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A highly efficient general synthesis of phosphine–borane complexes

James McNulty[a,*] and Yuehui Zhou[b]

[a]*Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4M1*
[b]*Cytec Canada Inc., PO Box 240, Niagara Falls, Ontario, Canada L2E 6T4*

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Abstract—A general synthesis of phosphine–borane complexes proceeding in high yield in a safe, green process from borane generated in situ from sodium borohydride is described. The procedure also allows simultaneous carbonyl reduction and phosphine–borane formation on air-sensitive bulky phosphine derivatives.

Since the first reported synthesis of a phosphine–borane complex over 50 years ago[1] there has been considerable interest in the preparation and controlled reactivity inherent in these air-stable complexes. Applications have been pioneered by Imamoto[2] over the last 20 years or so and now include their use in carbonyl addition,[2] alkylation,[2,3] hydrophosphination[4] and conjugate addition[5] processes as well as metal-mediated couplings.[6] Two recent reviews[7a,b] highlight the scope of these processes and clearly demonstrate the importance of protection of trivalent phosphorous in the synthesis of chiral phosphine ligands as well as the expanded range of controlled synthetic possibilities available with phosphine–borane complexes in comparison with the parent phosphines.

We have recently been involved in the synthesis of several phosphine–borane adducts and the resulting process chemistry associated with their scale-up. Like amine–boranes,[8] the most common approaches towards the synthesis of phosphine–boranes employ the reaction of the parent phosphine with borane sources such as borane–tetrahydrofuran and most often borane–dimethylsulfide.[7a,b] These procedures were not convenient for us on scale-up due to the instability of the THF complex as well as the release of dimethylsulfide from the latter process, which would require scrubbing. We also noted that residual dimethylsulfide in the phosphine–borane complexes so produced is difficult to eradicate resulting in odoriferous products. The use of sodium borohydride as a borane source in conjunction with a hydride acceptor such as acetone[9] or acetic acid[10] in the presence of an amine results in the formation of intermediate amine–boranes. Similar procedures have been reported for the synthesis of phosphite–boranes[11a] and phosphorous triamide boranes[11b] using carbon dioxide or hydrogen chloride as hydride acceptor and, in one case,[12] a tertiary phosphine borane from sodium borohydride and carbon dioxide. The only other direct synthesis of phosphine–boranes from phosphines employing sodium borohydride as borane source is the process reported by Imamoto et al.[13] that requires the stoichiometric addition of cerium trichloride. Thus earlier methods that allow evolution of borane from sodium borohydride through addition of simple protic solvents[9,10] have not been applied to the synthesis of phosphine–boranes. We now report on the development of a simple, general, economical synthesis of phosphine–borane complexes that uses solid sodium borohydride as a convenient source of borane.

We first determined that a suspension of sodium borohydride and a suitable phosphine in THF, used both as solvent and 'borane-shuttle', reacted slowly to produce the phosphine–borane adduct when dry methanol was slowly added.[9] Further experimentation showed that the reaction was much more efficient when an acetic acid solution in THF was used as proton source. A general procedure evolved from our studies on the reaction using dicyclohexylphosphine. With methanol as proton source, a maximum yield of 78% of the phosphine–borane is produced and the reaction comes to a halt despite the addition of excess sodium borohydride and methanol. In contrast, when acetic acid is

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* Corresponding author. Tel.: +1-905-525-9140x27393; fax: +1-905-522-2509; e-mail: jmcnult@mcmaster.ca

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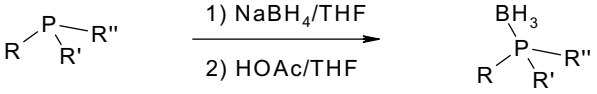
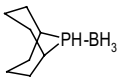
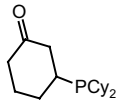
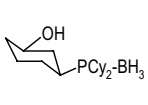
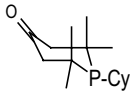
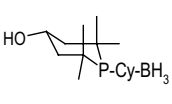
employed, the reaction proceeds rapidly to full conversion within 1 h.

Further experimentation with the stoichiometry of the reaction allowed the evolution of a general protocol whereby 1 equiv of the phosphine at 1.0 M in dry THF at 0 °C is treated with 1.5 equiv of solid sodium borohydride followed by addition of 1.7 equiv of acetic acid in 40% of the original volume of THF over 30 min at 0 °C, followed by 1 h at room temperature.[16]

The overall results from our study are reported in Table 1. As can be seen, primary, secondary and tertiary alkyl phosphines (entries 1–6) react readily to give the corresponding phosphine boranes in very high yield. Aryl and mixed alkyl/aryl phosphines (entries 7–9) react similarly as did the phosphabicyclo[3.3.1]nonane (entry 10). Two different work-up protocols were utilized depending upon whether the product phosphine–borane is a solid or liquid. When the product is a solid, addition of water and excess acetic acid followed by filtration allows the direct isolation of the borane adduct in high yield and purity. Where the product is an oil, partition between water and dichloromethane allows the separation of the borane adduct from the inorganic salts. The phosphine–borane complexes prepared in this way are formed in essentially quantitative yield in all cases so far investigated and are typically isolated in 95% yield requiring no chromatographic purification and could be directly used in alkylation and addition processes according to standard procedures.[2–7] All of the phosphine–borane complexes reported in Table 1 were stable at room temperature with the exception of the mixed isobutylphenyl derivative (entry 9), with which a very slow evolution of borane was noted. This complex was stable when stored at −5 °C or when pressurized at room temperature.

