Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5213–5216

TETRAHEDRON LETTERS

Mild reduction of chlorophosphine boranes to secondary phosphine boranes

Hubert Lam,[a] David J. Aldous[b] and King Kuok (Mimi) Hii[a,*]

[a]*Department of Chemistry, King's College London, Strand WC2R 2LS, UK*
[b]*Aventis Pharmaceuticals, Route 202-206, Bridgewater, NJ 08807, USA*

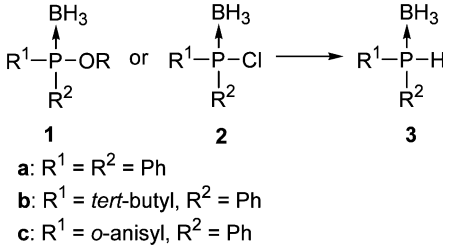
Received 26 March 2003; revised 9 May 2003; accepted 19 May 2003

Abstract—A number of reducing reagents were assessed in the transformation of chlorophosphine boranes to secondary phosphine boranes. The efficiency of the process requires judicious matching between steric and electronic requirements of reductant and the substrate. The stereochemistry of the reduction was investigated by using a chiral precursor.

Secondary phosphine boranes ($R_2PH{\cdot}BH_3$) are important precursors for the preparation of tertiary phosphines. They may be deprotonated to provide a source of phosphide-borane anions for electrophilic substitutions.[1] An elegant synthesis of enantiomerically pure *P*-chiral phosphine boranes was reported by Livinghouse et al., whereby racemic lithiated *tert*-butylphenylphosphine borane was subjected to a dynamic resolution process in the presence of alkylating reagents.[2] Alternatively, $R_2PH{\cdot}BH_3$ may be subjected to electrophilic arylation reactions with aryl iodides (under palladium catalysis).[3] Optically active phosphine borane precursors undergo such processes with excellent stereocontrol, and have been subsequently used for the preparation of a number of *P*-chirogenic phosphines.[4,5]

Despite burgeoning interests in these compounds, general procedures for the preparation of secondary phosphine boranes **3** are relatively unexplored. During the course of our studies on the synthesis and catalytic activities of aminophosphine ligands,[6] we required a general procedure for accessing these precursors, either by the reduction of **1**, or chlorophosphine boranes **2** (Scheme 1).

The reduction of phosphinite boranes **1** is usually achieved by cleavage of the P–O bond using single electron reductants such as lithium naphthalenide, di-*tert*-butyl biphenylide (LDBB), or NH_3, followed by reaction with a protic solvent.[1,2] Reduction of **1** by metal hydrides such as $NaBH_4$ and $LiAlH_4$ were reported to proceed sluggishly.[3] We have found that DIBAL-H was also ineffective in the reduction of diphenylphosphinite borane (**1a**, R = Me), affording only 2% conversion in 4 h.



Scheme 1. Reduction of phosphinite boranes **1** or chlorophosphine boranes **2**.

In comparison, chlorophosphine boranes **2** are generally more accessible from commercially available chlorophosphines. However, as far as we are aware, there were no reported procedures of their direct transformation to secondary phosphine boranes.

In this paper, we report the reduction of **2** by various reducing agents. Diphenylphosphine borane **2a** was chosen as the substrate in our initial investigation. The progress of the reactions may be easily monitored using ^{31}P NMR spectroscopy, by comparing relative intensities of the resonance peaks due to product **3a** (δ 2 ppm) and the starting material (δ 105 ppm) (Table 1).

