ref	product	yield, %	ref
	46	40		96	44
	88, 89	14		85	47
	84	40		90	45
	87, 83	14		93	46
	>46	42		70, 70	14
	41	43		42	41b
	81	14			
	68, 74	14			

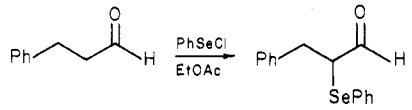
selenium compounds provides the mildest available procedure for the preparation of the corresponding α,β-unsaturated derivatives. Selected examples are shown in Table I.[42-47]

The selenenylation of carbanionic species is the most widely used method for introducing phenylseleno α to a functional group. The reaction is particularly clean



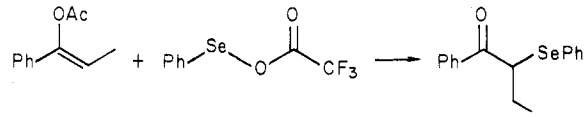
when R_2 is not hydrogen, since proton transfers cannot intervene to complicate the reaction. As one proceeds down the spectrum of carbanion reactivities from alkyllithium and Grignard reagents through anions prepared by deprotonation of sulfones, carboxylic acids, amides, esters, cyanides, lactones, and ketones to β-keto sulfoxide, β-keto selenoxide, β-keto ester and β-diketone enolates, one finds that diphenyl diselenide will selenenylate those anions more reactive than ketone enolates, but for the latter and less reactive anions the selenenyl halides are required.

Sharpless, Lauer, and Teranishi[40] have developed a procedure for the selenenylation of ketones and aldehydes under acid-catalyzed conditions using PhSeCl.



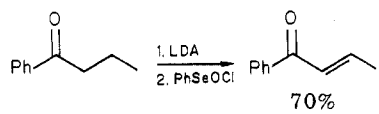
(PhSeBr behaves primarily as a brominating agent toward ketones.) This procedure nicely complements the enolate route since acidic rather than basic conditions are used and different regioisomers are sometimes formed.

A third method which has proved advantageous in some cases is the reaction of enol acetates (enol ethers and enol silanes also work) with electrophilic selenium species, in particular selenenyl trifluoroacetate.[21a,b]



The selenoxide syn elimination is not free of side reactions, and appropriate conditions must be chosen for this step.[14] It is sometimes advantageous to carry out the syn eliminations of keto selenides under weakly basic conditions to avoid interference by Pummerer-like reactions and difficulties with side reactions involving selenenic acids (PhSeOH). For example, cyclooctenone and cycloheptenone can be isolated in good yield only if the syn elimination is carried out in the presence of diethylamine to trap PhSeOH as $PhSeNEt_2$.[14]

The direct introduction of a selenoxide function by seleninylation of enolates with seleninyl chloride[14] or

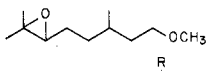
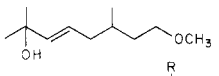
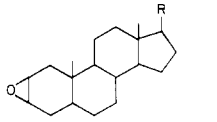
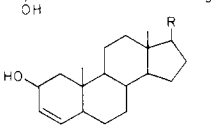
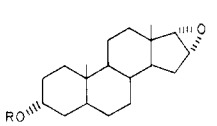
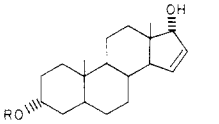
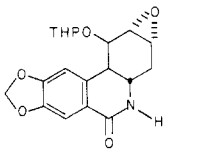
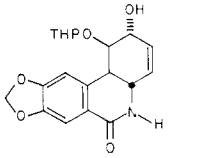
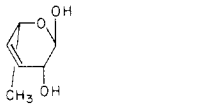
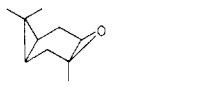
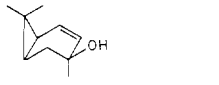
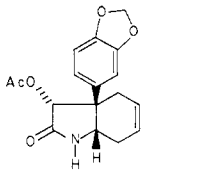
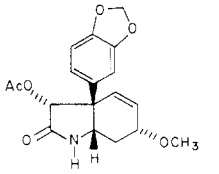
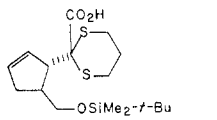
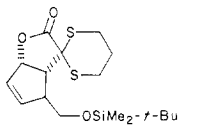
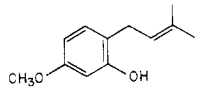
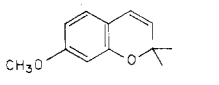


seleninic anhydride,[48] followed by in situ syn elimination, can be accomplished in satisfactory yields, although the great sensitivity of keto selenoxides to base can cause unwanted side reactions.

