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Regioselective alkylation reactions of hydrazones derived from phosphine oxides and phosphonates. Synthesis of phosphorus substituted 1-amino-pyrrolones, pyridinones and pyrroles

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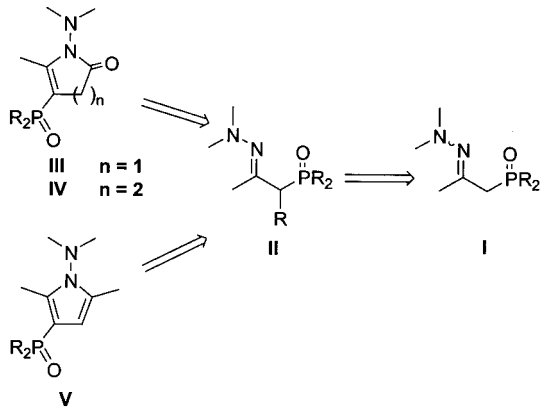
Abstract—Functionalized hydrazones derived from phosphine oxides or phosphonates were obtained from azaenolates of hydrazones and alkyl halides. The regioselectivity of alkylation of α-phosphorylated hydrazones can be controlled by phosphorus moiety. α-Alkylated compounds were used for the synthesis of heterocycles such as 1-aminopyrrol-2-ones, 1-amino-3,4-dihydropyridin-2-ones and 1-amino-pyrroles containing phosphinyl or phosphoryl substituents.

1. Introduction

Hydrazones constitute an important class of compounds due to the rich chemistry of the hydrazono group and have attracted a great deal of attention in recent years because of their range of applications.[1] They form part of the structure of new azapeptides,[2] biologically active antibiotic compounds such as cirratiomycin,[3a] antrimycin,[3b,c] azinothrycin,[3d] citropeptin[3e] and megamycin[3f] as well as potent anticancer[3g] and antimalarial agents.[3h] Hydrazones have also been extensively used as versatile precursors in heterocyclic synthesis,[4] and in the synthesis of chiral amines,[5a,b] α-aminoacids,[5c] and ligands for asymmetric homogeneous catalysis.[5d] In particular, the usefulness of carbanions derived from hydrazones for carbon–carbon bond formation reaction, has been well documented.[1,6] Besides enantioselective α-alkylations of aldehydes and ketones, the carbanion hydrazone method can be successfully applied, for instance, to the synthesis of α-hydroxy ketones,[7a] α-substituted nitriles,[7b,c] α,β-epoxy ketones,[7d] oxosulfones,[7e] pheromones,[7f,g] the potassium channel opener RP66471,[7h] sphingosine,[7i] phosphino alcohols,[7j] and of natural products such as ephotilones A and B,[8a] stigmatellin A,[8b] streptenol A,[8c] the antifungal antibiotics (−)-oudemansin A[8d] and (+)-pectinatone,[8e] as well as the ionophore antibiotic indanomycin.[8f]

We are interested in the design of new acyclic and cyclic derivatives, bearing a phosphine oxide or phosphonate moiety. This substituent could regulate important biological functions and increase the biological activity of these compounds, in a similar way to that reported for other pharmaceuticals.[9] In this context and in connection with our interest in the synthesis of three,[10] five[11] and six[12] membered phosphorylated nitrogen heterocycles, we have used β-functionalized enamines and hydrazones derived from phosphazenes, phosphine oxides and phosphonates as synthetic intermediates in the synthesis of acyclic derivatives such as oximes[13a] allylamines,[13b] hydrazones,[13c] and β-amino functionalized compounds[13d] as well as of phosphorus containing heterocycles.[14] Continuing with our interest in the chemistry of new phosphorus substituted compounds, we report here an easy and regioselective synthesis of phosphorylated α-functionalized hydrazones (II) from hydrazones (I) derived from phosphine oxide (R=Ph) or phosphonate (R=OEt) (Scheme 1). These α-functionalized hydrazones (II) are a versatile tool for



Scheme 1. Synthesis and applications of phosphorylated α-functionalized hydrazones II.

Keywords: alkylation; 1-amino-3,4-dihydropyridin-2-ones; 1-aminopyrroles; 1-aminopyrrol-2-ones; hydrazones; phosphine oxides; phosphonates.

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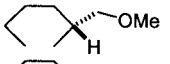
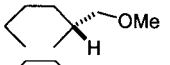
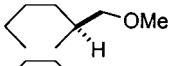
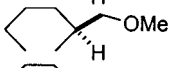
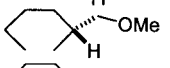
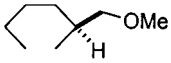
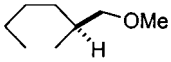
Table 1. α-Functionalized hydrazones **3** and **4** obtained

Entry	Compound	R	R^1	R^2	R^3	R^4	% de[a]	Yield (%)	Mp (°C)
1	**3a**	Ph	Me	Me	H	$CH{\equiv}C{-}CH_2$		77[b]	115–116
2	**3b**	Ph	Me	Me	Me	$CH{\equiv}C{-}CH_2$		82[b]	99–100
3	**3c**	Ph	Me	Me	*p*Me–Ph	$CH{\equiv}C{-}CH_2$		64[b]	103–104
4	**3d**	Ph	Me	Me	H	$(CH_2)_3{-}CH{=}CH_2$		68[b]	87–88
5	**3e**	Ph	Me	Me	H	$(CH_2)_2{-}CO_2Et$		72[b]	130–131
6	**3f**	Ph	Me	Me	H	$CH_2{-}CO_2Et$		79[b]	66–67
7	**3g**	Ph			H	Me	6	42[b]	87–89
8	**3h**	Ph			H	$CH_2{-}CO_2Et$	22	44[b]	Oil[c]
9	**3i**	Ph			H	Me	6	61[d]	87–89
10	**3j**	Ph			H	$CH_2{-}CO_2Et$	50	67[d]	Oil[c]
11	**3k**	Ph			H	$CH{\equiv}C{-}CH_2$	0	89[b]	Oil[c]
12	**3l**	Ph			H	$CH{\equiv}C{-}CH_2$	0	84[b]	Oil[c]
13	**4a**	OEt	Me	Me	H	$CH{\equiv}C{-}CH_2$		82[b]	Oil[c]
14	**4b**	OEt	Me	Me	H	$CH_2{-}CO_2Me$		89[b]	Oil[c]
15	**4c**	OEt	Me	Me	H	$(CH_2){-}CO_2Me$		56[b], 75[d]	Oil[c]
16	**4d**	OEt	Me	Me	H	$CH_2{-}CO_2Et$		78[d]	Oil[c]
17	**4e**	OEt			H	$CH_2{-}CO_2Et$	30	60[d]	Oil[c]

[a] Diastereoselectivity ratio determined by integration in ^{31}P NMR spectra of crude products.
[b] Yield of isolated purified compounds **3** and **4** using LDA.
[c] Purified by flash chromatography.
[d] Yield of isolated purified compounds **3** and **4** using $^nBu_2CuLi$.

the construction of phosphorus containing five and six membered heterocycles such as 1-aminopyrrol-2-ones (III), 1-amino-3,4-dihydropyridin-2-ones (IV) and 1-aminopyrroles (V).

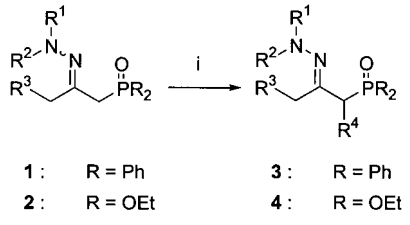
2. Results and discussion

2.1. Reaction of hydrazone carbanions derived from phosphine oxides and phosphonates with alkyl halides

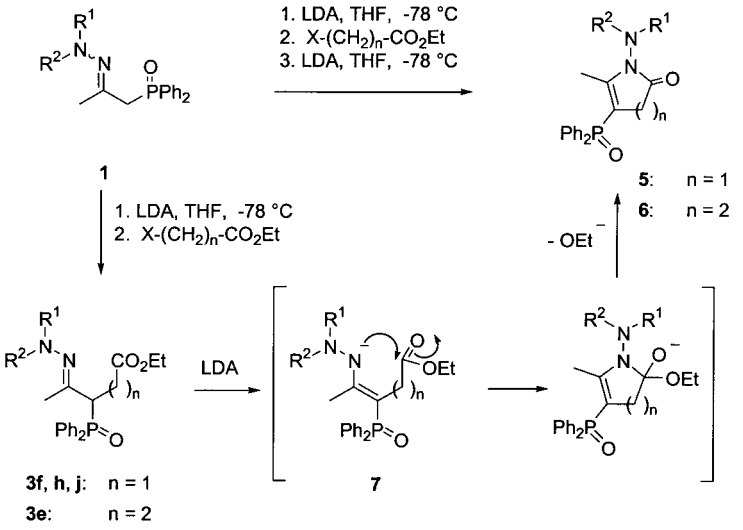
Simple hydrazones will deprotonate regioselectively on the less substituted side, forming an azaenolate[6,15] which can then be alkylated. Conversely, α-silyl substituents in hydrazones seem to favor the regioselective alkylation at the internal carbon adjacent to the silyl group when (*S*)-1-amino-2(methoxymethyl)pyrrolidine (SAMP)[16a] or (*R*)-1-amino-2(methoxymethyl)pyrrolidine (RAMP)[16] hydrazones are used, while in the alkylation of deprotonated α-silyl hydrazones derived from *N*,*N*-dimethylhydrazine mixtures of the two possible alkylation products were reported.[16b] Moreover, in our case, the presence of excellent anion stabilizing groups such as phosphine oxide I (R=Ph) or phosphonate I (R=OEt) could control the deprotonation at the internal less-substituted carbon.

