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Conjugate Addition to 1-Phosphono-2-aza-1,3-butadienes: Synthesis of Phosphonylated γ-Lactams

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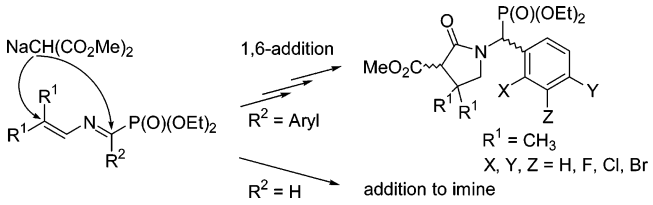

Several 1-phosphono-2-aza-1,3-butadienes, **1** and **13**−**20**, were evaluated in the reaction with different enolate-type nucleophiles to induce addition at the 1- or the 4-position of the azadiene. 1-Phosphono-2-azadienes **1** react with sodium malonate at the 1-position, leading to the formation of bisenamines **12** after elimination of the phosphonate moiety. On the contrary, sodium malonate adds at the 4-position of 1-aryl-1-phosphono-2-azadienes **14**−**19** when the azadienes bear a halogenated phenyl substituent, and the resulting addition products **21**−**26** are easily transformed into the corresponding phosphonylated γ-lactams **35**−**40**. The regioselectivity of the addition is explained by reversal of polarization of the azadiene due to the electron-withdrawing character of the halogenated phenyl substituents.

Introduction

Being key intermediates in organic synthesis for the construction of both heterocyclic systems and acyclic polyfunctionalized compounds, substituted 2-aza-1,3-butadienes have proven to be an important class of compounds.[1] Although the synthesis and reactivity of 2-azadienes is well established, they mainly focus on electron-rich[1,2] and electronically neutral 2-azadienes.[1,3] Probably owing to the lack of general methods for their synthesis, electron-poor 2-azadienes have received much less attention.[1,4] Phosphonylated 2-aza-1,3-butadienes represent an interesting class of such electron-poor 2-azadienes and may be useful intermediates for the synthesis of cyclic as well as acyclic α-aminophosphonate derivatives.[1] α-Aminophosphonates are promising bioactive compounds[5,6] since they mimic the transition states during peptide hydrolysis[6] and can be considered as surrogates for α-amino acids.[7] In fact, several α-aminophosphonic acids are reported to act as enzyme inhibitors,[8] antibacterial agents,[9] or neurotransmitters[10] and have been used as haptens for the generation of catalytic monoclonal antibodies.[11] Also, some aminoalkylbisphosphonic acid derivatives have gained importance as anti-inflammatory agents and can be used for the treatment of disorders in calcium metabolism.[12] Nevertheless, the

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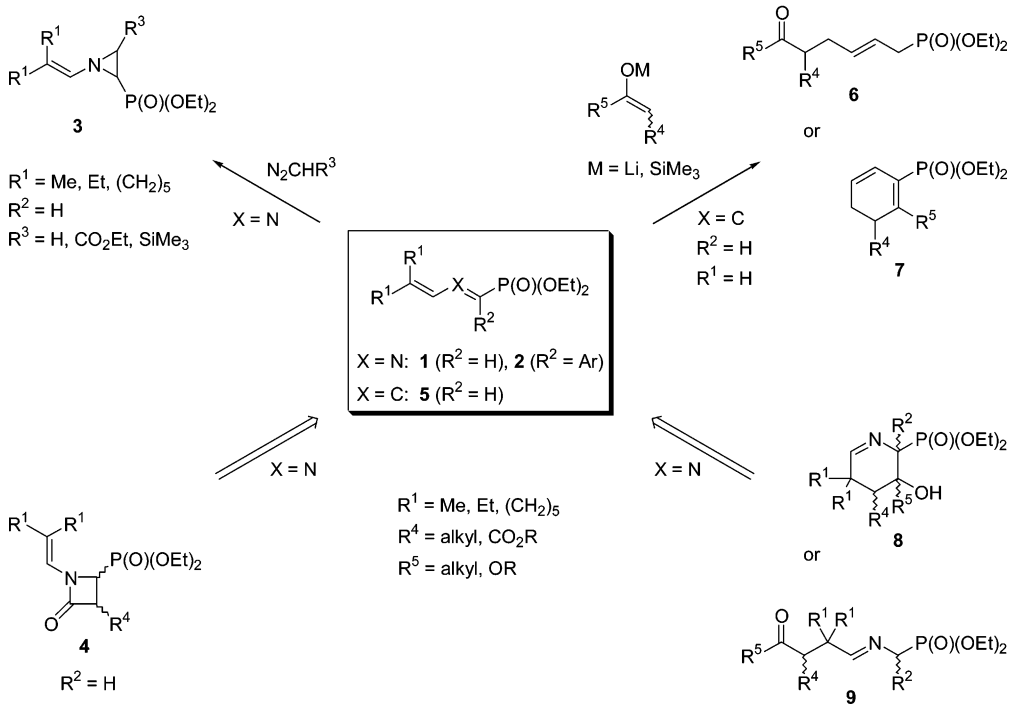
SCHEME 1. Retrosynthetic Analysis of Novel Amino Phosphonates from 1-Phosphono-2-azadienes 1 and 2



synthesis of phosphonylated 2-azadienes and its modification toward new α-aminophosphonates have been rarely reported in the literature.[13−15]

In connection with our interest in the synthesis of heterocyclic aminophosphonates, we recently evaluated the synthesis of 2-phosphonoaziridines **3** from 1-phosphono-2-azadienes **1** and **2**.[13] It was shown that nonaromatic 1-phosphono-2-azadienes **1** act as imines toward diazo compounds (Scheme 1). Hence, 1-phosphono-2-azadienes **1** could be useful compounds for the construction of phosphono β-lactams **4** using appropriate nucleophiles (Scheme 1). A lot of attention is still directed toward the synthesis of β-lactams because of their importance in the field of elastase inhibitors[16] and monobactam antibiotics.[17] Various phosphono β-lactams have also been prepared; however, these derivatives did not possess promising antibacterial properties.[18] On the other hand, 1,3-butadiene phosphonates **5** react with ketone[19a] and aldehyde[19b] enolates via 1,6-addition, leading to the corresponding alkenyl or cyclohexadienyl phosphonates **6** and **7**, respectively (Scheme 1). More recently, a diastereoselective addition of lithiated Schöllkopf's bislactim ether to 1,3-butadiene phosphonates was reported.[20] To the best of our knowledge, no Michael additions of this type have been applied to phosphonylated 2-azadienes, nor to 2-azadienes bearing another electron-withdrawing group at the 1-position. So, considering this reaction pattern, 1-phosphono-2-aza-1,3-butadienes **1** and **2** could lead to a new entry toward cyclic and/or acyclic α-aminophosphonates **8** and **9** (Scheme 1).

Moreover, reduction of the imine functionality of acyclic α-aminophosphonates **9** and subsequent ring closure would lead to new phosphonylated γ-lactams. Despite some promising exceptions,[21,22] γ-lactams generally exhibit only low antibacterial activity when compared with their β-lactam analogues.[23] Further, certain γ-lactam derivatives show antiviral activity against HIV-1[24] or act as cholesterol absorption inhibitors.[25] Phosphonylated γ-lactams are quite rarely reported in the literature,[26]

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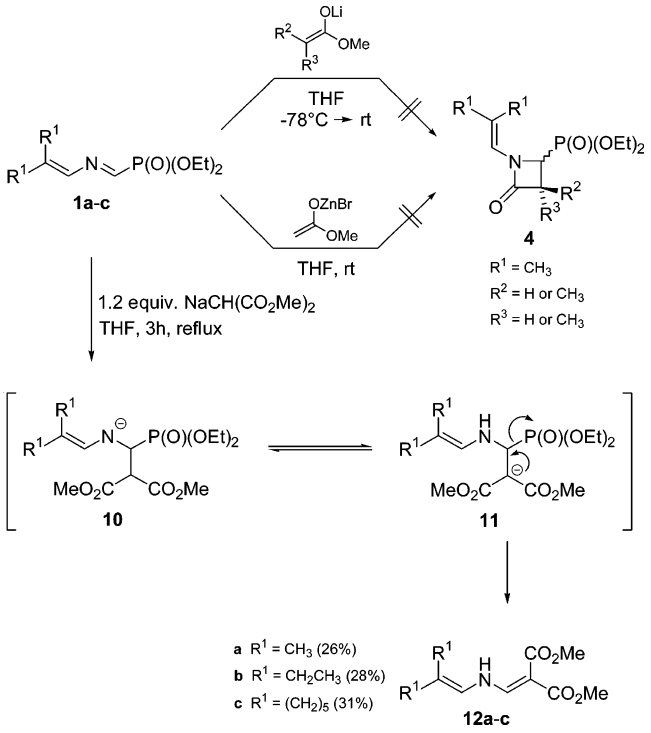
although the presence of a phosphonate functionality could render these compounds interesting properties associated with α-amino phosphonates.[5,6]

Results and Discussion

Addition of Sodium Malonate to 1-Phosphono-2-aza-1,3-dienes. To evaluate the preparation of phosphonylated β-lactams **4**, 1-phosphono-2-azadienes **1** were prepared according to a procedure recently reported by our group.[13] Different nucleophiles allowing the synthesis of the corresponding β-lactams via nucleophilic addition at the imine functionality were applied. Adding 1-phosphono-2-azadiene **1a** to the lithium enolate of methyl esters led to mixtures containing neither addition product nor the β-lactam **4** after workup (Scheme 2). Since β-lactams can be formed employing imines as electrophiles in Reformatsky reactions with α-halo esters,[27] 1-phosphono-2-azadiene **1a** was treated with the zinc enolate of methyl 2-bromoacetate (Scheme 2). However, the reaction did not furnish the expected β-lactam **4**, but a complex reaction mixture was formed.

