Synthesis of Amidines Derived from Phosphonates and Phosphane Oxides − Amidine-Mediated Preparation of Phosphorylated Oxazolines

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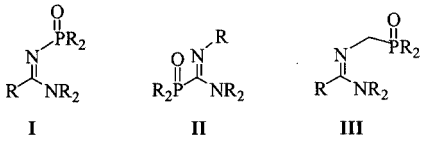
Alkylation of *N*-(phosphorylalkyl)phosphazenes **2** with methyl iodide and allyl bromide and acylation with ethyl chloroformate leads to the formation of aminophosphonium salts **4** derived from (aminoalkyl)phosphonates. *N*-(Phosphorylalkyl)amidines **8** were obtained by reaction of phosphazenes derived from aminophosphonates with benzoyl chloride and subsequent addition of amines. These functionalized amidines were used as key intermediates in the synthesis of oxazolin-4-ylphosphonates **9** and **10**. In a similar manner, oxazolin-4-ylphosphane oxides **17** and **18** were prepared from *N*-(phosphanylalkyl)amidines **16**, which were obtained by reaction of phosphazenes derived from phosphane oxides **15** with benzoyl chloride and amines.

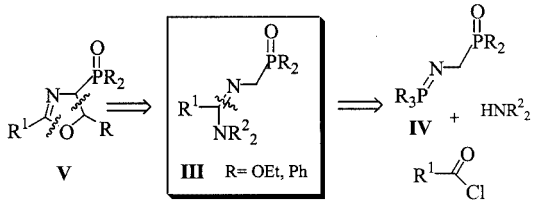
Introduction

Amidines are interesting intermediates in functional group transformations[1] and are used widely in medicinal chemistry.[2] Molecular modifications involving the introduction of organophosphorus functionalities could increase their biological activities.[3] Very few examples have been described of syntheses of phosphorus-substituted amidines, such as *N*-phosphoryl-[4] (**I**, Scheme 1) and *C*-phosphorylamidines[5] (**II**, Scheme 1). Moreover, as far as we know, the preparation of *N*-(phosphorylalkyl)amidines (**III**, Scheme 1) has not been reported.[1]



Scheme 1

On the other hand, phosphazenes[6,7] are an important class of compounds that have attracted a great deal of attention in recent years because of their broad range of uses in the construction of acyclic compounds[8] and in the preparation of heterocycles.[9] Furthermore, α-aminophosphonates can be considered as surrogates for α-amino acids,[10a] and have been used as haptens for the generation of catalytic antibodies,[10b] as enzyme inhibitors[10c,10d] and as antibacterial agents.[10e] In this context, we have been involved in the study of simple and functionalized phosphazenes[6e] as well as of their use in the construction of carbon−nitrogen double bonds[11] and in the preparation of acyclic[12] and heterocyclic compounds.[13] Following on from our previous studies on the reactivity and the synthetic utility of phosphazenes,[6e,11−13] here we aim to explore a new and effective strategy for the preparation of phosphorylated amidines (**III**, Scheme 2) from functionalized phosphazenes **IV**, as well as their synthetic utility in the preparation of oxazolinylphosphonates **V** (R = OEt) and oxazolinylphosphane oxides **V** (R = Ph). Retrosynthetically, we envisaged the preparation of amidines **III** by reaction of phosphazenes with acyl halides and subsequent addition of amines in a similar manner to the strategy previously used for the preparation of 2-azadienes.[14]



Scheme 2

Results and Discussion

Synthesis of *N*-(Phosphorylalkyl)amidines

The required phosphazene **2**, derived from an alkylphosphonate, is a functionalized *N*-alkylphosphazene and a very unstable compound.[6e,15] For this reason, phosphazene **2** was generated in situ by a Staudinger reaction of diethyl azidomethylphosphonate[16] (**1**) with triphenylphosphane

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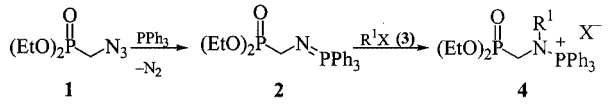


