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# Phosphonodifluoromethyl and Phosphonothiodifluoromethyl Radicals. Generation and Addition onto Alkenes and Alkynes

Sébastien Pignard, Chrystel Lopin, Géraldine Gouhier, and Serge R. Piettre*

*Laboratoire des Fonctions Azotées et Oxygénées Complexes, UMR CNRS 6014, IRCOF-Université de Rouen, Rue Tesnières, F-76821 Mont Saint Aignan, France*

*serge.piettre@univ-rouen.fr*

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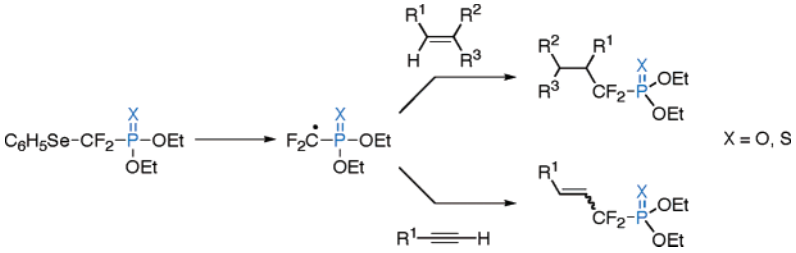


Selanylated difluoromethylphosphonates and difluoromethylphosphonothioates are good precursors to phosphonodifluoromethyl and phosphonothiodifluoromethyl radicals, respectively. When generated in the presence of alkenes and a hydrogen donor, the corresponding α,α-difluorinated alkylphosphonates or alkylphosphonothioates are produced in fair to good yields. The use of alkynes results in the formation of α,α-difluorinated allyl derivatives in useful yields. The presence of the sulfur atom in phosphonothiodifluoromethyl radicals usually translates into higher isolated yields.

## Introduction

Increasing the efficacy of a bioactive molecule may be achieved by fine-tuning its interactions with the biomolecular target. In this context, the search for the ideal phosphate mimic has been the focus of many scientists for the past decade. Indeed, this functional group **1** is involved in many biochemical processes, including those addressing the replication and transposition of nucleic acids (Figure 1). Phosphonates **2a**, phosphonothioates **2b**, and phosphonodithioates **2c**, in which an esterified oxygen has been replaced with a methylene, as well as phosphinates **3**, featuring two carbon−phosphorus bonds, have been much studied, and many applications have flourished.[1] The generally positive impact of the presence of fluorine in bioactive molecules led Blackburn and McKenna to independently introduce the difluorophosphonates **4a** more than 20 years ago.[2] Numerous analogues of natural phosphates encompassing this fluorinated functional group have since then been prepared and shown to be bioactive.[3] Chambers and O'Hagan underlined the closer electronic and structural similarities between fluorinated phosphonates **4a** and the corresponding phosphates.[4] Thatcher showed that the apicophilicities of both fluorinated methylenes, CHF and $CF_2$, are analogous to that of an esterified oxygen.[5] This would translate into similar geometries for the phosphorus atom in the functional groups **1** and **4**. In addition and despite the fact that this is still subject to debate, the possibility for carbon-bound fluorine atoms to establish hydrogen bonds, much as oxygen atoms, has been suggested.[5,6]

More recently we have introduced the α,α-difluorophosphonothioates **4b**, a new variant in which the phosphorus atom is doubly bonded to sulfur.[7] The presence of the sulfur atom may both help to modulate the binding to metallic enzymes and result in higher resistance of the functional group toward enzymatic

(1) (a) Edmundson, R. S. *The Chemistry of Organophosphorus Compounds. Vol. 4. Ter- and Quinque-valent Phosphorus Acids and Their Derivatives*; Hartley, F., Ed.; Wiley & Sons: Chichester, 1996; pp 47−652. (b) Kalir, A.; Kalir, H. H. In *The Chemistry of Organophosphorus Compounds. Vol. 4. Ter- and Quinque-valent Phosphorus Acids and Their Derivatives*; Hartley, F., Ed.; Wiley&Sons: Chichester, 1996; pp 767−780. (c) Tang, C. C.; Ma, F. P.; Zhang, K.; Zheng, J.; Jin, Y. C. *Heteroat. Chem.* **1995**, *6*, 413−417. (d) Rodriguez, O. P.; Thompson, C. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *117*, 101−110. (e) Collingwood, S. P.; Taylor, R. J. *Synlett* **1998**, 283−285. (f) Lu, H.; Berkman, C. E. *Bioorg. Med. Chem.* **2001**, *9*, 395−402. (g) An, H.; Wang, T.; Maier, M. A.; Manoharan, M.; Ross, B. S.; Cook, P. D. *J. Org. Chem.* **2001**, *66*, 2789−2801. (h) Dubert, O.; Gautier, A.; Condamine, E.; Piettre, S. R. *Org. Lett.* **2002**, *4*, 359−362. (i) Renard, P.-Y.; Schwebel, H.; Vayron, P.; Josien, L.; Valleix, A.; Mioskowski, C. *Chem. Eur. J.* **2002**, *8*, 2910−2916. (j) Savignac, P.; Bogdan, I. *Modern Phosphonate Chemistry*; CRC Press: Boca Raton, 2003.

(2) (a) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511−513 (b) Blackburn, G. M.; England, D. A.; Kolmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930−932. (c) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 1188−1190. (d) McKenna, C. E.; Shen, P.-D. *J. Org. Chem.* **1981**, *46*, 4573−4576. (e) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913−917.

