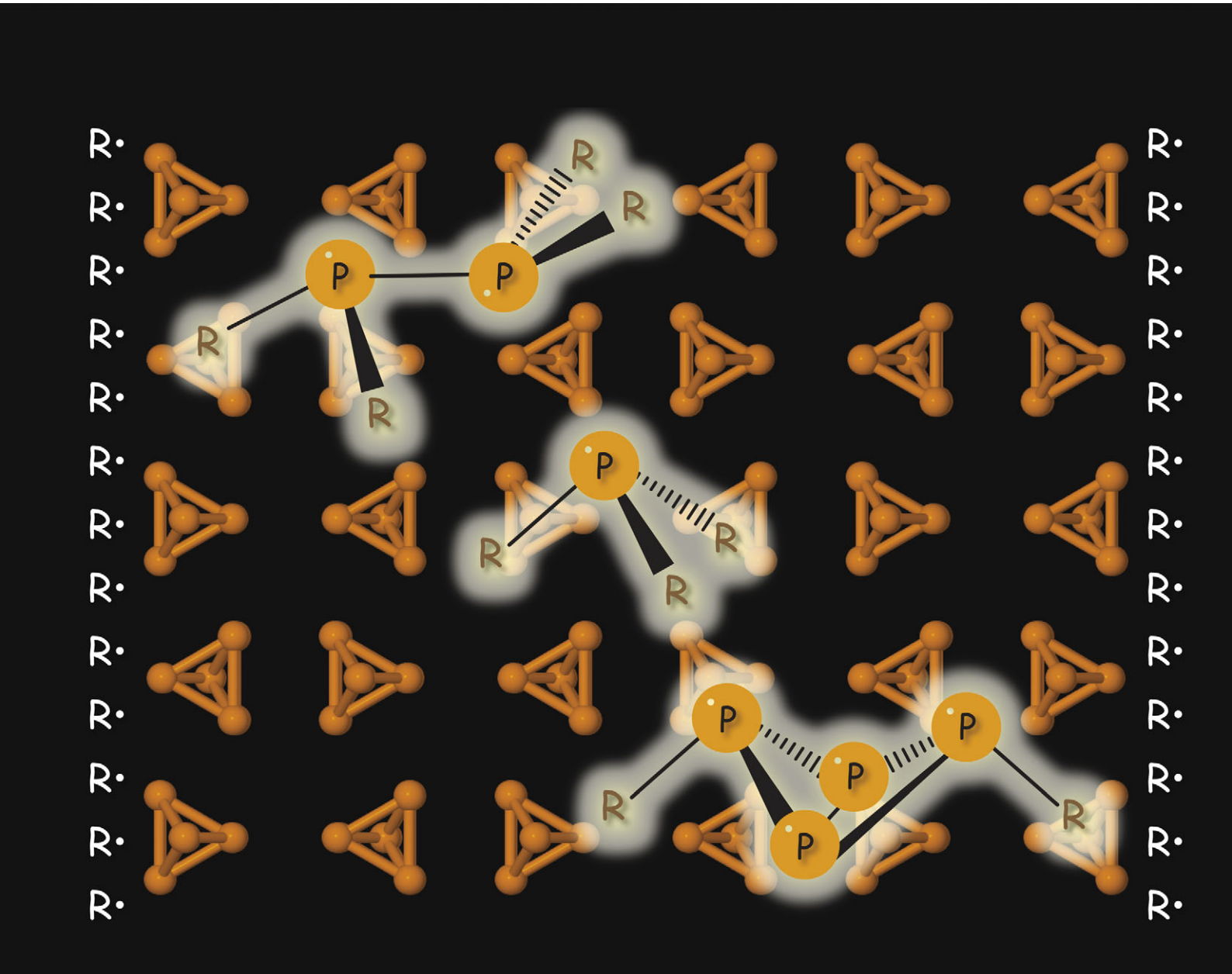
NJC

New Journal of Chemistry

An international journal of the chemical sciences

www.rsc.org/njc

Volume 34 | Number 8 | August 2010 | Pages 1493–1784



Themed Issue: Main Group chemistry

ISSN 1144-0546

RSC Publishing

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LETTER

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1144-0546(2010)34:8;1-K

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

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Received (in Montpellier, France) 15th February 2010, Accepted 16th March 2010
DOI: 10.1039/c0nj00124d

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 the direct radical functionalization of white phosphorus without the 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 of organic synthesis. The most prominent example of this was the demonstration that phosphonic acids may be prepared from their 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 work-up, 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 the 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]

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 work-up.[4] For our part, we have previously shown that the three-coordinate Ti(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 (Fig. 1). In the present work, we sought to develop a high yielding 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 eqn (1)). Success in this arena would demonstrate that it is possible to synthesize valuable tertiary phosphanes, PR_3, through the 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 previous study of the 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 the treatment of $Ti(N[^tBu]Ar)_3$ with a stoichiometric amount of PhBr or PhI effected the conversion to $XTi(N[^tBu]Ar)_3$, X-**1**, rapidly at room temperature, while the 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 with stirring overnight at room temperature did effect the complete conversion to $ClTi(N[^tBu]Ar)_3$, however. A radical cyclization experiment using *o*-bromophenyl allyl ether as the RX substrate for $Ti(N[^tBu]Ar)_3$ was used to substantiate the hypothesis that phenyl radicals are indeed generated upon