3, 4 a R^1 = Me, X = I
b R^1 = CH_2-CH=CH_2 , X = Br
c R^1 = CO_2Et, X = Cl

Scheme 3

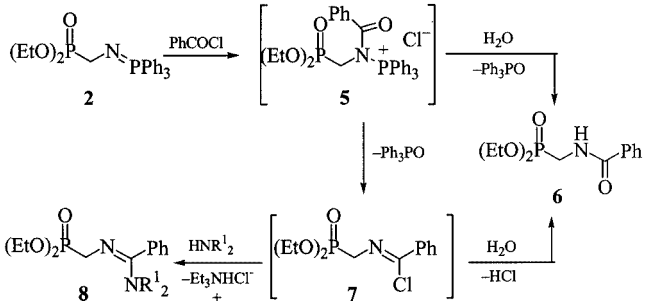
(Scheme 3), and the crude reaction mixture was used satisfactorily in the following steps. The presence of phosphazene **2** in the crude reaction mixture was monitored by ^{31}P NMR spectroscopy.[17] In order to know the chemical behaviour of phosphazene **2**, and confirm its presence in the reaction mixture, the formation of alkyl and acyl derivatives was explored. Thus, treatment of crude phosphazene **2** with alkyl halides, such as methyl iodide **3a** (R^1 = Me; X = I) or allyl bromide **3b** (R^1 = $CH_2CH{=}CH_2$; X = Br), in refluxing benzene gave *N*-alkylated aminophosphonium salts **4a** (R^1 = Me; X = I) and **4b** (R^1 = $CH_2CH{=}CH_2$; X = Br) in very good yields (Scheme 3, Table 1, Entries 1, 2). Compounds **4a**,**b** were characterized on the basis of their spectroscopic data, which are consistent with reported data of alkylated aminophosphonium salts.[12c,18] For example, the ^{31}P NMR spectrum shows signals at δ_P = 22.1 and 49.3 ppm ($^3J_{P,P}$ = 9.3 Hz) for the phosphonate and the phosphonium salt (**4a**), respectively, and the ^{1}H and ^{13}C NMR spectra displayed doublets for the *N*-methyl group (δ_H = 3.26 ppm, $^3J_{PH}$ = 9.3 Hz; δ_C = 39.6 ppm, $^2J_{P,C}$ = 3.0 Hz, respectively) of phosphonium salt **4a**. Because of the high basicity of the phosphazene linkage, formation of these derivatives **4** can be explained by selective *N*-alkylation of the phosphazene, in a manner similar to that of simply functionalized phosphazenes.[8a,12c] A similar behaviour was observed when *N*-(phosphorylalkyl)phosphazene **2** reacted with ethyl chloroformate **3c** (R^1 = CO_2Et; X = Cl) in THF to afford the hygroscopic phosphonium salt **4c** (R^1 = CO_2Et; X = Cl) in good yield (Scheme 3, Table 1, Entry 3).

Table 1. Aminophosphonium salts and amidines

Entry	Compd.	R^1	Yield (%)	M.p. [°C]
1	**4a**	Me	85[a]	125−126
2	**4b**	$CH_2{=}CHCH_2$	80[b]	55−56
3	**4c**	CO_2Et	70[c]	107−108
4	**8a**	$[CH_2]_5$	78[d]	oil
5	**8b**	$CHMe_2$	50[d]	oil
6	**16**	$[CH_2]_5$	80[d]	oil

[a] Yield after purification by recrystallization from ethyl acetate. [b] Yield after purification by recrystallization from diethyl ether/dichloromethane. [c] Yield after purification by recrystallization from THF. [d] Yield after purification by flash chromatography.

Having obtained these results, we tried to explore whether *N*-(phosphorylalkyl)phosphazene **2** could be acylated with acyl halides and if the corresponding phosphonium salts be used as intermediates for the preparation of amidines. When phosphazene **2** was treated with benzoyl chloride in THF (28 h) at room temperature, however, acylated aminophosphonium salt **5** was not isolated and, instead, a mixture of triphenylphosphane oxide and amide **6** was obtained after evaporation of the solvent (Scheme 4). Formation of the amide **6** may occur via an unstable imidoyl chloride **7**, generated from salt **5** by intramolecular loss of triphenylphosphane oxide, and subsequent addition of water to the imidoyl chloride, in a manner similar to that observed in simple[8e,15a] and functionalized phosphazenes.[14] We cannot exclude, however, that hydrolysis of the phosphonium salts **5** might occur, with cleavage of the nitrogen−phosphorus bond, during the workup (Scheme 4).



Scheme 4

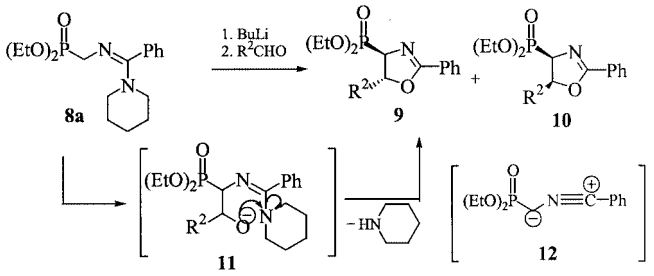
Having obtained these results, we studied the synthesis of amidines. We thought that if imidoyl chloride **7** is formed, this reactive intermediate could be trapped in situ by the addition of simple nucleophilic reagents such as amines. Benzoyl chloride was added to phosphazene **2** and the crude reaction mixture was treated with piperidine in the presence of triethylamine to give *N*-(phosphorylalkyl)amidine **8a** [R^1_2 = $(CH_2)_5$] (Scheme 4, Table 1, Entry 4). Spectroscopic data are in agreement with the structure of compound **8a**. The mass spectrum of **8a** shows the molecular ion [*m*/*z* (%) = 338 (60)], the ^{1}H NMR spectrum displays a doublet at δ_H = 3.40 ppm with a coupling constant $^2J_{PH}$ = 15.3 Hz for the methylene protons, and the ^{13}C NMR spectrum gave well-resolved doublets at δ_C = 47.9 ppm ($^1J_{P,C}$ = 163.3 Hz), for the methylene carbon atom bonded to the phosphorus atom, and at δ_C = 164.3 ppm ($^3J_{P,C}$ = 17.3 Hz), for the imidoyl carbon atom. The formation of amidine **8a** suggests that the amine could indeed trap the unstable imidoyl chloride **7** (Scheme 4).

