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Regioselective synthesis of pyridines and dihydropyridines derived from β-amino acids and aminophosphonates by reaction of *N*-vinylic phosphazenes with α,β-unsaturated ketones

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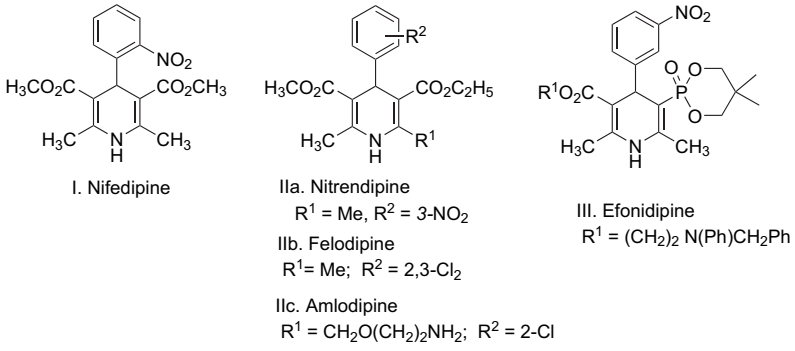
Abstract—Reaction of *N*-vinylic phosphazenes with α,β-unsaturated ketones leads to the formation of pyridines derived from β-amino acids in a regioselective fashion. The use of functionalized enones derived from α-acylstyryl-carboxylates or -phosphonates affords biologically active asymmetrical and symmetrical dihydropyridines substituted with carboxylate or phosphonate groups including nitrendipine, felodipine, MRS 1097, and efonidipine analogs.

1. Introduction

1,4-Dihydropyridine derivatives (1,4-DHPs) are versatile intermediates in organic synthesis.[1,2] Moreover, compounds based on this heterocycle play key roles in therapeutic and bioorganic chemistry[3] as calcium channel modulators.[4,5] Many natural products as well as first, second, and third generation calcium channel blockers such as nifedipine **I**,[6] nitrendipine **IIa**,[7] felodipine **IIb**,[8] amlodipine **IIc**,[9] and efonidipine **III** [10] are 1,4-DHPs (see Chart 1). Hantzsch reaction[1] as well as the reduction of *N*-alkylpyridinium salts[11] or the regioselective addition of nucleophilic reagents to *N*-acylpyridinium ions[12] is a method for the formation of 1,4-DHP derivatives.

N-vinylic phosphazenes[13] have proved to be useful building blocks for the synthesis of electronically neutral 2-azadienes,[14] 3-fluoroalkyl-2-azadienes,[15] electron-poor 2-azadienes derived from aminophosphorus derivatives,[16] α-[17] or β-amino acids,[18] and to be key intermediates in the preparation of cyclic compounds[19] and in the construction of the framework of pharmacologically active alkaloids.[20]

Continuing with our interest in the chemistry of phosphazenes,[21] we report here the use of *N*-vinylic phosphazenes with α,β-unsaturated ketones as key intermediates in the synthesis of dihydropyridine and pyridine compounds derived from β-amino acids.



I. Nifedipine

IIa. Nitrendipine
R^1 = Me, R^2 = 3-NO_2

IIb. Felodipine
R^1= Me; R^2 = 2,3-Cl_2

IIc. Amlodipine
R^1 = $CH_2O(CH_2)_2NH_2$; R^2 = 2-Cl

III. Efonidipine
R^1 = $(CH_2)_2$ N(Ph)CH_2Ph

Chart 1. Some pharmacologically active 1,4-DHPs.

Keywords: *N*-Vinylic phosphazenes; Dihydropyridines; Pyridines.
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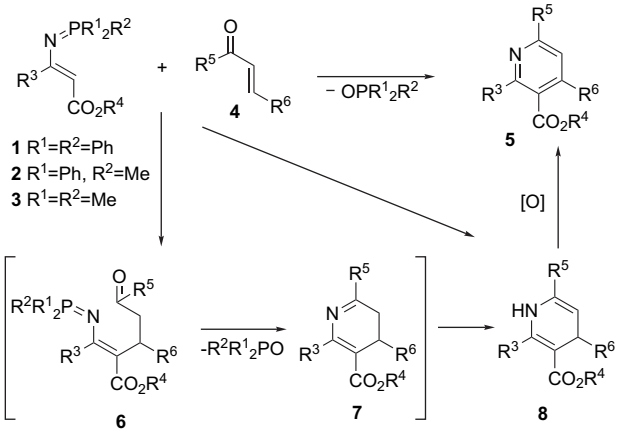
2. Results and discussion

2.1. Reaction of phosphazenes with α,β-unsaturated ketones 4

The treatment of ethyl 3-triphenylphosphazenyl-acrylate **1a** (R^1=R^2=Ph, R^3=H, R^4=Et) with methylvinylketone **4a** (R^5=Me, R^6=H) in refluxing toluene gave pyridine **5a** (R^3=H, R^4=Et, R^5=Me, R^6=H) in moderate yield (Scheme 1; Table 1, entry 1). The value of the coupling constant (8.5 Hz) of the vicinal 4- and 5-hydrogen in this compound **5a** is consistent with the literature.[22,23]



Scheme 1. Reaction of phosphazenes **1–3** with α,β-unsaturated ketones **4**.

