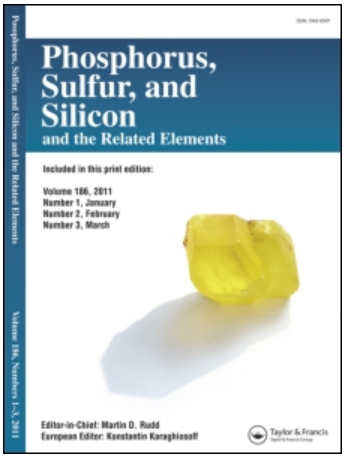

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REACTIONS OF CHIRAL PHOSPHORUS ACID DIAMIDES: LEWIS ACID CATALYZED ADDITION TO IMINES AND OXIDATION WITH $SnCl_4$

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REACTIONS OF CHIRAL PHOSPHORUS ACID DIAMIDES: LEWIS ACID CATALYZED ADDITION TO IMINES AND OXIDATION WITH $SnCl_4$

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Dedicated to Professor Reinhard Schmutzler on the occasion of his 60th birthday

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Lewis acid catalyzed addition of chiral phosphorus acid diamides to imines gave 1-aminophosphonamides in good yields and modest diastereoselectivity (up to 54%). Reaction of phosphorus acid diamide **1a** with $SnCl_4$ yielded a chlorophosphonamide. The crystal structure of the chlorophosphonamide, 2-chloro-2,3,3a,4,5,6,7,7a-octahydro-1,3-bis-benzyl-1H-1,3,2-benzodiazaphosphole-2-oxide has been determined by X-ray diffraction.

Key words: Phosphorous acid, diamide, chiral, alkylation, 1-aminoalkyl phosphonamide, chlorophosphonamide, imine, Lewis acid.

INTRODUCTION

1-Aminophosphonic acids are of interest due to their biological activity, which has been shown to be dependent upon the absolute configuration of the α carbon.[1] The synthesis of non racemic 1-aminophosphonic acid derivatives has been widely reported,[2] and a range of methods have been employed to control the stereodifferentiating step.[3] Asymmetric addition of a chiral phosphite nucleophile to imines, and hydrolysis of the resulting amino phosphonate, would represent a direct and general route to structurally varied 1-aminophosphonic acids. To our knowledge only one example of this approach has been reported,[4] wherein chiral cyclic phosphites were added to a cyclic imine with low stereoselectivity (up to 33% d.e.). We recently reported the preparation and alkylation of chiral phosphorous acid diamides.[5] The anions of these diamides add to aldehydes to give 1-hydroxy phosphonamides with up to 93% d.e.[6] Therefore, chiral phosphorus acid diamides appeared to be promising candidates as nucleophiles for diastereoselective additions to imines.

RESULTS

In contrast to the reaction with aldehydes, the lithium salt of the phosphorous acid diamide **1a** did not react with imines **2**. However, addition of the neutral phosphorus acid diamide to imines was achieved with Lewis acid catalysis to yield 1-amino-

phosphonamides **3**. A series of reactions were performed with the N-benzyl substituted diamide **1a** and variety of substituted imines (Table I). The diastereoisomeric pair **3** were easily distinguishable from each other by ^{31}P NMR spectroscopy thereby providing a suitable method for the determination of isomeric ratios. The $^{31}P\{^1H\}$ NMR spectra of the crude phosphonamide mixtures appeared as two singlets (one for each diastereoisomer) in the range of +42.6 to 29.3 ppm. Derivatives of the N-benzyl diamide **1a**, showed greater shielding of phosphorus by P-benzylic (**3a**, **d**, **e**) than by the analogous P-alkyl (**3b**, **c**, **f**) groups.

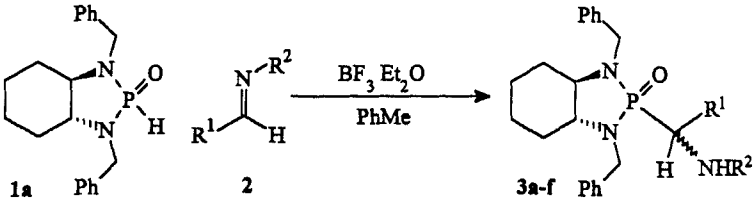
Unfortunately, the stereoselectivities were generally low, and the observed substituent effects were small. However, reaction of the anion of N-benzyl diamide **1a** with aldehydes was previously shown to proceed at best with modest selectivity (69% d.e.), and was unselective with benzaldehyde (1.1:1).[6c] Whereas, reaction of **1a** with benzaldehyde derived imines **2a**, **2d**, and **2e** gave aminophosphonamides with 35%, 37% and 0% d.e., respectively. As a comparison, the Lewis acid catalyzed addition of diamide **1a** to benzaldehyde was performed and hydroxy phophonamide **4** was formed with 33% d.e., an improvement over the anion addition.

