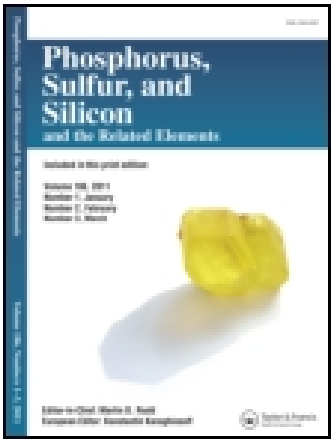

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

A Simple Procedure to Ditertiary Phosphinocarboxylic Acids and Their Bisphosphine Oxides

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Published online: 08 May 2013.

To cite this article: Mark R. J. Elsegood, Thomas A. Noble, Salem Talib & Martin B. Smith (2013) A Simple Procedure to Ditertiary Phosphinocarboxylic Acids and Their Bisphosphine Oxides, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:1-3, 121-127, DOI: 10.1080/10426507.2012.743133

To link to this article: http://dx.doi.org/10.1080/10426507.2012.743133

Phosphorus, Sulfur, and Silicon, 188:121–127, 2013

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.743133

A SIMPLE PROCEDURE TO DITERTIARY PHOSPHINOCARBOXYLIC ACIDS AND THEIR BISPHOSPHINE OXIDES

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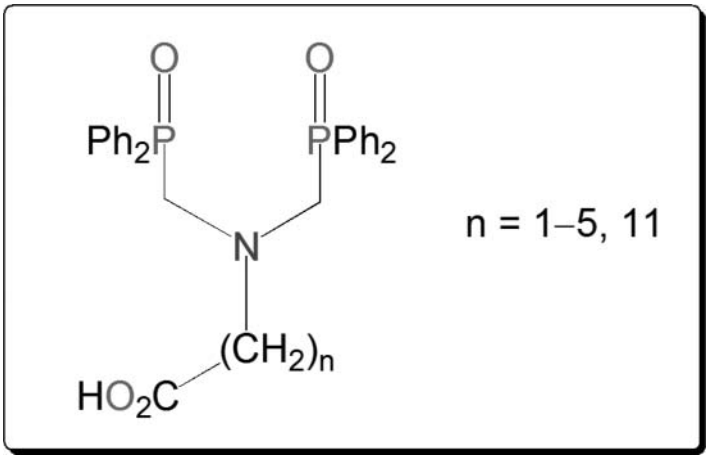
GRAPHICAL ABSTRACT



Abstract *A simple two-step route to a series of carboxylic acid functionalized ditertiary phosphine oxides is described, including the X-ray crystal structures of three representative examples namely* $\{Ph_2P(O)CH_2\}_2N(CH_2)_nCO_2H$ *(n = 3–5). Strong intermolecular O–H···O H-bonding is observed in all cases leading to distinct packing arrangements.*

Keywords Tertiary phosphine oxides; ligands; hydrogen bonding; NMR spectroscopy; X-ray crystallography

INTRODUCTION

Phosphine oxides are versatile compounds for diverse applications in organic synthesis,[1–3] photoinitiators for surface modification,[4] preparation of quantum dots,[5] coordination chemistry,[6] and industrial processes such as selective metal extraction.[7] Some

Received 4 September 2012; accepted 18 October 2012.
We would like to thank Loughborough University and The Leverhulme Trust (S.T.) for funding.
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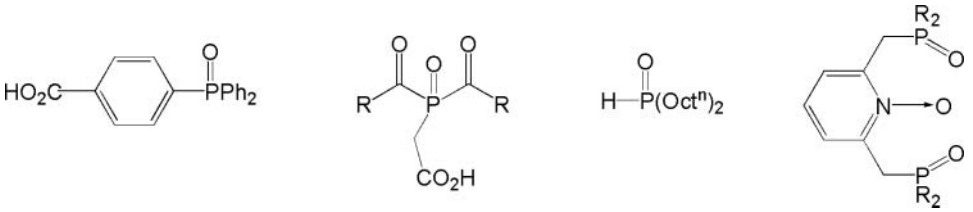
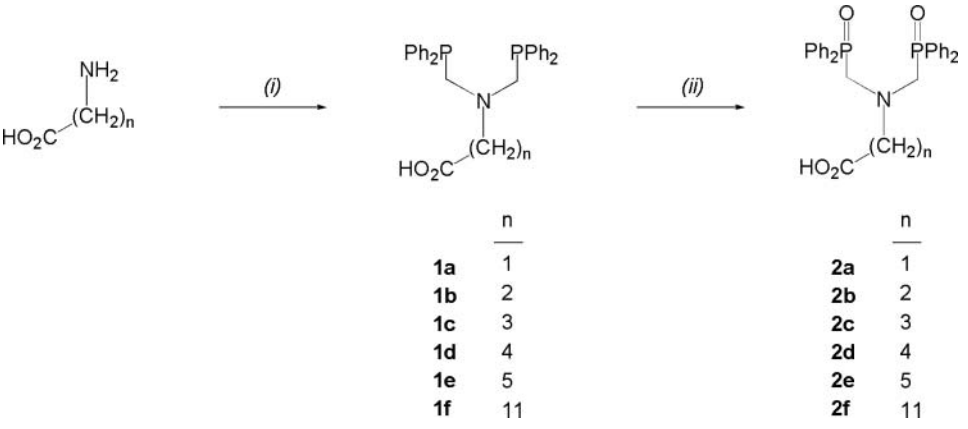


