JOC Article

Synthesis of P,N-Heterocycles from ω-Amino-*H*-Phosphinates: Conformationally Restricted α-Amino Acid Analogs

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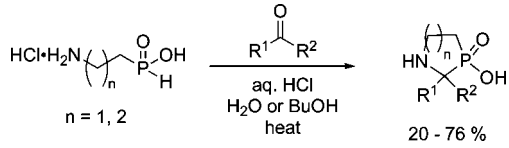

P,N-Heterocycles (3-hydroxy-1,3-azaphospholane and 3-hydroxy-1,3-azaphosphorinane-3-oxide) are synthesized in moderate yield from readily available ω-amino-*H*-phosphinates and aldehydes or ketones via an intramolecular Kabachnik−Fields reaction. The products are conformationally restricted phosphinic analogs of α-amino acids. The multigram-scale syntheses of the $H_2N(CH_2)_nPO_2H_2$ phosphinic precursors ($n = 1, 2, 3$) and some derivatives are also described.

Introduction

Analogs of α-amino acids for use in peptidomimetics are an important and well-studied area of research. The reason rests in the importance of peptidomimetics for the design of medicinally useful compounds.[1] At the same time, the Kabachnik−Fields reaction, which is the "phospha-Mannich" reaction of phosphinylidene [P(O)H] compounds, has been investigated and used extensively since its initial discovery in the early 1950s.[2] However, applications of the reaction to intramolecular cases is surprisingly lacking. In addition, very few P,N-heterocycles have been described in the literature, and there are only two known examples of simple 3-hydroxy-1,3-azaphospholane and 3-hydroxy-1,3-azaphosphorinane-3-oxides (both P−O esters, **1** and **2**, respectively, Figure 1).[3] Other related heterocycles **3**−**5** have been reported.[4] In terms of simple ring systems, aminophosphines react with carbonyl compounds to provide heterocycles **6** and **7** in a lower oxidation state than compound **2** (Figure 1).[5] In general, these syntheses are lengthy and/or inconvenient and proceed in low overall yields.

Over the past several years, we have developed various methodologies for the synthesis of *H*-phosphinates,[6] and we became interested in the preparation of ω-amino-*H*-phosphinates, which have value in their own right.[7] Herein, we describe the syntheses of three ω-amino-*H*-phosphinates and, prompted by the availability of these precursors, their reactions with carbonyl compounds.

Results and Discussion

Synthesis of the ω-Amino-*H*-phosphinates Precursors. Since ω-amino-*H*-phosphinates have potential value for various applications, the multigram syntheses of the three precursors **8**−**10** (Figure 2) were developed. Several literature prepara-

(1) For some references on peptidomimetics and amino acid analogs, see: (a) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, published ASAP, DOI 10.1021/ar700263g. (b) Robinson, J. A. *Acc. Chem. Res.* **2008**, published ASAP, DOI 10.1021/ar700259k. (c) Avendano, C.; Menendez, J. C. *Clin. Trans. Oncol.* **2007**, *9*, 563. (d) Garner, J.; Harding, M. M. *Org. Biomol. Chem.* **2007**, *5*, 3577. (e) Murphy, P. V. *Eur. J. Org. Chem.* **2007**, 4177. (f) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. (g) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039. (h) Gante, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1699. (i) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

(2) (a) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079. (b) Matveeva, E. D.; Zefirov, N. S. *Dokl. Chem.* **2008**, *420*, 137. (c) Belakhov, V. V.; Shenin, Y. D.; Ionin, B. I. *Russ. J. Gen. Chem.* **2008**, *78*, 305. (d) Zefirov, N. S.; Matveeva, E. D. *ARKIVOC* **2008**, 1. (e) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263. (f) Matveeva, E. D.; Podrugina, T. A.; Prisyajnoy, M. V.; Zefirov, N. S. *Russ. Chem. Bull.* **2006**, *55*, 1209. (g) Cristau, H.-J.; Herve, A.; Virieux, D. *Tetrahedron* **2004**, *60*, 877. (h) Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, 2321. (i) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *381*, 643–644. (j) Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.* **1998**, *67*, 857.