Seleninic anhydride and/or seleninyl chloride have also been used for the oxidation of amines to imines[24]

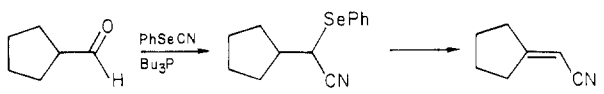
(41) (a) D. N. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974); (b) D. N. Brattesani and C. H. Heathcock, *J. Org. Chem.*, **40**, 2165 (1975).
(42) G. Stork and S. Raucher, *J. Am. Chem. Soc.*, **98**, 1583 (1976).
(43) P. A. Grieco, Y. Ohfune, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 7393 (1977).
(44) F. M. Dean and B. K. Park, *J. Chem. Soc., Chem. Commun.*, 142 (1975).
(45) D. Buddhsukh and P. D. Magnus, *J. Chem. Soc., Chem. Commun.*, 952 (1975).
(46) P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, **42**, 1717 (1977).
(47) P. J. Kocienski, G. Cernigliaro, and G. Feldstein, *J. Org. Chem.*, **42**, 353 (1977).
(48) D. H. R. Barton, P. D. Magnus, and M. N. Rosenfeld, *J. Chem. Soc., Chem. Commun.*, 301 (1975).

Table II
Conversion of Epoxides and Olefins to Allyl Alcohols, Ethers, and Esters

epoxide or olefin	product	yield, %	ref
		79	53
		51	53
		50	55
		63	56
		80	57
		93	58
		35	59
		86, 92	33b
		81, 54	54b

and phenols to *o*-quinones[48] and for the oxidative hydrolysis of hydrazones, oximes,[49] and dithiolanes.[50]

Grieco and Yokoyama[51] have developed an elegant procedure for the conversion of aldehydes to unsaturated nitriles. The intermediate α-phenylseleno nitriles

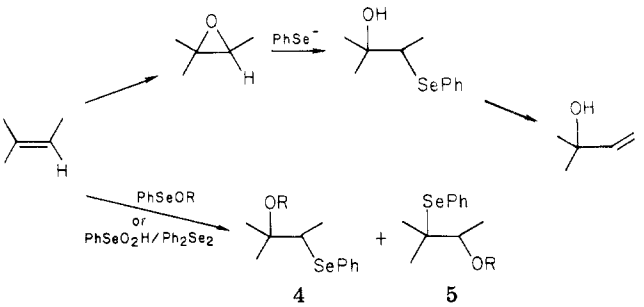


89% 95%

can be alkylated via the α-lithio nitrile.[52]

Conversion of Olefins to Allyl Alcohols. Two pathways are available for the conversion of olefins to β-hydroxy selenides and hence to allyl alcohols by selenoxide syn elimination: the opening of epoxides by selenolate anion.[53] or the addition of the elements of selenenic acid (PhSeOH) directly to olefins.

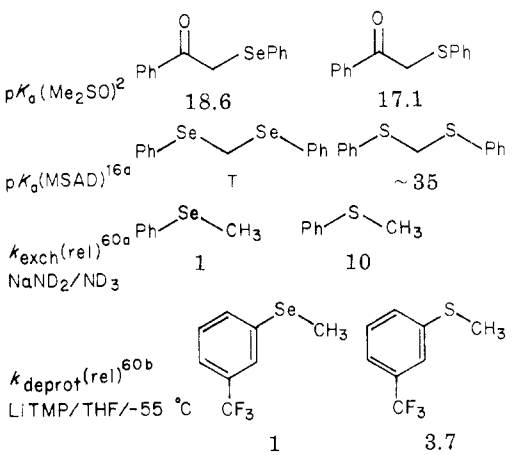
Several procedures are available for the electrophilic addition of PhSeOH to olefins: reaction with



4 5

$PhSeO_2CCH_3$,[22] $PhSeO_2CCF_3$,[21a,c] or a 1:1 mixture of Ph_2Se_2 and $PhSeO_2H$ (this apparently generates PhSeOH or a related species by comproportionation).[4b,19d] The last procedure can be carried out to give the thermodynamically more stable alcohol **4**. Intramolecular capture of episelenonium ions leads to lactones and cyclic ethers.[33b,54] Table II presents examples of the conversion of epoxides and olefins to allylic alcohols, ethers, and lactones.[55-59]