Guided by the findings by Pudovik et al. concerning the nature of nucleophiles for successful addition to 1,3-butadiene phosphonates **5**,[19c] the less basic carbanion of methyl malonate was evaluated for addition to 1-phosphono-2-azadiene **1a**. The azadiene was added to 1.2 equiv of sodium malonate, which was prepared using sodium hydride as base. After workup, a liquid was isolated which could be purified by flash chromatography; however, elucidation of the structure did not confirm the formation of the corresponding phosphono β-lactam **4**. In fact, the addition of sodium malonate to 1-phosphono-2-azadiene **1a** was followed by an intramolecular proton shift, after which the phosphonate moiety was eliminated, furnishing bisenamine **12a** (Scheme 2). The reaction was accelerated when performed in refluxing THF (3 h instead of 24 h at room temperature) and was also

SCHEME 2. Addition of Sodium Malonate to 1-Phosphono-2-azadienes 1a−c



successfully employed for the preparation of bisenamines **12b** and **12c** (Scheme 2). Although all the crude reaction mixtures mainly contain the corresponding bisenamines **12** (>80%, estimated by ^{1}H NMR), the isolated yields of pure compounds were rather poor, possibly due to the instability of the enamine functionality. To avoid the intramolecular proton shift and direct the reaction toward ring closure, sodium 2-methylmalonate was applied as nucleophile. Unfortunately, at room temperature or in refluxing THF, only complex reaction mixtures were obtained after workup.

Addition of Sodium Malonate to 1-Aryl-1-phosphono-2-aza-1,3-dienes. Considering the lack of reactivity of 1-aryl-1-phosphono-2-aza-1,3-dienes **2** toward diazo compounds,[13a] enolate nucleophiles were not expected to add to the imine functionality of these derivatives. However, prompted by the reports of Darling and coworkers about 1,6-additions to 1,3-butadiene phosphonates **5**,[19a,b] 1-aryl-1-phosphono-2-azadienes **2** were thought to be susceptible to this type of Michael addition (Scheme 1). Since sodium malonate was an appropriate nucleophile for the addition to 1-phosphono-2-azadienes **1**, this enolate was chosen for an initial evaluation of the 1,6-addition. So, 1-phenyl-1-phosphono-2-azadiene **13** was added to 3 equiv of sodium malonate in THF, and the solution was heated to reflux temperature. Monitoring the reaction for 48 h by TLC clearly showed that no reaction took place and that the starting material was recovered (Scheme 3).

Next, 1-(4-bromophenyl)-1-phosphono-2-azadiene **14a** was subjected to the same reaction conditions. The presence of a bromine atom at the *para*-position of the phenyl ring was presumed to increase the polarization of the azadiene system, promoting attack at C-4 of the diene system. Indeed, after 48 h of reflux, a mixture was recovered containing addition product, i.e., imine **21a**,

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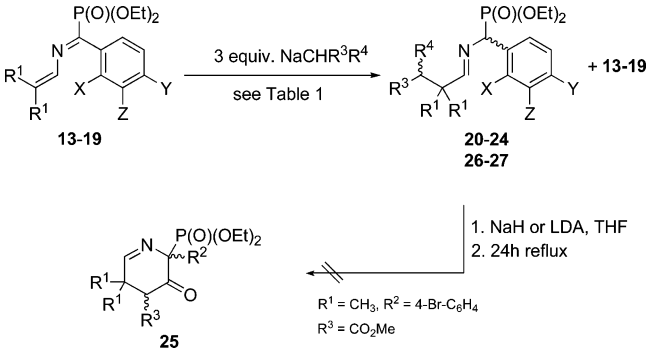
TABLE 1. Addition of Dimethyl Malonate and Malononitrile to 1-Aryl-1-phosphono-2-azadienes 13−20

azadiene **13−20**	R^1	X, Y, Z	R^3, R^4	product **21−29**, yield[a] (%)	azadiene **13−20** in crude mixture[c] (%)
13	CH_3	X = H, Y = H, Z = H	R^3, R^4 = CO_2Me	no reaction	100
14a	CH_3	X = H, Y = Br, Z = H	R^3, R^4 = CO_2Me	**21a**, 50 (69)	9
15	CH_3	X = Br, Y = H, Z = H	R^3, R^4 = CO_2Me	**22**, 51 (91)	6
16	CH_3	X = Cl, Y = H, Z = H	R^3, R^4 = CO_2Me	**23**, 45 (89)	7
17	CH_3	X = H, Y = F, Z = H	R^3, R^4 = CO_2Me	**24**, 49 (67)	6
18	CH_3	X = F, Y = H, Z = H	R^3, R^4 = CO_2Me	**25**, 47 (82)	5
19	CH_3	X = H, Y = H, Z = F	R^3, R^4 = CO_2Me	**26**, 44 (90)	1
20	CH_3	X = H, Y = OMe, Z = H	R^3, R^4 = CO_2Me	no reaction	100
14b	CH_2CH_3	X = H, Y = Br, Z = H	R^3, R^4 = CO_2Me	**21b**, 9[b]	91[b]
14c	$(CH_2)_5$	X = H, Y = Br, Z = H	R^3, R^4 = CO_2Me	no reaction	100
14a	CH_3	X = H, Y = Br, Z = H	R^3 = CO_2Me, R^4 = C(O)Me	no reaction	100
14a	CH_3	X = H, Y = Br, Z = H	R^3 = CO_2Me, R^4 = P(O)$(OEt)_2$	no reaction	100
14a	CH_3	X = H, Y = Br, Z = H	R^3, R^4 = CN	**28**, 53 (81)	<1
16	CH_3	X = Cl, Y = H, Z = H	R^3, R^4 = CN	**29**, 50 (79)	<1

[a] The crude yield is give in parentheses. [b] The amounts of addition product **21b** and azadiene **14b** were estimated from the ^{31}P NMR spectrum. [c] Estimated from the ^{31}P NMR spectra of the crude reaction mixtures.

SCHEME 3. Addition of Dimethyl Malonate and Malononitrile to 1-Aryl-1-phosphono-2-azadienes 13−20 (See Table 1)



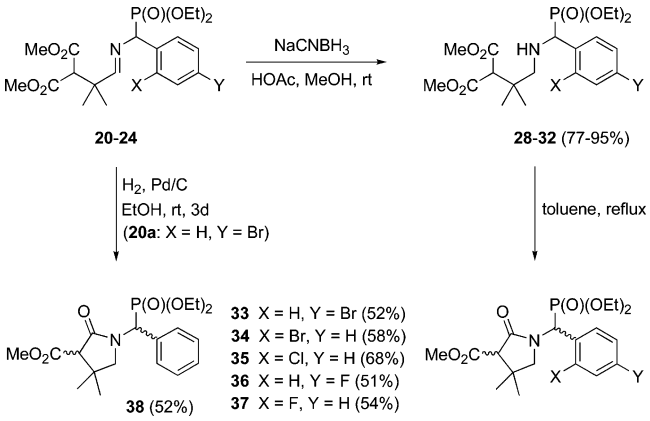
and 9% of the starting material **14a**. Prolonged heating (96 h) of the reaction mixture did not drive the reaction to completion, and moreover, no formation of ring-closed compound **27** was observed (Scheme 3). In an attempt to prepare cyclic imine **27**, addition product **21a** was purified (by means of flash chromatography) and treated with base. After 24 h of reflux, sodium hydride as well as LDA gave rise to the formation of a mixture of the acyclic imine **21a**, 1-phosphono-2-azadiene **14a**, and dimethyl malonate (Scheme 3).

To extend the reaction toward different derivatives and to confirm the necessity of an electron-withdrawing halogen atom on the phenyl substituent, several 1-aryl-1-phosphono-2-azadienes **15−20** were prepared[13a] and employed in the addition reaction (Scheme 3, Table 1). The reactions with azadienes bearing a halogenated phenyl substituent all result in a mixture of the corresponding imine **22−26** and a small amount of starting material (Table 1). On the other hand, reaction of sodium malonate with 1-(4-methoxyphenyl)-1-phosphono-2-azadiene **20** led to the recovery of starting material. This observation is in accordance with the decreased polarization of the azadiene due to the electron-donating nature of the methoxy group. Although also halogen atoms are mesomeric donating functionalities, they are considered as mainly electron-withdrawing when positioned on an aromatic ring. Indeed, the addition of sodium malonate to azadiene **19**, possessing a fluorine atom in the *meta*-position, was also successful. Hence, it was reasoned that the halogenated aromatic substituents on azadienes **14a−19** can be considered as electron-withdrawing functionalities and, consequently, induce attack at the 4-position of the diene system. All the imines were purified by flash chromatography and isolated in moderate yield (Table 1).