* Corresponding author. Tel.: +44-20-7848-1183; fax: +44-20-78482810; e-mail: mimi.hii@kcl.ac.uk

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01225-5

Table 1. Reduction of **2a** to **3a**

Entry	Reagent	T (°C)	t (h)	%Conversion[a]
1	Li/NH_3	−20	4	0
2	$NaBH(OAc)_3$	rt	24	0
3	Red-Al®	−40	2.5	[c]
4	L-Selectride®	−40	2.5	[d]
5	DIBAL-H	−40	1	>95
6	$LiAlH_4$	−40	<2.5[b]	>95
7	$LiBH_4$	−40	2[b]	>95
8	$^nBu_4NBH_4$	−40	2.5[b]	>95
9	$NaBH_4$ (THF)	−40	17	>95
10	$NaBH_4/CeCl_3$	rt	36	0

[a] Monitored by ^{31}P NMR. As the peaks were broad, a ±5% error was allowed in the calculation of conversion values.
[b] Unoptimised.
[c] A complex mixture of products was obtained.
[d] A single resonance peak at −14.5 ppm was observed.

Rather surprisingly, we found that Li/NH_3 was ineffective for the reduction of $Ph_2PCl{\cdot}BH_3$ **2a** (Table 1, entry 1). No reaction was detectable by ^{31}P NMR, even after 4 h at −20°C. In contrast, metal hydrides were found to be very potent reducing agents. A selection of these was subsequently examined for this transformation (Table 1).

Sodium triacetoxyborohydride was the only hydride reducing agent that gave no detectable conversion in this study (entry 2). Use of sodium bis-(2-methoxyethoxy)aluminium hydride (Red-Al®) led to a complex mixture of products (entry 3). Amongst the ^{31}P resonances observed were signals attributed to oxidised adducts ($\geq\delta$ 30 ppm) and diphenylphosphine (δ −40 ppm), suggesting dissociation of borane from the product. On the other hand, lithium tri-*sec*-butylborohydride (L-Selectride®) gave an unexpected product with a sharp resonance peak at −14.5 ppm (entry 4), reminiscent of a tertiary phosphine species. These observations led us to postulate that competing alkoxy and alkyl transfer processes occurred using these anionic aluminohydride and borohydride reagents.

Indeed, using the less nucleophilic DIBAL-H, the hydride moiety was selectively delivered with no formation of any side products (entry 5). Subsequent workup of this reaction afforded diphenylphosphine borane **3a** in 90% isolated yield.

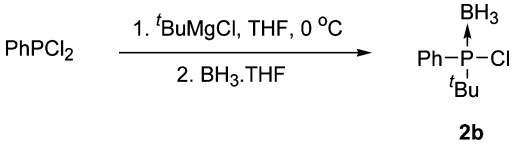
All other MH_4^- metal hydrides (where M = B or Al) afforded clean conversions to the expected product (entries 6–9). A significant counterion effect was observed using the lithium, tetra-*n*-butyl ammonium and sodium salts of borohydride in THF—the last being the least reactive (entries 7–9). Interestingly, the reactivity of $NaBH_4$ was totally inhibited in the presence of $CeCl_3$ (entry 10).

Chloro-*tert*-butylphenylphosphine borane **2b**, the chosen substrate in the next part of our study, was prepared by successive addition of equimolar equivalents of *tert*-butylmagnesium chloride and $BH_3{\cdot}THF$ to dichlorophenylphosphine (Scheme 2).[7]

The successful hydride reducing agents identified above were used in this part of the study (Table 2). With the sterically demanding substrate **2b**, interesting differences in reactivity started to emerge.

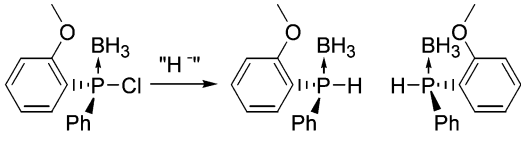
Perhaps unsurprisingly, the reaction with the bulkier reductant DIBAL-H was considerably slower (entry 1). Lithium triethylborohydride (Super Hydride®) was also slow, but gave a good conversion to the product after 14 h (entry 2)—in contrast with the previous system, no alkyl transfer from the anionic alkylborohydride occurred on this occasion. The aluminohydride reagents showed higher reactivity than their borohydride counterparts. Reduction using lithium aluminium hydride was quickest, even at −78°C (entries 3 and 4), furnishing the product **3b** in high yields. A counterion effect was again observable with the borohydrides (entries 5, 6 and 7). The lithium salt was considerably less reactive than the tetra-*n*-butyl ammonium salt, whereas sodium borohydride was completely inactive in the reduction, unless it was activated by using a protic solvent (entries 7 and 8).