The nucleophilic character of the nitrogen atom of *N*-vinylic phosphazenes depends on the influence of phosphorus atom substituents.[23] The use of the more reactive phosphazenes **2a** derived from diphenylmethylphosphine (R^1=Ph, R^2=Me, R^3=H, R^4=Et) with the same ketone **4a** led also to the formation of pyridine **5a** at room temperature in low yield (Table 1, entry 2), and even when the reaction was performed with very reactive phosphazenes **3a** derived from trimethylphosphine[24] (R^1=R^2=Me, R^3=H, R^4=Et) at room temperature, pyridine **5a** was obtained in low yield (entry 3) along with hydrolysis products of the starting phosphazene.[24]

The scope of this reaction was not limited to the phosphazenes derived from ethyl β-azidoacrylate, given that 3-phenyl- **1b**, -**3b** (R^3=Ph), and 3-methoxycarbonyl-substituted *N*-vinylic phosphazenes **1c** (R^3=CO_2Me) also reacted with ketone **4a** (R^5=Me, R^6=H) in refluxing toluene and **4b** (R^5=Me, R^6=Ph) in refluxing DMF leading to the formation of pyridines **5b**, **5c**, and **5d**, respectively (Scheme 1; Table 1, entries 4–6). The presence of an electron-releasing group in the phosphazene (R^3=Me) allowed the isolation of dihydropyridine **8e**, precursor of pyridine **5e**. Thus, reaction of *N*-vinylic phosphazene **1d** (R^3=Me), with chalcone **4c** (R^5=R^6=Ph) performed in refluxing DMF, gave dihydropyridine **8e** (entry 7). Oxidation of dihydropyridine **8e** with quinone led to the formation of pyridine **5e** derived from β-amino acids (entry 8).

Given these results and in accordance with the literature,[13,25,26] the formation of pyridines **5** could be explained by an initial Michael addition (1,4-addition) of phosphazenes **1–3** to the β-carbon atom of unsaturated ketones **4** followed by intramolecular aza-Wittig reaction of the functionalized phosphazenes **6** to give 4,5-dihydropyridines **7**. Tautomerization of these heterocycles **7** to the isomeric 1,4-dihydropyridines **8** and subsequent aromatization could afford pyridines **5**.

This process can be applied to the synthesis of pyridines **5** containing two carboxylate groups (R^6=CO_2Me) when the corresponding, commercially available, unsaturated ketone **4d** (R^5=Me, R^6=CO_2Me) was used (Scheme 1). The reaction of phosphazenes derived from ethyl β-azidoacrylate **1a** (R^3=H) and from dehydroaspartic ester **1c** (R^3=CO_2Me) with methyl *trans*-4-oxo-2-pentenoate **4d** (R^5=Me, R^6=CO_2Me) in refluxing toluene gave highly functionalized pyridines **5f** and **5g** (Scheme 1; Table 1, entries 9 and 10). Dihydropyridine **8h** (R^6=CO_2Me) was also isolated when the reaction of phosphazene **1d** (R^3=Me) with ketone **4d** (R^5=Me, R^6=CO_2Me) was performed in toluene, leading to the formation of a mixture of both the dihydropyridine **8h** and the corresponding pyridine **5h** (Scheme 1; Table 1, entry 11). Oxidation of dihydropyridine **8h** with quinone led to the formation of pyridine **5h** (entry 12).

2.2. Reaction of phosphazenes with functionalized α,β-unsaturated ketones 9 and 11

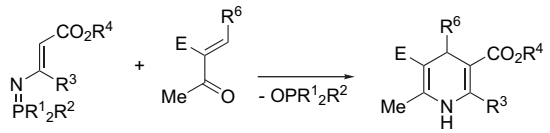
In order to explore the synthetic usefulness of *N*-vinylic phosphazenes **1–3** for the preparation of biologically active 1,4-DHPs,[4–10] we studied the reactions of these

Table 1. Pyridines **5** and dihydropyridines **8** obtained via Scheme 1

Entry	Starting materials		Products	R^3	R^4	R^5	R^6	Conditions		Yield[a] %
								T (°C)	Time (h)	
1	**1a**	**4a**	**5a**	H	Et	Me	H	110	110	40
2	**2a**	**4a**	**5a**	H	Et	Me	H	25	120	8
3	**3a**	**4a**	**5a**	H	Et	Me	H	25	5	15
4	**1b**	**4b**	**5b**	Ph	Et	Me	Ph	153	150	48
5	**3b**	**4a**	**5c**	Ph	Et	Me	H	110	96	67
6	**1c**	**4a**	**5d**	CO_2Me	Me	Me	H	110	140	60
7	**1d**	**4c**	**8e**	Me	Me	Ph	Ph	153	40	61
8	**8e**	—	**5e**	Me	Me	Ph	Ph	101	48	88[b]
9	**1a**	**4d**	**5f**	H	Et	Me	CO_2Me	110	168	50
10	**1c**	**4d**	**5g**	CO_2Me	Me	Me	CO_2Me	110	336	59
11	**1d**	**4d**	**5h/8h**	Me	Me	Me	CO_2Me	110	168	20/36
12	**8h**	—	**5h**	Me	Me	Me	CO_2Me	101	24	92[b]

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

phosphazenes with functionalized α,β-unsaturated ketones containing an electron-withdrawing group (E=CO_2R^5) in the α-position such as 2-arylmethyleneacetoacetates **9** (Scheme 2). This reaction could afford a new strategy for the preparation of symmetrical and asymmetrical 4-aryl-1,4-dihydro-3,5-pyridinedicarboxylates **10** (E=CO_2R) under mild reaction conditions.