Table 1. General synthesis of phosphine–borane complexes; Cy = cyclohexyl



Entry	Phosphine	Phosphine–borane	Isolated yield (%)
1	Bu_2PH	$Bu_2PH–BH_3$	99.0
2	Bu_3P	$Bu_3P–BH_3$	97.8
3	$CyPH_2$	$CyPH_2–BH_3$	99.5
4	Cy_2PH	$Cy_2PH–BH_3$	94.7
5	Cy_3P	$Cy_3P–BH_3$	95.0
6	^{i}BuCyPH	^{i}BuCyPH–BH_3	98.0
7	Ph_2PH	$Ph_2PH–BH_3$	95.0
8	Ph_3P	$Ph_3P–BH_3$	94.7
9	^{i}BuPhPH	^{i}BuPhPH–BH_3	99.8
10			95.1
11			84.0
12			79.7

The synthesis of polymer-supported phosphines is becoming increasingly important for the preparation of recoverable and recyclable catalysts.[14] Few reports describe the synthesis of resin-linkable hindered trialkyl phosphines.[15] We were thus delighted to find that reduction of the air-sensitive ketone containing phosphines (entries 11 and 12) using a slight modification of our protocol proceeded to give the corresponding alcohols with simultaneous protection of the phosphine as its boron adduct. In these cases, 2.0 and 2.3 equiv of sodium borohydride and acetic acid, respectively, were employed per equivalent of keto-phosphine. Thus resin-linkable analogues of tricyclohexyl phosphine and di-*tert*-butylalkyl phosphines are available through our reduction–protection protocol. The reduction of the cyclohexyl ketone derivative (entry 11) was extensively studied. When methanol was used as the proton source, two phosphine–borane alcohols were isolated in 39% yield as an 85:15 mixture of equatorial/axial alcohols. In contrast, the use of acetic acid provided a significantly higher yield of the reduction product and with almost complete diastereoselectivity (>98%) in favor of the equatorial alcohol.

In conclusion, we have demonstrated an efficient protocol for the preparation of phosphine–borane complexes from the free phosphines using sodium borohydride and addition of a solution of acetic acid in THF. The procedure also allows for the reduction of remote carbonyl functions with simultaneous P–borane formation allowing access to air-stable linkable alkyl phosphine derivatives. Sodium borohydride is very inexpensive on a cost-per-mole basis in comparison to borane–THF or borane–dimethylsulfide solutions. The use of stoichiometric quantities of cerium salts[13] is not required and the process allows for the elimination of environmentally offensive dimethylsulfide. Lastly, several examples have been scaled up to molar quantities demonstrating the methods suitability for the safe and efficient production of phosphine–boranes. For those phosphines that form crystalline boranes (entries 4, 5, 7, 11 and 12) direct recrystallization of the product allows ready isolation of the borane complex without the need for additional solvent. Applications of the phosphine–borane complexes towards the synthesis of hindered phosphine ligands and polymer-linked hindered phosphines is under active investigation in our laboratories.

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16. Sample procedure (Table 1, entry 4): To a solution of dicyclohexylphosphine (4.03 g, 20.3 mmol) in dry THF (20 mL) at 0 °C under nitrogen was added solid sodium borohydride (1.15 g, 30.5 mmol) in one portion followed by a solution of glacial acetic acid (2.1 g, 34.5 mmol) in THF (8.0 mL) dropwise over 30 min. Frothing occurs but is readily controllable through magnetic or overhead stirring of the solution. Subsequent to the acid addition, the reaction mixture was stirred at room temperature for 1 h at which time TLC analysis indicated complete conversion. TLC: hexane/EtOAc 85:15, Cy_2PH $R_f = 0.85$, $Cy_2PH–BH_3$ $R_f = 0.73$. (Note: All compounds investigated are cleanly visible on TLC upon plate development with 1% ethanolic anisaldehyde containing 0.5% H_2SO_4 and gentle heating.) Water (20 mL) was slowly added to the reaction followed by acetic acid (2.0 g) in water (25 mL). Crystallization occurs spontaneously or by brief storage in the refrigerator. The crystals were filtered by suction, washed with water and dried to give $Cy_2PH–BH_3$ in 89.0–99.9% yield, mp 81–83 °C, lit.[3a] 78.6–80.9 °C. All compounds reported were characterized by ^1H, ^{13}C and ^{31}P NMR as well as MS and HRMS data. Selected data: (Table 1, entry 9): ^1H NMR ($CDCl_3$) δ 7.68 (2H, m), 7.45 (3H, m), 5.48 (1H, dq, $J = 367$, 6.5 Hz), 1.95 (3H, m), 1.01 (6H, collapsed dd), 0.92 (3H, br q, $J = 90$ Hz); ^{31}P NMR δ −8.3; EIMS 166 (100), 124 (38), 110 (46); HREIMS calcd for $C_{10}H_{15}P$ ($M-BH_3$) 166.0911, found: 166.0913 (Table 1, entry 11); ^1H NMR ($CDCl_3$) δ 3.51 (1H, m), 2.10 (1H, m), 1.97 (1H, m), 1.2–1.8 (29H, m), 0.25 (3H, br q, $J = 120$ Hz); ^{31}P NMR δ 28.7; EIMS 296 (100), 279 (8), 214 (51), 198 (91), 117 (58); HREIMS calcd for $C_{18}H_{33}PO$ ($M-BH_3$) 296.2269, found: 296.2266.