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A Convenient Synthetic Protocol to 1,2-Bis(dialkylphosphino)-ethanes

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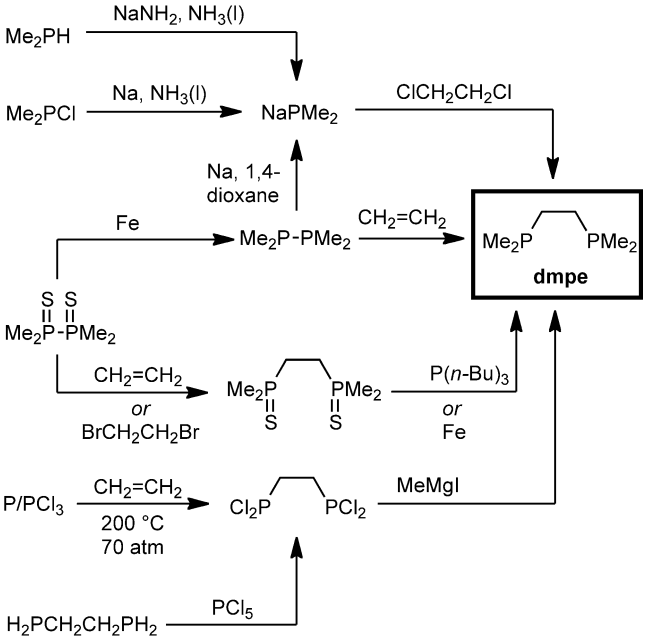
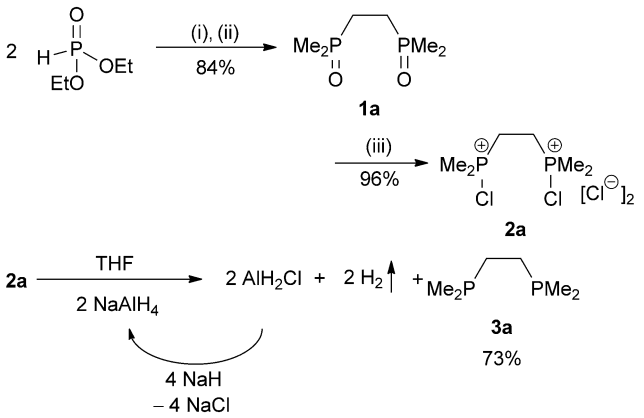
Abstract: 1,2-Bis(dialkylphosphino)ethanes are readily prepared from the parent phosphine oxides, *via* a novel sodium aluminium hydride/sodium hydride reduction protocol of intermediate chlorophosphonium chlorides. This approach is amenable to multi-gram syntheses, utilises readily available and inexpensive reagents, and benefits from a facile non-aqueous work-up in the final reductive step.

Keywords: aluminium; hydrides; phosphane ligands; reduction; synthetic methods

Organophosphines (R_3P) are prime candidates for use as ancillary ligands in many transition metal-catalysed transformations, and are arguably the most important class of ligator in organometallic chemistry.[1] Substitution at the phosphorus atom has a considerable effect on the electronic and steric influence of the ligand over the metal centre, which enables fine tuning of catalyst reactivity and stability.[2] Alkylphosphines are more electron-donating than their arylphosphine counterparts and therefore more effective in promoting key oxidative addition steps common to catalytic cycles (e.g., alkene hydrogenation, hydroformylation).[3] In particular, 1,2-bis(dialkylphosphino)-ethanes ($R_2PCH_2CH_2PR_2$) have found myriad applications in a number of important transformations as electron-rich chelating ligands. These include heterolytic H_2 activation (Co, Rh, Group 10 triad),[4] C–H bond activation (Pt),[5] CO_2 reduction (Fe, Ni),[6] N_2 fixation (Fe, Mo),[7] and have facilitated the isolation of structurally interesting molecules incorporating ligand C–H agostic interactions (Ti)[8] and recently a σ-alkane complex (Rh).[9] Despite their utility, the syntheses of these simple yet versatile ligands can be lengthy and involve dangerous (highly toxic and pyrophoric) or costly reagents; subsequently, related arylphosphine ligands that are far less air-sensitive and more readily prepared have hitherto been utilised to a greater extent. The difficulty in preparing alkyl bisphosphines is conveniently illustrated by the synthetic protocols reported for 1,2-bis(dimethylphosphi-



Scheme 1. Previous synthetic routes to $Me_2PCH_2CH_2PMe_2$ (dmpe; **3a**).