TABLE I

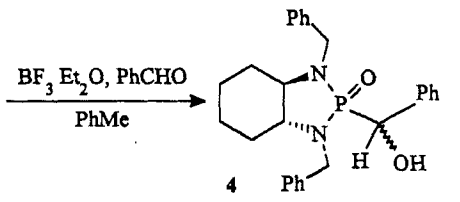
Boron trifluoride catalyzed reaction of phosphorous acid diamide **1a** with imines

Entry	Imine	R^1	R^2	Product	Reaction Temp.	Yield %	Isomeric Ratio	^{31}P NMR δ, ppm
1	2a	Ph	$PHCH_2$	3a	-70	82	2.1 : 1	37.3/35.5
2	2b	$(CH_3)_2CH$	$PHCH_2$	3b	-75	30	1.4 : 1	43.4/41.0
3	2c	CH_3	$PhCH_2$	3c	-70	53	1.9 : 1	43.3/41.1
4	2d	Ph	$CH_2CH{=}CH_2$	3d	-60	73	1.9 : 1	37.2/35.2
5	2e	Ph	$Si(CH_3)_3$	3e	-75	51	1 : 1	34.4/34.3
6	2f	pyrroline	trimer	3f	-65	44	1.4 : 1	41.3/40.6

The 1-aminophosphonamides were purified by column chromatography on silica gel. The conversion and crude yields were generally good. In all examples, the isolated phosphonamides were viscous oils. Diastereoisomeric ratios were determined by $^{31}P\{^1H\}$ or ^1H NMR spectroscopy of the crude products.



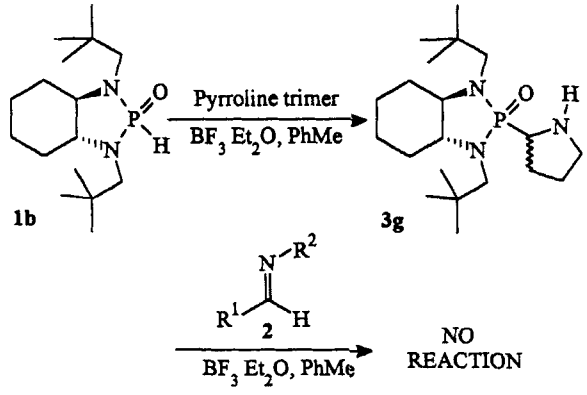
(for R^1 and R^2 see Table 1)



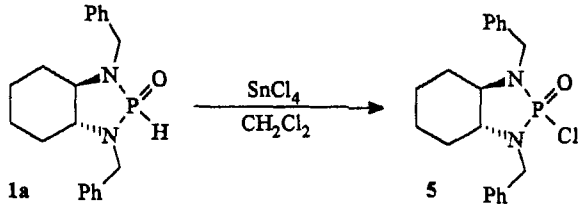
SCHEME I

The ^{31}P resonance of the major isomer was at δ 36.9 ppm indicating that the stereochemical preference in the Lewis acid catalyzed addition was the same as the anion addition to aldehydes. Unfortunately, the N-neopentyl diamide **1b**, which (as the anion) gave high selectivity upon addition to aldehydes (60–93% d.e.), failed to react with *trans* imines **2a–d** over extended periods of time at room temperature. This lack of reactivity was attributed to severe steric hindrance caused by the bulky neopentyl groups. However, the diamide **1b**, did successfully react with 1-pyrroline trimer (Scheme II) to give aminophosphonamide **3g**. Petrillo and Spitzmiller have reported the addition of diethyl phosphite to 1-pyrroline trimer.[7] The trimer is thought to exist in equilibrium with the cyclic imine monomer in acid conditions, which by its cyclic nature is *cis*.[8] The addition of **1b** to pyrroline was best achieved using $TiCl_4$ in CH_2Cl_2 solution. These conditions produced a 100% conversion (44% isolated), but virtually no stereoselectivity. The use of $BF_3 \cdot OEt_2$ resulted in a much slower reaction, giving only 23% conversion after 19 hours, but with improved stereoselectivity (3:1).

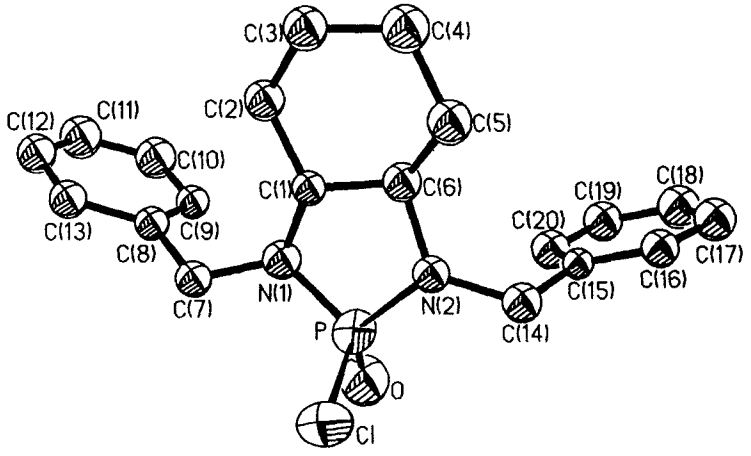
Although the best results were obtained with three equivalents of $BF_3 \cdot OEt_2$ in toluene at $-70°C$, other Lewis acids were examined. Whereas $TiCl_4$ greatly enhanced the reactivity of the neopentyl diamide **1b**, similar results to $BF_3 \cdot OEt_2$ were observed with benzyl diamide **1a** and imines **2a** and **2b**. The N-benzyl diamide **1a** failed to react with imine **2a** using $AlMe_3$ and $SnCl_2$ as catalyst. An unexpected product was formed when attempting to catalyze the addition of phosphorus acid diamide **1a** to imine **2a**, with $SnCl_4$. None of the expected 1-aminophosphonamide was formed, but a chlorophosphonamide **5** was obtained in moderate yield (30%). Further studies showed that the presence of imine has no effect on this reaction.



SCHEME II



SCHEME III



STRUCTURE 1 Thermal ellipsoid plot (*SHELXTL-Plus*) of the chlorophosphonamide **5**. Ellipsoid are scaled to enclose 50% probability (P and Cl only).

