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Preparation and reactions of 3-phosphinyl-1-aza-1,3-butadienes. Synthesis of phosphorylated pyridine and pyrazole derivatives

Francisco Palacios,[a,*] Domitila Aparicio,[a] Yago López,[a] Jesús M. de los Santos[a] and José M. Ezpeleta[b]

[a]*Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain*
[b]*Departamento de Física Aplicada II, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain*

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Abstract—3-Phosphinyl 1-aza-1,3-butadienes **2** are obtained by aldol condensation between hydrazonoalkyl phosphine oxides and *N*,*N*-dimethylformamide dimethyl acetal. Transamination reaction of these azadienes with amines yields functionalized 1-aza-1,3-butadienes **3**. Cycloaddition processes of these azadienes **2a** with electron-poor dienophiles to give phosphorylated pyridine derivatives **9** and **15** are also reported, while intramolecular cyclization reaction of heterodiene **2b** affords phosphorylated pyrazole **17**.

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 have been extensively used as versatile precursors in acyclic[2] and heterocyclic synthesis,[3] and also form part of the structure of new azapeptides,[4] as well as biologically active compounds.[5]

Aza-Diels–Alder (ADA) reactions[6,7] of 1-azabutadienes are gaining widespread acceptance as tools in heterocyclic synthesis and have found use in the preparation of compounds containing pyridine, quinoline, mono- and diazaanthracene and other nitrogen rings. In particular, α,β-unsaturated dimethylhydrazones have been widely used in hetero Diels–Alder reactions, as 1-azadienes[8] (**I**, $R^1=NMe_2$) (Fig. 1) with electron-deficient partners, as key steps in a variety of syntheses of natural products and other biologically relevant heterocycles.[9]

In this context, we have been involved in the synthesis of 1-aza (**I**),[10] 2-aza-(**II**),[11] and 1,2-diaza-1,3-butadienes (**III**)[12] (Fig. 1) as well as new strategies for the preparation of nitrogen heterocyclic compounds.[13]

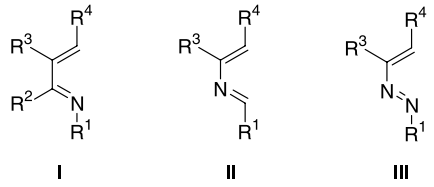

Figure 1.

However, as far as we know no examples of aza-Diels–Alder (ADA) reaction of 1-azadienes containing a phosphorus substituent at *C*-3 position (**I**, $R^1=NMe_2$, $R^3=P(O)Ph_2$, Fig. 1), have been reported. Furthermore, it is known that phosphorus substituents regulate important biological functions,[14] and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting for the preparation of biologically active compounds.

As a continuation of our work on the cycloaddition reaction of 1-azadienes and on the chemistry of new phosphorus- and nitrogen-substituted heterocycles, here we aim to explore the behaviour of 1-azadienes derived from dimethylhydrazones, such as 3-phosphinyl-1-aza-1,3-butadiene **Ia** (**I**, $R^1=R^4=NMe_2$, $R^3=P(O)Ph_2$) towards dienophiles (a=b), for the preparation of phosphorus-substituted heterocycles **IV** (Scheme 1), as well as the effect of subtituents at *C*-2 position of the azadiene. This strategy could open new entries for the preparation of substituted six-membered heterocycles.

Keywords: Hydrazones; 1-Aza-1, 3-buladienes; Phosphorylated heterocycles; Aza-Diels–Alder.
* Corresponding author. Tel.: +34 945 013103; fax: +34 945 013049; e-mail: francisco.palacios@ehu.es

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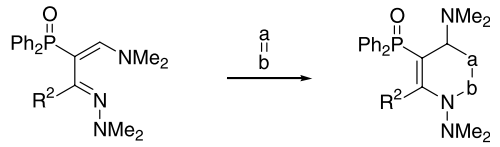


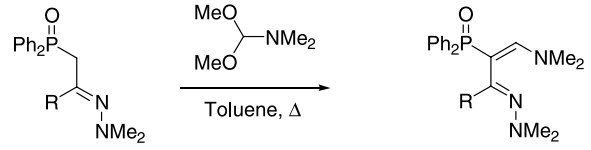
Ia **IV**

Scheme 1.