In all the reactions where reduction occurred, clean conversions to **3b** were observed (Fig. 1). The product could be obtained, typically in 75% yield, following workup of the reaction mixtures.[8]



2b

Scheme 2. Preparation of **2b**.



(*R*)-**2c** (*R*)-**3c** (*S*)-**3c**

Scheme 3. Reduction of (*R*)-**2c**.

Table 2. Reduction of **2b** to **3b**

Entry	Reagent	T (°C)	t (h)	%Conversion[a]
1	DIBAL-H	−40[b]	48	60
2	Super Hydride®	−20	14	>95
3	$LiAlH_4$	−78	1	>95
4	$LiAlH_4/CeCl_3$	−78	1	>95
5	$LiBH_4$	rt[b]	48	>95
6	$^nBu_4NBH_4$	rt[b]	16	>95
7	$NaBH_4$ (THF)	rt	48	0
8	$NaBH_4$ (EtOH)	−20	48	>95

[a] Monitored by ^{31}P NMR, as before.
[b] Kept at −40°C for 7 h (little/no reaction), then at rt.

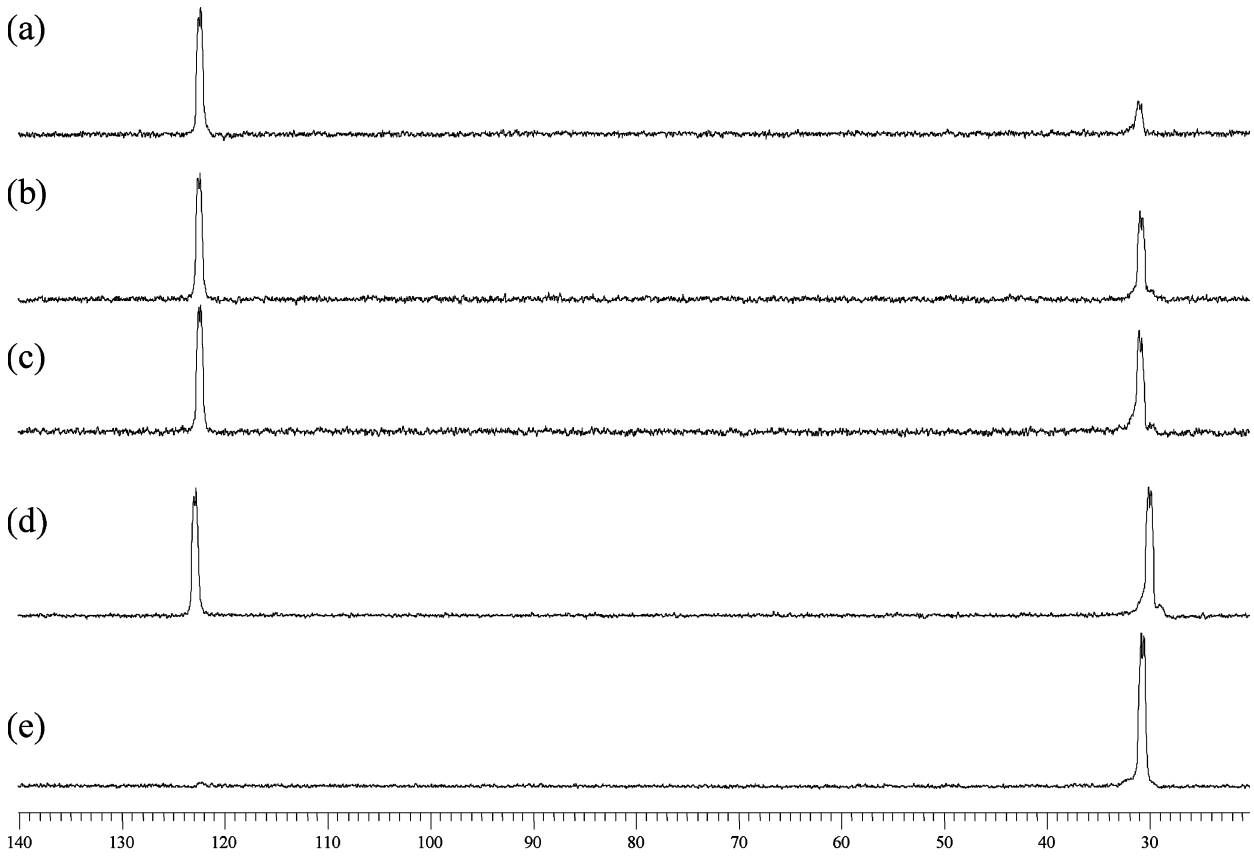


Figure 1. Progress of the reduction of **2b** (δ 123 ppm) to **2c** (δ 31 ppm) using $^{n}Bu_4NBH_4$, monitored by ^{31}P NMR spectroscopy at (a) 1 h, (b) 3 h, (c) 4 h, (d) 6 h and (e) 16 h.

The stereoselectivity of these reductions was investigated by employing the optically pure substrate (*R*)-chloro-*ortho*-anisylphenylphosphine borane (*R*)-**2c** (Scheme 3).[9]

The reductants previously used were once again evaluated (Table 3). The reactions were facile and clean. Optical purity of the product **3c** was determined by chiral HPLC,[10] corroborated by comparison of the measured optical rotation with reported literature values.[3a]

With the exception of tetra-*n*-butyl ammonium borohydride (entry 6), most of the conversions were facile at low temperature and were complete within 2 h. However, the reductions appear to be unselective—the optical purity of the product was found to be disappointingly low, with ee's of no more than 27% (racemisation of the product was ruled out as the product is configurationally stable for at least 3 months).

