Reduction of Phosphinites, Phosphinates, and Related Species with DIBAL-H

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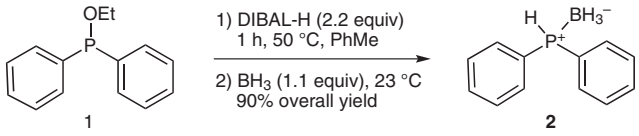
Abstract: Diisobutylaluminium hydride has been found to be an excellent reducing agent for phosphinites, phosphinates, and chlorophosphines. By performing reductions in situ, direct synthesis of secondary phosphine boranes from Grignard reagents has been achieved without isolation or purification of any intermediates.

Key words: phosphorus, phosphines, phosphine boranes, reductions

Diisobutylaluminium hydride is one of the least expensive reducing agents available due to its widespread application in the polymer industry. We have recently reported the use of DIBAL-H in efficient reductions of secondary phosphine oxides[1] and tertiary phosphine oxides,[2] including detailed experimental procedures for these new methodologies.[3] As part of a general program to expand the use of DIBAL-H in organophosphorus chemistry, we chose to first examine the reactivity of phosphinites. The reduction of phosphinites to secondary phosphines has been previously reported with LAH and AlH_3,[4] though both of these reagents pose significant problems for large-scale use.[1,3] The reduction of phosphinite borane complexes have also been described with lithium naphthalenide and related reductants, though these reagents are not practical for scale-up either.[5]

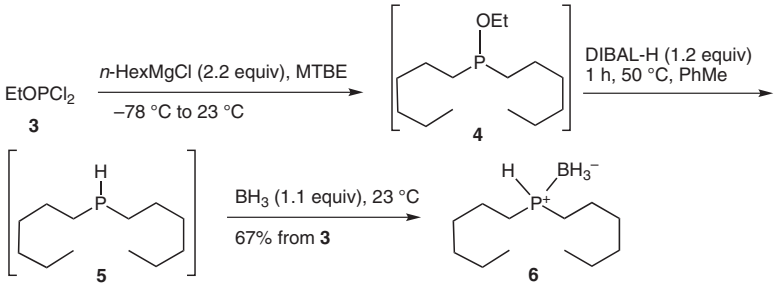
The ^{31}P NMR experiments rapidly established that 2.2 equivalents of DIBAL-H would reduce commercial ethyldiphenylphosphinite quantitatively to diphenylphosphine in one hour at 50 °C in C_6D_6. Addition of 1.1 equivalents of $BH_3{\cdot}SMe_2$ to this solution at ambient temperature led to clean formation of the secondary phosphine borane, and the product was obtained in high yield on gram scale, as shown in Scheme 1.



Scheme 1

We wanted to examine a dialkylphosphinite next. Since none are commercially available, we treated ethyldichloro phosphite in MTBE with 2.2 equivalents of *n*-hexyl Grignard at –78 °C, and warmed to ambient temperature. A thick slurry due to the precipitation of $MgCl_2$ ether complex formed. Attempted standard filtration of this slurry revealed that the intermediate phosphinite **4** (Scheme 2) was not stable in air. We therefore developed a simple in-line filtration to remove these salts while maintaining an inert atmosphere. Vacuum transfer of the reaction slurry through a commercial air-free filter we have previously described[3] into a second flask effectively removed the salts. Toluene was then added to this solution and the ethers removed by vacuum distillation. This furnished a toluene solution of the phosphinite ready for DIBAL-H reduction. Reduction was then carried out in one hour at 50 °C, and the synthesis completed by addition of 1.1 equivalents of BH_3 and overnight aging at ambient temperature. The overall isolated yield of target **6** from **3**, after chromatography, was 67%.

There are several items of note associated with this secondary phosphine borane synthesis. The route is efficient, with >90% average yield per step. In addition, no isolation of air-sensitive intermediates **4** or **5** was made, and only the stable borane complex was handled. Although we