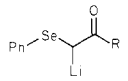
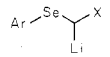
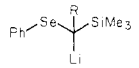
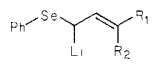
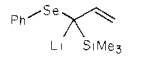
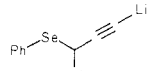
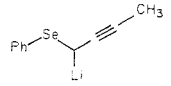
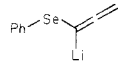
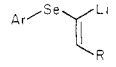
Selenium-Stabilized Anions. In addition to serving as a tool for functional group interconversion, selenium substituents can also activate adjacent hydrogens toward deprotonation, creating the potential for C–C bond formation. What little data are available suggests that selenium stabilizes negative charge on neighboring carbon slightly less effectively than does sulfur,[60] in contrast to a theoretical prediction.[61]



A major limitation in the chemistry of selenium-stabilized anions is evident from the early work of Gilman[15] and Seebach;[16a] i.e., unlike sulfides, many selenides are attacked *at selenium* by alkyllithium reagents; deprotonation is sometimes only a minor pathway. We have confirmed these results in a number of systems. In certain cases, even amide bases can cause C–Se bond cleavage.

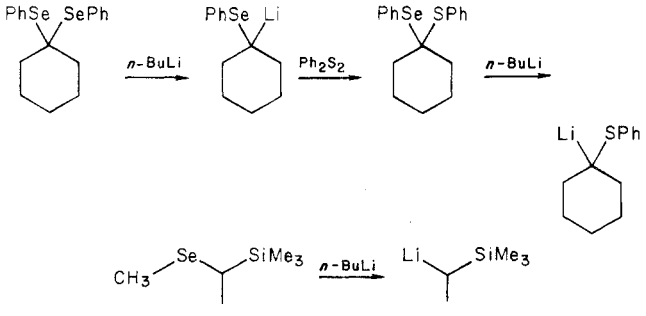
(49) D. H. R. Barton, D. J. Lester, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 445 (1977).
(50) D. H. R. Barton, N. J. Cussans, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 751 (1977).
(51) P. A. Grieco and Y. Yokoyama, *J. Am. Chem. Soc.*, **99**, 5210 (1977).
(52) Y. Masuyama, Y. Ueno, and M. Okawara, *Chem. Lett.*, 835 (1977).
(53) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).
(54) (a) D. L. J. Clive and G. Chittattu, *J. Chem. Soc., Chem. Commun.*, 484 (1977); (b) D. L. J. Clive, G. Chittattu, N. J. Curtis, W. A. Kiel, and C. K. Wong, *ibid.*, 725 (1977); (c) M. D. M. Campos, and N. Petragnani, *Chem. Ber.*, **93**, 317 (1960).
(55) V. Balogh, J.-C. Beloeil, and M. Fetizon, *Tetrahedron*, **33**, 1321 (1977).
(56) S. Ohta and S. Kimoto, *Tetrahedron Lett.*, 2279 (1975).
(57) S. David and A. Lubineau, *Nouv. J. Chim.*, 1, 375 (1977).
(58) S. Uzarewicz and E. Zientek, *Roczn. Chem.*, **51**, 181 (1977).
(59) K. Isobe, J. Taga, and Y. Tsuda, *Tetrahedron Lett.*, 2331 (1976).
(60) (a) A. I. Shatenshtein and H. A. Gvozdeva, *Tetrahedron*, **25**, 2749 (1969); (b) S. K. Shah, Ph.D. Thesis, University of Wisconsin—Madison, 1977.
(61) J.-M. Lehn, G. Wipff, and J. Demuynck, *Helv. Chim. Acta*, **60**, 1239 (1977).

Table III
α-Lithio Selenides Prepared by Deprotonation

lithium reagent			base, temp °C	ref
		R		
		OEt	$LiNR_2$,[a] −78	40
		OLi	LDA, −78	63
		Ph	LDA, −78	32
	Ar	X		
	*b*	H	LTMP, −40	60b
	Ph	SePh	$LiNR_2$,[c] −78	16a
	Ph	$SiMe_3$	sec-BuLi, 25	16e
	b	$SiMe_3$	LTMP, −40	28a
	b	OCH_3	LTMP, −78	63
	Ph	Ph	LDA, −78	16e,f
	R = Ph		$LiNEt_2$, 0	28a
	SePh		LDA, 0	64
	R_1	R_2		
	H	H	LDA, −78	6a
	CH_3	H	LDA, −78	6a
	CH_3	CH_3	LDA, 0	6a
	CH_3	Cl	LDA, −78	6a
			$LiNEt_2$, −78	6a
			LDA, −78	6b
			LDA, −78	60b
			LDA, −78	60b[d]
	Ar	R		
	Ph	H	LDA, −50	60b
	b	H	LDA, −78	65
	Ph	Ph	LDA, −78	65
	b	*i*-Pr	LTMP, −78	65

[a] Lithium isopropylcyclohexylamide. [b] Ar = *m*-trifluoromethylphenyl. [c] Lithium diisobutylamide. [d] This lithium reagent can be prepared by deprotonation of phenylselenoallene, 1-phenylselenopropyne, or 2-chloro-3-phenylselenopropene (2 equiv of LDA are required for consecutive dehydrohalogenation and deprotonation).

