JOC Article

Phosphonyl, Phosphonothioyl, Phosphonodithioyl, and Phosphonotrithioyl Radicals: Generation and Study of Their Addition onto Alkenes†

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The treatment of benzyl dialkyl phosphites and dithiophosphites with benzeneselanyl chloride generates an Arbuzov-type transformation leading to the dialkyl selenophosphates **19a** and **19b** and to selenophosphorodithioates **21a** and **21b**. Interaction of these substrates with Lawesson's reagent yields the corresponding selenophosphorothioates **20a** and **20b** and the selenophosphorotrithioates **22a** and **22b**. When treated with a radical initiator in the presence of a hydrogen donor and an alkene, all eight phosphorus(V) precursors undergo homolytic cleavage of the P−Se bond to generate the phosphonyl, phosphonothioyl, phosphonodithioyl, or phosphonotrithioyl radicals. Most of these are shown to add onto electron-rich and electron-poor alkenes to deliver the expected adducts in fair to excellent yields. Cyclic precursor **19b** displays peculiar behavior and, under the reaction conditions, produces only the corresponding cyclic phosphite. Application of this radical chain process is carried out on furanosyl 3-*exo*-methylene derivative **37** to diastereoselectively furnish five new 3-phosphonomethyl-, 3-phosphonothiomethyl-, and 3-phosphonodithiomethyl-3-deoxofuranoses **38a**−**c** and **38f**,**g**. The possibility of conducting tandem processes is also discussed through experiments involving (1*R*)-(+)-α-pinene (**39**) and diallylamine **41**.

Introduction

Phosphonates **2** have attracted much attention during the past decades because of their similarities with the phosphate functional group **1** (Figure 1).[1] The central role played by the latter in numerous biological processes and its position as a crucial constituent of many major biomolecules have resulted in the development of various synthetic methodologies designed at producing **2** as mimics of the parent phosphate. The replacement of one or more oxygen atom(s) in phosphonates by sulfur generates phosphonothioates, phosphonodithioates, or phosphonotrithioates (**3**, **4**, or **5**, respectively).

The large range of organophosphorus compounds containing sulfur have found widespread use as pesticides, in petroleum technology, and in metal ore extraction techniques.[2] The reported preparations of species **3**−**5** enter in two categories: the first ones rely on phosphorus−carbon bond formation, while the others exploit modifications at phosphorus in phosphorus−carbon-bonded compounds.[3] The approach relying on the addition of phosphorus-centered radicals onto alkenes was first introduced in the early 1950s on substrates devoid of sulfur and, more recently, was extended to substrates

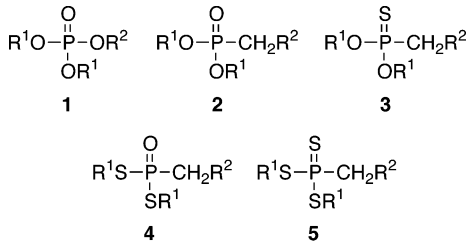

FIGURE 1. Structures of phosphates **1**, phosphonates **2**, phosphonothioates **3**, phosphonodithioates **4,** and phosphonotrithioates **5**.

encompassing single or double phosphorus−sulfur bond(s). Thus, several reports have since then demonstrated the efficiency of the method, when applied to *O*,*O*-dialkylphophites **6** or *O*,*O*-dialkylthiophosphites **7**; *O*,*O*-dialkylphosphonates and phosphonothioates are generally obtained in good to excellent yields (Scheme 1).[4]

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(1) Hartley, F. R., Ed. *The Chemistry of Organophosphorus Compounds, Vol. 4, Ter- and Quinque-valent Phosphorus Acids and Their Derivatives*; John Wiley & Sons: Chichester, 1996.

(2) See, for instance: (a) Shell, D. C.; Hayward, E. C. U.S. Patent 4,024,049 (19770517), 1977. (b) Ukeles, S. D.; Ben-Yoseph, E.; Finkelstein, N. P. Eur. Patent 89-302,625 (19890316), 1989. (c) Kazama, H.; Matsuoka, S. Jpn. Patent 04,330,083 (92,330,383), 1992. (d) Kazama, H.; Matsuoka, S. Jpn. Patent 05,39,296 (93 39,296), 1993. (e) Nakanishi, H.; Kuribayashi, T. Jpn. Patent 05 09,490 (93 09,490), 1993. (f) Tang, C. C.; Ma, F. P.; Zhang, K.; He, Z. J.; Jin, Y. C. *Heteroatom Chem.* **1995**, *6*, 413−417. (g) Rodriguez, O. P.; Thompson, C. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *117*, 101−110. (h) Kalir, A.; Kalir, H. H. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: Chichester, New York, 1996; pp 767−780.

(3) Edmundson, R. S. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; John Wiley & Sons: Chichester, 1996; Vol. 4, Chapter 5, pp 400−412.

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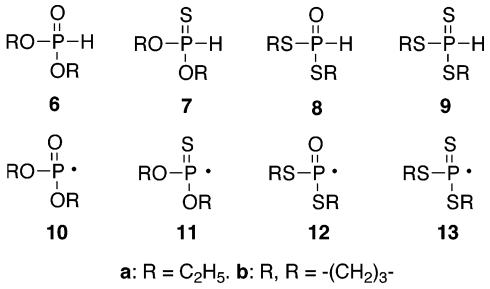
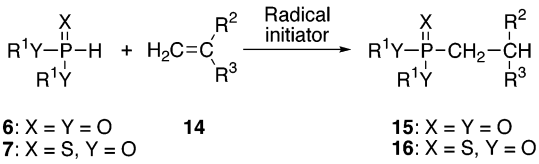


FIGURE 2. Phosphites **6**, thiophosphites **7**, dithiophosphites **8,** and trithiophosphites **9**, as well as radicals **10**−**13** generated therefrom.

SCHEME 1. Addition of Phosphites 6 and Thiophosphites 7 onto Alkenes 14



Our own studies on the radical chain addition of species **6** and **7** onto 1,1-difluoroalkenes showed the positive effect of the sulfur atom in **11** on the course of the reaction, when compared to the fully oxygenated analogue (i.e., **10**) (Figure 2).[5] More recently, we described the addition of *S*,*S*-dialkylphosphonodithioyl radicals **12** onto alkenes.[6] In this paper, we report a more complete and comparative study on the generation of radicals **10**, **11**, **12**, and **13** as well as on their behavior toward terminal alkenes.