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hydrolysis when compared to the fully oxygenated analogue.[8] In addition, the synthetic methodologies developed to construct or introduce this functional group have pointed the finger at the advantages brought by the sulfur atom: increased stability of the reagents, higher yields in product, reproducibility, and ease of purification when compared to the fully oxygenated reagents and products.[9] This positive role of sulfur was highlighted in a successful synthesis of phosphonodifluoromethyl analogues of nucleoside-3′-phosphates.[7d]

Recently, we reported that *O*,*O*-dialkylphosphonodifluoromethyl radicals **5a** generated from selanyl (or sulfanyl) precursors **6a** in the presence of a hydrogen donor add to variously substituted alkenes through a chain-reaction process to deliver the expected adducts in fair to good yields (Figure 2).[10] Phosphonodifluoromethyl radicals have also been postulated as intermediates in either metal- or oxone-mediated addition of either bromo- or iododifluoromethylphosphonates to alkenes and alkynes, leading to 1:1 adducts.[11]

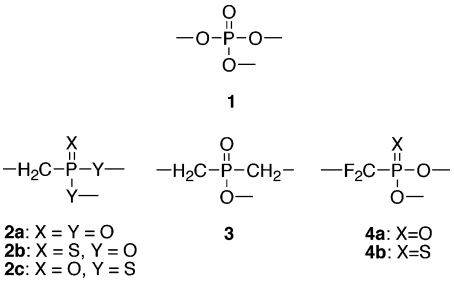


**FIGURE 1.** Structures of phosphate and various isosteres such as phosphonates and phosphinates.

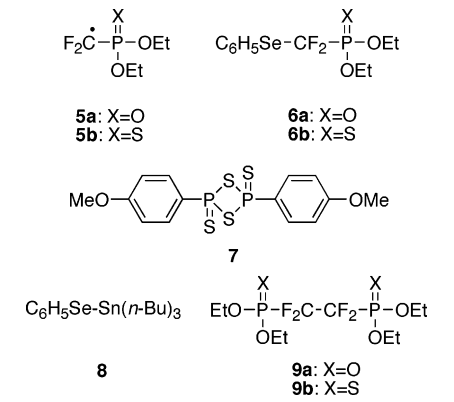


**FIGURE 2.** Structures of radicals **5**, their precursors **6**, Lawesson reagent **7**, and side products **8** and **9**.

We now report an extension of our previous work and show that addition onto alkynes leads to $\beta,\gamma$-unsaturated-$\alpha,\alpha$-difluorophosphonates. Not surprisingly, the previously unreported *O*,*O*-dialkylphosphonothiodifluoromethyl radicals **5b** can be generated from the corresponding thioanalogue **6b** of precursor **6a**: in the presence of alkenes or alkynes, the expected alkyl- or vinyl-$\alpha,\alpha$-difluorophosphonothioates, respectively, are produced.

(3) (a) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119−1125. (b) Blackburn, G. M.; Guo, M.-J.; Langston, S. P.; Taylor, G. E. *Tetrahedron Lett*. **1990**, *31*, 5637−5640. (c) Blackburn, G. M.; Langston, S. P. *Tetrahedron Lett.* **1991**, *32*, 6425−6428. (d) Burke, T. R., Jr.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. P. *J. Org. Chem.* **1993**, *58*, 1336−1340. (e) Matulic-Adamic, J.; Usman, N. *Tetrahedron Lett.* **1994**, *35*, 3227−3230. (f) Martin, S. F.; Wong, Y.-L.; Wagman, A. S. *J. Org. Chem*. **1994**, *59*, 4821−4831. (g) Berkowitz, D. B.; Shen, Q.; Maeng, J.-H. *Tetrahedron Lett.* **1994**, *35*, 6445−6448. (h) Matulic-Adamic, J.; Haeberli, P.; Usman, N. *J. Org. Chem*. **1995**, *60*, 2563−2569. (i) Levvy, S. G.; Wasson, B.; Carson, D. A.; Cottam, H. B. *Synthesis* **1996**, 843−846. (j) Burke Jr., T. R.; Ye, B.; Akamatsu, M.; Ford, H., Jr.; Yan, X.; Kole, H. K.; Wolf, G.; Shoelson, S. E.; Roller, P. P. *J. Med. Chem*. **1996**, *39*, 1021−1027. (k) Berkowitz, D. B.; Eggen, M.; Shen, Q.; Shoemaker, R. K. *J. Org. Chem*. **1996**, *61*, 4666−4675. (l) Ye, B.; Burke, T. R., Jr. *Tetrahedron* **1996**, *52*, 9963−9970. (m) Qabar, M. N.; Urban, J.; Khan, M. *Tetrahedron* **1997**, *53*, 11171−11178. (n) Hamilton, C. J.; Roberts, S. M.; Shipitsin, A. *J. Chem. Soc., Chem. Commun.* **1998**, 1087−1088. (o) Hamilton, C. J.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1051−1056. (p) Yokomatsu, T.; Abe, H.; Yamagishi, T.; Suemune, K.; Shibuya, S. *J. Org. Chem*. **1999**, *64*, 8413−8418. (q) Butt, A. H.; Percy, J. M.; Spencer, N. S. *Chem. Commun.* **2000**, 1691−1692. (r) Murano, T.; Muroyama, S.; Yokomatsu, T.; Shibuya, S. *Synlett* **2002**, 1657−1660. (s) Burke Jr., T. R.; Lee, K. *Acc. Chem. Res*. **2003**, *36*, 426−433. (t) Yokomatsu, T.; Kato, J.; Sakuma, C.; Shibuya, S. *Synlett* **2003**, 1407−1410. (u) Yokomatsu, T.; Kato, J.; Sakuma, C.; Shibuya, S. *Synlett* **2003**, 1407−1410. (v) Murano, T.; Yuasa, Y.; Kobayakawa, H.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2003**, *59*, 10223−10230. (w) Gautier, A.; Garipova, G.; Salcedo, C.; Balieu, S.; Piettre, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5963−5967.

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(5) Thatcher, G. R.; Campbell, A. S. *J. Org. Chem*. **1993**, *58*, 2272−2281.

