Organocatalyzed Synthesis of α-(Substituted Methyl)vinylphosphonates

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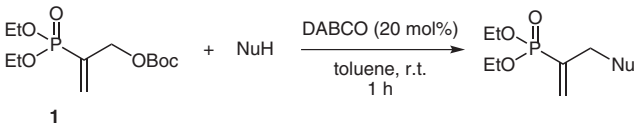
Abstract: α-(Substituted methyl)vinylphosphonates are obtained by a DABCO-catalyzed substitution reaction of diethyl α-(*tert*-butoxycarbonyloxymethyl)vinylphosphonate and (*N*-protected) amino- or soft pronucleophiles. The reactions are easily performed under mild conditions (r.t., 1 h), and give good to excellent yields of the title compounds. A diphosphonate by-product was isolated in some examples, when the nucleophile has a less pronounced nucleophilic character.

Key words: α-(substituted methyl)vinylphosphonates, organocatalysis, diethyl α-(*tert*-butoxycarbonyloxymethyl)vinylphosphonate, pronucleophiles, 1,4-diazabicyclo[2.2.2]octane

Functionalized vinylphosphonates constitute an important class of building blocks for which numerous synthetic methods have been reported.[1] However, α-(substituted methyl)vinylphosphonates have received less attention[2] although they can be used for the preparation of biologically active β-aminophosphonic acid derivatives[3] and 2,4-disubstituted tetrahydrothiophenes.[4] We recently reported the synthesis of aminovinylphosphonates through an organocatalyzed displacement reaction of acetate by amines in diethyl (α-acetoxymethyl)vinylphosphonate.[5] Although quite general, this method suffered from a lack of selectivity when using primary amines, which yielded mixtures of mono- and dialkylated products. Furthermore, the use of other (less) nucleophilic reagents (e.g., soft carbon nucleophiles) did not give satisfactory results. Recently, the organic Lewis base catalyzed substitution of *O*-Boc Morita–Baylis–Hillman (MBH) adducts has emerged as a powerful method for the synthesis of multifunctional compounds in one step.[6] In order to circumvent the above limitations associated with the use of diethyl (α-acetoxymethyl)vinylphosphonate, we turned our attention to a more reactive related substrate, namely, diethyl α-(*tert*-butoxycarbonyloxymethyl)vinylphosphonate (**1**), in a 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed substitution by amine derivatives and soft carbon nucleophiles (Equation 1).



1

Equation 1

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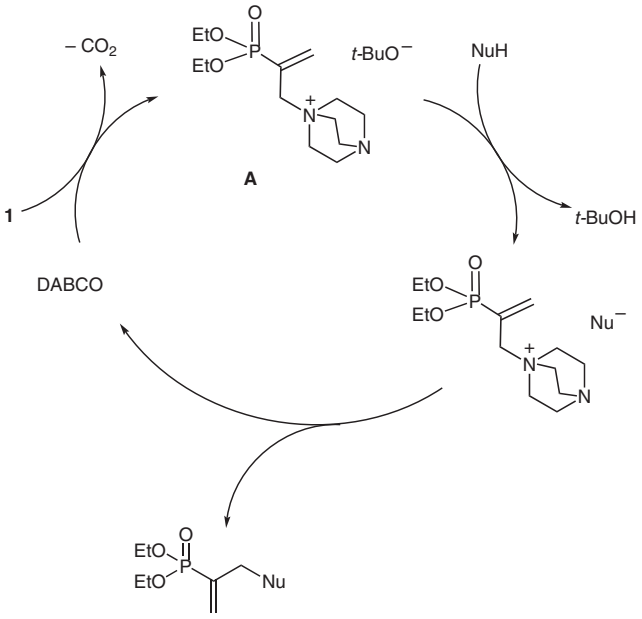
According to the general trends for this reaction, **1** reacts with DABCO to produce the ammonium salt **A** and *tert*-butoxide anion (after CO_2 extrusion), which will deprotonate the pronucleophile (NuH) to afford an activated species (Nu^-). The latter will react with **A** to yield finally the expected product together with regeneration of DABCO (Scheme 1).



