Radical synthesis of trialkyl, triaryl, trisilyl and tristannyl phosphines from P_4

Radical Synthesis of Trialkyl, Triaryl, Trisilyl, and Tristannyl Phosphines from P_4*

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March 12, 2010

Abstract

A reaction scheme has been devised according to 3 RX + 3 Ti(III) + 0.25 P_4 → PR_3 + 3 XTi(IV) wherein RX = PhBr, CyBr, Me_3SiI, or Ph_3SnCl with contrasting results in the case of more hindered RX; the scheme accomplishes direct radical functionalization of white phosphorus without intermediacy of PCl_3.

It is known that P_4, white phosphorus, has excellent properties as a trap for carbon-centered radicals in solution and under the mild conditions that are typical for organic synthesis. The most prominent example of this was the demonstration that phosphonic acids may be prepared from corresponding carboxylic acids by way of *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone (Barton PTOC esters).[1] The latter provide carbon centered radicals in an oxygen-initiated chain reaction, and these are consumed upon combination with P_4 as the critical P–C bond-forming event; upon oxidative workup, any remaining P–P bonds are cleaved and the phosphonic acid $RP(O)(OH)_2$ is the end product.[2] It is also known that P–P bonds *other* than those in P_4 may serve as traps for organic radicals. This has been shown by Sato et al. in a scheme for radical phosphination of organic halides wherein ArX serves as a source of Ar· which in turn attacks Ph_2P–PPh_2, yielding $ArPPh_2$.[3]

*We dedicate this work to the memory of Sir Derek Barton.

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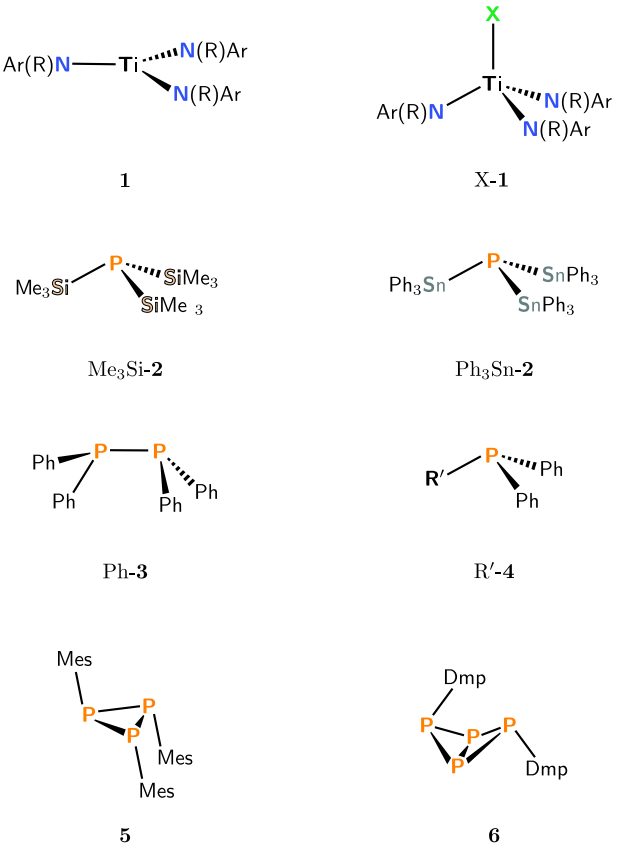

Figure 1: Ti(N[^{t}Bu]Ar)$_3$ together with various P_4-derived phosphanes and polyphosphorus products. R = ^{t}Bu; X = Cl, Br, I; R′ = Ph, Mes, Cy, Ph_3Sn; Mes = 2,4,6-$Me_3C_6H_2$; Dmp = 2,6-$Mes_2C_6H_3$.