The dependence of the 1,6-addition on steric hindrance was examined by reacting 1-phosphono-2-azadienes **14b** and **14c** with sodium malonate (Scheme 3, Table 1). The addition is shown to be rather sensitive to steric hindrance, since after 4 days of reflux, azadiene **14b** gives rise to the formation of only 9% of addition product **21b**. Further, azadiene **14c** appears to be completely unreactive toward nucleophilic addition under these reaction conditions. Keeping the nature of sodium malonate in mind, some other nucleophiles were also evaluated for the addition to 1-(4-bromophenyl)-1-phosphono-2-azadiene **14a**. Triethyl phosphonoacetate and methyl acetoacetate were both deprotonated with sodium hydride in THF, after which azadiene **14a** was added. After 48 h of reflux, only starting material was isolated. Taking into account the sensitivity of the addition reaction to steric hindrance, the unsuccessful addition of triethyl phosphonoacetate could be explained by the larger dimensions of this nucleophile compared to dimethyl malonate. The reason for the observed unreactivity of acetoacetate toward azadienes **14a** is not clear. On the contrary, malononitrile cleanly adds to both 1-phosphono-2-azadiene **14a** and **16** when deprotonated with sodium hydride. The addition was complete after 24 h of reflux, and the crude reaction mixtures only contained traces of starting material (Table 1). In contrast to the imines **21a−26**, addition products **28** and **29** are rather unstable, especially when dried over magnesium sulfate after workup. Utilizing potassium carbonate as drying agent gave better results so that the imines could be isolated.

Preparation of Phosphonylated γ-Lactams from 1-Aryl-1-phosphono-2-aza-1,3-dienes. With imines **21a−25** in hand, it was decided to explore the synthesis of phosphonylated γ-lactams **35−40** (Scheme 4). Therefore, imines **21a−25** were reduced to the corresponding amines **30−34** using sodium cyanoborohydride in the presence of 1 equiv of glacial acetic acid. Subsequently, amines **30−34** were heated in refluxing toluene to induce ring closure to the corresponding γ-lactams **35−39** (Scheme 4). Reduction of imine **21a** with molecular

SCHEME 4. Synthesis of Phosphonylated γ-Lactams 35−40 from the Corresponding Imines 21a−25



hydrogen in the presence of a catalytic amount (0.1 equiv) of palladium on carbon immediately leads to the isolation of γ-lactam **40**. As a result, nonhalogenated phosphono γ-lactam **40** can be prepared despite the fact that the addition of sodium malonate to 1-phenyl-1-phosphono-2-azadiene **13** was not successful (Table 1).

Since the separation of imines **21a−25** from 1-phosphono-2-azadienes **14−19** by flash chromatography leads to some loss of product, the γ-lactam synthesis was performed starting from the crude mixtures obtained after the addition reaction. The presence of minor amounts of the starting azadienes did not negatively influence the reduction of the imines **21a−25** nor the ring closure of amines **30−34**. Following this procedure, γ-lactams **35−40** were prepared as equimolar mixtures of both diastereoisomers and obtained in good yield after purification by means of flash chromatography (Scheme 4). Several attempts were made to separate both diastereoisomers of the γ-lactams **35−40**, but unfortunately all efforts failed.

Conclusion

The study of the reactivity of 1-phosphono-2-aza-1,3-butadienes **1** and **13−20** toward enolate nucleophiles consolidates the concept that these 2-azadienes are interesting compounds for the synthesis of new cyclic and acyclic α-aminophosphonates. On one hand, non-aromatic-substituted 1-phosphono-2-azadienes **1** act as activated imines toward sodium malonate and diazo compounds,[13] leading to the formation of bisenamines **12** and aziridines, respectively. However, the synthesis of phosphonylated β-lactams **4** is obstructed by an intramolecular proton shift and the leaving group capacity of the phosphonate moiety. On the other hand, the polarization of 1-phosphono-2-azadienes is reversed when substituted with a halogenated phenyl group activating the 4-position of the diene system. These halogenated substrates allow a not yet reported Michael-type addition of malonates to 1-phosphono-2-azadienes. Finally, this reaction pattern offers a new entry to rarely reported phosphonylated γ-lactams **35−40** from 1-phosphono-2-azadienes **14a−18**.

Experimental Section

General Methods. Flash chromatography was performed on silica gel (0.035−0.070 mm). ^{1}H NMR spectra were recorded at 270 MHz. ^{13}C NMR and ^{31}P NMR experiments were acquired at 68 and 109 MHz, respectively. The relative proportions between two diastereoisomers were measured by integration of the ^{1}H peaks. Chemical shifts (δ) are reported in parts per million from the peak for TMS as an internal reference. Coupling constants (*J*) are given in hertz. IR spectra were recorded with an FT-IR spectrometer. Low-resolution mass spectra (MS) were obtained at 70 eV or using ES (4000 V). All solvents were dried extensively over sodium/benzophenone ketyl (THF, toluene) or used as such (absolute ethanol). The 1,6-addition experiments were performed under an inert nitrogen atmosphere.

General Procedure for the Preparation of Bisenamines 12a−c. In a flask of 25 mL, sodium hydride (1.2 mmol) was added to anhydrous THF (5 mL). The suspension was placed under a dry nitrogen atmosphere, and dimethyl malonate (1.2 mmol), dissolved in 5 mL of anhydrous THF, was added using a syringe. After 15 min of stirring at room temperature, the corresponding azadiene **1a−c** (2 mmol), dissolved in 5 mL of THF, was added to the reaction mixture using a syringe. Subsequently, the reaction mixture was heated to reflux temperature and stirred for 3 h. Silica was added to the reaction mixture, and the solvent was removed under reduced pressure. Purification by flash chromatography afforded bisenamines **12a−c** as white solids (yield 26−31%).

Data for dimethyl 2-{[(2-methyl-1-propenyl)amino]methylene}malonate (12a): ^{1}H NMR ($CDCl_3$) δ 1.74 (3H, d, *J* = 2.0 Hz, CH_3), 1.75 (3H, s, CH_3), 3.73 (3H, d, *J* = 1.3 Hz, OCH_3), 3.82 (3H, d, *J* = 1.6 Hz, OCH_3), 6.03 (1H, dd, *J* = 10.9 Hz, *J* = 1.3 Hz, CH), 8.02 (1H, d, *J* = 13.7 Hz, *J* = 1.1 Hz, CH), 10.83 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ 16.4, 21.9, 50.8, 51.1, 89.8, 118.6, 122.7, 154.4, 165.7, 169.3; IR (KBr) 3427, 1673, 1630, 1596 cm^{-1}; MS *m/z* 213 [M$^+$]; mp 105 °C; R_f(EtOAc/PET, 8/2) = 0.28. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33, H, 7.09. Found: C, 56.40, H, 7.17.

Data for dimethyl 2-{[(2-ethyl-1-butenyl)amino]methylene}malonate (12b): ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, t, *J* = 7.4 Hz, CH_3), 1.08 (3H, t, *J* = 7.7 Hz, CH_3), 2.08 (2H, qd, *J* = 7.2 Hz, *J* = 1.0 Hz, CH_2), 2.16 (2H, q, *J* = 7.5 Hz, CH_2), 3.74 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.98 (1H, d, *J* = 10.9 Hz, CH), 8.05 (1H, d, *J* = 13.5 Hz, CH), 10.88 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ 12.1, 12.6, 22.5, 26.6, 51.2, 51.5, 90.2, 121.8, 130.3, 154.9, 166.1, 169.6; IR (KBr) 3436, 1672, 1635, 1595 cm^{-1}; MS *m/z* 241 [M$^+$]; mp 53 °C; R_f(EtOAc/PET, 8/2) = 0.22. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73, H, 7.94. Found: C, 59.75, H, 7.91.

Data for dimethyl 2-{[(cyclohexylidenemethyl)amino]methylene}malonate (12c): ^{1}H NMR ($CDCl_3$) δ 1.58 (6H, s, CH_2), 2.10 (2H, s, CH_2), 2.21 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.00 (1H, d, *J* = 11.2 Hz, CH), 8.04 (1H, d, *J* = 13.9 Hz, CH), 10.88 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.9, 27.6, 28.1, 33.2, 51.2, 51.5, 90.0, 120.0, 127.1, 154.8, 166.0, 169.7; IR (KBr) 3435, 1677, 1629, 1596 cm^{-1}; MS *m/z* 253 [M$^+$]; mp = 129 °C; R_f(EtOAc/PET, 8/2) = 0.29. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64, H, 7.56. Found: C, 61.48, H, 7.67.

