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# Cyclisation of Dienes and Enynes using Phosphorus-Centred Radicals

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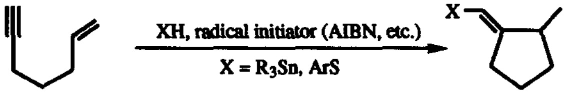
**Abstract:** Reaction of diphenylphosphine with suitable 1,6-diene or enyne systems, under free radical conditions, results in addition of a phosphorus-centred radical and cyclisation to form substituted phosphines and vinyl phosphines respectively.

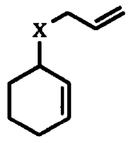
The use of carbon-centred radicals in cyclisation reactions has recently been an area of intense interest in the organic synthesis community. For the most part, the radicals required for these reactions have been generated from alkyl halides (or similar groups such as selenides) using reagents such as tin hydrides (or equivalent reagents such as $(Me_3Si)_3SiH$).[1] A range of alternative protocols has also been developed to a lesser extent, including reactions in which the radical cyclisation is initiated by the addition of a sulphur- or tin-centred radical to a multiple bond in a doubly unsaturated precursor, e.g. Scheme 1.[2,3]



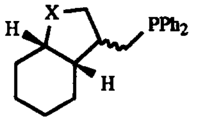
**Scheme 1**

Additional scattered reports describe alternative radical-generating conditions for analogous cyclisations of 1,6-diene or enyne systems, including the use of PhSeSePh,[4] or $(Me_3Si)_3SiH$.[5] We were attracted to this type of cyclisation, which can enable the introduction of synthetically useful functionality into simple starting materials, and recently examined the $Bu_3SnH$-mediated reactions as part of our study of spiroether synthesis.[6] Here we describe an unexplored variant of this type of radical cyclisation protocol which utilises diphenylphosphine as the radical-generating species.

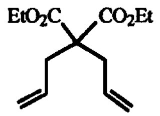
The free radical addition of phosphines to unsaturated systems, mainly alkenes, is a very well established, but rather under-utilised method of preparing alkyl phosphines.[7] Two isolated reports supported our expectation that the phosphorus-centred radicals involved in this type of reaction would enable cyclisations such as that outlined in Scheme 1 to be carried out to give phosphorus-containing products.[8] In order to examine this possibility in detail we prepared a series of diene and enyne substrates and exposed them to standard radical-generating conditions (AIBN in benzene at reflux) in the presence of $Ph_2PH$.[9] Under these conditions the cyclisation of 1,6-dienes appears to rather inefficient, as indicated by the modest yields of cyclised products **3**, **4** and **6** obtained from **1**, **2** and **5** respectively. In addition, we were unable to obtain any of the product expected by transannular cyclisation of 1,5-cyclooctadiene, which had been previously reported as a minor by-product from the corresponding reaction involving $^{n}C_{20}H_{41}PH_2$.[8b]



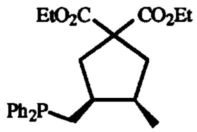
**1** X = O
**2** X = $NCO_2Me$



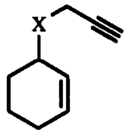
**3** X = O, 19% (1.2:1)
**4** X = $NCO_2Me$, 35% (1.2:1)



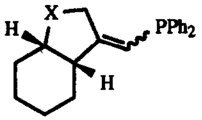
**5**



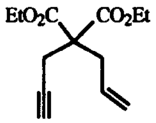
**6** 21% (36%)[a]



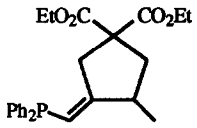
**7** X = O
**8** X = $NCO_2Me$



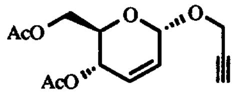
**9** X = O, 66% (1.7:1)
**10** X = $NCO_2Me$
55% major isomer
9% minor isomer



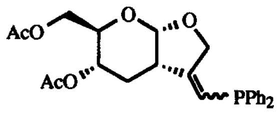
**11**



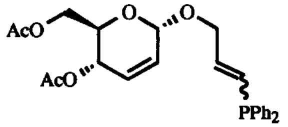
**12** 74%[b]