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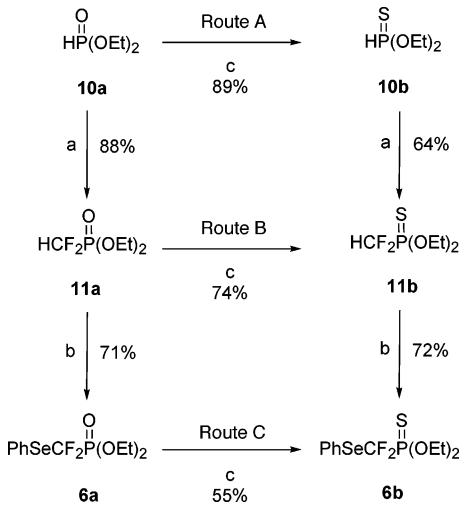
(8) By analogy, phosphorothioates are more stable than the corresponding phosphates. See: (a) Eckstein, F. *J. Am. Chem. Soc.* **1970**, *92*, 4718−4723. (b) Eckstein, F. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 423−506. (c) Eckstein, F. *Annu. Rev. Biochem.* **1985**, *54*, 367−402. (d) Matsukura M.; Shinozuka, K.; Zon, G.; Mitsuya, H.; Reitz, M.; Cohen, J. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7706−7710. (e) Cooke, A. M.; Noble, N. J.; Payne, S.; Gigg, R.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1989**, 269−271. (f) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543−584. (g) Baker, G. R.; Billington, D. C.; Gani, D. *Tetrahedron* **1991**, *47*, 3895−3908. (h) Billington, D. C. *The Inositol Phosphates*; VCH Weinheim: New York, 1993; p 69. (i) Szczepanik, M. B.; Désaubry, L.; Johnson, R. A. *Tetrahedron Lett.* **1998**, *39*, 7455−7458. (j) Marwic, C. *J. Am. Med. Assoc.* **1998**, *280*, 871. (k) Stix, G. *Sci. Am.* **1998**, *297*, 46−50. (l) Cook, P. D. *XIV International Roundtables: Nucleosides, Nucleotides and Their Biological Applications*, Sept. 10−14, 2000, San Francisco, N° 34, p 31.

(9) See, for example, refs 7d and 7e. In addition and despite their complete stability at room temperature, difluorinated phosphonothioates more readily react with strong oxidants than the corresponding phosphonates, thereby greatly facilitating the monitoring of both reactions and column chomatography purifications by TLC.

(10) Lequeux, T.; Lebouc, F.; Lopin, C.; Yang, H.; Gouhier, G.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 185−188.

(11) (a) Yang, Z.-Y.; Burton, D. *Tetrahedron Lett.* **1991**, *32*, 1019−1022. (b) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1992**, *57*, 4676−4683. (c) Hu, C.-M.; Chen, J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 327−330. (d) Li, A.-R.; Chen, Q.-Y. *Synthesis* **1996**, 606−608. (e) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. *J. Org. Chem.* **1996**, *61*, 7207−7211.

**SCHEME 1**[a]




[a] Reagents and conditions: (a) (i) Na, THF, (ii) $HCF_2Cl$; (b) (i) 1.5 equiv LDA, THF, −78 °C, (ii) 1.5 equiv PhSeCl, THF, −78 °C; (c) Lawesson reagent, toluene, 110 °C.

## Results and Discussion

Selanylated compounds **6a** and **6b** were selected as the precursors of choice of radicals **5a** and **5b**, respectively. Indeed, both the weaker C−Se bond, when compared to C−S and C−Br bonds, for instance, and the high polarizability of selenium were expected to generate the most efficient homolytic cleavage, and to decrease the probability of radical addition onto the $sp^2$-hybridized sulfur atom in **6b**, a potentially competitive reaction.[12,13] The preparation of precursors **6a** and **6b** is summarized in Scheme 1. The fully oxygenated precursor **6a** was synthesized in two steps from commercially available diethyl phosphite **10a** (62% overall yield). Three different preparations of **6b** from **10a** may be envisioned, depending on the stage at which Lawesson reagent **7** (LR) is used to transform the P═O bond into a P═S one.[14] Thus, either phosphite **10a** (Route A), difluorophosphonate **11a** (Route B), or precursor **6a** (Route C) can be subjected to the action of LR, with different outcomes. The results clearly indicate that Route B affords the highest overall yield to precursor **6b** (47%, versus 41% and 34% for Routes A and C, respectively). These syntheses can easily be carried out on multigram scales.

In accordance with the original procedure, slow addition of a toluene solution of tri-*n*-butyltin hydride (1.4 equiv) and azobisisobutyronitrile (0.5 equiv) to a toluene solution of either **6a** or **6b** (1 equiv) and *n*-octene (**12**) (10 equiv) at 90 °C resulted in a total consumption of either precursor and the generation of the desired adducts along with various amount of the reduced phosphonate **11a** or phosphonothioate **11b**.[10] Optimization of this first procedure eventually led to the use of a 1:1 mixture of **6a** or **6b** and the requisite alkene and of 1.1 equiv of *n*-$Bu_3$SnH. This furnished the desired products **18a** and **19a** in 45% and 54%, respectively, as well as 50−40% of reduced precursors **11a** or **11b** (Table 1, entries 1 and 7). The addition reaction was then extended to other alkenes **13**−**17**, featuring alkyl, electron-donating, or electron-withdrawing substituents (Table 1). Both electronic and steric factors play a role in the reaction. Classic and electron-rich alkenes furnished the products in higher yields than electron-poor substrates (compare entries 1, 2, 4, and 5 with 6, and 7, 8, 10 and 11 with 12). The rate of addition of 1,2-disubstituted alkenes is apparently slowed enough to mainly induce hydrogen quenching of radicals **5a** and **5b** (entries 3 and 9); however, replacing one of the alkyl substituent with an electron-donating atom results in a reversal of this deleterious steric effect (compare entries 3 and 5, and 9 and 11). Difluorophosphonates **18** and difluorophosphonothioates **19** were easily separated from tri-*n*-butyltin selenide **8** by flash chromatography. Dimeric species **9** were never isolated from these reactions nor even observed in the crude samples.

