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Synthetic Methods

# Homolytic Substitution at Phosphorus for the Synthesis of Alkyl and Aryl Phosphanes**

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During the past thirty years phosphanes and their derivatives have received much attention in many fields of chemistry. In particular in homogeneous catalysis they are highly important as ligands in various metal complexes. Although different approaches for the synthesis of phosphanes have been reported, the development of new methods for their preparation is still important owing to the lack of generality of the known methods, the harsh reaction conditions often applied, and the necessity for expensive metal catalysts.[1] In this context, radical-based methods appear to be a promising alternative to polar and transition-metal-mediated reactions.[2]

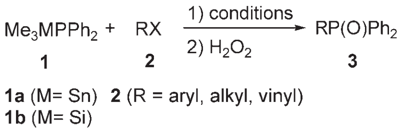
The reactivity of free radicals towards tricoordinated phosphorus ($PR_3$) has been studied.[3] With trialkylphosphites as radical-trapping reagents, efficient P transfer to the radical only occurs to reactive alkoxyl or σ-type vinylic or aryl radicals.[4] Another paper discusses the radical addition of stannylated phosphanes to C–C triple bonds. The reactive vinyl radical intermediates undergo homolytic substitution at phosphorus.[5] Very recently, Oshima et al. published the reaction of aryl radicals with diphosphane ($Ph_2P\text{-}PPh_2$) generated in situ for the synthesis of aryl phosphane derivatives.[6] Importantly, $Ph_2P\text{-}PPh_2$ was reported to react with the less reactive π-type alkyl radicals.[6] Encouraged by these results we initiated a program to study homolytic substitution[7] at P for C–P bond formation. Herein we wish to report our first results on the mild radical phosphonation with σ- as well as π-type C radicals using stannylated and silylated phosphanes as radical acceptors. Importantly, transition metals are not necessary for these reactions. Our results are further supported by DFT calculations of the reaction mechanism.

The reaction of the readily prepared $Me_3SnPPh_2$ (**1a**)[8,9] with phenyl halides was studied first (Table 1). The phosphonations were conducted in sealed tubes in benzene at 80 °C (0.083 M). For analysis, the product phosphanes were oxidized with $H_2O_2$ to triarylphosphane oxide [Eq. (1)].

**Table 1:** Phosphonation of PhX with **1a** under various conditions.[a]

| Entry | X | **1a** [equiv] | Initiator | *t* [h] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | I | 1.7 | AIBN | 2.5 | 41 |
| 2 | I | 1.7 | V-40 | 2.5 | 61 |
| 3 | I | 1.7 | V-40 | 16 | 66 |
| 4 | I | 4.0 | V-40 | 16 | 87 |
| 5 | Br | 4.0 | V-40 | 16 | 54 |
| 6 | Cl | 4.0 | V-40 | 16 | <2 |

[a] All reactions were performed in benzene at 80 °C at 0.083 M with 0.15 mol% initiator. [b] Determined by GC analysis.



$$\underset{\mathbf{1}}{Me_3MPPh_2} + \underset{\mathbf{2}}{RX} \xrightarrow[2)\ H_2O_2]{1)\ \text{conditions}} \underset{\mathbf{3}}{RP(O)Ph_2} \qquad (1)$$

**1a** (M= Sn) **2** (R = aryl, alkyl, vinyl)
**1b** (M= Si)

We were delighted to see that reaction of iodobenzene with reagent **1a** (1.7 equiv) and α,α′-azobisisobutyronitrile (AIBN) delivered after oxidation $Ph_3PO$ in 41% yield (Table 1, entry 1). The yield could be improved to 61% by switching to V-40 (1,1′-azobis(cyclohexane)-1-carbonitrile) as initiator (Table 1, entry 2). Extension of the reaction time to 16 h gave $Ph_3PO$ in 66% yield (Table 1, entry 3). A further improvement (87% yield) was achieved upon using a fourfold excess of **1a** (Table 1, entry 4). A lower yield was obtained with bromobenzene (Table 1, entry 5), while only traces of $Ph_3PO$ were formed with chlorobenzene (entry 6).