Scheme 2

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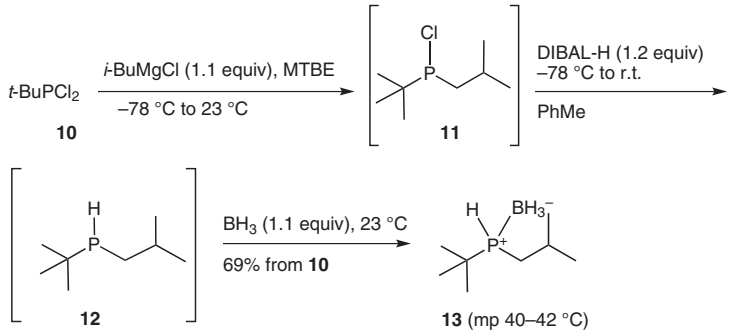
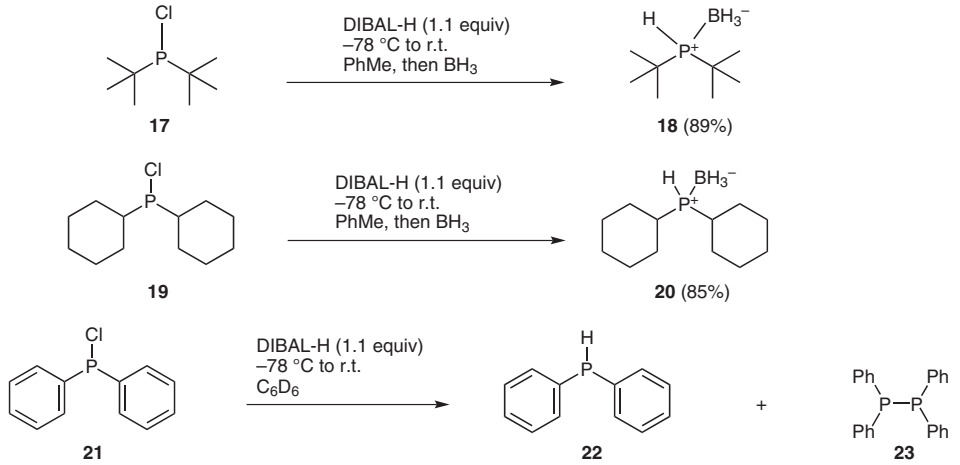


Scheme 3



Scheme 4

found the sequence could be carried out in one pot without removal of the magnesium salts, this led to a very difficult workup following quench with aqueous NaOH.[1] This was caused by the presence of both Mg and Al salts in water. The Mg(II) salts are best solubilized by acid, while aqueous base is essential to the production of aluminum hydroxide from the organoaluminum component.[1,3] Since these two pH values are mutually exclusive, gel formation occurred under basic conditions. In contrast, removal of the Mg salts allows for a smooth quench and extraction under basic conditions. We also observed that the DIBAL-H charge could generally be reduced by one full equivalent when the Mg salts were removed first. This in turn led to a faster quench and easier workup.

Table 1 (entries 2–5) shows the preparation of a series of dialkyl secondary phosphine boranes (**6**–**9**) using the same protocol described here. In the case of the more sterically hindered dicyclohexyl target **9**, 2.2 equivalents of DIBAL-H were required.

We were interested in the preparation of unsymmetrical dialkylphosphine boranes as well, and explored their formation from commercial dichlorophosphines. Scheme 3 shows the synthesis of the novel species *tert*-butyl(isobutyl)phosphine borane **13** from *tert*-$BuPCl_2$ and *i*-BuMgCl. In-line filtration of $MgCl_2$ was performed as described above, and the solvent was switched to toluene. The reduction of the intermediate chlorophosphine was then effected with 1.2 equivalents of reductant from –78 °C to room temperature, followed by in situ borane complex formation as before.[6] A yield of 69% of the crystalline target was achieved for the three-step sequence. Once again, no isolation of the air-sensitive intermediates was performed. The *tert*-butyl(cyclohexyl) analogue **14**, was prepared similarly (Table 1, entries 6 and 7).

Entries 8 and 9 of Table 1 show secondary phosphine boranes **15** and **16** prepared from their respective dichlorophosphines. These mixed aryl/alkyl complexes could be prepared with either order of nucleophile addition.