The cleavage of selenides, a reaction which resembles the metal–halogen and other metal–metaloid exchange reactions, has been used to prepare α-lithio selenides,[16a-c] sulfides,[16b,c] and silanes[62] as well as α-lithio vinyl selenides[16g] and sulfides, most of which are not available by other techniques.



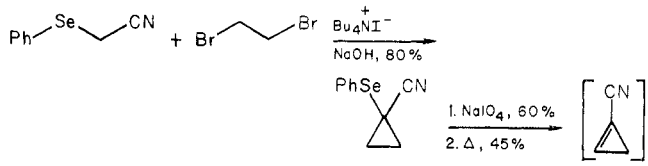
Lithium amide bases show a much lower tendency to attack at the soft electrophile selenium and can therefore be used to deprotonate the series of selenides shown in Table III (see ref 6, 16,a,e,f, 28a, 40, 60b, 63-65). Lithium diisopropylamide (LDA) suffices for most of the compounds, but the use of lithium tetramethylpiperidide (LiTMP)[66] is necessary for some deprotonations. LiTMP is kinetically at least a power of ten more basic than LDA. The range of accessible α-lithio selenides is further broadened by using an electron-withdrawing substituent (CF_3) on the phenylseleno group.[60b]

Unfortunately, the effect of alkyl substituents on kinetic and thermodynamic acidities is very large, and most of the selenides in Table III can no longer be deprotonated if an alkyl group is introduced at the α position.

Since alkyl selenides other than methyl phenyl are not deprotonated either by lithium amide or by alkyllithium bases, α-lithio alkyl selenides must be prepared by the cleavage of selenoacetals and -ketals described above. An alternative procedure (which uses more readily available selenides as starting materials and avoids the formation of byproduct butyl phenyl selenide) employs α-lithio selenoxides, prepared by deprotonation of selenoxides with LDA. Because many alkyl selenoxides are unstable at room temperature, they are best prepared by in situ oxidation with *m*-chloroperbenzoic acid. The lithium reagents prepared in this way[16e] react rapidly with ketones and aldehydes and can be alkylated with reactive primary halides.

Synthesis of Olefins and Dienes. The application of selenium-stabilized anions to the synthesis of olefins can be accomplished by using either the selenoxide syn elimination or the β-hydroxy selenide "reductive elimination" as the olefin-forming step. The former requires alkylation of a lithium reagent, the latter reaction with an aldehyde or ketone.

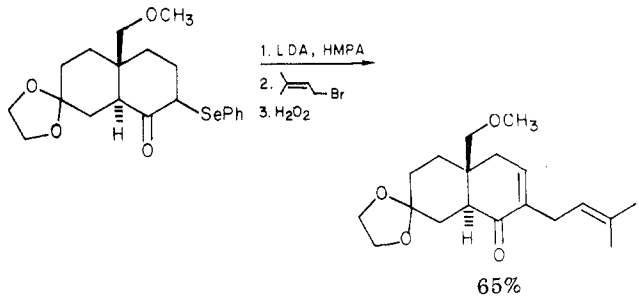
Selenoxide Syn Elimination. The alkylation of α-lithio selenides and selenoxides becomes a useful process only when some inherent feature of the molecule results in predominant formation of a single double bond regioisomer during the syn elimination. The first application was the alkylation of ethyl phenylselenoacetate reported by Sharpless, Lauer, and Teranishi.[40] α-Phenylselenonitriles have been alkylated using both preformed enolates[51] and phase transfer techniques.[52] The latter has led to the first synthesis of a cyclopropene by selenoxide syn elimination (the cyanocyclopropene was trapped by Diels–Alder reaction with anthracene).



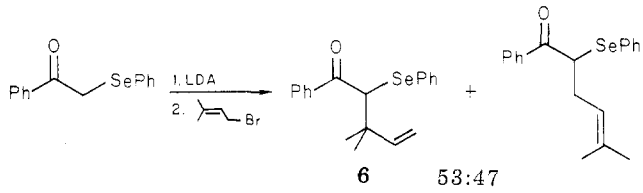
Successful alkylations of lactones[67] and ketones[37b] have been reported, the latter in connection with Grieco's synthesis of vernolepin. We have observed an interesting side reaction during alkylation of enolates prepared from seleno- and thioketones: i.e., alkylation

(62) W. Dumont and A. Krief, *Angew. Chem.*, **88**, 184 (1976).

