product of a putative alkoxyl radical (Scheme I). 10-Oxo-8,12-octadecadienoic acid (**3**) was produced in 8% yield but 10-hydroxy-8,12-octadecadienoic acid (**4**) was not detected. Reaction of 10-hydroperoxy-8-octadecenoic acid under similar conditions produced **2** in 20% yield, illustrating the importance of the allylic double bond on β-scission. 10-Oxo-8-octadecenoic acid and 10-hydroxy-8-octadecenoic acid were formed from 10-hydroperoxy-8-octadecenoic acid in 79% and 1%, respectively. Support for the intermediacy of an alkoxyl radical in the formation of **2** was provided by detection of the β-scission products octenal and 2-octenol in a total yield of 10% relative to **2** following reaction of **1** with ferric chloride–cysteine. Reaction of **1** with $FeSO_4$, hematin, or ferrihemoglobin produced **2**, **3**, and **4** in yields that are summarized in Table I. In all cases, **2** was the major product. In contrast to the reaction of **2** with iron protoporphyin IX, zinc protoporphyrin IX did not produce any aldehyde, suggesting that acid catalysis is not responsible for metalloporphyrin-catalyzed β-scission of **2**.

The data in Table I indicate that hematin and ferrihemoglobin catalyze *homolytic* cleavage of the O–O bond of **1**. Literature precedents indicate that hemeperoxidases catalyze *heterolytic* cleavage of the O–O bond of hydroperoxides.[1d-f] We, therefore, reacted prostaglandin H synthase, a heme-containing peroxidase, with **1** in the presence of phenol. Under these conditions, the alcohol **4** was produced in 95% yield.[8] The dramatic difference in product profiles between ferrihemoglobin and PGH synthase is consistent with homolytic vs. heterolytic hydroperoxide reduction and demonstrates the ability of **1** to differentiate one- and two-electron reduction pathways. This experiment also illustrates the importance of the protein component in determining the mechanism of hydroperoxide reduction by hemeproteins.

10-Hydroperoxy-8,12-octadecadienoic acid offers several advantages as a diagnostic probe for alkoxyl radical formation during the reaction of hydroperoxides with metals or metalloproteins. It is soluble in organic solvents or aqueous buffers, which makes it useful for investigating a variety of catalytic systems. A single major product (**2**) results from its conversion to alkoxyl radicals, which is easily separated by HPLC. The hydroperoxide is readily synthesized by photooxygenation of linoleic acid, and radioactively labeled material of high specific activity can be prepared from commercially available [^{14}C]- or [^{3}H]linoleic acid. This greatly facilitates quantitation of reaction products at virtually any starting concentration of **1**. Finally, **1** is an analogue of naturally occurring fatty acid hydroperoxides and should be able to probe the redox environment of the membrane phase of cells, the site at which most cellular hydroperoxide biosynthesis occurs.[9] We are currently employing **1** to determine the fate of hydroperoxides in chemical, biochemical, and biological systems.

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(7) Products of the reaction of **1** with different metal complexes were separated by HPLC by using the conditions described above and quantitated by using a radioactive flow detector. The purified products were methylated with diazomethane and analyzed by GC-MS. Methoximes were formed from carbonyl-containing compounds by treatment of the products (100 μg) with methoxyamine hydrochloride (5 mg) in pyridine (0.5 mL) for 15 h at 25 °C. Silyl ether derivatives of hydroxy compounds were prepared by treatment of dry samples with an excess of bis(trimethylsilyl)trifluoroacetamide. The proposed structure of **2** was confirmed by ^{1}H NMR [($CDCl_3$) δ 9.5 (d, J = 8 Hz, 1 H), 6.8 (dt, J = 15.5, 6.8 Hz, 1 H), 6.1 (ddt, J = 15.5, 8, 1.3 Hz, 1 H)] and by IR (2740, 1710, 1690 cm^{-1}).