1 R^1=R^2=Ph
2 R^1=Ph, R^2=Me
3 R^1=R^2=Me

9 E=CO_2R^5
11 E=PO(OEt)$_2$

10 E=CO_2R^5
12 E=PO(OEt)$_2$

Scheme 2. Synthesis of 1,4-DHPs **10** and **12**.

Reaction of *N*-vinylic phosphazenes derived from triphenylphosphine **1a** (R^3=H, R^4=Et, Scheme 2) with methyl 2-(*p*-nitrophenyl)methyleneacetoacetate **9a** (R^6=*p*-NO_2–C_6H_4) was performed at room temperature to give 3-methyl-5-methyl-1,4-dihydro-6-methyl-4-(*p*-nitrophenyl)-3,5-pyridinedicarboxylate **10a** (R^3=H, R^6=*p*-NO_2–C_6H_4) in excellent yields and in a regioselective fashion (Table 2, entry 1).

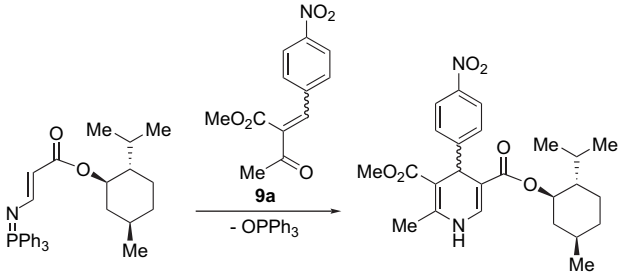
Similar results were obtained when phosphazenes derived from diphenylmethylphosphine **2a** and from trimethylphosphine **3a** were used. However, in the case of the more reactive phosphazene **3a** lower reaction time was necessary for the process (Table 2, entries 2 and 3). The formation of dihydropyridine **10a** could start with a Michael addition of phosphazenes **1a** to the enone **9** followed by intramolecular aza-Wittig reaction in a similar way to that described in Scheme 1.

The scope of this reaction was not limited to the preparation of this 1,4-DHP **10a** given that the strategy can also be used for the synthesis not only of calcium channel blockers such as nitrendipine[7] **10c** or felodipine[8] **10d**, but also for the synthesis of selective A_3 adenosine receptor antagonist MRS 1097[27] **10b** when appropriate unsaturated ketones **9b** (R^6=CH=CH–C_6H_5), **9c** (R^6=3-NO_2–C_6H_4), **9d** (R^6=2,6-Cl_2–C_6H_5), and *N*-vinylic phosphazenes **1b** or **1d** were used (Table 2, entries 4–6).

Furthermore, a phosphonate substituent[28] could regulate important biological functions and increase the biological activity of this type of compounds in a similar way to that reported for other pharmaceuticals.[29] Therefore, in connection with our interest in the chemistry of aminophosphonate derivatives and the design of new cyclic derivatives bearing a phosphonate group,[30] we aimed to extend the process for the preparation of 1,4-DHPs **12** containing a phosphonate group as substituent, since compounds with this substructure are shown hypotensive and selective cerebral vasodilating activities.[10]

Thus, the reaction of *N*-vinylic phosphazenes derived from triphenylphosphine **1a**, **1d** with diethyl α-acetylstyrylphosphonate **11a** (R^6=2,6-Cl_2–C_6H_3), and **11b** (R^6=3-NO_2–C_6H_4) at room temperature gave compounds **12a** (R^3=H, R^6=2,3-Cl_2–C_6H_3) and the efonidipine[10] analog **12b** (R^3=H, R^6=3-NO_2–C_6H_4) in good yields and in a regioselective fashion (Scheme 2; Table 2, entries 7 and 8).

Finally, we extended the process to optically active phosphazenes derived from β-amino esters of (1*R*,2*S*,5*R*)-(−)menthol, in order to know if the presence of a chiral auxiliary could afford optically enriched 1,4-DHPs. The preparation of the required *N*-vinylic phosphazene **13** was accomplished through the Staudinger reaction[21] involving chiral vinyl azide[18a] and triphenylphosphine (Scheme 3). The reaction of *E*-vinylic phosphazene **13** with methyl 2-(*p*-nitrophenyl)methyleneacetoacetate **9a** in CH_2Cl_2 at room temperature was explored and 1,4-DHP **14** was obtained as a mixture (64:34) of two diastereoisomers (Table 2, entry 9).



Scheme 3. Synthesis of optically enriched 1,4-DHP **14**.

