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Generation of Phosphorus-Centered Radicals via Homolytic Substitution at Sulfur

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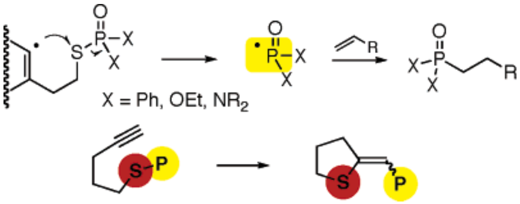
ABSTRACT



A novel radical domino process relying on the homolytic cleavage of P–S bonds allows the preparation of phosphorus-containing molecules through addition of P-centered radicals onto olefins. The key step of this reaction is a homolytic substitution on a sulfur atom. The scope of the reaction is broad. Diaminophosphonyl radicals whose reactivity was unknown react smoothly with olefins. Use of tin hydride can be avoided. A radical thiophosphinoylation of triple bonds has been uncovered.

The formation of C−P bonds has become an extremely important tool in modern synthesis. For example, the need for new phosphine-based ligands or phosphorus-containing biomolecules has created a strong demand for such methodologies. Because they are very mild, radical reactions are good candidates for such a purpose and have been shown to be especially suitable to phosphorus. As a consequence, various methods have been devised for radical-based formation of C−P bonds. The two main options available are addition of P-centered radicals to unsaturated compounds[1] or addition of carbon radicals to phosphorus moieties.[2] The former is a very old reaction,[3] and it has been reinvestigated recently.[4] The P-centered radicals have been prepared mainly by abstraction of a hydrogen atom from the corresponding P−H bond and by deselenylation. Both those methods have limitations: selenium-containing molecules are expensive and toxic. Some P−H bonds may be difficult to cleave. For example, in our hands, no radicals were formed via P−H bond cleavage of diaminophosphonates.

Our attention was attracted by the highly original work of Oshima and Yorimitsu, who introduced diphosphanes as a source of both P-radicals and phosphinylation agents.[5] The key feature of the reaction is a homolytic substitution on

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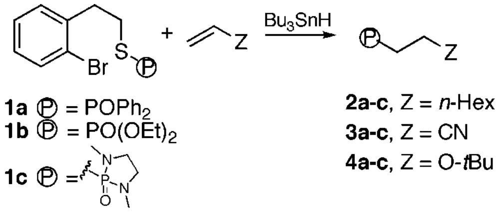
one phosphorus atom, which releases a phosphinyl radical that can add to terminal alkynes or be reduced to afford phosphinated products.[6] Because of our previous interest in the elimination of oxidized $P^\bullet$ radicals,[7] we wondered whether homolytic substitution could enable us to generate those radicals in a convenient way.

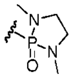
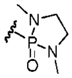
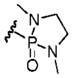
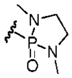
We turned our attention to thiophosphonates **1a**−**c**. It has been shown early on that sulfur is a very good target for rapid homolytic substitution.[8] Crich[9] and Spagnolo/Benati (for a tin-free version)[10] used that particular reaction to prepare acyl radicals. We felt that a related reaction could take place with phosphorus analogues, thus affording the corresponding P-centered radicals that could further react with olefins. This approach would add a new method to the existing tools available to generate and use P-centered radicals (the key radical fragmentation would now be a P−S bond cleavage). We also wished to gain insight on radicals which have so far not been used in synthesis, such as the diaminophosphonyl ones. To achieve this goal, a rapid substitution on phosphorus is needed to avoid unproductive early reductions. An intramolecular reaction meets this criterion. We present herein our results.

Substrates **1a**−**c** were chosen for this study, as they represent a good sample of phosphorus(v) moieties. The reactions were carried out under standard radical conditions, i.e., slow addition of tributyltin hydride (TBTH) in the presence of AIBN and an olefin in refluxing benzene (Table 1, method A). We selected an array of olefins with different electronic properties (electron-poor, -rich, and neutral) to get additional data on the philicity of the phosphorus-centered radicals.

A typical example is shown in Table 1, entry 1. In the presence of TBTH, 1-octene, and AIBN in refluxing benzene, substrate **1a** yielded 84% of the expected diphenyloctyl phosphine oxide. The reaction proved quite general. Both phosphinoyl and phosphonyl radicals led to the corresponding P−C bond formation, and the dihydrobenzothiophene byproduct could be easily separated from the desired products.

Table 1. Formation of C−P Bonds through a Homolytic Substitution/P-Centered Radical Addition Tandem



entry	Ⓟ	Z	cond	product, yield (%)[a]
1	$POPh_2$	*n*-Hex	A[b]	**2a**, 84
2	$POPh_2$	*n*-Hex	B[c]	**2a**, 58
3	$POPh_2$	CN	A[c]	**3a**, 39
4	$POPh_2$	CN	B[c]	**3a**, 50
5	$POPh_2$	O-*t*Bu	A[b]	**4a**, 71[d]
6	$POPh_2$	O-*t*Bu	B[b]	**4a**, 47[e]
7	$PO(OEt)_2$	*n*-Hex	A[b]	**2b**, 75
8	$PO(OEt)_2$	*n*-Hex	B[b]	**2b**, 70
9	$PO(OEt)_2$	CN	A[b]	**3b**, 74[f]
10	$PO(OEt)_2$	O-*t*Bu	B[b]	**4b**, 56
11		*n*-Hex	A[b]	**2c**, 60[g]
12		*n*-Hex	B[b]	**2c**, 48
13		CN	A[c]	**3c**, 82
14		O-*t*Bu	A[b]	**4c**, 40[h]

[a] Method A: Bu_3SnH, AIBN cat., slow addition, PhH reflux. Method B: Bu_3SnCl (10 mol %), $NaBH_4$, *t*-BuOH, reflux. [b] 10 equiv of olefin was used. [c] 2 equiv of olefin was used. [d] Product was contaminated by approximately 17% of byproduct. [e] Product was contaminated by approximately 9% of byproduct. [f] Some polymerized product was also isolated. [g] 10−30% of reduced starting material was also observed. [h] Product is not stable.