Synthesis of Oxazolinylphosphonates

Oxazolines are common heterocycles with a wide range of uses as building blocks in organic synthesis and as ligands in organometallic chemistry.[19,20] Although it is known, however, that phosphorus substituents regulate important biological functions,[3] and increase their biological activity, the synthesis has been described only[21,22] of 2-unsubstituted oxazolinylphosphonates by the reaction of isocyanomethylphosphonates and aldehydes and, as far as

we know, no examples of 2-substituted oxazolinylphosphonates have been reported. In this context, we are interested in the design of new nitrogen-containing acyclic and cyclic derivatives bearing either a phosphane oxide or a phosphonate moiety, and previously we have described the synthesis of three-,[23] five-,[24] and six-membered[25] phosphorus-substituted nitrogen heterocycles from enamines and imines derived from phosphazenes, phosphane oxides, or phosphonates, as well as of phosphorus-containing heterocycles.[26] Continuing with our interest in the chemistry of new phosphorus-substituted heterocyclic compounds, we thought that *N*-(phosphorylalkyl)amidine (**III**, Scheme 2) could be used for the preparation of oxazolines containing a phosphonate group as a substituent (**V**, Scheme 2).

Treatment of amidine **8a** with *n*-butyllithium followed by the addition of *p*-tolylaldehyde led to the formation of diethyl *trans*- and *cis*-2-phenyl-5-(*p*-tolyl)-2-oxazolin-4-ylphosphonates (R^2 = *p*-$CH_3C_6H_4$) (**9a** and **10a**, respectively) in good yields (Scheme 5, Table 2, Entry 1). These isomers can be separated by flash chromatography, and spectroscopic data are in agreement with their assigned structures. Mass spectrometry of both derivatives showed their molecular ions [*m*/*z* (%) = 373 (2)], while in their ^{31}P NMR spectra the phosphonate group resonates at δ_P = 21.5 ppm for the *trans* isomer and at δ_P = 19.1 ppm for the *cis* isomer. The ^1H NMR spectrum of *trans*-oxazoline **9a** displays a typical double doublet at δ_H = 4.38 ppm corresponding to the proton in position 4 bonded to the phosphonate group ($^2J_{PH}$ = 14.1 Hz) and with a second coupling constant ($^3J_{H,H}$ = 7.5 Hz) characteristic of a *trans* configuration in oxazolines,[22] and the signal of the 5-H proton appears at δ = 5.80 ppm as a double doublet ($^2J_{PH}$ = 19.8, $^3J_{HH}$ = 7.5 Hz). Conversely, in the isomer **10a**, the protons 4-H and 5-H display a coupling constant ($^3J_{HH}$ = 10.8 Hz) that is in agreement with a *cis* arrangement between substituent in positions 4 and 5 of the heterocycle. Also, the ^{13}C NMR spectra of products **9a** and **10a** display very characteristic signals for C-4 and C-5: the spectrum of oxazoline **9a** shows doublets at δ_C = 72.4 ppm ($^1J_{P,C}$ = 162.16 Hz) and at δ_C = 81.9 ppm ($^2J_{P,C}$ = 2.4 Hz) for C-4 and C-5, respectively, while in the spectrum of *cis*-oxazoline **10a** these signals appear as a doublet at δ_C = 69.1 ppm ($^1J_{P,C}$ = 164.68 Hz) for C-4 and as a singlet at δ_C = 82.7 ppm for C-5. The scope of the reaction is not limited to aromatic aldehydes, since the aliphatic aldehyde ethanal also reacted with amidine **8a** to yield diethyl 5-methyl-2-phenyl-2-oxazolin-4-ylphosphonates (R^2 = Me) **9/10b** (Table 2, Entry 2). The formation of oxazolines **9** and **10** can be explained by deprotonation of amidine **8a** in the presence of the base (butyllithium) followed by nucleophilic addition of the stabilized carbanion phosphonate to the aldehyde with formation of intermediate **11**. Cyclization of this intermediate **11** with the loss of piperidine would afford oxazolines **9** and **10**. We cannot exclude totally, however, an alternative mechanism involving the formation of an unstable nitrile ylide **12**, from the amidine and the base, and subsequent 1,3-dipolar cycloadditions[27] of this dipole to the aldehydes with the formation of oxazolines (Scheme 5).