To gain a deeper understanding of the scope of DIBAL-H reductions of chlorophosphines, three commercial substrates were examined (Scheme 4). The hindered di-*tert*-butyl- and dicyclohexyl-chlorophosphines were cleanly reduced to the desired secondary phosphines, and the phosphine boranes were isolated in good overall yield. For the less hindered Ph_2PCl, however, ^{31}P NMR showed that the desired product was accompanied by a second component. We ultimately determined that this byproduct was the bisphosphine **23**. Presumably, the secondary phosphine product reacted rapidly once formed with the chlorophosphine starting material.[7] We found that these bisphosphine byproducts could also be reduced to the secondary phosphines by DIBAL-H. For the diaryl substrate,

Table 1 Preparation of Secondary Phosphine Boranes

Entry	SM[a]	Product	Product (equiv)[b]	Temp (°C)[c]	Mp (°C)	Yield (%)[d–h]	^{31}P NMR (C_6D_6),[j] δ (ppm)
1	Ph_2POEt	Ph_2PH-BH_3	**2** (2.2)	50	46–47	90[d]	2.13
2	$EtOPCl_2$	*n*-Hex_2PH-BH_3	**6** (1.2)	50	– (oil)	67[f]	–7.04
3	$EtOPCl_2$	*i*-Bu_2PH-BH_3	**7** (1.1)	50	– (waxy)	75[f]	–18.99
4	$EtOPCl_2$	*t*-Bu-MePH-BH_3	**8** (2.2)	50	– (oil)	30[f]	12.95
5	$EtOPCl_2$	*c*-Hex_2PH-BH_3	**9** (2.2)	50	80–81	50[f]	19.20
6	*t*-$BuPCl_2$	*t*-Bu-*i*-BuPH-BH_3	**13** (1.1)	23[i]	40–42	69[e]	17.79
7	*t*-$BuPCl_2$	*t*-Bu-*c*-HexPH-BH_3	**14** (1.1)	23[i]	– (oil)	50[e]	36.73
8	*c*-$HexPCl_2$	*c*-Hex-*m*-xylPH-BH_3	**15** (1.2)	23[i]	– (oil)	60[e]	12.94
9	$PhPCl_2$	Ph-*i*-BuPH-BH_3	**16** (1.1)	23[i]	– (oil)	49[e]	–8.08
10	*t*-Bu_2PCl	*t*-Bu_2PH-BH_3	**18** (1.1)	23[i]	62–63	97[d]	49.15
11	*c*-Hex_2PCl	*c*-Hex_2PH-BH_3	**9** (1.1)	23[i]	80–81	78[d]	19.20
12	Ph_2PCl	Ph_2PH-BH_3	**2** (2.2)	50	46–47	84[d]	2.13
13	PhMeP(O)(OMe)	PhMePH-BH_3	**26** (2.2)	50	– (oil)	80[d]	–14.76
14	Ph-2-NaphP(O)(OEt)	Ph-2-NaphPH-BH_3	**27** (3.2)	50	53–54	63[d]	2.37
15	Ph-(*m*-xyl)P(O)(OEt)	Ph-(*m*-xyl)-PH-BH_3	**28** (2.2)	75	– (oil)	54[d]	2.07
16	Ph-NBNP(O)(OEt)[k]	Ph-NBN-PH-BH_3[k]	**29** (3.5)	90	– (oil)	40[d]	11.06, 7.83[l]

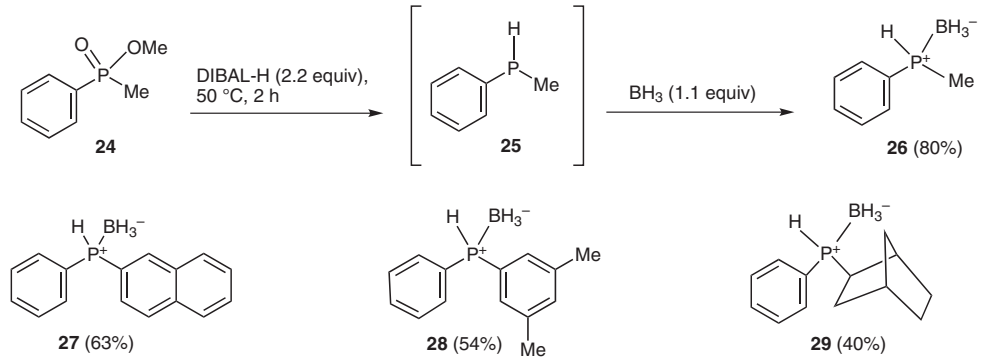
[a] Starting material.
[b] Equiv DIBAL-H.
[c] Reduction temp.
[d] Isolated yield over 2 steps.
[e] Isolated yield over 3 steps.
[f] Isolated yield over 4 steps.
[g] Distilled yield.
[h] Crude yield.
[i] –78 °C to r.t.
[j] Calibrated to 85% H_3PO_4 (0.0 ppm).
[k] NBN = norbornyl.
[l] Mixture of diastereomers; free secondary phosphines: δ = –36.23, –38.12 ppm.

we thus added a Ph_2PCl solution over two hours to 2.2 equivalents of DIBAL-H at 23 °C, and then aged one hour at 50 °C, furnishing the diarylphosphine cleanly. Gram-scale reductions of all three chlorides could thus be efficiently performed, as shown in entries 10–12 of Table 1.

