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Regioselective cycloaddition of 3-azatrienes with enamines. Synthesis of pyridines derived from β-aminoacids

Francisco Palacios,* Esther Herrán, Concepción Alonso and Gloria Rubiales

Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080, Spain

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Abstract—Aza-Wittig reaction of *N*-vinylic phosphazenes with α,β-unsaturated aldehydes leads to the formation of 3-azatrienes through a [2+2]-cycloaddition–cycloreversion process. Subsequent, regioselective [4+2]-cycloaddition of 3-azatrienes with pyrrolidinocycloalkanone affords bicyclic dihydropyridines and pyridines in a regioselective fashion. 2-Heterodiene moiety of azatriene is involved in the formation of the six-membered ring skeleton of pyridine derivatives.

1. Introduction

Aza-Wittig reaction of *N*-vinylic phosphazenes with carbonyl compounds represents an easy method for the preparation of 2-azadienes. Therefore, *N*-vinylic phosphazenes[1] have proved to be useful building blocks for the synthesis of functionalized imine compounds such as electronically neutral-2-azadienes **I** (Fig. 1),[2] electron-poor 2-azadienes derived from aminophosphorus derivatives,[3] electron-poor 2-azadienes **II** (Fig. 1) derived from α-[4] or β-aminoacids,[5] and 3-fluoroalkyl-2-azadienes **III** (Fig. 1).[6] *N*-vinylic phosphazenes have also been used as key intermediates in the preparation of glycosides[7] and cyclic compounds[8–11] as well as in the construction of the framework of pharmacologically active alkaloids.[12]

Functionalized 2-azabutadienes have proved to be efficient key intermediates in organic synthesis for the preparation of heterocycles although the great majority of 2-azadienes studied are substituted with electron-donating groups being excellent reagents in aza-Diels–Alder (ADA) reactions with electron-poor dienophiles.[13–15]

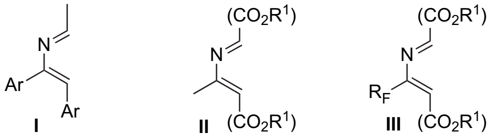
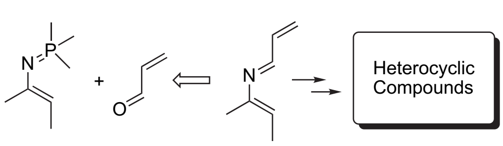


Figure 1.

In this context, we have described new methods for the preparation of nitrogen heterocyclic compounds by the use of 2-azabutadiene systems.[2,5,6] Therefore, we report here the preparation of 3-azatrienes by aza-Wittig reaction of *N*-vinylic phosphazenes with α,β-unsaturated aldehydes. Moreover, we report that 3-azatrienes can be used as key intermediates in the synthesis of dihydropyridine and pyridine compounds derived from β-aminoacids (Scheme 1) through [4+2] cycloaddition processes. It is known that 3-azatriene systems give heterocyclic compounds through electrocyclic ring closure.[16,17] However, as far as we know no examples of aza-Diels–Alder (ADA) reaction of 3-azatrienes have been reported.



Scheme 1.

2. Results and discussion

2.1. Aza-Wittig reaction of phosphazenes 1 with α,β-unsaturated aldehydes 2. Synthesis of 3-azatrienes

Reaction of *N*-vinylic phosphazenes **1a** (R=Ph, R^1=Et, R^2=H) and **1b** (R=Ph, R^1=Me, R^2=CO_2Me) with cinnamaldehyde **2a** (R^3=H, R^4=Ph), crotonaldehyde **2b** (R^3=H, R^4=Me) or methacrolein **2c** (R^3=Me, R^4=H) at room temperature, gave the [2+2]-aza-Wittig[18] products **3a–d** in excellent yields (Scheme 2, Table 1, entries 1–4). However, these azatrienes **3** were unstable during distillation

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* Corresponding author. Tel.: +34 945 013103; fax: +34 945 013049; e-mail: francisco.palacios@ehu.es

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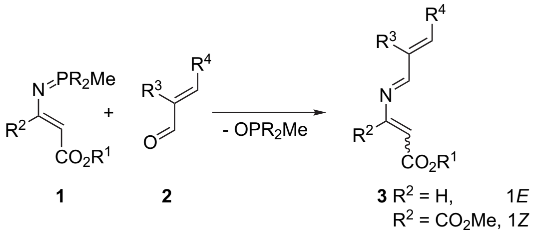
Table 1. Azatrienes **3** obtained