Scheme 5

Table 2. Oxazolidines obtained from **8a**

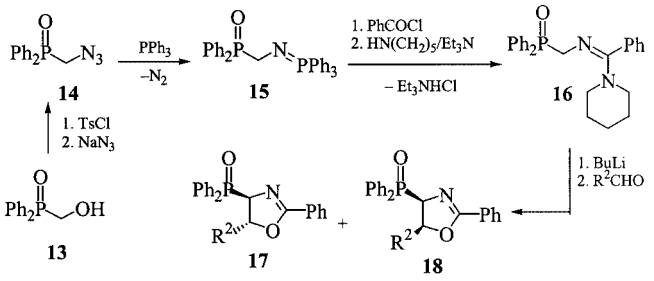
Entry	Compd.	R^2	Yield (%)[a]	M.p. [°C]
1	**9/10a**	*p*-MeC_6H_4	74	oil
2	**9/10b**	Me	80	oil
3	**17/18a**	*p*-MeC_6H_4	80	oil
4	**17/18b**	Me	86	oil

[a] Yield after purification by flash chromatography.

Synthesis of *N*-(Phosphinylalkyl)amidines and Oxazolinylphosphane Oxides

This methodology that we have used for the preparation of amidines **8** and oxazolines derived from phosphonates **9** and **10**, can be extended also to the synthesis of amidines and oxazolines containing a phosphane oxide group. According to a similar strategy to that described for the synthesis of amidines **8**, the generation of phosphazene **15** in situ is necessary for the preparation of *N*-[(diphenylphosphanyl)methyl]amidine **16** and, therefore, the synthesis of (azidomethyl)diphenylphosphane oxide (**14**) is required. Preparation of azide **14** was achieved by reaction of (hydroxymethyl)phosphane oxide[28] **13** with tosyl chloride and subsequent addition of sodium azide in dimethyl sulfoxide. Azide **14** was used then for the one-pot synthesis of amidine **16**. Thus, benzoyl chloride was added to the phosphazene **15**, which was prepared easily by the Staudinger reaction of (azidoalkyl)phosphane oxide **14** and triphenylphosphane, and the crude reaction mixture was treated with piperidine in the presence of triethylamine to give *N*-(phosphanylalkyl)-amidine **16** (Scheme 6, Table 1, Entry 6). Spectroscopic data are consistent with the structure of compound **16**. Mass spectrometry shows the molecular ion [*m*/*z* (%) = 402 (2)], while the ^1H and ^{13}C NMR spectra showed well-resolved doublets at δ_H = 3.90 ppm ($^2J_{PH}$ = 12.4 Hz) and at δ_C = 51.9 ppm ($^1J_{P,C}$ = 87.6 Hz) for the methylene group bonded to the phosphane oxide group.

Amidines derived from phosphane oxides **16** were then used for the preparation of oxazolinylphosphane oxides **17** and **18**. Treatment of amidine **16** with butyllithium followed by the addition of aromatic (R^2 = *p*-MeC_6H_4) and aliphatic (R^2 = Me) aldehydes gave (2-phenyl-2-oxazolin-4-yl)phosphane oxides, isolated as mixtures of *trans* (**17**) and *cis* isomers (**18**), in good yields (Scheme 6, Table 2, Entries 3, 4). These isomers can be separated by flash chromatography



Scheme 6

and spectroscopic data are in agreement with the assigned structures. For **17a** and **18a**, their mass spectra show their molecular ions [*m*/*z* (%) = 437 2%], and in their ^{31}P NMR spectra the signal of the phosphane oxide group appeared at $\delta_P = 28.1$ ppm for the *trans* isomer and at $\delta_P = 22.8$ ppm for the *cis* isomer. The formation of oxazolines **17** and **18** can be explained, as in the case of phosphorylamidines **8**, by nucleophilic addition of the stabilized carbanion derived from the amidine **16** to the aldehyde, followed by cyclization with the loss of piperidine (Scheme 6). As far as we know, this is the first synthesis of oxazolines containing a phosphane oxide group directly bonded to the heterocyclic ring.

In conclusion, the strategy described in this paper outlines an efficient and simple route to the first synthesis of amidines containing either alkylphosphonate or alkylphosphane oxide groups, and makes use of readily available starting materials. These amidines can be used for the preparation of oxazolinylphosphonates and oxazolinylphosphane oxides, some of which have been prepared for the first time. Functionalized amidines and oxazolines are important building blocks in organic synthesis and in the preparation of biologically active compounds of interest to medicinal chemistry.[1,2,18,19]

Experimental Section

General: Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallised or distilled as necessary. All reactions were performed under dry nitrogen. Analytical TLC was performed on Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out on Merck silica gel 60 (230−400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^1H (300 MHz), ^{13}C (75 MHz), and ^{31}P NMR (120 MHz) spectra were recorded with a Varian VXR 300 MHz spectrometer using $CDCl_3$ or CD_3OD solutions, with TMS as an internal reference ($\delta = 0.00$ ppm) for ^1H and ^{13}C NMR spectra and phosphoric acid (85%) ($\delta = 0.00$ ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hz. Low-resolution mass spectra (MS) were obtained at 50−70 eV by electron impact (EIMS) with a Hewlett−Packard 5971 or 5973 spectrometer and by chemical ionization (CI) with a Hewlett−Packard 1100MSD. Data are reported in the form *m*/*z* (intensity relative to base = 100). Infrared spectra (IR) were taken with 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 with a LECO CHNS-932 apparatus. Diethyl (azidomethyl)phosphonate (**1**) was synthesized according to a literature procedure.[16]

General Procedure for the Synthesis of Aminophosphonium Salts 4: To a solution of triphenylphosphane (4.5 mmol) in benzene (for **4a**, **4b**) or THF (for **4c**) (10 mL) was added dropwise with stirring and to a cooled (ice bath) solution of diethyl (azidomethyl)phosphonate (**1**) (5 mmol). Phosphazene **2** was generated in situ and the presence of **2** in the crude reaction mixture was monitored by ^{31}P NMR spectroscopy.[17] Alkyl halides **3** were added to the crude reaction mixture, which was then stirred under reflux for 17−20 h. The mixture was concentrated under vacuum and the crude residue was purified by recrystallization.