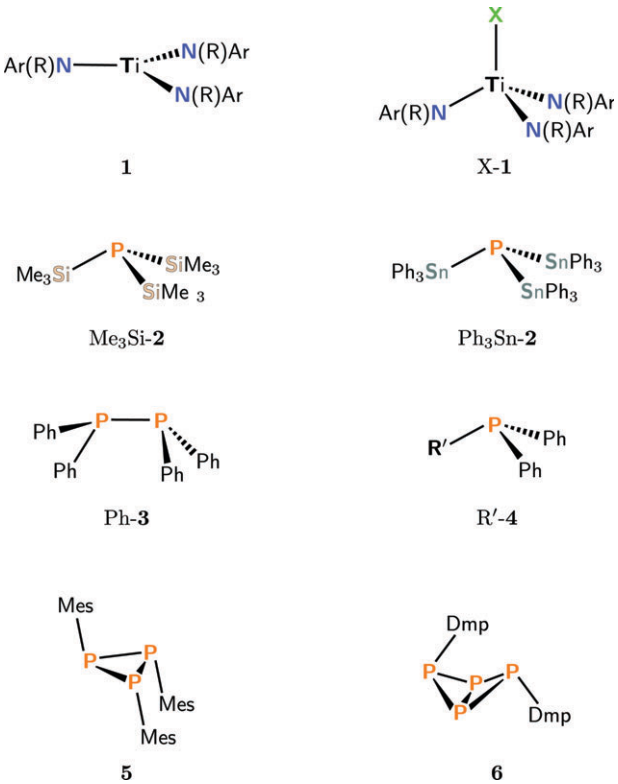

Fig. 1 $Ti(N[^tBu]Ar)_3$ together with various P_4-derived phosphanes and polyphosphorus products. R = ^{t}Bu; X = Cl, Br, I; R′ = Ph, Mes, Cy, Ph_3Sn; Mes = 2,4,6-$Me_3C_6H_2$; Dmp = 2,6-$Mes_2C_6H_3$.

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† We dedicate this work to the memory of Sir Derek Barton. This article is part of a themed issue on Main Group chemistry.
‡ Electronic supplementary information (ESI) available: Additional synthetic and characterization details. See DOI: 10.1039/c0nj00124d

halogen atom abstraction from PhX by Ti(N[^{t}Bu]Ar)$_3$.[5,6] On the basis of this information, together with the knowledge from recent independent work that Ti(N[^{t}Bu]Ar)$_3$ engages in a negligible reaction 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$^\bullet$ 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$^\bullet$ abstraction, *e.g.* CoCl(PPh$_3$)$_3$, SmI$_2$ or Cp$_2$TiCl, simply gave no reaction with substrates such as PhBr.§‡

In a first reaction targeted at generating PPh$_3$, it was found that the 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 resulted in the 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.¶ In order to convert the full equivalent of P_4 to PPh$_3$, 5 equiv. of PhBr and Ti(N[^{t}Bu]Ar)$_3$ were used, giving 95% conversion and an isolated yield of 72% (Table 1). We could also selectively target P_2Ph_4 by the 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 gave 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.‡ It was found that PhI could be used in place of PhBr with similar results, however PhCl did 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 limited to aryl substituents. The treatment of a 0.04 M solution of 0.25 equiv. P_4 with 5 equiv. of **1** and 5 equiv. of CyBr resulted 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$_3$SiI or Ph$_3$SnCl resulted in the clean and quantitative formation of known phosphines P(SiMe$_3$)$_3$ or P(SnPh$_3$)$_3$, respectively, as the sole products (Table 1, Fig. 1).[9,10] The P(SiMe$_3$)$_3$ produced here was easily separated from the reaction co-products by vacuum transfer from the crude reaction mixture in 86% yield, while highly crystalline P(SnPh$_3$)$_3$ can be isolated in 75% yield.

Table 1 Synthesis of PR$_3$ from n(RX + Ti(N[^{t}Bu]Ar)$_3$) and 0.25P_4 in benzene solvent at 20 °C

Entry	n^a	R	X	δ_{PR_3}/ppm^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$_3$Sn	Cl	−325^d	96
7	3	Me$_3$Si	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.