(3) (a) compound **1** Maier, L. *Phosphorus Sulfur* **1981**, *11*, 149. (b) compound **2** Hewitt, D. G.; Teese, M. W. *Aust. J. Chem.* **1984**, *37*, 205.

(4) Compound **3**: Trishin, Y. G.; Namestnikov, V. I.; Bel'skii, V. K. *Russ. J. Gen. Chem.* **1999**, *69*, 1588. (b) Compound **4**: Campbell, M. M.; Carruthers, N. I.; Mickel, S. J.; Winton, P. M. *J. Chem. Soc., Chem. Commun.* **1984**, 200. (c) Compound **5a**: Yiotakis, A.; Vassiliou, S.; Jiracek, J.; Dive, V. *J. Org. Chem.* **1996**, *61*, 6601. (d) Compound **5b**: Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641.

(5) (a) Compound **6**: Issleib, K.; Winkelmann, H.; Abicht, H.-P. *Synth. React. Inorg., Met.-Org. Chem.* **1974**, *4*, 191. (b) Compound **7**: Issleib, K.; Oehme, H.; Lei*β*ring, E. *Chem. Ber.* **1968**, *101*, 4032.

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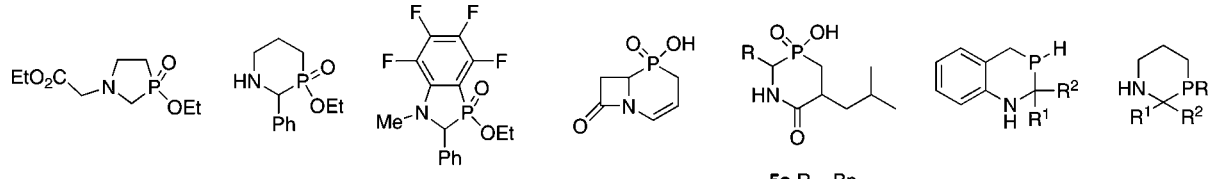


FIGURE 1. Some examples of known 1,3-azaphospho-heterocycles.

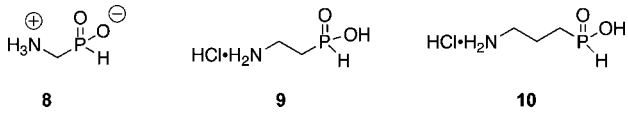


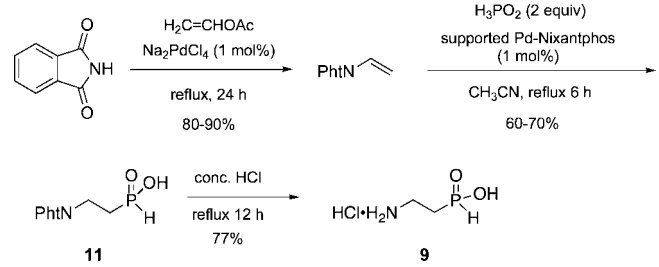
FIGURE 2. The three precursors used in this study.

tions of protected versions of **8** have appeared,[8] because of the utility of the synthons for phosphinopeptide synthesis.[9] A synthesis of aminomethyl-*H*-phosphinic acid **8** and some derivatives is described in Supporting Information.

2-Aminoethyl-*H*-phosphinic Acid. 2-Aminoethyl-*H*-phosphinic acid **9** was synthesized using our hydrophosphinylation of *N*-vinylphthalimide with hypophosphorous acid H_3PO_2 (Scheme 1).[10]

Phthalimide reacted with vinyl acetate according to the literature procedure.[11] Palladium-catalyzed hydrophosphinylation with H_3PO_2 using our reusable polymer-supported catalyst[10] gave phosphinic acid **11** in 60−70% yield. When the homogeneous catalyst (0.25 mol % Pd/xantphos) was used, **11** was obtained in 72−87% yield. Simple acid hydrolysis of phthalimide **11** gave hydrochloride **9** as a white solid. Other syntheses of 2-aminoethyl-*H*-phosphinic acid **9** and some derivatives have been reported previously.[12] Kafarski reported[8c] a nice preparation of **9** via Hoffman degradation (NaOH, Br_2, −15 °C, 77% yield after propylene oxide treatment) of $H_2PO_2CH_2CH_2$-$C(O)NH_2$ itself prepared by thermal conjugate addition of H_3PO_2 with acrylamide.[13]