The lower stability of the P−S bond (45−50 kcal/mol versus 90−100 kcal/mol for the P−O bond) precluded us from using *S*,*S*-dialkyl dithiophosphites and trithiophosphites (**8** and **9**, respectively) as precursors of radicals **12** and **13**. Thus, for instance, dithiophosphites **8** are notoriously difficult to prepare and handle and have been reported to disproportionate and to be prone to decomposition upon hydrolysis.[7] In addition, the more stable, cyclic 1,3,2-dithiaphosphinane 2-oxide (**8b**, R, R = $-CH_2-CH_2CH_2-$) has been shown to easily form oligomers or polymers.[8,9] Analogously, attempts to prepare trithiophosphites have been reported to be unsuccessful, due to a rapid disproportionation process.[10] Hence, we elected to rely on precursors encompassing a P−Se bond. Indeed, *O*,*O*-diethylphenylselenophosphate (**19a**) has been prepared by Petragnani and used by Motherwell to generate the corresponding phosphonyl radical **10a** (Figure 3).[11] Thus, radical **10a**, when generated from **19a** and a radical initiator in the presence of a hydrogen donor, was shown to add onto carbohydrate *gem*-difluoroenol ethers to deliver the expected adducts in fair yields.

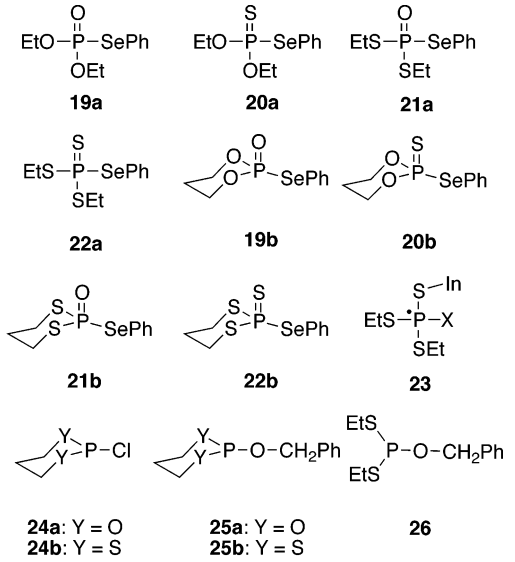


FIGURE 3. Structures of radical precursors **19**−**22**, of radical **23**, and of intermediates **24**−**26**.

These literature data constitute the starting point of this study. The corresponding diethylphenylselenophosphorothioate (**20a**), diethylphenylselenophosphorodithioate (**21a**), and diethylphenylselenophosphorotrithioate (**22a**), as well as the four related cyclic derivatives **19b**−**22b**, were considered as good precursors of radicals **10**−**13**. The choice of a selenoether group (rather than halogen atoms) stemmed from the consideration that a competitive addition process or a competitive homolytic cleavage could arise under the reaction conditions with some of these precursors.[12] Thus, for instance, homolytic cleavage of the P−Se bond in **22a** would give rise to the desired phosphonotrithioyl radical **13a** while addition of the initiator on the sulfur end of the P═S bond would generate an undesired, stabilized phosphorus radical of the type **23**.[13]

(4) (a) Stiles, A. R.; Vaughan, W. E.; Rust, F. F. *J. Am. Chem. Soc.* **1958**, *80*, 714−716. (b) Pudovik, A. N.; Konovalova, I. V. *Zh. Obshch. Khim.* **1959**, *29*, 3338−3342; *Chem. Abstr.* **1960**, *54*, 15224b. (c) Kenny, R. L.; Fisher, G. S. *J. Org. Chem.* **1974**, *39*, 682−686. (d) Battiste, D. R.; Haseldine, D. L. *Synth. Commun.* **1984**, *14*, 993−1000. (e) Finke, M.; Kleiner, H.-J. *Liebigs Ann. Chem.* **1974**, 741−750. (f) Dingwall, J. G.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2081−2090.

(5) Piettre, S. R. *Tetrahedron Lett.* **1996**, *37*, 2233−2236.

(6) Lopin, C.; Gautier, A.; Gouhier, G.; Piettre, S. R. *Tetrahedron Lett.* **2000**, *41*, 10195−10200.

(7) (a) Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1956**, 3269−3271. (b) Kardanov, N. A.; Provotorova, N. P.; Petrovskii, P. V.; Godoviloc, N. N.; Kabachnik, M. I. *Izv. Akad. Nauk. SSSR* **1983**, 2114−2121. (c) Al'fonsov, V. A.; Trusenev, A. G.; Batyeva, E. S.; Pudovic, M. A. *Ivz. Akad. Nauk. SSSR* **1991**, 2103-2111.

(8) (a) Nifant'ev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Chernyak, S. M. *Dolk. Akad. Nauk. SSSR* **1972**, *203*, 593−595. (b) Sorokina, S. F.; Zavalishina, A. I.; Nifant'ev, E. E. *Zh. Obshch. Khim.* **1973**, *43*, 750−752. (c) Nifant'ev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Blagoveshchenskii, V. S.; Yakovleva, O. P.; Esenina, E. V. *Zh. Obshch. Khim.* **1974**, *44*, 1694−1697.

(9) In our hands, compound **8b** was formed in very poor yields (<10%), and large amounts of insoluble, colorless material were obtained.

(10) Nifant'ev, E. E.; Chechetkin, A. S.; Blagoveshchenskii, V. S.; Sokurenko, A. M. *Zh. Obsch. Khim.* **1983**, *53*, 2695−2697.

(11) (a) Petragnani, N.; Toscano, V. G.; Moura Campos, M. *Chem. Ber.* **1968**, *101*, 3070−3078. (b) Herpin, T. F.; Houlton, J. S.; Motherwell, W. B.; Roberts, B. P.; Weibel, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 613−614. (c) Herpin, T. F.; Motherwell, W. B.; Roberts, B. P.; Roland, S.; Weibel, J.-M. *Tetrahedron* **1997**, *53*, 15085−15100.

