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Air-Stable Trialkylphosphonium Salts: Simple, Practical, and Versatile Replacements for Air-Sensitive Trialkylphosphines. Applications in Stoichiometric and Catalytic Processes

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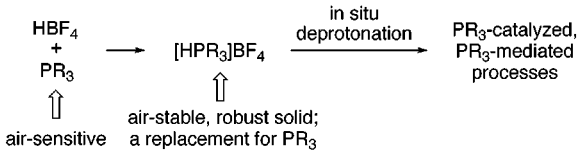
ABSTRACT



Trialkylphosphines furnish unusual, sometimes unique, reactivity in a range of transformations. Unfortunately, their utility is compromised by their sensitivity to oxidation. We have examined a simple but powerful strategy for addressing this problem: convert air-sensitive trialkylphosphines into air-stable phosphonium salts via protonation on phosphorus. These robust salts serve as direct replacements for the corresponding phosphines (simple deprotonation under the reaction conditions by a Brønsted base liberates the trialkylphosphine) in a diverse set of applications.

Phosphines serve as useful catalysts, reagents, and ligands in a wide array of important organic transformations. Until now, triarylphosphines (e.g., PPh_3), which are typically air-stable, have been the predominant focus of study. Trialkylphosphines, on the other hand, have been relatively neglected, probably as a result in large part of the fact that many are air-sensitive, which renders them more difficult to handle than triarylphosphines. For example, the *Encyclopedia of Reagents for Organic Synthesis* provides the following description for P(*n*-Bu)$_3$:[1]

"Improperly stored bottles of Bu_3P are invariably contaminated with tributylphosphine oxide and butyl dibutylphosphinate.... Oxygen should be rigorously excluded to avoid free radical chain oxidation. Tributylphosphine is pyrophoric...."

There is, however, growing evidence that trialkylphosphines can furnish reactivity that is not generally accessible with triarylphosphines; this dichotomy presumably arises from differences between these two families of phosphines in electron-richness (in general, trialkylphosphines ≫ triarylphosphines) and shape/sterics. In particular, P(*n*-Bu)$_3$[2] and P(*t*-Bu)$_3$[3] have proved to be useful in a number of

(1) Diver, S. T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, pp 5014−5016.

(2) For example, see: (a) Reduction of disulfides: Ayers, J. T.; Anderson, S. R. *Synth. Commun.* **1999**, *29*, 351−358. Grayson, M.; Farley, C. E. *Chim. Organ. Phosphore, Colloq. Int. C.N.R.S.* **1969**, *182*, 275−284. (b) Reduction of azides: Afonso, C. A. M. *Tetrahedron Lett.* **1995**, *36*, 8857−8858. Szmuszkovicz, J.; Kane, M. P.; Laurian, L. G.; Chidester, C. G.; Scahill, T. A. *J. Org. Chem.* **1981**, *46*, 3562−3564. (c) Catalyst for Baylis−Hillman reaction: Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165−2169. Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M. *Synth. Commun.* **1984**, *14*, 1267−1273. (d) Catalyst for acylation of alcohols: Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286−7288. See also: Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358−3359.

(3) For early studies, see: (a) Buchwald−Hartwig reaction: Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (b) Suzuki reaction: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (c) Heck reaction: Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. Littke,

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important processes, including palladium-catalyzed couplings and Baylis−Hillman reactions. Unfortunately, P(*n*-Bu)$_3$ and P(*t*-Bu)$_3$ cannot readily be handled in air because of the ease with which they undergo oxidation.

It occurred to us that a simple but powerful strategy for handling these phosphines would be to protect them as their conjugate acids. According to this approach, an oxidation-stable, easily handled phosphonium salt would be employed as a catalyst/reagent precursor, and a weak base (e.g., (*i*-Pr)$_2$NEt) in the reaction mixture would liberate the desired phosphine through simple acid−base chemistry.[4,5]

A survey of the literature revealed a precedent for the use of a phosphonium salt as a precursor to a phosphine reagent. In 1991, Whitesides applied tris(2-carboxyethyl)phosphine hydrochloride as a water-soluble stoichiometric reducing agent for disulfides.[6] To the best of our knowledge, however, the versatility of this phosphonium-salt strategy has not been determined.