The possibility of carrying out tandem radical additions was demonstrated by using *N*-tosyl bisallylamine **20** (Scheme 2).[15] Products **21a** were isolated in a disappointing 16% yield (a 7:3 mixture of *cis* and *trans* diastereomers); however, radical **5b** proved more efficient, affording the corresponding phosphonothioate **21b** in 51% isolated yield (a 7:3 mixture of *cis* and *trans* diastereomers).[16] Despite the lack of kinetic data, the results are indicative of the probable electrophilic nature of radicals **5a** and **5b**. According to the putative radical chain reaction and the catalytic cycle suggested in Scheme 3, a slower addition of radicals **5a** or **5b** onto the reacting alkene would favor its hydrogen quenching by *n*-$Bu_3$SnH. Indeed, in reactions producing less of the desired addition product, more **11a** or **11b** was generally isolated. Thus, a high yield of desired product probably reflects a favorable frontier molecular orbital interaction (and a high addition rate), and conversely, lower yields may be indicative of less favorable such orbital interactions, resulting in a competitive reduction of the precursor.

The most salient feature emerging from Table 1 is the consistently higher yields obtained from precursor **6b** when compared to those of **6a**, presumably due to the higher stability of the phosphonothiodifluoromethyl radical **5b**. This observation is in line with previous data from the literature on the corresponding anions and on phosphon(othio)yl radicals.[7] The use of tris(trimethylsilyl)silane (TTMSSH), a hydrogen donor slightly weaker than *n*-$Bu_3$SnH, resulted in a significant increase in the isolated yield of **18a**, **19a**, **18c**, and **19c**; this could be the result of the stronger Si−H bond, when compared to Sn−H, favoring the addition of **5a** or **5b** onto alkenes over the mere hydrogen quenching of these radicals.[17] However, when enol ether **16** was used, the main reaction turned out to be the reduction of both precursors **6a** and **6b**, possibly due to an

(12) Dissociation energies of C−X bonds are as follows: X = Br, 68 kCal/mol; X = S, 65 kCal/mol; X = Se, 58 kCal/mol. See ref 14f.

(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.

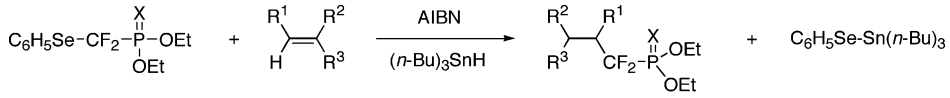
(14) (a) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223−228. (b) Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229−234. (c) Horner, L.; Lindel, H. *Phosphorus Sulfur* **1982**, *12*, 259−261. (d) Piettre, S. R.; Raboisson, P. *Tetrahedron Lett.* **1996**, *37*, 2229−2232. (e) Piettre, S. R. *Tetrahedron Lett.* **1996**, *37*, 4707−4710. (f) Lopin, C.; Gouhier, G.; Gautier, A.; Piettre, S. *J. Org. Chem.* **2003**, *68*, 9916−9923.

(15) For examples of such tandem radical processes, see: (a) Hanessian, S.; Rheinhold, U.; Ninkovic, S. *Tetrahedron Lett.* **1996**, *37*, 8967−8970. (b) Hanessian, S.; Ninkovic, S.; Rheinhold, U. *Tetrahedron Lett.* **1996**, *37*, 8971−8974. (c) Parsons, A. F.; Williams, D. A. J. *Tetrahedron* **1998**, *54*, 13405−13420. (d) Barks, J. M.; Gilbert, B. C.; Parsons, A. F.; Upeandran, B. *Tetrahedron Lett.* **2001**, *42*, 3137−3140. (e) Gautier, A.; Garipova, G.; Dubert, O.; Oulyadi, H.; Piettre, S. R. *Tetrahedron Lett.* **2001**, *42*, 5673−5676. (f) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2003**, *44*, 479−483.

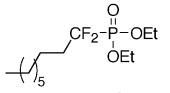
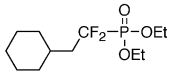
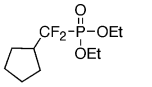
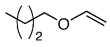
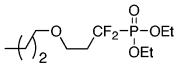
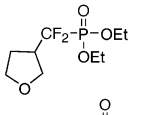
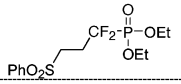
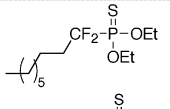
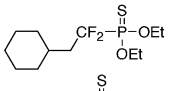
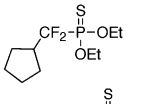
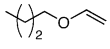
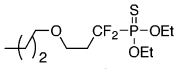
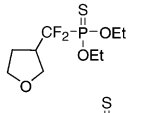
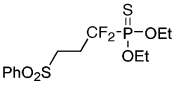
(16) Phosphonate **11a** and phosphonothioate **11b**, resulting from competitive reduction, were the only other products observed by NMR spectrometry.