SCHEME 1. Synthesis of 2-Aminoethyl-*H*-phosphinic Acid 9



3-Aminopropyl-*H*-phosphinic Acid. We[14] and others[15] have reported previously the preparation of the biologically active GABA analog 3-aminopropyl-*H*-phosphinic acid and related compounds. For the present study, we opted for a simple synthesis using our Pd-catalyzed hydrophosphinylation on ethyl *N*-allylcarbamate **12** in place of the more expensive benzyl and *tert*-butyl carbamates, since acid hydrolysis would ultimately be employed to form compound **10**. Scheme 2 shows the preparation of **10** from allylamine. As with *N*-vinylphthalimide, this reusable polymer catalyst[10] was employed to directly deliver *H*-phosphinic acid **13**. Hydrolysis then provided hydrochloride **10**. If the synthesis of **10** is desired, alternate routes via other intermediates[14] are more expensive, atom-wasteful, and lower-yielding in the case of **14**.[14a]

Overall, compounds **8**−**10** were synthesized in reasonable yields and on a multigram scale, using some methodologies we had developed previously. The syntheses are generally simpler than comparable literature approaches, and ion-exchange chromatography is avoided in all cases. With the compounds in hand,

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(9) For selected references, see: (a) Nasopoulou, M.; Georgiadis, D.; Matziari, M.; Dive, V.; Yiotakis, A. *J. Org. Chem.* **2007**, *72*, 7222. (b) Ye, Y.; Liu, M.; Kao, J. L.-F.; Marshall, G. R. *Biopolymers* **2007**, *89*, 72. (c) Li, B.; Cai, S.; Du, D.-M.; Xu, J. *Org. Lett.* **2007**, *9*, 2257. (d) Nasopoulou, M.; Matziari, M.; Dive, V.; Yiotakis, A. *J. Org. Chem.* **2006**, *71*, 9525. (e) Fisher, J. F.; Mobashery, S. *Cancer Metastasis Rev.* **2006**, *25*, 115. (f) Yiotakis, A.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135. (g) Palacios, F.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2004**, *8*, 1481. (h) Kruger, R. G.; Barkallah, S.; Frankel, B. A.; McCafferty, D. G. *Bioorg. Med. Chem.* **2004**, *12*, 3723. (i) Makaritis, A.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Chem. Eur. J.* **2003**, *9*, 2079. (j) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *Tetrahedron Lett.* **2001**, *42*, 4491. (k) Tokutake, N.; Hiratake, J.; Katoh, M.; Irie, T.; Kato, H.; Oda, J. *Bioorg. Med. Chem.* **1998**, *6*, 1935. (l) Jouin, P.; Coste, J.; Galeotti, N.; Campagne, J.-M.; Bedos, P.; Guillou, L. *Lett. Peptide Sci.* **1995**, *2*, 233. (m) Peyman, A.; Budt, K. H.; Spanig, J.; Ruppert, D. *Angew. Chem., Int. Ed.* **1993**, *32*, 1720. (n) Campagne, J. M.; Coste, J.; Guillou, L.; Heitz, A.; Jouin, P. *Tetrahedron Lett.* **1993**, *34*, 4181. (o) Campbell, M. M.; Carruthers, N. I.; Mickel, S. J. *Tetrahedron* **1982**, *38*, 2513.

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(12) (a) Livantsova, L. I.; Prishchenko, A. A.; Livantsov, M. V.; Nikolaev, S. N.; Grigor'ev, E. V. *Russ. J. Gen. Chem.* **2000**, *70*, 1484. (b) Maier, L.; Diel, P. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **1989**, *45*, 165. (c) See also refs 8c and 8d.

(13) Cates, L. A.; Li, V.-S. *Phosphorus, Sulfur Silicon* **1984**, *21*, 187.

