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An Improved Synthesis of ^{Me4}PCP and DMPE

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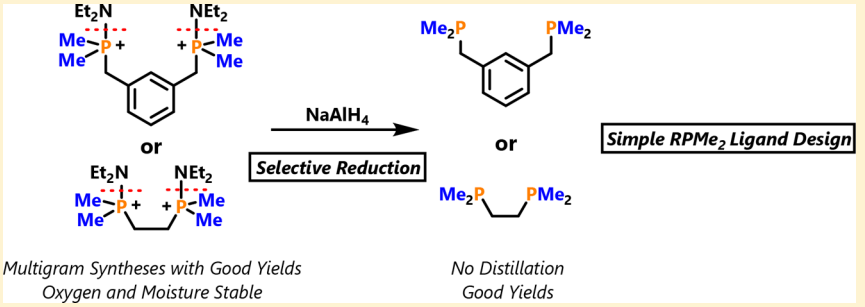
Supporting Information



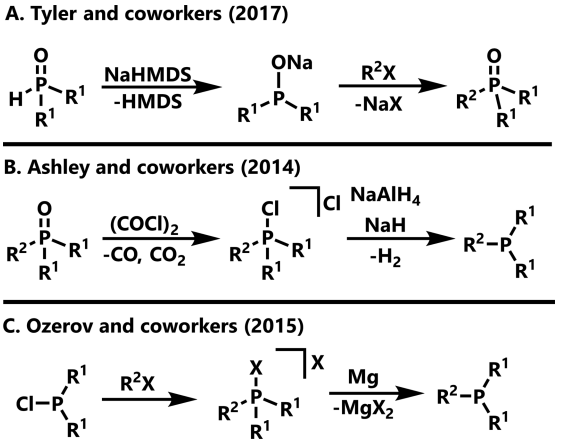
ABSTRACT: We present a new synthetic method for the bis(dimethyl)phosphines ^{Me4}PCP (C_6H_4-2,6-$(CH_2P(CH_3)_2)_2$) and DMPE ($(CH_3)_2PCH_2CH_2P(CH_3)_2$) that starts from an aminophosphine, Et_2NPMe_2. Two equivalents of Et_2NPMe_2 react with the corresponding bis(alkyl bromide) to afford an oxygen- and moisture-stable aminophosphonium salt. $NaAlH_4$ selectively reduces the aminophosphonium salt to the desired phosphine. Each step is high yielding and requires minimal purification.

Ligands featuring dimethylphosphino (Me_2P−) moieties offer an open steric environment but are underexplored because their syntheses have involved dangerous reagents and cumbersome methods.[1,2] Previous syntheses of DMPE ($(CH_3)_2PCH_2CH_2P(CH_3)_2$)) have proceeded through pyrophoric primary phosphines or $Me_2P(S)P(S)Me_2$, whose synthesis has caused laboratory accidents.[3−6] A derivative of the commonly used pincer PCP ligand framework, ^{Me4}PCP (C_6H_4-2,6-$(CH_2P(CH_3)_2)_2$), has seen minimal use because of its previously low yielding synthesis, which proceeds through the pyrophoric gas $HPMe_2$.[7,8] Greater use of these ligands and exploitation of their steric properties require a safer and more convenient synthetic protocol.

Newly developed syntheses of heteroleptic phosphines (R_2PR') solve some of these issues but introduce other difficulties when R = Me. These synthetic strategies, shown in Scheme 1, involve treating an alkyl halide with a nucleophilic phosphorus(III) precursor to afford a phosphine oxide or halophosphonium halide.[9−12] The phosphine oxides can be converted to halophosphonium halides and then reduced with aluminum hydride reagents, magnesium, or nickel.[10,11]

We hypothesized that an aminophosphine, a common precursor to small $ClPR_2$ derivatives, could be used in place of $ClPR_2$ in a pathway like that described by Ozerov and coworkers, and may be beneficial, as $ClPMe_2$ is difficult to obtain in large quantities.[2,11,13−17] Aminophosphines and their precursors, aminodichlorophosphines, are oxygen and water sensitive but can be safely prepared and stored in large quantities with the commercially available reagents PCl_3, HNR_2, and MR′ (M = Li, MgX (X = Cl, Br, I)).[13,17−19] Here, we use an aminophosphine, Et_2NPMe_2, as a convenient synthetic precursor to ^{Me4}PCP and DMPE, which are representative of commonly used ligand frameworks.