Such a vision for phosphine synthesis *via* homolytic substitution at a phosphorus center has also been developed by Vaillard et al., who employed Me_3MPPh_2 (M = Si or Sn) as the phosphorus substrate and RX as the carbon-radical source, together with a radical initiator, to produce $RP(O)Ph_2$ efficiently after an oxidative workup.[4] For our part, we have previously shown that the three-coordinate titanium(III) complex $Ti(N[^tBu]Ar)_3$ (Ar = 3,5-$C_6H_3Me_2$), **1**, is a potent halogen-atom abstractor, capable of abstracting X· (X = Cl, Br, or I) from various donor molecules at room temperature or below, in aprotic organic media (Figure 1). With the present work, we sought to develop a high-yield synthesis of phosphines PR_3 from 3 RX and 0.25 P_4, using $Ti(N[^tBu]Ar)_3$ as a halogen atom sink (see idealized Equation 1). Success in this arena would demonstrate that it is possible to synthesize valuable tertiary phosphanes PR_3 through direct functionalization and complete consumption of P_4 by a radical mechanism.

$$3\ RX + \tfrac{1}{4}\ P_4 \xrightarrow[-3\ XTi(N[^tBu]Ar)_3]{3\ Ti(N[^tBu]Ar)_3} PR_3 \qquad (1)$$

In the course of a prior study of radical cleavage of symmetrical 1,4-dicarbonyl compounds by $Ti(N[^tBu]Ar)_3$, the propensity was examined of $Ti(N[^tBu]Ar)_3$ to abstract X· from halobenzenes.[5] This study revealed that treatment of $Ti(N[^tBu]Ar)_3$ with the stoichiometric amount of PhBr or PhI effected conversion to $XTi(N[^tBu]Ar)_3$ X-**1**, rapidly at room temperature, while conversion to $ClTi(N[^tBu]Ar)_3$ upon treatment with PhCl was considerably slower. Dissolution of $Ti(N[^tBu]Ar)_3$ in *neat* chlorobenzene and stirring overnight at room temperature did effect complete conversion to $ClTi(N[^tBu]Ar)_3$, however. A radical cyclization experiment using *o*-bromophenyl allyl ether as the RX substrate for $Ti(N[^tBu]Ar)_3$ has been used to substantiate the hypothesis that phenyl radicals are indeed generated upon halogen atom abstraction from PhX by $Ti(N[^tBu]Ar)_3$.[5,6] On the basis of this information, together with the knowledge from recent independent work that $Ti(N[^tBu]Ar)_3$ engages in negligible re-

action with P_4,[7] we realized that Ti(N[^{t}Bu]Ar)$_3$ is an unusual reducing agent in that it could be selective for RX activation in the presence of P_4. This is unusual because most chemical reducing agents capable of X· abstraction from RX would not be expected to be selective for this reactivity channel in the presence of P_4. An aspect of this type of special selectivity in reactions of Ti(N[^{t}Bu]Ar)$_3$ has been demonstrated previously wherein 7-chloronorbornadiene was treated with a 1:1 mixture of Ti(N[^{t}Bu]Ar)$_3$ and Mo(N[^{t}Bu]Ar)$_3$; in this instance Ti(N[^{t}Bu]Ar)$_3$ was entirely selective for Cl-atom abstraction giving ClTi(N[^{t}Bu]Ar)$_3$, while exhibiting no propensity for trapping the 7-norbornadienyl radical which was seen to interact selectively with the molybdenum complex.[8] In addition, typical one-electron reducing agents that might be used for effecting X· abstraction, e.g. CoCl(PPh_3)$_3$, SmI_2, or Cp_2TiCl, simply give no reaction with a substrate such as PhBr.[9,10]

In a first reaction targeted at generating PPh_3, it was found that addition of 3 equiv of PhBr by microsyringe to a 0.04 M solution of 0.25 equiv P_4 containing 3 equiv of **1** in benzene results in immediate formation of a bright orange solution containing BrTi(N[^{t}Bu]Ar)$_3$ (Br-**1**), PPh_3 (Ph-**2**, 71% of the P-containing product), and P_2Ph_4 (Ph-**3**, 29% of the P-containing product, Table 1). P_2Ph_4 is one of the four possible stable intermediates en route to complete P_4 degredation by P_4 to give PPh_3 and is present in this stoichiometric treatment because the trapping of the highly reactive phenyl radicals is not completely efficient in this system.[11] In order to convert the full equivalent of P_4 to PPh_3, 5 equiv of PhBr and Ti(N[^{t}Bu]Ar)$_3$ are used, giving 95% conversion and an isolated yield of 72% (Table 1). We could also selectively target P_2Ph_4 by treatment of 0.25 equiv of 0.04 M P_4 in benzene with 2 equiv of **1** followed by 2 equiv of PhBr, which gives P_2Ph_4 in 80% yield with small amounts of PPh_3 and P_4Ph_4 being observed as well. Evidence for the intermediacy of P_2Ph_4 along the reaction pathway was provided by the use of P_2Ph_4 itself as a starting material for PPh_3 synthesis.[10] It was found that PhI can be used in place of PhBr with similar results, however PhCl does not lead to any PPh_3 or P_2Ph_4 formation as Ti(N[^{t}Bu]Ar)$_3$ reacts very slowly with PhCl under these conditions.[5]