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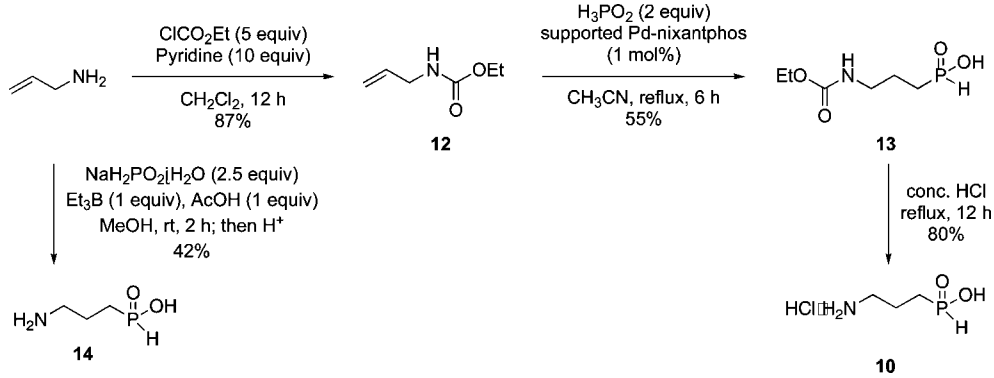
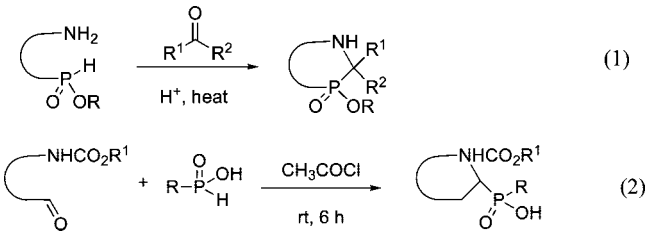
(15) (a) Gallop, M. A.; Xu, F.; Phan, T.; Dilip, U.; Peng, G. PCT Int. Appl. (2008),WO 2008033572 A1 20080320. (b) Hall, R. G.; Kane, P. D.; Bittiger, H.; Froestl, W. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 129. (c) Broan, C. J.; Cole, E.; Jankowski, K. J.; Parker, D.; Pulukkody, K.; Boyce, B. A.; Beeley, N. R. A.; Millar, K.; Millican, A. T. *Synthesis* **1992**, 63. (d) Baylis, E. K.; Bittiger, H.; Froestl, W.; Hall, R. G.; Maier, L.; Mickel, S. J.; Olpe, H. R. Eur. Pat. Appl. (1989),EP 319479 A2 19890607. (e) See also ref 8d.

SCHEME 2. Synthesis of 3-Aminopropyl-*H*-phosphinic Acid 10



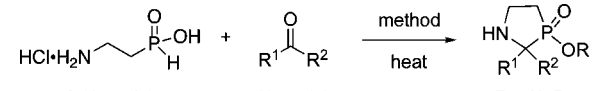
we then set out to study their reactions with carbonyl compounds for the formation of P,N-heterocycles (eq 1). Yiotakis, Dive, and co-workers have recently reported a different approach toward phosphinic peptidomimetics where the phosphorus atom is exocyclic, also using *H*-phosphinic acids, amines, and aldehydes (eq 2);[9a] however, in their case the aldehyde and amine functionalities are linked with a tether, whereas in our case, the amine and *H*-phosphinic acid are linked by a tether.

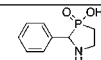
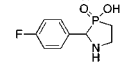
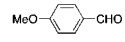
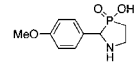
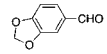
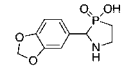
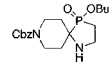


Reactions of ω-Amino-*H*-phosphinates 8−10 with Aldehydes and Ketones. The intramolecular Kabachnik−Fields reaction of synthons **8**−**10** was investigated with aldehydes and ketones. Maybe not surprisingly, the reaction of aminomethylphosphinate **8** resulted in intractable mixtures of products, although ^{31}P NMR peaks in the phosphetanic acid[16] range (δ 28 ppm) may indicate some cyclization. The results are not unexpected since the 3-hydroxy-1,3-azaphosphetane oxide ring system is apparently unknown. There are, however, a few four-membered P,N-heterocycles that have been described.[17] Instead, focus was shifted on the more promising five- and six-membered ring precursors **9** and **10**.