(12) In particular, the dissociation energies of the analogous C−X bonds (X = Br: 68 kcal/mol; X = S: 65 kcal/mol; X = Se: 58 kcal/mol) and literature data allow one to expect a cleaner and more selective homolytic cleavage with selenophosphorodithioate **21** and selenophosphorotrithioate **22** than with the corresponding phosphorodithioyl bromide **i** and phosphorotrithioyl bromide **ii**. The same can be said for the phosphorotrithioate **iii** and phosphorotetrathioate **iv**.

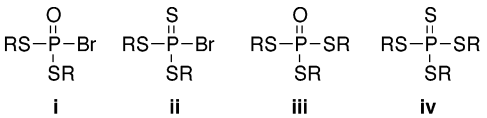


TABLE 1. Optimization of the Reaction Conditions in the Case of Precursor 19a and *n*-Oct-1-ene (27)

entry	procedure	*n*-octene **27** (equiv)	**19a** (equiv)	hydrogen donor[a] (equiv)	AIBN (equiv)	addition time (h)	yields[b] (%)
1	A	1	3	*n*-Bu_3SnH (4) or TTMSSH (4)	0.5	8	60
2	B	1	2	TTMSSH (3)	0.25	2	59
3	C	1	3	*n*-Bu_3SnH (4)	0.5	0.2	50
4	D	10	1	*n*-Bu_3SnH (1)	0.5	8	20

[a] TTMSSH: tris(trimethylsilyl)silane. [b] Isolated yields.

Results and Discussion

Preparation of Radical Precursors 19−22. In analogy to the reported preparation of **19a**, we used an approach relying on an Arbuzov process on trialkyl phosphites and *O*,*S*,*S*-trialkyl dithiophosphites. Thus, triethyl phosphite was reacted with benzeneselanyl chloride in toluene at 0 °C to afford precursor **19a** (77% yield).[14] 2-Chloro-1,3,2-phosphinane (**24a**)[15] and 2-chloro-1,3,2-dithiaphosphinane (**24b**)[16] were quantitatively transformed into the 2-benzyloxy derivatives **25a** and **25b**, respectively, by interaction with benzyl alcohols in diethyl ether, under basic conditions (procedures of Banwarth and Holmes, respectively).[17] To avoid any oxidation of the phosphorus(III), these compounds were engaged without further purification in the next step. Not unexpectedly, benzeneselanyl chloride was found to selectively and efficiently react on the benzyloxy unit to deliver selenophosphate **19b** and selenophosphorodithioate **21b** in 76 and 70% isolated yields. Precursor **21a** was generated in a somewhat different manner. Phosphorus trichloride was sequentially reacted with benzyl alcohol and ethanethiol (2 equiv) under basic conditions. Direct treatment of the thereby isolated and highly oxygen-sensitive *O*-benzyl-*S*,*S*-diethyl dithiophophite (**26**) with benzeneselanyl chloride delivered **21a** in 54% yield.[18] The P═O bond in all four precursors **19a**, **19b**, **21a**, and **21b** were then converted into a P═S bond by reaction with 1 equiv of Lawesson's reagent in refluxing toluene (**19a**, **19b**) or refluxing CH_2Cl_2 (**21a**, **21b**); isolated yields were found to be 72, 58, 56, and 86%, respectively.[19]

Additions Reactions of Radicals 10−13 onto Alkenes. In his paper describing the interaction between precursor **19a** and difluoroalkenes in the presence of a radical initiator, Motherwell and his collaborators report a procedure calling for the use of 0.5, 1, 3, and 4 equiv of azobisisobutyronitrile (AIBN), alkene, **19a**, and tri(*n*-butyl)tin hydride (*n*-Bu_3SnH), respectively, and an addition time of 8−10 h (Table 1, entry 1).[11c] In view of both the probable higher reactivity of the unfluorinated alkenes considered in the present study and the purification problems associated with the use of tin compounds, a somewhat different procedure was worked out with **19a** and *n*-oct-1-ene (**27**). Replacement of tris(*n*-butyl)tin hydride with tris(trimethylsilyl)silane (TTMSSH),[20] and decreasing the amount of AIBN to 0.25 equiv did not induce any change in the course of the reaction. The amount of precursor was also decreased, as was the addition time of the TTMSSH/AIBN solution. Thus, it was found that slow addition of 3 equiv of TTMSSH and 0.25 equiv of AIBN over a period of 2 h resulted in the formation of the desired product in essentially the same yield as with the original procedure (Table 1, entry 2). Further diminishing the addition time resulted in a drop of the yields (Table 1, entry 3). Conditions calling for a large excess of alkene also produced a deleterious effect on the course of the reaction (entry 4). Similar results were obtained with precursors **20a**, **21b**, and **22b**.

The eight precursors were then engaged in reactions with *n*-oct-1-ene (**27**), methylenecyclohexane (**28**), phenyl acrylate (**29**), and *n*-butyl vinyl ether (**30**). The results are compiled in Table 2.

In all cases but one, the selanylated precursors were found to be totally consumed. Precursor **19b** constantly led to 60−65% consumption, thus demonstrating that the homolytic cleavage is, in this particular case, a slower process (see below). The facile homolytic cleavage of the P−Se bond in the seven other precursors is in line with the available literature data on the analogous C−Se bond.[21] The expected adducts, when formed, were easily isolated by chomatography on silica in yields ranging from 15 to 99%; complete regioselectivity was observed in all cases. Byproducts included *n*-$Bu_3SnSePh$ or $(Me_3Si)_3SiSePh$, and the corresponding phosphites **6** or thiophosphites **7** resulted from partial, competitive hydrogen quenching of the phosphorus-centered radicals (10−100% in the ^1H and ^{31}P NMR spectra).[22] The corresponding dithiophosphites and trithiophosphites were not observed, due to their propensity to disproportionate, to dimerize and oligomerize, and to the low solubility of these oligomers.[8,10,23] The lower yields observed with phenyl acrylate may more reflect a competitive polym-

(13) For an example of a radical addition on a S═P bond, see: Romeo, R.; Wozniak, L. A.; Chatgilialoglu, C. *Tetrahedron Lett.* **2000**, *41*, 9899−9902.

(14) Reference 11a reports the preparation of compound **19a** from triethyl phosphite and benzeneselanyl bromide. We satisfactorily used the commercially available analogous chloride to achieve this transformation; see the Experimental Section.