Hydrazones derived from phosphine oxides **1** (R=Ph) and phosphonates **2** (R=OEt) were easily prepared by addition of achiral and chiral hydrazines to allenes.[13c] Deprotonation of functionalized hydrazones **1** or **2** with lithium diisopropylamide (LDA) in THF at −78°C (Procedure A) gave an azaenolate which was alkylated by alkyl halides. After aqueous work-up, the α-substituted hydrazones **3** (R=Ph) (see Table 1, entries 1–8 and 11–12) and **4** (R=OEt) (see Table 1, entries 13–15) were obtained in moderate to good yields and in a regioselective fashion. Compounds **3** and **4** were characterized on the basis of their spectroscopic data. Thus, the ^{31}P NMR spectrum of compound **3a** showed an absorption at δ_P=30.6 ppm. Likewise, the ^1H and ^{13}C NMR spectra gave a multiplet for the methine proton (δ_H=3.54 ppm) and a well resolved doublet at δ_C=48.4 ppm with a coupling constant of $^1J_{PC}$=63.9 Hz for the carbon atom directly bonded to the phosphinyl moiety of compound **3a**.

This methodology can also be extended to chiral α-functionalized hydrazones when the corresponding chiral hydrazones are used. Regioselective alkylation of RAMP hydrazone **1** was accomplished using LDA as the base followed by addition of alkyl halides, but the α-alkylated hydrazones **3g** and **h** were isolated with low diastereoselectivity (see Table 1, entries 7 and 8). In all cases, alkylation of these dimethyl and RAMP hydrazones **1** and **2**



Scheme 2. Regioselective alkylation of hydrazone phosphine oxides **1** and phosphonates **2**.



Scheme 3. Preparation of phosphinylated pyrrol-2-ones **5** and 3,4-dihydropyridin-2-ones **6**.

under LDA conditions with different alkyl halides occurred adjacent to the phosphoryl or phosphinyl group to form exclusively products **3** and **4** (Scheme 2).

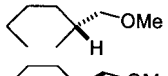
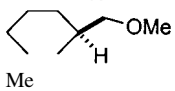
Enantiomerically enriched α-substituted hydrazones derived from phosphine oxides **3i** and **j** (see Table 1, entries 9 and 10) and phosphonates **4c–e** (see Table 1, entries 15–17) can also be prepared by deprotonation of the SAMP hydrazone **1** or phosphoryl hydrazone **2** using $^{n}Bu_2CuLi$ in THF/Et_2O at −50°C (Procedure B) followed by addition of alkyl halide and aqueous work-up. The same regioselectivity was observed to that obtained when LDA was used as base. Using this methodology for the alkylation of chiral SAMP hydrazones afforded α-alkylated hydrazones, but, in low diastereoselectivity. When a bulkier electrophile ($CH_2–CO_2Et$) is used, higher diastereoselectivity is observed (see Table 1, entries 8, 10 and 17) than in the case of the use of a smaller electrophile such as methyl (see Table 1, entries 7 and 9). The influence of the base (organolithium or organocopper reagent) does not seem to be crucial for this diastereoselectivity. However, the presence of an anion stabilizing group such as phosphine oxide (R=Ph) or phosphonate (R=OEt) could control the deprotonation at the internal less-substituted carbon not only in chiral (SAMP, RAMP), but also in achiral (*N*,*N*-dimethyl) hydrazones.

2.2. Cyclocondensation of α-functionalized hydrazones 3e, f, h and j: synthesis of phosphinylated 1-amino-pyrrol-2-ones 5 and 1-amino-3,4-dihydropyridin-2-one 6

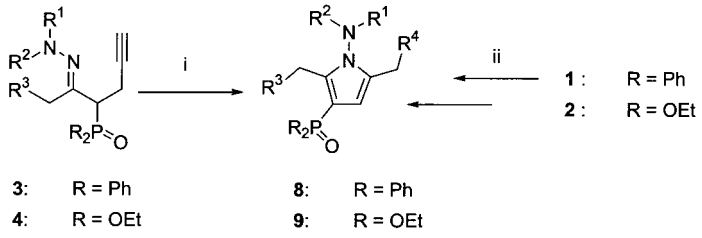
Phosphinylhydrazones with ester functions such as **3e**, **f**, **h** and **j** can be used for heterocycle formation containing a phosphinyl substituent in the 4-position of the heterocyclic system. Thus, carbethoxymethyl-substituted hydrazones **3f**, **h** and **j** when treated with LDA followed by aqueous work-up, gave high yields of 1-aminopyrrol-2-ones **5** (Scheme 3, Table 2, entries 1–3). On the other hand carbethoxyethyl-subtituted compound **3e** was cyclocondensed using LDA to lead 5-phosphinylated-1-amino-3,4-dihydropyridin-2-ones **6** in excellent yield (Table 2, entry 4). However, attempts for the cyclocondensation of phosphoryl hydrazones **4b–e** by using different bases (HNa, LDA) and heating (60°C) did not give the corresponding five or six membered heterocycles and the starting hydrazones were recovered. Compounds **5** and **6** were characterized on the basis of their spectroscopic data. Thus, the ^{31}P NMR of compound **5a** showed an absorption at δ_P=21.7 ppm, while the ^{1}H NMR showed well resolved doublet for the methylene proton (δ_H=2.88 ppm with a coupling constant of $^{3}J_{PH}$=19.7 Hz) and ^{13}C NMR gave two well resolved doublets at δ_C=38.4 ppm with a coupling constant of $^{2}J_{PC}$=8.5 Hz for the methylene carbon and at δ_C=97.9 ppm with a coupling constant of $^{1}J_{PC}$=125.9 Hz for the carbon atom directly bonded to the phosphinyl moiety. As far as we know, this strategy leads to the first examples of 1-aminopyrrol-2-ones **5** and 1-amino-3,4-dihydropyridin-2-ones **6** containing phosphinyl substituents in the ring system. The formation of these heterocycles **5** and **6** can be explained by cyclocondensation reaction of the azaenolate **7** derived from α-functionalized hydrazones **3** followed by the loss of ethanol (Scheme 3).

Likewise, phosphinylated 1-aminopyrrol-2-ones **5** and 1-amino-3,4-dihydropyridin-2-ones **6** were alternatively prepared in a 'one pot' reaction from β-hydrazones **1**, two equivalents of a base (LDA) and ethyl bromoacetate or bromopropionate (Table 2, entries 1 and 4). Pyrrol-2-ones are used in biochemical studies,[17a] pharmaceutical formula-

Table 2. Pyrrol-2-ones **5** and 3,4-dihydropyridin-2-one **6** obtained

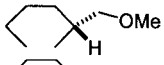
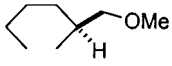
Entry	Compound	R^1	R^2	Yield (%)	Mp (°C)
1	**5a**	Me	Me	89[a], 65[b]	162–163
2	**5b**			86[a]	Oil[c]
3	**5c**			84[a]	Oil[c]
4	**6**	Me	Me	88[a], 68[b]	145–146

[a] Yield of isolated purified compounds **5** and **6** from hydrazones **3**.
[b] Yield of isolated purified compounds **5a** and **6** in 'one pot' reaction from **1**.
[c] Purified by flash chromatography.



Scheme 4. Regioselective synthesis of phosphinylated and phosphorylated 1-aminopyrroles **8** and **9**.

Table 3. 1-Aminopyrroles **8** and **9** obtained

Entry	Compound	R	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
1	**8a**	Ph	Me	Me	H	Ph	65[a]	129–130
2	**8b**	Ph	Me	Me	Me	Ph	64[a], 48[b]	179–180
3	**8c**	Ph	Me	Me	*p*Me–Ph	Ph	63[a]	89–90
4	**8d**	Ph	Me	Me	H	H	62[a]	119–120
5	**8e**	Ph	Me	Me	Me	H	73[a]	130–131
6	**8f**	Ph	Me	Me	*p*Me–Ph	H	63[a]	142–143
7	**8g**	Ph			H	Ph	74[a]	Oil[c]
8	**8h**	Ph			H	Ph	72[a]	Oil[c]
9	**9a**	OEt	Me	Me	H	Ph	60[a], 51[b]	Oil[c]
10	**9b**	OEt	Me	Me	H	H	61[a], 52[b]	Oil[c]

[a] Yield of isolated purified 1-aminopyrroles **8** from hydrazones **3a–c**, **k**, **l** and **4a**.
[b] Yield of isolated purified 1-aminopyrroles **8** and **9** in 2 step-reactions without purification from hydrazones **1** and **2**.
[c] Purified by flash chromatography.

tions[17b] and for polymeric materials;[17c] while the pyridin-2-one substructure is found in many biologically active natural and synthetic compounds that possess medicinal properties.[18]