Figure 1 Some examples of phosphine oxides.

representative examples of phosphine oxides used in these scenarios are illustrated in Figure 1. Bis(phosphine) oxides are known[2,8] and often incorporate a carbon connectivity between both $-P(O)R_2$ groups (where R = Ph typically). Carboxylic acid bearing ditertiary phosphines and their oxides are attractive targets, yet their ease of preparation and suitability to our program were inappropriate.[2,8] Phosphorus based Mannich transformations are an extremely useful synthetic method for accessing new "hybrid" ligands.[9,10] Keglevich and coworkers[9] recently showed bis(phosphine) oxides of the type $\{Ph_2P(O)CH_2\}_2N(R)$ are accessible via the microwave assisted double phospha-Mannich reaction of $HP(O)Ph_2$, $(CH_2O)_n$ and various arylamines. Our research group[10] is also interested in P−C−N(R)−C−P based ligands and we required access to readily amenable ditertiary phosphine bisoxides, bearing *N*-backbone functionality for further modification. Herein we describe a simple, high yielding, two-step method for the synthesis of new carboxylic acid modified ditertiary phosphine bisoxides derived from cheap, commercially available, starting materials. The structures of $\{Ph_2P(O)CH_2\}_2N(CH_2)_nCO_2H$ ($n = 3$ **2c**; $n = 4$ **2d**, and $n = 5$ **2e**) have been determined by single crystal X-ray diffraction and reveal different structural H-bonding motifs as a function of alkyl spacer chain length.

RESULTS AND DISCUSSION

Using a procedure similar to that recently developed by us[10] for preparing novel carboxylic acid functionalized ditertiary phosphines, reaction of two equivalents of Ph_2PCH_2OH (readily preformed from equimolar amounts of $[CH_2O]_n$ and Ph_2PH)[11] with one equivalent of $H_2N(CH_2)_nCO_2H$ ($n = 1-5, 11$) in refluxing CH_3OH, gave the condensed ligands $\{Ph_2PCH_2\}_2N(CH_2)_nCO_2H$ **1a–f** (Scheme 1). Compounds **1a–f** were characterized in situ by $^{31}P\{^1H\}$ NMR spectroscopy (Table 1). As demonstrated by the facile synthesis of **1a–f**, this simple method unsurprisingly appears insensitive to alkyl chain length with no significant amounts of other phosphorus species observed by $^{31}P\{^1H\}$ NMR spectroscopy. Oxidation of **1a–f**, under standard conditions (aq. H_2O_2/THF/r.t.)[12] and subsequent work-up, gave the corresponding ditertiary phosphine bisoxides **2a–f** (Scheme 1) as colorless solids. The unoptimized yields for **2a–f** are in the range 60–77% (Table 1). The $^{31}P\{^1H\}$ NMR data (Table 1) confirm oxidation of both phosphorus centers since only one singlet ^{31}P resonance is observed at ca. δ(P) 30 ppm. Our data is in good agreement with those of known phosphine oxides[9] and, moreover, these ^{31}P NMR resonances are some 50 ppm downfield with respect to the trivalent precursors **1a–f**. All compounds were further characterized by ^1H NMR, FT−IR and elemental analysis (see Experimental Section for selected data). Compounds **2a–f** are freely soluble in CH_2Cl_2, THF, and CH_3OH, but show limited solubility in CH_3CN and H_2O (the lower alkyl chain members are soluble in basic media).



	n
1a	1
1b	2
1c	3
1d	4
1e	5
1f	11

	n
2a	1
2b	2
2c	3
2d	4
2e	5
2f	11

Scheme 1 (i) 2 Ph_2PCH_2OH, CH_3OH, reflux (ii) aq. H_2O_2, THF.