(8) Prostaglandin H synthase was purified from ram seminal vesicles. The enzyme exhibits heme-dependent cyclooxygenase and peroxidase activities. Recent studies indicate that hydroperoxides oxidize the heme by two electrons to a ferryl–oxo complex that undergoes stepwise one–electron reduction to resting enzyme if a reducing substrate is present. Lambeir, A.-M.; Markey, C. M.; Dunford, H. B.; Marnett, L. J. *J. Biol. Chem.* **1985**, *260*, 14894–14896. Phenol was included to support catalytic turnover of the higher oxidation states of the peroxidase. Phenol has no effect on the products of reaction of **1** with ferrihemoglobin. The small amount of **2** formed in the experiments with PGH synthase (4%) is due to free heme in the enzyme preparation.

(9) Hydroperoxyoctadecadienoic acids partition into the membrane phase of cells but do not appear to be incorporated into phospholipids by esterification into the glycerol component. Funk, C. D.; Powell, W. S. *J. Biol. Chem.* **1985**, *260*, 7481–7488.

Vinyl Radical Cyclizations Mediated by the Addition of Stannyl Radicals to Triple Bonds

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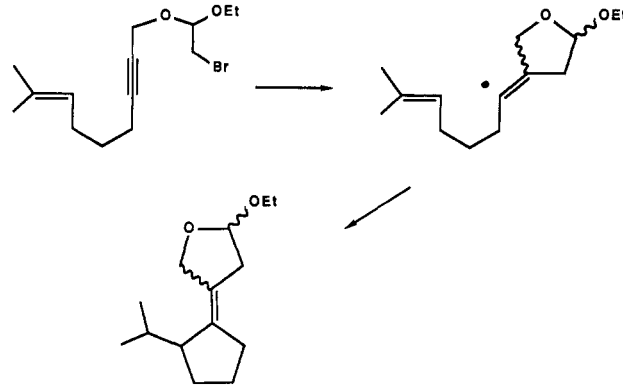
In our original report[1] of the vinyl radical cyclization, the vinyl radical was produced by the reaction of a vinyl bromide with a stannyl radical. We now describe an alternative.

It occurred to us that an attractive route would be opened if one could direct the addition of a radical species selectively to the triple bond of a suitable enyne. We have described elsewhere a rather special solution to this problem, in which the desired regioselectivity was achieved by tethering the initiating radical so as to enforce its addition to the triple bond.[2]



We now illustrate the more general process shown in Scheme I, in which the external radical A is a stannyl radical.[3] For example, refluxing a 0.02 M benzene solution of enyne **1** containing tributylstannane (1.1 equiv) and AIBN (0.04 equiv) for 3–4 h led to 85% yield of the tin-substituted methylenecyclopentane **2**. It is of particular interest, of course, that the tin substituent can readily be removed without effecting other structural changes: simple stirring with dry silica in methylene chloride caused protiodestannylation[4] to **3**. Even on a 20-g scale,[5] the cyclization of **1** can be run, without isolation of the intermediate[2,6,7] to produce pure **3**, bp 80–85 °C (0.2 mm), in 90%

(1) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.
(2) Stork, G.; Mook R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720.
(3) For previous reports of the cyclization of acetylenic olefins by stannyl radicals, see: (a) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529. See also: Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. (b) Stork, G. In *Selectivity—A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Basel, 1984; pp 292–293. (c) "Vinyl Radical Cyclization Initiated by Free Radical Addition to Triple Bonds"; Mook, R., Jr., Ph.D. Dissertation, Columbia University, 1985, Cf. *Diss. Abstr. Int., B* **1986**, *46B*, 2669.
(4) See: Fung, N. Y. M; de Mayo, P.; Schauble, J. H.; Weedon, A. C. *J. Org. Chem.* **1978**, *43*, 3977. Leibner, J. E.; Jacobus, J *J. Org. Chem.* **1979**, *44*, 449.
(5) Mook, R., Jr.; Sher, P. M. *Org. Synth.*, in press.
(6) The vinylstannane **2** may be isolated by flash chromatography. ^{1}H NMR δ 5.62 (br s, 1 H) with satellites, 3.73 (s, 3 H), 3.71 (s, 3 H).