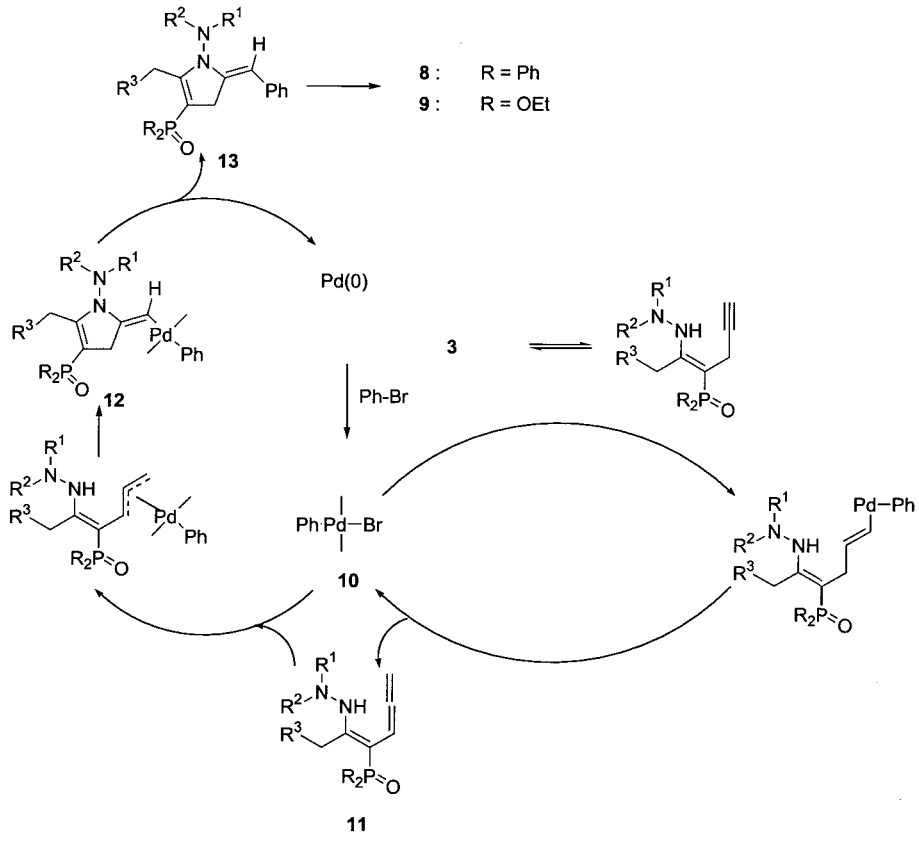
2.3. Palladium-catalyzed cyclization reaction of α-propargyl hydrazones 3a–c, k, l and 4a: synthesis of phosphinylated and phosphorylated 1-aminopyrroles 8 and 9

Pyrrole ring systems are important in organic chemistry because they constitute the skeleton of natural products, alkaloids, antibiotics and polymers.[19] 1-Aminopyrrole derivatives have been used in the preparation of nanocomposites,[20a] pyrrolo[1,2-*b*][1,2,4]triazines,[20b,c] phytochromes,[20d] analgesics,[20e] as well as NMDA receptor[20f] and angiotensin II antagonists.[20g] Despite these applications, the limited presence of 1-aminopyrroles in the literature can be ascribed to the few procedures which exist for their preparation,[21,22] and only two examples of phosphor substituted aminopyrroles[23,24] have been described, obtained from azoalkenes and phosphorus ylides[23] or enamines.[24]

The palladium-catalyzed allylation of carbon, oxygen or nitrogen nucleophiles is well-recognized as one of the most powerful synthetic tools for the construction of carbon–carbon, carbon–oxygen or carbon–nitrogen bonds from allenes[25] or propargyl derivatives.[26] Similarly, electrophile-mediated cyclization is an efficient route to nitrogen-containing heterocycles[27] and palladium-mediated cyclizations are particularly attractive in this sense when allene[28] or propargyl[22c,29] systems as π-component are used. For this reason, we envisaged that propargylic substituted hydrazones derived from phosphine oxides **3a–c**, **k**, **l** and phosphonate **4a** could be used for the synthesis of phosphinylated and phosphorylated 1-aminopyrroles through their Pd(0)- and Pd(II)-catalyzed regioselective heterocyclization reactions. Thus, when phosphinylated hydrazones **3a–c** were treated with bromobenzene, catalytic amounts of $Pd(PPh_3)_4$ and K_2CO_3 in DMF at 60°C and aqueous work-up, led to formation of 1-aminopyrroles **8a–c** (R^4=Ph) in moderate yields and in a regioselective fashion (see Scheme 4, Table 3, entries 1–3). A similar behavior was observed in the case of phosphonate **4a** to give phosphoryl 1-aminopyrrole **9a** (R^4=Ph) (see Scheme 4, Table 3, entry 9).

Spectroscopic data and mass spectrometry were in agreement with the proposed structure for 1-aminopyrroles **8** and **9**. In the ^{1}H NMR spectrum of 1-aminopyrrole **8a**, the signal for the methine proton appeared at δ_H=5.43 ppm with a coupling constant of $^3J_{PH}$=4.4 Hz, while the ^{13}C NMR spectrum showed absorption at δ_C=106.4 ppm as a doublet with coupling constant $^1J_{PC}$=128.9 Hz for the carbon atom directly bonded to the phosphinyl moiety (C-3), as well as doublets at δ_C=109.0 ppm with a $^2J_{PC}$=11.5 Hz and at δ_C=136.7 ppm with a $^2J_{PC}$=16.6 Hz and a singlet at δ_C=139.9 ppm for the heterocyclic carbon atoms C-4, C-2 and C-5.

The formation of these heterocycles may be supposed to proceed through generation of the σ-vinylpalladium complex **12** via regio-chemoselective *trans* addition of the enehydrazino NH and palladium across the allene system (*exo-dig* process)[28] in the π-complex derived from a σ-phenylpalladium complex **10** and propargyl-isomerized allene **11**. Reductive elimination of **13** followed by



Scheme 5. Mechanism for aminopalladation and cross coupling of α-functionalized hydrazones **3** and **4**.

isomerization would afford 1-aminopyrroles **8** and **9** (Scheme 5). This process can be extended to the preparation of 1-aminopyrroles **8d–f** and **9b** (R^4=H) when the reactions were carried out under the presence of catalytic amounts of $Pd(OAc)_2$ and K_2CO_3 in DMF at 60°C without bromobenzene (Scheme 4; Table 3, entries 4–6 and 10).

Alternatively, phosphinylated 1-aminopyrroles **8** and **9** were prepared in just two step-reactions without purification from β-hydrazones **1** and **2** and propargyl bromide, when crude adducts **3b** and **4a** are directly treated, without their isolation, with bromobenzene, catalytic amounts of $Pd(PPh_3)_4$ and K_2CO_3 in DMF (R^4=Ph) or catalytic amounts of $Pd(OAc)_2$ and K_2CO_3 in DMF (R^4=H) and aqueous work-up (Table 3, entries 2, 9 and 10).

3. Conclusion

In conclusion, the synthesis described in this paper provides an efficient and easy access to α-functionalized β-hydrazones substituted with a phosphine oxide **3** (R=Ph) or a phosphonate **4** (R=OEt) group, making use of readily available starting materials. These hydrazones can serve as intermediates in the synthesis of new nitrogen heterocycle compounds such as 4-phosphinylated-1-aminopyrrol-2-ones **5**, 5-phosphinylated-1-amino-3,4-dihydropyridin-2-ones **6**, as well as 3-phosphinylated- or 3-phosphorylated-1-aminopyrroles **8**. Compounds with these structures could be useful in the synthesis of biologically active compounds with interest as agrochemicals and in medicinal chemistry.[17–20]

4. Experimental

4.1. General

Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light and $KMnO_4$ solution. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with a Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CDCl_3$ solutions with TMS as an internal reference for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) for ^{31}P NMR spectra. Coupling constants (*J*) are reported in Hz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Data are reported in the form *m/z* (intensity relative to base=100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. $[\alpha]^{20}_D$ were taken on a Perkin Elmer 341 polarimeter using a Na/HaI lamp. Hydrazone phosphine oxides **1**[13c] and

phosphonates **2**[13c] were synthesized according to literature procedures, except for *syn*- and *anti*-diethyl-2-(*N*-(*S*)-2-methoxymethylpyrrolidinimino)propylphosphonate which were not previously reported.

4.1.1. *syn*- and *anti*-Diethyl-2-(*N*-(*S*)-2-methoxymethylpyrrolidinimino) propylphosphonate. 92%. Obtained as a colorless oil using general procedure:[13c] R_f (AcOEt) 0.13; ^{1}H NMR (300 MHz) 4.65 and 4.44 (d, $^2J_{PH}$=11.6, 9.9 Hz, 2H), 4.16–4.04 (m, 4H), 3.87–3.79 (m, 2H), 3.68–3.51 (m, 2H), 3.47 and 3.31 (d, $^4J_{PH}$=5.5, 10.0 Hz, 3H), 3.32 (s, 3H), 2.57–2.43 (m, 1H), 2.19–1.46 (m, 4H), 1.14–1.32 (m, 6H); ^{13}C NMR (75 MHz) 143.8 and 138.6 (d, $^3J_{PC}$=2.7, 2.4 Hz), 73.8 and 73.0, 71.5 and 70.4, 65.7, 60.7 and 56.7, 57.9 and 57.1, 51.2 and 49.0 (d, $^1J_{PC}$=121.4, 83.1 Hz), 26.0 and 24.7, 22.8 and 21.9, 20.8 and 20.0, 15.5 and 15.2; ^{31}P NMR (120 MHz) 7.8 and 8.1; IR (film) 1664, 1453, 1256; EIMS *m*/*z* 306 (M^+, 5.8). Anal. Calcd for $C_{13}H_{27}N_2O_4P$: C, 50.98; H, 8.82; N, 9.15. Found: C, 51.08; H, 8.80; N, 9.17.