We next studied the scope and limitations of the radical P–C bond formation. Electron-withdrawing (see **2b–d**, **2f**) and also electron-releasing groups (see **2a**,**e**) in the *o* and *p* position are tolerated in the reaction with reactive aryl radicals. Good yields of the corresponding triarylphosphane oxides **3a–f** were obtained (59–79%, Table 2, entries 1–6). Vinyl radicals efficiently react with $Me_3SnPPh_2$ as shown for the transformation of 2-bromopropene (Table 2, entry 7, → **3g**, 76%). We then focused on less reactive π-type radicals. Pleasingly, the primary and secondary alkyl iodides **2h**,**i**, 1-bromoundecane, and *tert*-butyl bromide were readily phosphonated in high yields (→**3h** (79%), **3i** (94%), **3j** (54%), **3k** (83%), Table 2, entries 8, 10, 12, and 14). Other typical radical precursors such as thionocarbonate **2l** and phenyl selenide **2m** can be transformed to the phosphane oxides **3i** and **3h** in good yields (Table 2, entries 16 and 17). Reducing the amount of reagent **1a** from 4 equiv to 1.5 equiv resulted in slightly

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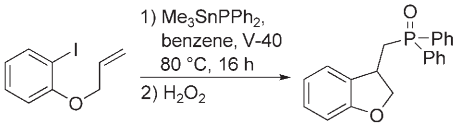
*Table 2:* Radical phosphonations using reagent **1a**.[a]

| Entry | Radical precursor | R | X | Product (Yield [%])[b] |
|---|---|---|---|---|
| 1 | **2a** | *p*-MeO-$C_6H_4$ | I | **3a** (73) |
| 2 | **2b** | *p*-NC-$C_6H_4$ | I | **3b** (79) |
| 3 | **2c** | *p*-$F_3C$-$C_6H_4$ | I | **3c** (75) |
| 4 | **2d** | *p*-Cl-$C_6H_4$ | I | **3d** (72) |
| 5 | **2e** | *o*-MeO-$C_6H_4$ | I | **3e** (59) |
| 6 | **2f** | *o*-$MeO_2C$-$C_6H_4$ | I | **3f** (73) |
| 7 | **2g** | $CH_3C{=}CH_2$ | Br | **3g** (76) |
| 8 | **2h** | *n*-pentyl | I | **3h** (79) |
| 9[c] | **2h** | *n*-pentyl | I | **3h** (64) |
| 10 | **2i** | cyclohexyl | I | **3i** (94) |
| 11[c] | **2i** | cyclohexyl | I | **3i** (82) |
| 12 | **2j** | *n*-undecyl | Br | **3j** (54) |
| 13[c] | **2j** | *n*-undecyl | Br | **3j** (33) |
| 14 | **2k** | *tert*-butyl | Br | **3k** (83) |
| 15[c] | **2k** | *tert*-butyl | Br | **3k** (64) |
| 16 | **2l** | cyclohexyl | OC(S)imidazolyl | **3i** (57) |
| 17 | **2m** | *n*-pentyl | SePh | **3h** (60) |

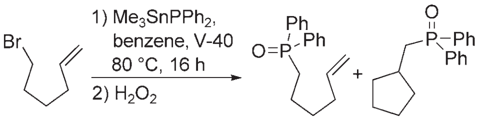
[a] All reactions were performed in benzene at 80°C at 0.083 M using a fourfold excess of **1a** and 16 mol% of V-40. [b] Yield of isolated product. [c] Reaction conducted with 1.5 equiv of **1a**.

diminished but still good yields, as shown for the reactions with alkyl iodides and bromides (Table 2, entries 9, 11, 13, and 15).

To prove the radical nature of the process, iodide **4** was reacted with $Me_3SnPPh_2$ to afford the cyclization/phosphonation product **5** in 72% yield [Eq. (2)]. Moreover, reaction of 5-hexenyl bromide under the same conditions provided the radical-cyclization product **6b** in 85% yield along with uncyclized phosphane oxide **6a** (6%) [Eq. (3)]. From the ratio of **6a** to **6b** the rate constant for the trapping of a primary alkyl radical with $Me_3SnPPh_2$ at 80°C is calculated to be $3\times10^5\,\text{M}^{-1}\,\text{s}^{-1}$ by applying radical-clock methodology.[10] To our surprise, reaction of **1a** (4 equiv) with iodobenzene without initiator provided after oxidation triphenylphosphane oxide in 30% yield. Probably, thermal Sn–P bond homolysis occurs eventually initiating the radical-chain reaction. Indeed, reaction of 5-hexenyl bromide with $Me_3SnPPh_2$ (1.5 equiv) in benzene without initiator at 80°C for 16 h afforded **6b** (39%) and **6a** (2%), clearly showing that thermal initiation occurs. Hence, $Me_3SnPPh_2$ can act as a radical phosphonation reagent and also as a radical initiator.