Scheme 1

Vinylphosphonate **1** was obtained by treating diethyl (α-hydroxymethyl)vinylphosphonate with di-*tert*-butyl dicarbonate under standard conditions and was isolated as a colorless oil, stable to air and moisture. In a first set of experiments, *N*-protected primary amine equivalents were used in order to set up a stereoselective synthesis of monoalkylated α-(aminomethyl)vinylphosphonates (Table 1). Thus, *N*-tosylamides (Table 1, entries 1–4) as well as succinimide (entry 5) or a chiral oxazolidinone (entry 6) yielded the corresponding *N*-protected α-(aminomethyl)vinylphosphonates as the sole products in very good yields, the reactions being completed after one hour at room temperature. Among the different solvents tested, toluene was the most effective, whereas THF, dichloromethane, and diethyl ether led to lower yields with formation of unidentified by-products (as evidenced by ^{31}P NMR analysis of the crude products). Thus, this provides a valuable selective synthesis of monoalkylated aminovi-

Table 1 Synthesis of N-Protected α-(Aminomethyl)vinylphosphonates

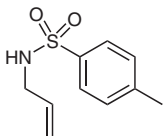
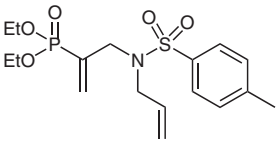
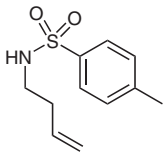
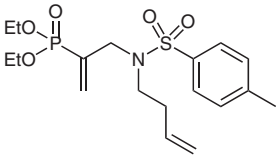
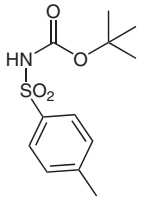
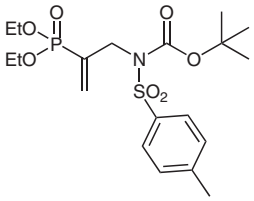
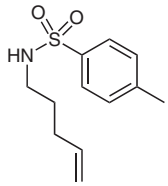
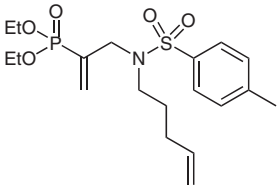
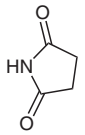
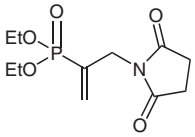
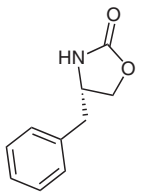
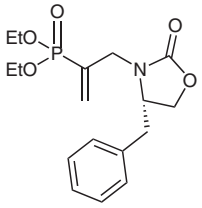
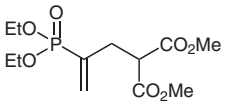
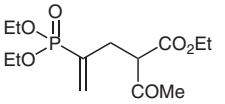
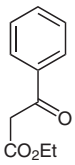
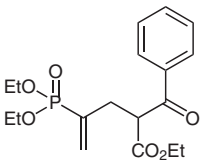
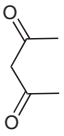
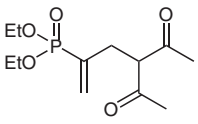
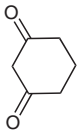
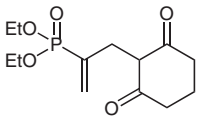
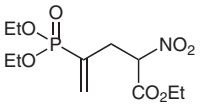
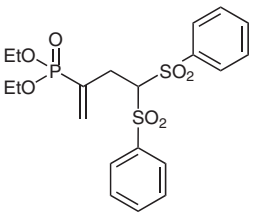
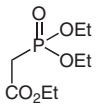
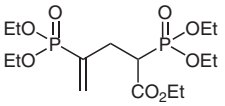
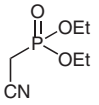
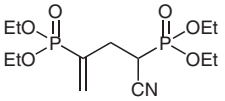
Entry	Pronucleophile	Product	Yield (%)
1		**2** 	90
2		**3** 	97
3		**4** 	99
4		**5** 	94
5		**6** 	96
6		**7** 	89

