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A Universally Applicable Methodology for the Gram-Scale Synthesis of Primary, Secondary, and Tertiary Phosphines

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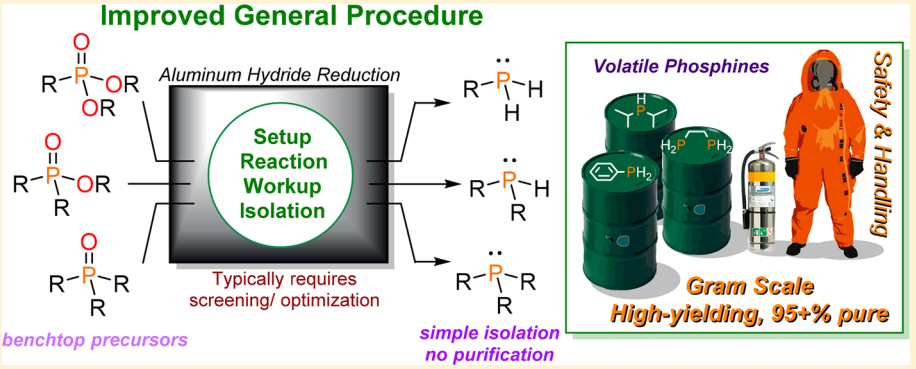
Supporting Information



ABSTRACT: Although organophosphine syntheses have been known for the better part of a century, the synthesis of phosphines still represents an arduous task for even veteran synthetic chemists. Phosphines as a class of compounds vary greatly in their air sensitivity, and the misconception that it is trivial or even easy for a novice chemist to attempt a seemingly straightforward synthesis can have disastrous results. To simplify the task, we have previously developed a methodology that uses benchtop intermediates to access a wide variety of phosphine oxides (an immediate precursor to phosphines). This synthetic approach saves the air-free handling until the last step (reduction to and isolation of the phosphine). Presented herein is a complete general procedure for the facile reduction of phosphonates, phosphinates, and phosphine oxides to primary, secondary, and tertiary phosphines using aluminum hydride reducing agents. The electrophilic reducing agents $(^{i}Bu)_2AlH$ and AlH_3 were determined to be vastly superior to $LiAlH_4$ for reduction selectivity and reactivity. Notably, it was determined that AlH_3 is capable of reducing the exceptionally resistant tricyclohexylphosphine oxide, even though $LiAlH_4$ and $(^{i}Bu)_2AlH$ were not. Using this new procedure, gram-scale reactions to synthesize a representative range of primary, secondary, and tertiary phosphines (including volatile phosphines) were achieved reproducibly with excellent yields and unmatched purity without the need for a purification step.

INTRODUCTION

Phosphines are ubiquitous in inorganic, organometallic, and catalysis chemistry.[1−4] The chief reason phosphines are so useful as ligands is that they endow metal centers with steric and electronic properties that can be tuned by altering the substituents on the phosphines and the structures of the phosphines.[3,5] The growing demand for new complexes and catalysts with novel properties requires increasingly exotic phosphine ligands.[6] The synthesis of new phosphine ligands, however, is often frustrated by the rigorous synthetic methods required to produce these ligands and the often imprecise synthetic techniques and procedures reported in the literature.[7] Any novice researcher will quickly discover that the *details* are essential in organophosphorus chemistry.

Our laboratory recently developed several new benchtop methodologies for the synthesis of air-stable phosphine precursors, namely, phosphine oxides.[8,9] The motivation for our ongoing effort is to make traditionally difficult chemical preparations benchtop friendly. A synthetic route to phosphines that goes through a phosphine oxide intermediate avoids most of the air, water, and silica instability of typical phosphine ligand preparations (Figure 1). The new methodologies[8,9] significantly simplify phosphine syntheses on the laboratory scale because the reduction from a phosphine oxide to a phosphine is the *final* synthetic step, only requiring air-free handling once the desired product is in hand.[2]

A reliable reduction method is key to the successful completion of the benchtop synthetic routes shown in Figure 1, and for that reason, we sought to develop dependable, reproducible, and universally applicable methods for the reduction step. Despite running a gamut of reaction conditions and purification methods,[10−16] our initial foray into reducing phosphine oxides was fraught with unforeseen difficulties, including low yields, numerous side reactions, difficult purifications, and persistent impurities. Iterative optimization

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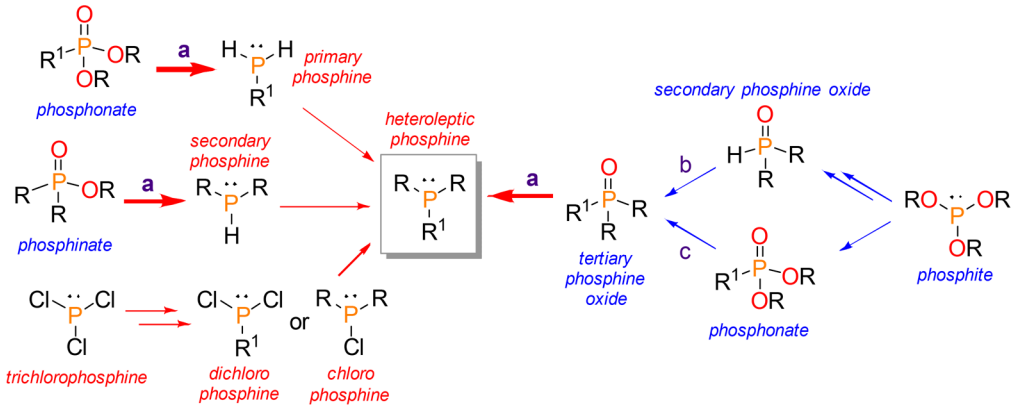