2. Results and discussion

2.1. Preparation of 3-phosphinyl 1-aza-1,3-butadienes 2

1-Aza-1,3-butadienes **2** (R=H, Me), containing electron-donating groups at *N*-1 and *C*-4 as well as an electron-withdrawing group at *C*-3 position, were prepared by aldol condensation between hydrazonoalkyl phosphine oxides **1** (R=H, Me) and *N*,*N*-dimethylformamide dimethyl acetal (Scheme 2). Thus, reaction of β-hydrazono phosphine oxide **1a** (R=H), prepared from methyl diphenylphosphine oxide, DMF and *N*,*N*-dimethylhydrazine (see Section 3), with *N*,*N*-dimethylformamide dimethyl acetal in refluxing toluene (TLC control) led to the formation of 1-azadiene **2a** (R=H) in good yield (Scheme 2). In the same way, 2-methyl-substituted 1-azadiene **2b** (R=Me) can be obtained by reaction of hydrazonoalkyl phosphine oxide **1b** (R=Me)[10b] with *N*,*N*-dimethylformamide dimethyl acetal. These compounds **2** were characterized by their spectroscopic data, and the vicinal coupling constant ($^3J_{PH}$) in the range of 15.0 Hz indicate a cis-relationship between the phosphorus atom and the vinylic proton, being consistent with an *E*-configuration for the carbon–carbon double bond.[15] ^{31}P NMR spectrum of **2a** showed one absorption at δ_P 33.1 ppm. Likewise, the ^{1}H NMR spectra of **2a** gave a well resolved doublet for the vinylic proton at δ_H 7.12 ppm ($^3J_{PH}$=15.0 Hz), while in ^{13}C NMR a doublet appeared at δ_C 146.0 ppm ($^2J_{PC}$=16.6 Hz) for the methine carbon.



1a R = H
1b R = Me

2a R = H
2b R = Me

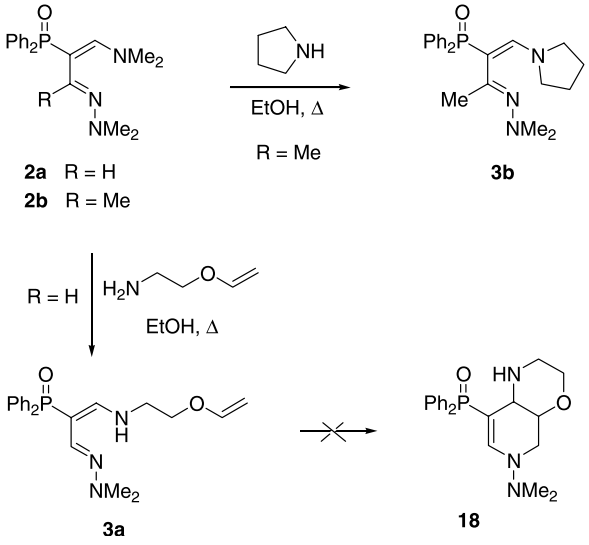
Scheme 2.

As far as we know, this process represents the first example for the preparation of 1-aza-1,3-butadienes containing a phosphorus electron-withdrawing group (Scheme 2).

These results prompted us to extend this reaction and to explore whether other phosphorylated 1-aza-1,3-butadienes can be obtained by transamination reaction of these 1-azadienes **2** with amine derivatives.

2.2. Transamination reaction of 4-dimethylamino 3-phosphinyl 1-aza-1,3-butadienes 2

We studied the transamination reaction between 1-azadienes **2** and simple and functionalized amines. Treatment of 1-azadiene **2b** (R=Me) with pyrrolidine in refluxing EtOH gave the transamination product **3b** in almost quantitative yield (Scheme 3). The spectroscopic data are in agreement with the assigned structure for compound **3b**. This process was extended to other functionalized amine derivatives. Thus, 2-vinyloxy ethylamine reacted with 1-azadiene **2a** (R=H) and gave, after purification, *N*-functionalized 1-aza-1,3-butadiene **3a** in 76% yield (Scheme 3).



2a R = H
2b R = Me

3b **3a** **18**

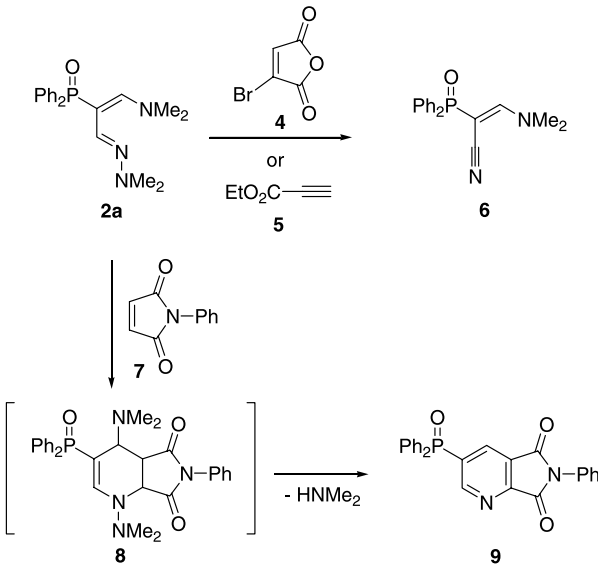
Scheme 3.