(15) Arbuzov, A. E.; Zoroastrova, V. H. *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.* **1952**, *6*, 770−778.

(16) This compound has been described in the past: (a) See refs 8b and 14. (b) Martin, J.; Robert, J. B.; Taieb, C. *J. Phys. Chem.* **1976**, *80*, 2417−2421. However, we found these procedures nonreproducible and yielding the desired compound in yields <35%. In the end, dithiaphosphinane **24b** was prepared in 45% yield by using the conditions described for the corresponding phospholane: (c) Martin, S. F.; Wagman, A. S. *J. Org. Chem.* **1996**, *61*, 8016−8023. See the Experimental Section.

(17) (a) Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175−186. (b) Swamy, K. C. K.; Holmes, J. M.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6092−6094.

(18) Compound **26** was isolated by evaporation of the volatiles and used without further purification. ^1H and ^{31}P NMR data indicated a purity of 92−95%.

(19) (a) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223−228. (b) Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229−234. (c) Horner, L.; Lindel, H. *Phosphorus Sulfur* **1982**, *12*, 259−261. (d) Piettre, S. R.; Raboisson, P. *Tetrahedron Lett.* **1996**, *37*, 2229−2232. (e) Piettre, S. R. *Tetrahedron Lett.* **1996**, *37*, 4707−4710.

(20) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678−683.

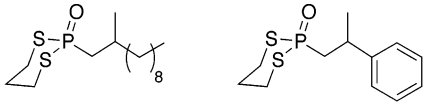
(21) Although this particular point is not discussed in ref 11b,c, one can assume that the authors observed a total consumption of precursor **19a**.

(22) After evaporation of the volatiles; at least 2 equiv of precursor was used in each reaction; see the Experimental Section.

TABLE 2. Yields of Products Resulting from the Addition Reactions of Radicals 10−13 onto Alkenes 27−30

entry	radical precursor 19-22	radical 10-13	procedure[a]	(27)		(28)		(29)		(30)	
				product	yields (%)[b]	product	yields (%)[b]	product	yields (%)[b]	product	yields (%)[b]
1	**19a**	**10a**	B	**31a**	60	**32a**	82	**33a**	0	**34a**	73
2	**20a**	**11a**	B	**31b**	76	**32b**	99	**33b**	55	**34b**	43
3	**21a**	**12a**	B	**31c**	89	**32c**	99	**33c**	70	**34c**	15
4	**22a**	**13a**	B	**31d**	73	**32d**	72	**33d**	22	**34d**	0
5	**19b**	**10b**	B	**31e**	0	**32e**	0	**33e**	0	**34e**	0
6	**20b**	**11b**	B	**31f**	46	**32f**	78	**33f**	53	**34f**	54
7	**21b**	**12b**	A	**31g**	60	**32g**	60	**33g**	48	**34g**	0
8	**22b**	**13b**	A	**31h**	84	**32h**	90	**33h**	57	**34h**	traces

[a] See text. [b] Isolated yields.



35 **36**

FIGURE 4. Structures of adducts **35** and **36**.

erization process (and thus a competitive consumption of the alkene) than a competitive reduction of the phosphorus-centered radical by TTMSSH. It is noteworthy that phosphonodithioyl and phosphonotrithioyl radicals (**12** and **13**) reacted sluggishly with *n*-butyl vinyl ether (**30**).

Other alkenes also react in an analogous way. Thus radical **12b** was successfully added onto 2-methylundec-1-ene and α-methylstyrene to deliver the corresponding adducts **35** and **36** in 70 and 75% isolated yields, respectively (Figure 4).

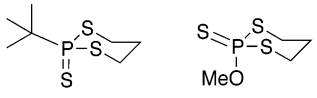
Several reasons may be invoked to explain the striking differences observed in the behavior of both precursor **19b** and radical **10b** generated from it: in addition to the uncomplete consumption of precursors **19b**, no adduct could be isolated, even in minor amounts, from the addition reactions on alkenes **27**−**30** (Table 2, entry 5). The first observation can be the translation of a stronger P−Se bond in **19b** than in the seven other precursors. Conformational analysis of the chairlike cyclic precursors **19b**, **20b**, **21b**, and **22b** indicates that, in solution, conformation A may be preferred over conformation B due to the stabilizing overlap of the antibonding orbital σ* of the P−Se bond with the lone pair of the Y atom(s) (Figure 5).[24−26] Obviously, such antiperiplanar arrangements of the lone pairs of Y atoms and the P−Se bond in precursors **19b**−**22b** would result in different stabilizations, depending on the identity of atoms Y. The partial transfer of electron density from a heteroatom (Y) to another heteroatom (Se) would be expected to be enhanced when the former heteroatom is less electronega-

(23) For example, dithiophosphite dimers and oligomers are soluble only in DMSO. See refs 8a and 10.

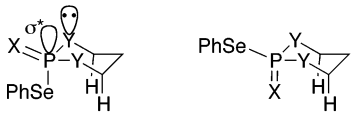
(24) For a discussion on stereoelectronic effects, see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.

(25) Stereoelectronic effects in cyclic phosphates have been extensively studied, particularly in the context of hydrolysis. Thus, six-membered monocyclic phosphates are in a chair conformation with an axial ester bond, a reflection of the ground-state stereoelectronic effect ($n_O \rightarrow \sigma^*_{P-O}$). See: (a) Lehn, J.-M.; Wipff, G. *J. Chem. Soc., Chem. Commun*. **1975**, 800−802. (b) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059−2095. (c) Gorenstein, D. G. *Chem. Rev*. **1987**, *87*, 1047−1077.