Table 2. Dihydropyridines (1,4-DHPs) **10**, **12**, and **14** obtained

Entry	Starting materials		Products	R^3	R^4	R^5	R^6	Conditions		Yield[a] %
								T (°C)	Time (h)	
1	**1a**	**9a**	**10a**	H	Et	Me	4-NO_2–C_6H_4	25	3	93
2	**2a**	**9a**	**10a**	H	Et	Me	4-NO_2–C_6H_4	25	3	95
3	**3a**	**9a**	**10a**	H	Et	Me	4-NO_2–C_6H_4	25	0.5	96
4	**1b**	**9b**	**10b**[b]	Ph	Et	Et	(*E*) CH=CH–C_6H_5	60	30	71
5	**1d**	**9c**	**10c**[c]	Me	Me	Et	3-NO_2–C_6H_4	25	0.5	77
6	**1d**	**9d**	**10d**[d]	Me	Me	Et	2,3-Cl_2–C_6H_3	40	24	82
7	**1a**	**11a**	**12a**	H	Et	—	2,3-Cl_2–C_6H_3	60	36	65
8	**1d**	**11b**	**12b**	Me	Me	—	3-NO_2–C_6H_4	60	24	87
9	**13**	**9a**	**14**				—	25	2.5	92

[a] Purified by chromatography.
[b] MRS 1097.
[c] Nitrendipine.
[d] Felodipine.

3. Conclusion

We conclude that *N*-vinylic phosphazenes **1**–**3** are intermediates in the regioselective preparation of pyridines **5** derived from β-amino acids, when they react with enones **4**. Enamine type addition (1,4-addition) of *N*-vinylic phosphazenes with the β-carbon atom of unsaturated ketones leads to a regioselective synthesis of functionalized pyridines **5**. This strategy can be used for an efficient synthesis of symmetrical and asymmetrical 1,4-DHPs derived from amino esters **10** and aminophosphonates **12** including biologically active nitrendipine,[7] felodipine,[8] MRS 1097,[27] and efonidipine[10] analogs, as well as for the preparation of optically enriched 1,4-DHP **14**. It is worth noting that pyridine compounds derived from β-amino acids are also useful heterocycles not only for their biological activities[31] but also because the pyridine nucleus is a structural unit appearing in many natural products.[32]

4. Experimental section

4.1. 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 $60F_{254}$ plates. Visualization was accomplished by UV light. Flash chromatography was carried out using silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H NMR (300 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 (EI) 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 **1**, **2**, and **3** were synthesized according to literature procedures.[18b,23]

4.2. General procedure for the preparation of pyridines 5 and dihydropyridines 8

Unsaturated ketone **4** (3 mmol) was added to a 0–10 °C solution of phosphazene **1**, **2**, or **3** (3 mmol) in $CHCl_3$, toluene or DMF (9 mL) under N_2. The mixture was stirred at rt, 110, or 153 °C until TLC indicated the disappearance of phosphazene. Evaporation of solvent under reduced pressure afforded an oil that was chromatographed on silica gel to give the compounds **5** and/or **8**.

4.2.1. Ethyl 6-methyl-3-pyridinecarboxylate (5a). The general procedure was followed using phosphazene **1a** (1.127 g, 3 mmol), **2a** (0.940 g, 3 mmol) or **3a** (3 mmol), prepared 'in situ', and methylvinylketone **4a** (0.250 mL, 3 mmol). The reaction mixture was stirred at 110 °C for 110 h for phosphazene **1a** (toluene), at rt for 120 h for phosphazene **2a** (chloroform), and at rt for 5 h for phosphazene **3a** (chloroform). The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give the pyridine **5a** as a yellow oil [0.198 g (40%) for phosphazene **1a**, 0.039 g (8%) for phosphazene **2a**, and 0.074 g (15%) for phosphazene **3a**] (R_f=0.30, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, $^3J_{HH}$=7.1 Hz, 3H), 2.56 (s, 3H), 4.30 (q, $^3J_{HH}$=7.1 Hz, 2H), 7.17 (d, $^3J_{HH}$=8.1 Hz, 1H), 8.11 (d, $^3J_{HH}$=8.1 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 14.1, 24.5, 61.0, 122.7, 123.4, 137.0, 150.2, 162.8, 165.2; IR (NaCl): 1722; MS (EI): m/z 165 (M^+, 93). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.50; H, 6.69; N, 8.47.

4.2.2. Ethyl 6-methyl-2,4-diphenyl-3-pyridinecarboxylate (5b). The general procedure was followed using phosphazene **1b** (1.355 g, 3 mmol) and benzylideneacetone **4b** (0.438 g, 3 mmol) in DMF. The mixture was stirred at 153 °C for 150 h. The crude oil was chromatographed on silica gel (40:1 hexane/AcOEt) to give 0.457 g (48%) of **5b** as a yellow oil (R_f=0.53, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.60 (s, 3H), 3.86 (q, $^3J_{HH}$=7.2 Hz, 2H), 7.09 (s, 1H), 7.29–7.59 (m, 10H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 13.4, 24.6, 61.2, 122.3, 125.9, 127.9–129.3, 138.4, 140.0, 148.8, 156.5, 158.9, 168.7; IR (NaCl): 1731; MS (EI): m/z 317 (M^+, 9). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.51; H, 6.03; N, 4.42.

