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PALLADIUM-CATALYZED PHOSPHORYLATION OF ALKENYL TRIFLATES

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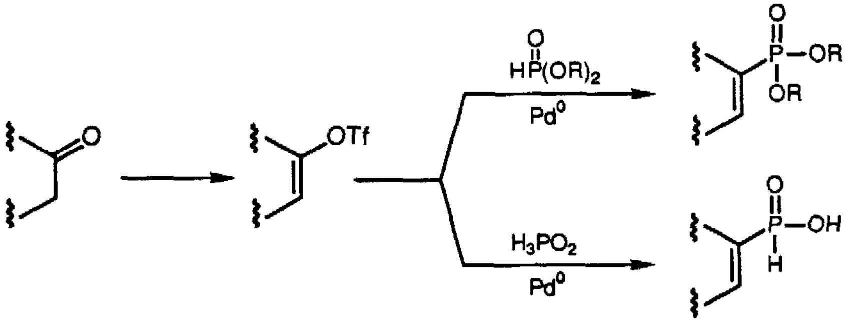
Summary: A method is described for the efficient preparation of α,β-unsaturated phosphonates and phosphinates from alkenyl triflates via palladium(0)-catalyzed coupling with dialkylphosphites or hypophosphorous acid.

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] Whereas the chemical literature is rich with methodology for the preparation of compounds containing sp^3-carbon-phosphorus bonds, examples of sp^2(particularly alkenyl)-carbon-phosphorus bond forming reactions are notably scarce.[2] Our interest in studying the behavior of unsaturated organophosphorus compounds with enzymes prompted our development of a versatile method for synthesizing alkenyl phosphorus acid derivatives. Specifically, we have found that alkenyl triflates undergo very facile and efficient palladium(0)-catalyzed coupling with dialkyl phosphites and with hypophosphorous acid to provide alkenyl phosphonates and alkenyl phosphinates in high isolated yields, ordinarily in less than one hour at room temperature.



Formal phosphorus displacements of vinyl chlorides or bromides mediated by nickel,[3] palladium,[4] or copper[5] have been reported. The general utility of these methods is attenuated, however, by the limited accessibility of the vinyl halides and, to a lesser extent, moderate yields and relatively harsh reaction conditions. On the other hand, the chemistry of alkenyl-palladium(II) intermediates derived from *alkenyl triflates* has been extensively explored and applied in recent years.[6] Not only are alkenyl triflates generally more reactive in palladium(0)-catalyzed couplings than the corresponding vinyl halides, but also, as enol derivatives, they are readily available in regiocontrollable fashion from ketones.[7]

A typical phosphorylation procedure is as follows. A mixture of triflate **2**[7] (100 mg, 0.193 mmol), dimethyl phosphite (25 µL, 0.273 mmol), triethylamine (120 µL, 0.863 mmol), and tetrakis(triphenylphosphine)palladium (10 mg, 0.009 mmol) in DMF (4 mL) was stirred under an argon atmosphere for 1 h. The reaction mixture was then diluted with chloroform and washed with 10% aqueous HCl and brine, dried over sodium sulfate, and concentrated *in vacuo*. Flash column chromatography (silica gel, 10% *i*-PrOH in hexanes) afforded dimethyl phosphonate **10** as a white crystalline solid (90 mg, 98%), mp 151-155° C. Table I contains illustrative examples.

Phosphinic acids (e.g., **9**) can similarly be prepared by substitution of 95% hypophosphorous acid[8] in place of the dialkyl phosphite. Electron-deficient triflates such as **5** and **6** required slightly elevated temperatures for complete conversion to occur within a convenient time span. Tris(dibenzylideneacetone)dipalladium(0), with or without added 1,3-bis(diphenylphosphino)propane[9] was also effective in catalyzing the phosphorylation (data not shown), although higher yields and cleaner reaction mixtures generally resulted from the use of tetrakis(triphenylphosphine)palladium. In contrast to palladium-catalyzed carbonylations[6f] and alkylations[6a,e], bis(triphenylphosphine)palladium(II) acetate was ineffective as a phosphorylation catalyst as only recovered triflate was obtained after 24 hours.

In conclusion, we have reported a versatile and efficient means of preparing α,β-unsaturated phosphonic and phosphinic acid derivatives from ketones through the intermediacy of alkenyl triflates.[10] In view of the ready availability of alkenyl triflates and the relatively mild catalytic palladium(0) reaction conditions, this protocol represents a useful new tool of general applicability for the organophosphorus chemist.