The ability of P_4 to act as a radical trap in combination with the work of Sato and co-workers 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. The treatment of 0.5 equiv. of P_2Ph_4 with 1 equiv. of PhBr, MesBr, CyBr or Ph$_3$SnCl and 1 equiv. of **1** quantitatively produced 1 equiv. of Ph-**2** (δ 4.9 ppm), P(Ph$_2$)Mes (Mes-**4**, δ 16.0 ppm),[11] P(Ph$_2$)Cy (Cy-**4**, δ 3.4 ppm)[12] or P(Ph$_2$)SnPh$_3$ (Ph$_3$Sn-**4**, δ 56.2 ppm, $^1J_{119_{Sn-P}}$ = 715 Hz, $^1J_{117_{Sn-P}}$ = 682 Hz),[13] respectively (Fig. 1).‡ 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 the 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, gave P_3Mes_3 (**5**) as the major product and small amounts of P_2Mes_4 (Mes-**3**).[14–16] P_3Mes_3 could be isolated from the reaction mixture in 61% yield. Increasing the steric pressure further, we found that the 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$_2$C$_6$H$_3$) gave *cis*,*trans*-DmpP$_4$Dmp (**6**) as the exclusive product, isolated in 78% yield.[17]‡ 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 the coupling of two substituted diphosphanes[18] or the activation of P_4 by some highly designed substrate.[17,19–21] 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 by-products from these syntheses, it is worth noting that X-**1** (X = I, Br, Cl) are cleanly reduced back to Ti(N[^{t}Bu]Ar)$_3$ by reduction with Na/Hg amalgam.[22,23] This ability to easily recycle the titanium by-products generates a closed cycle for the synthesis of

trisubstituted 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 susceptible to reduction to Na_3P by the 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.‡

The present day synthesis of many organophosphorus compounds is a multi-step process in which P_4 is first chlorinated to generate PCl_3.[24] PCl_3 is then functionalized *via* salt elimination reactions with appropriate Grignard or organolithium reagents, or with an organohalide and a harsh reducing agent.[24] For example, the industrial method for PPh_3 preparation is based on the high temperature reaction of chlorobenzene with PCl_3 in the presence of molten sodium.[25] Manufacturers of organophosphorus compounds have recognized that the direct functionalization of white phosphorus is one of the major challenges in this field.[25,26] New studies are needed to work out alternative direct routes to organophosphorus compounds that avoid the chlorination of white phosphorus. Strides have been made with regard to the electrosynthesis of trisubstituted phosphines directly from P_4,[27] but facile solution methods are lacking. It is our hope that this work will inspire 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 phosphorus. Meanwhile, the syntheses reported herein represent novel methodologies for the direct functionalization of P_4 and will themselves be the subject of further investigation.

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

Experimental

A representative protocol for the reaction between $Ti(N[^tBu]Ar)_3$, RX (RX = PhBr, MesBr, DmpI, CyBr, Me_3SiI and Ph_3SnCl) and P_4: the synthesis of PPh_3

$Ti(N[^tBu]Ar)_3$ (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 a microlitre syringe. Over the course of a minute, the originally green reaction mixture took on a bright orange color. The reaction mixture was analyzed by ^1H, ^{13}C and ^{31}P NMR spectroscopy. 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 being made up of P_2Ph_4 (−14 ppm). GC-MS analysis confirmed this assignment. Solvent screening (benzene, toluene, THF, Et_2O, n-hexane) and concentration screening (0.01, 0.02, 0.03, 0.04 and 0.05 M P_4) indicated that these conditions were optimal for the conversion of 0.25 equiv. P_4 to 1 equiv. PPh_3 using 3 equiv. $Ti(N[^tBu]Ar)_3$ 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 $Ti(N[^tBu]Ar)_3$ 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 ^1H, ^{13}C and ^{31}P NMR spectroscopy. 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 this assignment. A screening of the reaction stoichiometry showed 5 equiv. of $Ti(N[^tBu]Ar)_3$ and 5 equiv. BrC_6H_5 were necessary for the complete conversion of P_4 to PPh_3; when fewer equivalents were used, small amounts of P_2Ph_4 were observed. When the optimized conditions were 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 $RX/Ti(N[^tBu]Ar)_3$ were effective for both PPh_3 and PCy_3 syntheses. For $P(SiMe_3)_3$ and $P(SnPh_3)_3$, the same conditions were used, but with only 3 equiv. (stoichiometric) of $RX/Ti(N[^tBu]Ar)_3$. 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$_4$Dmp, the same conditions were used, but with only 1.5 equiv. of $RX/Ti(N[^tBu]Ar)_3$. P_3Mes_3 was isolated by repeated crystallization from Et_2O in 61% yield starting from 50 mg of P_4. *cis*,*trans*-DmpP$_4$Dmp was isolated by repeated crystallization from Et_2O in 78% yield starting from 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 could be used. The treatment of a 0.04 M solution of P_2Ph_4 (5 mg, 0.014 mmol, 0.5 equiv.) with $Ti(N[^tBu]Ar)_3$ (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 ^1H, ^{13}C and ^{31}P NMR spectroscopy. 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.

Notes and references

§ It is well documented that SmI_2 is capable of slowly reducing aryl halides in the presence of HMPA, however the slow rate of this transformation did not allow for a radical synthesis of trisubstituted phosphines.
¶ The fate of the untrapped radicals is unknown.

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