Table 2 Synthesis of α-(Substituted Methyl)vinylphosphonates

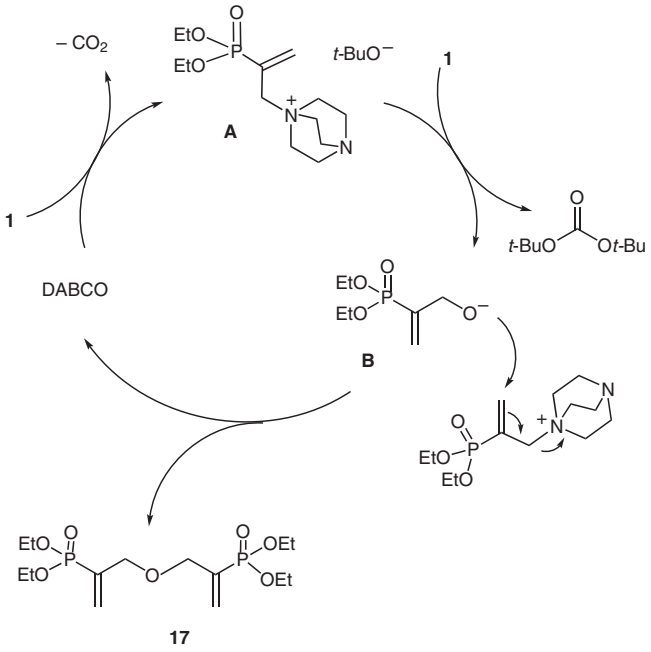
Entry	Pronucleophile	Product	Yield (%)
1		**8** 	83
2		**9** 	84
3		**10** 	99
4		**11** 	79
5		**12** 	99
6		**13** 	89
7	$CH_2(SO_2Ph)_2$	**14** 	99
8		**15** 	63
9		**16** 	79

nylphosphonates upon removal of the protecting tosyl group.

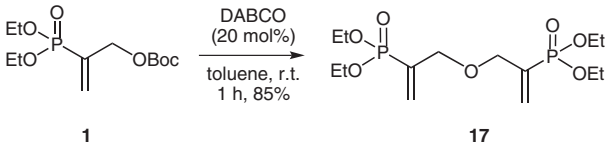
Next, our attention was turned to the use of carbon pronucleophiles, which lead to α-(substituted methyl)vinylphosphonates (Table 2) under the same experimental conditions. Similar compounds were already prepared by halogen substitution in 3-chloroprop-1-en-2-ylphosphonates, but these reactions were not selective, yielding mixtures of mono- and dialkylation products.[2d] Alternatively, Horner–Wadsworth–Emmons olefination leads to analogous derivatives.[7]

In the reactions studied, very good to quantitative yields were obtained with dimethyl malonate (Table 2, entry 1), β-keto esters (entries 2 and 3), and β-diketones (entries 4 and 5). Ethyl nitroacetate (entry 6) and bis(phenylsulfonyl)methane (entry 7) also gave good results. However, the use of triethyl phosphonoacetate (entry 8) and diethyl cyanomethylphosphonate (entry 9) led to somewhat lower yields, and chromatographic purification allowed the isolation of a by-product whose structure was assigned as **17** on the basis of its spectral data. We suspected that **17** could arise from the nucleophilic attack of *tert*-butoxide onto **1**, followed by reaction of the generated alkoxy anion **B** with intermediate **A** (Scheme 2). This assumption was supported by the presence of small amounts of diethyl (α-hydroxymethyl)vinylphosphonate in the crude reaction mixtures as evidenced by ^{31}P NMR analysis.

In order to check this hypothesis, **1** was submitted to the DABCO-catalyzed reaction in the absence of pronucleo-



Scheme 2



Equation 2

phile (Equation 2), which led to the formation of **17** in 85% yield.

To our knowledge, this is the first report of such a side reaction during an organocatalyzed reaction of a Boc derivative of a MBH adduct. The formation of **17** during some of the above reactions can be accounted for by the use of less nucleophilic reagents (Table 2, entries 8 and 9) for which the side reaction leading to **17** may occur to some extent. Indeed, trace amounts of **17** were also detected in the syntheses corresponding to entries 1–7 (Table 2).

In conclusion, we have developed a general synthesis of α-(substituted methyl)vinylphosphonates using a DABCO-catalyzed substitution of the *tert*-butoxycarbonyloxy moiety in **1** by amino and soft carbon nucleophiles. The reactions are completed in usually one hour at room temperature in the presence of 20 mol% of organocatalyst. Despite the fact that a diphosphonate by-product is formed in some experiments, its easy removal together with the high yields of expected products still enable a useful synthesis of the title compounds.