Scheme 1. Summary of Recently Reported Methods for Heteroleptic Phosphines and Phosphine Oxides



Two equivalents of methyllithium alkylate (diethylamino)-dichlorophosphine (Et_2NPCl_2) to afford (diethylamino)-dimethylphosphine (Et_2NPMe_2).[17,18] Aminophosphines can be conveniently prepared in multigram quantities.[13,18]

Like most phosphines, aminophosphines are known to oxidatively add alkyl halides to form phosphonium salts.[13,17,20] Thus, two equivalents of Et_2NPMe_2 react with 1,2-dibromoethane or α,α′-dibromo-*m*-xylene to afford the respective bis(aminophosphonium) bromide, **1a** or **1b**, shown in Table

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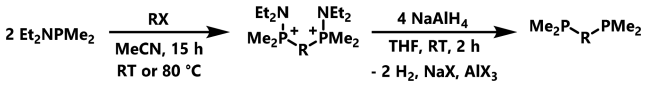
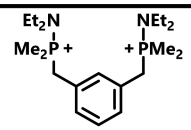
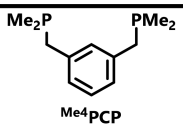
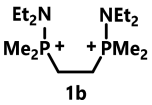
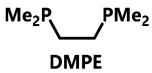
1. These bis(aminophosphonium) salts are air and moisture stable. X-ray crystallography confirmed the structure of **1a**, as shown in Figure S18 in the Supporting Information.

Table 1. Synthesized Aminophosphonium Salts and Phosphines with Their Respective Yields



Aminophosphonium	Yield (%)	Phosphine	Yield (%)
 1a	90[b]	 ^{Me4}PCP	88[c]
 1b	75[a]	 DMPE	81[c]

[a]Conditions: 80 °C in MeCN for 15 h. [b]Conditions: room temperature in MeCN for 15 h. [c]Conditions: 4 equiv of $NaAlH_4$, room temperature in THF for 2 h.

We hypothesized that traditional reagents for reducing phosphoniums should also reduce aminophosphoniums.[10,21] Four equivalents of $NaAlH_4$ provided the highest purity and yield of ^{Me4}PCP and DMPE. Table 1 summarizes the reaction conditions and yields for these syntheses. We observed side products, likely the mono- or bis-ylide, when **1a** was reduced with $LiAlH_4$ in THF. In contrast, we did not observe undesired products when reducing **1b** with excess $LiAlH_4$ in THF. Others have attributed the differences in reactivity between $NaAlH_4$ and $LiAlH_4$ to the differing solubilities of the resulting NaX or LiX salt and variable speciation in solution.[22−25] Unlike the reduction of halophosphonium halides reported by Ozerov and co-workers, we found that nonhydridic reductants, such as Mg, do not reduce **1a** or **1b** in MeCN or THF.

The presented synthetic method provides a straightforward template to synthesize dimethyl (aliphatic and benzyl) heteroleptic phosphines starting from an aminophosphine, which can be prepared and stored in large quantities. We hypothesize that these methods may be generalized to synthesize a variety of heteroleptic and mixed phosphines. Further research from our group will focus on the coordination and catalytic chemistry of the corresponding ^{Me4}PCP complexes with late transition metals and application of this synthetic method to other ligands.

EXPERIMENTAL SECTION

General Considerations. All manipulations and reactions used standard Schlenk techniques under an argon atmosphere unless otherwise stated. Glassware, diatomaceous earth, and sodium sulfate were stored in an oven maintained at 140 °C for at least 24 h prior to use. All protio solvents were passed through activated alumina and activated 3 Å molecular sieves prior to use. Deuterated solvents (C_6D_6 and THF-d_8) were dried over calcium hydride or sieves. CD_3CN was used as received. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker AV-500, DRX-499, or AV-300 instrument. ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra were referenced to residual solvent signals.[26] $^{31}P\{^1H\}$ NMR spectra were referenced to an 85% H_3PO_4 standard. Et_2NPMe_2 was synthesized as previously described.[18,19] Reagents MeLi (in Et_2O), PCl_3, $HNEt_2$, 1,2-dibromoethane, α,α'-dibromo-*m*-xylene, and reagent grade 90% $NaAlH_4$ were purchased from Sigma-Aldrich. MeLi solutions in Et_2O were titrated with salicylaldehyde phenylhydrazone to determine their concentrations prior to use.[27] 1,2-Dibromoethane and $HNEt_2$ were stored over activated 3 Å molecular sieves prior to use. α,α'-Dibromo-*m*-xylene was recrystallized from hexanes prior to use. Elemental analysis was completed at the CENTC facility at the University of Rochester (funded by NSF CHE-0650456) and at Atlantic Microlab, Norcross, GA.