4.2.3. Ethyl 6-methyl-2-phenyl-3-pyridinecarboxylate (5c). The general procedure was followed using phosphazene **3b** (3 mmol), prepared 'in situ', and methylvinylketone **4a** (0.250 mL, 3 mmol) in toluene. The reaction mixture was stirred at 110 °C for 96 h. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.484 g (67%) of **5c** as a yellow oil (R_f=0.51, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.57 (s, 3H), 4.05 (q, $^3J_{HH}$=7.2 Hz, 2H), 7.11 (d, $^3J_{HH}$=7.9 Hz, 1H), 7.19–7.42 (m, 5H), 7.91 (d, $^3J_{HH}$=7.9 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 13.5, 24.7, 61.1, 121.1, 124.3, 127.9, 128.2, 128.5, 138.1, 140.5, 158.6, 160.6, 168.0; IR (NaCl): 1725; MS (EI): m/z 241 (M^+, 10). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.69; H, 6.26; N, 5.81.

4.2.4. Dimethyl 6-methyl-2,3-pyridinedicarboxylate (5d). The general procedure was followed using phosphazene **1c** (1.257 g, 3 mmol) and methylvinylketone **4a** (0.250 mL, 3 mmol) in toluene. The mixture was stirred at 110 °C for 140 h. The crude oil was chromatographed on silica gel (20:1 hexane/AcOEt) to give 0.376 g (60%) of **5d** as a white solid. Mp 68–69 °C (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 7.25 (d, $^3J_{HH}$=8.1 Hz, 1H), 8.04 (d, $^3J_{HH}$=8.1 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 24.5, 52.6, 52.9, 122.5, 124.3, 137.9, 151.2, 162.1, 165.4, 167.1; IR (KBr): 1749, 1713; MS (EI): m/z 209 (M^+, 2). Anal. Calcd for

$C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.46; H, 5.29; N, 6.71.

4.2.5. Methyl 2-methyl-4,6-diphenyl-1,4-dihydro-3-pyridinecarboxylate (8e). The general procedure was followed using phosphazene **1d** (1.127 g, 3 mmol) and benzylideneacetophenone **4c** (0.626 g, 3 mmol) in DMF. The mixture was stirred at 153 °C for 40 h. The crude oil was chromatographed on silica gel (hexane) to give 0.558 g (61%) of **8e** as a yellow oil (R_f=0.50, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.51 (s, 3H), 4.62 (d, $^3J_{HH}$=5.5 Hz, 1H), 5.13 (d, $^3J_{HH}$=5.5 Hz, 1H), 5.56 (s, 1H), 7.06–7.45 (10H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 20.7, 40.8, 50.6, 98.9, 105.1, 125.0–130.9, 144.1, 146.9, 148.6, 168.8; IR (NaCl): 3376, 1692; MS (EI): *m/z* 209 (M^+, 2). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.70; H, 6.26; N, 4.60.

4.2.6. 3-Ethyl 4-methyl 6-methyl-3,4-pyridinedicarboxylate (5f). The general procedure was followed using phosphazene **1a** (1.126 g, 3 mmol) and ketone **4d** (0.384 g, 3 mmol) in toluene. The mixture was stirred at 110 °C for 168 h. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.335 g (50%) of **5f** as a yellow oil (R_f=0.31, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.58 (s, 3H), 3.87 (s, 3H), 4.32 (q, $^3J_{HH}$=7.2 Hz, 2H), 7.25 (s, 1H), 8.92 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 14.0, 24.6, 52.9, 61.8, 121.2, 122.1, 141.0, 150.3, 162.8, 165.0, 167.2; IR (NaCl): 1752; MS (EI): *m/z* 223 (M^+, 9). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.15; H, 5.86; N, 6.28.

4.2.7. Trimethyl 6-methyl-2,4,5-pyridinetricarboxylate (5g). The general procedure was followed using phosphazene **1c** (1.257 g, 3 mmol) and ketone **4d** (0.384 g, 3 mmol) in toluene. The mixture was stirred at 110 °C for 336 h. The crude oil was chromatographed on silica gel (4:1 hexane/AcOEt) to give 0.473 g (59%) of **5g** as an orange oil (R_f=0.20, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 7.79 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 24.4, 52.9, 53.1, 53.3, 125.7, 126.8, 137.1, 145.8, 160.5, 164.0, 164.5, 167.0; IR (NaCl): 1736; MS (EI): *m/z* 267 (M^+, 3). Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.96; H, 4.91; N, 5.23.

4.2.8. Dimethyl 2,6-dimethyl-3,4-pyridinedicarboxylate (5h). The general procedure was followed using phosphazene **1d** (1.127 g, 3 mmol) and methyl *trans*-4-oxo-2-pentenoate **4d** (0.384 g, 3 mmol) in toluene. The mixture was stirred at 110 °C for 168 h. The crude oil was chromatographed on silica gel (4:1 hexane/AcOEt) to give 0.134 g (20%) of **5h** as a yellow oil (R_f=0.45, hexane/AcOEt 2:1) and dihydropyridine **8h**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H), 2.53 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 7.40 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 22.5, 24.4, 52.7, 52.9, 119.6, 126.0, 136.3, 155.8, 159.8, 165.8, 168.5; IR (NaCl): 1739; MS (EI): *m/z* 223 (M^+, 12). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.25; H, 5.85; N, 6.26.