Next, we explore whether new phosphorylated 1-aza-1, 3-butadienes could be used as versatile tools for the construction of nitrogen-containing heterocycles through the cycloaddition reaction of these azadienes.

2.3. Cycloaddition reaction of 3-phosphinyl 1-aza-1,3-butadienes 2

The presence of electron-rich groups such as dimethylamino substituents on the terminal nitrogen atom (*N*-1) and on the terminal carbon atom (*C*-4) of the heterodiene system, may favour the Aza-Diels–Alder (ADA) cycloaddition of these substrates. In this way, 1-azadiene systems have been used as building blocks for the preparation of a wide range of heterocycles.[16] However, aza-Diels–Alder (ADA) reaction of 1-aza-1,3-butadienes **2** containing phosphorus substituents has not been reported, although, this strategy could be very useful for the preparation of phosphorylated azaheterocycles.[17]

Initially, we studied the cycloaddition reaction of electron-poor dienophiles such as tetracyanoethylene, naphthoquinone, diethyl azodicarboxylate, tosylisocyanate, diethyl fumarate, diethyl maleate, or maleic anhydride to azadiene **2a**. However, the formation of cyloadducts was not observed and decomposition products were obtained. In the same way, the addition of bromomaleic anhydride **4** or ethyl propiolate **5** to 1-azadiene **2a** gave the phosphorylated α,β-unsaturated nitrile **6** in moderate to good yield (Scheme 4). The formation of this nitrile **6** could be explained by transfer of the dimethylamino group of the azadienic system to the dienophile followed by oxidation to nitrile **6** as reported before for other authors.[18]



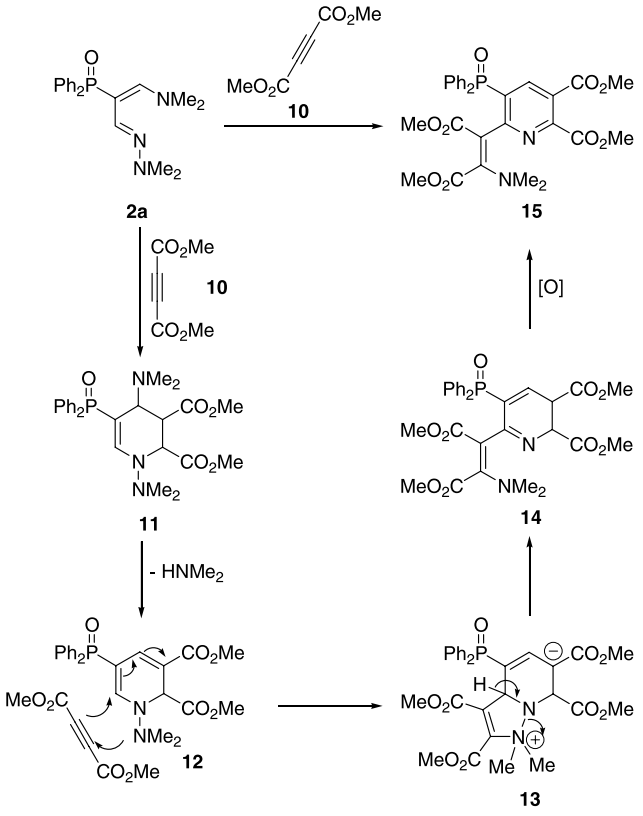
Scheme 4.

The addition of *N*-phenylmaleimide **7** to 1-aza-1,3-butadiene **2a** in the absence of solvent and at 100 °C led to the formation of the functionalized bicyclic cycloadduct **9** (yield of isolated compound 37%, Scheme 4). All attempts to increase the yield of this cycloaddition by addition of Lewis acids such as BF_3, $AlCl_3$, $Cu(OTf)_2$, $InCl_3$ or $LiClO_4$ were unsuccessful giving to the decomposition of the starting 1-azadiene **2a**. As before, the structure of compound **9** was assigned on the basis of NMR spectroscopic data, including MS data and its formation could be rationalized through a initial [4+2] cycloaddition reaction of 1-azadiene **2a** with *N*-phenylmaleimide **7** as dienophile to give tetrahydropyridine **8**, which aromatization with the loss of dimethylamine afforded substituted fused-pyridine **9** (Scheme 4).

A different behaviour was observed when 1-azadiene **2a** (R=H) was treated with an excess of diethyl acetylenedicarboxylate (DEAD) **10** in the absence of solvent and at room temperature to give, in moderate yield the substituted vinyl pyridine **15**, instead of the expected phosphorylated pyridine derivative **11** (Scheme 5).