Entry	Starting materials		Product	R^1	R^2	R^3	R^4	Reaction conditions		Yield (%)[a]
	Phosphazene	Aldehyde						*T* (°C)	Time (h)	
1	**1a/1c**	**2a**	**3a**	Et	H	H	Ph	rt	7/1	75/98
2	**1a/1c**	**2b**	**3b**	Et	H	H	Me	rt	24/5	65/90
3	**1a/1c**	**2c**	**3c**	Et	H	Me	H	rt	30/4	90/62
4	**1b**	**2a**	**3d**	Me	CO_2Me	H	Ph	70	30	85

[a] Yield calculated by ^1H NMR.

and/or chromatography and were used without purification.[19] The use of conjugated phosphazenes **1c** derived from trimethylphosphine (R=Me, R^1=Et, R^2=H) was more favorable because the formation of azatrienes **3** took place in shorter periods of time and the elimination of trimethylphosphine oxide from the reaction mixture was easier (Table 1, entries 1–3). Next, we explored the synthetic utility of these 3-azatrienes **3** and whether new azatrienes **3** could be used as versatile tools for the construction of nitrogen-containing heterocycles through their cycloaddition reaction.

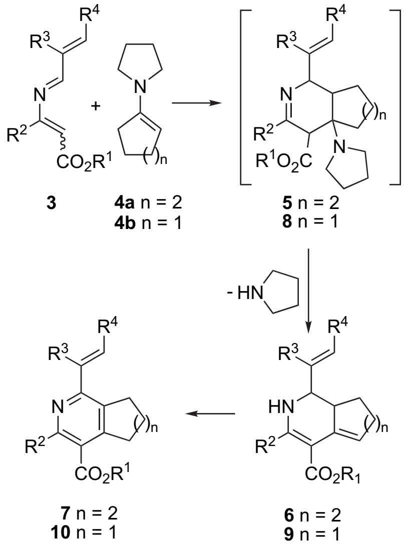


Scheme 2.

2.2. Cycloaddition reaction of azatrienes 3 with enamines

The presence of a third double bond in 3-azatrienes conjugated with 2-azadiene may have influence in the reactivity of the new systems. As it has been reported previously, 3-azatrienes through a thermal electrocyclic ring closure afford the corresponding heterocyclic compounds.[16,17,20] Therefore, we studied the synthetic usefulness of these new azatrienes **3** as heterodienes for heterocyclic synthesis.[13,20] At this point, it is noteworthy that these substrates would be an interesting starting material for the preparation of pipecolic acid derivatives.[21]

We then turned our attention to study the cycloaddition reaction of electron-deficient 3-azatrienes **3** with enamines (Scheme 3). Pyrrolidinecyclohexanone **4a** (*n*=2) reacted with heterodienes **3a**,**b** (R^2=H) at room temperature affording 1,2,6,7,8,8a-hexahydroisoquinoline compounds **6** (Table 2, entries 1 and 2). Spectral data were in agreement with the enamine structure of a bicyclic heterocycle.



Scheme 3.

The formation of these hexahydroisoquinolines **6** can be explained through a [4+2] cycloaddition reaction of 3-azatriene **3** with enamine **4a**, formation of a cycloadduct **5** followed by the loss of pyrrolidine and prototropic tautomerization under the reaction conditions. Oxidation of bicyclic heterocycles **6** with quinone or $Mn(AcO)_3$[22] led to the formation of 5,6,7,8-tetrahydroisoquinoline **7** derived from β-aminoacids (Table 2, entries 3 and 4).

Then, we tried to extend the process to other enamine, pyrrolidinecyclopentanone **4b**. Thus, 3-azatriene **3c** (R^2=H) reacted with *N*-cyclopent-1-enylpyrrolidine **4b** (*n*=1) at room temperature until disappearance of starting material, affording bicyclic compound **9** (Table 2, entry 5). Similarly,

Table 2. Bicyclic heterocycles **5–8** obtained

Entry	Starting material	Products	R^1	R^2	R^3	R^4	Reaction conditions		Yield (%)[a]
							T (°C)	Time (h)	
1	**3a**	**6a**	Et	H	H	Ph	rt	18	42
2	**3b**	**6b**	Et	H	H	Me	rt	18	42
3	**6a**	**7a**	Et	H	H	H	100	24	84[b]
4	**6b**	**7b**	Et	H	H	Me	rt	0.5	83[c]
5	**3c**	**9**	Et	H	Me	H	rt	14	35
6	**3d**	**10**	Me	CO_2Me	H	Ph	rt	20	40

[a] Purified by chromatography.

[b] Obtained by oxidation with *p*-benzoquinone.

[c] Obtained by oxidation with $Mn(AcO)_3$.