2-Substituted 3-Hydroxy-1,3-azaphospholane-3-oxides. The reaction of 2-aminoethyl-*H*-phosphinate **9** with carbonyl compounds took place smoothly, in acceptable yields (Table 1). Although the isolated yields are relatively low, the compounds were obtained directly as pure solids by precipitation from the reaction mixtures (entries 1−4) or after chromatography on silica gel for the phosphinic esters (entries 5−7). Reaction with benzaldehyde under method B provided the butyl ester, which could be isolated after acetylation (entry 5). In general, prior esterification of **9** via azeotropic water removal in a Dean−Stark trap gave better results than the direct reaction; however direct heating of **9** with benzaldehyde (entry 1b, Method C) gave an improved yield of heterocycle **15**, although this was not true with other substrates. Thus, minor changes in the reaction conditions sometimes resulted in significant differences in isolated yields depending on the carbonyl compounds. Method B was employed with ketones because method A failed to deliver the phosphinic acids as precipitates in these cases. Thus, in order to isolate the products **19**, **20**, and **21**, it was necessary to preserve the butyl ester.

TABLE 1. Formation of the Five-Membered P,N-Heterocycles[a]



Entry	Carbonyl	Method[b]	Product	Compound	Isolated yield %[c]
1a 1b		A C		15	22 55
2		A		16	44
3		A		17	55
4		A		18	42
5		B		19	24[d]
6		B		20	48
7		B		21	48

[a] Details are provided in the Experimental Section. [b] Method A: (a) BuOH, Dean−Stark, reflux, 12 h; (b) BuOH, reflux 16 h. Method B: (a) BuOH, Dean−Stark, reflux, 12 h; (b) BuOH (0.1 M), DIEA (1 equiv), microwave heating, 200 °C, 3−6 min. Method C: conc HCl, reflux, 16 h. [c] Isolated yield of pure compounds after precipitation (entries 1−4) or chromatography on silica gel (entries 6 and 7). [d] Chromatographic isolation after treatment of the crude with Ac_2O (2 equiv), DIEA (1 equiv), 3 h, rt.

2-Substituted 3-Hydroxy-1,3-azaphosphorinane-3-oxides. Not surprisingly, *H*-Phosphinate **10** also reacted with aldehydes to form six-membered heterocycles (Table 2). Again, the yields ranged from low to medium, but the compounds were easily isolated pure in all cases through simple filtration. Unfortunately, ketones failed to provide the desired products.

Method C did not result in a good yield of heterocycle **22** (Table 2, entry 1a), nor did methods A and B. However, changing the thermal heating used for the five-membered rings (Table 1) with microwave heating gave acceptable results with

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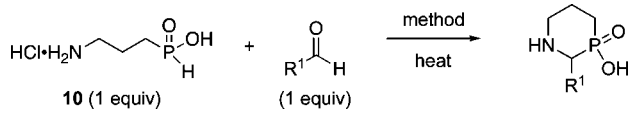
TABLE 2. Formation of the Six-Membered P,N-Heterocycles[a]



Entry	Aldehyde	Method[b]	Product	Compound	Isolated yield %[c]
1a		C			-[d]
1b	CHO	D		22	43
1c		E			76
1d		F			33
2	F, CHO	D	F	23	49
3	O, O, CHO	D	O, O	24	55
4	CHO, OH	D	OH	25	38
5	CHO, NO_2	D	NO_2	26	31
6	N, CHO	D	HCl • N	27	34
7	CHO	E	Ph	28	20