This substituted vinyl pyridine **15** were characterized by its NMR spectral data, where ^{1}H NMR spectrum of **15** showed a well resolved doublet at δ_H 7.89 ppm with coupling constant $^3J_{PH}=12.8$ Hz corresponding to *H*-4. The structure was finally determined by X-ray study of **15**[19] (Fig. 2). The process could be explained through an initial [4+2] cycloaddition reaction of 1-azadiene **2a** with DEAD **10** to give tetrahydropyridine **11**, followed by elimination of diethylamine and formation of dihydropyridine **12**. Subsequent addition of a second molecule of DEAD to this dihydropyridine **12** may give a bicyclic heterocycle **13**, which five-membered ring opening and aromatization led to the formation of pyridine **15**.

Next, the reaction of 1-azabutadienes **2b** substituted with a methyl group at *C*-2 position as heterodienes with electron-poor dienophiles such as diethyl acetylenedicarboxylate, diethyl azodicarboxylate, or benzoquinone was explored.



Scheme 5.

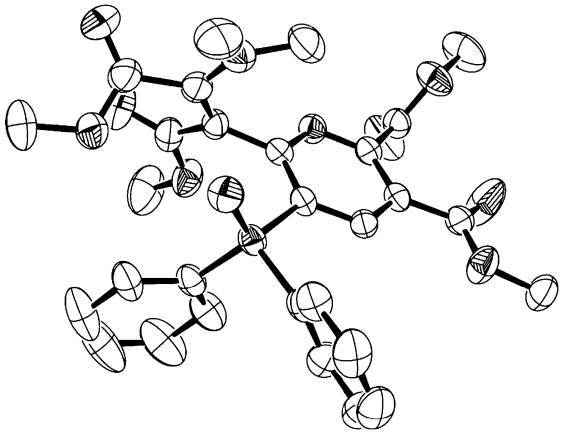
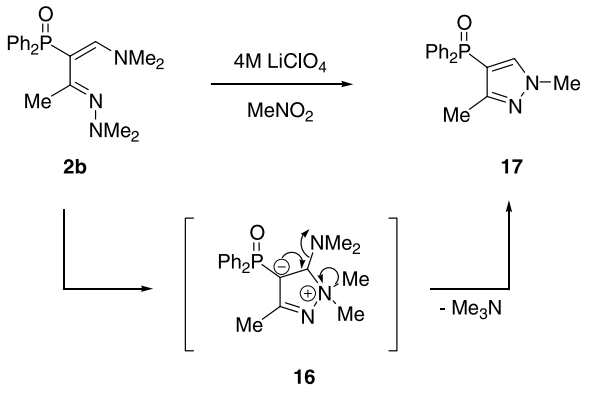


Figure 2. ORTEP view of compound **15**.

However, the formation of cyloadducts was not observed and decomposition products were obtained. As reported by Ghosez et al.,[20] the presence of a methyl group at *C*-2 of the 1-azadiene system **2b** shifts the dimethylamino group at *N*-1 out of the plane (steric inhibition of conjugation), deactivating the diene system and hindering the cycloaddition reaction with dienophiles.

For this reason, we explored the behaviour of these substrates **2b** in the presence of $LiClO_4$ as catalyst. Addition of $LiClO_4$ to methyl-substituted 1-azadiene **2b** in the presence or even in the absence of dienophile and using nitromethane as solvent led to the formation of 4-phosphorylated pyrazole **17** (Scheme 6). Mass spectrometry supported the molecular ion peak, while in the ^{31}P NMR



Scheme 6.

spectrum the phosphinyl group resonated at δ_P 19.2 ppm. The ^1H NMR spectrum showed an absorption at δ_H 7.07 ppm as a singlet for *H*-5 and ^{13}C NMR spectrum showed an absorption at δ_C 137.1 ppm as a doublet with coupling constant $^2J_{PC}=20.6$ Hz for *C*-5 and at δ_C 110.4 ppm as a doublet with coupling constant $^1J_{PC}=125.9$ Hz for the carbon atom directly bonded to the phosphorus atom (*C*-4). The formation of this pyrazole **17** could be explained by intramolecular cyclization involving nucleophilic atack of the dimethylamino group at *N*-1 to the carbon–carbon double bond to give pyrazolidine **16**. Subsequent loss of trimethylamine afforded 4-phosphorylated pyrazole **17** (Scheme 6).