General Procedure for the Preparation of Imines 21a−26, 28, and 29. In a flask of 50 mL, sodium hydride (6 mmol) was dissolved in anhydrous THF (10 mL). The suspension was placed under a dry nitrogen atmosphere, and dimethyl malonate (6 mmol) (or malononitrile (4 mmol) for the preparation of imines **26−29**), dissolved in 10 mL of anhydrous THF, was added using a syringe. After 15 min of stirring at room temperature, the corresponding azadiene **13−19** (2 mmol), dissolved in 10 mL of THF, was added to the reaction mixture using a syringe. Subsequently, the reaction mixture was heated to reflux temperature and stirred for 48 h. The reaction mixture was poured into 20 mL of aqueous sodium bicarbonate (0.1 M) and extracted with diethyl ether (3 × 20 mL). The combined organic fractions were dried over magnesium sulfate (potassium carbonate was used for the synthesis of **28** and **29**). Next, the magnesium sulfate was filtered off, and the solvent was evaporated under reduced pressure, affording the crude reaction product as a yellow oil. Purifica-

tion by flash chromatography yielded imine **21a**−**26** (or **28** or **29** when malononitrile was used) in moderate yield (yield 49−56%).

Data for dimethyl 2-((2*E*)-2-{[(*E*)-(4-bromophenyl)(diethoxyphosphoryl)methyl]imino}-1,1-dimethylethyl)malonate (21a): ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 6.9 Hz, P(O)OCH_2CH_3), 1.25 (3H, t, J = 6.9 Hz, P(O)OCH_2CH_3), 1.31 (3H, s, CH_3), 1.32 (3H, s, CH_3), 3.61 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.82 (1H, s, CH), 4.00 (4H, m, P(O)OCH_2CH_3), 4.63 (1H, d, J_{HP} = 18.5 Hz, CHP), 7.36 (2H, dd, J = 8.6 Hz, J_{HP} = 2.1 Hz, CH), 7.46 (2H, d, J = 8.3 Hz, CH), 7.82 (1H, d, J_{HP} = 4.9 Hz, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.3, 16.4, 23.2, 23.9, 41.7, 52.1, 52.2, 58.1, 62.9 (d, J_{CP} = 7.3 Hz), 63.0 (d, J_{CP} = 8.6 Hz), 71.6 (d, J_{CP} = 151.3 Hz), 121.5 (d, J_{CP} = 4.9 Hz), 130.0 (2C, d, J_{CP} = 6.1 Hz), 131.2 (2C, d, J_{CP} = 2.4 Hz), 135.4 (d, J_{CP} = 7.3 Hz), 168.4, 168.5, 173.1 (d, J_{CP} = 14.7 Hz); ^{31}P NMR ($CDCl_3$) δ 19.40; IR (neat) 1756, 1738, 1733 cm^{-1}; MS *m/z* 508/506 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.24. Anal. Calcd for $C_{20}H_{29}BrNO_7P$: C, 47.44, H, 5.77. Found: C, 47.66, H, 5.62.

Data for dimethyl 2-((2*E*)-2-{[(*E*)-(2-bromophenyl)(diethoxyphosphoryl)methyl]imino}-1,1-dimethylethyl)malonate (22): ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.28 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.31 (6H, s, CH_3), 3.57 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.81 (1H, s, CH), 4.02 (4H, m, P(O)OCH_2CH_3), 5.27 (1H, d, J_{HP} = 18.7 Hz, CHP), 7.12 (1H, tt, J = 7.7 Hz, J = 1.8 Hz, CH), 7.32 (1H, t, J = 7.6 Hz, CH), 7.54 (1H, d, J = 8.0 Hz, CH), 7.83 (2H, m, CH, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.36 (d, J_{CP} = 4.6 Hz), 16.42 (d, J_{CP} = 4.6 Hz), 23.2, 23.7, 41.8, 52.0, 52.2, 57.9, 62.9 (d, J_{CP} = 8.1 Hz), 63.1 (d, J_{CP} = 6.9 Hz), 70.4 (d, J_{CP} = 154.6 Hz), 123.8 (d, J_{CP} = 8.1 Hz), 127.3 (d, J_{CP} = 2.3 Hz), 129.0 (d, J_{CP} = 2.3 Hz), 131.4 (d, J_{CP} = 4.6 Hz), 132.6, 135.5 (d, J_{CP} = 6.9 Hz), 168.3, 168.5, 173.3 (d, J_{CP} = 15.0 Hz); ^{31}P NMR ($CDCl_3$) δ 19.97; IR (neat) 1758, 1735 cm^{-1}; MS *m/z* 508/506 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.21. Anal. Calcd for $C_{20}H_{29}BrNO_7P$: C, 47.44, H, 5.77. Found: C, 47.64, H, 5.66.

Data for dimethyl 2-((2*E*)-2-{[(*E*)-(2-chlorophenyl)(diethoxyphosphoryl)methyl]imino}-1,1-dimethylethyl)malonate (23): ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.27 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.31 (6H, s, CH_3), 3.57 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.82 (1H, s, CH), 4.05 (4H, m, P(O)OCH_2CH_3), 5.28 (1H, d, J_{HP} = 18.7 Hz, CHP), 7.20 (1H, t, J = 7.4 Hz, CH), 7.28 (1H, m, CH), 7.31 (1H, d, J = 8.0 Hz, CH), 7.83 (2H, m, CH, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.4 (d, J_{CP} = 3.5 Hz), 16.5 (d, J_{CP} = 3.5 Hz), 23.2, 23.9, 41.8, 52.1, 52.3, 58.0, 63.0 (d, J_{CP} = 6.9 Hz), 63.1 (d, J_{CP} = 6.9 Hz), 67.9 (d, J_{CP} = 154.6 Hz), 126.8 (d, J_{CP} = 3.5 Hz), 128.7 (d, J_{CP} = 3.5 Hz), 129.3, 131.1 (d, J_{CP} = 4.6 Hz), 133.3 (d, J_{CP} = 8.1 Hz), 133.9 (d, J_{CP} = 6.9 Hz), 168.5, 168.7, 173.5 (d, J_{CP} = 15.0 Hz); ^{31}P NMR ($CDCl_3$) δ 19.94; IR (neat) 1758, 1735 cm^{-1}; MS *m/z* 464/462 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.24. Anal. Calcd for $C_{20}H_{29}ClNO_7P$: C, 52.01, H, 6.33. Found: C, 52.35, H, 6.40.

Data for dimethyl 2-((2*E*)-2-{[(*E*)-(diethoxyphosphoryl)(4-fluorophenyl)methyl]imino}-1,1-dimethylethyl)malonate (24): ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.24 (3H, t, J = 6.8 Hz, P(O)OCH_2CH_3), 1.32 (6H, s, CH_3), 3.59 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.83 (1H, s, CH), 3.99 (2H, quintet, J = 7.4 Hz, P(O)OCH_2CH_3), 4.00 (2H, quintet, J = 7.3 Hz, P(O)OCH_2CH_3), 4.65 (1H, d, J_{HP} = 17.8 Hz, CHP), 7.02 (2H, t, J = 8.6 Hz, CH), 7.45 (2H, m, CH), 7.81 (1H, d, J_{HP} = 4.6 Hz, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.3, 16.4, 23.3, 23.9, 41.7, 52.1, 52.3, 58.1, 62.9 (d, J_{CP} = 7.3 Hz), 63.0 (d, J_{CP} = 7.4 Hz), 71.5 (d, J_{CP} = 153.8 Hz), 115.1 (2C, dd, J_{CF} = 21.9 Hz, J_{CP} = 2.4 Hz), 129.9 (2C, t, J = 7.3 Hz), 131.9 (t, J_{CP} = 3.7 Hz), 162.3 (dd, J_{CF} = 246.6 Hz, J_{CP} = 3.7 Hz), 168.5, 168.6, 172.8 (d, J_{CP} = 15.9 Hz; ^{31}P NMR ($CDCl_3$) δ 19.87 (d, J_{PF} = 5.4 Hz); IR (neat) 1756, 1738, 1732 cm^{-1}; MS *m/z* 446 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.17. Anal. Calcd for $C_{20}H_{29}FNO_7P$: C, 53.93, H, 6.56. Found: C, 53.58, H, 6.71.