[a] Details are provided in the Experimental Section. [b] Method C: conc HCl, reflux, 16 h. Method D: (a) BuOH (0.1 M), Dean−Stark, reflux, 12 h; (b) BuOH (0.1 M), microwaves, 200 °C, 3 min. Method E: BuOH, (0.2 M), reflux, 16 h. Method F: BuOH (0.2 M), microwaves, 200 °C, 10 min. [c] Isolated yield of pure compounds after precipitation. [d] No product formation.

the six-membered rings, and in some cases, simply heating the reagents in BuOH provided the products (entries 1c and 7). Again, as it was the case with the 1,3-azaphospholanes, small variations in conditions resulted in large changes in yield for the 1,3-azaphosphorinanes. One key to the success of these reactions is the use of butanol as a solvent. This allowed the precipitation of the heterocycles from the reaction mixture. While the reactions are intrinsically higher yielding than the isolated yields reflect, the conditions are adjusted to directly provide the products as solids and to avoid lengthy purification procedures. No attempt was made at purifying the filtrate in these reactions.

The 1,3-azaphosphorinanes were obtained simply via an intramolecular Kabachnik−Fields reaction as shown in eq 1. Because the aminopropyl-*H*-phosphinate starting material **10** can easily be prepared on a multigram scale, the heterocycles shown in Table 2 are still readily accessible.

Conclusions

Using our own methodologies, we have prepared three ω-amino-*H*-phosphinic acids ($H_2N(CH_2)_nPO_2H_2$, $n = 1, 2, 3$) and some variously protected derivatives. Previously unknown phosphinic P,N-heterocycles (3-hydroxy-1,3-azaphospholane- and 3-hydroxy-1,3-azaphosphorinane-3-oxides) were prepared directly from amino-*H*-phosphinates **9** and **10** and aldehydes or ketones using an intramolecular Kabachnik−Fields reaction, under thermal or microwave heating. Although the yields are low to moderate, the heterocycles are generally isolated easily as pure solids from readily available starting materials. These heterocycles are novel analogs of α-amino acids, and as such might be useful in the preparation of peptidomimetics. Other heterocyclic ring systems should be accessible using other amino-*H*-phosphinic acids as precursors and this will be the object of future studies.

Experimental Section

2-(Phthalimido)ethyl-*H*-phosphinic Acid, 11 (Scheme 1).[10] Pd_2dba_3 (0.132 g, 0.14 mmol, 0.25 mol % of Pd) and xantphos (0.2 g, 0.34 mmol, 0.3 mol %) were added to a solution of *N*-vinyl phthalimide (20 g, 115 mmol) and concentrated H_3PO_2 (15.2 g, 2 equiv, 231 mmol) in distilled CH_3CN (230 mL) under nitrogen. The mixture was refluxed for 3 h. On cooling, a brown powder appeared. This precipitate was filtered, washed with CH_3CN (3 × 50 mL) and dried in vacuo to afford **11** (21.3 g, 77%) as a tan powder: ^{1}H NMR (D_2O, 300 MHz) δ 7.60−7.70 (m, 4H), 6.92 (d, J = 538 Hz, 1H), 3.70−3.80 (m, 2H), 1.80−1.94 (m, 2H); ^{13}C NMR (D_2O, 75.45 MHz) δ 168.3, 135.0, 132.4, 123.7, 31.4, 29.5 (d, J_{PC} = 89 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 29.9 (dm, J = 538 Hz).

2-Aminoethyl-*H*-phosphinic Acid Hydrochloride, 9 (Scheme 1).[12] Hydrochloric acid (12 N, 400 mL) was added to (2-phthalimidoethyl)phosphinic acid **11** (20 g, 83.7 mmol). After 16 h of reflux, the mixture was concentrated under high vacuum. The residue was diluted with water and washed with ethyl acetate (3 × 50 mL). Concentration of the aqueous layer afforded product **9** (7 g, 77%) as a yellow oil: ^{1}H NMR (D_2O, 300 MHz) δ 6.91 (d, J = 531 Hz, 1H), 3.15−3.25 (m, 2H), 1.82−1.98 (m, 2H); ^{13}C NMR (D_2O, 75.45 MHz) δ 33.6, 28.0 (d, J_{PC} = 100 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 24.1 (dm, J = 531 Hz); HRMS (EI$^+$) calcd for $C_2H_8NO_2P$ 110.0371, found 110.0377.