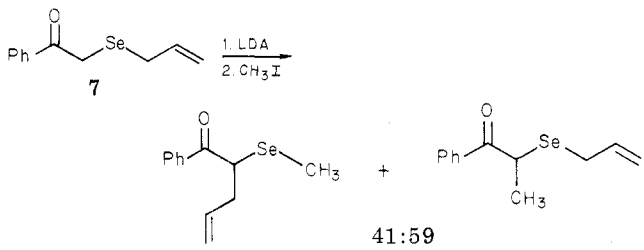
(63) H. J. Reich and F. Chow, unpublished results.
(64) B.-T. Gröbel and D. Seebach, *Chem. Ber.*, **110**, 852 (1977).
(65) H. J. Reich, P. D. Clark, and W. W. Willis, Jr., unpublished results.
(66) M. W. Rathke and R. Kow, *J. Am. Chem. Soc.*, **94**, 6854 (1972); R. A. Olofson and C. M. Dougherty, *ibid.*, **95**, 582 (1973).
(67) P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).



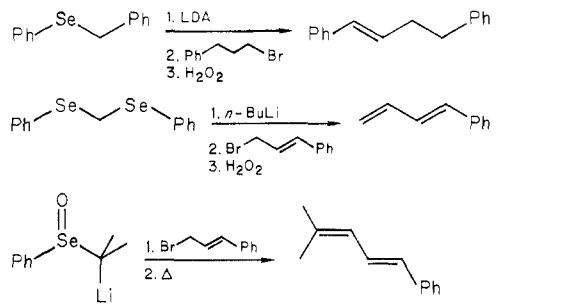
on the heteroatom.[32] Thus phenylselenoacetophenone gives some of the product (**6**) obtained by γ-alkylation of prenyl bromide.



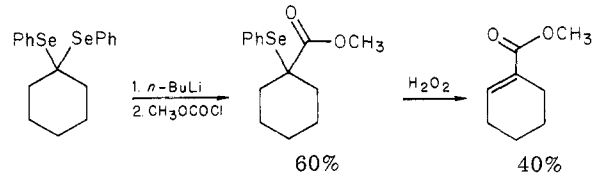
That this product is actually formed by Se-alkylation followed by [2,3] sigmatropic rearrangement of the ylide is shown by alkylations carried out with the *Se*-allyl compound **7**, for which *C*-allyl products were observed upon reaction with prenyl and methyl iodide.



Less highly stabilized α-lithio selenides can also be alkylated and oxidized to give variously substituted olefins.[16e,f] When the alkylating agent is an allyl halide,

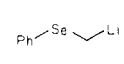
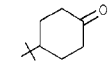
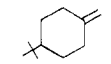
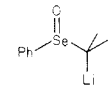
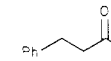
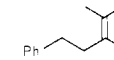
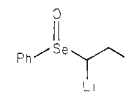
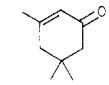
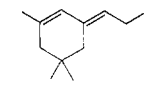
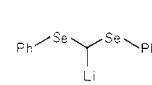
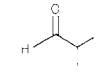
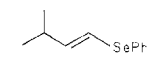
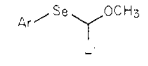
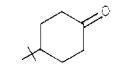
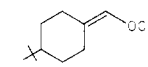


the syn elimination is usually sufficiently regioselective that pure products are obtained. α-Lithio selenium compounds can also be acylated and formylated to provide connective syntheses of α,β-unsaturated carbonyl compounds.[16e,68]

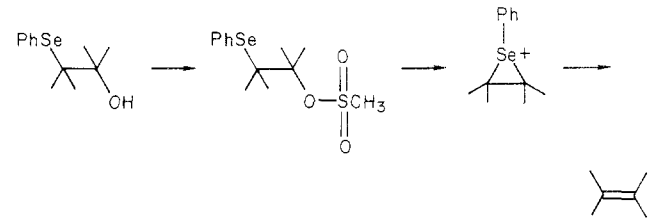


(68) J. N. Denis, W. Dumont, and A. Krief, *Tetrahedron Lett.*, 453 (1976).