[(Diethoxyphosphorylmethyl)(methyl)amino]triphenylphosphonium Iodide (4a): The general procedure was applied using methyl iodide **3** (6 mmol), affording **4a** (2.18 g, 85%) as a white solid. M.p. 125−126 °C. ^1H NMR: $\delta = 7.67-7.33$ (m, 15 H), 3.97 (m, 4 H), 3.72 (dd, $^3J_{PH} = 11.4$, $^2J_{PH} = 8.0$ Hz, 2 H) 3.26 (d, $^3J_{HP} = 9.3$ Hz, 3 H), 1.17 (m, 6 H) ppm. ^{13}C NMR: $\delta = 135.6-130.2$, 119.0 (d, $^1J_{P,C} = 103.0$ Hz), 62.6, 62.5, 46.2 (d, $^1J_{P,C} = 160.2$ Hz), 39.6 (d, $^2J_{P,C} = 3.0$ Hz), 16.3, 16.2 ppm. ^{31}P NMR: $\delta = 22.1$ (d, $^3J_{P,P} = 9.3$ Hz), 49.3 (d, $^3J_{P,P} = 9.3$ Hz) ppm. IR (KBr): $\tilde{\nu}$: 1247 cm^{-1}. MS: *m*/*z* (%) = 413 (12) $[M - I - Et]^+$. $C_{24}H_{30}INO_3P_2$ (569): calcd. C 50.62, H 5.27, N 2.46; found C 50.58, H 5.24, N 2.39.

[(Allyl)(diethoxyphosphorylmethyl)amino]triphenylphosphonium Bromide (4b): The general procedure was applied using allyl bromide **3** (4.5 mmol), affording **4b** (1.97 g, 80%) as a white solid. M.p. 55−56 °C. ^1H NMR: $\delta = 7.85-7.23$ (m, 15 H), 5.60 (m, 1 H), 5.21 (m, 2 H), 4.15 (m, 4 H), 3.70 (dd, $^3J_{PH} = 9.4$, $^2J_{PH} = 7.0$ Hz, 2 H), 3.40 (m, 2 H), 1.14 (m, 6 H) ppm. ^{13}C NMR: $\delta = 135.1-128.3$, 121.9, 60.2, 59.1, 51.4, 42.9 (d, $^1J_{P,C} = 149.5$ Hz), 16.6, 16.25 ppm. ^{31}P NMR: $\delta = 21.5$ (d, $^3J_{P,P} = 16.5$ Hz), 40.8 (d, $^3J_{P,P} = 16.5$ Hz) ppm. IR (KBr): $\tilde{\nu} = 1245$ cm^{-1}. MS: *m*/*z* (%) = 468 (2) $[M - Br]^+$. $C_{26}H_{32}BrNO_3P_2$ (548) calcd. C 56.93, H 5.84, N 2.55; found C 56.98, H 5.82, N 2.60.

[(Diethoxyphosphorylmethyl)(ethoxycarbonyl)amino]triphenylphosphonium Chloride (4c): The general procedure was applied using ethyl chloroformate **3** (4.5 mmol) affording **4c** (1.69 g, 70%) as a hygroscopic white solid. M.p. 107−108 °C. ^1H NMR: $\delta = 8.05-7.26$ (m, 15 H), 4.11 (m, 4 H), 3.93 (m, 4 H) 1.16 (t, $^3J_{H,H} = 7.0$ Hz, 6 H), 0.96 (t, $^3J_{H,H} = 6.9$ Hz, 3 H) ppm. ^{13}C NMR: $\delta = 153.1$, 135.5−128.0, 117.8 (d, $^1J_{P,C} = 103.0$ Hz), 65.4, 62.5, 62.4, 42.8 (d, $^1J_{P,C} = 158.1$ Hz), 16.3, 15.9, 15.8, 13.1 ppm. ^{31}P NMR: $\delta = 21.7$ (d, $^3J_{P,P} = 17.0$ Hz), 40.7 (d, $^3J_{P,P} = 17.0$ Hz) ppm. IR (KBr): $\tilde{\nu} = 1760$, 1252 cm^{-1}. MS: *m*/*z* (%) = 500 (1) $[M - Cl]^+$. $C_{26}H_{32}ClNO_5P_2$ (535.5) calcd. C 58.26, H 5.98, N 2.61; found C 58.29, H 5.90, N 2.58.