Figure 1. General synthetic methodologies to make heteroleptic tertiary phosphines:[6] (a) reductions developed in this work, (b) nucleophilic phosphorus addition to alkyl electrophiles,[9] (c) electrophilic phosphorus reacting with Grignard nucleophiles.[8] Red represents air- and water-free handling and workup, and blue represents air- and water-stable workup.

was required to achieve reasonable yield and purity for each new ligand. The most difficult cases involved the generation of volatile phosphines (boiling points below 150 °C at 760 Torr).[17−19] In addition, we found that most published methods worked well for a narrow range of compounds but lacked applicability across the organophosphorus spectrum. Overall, we concluded that the application of old methods to new phosphine ligand syntheses is generally unreliable.[20]

We report here a rational, reliable, detailed, and universally applicable procedure for reduction on the gram scale of air-stable precursors to primary, secondary, and tertiary phosphines. The troublesome phosphine characteristics that the new procedure addresses are pyrophoricity, toxicity, and volatility. The procedure (1) is high yielding, (2) gives pure phosphine products (>95%), (3) occurs at low reaction temperatures (close to 22 °C), (4) features short reaction times (≤24 h), (5) is selective for P−O over P−C bond cleavage (i.e., there are no side reactions), (6) uses commercially available reagents, (7) requires only stoichiometric equivalents of a single reducing reagent, (8) has a reliable and rationally designed quench and workup that is compatible with volatile phosphine products, (9) is applicable to a representative range of 1, 2, and 3° phosphines with varying steric and electronic profiles, and (10) is directly applicable to both discovery and laboratory scale syntheses.

EXPERIMENTAL SECTION

General Reduction Procedures. The reductions of the molecules in Table 1 and Figure 2 were carried out under an atmosphere of N_2 unless otherwise stated. The specific methods used for the reductions are indicated in Table 1 as methods A−F (see below). The methods used for the reductions in Figure 2 are described in detail in the Supporting Information (SI), pages S8−S12. For a more detailed step-by-step description of the reaction setup, methods, and safety issues, refer to the SI, pages S25−S32 and especially Figures S11 and S12.

Method A. A 500 mL two-neck Schlenk flask equipped with an addition funnel and reflux condenser was charged with the phosphonate in Et_2O (ca. 1.0 M solution, 4 to 35 mmol phosphorus). The solution was cooled to 0 °C, and then a 1.0−1.5 M solution of $(^iBu)_2AlH$ in Et_2O (5 equiv per phosphorus) was added dropwise to the reaction. The mixture was allowed to warm to room temperature and stirred for 2 h until conversion was complete, as judged by $^{31}P\{^1H\}$ NMR spectroscopy of the crude reaction mixture (for an example, see SI Figure S31). A degassed solution of $NaH_2PO_{4(aq)}$ (10 equiv/phosphorus at ca. 0.5 M) was added dropwise with vigorous stirring while being maintained at 22 °C. The reaction mixture was extracted with 20 mL of *n*-pentane five times, and the organic extracts were combined and distilled (in two 50 mL aliquots) out of a two-neck 100 mL round-bottom Schlenk flask equipped with a fractional distillation head leading to a 250 mL round-bottom flask. A gentle distillation of the organic solvents off of the products (35 °C at 760 Torr) was carried out, followed by a vacuum transfer of the remaining residue into a liquid-nitrogen-cooled receiving flask, yielding pure phosphine.

1,2-Bis(phosphino)ethane: ^1H NMR (500 MHz, chloroform-*d*) δ 2.77 (dt, J = 196.2, 6.3 Hz, 4H), 1.76−1.69 (m, 4H); $^{31}P\{^1H\}$ NMR (202 MHz, chloroform-*d*) δ −132.28; ^{31}P (^1H coupled) NMR (202 MHz, chloroform-*d*) δ −132.28 (tp, J = 195.1, 6.1 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, benzene-d_6) δ 17.51 (dd, J = 11.2, 3.3 Hz). All of these spectroscopic data matched literature values.[21]

Phenylphosphine: ^1H NMR (500 MHz, benzene-d_6) δ 7.27 (td, J = 7.5, 2.0 Hz, 2H), 6.99 (t, J = 5.4 Hz, 3H), 3.83 (d, J = 199.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 134.84 (d, J = 15.2 Hz), 128.65 (d, J = 7.3 Hz), 128.55 (d, J = 6.0 Hz), 128.22; $^{31}P\{^1H\}$ NMR (202 MHz, benzene-d_6) δ −123.81; ^{31}P (^1H coupled) NMR (202 MHz, benzene-d_6) δ −123.79 (tt, J = 199.3, 6.7 Hz). All of these spectroscopic data matched literature values.[22]

Method B. Same as method A except for the isolation procedure. Instead of distillation, the solvent was removed under reduced pressure, followed by a filtration through basic alumina using *n*-pentane. The solvent was then removed under reduced pressure to yield pure phosphine.