Toluene was distilled from Na and CH_2Cl_2 from CaH_2 immediately before use. Analytical TLC analyses were performed on Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or by dipping in 2% $KMnO_4$ aqueous solution. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). NMR spectra were recorded on a Bruker Avance 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.47 MHz, ^{31}P: 121.49 MHz) using residual proton signals of $CDCl_3$ as an internal standard for ^{1}H, the central triplet of $CDCl_3$ at 77.0 ppm for ^{13}C, and H_3PO_4 as external standard for ^{31}P. Mass spectra (EI) were recorded with a QStar Elite spectrometer. Optical rotation was measured with a P-2000 JASCO polarimeter. Diethyl (α-hydroxymethyl)vinylphosphonate was prepared as already described.[8] All other reagents were commercial grades and used as received. The starting *N*-tosylamines were prepared according to reported procedures.[9]

Diethyl α-(*tert*-Butoxycarbonyloxymethyl)vinylphosphonate (1)
To a cooled (0 °C) and stirred solution of diethyl (α-hydroxymethyl)vinylphosphonate (3 g, 15.5 mmol) and 4-dimethylaminopyridine (0.094 g, 0.77 mmol, 0.05 equiv) in anhyd CH_2Cl_2 (30 mL) was added dropwise a solution of di-*tert*-butyl dicarbonate (3.91 mL, 17 mmol, 1.1 equiv) in anhyd CH_2Cl_2 (25 mL). The mixture was then stirred at r.t. overnight. Aq 5% HCl (10 mL) was added, and the layers were decanted. The organic layer was washed with aq 10% $NaHCO_3$ (10 mL), brine (20 mL), and dried ($MgSO_4$). After filtration and removal of solvents in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc–MeOH, 95:5) to give **1** as a colorless oil; yield: 3.36 g (89%); R_f = 0.61 (EtOAc–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, CH_3), 1.48 (s, 9 H, *t*-C_4H_9), 4.10 (m, 4 H, OCH_2), 4.71 (dt, $^3J_{P,H}$ = 8.1 Hz, $^4J_{H,H}$ = 1.5 Hz, 2 H, CH_2), 6.10 (dq, $^3J_{H,P}$ = 45.9 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, =CH_2), 6.22 (dq, $^3J_{H,P}$ = 22.7 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, =CH_2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 27.7 [s, C(CH_3)$_3$], 62.1 (d, $^2J_{P,C}$ = 5.7 Hz, OCH_2), 65.0 (d, $^2J_{P,C}$ = 18.4 Hz, CH_2), 82.5 [s, *C*(CH_3)$_3$], 130.9 (d, $^2J_{P,C}$ = 6.3 Hz, =CH_2), 135.4 (d, $^1J_{P,C}$ = 177.3 Hz, PC=), 152.9 [s, OC(O)O].

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 16.1.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{12}H_{23}O_6P$: 295.1305; found: 295.1304.

Organocatalyzed Synthesis of α-(Substituted Methyl)vinylphosphonates; General Procedure
To a solution of **1** (0.1 g, 0.34 mmol) and the respective pronucleophile (0.37 mmol, 1.1 equiv) in anhyd toluene (1.5 mL) was added DABCO (0.0076 g, 0.068 mmol, 0.2 equiv) and the mixture was stirred at r.t. for ca. 1 h. The progress of the reaction can be monitored by TLC (for eluents, see individual listings below) or by ^{31}P NMR spectroscopy. After complete consumption of **1**, the volatiles were removed in vacuo, and the residue was purified by flash chromatography on silica gel (Tables 1 and 2).