General Procedure for the Synthesis of Amidines 8: A solution of diethyl (azidomethyl)phosphonate (**1**) (5 mmol) was added dropwise with stirring to a solution of triphenylphosphane (4.5 mmol) in THF (25 mL) cooled in an ice bath. Phosphazene **2** was generated in situ and the presence of **2** in the crude reaction mixture was monitored by ^{31}P NMR spectroscopy.[17] Benzoyl chloride was added to the crude reaction mixture, which was then allowed to stand at room temperature for 28 h. A solution of either a secondary amine (piperidine or diisopropylamine, 6 mmol) or of triethylamine (9 mmol) was added to the resulting mixture . The reaction mixture was then left at room temperature for 3 d. The resulting mixture was washed three times with water, extracted with CH_2Cl_2,

dried with anhydrous $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with diethyl ether/hexane (1:6).

***N*²-(Diethoxyphosphorylmethyl)-*N*¹-(pentamethylene)benzamidine (8a):** The general procedure was applied using piperidine (4.5 mmol), affording **8a** (1.19 g, 78%) as an oil. ^{1}H NMR: δ = 7.42−7.12 (m, 5 H), 4.07 (m, 4 H), 3.40 (d, $^2J_{PH}$ = 15.3 Hz, 2 H), 3.21 (m, 4 H), 1.54 (m, 2 H), 1.46 (m, 4 H), 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H) ppm. ^{13}C NMR: δ = 164.3 (d, $^3J_{P,C}$ = 17.3 Hz), 133.3−127.3, 61.9, 61.8, 47.9 (d, $^1J_{P,C}$ = 163.3 Hz), 46.5, 25.6, 22.8, 16.3, 16.2 ppm. ^{31}P NMR: δ = 26.5 ppm. IR (KBr): $\tilde{\nu}$ = 1239 cm^{-1}. MS: *m*/*z* (%) = 338 (60) [M$^+$]. $C_{17}H_{27}N_2O_3P$ (338): calcd. C 60.36, H 7.99, N 8.28; found C 60.30, H 7.94, N 8.23.

***N*²-(Diethoxyphosphorylmethyl)-*N*¹,*N*¹-diisopropylbenzamidine (8b):** The general procedure was applied using diisopropylamine (4.5 mmol), affording **8b** (0.72 g, 50%) as an oil. ^{1}H NMR: δ = 7.38−7.06 (m, 5 H), 4.05 (m, 4 H), 3.7 (m, 2 H), 3.25 (d, $^2J_{PH}$ = 14.6 Hz, 2 H), 1.15 (m,18 H) ppm. ^{13}C NMR: δ = 162.9 (d, $^3J_{P,C}$ = 17.6 Hz), 134.5−127.1, 76.5, 61.7, 61.6, 46.9 (d, $^1J_{P,C}$ = 163.7 Hz), 20.8, 16.5, 16.4 ppm. ^{31}P NMR: δ = 26.7 ppm. IR (KBr): $\tilde{\nu}$ = 1235 cm^{-1}. MS: *m*/*z* (%) = 354 (7) [M$^+$]. $C_{18}H_{31}N_2O_3P$ (354) calcd. C 61.01, H 8.75, N 7.90; found C 61.08, H 8.68, N 7.92.

Synthesis of (Azidomethyl)phosphane Oxide (14): Tosyl chloride (4.5 mmol) was added with stirring to an ice-cooled solution of (hydroxymethyl)phosphane oxide **13**[28] (4.5 mmol) in THF/dimethyl sulfoxide and the mixture stirred for 2 h. Sodium azide (5 mmol) was added to the crude reaction mixture, which was then heated at 70 °C for 24 h. The resulting mixture was washed three times with water, extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with ethyl acetate to afford **14** (0.7 g, 80%) as a white solid. M.p. 109−110 °C. ^{1}H NMR: δ = 7.75−7.37 (m, 10 H), 3.92 (d, $^2J_{PH}$ = 7.3 Hz, 2 H) ppm. ^{13}C NMR: δ = 132.3−128.5, 49.3 (d, $^1J_{P,C}$ = 76.0 Hz) ppm. ^{31}P NMR: δ = 27.9 ppm. IR (KBr): $\tilde{\nu}$ = 2480, 1340 cm^{-1}. MS: *m*/*z* (%) = 257 (2) [M$^+$]. $C_{13}H_{12}N_3OP$ (257): calcd. C 60.67, H 4.70, N 16.34; found C 60.62, H 4.69, N 16.28.