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

**TABLE 1. Addition of Radicals 5a and 5b to Alkenes 12−17**[a]

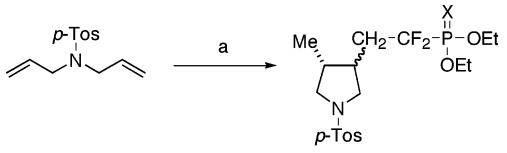



**6a**: X=O **6b**: X=S | **12-17** | **18a-f: X=O** **19a-f: X=S** | **8**

| entry | alkene | precursor | | product | | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 |  | **12** | **6a** |  | **18a** | 45 (70)[c] |
| 2 |  | **13** | **6a** |  | **18b** | 82 |
| 3 |  | **14** | **6a** |  | **18c** | 10 (20)[c] |
| 4 |  | **15** | **6a** |  | **18d** | 46 |
| 5 |  | **16** | **6a** |  | **18e** | 68 (10)[c] |
| 6 |  | **17** | **6a** |  | **18f** | 12 |
| 7 |  | **12** | **6b** |  | **19a** | 54 (87)[c] |
| 8 |  | **13** | **6b** |  | **19b** | 88 |
| 9 |  | **14** | **6b** |  | **19c** | 22 (35)[c] |
| 10 |  | **15** | **6b** |  | **19d** | 81 |
| 11 |  | **16** | **6b** |  | **19e** | 78 (21)[c] |
| 12 |  | **17** | **6b** |  | **19f** | 43 |

[a] **5a** or **5b** (1 equiv), *n*-$Bu_3SnH$ (1.1 equiv), AIBN (0.4 equiv), toluene, 110 °C. [b] Isolated yields. [c] Using TTMSSH (1.1 equiv).

**SCHEME 2**[a]




**20** **21a**: X = O **21b**: X = S

[a] Reagents and conditions: (a**) 5a** or **5b** (1 equiv), *n*-$Bu_3SnH$ (1.1 equiv), AIBN (0.4 equiv), toluene, 110 °C.

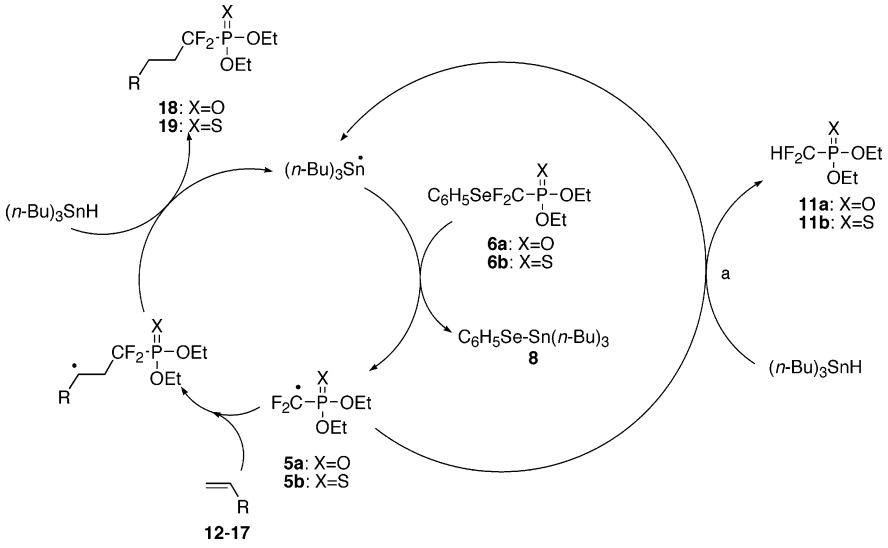
increase in the HOMO/SOMO gap induced by the Lewis acid properties of silylated species.

The possibility of adding radicals **5a** or **5b** onto alkynes was next considered. Of particular interest was the fact that the approach might generate a general method of synthesis of α,α-difluorinated allylphosphonates and allylphosphonothioates. Few preparations of such phosphonates have been reported so far, and the literature is devoid of the corresponding phosphonothioates. Thus, α,α-difluorinated allylphosphonates bearing an iodine atom on carbon $\gamma$ to the phosphorus atom have been prepared by addition of iododifluoromethanephosphonic esters on terminal alkynes in the presence of sodium dithionite.[11d] Shibuya has reported a copper-mediated coupling reaction between vinyliodides and zinc derivative **40a**, and a related addition across alkynes (Figure 3).[11e] Alternatively, a sequence involving (i) the cerium-mediated conjugate addition of lithium reagent **40b** to vinyl sulfoxides and (ii) a thermal *syn* elimination of sulfenic acid was developed by Percy.[18]

When the above procedure was applied to alkynes, difluorinated allylphosphonates and allylphosphonothioates were obtained in fair to good yields (Table 2). Here again, isolated yields of phosphonothioates **34**−**39** were found to be higher than in the case of the corresponding phosphonates **28**−**33**. Alterna-

(18) Blades, K.; Percy, J. M. *Tetrahedron Lett.* **1998**, *39*, 9085−9088.

**SCHEME 3 .**




tively, tris(trimethylsilyl)silane (TTMSSH) may be used as hydrogen donor: addition of radicals **5a** or **5b** on trimethylsilylacetylene **25**, following an otherwise identical procedure, led to the isolation of adducts **31** and **37**, in virtually identical yields (entries 4 and 10). Decreasing the addition time of the radical initiator/hydrogen donor solution from 10 to 3 h resulted in a significant drop in yields, demonstrating the advantage of slow addition here. In most cases, the *E* isomer was found to have formed predominantly, a reflection of the higher stability of radical-adduct **41**, when compared to **42**. Interestingly, in the case of propargyl ether **23**, the *Z* isomer was slightly favored (entries 2 and 8). Orbital interaction between the phosphorus-centered functional group and the propargylic oxygen may explain this apparent aberration. The use of internal alkynes mainly generated the reduced products **11a** and **11b**.[19]