Diethyl α-[(*N*-Allyl-*N*-tosyl)aminomethyl]vinylphosphonate (2)
Yield: 90%; colorless oil; R_f = 0.40 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, CH_3), 2.43 (s, 3 H, CH_3), 3.80 (br d, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH_2), 3.94 (dt, $^3J_{H,P}$ = 5.7 Hz, $^4J_{H,H}$ = 1.7 Hz, 2 H, CH_2), 4.07 (m, 4 H, OCH_2), 5.08 (m, 2 H, =CH_2), 5.51 (m, 1 H, CH=), 6.05 (dq, $^3J_{H,P}$ = 46.5 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.7 Hz, 1 H, =CH_2), 6.18 (dq, $^3J_{H,P}$ = 22.5 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.7 Hz, 1 H, =CH_2), 7.29 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}), 7.70 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 21.5 (s, CH_3), 47.2 (d, $^2J_{P,C}$ = 19.5 Hz, CH_2), 50.7 (s, CH_2), 62.1 (d, $^2J_{P,C}$ = 5.7 Hz, OCH_2), 119.8 (s, =CH_2), 127.2 (s, CH_{arom}), 129.7 (s, CH_{arom}), 130.5 (d, $^2J_{P,C}$ = 7.5 Hz, =CH_2), 131.9 (s, =CH), 134.5 (d, $^1J_{P,C}$ = 174.4 Hz, PC=), 137.0 (s, C_{arom}), 143.5 (s, C_{arom}).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 17.3.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{17}H_{26}NO_5PS$: 388.1342; found: 388.1346.

Diethyl α-[(*N*-(But-3-enyl)-*N*-tosyl)aminomethyl]vinylphosphonate (3)
Yield: 97%; colorless oil; R_f = 0.54 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.3 Hz, 6 H, CH_3), 2.18 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 3.20 (m, 2 H, CH_2), 3.96 (br d, $^3J_{H,P}$ = 5.5 Hz, 2 H, CH_2), 4.08 (m, 4 H, OCH_2), 4.98 (m, 2 H, $=CH_2$), 5.62 (m, 1 H, CH=), 6.08 (br d, $^3J_{H,P}$ = 46.4 Hz, 1 H, $=CH_2$), 6.18 (br d, $^3J_{H,P}$ = 22.6 Hz, 1 H, $=CH_2$), 7.30 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}), 7.69 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{P,C}$ = 6.6 Hz, CH_3), 21.5 (s, CH_3), 32.4 (s, CH_2), 48.2 (s, CH_2), 49.0 (d, $^2J_{P,C}$ = 19.8 Hz, CH_2), 62.2 (d, $^2J_{P,C}$ = 5.5 Hz, OCH_2), 117.2 (s, $=CH_2$), 127.2 (s, CH_{arom}), 129.7 (s, CH_{arom}), 130.6 (d, $^2J_{P,C}$ = 7.1 Hz, $=CH_2$), 134.4 (s, =CH), 134.9 (d, $^1J_{P,C}$ = 174.5 Hz, PC=), 136.8 (s, C_{arom}), 143.5 (s, C_{arom}).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 17.0.

HRMS (EI): *m*/*z* calcd [M + H^+] for $C_{18}H_{28}NO_5PS$: 402.1499; found: 402.1504.

Diethyl α-[(*N*-*tert*-Butoxycarbonyl-*N*-tosyl)aminomethyl]vinylphosphonate (4)
Yield: 99%; colorless oil; R_f = 0.63 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, $^3J_{H,H}$ = 5.7 Hz, 6 H, CH_3), 1.25 (s, 9 H, *t*-C_4H_9), 2.34 (s, 3 H, CH_3), 4.02 (m, 4 H, OCH_2), 4.53 (dt, $^3J_{H,P}$ = 4.7 Hz, $^4J_{H,H}$ = 1.7 Hz, 2 H, CH_2), 5.82 (br d, $^3J_{H,P}$ = 45.9 Hz, 1 H, $=CH_2$), 6.11 (br d, $^3J_{H,P}$ = 22.8 Hz, 1 H, $=CH_2$), 7.21 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}), 7.70 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 21.6 [s, C(CH_3)$_3$], 27.7 (s, CH_3), 47.7 (d, $^2J_{P,C}$ = 21.8 Hz, CH_2), 62.1 (d, $^2J_{P,C}$ = 5.2 Hz, OCH_2), 84.5 [s, $C(CH_3)_3$], 128.1 (s, CH_{arom}), 128.8 (d, $^2J_{P,C}$ = 7.5Hz, $=CH_2$), 129.2 (s, CH_{arom}), 135.1 (d, $^1J_{P,C}$ = 173.2Hz, PC=), 136.7 (s, C_{arom}), 144.5 (s, C_{arom}), 150.4 [s, NC(O)O].

HRMS (EI): *m*/*z* calcd [M + H^+] for $C_{19}H_{30}NO_7PS$: 448.1553; found: 448.1551.