Data for dimethyl 2-((2*E*)-2-{[(*E*)-(diethoxyphosphoryl)(2-fluorophenyl)methyl]imino}-1,1-dimethylethyl)-malonate (25): ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.26 (3H, t, J = 7.0 Hz, P(O)OCH_2CH_3), 1.31 (3H, s, CH_3), 1.32 (3H, s, CH_3), 3.57 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.83 (1H, s, CH), 4.03 (4H, m, P(O)OCH_2CH_3), 5.07 (1H, d, J_{HP} = 18.4 Hz, CHP), 7.03 (1H, t, J = 9.1 Hz, CH), 7.14 (1H, t, J = 7.4 Hz, CH), 7.24 (1H, m, CH), 7.73 (1H, tt, J = 7.4 Hz, J = 2.0 Hz, CH), 7.85 (1H, d, J_{HP} = 4.4 Hz, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.4, 16.5, 23.2, 24.0, 41.9, 52.2, 52.4, 58.2, 63.0 (d, J_{CP} = 6.9 Hz), 63.2 (d, J_{CP} = 6.9 Hz), 64.2 (d, J_{CP} = 152.3 Hz), 115.1 (dd, J = 21.9 Hz, J = 2.3 Hz), 123.7 (dd, J = 13.3 Hz, J = 7.5 Hz), 124.1 (t, J = 3.5 Hz), 129.1 (dd, J = 8.6 Hz, J = 2.9 Hz), 130.5 (t, J = 3.5 Hz), 159.9 (dd, J_{CF} = 246.3 Hz, J_{CP} = 6.3 Hz), 168.5, 168.7, 173.6 (d, J_{CP} = 15.0 Hz); ^{31}P NMR ($CDCl_3$) δ 19.85 (d, J_{PF} = 5.9 Hz); IR (neat) 1759, 1736 cm^{-1}; MS *m/z* 446 [M + H$^+$]; R_f(EtOAc/PET, 4/6) = 0.13. Anal. Calcd. for $C_{20}H_{29}FNO_7P$: C, 53.93, H, 6.56. Found: C, 54.26, H, 6.69.

Data for dimethyl 2-((2*E*)-2-{[(*E*)-(diethoxyphosphoryl)(3-fluorophenyl)methyl]imino}-1,1-dimethylethyl)-malonate (26): ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.0 Hz, P(O)OCH_2CH_3), 1.26 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.32 (3H, s, CH_3), 1.34 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.86 (1H, s, CH), 4.05 (4H, m, P(O)OCH_2CH_3), 4.67 (1H, d, J_{HP} = 18.4 Hz, CHP), 6.96 (1H, t, J = 8.0 Hz, CH), 7.29 (3H, m, CH), 7.82 (1H, d, J_{HP} = 4.7 Hz, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.4, 16.5, 23.1, 24.2, 41.8, 52.2, 52.4, 58.1, 63.1 (d, J_{CP} = 8.1 Hz), 63.2 (d, J_{CP} = 6.9 Hz), 71.9 (d, J_{CP} = 151.1 Hz), 114.5 (dd, J = 21.3 Hz, J = 2.9 Hz), 115.3 (dd, J = 23.1 Hz, J = 5.8 Hz), 124.0 (dd, J = 5.8 Hz, J = 2.3 Hz), 129.6 (dd, J = 8.1 Hz, J = 3.5 Hz), 138.8 (t, J = 7.5 Hz), 162.7 (dd, J_{CF} = 245.7 Hz, J_{CP} = 3.5 Hz), 168.6, 168.7, 173.2 (d, J_{CP} = 15.0 Hz); ^{31}P NMR ($CDCl_3$) δ 19.68 (d, J_{PF} = 2.2 Hz); IR (neat) 1758, 1735 cm^{-1}; MS *m/z* 446 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.22. Anal. Calcd for $C_{20}H_{29}FNO_7P$: C, 53.93, H, 6.56. Found: C, 54.23 H, 6.70.

Data for diethyl (4-bromophenyl){[(*E*)-3,3-dicyano-2,2-dimethylpropylidene]amino}methylphosphonate (28): ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.0 Hz, P(O)OCH_2CH_3), 1.25 (3H, t, J = 7.0 Hz, P(O)OCH_2CH_3), 1.41 (3H, s, CH_3), 1.44 (3H, s, CH_3), 4.01 (4H, m, P(O)OCH_2CH_3), 4.26 (1H, s, CH), 4.72 (1H, d, J_{HP} = 19.3 Hz, CHP), 7.42 (2H, dd, J = 8.5 Hz, J_{HP} = 2.2 Hz, CH), 7.50 (2H, d, J = 8.3 Hz, CH), 7.69 (1H, d, J_{HP} = 4.9 Hz, HC=N); ^{13}C NMR ($CDCl_3$) δ 16.4, 16.5, 22.7, 23.1, 31.4, 43.5, 63.3 (d, J_{CP} = 4.6 Hz), 63.4 (d, J_{CP} = 6.9 Hz), 71.3 (d, J_{CP} = 150.0 Hz), 112.02, 112.06, 122.2 (d, J_{CP} = 4.6 Hz), 129.9 (2C, d, J_{CP} = 5.8 Hz), 131.7 (2C, d, J_{CP} = 2.3 Hz), 134.1 (d, J_{CP} = 8.1 Hz), 167.9 (d, J_{CP} = 15.0 Hz); ^{31}P NMR ($CDCl_3$) δ 18.56; IR (neat) 2253, 2213, 1665 cm^{-1}; MS *m/z* 440/442 [M + H$^+$]; R_f(EtOAc/PET, 7/3) = 0.31. Anal. Calcd for $C_{18}H_{23}BrN_3O_3P$: C, 49.10, H, 5.27. Found: C, 48.97, H, 5.39.

Data for diethyl (2-chlorophenyl){[(*E*)-3,3-dicyano-2,2-dimethylpropylidene]amino}methylphosphonate (29): ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.1 Hz, P(O)OCH_2CH_3), 1.28 (3H, t, J = 7.0 Hz, P(O)OCH_2CH_3), 1.40 (3H, s, CH_3), 1.44 (3H, s, CH_3), 4.04 (4H, m, P(O)OCH_2CH_3), 4.27 (1H, s, CH), 5.37 (1H, d, J_{HP} = 19.5 Hz, CHP), 7.24 (1H, tt, J = 7.4 Hz, J = 1.9 Hz, CH), 7.32 (1H, d, J = 7.7 Hz, CH), 7.38 (1H, d, J = 8.5 Hz, CH), 7.74 (1H, d, J_{HP} = 4.7 Hz, HC=N), 7.90 (1H, dt, J = 7.7 Hz, J = 2.0 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 16.4 (d, J_{CP} = 4.6 Hz), 16.5 (d, J_{CP} = 5.8 Hz), 22.8, 23.0, 31.4, 43.5, 63.3 (d, J_{CP} = 6.9 Hz), 63.5 (d, J_{CP} = 6.9 Hz), 67.2 (d, J_{CP} = 153.4 Hz), 112.1 (2C), 127.2, 129.3, 129.5, 131.1 (d, J_{CP} = 4.6 Hz), 132.8 (d, J_{CP} = 8.1 Hz), 133.3 (d, J_{CP} = 6.9 Hz), 168.3 (d, J_{CP} = 13.8 Hz); ^{31}P NMR ($CDCl_3$) δ 18.98; IR (neat) 2254, 2200, 1668 cm^{-1}; MS *m/z* 398/396 [M + H$^+$]; R_f(EtOAc/PET, 6/4) = 0.38. Anal. Calcd for $C_{18}H_{23}ClN_3O_3P$: C, 54.62, H, 5.86. Found: C, 54.83, H, 5.75.

General Procedure for the Preparation of Amines 30−34. In a flask of 25 mL, imine **21a**−**25** (2 mmol) and glacial acetic acid (2.2 mmol) were dissolved in 10 mL of anhydrous methanol. The reaction mixture was stirred at room temperature, and sodium cyanoborohydride (2.1 mmol) was added

portionwise. The reaction mixture was protected from moisture by a calcium chloride tube and stirred for 12 h. To the reaction mixture were added 10 mL of aqueous sodium bicarbonate (0.1 M) and 20 mL of diethyl ether. The organic phase was separated from the water phase and washed with 2 × 10 mL of aqueous sodium bicarbonate (0.1 M). The organic fraction was dried over magnesium sulfate. Next, the magnesium sulfate was filtered off, and the solvent was evaporated under reduced pressure, affording the crude reaction product as a yellow oil with high purity (>98%). Purification by flash chromatography yielded amine **30**−**34** in good yield (77−95%).

Data for dimethyl 2-(2-{[(4-bromophenyl)(diethoxyphosphoryl)methyl]amino}-1,1-dimethylethyl)malonate (30): ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.16 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.30 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.71 (1H, br s, NH), 2.42 (1H, d, J = 10.9 Hz, CH_2), 2.48 (1H, d, J = 10.7 Hz, CH_2), 3.65 (3H, s, OCH_3), 3.69 (1H, s, CH), 3.71 (3H, s, OCH_3), 3.89 (1H, d, J_{HP} = 19.8 Hz, CHP), 3.90 (2H, m, P(O)OCH_2CH$_3$), 4.12 (2H, quintet, J = 7.3 Hz, P(O)OCH_2CH$_3$), 7.26 (2H, dd, J = 8.6 Hz, J_{HP} = 2.3 Hz, CH), 7.47 (2H, d, J = 8.3 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J_{CP} = 6.1 Hz), 16.5 (d, J_{CP} = 6.1 Hz), 23.6, 23.7, 37.5, 51.9, 52.0, 56.5, 57.5 (d, J_{CP} = 15.9 Hz), 61.3 (d, J_{CP} = 152.6 Hz), 62.7 (d, J_{CP} = 6.1 Hz), 63.0 (d, J_{CP} = 7.3 Hz), 121.7 (d, J_{CP} = 3.6 Hz), 130.1 (2C, d, J_{CP} = 6.1 Hz), 131.5 (2C), 135.5 (d, J_{CP} = 2.5 Hz), 168.8, 168.9; ^{31}P NMR ($CDCl_3$) δ 22.75; IR (neat) 3318, 1755, 1732 cm^{-1}; MS *m/z* 510/508 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.22. Anal. Calcd for $C_{20}H_{31}BrNO_7P$: C, 47.25, H, 6.15. Found: C, 47.43, H, 6.08.