In the majority of the cases (entries 1–5), an overall inversion of configuration was observed, i.e. the major isomer had the *S*-configuration. However, with the least active reducing agent $^{n}Bu_4NBH_4$, a curious retention of the *R*-configuration was observed (entry 6). This is especially surprising as its corresponding alkali metal salts afforded the inversion products (entries 4 and 5). The reason for this anomaly is unclear at this stage, although we speculate that the presence of the *ortho*-anisyl group may be responsible for the low stereoselectivity by stabilising competitive reactive intermediates.

Table 3. Reduction of optically active (*R*)-**2c**

Entry	Reagent	T (°C)	t (h)	% conversion[a]	*S*:*R*[b]
1	$LiAlH_4$	−78	1	>95 (50)	58:42
2	$LiAlH_4/CeCl_3$	−78	1	>95 (52)	63:37
3	DIBAL-H	−40	2	>95 (63)	60:40
4	$NaBH_4$	−40	2	>95 (62)	56:44
5	$LiBH_4$	−40	2	>95 (42)	63.5:36.5
6	$^{n}Bu_4NBH_4$	−40	4	>95 (65)	45:55

[a] Determined by ^{31}P NMR (as before). Values in parentheses correspond to isolated yields.
[b] Determined by chiral HPLC (see discussion).

In this study, we examined the suitability of several commercially available hydride reducing agents for the transformation of chlorophosphine boranes to secondary phosphine boranes. These reductions are sensitive to steric and electronic environments in the reagent and substrate. We believe that this procedure represents a clean, convenient route to the preparation of racemic/achiral secondary phosphine boranes from commercially available and/or easily accessible chlorophosphines. Very mild reducing agents such as borohydrides and DIBAL-H may be employed to afford the products in moderate to good yields. By avoiding the use of powerful reducing reagents, this method should provide an alternative route to the synthesis of many secondary phosphine boranes, which may contain functional groups that are not compatible with current methodologies.