Phosphinates are species readily produced by a number of synthetic methods including the Michaelis–Arbuzov reaction between phosphonites and alkyl halides,[8] radical hydrophosphination of olefins,[9] transition-metal-catalyzed cross-couplings,[10] and alkylation.[11] We began our research with commercial phenylmethyl methylphosphinate (**24**). As with all new substrate classes, we first examined reactivity with ^{31}P NMR, running reactions in septum-capped NMR tubes.[12] In this way we were able to quickly establish key reaction parameters such as reductant stoichiometry, temperature, optimum solvent, and reaction time before any 'true' reactions in flasks were performed.

As depicted in Scheme 5, the phosphinate was cleanly reduced with 2.2 equivalents of DIBAL-H at 50 °C for two hours in C_6D_6. In situ borane complex formation was again achieved with 1.1 equivalents of $BH_3{\cdot}SMe_2$ at ambient temperature. When the reaction was then performed on gram scale in toluene, 80% isolated yield of phenylmethylphosphine borane **26** was achieved following chromatographic purification (Table 1, entry 13). Two unsymmetrical diarylphosphinates were prepared by the known method,[10c] and similarly reduced to furnish novel diaryl phosphine boranes **27** and **28** in good overall yield (entries 14 and 15). Hydrophosphination of norbornene, followed by reduction and complex formation produced novel phenyl-norbornylphosphine borane **29** in similar fashion (entry 16).

In summary, the unique reducing abilities of DIBAL-H towards organophosphorus species have been successfully extended to include phosphinites, phosphinates, and



Scheme 5

chlorophosphines. Efficient and economical procedures to access secondary phosphine boranes have been developed that avoid isolation of all air-sensitive intermediates, giving these important targets in good overall yield.

General Procedure A: Synthesis of Secondary Phosphine Boranes from $EtOPCl_2$ (6)

A four-neck 500 mL flask was equipped with a mechanical stirrer, an addition funnel, a Claisen adapter with thermocouple and inert gas valve, and a Teflon transfer line to an air-free filter atop a second 500 mL flask. To the inerted reactor was then charged in succession through the addition funnel MTBE (50 mL), $EtOPCl_2$ (5.71 mL, 50 mmol, 1.0 equiv), and THF (50 mL). The solution was cooled in a –78 °C bath, then 2 M *n*-hexMgBr in Et_2O (55 mL, 110 mmol, 2.2 equiv) was charged to the addition funnel. At –65 °C, the Grignard was added dropwise over 30 min, then aged 30 min at ca. –78 °C. The slurry was then allowed to warm to 23 °C.

After 1.5 hours at 23 °C, MTBE (50 mL) was added, stirred 10 min, then vacuum was applied to the second flask, drawing the slurry through the airfree filter. The first reactor was then washed with MTBE (2 × 40 mL) to transfer the last of the slurry. The second reactor was then isolated from the first reactor. A clean, dry 1 L 4-neck flask was then installed with mechanical stirrer, short-path distillation head to a receiver flask, addition funnel, and thermocouple. The filtrate in the second reactor was then transferred via cannula under N_2 pressure to the 1 L flask, and then PhMe (50 mL) was added as a wash of the second reactor and transferred via cannula as before. The 1 L flask was then configured for house vacuum (ca. 0.11 bar) distillation by freezing the receiver (–78 °C) and flowing water through the still head. The temperature was raised in steps to 45 °C, collecting all the ethers in the receiver and leaving a toluene solution of the phosphinite in the reactor.

Vacuum was switched to argon and the flask cooled to 23 °C. To the phosphinite solution was then added 1.5 M DIBAL-H in PhMe (40 mL, 60 mmol, 1.2 equiv) via addition funnel over 3 min causing an exotherm to 51 °C. The batch was then heated at 50 °C for 2 h, then cooled to 23 °C. 10 M $BH_3{\cdot}SMe_2$ (6.0 mL, 60 mmol) was then added at once via syringe. The batch was then stirred overnight at ambient temperature.