This synthesis of phosphines from P_4 and a burst of radicals was found not to be

Table 1: Synthesis of PR_3 from n(RX + $Ti(N[^tBu]Ar)_3$) and 0.25 P_4 in benzene solvent at 20 °C.

Entry	n^a	R	X	δ $PR_3{}^b$	% yield^c
1	3	Ph	Br	−4.9	71
2	3.75	Ph	Br	−4.9	82
3	5	Ph	Br	−4.9	95
4	3	Ph	I	−4.9	65
5	3	Ph	Cl	n/a	0
6	3	Ph_3Sn	Cl	−325^d	96
7	3	Me_3Si	I	−252	97
8	3	Cy	Br	10.5	64
9	3.75	Cy	Br	10.5	77
10	5	Cy	Br	10.5	95

[a] Number of equivalents per phosphorus atom.

[b] ^{31}P NMR chemical shift for the PR_3 product referenced to external 85% H_3PO_4.

[c] Phosphorus-based yield of PR_3 as determined by ^{31}P NMR spectroscopy *via* integration with respect to an internal standard using a single-pulse experiment.

[d] $^1J_{^{119}Sn-P}$ = 442 Hz, $^1J_{^{117}Sn-P}$ = 425 Hz.

limited to aryl substituents. Treatment of a 0.04 M solution of 0.25 equiv P_4 with 5 equiv of **1** and 5 equiv of CyBr results in formation of PCy_3 (Cy-**2**) as the exclusive P-containing product (Table 1). The use of less than 5 equiv of CyBr resulted in mixtures of P_2Cy_4 (Cy-**3**) and Cy-**2**, much like what was seen for PhBr. When the radicals produced were longer lived, it was possible to obtain stoichiometric conversion of P_4 to the trisubstituted phosphine. For instance, treatment of a 0.04 M solution of 0.25 equiv P_4 with 3 equiv of **1** and 3 equiv of Me_3SiI or Ph_3SnCl results in clean and quantitative formation of the known phosphines $P(SiMe_3)_3$ or $P(SnPh_3)_3$, respectively, as the sole products (Table 1, Figure 1).[12,13] The $P(SiMe_3)_3$ produced here is easily separated from the reaction coproducts by vacuum transfer from the crude reaction mixture in 86% yield, while the highly crystalline $P(SnPh_3)_3$ can be isolated in 75% yield.

The ability of P_4 to act as a radical trap in combination with the work of Sato and coworkers on the radical phosphination of aryl halides suggests that P−P bonds, generally, may be competent radical traps.[3] This was found to be the case using our radical method, opening up the potential for the synthesis of asymmetric phosphines. Treatment of 0.5 equiv of P_2Ph_4 with 1 equiv of PhBr, MesBr, CyBr, or Ph_3SnCl and 1 equiv of **1** quantitatively produced 1 equiv of Ph-**2** (δ 4.9 ppm), $P(Ph_2)$Mes (Mes-**4**, δ16.0 ppm),[14] $P(Ph_2)$Cy (Cy-**4**, δ 3.4 ppm),[15] or $P(Ph_2)SnPh_3$ (Ph_3Sn-**4**, δ 56.2 ppm, $^1J_{^{119}Sn-P}$ = 715 Hz, $^1J_{^{117}Sn-P}$ = 682 Hz),[16] respectively (Figure 1).[10] This striking attribute of P−P single bond chemistry has great potential for further synthetic development.