Acknowledgements

We thank King's College London and Aventis Pharmaceuticals for a studentship and other support.

References

1. (a) Imamoto, T. *J. Syn. Org. Chem. Jpn.* **1993**, *51*, 223–231; (b) Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *180*, 665–698.
2. Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116–5117.
3. (a) Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroatom. Chem.* **1992**, *3*, 563–574; (b) Oshiki, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975–3977.
4. Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776–4778.
5. (a) Gaumont, A. C.; Hursthouse, M. B.; Coles, S. J.; Brown, J. M. *Chem. Commun.* **1999**, 63–64; (b) Moncarz, J. R.; Brunker, T. J.; Glueck, D. S.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 1180–1181.
6. (a) Hii, K. K.; Thornton-Pett, M.; Jutand, A.; Tooze, R. P. *Organometallics* **1999**, *18*, 1887–1896; (b) Qadir, M.; Möchel, T.; Hii, K. K. *Tetrahedron* **2000**, *56*, 7975–7979; (c) Rahman, M. S.; Steed, J. W.; Hii, K. K. *Synthesis* **2000**, 1320–1326; (d) Lam, H.; Cheng, X.; Steed, J. W.; Aldous, D. J.; Hii, K. K. *Tetrahedron Lett.* **2002**, *43*, 5875–5877; (e) Rahman, M. S.; Prince, P. D.; Steed, J. W.; Hii, K. K. *Organometallics* **2002**, *21*, 4927–4933.
7. *tert*-Butyl magnesium chloride (16.8 mL, 2.0 M in ether, 33.5 mmol) was added dropwise over 10 min at −78°C to a solution of dichlorophenylphosphine (4.55 mL, 33.5 mmol) in dry THF (30 mL). The reaction mixture was stirred for 1 h, before it was warmed up to room temperature. BH_3·THF complex (1.5 M in ether, 33 mL, 45.5 mmol) was added and stirring was continued for 2 h. The suspension was carefully filtered via cannula and the filtrate was evaporated under reduced pressure to afford a colourless oil, which was used in subsequent reductions without further purification.
8. **General procedure for reduction**: Chloro *tert*-butyl phenylphosphine borane **2b** (500 mg, 2.1 mmol) was added via a syringe over 10 min to a cooled suspension (–40°C) of the reducing agent (4.2 mmol, 2.1 equiv.) in 3 mL of THF under argon. The reaction mixture was stirred at this temperature for 3–36 h. The reduction was followed by ^{31}P NMR by extraction of aliquots of the reaction mixture every 3 h. The product (*rac*)-*tert*-butylphenylphosphine borane **3b** was isolated as a colourless oil after an acidic work up (285 mg, 75%). ^1H NMR (500 MHz): 0.58–1.35 (m, 3H, BH_3), 1.19 (d, 9H, $J_{PH}=16.2$ Hz, CH_3), 6.20 (dq, 1H, $J_{BH}=6.8$ Hz, $J_{PH}=379$ Hz, P–H), 7.39–7.51 (m, 5H); ^{31}P NMR (167 MHz): 2.38–2.77 ($J_{PB}=57$ Hz); ^{13}C NMR (90.5 MHz): 26.9 (d, CH_3, $J_{PC}=3$ Hz); 28.8 (d, CMe_3, $J_{PC}=32$ Hz); 129.0–134.4 (C_{Ar}).
9. Kaloun, E. B.; Merdès, R.; Genêt, J.-P.; Uziel, J.; Jugé, S. *J. Organomet. Chem.* **1997**, *529*, 455–463.
10. Daicel OD-H column, hexane/2-propanol, 98/2, 1 mL min^{-1}: $t_R=10$ min, $t_S=11.3$ min.