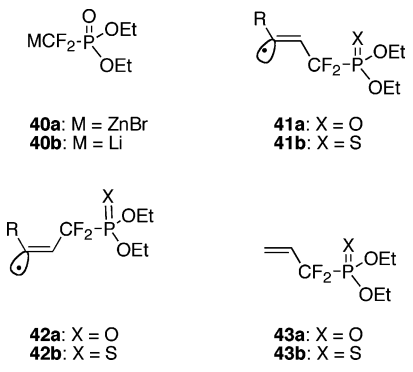



**FIGURE 3.** Structures of reagents **40**, radicals **41** and **42**, and products **43**.

Adducts **31** and **37** were quantitatively desilylated by treatment with tetra-*n*-butylammonium fluoride to give α,α-difluoroallylphosphonate **43a** and α,α-difluoroallylphosphonothioate **43b**. The approach developed in this paper thus allows the preparation of these products with an overall yield, from difluorophosphonate **11a** and difluorophosphonothioate **11b**, of 48% and 57%, respectively, and compares favorably with the literature approach to **43a** (39% overall yield).[18]

(19) For instance, attempted additions of radicals **5a** and **5b** onto *n*-oct-4-yne under otherwise identical conditions resulted in the formation of the desired adducts in 4% and 8%, respectively, based on $^{19}$F NMR spectra of the crude materials.

## Conclusion

Addition of dialkyl phosphonodifluoromethyl and phosphonothiodifluoromethyl radicals to alkenes represents a useful approach to the preparation of α,α-difluorinated alkylphosphonates and alkylphosphonothioates. The method can be applied to alkynes and generates the analogous *β*,*γ*-unsaturated adducts in fair to good yields. The use of these products in cycloaddition processes is under way in this laboratory, and will be reported in due course.

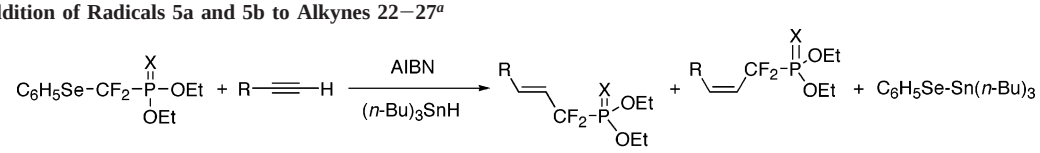
## Experimental Section

Unless otherwise stated, $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR, and $^{31}$P NMR spectra were recorded in deuterated chloroform on a spectrometer operating at 200, 50, 188, and 81 MHz, respectively, and relative to $(CH_3)_4Si$, $CDCl_3$, $C_6F_6$, and 85% $H_3PO_4$, respectively. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hertz (Hz). IR Spectra were recorded on a FT-IR spectrometer. Chemicals were used without further purification. Unless otherwise indicated, all drying of organic extracts were carried out over magnesium sulfate and all chromatographies were performed on silica. Abbreviations for the eluents are as follows: A (AcOEt), C ($CH_2Cl_2$), H (*n*-heptane), and E ($Et_2O$).

***O,O*-Diethyl difluoromethylphosphonothioate (11b)**. A solution of substrate **11a** (2.00 g, 7.81 mmol) and Lawesson's reagent (3.16 g, 7.81 mmol) in anhydrous toluene (16 mL) is refluxed under argon for 2 h, cooled to room temperature, and evaporated under reduced pressure. The crude product is filtered under a mixture of silica and celite and washed with heptane. The filtrate is evaporated under reduced pressure. Chromatography and elution with H/A (9:1) give **11b** as a colorless oil (1.55 g, 74%) ($R_f$ 0.31). $^1$H NMR $\delta$ 5.88 (dt, 1H, $^2J_{H-F}$ = 50.1, $^2J_{H-P}$ = 20.1), 4.31−4.15 (m, 4H, $^3J_{H-P}$ = 14.2, $^3J_{H-H}$ = 7.3), 1.33 (t, 6H, $^3J_{H-H}$ = 6.9). $^{31}$P NMR $\delta$ 72.99 (t, 1P, $^2J_{P-F}$ = 95.2).$^{19}$F NMR $\delta$ 29.62 (dd, 2F, $^2J_{F-P}$ = 94.7, $^2J_{F-H}$ = 47.2). $^{13}$C NMR $\delta$ 124.1 (dt, 1C), 65.6 (d, 2C, $^2J_{C-P}$ = 6.6), 16.0 (d, 2C, $^3J_{C-P}$ = 5.4). IR (NaCl) $\nu$ cm$^{-1}$ 1120 (C−F), 1046 (P−O), 807 (P═S). Exact mass (EI, 70 eV) *m*/*z* calcd for $C_5H_{11}O_2PF_2S$ 204.1773, found 204.1801. Anal. Calcd for $C_5H_{11}O_2PF_2S$: C, 40.37; H, 3.62. Found: C, 40.17; H, 4.27.

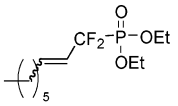
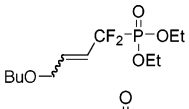
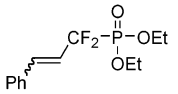
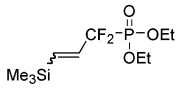
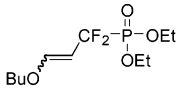
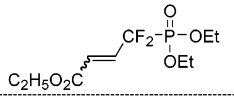
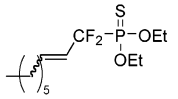
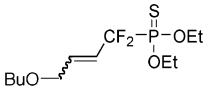
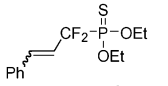
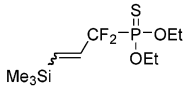
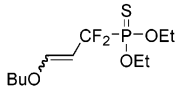
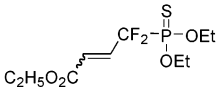
The same compound can also be prepared from diethylthiophosphite by the following procedure. To a solution of diethylthiophos-