4.2.9. Dimethyl 2,6-dimethyl-1,4-dihydro-3,4-pyridinedicarboxylate (8h). It was obtained as a yellow oil (0.243 g, 36%) (R_f=0.41, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (s, 3H), 2.21 (s, 3H), 3.57 (s, 3H), 3.61 (s, 3H), 4.16 (d, $^3J_{HH}$=4.7 Hz, 1H), 4.50 (d, $^3J_{HH}$=4.7 Hz, 1H), 5.45 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 18.7, 20.1, 42.1, 50.8, 51.9, 93.6, 97.1, 148.6, 153.0, 168.4, 175.0; IR (NaCl): 3349, 1745; MS (EI): *m/z* 225 (M^+, 4). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.70; H, 6.72; N, 6.21.

4.3. General procedure for the oxidation of 1,4-dihydropyridines 8

To a solution of dihydropyridine **8** (2 mmol) in dioxane (8 mL) was added 0.212 g (2 mmol) of *p*-benzoquinone and the mixture was stirred at 101 °C under N_2. The solvent was evaporated under reduced pressure and the resulting oil was purified by silica gel column chromatography.

4.3.1. Methyl 2-methyl-4,6-diphenyl-3-pyridinecarboxylate (5e). The general procedure was followed using dihydropyridine **8e** (0.610 g, 2 mmol) and stirred for 48 h. Evaporation of solvent under reduced pressure afforded an oil, which was chromatographed on silica gel (7:1 hexane/AcOEt) to give 0.533 g (88%) of **5e** as a brown oil (R_f=0.44, hexane/AcOEt 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.50 (s, 3H), 7.32–7.87 (m, 11H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 22.3, 52.1, 126.9, 127.7–130.9, 132.8, 134.7, 136.8, 144.4, 146.1, 146.8, 168.3; IR (NaCl): 1725; MS (EI): *m/z* 303 (M^+, 62). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.26; H, 5.64; N, 4.61.

4.3.2. Dimethyl 2,6-dimethyl-3,4-pyridinedicarboxylate (5h). The general procedure was followed using dihydropyridine **8d** (0.450 g, 2 mmol) and stirred for 24 h. The crude oil was chromatographed on silica gel (4:1 hexane/AcOEt) to give 0.410 g (92%) of **5h** as a yellow oil (R_f=0.45, hexane/AcOEt 2:1). See spectroscopy data of compound **5h**.

4.4. General procedure for the preparation of 1,4-dihydropyridines 10

Acetoacetate[33] **9** (3 mmol) was added to a 0–10 °C solution of phosphazene **1** or **2** (3 mmol) in $CHCl_3$ (9 mL) under N_2 and the mixture was stirred at rt, 40, or 60 °C until TLC indicated the disappearance of phosphazene. Evaporation of solvent under reduced pressure afforded an oil that was chromatographed on silica gel to give compounds **11**.

4.4.1. 3-Ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (10a). The general procedure was followed using phosphazene **1a** (1.126 g), **2a** (0.939 g) or **3a** (3 mmol, prepared 'in situ'), and 0.747 g of methyl 2-(4-nitrophenylmethylene)acetoacetate **9a**, the mixture was stirred at rt for 3/3/0.5 h, respectively. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give **10a** as a yellow solid (0.966 g (93%) for the phosphazene **1a**, 0.986 g (95%) for the phosphazene **2a**, and 0.996 g (96%) for the phosphazene **3a**. Mp 48–49 °C (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.31 (s, 3H), 3.55 (s, 3H), 3.98–4.12 (m, 2H), 5.00 (s, 1H), 6.19 (s, 1H), 7.24 (d, $^3J_{HH}$=5.5 Hz, 1H), 7.41 (d, $^3J_{HH}$=8.7 Hz, 2H), 8.04 (d,

$^3J_{HH}$=8.7 Hz, 2H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 14.2, 19.7, 39.0, 51.1, 60.2, 102.9, 107.7, 123.4, 128.9, 133.9, 144.9, 146.4, 154.4, 166.4, 167.5; IR (KBr): 3327, 1698, 1514; MS (EI): *m/z* 346 (M^+, 19). Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.90; H, 5.25; N, 8.08.