TABLE II

Bond lengths (Å) and bond angles (°)

P-Cl	2.016 (8)	P-O	1.488 (12)
P-N(1)	1.621 (14)	P-N(2)	1.619 (14)
N(1)-C(1)	1.581 (20)	N(1)-C(7)	1.442 (20)
N(2)-C(6)	1.496 (21)	N(2)-C(14)	1.474 (21)
C(1)-C(2)	1.518 (23)	C(1)-C(6)	1.483 (24)
C(2)-C(3)	1.581 (24)	C(3)-C(4)	1.506 (24)
C(4)-C(5)	1.527 (24)	C(5)-C(6)	1.602 (24)
C(7)-C(8)	1.493 (20)	C(8)-C(9)	1.394 (22)
C(8)-C(13)	1.407 (22)	C(9)-C(10)	1.379 (24)
C(10)-C(11)	1.347 (27)	C(11)-C(12)	1.346 (24)
C(12)-C(13)	1.373 (22)	C(14)-C(15)	1.452 (21)
C(15)-C(16)	1.335 (22)	C(15)-C(20)	1.457 (22)
C(16)-C(17)	1.383 (23)	C(17)-C(18)	1.426 (25)
C(18)-C(19)	1.340 (27)	C(19)-C(20)	1.378 (25)
Cl-P-O	105.5 (6)	Cl-P-N(1)	108.9 (5)
O-P-N(1)	115.8 (8)	Cl-P-N(2)	106.1 (5)
O-P-N(2)	121.3 (8)	N(1)-P-N(2)	98.5 (7)
P-N(1)-C(1)	104.3 (9)	P-N(1)-C(7)	123.0 (10)
C(1)-N(1)-C(7)	118.0 (12)	P-N(2)-C(6)	110.1 (10)
P-N(2)-C(14)	126.0 (11)	C(6)-N(2)-C(14)	123.5 (13)
N(1)-C(1)-C(2)	112.7 (12)	N(1)-C(1)-C(6)	102.0 (12)
C(2)-C(1)-C(6)	110.3 (14)	C(1)-C(2)-C(3)	104.3 (13)
C(2)-C(3)-C(4)	112.5 (15)	C(3)-C(4)-C(5)	114.0 (14)
C(4)-C(5)-C(6)	102.2 (14)	N(2)-C(6)-C(1)	103.7 (13)
N(2)-C(6)-C(5)	114.7 (13)	C(1)-C(6)-C(5)	107.8 (13)
N(1)-C(7)-C(8)	113.5 (12)	C(7)-C(8)-C(9)	120.2 (14)
C(7)-C(8)-C(13)	123.8 (14)	C(9)-C(8)-C(13)	115.6 (14)
C(8)-C(9)-C(10)	120.2 (15)	C(9)-C(10)-C(11)	122.8 (17)
C(10)-C(11)-C(12)	117.9 (18)	C(11)-C(12)-C(13)	121.7 (17)
C(8)-C(13)-C(12)	121.3 (15)	N(2)-C(14)-C(15)	115.9 (13)
C(14)-C(15)-C(16)	123.5 (14)	C(14)-C(15)-C(20)	121.2 (14)
C(16)-C(15)-C(20)	115.0 (14)	C(15)-C(16)-C(17)	127.6 (16)
C(16)-C(17)-C(18)	115.3 (16)	C(17)-C(18)-C(19)	120.2 (17)
C(18)-C(19)-C(20)	122.8 (17)	C(15)-C(20)-C(19)	119.1 (15)

The formation of a white precipitate (presumably $SnCl_2$) indicated that the $SnCl_4$ acted as a mild oxidizing agent for the P—H bond of phosphorus acid diamides. In contrast, exposure of dimethyl phosphite to excess $SnCl_4$ gave only starting materials. This is probably due to differences in oxidation potential between dimethylphosphite and the phosphorus acid diamide. Similar chlorophosphonamides, formed by addition of diamines to $P(O)Cl_3$ have been used to determine the optical purity of chiral alcohols and thiols.[9]

The ^{13}C and ^{1}H NMR spectra of chlorophosphonamide **5** appeared very similar to those of its parent phosphorous acid diamide **1a**. The only major change observed was the absence of the phosphorus-bound proton in the ^{1}H NMR spectrum. The ^{31}P resonance was downfield of the parent diamide by 14 ppm at δ 33.8. Mass spectroscopy and elemental analysis indicated the presence of chlorine in the molecule. Final proof of the structure was obtained by X-ray crystallography (Structure 1).

Clear, colorless crystals of chlorophosphonamide **5** suitable for X-ray analysis were obtained from EtOAc/hexanes solution at room temperature. Although the crystal was weakly diffracting, which resulted in a lack of observed data, the structure was solved (R = 8.78%), confirming our initial assignment as the chlorophosphonamide. The crystal structures of some related bicyclic phosphonamides have been reported.[10,11] The P—Cl bond length {2.016(8) Å} is in agreement with the expected value for a P(O)—Cl bond.[12]

DISCUSSION

Hanessian *et al.*[13] have studied the alkylation reactions of the α-anions of chiral N,N′-dimethyl bicyclic phosphonamides in the synthesis of α-amino, chloro and alkyl substituted alkyl phosphonic acids.[13] The bicyclic phosphonamides display high selectivity in many of these C—C bond formations. The selectivity has been rationalized on the basis of the topology of these bicyclic systems.[13] The geometry of the nitrogen atoms in the bicyclic phosphonamides[10] are midway between pyramidal and trigonal and the exocyclic nitrogen substitutents (Me) are syn to the axial cyclohexyl protons and thus anti to each other. In this conformation, the chiral nitrogen atoms adopt the opposite configuration to each other and act to project the chirality of the molecule closer to the reacting center. Thus, the phosphonamide C-1′ anion has one face blocked and one face accessible to an approaching electrophile (Figure 1).