Suitable crystals of **2c**, **2d**, and **2e** were obtained by vapor diffusion of diethyl ether into a $CDCl_3$ solution over the course of several days. The single crystal X-ray structures[13] of **2c** (Figure 2), **2d**, and **2e** have been determined with selected bond lengths and angles given in Table 2. In all cases, the X-ray structures confirm the presence of both $–P(O)Ph_2$ and $–CO_2H$ groups. The $–P(O)Ph_2$ groups adopt an *anti* configuration with respect to each other and the P═O bond lengths [1.486(2)–1.499(3) Å] are in the normal range.[9] Furthermore, in all three structures, the central nitrogen atom is clearly pyramidal as indicated by the ∑[N(1) angles] of 337° (**2c**), 341° (**2d**), and 339° (**2e**). The most unusual feature between all three X-ray structures, none of which incorporate solvent cocrystallization, are the different packing arrangements on going from **2c** (C_3) to **2d** (C_4) to **2e** (C_5) (Figures 3a–c). In **2c**, molecules are linked into a 1-D zig-zag chain through strong O─H···O intermolecular H-bonding [O(4)···O(2′) 2.621(4) Å, H(4)···O(2′)

Table 1 Selected experimental and $^{31}P\{^1H\}$ NMR data for **1a–f** and **2a–f**

Compound	Reaction time (h)	Yield (%)[a]	δ(P) (ppm)[c]
1a	19		−26.4
1b	5[b]		−27.8
1c	21		−27.6
1d	19		−27.8
1e	20		−27.9
1f	16		−27.7
2a	1.5	77	29.5
2b	1.5	70	30.0
2c	1.5	61	30.0
2d	1.5	62	30.6
2e	4	60	30.2
2f	4	60	30.1

[a] Yields for **1a**−**f** not determined.

[b] Reaction conducted at r.t.

[c] $^{31}P\{^1H\}$ NMR spectra were recorded (101.23, 161.97, or 202.46 MHz) in CH_3OH/C_6D_6 (for **1a**−**f**) and $CDCl_3$ (**2a**−**f**).

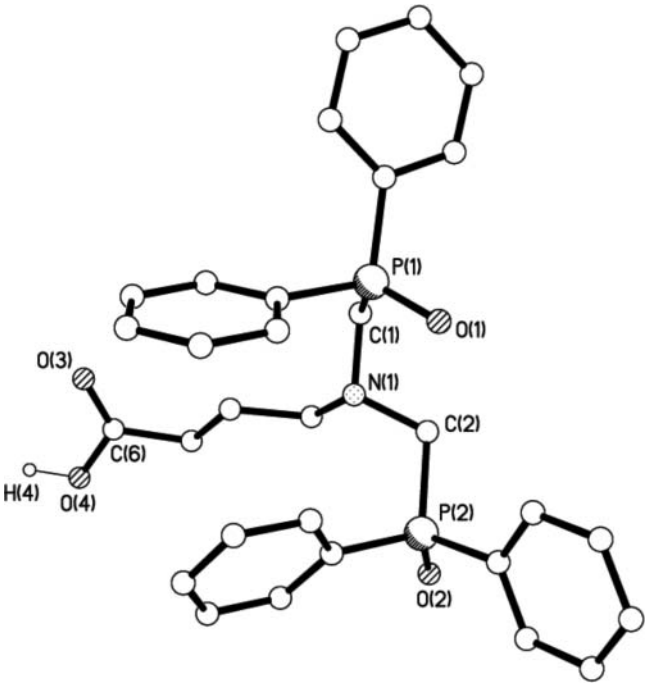


Figure 2 Crystal structure of **2c**. Compounds **2d** and **2e** are ostensibly similar and not shown. All hydrogen atoms except H(4) have been omitted for clarity.