Finally, the behaviour of functionalized 1-aza-1,3-butadiene **3a** (Scheme 3) as heterodiene in intramolecular aza-Diels–Alder (IADA) reaction was explored. However, the formation of cycloadducts **18** was not observed in this reaction and the starting compound **3a** was recovered unchanged. Neither standing the 1-azadiene in refluxing xylene nor the use of Lewis acids as catalyst led to the formation of cycloadducts, probably due to the unfavourable configuration of the amino group in position 4.

In conclusion, the synthesis of 1-dimethylamino-1-aza-1,3-butadienes containing a phosphine oxide group at *C*-3 **2** is described. The process implies aldol condensation between hydrazonoalkyl phosphine oxides and *N*,*N*-dimethylformamide dimethyl acetal. Electron-deficient dienophiles such as *N*-phenylmaleimide or diethyl acetylenedicarboxylate react with *C*-2 unsubstituted 1-azadienes **2a** to afford phosphorylated pyridine derivatives **9** and **15**. However, 1-azadienes **2b** substituted with a methyl group at *C*-2 of the azadiene system do not react with electron-poor dienophiles, and its cyclization in the presence of $LiClO_4$ to give phosphorylated pyrazole **17** has been described. Through these strategies reported in this paper, new access to polysubstituted nitrogen- and phosphorus-containing heterocycles can be designed.

3. Experimental

3.1. General

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC's were performed with silica gel 60 F_{254} plates. Spot visualization was accomplished by UV light or $KMnO_4$ solution. Flash chromatography was carried out using silica gel 60 (230–400 mesh). Melting points were determined with a Electrothermal IA9100 digital apparatus and are uncorrected. ^1H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian Unity Plus 300 MHz spectrometer, using tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.24 ppm) for ^1H NMR spectra, chloroform (77.0 ppm) for ^{13}C NMR spectra, and phosphoric acid (85%) (0.00 ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), br s (broad singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet) or m (multiplet). Coupling constants (*J*) are reported in Hertz. Low-resolution mass spectra (MS) were obtained on a Hewlett Packard 5971 MSD Series spectrometer at 50–70 eV by electron impact (EI) or on a Hewlett Packard 1100 MSD Series spectrometer by chemical ionization (CI). Data are reported in the form *m*/*z* (intensity relative to base peak = 100). Infrared spectra (IR) were taken on a Nicolet FTIR Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1}. Elemental analyses were performed in a Leco CHNS-932 instrument. Hydrazonoalkyl phosphine oxide **1b** was synthesized according to literature procedures.[10b]

3.1.1. Synthesis of 1-(dimethylhydrazono)ethenyl diphenylphosphine oxide (1a). To a −60 °C stirred solution of methyl diphenylphosphine oxide (10 mmol, 2.16 g) in THF (40 mL), a solution of butyllithium (1.6 M in hexanes, 11 mmol, 6.9 mL) in THF (2 mL) was added under a nitrogen atmosphere. After 30 min at the same temperature a solution of DMF (15 mmol, 1.16 mL) in THF (5 mL) was added dropwise and the reaction was kept to reach room temperature for 16 h. After this time, H_2O (10 mL) was added to the reaction mixture and stirred for 45 min. HCl (20%) was then added to the reaction mixture until pH = 1 and the mixture was stirred for 30 additional min. Then, the aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the organic phases were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The obtained aldehyde, without further purifications, was dissolved in dry chloroform (40 mL) and *N*,*N*-dimethylhydrazine (11 mmol, 0.85 mL) was then added at room temperature and stirred for 16 h. The reaction mixture was washed with water (2×10 mL) and the organic phase was dried over anhydrous $MgSO_4$ and evaporated under vacuum. Precipitation of the crude product from ethyl ether and recrystallization from a mixture of hexanes–CH_2Cl_2 (3/1) gave **1a** (2.40 g, 84% two steps) as a white solid: 90–92 °C; ^1H NMR ($CDCl_3$) δ 7.79–7.42 (m, 10H), 6.58–6.53 (m, 1H), 3.37 (dd, $^2J_{PH}=14.2$ Hz, $^3J_{HH}=5.9$ Hz, 2H), 2.66 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 133.1, 131.8, 131.7, 131.6, 131.5, 131.1, 131.0, 130.9, 128.6, 128.5, 128.3, 125.9 (d, $^2J_{PC}=7.5$ Hz), 42.8, 35.7 (d, $^1J_{PC}=68.5$ Hz); ^{31}P NMR ($CDCl_3$) δ 29.9; IR (KBr) 3065, 2959, 2853, 1434, 1182; MS (CI) *m*/*z* 287 (M^+ 1, 100). Anal. Calcd for $C_{16}H_{19}N_2OP$: C, 67.12; H, 6.69; N, 9.78. Found C, 67.10; H, 6.72; N, 9.77.