In the reaction of phosphorous acid diamides with imines, both reagents are probably complexed to BF_3, with the phosphorus diamide in the trivalent form

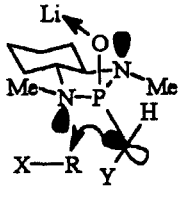
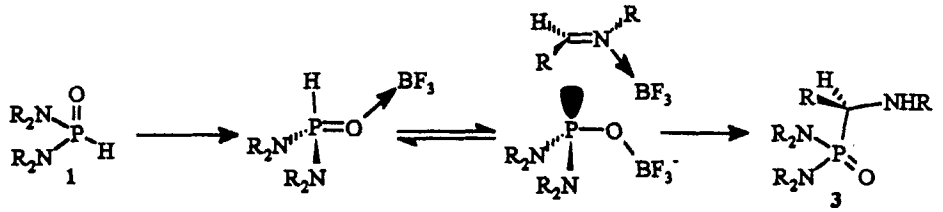


FIGURE 1 (Reference 13).



SCHEME IV

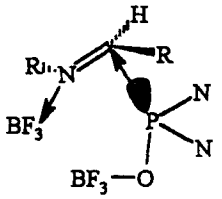


FIGURE 2

(Scheme IV). Although it is conceivable that the N-substituents serve the same stereodirecting function in the additional reactions of both the C-1′ anions and phosphorus acid diamide, there are several key differences between these reactions which may result in the diminished selectivities. The effective bonding distance of the C—C bond is considerably shorter than the P—C bond. The complexed imine is expected to react with the lone pair of phosphorus acid diamide in the trivalent form (Scheme IV), and thus approach from above and slightly in front of the plane of the five membered ring (Figure 2). These factors require that N-substitutents exert their stereodirecting effect at a greater distance and in a different orientation when compared to the C-1′ anions. The N-neopentyl substituent is able to perform this stereo directing function in the addition of diamide anions to aldehydes,[6] but the N,N′ neopentyl diamide **1b** is unreactive in Lewis acid catalyzed addition to imines. The N-benzyl diamide **1a**, which is reactive under the Lewis acid catalyzed conditions, gives lower selectivities in the anion chemistry. In general, the diamides **1a** and **1b** are less reactive than dimethylphosphite in Lewis acid catalyzed additions to imines.[14]

In conclusion, we have shown that chiral phosphorous acid diamides undergo Lewis acid catalyzed additions to imines to give 1-aminophosphonamides with moderate stereoselectivity. In addition, the phosphorous acid diamides are oxidized under mild, neutral conditions with $SnCl_4$ to give chlorophosphonamides.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian XL-300 spectrometer in $CDCl_3$ solution at 300, 75 and 121 MHz, respectively. The ^1H chemical shifts are reported in ppm downfield from Me_4Si, the ^{31}P chemical shifts are reported relative to external H_3PO_4, and the ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Mass spectra were determined on a Varian Mat 331A spectrometer and microanalyses were performed by Atlantic Microlab, Inc. High resolution mass spectra were performed by Monsanto Company. Toluene and methylene chloride were distilled from CaH_2. Imines were prepared

via condensation of aldehydes with primary amines and purified by vacuum distillation. 1-Pyrroline trimer was prepared according to the method of Nomura *et al.*,[15] and benzaldehyde N-trimethylsilylimine was prepared according to the method of Seebach and coworkers.[16] Chiral phosphorous acid diamides **1** were prepared according to the previously published procedure.[5]

General Procedure for 1-Aminophosphonamides

A solution of the phosphorous acid diamide **2** (0.100 g), and the imine **3** (see below) in toluene (3 mL) was cooled to −70°C. Boron trifluoride etherate (3 eq.) was added and the resulting suspension was stirred for 3.5–24 hrs (reaction progress was monitored by ^{31}P NMR spectroscopy). The reaction was quenched with triethylamine and the mixture was diluted with $CHCl_3$. The organic layer was washed twice with H_2O, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product. The product was isolated by column chromatography on SiO_2 eluting with $CHCl_3$ (unless otherwise indicated).

2-[(N-Benzylamino)-phenylmethyl]-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzodiazaphosphole-2-oxide (**3a**). Reaction of phosphorous acid **1a** (0.300 mol), imine **2a** (0.487 mmol) and $BF_3 \cdot OEt_2$ (0.902 mmol) at −72°C for 3.5 hrs gave amino phosphonamide **3a** as a mixture of diastereoisomers. An oil; IR ($CHCl_3$) 3682, 3619, 3020, 1522, 1220 cm^{-1}; ^1H NMR δ 7.54–7.12 (m, 20H), 4.80–4.66 (m, 1H), 4.24–4.10 (m, 2H), 3.99–3.71 (m, 2H), 3.63–3.42 (m, 2H), 2.65–2.54 (m, 2H), 2.24–2.15 (m, 1H), 1.80–1.60 (m, 2H), 1.52–1.24 (m, 3H), 0.98–0.55 (m, 3H); ^{13}C NMR δ 140.9–136.2 and 129.0–126.5 (complex multiplet, aromatic carbons), 64.25, 64.15, 64.0, 63.9, 63.7, 62.8, 62.7, 62.3, 62.1, 61.8, and 61.7 (C1′, C3a and C7a), 52.1 [d, J_{PC} = 16.6 Hz, NCH_2 (major)], 51.3 [d, J_{PC} = 16.4 Hz, NCH_2 (minor)], 47.8, 47.7, 46.9, 46.8, 46.7, and 46.6 ($P(O)NCH_2$), 29.7, 29.6, 29.5, 29.4, 28.8, 28.7 and, 28.6 (C4 and C7), 24.3, 24.2, 24.0 and, 23.9 (C5 and C6); ^{31}P NMR δ 37.3 (major), 35.5 (minor); MS(EI/DIP) m/z (rel. intensity) 197 (8), 196 (49), 92 (14), 91 (100), 65 (13), 28 (8). Anal. Calcd for $C_{34}H_{38}N_3OP \cdot 0.5H_2O$: C, 74.98; H, 7.22; N, 7.71. Found: C, 75.17; H, 7.23; N, 7.67.