Diethyl α-{[(*N*-(Pent-4-enyl)-*N*-tosyl]aminomethyl}vinylphosphonate (5)
Yield: 94%; colorless oil; R_f = 0.57 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 1.54 (qt, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2), 1.96 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2), 2.43 (s, 3 H, CH_3), 3.12 (m, 2 H, CH_2), 3.94 (dt, $^3J_{H,P}$ = 5.3 Hz, $^4J_{H,H}$ = 1.5 Hz, 2 H, CH_2), 4.09 (m, 4 H, OCH_2), 4.95 (m, 2 H, $=CH_2$), 5.68 (m, 1 H, CH=), 6.09 (m, 1 H, $=CH_2$), 6.18 (m, 1 H, $=CH_2$), 7.30 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}), 7.69 (br d, $^3J_{H,H}$ = 8.2 Hz, 2 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{P,C}$ = 6.0 Hz, CH_3), 21.5 (s, CH_3), 27.1 (s, CH_2), 30.7 (s, CH_2), 48.5 (s, CH_2), 48.7 (d, $^2J_{P,C}$ = 17.0 Hz, CH_2), 62.1 (d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 115.4 (s, $=CH_2$), 127.1 (s, CH_{arom}), 129.7 (s, CH_{arom}), 130.5 (d, $^2J_{P,C}$ = 7.7 Hz, $=CH_2$), 135.0 (d, $^1J_{P,C}$ = 174.0 Hz, PC=), 136.7 (s, =CH), 137.1 (s, C_{arom}), 143.4 (s, C_{arom}).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 17.1.

HRMS (EI): *m*/*z* calcd [M + H^+] for $C_{19}H_{30}NO_5PS$: 416.1655; found: 416.1654.

Diethyl α-[(2,5-Dioxopyrrolidin-1-yl)methyl]vinylphosphonate (6)
Yield: 96%; colorless oil; R_f = 0.31 (EtOAc–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 2.75 (s, 4 H, CH_2), 4.09 (m, 4 H, CH_2), 4.29 (dt, $^3J_{H,P}$ = 9.3 Hz, $^4J_{H,H}$ = 1.5 Hz, 2 H, OCH_2), 5.76 (br d, $^3J_{H,P}$ = 45.4 Hz, 1 H, $=CH_2$), 6.16 (br d, $^3J_{H,P}$ = 21.2 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 28.2 (s, CH_2), 39.6 (d, $^2J_{P,C}$ = 16.1 Hz, CH_2), 62.3 (d, $^2J_{P,C}$ = 5.2 Hz, OCH_2), 130.9 (d, $^2J_{P,C}$ = 8.0 Hz, $=CH_2$), 132.9 (d, $^1J_{P,C}$ = 177.3 Hz, PC=), 176.3 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 16.0.

HRMS (EI): *m*/*z* calcd [M + H^+] for $C_{11}H_{18}NO_5P$: 276.0995; found: 276.0994.

Diethyl (*S*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)prop-1-en-2-ylphosphonate (7)
Yield: 89%; slightly yellow oil; R_f = 0.46 (EtOAc–MeOH, 95:5); $[\alpha]_D^{25}$ +7.3 (*c* 0.44, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (2 t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 2.60 (dd, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 8.9 Hz, 1 H, CH_2Ph), 3.05 (dd, $^2J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 4.5 Hz, 1 H, CH_2Ph), 3.75 (m, 1 H, CH_2N), 4.00 (m, 2 H, CHN and 1 H of CH_2O), 4.08 (m, 4 H, OCH_2), 4.14 (m, 1 H, CH_2O), 4.40 (m, 1 H, CH_2N), 5.84 (br d, $^3J_{H,P}$ = 45.9 Hz, 1 H, $=CH_2$), 6.17 (br d, $^3J_{H,P}$ = 21.6 Hz, 1 H, $=CH_2$), 7.11 (m, 2 H_{arom}), 7.22 (m, 1 H_{arom}), 7.27 (m, 2 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.0 (2 d, $^3J_{P,C}$ = 6.0 Hz, CH_3), 38.2 (s, CH_2), 43.6 (d, $^2J_{P,C}$ = 14.8 Hz, CH_2), 55.4 (s, CHN), 62.0 (d, $^2J_{PC}$ = 6.0 Hz, OCH_2), 66.8 (s, CH_2), 126.9 (s, CH_{arom}), 128.6 (s, CH_{arom}), 128.8 (s, CH_{arom}), 131.8 (d, $^2J_{P,C}$ = 8.2 Hz, $=CH_2$), 134.0 (d, $^1J_{P,C}$ = 175.6 Hz, PC=), 135.3 (s, C_{arom}), 157.6 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 16.6.