3.2. General procedure for the synthesis of phosphorylated 1-azadienes (2)

To a stirred solution of β-hydrazono phosphine oxide **1a** or **1b** (1 mmol) in toluene (1 mL), was added *N*,*N*-dimethylformamide dimethyl acetal (1.2 mmol, 0.16 mL) under a nitrogen atmosphere, and the mixture was refluxed for 36 h. Then, the solvent was evaporated under vacuum and the crude product was purified by flash-chromatography (silica gel, AcOEt/MeOH 85:15).

3.2.1. [3-(Dimethylhydrazono)-2-(diphenylphosphinoyl)-propenyl]dimethylamine (2a). The title compound (0.24 g, 69%) obtained as a white solid from 2-(*N*,*N*-dimethylhydrazono)ethyldiphenylphosphine oxide (1 mmol, 0.29 g) as described in the general procedure: mp 92–93 °C; ^{1}H NMR ($CDCl_3$) δ 7.83–7.27 (m, 11H), 7.12 (d, $^{3}J_{PH}$=15.0 Hz, 1H), 3.07 (s, 6H), 2.47 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.0 (d, $^{2}J_{PC}$=16.6 Hz), 131.1, 129.7, 129.2 (d, $^{2}J_{PC}$=8.1 Hz), 127.8, 127.7, 127.3, 127.2, 126.1, 126.0, 124.0, 123.9, 123.8, 123.2, 123.0, 87.4 (d, $^{1}J_{PC}$=115.3 Hz), 39.5, 38.7; ^{31}P NMR ($CDCl_3$) δ 33.1; IR (KBr) 3436, 2906, 2793, 1600, 1527, 1122; MS (CI) *m*/*z* 342 (M^++1, 100). Anal. Calcd for $C_{19}H_{24}N_3OP$: C, 66.85; H, 7.09; N, 12.31. Found C, 66.63; H, 7.08; N, 12.34.

3.2.2. [3-(Dimethylhydrazono)-2-(diphenylphosphinoyl) but-1-enyl]dimethylamine (2b). The title compound (0.25 g, 70%) obtained as a white solid from 2-(*N*,*N*-dimethylhydrazono)propyldiphenylphosphine oxide (1 mmol, 0.30 g) as described in the general procedure: mp 78–80 °C; ^{1}H NMR ($CDCl_3$) δ 7.85–7.29 (m, 10H), 6.55 (d, $^{3}J_{PH}$=15.4 Hz, 1H), 2.80 (s, 6H), 2.21 (s, 6H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.0, 150.3 (d, $^{2}J_{PC}$=18.6 Hz), 133.8, 132.4, 131.6, 131.4, 130.8, 130.6, 130.4, 130.3, 130.2, 130.1, 127.0, 126.9, 95.6 (d, $^{1}J_{PC}$=115.3 Hz), 45.7, 42.1, 20.8; ^{31}P NMR ($CDCl_3$) δ 30.7; IR (KBr) 3409, 2952, 2653, 1613, 1440, 1241; MS (CI) *m*/*z* 356 (M^++1, 100). Anal. Calcd for $C_{20}H_{26}N_3OP$: C, 67.59; H, 7.37; N, 11.82. Found C, 67.75; H, 7.39; N, 11.83.

3.3. General procedure for the transamination reaction. Synthesis of phosphorylated 1-azadienes (3)

To a stirred solution of 1-azadiene **2a** or **2b** (1 mmol) in dry ethanol (4 mL), the corresponding amine (1.5–2 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred and refluxing for 8–24 h. The solvent was evaporated under vacuum, and the crude product was purified by flash-chromatography (silica gel, AcOEt/MeOH 95:5).

3.3.1. [3-(Dimethylhydrazono)-2-(diphenylphosphinoyl)-propenyl](2-vinyloxyethyl)amine (3a). The title compound (0.29 g, 76%) obtained as a yellow oil from 1-azadiene **2a** (1 mmol, 0.34 g) and 2-vinyloxy ethylamine (1.5 mmol, 0.17 g) after refluxing for 8 h as described in the general procedure: R_f=0.82, AcOEt/MeOH 3:1; ^{1}H NMR ($CDCl_3$) δ 9.39 (br s, 1H), 7.67–6.78 (m, 12H), 6.37 (dd, $^{3}J_{HH}$=6.1 and 14.0 Hz, 1H), 4.10 (d, $^{3}J_{HH}$=14.0 Hz, 1H), 3.96 (d, $^{3}J_{HH}$=6.1 Hz, 1H), 3.70–3.67 (m, 2H), 3.38–3.36 (m, 2H), 2.58 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 151.0, 149.5 (d, $^{2}J_{PC}$=17.6 Hz), 137.8 (d, $^{2}J_{PC}$=19.5 Hz), 134.5, 133.1, 131.8, 131.7, 131.1, 131.0, 128.2, 128.1, 127.9, 89.6 (d, $^{1}J_{PC}$=126.9 Hz), 87.0, 67.3, 47.4, 43.6; ^{31}P NMR ($CDCl_3$) δ 31.8; IR (NaCl) 3376, 2965, 1619, 1440, 1188; MS (EI) *m*/*z* 383 (M^+, 35). Anal. Calcd for $C_{21}H_{26}N_3O_2P$: C, 65.78; H, 6.83; N, 10.96. Found C, 65.96; H, 6.85; N, 10.93.