(26) Data from the literature also show that both phosphonotrithioate **v** and phosphorotrithioate **vi** adopt a chairlike conformation, with the *tert*-butyl group in **v** preferably equatorial. In the case of **vi**, however, the exclusive conformation is the one in which the methoxy group is in axial position (as depicted below), due to a stabilizing overlap analogous to the one discussed hereabove, and, most probably, weaker 1,3-diaxial interactions. See: Maryanoff, B. E.; MacPail, A. T.; Hutchins, R. O. *J. Am. Chem. Soc.* **1981**, *103*, 4432−4445.



v **vi**



19b: X=Y=O
20b: X=S, Y=O
21b: X=O, Y=S
22b: X=Y=S

FIGURE 5. Conformations of precursors **19b**−**22b**.

tive. Thus, a better overlap would occur with dithiaphosphinane oxide **21b** than with dioxaphosphinane oxide **19b**. In addition, the σ^* orbital of the P−Se bond and the *n* orbital of the singly bound heteroatoms Y are expected to be of closer energetic levels when Y = sulfur. Other points concern both the longer P−S bond (when compared to the P−O one) and the increasing atomic radii (O < S < Se); these are expected to have a direct impact on the 1,3-diaxial interactions and, therefore, play a role in the adoption of the most favored conformation.[27]

An attempt to shed light on this issue included submitting monocrystals of precursors **19b**, **20b**, **21b**, and **22b** to X-ray diffraction analysis. Figure 6 depicts the computer-generated ORTEP graphics for all four precursors and unambiguously shows that **19b**−**22b** actually all adopt conformations of the type A, i.e., with the selenoether group in axial position. Careful analysis of the data indicates that a subtle difference exists between these otherwise apparently similar conformations. Superimposition of structures **19b** and **22b** points the finger at the former structure in which the cycle undergoes a distortion to place the selenoether group away from the axial position (Figure 7). Measurement of the angles formed between the P−Se bond and a straight line joining C4 and the phosphorus atom, and comparison of the data with the value obtained for cyclohexane shows differences ranging from 3 to 9.6° (Table 3). Even though these distortions may look modest, they might constitute a basis to explain the observed behavior of **19b**. Indeed, a diminished overlap ($n_O \rightarrow \sigma^*_{P-Se}$) resulting from the higher deviation of the selenoether group from the dioxane axis would strengthened the P−Se bond and slower the homolytic process.[30−32]

The data in Table 2 clearly show that radicals **11a** and **11b**, featuring two P−O bonds and one P═S bond, add to a range of alkenes of different polarities to yield the desired monoadducts in fair to excellent yields (entries 2 and 6). While phosphonyl radical **10a** delivered the expected adducts when generated in the presence of neutral and electron-rich alkenes, no product was isolated or detected with phenyl acrylate, an electron-poor substrate (entry 1). Phosphonodithioyl radicals **12a** and **12b** as well as phosphonotrithioyl radicals **13a** and **13b**, however, were inert toward an electron-rich alkene such as *n*-butyl vinyl ether, and reacted well with neutral and electron-poor alkenes (entries 3, 4, 7, and 8). Polar factors are known to greatly influence the rate of radical additions, and their importance may be seen in the results obtained with *n*-butyl vinyl ether (**30**) (Table 2).[33] Inasmuch as no kinetic data are available at this time, one may cautiously argue against the electrophilic nature of phosphonodithioyl radicals **12a** and **12b**, as well as of phosphonotrithioyl radicals **13a** and **13b** (entries 3, 7, 4, and 8, respectively).[34] *The data indicate that it is possible to add a phosphorus-centered radical across a range of formal reactivities from electrophilic to nucleophilic by carefully choosing the precursor*. Functional group manipulation allows for the interconversion of the different groups and open access to virtually any of the four types of products.[35]

The peculiar reactivity of cyclic phosphonyl radical **10b** reflects a higher rate for hydrogen abstraction than for the addition process to the alkene, even though the latter must be accumulating in the medium. Most carbon-centered radicals are considered to be planar while phosphorus-centered radicals adopt a pyramidal configuration. Electron spin resonance spectrometry studies and theoretical evaluations have shown that more electronegative substituents on the phosphorus atom induce a more pronounced pyramidal configuration of the radical; such would be the case of radicals **10a** and **10b**, when compared to the others.[36] Comparison of the data from entries 1 and 5 suggests that the strain induced by the cyclic structure of radical **10b** would disfavor stabilization and promote faster reduction than addition onto the C═C bond of the alkenes, in accordance with the chain mechanism depicted in Scheme 2. The replacement of one or more oxygen atom(s) with sulfur changes this picture dramatically by inducing a positive effect in the course of the additions and is reminiscent of earlier observations from this laboratory and others.[5,11c]

The reactions between all eight precursors **19**−**22** and furanose derivative **37** were found to parallel the above-

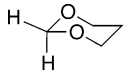
(27) Tedder has discussed the importance of polarity, bond strength, and steric effects on the rate of free radical substitution. See: Tedder, J. M. *Tetrahedron* **1982**, *38*, 313−329.

(28) All non-hydrogen atoms are represented by their displacement ellipsoids drawn at the 50% probability level.

(29) Hydrogen atoms are displayed with an arbitrary radius. Hydrogen is depicted in blue, carbon in black, oxygen in red, phosphorus in purple, sulfur in orange, and selenium in green.

(30) In the case of precursor **19b**, 35−40% of unconsumed **19b** were invariably recovered.

(31) In this context, data from the literature indicate that the lower bond dissociation energy of the axial C−H bond in **vii** (when compared to the equatorial one) is the result of an antiperiplanar orientation of one of the lone pairs of the cyclic oxygens with respect to that bond. See: (a) Belckwith, A. L. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615−619. (b) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609−614. (c) Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455−1459.



vii

(32) Results reporting that radicals at C-2 form faster from thioacetals and oxathiocycloalkanes than from the corresponding acetals are in line with our observations. See: (a) Batyrbaev, N. A.; Zorin, V. V.; Moravskii, A. P.; Shuvalov, V. F.; Zlot-skii, S. S.; Rakhmankulov, D. L. *J. Gen. Chem. USSR* **1983**, *53*, 364−369. (b) Lucken, E. A. C.; Poncioni, B. *J. Chem. Soc., J. Perkin Trans. 2* **1974**, 777−780.

(33) Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, *36*, 701−707.

(34) Physicochemical studies will soon be initiated using Flash Laser Photolysis and Electron Spin Resonance spectroscopy techniques, the results of which will be reported in due course.

(35) (a) Edmunson, R. S. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: Chichester, New York, 1996; pp 424−462. (b) Pietre, S. R. *Tetrahedron Lett.* **1996**, *37*, 4707−4710 and references therein.