ortho-Biphenylphosphine:[23] ^1H NMR (500 MHz, benzene-d_6) δ 7.36 (t, J = 7.1 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.16 (dt, J = 6.9, 1.2 Hz, 2H), 7.15−7.14 (m, 1H), 7.13 (d, J = 1.6 Hz, 0H), 7.13−7.10 (m, 1H), 7.10 (q, J = 2.0 Hz, 0H), 7.09−7.08 (m, 0H), 7.07−7.03 (m, 1H), 3.77 (d, J = 201.7 Hz, 1H); $^{31}P\{^1H\}$ NMR (202 MHz, benzene-d_6) δ −124.45; ^{31}P (^1H coupled) NMR (202 MHz, benzene-d_6) δ −124.44 (t, J = 201.7 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 135.45 (d, J = 8.5 Hz), 130.37, 129.93 (d, J = 2.0 Hz), 129.46, 129.28 (d, J = 10.3 Hz), 129.08 (d, J = 2.9 Hz), 128.41, 128.29 (d, J = 4.5 Hz), 128.14 (d, J = 2.0 Hz), 128.00 (d, J = 10.5 Hz), 127.61, 127.44 (dd, J = 7.6, 3.3 Hz), 127.26 (d, J = 3.1 Hz), 120.99, 115.96; HRMS TOF ESI$^+$ $[C_{12}H_{11}P]^+$ calcd 186.0598, found 186.0603.

Method C. A 500 mL two-neck Schlenk flask equipped with an addition funnel and reflux condenser was charged with phosphinate in Et_2O (ca. 1.0 M solution, 7 mmol phosphorus). The solution was cooled to 0 °C; a 1.0−1.5 M solution of $(^iBu)_2AlH$ in Et_2O (4 equiv per phosphorus) was added dropwise, and the reaction was allowed to warm to room temperature for 2 h. A degassed solution of $K_2HPO_{4(aq)}$ (10 equiv/phosphorus at ca. 0.5 M) was added dropwise with vigorous stirring while being maintained at 22 °C. The reaction mixture was extracted with 20 mL of *n*-pentane five times, and the organic extracts were combined and distilled (in two 50 mL aliquots) out of a two-neck 100 mL round-bottom Schlenk flask equipped with a fractional

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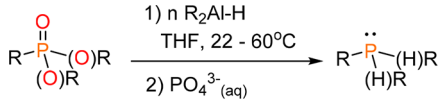
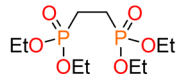
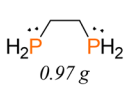
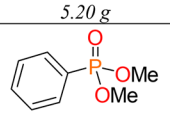
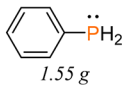
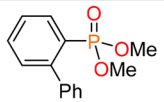
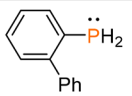
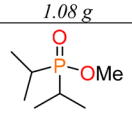
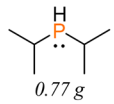
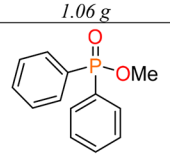
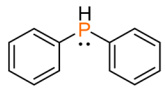
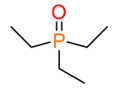
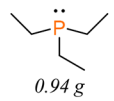
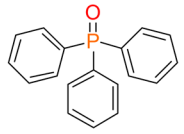
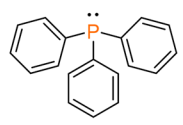
Table 1. Gram-Scale Reduction of Phosphorus Precursors To Yield 1°, 2°, and 3° Phosphines



Entry	Phosphine precursor	Phosphine product	Yield (%)[a]	Purity[c]	Method
1	 5.20 g	 0.97 g	61-72[b]	>99%	A
2	 3.15 g	 1.55 g	88-89[b]	>99%	A
3	 1.08 g	 0.55 g	71-72	95%	B
4	 1.06 g	 0.77 g	60-93[b]	>99%	C
5	 1.46 g	 1.01 g	75-95	>99%	D
6	 1.04 g	 0.94 g	70-72[b]	>99%	E
7	 1.06 g	 0.99 g	97-99	98%	F

[a]Range of isolated yields for multiple trials. [b]Yield determined from isolated mass and corrected using ^{1}H NMR (typically 10% *n*-pentane or Et_2O is present). [c]Purity determined by $^{31}P\{^1H\}$ NMR, with only minor solvent as impurities in the ^{1}H NMR.

distillation head leading to a 250 mL round-bottom flask. A gentle distillation of the organic solvents off of the products (35 °C at 760 Torr) was carried out, followed by a vacuum transfer of the remaining residue into a liquid-nitrogen-cooled receiving flask, yielding pure phosphine.

Diisopropylphosphine: ^{1}H NMR (500 MHz, benzene-d_6) δ 2.92 (dt, J = 192.1, 5.9 Hz, 1H), 1.79 (hd, J = 7.0, 1.4 Hz, 2H), 1.07−0.98 (m, 12H); $^{31}P\{^1H\}$ NMR (202 MHz, benzene-d_6) δ −16.54; ^{31}P (^{1}H coupled) NMR (202 MHz, benzene-d_6) δ −15.49 to −17.59 (dm); $^{13}C\{^1H\}$ NMR (126 MHz, benzene-d_6) δ 22.85 (d, J = 6.5 Hz), 21.76 (d, J = 20.1 Hz), 20.57 (d, J = 9.4 Hz). All of these spectroscopic data matched literature values.[24]

Method D. Same as method C except for the isolation procedure. Instead of distillation, the solvent was removed under reduced pressure, followed by a filtration through basic alumina using *n*-pentane. The solvent was then removed under reduced pressure to yield pure phosphine.