3-methoxycarbonyl-substituted azatriene **3d** also reacted with pyrrolidinecyclopentanone **4b** (n=1). However in this case, completely aromatized bicyclic pyridine **10** (Table 2, entry 6) was obtained. Formation of compounds **9** and **10** could be explained, as before, by formation of a [4+2]-cycloadduct **8** followed by the loss of pyrrolidine to give dihydropyridine **9** and oxidation to yield bicyclic compound **10** (Scheme 3).

In summary, we conclude that aza-Wittig reaction of *N*-vinylic phosphazenes with the carbonyl group of unsaturated aldehydes gives 3-azatrienes **3**. Hetero-Diels–Alder reaction of azatrienes **3** with enamines leads to the formation of bicyclic pyridine compounds derived from β-aminoacids. It is worth noting that pyridine compounds derived from β-aminoacids are useful heterocycles not only for their biological activities[23] but also because the pyridine nucleus is a structural unit appearing in many natural products.[24]

3. Experimental

3.1. General

Solvents for extraction and chromatography were of 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 silica gel 60 F_{254} and aluminum oxide N/UV_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using silica gel 60 (230–400 mesh ASTM) and aluminum oxide 90 active neutre (70–230 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H NMR (300 MHz, 250 MHz), ^{13}C NMR (75 MHz), and ^{31}P NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference (δ=0.00 ppm) for ^{1}H and ^{13}C NMR spectra, and phosphoric acid (85%) (δ=0.0 ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in hertz. 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. Phosphazenes **1a** and **1b** were prepared according to literature processes.[5]

3.2. 4-(Ethoxycarbonyl)-1,1,1-trimethyl-2-aza-1-λ^5-phosphabuta-1,3-diene (1c)

A solution of 0.705 g (5 mmol) of ethyl 3-azidoacrylate in anhydrous CH_2Cl_2 (3 mL) was added dropwise to a 0 °C solution of 5 mL (5 mmol) of trimethylphosphine (1.0 M solution in hexane) in anhydrous CH_2Cl_2 (8 mL), and the mixture was stirred for 30 min at 0 °C. Phosphazene **1c** is unstable during distillation and/or chromatography and was used without purification for the following reactions. It was obtained as a 85:15 diastereomeric mixture of *E*/*Z* isomers of **1c**. ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture δ 1.14–1.22 (m, 6H), 1.61 (d, $^{2}J_{PH}$=12.8 Hz, 9H) for isomer *E*, 1.81 (d, $^{2}J_{PH}$=12.8 Hz, 9H) for isomer *Z*, 3.98–4.09 (m, 4H), 4.59 (dd, $^{3}J_{HH}$=7.6 Hz, $^{4}J_{PH}$=3.1 Hz, 1H) for isomer *Z*, 4.99 (d, $^{3}J_{PH}$=12.4 Hz, 1H) for isomer *E*, 6.97 (dd, $^{3}J_{HH}$=7.6 Hz, $^{3}J_{PH}$=35.5 Hz, 1H) for isomer *Z*, 7.86 (dd, $^{3}J_{HH}$=12.4 Hz, $^{3}J_{PH}$=33.3 Hz, 1H) for isomer *E* ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture δ 13.4 (d, $^{2}J_{PC}$=66 Hz) for isomer *Z*, 13.5 (d, $^{2}J_{PC}$=66 Hz) for isomer *E*, 14.3 for isomer *E*, 14.5 for isomer *Z*, 56.7 for isomer *E*, 57.2 for isomer *Z*, 92.2 (d, $^{3}J_{PC}$=27 Hz) for isomer *E*, 95.5 (d, $^{3}J_{PC}$=29 Hz) for isomer *Z*, 153.7 (d, $^{2}J_{PC}$=5 Hz) for isomer *Z*, 156.2 (d, $^{2}J_{PC}$=4 Hz) for isomer *E*, 166.1 for isomer *E*, 169.4 for isomer *Z* ppm; ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.41 for isomer *Z*, 28.12 for isomer *E* ppm.

3.3. General procedure A for the preparation of 3-azatrienes 3

Unsaturated aldehyde **2** (4 mmol) was added to a 0–10 °C solution of phosphazene **1** (4 mmol) in $CHCl_3$ (10 mL) under N_2, and the mixture was stirred at room temperature or warmed at 70 °C until ^{1}H NMR indicated the disappearance of phosphazene. 3-Azatrienes **3** are unstable during distillation and/or chromatography and were used without purification for the following reactions.