Table IV
Synthesis of Olefin by Reductive Elimination of β-Hydroxy Selenides.[64,69]

lithium reagent	carbonyl compound	product	yield, %
			71, 87
			61
			56, 52
			65
			83, 62

Reductive Elimination of β-Hydroxy Selenides. The observation was made that many of the reaction products of $PhSeO_2CCF_3$ with olefins (β-trifluoroacetoxy selenides)[21a] were unstable and reverted readily to the olefins from which they were formed. Further experiments showed that a variety of reagents which had in common the ability to convert the hydroxyl to a better leaving group (of which the best was CH_3SO_2Cl/NEt_3) transformed β-hydroxy selenides to olefins.[69] Krief and co-workers[70] have subsequently



reported several other reagents which are useful, including $HClO_4$/ether, $(CF_3CO)_2O/NEt_3$, TsOH/pentane, $(C_6H_4O_2)PCl/NaH$, and $SOCl_2/NEt_3$. The reaction is the reverse of an electrophilic selenium addition and proceeds with anti stereochemistry.[63,70]

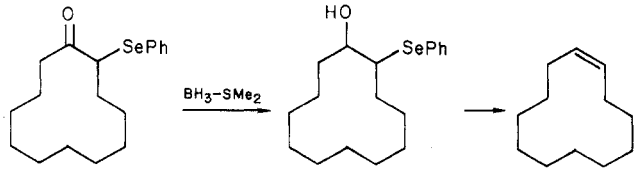
In conjunction with the addition of selenium-stabilized anions, the "reductive elimination" provides a Wittig-like procedure for the synthesis of olefins (Table IV). When α-lithio selenoxides are used, the selenoxide function must be reduced before syn elimination occurs. This can be easily accomplished in situ either with $I^-/NaHSO_3/HOAc$ or $P(OCH_3)_3/RCO_2H$. In favorable cases diastereomeric β-hydroxy selenides can be separated and each converted to a stereochemically pure olefin. The reaction has been extended to the preparation of vinyl selenides and vinyl ethers.[63,69]

Krief and co-workers have utilized reductive eliminations to deoxygenate epoxides (nucleophilic opening using $PhSe^-$, followed by reductive elimination) and convert α-seleno aldehydes to olefins by addition of organometallic reagents to the carbonyl groups.[70]

(69) H. J. Reich and F. Chow, *J. Chem. Soc., Chem. Commun.*, 790 (1975).

(70) (a) J. Remion, W. Dumont, and A. Krief, *Tetrahedron Lett.*, 1385 (1976); (b) A. M. Leonard-Coppens and A. Krief, *ibid.*, 3227 (1976); (c) J. Remion and A. Krief, *ibid.*, 3743 (1976).

α-Phenylseleno ketones suffer varying amount of deselenation when treated with lithium or Grignard reagents or nucleophilic hydride donors such as lithium aluminum hydride or sodium borohydride. Reduction to hydroxy selenides can, however, be achieved with diborane (must be free of $NaBH_4$), diisobutylaluminum hydride, or BH_3–SMe_2.[63]



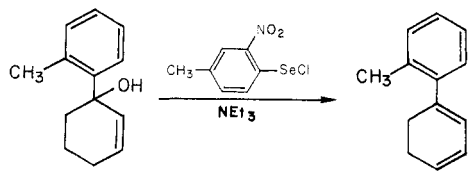
c/*t* = 1:1
88%

There are several situations in which the syntheses of olefins by the technique described above are superior to existing techniques. First of all, tetrasubstituted olefins can be prepared in situations where the Wittig reaction fails. Secondly, the great nucleophilicity and low basicity of $PhSe^-$ allow the preparation of selenides from alkyl halides and sulfonates when the analogous phosphonium salts and phosphonates would be difficult to prepare in satisfactory yield. Additional flexibility in the preparation of suitable reagents is provided by the conversion of ketones to selenoketals, which are precursors to α-lithio selenides.

Synthesis of Allyl Alcohols. The reaction of carbonyl compounds with α-lithio selenides or selenoxides followed by selenoxide syn elimination leads to allyl alcohols, a transformation equivalent to the addition of a vinyl anion to the carbonyl compound.[16e] Table V presents several examples of allyl alcohols prepared in this way. The corresponding sulfur methodology has not been developed since the brutal conditions required for syn elimination would in some cases destroy the sensitive products.

Phenylselenoallyllithium Reagents. A variety of allyl selenides are deprotonated by lithium amide bases (Table III). The resulting anions are powerful nucleophiles (some can be alkylated with secondary alkyl bromides) and usually react predominantly at the α position. Oxidation of allyl selenides results in formation of allyl alcohols by [2,3] sigmatropic rearrangement of the selenoxide, a reaction first reported by Sharpless and Lauer[5] and previously studied in the sulfur series by Evans[71] and others. The selenium compounds have the usual advantage of allowing the use of a cheap oxidizing agent (H_2O_2). Trapping agents for the allyl selenenate ester formed by [2,3] sigmatropic rearrangement are not required since hydrolysis occurs rapidly.