1.68(2) Å; O(4)−H(4)···O(2′) 166(4)°], whereas in **2d**, strong O−H···O intermolecular H-bonding O(4)···O(2′) 2.589(3) Å, H(4)···O(2′) 1.73(3) Å; O(4)−H(4)···O(2′) 164(3)°] leads to spirals (2_1 screw axis) that run along the crystallographic *a* axis.[14] In **2e**, molecules form discrete dimer pair through P=O···H−O hydrogen bonding [O(4)···O(1′) 2.585(2) Å, H(4)···O(1′) 1.73(3) Å; O(4)−H(4)···O(1′) 167(3)°]. This leads to formation of a large 24-membered ring as opposed to the more classical carboxylic acid-carboxylic acid head-to-tail 8-membered ring through pairs of C=O···H−O hydrogen bonds.[10, 15] Furthermore, additional weak intermolecular C−H···O contacts were observed in **2c**–**e**. All attempts to obtain suitable crystals of **2a**, **2b**, or **2f** were unsuccessful.

Table 2 Selected bond lengths (Å) and angles (°) for **2c–e**

	2c	**2d**	**2e**
P(1)−O(1)	1.489(3)	1.486(2)	1.4962(15)
P(2)−O(2)	1.499(3)	1.4911(18)	1.4902(16)
C−O(3)	1.202(5)	1.213(3)	1.209(3)
C−O(4)	1.325(4)	1.323(3)	1.325(2)
C(1)−N(1)−C(2)	112.0(3)	111.2(2)	111.24(15)