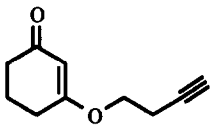
**13**



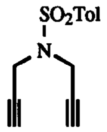
**14** 37% (6:1)



**15** 29%



**16**



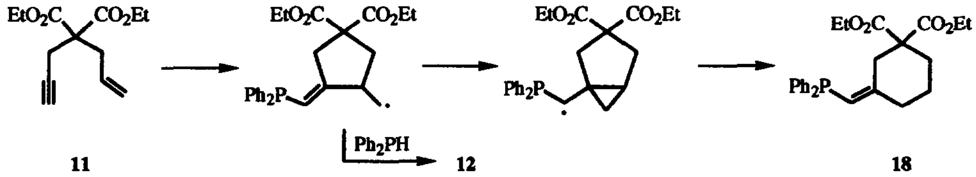
**17**

a - yield in brackets is based on recovered starting material

b - product is a mixture of **12** and **18** (see text)

In contrast, the reactions of the enyne systems **7**, **8**, **11** and **13**, to furnish the vinyl phosphine products **9**, **10**, **12** and **14**, proceeded in significantly higher yield.[10] Somewhat unexpectedly, considering the previous results employing $Bu_3SnH$ (in which only the *Z*-stannylalkenyl radical usually cyclises), the vinyl phosphine products were obtained with varying levels of stereoselectivity, ranging from only 1.7:1 for **9** to about 6:1 for **10** and **14**.[11] In the latter case a substantial amount of the uncyclised vinyl phosphine product **15** was also isolated, this type of product also being obtained in an unsuccessful attempt at cyclising vinylogous ester **16**.[6] The bis-propargylic sulphonamide **17** also failed to cyclise under our usual reaction conditions.

We consider the above results to be in accord with our expectation that a reversible addition of a $Ph_2P\cdot$ radical to a diene or enyne system will result in the formation of an intermediate alkyl or vinyl radical, which can then cyclise to give the desired products. The improved yields obtained in the enyne examples reflect the increased reactivity of the intermediate vinyl radical, which allows cyclisation (or hydrogen atom transfer in the case of **15**) to effectively compete with the elimination of $Ph_2P\cdot$ radical. In the case of enyne **11** the isolated product **12** (isolated as a single isomer) was accompanied by the corresponding six-membered (formally 6-*endo*) product **18**, which is assumed to arise by the type of rearrangement described previously by the groups of Stork and Beckwith, Scheme 2.[12]



**Scheme 2**

Our failure to observe analogous cyclohexenyl products from the reactions involving **7**, **8** and **13** presumably reflects the very highly strained nature of the tricyclic cyclopropylmethyl radicals required as intermediates.

In conclusion, the above results indicate that phosphorus-centred radicals can be useful for cyclising certain diene or enyne systems, thus opening a new route to cycloalkyl phosphines and vinyl phosphines. These compounds are readily converted into derivatives (such as the corresponding phosphine oxides) which are useful in C=C forming reactions. At present the modest yields in some of the reactions, and the mixtures of vinyl phosphine stereoisomers formed are a disadvantage, and may be attributed to the ease of hydrogen atom transfer from $Ph_2PH$ (the $Ph_2P\cdot$ radical is rather stable due to conjugation) and the fact the radical centre bears only two groups of modest size (i.e. comparing $Ph_2P$ with $Bu_3Sn$). We expect optimisation of this method to be possible by employing different phosphines, or alternative P–H-containing species, and work towards this end is under way.[13]

**Acknowledgements**

We are grateful to the Science and Engineering Research Council and Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK for support of JEB under the CASE scheme.