In this Letter, we establish the generality of this approach, focusing on the phosphonium salts of P(*n*-Bu)$_3$ and P(*t*-Bu)$_3$. We show that [(*n*-Bu)$_3$PH]BF$_4$ and [(*t*-Bu)$_3$PH]BF$_4$ are stable to oxygen and to moisture and that they can be stored in air for long periods of time (>4 months) without any detectable deterioration. Furthermore, we demonstrate that these phosphonium salts can be used interchangeably with the phosphines themselves in a broad spectrum of processes ranging from catalytic applications (palladium-catalyzed couplings, acylations of alcohols, and Baylis−Hillman reactions) to stoichiometric transformations (reductions of disulfides and azides). We anticipate that this study will spark the development of a wide array of applications of trialkylphosphonium salts (trialkylphosphines) in organic synthesis.

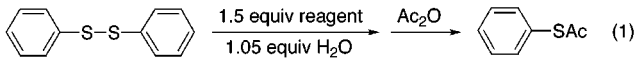
Phosphonium Salts. Preparation and Stability. The pK_a values of the conjugate acids of P(*n*-Bu)$_3$ and P(*t*-Bu)$_3$ are 8.4 and 11.4, respectively.[7] To maximize the likelihood that the chemistry of the phosphonium salts will mimic that of the free phosphines, we chose to investigate salts for which the counterion is noncoordinating (and therefore likely to simply serve as a spectator in the reaction of interest). Both [(*n*-Bu)$_3$PH]BF$_4$[8] and [(*t*-Bu)$_3$PH]BF$_4$[9] have been reported previously, as have many congeners with different counterions. To date, the utility of these phosphonium salts in synthetic organic chemistry has not been examined.

[(*n*-Bu)$_3$PH]BF$_4$ and [(*t*-Bu)$_3$PH]BF$_4$ can be synthesized in near-quantitative yield simply by mixing a solution of the phosphine in CH_2Cl_2 with a solution of aqueous HBF_4 (48 wt %; ~$40/kg from Alfa-Aesar).[10] Separation of the phases and concentration of the organic layer provide analytically pure phosphonium salt. Alternatively, the salts will soon be available from Strem Chemicals.[11]

Neither [(*n*-Bu)$_3$PH]BF$_4$ (mp 51−52 °C) nor [(*t*-Bu)$_3$PH]BF$_4$ (mp 261 °C, dec) shows any sign of deterioration after exposure to air for several months (^{31}P, ^{13}C, and ^{1}H NMR; elemental analysis). Indeed, NMR spectroscopy reveals no significant decomposition even after heating [(*t*-Bu)$_3$PH]BF$_4$ in air at 120 °C for 24 h. In view of the sensitivity of the free phosphines, the air-stability of these salts is particularly remarkable.[12] Neither salt is hygroscopic.

Applications of [(*n*-Bu)$_3$PH]BF$_4$. P(*n*-Bu)$_3$ has been employed in synthetic organic chemistry in a number of useful ways, including as a nucleophilic catalyst[2c,d] and as a stoichiometric reducing agent.[2a,b] As one test of the phosphonium-salt strategy, we have examined the substitution of P(*n*-Bu)$_3$ with [(*n*-Bu)$_3$PH]BF$_4$ in several of these applications.[13]

P(*n*-Bu)$_3$ serves as a mild reducing agent for a range of functional groups. For example, Anderson has described the synthesis of thioacetates via the reaction of disulfides with P(*n*-Bu)$_3$, followed by acylation with acetic anhydride (eq 1).[2a,14] We have applied this procedure to the reduction of diphenyl disulfide, and we have determined that [(*n*-Bu)$_3$PH]BF$_4$/(*i*-Pr)$_2$NEt furnishes a yield identical to that provided by the phosphine itself (eq 1).



(1)

Reagent	Yield
(*n*-Bu)$_3$P	91%
[(*n*-Bu)$_3$PH]BF$_4$ / (*i*-Pr)$_2$NEt (1:1)	91%

A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000. Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123−2132. (d) Stille reaction: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413. Littke, A. F.; Schwarz, L.; Fu, G. C. Manuscript in preparation. (e) Arylation of carbonyl compounds: Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (f) Arylation of alcohols: Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (g) Hiyama reaction: Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495−1498. (h) Sonogashira reaction: Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679−3681. (i) Kumada reaction: Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602−1604. (j) Negishi reaction: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(4) Dialkylphosphine oxides have been employed as precursors to dialkylphosphinous acids, via tautomerization: Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *41*, 1513−1516.

(5) In situ deprotonation has been used to generate metal-carbene complexes from imidazolium salts. For example, see: Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889−9890.

(6) Burns, J. A.; Butler, J. C.; Moran, J.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 2648−2650.

(7) For an extensive compilation of pK_a values for tertiary phosphines, see: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1−7.