(36) (a) Davies, A. G.; Griller, D.; Roberts, B. P. *J. Am. Chem. Soc.* **1972**, *94*, 1782−1783. (b) Roberts, B. P.; Singh, K. *J. Organomet. Chem.* **1978**, *159*, 31−35. (c) McLauchlan, K. A.; Simpson, N. J. K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1371−1377.

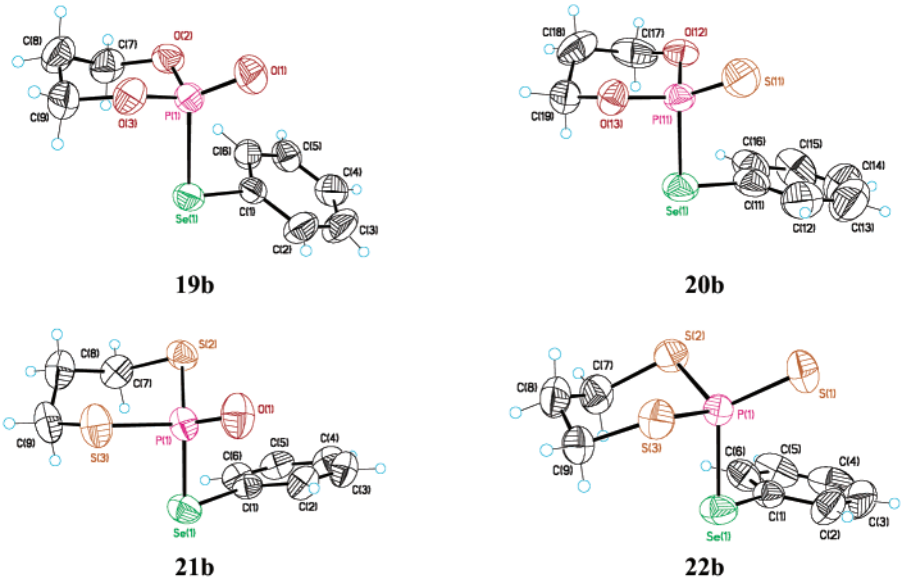


FIGURE 6. ORTEP drawings of precursors **19b**−**22b** with the adopted numbering scheme.[28,29]

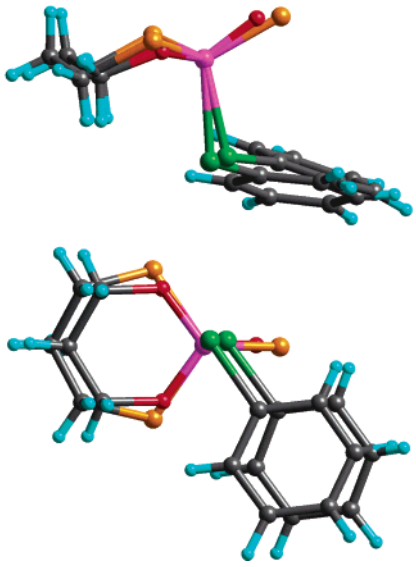


FIGURE 7. Side view and upper view of the superimposition of precursors **19b** and **22b**.[29]

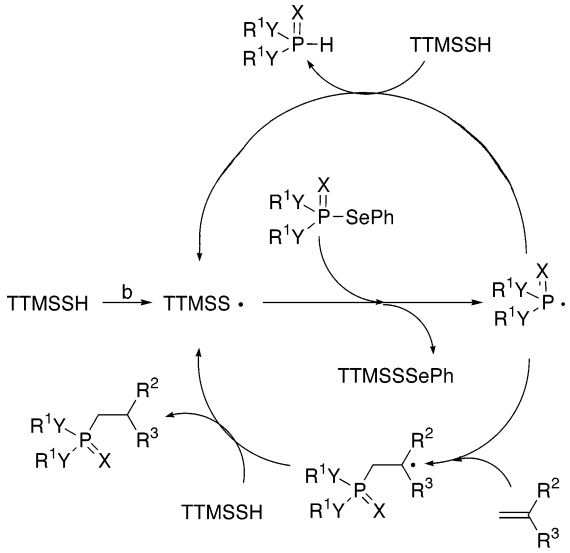
TABLE 3. Angle between the Axial C−H Bond and the C1−C4 Axis in Cyclohexane and Angles between the P−Se Bond and the C1−C4 Axis in Precursors 19b−22b

	C_6H_{12}	**19b**	**20b**	**21b**	**22b**
angle (deg)	100.0	103.9	96.6	100.9	94.3

discussed data (Table 4). Here again, precursor **19b** did not undergo complete homolytic cleavage, and no adduct was isolated in this case. This time, phosphonotrithioyl radical **13a** or **13b** failed to add onto alkene **37**, and this might be the result of increased steric hindrance in the furanosyl substrate. The reactions leading to products **38a**−**c**,**f**,**g** displayed a very good diastereoselectivity, the result of the known stereodirecting effect of the 2,3-diisopropylidene acetal unit.[6,37]

The above phosphorus-centered radicals can also be used in tandem cascade processes. Thus, interacting precursor **20a** and (1*R*)-(+)-α-pinene (**39**) under the same

SCHEME 2. Radical Chain Process of the Addition Reaction of Radicals 10−13 onto Alkenes[a]

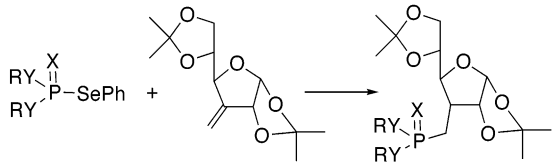


[a] TTMSS = $((CH_3)_3Si)_3Si$. [b]Radical initiator.

reaction conditions (procedure A) furnished the cyclic allylphosphonothioate **40** (30% isolated yield), the result of sequential radical addition, cyclobutane-ring fragmentation, and hydrogen quenching of the thereby-produced tertiary radical (Scheme 3).[38,39] Precursor **20a** was also