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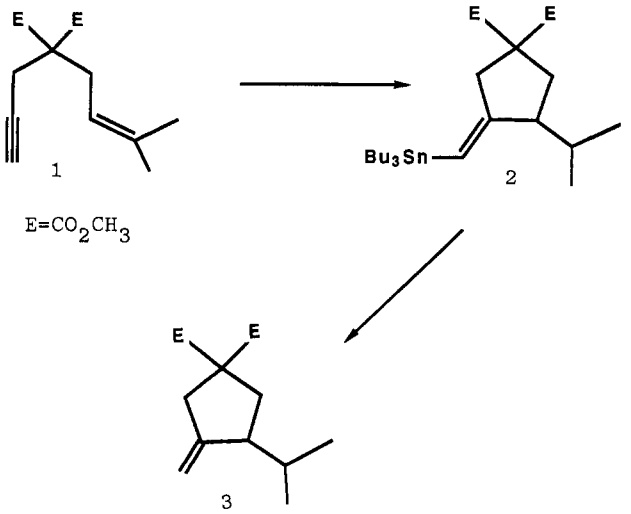
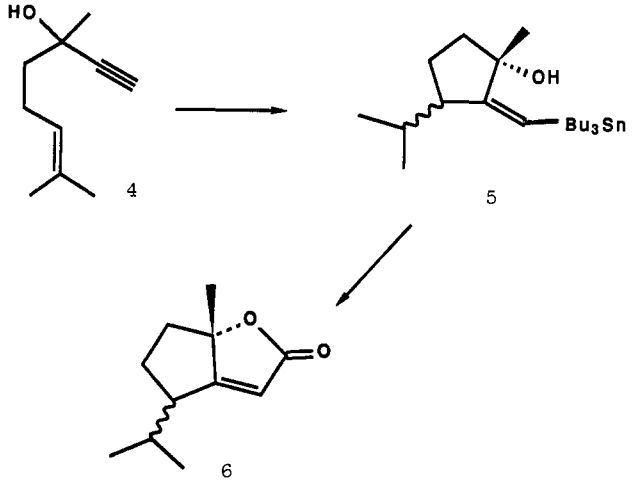
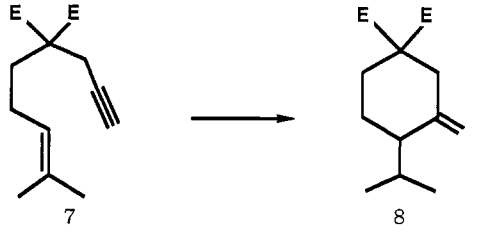
overall yield.[8]



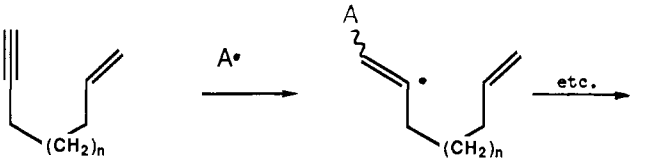
The (*Z*) stereochemistry of the vinylstannane **5**, obtained by the above procedure from the ethynyl carbinol **4** ("dehydrolinalol"), was proved by its transformation into the bicyclic lactone **6** obtained by cyclization of the unsaturated acid which is produced from **5** by tin–lithium exchange, followed by carbon dioxide.



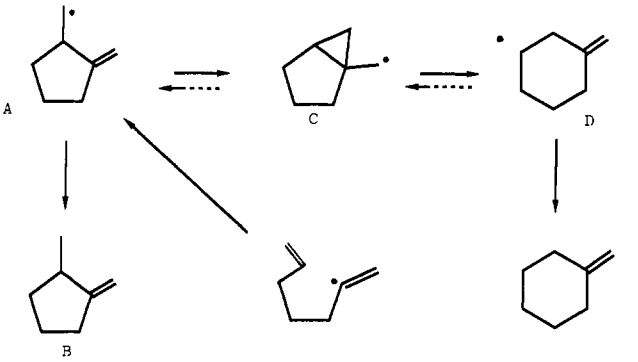
Competition between formation of a six- and a seven-membered ring leads, as expected, to the former as shown by the cyclization of **7** to **8**, obtained in 55% yield after silica destannylation of the intermediate. This particular result would be expected whether