HRMS (EI): *m*/*z* calcd [M + H^+] for $C_{17}H_{24}NO_5P$: 354.1465; found: 354.1467.

Dimethyl 2-[2-(Diethoxyphosphoryl)allyl]malonate (8)
Yield: 83%; yellow oil; R_f = 0.60 (EtOAc–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 2.86 (dd, $^3J_{P,H}$ = 15.1 Hz, $^3J_{H,H}$ = 7.8 Hz, 2 H, CH_2), 3.73 (s, 6 H, CH_3), 3.84 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, CH), 4.08 (m, 4 H, OCH_2), 5.82 (br d, $^3J_{H,P}$ = 47.2 Hz, 1 H, $=CH_2$), 6.09 (br d, $^3J_{H,P}$ = 22.4 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 31.6 (d, $^2J_{P,C}$ = 11.5 Hz, CH_2), 50.3 (d, $^3J_{P,C}$ = 4.0 Hz, CH), 52.6 (s, CH_3), 62.0 (d, $^3J_{P,C}$ = 5.7 Hz, OCH_2), 132.0 (d, $^2J_{P,C}$ = 9.2 Hz, $=CH_2$), 135.5 (d, $^1J_{P,C}$ = 175.5 Hz, PC=), 168.9 (s, CO_2).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 18.1.

HRMS (EI): *m*/*z* calcd [M + H^+] for $C_{12}H_{21}O_7P$: 309.1098; found: 309.1097.

Ethyl 2-Acetyl-4-(diethoxyphosphoryl)pent-4-enoate (9)
Yield: 84%; slightly yellow oil; R_f = 0.37 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 2.18 (s, 3 H, OCH_3), 2.71 (m, 2 H, CH_2), 3.88 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 4.01 (m, 4 H, OCH_2), 4.10 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2), 5.72 (br d, $^3J_{H,P}$ = 47.4 Hz, 1 H, $=CH_2$), 5.96 (br d, $^3J_{H,P}$ = 22.6 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.1 (d, $^3J_{P,C}$ = 6.6 Hz, CH_3), 18.9 (s, CH_3), 29.4 (s, CH_3), 30.7 (d, $^2J_{P,C}$ = 11.5 Hz, CH_2), 57.5 (d, $^3J_{P,C}$ = 3.8 Hz, CH), 61.3 (s, OCH_2), 61.9 (2 d, $^2J_{P,C}$ = 5.5 Hz, OCH_2), 131.6 (d, $^2J_{P,C}$ = 9.3 Hz, $=CH_2$), 135.5 (d, $^1J_{P,C}$ = 174.0 Hz, PC=), 168.5 (s, CO_2), 201.7 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 18.2.

HRMS (EI): *m*/z calcd [M + H^+] for $C_{13}H_{23}O_6P$: 307.1305; found: 307.1307.

Ethyl 2-Benzoyl-4-(diethoxyphosphoryl)pent-4-enoate (10)
Yield: 99%; colorless oil; R_f = 0.50 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 2.89 (dd, $^3J_{H,P}$ = 16.1 Hz, $^3J_{H,H}$ = 7.3 Hz, 2 H, CH_2), 4.00 (m, 4 H, OCH_2), 4.05 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2), 4.82 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH), 5.79 (br d, $^3J_{H,P}$ = 47.4 Hz, 1 H, $=CH_2$), 5.96 (br d, $^3J_{H,P}$ = 22.3 Hz, 1 H, $=CH_2$), 7.40 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H_{arom}), 7.51 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H_{arom}), 7.97 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.8 (s, CH_3), 16.1 (d, $^3J_{P,C}$ = 6.6 Hz, CH_3), 31.9 (d, $^2J_{P,C}$ = 11.5 Hz, CH_2), 52.2 (d, $^3J_{P,C}$ = 3.3 Hz, CH), 61.3 (s, OCH_2), 61.8 (2 d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 128.5 (s, CH_{arom}), 128.6 (s, CH_{arom}), 132.2 (d, $^2J_{P,C}$ = 9.3 Hz, $=CH_2$), 133.5 (s, CH_{arom}), 135.3 (d, $^1J_{P,C}$ = 174.0 Hz, PC=), 135.8 (s, C_{arom}), 168.7 (s, CO_2), 194.3 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 18.4.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{18}H_{25}O_6P$: 369.1462; found: 369.1461.