Diphenylphosphine: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.48 (ddd, J = 9.5, 5.1, 2.9 Hz, 4H), 7.33−7.31 (m, 6H), 5.25 (d, J = 219.0 Hz, 1H); $^{31}P\{^1H\}$ NMR (202 MHz, chloroform-*d*) δ −40.41; ^{31}P (^{1}H coupled) NMR (202 MHz, chloroform-*d*) δ −40.41 (dp, J = 219.1, 7.4 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 134.66 (d, J = 9.7 Hz), 133.96 (d, J = 16.8 Hz), 128.56 (d, J = 6.3 Hz), 128.46. All of these spectroscopic data matched literature values.[25]

Method E. A solution of AlH_3 was prepared in situ by dropwise addition of a solution of $LiAlH_4$ to a solution of $AlCl_3$ (3:1 $LiAlH_4$/$AlCl_3$) in glyme (ca. 0.2 M AlH_3).[26] The mixture was stirred for 30 min at room temperature. A solution of tertiary phosphine oxide (2.0 M in glyme) was added to the AlH_3 mixture dropwise while the temperature was maintained at 22 °C. The mixture was then heated to 65 °C for 12 h. The reaction was cooled to 22 °C, and a degassed solution of $Na_3PO_{4(aq)}$ (5 equiv/phosphorus at ca. 0.5 M) was added dropwise with vigorous stirring while being maintained at 22 °C. The reaction mixture was extracted with 20 mL of *n*-pentane five times, and the organic extracts were combined and distilled (in two 50 mL aliquots) out of a two-neck 100 mL round-bottom Schlenk flask equipped with a fractional distillation head leading to a 250 mL round-bottom flask. A gentle distillation of the organic solvents off of the products (35 °C at 760 Torr) was carried out, followed by a vacuum transfer of the remaining residue into a liquid-nitrogen-cooled receiving flask, yielding pure phosphine.

Triethylphosphine: ^{1}H NMR (500 MHz, benzene-d_6) δ 1.22 (q, J = 7.7 Hz, 6H), 0.97 (dt, J = 13.9, 7.7 Hz, 9H); $^{31}P\{^1H\}$ NMR (202 MHz, benzene-d_6) δ −19.67; ^{31}P (^{1}H coupled) NMR (202 MHz, benzene-d_6) δ −19.70 (dhept, J = 27.5, 13.8 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, benzene-d_6) δ 18.67 (d, J = 13.7 Hz), 9.39 (d, J = 13.5 Hz). All of these spectroscopic data matched literature values.[27]

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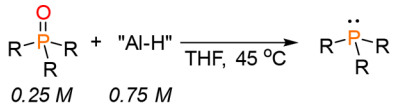

a)

"Al-H"	PCy_3	PEt_3	PPh_3
$(^iBu)_2AlH$	>>24[c]	6.0 ± 0.6	2.0 ± 0.4
AlH_3[a]	20 ± 2	1.6 ± 0.2	< 0.2
$LiAlH_4$[b]	N/R	>>24[d]	>24[e]

All values quantified using $^{31}P\{^1H\}$ NMR spectroscopy with an internal sealed capillary standard of 1,2-bis(diethylphosphonato)ethane in THF-d_8 and fit to kinetic curves in order to determine half-life (see S.I. Figures S1-S10). All run with equal concentrations of 3.0 equivalents aluminum per phosphorus.
[a]AlH_3 was prepared according to Method E. [b]$LiAlH_4$ was freshly recrystallized and prepared as an etherial solution. [c]Trace conversion (<1%) at 20 h. [d]3% Conversion at 20 h, no observable product. [e]9% Conversion at 22 h, trace product.

b)

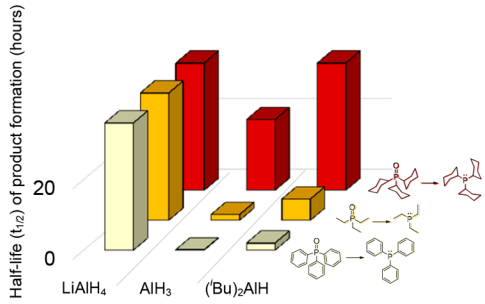

Figure 2. Kinetic half-life (in hours) of phosphine formation for a representative range of tertiary phosphine oxides reacting with aluminum hydrides. (a) Table showing kinetic values and errors with notes on the reactions and (b) visual representation of the data. Note that the vertical limit cuts off at 30 h. Also note that lower bars are faster reactions. The methods used for the reductions are described in the Supporting Information, pages S5 and S6.

Method F. A 50 mL flask was charged with THF and phosphine oxide (10 mL, ca. 0.4 M solution, 4 mmol phosphorus). $(^iBu)_2AlH$ (neat, 3.2 equiv per phosphorus) was added dropwise to the reaction mixture and heated to 60 °C for 12 h. The reaction was cooled to 22 °C, and a degassed solution of $K_3PO_{4(aq)}$ (12 equiv/phosphorus at ca. 0.5 M) was added dropwise with vigorous stirring while being maintained at 22 °C for 1 h. The reaction mixture was extracted with 20 mL of Et_2O five times, and the organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield pure phosphine.

Triphenylphosphine: ^1H NMR (500 MHz, chloroform-*d*) δ 7.40−7.29 (m, 15H); $^{31}P\{^1H\}$ NMR (202 MHz, chloroform-*d*) δ −5.35; ^{31}P (^1H coupled) NMR (202 MHz, chloroform-*d*) δ −5.34; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 137.33 (d, J = 10.8 Hz), 133.87 (d, J = 19.5 Hz), 128.83, 128.62 (d, J = 6.9 Hz). All of these spectroscopic data matched literature values.[28]

Reagents and Instrumentation. Complete details are provided in the Supporting Information (page S2).