(37) (a) Rees, R. D.; James, K.; Tatchell, A. R.; Williams, R. H. *J. Chem. Soc. C* **1968**, 2716−2721. (b) Sowa, W. *Can. J. Chem.* **1968**, *46*, 1586−1589. (c) Bourgeois, J. M. *Helv. Chim. Acta* **1975**, *53*, 363−372. (d) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69−134. (e) Giese, B.; Gonzàlez-Gomez, J. A.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 69−70. (f) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969−980. (g) Schmit, C. *Synlett* **1994**, 241−242. (h) Johnson, C. R.; Bhumralkar, D. R.; De Clercq, E. *Nucleosides Nucleotides* **1995**, *14*, 185-194. (i) Lavaire, S.; Plantier-Royon, R.; Portella, C. *J. Carbohydr. Chem.* **1996**, *15*, 361−370. (j) Lavaire, S.; Plantier-Royon, R.; Portella, C. *Tetrahedron: Asymmetry* **1998**, *9*, 213−226. (k) Gautier, A.; Garipova, G.; Dubert, O.; Oulyadi, H.; Piettre, S. R. *Tetrahedron Lett.* **2001**, *42*, 5673−5676. (l) Dubert, O.; Gautier, A.; Condamine, E.; Piettre, S. R. *Org. Lett.* **2002**, *4*, 359−362. (m) Lopin, C.; Gautier, A.; Gouhier, G.; Piettre, S. R. *J. Am. Chem. Soc.* **2002**, *124*, 14668−14675.

TABLE 4. Structures and Yields of Products 38a−38h

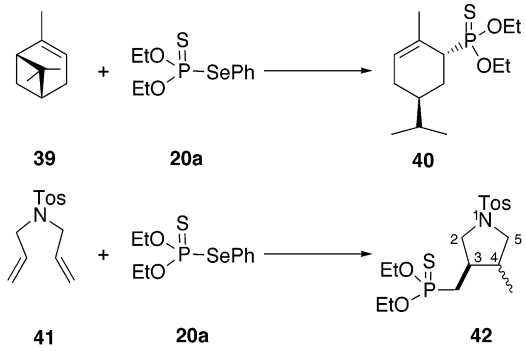


19-22 **37** **38**

entry	radical precursor **19−22**	X	Y	R, R	product[a]	yields[b] (%)
1	**19a**	O	O	Et, Et	**38a**	57
2	**20a**	S	O	Et, Et	**38b**	83
3	**21a**	O	S	Et, Et	**38c**	46
4	**22a**	S	S	Et, Et	**38d**	0
5	**19b**	O	O	-$(CH_2)_3$-	**38e**	0
6	**20b**	S	O	-$(CH_2)_3$-	**38f**	44
7	**21b**	O	S	-$(CH_2)_3$-	**38g**	65
8	**22b**	S	S	-$(CH_2)_3$-	**38h**	0

[a] Diastereoselection in excess of 95% was observed in all cases. [b] Isolated yields.

SCHEME 3. Addition Reactions of 20a to 39 and 41



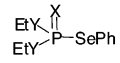
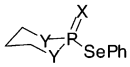
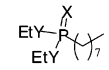
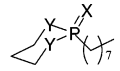
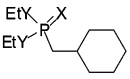
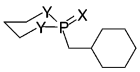
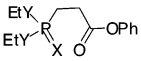
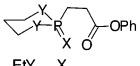
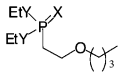
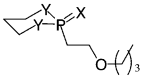
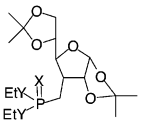
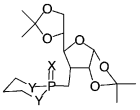
39 **20a** **40**

41 **20a** **42**

reacted with *N*-tosylbisallylamine (**41**) to generate pyrrolidine **42** through a cascade radical addition (45% isolated yield; a 7:3 mixture of cis and trans isomers, respectively).[40] Assignment of the diastereomeric ratio was achieved with the help of 1-D and 2-D NMR spectrometry ($^1H-^1H$ COSY, $^1H-^{13}C$ COSY, $^1H-^{31}P$ COSY, and NOESY experiments).[41] Thus, for instance, the spectra of the minor trans isomer displayed correlations between the hydrogen on carbon 5 cis to the methyl group, those of that methyl group, and the hydrogen on carbon 3, indicative of a trans relationship between the substituents; in the case of the cis isomer, however, the lack of any correlation between the 5-hydrogen atom cis to the methyl group and the 3-hydrogen atom demonstrated the cis relationship of the two substituents on carbon 3 and 4 of the pyrrolidinyl cycle.

The methodology described in this paper thus usefully completes literature data on phosphorus-centered radicals addition to alkenes by extending the scope of the reaction to phosphonodithioyl and phosphonotrithioyl radicals **12** and **13**. The synthesis of phosphonates and phosphonothioates have been largely dominated by the Michaelis−Arbusov and the Michaelis−Becker processes involving the interaction between alkyl halides and trialkyl phosphites or metalated dialkyl phosphites, respectively.[42] Other methods involving phosphoaldol and Michael reactions have also been traditionally exploited to create carbon−phosphorus bonds (Abramov and Pudovik reactions, respectively). These reactions have been much less used for the preparation of phosphonodithioates and phosphonotrithioates due to the lability of the P−S bond, as mentionned earlier. Classical Michaelis−Arbusov reaction between alkyl halides and trithiophosphites ($(RS)_3P$) have been reported to be slow and to require a large excess of alkyl halide.[43] The efficient approach developed in this paper thus successfully fills

TABLE 5. Chemical Shifts of Compounds 19−22, 31−34, and 38

entry	product	δ (ppm)[a] X=O Y=O	X=S Y=O	X=O Y=S	X=S Y=S
1		18.32	81.52	49.97	73.26
2		10.24	76.11	51.89	57.37
3		33.08	100.29	68.47	90.94
4		-	103.23	62.39	74.04
5		32.34	99.63	67.40	89.13
6		-	103.28	59.14	72.04
7		-	96.81	66.40	87.73
8		-	99.09	61.71	69.85
9		29.26	95.83	64.65	-
10		-	98.38	-	-
11		30.47	97.02	66.68	-
12		-	99.22	59.08	-

[a] Downfield from H_3PO_4.

(38) For a related example of phosphorylation, see: Battiste, D. R.; Haseldine, D. L. *Synth. Commun.* **1984**, *14*, 993−1000.

(39) An identical result was obtained from diethyl thiophosphite and (1*R*)-(+)-α-pinene in the presence of Et_3B/O_2. See ref 37k. For the opening of (1*S*)-(−)-*β*-pinene following a phosphorus-centered radical addition, see: Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun.* **2003**, 2928−2929.