Scheme 2. Synthesis of $Me_2PCH_2CH_2PMe_2$ (dmpe; **3a**): (i) 6 equiv. MeMgCl/THF; (ii) 0.5 equiv. $ClCH_2CH_2Cl$, reflux then K_2CO_3(aq.); (iii) 2.1 equiv. $(COCl)_2/CH_2Cl_2$.

no)ethane ($Me_2PCH_2CH_2PMe_2$, dmpe; Scheme 1). Generation of a phosphide precursor involves either $NaNH_2/NH_{3(l)}$ deprotonation of pyrophoric Me_2PH (from PH_3),[10] or Na reduction of $Me_2PCl/Me_2P{-}PMe_2$.[11] Other modifications have utilised $Me_2P(S){-}P(S)Me_2$,[12,13] a precursor to $Me_2P{-}PMe_2$, which is prepared *via* a dangerous reaction of MeMgI with $P(=S)Cl_3$, that has in one case led to a severe accident.[14] Alkylation of $Cl_2PCH_2CH_2PCl_2$ affords $R_2PCH_2CH_2PR_2$ species in moderate yields, yet synthesis of the precursor requires specialised autoclave apparatus ($P/PCl_3/CH_2{=}CH_2$; 200 °C, 70 atm)[15] or chlorination of highly pyrophoric $H_2PCH_2CH_2PH_2$.[16] Whilst $Cl_2PCH_2CH_2PCl_2$ is commercially available, its expense limits large-scale syntheses of $R_2PCH_2CH_2PR_2$.

We required multi-gram quantities of dmpe (and related alkylphosphines), and envisioned a route *via* reduction of the bisphosphine oxide $Me_2P(=O)CH_2CH_2P(=O)Me_2$ (**3a**, Scheme 2). However, common strategies used for the deoxygenation of phosphine oxides [for example, electrophilic aluminium hydrides,[17] hydrosilanes][18] require aqueous work-ups that can result in considerable by-product waste, separation and purification issues on scale-up, and accordingly we wished to devise a novel reduction strategy which would avoid an aqueous work-up in the final step.

$(n\text{-Bu})_2P(=O)CH_2CH_2P(=O)(n\text{-Bu})_2$ has previously been prepared from the condensation of $(n\text{-Bu})_2P(=O)H$ with XCH_2CH_2X (X = Cl, Br) using concentrated $KOH_{(aq)}$ in DMSO.[19] Hays et al. documented the synthesis of secondary phosphine oxides [$R_2P(=O)H$; R = Me, Et][20] from the reaction of RMgCl and inexpensive diethyl phosphite [$HP(=O)(OEt)_2$], postulating formation of a solution-phase active intermediate of the form [$R_2P(=O)MgCl$]. This species also acts as a P-centred nucleophilic synthon $[R_2P(=O)]^-$ in $R_2P(=O){-}C$ bond formation, yet very few examples of directly producing tertiary phosphine oxides using this method have been documented.[21]

In order to avoid the prior synthesis of $Me_2P(=O)H$, we reacted MeMgCl and $HP(=O)(OEt)_2$ (3:1) in THF, which led to evolution of CH_4 and proposed formation of [$Me_2P(=O)MgCl$]. Electrophilic trapping of the latter *in situ* with 1,2-dichloroethane and subsequent $K_2CO_{3(aq)}$ work-up afforded the target $Me_2P(=O)CH_2CH_2P(=O)Me_2$ (**1a**) in excellent yield (Scheme 2). Hence the entire carbon-phosphorus skeleton of the target phosphine can be assembled in a one-pot protocol.