4.4.2. Diethyl 6-methyl-2-phenyl-4-(2-phenylethenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (10b). The general procedure was followed using phosphazene **1b** (1.624 g, 3 mmol) and ethyl 2-(3-phenylpropylene)acetoacetate **9b** (0.732 g, 3 mmol). The mixture was stirred at 60 °C for 30 h. The crude oil was chromatographed on silica gel (20:1 hexane/AcOEt) to give 0.889 g (71%) of **10b** as a yellow solid. Mp 123–124 °C (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.24 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.29 (s, 3H), 3.81–3.92 (m, 2H), 4.08–4.22 (m, 2H), 4.68 (d, $^3J_{HH}$=6.1 Hz, 1H), 5.75 (s, 1H), 6.21 (dd, $^3J_{HH}$=6.1, 15.9 Hz, 1H), 7.08–7.34 (m, 10H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 13.7, 14.4, 19.4, 36.8, 59.7, 59.8, 101.4, 102.3, 126.3–131.6, 136.9, 137.8, 146.2, 144.9, 166.8, 167.4; IR (KBr): 3444, 1694, 1646; MS (EI): *m/z* 417 (M^+, 13); Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.85; H, 6.51; N, 3.36.

4.4.3. 3-Ethyl 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (10c). The general procedure was followed using phosphazene **1d** (1.126 g, 3 mmol) and ethyl 2-(3-nitrophenylmethylene)acetoacetate **9c** (1.185 g, 3 mmol). The mixture was stirred at rt for 30 min. The crude oil was chromatographed on silica gel (7:1 hexane/AcOEt) to give 0.832 g (77%) of **10c** as a yellow solid. Mp 157–158 °C (recrystallized from AcOEt/hexane).[34]

4.4.4. 3-Ethyl 5-methyl 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (10d). The general procedure was followed using phosphazene **1d** (1.126 g, 3 mmol) and ethyl 2-(2,3-dichlorophenylmethylene)acetoacetate **9d** (0.862 g, 3 mmol). The mixture was stirred at 40 °C for 24 h. The crude oil was chromatographed on silica gel (15:1 hexane/AcOEt) to give 0.945 g (82%) of **10d** as a yellow solid. Mp 143–144 °C (recrystallized from AcOEt/hexane).[34]

4.5. General procedure for the preparation of 1,4-dihydropyridines 12

α-Acetylstyrylphosphonate[35] **11** (3 mmol) was added to a 0–10 °C solution of phosphazene **1** (3 mmol) in $CHCl_3$ (9 mL) under N_2 and the mixture was stirred at 60 °C until TLC indicated the disappearance of phosphazene. Evaporation of solvent under reduced pressure afforded an oil that was chromatographed on silica gel (AcOEt) to give the compounds **12**.

4.5.1. Ethyl 4-(2,3-dichlorophenyl)-5-(diethoxyphosphonoyl)-6-methyl-1,4-dihydro-3-pyridinecarboxylate (12a). The general procedure was followed using phosphazene **1a** (1.126 g, 3 mmol) and diethyl α-acetyl-2,3-dichlorostyrylphosphonate **11a** (1.053 g, 3 mmol) for 36 h. It was obtained as a white solid (0.814 g, 65%). Mp 134–135 °C (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $^3J_{HH}$=7.0 Hz, 3H), 1.13 (t, $^3J_{HH}$=7.0 Hz, 3H), 2.25 (s, 3H), 1.25 (t, $^3J_{HH}$=7.0 Hz, 3H), 2.24 (s, 3H), 3.27–3.38 (m, 1H), 3.63–3.73 (m, 1H), 3.87–4.10 (m, 4H), 5.16 (d, $^3J_{PH}$=8.4 Hz, 1H), 6.87 (s, 1H), 7.03 (t, $^3J_{HH}$=7.8 Hz, 1H), 7.18–7.28 (m, 3H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 14.1, 15.5 (d, $^6J_{PC}$=7.6 Hz), 16.2, 18.5, 37.2 (d, $^2J_{PC}$=9.1 Hz), 59.9, 60.7, 61.2, 96.3 (d, $^1J_{PC}$=200.9 Hz), 105.4 (d, $^3J_{PC}$=9.6 Hz), 126.9, 128.2, 129.6, 130.9, 132.5, 135.3, 146.6 (d, $^2J_{PC}$=24.7 Hz), 147.9, 166.9; ^{31}P NMR ($CDCl_3$, 120 MHz): δ 20.81; IR (KBr): 3250, 3184, 1692, 1222, 1029; MS (EI): *m/z* 448 (M^+, 5). Anal. Calcd for $C_{19}H_{24}NCl_2O_5P$: C, 50.91; H, 5.40; N, 3.12. Found: C, 50.98; H, 5.42; N, 3.13.

4.5.2. Methyl 5-(diethoxyphosphonoyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (12b). The general procedure was followed using phosphazene **1d** (1.126 g, 3 mmol) and diethyl α-acetyl-3-nitrostyrylphosphonate **11b** (0.982 g, 3 mmol) for 24 h. It was obtained as a yellow solid (1.107 g, 87%). Mp 159–160 °C (recrystallized from AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.17 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 3.59 (s, 3H), 3.73–3.89 (m, 4H), 4.79 (d, $^3J_{PH}$=10.1 Hz, 1H), 6.07 (s, 1H), 7.29–7.34 (m, 1H), 7.61 (d, $^3J_{HH}$=7.6 Hz, 1H), 7.95 (d, $^3J_{HH}$=8.2 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 16.0, 16.1, 18.2, 19.2, 40.0 (d, $^2J_{PC}$=9.6 Hz), 50.9, 61.1, 61.3, 96.7 (d, $^1J_{PC}$=201.4 Hz), 100.9 (d, $^3J_{PC}$=9.6 Hz), 121.3, 122.7, 128.6, 134.2, 146.1, 146.4, 148.1, 149.6, 167.5; ^{31}P NMR ($CDCl_3$, 120 MHz): δ 20.67; IR (KBr): 3283, 3224, 1705, 1530, 1241, 1023; MS (EI): *m/z* 424 (M^+, 5); Anal. Calcd for $C_{19}H_{25}N_2O_7P$: C, 53.77; H, 5.94; N, 6.60. Found: C, 53.82; H, 5.95; N, 6.59.