(3-Ethoxycarbonylamino-propyl)-*H*-phosphinic Acid, 13 (Scheme 2). $Pd(OAc)_2$ (0.348 g, 1.55 mmol, 1 mol % of Pd) and nixantphos (4.37 g, 1.705 mmol, 1.1 mol %) were added to a solution of (ethylcarbamate)allyl amine (20 g, 155 mmol) and concentrated H_3PO_2 (20.5 g, 2 equiv, 310 mmol) in distilled CH_3CN (300 mL) under nitrogen. The mixture was refluxed for 6 h. After cooling and filtration the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate then washed with brine (2×). Drying and concentration afforded product **13** as an oil (16.6 g, 55%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 548 Hz, 1H), 4.02−4.20 (m, 2H), 3.20−3.40 (m, 2H), 1.65−1.95 (m, 2H), 1.24 (t, J = 7 Hz, 3H); ^{13}C NMR (D_2O, 75.45 MHz) δ 159.0, 61.9, 40.8 (d, J_{PCC} = 18 Hz), 26.7 (d, J_{PC} = 91 Hz), 20.9, 13.9; ^{31}P NMR (D_2O, 121.47 MHz) δ 37.7 (d, J = 548 Hz); HRMS (EI$^+$) calcd for $C_6H_{14}NO_4P$ 196.0738, found 196.0729.

3-Aminopropyl-*H*-phosphinic Acid Hydrochloride, 10 (Scheme 2).[14a] Hydrochloric acid (12 N, 400 mL) was added to 3-ethoxycarbonylamino-propyl)-*H*-phosphinic acid **13** (16 g, 81.9 mmol). After 16 h of reflux, the mixture was concentrated under high vacuum. The residue was diluted with water and washed with ethyl acetate (3 × 50 mL). Concentration of the aqueous layer afforded product **10** as a yellow oil (10.5 g, 80%): ^{1}H NMR (D_2O, 300 MHz) δ 6.86 (d, J = 535 Hz, 1H), 2.91 (t, J = 7 Hz, 2H), 1.50−1.80 (m, 4H); ^{13}C NMR (D_2O, 75.45 MHz) δ 39.9 (d, J_{PCCC} = 19 Hz), 26.7 (d, J_{PC} = 91 Hz), 19.0; ^{31}P NMR (D_2O, 121.47 MHz) δ 33.2 (dm, J = 535 Hz); HRMS (EI$^+$) calcd for $C_3H_{10}NO_2P$ 124.0527, found 124.0527.

General Procedure for the Cyclizations (Tables 1 and 2). Method A. Compound **9** was dissolved in a mixture of HCl (1 N, 1.5−2.0 equiv) and *n*-butanol (0.1 M). Under strong stirring, the solution was refluxed with a Dean−Stark for 12 h. After cooling to room temperature, the solution was used as is: ^{31}P NMR δ 34.2 (dm). To that solution (10 mL, 0.1 M, 1 mmol) in *n*-butanol was added one equivalent of the aldehyde. The mixture was refluxed for 12−18 h. After cooling, the precipitate was filtered and washed with *n*-butanol and then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

Method B. Compound **9** was dissolved in a mixture of HCl (1 N, 1.5−2.0 equiv) and *n*-butanol (0.1 M). Under vigorous stirring,

the solution was refluxed with a Dean−Stark trap for 12 h. After cooling at room temperature, the solution was used as is: ^{31}P NMR δ 34.2 (dm). To that solution (10 mL, 0.1 M, 1 mmol) in *n*-butanol was added 1 equiv of diethylamine and 1 equiv of the aldehyde. After a brief stirring at room temperature, the mixture was irradiated by microwaves for 3 min at 200 °C. Concentration under high vacuum and purification by silica gel chromatography (EtOAc/Et_3N 100:0.5 v/v to EtOAc/EtOH/Et_3N 90:10:0.5 v/v) afforded the product as a colorless oil.