Surprisingly, the yield of the phosphinoyl radical addition to enol ether (entry 5) was better than the one obtained with acrylonitrile (entry 3). Indeed, phosphinoyl radicals are thought to be moderately nucleophilic[11] and thus should react best with electron-poor olefins. This may be due to polymerization.[11] Nevertheless, the yield remained low even when the amount of olefins was reduced to two equivalents to avoid excessive polymerization of acrylonitrile. We will investigate this aspect more thoroughly, but initial competition experiments (acrylonitrile vs enol ether) tend to confirm the

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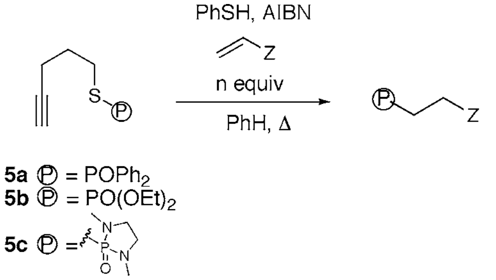
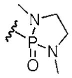
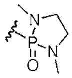
nucleophilic character of the phosphinoyl radical. In the enol ether case, a minor unidentified phosphorus-containing byproduct was also observed. Phosphonyl radicals also gave fair yields of products (entries 7−10). Our methodology was extended to diaminophosphonyl radicals (entries 11−14), thus demonstrating their synthetic potential.

Encouraged by these results, we decided to eliminate TBTH, as tin byproducts are difficult to remove and toxic. As a first step toward that goal, we decided to use Stork's catalytic conditions (Bu_3SnCl (10 mol %), $NaBH_4$, *t*-BuOH, reflux; method B).[12] The additions still worked, albeit generally in slightly reduced yields. To eliminate tin entirely, we took advantage of the Benati/Spagnolo trick and replaced the radical trigger with a triple bond (see **5a**−**c**, Table 2).

Table 2. Tin-Free Formation of C−P Bonds



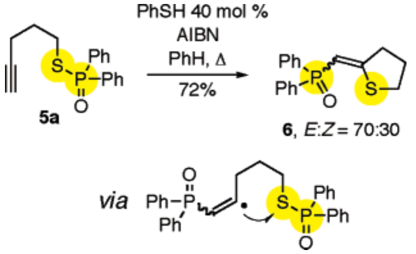
entry	Ⓟ	Z	n	product, yield (%)[a]
1	$POPh_2$	*n*-Hex	10	**2a**, 87
2	$POPh_2$	CN	5	**3a**, 66
3	$PO(OEt)_2$	*n*-Hex	10	**2b**, 58[a]
4		*n*-Hex	10	**4a**, 85[b]
5		O-*t*Bu	5	**4c**, 80[c]

[a] 28% of the hydrothiolation of the triple bond was also observed. [b] 5% of the hydrothiolation of the triple bond was also observed. [c] 10% of the hydrothiolation of the triple bond was also observed.

The homolytic substitution was neatly triggered by the thiyl radical addition onto the triple bonds. Except in the phosphonyl case (Table 2, entry 3), this new cascade delivered much better yields of phosphorus-containing products, especially with acrylonitrile. Some reactions delivered byproducts arising from reduction of the intermediate vinyl radicals (Table 2, entries 3−5), which complicated the purification process. Nonetheless, the elimination of tin reagents increases the synthetic interest of our procedure.

Phosphinoyl radicals are also known to add onto triple bonds.[4g] When only two equivalents of olefins was employed with **5a** and hexene, we isolated some products arising from trapping of phosphinoyl radicals by **5a**. This side reaction attracted our attention, as it could be used to our advantage (Scheme 1). Indeed, removal of the olefin led to a clean formal cycloisomerization of thiophosphine oxide **5a** (72% yield), during which the C−P bond formation from phosphinoyl radicals formed in the initiation process triggered the homolytic substitution that installed the sulfur moiety. Cyclic sulfide **6** was obtained as a 70:30 mixture of isomers, whose geometry was determined by NOE. This last reaction opens new perspectives to our homolytic substitution: to the best of our knowledge, this is the first example of a thiophosphinoylation of triple bonds, during which the two different heteroatoms are introduced on the hydrocarbon backbone in the same synthetic step.

Scheme 1. Thiophosphorylation of Triple Bonds



To conclude, we have devised a new way of generating phosphorus-centered radicals. Homolytic substitution of thiophosphine oxides, thiophosphonates, and thiodiaminophosphonates led to the corresponding radicals, which added smoothly onto olefins. The diaminophosphonyl radical additions to olefins have not been previously reported. We could avoid using tin hydride by switching to derivatives of pent-4-ynethiol and thiophenol as the mediator. The efficient addition of $P^\bullet$ onto unsaturated compounds led us to uncover an unprecedented thiophosphinoylation reaction, in which both heteroatoms are introduced at both ends of the triple bond. We are currently assessing the full scope of this new process, particularly when chiral phosphorus-containing moieties are involved. Our results will be presented in due course.

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Supporting Information Available: Full characterization (including NMR spectra) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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