The mixture was cooled in a –78 °C bath, then quenched by the dropwise addition of 4 N NaOH (45 mL) over 15 min, then warmed to 23 °C. After 1 h at ambient temperature, the mixture was poured into a separatory funnel and allowed to settle, giving a PhMe solution above an aqueous suspension. The aqueous phase was filtered through a Celite pad while agitating with a spatula, and the organic phase was separated and saved. The Celite pad was washed with PhMe (2 × 40 mL) and the filtrate was transferred to a separatory funnel and the phases separated. All organics were combined, washed with half-saturated NaCl (1 × 100 mL), dried ($MgSO_4$), and concentrated on the rotary evaporator to ca. 15 mL final volume (do NOT concentrate to dryness[2]). This solution was then filtered in 5 min through a short silica gel column, eluting with MTBE (150 mL). The eluent was stripped in vacuo to give a colorless oil. The oil was then chromatographed on SiO_2 eluting with hexane–EtOAc (20:1) and staining with $KMnO_4$ to give, after drying under high vacuum, 7.21 g of **6** (67% over 4 steps) as a colorless oil.

General Procedure B: Synthesis of Secondary Phosphine Boranes from Phosphinates (27)

Part 1. A three-neck 500 mL flask was charged with $PdCl_2$(dppf) (1.013 g, 1.24 mmol, 0.03 equiv), 2-bromonaphthalene (8.28 g, 40.0 mmol, 1 equiv), and ethylphenylphosphinate (6.03 mL, 40.0 mmol, 1 equiv). The flask was evacuated/Ar filled (3×), then MeCN (160 mL) and Et_3N (11.19 mL, 80.0 mmol, 2 equiv) were added via syringe in the order given. The resulting mixture was then placed in a pre-equilibrated 65 °C oil bath under Ar. After 16 h, the mixture was cooled to ambient temperature, diluted with EtOAc (200 mL), and then filtered to remove $Et_3N{\cdot}HBr$. The filtrate was concentrated in vacuo, and the residue chromatographed on SiO_2 eluting with hexane–EtOAc (1:1) to give, after drying under high vacuum, 9.40 g of the phenyl-2-naphthyl phosphinate (79%) as a viscous, yellow oil. ^{31}P NMR (202 MHz, C_6D_6): δ = 29.38 ppm.

Part 2. A three-neck 100 mL flask with an addition funnel was charged with the phenyl-2-naphthyl phosphinate (2.4 g, 8.1 mmol, 1 equiv) described above, then evacuated/Ar filled (2×), then PhMe (15 mL) was added via syringe. 1.5 M DIBAL-H in PhMe (17.8 mL, 26.7 mmol, 3.3 equiv) was then added via addition funnel over ca. 5 min, causing an orange mixture to form. The flask was then placed in a pre-equilibrated 50 °C oil bath under Ar. After 6 h, an aliquot was transferred to a screw-cap NMR tube containing C_6D_6. To this NMR tube was then cautiously added *N*,*N*-dimethylaminoethanol (ca. 0.1 mL) as a quench. ^{31}P NMR showed nearly pure secondary phosphine at δ = –27 ppm. 10 M $BH_3{\cdot}SMe_2$ (1.2 mL, 12 mmol, 1.5 equiv) was then added at once to the reactor via syringe, and the mixture allowed to stir overnight at r.t.

The reaction mixture was cooled to –78 °C, then 4 N NaOH (14 mL) was added cautiously via the addition funnel. The cold bath was then removed and the mixture allowed to warm to r.t., and stirred 1 h at r.t. The mixture was then poured into a separatory funnel, giving a clear organic phase on top of an aqueous suspension. The upper organic phase was separated and saved, while the lower aqeuous phase was filtered through a Celite pad, washing the pad with PhMe (2 × 20 mL). All organics were combined, washed with half-saturated NaCl (2 × 25 mL), and then dried over $MgSO_4$. The PhMe solution was then concentrated on the rotary evaporator to ca. 20 mL (do NOT concentrate to dryness[2]), then filtered by gravity through a short column of SiO_2 in a fritted funnel, eluting with ad-

ditional PhMe (ca. 50 mL). The eluents were then concentrated in vacuo to give a yellow oil which was azeotroped with heptane on the rotary evaporator and finally dried under high vacuum on the rotary evaporator to give 1.25 g of pure **27** (63%) as a colorless oil which crystallized on standing; mp 53–54 °C.

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