Synthesis of *N*²-(Diphenylphosphanylmethyl)-*N*¹-(pentamethylene)benzamidine (16): A solution of triphenylphosphane (4.5 mmol) was added dropwise with stirring to a solution of (azidomethyl)phosphane oxide **14** (4.5 mmol) in THF (20 mL) cooled in an ice bath. The mixture was allowed to warm to room temperature for 22 h, phosphazene **15** was generated in situ. Benzoyl chloride was added to the crude reaction mixture, which was allowed to stand at room temperature for 7 h. A solution of either piperidine (6 mmol) or triethylamine (9 mmol) was added to the resulting mixture. The reaction mixture was then left at room temperature for 3 d. The resulting mixture was washed three times with water, extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, and the solvents were evaporated under vacuum. The crude residue was purified by flash column chromatography eluting with diethyl ether/hexane (1:6) to afford of **16** (0.59 g, 80%) as an oil. ^{1}H NMR: δ = 7.82−7.17 (m, 15 H), 3.91 (d, $^2J_{PH}$ = 12.4 Hz, 2 H), 3.10 (m, 4 H), 1.50 (m, 2 H), 1.34 (m, 4 H) ppm. ^{13}C NMR: δ = 164.0 (d, $^3J_{P,C}$ = 12.6 Hz), 136.9−127.1, 51.9 (d, $^1J_{P,C}$ = 87.6 Hz), 46.7, 25.8, 24.7 ppm. ^{31}P NMR: δ = 30.8 ppm. IR (KBr): $\tilde{\nu}$ = 1350 cm^{-1}. MS: *m*/*z* (%) = 402 (2) [M$^+$]. $C_{25}H_{27}N_2OP$ (402): calcd. C 74.62, H 6.71, N 6.96; found C 74.59, H 6.74, N 6.93.

General Procedure for the Synthesis of Phosphorylated Oxazolines 9, 10, 17, 18: Butyllithium (1.6 M in hexanes, 2.4 mmol) was added dropwise to a solution of amidine **8a** or **16** (2 mmol) in THF (15 mL) stirred at −78 °C. After 1 h at −78 °C, the corresponding aldehyde (4 mmol) was added. The reaction mixture was warmed to room temperature and stirred until TLC showed the disappearance of the amidine. The resulting mixture was washed three times with water, extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash column chromatography eluting with ethyl acetate/hexane (1:5) to afford isomeric compounds **9** and **10** or **17** and **18**.

Diethyl [2-Phenyl-5-(*p*-tolyl)-2-oxazolin-4-yl]phosphonate (9/10a): The general procedure was applied using amidine **8a** (2 mmol) and *p*-tolylaldehyde (4 mmol), affording a mixture of oxazolines *trans*-**9a** and *cis*-**10a** (0.54 g, 74%) as an oil. ^{1}H NMR: **9a**: δ = 8.11−7.00 (m, 9 H), 5.80 (dd, $^3J_{H,H}$ = 7.5, $^2J_{PH}$ = 19.8 Hz, 1 H), 4.38 (dd, $^3J_{H,H}$ = 7.5, $^2J_{PH}$ = 14.0 Hz, 1 H), 4.15 (m, 4 H), 2.28 (s, 3 H), 1.25 (m, 6 H) ppm. **10a**: δ = 8.11− 7.00 (m, 9 H), 5.89 (dd, $^3J_{H,H}$ = 10.8, $^2J_{PH}$ = 23.8 Hz, 1 H), 4.78 (dd, $^3J_{H,H}$ = 10.8, $^2J_{PH}$ = 16.9 Hz, 1 H), 3.85 (m, 4 H), 2.27 (s, 3 H), 1.06 (m, 6 H) ppm. ^{13}C NMR: **9a**: δ = 138.3 (d, $^3J_{P,C}$ = 19.1 Hz), 133.3−125.5, 81.9 (d, $^2J_{P,C}$ = 2.4 Hz), 72.3 (d, $^1J_{P,C}$ = 162.1 Hz), 63.1, 63.0, 21.1, 16.5, 16.4 ppm. **10a**: δ = 137.3 (d, $^3J_{P,C}$ = 11.6 Hz), 133.3−125.5, 82.6, 69.1 (d, $^1J_{P,C}$ = 164.6 Hz), 62.5, 62.3, 21.1, 16.3, 16.2 ppm. ^{31}P NMR: **9a**: δ = 21.51 ppm; **10a**: δ = 19.03 ppm. IR (KBr): $\tilde{\nu}$ = 1228 cm^{-1}. MS: *m*/*z* (%) = 373 (1) [M$^+$]. $C_{20}H_{24}NO_4P$ (373): calcd. C 64.34, H 6.43, N 3.75; found C 64.38, H 6.42, N 3.77.