3.4. General procedure B for the preparation of 3-azatrienes 3

Unsaturated aldehyde **2** (4 mmol) was added to a 0–10 °C solution of phosphazene **1** (4 mmol), prepared 'in situ' in $CHCl_3$ (10 mL) under N_2, and the mixture was stirred at room temperature until ^{1}H NMR indicated the disappearance of phosphazene. 3-Azatrienes **3** are unstable during distillation and/or chromatography and were used without purification for the following reactions.

3.4.1. 1-(Ethoxycarbonyl)-6-phenyl-3-azahexa-1,3,5-triene (3a). The general procedure A was followed using phosphazene **1a** (1.252 g, 4 mmol) and cinnamaldehyde **2a** (0.504 mL, 4 mmol) (room temperature/7 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3a**+Ph_2MePO) δ 1.25 (t, $^{3}J_{HH}$=7.2 Hz, 3H), 1.96 (d, $^{2}J_{PH}$=13.0 Hz, 3H), 4.17 (q, $^{3}J_{HH}$=7.2 Hz, 2H), 6.08 (d, $^{3}J_{HH}$=13.1 Hz, 1H), 6.98 (dd, $^{3}J_{HH}$=9.0, 16.0 Hz, 1H), 7.14 (d, $^{3}J_{HH}$=16.0 Hz, 1H), 7.31–7.70 (m, 15H), 7.77 (d, $^{3}J_{HH}$=13.1 Hz, 1H), 8.14 (d, $^{3}J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3a**+Ph_2MePO) δ 14.2, 16.5 (d, $^{1}J_{PC}$=74.0 Hz), 60.3, 118.6, 126.3–131.7, 147.1, 152.6, 155.5, 167.5, 169.4 ppm. The general procedure B was followed using phosphazene **1c** (4 mmol), prepared 'in situ', and 0.504 mL (4 mmol) of cinnamaldehyde **2a** (room temperature/1 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3a**+Me_3PO) δ 1.25 (t, $^{3}J_{HH}$=7.2 Hz, 3H), 1.47 (d, $^{2}J_{PH}$=12.8 Hz, 9H), 4.17 (q, $^{3}J_{HH}$=7.2 Hz, 2H), 6.08 (d, $^{3}J_{HH}$=13.1 Hz, 1H), 6.98 (dd, $^{3}J_{HH}$=9.0, 16.0 Hz, 1H), 7.14 (d, $^{3}J_{HH}$=16.0 Hz, 1H), 7.30–7.51 (m, 5H), 7.77 (d, $^{3}J_{HH}$=13.1 Hz, 1H), 8.14 (d, $^{3}J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$)

of crude reaction mixture (**3a**+Me$_3$PO) δ 14.2, 17.8 (d, $^{1}J_{\mathrm{PC}}$=70.0 Hz), 60.3, 118.6, 126.3–131.7, 147.1, 152.6, 155.5, 167.5, 169.4 ppm.

3.4.2. 1-(Ethoxycarbonyl)-3-azahepta-1,3,5-triene (3b). The general procedure A was followed using phosphazene **1a** (1.252 g, 4 mmol) and crotonaldehyde **2b** (0.328 mL, 4 mmol) (room temperature/24 h). ^{1}H NMR (300 MHz, CDCl$_3$) of crude reaction mixture (**3b**+Ph$_2$MePO) δ 1.23 (t, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 3H), 1.92 (dd, $^{4}J_{\mathrm{HH}}$=1.2 Hz, $^{3}J_{\mathrm{HH}}$=6.7 Hz, 3H), 1.96 (d, $^{2}J_{\mathrm{PH}}$=13.0 Hz, 3H), 4.15 (q, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 2H), 6.00 (d, $^{3}J_{\mathrm{HH}}$=13.1 Hz, 1H), 6.33 (ddd, $^{4}J_{\mathrm{HH}}$=1.2 Hz, $^{3}J_{\mathrm{HH}}$=15.3, 9.0 Hz, 1H), 6.48 (dq, $^{3}J_{\mathrm{HH}}$=6.7, 15.3 Hz, 1H), 7.36–7.74 (m, 11H), 7.95 (d, $^{3}J_{\mathrm{HH}}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) of crude reaction mixture (**3b**+Ph$_2$MePO) δ 14.0, 16.5 (d, $^{1}J_{\mathrm{PC}}$=74.0 Hz), 18.8, 60.0, 117.8, 128.3–134.5, 147.4, 153.7, 155.5, 166.8, 169.4 ppm. The general procedure B was followed using phosphazene **1c** (4 mmol), prepared ‘in situ’, and 0.328 mL (4 mmol) of crotonaldehyde **2b** (room temperature/5 h). ^{1}H NMR (300 MHz, CDCl$_3$) of crude reaction mixture (**3b**+Me$_3$PO) δ 1.23 (t, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 3H), 1.47 (d, $^{2}J_{\mathrm{PH}}$=12.8 Hz, 9H), 1.92 (dd, $^{4}J_{\mathrm{HH}}$=1.2 Hz, $^{3}J_{\mathrm{HH}}$=6.7 Hz, 3H), 4.15 (q, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 2H), 6.00 (d, $^{3}J_{\mathrm{HH}}$=13.1 Hz, 1H), 6.33 (ddd, $^{4}J_{\mathrm{HH}}$=1.2 Hz, $^{3}J_{\mathrm{HH}}$=15.3, 9.0 Hz, 1H), 6.48 (dq, $^{3}J_{\mathrm{HH}}$=6.7, 15.3 Hz, 1H), 7.68 (d, $^{3}J_{\mathrm{HH}}$=13.1 Hz), 7.95 (d, $^{3}J_{\mathrm{HH}}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) of crude reaction mixture (**3b**+Me$_3$PO) δ 14.0, 17.8 (d, $^{1}J_{\mathrm{PC}}$=70.0 Hz), 18.8, 60.0, 117.8, 147.4, 153.7, 155.5, 166.8, 169.4 ppm.