RESULTS AND DISCUSSION

The reduction techniques reported here were determined over many years of internal laboratory refinement. Applying process development principles to these reactions, we continually strove for high-purity products, low purification demands, and high yields across an array of substrates.[29] To demonstrate the applicability of the reductions, eight representative molecules were studied, representing six different categories of molecules: two aryl phosphonates, an alkyl phosphonate, an aryl phosphinite, an alkyl phosphinite, an aryl phosphine oxide, and two alkyl phosphine oxides (Table 1 and Figure 2).[30] Within the overall methodology, experimental and preparative details were nominally permuted to allow the application of the methodology to the six categories of molecules.[31] The sections below present the chemical context for the steps in the reduction methods and also serve as a general overview of the reduction of phosphonates, phosphinates, and phosphine oxides with aluminum hydride reducing agents.

Reduction of Organophosphorus Oxides to Phosphines: Typical Methods. Many reagents, conditions,[32−36] additives,[37−39] catalysts,[40−42] and exotic reducing agents[43−45] have been reported for the reduction of phosphine precursors. Lithium aluminum hydride ($LiAlH_4$) is one of the most common reagents used for this purpose. As initially reported by Mallion and Mann,[46] we too found that $LiAlH_4$ has several drawbacks, including slow reaction rates,[47] a propensity for side reactions (namely, dehydrocoupling to form P−P bonds and excessive P−C bond cleavage[48]), and low functional group tolerance. To alleviate these problems, a myriad of stoichiometric additives (e.g., Me_3SiCl[16]) or catalysts are typically used in $LiAlH_4$ reductions to improve the yields or increase the rates. However, when additives are used, the workup produces stoichiometric salts and surfactants that often hinder filtrations and extractions and that otherwise complicate isolation procedures.

Reductions Using $(^iBu)_2AlH$ and AlH_3. Unlike the action of $LiAlH_4$ on carbonyl species, where the C=O will directly react with a hydride, phosphine oxide reduction is dependent on first forming a phosphine oxide−aluminum adduct intermediate ($R_3P{=}O \rightarrow Al$).[37,46] Consequently, the reduction of a phosphine oxide with $LiAlH_4$ first requires the formation of AlH_3 in solution (see eq 1—the Paddock reaction).[49] For this reason, we studied the direct use of electrophilic aluminum hydrides for organophosphorus reductions to phosphines. Specifically, AlH_3[50−53] and the commercially available $(^iBu)_2AlH$[37,54−56] were investigated because they have been shown to perform clean and selective organophosphorus reductions with fast reaction rates at low temperatures. In addition, these reagents have better functional group tolerance than $LiAlH_4$.[50,51,57] Note that $(^iBu)_2AlH$ does not cause racemization when reducing chiral phosphine oxides, as $LiAlH_4$ does, making it a viable reducing agent for chiral phosphine syntheses.[11,58]

$$LiAlH_4 \rightleftharpoons Li^+H^- + AlH_3 \quad (1)$$

To determine the synthetic usefulness of $(^iBu)_2AlH$ and AlH_3 (compared to $LiAlH_4$), the relative reduction kinetics of these reagents were determined across a representative range of tertiary phosphine oxides (Figure 2). (The results in Figure 2 are reported as half-lives for the formation of product. Thus, a lower bar height indicates a faster reaction. The half-lives were obtained by fitting the growth of the product phosphine to first-order kinetics.) The phosphine oxides in Figure 2 were chosen

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because tertiary phosphine oxides are chemically more difficult to reduce than the analogous reduction of phosphonates and phosphinates to primary and secondary phosphines, respectively. $P(O)Cy_3$ was specifically included because it is an exceptionally difficult to reduce phosphine oxide, and it does not react with typical aluminum hydrides.[37] To our knowledge, a reaction profile comparison of aluminum hydrides reacting with phosphine oxides has never been quantified.

As shown in Figure 2, the two electrophilic aluminum hydrides (AlH_3 and $(^iBu)_2AlH$) reduce phosphine oxides with faster rates than $LiAlH_4$. This result is perhaps surprising because the reactivity of these aluminum hydrides for most organic reductions follows the reactivity trend $LiAlH_4 > AlH_3 > (^iBu)_2AlH$.[59] The findings in Figure 2 lend credence to the idea that an electrophilic aluminum species first forms a $R_3P{=}O \rightarrow Al$ intermediate as the key step in reducing phosphine oxides.

$(^iBu)_2AlH$ and AlH_3 appear to follow their expected reactivity, with $(^iBu)_2AlH$ being somewhat less reactive than AlH_3. It is also possible that AlH_3 reacts faster because there are more available hydrides for reduction; however, these reactions were all run with excess aluminum hydrides, so the effect of multiple hydrides on the Al center should be minimized. Note that AlH_3 was the only reducing agent capable of reducing $P(O)Cy_3$ to PCy_3, albeit with incomplete conversion (up to 62% yield before reaction stalling, see the SI, Figures S73 and S74S). This result shows that AlH_3 is a superior reducing agent compared to $LiAlH_4$ and $(^iBu)_2AlH$ for chemically difficult phosphine oxide reductions.

With $(^iBu)_2AlH$ and AlH_3, the formation of the $R_3P{=}O \rightarrow Al$ intermediates was directly observable at room temperature by $^{31}P\{^1H\}$ NMR spectroscopy (SI Figures S1–S10; addition of the aluminum reagent to the phosphine oxide shifted the resonances downfield by 15 to 30 ppm). When these intermediate species were hydrolyzed, the phosphine oxides were cleanly recoverable, consistent with the intermediate species having a $R_3P{=}O \rightarrow Al$ structure. In the absence of water, the $R_3P{=}O \rightarrow Al$ resonances cleanly converted to the sharp upfield resonances of the expected phosphine products.