Scheme I

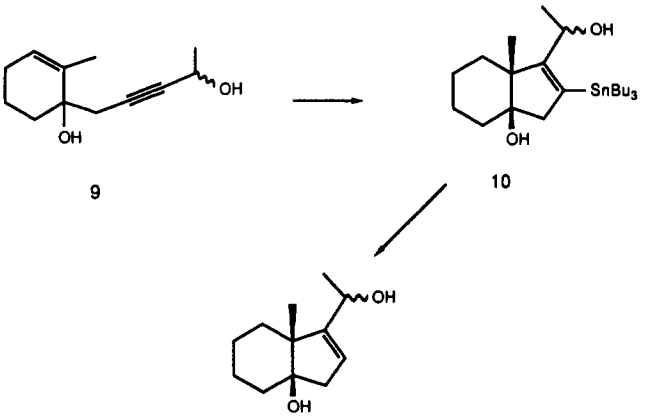


cyclization is under kinetic or thermodynamic control. On the other hand, when the competition is between the formation of a methylenecyclopentane or a methylenecyclohexane, the cyclopentyl system (cf. A) that is the expected kinetic product from the cyclization of a *vinyl* radical into an olefin can easily rearrange to a cyclohexyl ring (cf. D),[3a] as illustrated below:



For practical purposes, it is often possible to steer the cyclization reaction to either the five- (normally kinetic) or six-ring (normally thermodynamic) product because the rearrangement rate, A → C → D, though expected to be fast, is independent of tin hydride concentration, in contrast to the A to B rate.[3a]

A particularly striking example of regiocontrol in these tin radical-mediated cyclizations of acetylenic olefins underlines the potential scope of the reaction: cyclization of the unsymmetrical acetylenic diol **9**[9] under the usual 0.02 M conditions gave, in 70% yield, the bicyclic tin compound **10**,[10] which led to the indene **11** after destannylation (BuLi, −78 °C, pH 7 buffer).[11]



The regioselectivities implied by the cyclizations of **1** to **2** and of **9** to **10** are surprising. First, because they appear to imply preference of a stannyl radical for a triple rather than for a double bond. Second, because of the apparent preference of the stannyl radical for that end of the triple bond which leads to **10**. We now

(7) The cyclized vinylstannanes are, of course, useful for various transformations, as intermediates, inter alia (a) to vinyl carbanions: Negishi, E.-i. *Organometallics in Organic Synthesis*; Wiley-Interscience: New York, 1980; Vol. 1, pp 394–454. Pereyre, M.; Quintard, J.-P. *Pure Appl. Chem.* **1981**, *53*, 2401 and references therein. Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404 and references therein. (b) To acylated and alkylated olefins via Pd(0) chemistry: Stille, J. K.; Labodie, J. W. *Tetrahedron Lett.* **1983**, 4283. Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* **1983**, 839. Stille, J. K.; Scott, W. J.; Crisp, G. T. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (c) To carbonyl compounds: Ikegami, S.; Nishida, A.; Shibasaki, M. *Tetrahedron Lett.* **1981**, 4819. (d) To vinyl halides: Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, 3851 and references therein.

(8) IR (neat) 3085, 2975, 2875, 1735, 1655, 1430, 1380, 1365, 855 cm^{-2}; MS (CI), *m/z* M + 1 = 241; ^1H NMR (200 MHz, $CDCl_3$) δ 5.04 (br s, 1 H), 4.84 (br s, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 0.96 (d, 3 H, *J* = 7 Hz), 0.85 (d, 3 H, *J* = 7 Hz).

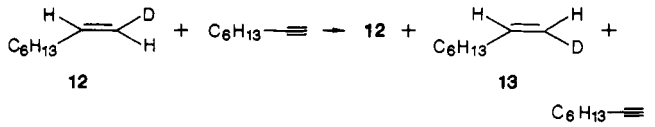
(9) Made by addition of the aluminum complex of propyne (Eiter, K.; Oediger, H. *Justus Liebigs Ann. Chem.* **1965**, *682*, 62) to 2-methyl-2-cyclohexenone, followed by reaction of the lithio derivative of the resulting acetylide with acetaldehyde.