3.4.3. 1-(Ethoxycarbonyl)-5-methyl-3-azahexa-1,3,5-triene (3c). The general procedure A was followed using phosphazene **1a** (1.252 g, 4 mmol) and methacrolein **2c** (0.238 mL, 4 mmol) (room temperature/30 h). ^{1}H NMR (300 MHz, CDCl$_3$) of crude reaction mixture (**3c**+Ph$_2$MePO) δ 1.23 (t, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 3H), 1.91 (s, 3H), 1.96 (d, $^{2}J_{\mathrm{PH}}$=13.0 Hz, 3H), 4.15 (q, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 2H), 5.58 (s, 1H), 5.77 (s, 1H), 6.03 (d, $^{3}J_{\mathrm{HH}}$=13.3 Hz, 1H), 7.27–7.09 (m, 10H), 7.76 (d, $^{3}J_{\mathrm{HH}}$=13.3 Hz, 1H), 7.99 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) of crude reaction mixture (**3c**+Ph$_2$MePO) δ 14.1, 16.4, 16.5 (d, $^{1}J_{\mathrm{PC}}$=74.0 Hz), 60.1, 118.1, 128.4–132.4, 133.2, 155.1, 166.8, 170.1 ppm. The general procedure B was followed using phosphazene **1c** (4 mmol), prepared ‘in situ’, and 0.238 mL (4 mmol) of methacrolein **2c** (room temperature/4 h). ^{1}H NMR (300 MHz, CDCl$_3$) of crude reaction mixture (**3c**+Me$_3$PO) δ 1.23 (t, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 3H), 1.47 (d, $^{2}J_{\mathrm{PH}}$=12.8 Hz, 9H), 1.91 (s, 3H), 4.15 (q, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 2H), 5.58 (s, 1H), 5.77 (s, 1H), 6.03 (d, $^{3}J_{\mathrm{HH}}$=13.3 Hz, 1H), 7.76 (d, $^{3}J_{\mathrm{HH}}$=13.3 Hz, 1H), 7.99 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) of crude reaction mixture (**3c**+Me$_3$PO) δ 14.1, 16.4, 17.8 (d, $^{1}J_{\mathrm{PC}}$=70.0 Hz), 60.1, 118.1, 129.4, 133.2, 155.1, 166.8, 170.1 ppm.

3.4.4. 1,2-(Dimethoxycarbonyl)-6-phenyl-3-azahexa-1,3,5-triene (3d). The general procedure A was followed using phosphazene **1b** (1.428 g, 4 mmol) and cinnamaldehyde **2a** (0.504 mL, 4 mmol) (70 °C/30 h). ^{1}H NMR (300 MHz, CDCl$_3$) of crude reaction mixture (**3d**+Ph$_2$MePO) δ 1.96 (d, $^{2}J_{\mathrm{PH}}$=13.0 Hz, 3H), 3.59 (s, 3H), 3.73 (s, 3H), 6.22 (s, 1H), 6.91–7.87 (m, 17H), 7.95 (d, $^{3}J_{\mathrm{HH}}$=8.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) of crude reaction mixture (**3d**+Ph$_2$MePO) δ 16.5 (d, $^{1}J_{\mathrm{PC}}$=74.0 Hz), 51.2, 52.7, 108.4, 124.9–134.6, 146.2, 152.3, 163.7, 165.0 ppm.