Reductions Using $LiAlH_4$. When $LiAlH_4$ was added to phosphine oxides in solution at room temperature and the reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy, a small resonance attributed to $R_3P{=}O \rightarrow AlH_3$ developed slowly that was shifted downfield by 15–30 ppm relative to the original P resonance. (The assignment to $R_3P{=}O \rightarrow AlH_3$ is based on the formation of similar resonances that form with AlH_3; see the SI, Figures S9 and S10.) The formation of the species identified as $R_3P{=}O \rightarrow AlH_3$ preceded product formation for all of the $LiAlH_4$ reduction reactions in this study.

For triphenylphosphine oxide, a cluster of downfield resonances at 90 ppm (attributed to unwanted side reactions) was also observed (see SI Figure S2). Hydrolysis of the intermediates yielded a mixture of primary phosphine, secondary phosphine, secondary phosphine oxide, tertiary phosphine, tertiary phosphine oxide, and several other species. These observed byproducts are suggested to be the result of P–C bond cleavage (Figure 3). No such byproducts were observed when identical reductions were performed using $(^iBu)_2AlH$ and AlH_3. Compared to $(^iBu)_2AlH$ and AlH_3, $LiAlH_4$ has a strong propensity to reduce P–C bonds over P–O bonds, even at room temperature.

Based on the in situ NMR spectroscopy of $(^iBu)_2AlH$, AlH_3, and $LiAlH_4$ reductions showing similar intermediate species (see the SI, Figures S1, S5, and S8), we propose the reduction

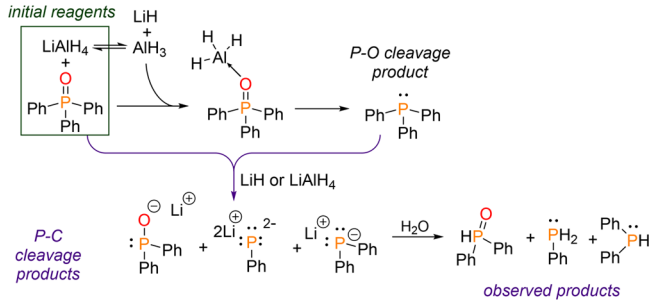

Figure 3. Chemical steps and intermediates for triphenylphosphine oxide reaction with $LiAlH_4$. All species based on NMR spectroscopy, literature, and hydrolysis products (see SI Figure S2 for NMR spectra).

of tertiary phosphine oxides to tertiary phosphines using $LiAlH_4$ proceeds through the in situ formation of AlH_3 via the Paddock mechanism (Figure 3, upper scheme), consistent with Paddock's initial report.[49] Because AlH_3 reactions proceed via $R_3P{=}O \rightarrow AlH_3$ formation and subsequent P–O bond cleavage to yield tertiary phosphines but lack the other side reactivity observed with $LiAlH_4$, it is likely that P–C bond cleavage in the $LiAlH_4$ reaction is primarily caused by either LiH or $LiAlH_4$ (Figure 3, lower scheme). These results demonstrate the advantages of using the electrophilic aluminum hydrides instead of $LiAlH_4$ for tertiary phosphine oxide reduction.

Improved Quench and Workup. Perhaps the most crucial steps to an organophosphorus reduction are the quench and workup. Because these steps require air-free techniques to preserve the free phosphine, any mistakes can be irrecoverable and potentially dangerous. We suggest that the lack of vital *chemical* details (i.e., knowledge of the species that are present) and the lack of chemical sense in reported quench and workup procedures are the primary causes of low yields in typical reductions. For example, some reported workups involve aqueous quenches ranging from 6 M HCl[60,61] (conditions that protonate many phosphines) to 2 M NaOH[62] (conditions that cause significant gelation of the aqueous workup mixture) to no quenching but with a dangerous distillation of product off of residual neat $LiAlH_4$.[63−65] (*Note that the direct distillation of phosphines off of unquenched $LiAlH_4$ is* ***extremely dangerous*** *and should never be attempted.)*

To address the causes of low yields in aluminum hydride reduction reactions, the chemical details of the reaction mixture must be considered, in particular, the byproducts. The byproducts of P=O reduction (Figure 4a) are typically gases and aluminum salts. (The aluminum salts are nondiscrete species that are water-soluble and whose speciation is dependent on concentration, pH, and the presence of other small molecules such as alcohols.) This would seemingly make isolation of the organic phosphine straightforward by using an organic solvent extraction of an aqueous layer. However, the mixture of aluminum species acts as a surfactant and causes gelation of the aqueous layer through the formation of aluminum hydrogels, leading to intractable separations and filtrations.