Acknowledgments

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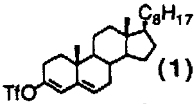
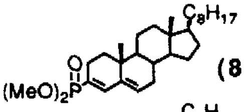
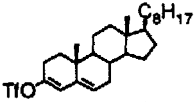
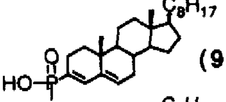
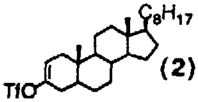
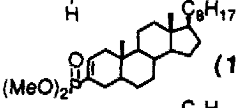
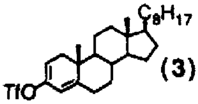
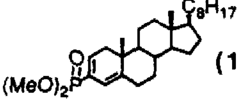
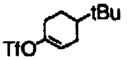
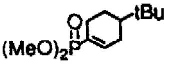
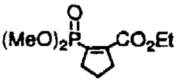
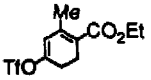
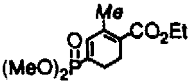
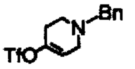
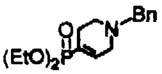
Table I.

Triflate[a]	Phosphorylation Reagent	Product[a,b]	% Yield[c]
 (1)	$(MeO)_2P(O)H$	 (8)	90
	H_3PO_2	 (9)	80
 (2)	$(MeO)_2P(O)H$	 (10)	98
 (3)	$(MeO)_2P(O)H$	 (11)	93
 (4)	$(MeO)_2P(O)H$	 (12)	91
 (5)	$(MeO)_2P(O)H$	 (13)[d]	89
 (6)	$(MeO)_2P(O)H$	 (14)[d]	87
 (7)	$(EtO)_2P(O)H$	 (15)	84

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[a] All new compounds gave satisfactory NMR, IR, and mass spectra and elemental analyses.

[b] Except where noted, reactions were carried out at 25° C for 1 hour with 5 mole % catalyst.

[c] Yields are based on chromatographically isolated, analytically pure products.

[d] Reaction conducted at 65° C for 4 hours.

References and Footnotes

1. For example: Drake, G.L., Calamaria, T.A., *The Role of Phosphonates in Living Systems*, Hilderbrand, R.L., Ed., CRC Press: Boca Raton, FL, 1983; chap 7.
2. Engel, R., *Synthesis of Carbon-Phosphorus Bonds*, CRC Press: Boca Raton, FL, 1988.
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6. (a) Andersson, C.-M., Hallberg, A., *J. Org. Chem.*, **1989**, *54*, 1502; (b) Karabelas, K., Hallberg, A., *J. Org. Chem.*, **1988**, *53*, 4909; (c) Orsini, F., Pelizzoni, F., *Synthetic Commun.*, **1987**, *17*, 1389; (d) Wulff, W.D., Peterson, G.A., Bauta, W.E., Chan, K.-S., Faron, K.L., Gilbertson, S.C., Kaesler, R.W., Yang, D.C., Murray, C.K., *J. Org. Chem.*, **1986**, *51*, 279; (e) Cacchi, S., Morera, E., Ortar, G., *Synthesis*, **1986**, 320; (f) Cacchi, S., Morera, E., Ortar, G., *Tetrahedron Lett.*, **1985**, *26*, 1109; (g) Scott, W.J., Crisp, G.T., Stille, J.K., *J. Am. Chem. Soc.*, **1984**, *106*, 4630; (h) Cacchi, S., Morera, E., Ortar, G., *Tetrahedron Lett.*, **1984**, *25*, 2271; (i) Cacchi, S., Morera, E., Ortar, G., *Tetrahedron Lett.*, **1984**, *25*, 4821; (j) Stille, J.K., *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508.
7. Mc Murry, J.E., Scott, W.J., *Tetrahedron Lett.*, 1983, 24, 979;
8. Commercially available (Aldrich) 50% aqueous hypophosphorous acid was distilled at 38 mmHg, 30-35° C. The distillate solidified upon cooling to -20° C and thereafter was handled as a hygroscopic solid using ordinary precautions to exclude moisture. See also: Zeches, M., Ledouble, G., Albert, O., Wiczewski, M., *Eur. J. Med. Chem.-Chimica Therapeutica*, **1975**, *10*, 309.
9. Bidentate phosphine ligands have been reported to accelerate aryl triflate-palladium-catalyzed carbonylation reactions, however no rate enhancement was observed for the phosphorylations of alkenyl triflates. See: Dolle, R.E., Schmidt, S.J., Kruse, L.I., *J.Chem. Soc., Chem. Comm.*, **1987**, 904, and references cited therein.
10. Recently two groups have reported on the preparation of aryl phosphonates from aryl triflates facilitated by palladium(0)[11]. We find that our phosphorylation protocol also allows for the preparation of aryl phosphonates and, additionally, *aryl phosphinates* from aryl triflates provided that one mole-equivalent per palladium of 1,3-bis(diphenylphosphino)propane is added and the reaction temperature is held at 90° C for 4-5 hours.
11. Petrakis, K.S., Nagabhushan, T.L., *J. Am. Chem. Soc.*, **1987**, *109*, 2831; Lu, X., Zhu, J., *Synthesis*, **1987**, 726.

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