3.5. General procedure for [4+2] cycloaddition reaction of 3-azatrienes 3 with cyclic enamines 4a,b

Cyclic enamine **4** (4 mmol) was added to a 0–10 °C solution of 3-azatriene **3** (4 mmol), prepared ‘in situ’, in CHCl$_3$ (10 mL) under N$_2$, and the mixture was stirred at room temperature until ^{1}H NMR indicated the disappearance of 3-azatriene. Evaporation of solvent under reduced pressure afforded an oil that was chromatographed on silica gel to give the compounds **6**, **9**, and **10**.

3.5.1. Ethyl 1-(2-phenylethenyl)-1,2,6,7,8,8a-hexahydro-4-isoquinolinecarboxylate (6a). The general procedure was followed using 3-azatriene **3a** and 1-pyrrolidine-1-cyclohexene **4a** (0.605 g, 4 mmol) for 18 h at room temperature. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.381 g (42%) of **6a** as a white solid: mp 169–170 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.02–1.19 (m, 1H), 1.21 (t, $^{3}J_{\mathrm{HH}}$=7.2 Hz, 3H), 1.48–2.21 (m, 6H), 3.45–3.51 (m, 1H), 4.04–4.15 (m, 2H), 4.23 (d, $^{3}J_{\mathrm{HH}}$=6.1 Hz, 1H), 6.01 (dd, $^{3}J_{\mathrm{HH}}$=8.6, 15.7 Hz, 1H), 6.47 (s, 1H), 6.55 (d, $^{3}J_{\mathrm{HH}}$=15.7 Hz, 1H), 7.18–7.34 (m, 5H), 7.44 (d, $^{3}J_{\mathrm{HH}}$=6.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.6, 21.8, 25.9, 27.2, 38.4, 59.1, 60.4, 99.1, 120.6, 126.5, 128.0, 128.7, 128.8, 134.2, 136.1, 142.0, 142.1, 167.3 ppm; IR (KBr) 3423, 1656; MS (EI) *m/z* 309 (M^{+}, 14). Anal. Calcd for C$_{20}$H$_{23}$NO$_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.68; H, 7.48; N, 4.52.

3.5.2. Ethyl 1-(1-propenyl)-1,2,6,7,8,8a-hexahydro-4-isoquinolinecarboxylate (6b). The general procedure was followed using 3-azatriene **3b** and 1-pyrrolidine-1-cyclohexene **4a** (0.605 g, 4 mmol) for 18 h at room temperature. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.594 g (42%) of **6b** as a white solid: mp 134–135 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89–1.00 (m, 1H), 1.20 (t, $^{3}J_{\mathrm{HH}}$=7.1 Hz, 3H), 1.26–2.21 (m, 9H), 3.23–3.29 (m, 1H), 4.02–4.17 (m, 2H), 4.35 (s, 1H), 5.28 (dd, $^{3}J_{\mathrm{HH}}$=8.7, 15.3 Hz, 1H), 5.61–5.72 (m, 1H), 6.43 (s, 1H), 7.40 (d, $^{3}J_{\mathrm{HH}}$=6.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.6, 17.7, 21.8, 25.9, 27.1, 38.1, 59.0, 60.2, 98.5, 120.1, 130.5, 130.7, 142.2, 142.3, 167.4 ppm; IR (KBr) 3320, 1690; MS (EI) *m/z* 247 (M^{+}, 31). Anal. Calcd for C$_{15}$H$_{21}$NO$_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.87; H, 8.57; N, 5.65.

3.5.3. Ethyl 6-(1-methylethenyl)-5,4-(1-propanyl-3-yliden)-1,4,5,6-tetrahydro-3-pyridinecarboxylate (9). The general procedure was followed using 3-azatriene **3c** (4 mmol), prepared ‘in situ’, and 1-pyrrolidine-1-cyclopentene **4b** (0.496 g, 4 mmol) for 14 h at room temperature. The crude oil was chromatographed on silica gel (7:1 hexane/AcOEt) to give 0.594 g (35%) of **9** as a white solid: mp 120–121 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.17–1.31 (m, 4H), 1.72 (s, 3H), 1.90–1.99 (m, 1H), 2.36–2.38 (m, 2H), 2.66–2.72 (m, 1H), 3.39 (d, $^{3}J_{\mathrm{HH}}$=10.5 Hz, 1H), 4.09–4.18 (m, 2H), 4.50 (s, 1H), 4.91 (s, 1H), 4.95 (s, 1H), 5.97 (s, 1H), 7.46

(d, $^3J_{HH}$=6.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 17.7, 28.4, 31.8, 46.3, 59.2, 65.2, 97.3, 115.0, 120.5, 133.7, 143.2, 144.1, 167.3 ppm; IR (KBr) 3325, 1700; MS (EI) *m/z* 233 (M^+, 100). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.19; N, 6.01.