(8) (a) Muskopf, J. W.; Bertram, J. L.; Walker, L. L. U.S. Patent 5,140,079, 1992. (b) Perron, R.; Mutez, S. U.S. Patent 4,927,957, 1990. (c) Grenouillet, P.; Neibecker, D.; Tkatchenko, I. U.S. Patent 4,889,949, 1989.

(9) Jia, G.; Morris, R. H. *J. Am. Chem. Soc.* **1991**, *113*, 875−883.

(10) Roberts, N. K.; Wild, S. B. *J. Am. Chem. Soc.* **1979**, *101*, 6254−6260.

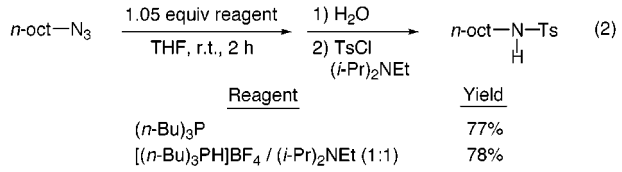
(11) Dr. Mike Strem, personal communication.

(12) Approximately half of the trialkylphosphine is consumed in 20 min for P(*n*-Bu)$_3$ and 4 min for P(*t*-Bu)$_3$, when a 0.1 M solution in THF is vigorously stirred in air. In contrast, the corresponding phosphonium salts show no decomposition after weeks in solution.

(13) Notes: (a) Each reaction was first conducted according to the published conditions. Then, it was repeated using [(*n*-Bu)$_3$PH]BF$_4$/base in place of P(*n*-Bu)$_3$, with all other reaction parameters unchanged. (b) In each instance, the Brønsted base was required in order for the phosphonium salt to serve as a suitable substitute for the phosphine.

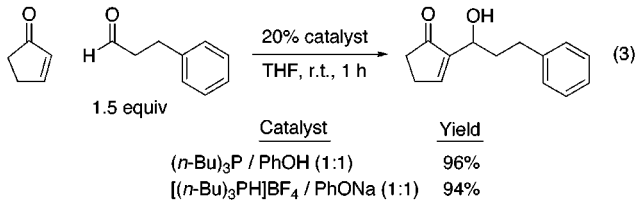
(14) The PBu$_3$-mediated reduction of a disulfide to a thiol is a key step in Bristol-Myers Squibb's synthesis of Vanlev, a vasopeptidase inhibitor that is currently in Phase 3 clinical trials: Scott, John W. Presented at Chiral USA 2000, Boston, MA, 2000.

Trialkylphosphines such as P(*n*-Bu)$_3$ are often employed in the reduction of azides to amines,[2b,15,16] which can be tosylated in situ to produce sulfonamides (eq 2). For *n*-octyl



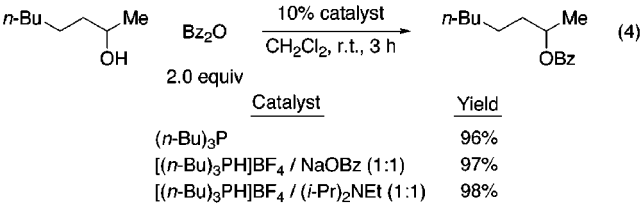
azide, P(*n*-Bu)$_3$ and [(*n*-Bu)$_3$PH]BF$_4$/(*i*-Pr)$_2$NEt achieve this one-pot transformation with similar efficiency (eq 2).

P(*n*-Bu)$_3$ has been applied in organic synthesis not only as a stoichiometric reagent but also as a catalyst. For example, Ikegami has recently described the use of P(*n*-Bu)$_3$/PhOH in Baylis−Hillman reactions (eq 3).[2c] We have



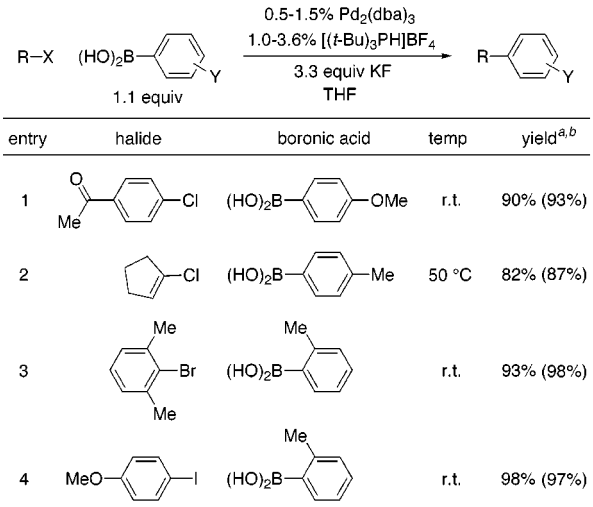
established that [(*n*-Bu)$_3$PH]BF$_4$/PhONa affords the desired product with an isolated yield that is comparable to that furnished by Ikegami's procedure (eq 3). Within minutes of mixing [(*n*-Bu)$_3$PH]BF$_4$ with PhONa, a white precipitate (NaBF$_4$) appears, signaling that free phosphine has been generated.