3.3.2. [3-(Dimethylhydrazono)-2-(diphenylphosphinoyl)-but-1-enyl]pyrrolidine (3b). The title compound (0.36 g, 94%) obtained as a yellow oil from 1-azadiene **2b** (1 mmol, 0.36 g) and pyrrolidine (2 mmol, 0.17 mL) after refluxing for 24 h as described in the general procedure: R_f=0.84, AcOEt/MeOH 3:1; ^{1}H NMR ($CDCl_3$) δ 7.86–7.21 (m, 10H), 6.57 (d, $^{3}J_{PH}$=15.0 Hz, 1H), 3.16–3.14 (m, 4H), 2.27 (s, 6H), 1.89 (s, 3H), 1.76–1.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.2 (d, $^{2}J_{PC}$=9.6 Hz), 146.9 (d, $^{2}J_{PC}$=19.6 Hz), 134.0, 132.6, 132.1, 132.0, 131.9, 131.8, 131.0, 130.9, 130.6, 130.5, 130.1, 130.0, 127.5, 127.4, 127.3, 127.2, 97.6 (d, $^{1}J_{PC}$=115.3 Hz), 51.4, 46.4, 24.8, 21.1; ^{31}P NMR ($CDCl_3$) δ 29.7; IR (NaCl) 2945, 2859, 1606, 1175; MS (CI) *m*/*z* 382 (M^++1, 100). Anal. Calcd for $C_{22}H_{28}N_3OP$: C, 69.27; H, 7.40; N, 11.02. Found C, 69.03; H, 7.41; N, 10.98.

3.3.3. Synthesis of 3-dimethylamino-2-(diphenylphosphinoyl)acrylonitrile (6). A mixture of 1-azadiene **2a** (1 mmol, 0.34 g) in xylene (3 mL) and the corresponding dienophile (2 mmol) was stirred at room temperature under a nitrogen atmosphere for 36 h. The solvent was evaporated under vacuum and the crude product was purified by flash-chromatography (silica gel, AcOEt/MeOH 95:5) to afford compound **6** (76–83%) as a yellow oil: R_f=0.65, AcOEt/MeOH 3:1; ^{1}H NMR ($CDCl_3$) δ 7.76–7.33 (m, 11H), 3.31 (s, 3H), 3.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.0 (d, $^{2}J_{PC}$=12.6 Hz), 133.0, 131.8, 131.7, 131.6, 131.4, 131.2, 128.3, 128.1, 119.0 (d, $^{2}J_{PC}$=12.6 Hz), 62.0 (d, $^{1}J_{PC}$=122.5 Hz), 46.9, 38.0; ^{31}P NMR ($CDCl_3$) δ 28.1; IR (NaCl) 3423, 2925, 2182, 1613, 1434, 1367; MS (EI) *m*/*z* 295 (M^+−1, 100). Anal. Calcd for $C_{17}H_{17}N_2OP$: C, 68.91; H, 5.78; N, 9.45. Found C, 68.78; H, 5.77; N, 9.47.

3.4. General procedure for the cycloaddition reaction. Synthesis of phosphorylated pyridine derivatives (9) and (15)

A mixture of 1-azadiene **2a** (1 mmol, 0.34 g) and the corresponding dienophile (5–6 mmol) was stirred, without solvent, at room temperature or 100 °C under a nitrogen atmosphere. The reaction mixture was stirred for 3–5 h and the crude product was purified by flash-chromatography (silica gel).