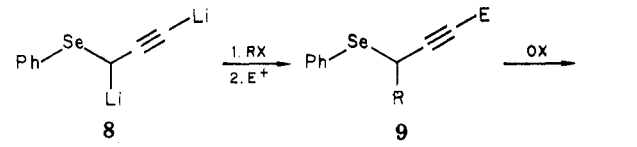
In a few cases syn elimination has been shown to compete with [2,3] sigmatropic rearrangement of allyl selenoxides.[6,27] The reaction can become an effective diene synthesis in favorable circumstances:[72]



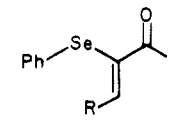
50%

(71) D. A. Evans, *Acc. Chem. Res.*, 7, 147 (1974).

Phenylselenopropargyllithium Reagents. In contrast to the allyl selenides discussed above, chemistry quite divergent from that found for similar sulfur compounds[73] was observed for propargyl selenides.[6b]

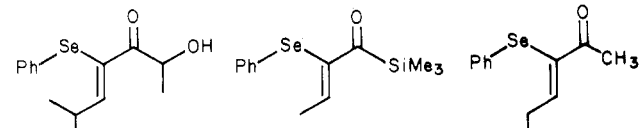


8 **9**



10

The dianion **8** can be sequentially alkylated and treated with a second electrophile to give disubstituted propargyl selenides (**9**). Oxidation of these to the selenoxide under controlled conditions leads to α-phenylseleno enones **10** in fair to good yields.[6b] The reaction

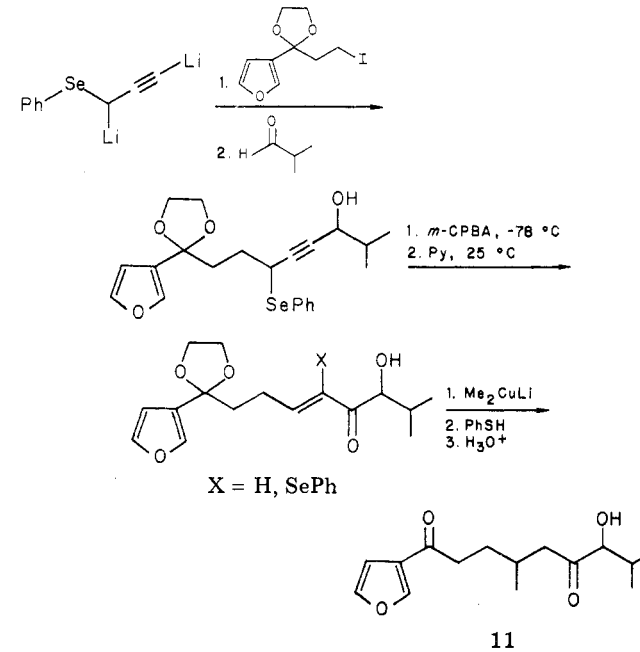


10a
RX = *i*-PrI
E = H_2O

10b
RX = CH_3I
E = $SiMe_3Cl$

10c
RX = $Ph(CH_2)_3I$
E = CH_3I

provides facile access to rather complicated enone systems. A synthesis of the toxic furanosesquiterpene 7-hydroxymyoporone[74] (**11**) has been completed using this anion.[75] The cuprate addition product is a 70:30 mixture of the unnatural and natural diastereomers of racemic 7-hydroxymyoporone.



11

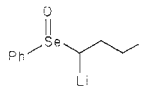
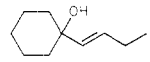
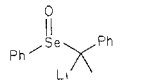
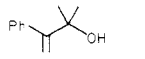
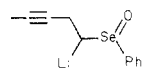
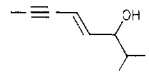
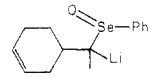
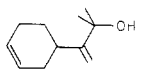
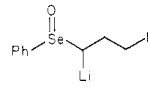
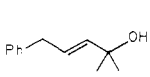
(72) H. J. Reich, I. L. Reich, and S. Wollowitz, *J. Am. Chem. Soc.*, 100, 5981 (1978).

(73) K. C. Majumdar and B. S. Thyagarajan, *J. Chem. Soc., Chem. Commun.*, 83 (1972); Y. Makisumi and S. Takada, *ibid.*, 848 (1972).

(74) L. T. Burka, R. M. Bowen, B. J. Wilson, and T. M. Harris, *J. Org. Chem.*, 39, 3241 (1974).

(75) H. J. Reich and P. Gold, unpublished results.