(10) The indenylstannane **10** was obtained as a white solid (mixture of diastereomers), mp 70–72 °C after flash chromatography.

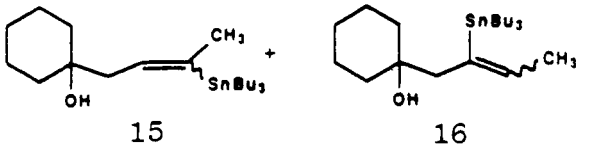
(11) Destannylation was unsuccessful with silica gel in this case and in similarly hindered cases. Indene **11** was obtained as a mixture of diastereomers at the secondary carbinol center. ^1H NMR δ 5.68 (br s, 1 H); 1.38, 1.35 (d, *J* = 7 Hz, 3 H); 1.13, 1.12, (s, 3 H).

show that these results are the consequence of the reversibility of the addition of stannyl radicals not only to double bonds[12] but *to triple bonds as well.* The operational selectivity for addition of a trialkylstannyl radical to an alkyne in the presence of a double bond suitable for cyclization was not anticipated since radical additions to isolated alkenes and alkynes either show no great selectivity or are faster with the former.[13]

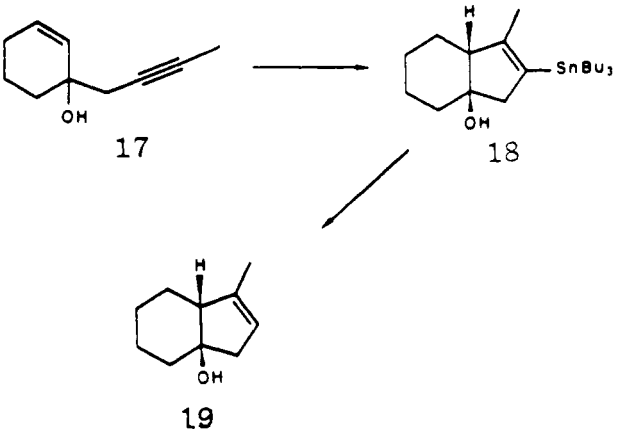
The following experiment shows that the enyne cyclizations are successful because cyclization is faster, and reversal slower, for vinyl radicals than for their alkyl counterparts, so that the whole cyclization pathway is via the adduct of the stannyl radical to the acetylene rather than to the olefin: A 1:1 mixture of *trans*-1-deuterio-1-octene (**12**)[12a] and 1-octyne was heated under argon for 1 h at 80 °C, with 0.85 equiv of tributylstannane and 1 mol % of AIBN. The products consisted, in addition to a considerable recovery of 1-octyne, of a mixture of (*E*)- and (*Z*)-deuterio-1-octene. This was deduced by the presence in the infrared spectrum of the reaction products of an absorption band at 2250 cm^{-1} due to the *Z* isomer **13**,[12a] in addition to that at 2270 cm^{-1} corresponding to the *E* isomer **12**.



The surprising regioselectivity toward one end of the triple bond in the cyclization of **9** to **10** implies that the addition of stannyl radicals to the *triple bond* of an olefinic acetylene is *also reversible* under the reaction conditions. This is demonstrated by the following two experiments. (1) No addition of tributylstannane to the ethynyl carbinol **14** took place under the usual 0.02 M conditions in benzene with AIBN, but increasing the stannane concentration to 0.77 M now gave a 1.2 to 1 mixture of the two possible vinylstannanes **15** and **16**, in addition to some recovered **14**. (2) When **17**, the cyclohexenyl analogue of **14**, was submitted



to the 0.02 M cyclization conditions which left **14** unchanged, it was cyclized to give **18**, which was destannylated to **19**[14] with silica gel, in an overall yield of 76% from **17**. It, thus, is the reversibility of the addition of stannyl radicals to the triple bonds of **9** and **17**, which leads to selection of the more rapidly formed ring (in the case of **9** to **10** and of **17** to **18**, to a five-membered rather than a four-membered ring).



Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for their support of this work.