When a secondary or primary phosphine is the product of reduction (Figure 4b), then R^3OH is an additional stoichiometric byproduct. Typically, R^3OH is EtOH or MeOH, both of which are miscible with organic and aqueous layers, which are surfactants that carry over salts and hinder filtrations and extractions. (Likewise, the problem with silyl reducing agents is

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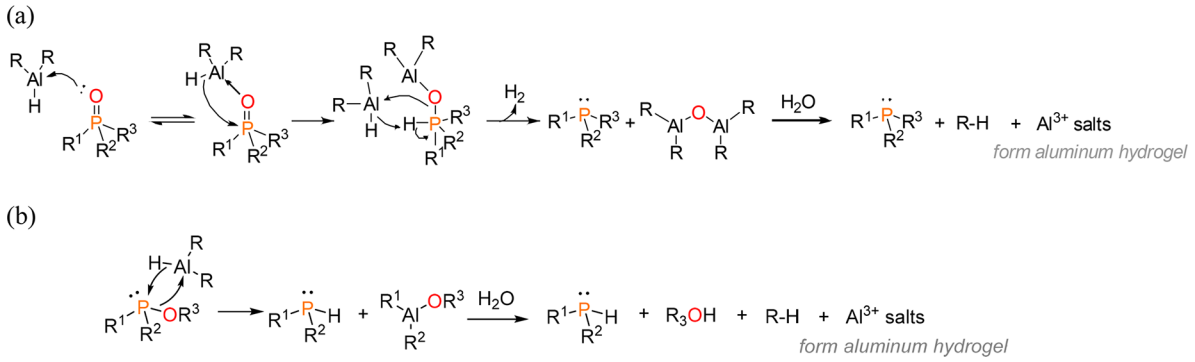


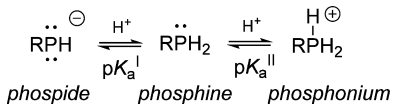
Figure 4. Mechanism of electrophilic aluminum hydride reduction of (a) tertiary phosphine oxide to a phosphine and (b) representative reduction of a phosphinite to secondary phosphine showing chemical intermediates and subsequent byproducts. R_1, R_2, and R_3 = carbon functional groups; R = ^{i}Bu or H.

not the reduction, per se, rather the subsequent workup and isolation of pyrophoric phosphines.) For these reasons, the presence of stoichiometric alcohols complicates the air-free isolation. When additives such as silanes and silyl chlorides are used (which are always used in 5−100-fold excess), additional complications in the workup are caused by the super-stoichiometric byproducts that form. For example, quenching of silyl chlorides gives silanol species, which are pervasive surfactants that carry Al^{3+} salts into the organic layer, promoting gelation. Alcohols and silanols are also particularly difficult to remove from volatile phosphine products because they have similar boiling points.

Of all the issues discussed in the preceding paragraph that lead to problems with the workup and low yields, the most pressing problem is the presence of the aluminum salts. To solve this problem, aluminum needs to be removed from the reaction mixture. Rochelle's salt (sodium potassium L-(+)-tartrate tetrahydrate) has been reported to precipitate the Al^{3+} ion;[66] however, we found that it may add to the surfactant problem when used at the wrong concentration,[67] and that it is generally unreliable at reducing the gelation of the reaction mixture. As an alternative, experiments showed that the addition of sodium phosphate (Na_3PO_4) cleanly precipitated the aluminum salts as $AlPO_{4(s)}$, thereby solving the problem. Solutions of $Na_3PO_{4(aq)}$ also buffer the aqueous layer to keep almost all phosphines in a nonionic form (Table 2), which makes them isolable using an organic extraction. Based on the pK_a values for the formation of phosphonium species (Table 2, pK_a^{II}), it is clear that a large number of tertiary phosphine derivatives are protonated at pH values below 12. Based on known pK_a values (Table 2, pK_a^{I}), the phosphide form is inaccessible in water. Overall, the workup strategy of adding Na_3PO_4 led to clean and near-quantitative extractions.

Improved Isolation of Volatile Phosphines. Although large-scale (>50 g) preparations allow a high-yielding fractional distillation of a volatile phosphine, preparatory to gram-scale distillation is impractical and typically ineffective (even with specialized glassware). Because electrophilic aluminum hydride reductions yield only phosphine product, the method reported here has consistently provided clean material with high yields and without the need for elaborate purifications. After an extraction with *n*-pentane,[74] the crude product can be isolated by very mild air-free distillation of the bulk solvents off of the volatile phosphine, followed by a vacuum transfer. The only chemicals present after the vacuum transfer are 10−15% organic solvent (*n*-pentane from the extraction step or Et_2O from the reaction) and the product phosphine (>95% pure after removal of the solvent, which is superior to most purchased samples). The solvent contaminants can easily be removed using a Kügelrohr distillation apparatus; however, this is oftentimes synthetically unnecessary because *n*-pentane and Et_2O are easily quantified by ^{1}H NMR spectroscopy and chemically compatible with most subsequent chemical manipulations.

Table 2. pK_a Values of a Representative Range of Phosphines for the Protonation of Phosphide to Phosphine and Phosphine to Phosphonium[a]



	phosphine	pK_a^{I}[b]	pK_a^{II}[d]	ref
primary	PH_3	24.1[c]	−14[h]	68,69
	$MePH_2$	29.6[c]	−3.2[e]	68,70
	$CyPH_2$	32.3	0.27[h]	69,71
	$PhPH_2$	24.5	−1.3[f]	61,35
secondary	Me_2PH	34.8[c]	3.91	34,66
	Cy_2PH	35.7	4.55	34,69,72
	Ph_2PH	21.7	0.03	69,70
tertiary	Me_3P		7.2	35
	Cy_3P		9.7	72
	Ph_3P		2.7	35,72
	$^tBu_3P$		11.4[g]	73

[a]Note only phosphines in a nonionic form can be isolated using an organic extraction. [b]pK_a in THF. [c]pK_a in DMSO. [d]pK_a in H_2O. [e]pK_a in CH_2Cl_2. [f]pK_a in EtOH. [g]pK_a in CH_3NO_2. [h]pK_a estimate obtained by gas-phase basicity measurements combined with solution enthalpy of formation of protonated species using HSO_3F.