Direct deoxygenation of **1a** was attempted using a variety of standard protocols: $LiAlH_4$ and MeOTf/MeI/Me_3SiCl,[22] DIBAL-H,[23] AlH_3,[24] $Ti(O\text{-}i\text{-}Pr)_4$ and PMHS,[25] $Cu(OTf)_2$ and TMDS;[18i] in each case poor conversions (< 10%) and product separation difficulties were encountered. This latter effect is attributed to the strongly electron-donating character of the chelating alkylphosphine. Rajendran and Gilheany recently reduced a variety of phosphorus(V) oxides to their corresponding phosphorus(III) boranes using $NaBH_4$, *via* their chlorophosphonium(V) chlorides.[26] Accordingly, reaction of **1a** with $(COCl)_2$ in CH_2Cl_2 rapidly affords [$Me_2P(Cl)CH_2CH_2P(Cl)Me_2$] $[Cl]_2$ (**2a**) as a poorly soluble moisture-sensitive solid, in almost quantitative yield (Scheme 2). Whilst the $NaBH_4$ reduction of **2a** reaction did cleanly form $(dmpe)\cdot(BH_3)_2$ (^{31}P NMR: $\delta = 8.52$ ppm; THF), dissociation of this strong adduct could neither be achieved by heating in vacuum (150 °C, 10^{-3} mbar), nor using DABCO deprotection.[27] Other methods for deboronation of electron-rich phosphines using strong acids (e.g., $HBF_4\cdot OMe_2$, CF_3SO_3H) and subsequent alkaline hydrolysis[28] were deemed incommensurate with the goals of our synthetic methodology.

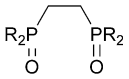
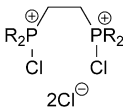
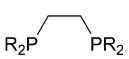
Recognising that the soft-soft interaction between BH_3 and a tertiary alkylphosphine might be too strong to permit isolation of our target phosphines, our attention turned to the use of $NaAlH_4$ whereby the harder AlH_3 by-product should lead to weaker donor-acceptor adducts. Gratifyingly, an NMR-scale reaction of **2a** with $NaAlH_4$ in THF afforded uncoordinated dmpe (**3a**) in quantitative yield (calibrated PPh_3 insert), as ascertained by the strongly shielded ^{31}P NMR resonance ($\delta = -48.3$ ppm). 2 equivalents of $NaAlH_4$ are necessary to effect full conversion of **2a** to **3a** as judged by the disappearance of AlH_4^- (^{27}Al NMR: $\delta = 98.7$ ppm, quintet, $^1J_{Al,H} = 174$ Hz) in solution, thus implying that AlH_2Cl is the end-product after hydride transfer under this stoichiometry. Although **3a** is hydrocarbon-soluble, it could not be isolated from NaCl and $AlH_2Cl\cdot$THF by pentane extraction of the residue obtained upon removal of THF solvent. However, upon re-addition of THF to the solids, free **3a** was again observed by ^{31}P NMR spectroscopy. Thus, it appears that the Lewis acidic

AlH_2Cl preferentially binds the harder O-donor THF when it is in excess, but upon solvent removal it binds the softer phosphine, rendering it a hydrocarbon-insoluble strongly bound adduct that inhibits mechanical separation.

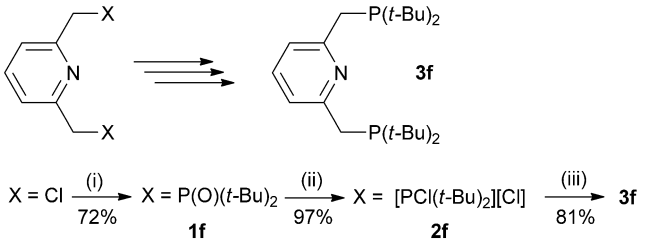
In order to solve this predicament, we adapted the known reaction of $AlCl_3$ and MH (M = Li, Na, K) to form MCl and $MAlH_4$ salts,[29] recognising that incipiently formed AlH_2Cl or AlH_3 could regenerate AlH_4^-, thus blocking Al Lewis acids from binding **3a**. Satisfyingly, addition of activated NaH[30a,b] to the reaction mixture of **3a** formed from $2\,NaAlH_4$/**2a** resulted in immediate appearance of the AlH_4^- resonance in the ^{27}Al NMR spectrum, demonstrating that regeneration of $NaAlH_4$ by NaH is facile under these conditions. Additionally, **2a** could be reacted on a 5–20-gram scale with $NaAlH_4$/activated NaH (1:2:4 ratio) to afford **3a** in high yield (Scheme 2), which was purified by vacuum distillation. Work-up is facile and consists of simple filtration from NaCl, pentane extraction, and removal of volatiles. $NaAlH_4$ was used in place of $LiAlH_4$ since it is considerably less hazardous[31] due to its greater thermal stability and furthermore, the poorly soluble NaCl by-product precipitates from THF solution, thus simplifying the extraction process. Advantageously, $NaAlH_4$ was readily recovered in near quantitative yield (>95%), and could be used in further reactions with no impaired reactivity.[32]