(12) (a) Sommer, R.; Kuivila, H. G.; *J. Org. Chem.* **1968**, *33*, 802. (b) Neumann, W. P.; Albert, H. J.; Kaiser, W. *Tetrahedron Lett.* **1967**, 2041. (c) Kuivila, H. G., Sommer, R. *J. Am. Chem. Soc.* **1967**, *89*, 5616. (d) Albert, H. G.; Neumann, W. P.; Kaiser, W.; Ritter, H. P. *Chem. Ber.* **1970**, *103*, 1372. (e) Mitchell, T.; Amamrin, A. *J. Organomet. Chem.* **1980**, *199*, 49. (f) Podesta, J. C.; Chopa, a. B.; Ayala, A. D. *J. Organomet. Chem.* **1981**, *212*, 163.

(13) (a) Kharasch, M. S.; Jerome, J. J.; Urry, W. H. *J. Org. Chem.* **1950**, *15*, 966. (b) Gazith, M.; Szwarc, M. *J. Am. Chem. Soc.* **1957**, *79*, 3339. (c) Abell, P. I. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tripper, C. F. H., Eds.; Elsevier: Amsterdam, 1976; Vol. 18. (d) Giese, B.; Lachein, S. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 768. Giese, B.; Meixner, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 965. Giese, B.; Lachein, S.; Meixner, J. *Tetrahedron Lett.* **1980**, *21*, 2505. (e) Heiba, E. I.; Dessau, R. M.; *J. org. Chem.* **1967**, *32*, 3837. (f) Ito, O.; Matsuda, M. *J. Org. Chem.* **1984**, *49*, 17 and references therein.

(14) The stannylindene **18** was purified by flash chromatography on silica gel with 7% ethyl acetate–petroleum ether (R_f 0.65; starting hydroxyenyne **17**, R_f 0.35). Destannylation was effected by stirring overnight with silica gel to give **19** in 76% yield after chromatography. ^1H NMR δ 5.27 (br s, 1 H), 2.48 (br d, J = 16 Hz, 1 H), 2.16 (d, J = 16 Hz) 2.16 (m), 1.71 (br s, 3 H); MS (EI), m/z 152 (M^+), 137 ($M^+ - CH_3$), 135 (M^+ – OH).

Palladium-Catalyzed Substitutions of Triflates Derived from Tyrosine-Containing Peptides and Simpler Hydroxyarenes Forming 4-(Diethoxyphosphinyl)phenylalanines and Diethyl Arylphosphonates†

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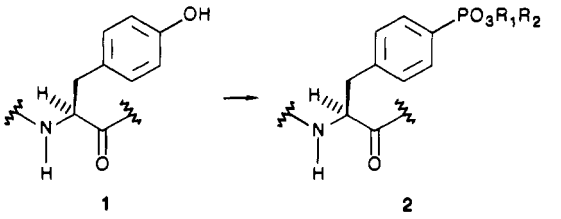
Inhibitors of tyrosine protein kinases which oncogenes or retroviruses encode may lead to avant garde, *mechanism-based anticancer and antiviral drugs.* These kinases are of central importance in retroviral or oncogenic cell transformation, and their cellular homologues with the associated phosphatases regulate normal cell growth.[1] Together the kinases and phosphatases catalyze reversible transfer of phosphate to tyrosyl residues of proteins and enzymes. Thus, to design inhibitors of enzymes catalyzing phosphate transfer, we sought to change tyrosyl peptides to 4-phosphonophenylalanyl derivatives (**1** → **2**). Here we report



that tyrosine-containing peptides and certain functionalized hydroxyarenes formed 4-(diethoxyphosphinyl)phenylalanines and diethyl arylphosphonates in a novel, two-step sequence.[2]

Direct replacement of an aryl C–O bond by a C–P bond is, to our knowledge, unprecedented. This is in sharp contrast to analogous processes involving the aryl carbon–metal,[3] –halogen,[4]

† In memoriam Stylianos K. Petrakis.

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(2) Tf = (trifluoromethyl)sulfonyl; TfO = [(trifluoromethyl)sulfonyl]oxy; MeMorph = *N*-methylmorpholine; Boc = *tert*-butyloxycarbonyl; Bzl = benzyl; Z = benzyloxycarbonyl; MeO = methyl ester.

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