Another process for which P(*n*-Bu)$_3$ serves as a catalyst is the acylation of alcohols by anhydrides, a reaction discovered by Vedejs (eq 4).[2d] We have determined that [(*n*-Bu)$_3$PH]BF$_4$, in the presence of a mild base such as NaOBz or (*i*-Pr)$_2$NEt, is as effective as the phosphine itself (eq 4).



Applications of [(*t*-Bu)$_3$PH]BF$_4$. During the past few years, P(*t*-Bu)$_3$ has emerged as an unusually powerful ligand for a broad spectrum of palladium- and nickel-catalyzed coupling reactions.[3] However, as with P(*n*-Bu)$_3$, the air-sensitivity of P(*t*-Bu)$_3$ has impeded the application of this useful reagent. As a second test of the phosphonium-salt strategy, we have investigated the replacement of P(*t*-Bu)$_3$ with [(*t*-Bu)$_3$PH]BF$_4$ in a representative cross section of palladium-catalyzed processes.[17]

Table 1. Suzuki Cross-Couplings Using [(*t*-Bu)$_3$PH]BF$_4$



[a] Isolated yields; average of two runs. [b] Literature yields, using P(*t*-Bu)$_3$ (ref 3b), are reported in parentheses.

Because most palladium-catalyzed coupling reactions that employ P(*t*-Bu)$_3$ as a ligand also require Brønsted-base additives, we envisioned that simply substituting the P(*t*-Bu)$_3$ in the original Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$ protocols with [(*t*-Bu)$_3$PH]BF$_4$ would lead to comparable results. To furnish support for this hypothesis, we undertook a series of ^{31}P NMR studies.

In the absence of a Brønsted base, the addition of Pd$_2$(dba)$_3$ to a solution of [(*t*-Bu)$_3$PH]BF$_4$ in THF (δ 52; slightly soluble) leads to no change in the ^{31}P NMR spectrum. After KF, Cy$_2$NMe, CsF, or HN(*i*-Pr)$_2$ is added, the resonance for [(*t*-Bu)$_3$PH]BF$_4$ disappears, and one new signal appears (δ 86), corresponding to Pd(P(*t*-Bu)$_3$)$_2$.[18] In the case of amines, this transformation occurs rapidly at room temperature and is accompanied by precipitation of the ammonium tetrafluoroborate salt. In the case of non-amine (heterogeneous) bases, the reaction is slower, requiring up to 2 h to proceed to completion.

We have evaluated four palladium-catalyzed coupling processes for which Pd/P(*t*-Bu)$_3$ has been shown to be an active catalyst (Suzuki,[3b] Heck,[3c] Stille,[3d] and Sonogashira[3h] reactions). In each instance, we have replaced P(*t*-Bu)$_3$ with an equimolar amount of [(*t*-Bu)$_3$PH]BF$_4$, and we have kept the quantities of all other components the same.

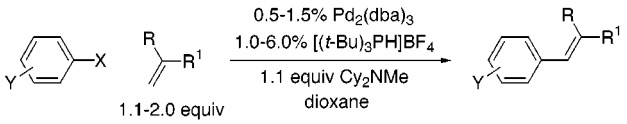
The data in Table 1 establish that air-stable [(*t*-Bu)$_3$PH]-

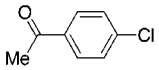
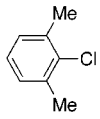
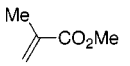
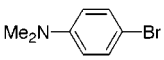
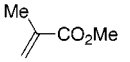
(15) The PMe$_3$-mediated reduction of an azide to an amine is a key step in Bristol-Myers Squibb's synthesis of epothilone B-lactam (BMS-247550), an anticancer agent that is currently undergoing clinical trials: Borzilleri, R. M.; Zheng, X.; Schmidt, R. J.; Johnson, J. A.; Kim, S.-H.; DiMarco, J. D.; Fairchild, C. R.; Gougoutas, J. Z.; Lee, F. Y. F.; Long, B. H.; Vite, G. D. *J. Am. Chem. Soc.* **2000**, *122*, 8890−8897. Other methods (including PPh$_3$) for reducing the azide are less effective. We have synthesized [Me$_3$PH]BF$_4$ (from PMe$_3$ and HBF$_4$ (52 wt % in Et$_2$O) in THF) and determined that, like [(*n*-Bu)$_3$PH]BF$_4$ and [(*t*-Bu)$_3$PH]BF$_4$, it is an air-stable, crystalline solid (mp 212−213 °C).