2-[1-(N-Benzylamino)-2-methylpropyl]-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzodiazaphosphole-2-oxide (**3b**). Reaction of phosphorous acid **1a** (0.294 mmol), imine **2b** (0.477 mmol) and $BF_3 \cdot OEt_2$ (0.894 mmol) at −75°C for 6.5 hrs gave amino phosphonamide **3b** as mixture of diastereoisomers. An oil; IR ($CHCl_3$) 3682, 3620, 2020, 2975, 1520, 1425, 11215, 765 (brd), 670 cm^{-1}; ^1H NMR δ 7.50–7.12 (m, 15H), 4.60–4.30 (m, 2H), 4.20–3.67 (m, 4H), 3.20–2.97 (m, 1H), 2.89–2.70 (m, 2H), 2.35–2.21 (m, 1H), 2.19–2.03 (m, 1H), 1.70–1.50 (m, 4H), 1.29–1.15 (m, 1H), 0.80–1.15 (m, 9H); ^{13}C NMR δ 140.9–138.4 and 128.4–126.57 (complex multiplet, aromatic carbons), 65.53, 65.47, 64.4, 64.3, 64.21, 64.18, 64.0, 63.9, 62.6, and 61.0 (C1′, C3a and C7a), 54.8 [d, J_{PC} = 8.6 Hz, NCH_2 (minor)], 54.3 [d, J_{PC} = 11.3 Hz, NCH_2 (major)], 49.3, 48.5, 46.6, and 46.2 ($P(O)NCH_2$), 30.3–28.1 (complex multiplet, C4, C7 and C2′), 24.6, 24.5, 24.4, 24.3, and 22.74 (C5 and C6), 22.7 (d, J_{PC} = 3.5 Hz), 22.5, 18.6 (d, J_{PC} = 3.1 Hz), and 17.9 (d, J_{PC} = 2.0 Hz) (methyls); ^{31}P NMR δ 43.4 (major), 41.9 (minor); MS(EI/DIP) m/z (rel. intensity) 341 (39), 294 (16), 250 (68), 237 (29), 107 (25), 91 (100). Anal. Calcd for $C_{31}H_{40}N_3OP \cdot 0.5Et_2O$: C, 73.58; H, 8.42; N, 7.80. Found: C, 73.58; H, 8.13; N, 7.69.

2-[1-(N-Benzylamino)-ethyl]-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzodiazaphosphole-2-oxide (**3c**). Reaction of phosphorous acid **1a** (0.294 mmol), imine **2c** (0.766 mmol) and $BF_3 \cdot OEt_2$ (0.894 mmol) at −70°C for 5.0 hrs gave amino phosphonamide **3c** as mixture of diastereoisomers. An oil; IR ($CHCl_3$) 4215, 3620, 3020, 1525, 1425, 1215, 910, 760 (brd), 670 cm^{-1}; ^1H NMR δ 7.50–7.15 (m, 15H), 4.63–4.41 (m, 2H), 4.12–3.81 (m, 3H), 3.65 (d, J = 9.0 Hz, major), 3.61 (d, J = 9.0 Hz, minor), 3.20–3.05 (m, 1H), 3.04–2.80 (m, 1H), 1.87 (br s, 1H), 1.80–1.51 (m, 4H), 1.34–1.24 (m, 4H), 1.20–1.02 (m, 2H), 1.01–0.80 (m, 2H); ^{13}C NMR δ 140.5–139.0 and 128.2–126.6 (complex multiplet, aromatic carbons), 65.6, 65.5, 65.15, 65.09, 64.41, 64.37, 64.34, and 64.28 (C3a and C7a), 53.2, 52.2, 51.9, 51.74, 51.67, 51.5, 51.4, and 50.5, (C1′ and NCH_2) 48.6, 48.5, 48.4, 46.9, 46.8, 46.4, and 46.3 ($P(O)NCH_2$), 30.3, 30.2, 30.1, 30.0, 29.9, 29.8, 29.7, 29.5, and 29.4 (C4 and C7), 24.4 and 24.3 (C5 and C6), 14.8 and 14.4 (Me); ^{31}P NMR δ 43.3 (major), 41.1 (minor); MS(EI/DIP) m/z (rel. intensity) 341 (7), 250 (10), 134 (44), 92 (15), 91 (100), 65 (11). HRMS(FAB/PEG-300), $(M + 1)^+$ Calcd for $C_{29}H_{36}N_3OP$: 474.2674. Found: 474.2683.