In order to test the scope of our reaction sequence, we synthesised the corresponding $R_2P(=O)CH_2CH_2P(=O)R_2$ (**1b–e**) from RMgCl (R = Et, *i*-Pr, *i*-Bu) or RLi (R = *t*-Bu),[33] and reduced them to $R_2PCH_2CH_2PR_2$ (**3b–e**) *via* **2b–e** respectively; comparable yields are obtained in each case (Table 1). Particularly noteworthy is that all reactions scale-up linearly with no ensuing complications, even for sterically bulky substrates (R = *i*-Pr, *t*-Bu), and the syntheses have frequently been performed on a 5-30-gram manipulation.

Table 1. ^{31}P NMR spectral data and yields for compounds.

Compound		R	^{31}P (δ [ppm])[a]	Yield [%][c]
	**1a**	Me	42.05	84
	1b	Et	51.21	78
	1c	*i*-Pr	56.07	76
	1d	*i*-Bu	46.43	92
	1e	*t*-Bu	60.09	85
	**2a**	Me	–[b]	96
	2b	Et	107.21	97
	2c	*i*-Pr	114.47	94
	2d	*i*-Bu	99.03	96
	2e	*t*-Bu	120.01	96
	**3a**	Me	−48.79	73
	3b	Et	−18.77	84
	3c	*i*-Pr	9.12	85
	3d	*i*-Bu	−35.96	73
	3e	*t*-Bu	35.72	85

[a] NMR spectra for compounds **1a–e**, **2b–e** were recorded in $CDCl_3$; those of **3a–e** were recorded in C_6D_6.
[b] Compound insoluble in all common solvents attempted.
[c] Purified yields (distillation/sublimation).



Scheme 3. Novel synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)pyridine (**3f**); (i) 6 equiv. *t*-BuLi/Et_2O/2 equiv. $HP(=O)(OEt)_2$; (ii) excess $(COCl)_2/CH_2Cl_2$; (iii) 2 equiv. $NaAlH_4$/4 equiv. NaH/THF.

Subsequently we sought to investigate the possibility of extending the protocol to bisphosphines with greater functionality. The tridentate 'pincer' ligand 1,2-bis(di-*tert*-butylphosphinomethyl)pyridine (**3f**) has shown itself to be a strongly electron-donating framework which forms structurally interesting and catalytically active complexes with an extensive range of transition metals.[34] Pyridine **3f** is currently prepared from expensive $HP(t\text{-}Bu)_2$ or $ClP(t\text{-}Bu)_2$ using the methods of Kawatsura and Hartwig[34a] or Milstein.[34c] In view of the ability of $LiAlH_4$ to attack pyridine and form lithium tetrakis(*N*-dihydropyridyl)aluminate isomers,[34] we thought that **3f** would be a viable target to test the selectivity of our reductive step. Gratifyingly, 2,6-bis(chloromethyl)pyridine was phosphorylated with the $[(t\text{-}Bu)_2P(=O)Li]$ reagent to provide 1,2-bis(di-*tert*-butylphosphinomethyl)pyridine *P,P′*-dioxide (**1f**; 72% yield from diethyl phosphite), which was successfully converted (*via* **2f**) to **3f** in 79% yield on a multi-gram scale (Scheme 3).