Based on our hypothesis that the radical-degradation of the P_4 tetrahedron occurs in a stepwise manner, we thought that it might be possible to target intermediate structures by tuning the steric properties of the RX substrate. It was found that treatment of 0.25 equiv of 0.04 M P_4 in benzene with 1.5 equiv **1**, followed by 1.5 equiv of MesBr gives P_3Mes_3, **5**, as the major product and small amounts of P_2Mes_4 (Mes-**3**).[17–19] P_3Mes_3 could be isolated from the reaction mixture in 61% yield. Increasing the steric pressure further, we found that treatment of 0.25 equiv of 0.04 M P_4 with 1.5 equiv of **1** and 1.5 equiv of DmpI (Dmp = 2,6-$Mes_2C_6H_3$) gives cis,trans-DmpP_4Dmp, **6**, as the

exclusive product and isolated in 78% yield.[10,20] This latter reaction represents a facile approach for the synthesis of novel substituted tetraphosphabicyclobutane molecules directly from P_4 in a single step. Many of the previously reported syntheses of stable tetraphosphabicyclobutanes involve coupling of two substituted diphosphanes,[21] or activation of P_4 by some highly designed substrate.[20,22–24] Our synthesis is unique in that a large number of sterically hindered aryl or alkyl halides could be employed in a general synthesis.

In terms of recycling the titanium byproducts from these syntheses, it is worth noting that X-**1** (X = I, Br, Cl) are cleanly reduced back to $Ti(N[^tBu]Ar)_3$ by reduction with Na/Hg amalgam.[25,26] This ability to easily recycle the titanium-byproducts generates a closed cycle for the synthesis of trisubtituted phosphines from P_4. One might begin to contemplate a catalytic cycle using this system, however, the reduction of $XTi(N[^tBu]Ar)_3$ is slow and P_4 is itself suseptible to reduction to Na_3P by Na/Hg amalgam under such conditions. As such, other halogen atom abstractors are currently being screened as potential entry points into the catalytic generation of trisubstituted phosphines from P_4 by this radical trapping method.[10]

The present day synthesis of organophosphorus compounds is a multistep process in which P_4 is first chlorinated to generate PCl_3.[27] PCl_3 is then functionalized via salt elimination reactions with appropriate Grignard or organolithium reagents, or with the organohalide and a harsh reducing agent.[27] For example, the industrial method for triphenylphosphine preparation is based on the high temperature reaction of chlorobenzene with phosphorus trichloride in the presence of molten sodium.[28] Manufacturers of organophosphorus compounds have recognized that the direct functionalization of white phosphorus is one of the major challenges in this field.[28,29] New studies are needed to work out alternative direct routes to organophosphorus compounds avoiding chlorination of white phosphorus. Strides have been made with regard to the electrosynthesis of trisubstituted phosphines directly from P_4,[30] but facile solution methods are lacking. It is our hope that this work will inspire a renewed interest in the use of P−P bonds as efficient radical traps and will eventually lead to a robust catalytic system for the synthesis of organophosphorus compounds directly from white phopshorus.

Meanwhile, the syntheses reported herein represent novel methodologies for the direct functionalization of P_4 and will themselves be the subject of further investigation.

Experimental

Representative protocol for reaction between Ti(N[^{t}Bu]Ar)$_3$, RX (RX = PhBr, MesBr, DmpI, CyBr, Me$_3$SiI, and Ph$_3$SnCl), and P$_4$: Synthesis of PPh$_3$

Ti(N[^{t}Bu]Ar)$_3$ (279 mg, 0.484 mmol) was added to a 0.04 M solution of P_4 in benzene (5 mg total P_4, 0.040 mmol). BrC_6H_5 (76 mg, 0.484 mmol) was then added to the reaction mixture at room temperature by microliter syringe. Over the course of a minute, the originally green reaction mixture took on a bright orange color. The reaction mixture was analyzed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies. Using $OPPh_3$ (26 ppm) as an internal standard, a single pulse ^{31}P NMR experiment showed 71% conversion to PPh_3 (s, -4.9 ppm) with the balance made up by P_2Ph_4 (-14 ppm). GC-MS analysis confirmed that assignment. A solvent screening (benzene, toluene, THF, Et_2O, *n*-hexane) and concentration screening (0.01 M P_4, 0.02 M P_4, 0.03 M P_4, 0.04 M P_4, and 0.05 M P_4) indicated these conditions as optimal for conversion of 0.25 equiv P_4 to 1 equiv PPh_3 using 3 equiv Ti(N[^{t}Bu]Ar)$_3$ and 3 equiv PhBr.