Data for dimethyl 2-(2-{[(2-bromophenyl)(diethoxyphosphoryl)methyl]amino}-1,1-dimethylethyl)malonate (31): ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.08 (3H, t, J = 7.0 Hz, P(O)OCH$_2$CH_3), 1.36 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.72 (1H, br s, NH), 2.39 (1H, d, J = 12.4 Hz, CH_2), 2.46 (1H, d, J = 12.6 Hz, CH_2), 3.65 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.73 (1H, s, CH), 3.74 (1H, m, P(O)OCH_2-CH$_3$), 3.89 (1H, m, P(O)OCH_2CH$_3$), 4.23 (2H, m, P(O)OCH_2-CH$_3$), 4.62 (1H, d, J_{HP} = 22.3 Hz, CHP), 7.15 (1H, tt, J = 7.1 Hz, J = 1.6 Hz, CH), 7.35 (1H, t, J = 7.3 Hz, CH), 7.57 (2H, m, CH); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J_{CP} = 5.8 Hz), 16.5 (d, J_{CP} = 6.9 Hz), 23.6, 23.7, 37.7, 51.98, 52.04, 56.4, 57.3 (d, J_{CP} = 16.1 Hz), 59.8 (d, J_{CP} = 154.6 Hz), 62.8 (d, J_{CP} = 6.9 Hz, 63.2 (d, J_{CP} = 6.9 Hz), 125.3 (d, J_{CP} = 9.2 Hz), 127.8 (d, J_{CP} = 3.5 Hz), 129.2 (d, J_{CP} = 2.3 Hz), 129.4 (d, J_{CP} = 3.5 Hz), 132.8, 136.3, 168.9, 169.0; ^{31}P NMR ($CDCl_3$) δ 23.21; IR (neat) 3312, 1755, 1733 cm^{-1}; MS *m/z* 510/508 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.30. Anal. Calcd for $C_{20}H_{31}BrNO_7P$: C, 47.25, H, 6.15. Found: C, 47.28, H, 6.13.

Data for dimethyl 2-(2-{[(2-chlorophenyl)(diethoxyphosphoryl)methyl]amino}-1,1-dimethylethyl)malonate (32): ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.09 (3H, t, J = 7.0 Hz, P(O)OCH$_2$CH_3), 1.36 (3H, t, J = 7.0 Hz, P(O)OCH$_2$CH_3), 2.08 (1H, br s, NH), 2.40 (1H, d, J = 12.6 Hz, CH_2), 2.47 (1H, d, J = 12.4 Hz, CH_2), 3.66 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.73 (1H, s, CH), 3.76 (1H, m, P(O)OCH_2-CH$_3$), 3.91 (1H, m, P(O)OCH_2CH$_3$), 4.24 (2H, m, P(O)OCH_2-CH$_3$), 4.63 (1H, d, J_{HP} = 22.3 Hz, CHP), 7.23 (1H, t, J = 7.5 Hz, CH), 7.31 (1H, m, CH), 7.37 (1H, d, J = 7.8 Hz, CH), 7.60 (1H, d, J = 7.7 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J_{CP} = 5.8 Hz), 16.6 (d, J_{CP} = 5.8 Hz), 23.6, 23.7, 37.8, 52.06, 52.09, 56.5, 57.1 (d, J_{CP} = 155.8 Hz), 57.5 (d, J_{CP} = 16.1 Hz), 62.8 (d, J_{CP} = 6.9 Hz), 63.3 (d, J_{CP} = 6.9 Hz), 127.2 (d, J_{CP} = 2.3 Hz), 128.9 (d, J_{CP} = 2.3 Hz), 129.3 (d, J_{CP} = 3.5 Hz), 129.5, 134.5, 134.6, 169.0 (2C); ^{31}P NMR ($CDCl_3$) δ 23.22; IR (neat) 3311, 1755, 1732 cm^{-1}; MS *m/z* 466/464 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.33. Anal. Calcd for $C_{20}H_{31}ClNO_7P$: C, 51.78, H, 6.74. Found: C, 51.79, H, 6.71.

Data for dimethyl 2-(2-{[(diethoxyphosphoryl)(4-fluorophenyl)methyl]amino}-1,1-dimethylethyl)malonate (33): ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.14 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.31 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.72 (1H, br s, NH), 2.41 (1H, d, J = 12.2 Hz, CH_2), 2.48 (1H, d, J = 12.5 Hz, CH_2), 3.65 (3H, s, OCH_3), 3.70 (1H, s, CH), 3.71 (3H, s, OCH_3), 3.88 (2H, m, P(O)OCH_2CH$_3$), 3.91 (1H, d, J_{HP} = 20.8 Hz, CHP), 4.12 (2H, quintet, J = 7.2 Hz, P(O)OCH_2CH$_3$), 7.03 (2H, t, J = 8.6 Hz, CH), 7.35 (2H, m, CH); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J_{CP} = 4.9 Hz), 16.5 (d, J_{CP} = 4.9 Hz), 23.6, 23.8, 37.6, 51.98, 52.04, 56.6, 57.5 (d, J_{CP} = 17.1 Hz), 61.2 (d, J_{CP} = 152.6 Hz), 62.7 (d, J_{CP} = 7.3 Hz), 63.0 (d, J_{CP} = 7.3 Hz$_3$), 115.3 (2C, d, J_{CF} = 23.2 Hz), 130.1 (2C, t, J = 7.3 Hz), 132.1 (t, J = 3.0 Hz), 162.4 (dd, J_{CF} = 246.0 Hz, J_{CP} = 3.1 Hz), 168.9, 169.0; ^{31}P NMR ($CDCl_3$) δ 23.32 (d, J_{PF} = 4.0 Hz); IR (neat) 3318, 1755, 1732 cm^{-1}; MS *m/z* 448 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.16. Anal. Calcd for $C_{20}H_{31}FNO_7P$: C, 53.69, H, 6.98. Found: C, 53.91, H, 7.89.

Data for dimethyl 2-(2-{[(diethoxyphosphoryl)(2-fluorophenyl)methyl]amino}-1,1-dimethylethyl)malonate (34): ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.11 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.34 (3H, t, J = 7.0 Hz, P(O)OCH$_2$CH_3), 2.01 (1H, br s, NH), 2.42 (1H, d, J = 12.4 Hz, CH_2), 2.51 (1H, d, J = 12.6 Hz, CH_2), 3.66 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.73 (1H, s, CH), 3.82 (1H, m, P(O)OCH_2CH$_3$), 3.95 (1H, m, P(O)OCH_2CH$_3$), 4.21 (2H, quintet, J = 7.0 Hz, P(O)OCH_2CH$_3$), 4.37 (1H, d, J_{HP} = 22.0 Hz, CHP), 7.04 (1H, t, J = 9.0 Hz, CH), 7.17 (1H, t, J = 7.1 Hz, CH), 7.27 (1H, m, CH), 7.51 (1H, tt, J = 7.4 Hz, J = 1.9 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J_{CP} = 5.8 Hz), 16.5 (d, J_{CP} = 5.8 Hz), 23.6, 23.7, 37.8, 52.00, 52.03, 53.8 (d, J_{CP} = 156.9 Hz), 56.5, 57.7 (d, J_{CP} = 16.1 Hz), 62.7 (d, J_{CP} = 6.9 Hz), 63.2 (d, J_{CP} = 6.9 Hz), 115.3 (d, J_{CP} = 20.8 Hz), 123.9 (d, J = 13.8 Hz), 124.4, 129.2 (d, J = 3.5 Hz), 129.3 (d, J = 2.3 Hz), 161.0 (dd, J_{CF} = 245.7 Hz, J_{CP} = 6.9 Hz), 169.0 (2C); ^{31}P NMR ($CDCl_3$) δ 23.09 (d, J_{PF} = 5.9 Hz); IR (neat) 3311, 1755, 1733 cm^{-1}; MS *m/z* 448 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.26. Anal. Calcd for $C_{20}H_{31}FNO_7P$: C, 53.69, H, 6.98. Found: C, 53.71, H, 6.99.

General Procedure for the Preparation of γ-Lactams 35−39. In a flask of 25 mL, amine **30**−**34** (1 mmol) was dissolved in 10 mL of anhydrous toluene and was heated under reflux. The reaction mixture was protected from moisture by a calcium chloride tube on top of the condenser. The reaction was followed by ^{31}P NMR, taking samples out of the reaction mixture. When ring closure was observed to be complete (the required reaction time is mentioned with the spectral data for each derivative), the solvent was evaporated under reduced pressure, affording the crude γ-lactam **35**−**39** as a yellow oil. Purification by flash chromatography yielded the pure lactam in moderate yield (51−68%).