In conclusion, we have developed a new, high yielding and facile synthetic route to 1,2-bis(dialkylphosphino)ethanes which uses inexpensive reagents,[35] mild conditions, and demonstrates versatility for modulation of the alkyl groups and ligand backbone. Advantageously, the phosphine oxide and chlorophosphonium chloride precursors are readily handled solids, and amenable to large-scale syntheses. The novel $NaAlH_4$/NaH reductive protocol is highly economical, and avoids issues encountered with other common reduction methods (boranes and silanes), for a convenient extraction process that obviates the need for an aqueous work-up. We anticipate the improved availability of these desirable alkylated bisphosphines will stimulate an enhanced interest in the study of their diverse and effectual coordination

chemistry, which can be extended to other substrates incorporating dialkylphosphine moieties.

Experimental Section

General Remarks

All chemical manipulations were performed under an N_2 atmosphere either using standard Schlenk-line techniques or in a MBraun Labmaster DP glovebox, unless stated otherwise; in particular, the phosphine compounds **3a–f** are highly oxygen sensitive. Solvents were purchased from VWR: pentane and CH_2Cl_2 were dried using an Innovative Technology Pure Solv SPS-400; THF and Et_2O were distilled from purple Na/benzophenone indicator. Solvents were degassed by thorough sparging with N_2 gas followed by storage in gas-tight ampoules over suitable drying agents: CH_2Cl_2 (4 Å molecular sieves); pentane, Et_2O (K mirror). Deuterated solvents were freeze-thaw degassed, dried, and stored under N_2 in gas-tight ampoules: C_6D_6 (Sigma–Aldrich, 99.6% D; K mirror); $CDCl_3$ (Merck, 99.8% D; 4 Å molecular sieves). Diethyl phosphite (Sigma–Aldrich, 98%) and 1,2-dichloroethane (Sigma–Aldrich, ≥99.0%) were degassed by thorough sparging with N_2 and stored over 4 Å molecular sieves. Oxalyl chloride (Sigma–Aldrich, 98%), $NaAlH_4$ (Sigma–Aldrich, hydrogen-storage grade) and NaH (60 wt% dispersion in oil) were used as supplied. MeMgCl (3.0 M in THF), EtMgCl (2.0 M in THF), (*i*-Pr)MgCl (2.0 M in THF), (*i*-Bu)MgCl (2.0 M in THF), and *t*-BuLi (1.7 M in pentane) were purchased from Sigma–Aldrich and freshly titrated against *sec*-butanol/1,10-phenanthroline indicator prior to use. 2,6-Bis(chloromethyl)pyridine was prepared according to a literature procedure.[36]

NMR, HR-MS, IR and elemental analysis data for the compounds are presented in the Supporting Information. NMR spectra were recorded using Bruker AV-400 (400 MHz) spectrometers. Chemical shifts, δ, are reported in parts per million (ppm). ^1H and $^{13}C\{^1H\}$ chemical shifts are given relative to Me_4Si and referenced internally to the residual proton shift of the deuterated solvent employed. ^{27}Al and $^{31}P\{^1H\}$ NMR chemical shifts were referenced ($\delta = 0$) externally to 1 M $AlCl_3$ (aq.) and 85% H_3PO_4 (aq.). Air or moisture sensitive samples were prepared inside the glovebox using NMR tubes fitted with J. Young valves. High resolution mass spectrometry samples (HR-MS; EI and ESI) were recorded using either a Micromass Autospec Premier or a Micromass LCT Premier spectrometer. Infrared (IR) spectra were recorded as Nujol mulls using a Perkin–Elmer FT-IR Spectrum GX spectrometer. Elemental analysis was performed by Mr. S. Boyer of the London Metropolitan University.

General Procedure for the Synthesis of 1,2-Bis(dialkylphosphoryl)ethanes (1a–e)