3.5.4. Dimethyl 6-(phenylethenyl)-4,5-trimethylene-2,3-pyridinedicarboxylate (10). The general procedure was followed using 3-azatriene **3d** (4 mmol), prepared 'in situ', and 1-pyrrolidine-1-cyclopentene **4b** (0.496 g, 4 mmol) for 20 h at room temperature. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.540 g (40%) of **10** as a white solid: mp 145–146 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09–2.19 (m, 2H), 3.03–3.13 (m, 4H), 3.85 (s, 3H), 3.93 (s, 3H), 7.11 (d, $^3J_{HH}$=15.8 Hz, 1H), 7.23–7.56 (m, 5H), 7.82 (d, $^3J_{HH}$=15.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 30.7, 33.0, 52.5, 52.9, 122.2, 123.7, 127.5, 128.7, 128.9, 136.4, 136.6, 140.0, 147.9, 152.1, 155.6, 166.8, 167.3 ppm; IR (KBr) 1751, 1707; MS (EI) *m/z* 337 (M^+, 100). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.18; H, 5.70; N, 4.14.

3.6. Oxidation with *p*-benzoquinone. Synthesis of ethyl 1-(2-phenylethenyl)-5,6,7,8-tetrahydro-4-isoquinolinecarboxylate (7a)

To a solution of bicyclic compound **6a** (0.619 g, 2 mmol) in dioxane (8 mL) was added 0.212 g (2 mmol) of *p*-benzoquinone, and the mixture was stirred for 24 h at 100 °C under N_2. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (10:1 hexane/AcOEt) to give 0.515 g (84%) of **7a** as a white solid: mp 126–127 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, $^3J_{HH}$=7.0 Hz, 3H), 1.74–1.81 (m, 4H), 2.82–2.86 (m, 2H), 3.03–3.07 (m, 2H), 4.30 (q, $^3J_{HH}$=7.0 Hz, 2H), 7.22–7.56 (m, 6H), 7.81 (d, $^3J_{HH}$=15.4 Hz, 1H), 8.82 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.8, 22.1, 28.1, 29.7, 60.9, 123.3–128.7, 130.2, 136.2, 136.9, 148.2, 148.6, 150.1, 166.3 ppm; IR (KBr) 1705; MS (EI) *m/z* 307 (M^+, 100). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.18; H, 6.90; N, 4.57.

3.7. Oxidation with manganese triacetate. Ethyl 1-(1-propenyl)-5,6,7,8-tetrahydro-4-isoquinolinecarboxylate (7b)[22]

To a solution of manganese triacetate (0.536 g, 2 mmol) in acetic acid (5 mL) was added the bicyclic compound **6b** (0.247 g, 1 mmol). The reaction mixture was stirred at room temperature for 30 min. After completion of the reaction, as indicated by TLC examination, manganese diacetate was filtered off and the reaction mixture poured into water. The contents were then neutralized by $NaHCO_3$, extracted with dichloromethane (2×10 mL) of **7b** and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting crude product was purified by silica gel column chromatography (20:1 hexane/AcOEt) to give 0.204 g (83%) of **7b** as a white solid: mp 51–52 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.63–1.83 (m, 4H), 1.90 (dd, $^3J_{HH}$=6.9 Hz, $^4J_{HH}$=1.7 Hz, 3H), 2.68 (t, $^3J_{HH}$=6.1 Hz, 2H), 3.01 (t, $^3J_{HH}$=6.1 Hz, 2H), 4.28 (q, $^3J_{HH}$=7.2 Hz, 2H), 6.59 (dd, $^3J_{HH}$=15.1 Hz, $^4J_{HH}$=1.7 Hz, 1H), 6.91 (dd, $^3J_{HH}$=15.1, 6.9 Hz, 1H), 8.73 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.7, 21.6, 22.0, 25.9, 27.9, 60.6, 123.5, 126.8, 128.9, 134.6, 147.9, 148.2, 156.2, 166.5 ppm; IR (KBr) 1725; MS (EI) *m/z* 245 (M^+, 99). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.79; N, 5.70.