Compound 1a. 2,6-Dibromomethylbenzene (1.53 g, 5.77 mmol) was added to a solution of *N*,*N*-diethylamino-*P*,*P*-dimethylphosphine (1.69 g, 12.7 mmol) in MeCN (30 mL). The solution was stirred for 15 h. The resulting white precipitate was collected by vacuum filtration in air and then washed with cold MeCN (0 °C, 3 × 5 mL) and diethyl ether (3 × 5 mL) to afford **1a** (2.76 g, 5.19 mmol, 90% yield). Crystals of **1a** suitable for X-ray diffraction were grown from a saturated MeCN solution at −30 °C. ^{1}H NMR (300 MHz, CD_3CN): δ 7.52−7.29 (m; 4H; Ar-*H*), 3.83 (d; $^2J_{HP}$ = 15.5 Hz; 4H; Ar(−CH_2−)), 3.10 (m; 8H; −N((CH_2)CH$_3$)$_2$), 1.96 (d; $^2J_{HP}$ = 14.8 Hz; 12H; −P(CH_3)$_2$), 1.02 (t; $^3J_{HH}$ = 7.3 Hz; −N((CH$_2$)CH_3)$_2$). $^{31}P\{^1H\}$ NMR (121 MHz, CD_3CN): δ 60.0. $^{13}C\{^1H\}$ NMR (125.8 MHz, CD_3CN): δ 131.0 (t, $^2J_{CP}$ = 2.7 Hz, C_{Ar}), 130.8 (t; $^2J_{CP}$ = 3.7 Hz; C_{Ar}), 41.73 (s; −N((CH$_2$)CH$_3$)$_2$), 33.89 (d; $^1J_{CP}$ = 49.1 Hz; Ar(−CH_2−)), 14.77(s; −N((CH$_2$)CH_3)$_2$) 10.03 (d; $^1J_{CP}$ = 65.8 Hz; −P(CH_3)$_2$). Anal. Calcd: C, 45.30; H, 7.60; N, 5.28. Found: C, 45.20; H, 7.53; N, 5.27.

^{Me4}PCP. Compound **1a** (2.14 g, 4.03 mmol) and $NaAlH_4$ (0.87 g, 16.0 mmol) were stirred together in THF (15 mL) for 2 h at room temperature. The reaction mixture was cooled to 0 °C, and a 15% NaOH aqueous solution was added dropwise to quench the reductant and byproducts. The volume of the solution was reduced under vacuum, and pentane (3 × 10 mL) was used to extract from the aqueous layer. The organic layer was dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the volatiles were removed under vacuum to afford ^{Me4}PCP (0.80 g, 88% yield). The spectroscopic data are consistent with previous reports.[7,8] ^{1}H NMR (300 MHz, C_6D_6): δ 7.11 (t; $^3J_{HH}$ = 7.8 Hz; 1H), 6.90 (d; $^3J_{HH}$ = 7.8 Hz; 2H), 2.50 (br s; 4H), 0.79 (d; $^2J_{HP}$ = 3.4 Hz; 12H). $^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ −49.0. $^{13}C\{^1H\}$ NMR (125.8 MHz, C_6D_6): δ 138.4 (s; C_{Ar}), 130.2 (t; $^3J_{cp}$ = 4.0 Hz; C_{Ar}), 128.5 (s; C_{Ar}), 126.8 (d; $^3J_{CP}$ = 3.6 Hz, C_{Ar}), 39.09 (d; $^2J_{CP}$ = 15.5 Hz; Ar(−CH_2- 68 (d; $^2J_{CP}$ = 16.5 Hz; −P(CH_3)$_2$).

Compound 1b. 1,2-Dibromoethane (1.76 g, 9.37 mmol) was added to a solution of *N*,*N*-diethylamino-*P*,*P*-dimethylphosphine (2.74 g, 20.6 mmol) in MeCN (30 mL). The solution was stirred for 15 h at 80 °C. The volatiles were removed under vacuum, and the resulting white solid was washed with cold MeCN (−45 °C, 3 × 5 mL) and diethyl ether (3 × 5 mL) to afford **1b** (3.20 g, 7.04 mmol, 75% yield). ^{1}H NMR (300 MHz, CD_3CN): δ 3.20 (m; 8H; −N((CH_2)CH$_3$)$_2$), 2.81 (d; $^2J_{HP}$ = 4.5 Hz; 4H; −CH_2CH_2−), 2.18 (vt; 12H; −P(CH_3)$_2$), 1.16 (t; $^3J_{HH}$ = 7.0 Hz; 12H; −N((CH$_2$)CH_3)$_2$). $^{31}P\{^1H\}$ NMR (121 MHz, CD_3CN): δ 61.4. $^{13}C\{^1H\}$ NMR (125.8 MHz, CD_3CN): δ 40.62 (s; −N((CH_2)CH$_3$)$_2$), 18.75 (vt; −CH_2CH_2−), 13.90 (s; −N((CH$_2$)CH_3)$_2$), 9.55 (vt; −P(CH_3)$_2$). Anal. Calcd: C, 37.02; H, 7.99; N, 6.17. Found: C, 36.99; H, 8.11; N, 6.05.