*Examplary synthesis of 1,2-bis(dimethylphosphoryl)ethane (**1a**):* diethyl phosphite (51.5 mL, 0.40 mol) was added dropwise *via* a dropping funnel to a 3.01 M THF solution of MeMgCl (400 mL, 1.20 mol) at 0 °C. CH_4 gas was evolved during addition and the excess pressure vented *via* a paraffin oil bubbler. The mixture was stirred at 0 °C for 30 min followed by 6 h at room temperature. The resulting grey suspension was cooled to 0 °C and 1,2-dichloroethane (15.8 mL, 0.201 mol) was added slowly. The mixture was heated to reflux for 12 h yielding a viscous grey suspension which was poured into aqueous K_2CO_3 (166 g, 1.20 mol, 200 mL) and the THF/H_2O mixture removed by decanting. The remaining white precipitate was washed with hot MeOH (6× 300 mL) and the combined MeOH washings were concentrated under vacuum. The oily solid obtained was dissolved in $CHCl_3$ (300 mL) and the solution dried over Na_2SO_4, filtered and evaporated. The resulting solids were dried under vacuum at 80 °C to yield **1a** as a hygroscopic white powder; yield: 30.2 g (84%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.98$ (d, $J = 2.6$ Hz, 4 H, CH_2), 1.53 (m, 12 H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 24.3$–23.1 (m), 16.8–15.7 (m); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): $\delta = 42.1$ (s). HR-MS (ESI): $m/z = 183.0704$, calcd. for $C_6H_{17}O_2P_2$: 183.0704; IR (nujol): $\nu = 115$ cm^{-1}:6 (s, ν_{PO}); anal. calcd. for $C_6H_{16}O_2P_2$: C 39.57, H 8.85; found: C 39.66, H 8.78.

General Procedure for the Synthesis of Ethylenebis(dialkylchlorophosphonium) Dichlorides (2a–e)

*Examplary synthesis of ethylenebis(dimethylchlorophosphonium) dichloride (**2a**):* to a solution of **1a** (20 g, 110 mmol) in CH_2Cl_2, was added dropwise $(COCl)_2$ (19.5 mL, 230 mmol) with stirring (caution: gas evolution) resulting in precipitation. The reaction was allowed to stir for 1 h at room temperature after which the suspension was filtered, washed with Et_2O, and dried under vacuum to afford **2a** as a white powder; yield: 30.7 g (96%); anal. calcd. for $C_6H_{16}Cl_4P_2$: C 24.68, H 5.52; found: C 24.76, H 5.46.

General Procedure for the Synthesis of 1,2-Bis(dialkylphosphino)ethanes (3a–e)

*Examplary synthesis of 1,2-bis(dimethylphosphino)ethane (**3a**):* NaH (60 wt% in mineral oil, 11.52 g, 288 mmol) was placed in a Schlenk tube and washed with THF (2×50 mL) to remove mineral oil. Subsequent activation[30] of NaH was achieved by stirring with a 1 M solution of $LiAlH_4$ in THF (30 mL, 30 mmol) for 2 h, which was then removed by cannula filtration and the solid rinsed with a further 2×20 mL portions of THF. 100 mL of fresh THF were then added and the suspension cooled to −78 °C before addition of $NaAlH_4$ (8.14 g, 151 mmol) as a solid under a flush of N_2. **2a** (20 g, 68.5 mmol) was then added as a suspension in 150 mL of THF at −78 °C *via* a wide Teflon cannula. Reaction proceeded immediately with accompanying gas evolution (caution). The mixture was allowed to warm to room temperature, stirred for a further 1 h, and then filtered through a glass frit with a pad of Celite® and washed with THF (2×50 mL). THF was removed under reduced pressure (20 mmHg) and the resulting white solids extracted with pentane (4× 150 mL); remaining solid $NaAlH_4$ was washed with cold Et_2O and reused in further reactions (recovery: 7.7 g; 95%). The pentane was then removed under reduced pressure (20 mmHg), leaving behind a colourless oil which was vacuum distilled at 58 °C (5 mmHg) to afford **3a** as a colourless oil; yield: 7.44 g (72%). ^1H NMR (400 MHz, C_6D_6): $\delta = 1.30$ (m, 4 H, CH_2), 0.81 (t, $J = 1.5$ Hz, 12 H, CH_3); $^{13}C\{^1H\}$ NMR

(100 MHz, C_6D_6): $\delta = 28.2$ (s), 13.9–14.1 (m); $^{31}P\{^1H\}$ NMR (162 MHz, C_6D_6): $\delta = -48.8$ (s); HR-MS (EI): $m/z =$ 150.0726, calcd. for $C_6H_{16}P_2$: 150.0727; anal. calcd. for $C_6H_{16}P_2$: C 48.00, H 10.74; found: C 48.23, H 10.64.

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