Method C. To a solution of compound **9** (1 mmol) in hydrochloric acid (12 N, 10 mL) was added 1 equiv of the aldehyde. The mixture was refluxed for 16 h. After cooling, the mixture was concentrated. After precipitation in *n*-butanol, the solid was dried under high vacuum to yield the expected compound as a white solid.

Method D. Dry HCl(g) was bubbled through a solution of compound ethyl (3-tert-butoxycarbonylamino-propyl)-*H*-phosphinate (2.4 g, 9.6 mmol) in 50 mL of distilled dichloromethane for 1 h 30. The solution was then stirred for 12 h at room temperature. After concentration, the residue was diluted with 47 mL of *n*-butanol (0.1 M) and refluxed overnight with a Dean−Stark system. This solution was used directly for the cyclization step (^{31}P NMR δ 37.5). To that solution (10 mL, 0.1 M, 1 mmol) in *n*-butanol was added 1 equiv of the aldehyde. The mixture was irradiated by microwaves for 3 min at 200 °C. After cooling, the precipitate was filtered and washed with *n*-butanol and then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

Method E. To a solution of compound **10** (1 mmol) in *n*-butanol (0.2 M) was added 1 equiv of the aldehyde. The mixture was refluxed for 16 h. After cooling, the precipitate was filtered and washed with *n*-butanol and then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

Method F. To a solution of compound **10** (1 mmol) in *n*-butanol (0.2 M) was added 1 equiv of the aldehyde. The mixture was irradiated by microwaves 10 min at 200 °C. After cooling, the precipitate was filtered and washed with *n*-butanol and then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

3-Hydroxy-2-(4-methoxy-phenyl)-1,3-azaphospholane-3-oxide, 17 (Table 1, Method A). Yield: 55%. Mp > 300 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.18 (d, J = 8 Hz, 2H), 6.87 (d, J = 8 Hz, 2H), 4.04 (d, J_{PCH} = 11 Hz, 1H), 3.65 (s, 3H), 3.45−3.70 (m, 1H), 3.25−3.45 (m, 1H), 1.80−2.10 (m, 2H); ^{13}C NMR (D_2O, 75.45 MHz) δ 159.4, 129.8 (d, J_{PCCC} = 4 Hz, 2C), 122.7, 114.7 (2C), 57.5 (d, J_{PC} = 93 Hz), 55.5, 41.9, 23.8 (d, J_{PC} = 86 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 42.3 (s); HRMS (EI^+) calcd for $C_{10}H_{14}NO_3P$ 228.0789, found 228.0792.

2-(4-Fluoro-phenyl)-3-hydroxy-1,3-azaphosphorinane-3-oxide, 23 (Table 2, Method D). Yield: 49%. Mp > 300 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.28 (dd, J = 7 Hz, J = 5 Hz, 2H), 7.03 (dd, J = 9 Hz, 2H), 4.19 (d, J_{PCH} = 7 Hz, 1H), 3.37 (dm, J_{gem} = 13 Hz, 1H), 2.95−3.10 (m, 1H), 1.95−2.20 (m, 2H), 1.60−1.85 (m, 2H); ^{13}C NMR (D_2O, 75.45 MHz) δ 163.0 (d, J_{FC} = 244 Hz), 130.4 (d, J_{FCC} = 4 Hz, 2C), 126.0 (d, J_{PCC} = 6 Hz), 115.9 (d, J_{PCCC} = 22 Hz, 2C), 60.8 (d, J_{PC} = 85 Hz), 46.6 (d, J_{PCCC} = 5 Hz), 27.3 (d, J_{PC} = 90 Hz), 21.7 (d, J_{PCC} = 6 Hz); ^{31}P NMR (D_2O, 121.47 MHz) δ 24.9 (s); ^{19}F NMR (D_2O, 282.306 MHz) δ −115.1 (s); HRMS (EI^+) calcd for $C_{10}FH_{13}NO_2P$ 230.0476, found 230.0749.

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Supporting Information Available: Additional experimental procedures and detailed spectroscopic data (^{31}P, ^{1}H and ^{13}C NMR spectra, and HRMS data) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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