CONCLUSIONS

An improved general methodology involving the use of electrophilic Al−H reagents for the reduction of phosphonates, phosphinates, and phosphine oxides to primary, secondary, and tertiary phosphines was developed. It was demonstrated that $(^iBu)_2AlH$ is the best reagent for the reduction of phosphonates, phosphinates, and triarylphosphine oxides to primary, secondary, and tertiary phosphines, respectively. In addition, it was demonstrated that AlH_3 is a stronger reducing agent when commercially available $(^iBu)_2AlH$ is insufficient. NMR spectroscopy and reactivity evidence imply AlH_3 as the active species in the mechanism of tertiary phosphine oxide

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reduction by $LiAlH_4$ (via the Paddock reaction equilibrium in eq 1). By using AlH_3 directly, even the reduction of the otherwise unreactive $P(O)Cy_3$ was accomplished (Figure 2).[75]

The electrophilic aluminum hydrides $(^iBu)_2AlH$ and AlH_3 have superb selectivity when reacted near room temperature. These reagents avoid side reactions such as P−C bond cleavage, leading to clean product formation. Quenching the reaction with a basic phosphate salt leads to the removal of Al^{3+} salts that otherwise form aluminum oxy/hydroxyl gels that hinder the workup. Maintaining a pH >12 prevents product loss in the aqueous layer. Finally, azeotropic removal of volatile byproducts such as alcohols[74] followed by vacuum transfer of volatile phosphines affords excellent yields and purities without the need for purification of the phosphine. Nonvolatile phosphines were pure after a simple filtration. The representative array of phosphine precursors reduced in this study suggest that the reduction methodology is broadly applicable to diverse and new phosphine syntheses. Although this methodology focuses on air-stable precursors to phosphines, applications could easily extend to the reduction of phosphonites, phosphinites, chlorophosphonium salts, chlorophosphines, phosphine sulfides, P−N, P−S, P−X bonds, etc. Because electrophilic aluminum hydrides are known to retain chirality for 2 and 3° phosphine oxides, a natural extension of this work is the low-temperature reduction to chiral phosphines.[57]

The reduction methodology described here completes the reaction sequence from all air-, water-, and silica-stable intermediates to phosphines with complete benchtop handling until the final synthetic step (Figure 1). In total, these studies are a new synthetic benchtop strategy to clean and isolable phosphines. This synthetic strategy follows the core tenants of process development (specifically quality by design) to make the synthesis of phosphines reliable and high-yielding on the laboratory scale while avoiding demanding purifications and minimizing air-free handling. Overall, these studies will simplify future organophosphorus syntheses and provide a blueprint from which novice organophosphorus chemists may reliably work.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00684.

Additional discussion of general considerations, specific synthesis descriptions, additional commentary on the reactions, additional references, and complete spectroscopic data for the products (PDF)

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Notes

The authors declare no competing financial interest.

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(29) We specifically chose target compounds like phenylphosphine, bis(phosphino)ethane, and diisopropylphosphine because these are

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exquisitely pyrophoric (and toxic) compounds that present a real challenge for synthesis and isolation even by experienced chemists. A simple error in handling, miscalculation, or careless reaction setup can lead to lab fires and chemical exposure.

(30) Note that [1,1′-biphenyl]-2-ylphosphane (*o*-biphenylphosphine, see entry 3 in Table 1 and Figure S13 in the SI) is a key synthetic intermediate (previously reported as 40−85% pure by ^{31}P NMR spectroscopic estimate) for many academically and industrially valuable ligands.[23,76−79] The isolation of this phosphine grants access to new Buchwald-type[80] ligands—the synthesis of which would not be feasible with technical grade *o*-biphenylphosphine.

(31) When compared to the variety of reagents, catalysts, conditions, and publications on reducing phosphines, the methodology represents a consolidation of necessary and new information that is applicable unilaterally for this chemical transformation.

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(47) Note that $LiAlH_4$ is metastable and if used as purchased from chemical companies often contains a mixture of Et_2O-soluble material ($LiAlH_4$) and insoluble materials (Li_3AlH_6 and other species).[81,82] The insoluble aluminum species likely contribute to the slow reaction rates and side reactions due to their insoluble and unspecified nature. Pure $LiAlH_4$ can be purchased as a solution or extracted from the commercially available $LiAlH_4$ using Et_2O and recrystallized.[83]

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(74) Note that *n*-pentane has several superior properties as the extracting solvent: (1) most primary, secondary, and tertiary phosphines are very soluble in nonpolar hydrocarbons; (2) *n*-pentane has a high vapor pressure and is easily removed with gentle heating and (3) *n*-pentane azeotropes with both ethanol and methanol (which are typical contaminates from the reduction to primary and secondary phosphines, see Figure 3b).

(75) A reviewer suggests that AlH_3 is also the reductant generated when using the reducing mixture of $LiAlH_4$ and Me_3SiCl. However, research has shown that AlH_3 is not the active reductant in these reactions. See: Hérault, D.; Nguyen, D. H.; Nuel, D.; Buono, G. *Chem. Soc. Rev.* **2015**, *44*, 2508. Rather, the reductants are Si−H species, which are capable of reducing aryl substituted tertiary phosphine oxides and phosphonates. The same reviewer also notes that $LiAlH_4$ and Me_3SiCl can lead to quantitative reductions of phosphine oxides in multigram amounts in high yields. In fact, these papers pertain to a narrow subset of phosphines, namely aryl-phosphines that are air-stable (see ref 20 for further discussion of this point). These phosphines lack the core properties that the developments of our manuscript seeks to address: pyrophoricity, toxicity, and volatility.

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