**4** **5** (72%) (2)



**6a** (6%) **6b** (85%) (3)

Given the toxicity of organotin compounds[11] and difficulty in removal of tin by-products from the reaction mixture, we turned our attention to the silylphosphane **1b**, which is commercially available and can be efficiently prepared from readily available starting materials.[12,13]

We switched to *n*-heptane as a solvent, because silyl radicals are known to react with benzene and would therefore be prevented from propagating the chain.[14] To our delight, the reaction of pentyl iodide with $Me_3SiPPh_2$ (4 equiv) and V-40 (0.25 equiv) in heptane (0.1 M) at 100°C for 72 h provided after oxidation **3h** in 86% yield (Table 3, entry 1). A slightly lower yield was obtained for the phosphonation of cyclohexyl iodide (Table 3, entry 4). The reactions conducted without initiator afforded the desired compounds in less than 10% yield supporting a radical mechanism (Table 3, entries 2 and 5). Even with 1.5 equiv of reagent **1b** good yields are obtained (Table 3, entries 3 and 6). Bromides and thionocarbonates are also acceptable as radical precursors (Table 3, entries 7 and 8). Unfortunately, *tert*-butyl bromide and iodobenzene were not phosphonated under optimized conditions.

*Table 3:* Radical phosphonations using reagent **1b**.[a]

| Entry | Radical precursor | R | X | Product (Yield [%])[b] |
|---|---|---|---|---|
| 1 | **2h** | *n*-pentyl | I | **3h** (86) |
| 2 | **2h** | *n*-pentyl | I | **3h** (4)[c] |
| 3 | **2h** | *n*-pentyl | I | **3h** (74)[d] |
| 4 | **2i** | cyclohexyl | I | **3i** (70) |
| 5 | **2i** | cyclohexyl | I | **3i** (9)[c] |
| 6 | **2i** | cyclohexyl | I | **3i** (58)[d] |
| 7 | **2j** | *n*-undecyl | Br | **3j** (41) |
| 8 | **2l** | cyclohexyl | OC(S)imidazolyl | **3i** (44) |

[a] All reactions were performed in *n*-heptane at 100°C at 0.1 M using a fourfold excess of **1b** and 25 mol% of V-40 for 72 h. [b] Yield of isolated product. [c] Reaction was conducted without V-40. [d] Reaction conducted with 1.5 equiv of **1b**.

To gain further insight into the mechanism of the reaction we conducted density functional theory (DFT) calculations. We used the PBE functional[15] together with a basis set of triple zeta quality (TZVP)[16] for geometry optimizations. The energies were then recalculated with the double-hybrid density functional B2-PLYP[17] adding additional polarization functions (TZVPP). An empirical correction accounting for long-range dispersion interactions was added during all the calculations ("PBE-D" and "B2-PLYP-D").[18]

The reaction of three different radicals (phenyl, ethyl and *tert*-butyl) with phosphanes **1a** and **1b** was found to proceed by a two-step mechanism [Eq. (4)]. The radical intermediate **7** with a tetracoordinate phosphorus atom and an elongated P–M bond (M = Si, Sn) is stable, at least under our model conditions (gas phase). The direct homolytic substitution can thus be disregarded.[19]

$$\mathrm{Me_3MPPh_2} + \mathrm{R}^{\bullet} \longrightarrow \underset{\mathbf{7}}{\left[\mathrm{Me_3MPRPh_2}\right]^{\bullet}} \longrightarrow \mathrm{Me_3M}^{\bullet} + \mathrm{RPPh_2} \qquad (4)$$

Table 4 reports the energies of the first ($\Delta E_{\mathrm{add}}$) and second step ($\Delta E_{\mathrm{diss}}$) of the homolytic substitution. B2-PLYP-D predicts the intermediates **7** to be about 1–5 kcal mol$^{-1}$ less stable than PBE-D does, but the overall reaction energy is similar. The formation of **7** is exothermic (Table 4, entries 1–5), except for R = *t*Bu and M = Si where $\Delta E_{\mathrm{add}}$ is 3.5 kcal mol$^{-1}$ (entry 6). This is probably the reason why in the experiment *tert*-butyl radical was not able to replace $SiMe_3$ in **1b** in a homolytic substitution reaction. Interestingly, although ethyl radical addition to **1b** is only slightly exothermic (Table 4, entry 4), good experimental yields were obtained for the reaction of the pentyl radical with **1b**. For all radicals investigated, the addition reaction is more exothermic for the Sn compound as compared to the corresponding Si–P derivative.