**References**

1. (a) Geise, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986; (b) Regitz, M.; Geise, B. Eds. *Methoden Der Organischen Chemie (Houben-Weyl)*; Thieme: Stuttgart, 1989; Vol. E19a; (c) Curran, D. P. *Synthesis* **1988**, 417 and 489; (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
2. Cyclisations using thiols: (a) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J-L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647; (b) Broka, C. A.; Reichert, D. E. C. *Tetrahedron Lett.* **1987**, *28*, 1503; (c) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
3. Cyclisations using $R_3SnH$: (a) Stork, G.; Mook, Jr., R. *J. Am. Chem. Soc.* **1987**, *109*, 2829; (b) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.
4. Ogawa, A.; Takami, N.; Sekiguchi, M.; Yokoyama, H.; Kuniyasu, H.; Ryu, I.; Sonoda, N. *Chem. Lett.* **1991**, 2241.
5. Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Geise, B. *J. Org. Chem.* **1992**, *57*, 3994.
6. Middleton, D. S.; Simpkins, N. S.; Begley, M. J.; Terrett, N. K. *Tetrahedron* **1990**, *46*, 545.
7. For reviews of this area, see: (a) Kirby, A.J.; Warren, S. G.; *The Organic Chemistry of Phosphorus*; Elsevier: Amsterdam, 1967; pp. 158–183; (b) Bentrude, W. G. Phosphorus Radicals. In *Free Radicals (Vol. 2)*; Kochi, J. K. Ed.; John Wiley and Sons, Inc.: New York, 1973; pp. 595–663; (c) Stacey, F. W.; Harris, Jr., J. F. *Org. React.* **1963**, *13*, 150; (d) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; Harper and Row Ltd.: London, 1976; pp. 352–378.
8. (a) Cadogan, J. I. G.; Hey, D. H.; Hock, A. O. S. *Chem. Ind. (London)* **1964**, 753; (b) Van Winkle, J. L. GB Patent 1191815 (1970/1968), Shell.
9. Typical experimental conditions involve heating a solution of the starting diene or enyne (*ca.* 0.085M) in benzene under reflux, in the presence of $Ph_2PH$ (1 eq.) and AIBN (0.1 eq.), under an atmosphere of dry nitrogen. Reflux is maintained until reaction is complete (as monitored by TLC, 3–24h), with additional portions of AIBN (0.1 eq.) being added at intervals for longer reactions. The solvent is then removed under reduced pressure, and the residue subjected to column chromatography to give the pure phosphine product.
10. Selected data for products: **3** (Found: $M^+$, 324.1674. $C_{21}H_{25}OP$ requires *M*, 324.1643). **9** $\nu_{max}$ (film)/$cm^{-1}$ 3069, 2932, 1641, 1586, 1434, 1052, 741 and 697; (Found: $M^+$, 322.1473. $C_{21}H_{23}OP$ requires *M*, 322.1486); a sample was oxidised to give the corresponding phosphine oxide (Found: C, 74.39; H, 6.99. $C_{21}H_{23}O_2P$ requires C, 74.54; H, 6.85%). **10** $\delta_H$ (400 MHz, $CDCl_3$, 338K) 1.05 (1H, m), 1.18–1.32 (2H, m), 1.43–1.53 (1H, m), 1.63–1.72 (2H, m), 1.96 (1H, m), 2.12 (1H, d, *J* 14.5), 2.88 (1H, br.s, C=C–C*H*), 3.67 (3H, s), 4.02 (1H, m, C*H*NCO$_2$Me), 4.16 (1H, d, *J* 17, NC*H*$_2$C=C), 4.30 (1H, dd, *J* 17 and 1.5, NC*H*$_2$C=C), 6.06 (1H, m, C=C*H*) and 7.25–7.41 (10H, m); (Found: $M^+$, 379.1713. $C_{23}H_{26}NO_2P$ requires *M*, 379.1702).
11. For a related cyclisation of **13**, see Moufid, N.; Chapleur, Y. *Tetrahedron Lett.* **1991**, *32*, 1799.
12. (a) Stork, G.; Mook, Jr., R. *Tetrahedron Lett.* **1986**, *27*, 4529; (b) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

13 Radicals derived from dialkyl phosphites and related compounds appear promising. For recent use of these compounds in radical chemistry, see Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 2311 and 5709.

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