In order to convert all of the P_4 to PPh_3, the reaction was repeated using a 0.04 M solution of P_4 (5 mg total P_4, 0.040 mmol, 0.25 equiv), 5 equiv (465 mg, 0.807 mmol) of Ti(N[^{t}Bu]Ar)$_3$ and 5 equiv (126 mg, 0.807 mmol) of BrC_6H_5. Again, over the course of a minute, the originally green reaction mixture took on a bright orange color. The reaction mixture was analyzed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies. Using $OPPh_3$ (26 ppm) as an internal standard, a single pulse ^{31}P NMR experiment showed 98% conversion to PPh_3 (s, -4.9 ppm). GC-MS analysis confirmed that assignment. A screening of reaction stoichiometry showed 5 equiv of Ti(N[^{t}Bu]Ar)$_3$ and 5 equiv BrC_6H_5 was necessary for the complete conversion of P_4 to PPh_3; when fewer equivalents were used, small amounts of P_2Ph_4 were still observed. When the optimized

conditions are scaled up 10-fold, PPh_3 was isolated by repeated crystallizations at −35 °C in Et_2O in 72% yield (304 mg).

These optimized conditions of 0.04 M P_4 (0.25 equiv), benzene, and 5 equiv of RX/Ti(N[^{t}Bu]Ar)$_3$ are effective for both PPh_3 and PCy_3 syntheses. For $P(SiMe_3)_3$ and $P(SnPh_3)_3$ the same conditions are used but with only 3 equiv (stoichiometric) RX/Ti(N[^{t}Bu]Ar)$_3$. Starting with 50 mg of P_4, $P(SiMe_3)_3$ was isolated by vacuum transfer in 86% yield (348 mg) and $P(SnPh_3)_3$ was isolated in 75% yield (1.30 g) by repeated recrystallization from Et_2O. For the synthesis of P_3Mes_3 and *cis*,*trans*-DmpP_4Dmp, the same conditions are used but with only 1.5 equiv of RX/Ti(N[^{t}Bu]Ar)$_3$. P_3Mes_3 was isolated by repeated crystallization from Et_2O in 61% yield starting with 50 mg of P_4. *cis*,*trans*-DmpP_4Dmp was isolated by repeated crystallization from Et_2O in 78% yield starting with 50 mg of P_4.

In order to use P_2Ph_4 as the starting material for PPh_3 synthesis, the same reaction protocol and conditions can be used. Treatment of a 0.04 M solution of P_2Ph_4 (5 mg, 0.014 mmol, 0.5 equiv) with Ti(N[^{t}Bu]Ar)$_3$ (93 mg, 0.16 mmol, 1 equiv) followed by BrPh (60 mg, 0.16 mmol, 1 equiv) resulted in a rapid color change from green to orange upon stirring. The reaction mixture was analyzed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies. Using $OPPh_3$ (26 ppm) as an internal standard, a single pulse ^{31}P NMR experiment showed 97% conversion to PPh_3 (s, −4.9 ppm). Similar results were found when 0.5 equiv P_2Ph_4 was treated with 1 equiv of MesBr, CyBr, or Ph_3SnCl, which produced 1 equiv of $P(Ph_2)$Mes (−16.0 ppm), $P(Ph_2)$Cy (−3.4 ppm), or $P(Ph_2)SnPh_3$ (−56.2 ppm, $^1J_{^{119}Sn-P}$ = 715 Hz, $^1J_{^{117}Sn-P}$ = 682 Hz) , respectively, each in greater than 95% yield.

Please see the Supporting Information accompanying this manuscript for additional synthetic and characterization details.

Acknowledgements

We gratefully acknowledge the US National Science Foundation (grant CHE-719157) and Thermphos International for support.

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[10] Please see the supporting information document accompanying this text for additional details.

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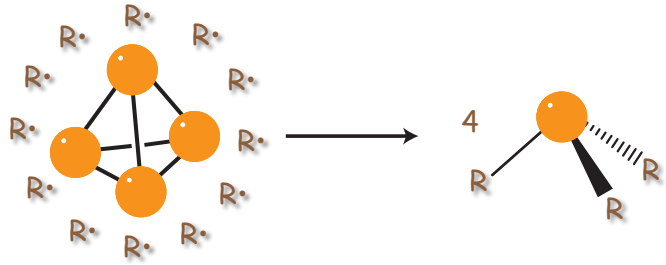
Table of Contents Material



A reaction scheme has been developed that accomplishes direct radical functionalization of white phosphorus without the intermediacy of PCl_3.