**TABLE 2. Addition of Radicals 5a and 5b to Alkynes 22−27**[a]




**6a**: X=O
**6b**: X=S

**22-27** **28a-39a** **28b-39b** **8**

| entry | R | precursor | | product | | Yield (%)[b] | *E*/*Z* ratio |
|---|---|---|---|---|---|---|---|
| 1 | $CH_3$-$(CH_2)_5$- | **22** | **6a** |  | **28** | 55 | 88:12 |
| 2 | *n*-BuO-$CH_2$- | **23** | **6a** |  | **29** | 30 | 40:60 |
| 3 | $C_6H_5$- | **24** | **6a** |  | **30** | 68 | 73:27 |
| 4 | $(CH_3)_3$Si- | **25** | **6a** |  | **31** | 67 (64)[c] | 100:0 (95:5) |
| 5 | *n*-BuO- | **26** | **6a** |  | **32** | 63 | 83:15 |
| 6 | $C_2H_5O_2C$- | **27** | **6a** |  | **33** | 0 | - |
| 7 | $CH_3$-$(CH_2)_5$- | **22** | **6b** |  | **34** | 50 | 79:21 |
| 8 | *n*-BuO-$CH_2$- | **23** | **6b** |  | **35** | 37 | 45:55 |
| 9 | $C_6H_5$- | **24** | **6b** |  | **36** | 77 | 9:1 |
| 10 | $(CH_3)_3$Si- | **25** | **6b** |  | **37** | 80 (82)[c] | 93:7 (91:1) |
| 11 | *n*-BuO- | **26** | **6b** |  | **38** | 75 | 100:0 |
| 12 | $C_2H_5O_2C$- | **27** | **6b** |  | **39** | 0 | - |

[a] **5a** or **5b** (1 equiv), *n*-$Bu_3SnH$ (1.1 equiv), AIBN (0.4 equiv), toluene, 110 °C. [b] Isolated yields. [c] Using TTMSSH (1.1 equiv).

phite (22.33 g, 0.145 mol) in anhydrous THF (90 mL) is added sodium wire (3.5 g, 1.5 mol) in portions. The solution is stirred for 24 h at room temperature. After the disappearance of all of the sodium, chlorodifluoromethane (40 g, 0.33 mol) is bubbled through the reaction mixture over a period of time of 3 h. The solution is stirred under nitrogen for 12 h. Addition of a 1:1 mixture of silica and celite (100 g), filtration, washing of the solid with heptane (3 × 100 mL), and evaporation of the filtrate affords a liquid that is purified as above to give **11b** as a colorless oil (18.94 g, 64%).

***O,O*-Diethyl (phenylselanyl)difluoromethylphosphonate (6a).** A solution of phosphonate **11a** (0.42 g, 2.23 mmol; see Supporting Information) in anhydrous THF (6 mL) is added to a cold (−78 °C) solution of LDA (2.60 mmol, prepared from *N*,*N*-di*iso*propylamine (0.36 mL, 2.60 mmol), THF (10 mL), and *n*-butyllithium (1.79 mL of a 1.6 M solution in *n*-hexane, 2.86 mmol). After 15 min of stirring, a solution of freshly sublimated phenylselanyl chloride (0.64 g, 3.34 mmol) in anhydrous THF (6 mL) cooled at −78 °C is added under argon over a period of time of 3 h (cannula). The resultant mixture is stirred for 4 h at −78 °C, warmed to room temperature, and quenched with a saturated NaCl aqueous solution. The mixture is extracted with $CH_2Cl_2$ (3 × 10 mL), dried, and evaporated under reduced pressure. The crude material is chromatographed and eluted with a 4:1 mixture of H/A to give 0.55 g (71% yield) of **11a** as a colorless oil ($R_f$ 0.2). $^1$H NMR $\delta$ 7.68−7.65 (m, 2H), 7.37−7.26 (m, 3H), 4.27−4.14 (m, 4H), 1.28 (t, 6H, $^3J_{H-H}$ = 6.9). $^{31}$P NMR $\delta$ 4.39 (t, 1P, $^2J_{P-F}$ = 95.2). $^{19}$F NMR $\delta$ 77.84 (d, 2F, $^2J_{F-P}$ = 94.8). $^{13}$C NMR $\delta$ 136.6 (s, 2C), 128.8 (s, 1C), 128.1 (s, 2C), 121.7 (dt, 1C), 64.3 (d, 2C, $^2J_{C-P}$ = 6.6), 15.3

(d, 2C, $^3J_{C-P}$ = 5.5). IR (NaCl) $\nu$ (cm$^{-1}$) 1270 (P═O), 1042 et 1035 (C−F). M. S. (EI) *m*/*z* (rel int) 344 ($M^+$ ($^{80}$Se), 37), 186 ($M^+$ − $C_6H_5Se$, 22), 157 (57), 121 (100). Exact mass (CI, 200 eV) *m*/*z* calcd $C_{11}H_{15}F_2O_3PSe$ ($^{80}$Se) 344.9970, found 344.9990. Anal. Calcd for $C_{11}H_{15}F_2O_3PSe$: C, 38.50; H, 4.41. Found: C, 38.49; H, 4.42.

***O,O*-Diethyl (phenylselanyl)difluoromethylphosphonothioate (6b)**. Prepared from phosphonothioate **11b** by the same procedure; obtained as a greenish oil (0.58 g, 72% yield) ($R_f$ 0.34). $^1$H NMR $\delta$ 7.72−7.68 (m, 2H), 7.45−7.24 (m, 3H), 4.32−4.20 (m, 4H), 1.32 (t, 6H, $^3J_{H-H}$ = 6.9). $^{31}$P NMR $\delta$ 73.01 (t, 1P, $^2J_{P-F}$ = 96.4). $^{19}$F NMR $\delta$ 79.14 (d, 2F, $^2J_{F-P}$ = 94.9). $^{13}$C NMR $\delta$ 138.0 (s, 2C), 130.1 (s, 1C), 129.5 (s, 2C), 123.4 (dt, 1C), 65.8 (d, 2C, $^2J_{C-P}$ = 6.7), 16.6 (d, 2C, $^3J_{C-P}$ = 5.6). IR (NaCl) $\nu$ cm$^{-1}$ 1137 (C−F), 907 (P−O), 753 (P═S). Exact mass (EI, 70 eV) *m*/*z* calcd for $C_{11}H_{15}O_2PF_2SSe$ 359.2349, found 359.2353. Anal. Calcd for $C_{11}H_{15}O_2PF_2SSe$: C, 36.78; H, 4.21; S, 8.93. Found: C, 36.82; H, 4.24; S, 8.96.