4.1.2. Preparation of α-functionalized hydrazonophosphine oxides 3 and hydrazono phosphonates 4. *Procedure A*. To a −78°C solution of LDA (5 mmol) (previously prepared from diisopropylamine and a 1.6 M solution of ^{n}BuLi in hexanes) in THF (25 mL), a solution of hydrazono phosphine oxide **1** or hydrazono phosphonate **2** (5 mmol) in THF (25 mL) was added. The mixture was stirred at that temperature for 1 h and a solution of alkyl halide (6 mmol) in THF (5 mL) was then added at the same temperature. After the mixture was allowed to warm to rt, the reaction mixture was stirred at rt until TLC indicated the disappearance of compound **1** or **2**. The mixture was then diluted with water (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes for α-functionalized hydrazone phosphonates **4** and hydrazono phosphine oxides **3g**, **h** and **3k**, **l** or by recrystallization from CH_2Cl_2/hexanes for α-functionalized hydrazono phosphine oxides **3a**–**f**.

Procedure B. To a −50°C suspension of CuI (0.95 g, 5 mmol) in diethyl ether (25 mL), a 1.6 M solution of ^{n}BuLi in hexanes (10 mmol) was added. The mixture was stirred at that temperature for 10 min and a solution of hydrazono phosphine oxide **1** or hydrazono phosphonate **2** (5 mmol) in THF (25 mL) was added at the same temperature. The mixture was stirred at that temperature for 1 h and a solution of alkyl halide (6 mmol) in diethyl ether (10 mL) was added at the same temperature. After the mixture was allowed to warm to −30°C, the reaction mixture was stirred at that temperature until TLC indicated the disappearance of compound **1** or **2**. Water (50 mL) was then added to the mixture and was filtered through celite. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes.

4.1.3. 2-(*N*,*N*-Dimethylhydrazono)-1-propargylpropyldiphenylphosphine oxide (3a). Using procedure A from the corresponding β-hydrazono phosphine oxide **1** (1.50 g, 5 mmol) and propargyl bromide (0.54 mL, 6 mmol), affording 1.30 g (77%) of **3a** as a white solid: mp 115–116°C; ^{1}H NMR (300 MHz) 7.83–7.35 (m, 10H), 3.54 (m, 1H), 2.93 (m, 1H), 2.44 (m, 1H), 2.10 (s, 6H), 2.00 (d, $^4J_{PH}$=1.7 Hz, 3H), 1.90 (dd, $^4J_{HH}$=2.9, 1.4 Hz, 1H); ^{13}C NMR (75 MHz) 163.0 (d, $^2J_{PC}$=4.0 Hz), 132.0–128.2 (m), 79.8 (d, $^4J_{PC}$=19.1 Hz), 70.9, 48.4 (d, $^1J_{PC}$=63.9 Hz), 46.6, 16.1, 15.6; ^{31}P NMR (120 MHz) 30.6; IR (KBr) 1434, 1191; EIMS *m*/*z* 338 (M^+, 0.5). Anal. Calcd for $C_{20}H_{23}N_2OP$: C, 70.99; H, 6.85; N, 8.28. Found: C, 70.92; H, 6.83; N, 8.30.

4.1.4. 2-(*N*,*N*-Dimethylhydrazono)-1-propargylbutyldiphenylphosphine oxide (3b). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.57 g, 5 mmol) and propargyl bromide (0.54 mL, 6 mmol), affording 1.44 g (82%) of **3b** as a white solid: mp 99–100°C; ^{1}H NMR (300 MHz) 7.90–7.20 (m, 10H), 5.01 (m, 1H), 2.95 (m, 1H), 2.59–2.17 (m, 3H), 2.13 (s, 6H), 1.88 (dd, $^4J_{HH}$=2.6, 1.8 Hz, 1H), 0.99 (t, $^3J_{HH}$=7.3 Hz, 3H); ^{13}C NMR (75 MHz) 166.4 (d, $^2J_{PC}$=3.5 Hz), 131.5–127.5 (m), 80.5 (d, $^4J_{PC}$=19.1 Hz), 70.8, 46.8, 40.2 (d, $^1J_{PC}$=61.9 Hz), 26.2, 15.3, 10.0; ^{31}P NMR (120 MHz) 30.7; IR (KBr) 2110, 1620, 1441; EIMS *m*/*z* 352 (M^+, 24.4). Anal. Calcd for $C_{21}H_{25}N_2OP$: C, 71.57; H, 7.15; N, 7.95. Found: C, 71.62; H, 7.13; N, 7.97.

4.1.5. 2-(*N*,*N*-Dimethylhydrazono)-1-propargyl-3-(*p*-tolyl)-propyldiphenylphosphine oxide (3c). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.95 g, 5 mmol) and propargyl bromide (0.54 mL, 6 mmol), affording 1.37 g (64%) of **3c** as a white solid: mp 103–104°C; ^{1}H NMR (300 MHz) 7.80–6.93 (m, 14H), 4.05 (d, $^2J_{HH}$=14.5 Hz, 1H), 3.56 (m, 1H), 3.41 (d, $^2J_{HH}$=14.5 Hz, 1H), 2.83 (m, 1H), 2.44 (m, 1H), 2.34 (s, 6H), 2.31 (s, 3H), 1.76 (dd, $^4J_{HH}$=2.4 Hz, 1.5 Hz, 1H); ^{13}C NMR (75 MHz) 164.0 (d, $^2J_{Pc}$=6.0 Hz), 150.1–128.8 (m), 81.6 (d, $^4J_{PC}$=17.1 Hz), 69.9, 47.3, 45.5 (d, $^1J_{PC}$=64.0 Hz), 37.0, 21.6, 18.1; ^{31}P NMR (120 MHz) 31.6; IR (KBr) 2120, 1447, 1189; EIMS *m*/*z* 428 (M^+, 17.5). Anal. Calcd for $C_{27}H_{29}N_2OP$: C, 75.68; H, 6.82; N, 6.54. Found: C, 75.62; H, 6.83; N, 6.52.

4.1.6. 2-(*N*,*N*-Dimethylhydrazono)-1-(4-pentenyl)propyldiphenylphosphine oxide (3d). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.50 g, 5 mmol) and 4-pentenyl bromide (1.80 g, 6 mmol), affording 1.25 g (68%) of **3d** as a white solid: mp 87–88°C; ^{1}H NMR (300 MHz) 7.90–7.26 (m, 10H), 5.72–5.61 (m, 1H), 4.95–4.85 (m, 2H), 3.45–3.36 (m, 1H), 2.15 (s, 6H), 2.01 (s, 3H), 2.15–1.29 (m, 6H); ^{13}C NMR (75 MHz) 164.6, 137.8, 131.6–128.1 (m), 49.5 (d, $^1J_{PC}$=64.5 Hz), 114.9, 46.6, 32.9, 26.8 (d, $^3J_{PC}$=14.0 Hz), 24.3, 15.4; ^{31}P NMR (120 MHz) 31.5; IR (KBr) 1650, 1446, 1203, 1124; EIMS *m*/*z* 368 (M^+, 20.0). Anal. Calcd for $C_{22}H_{29}N_2OP$: C, 71.70; H, 7.93; N, 7.60. Found: C, 71.49; H, 7.92; N, 7.62.

4.1.7. 1-(2-Ethoxycarbonylethyl)-2-(*N*,*N*-dimethylhydrazono)propyldiphenylphosphine oxide (3e). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.50 g, 5 mmol) and ethyl bromopropionate (0.77 mL, 6 mmol), affording 1.44 g (72%) of **3e** as a white solid: mp 130–131°C; ^{1}H NMR (300 MHz)

7.88–7.32 (m, 10H), 4.03 (q, $^3J_{HH}$=7.2 Hz, 2H), 3.48–3.28 (m, 1H), 2.34–1.97 (m, 4H), 2.09 (s, 6H), 1.96 (s, 3H), 1.15 (t, $^3J_{HH}$=7.2 Hz, 3H); ^{13}C NMR (75 MHz) 172.3, 163.6, 132.4–128.1 (m), 60.5, 48.5 (d, $^1J_{PC}$=65.1 Hz), 46.5, 31.8 (d, $^3J_{PC}$=13.5 Hz), 20.6, 15.7, 14.1; ^{31}P NMR (120 MHz) 30.9; IR (KBr) 1728, 1444, 1188; EIMS *m/z* 400 (M^+, 9.0). Anal. Calcd for $C_{22}H_{29}N_2O_3P$: C, 65.99; H, 7.30; N, 7.00. Found: C, 65.81; H, 7.32; N, 6.98.