Diethyl (5-Methyl-2-phenyl-2-oxazolin-4-yl)phosphonate (9/10b): The general procedure was applied using amidine **8a** (2 mmol) and acetaldehyde (4 mmol), affording a mixture of oxazolines *trans*-**9b** and *cis*-**10b** (0.5 g, 80%) as an oil. ^{1}H NMR: **9b**: δ = 7.90−7.21 (m, 5 H), 4.98 (m, 1 H), 4.14 (m, 4 H), 4.03 (dd, $^3J_{H,H}$ = 8.0, $^2J_{PH}$ = 13.8 Hz, 1 H), 1.44 (d, $^2J_{H,H}$ = 6.3 Hz, 3 H), 1.24 (m, 6 H) ppm; **10b**: δ = 7.90−7.21 (m, 5 H), 5.07 (m, 1 H), 4.47 (dd, $^3J_{H,H}$ = 10.2, $^2J_{PH}$ = 16.0 Hz, 1 H), 4.14 (m, 4 H), 1.56 (d, $^2J_{H,H}$ = 6.4 Hz, 3 H), 1.16 (m, 6 H) ppm. ^{13}C NMR: **9b**: δ = 131.5−128.2, 77.6, 70.5 (d, $^1J_{P,C}$ = 163.17 Hz), 63.1, 62.9, 21.5, 16.5 ppm; **10b**: δ = 131.5−128.2, 77.9, 66.6 (d, $^1J_{P,C}$ = 161.66 Hz), 62.7, 62.4, 21.4, 16.4 ppm. ^{31}P NMR: **9b**: δ = 21.91 ppm; **10b**: δ = 20.27 ppm. IR (KBr): $\tilde{\nu}$ = 1238 cm^{-1}. MS: *m*/*z* (%) = 297 (4) [M$^+$]. $C_{14}H_{20}NO_4P$ (297): calcd. C 56.56, H 6.73, N 4.71; found C 56.59, H 6.77, N 4.75.

Diphenyl[2-phenyl-5-(*p*-tolyl)-2-oxazolin-4-yl]phosphane Oxides 17/18a: The general procedure was applied using amidine **16** (2 mmol) and *p*-tolualdehyde (4 mmol), affording a mixture of oxazolines *trans*-**17a** and *cis*-**18a** (0.72 g, 80%) as an oil. ^{1}H NMR: **17a**: δ = 8.05−7.04 (m, 19 H), 5.90 (dd, $^3J_{H,H}$ = 6.5, $^2J_{PH}$ = 18.2 Hz, 1 H), 4.92 (dd, $^3J_{H,H}$ = 6.5, $^2J_{PH}$ = 6.5 Hz, 1 H), 2.24 (s, 3 H) ppm; **18a**: δ = 8.03−7.03 (m, 19 H), 6.10 (dd, $^3J_{H,H}$ = 10.7, $^2J_{PH}$ = 12.6 Hz, 1 H), 5.34 (dd, $^3J_{H,H}$ = 10.7, $^2J_{PH}$ = 11.4 Hz, 1 H), 2.16 (s, 3 H) ppm. ^{13}C NMR: **17a**: δ = 165.2 (d, $^3J_{P,C}$ = 8.6 Hz), 138.1−125.2, 80.8, 76.4 (d, $^1J_{P,C}$ = 79.6 Hz), 21.1 ppm; **18a**: δ = 165.8 (d, $^3J_{P,C}$ = 13.6 Hz), 137.7−125.3, 83.0, 71.6 (d, $^1J_{P,C}$ = 87.1 Hz), 21.1 ppm. ^{31}P NMR: **17a**: δ = 28.06 ppm; **18a**: δ = 22.82 ppm. IR (KBr): $\tilde{\nu}$ = 1325 cm^{-1}. MS: *m*/*z* (%) = 437 (2) [M$^+$]. $C_{28}H_{24}NO_2P$ (437): calcd. C 76.88, H 5.49, N 3.20; found C 76.84, H 5.42, N 3.12.

(5-Methyl-2-phenyl-2-oxazolin-4-yl)diphenylphosphane Oxides 17/18b: The general procedure was applied using amidine **16** (2 mmol) and acetaldehyde (4 mmol), affording a mixture of oxazolines *trans*-**17b** and *cis*-**18b** (0.61 g, 86%) as an oil. ^{1}H NMR: **17b**: δ = 8.14−7.19 (m, 15 H), 5.26 (m, 1 H), 4.60 (dd, $^3J_{H,H}$ = 7.5, $^2J_{PH}$ = 7.5 Hz, 1 H), 1.44 (d, $^2J_{H,H}$ = 6.6 Hz, 3 H) ppm; **18b**: δ = 8.14−7.19 (m, 15 H), 5.21(m, 1 H), 5.04 (dd, $^3J_{H,H}$ = 10.4, $^2J_{PH}$ = 10.4 Hz, 1 H), 1.40 (d, $^2J_{H,H}$ = 6.3 Hz, 3 H) ppm. ^{13}C NMR: **17b**:

δ = 165.1 (d, $^3J_{P,C}$ = 9.6 Hz), 134.4−127.2, 79.4, 73.8 (d, $^1J_{P,C}$ = 81.6 Hz), 22.09 (d, $^3J_{P,C}$ = 10.6 Hz) ppm; **18b**: δ = 165.5 (d, $^3J_{P,C}$ = 12.1 Hz), 134.4−127.2, 76.9, 69.8 (d, $^1J_{P,C}$ = 83.6 Hz), 17.1 (d, $^3J_{P,C}$ = 7.6 Hz) ppm. ^{31}P NMR: **17b**: δ = 28.33 ppm; **18b**: δ = 24.69 ppm. IR (KBr): $\tilde{\nu}$ = 1238 cm^{-1}. MS: *m*/*z* (%) = 361 (1) [M$^+$]. $C_{22}H_{20}NO_2P$ (361): calcd. C 73.13, H 5.54, N 3.87; found C 73.19, H 5.49, N 3.88.

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