Compound **6b** can also be prepared from precursor **6a** by the following procedure. A solution of substrate **6a** (2.69 g, 7.81 mmol) and Lawesson's reagent (3.16 g, 7.81 mmol) in anhydrous toluene (16 mL) is refluxed under argon for 2 h, cooled to room temperature, and evaporated under reduced pressure. The crude product is filtered under a 1:1 mixture of silica and celite and washed with heptane. The filtrate is evaporated under reduced pressure. This material is then subjected to chromatography and elution with a 4:1 mixture of H/A to give **6b** as a greenish oil (1.54 g, 55% yield).

**Radical Addition of Precursor 6a and 6b onto Alkenes 12−17 or Alkynes 22−27. General Procedure**. To a degassed refluxing solution of the requisite precursor (1 equiv; **6a** or **6b** 0.185 mol/L) and the requisite alkene (1 equiv; **12**−**17** 0.185 mol/L) or alkyne (1 equiv; **22**−**27** 0.185 mol/L) in anhydrous toluene is added a toluene solution of tri-*n*-butyltin hydride (1.1 equiv; 0.203 mol/L) and AIBN (0.4 equiv, 0.074 mol/L) over a period of time of 10 h (syringe pump). After completion of the addition, the resultant mixture is refluxed for an additional 2 h, cooled to room temperature, and evaporated under pressure. The crude material is chromatographed and eluted with the solvents indicated in Supporting Information.

***O,O*-Diethyl 1,1-difluoro-prop-2-enylphosphonate (43a)**. At 0 °C, 1.33 mL of tetra-*n*-butylammonium fluoride (1.33 mmol, 1 M in THF containing 5% water) is added to **31** (100 mg, 0.33 mmol) in solution in anhydrous THF (2 mL). The mixture is stirred for 1 h at 0 °C and quenched with NaCl solution (3 mL) at room temperature. The crude mixture is extracted with ethyl acetate (2 × 5 mL), dried under $MgSO_4$, and evaporated under reduced pressure to afford **43a** as a pale green oil (75.9 mg, 100%). $^1$H NMR $\delta$ 6.31−6.13 (m, 1H), 6.02−5.85 (m, 1H), 5.63−5.38 (m, 1H), 4.32−4.15 (m, 4H), 1.42 (t, 6H, $^3J_{H-H}$ = 7.2). $^{31}$P NMR $\delta$ 7.55 (t, 1P, $^2J_{F-P}$ = 110.3). $^{19}$F NMR $\delta$ 57.35 (dd, 2F, $^2J_{F-P}$ = 115.4, $^3J_{F-H}$ = 14.5). $^{13}$C NMR $\delta$ 137.8 (s, 1C), 133.2 (s, 1C), 124.5 (dt, 1C), 64.4 (d, 2C, $^2J_{C-P}$ = 6.4), 15.4 (d, 2C, $^3J_{C-P}$ = 4.8). IR (NaCl) $\nu$ cm$^{-1}$ 1187 (P═O), 1092 (C−F), 1069 (P−O). Exact (EI, 70 eV) *m*/*z* calcd for $C_7H_{13}O_3PF_2$ 214.1485, found 214.1533. Anal. Calcd for $C_7H_{13}O_3PF_2$: C, 39.26; H, 6.12. Found: C, 39.35; H, 6.08.

***O,O*-Diethyl 1,1-difluoro-prop-2-enylphosphonothioate (43b)**. The procedure described above is applied to **37** to quantitatively deliver **43b** as a colorless liquid. $^1$H NMR $\delta$ 6.43−6.19 (m, 1H), 6.04−5.82 (m, 1H), 5.59−5.34 (m, 1H), 4.43−4.21 (m, 4H), 1.38 (t, 6H, $^3J_{H-H}$ = 6.9). $^{31}$P NMR $\delta$ 78.11 (t, 1P, $^2J_{F-P}$ = 109.7). $^{19}$F NMR $\delta$ 59.06 (dd, 2F, $^2J_{F-P}$ = 112.9, $^3J_{F-H}$ = 15.2). $^{13}$C NMR $\delta$ 140.1 (s, 1C), 135.6 (s, 1C), 122.5 (dt, 1C), 63.8 (d, 2C, $^2J_{C-P}$ = 6.8), 16.4 (d, 2C, $^3J_{C-P}$ = 5.2). IR (NaCl) $\nu$ cm$^{-1}$ 1092 (C−F), 1069 (P−O), 836 (P═S). Exact (EI, 70 eV) *m*/*z* calcd for $C_7H_{13}O_2PF_2S$ 230.2151, found 230.2134. Anal. Calcd for $C_7H_{13}O_2PF_2S$: C, 36.52; H, 5.69; S, 13.93. Found: C, 36.57; H, 5.73; S, 13.85.

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**Supporting Information Available:** Experimental procedure for compound **11a**; anatytical data for compounds **18a**−**18f**, **19a**−**19f**, **21a**−**21b**, **28**−**32**, and **34**−**38**; and $^1$H, $^{13}$C, $^{19}$F, and $^{31}$P NMR spectra for compounds **18f**, **31** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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