4.5.3. 4-[(1*R*,2*S*,5*R*)-(−)-menthyl]-1,1,1-triphenyl-2-aza-1λ^5-phosphabuta-1,3-diene (13). A solution of (1*R*,2*S*,5*R*)-(−)menthyl 3-azidoacrylate[18a] (1.257 g, 5 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise to a solution of triphenylphosphine (5 mmol) for 1 h in anhydrous CH_2Cl_2 (8 mL) under N_2 and the mixture was stirred at room temperature. Evaporation of solvent under reduced pressure afforded an oil, which was recrystallized from hexane/CH_2Cl_2 to give 2.088 g (86%) of **13** as a white solid (mp 86–87 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.64–1.97 (m, 18H), 4.55 (dt, $^3J_{HH}$=4.4, 10.8 Hz, 1H), 5.33 (d, $^3J_{HH}$=12.4 Hz, 1H), 7.39–7.60 (m, 15H), 7.78 (dd, $^3J_{HH}$=12.4 Hz, $^3J_{PH}$=27.0 Hz, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 16.5, 20.5, 21.9, 23.6, 26.1, 31.2, 34.3, 41.3, 47.1, 71.6, 99.7 (d, $^3J_{PC}$=29.2 Hz), 127.6 (d, $^1J_{PC}$=99.2 Hz), 128.6–132.6 (m), 156.9, 170.1 (d, $^4J_{PC}$=3.5 Hz); ^{31}P NMR ($CDCl_3$): δ19.4; IR (KBr): 1686, 1580; $[\alpha]_D^{20}$ −47.4 (*c*, 1.00, CH_2Cl_2); MS (EI): *m/z* 485 (M^+, 5); Anal. Calcd for $C_{31}H_{36}NO_2P$: C, 76.68; H, 7.42; N, 2.88. Found: C, 76.72; H, 7.43; N, 2.88.

4.5.4. 5-[(1*R*,2*S*,5*R*)-(−)-menthyl] 3-methyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate (14). Methyl 2-(4-nitrophenyl)acetoacetate (0.748 g, 3 mmol) was added to a solution of phosphazene **13** (1.456 g, 3 mmol) in CH_2Cl_2 (5 mL) at 0 °C under N_2. The mixture was stirred for 2.5 h. Evaporation of solvent under reduced pressure afforded a solid that was chromatographed on silica gel (10:1 hexane/AcOEt) to give a diastereomeric mixture (36:64, **a/b**) of compound **14** (1.261 g, 92%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.49–1.98

(m, 36H), 2.28 (s, 3H) for **b**, 2.30 (s, 3H) for **a**, 3.55 (s, 3H) for **a**, 3.57 (s, 3H) for **b**, 4.53–4.66 (m, 2H), 4.98 (s, 1H) for **b**, 4.99 (s, 1H) for **a**, 6.06 (s, 2H), 7.21 (d, $^3J_{HH}$=3.1 Hz, 1H) for **a**, 7.28 (d, $^3J_{HH}$=5.5 Hz, 1H) for **b**, 7.39 (d, $^3J_{HH}$=8.8 Hz, 2H) for **a**, 7.40 (d, $^3J_{HH}$=8.8 Hz, 2H) for **b**, 8.03 (d, $^3J_{HH}$=8.7 Hz, 4H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 15.8 for **b**, 16.6 for **a**, 19.8 for **a**, 19.9 for **b**, 20.7 for **a**, 20.8 for **b**, 21.9, 23.0 for **b**, 23.7 for **a**, 25.7 for **b**, 26.6 for **a**, 31.3 for **a**, 31.4 for **b**, 34.1 for **b**, 34.2 for **a**, 39.1, 40.9 for **a**, 41.2 for **b**, 47.3 for **b**, 47.4 for **a**, 51.1, 73.8 for **b**, 74.3 for **a**, 102.8 for **a**, 103.1 for **b**, 108.0 for **b**, 108.3 for **a**, 123.2 for **a**, 123.3 for **b**, 128.9 for **a**, 129.0 for **b**, 133.5 for **a**, 134.0 for **b**, 144.7 for **b**, 144.9 for **a**, 146.4, 154.4 for **b**, 154.5 for **a**, 166.0 for **b**, 166.1 for **a**, 167.5; IR (KBr): 3337, 1692, 1520; MS (EI): *m/z* 456 (M^+, 8). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.85; H, 7.07; N, 6.14. Found: C, 65.88; H, 7.06; N, 6.15.

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