(16) For an overview of the Staudinger reaction, see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1406.

(17) We have recently established that use of air-stable Pd(P(*t*-Bu)$_3$)$_2$, sometimes in conjunction with Pd$_2$(dba)$_3$, can circumvent the need to handle P(*t*-Bu)$_3$ in palladium-catalyzed coupling reactions: (a) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

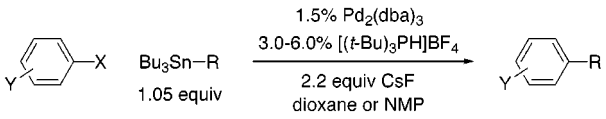
Table 2. Heck Reactions Using $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$

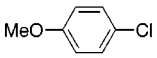
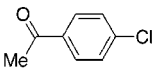
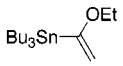
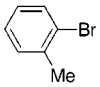


entry	aryl halide	olefin	temp	yield[a,b,c]
1			r.t.	92% (78%)
2			120 °C	90% (80%)
3			r.t.	96% (96%)

[a] Isolated yields; average of two runs. [b] Literature yields, using $P(t\text{-Bu})_3$ (ref 3c), are reported in parentheses. [c] The E olefin is produced with >20:1 E:Z selectivity.

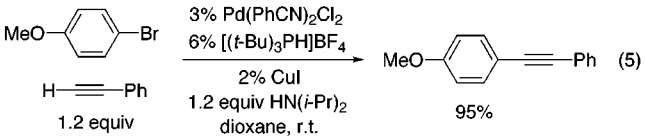
Table 3. Stille Cross-Couplings Using $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$



entry	aryl halide	organostannane	temp	yield[a,b]
1		Bu_3Sn–Ph	100 °C	93% (94%)
2			r.t.	89% (85%)
3		Bu_3Sn–Ph	r.t.	88% (94%)

[a] Isolated yields; average of two runs. [b] Literature yields, using $P(t\text{-Bu})_3$ (ref 3d), are reported in parentheses.

BF_4 is indeed a suitable substitute for air-sensitive $P(t\text{-Bu})_3$ in Suzuki cross-coupling reactions. Thus, we obtain comparable (within 5%) isolated yields for a cross section of aryl and vinyl halides under the same mild conditions. Table 2 demonstrates that the phosphonium salt may also be used instead of the free phosphine in Heck couplings of chlorides and bromides, with similar or even improved efficiency (up to 14% higher yield). Furthermore, we can replace $P(t\text{-Bu})_3$ with $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$ in Stille reactions of aryl halides (Table 3). Finally, we have determined that the phosphine and the phosphonium salt are interchangeable in Sonogashira couplings of aryl bromides (eq 5), furnishing comparable yields.[19]



Conclusions. Trialkylphosphines are beginning to emerge as important reagents in organic synthesis as a result of their unusual, sometimes unique, reactivity in an array of processes. Unfortunately, the practical utility of many trialkylphosphines is compromised by their sensitivity to oxidation, which can render them difficult to handle. To address this problem, we have examined a simple but powerful strategy: conversion of air-sensitive trialkylphosphines into storable, air-stable phosphonium salts by way of protonation on phosphorus.

We have demonstrated that these robust salts can indeed serve as direct replacements for the corresponding phosphines; simple deprotonation under the reaction conditions by a Brønsted base liberates the trialkylphosphine. Thus, phosphonium salts are interchangeable with phosphines in a diverse set of processes ranging from stoichiometric to catalytic uses. We anticipate that this study will provide a powerful stimulus to the development of applications of trialkylphosphines in organic synthesis.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Notes: (a) For the couplings in Tables 1−3 that require elevated temperature, the reaction mixtures are first stirred at room temperature for 1 h, and then they are heated to the indicated temperature. This ensures that free $P(t\text{-Bu})_3$ is available to coordinate to the low-valent metal complex. (b) For each coupling process in Tables 1−3 and eq 5, the reaction proceeds to completion in comparable time with Pd/$P(t\text{-Bu})_3$ and Pd/$[(t\text{-Bu})_3\text{PH}]\text{BF}_4$.