***Table 4:*** Radical substitution energies[a] for different alkyl radicals.

| Entry | Phosphane | Radical (R) | d$_{\mathrm{int}}$ (P–M) [pm][b] | $\Delta E_{\mathrm{add}}$ [kcal mol$^{-1}$] | $\Delta E_{\mathrm{diss}}$ [kcal mol$^{-1}$] |
|---|---|---|---|---|---|
| 1 | $Me_3SnPPh_2$ | Ph | 308.0 | −28.2 (−29.2) | 4.2 (7.2) |
| 2 | $Me_3SiPPh_2$ | Ph | 246.8 | −16.6 (−19.9) | 5.7 (9.6) |
| 3 | $Me_3SnPPh_2$ | Et | 313.3 | −12.5 (−15.8) | 5.0 (7.8) |
| 4 | $Me_3SiPPh_2$ | Et | 252.7 | −0.7 (−5.8) | 5.5 (9.4) |
| 5 | $Me_3SnPPh_2$ | *t*Bu | 307.9 | −7.2 (−9.3) | 5.5 (8.5) |
| 6 | $Me_3SiPPh_2$ | *t*Bu | 244.6 | 3.5 (−0.4) | 6.9 (11.3) |

[a] B2-PLYP-D/TZVPP//PBE-D/TZVP, including PBE-D/TZVP zero-point vibrational energies (in brackets: PBE-D/TZVP energies). [b] M–P distance in intermediate **7**; calculated distances in phosphanes **1a** and **1b** are 257.3 pm (**1a**, M = Sn) and 230.3 pm (**1b**, M = Si).

For reactions with **1a**, the dissociation of the radical complex liberating the $Me_3Sn$ radical requires less energy than is obtained in the addition step. However, for the homolytic substitution of the $Me_3Si$ radical with the ethyl and *tert*-butyl radicals the overall process is endothermic. As expected, the energy required for dissociation is 2–3 kcal mol$^{-1}$ less for the Sn derivatives (M = Sn) than for the corresponding Si intermediates, reflecting the higher intrinsic radical stability of $SnMe_3$ versus $SiMe_3$. This difference has also an effect on the geometry and electronic structure of the intermediates **7**. The P–Sn bond in **7** (M = Sn) is more elongated (about 20%) than the P–Si bond in **7** (M = Si), relative to bond lengths of the starting phosphanes **1a** and **1b**. Figure 1 depicts the geometry and the spin density of the intermediates **7**. It is apparent that the spin density (the difference between α and β electron densities) in the intermediate **7** is more localized on Sn than on Si if the two intermediates are compared. The excess spin density on the phosphorus atom is found in the equatorial position of a distorted trigonal-prismatic coordination sphere.

In conclusion we have described a highly efficient radical phosphonation of alkyl and aryl radicals using readily available $Me_3SnPPh_2$. Moreover, phosphonations of primary and secondary alkyl radicals can also be performed using the less toxic commercially available $Me_3SiPPh_2$. To our knowledge, this is the first report on a homolytic substitution at phosphorus with a trialkylsilyl radical as a leaving group. Importantly, expensive transition metals are not necessary to conduct these reactions. The results of our experimental investigations are further supported by DFT calculations of the reaction mechanism.

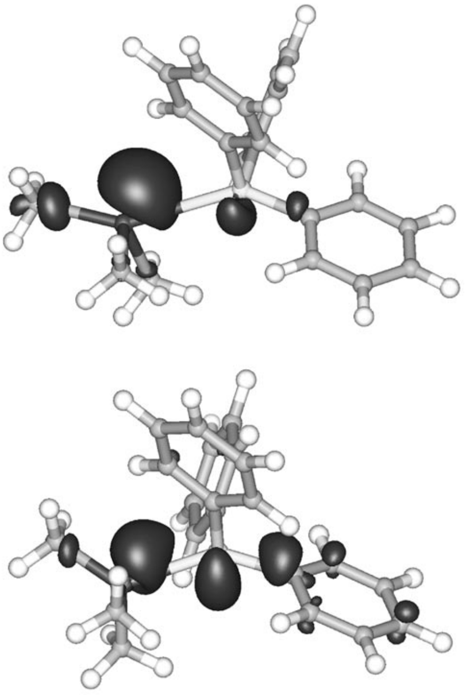


***Figure 1.*** Spin densities (PBE-D/TZVP) for radical intermediates **7** with R = Ph, M = Sn (top) and R = Ph, M = Si (bottom) (isosurface value = + 0.005 a.u.).

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[19] Indeed, phosphoranyl radicals generated upon addition of reactive radicals to trialkylphosphites have been experimentally detected, see Ref. [3b].