2-[(N-Prop-2-enylamino)-phenylmethyl]-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzoidiazaphosphole-2-oxide (**3d**). Reaction of phosphorous acid **1a** (0.295 mmol), imine **2d** (0.606 mmol) and $BF_3 \cdot OEt_2$ (0.984 mmol) at −65°C for 7.3 hrs gave, after column chromatography (SiO_2 eluting with 9:0.6:0.3; hexanes, CH_2Cl_2, CH_3OH), amino phosphonamide **3d** as a mixture of diastereoisomers. An oil; IR ($CHCl_3$) 306, 3030, 2940, 2865, 1495, 1455, 1210, 1180, 915, 725 (brd), cm^{-1}; ^1H NMR δ 7.60–7.10 (m, 15H), 5.88–5.72 (m, 1H), 5.11–5.02 (m, 2H), 4.81–4.67 (m, 1H), 4.28–4.13 (m, 3H), 3.81 (dd, J = 16.1, 6.6 Hz, minor), 3.58 (dd, J = 16.4, 7.6 Hz, major), 3.27–3.13 (m, 1H), 2.97–2.85

(m, 1H), 2.67–2.55 (m, 1H), 2.40–2.20 (m, 1H), 1.77–1.55 (m, 2H), 1.52–1.25 (m, 3H), 0.53–1.12 (m, 4H); ^{13}C NMR δ 140.8 [d, J_{PC} = 3.6 Hz, (major)], 140.6 [d, J_{PC} = 4.1 Hz, (minor)], 137.6 (d, J_{PC} = 2.3 Hz), and 137.5 (aromatic ipso carbons), 137.1, 136.3, 136.2 and 136.0 (CH=CH_2), 128.8–126.4 (complex multiplet, aromatic carbons), 116.0 and 115.9 (CH=CH_2), 64.2, 64.1, 64.0, 63.9, 63.8, 63.7, 62.7, 62.6, 62.2, 62.1, 61.8, and 61.7 (C1′, C3a and C7a), 50.6 [d, J_{PC} = 16.4 Hz, NCH_2 (major)], 49.8 [d, J_{PC} = 16.3 Hz, NCH_2 (minor)], 47.8 [d, J_{PC} = 2.5 Hz, (minor)], 47.6 [d, J_{PC} = 2.3 Hz, (major)], 46.8 (d, J_{PC} = 5.0 Hz), and 46.6 (d, J_{PC} = 5.2 Hz) (P(O)NCH_2), 29.7 (minor), 29.6 (major), 29.5 (minor), 28.7 (minor), and 28.6 (major) (C4 and C7), 24.2 (minor), 24.1 (major), 24.0 (major), and 23.9 (minor) (C5 and C6); ^{31}P NMR δ 37.2 (major), 35.2 (minor); MS(EI/DIP) m/z (rel. intensity) 340 (16), 249 (22), 236 (10), 92 (10), 91 (100), 65 (13). HRMS(FAB/PEG-300), $(M + 1)^+$ Calcd for $C_{30}H_{36}N_3OP$: 486.2674. Found: 486.2677.

2-(Aminophenylmethyl)-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzodiazaphosphole-2-oxide (**3e**). Reaction of phosphorous acid **1a** (0.294 mmol), imine **2e** (0.739 mmol), and $BF_3 \cdot OEt_2$ (0.894 mmol) at −75°C for 5.5 hrs gave amino phosphonamide **3e** as a mixture of diastereoisomers. An oil; IR ($CHCl_3$) 3025, 2940, 2865, 1640, 1455, 1105, 915, 750 (brd), 650 cm^{-1}; ^{1}H NMR δ 8.27–8.14 (m, 1H), 7.78–7.52 (m, 1H), 7.48–7.03 (m, 13H), 5.00 (d, J_{PH} = 15.8 Hz, minor), 4.91 (d, J_{PH} = 16.5 Hz, major), 4.80–4.49 (m, 1H), 4.47–4.10 (m, 2H), 4.08–3.84 (m, 2H), 3.69–3.61 (m, 1H), 2.64–2.51 (m, 1H), 2.33–2.22 (m, 1H), 1.70–1.50 (m, 1H), 1.45–1.28 (m, 3H), 0.51–0.93 (m, 4H); ^{13}C NMR δ 140.71–130.7 (complex multiplet, aromatic ipso carbons), 128.9–126.6 (complex multiplet, aromatic carbons), 64.3 (d, J_{PC} = 7.1 Hz), 64.0 (d, J_{PC} = 7.1 Hz), 63.1 (d, J_{PC} = 5.0 Hz), and 62.3 (d, J_{PC} = 5.9 Hz) (C3a and C7a), 48.0, 47.8, 46.8, and 46.2 (P(O)NCH_2), 29.7, 29.1, 29.0, and 28.9 (C4 and C7), 24.3 and 24.0 (C5 and C6); ^{31}P NMR δ 34.4 (major), 34.3 (minor); MS(EI/DIP) m/z (rel. intensity) 443 (16), 341 (20), 248 (11), 195 (29), 91 (100), 89 (11). HRMS(EI/DIP), Calcd for $C_{27}H_{32}N_3OP$: 445.2283. Found: 445.2227.