4.1.8. 1-Ethoxycarbonylmethyl-2-(*N*,*N*-dimethylhydrazono)propyldiphenylphosphine oxide (3f). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.50 g, 5 mmol) and ethyl bromoacetate (0.67 mL, 6 mmol), affording 1.53 g (79%) of **3f** as a white solid: mp 66–67°C; ^{1}H NMR (300 MHz) 7.84–7.35 (m, 10H), 3.97 (q, $^3J_{HH}$=7.0 Hz, 2H), 3.81 (m, 1H), 3.04 (m, 1H), 2.56 (m, 1H), 2.13 (s, 6H), 1.91 (s, 3H), 1.12 (t, $^3J_{HH}$=7.0 Hz, 3H); ^{13}C NMR (75 MHz) 170.3 (d, $^3J_{PC}$=17.1 Hz), 161.9 (d, $^2J_{PC}$=5.5 Hz), 131.5–127.7 (m), 60.2, 46.0, 45.9 (d, $^1J_{PC}$=64.5 Hz), 31.2, 16.7, 13.6; ^{31}P NMR (120 MHz) 31.3; IR (KBr) 1759, 1401; EIMS *m/z* 386 (M^+, 8.8). Anal. Calcd for $C_{21}H_{27}N_2O_3P$: C, 65.27; H, 7.04; N, 7.25. Found: C, 65.30; H, 7.05; N, 7.23.

4.1.9. 1-Methyl-2-(*N*-(*R*)-2-methoxymethylpyrrolidinimino)propyldiphenylphosphine oxide (3g). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.85 g, 5 mmol) and methyl iodide (0.37 mL, 6 mmol), affording 0.81 g (42%) of a mixture of diastereoisomers **3g** (de=6%) as a white solid: mp 87–89°C; ^{1}H NMR (300 MHz) 7.83–7.31 (m, 10H), 3.59–3.42 (m, 1H), 3.24 and 3.14 (s, 3H), 3.30–2.81 (m, 3H), 2.74–2.65 (m, 1H), 2.29–2.21 (m, 1H), 1.97 and 1.87 (d, $^4J_{PH}$=2.14, 1.83 Hz, 3H), 1.75–1.41 (m, 4H), 1.22–1.38 (m, 3H); ^{13}C NMR (75 MHz) 162.4 and 161.7, 132.6–127.9 (m), 75.8 and 75.1, 66.3 and 66.2, 59.1 and 58.9, 54.0 and 53.8, 43.8 (d, $^1J_{PC}$=64.5 Hz), 26.8 and 26.7, 22.6 and 22.5, 17.0 and 16.3, 11.9 and 11.3 (d, $^2J_{PC}$=4.0, 4.0 Hz); ^{31}P NMR (120 MHz) 33.1 and 32.4; IR (KBr) 1613, 1428, 1189, 1116; EIMS *m/z* 384 (M^+, 3.9). Anal. Calcd for $C_{22}H_{29}N_2O_2P$: C, 68.73; H, 7.60; N, 7.29. Found: C, 68.84; H, 7.58; N, 7.26.

4.1.10. 1-Ethoxycarbonylmethyl-2-(*N*-(*R*)-2-methoxymethylpyrrolidinimino)propyldiphenyl phosphine oxide (3h). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.85 g, 5 mmol) and ethyl bromoacetate (0.67 mL, 6 mmol), affording 1.01 g (44%) of a mixture of diastereoisomers **3h** (de=22%) as a pale yellow oil: R_f (AcOEt) 0.41; ^{1}H NMR (300 MHz) 7.83–7.40 (m, 10H), 4.06–3.95 (q, $^3J_{HH}$=7.2 Hz, 2H), 3.90–3.76 (m, 1H), 3.25 and 3.16 (s, 3H), 3.24–2.89 (m, 4H), 2.85–2.79 (m, 1H), 2.61–2.47 (m, 1H), 2.26–2.14 (m, 1H), 1.84 and 1.80 (d, $^4J_{PH}$=2.1, 1.8 Hz, 3H), 1.70–1.63 (m, 2H), 1.54–1.42 (m, 2H), 1.15 (t, $^3J_{HH}$=7.2 Hz, 3H); ^{13}C NMR (75 MHz) 170.9 and 170.8, 158.0 and 157.4, 131.8–128.1 (m), 75.2 and 75.1, 66.3 and 66.2, 60.6, 59.0 and 58.9, 53.7, 46.4 (d, $^1J_{PC}$=65.0 Hz), 32.0 and 31.9, 26.6 and 26.5, 22.3 and 22.2, 19.1, 14.0; ^{31}P NMR (120 MHz) 31.5 and 31.2; IR (film) 1726, 1441, 1202, 1116; EIMS *m/z* 456 (M^+, 3.9). Anal. Calcd for $C_{25}H_{33}N_2O_4P$: C, 65.77; H, 7.29; N, 6.14. Found: C, 65.70; H, 7.28; N, 6.12.

4.1.11. 1-Methyl-2-(*N*-(*S*)-2-methoxymethylpyrrolidinimino)propyldiphenylphosphine oxide (3i). Using procedure B from the corresponding hydrazono phosphine oxide **1** (1.85 g, 5 mmol) and methyl iodide (0.37 mL, 6 mmol), affording 1.17 g (61%) of a mixture of diastereoisomers **3i** (de=6%) as a white solid. For physical and spectral data see compound **3g**.

4.1.12. 1-Ethoxycarbonylmethyl-2-(*N*-(*S*)-2-methoxymethylpyrrolidinimino)propyldiphenyl phosphine oxide (3j). Using procedure B from the corresponding hydrazono phosphine oxide **1** (1.85 g, 5 mmol) and ethyl bromoacetate (0.67 mL, 6 mmol), affording 1.53 g (67%) of a mixture of diastereoisomers **3j** (de=50%) as a pale yellow oil. For physical and spectral data see compound **3h**.

4.1.13. 2-(*N*-(*S*)-2-Methoxymethylpyrrolidinimino)-1-propargylpropyldiphenylphosphine oxide (3k). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.85 g, 5 mmol) and propargyl bromide (0.54 mL, 6 mmol), affording 1.81 g (89%) of a mixture of diastereoisomers **3k** (de=0%) as a pale yellow oil: R_f (AcOEt) 0.61; ^{1}H NMR (300 MHz) 7.85–7.36 (m, 10H), 3.67–3.51 (m, 1H), 3.36–3.26 (m, 1H), 3.15 and 3.25 (s, 3H), 3.14–3.06 (m, 1H), 2.93–2.85 (m, 2H), 2.78–2.72 (m, 1H), 2.41–2.53 (m, 1H), 2.38–2.27 (m, 1H), 2.00 (m, 1H), 1.97 and 1.87 (d, $^4J_{PH}$=2.1, 2.1 Hz, 3H), 1.74–1.48 (m, 4H); ^{13}C NMR (75 MHz) 158.0 and 157.5 (d, $^2J_{PC}$=6.0, 7.1 Hz), 131.6–127.1 (m), 79.7 and 79.5 (d, $^3J_{PC}$=17.1, 18.1 Hz), 74.4, 70.5 and 70.3, 65.6 and 65.5, 58.2 and 58.1, 53.2 and 52.9, 48.0 and 47.5 (d, $^1J_{PC}$=64.5, 63.5 Hz), 26.1 and 25.9, 21.6 and 21.5, 16.5 and 15.9, 13.7 and 13.4; ^{31}P NMR (120 MHz) 30.7 and 31.3; IR (film) 2117, 1659, 1434, 1191; EIMS *m/z* 408 (M^+, 3.8); Anal. Calcd for $C_{24}H_{29}N_2O_2P$: C, 70.57; H, 7.16; N, 6.86. Found: C, 70.66; H, 7.14; N, 6.83.

4.1.14. 2-(*N*-(*R*)-2-Methoxymethylpyrrolidinimino)-1-propargylpropyldiphenylphosphine oxide (3l). Using procedure A from the corresponding hydrazono phosphine oxide **1** (1.85 g, 5 mmol) and propargyl bromide (0.54 mL, 6 mmol), affording 1.71 g (84%) of a mixture of diastereoisomers **3l** (de=0%) as a pale yellow oil. For physical and spectral data see compound **3k**.

4.1.15. Diethyl 2-(*N*,*N*-dimethylhydrazono)-1-propargylpropylphosphonate (4a). Using procedure A from the corresponding hydrazono phosphonate **2** (1.18 g, 5 mmol) and propargyl bromide (0.54 mL, 6 mmol), affording 1.12 g (82%) of **4a** as a colorless oil: R_f (AcOEt) 0.15; ^{1}H NMR (300 MHz) 4.03 (m, 4H), 3.06–2.61 (m, 3H), 2.40 (s, 6H), 2.03 (d, $^4J_{PH}$=2.1 Hz, 3H), 1.89 (t, $^4J_{HH}$=2.6 Hz, 1H), 1.23 (m, 6H); ^{13}C NMR (75 MHz) 161.3 (d, $^3J_{PC}$=6.6 Hz), 80.5 (d, $^4J_{PC}$=22.2 Hz), 69.8, 62.3, 62.0, 46.6, 37.8 (d, $^1J_{PC}$=134.9 Hz), 17.2, 16.3, 16.1, 16.0; ^{31}P NMR (120 MHz) 24.8; IR (film) 1739, 1250, 1022; EIMS *m/z* 274 (M^+, 0.5). Anal. Calcd for $C_{12}H_{23}N_2O_3P$: C, 52.55; H, 8.45; N, 10.21. Found: C, 52.62; H, 8.44; N, 10.19.