DMPE. Compound **1b** (2.32 g, 4.91 mmol) and $NaAlH_4$ (1.06 g, 19.6 mmol) were stirred together in THF (15 mL) for 2 h at room temperature. The reaction mixture was cooled to 0 °C, and a 15% NaOH aqueous solution was added dropwise to quench the reductant and byproducts. The volume of the solution was reduced under vacuum, and pentane (3 × 10 mL) was used to extract from the aqueous layer. The organic layer was dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the volatiles were removed under vacuum to afford DMPE (0.60 g, 4.00 mmol, 81% yield). The spectroscopic data are consistent with previous reports.[10] ^{1}H NMR (300 MHz, C_6D_6): δ 1.30 (vt; 4H; −CH_2CH_2−), 0.81 (vt; 12H; −P(CH_3)$_2$). $^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ −47.3. $^{13}C\{^1H\}$ NMR (125.8 MHz, C_6D_6): δ 28.16 (vt; −CH_2CH_2−), 14.01 (dd; −P(CH_3)$_2$).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00780.

NMR spectra and crystallographic structure and data (PDF)

Accession Codes

CCDC 1580835 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Roddick, D. M. In *Organometallic Pincer Chemistry*; Springer: Berlin, 2012; pp 49−88.

(2) Kendall, A. J.; Tyler, D. R. *Dalton Trans.* **2015**, *44* (28), 12473−12483.

(3) Parshall, G. W. *J. Inorg. Nucl. Chem.* **1960**, *14* (3−4), 291−292.

(4) Butter, S. A.; Chatt, J.; Wonchoba, E. R.; Parshall, G. W. *Inorg. Synth.* **2007**, *15*, 185−191.

(5) Bercaw, J. E.; Parshall, G. W. *Inorg. Synth.* **1985**, *23*, 199−200.

(6) Tavtorkin, A. N.; Toloraya, S. A.; Nifant'Ev, E. E.; Nifant'Ev, I. E. *Tetrahedron Lett.* **2011**, *52* (7), 824−825.

(7) Creaser, C. S.; Kaska, W. C. *Inorg. Chim. Acta* **1978**, *30* (C), L325−L326.

(8) Wang, K.; Goldman, M. E.; Emge, T. J.; Goldman, A. S. *J. Organomet. Chem.* **1996**, *518* (1−2), 55−68.

(9) Hays, H. R. *J. Org. Chem.* **1968**, *33* (10), 3690−3694.

(10) Doyle, L. R.; Heath, A.; Low, C. H.; Ashley, A. E. *Adv. Synth. Catal.* **2014**, *356* (2−3), 603−608.

(11) Shih, W. C.; Ozerov, O. V. *Organometallics* **2015**, *34* (18), 4591−4597.

(12) Kendall, A. J.; Seidenkranz, D. T.; Tyler, D. R. *Organometallics* **2017**, *36* (13), 2412−2417.

(13) Burg, A. B.; Slota, P. J. J. *J. Am. Chem. Soc.* **1958**, *80* (5), 1107−1109.

(14) Ferron, J. L. *Nature* **1961**, *189*, 916.

(15) Wolfsberger, W. *J. Organomet. Chem.* **1986**, *317* (2), 167−173.

(16) Burg, A. B.; Slota, P. J. *J. Am. Chem. Soc.* **1958**, *80* (5), 1107−1109.

(17) Gopalakrishnan, J. *Appl. Organomet. Chem.* **2009**, *23* (8), 291−318.

(18) Maier, L. *Helv. Chim. Acta* **1964**, *47* (8), 2129−2137.

(19) Muraishi, K.; Sueto, K.; Gao, Y. Ionic Liquid Containing Phosphonium Cation Having P-N Bond and Method for Producing Same. US Patent 20090163394, 2007.

(20) Sisler, H. H.; Smith, N. L. Novel Diquaternary Aminophosphonium Compounds. US Patent 3131204, 1962.

(21) Maier, L. *Prog. Inorg. Chem.* **1963**, *5*, 27−210.

(22) Ashby, E. C.; Sanders, J. R.; Claudy, P.; Schwartz, R. D. *Inorg. Chem.* **1973**, *12* (12), 2860−2868.

(23) Ashby, E. C.; Prather, J. *J. Am. Chem. Soc.* **1966**, *88* (4), 729−733.

(24) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41* (17), 2890−2903.

(25) Wiegers, K. E.; Smith, S. G. *J. Org. Chem.* **1978**, *43* (6), 1126−1131.

(26) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29* (9), 2176−2179.

(27) Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64* (10), 3755−3756.

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