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References and notes

1. For a review see: (a) Wamhoff, H.; Richard, G.; Stoelben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159; (b) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; (c) Nitta, M. *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1993; Vol. 9, p 87.
2. (a) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941; (b) Palacios, F.; Alonso, C.; Rubiales, G. *J. Org. Chem.* **1997**, *62*, 1146.
3. Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; Rodríguez, M.; Pagalday, J. *Tetrahedron* **2003**, *59*, 2617.
4. (a) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 3497; (b) Barluenga, J.; Ferrero, M.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2193; (c) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1988**, *29*, 4863.
5. (a) Palacios, F.; Herrán, E.; Rubiales, G.; Ezpeleta, J. M. *J. Org. Chem.* **2002**, *67*, 2131; (b) Palacios, F.; Herrán, E.; Rubiales, G. *J. Org. Chem.* **1999**, *64*, 6239; (c) Palacios, F.; Pérez de Heredia, I.; Rubiales, G. *J. Org. Chem.* **1995**, *60*, 2384.
6. (a) Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2005**, *61*, 2779; (b) Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron Lett.* **2004**, *45*, 4031.
7. Wamhoff, H.; Warnecke, H.; Sohar, P.; Csámpai, A. *Synlett* **1998**, 1193.
8. (a) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron* **1997**, *53*, 4521; (b) Barluenga, J.; Ferrero, M.; Lopez, F.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 615.
9. (a) Katritzky, A. R.; Mazurkiewicz, R.; Stevens, C. V.; Gordeev, M. F. *J. Org. Chem.* **1994**, *59*, 2740; (b) Molina, P.; Pastor, A.; Vilaplana, M. J. *Tetrahedron Lett.* **1993**, *34*, 3773; (c) Oikawa, T.; Kanomata, N.; Tada, M. J. *J. Org. Chem.* **1993**, *58*, 2046; (d) Krutosikova, A.; Dandarova, M.; Chylova, J.; Vegh, D. *Monatsh. Chem.* **1992**, *123*, 807.
10. Palacios, F.; Alonso, C.; Rubiales, G. *Tetrahedron* **1995**, *51*, 3683.
11. (a) Wamhoff, H.; Schmidt, A. *J. Org. Chem.* **1993**, *58*, 6976; (b) Nitta, M.; Iino, Y.; Mori, S.; Takayasu, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1001.
12. (a) Eguchi, S. *Arkivoc* **2005**, *ii*, 98; (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1; (c) Rodrigues, J.; Augusto, R.; Leiva, G. C.; de Sousa, D. F. *Tetrahedron Lett.* **1995**, *36*, 59; (d) Chavignon, O.; Teulade, J. C.; Roche, D.; Madesclaire, M.;

Blache, Y.; Gueiffier, A.; Chabard, J. L.; Dauphin, G. *J. Org. Chem.* **1994**, *59*, 6413.

13. For reviews see: (a) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078; (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668; (c) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379; (d) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099; (e) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1; (f) *Stereocontrolled Organic Synthesis*; Ghosez, L., Ed.; Blackwell: Oxford, 1994; pp 193–233.
14. For recent contributions, see: (a) Nicolau, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zecri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159; (b) Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2005**, *46*, 6111; (c) Bongini, A.; Panunzio, M.; Tamanini, E.; Martelli, G.; Vicennati, P.; Moneri, M. *Tetrahedron: Asymmetry* **2003**, *14*, 993; (d) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941; (e) Ntirampebura, D.; Ghosez, L. *Synthesis* **2002**, 2043.
15. (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617; (b) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Synlett* **1999**, 1735; (c) Ntirampebura, D.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 7079.
16. Palacios, F.; Gil, M. J.; Martinez de Marigorta, E.; Rodriguez, M. *Tetrahedron* **2000**, *56*, 6319.
17. (a) Bonini, C.; D'Auria, M.; Funicello, M.; Romaniello, G. *Tetrahedron* **2002**, *58*, 3507; (b) Rossi, E.; Abbianti, G.; Pini, E. *Synlett* **1999**, 1265; (c) Molina, P.; Pastor, A.; Vilaplana, M. J. *J. Org. Chem.* **1996**, *61*, 8094.
18. Cossio, F.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839.
19. The reaction was monitored by ^{31}P and ^{1}H NMR showing the disappearance of phosphazene **1** and the formation of azatrienes **3**.
20. For a review, see: Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic: New York, NY, 1980.
21. (a) Hofle, G.; Glaser, N.; Leibold, T.; Karama, U.; Sasse, F.; Steinmetz, H. *Pure Appl. Chem.* **2003**, *75*, 167; (b) Cativiela, C.; Diaz de Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645; (c) Couty, F. *Amino Acids* **1999**, *16*, 197.
22. Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 21.
23. For reviews see: (a) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581; (b) Numata, A.; Ibuka, T. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1987; Vol. 31; (c) Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 77; (d) Daly, J. L.; Spande, T. F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, NY, 1986; Vol. 4, pp 1–274.
24. For recent reviews see: (a) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155–299; (b) Shipman, M. *Contemp. Org. Synth.* **1995**, *2*, 1.