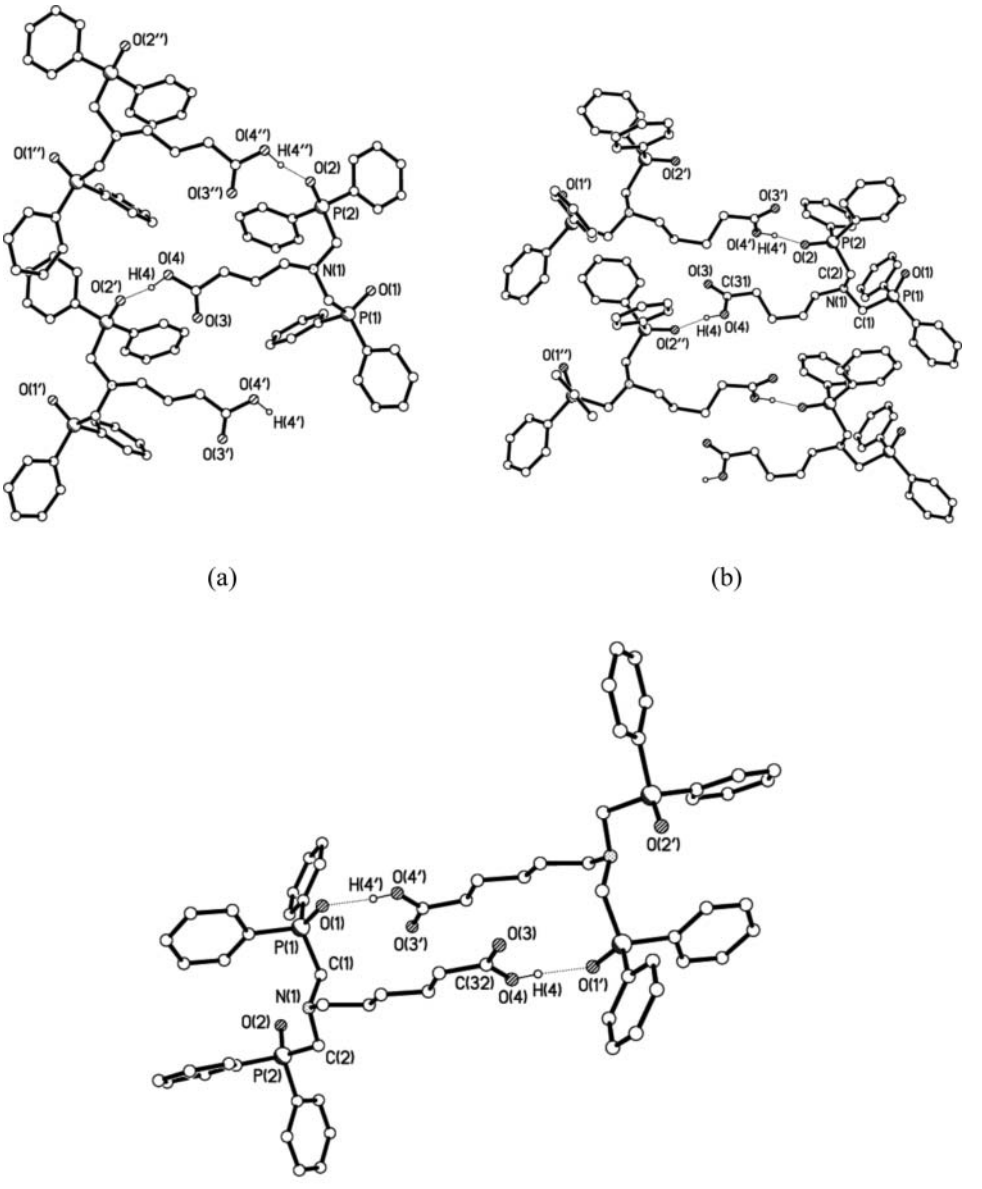


Figure 3 Packing diagrams of (a) **2c**, (b) **2d**, and (c) **2e**. All hydrogen atoms except those on $-CO_2H$ groups have been omitted for clarity.

In summary, we have shown, new carboxylic acid modified ditertiary phosphine bisoxides are readily accessible. This procedure should be tolerant to other reactive functional groups, and current efforts are directed toward tagging these precursors onto bioconjugate and polymeric supports. Related hydroxyalkyl aminophosphonic acids have recently been used to prepare novel composite films.[16]

EXPERIMENTAL

The following method was used for the synthesis of **2a**. To the solids Ph_2PCH_2OH (0.513 g, 2.37 mmol) and $H_2NCH_2CO_2H$ (0.085 g, 1.13 mmol) was added oxygen-free CH_3OH (20 mL). The solution was refluxed for 19 h under a N_2 atmosphere. The solvent was evaporated to dryness under reduced pressure to afford **1a**. THF (15 mL) was added followed by H_2O_2 (1.5 mL, 27.5 wt% solution in water) and the solution stirred at r.t. for 1.5 h. The solvent was evaporated to dryness, the residue taken up in CH_2Cl_2 (30 mL) and washed with H_2O (30 mL). The organic layer was dried over anhydrous $MgSO_4$, the solvent reduced to ca. 5 mL and Et_2O (30 mL) added. Yield: 0.46 g, 77%. Selected data for **2a**: ^{1}H NMR [$CDCl_3$, 298 K]: $\delta = 7.76-7.34$ (m, 20H, arom-H), 3.76 (d, $^2J_{PH} = 4.9$ Hz, 4H, PCH_2), 2.97 (t, 2H, CH_2). FT−IR (KBr): 1715 cm^{-1} (ν_{CO}). Calcd. for $C_{28}H_{27}NO_4P_2$: C, 66.80; H, 5.42; N, 2.78. Found: C, 66.46; H, 5.75; N, 2.40. Selected data for **2b**: ^{1}H NMR [$CDCl_3$, 298 K]: $\delta = 7.73-7.36$ (m, 20H, arom-H), 3.79 (s, 4H, PCH_2), 3.23 (s, 2H, CH_2), 2.53 (s, 2H, CH_2). FT−IR (KBr): 1717 cm^{-1} (ν_{CO}). Calcd. for $C_{29}H_{29}NO_4P_2$: C, 67.30; H, 5.66; N, 2.71. Found: C, 66.92; H, 5.60; N, 2.74. Selected data for **2c**: ^{1}H NMR [$CDCl_3$, 298 K]: $\delta = 7.86-7.32$ (m, 20H, arom-H), 3.76 (d, $^2J_{PH} = 3.6$ Hz, 4H, PCH_2), 2.97 (t, 2H, CH_2), 2.15 (t, 2H, CH_2), 1.69 (m, 2H, CH_2). FT−IR (KBr): 1715 cm^{-1} (ν_{CO}). Calcd. for $C_{30}H_{31}NO_4P_2$: C, 67.78; H, 5.89; N, 2.64. Found: C, 67.12; H, 5.84; N, 2.67. Selected data for **2d**: ^{1}H NMR [$CDCl_3$, 298 K]: $\delta = 7.74-7.25$ (m, 20H, arom-H), 3.66 (d, $^2J_{PH} = 4.0$ Hz, 4H, PCH_2), 2.89 (t, 2H, CH_2), 2.21 (t, 2H, CH_2), 1.39 (m, 2H, CH_2), 1.31 (m, 2H, CH_2). FT−IR (KBr): 1716 cm^{-1} (ν_{CO}). Calcd. for $C_{31}H_{33}NO_4P_2$: C, 68.24; H, 6.11; N, 2.57. Found: C, 67.83; H, 5.93; N, 2.59. Selected data for **2e**: ^{1}H NMR [$CDCl_3$, 298 K]: $\delta = 7.87-7.32$ (m, 20H, arom-H), 3.75 (d, $^2J_{PH} = 4.4$ Hz, 4H, PCH_2), 2.97 (t, 2H, CH_2), 2.22 (t, 2H, CH_2), 1.52 (m, 2H, CH_2), 1.34 (m, 2H, CH_2), 1.08 (m, 2H, CH_2). FT−IR (KBr): 1700 cm^{-1} (ν_{CO}). Calcd. for $C_{32}H_{35}NO_4P_2$: C, 68.68; H, 6.32; N, 2.50. Found: C, 67.68; H, 6.15; N, 2.60. Selected data for **2f**: ^{1}H NMR [$CDCl_3$, 298 K]: $\delta = 7.80-7.37$ (m, 20H, arom-H), 3.76 (d, $^2J_{PH} = 4.4$ Hz, 4H, PCH_2), 2.97 (t, 2H, CH_2), 2.36 (t, 2H, CH_2), 1.69−1.06 (m, 18H, CH_2). FT−IR (KBr): 1718 cm^{-1} (ν_{CO}). Calcd. for $C_{38}H_{47}NO_4P_2$: C, 70.89; H, 7.37; N, 2.18. Found: C, 70.93; H, 7.37; N, 2.32.