2-(Pyrrolidin-2-yl)-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzodiazaphosphole-2-oxide (**3f**). Reaction of phosphorous acid **1a** (0.299 mmol), imine **2f** (0.289 mmol), and $BF_3 \cdot OEt_2$ (0.903 mmol) at −65°C for 6.0 hrs gave amino phosphonamide **3f** as a mixture of diastereoisomers. An oil; IR ($CHCl_3$) 3155, 2940, 2865, 1455, 1380, 1205, 1105, 900, 750, 650 cm^{-1}; ^{1}H NMR δ 7.45–7.10 (m, 10H), 4.63–4.40 (m, 2H), 4.06–3.87 (m, 2H), 3.35–3.25 [m, (major)], 3.20–3.10 [m, (minor)], 3.03–2.90 (m, 1H), 2.89–2.65 (m, 3H), 2.35–2.05 (br s, 1H), 1.99–1.63 (m, 1H), 1.63–1.40 (m, 7H), 1.20–0.80 (m, 4H); ^{13}C NMR δ 140.3 [d, J_{PC} = 4.3 Hz, (minor)], 140.1 [d, J_{PC} = 4.0 Hz, (major)], 139.3 [d, J_{PC} = 5.3 Hz, (major)], and 139.1 [d, J_{PC} = 5.6 Hz, (minor)] (aromatic ipso carbons), 128.2–126.7 (complex multiplet, aromatic carbons), 65.1 [d, J_{PC} = 4.7 Hz, (major)], 64.6 [d, J_{PC} = 4.8 Hz, (minor)], 64.4 [d, J_{PC} = 7.0 Hz, (major)], and 64.0 [d, J_{PC} = 7.2 Hz, (minor)] (C3a and C7a), 57.9 [d, J_{PC} = 132 Hz, C2′ (minor)], 56.9 [d, J_{PC} = 131 Hz, C2′ (major)], 48.9, 48.5, 48.0, 47.8, 47.6, 46.8, 46.7, 46.7, and 46.6 (P(O)NCH_2 and C5′), 30.3–29.5 (complex multiplet, C4 and C7), 27.62 and 27.58 (C3′), 25.92, 25.87, 25.79, and 25.72 (C4′), 24.34 and 24.28 (C5 and C6); ^{31}P NMR δ 41.3 (major), 40.6 (minor); MS(EI/DIP) m/z (rel. intensity) 341 (26, 250 (29), 237 (14), 106 (13), 92 (11), 91 (100). Anal. Calcd for $C_{24}H_{32}N_3OP \cdot 0.5H_2O$: C, 68.88; N, 7.95; N, 10.04. Found: C, 68.79; H, 7.95; N, 9.64.

2-(Pyrrolidin-2-yl)-2,3,3a,4,5,6,7,7a-octahydro-1,3-bis(2,2-dimethylpropyl)-1H-1,3,2-benzodiazaphosphole-2-oxide (**3g**). Reaction of phosphorous acid **1b** (0.333 mmol), imine **2f** (0.506 mmol), and $TiCl_4$ (0.669 mmol) in CH_2Cl_2 at 3°C for 63 hrs gave amino phosphonamide **3g**, after column chromatography (SiO_2 eluting with 98:2; $CHCl_3$, CH_3OH), as a mixture of diastereoisomers. An oil; IR($CHCl_3$) 3020, 2955, 1525, 1480, 1425, 1220, 910 cm^{-1}; ^{1}H NMR δ 3.50–3.17 (m, 1H), 3.12–3.00 (m, 2H), 2.95–2.58 (m, 3H), 2.47–2.20 (m, 3H), 2.10–1.82 (m, 4H), 1.80–1.65 (m, 4H), 1.30–1.15 (m, 5H), 0.92 (s, 9H), 0.90 (s, 4.5H), 0.89 (s, 4.5H); ^{13}C NMR δ 65.3 (d, J_{PC} = 6.5 Hz), 65.1, 64.1 (d, J_{PC} = 6.9 Hz), 58.3 (d, J_{PC} = 11.5 Hz) (C3a and C7a), 56.7, 56.54 (minor), 56.50 (major), 55.15 (major), 55.12 (minor), 54.62 (major), 54.59 (minor), and 54.2 (major), 54.1 (minor) (P(O)NCH_2 and C2′), 47.53 [d, J_{PC} = 14.5 Hz, (major)], and 47.48 [d, J_{PC} = 13.6 Hz, (minor)] (C5′), 33.0, 32.7, and 31.8 ($Me_3\underline{C}$), 31.0–28.2 (complex multiplet, C4, C7, and C3′), 29.1 ($\underline{Me}_3C$), 28.4 ($\underline{Me}_3C$), 25.7 and 25.6 (C4′), 24.7 and 24.5 (C5 and C6); ^{31}P NMR δ 42.0 (minor), 41.5 (major); MS(EI/DIP) m/z (rel. intensity) 243 (100), 81 (16), 70 (88), 57 (28), 44 (17), 42 (44). HRMS(FAB/PEG-300), $(M + 1)^+$ Calcd for $C_{20}H_{40}N_3OP$: 370.2987. Found: 370.2993.

2-Chloro-2,3,3a,4,5,6,7,7a-octahydro-1,3-bis(phenylmethyl)-1H-1,3,2,-benzoidiazaphosphole-2-oxide (**5**). To a solution of phosphorous acid **1a** (0.101 g, 0.297 mmol) in toluene (3 mL) was added 1.0 M $SnCl_4$ in CH_2Cl_2 (0.893 mL, 0.893 mmol). The resulting solution was stirred magnetically at room temp.