Data for methyl 1-[(4-bromophenyl)(diethoxyphosphoryl)methyl]-4,4-dimethyl-2-oxo-3-pyrrolidinecarboxylate (35): synthesized according to the general procedure applying 2 days of reflux; ^{1}H NMR ($CDCl_3$) δ 0.99 (6H, s, 2 × CH_3), 1.10 (3H, s, CH_3), 1.17 (3H, t, J = 7.2 Hz, P(O)OCH$_2$CH_3), 1.19 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.27 (3H, s, CH_3), 1.34 (3H, t, J = 7.3 Hz, P(O)OCH$_2$CH_3), 1.37 (3H, t, J = 7.3 Hz, P(O)OCH$_2$CH_3), 2.96 (1H, d, J = 9.9 Hz, CH_2), 3.06 (1H, s, CH), 3.08 (2H, m, CH, CH_2), 3.53 (1H, d, J = 9.6 Hz, CH_2), 3.63 (3H, s, OCH_3), 3.70 (1H, d, J = 9.9 Hz, CH_2), 3.74 (3H, s, OCH_3), 4.03 (4H, m, 2 × P(O)OCH_2CH$_3$), 4.20 (4H, m, 2 × P(O)-OCH_2CH$_3$), 5.70 (1H, d, J_{HP} = 21.1 Hz, CHP), 5.73 (1H, d, J_{HP} = 21.1 Hz, CHP), 7.50 (8H, d, J = 2.6 Hz, 8 × CH); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.2 (d, J_{CP} = 3.7 Hz), 16.4 (d, J_{CP} = 2.4 Hz), 16.5 (d, J_{CP} = 2.4 Hz), 22.4, 22.7, 27.8, 28.5, 36.9, 37.2, 51.0 (d, J_{CP} = 159.9 Hz), 51.1 (d, J_{CP} = 159.9 Hz), 52.0 (2C), 56.4, 56.7, 59.7, 59.8, 62.7 (d, J_{CP} = 7.4 Hz), 63.0 (d, J_{CP} = 6.1 Hz), 63.1 (d, J_{CP} = 7.4 Hz), 63.2 (d, J_{CP} = 6.1 Hz), 122.8, 122.9, 131.2 (d, J_{CP} = 3.6 Hz), 131.4 (2C, d, J_{CP} = 8.5 Hz), 131.5 (2C, d, J_{CP} = 8.6 Hz), 131.8 (d, J_{CP} = 3.6 Hz), 131.9 (2C), 132.0 (2C), 168.7, 168.9, 169.7 (d, J_{CP} = 6.1 Hz), 170.2 (d, J_{CP} = 6.1 Hz); ^{31}P NMR ($CDCl_3$) δ 18.65, 19.32; IR (neat) 1738, 1732, 1704, 1694 cm^{-1}; MS *m/z* 478/476 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.17. Anal. Calcd for $C_{19}H_{27}BrNO_6P$: C, 47.91, H, 5.71. Found: C, 47.83, H, 5.79.

Data for methyl 1-[(2-bromophenyl)(diethoxyphosphoryl)methyl]-4,4-dimethyl-2-oxo-3-pyrrolidinecarbox-

ylate (36): synthesized according to the general procedure applying 6 days of reflux; ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.17 (6H, t, J = 7.1 Hz, 2 × P(O)OCH$_2$CH_3), 1.27 (3H, s, CH_3), 1.38 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.39 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 2.74 (1H, d, J = 9.6 Hz, CH_2), 2.92 (1H, d, J = 9.2 Hz, CH_2), 3.08 (1H, d, J = 2.6 Hz, CH), 3.11 (1H, s, CH), 3.52 (1H, d, J = 9.2 Hz, CH_2), 3.64 (3H, s, OCH_3), 3.65 (1H, d, J = 9.6 Hz, CH_2), 3.74 (3H, s, OCH_3), 4.07 (4H, m, 2 × P(O)OCH_2CH$_3$), 4.26 (4H, m, 2 × P(O)OCH_2CH$_3$), 6.11 (1H, d, J_{HP} = 20.5 Hz, CHP), 6.17 (1H, d, J_{HP} = 20.5 Hz, CHP), 7.22 (2H, td, J = 7.5 Hz, J = 1.5 Hz, 2 × CH), 7.35 (2H, t, J = 7.6 Hz, 2 × CH), 7.65 (2H, t, J = 7.0 Hz, 2 × CH), 8.06 (2H, t, J = 7.6 Hz, 2 × CH); ^{13}C NMR ($CDCl_3$) δ 16.1 (2C, d, J_{CP} = 3.6 Hz), 16.5 (2C, d, J_{CP} = 4.9 Hz), 22.5, 22.8, 28.0, 28.5, 37.0, 37.1, 51.4 (d, J_{CP} = 161.1 Hz), 51.4 (d, J_{CP} = 161.1 Hz), 51.9 (2C), 56.7 (2C), 59.7, 60.1, 62.9 (d, J_{CP} = 7.3 Hz), 63.0 (d, J_{CP} = 6.1 Hz), 63.2 (2C, d, J_{CP} = 7.3 Hz), 125.7 (d, J_{CP} = 14.6 Hz), 126.0 (d, J_{CP} = 14.6 Hz), 127.3, 127.4, 130.3 (2C), 131.7 (d, J_{CP} = 6.1 Hz), 131.8 (2C, d, J_{CP} = 3.6 Hz), 132.0 (d, J_{CP} = 6.1 Hz), 133.6 (2C), 168.7, 168.8, 169.0 (d, J_{CP} = 2.4 Hz), 169.2 (d, J_{CP} = 3.7 Hz); ^{31}P NMR ($CDCl_3$) δ 19.07, 19.58; IR (neat) 1739, 1704, 1699 cm^{-1}; MS *m/z* 478/476 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.16. Anal. Calcd for $C_{19}H_{27}BrNO_6P$: C, 47.91, H, 5.71. Found: C, 47.79, H, 5.80.

Data for methyl 1-[(2-chlorophenyl)(diethoxyphosphoryl)methyl]-4,4-dimethyl-2-oxo-3-pyrrolidinecarboxylate (37): synthesized according to the general procedure applying 9 days of reflux; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.17 (6H, t, J = 6.9 Hz, 2 × P(O)OCH$_2$CH_3), 1.27 (3H, s, CH_3), 1.38 (3H, t, J = 7.1 Hz, P(O)OCH$_2$CH_3), 1.39 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 2.74 (1H, d, J = 9.6 Hz, CH_2), 2.92 (1H, d, J = 9.2 Hz, CH_2), 3.07 (1H, d, J = 2.6 Hz, CH), 3.10 (1H, s, CH), 3.52 (1H, d, J = 9.2 Hz, CH_2), 3.64 (3H, s, OCH_3), 3.65 (1H, d, J = 9.6 Hz, CH_2), 3.74 (3H, s, OCH_3), 4.05 (4H, m, 2 × P(O)OCH_2CH$_3$), 4.25 (4H, m, 2 × P(O)OCH_2CH$_3$), 6.16 (1H, d, J_{HP} = 20.8 Hz, CHP), 6.20 (1H, d, J_{HP} = 20.5 Hz, CHP), 7.31 (4H, m, 4 × CH), 7.45 (2H, m, 2 × CH), 8.05 (2H, m, 2 × CH); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, J_{CP} = 2.4 Hz), 16.2 (d, J_{CP} = 2.5 Hz), 16.4, 16.5, 22.4, 22.7, 27.9, 28.5, 36.9, 37.1, 48.6 (d, J_{CP} = 161.1 Hz), 48.7 (d, J_{CP} = 162.3 Hz), 51.7 (2C), 56.7 (2C), 59.8, 60.1, 62.8 (d, J_{CP} = 7.3 Hz), 62.9 (d, J_{CP} = 7.3 Hz), 63.1 (d, J_{CP} = 7.3 Hz), 63.2 (d, J_{CP} = 7.3 Hz), 126.7, 126.8, 130.2 (6C), 131.5 (d, J_{CP} = 3.6 Hz), 131.7 (d, J_{CP} = 3.7 Hz), 135.2 (d, J_{CP} = 13.5 Hz), 135.5 (d, J_{CP} = 13.4 Hz), 168.7, 168.8, 169.0 (d, J_{CP} = 3.7 Hz), 169.3 (d, J_{CP} = 3.6 Hz); ^{31}P NMR ($CDCl_3$) δ 18.97, 19.52; IR (neat) 1739, 1703, 1700 cm^{-1}; MS *m/z* 434/432 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.11. Anal. Calcd for $C_{19}H_{27}ClNO_6P$: C, 52.84, H, 6.30. Found: C, 52.80, H, 6.35.