Crystal data for **2c**: $C_{30}H_{31}NO_4P_2$, $M = 531.50$; monoclinic, $P2_1/n$, $a = 7.7628(7)$, $b = 35.747(3)$, $c = 10.2069(9)$ Å, $\beta = 108.2102(17)^\circ$, $V = 2690.5(4)$ Å^3; $Z = 4$, ρ_{cal} 1.312 g cm^{-3}; μ(Mo-Kα) = 0.198 mm^{-1}; $\lambda = 0.71073$ Å, $T = 150(2)$ K; 19529 reflections were collected on a Bruker SMART 1000 CCD diffractometer[13] using narrow ω-scans, 4743 of which were independent ($R_{int} = 0.0785$). The structure was solved by direct methods and refined on F^2 values to give a final $R1 = 0.0577$ for 2837 data with $F^2 > 2\sigma$ (F^2); $wR_2 = 0.1497$ for all data.[17, 18] Crystal data for **2d**: $C_{31}H_{33}NO_4P_2$, $M = 545.52$; orthorhombic, $P2_12_12_1$, $a = 7.9895(5)$, $b = 16.9972(10)$, $c = 20.1654(12)$ Å, $V = 2738.4(3)$ Å^3; $Z = 4$, ρ_{cal} 1.323 g cm^{-3}; μ(Mo-Kα) = 0.197 mm^{-1}; $\lambda = 0.71073$ Å, $T = 150(2)$ K; 24123 reflections were collected on a Bruker SMART 1000 CCD diffractometer using narrow ω-scans, 6677 of which were independent ($R_{int} = 0.0532$). The structure was solved by direct methods and refined on F^2 values to give a final $R1 = 0.0507$ for 4723 data with $F^2 > 2\sigma$ (F^2); $wR_2 = 0.1044$ for all data. Flack x = 0.01(10). Crystal data for **2e**: $C_{32}H_{35}NO_4P_2$, $M = 559.55$; monoclinic, $P2_1/n$, $a = 7.9659(5)$, $b = 17.8259(11)$, $c = 20.7005(13)$ Å, $\beta = 96.0029(11)^\circ$, $V = 2923.3(3)$ Å^3; $Z = 4$, ρ_{cal} 1.271 g cm^{-3}; μ(Mo-Kα) = 0.186 mm^{-1}; $\lambda = 0.71073$ Å, $T = 150(2)$ K; 25371 reflections were collected on a Bruker SMART 1000 CCD diffractometer using narrow ω-scans, 6995 of which were independent ($R_{int} = 0.0398$). The structure was solved by direct methods and refined on F^2 values to give a final $R1 = 0.0448$ for 4762

data with $F^2 > 2\sigma\ (F^2)$; $wR_2 = 0.1181$ for all data. A complete set of X-ray crystallographic structural data for compounds **2c–e** (CCDC numbers 897295, 897296, and 214336) are available at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.ac.uk) on request, quoting the deposition number.

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