4.1.16. Diethyl 2-(*N*,*N*-dimethylhidrazono)-1-methoxycarbonylmethylpropylphosphonate (4b). Using procedure A from the corresponding hydrazono phosphonate **2** (1.18 g, 5 mmol) and methyl bromoacetate (0.57 mL, 6 mmol), affording 1.37 g (89%) of **4b** as a colorless oil: R_f (AcOEt) 0.22; ^{1}H NMR (300 MHz) 4.05 (m, 4H), 3.59 (s,

3H), 3.26–2.98 (m, 2H), 2.67 (m, 1H), 2.34 (s, 6H), 2.06 (d, $^4J_{PH}$=2.4 Hz, 3H), 1.31–1.19 (m, 6H); ^{13}C NMR (75 MHz) 171.8 (d, $^3J_{PC}$=19.6 Hz), 161.4 (d, $^2J_{PC}$=8.0 Hz), 62.5, 62.0, 51.5, 46.6, 43.0 (d, $^1J_{PC}$=135.5 Hz), 32.1 (d, $^2J_{PC}$=2.5 Hz), 18.3, 16.2, 16.1; ^{31}P NMR (120 MHz) 25.4; IR (film) 1738, 1250, 1169, 1023; EIMS *m/z* 308 (M^+, 55.4). Anal. Calcd for $C_{12}H_{25}N_2O_5P$: C, 46.75; H, 8.17; N, 9.09. Found: C, 46.80; H, 8.16; N, 9.05.

4.1.17. Diethyl 2-(*N*,*N*-dimethylhydrazono)-1-(2-methoxycarbonylethyl)propylphosphonate (4c). Using procedure A from the corresponding hydrazono phosphonate **2** (1.18 g, 5 mmol), methyl acrylate (0.54 mL, 6 mmol) and TMEDA (0.76 mL, 5 mmol), affording 0.91 g (56%) of **4c** as a colorless oil. Using procedure B from the corresponding hydrazono phosphonate **2** (1.18 g, 5 mmol), methyl bromopropionate (0.68 mL, 6 mmol), affording 1.21 g (75%) of **4c** as a colorless oil: R_f (AcOEt) 0.23; ^{1}H NMR (300 MHz) 4.11–3.99 (m, 4H), 3.60 (s, 3H), 2.82 (m, 1H), 2.39 (s, 6H), 2.35–2.26 (m, 1H), 2.22–2.09 (m, 1H), 1.98 (d, $^4J_{PH}$=2.29 Hz, 3H), 1.36–1.16 (m, 8H); ^{13}C NMR (75 MHz) 172.9, 162.2, 62.2, 61.9, 51.5, 46.7, 46.6 (d, $^1J_{PC}$=135.0 Hz), 31.8 (d, $^2J_{PC}$=15.1 Hz), 21.9, 16.2, 16.1, 14.1; ^{31}P NMR (120 MHz) 26.9; IR (film) 1732, 1461, 1241; EIMS *m/z* 322 (M^+, 23.3). Anal. Calcd for $C_{13}H_{27}N_2O_5P$: C, 48.44; H, 8.44; N, 8.69. Found: C, 48.49; H, 8.42; N, 8.67.

4.1.18. Diethyl 2-(*N*,*N*-dimethylhydrazono)-1-ethoxycarbonylmethylpropylphosphonate (4d). Using procedure B from the corresponding hydrazono phosphonate **2** (1.18 g, 5 mmol) and ethyl bromoacetate (0.67 mL, 6 mmol), affording 1.21 g (78%) of **4d** as a colorless oil: R_f (AcOEt) 0.22; ^{1}H NMR (300 MHz) 4.12–4.00 (m, 6H), 3.25–2.99 (m, 2H), 2.67 (m, 1H), 2.35 (s, 6H), 2.06 (d, $^4J_{PH}$=2.4 Hz, 3H), 1.32–1.15 (m, 9H); ^{13}C NMR (75 MHz) 171.4 (d, $^3J_{PC}$=19.6 Hz), 161.6 (d, $^2J_{PC}$=8.0 Hz), 62.6, 62.0, 60.5, 46.7, 44.1 (d, $^1J_{PC}$=135.5 Hz), 32.4 (d, $^2J_{PC}$=2.0 Hz), 18.5, 16.3, 14.1; ^{31}P NMR (120 MHz) 25.6; IR (film) 1732, 1268, 1029; EIMS *m/z* 322 (M^+, 32.0). Anal. Calcd for $C_{13}H_{27}N_2O_5P$: C, 48.44; H, 8.44; N, 8.69. Found: C, 48.39; H, 8.41; N, 8.74.

4.1.19. Diethyl 1-ethoxycarbonylmethyl-2-(*N*-(*S*)-2-methoxymethylpyrrolidinimino)propyl phosphonate (4e). Using procedure B from the corresponding β-hydrazono phosphonate **2** (1.53 g, 5 mmol) and ethyl bromoacetate (0.67 mL, 6 mmol), affording 1.18 g (60%) of a mixture of diastereoisomers **4e** (de=30%) as a colorless oil: R_f (AcOEt) 0.38; ^{1}H NMR (300 MHz) 4.15–3.97 (m, 6H), 3.27 and 3.26 (s, 3H), 3.37–2.86 (m, 6H), 2.67–2.58 (m, 1H), 2.33–2.24 (m, 1H), 2.00 (d, $^4J_{PH}$=2.75 Hz, 3H), 1.96–1.45 (m, 4H), 1.31–1.15 (m, 9H); ^{13}C NMR (75 MHz) 171.5 and 171.4 (d, $^3J_{PC}$=20.1, 20.1 Hz), 158.0 and 156.9 (d, $^2J_{PC}$=7.6, 9.6 Hz), 75.4 and 75.3, 66.5, 62.6 and 62.5, 61.9 and 61.8, 60.4, 59.0, 53.8 and 53.7, 43.5 and 42.8 (d, $^1J_{PC}$=137.0, 135.0 Hz), 32.0 and 32.9, 26.7 and 26.6, 22.4 and 22.3, 20.1 and 19.5, 16.4 and 16.3, 14.1 and 14.0; ^{31}P NMR (120 MHz) 26.1 and 26.0; IR (film) 1732, 1255, 1017; EIMS *m/z* 392 (M^+, 2.9). Anal. Calcd for $C_{17}H_{33}N_2O_6P$: C, 52.04; H, 8.42; N, 7.14. Found: C, 52.03; H, 8.47; N, 7.12.

4.1.20. General procedure for the synthesis of phosphinylated pyrrolones 5 and pyridinone 6. To a −78°C solution of LDA (5 mmol) (previously prepared from diisopropylamine and a 1.6 M solution of ^{n}BuLi in hexanes) in THF (25 mL), a solution of α-functionalized hydrazono phosphine oxide **3f**, **h**, **j** or **e** (5 mmol) in THF (25 mL) was added. The mixture was stirred at that temperature for 1 h. After the mixture was allowed to warm to rt, the reaction mixture was stirred at rt until TLC indicated the disappearance of compound **3**. The mixture was then diluted with water (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes to afford pyrrolones **5** and pyridinone **6**.

4.1.21. 1-Dimethylamino-4-diphenylphosphinyl-5-methyl-1,3-dihydropyrrol-2-one (5a). Using general procedure from α-functionalized hydrazono phosphine oxide **3f** (1.93 g, 5 mmol), affording 1.51 g (89%) of **5a** as a white solid: mp 162–163°C; ^{1}H NMR (300 MHz) 7.70–7.26 (m, 10H), 2.89 (s, 6H), 2.88 (d, $^3J_{PH}$=19.7 Hz, 2H), 2.13 (d, $^4J_{PH}$=2.0 Hz, 3H); ^{13}C NMR (75 MHz) 175.9, 157.6 (d, $^2J_{PC}$=12.6 Hz), 131.9–128.6 (m), 97.9 (d, $^1J_{PC}$=125.9 Hz), 43.8, 38.4 (d, $^2J_{PC}$=8.5 Hz), 12.8; ^{31}P NMR (120 MHz) 21.7; IR (KBr) 1714, 1619, 1439, 1177; EIMS *m/z* 340 (M^+, 91.0). Anal. Calcd for $C_{19}H_{21}N_2O_2P$: C, 67.05; H, 6.22; N, 8.23. Found: C, 66.99; H, 6.23; N, 8.20.

4.1.22. 4-Diphenylphosphinyl-(+)-(*R*)-2′-methoxymethyl-5-methyl-2′,3′,4′,5′-tetrahydro-3*H*-[1,1′]bipyrrolyl-2-one (5b). Using general procedure from α-functionalized hydrazono phosphine oxide **3h** (2.28 g, 5 mmol), affording 1.77 g (86%) of **5b** as a pale yellow oil: R_f (AcOEt) 0.26; $[\alpha]^{20}_D$=+31.5 (*c* 1.27, CH_2Cl_2); ^{1}H NMR (300 MHz) 7.67–7.40 (m, 10H), 3.86–3.90 (m, 1H), 3.45–3.37 (m, 1H), 3.23 (s, 3H), 3.28–3.18 (m, 2H), 3.08–3.02 (m, 1H), 2.77 (t, $^3J_{HH}$=2.29 Hz, 2H), 2.10 (d, $^4J_{PH}$=1.8 Hz, 3H), 2.06–1.43 (m, 4H); ^{13}C NMR (75 MHz) 175.2 (d, $^3J_{PC}$=10.1 Hz), 159.3 (d, $^2J_{PC}$=12.6 Hz), 128.5–132.8 (m), 96.9 (d, $^1J_{PC}$=127.4 Hz), 76.5, 59.3, 58.9, 52.5, 38.3 (d, $^2J_{PC}$=80.6 Hz), 26.9, 22.7, 12.9; ^{31}P NMR (120 MHz) 22.1; IR (film) 1712, 1434, 1116; EIMS *m/z* 410 (M^+, 5.8). Anal. Calcd for $C_{23}H_{27}N_2O_3P$: C, 67.30; H, 6.63; N, 6.83. Found: C, 67.39; H, 6.65; N, 6.80.