3.4.1. 3-(Diphenylphosphinoyl)-6-phenyl pyrrolo[3,4,-*b*]-pyridine-5,7-dione (9). The title compound (0.16 g, 37%) obtained as a white solid from 1-azadiene **2a** and *N*-phenylmaleimide (6 mmol, 1.1 g) after 5 h at 100 °C as described in the general procedure. The crude product was purified by flash-chromatography (silica gel, AcOEt/hexanes 1:1): mp 193–195 °C; ^{1}H NMR ($CDCl_3$) δ 9.18 (d, $^{3}J_{PH}$=6.1 Hz, 1H), 8.34 (d, $^{3}J_{PH}$=10.5 Hz, 1H), 7.59–7.27 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 176.3, 158.7 (d, $^{2}J_{PC}$=12.1 Hz), 135.9, 135.3, 135.2, 134.7, 133.1, 132.0, 131.9, 131.0, 130.8, 129.6, 129.3, 129.2, 129.1, 128.8, 126.4; ^{31}P NMR ($CDCl_3$) δ 25.7; IR (KBr) 3320, 2975, 1689, 1420, 1267; MS (CI) *m*/*z* 425 (M^++1, 100). Anal.

Calcd for $C_{25}H_{17}N_2O_3P$: C, 70.75; H, 4.04; N, 6.60. Found C, 70.66; H, 4.08; N, 6.64.

3.4.2. 6-(2-Dimethylamino-1,2-bis-methoxycarbonyl-vinyl)-5-(diphenylphosphinoyl)pyridine-2,3-dicarboxylic acid dimethyl ester (15). The title compound (0.37 g, 63%) obtained as a white solid from 1-azadiene **2a** and dimethyl acetylenedicarboxylate (5 mmol, 0.62 mL) after 3 h at room temperature as described in the general procedure. The crude product was purified by flash-chromatography (silica gel, AcOEt) and recrystallized from a mixture of CH_2Cl_2–hexanes (1/5): mp 184–186 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, $^3J_{PH}$=12.8 Hz, 1H), 7.61–7.33 (m, 10H), 3.85 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 2.97 (s, 3H), 2.50 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.3, 165.7, 164.6, 163.3, 163.2, 155.0, 152.4, 142.5 (d, $^2J_{PC}$=12.6 Hz), 133.2, 132.1, 132.0, 131.9, 131.8, 130.8, 130.6, 129.2, 128.8, 128.6, 127.9, 127.8, 121.6, 121.5, 53.1, 52.9, 52.3, 50.6, 42.6; ^{31}P NMR ($CDCl_3$) δ 25.0; IR (KBr) 3356, 2925, 1739, 1440, 1195; MS (EI) *m/z* 580 (M^+, 3). Anal. Calcd for $C_{29}H_{29}N_2O_9P$: C, 60.00; H, 5.04; N, 4.83. Found C, 59.77; H, 5.02; N, 4.82.

X-ray analysis of compound **15**. A yellow prismatic crystal of $C_{29}H_{29}N_2O_9P$ having approximate dimensions of 0.31×0.22×0.16 mm^3 was mounted on a glass fiber. All measurements were carried out by means of a Nonius KappaCCD diffractometer with graphite monochromated Mo Kα radiation. Crystal data: $C_{29}H_{29}N_2O_9P$, T=293 K, monoclinic, space group $P2_1/n$, with a=8.9660(10) Å, b=28.402(3) Å, c=12.031(9) Å, β=110.111(12)°, V=2877(2) Å^3 and Z=4 (d_{calcd}=1.340 g cm^{-3}), μ(Mo Kα)=0.152 mm^{-1}, no absorption correction; 5072 unique reflections, 3828 with $I>2\sigma(I)$; R=5.7%, R_w=15.4% for reflections with $I>2\sigma(I)$. Crystal data for the structure of this paper have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 283335).

3.4.3. Synthesis of 4-(diphenylphosphinoyl)-1,3-dimethyl-1*H*-pyrazole (17). To a stirred solution of 1-azadiene **2b** (1 mmol, 0.36 g) in nitromethane (3 mL), lithium perchlorate was added until a 4 M solution of the salt was formed under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h, washed with H_2O (2×5 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL). The organic layer was dried over $MgSO_4$ and evaporated under vacuum, and the crude product was purified by flash-chromatography (silica gel, AcOEt) affording compound **17** (0.22 g, 74%) as a white solid: 176–178 °C; ^{1}H NMR ($CDCl_3$) δ 7.68–7.40 (m, 10H), 7.07 (s, 1H), 3.74 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.2 (d, $^2J_{PC}$=9.5 Hz), 137.1 (d, $^2J_{PC}$=20.6 Hz), 134.1, 132.6, 131.8, 131.7, 131.6, 131.4, 128.6, 128.4, 110.4 (d, $^1J_{PC}$=125.9 Hz), 38.7, 13.5; ^{31}P NMR ($CDCl_3$) δ 19.2; IR (KBr) 3104, 3051, 1527, 1440, 1195; MS (EI) *m/z* 295 (M^+-1, 100). Anal. Calcd for $C_{17}H_{17}N_2OP$: C, 68.91; H, 5.78; N, 9.45. Found C, 69.10; H, 5.76; N, 9.43.

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