Data for methyl 1-[(diethoxyphosphoryl)(4-fluorophenyl)methyl]-4,4-dimethyl-2-oxo-3-pyrrolidinecarboxylate (38): synthesized according to the general procedure applying 2 days of reflux; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.15 (3H, t, J = 6.9 Hz, P(O)-OCH$_2$CH_3), 1.17 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.27 (3H, s, CH_3), 1.35 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.38 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 2.97 (1H, d, J = 9.6 Hz, CH_2), 3.06 (1H, s, CH), 3.08 (2H, m, CH, CH_2), 3.54 (1H, d, J = 9.2 Hz, CH_2), 3.63 (3H, s, OCH_3), 3.72 (1H, d, J = 9.9 Hz, CH_2), 3.74 (3H, s, OCH_3), 4.02 (4H, m, 2 × P(O)OCH_2CH$_3$), 4.21 (4H, m, 2 × P(O)OCH_2CH$_3$), 5.73 (1H, d, J_{HP} = 21.4 Hz, CHP), 5.76 (1H, d, J_{HP} = 21.4 Hz, CHP), 7.06 (2H, t, J = 8.6 Hz, 2 × CH), 7.07 (2H, t, J = 8.6 Hz, 2 × CH), 7.61 (4H, m, 4 × CH); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.2 (d, J_{CP} = 4.9 Hz), 16.4 (d, J_{CP} = 2.4 Hz), 16.5 (d, J_{CP} = 2.4 Hz), 22.4, 22.8, 27.8, 28.5, 36.9, 37.2, 50.9 (d, J_{CP} = 159.9 Hz), 51.1 (d, J_{CP} = 161.1 Hz), 52.0 (2C), 56.5, 56.7, 59.8, 60.0, 62.7 (d, J_{CP} = 7.4 Hz), 63.1 (2C, d, J_{CP} = 7.3 Hz), 63.3 (d, J_{CP} = 7.4 Hz), 115.7 (2C, d, J_{CF} = 21.9 Hz), 115.8 (2C, d, J_{CF} = 22.0 Hz), 128.0 (d, J = 3.7 Hz), 128.6 (d, J = 3.7 Hz), 131.6 (2C, d, J = 8.5 Hz), 131.9 (2C, d, J = 7.3 Hz), 162.7 (2C, d, J_{CF} = 245.4 Hz), 168.8, 169.0, 169.8 (d, J_{CP} = 4.9 Hz), 170.3 (d, J_{CP} = 6.1 Hz); ^{31}P NMR ($CDCl_3$) δ 19.08, 19.73; IR (neat) 1739, 1733, 1703, 1695 cm^{-1}; MS *m/z* 416 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.14. Anal. Calcd for $C_{19}H_{27}FNO_6P$: C, 54.94, H, 6.55. Found: C, 55.15, H, 6.49.

Data for methyl 1-[(diethoxyphosphoryl)(2-fluorophenyl)methyl]-4,4-dimethyl-2-oxo-3-pyrrolidinecarboxylate (39): synthesized according to the general procedure applying 3 days of reflux; ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.16 (3H, t, J = 7.0 Hz, P(O)-OCH$_2$CH_3), 1.17 (3H, t, J = 7.0 Hz, P(O)OCH$_2$CH_3), 1.27 (3H, s, CH_3), 1.37 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.39 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 2.90 (1H, d, J = 9.6 Hz, CH_2), 3.06 (1H, d, J = 9.4 Hz, CH_2), 3.07 (1H, d, J = 2.5 Hz, CH), 3.08 (1H, s, CH), 3.59 (1H, d, J = 9.4 Hz, CH_2), 3.62 (3H, s, OCH_3), 3.70 (1H, d, J = 9.6 Hz, CH_2), 3.74 (3H, s, OCH_3), 4.04 (4H, m, 2 × P(O)OCH_2CH$_3$), 4.24 (4H, m, 2 × P(O)OCH_2CH$_3$), 6.09 (1H, d, J_{HP} = 20.9 Hz, CHP), 6.10 (1H, d, J_{HP} = 20.6 Hz, CHP), 7.10 (1H, tt, J = 8.2 Hz, J = 1.4 Hz, CH), 7.13 (1H, tt, J = 8.0 Hz, J = 1.6 Hz, CH), 7.17 (2H, t, J = 7.7 Hz, 2 × CH), 7.35 (1H, t, J = 6.9 Hz, CH), 7.37 (1H, t, J = 7.4 Hz, CH), 7.89 (1H, t, J = 7.9 Hz, CH), 7.92 (1H, t, J = 7.7 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J_{CP} = 2.3 Hz), 16.3 (d, J_{CP} = 2.3 Hz), 16.5, 16.6, 22.5, 22.8, 27.9, 28.5, 37.0, 37.3, 44.72 (d, J_{CP} = 162.7 Hz), 44.74 (d, J_{CP} = 163.8 Hz), 52.1 (2C), 56.8, 56.9, 59.8, 60.1, 63.0 (d, J_{CP} = 8.1 Hz), 63.1 (d, J_{CP} = 6.9 Hz), 63.3 (2C, d, J_{CP} = 6.9 Hz), 116.0 (2C, J = 21.9 Hz), 119.6 (d, J_{CP} = 15.0 Hz, J_{CF} = 4.6 Hz), 121.0 (d, J_{CP} = 14.4 Hz, J_{CF} = 5.2 Hz), 124.1 (d, J = 3.5 Hz), 124.2 (d, J = 3.5 Hz), 130.7, 130.8, 131.4 (d, J = 3.5 Hz), 131.5 (d, J = 2.3 Hz), 160.9 (dd, J_{CF} = 249.8 Hz, J_{CP} = 6.3 Hz), 161.0 (dd, J_{CF} = 249.8 Hz, J_{CP} = 6.3 Hz), 168.9 (2C), 169.5 (d, J_{CP} = 4.6 Hz), 169.9 (d, J_{CP} = 4.6 Hz); ^{31}P NMR ($CDCl_3$) δ 19.10 (d, J_{PF} = 3.7 Hz), 19.69 (d, J_{PF} = 4.5 Hz); IR (neat) 1739, 1704, 1699 cm^{-1}; MS *m/z* 416 [M + H$^+$]; R_f(EtOAc/PET, 4/6) = 0.10. Anal. Calcd for $C_{19}H_{27}FNO_6P$: C, 54.94, H, 6.55. Found: C, 54.98, H, 6.52.

General Procedure for the Preparation of γ-Lactam 40. Imine **21a** (1 mmol) was dissolved in 10 mL of anhydrous ethanol together with 10 mol % palladium on carbon, and the reaction mixture was brought under a hydrogen atmosphere for 3 days. After filtration over Celite and evaporation of the solvent under reduced pressure, the crude γ-lactam **40** was isolated as a yellow oil. Purification by flash chromatography yielded the pure lactam in 52% yield.

Data for methyl 1-[(diethoxyphosphoryl)(phenyl)methyl]-4,4-dimethyl-2-oxo-3-pyrrolidinecarboxylate (40): ^{1}H NMR ($CDCl_3$) δ 0.98 (6H, s, 2 × CH_3), 1.10 (3H, s, CH_3), 1.13 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.16 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.27 (3H, s, CH_3), 1.35 (3H, t, J = 6.9 Hz, P(O)OCH$_2$CH_3), 1.37 (3H, t, J = 7.3 Hz, P(O)OCH$_2$CH_3), 3.00 (1H, d, J = 9.6 Hz, CH_2), 3.06 (1H, s, CH), 3.08 (1H, d, J = 2.6 Hz, CH), 3.09 (1H, d, J = 9.6 Hz, CH_2), 3.56 (1H, d, J = 9.6 Hz, CH_2), 3.62 (3H, s, OCH_3), 3.73 (1H, d, J = 9.6 Hz, CH_2), 3.74 (3H, s, OCH_3), 4.02 (4H, m, 2 × P(O)OCH_2CH$_3$), 4.21 (4H, m, 2 × P(O)OCH_2CH$_3$), 5.75 (1H, d, J_{HP} = 21.1 Hz, CHP), 5.78 (1H, d, J_{HP} = 20.8 Hz, CHP), 7.36 (6H, m, 6 × CH), 7.61 (4H, m, 4 × CH); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.2 (d, J_{CP} = 4.8 Hz), 16.4, 16.5, 22.4, 22.8, 27.7, 28.5, 36.9, 37.2, 51.7 (d, J_{CP} = 158.7 Hz), 51.9 (d, J_{CP} = 158.7 Hz), 51.97, 52.00, 56.6, 56.8, 59.8, 60.0, 62.6 (d, J_{CP} = 7.3 Hz), 62.97 (d, J_{CP} = 6.1 Hz), 63.04 (d, J_{CP} = 6.1 Hz), 63.2 (d, J_{CP} = 7.3 Hz), 128.7 (6C, t, J = 8.5 Hz), 129.8 (4C, J = 7.9 Hz), 132.0 (d, J_{CP} = 3.7 Hz), 132.6 (d, J_{CP} = 3.7 Hz), 168.8, 169.0, 169.7 (d, J_{CP} = 6.1 Hz), 170.2 (d, J_{CP} = 4.9 Hz); ^{31}P NMR ($CDCl_3$) δ 19.35, 19.97; IR (neat) 1738, 1694 cm^{-1}; MS *m/z* 398 [M + H$^+$]; R_f(EtOAc/PET, 1/1) = 0.20. Anal. Calcd for $C_{19}H_{28}NO_6P$: C, 57.42, H, 7.10. Found: C, 57.25, H, 7.19.

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