4.1.23. 4-Diphenylphosphinyl-(−)-(*S*)-2′-methoxymethyl-5-methyl-2′,3′,4′,5′-tetrahydro-3*H*-[1,1′]bipyrrolyl-2-one (5c). Using general procedure from α-functionalized hydrazono phosphine oxide **3j** (2.28 g, 5 mmol), affording 1.72 g (84%) of **5c** as a pale yellow oil: $[\alpha]^{20}_D$=−31.5 (*c* 1.14, CH_2Cl_2). For physical and spectral data see compound **5b**.

4.1.24. 1-Dimethylamino-5-diphenylphosphinyl-6-methyl-1,3-dihydro-2-pyridone (6). Using general procedure from α-functionalized hydrazono phosphine oxide **3e** (2.00 g, 5 mmol), affording 1.56 g (88%) of **6** as a white solid: mp 145–146°C; ^{1}H NMR (300 MHz) 7.65–7.21 (m, 10H), 2.79 (s, 6H), 2.40–2.34 (m, 2H), 2.19 (d, $^4J_{PH}$=1.8 Hz, 3H), 1.96–1.93 (m, 2H); ^{13}C NMR (75 MHz) 169.4, 153.9 (d, $^2J_{PC}$=13.3 Hz), 128.5–133.9 (m), 103.8 (d, $^1J_{PC}$=110.2 Hz), 43.5, 32.8 (d, $^3J_{PC}$=8.0 Hz), 23.6 (d, $^2J_{PC}$=11.0 Hz), 17.7 (d, $^3J_{PC}$=5.0 Hz); ^{31}P NMR (120 MHz) 30.8; IR (KBr) 1690,

1609, 1434, 1354, 1280, 1179; EIMS *m/z* 354 (M^+, 10.0). Anal. Calcd for $C_{20}H_{23}N_2O_2P$: C, 67.78; H, 6.54; N, 7.90. Found: C, 67.73; H, 6.56; N, 7.89.

Pyrrolidone **5a** and pyridone **6** can also be obtained in 'one pot' reaction from hydrazone **1**. To a −78°C solution of LDA (10 mmol) (previously prepared from diisopropylamine and a 1.6 M solution of ^{n}BuLi in hexanes) in THF (25 mL), a solution of the corresponding hydrazono phosphine oxide **1** (5 mmol) in THF (25 mL) was added. The mixture was stirred at that temperature for 1 h and a solution of ethyl bromoacetate (0.67 mL, 6 mmol) or ethyl bromopropionate (0.77 mL, 6 mmol) in THF (5 mL) was then added at the same temperature. After the mixture reaction was allowed to warm to rt and stirred at this temperature for 2 days, was diluted with water (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes affording 1.20 g (65%) of **5a** as a white solid and 1.20 g (68%) of **6**.

4.1.25. Synthesis of phosphinylated and phosphorylated 1-aminopyrroles 8 and 9. *Procedure A*. A solution of K_2CO_3 (3.46 g, 25 mmol), phenyl bromide (1.05 mL, 10 mmol), $Pd(PPh_3)_4$ (0.115 g, 0.1 mmol) and the α-propargyl hydrazone **3a–c**, **k**, **l** or **4a** in DMF (30 mL) was stirred at 60°C until TLC indicated the disappearance of compounds **3a–c**, **k**, **l** or **4a** (3–7 h). The mixture was diluted with water (50 mL) and extracted with AcOEt (3×30 mL). The combined organic layers were washed with water (40 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes.

Procedure B. A solution of K_2CO_3 (3.46 g, 25 mmol), $Pd(OAc)_2$ (0.023 g, 0.1 mmol) and the α-propargyl hydrazone **3a–c** or **4a** in DMF (30 mL) was stirred at 60°C until TLC indicated the disappearance of compounds **3a–c** or **4a** (3–7 h). The mixture was diluted with water (50 mL) and extracted with AcOEt (3×30 mL). The combined organic layers were washed with water (40 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes.

4.1.26. 5-Benzyl-1-dimethylamino-3-diphenylphosphinyl-2-methylpyrrole (8a). Using procedure A from α-functionalized hydrazono phosphine oxide **3a** (1.69 g, 5 mmol), affording 1.35 g (65%) of **8a** as a white solid: mp 129–130°C; ^{1}H NMR (300 MHz) 7.67–7.02 (m, 15H), 5.43 (d, $^3J_{PH}$=4.4 Hz, 1H), 3.78 (s, 2H), 2.67 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (75 MHz) 139.9, 136.7 (d, $^2J_{PC}$=16.6 Hz), 134.5–125.9 (m), 109.0 (d, $^2J_{PC}$=11.5 Hz), 106.4 (d, $^1J_{PC}$=128.9 Hz), 44.9, 32.7, 12.8; ^{31}P NMR (120 MHz) 25.0; IR (KBr) 2939, 1441, 1182, 1116, 701; EIMS *m/z* 414 (M^+, 27.0). Anal. Calcd for $C_{26}H_{27}N_2OP$: C, 75.34; H, 6.57; N, 6.76. Found: C, 75.27; H, 6.61; N, 6.78.

4.1.27. 5-Benzyl-1-dimethylamino-3-diphenylphosphinyl-2-ethylpyrrole (8b). Using procedure A from α-functionalized hydrazono phosphine oxide **3b** (1.76 g, 5 mmol), affording 1.37 g (64%) of **8b** as a white solid: mp 179–180°C; ^{1}H NMR (300 MHz) 7.68–7.03 (m, 15H), 5.43 (d, $^3J_{PH}$=4.7 Hz, 1H), 3.87 (s, 2H), 2.74 (s, 6H), 2.72 (q, $^3J_{HH}$=7.3 Hz, 2H), 0.92 (t, $^3J_{HH}$=7.3 Hz, 3H); ^{13}C NMR (75 MHz) 143.6 (d, $^2J_{PC}$=16.6 Hz), 139.4, 134.9–126.0 (m), 110.8 (d, $^2J_{PC}$=12.0 Hz), 104.9 (d, $^1J_{PC}$=128.4 Hz), 45.6, 33.0, 19.3, 14.9; ^{31}P NMR (120 MHz) 24.2; IR (KBr) 1435, 1183, 1109, 692; EIMS *m/z* 428 (M^+, 28.2). Anal. Calcd for $C_{27}H_{29}N_2OP$: C, 75.68; H, 6.82; N, 6.54. Found: C, 75.61; H, 6.79; N, 6.56.

4.1.28. 5-Benzyl-1-dimethylamino-3-diphenylphosphinyl-2-(*p*-tolylmethyl)pyrrole (8c). Using procedure A from α-functionalized hydrazono phosphine oxide **3c** (2.14 g, 5 mmol), affording 1.59 g (63%) of **8c** as a white solid: mp 89–90°C; ^{1}H NMR (300 MHz) 7.72–6.77 (m, 19H), 5.50 (d, $^3J_{PH}$=4.6 Hz, 1H), 4.06 (s, 2H), 3.89 (s, 2H), 2.51 (s, 6H), 2.15 (s, 3H); ^{13}C NMR (75 MHz) 140.5 (d, $^2J_{PC}$=16.1 Hz), 139.1, 134.8–126.2 (m), 111.2 (d, $^2J_{PC}$=11.5 Hz), 106.2 (d, $^1J_{PC}$=128.9 Hz), 45.2, 33.1, 31.9, 22.7; ^{31}P NMR (120 MHz) 24.1; IR (KBr) 1726, 1467, 1381, 1282; EIMS *m/z* 504 (M^+, 14.6). Anal. Calcd for $C_{33}H_{33}N_2OP$: C, 78.55; H, 6.59; N, 5.55. Found: C, 78.65; H, 6.55; N, 5.57.

4.1.29. 2,5-Dimethyl-1-dimethylamino-3-diphenylphosphinyl-pyrrole (8d). Using procedure B from α-functionalized hydrazono phosphine oxide **3a** (1.69 g, 5 mmol), affording 1.05 g (62%) of **8d** as a white solid: mp 119–120°C; ^{1}H NMR (300 MHz) 7.70–7.39 (m, 10H), 5.36 (d, $^3J_{PH}$=4.4 Hz, 1H), 2.90 (s, 6H), 2.27 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz) 150.0, 136.7 (d, $^2J_{PC}$=16.1 Hz), 134.6–127.9 (m), 108.9 (d, $^2J_{PC}$=11.5 Hz), 105.0 (d, $^1J_{PC}$=128.9 Hz), 44.9, 12.8, 12.1; ^{31}P NMR (120 MHz) 25.0; IR (KBr) 1427, 1188; EIMS *m/z* 338 (M^+, 22.0). Anal. Calcd for $C_{20}H_{23}N_2OP$: C, 70.99; H, 6.85; N, 8.28. Found: C, 71.07; H, 6.87; N, 8.31.