(40) Baldwin, J. E. *Chem. Commun.* **1976**, 734−736. For a synthesis of pyrrolidine by a *5-exo-trig* radical cyclization, see: Berlin, S.; Engman, L. *Tetrahedron lett.* **2000**, *41*, 3701−3704.

(41) (a) Bax, A.; Griffey, R. H.; Hawkins, B. L. *J. Magn. Reson.* **1983**, 55, 301−315. (b) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, 67, 565−569. (c) Marion, D.; Wuthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 967−974.

(42) For a general discussion concerning these methods, see: Edmunson, R. S. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: Chichester, New York, 1996; Chapters 2−5, pp 47−494.

(43) Al'fonsov, V. A.; Zamaletdinova, G. U.; Batyeva, E. S.; Pudovik, A. N. *J. Gen. Chem. USSR* **1986**, *56*, 634−639.

a gap in the synthesis of phosphonodithioates and phosphonotrithioates via the direct formation of a P−C bond.

NMR Spectrometric Analysis. The ^{31}P NMR data for all precursors and the obtained adducts are compiled in Table 5. Several points are worth noting. In a given series, the known deshielding effect of a double-bonded sulfur on the ^{31}P NMR chemical shift is larger when two oxygen atoms are single-bonded to the phosphorus (63−67 ppm) than when two sulfur atoms are linked to the phosphorus (5.5−22 ppm). Interestingly, the phosphorus nucleus of the selenophosphorotrithioate **22b** is strongly shielded when compared to the acyclic analogue **22a** (entries 1 and 2, column 6; see below).

In the case of the adducts (entries 3−12), comparing the acyclic series to the cyclic ones indicates a slight deshielding effect in the phosphonothioate cases (∼−3 ppm; column 4), a shielding effect in the phosphonodithioate cases (∼+7 ppm; column 5) and a larger shielding effect in the phosphonotrithioate cases (∼+17 ppm; column 6). Clearly, placing the sulfur atoms within a six-membered cycle has a stronger impact on the chemical shifts of the phosphorus nucleus in the case of a P═S bond. The explanation of this interesting effect lies, however, beyond the scope of the present study; the issue will be addressed in a forthcoming paper.

Conclusion

The new selenophosphate **19b**, selenophosphorothioates **20a** and **20b**, selenophosphorodithioates **21a** and **21b**, and selenophosphorotrithioates **22a** and **22b** are easily generated in good overall yields from readily available starting substrates and reagents, by a three- or four-step sequence of reactions. These compounds show good thermal stability and may be used as precursors of the corresponding phosphorus-centered radicals by homolytic cleavage of the P−Se bond. In particular, this approach allows us to generate the hiterto unreported phosphonotrithioyl radicals. When radicals **10a**−**13a** and **10b**−**13b** are produced in the presence of a range of alkenes of different formal reactivities (from nucleophilic to electrophilic), most of the expected adducts are formed in good to excellent yields. Cyclic precursor **19b** and radical **10b** feature unusual behavior, undergoing uncomplete homolytic cleavage and complete reduction, respectively. Inspection of data gathered from X-ray diffraction on monocrystals of the cyclic precursors indicates a higher twisting of the six-membered ring in **19b** and points at this feature as a possible reason for this precursor behavior. Noteworthy is the fact that the corresponding thioyl entities **20b** and **11b** produce the expected adducts, thus pointing out the beneficial effect of the double-bonded sulfur atom. The possibility of carrying out tandem processes is demonstrated through the use of substrates featuring two C═C bonds, i.e., (1*R*)-(+)-α-pinene (**39**) and diallylamine **41**. The approach thus allows the clean production of phosphonates, phosphonothioates, phosphonodithioates, and phosphonotrithioates and may find application in the field of nucleotide analogues, as illustrated by the use of furanosyl derivative **37**.

Experimental Section

General procedures for all new compounds are given below. Purifications and physical data are included in the Supporting Information.

Synthesis of Precursors 19b, 21a, and 21b. General Procedure. A solution of the requisite substrate (**25a**, **25b**, or **26)** (43.0 mmol) in toluene (25 mL) was added dropwise to an ice-cold solution of phenylselanyl chloride (8.31 g, 43.0 mmol) in anhydrous toluene (25 mL) under argon. The resultant mixture was stirred for 2 h at 0 °C, warmed to room temperature, and evaporated under reduced pressure.

Preparation of Precursors 20a, 20b, 22a and 22b. General Procedure. A solution of the requisite phosphoroselenoate (**19a** or **19b**) or phosphoroselenodithioate (**21a** or **21b**) (7.63 mmol) and Lawesson's reagent (3.10 g, 7.63 mmol) in anhydrous CH_2Cl_2 (60 mL) was refluxed under argon for 2 h.

Radical Addition of Precursors 19a−22a and 19b−22b onto Alkenes. General Procedure B. To a degassed refluxing solution of the requisite precursor (2 equiv; **19a**−**22a** and **19b**−**20b**: 0.36 mol/L; **21b**−**22b**: 0.42 mol/L) and alkene (1 equiv; **19a**−**22a** and **19b**−**20b**: 0.18 mol/L; **21b**−**22b**: 0.14 mol/L) in anhydrous C_6H_6 was added a solution of TTMSSH (3 equiv; **19a**−**22a** and **19b**−**20b**: 0.39 mol/L; **21b**−**22b**: 1.0 mol/L) and AIBN (0.25 equiv; **19a**−**22a** and **19b**−**20b**: 0.032 mol/L; **21b**−**22b**: 0.12 mol/L) in C_6H_6 over a period of time of 2 h (syringe-pump). After completion of the addition, the resultant solution was refluxed for another hour, cooled to room temperature, and evaporated under reduced pressure. The crude material was chromatographed and eluted with the solvents indicated in each case.

Procedure A can similarly be carried out by using the number of equivalents in Table 1.

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Supporting Information Available: Purification procedures and physical data for all new compounds as well as ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **20b**, **22a**, **31a**−**d**, **31f**−**h**, **32b**,**d**,**f**,**h**, **33c**,**d**,**f**−**h**, **34b**,**c**, **35**, **36**, **38a**−**c**,**f**,**g**, **40**, and **42**; 2D H/H correlations for compounds **38g**, **40**, and **42**; and 2D H/C correlation for compound **38g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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