Table V
Synthesis of Allyl Alcohols by Addition of α-Lithio Selenoxides to Ketones and Aldehydes[16e,60b]

lithium reagent	carbonyl compound	allyl alcohol	yield, %
			78
			74
			68
			69
			76

Summary. The combination of readily accessible reagents and convenient reactions for the introduction of selenium, the air stability and ease of manipulation of most organoselenium compounds, and the availability of mild oxidative and reductive reactions for the removal of selenium has begun to make selenium one of the more valuable of the heavier elements to the synthetic organic chemist. It is expected that refinement and elaboration of the methods outlined here will continue and that additional new procedures based on the sometimes unique reactivity of organoselenium compounds will be developed.

It is a pleasure to thank my co-workers (J. M. Renga, I. L. Reich, S. K. Shah, F. Chow, J. E. Trend, P. D. Clark, S. Wollowitz, P. A. Gold, M. L. Cohen and S. L. Peake) for their conceptual and experimental contributions to this work, and to the National Science Foundation, The Petroleum Research Fund, administered by the American Chemical Society, and the Wisconsin Alumni Research Foundation for financial support.

Poly(iminomethylenes): Rigid Rod Helical Polymers

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Laboratory for Organic Chemistry of the University, Utrecht, The Netherlands

Received May 3, 1978

Isocyanides, also called isonitriles, have an electronic configuration which resembles that of carbon monoxide.

$$:\ddot{O}{=}C: \leftrightarrow :\overset{+}{O}{\equiv}\overset{-}{C}:$$

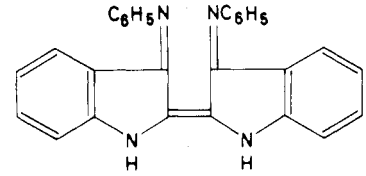
$$R{-}\ddot{N}{=}C: \leftrightarrow R{-}\overset{+}{N}{\equiv}\overset{-}{C}:$$

The contribution of the dipolar structure is important, as can be seen from the value of the N≡C stretching vibration which is in the triple bond region of the infrared, viz. 2100–2200 cm^{-1}. At the same time the carbenic structure of isocyanides is apparent from their ability to give α additions easily.

$$R{-}N{=}C + X{-}Y \rightarrow R{-}N{=}C\begin{matrix}X\\Y\end{matrix}$$

The organic chemistry of isocyanides has been reviewed in several places; refer to the 1971 book edited by Ugi.[1]

Ever since Gautier[2] and Hofmann[3] discovered isocyanides in 1867, many authors have noted their tendency to form oligomers and polymers. In only a few cases have these products actually been characterized. For instance, the blue color appearing in phenyl isocyanide at ambient temperature has been proved to be from the tetramer, indigodianil, **1**.[4]



1

The first reports on polymers of isocyanides are to be found in an article in Japanese by Yamamoto[5] and in a paper given by Millich[6] at an ACS meeting. Yamamoto tested the activity of radical initiators, anions, and Lewis acids as catalysts for polymerization. Only Lewis acids, e.g., boron trifluoride, were found to be active. The yields varied from 13 to 45% with an exceptionally high yield of 100% for the polymer of cyclohexyl isocyanide. *tert*-Butyl isocyanide did not polymerize with boron trifluoride but partly oligomerized and partly isomerized to *tert*-butyl cyanide. From spectroscopic data it was suggested that the polymers have structure **2**.

$$[R{-}N{=}C<]_n$$

2

Wiendelt Drenth was born in Groningen, The Netherlands, in 1925. He received his Ph.D. degree with E. H. Wiebenga on X-ray structure determinations of α,ω-diphenylpolyenes. He then switched to physical organic chemistry, and gained experience in working with S. Winstein, J. F. Arens, and G. J. M. van der Kerk. He is a Professor of Organic Chemistry at the University of Utrecht and editor-in-chief of *Recueil des Travaux Chimiques des Pays-Bas*.

Roeland Nolte was born in 's-Heerenberg, The Netherlands, in 1944. He obtained his Ph.D. degree with Professor Drenth on poly(iminomethylenes).

(1) I. Ugi, "Isonitrile Chemistry", Academic Press, New York, N.Y., 1971.
(2) A. Gautier, *Justus Liebigs Ann. Chem.*, **142**, 289 (1867).
(3) A. W. Hofmann, *Justus Liebigs Ann. Chem.*, **144**, 114 (1867).
(4) C. Grundmann, *Chem. Ber.*, **91**, 1380 (1958).
(5) Y. Yamamoto, T. Takizawa, and N. Hagihara, *Nippon Kagaku Zasshi*, **87**, 1355 (1966).
(6) F. Millich and R. G. Sinclair, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1965. For an historical account, see F. Millich, "Encyclopedia of Polymer Science and Technology", Supplement, Vol. 15, H. Mark, N. G. Gaylord, and N. M. Bikales, Eds., Wiley-Interscience, New York, N.Y., 1971, p 395.

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