4.1.30. 1-Dimethylamino-3-diphenylphosphinyl-2-ethyl-5-methylpyrrole (8e). Using procedure B from α-functionalized hydrazono phosphine oxide **3b** (1.76 g, 5 mmol), affording 1.29 g (73%) of **8e** as a white solid: mp 130–131°C; ^{1}H NMR (300 MHz) 7.73–7.20 (m, 10H), 5.36 (d, $^3J_{PH}$=4.6 Hz, 1H), 2.88 (s, 6H), 2.63 (q, $^3J_{HH}$=7.3 Hz, 2H), 2.21 (s, 3H), 0.88 (t, $^3J_{HH}$=7.3 Hz, 3H); ^{13}C NMR (75 MHz) 150.1, 143.4 (d, $^2J_{PC}$=16.6 Hz), 132.0–127.7 (m), 110.3 (d, $^2J_{PC}$=12.1 Hz), 104.0 (d, $^1J_{PC}$=128.4 Hz), 45.3, 19.2, 14.8, 13.5; ^{31}P NMR (120 MHz) 24.3; IR (KBr) 1706, 1441, 1182, 1123; EIMS *m/z* 352 (M^+, 28.2). Anal. Calcd for $C_{21}H_{25}N_2OP$: C, 71.57; H, 7.15; N, 7.95. Found: C, 71.69; H, 7.12; N, 7.92.

4.1.31. 1-Dimethylamino-3-diphenylphosphinyl-5-methyl-2-(*p*-tolylmethyl)pyrrole (8f). Using procedure B from α-functionalized hydrazono phosphine oxide **3c** (2.14 g, 5 mmol), affording 1.35 g (63%) of **8f** as a white solid: mp 142–143°C; ^{1}H NMR (300 MHz) 7.69–6.79 (m, 14H), 5.45 (d, $^3J_{PH}$=4.6 Hz, 1H), 4.02 (s, 2H), 2.61 (s, 6H), 2.18 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz) 140.5 (d, $^2J_{PC}$=16.6 Hz), 137.1, 135.0–128.0 (m), 110.4 (d, $^2J_{PC}$=11.5 Hz), 105.1 (d, $^1J_{PC}$=129.4 Hz), 44.8, 31.3, 20.9, 13.5; ^{31}P NMR (120 MHz) 24.3; IR (KBr) 1500, 1428, 1196, 1123, 698; EIMS *m/z* 428 (M^+, 19.5). Anal. Calcd for $C_{27}H_{29}N_2OP$: C, 75.68; H, 6.82; N, 6.54. Found: C, 75.76; H, 6.83; N, 6.56.

4.1.32. 5′-Benzyl-3′-diphenylphosphinyl-(+)-(*R*)-2-methoxymethyl-2′-methyl-2,3,4,5-tetrahydro-[1,1′]bipyrrolyl (8g). Using procedure B from α-functionalized hydrazono phosphine oxide **3k** (2.04 g, 5 mmol), affording 1.79 g (74%) of **8g** as a pale yellow oil: R_f (AcOEt) 0.23; $[\alpha]^{20}_D$=+25.0 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (300 MHz) 7.71–7.01 (m, 15H), 5.46 (d, $^3J_{PH}$=4.6 Hz, 1H), 3.61–3.54 (m, 2H), 3.23 (s, 3H), 3.13 (s, 2H), 3.15–3.04 (m, 1H), 3.00–2.91 (m, 1H), 2.51–2.46 (m, 1H), 2.26 (s, 3H), 2.06–1.61 (m, 4H); ^{13}C NMR (75 MHz) 144.8, 135.9 (d, $^2J_{PC}$=16.1 Hz), 140.2–123.1 (m), 108.0 (d, $^2J_{PC}$=12.8 Hz), 106.8 (d, $^1J_{PC}$=127.9 Hz), 74.9, 61.9, 58.7, 53.2, 32.4, 27.6, 22.7; ^{31}P NMR (120 MHz) 22.1; IR (film) 1706, 1434, 1109; EIMS *m*/*z* 484 (M^+, 8.2). Anal. Calcd for $C_{30}H_{33}N_2O_2P$: C, 74.36; H, 6.86; N, 5.78. Found: C, 74.40; H, 6.83; N, 5.80.

4.1.33. 5′-Benzyl-3′-diphenylphosphinyl-(−)-(*S*)-2-methoxymethyl-2′-methyl-2,3,4,5-tetrahydro-[1,1′]bipyrrolyl (8h). Using procedure B from α-functionalized hydrazono phosphine oxide **3l** (2.04 g, 5 mmol), affording 1.75 g (72%) of **8h** as a pale yellow oil $[\alpha]^{20}_D$=−25.0 (*c* 0.50, CH_2Cl_2). For physical and spectral data see compound **8g**.

4.1.34. 3-Diethoxyphosphoryl-1-dimethylamino-2-methyl-5-phenylmethylpyrrole (9a). Using procedure A from α-functionalized hydrazono phosphonate **4a** (1.37 g, 5 mmol), affording 1.05 g (60%) of **9a** as a colorless oil: R_f (AcOEt) 0.38; ^{1}H NMR (300 MHz) 7.40–7.09 (m, 5H), 5.86 (d, $^3J_{PH}$=5.0 Hz, 1H), 4.02 (q, $^3J_{HH}$=7.0 Hz, 4H), 3.82 (s, 2H), 2.72 (s, 6H), 2.43 (s, 3H), 1.24 (t, $^3J_{HH}$=7.0 Hz, 6H); ^{13}C NMR (75 MHz) 136.3 (d, $^2J_{PC}$=24.2 Hz), 132.5 (d, $^3J_{PC}$=12.6 Hz), 139.7–126.0 (m), 108.0 (d, $^2J_{PC}$=10.6 Hz), 102.4 (d, $^1J_{PC}$=217.6 Hz), 61.3, 61.2, 44.7, 32.9, 16.3, 16.2, 12.2; ^{31}P NMR (120 MHz) 19.9; IR (film) 1454, 1235, 1036; EIMS *m*/*z* 350 (M^+, 47.6). Anal. Calcd for $C_{18}H_{27}N_2O_3P$: C, 61.70; H, 7.77; N, 7.99. Found: C, 61.64; H, 7.78; N, 7.96.

4.1.35. 3-Diethoxyphosphoryl-2,5-dimethyl-1-dimethylaminopyrrole (9b). Using procedure B from α-functionalized hydrazono phosphonate **4a** (1.37 g, 5 mmol), affording 0.84 g (61%) of **9b** as a colorless oil: R_f (AcOEt) 0.31; ^{1}H NMR (300 MHz) 5.86 (d, $^3J_{PH}$=4.9 Hz, 1H), 3.99 (q, $^3J_{HH}$=7.0 Hz, 4H), 2.86 (s, 6H), 2.37 (s, 3H), 2.19 (s, 3H), 1.24 (t, $^3J_{HH}$=7.0 Hz, 6H); ^{13}C NMR (75 MHz) 136.5 (d, $^2J_{PC}$=24.2 Hz), 128.6 (d, $^3J_{PC}$=12.6 Hz), 107.9 (d, $^2J_{PC}$=10.6 Hz), 100.6 (d, $^1J_{PC}$=218.6 Hz), 61.6, 61.0, 44.8, 16.2, 16.1, 12.8, 11.5; ^{31}P NMR (120 MHz) 20.1; IR (film) 1705, 1430, 1241, 1023; EIMS *m*/*z* 274 (M^+, 69.4). Anal. Calcd for $C_{12}H_{23}N_2O_3P$: C, 52.56; H, 8.39; N, 10.22. Found: C, 52.55; H, 8.40; N, 10.21.

Phosphinylated 1-aminopyrrole **8b** and phosphorylated 1-aminopyrroles **9a** and **b** can also be obtained in 2 step-reactions without purification from hydrazones **1** and **2**. To a −78°C solution of LDA (5 mmol) (previously prepared from diisopropylamine and a 1.6 M solution of ^{n}BuLi in hexanes) in THF (25 mL), a solution of the corresponding hydrazono phosphine oxide **1** (5 mmol) or hydrazono phosphonate **2** (5 mmol) in THF (25 mL) was added. The mixture was stirred at that temperature for 1 h and a solution of propargyl bromide (0.54 g, 6 mmol) in THF (5 mL) was then added at the same temperature. After the mixture was allowed to warm to rt, the reaction mixture was stirred at rt for 12 h. The resulting solution was then concentrated under vacuum and diluted with DMF (30 mL). K_2CO_3 (3.46 g, 25 mmol) and $Pd(OAc)_2$ (0.026 g, 0.1 mmol) was added and the mixture reaction was stirred for 6 h at 60°C. The mixture was then diluted with water (50 mL) and extracted with AcOEt (3×30 mL). The combined organic layers were washed with water (40 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with 2:1 AcOEt/hexanes affording 1.03 g (48%) of **8b**, 0.64 g (51%) of **9a** and 0.71 g (52%) of **9b**.

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