for 23 hrs during which time a white precipitate formed. The reaction was quenched with triethylamine and the mixture was diluted with $CHCl_3$. The organic layer was washed twice with H_2O, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product. The product was isolated by column chromatography (SiO_2 eluting with $CHCl_3$) to give the chlorophosphonamide **5** (30%); mp 220.5–222.5°C; $[\alpha]_D$ −20.8° (c = 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.50–7.20 (m, 10H), 4.57–4.39 (m, 2H), 4.20 (dd, 1H, *J* = 15.9, 10.5 Hz), 3.74 (dd, 1H, *J* = 15.6, 7.6 Hz), 3.02–2.86 (m, 2H), 1.80–1.55 (m, 4H), 1.28–0.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 137.9 (d, J_{PC} = 9.7 Hz) and 137.4 (d, J_{PC} = 3.5 Hz) (aromatic ipso carbons), 128.4–127.26 (aromatic carbons), 63.4 (d, J_{PC} = 10.3 Hz) and 63.1 (d, J_{PC} = 10.4 Hz) (C3a and C7a), 47.5 (d, J_{PC} = 2.7 Hz) and 46.7 (d, J_{PC} = 4.4 Hz) ($P(O)NCH_2$), 29.2 (d, J_{PC} = 10.4 Hz) and 29.1 (d, J_{PC} = 5.5 Hz) (C4 and C7), 24.2, 23.9 and 23.8 (C5 and 6); ^{31}P NMR ($CDCl_3$) δ 33.8; MS(CI/GC/CH_4) m/z (rel. intensity) 375 ($[M + 1]^+$, 100), 340 (10), 339 (41). HRMS(EI/DIP), Calcd for $C_{20}H_{24}N_2OPCl$: 374.1315. Found: 374.1363.

X-Ray crystal structure determination. Clear, colorless crystals of 2-Chloro-2,3,3a,4,5,6,7,7a-octahydro-1,3-dibenzyl-1H-1,3,2-benzodiazaphosphole-2-oxide suitable for X-ray analysis were obtained from EtOAc/hexanes solution at room temperature. The details for the crystal structure determination are listed in Table III, the final atomic coordinates are given in Table IV. Data reduction, structure solution and refinement were carried out using *SHELXTL-Plus*.[17] The structure was solved by direct methods and refined successfully in the space group $P2_1$. Full-matrix least-squares refinement was carried out by minimizing $w(F_o - F_c)$.[2] All the non-H atoms were refined isotropically, except for P and Cl which were refined anisotropically to convergence. All H-atoms were included in calculated positions in the final refinement. The crystal data hae been deposited at the Cambridge Crystallographic Data Center.[18]

TABLE III

Summary of the crystal structure determination

Crystal data	
$C_{20}H_{24}N_2OPCl$	MoKα radiation
M_r = 374.8	λ = 0.71073 Å
Monoclinic	2θ = 3-60°
$P2_1$	μ' = 0.298 mm^{-1}
a = 10.998 (9) Å	*T* = 298 K
b = 7.712 (4) Å	Needle-shaped
c = 11.159 (7) Å	0.5 x 0.1 x 0.1 mm
β = 94.83 (6)°	
V = 943.1 (11) $Å^3$	
Z = 2	
D_x = 1.320 Mg/m^3	
F(000) = 396	
Data collection	
Siemens *R3m/V* diffractometer	R_{int} = 0.0561
θ-2θ scans	θ_{max} = 30 °
Absorption correction: none	*h* = -15 to 14
5223 measured reflections	*k* = -9 to 10
4478 independent reflections	*l* = -15 to 15
1138 observed reflections [F > 4.0σ(F)]	3 standard reflections measured for every 100 reflections
Refinement	
Final *R* = 0.0878	$(\Delta/\sigma)_{max}$ = 0.317
wR = 0.1003	$\Delta\rho_{max}$ = 0.80 e $Å^{-3}$
S = 1.17	$\Delta\rho_{min}$ = 0.62 e $Å^{-3}$
1138 reflections	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
112 parameters	
All H-atom parameters fixed	
$w = 1/[\sigma^2(F) + 0.0025F^2]^{1/2}$	

TABLE IV

Fractional atomic coordinates and equivalent isotropic thermal parameters (Å^2). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U_{eq}
P	7811 (5)	1320	7906 (5)	44 (2)
Cl	9177 (5)	518 (10)	9094 (5)	76 (2)
O	7787 (14)	3242 (16)	8020 (13)	70 (4)
N(1)	8042 (11)	575 (18)	6587 (11)	39 (4)
N(2)	6637 (11)	150 (16)	8158 (11)	34 (4)
C(1)	7442 (15)	-1289 (19)	6552 (14)	28 (4)
C(2)	7200 (17)	-1989 (20)	5283 (15)	39 (5)
C(3)	6535 (14)	-3779 (23)	5450 (15)	44 (5)
C(4)	5430 (15)	-3600 (26)	6151 (15)	52 (5)
C(5)	5700 (16)	-2799 (23)	7397 (15)	45 (5)
C(6)	6274 (15)	-960 (21)	7088 (16)	37 (5)
C(7)	9180 (14)	791 (22)	6049 (13)	34 (4)
C(8)	9021 (14)	1153 (22)	4731 (13)	32 (4)
C(9)	8101 (14)	2267 (23)	4267 (14)	33 (4)
C(10)	7983 (17)	2655 (23)	3056 (17)	52 (5)
C(11)	8789 (16)	2117 (25)	2290 (18)	55 (5)
C(12)	9677 (15)	1024 (22)	2713 (15)	43 (5)
C(13)	9839 (14)	586 (22)	3909 (13)	38 (4)
C(14)	5918 (14)	285 (24)	9211 (14)	39 (5)
C(15)	4671 (13)	892 (18)	8970 (13)	26 (4)
C(16)	3752 (14)	373 (24)	9592 (14)	38 (4)
C(17)	2563 (15)	971 (22)	9491 (15)	48 (5)
C(18)	2306 (18)	2307 (28)	8624 (16)	54 (5)
C(19)	3189 (16)	2894 (22)	7971 (16)	46 (5)
C(20)	4370 (16)	2283 (24)	8112 (15)	44 (5)

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