Diethyl (4-Acetyl-5-oxo)hex-1-en-2-ylphosphonate (11)
Yield: 79%; yellow oil; R_f = 0.43 (EtOAc–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 1.98 (s, 6 H, CH_3), 2.71 (dd, $^3J_{H,P}$ = 15.1 Hz, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2), 4.03 (m, 4 H, OCH_2), 4.11 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH), 5.69 (dq, $^3J_{H,P}$ = 47.2 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.3 Hz, 1 H, $=CH_2$), 6.20 (br d, $^3J_{H,P}$ = 22.1 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.7 (d, $^3J_{P,C}$ = 6.0 Hz, CH_3), 22.6 (s, CH_3), 30.8 (d, $^2J_{P,C}$ = 12.1 Hz, CH_2), 62.0 (d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 65.9 (d, $^3J_{P,C}$ = 3.8 Hz, CH), 131.4 (d, $^2J_{P,C}$ = 8.8 Hz, $=CH_2$), 135.6 (d, $^1J_{P,C}$ = 175.1 Hz, PC=), 202.8 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 18.3.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{12}H_{21}O_5P$: 277.1199; found: 277.1198.

Enol Form of 11
The enol form of **11** displayed specific chemical shifts.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 1.98 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 3.12 (dt, $^3J_{H,P}$ = 6.4 Hz, $^4J_{H,H}$ = $^4J_{H,H}$ = 1.9 Hz, 2 H, CH_2), 4.03 (m, 4 H, OCH_2), 5.54 (dq, $^3J_{H,P}$ = 47.8 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.9 Hz, 1 H, $=CH_2$), 6.01 (br d, $^3J_{H,P}$ = 22.3 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.7 (d, $^3J_{P,C}$ = 6.0 Hz, CH_3), 22.6 (s, CH_3), 29.5 (s, CH_3), 29.6 (d, $^2J_{P,C}$ = 13.2 Hz, CH_2), 61.8 (d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 105.2 (s, =C), 127.9 (d, $^2J_{P,C}$ = 9.9Hz, $=CH_2$), 137.6 (d, $^1J_{P,C}$ = 172.9 Hz, PC=), 191.8 (s, =COH), 202.8 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 18.9.

Diethyl α-(2,6-Dioxocyclohexylmethyl)vinylphosphonate (12)
Yield: 99%; orange oil; R_f = 0.23 (EtOAc–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, CH_3), 1.97 (qt, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2), 2.53 (t, $^3J_{H,H}$ = 6.4 Hz, 4 H, CH_2), 3.22 (d, $^3J_{H,P}$ = 12.6 Hz, 2 H, CH_2), 4.08 (qt, $^3J_{H,H}$ = $^3J_{H,P}$ = 7.1 Hz, 4 H, OCH_2), 5.86 (br d, $^3J_{H,P}$ = 22.3 Hz, 1 H, $=CH_2$), 5.91 (br d, $^3J_{H,P}$ = 48.3 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 15.7 (d, $^3J_{P,C}$ = 6.6 Hz, CH_3), 19.8 (s, CH_2), 23.6 (d, $^2J_{P,C}$ = 12.6 Hz, CH_2), 31.4 (s, CH_2), 64.4 (d, $^2J_{P,C}$ = 6.6 Hz, OCH_2), 112.3 (d, $^3J_{P,C}$ = 7.7 Hz, =C), 132.4 (d, $^2J_{P,C}$ = 8.8 Hz, $=CH_2$), 132.8 (d, $^1J_{P,C}$ = 176.2 Hz, PC=), 195.7 (s, C=O).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 21.4.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{13}H_{21}O_5P$: 289.1199; found: 289.1197.

Ethyl 4-(Diethoxyphosphoryl)-2-nitropent-4-enoate (13)
Yield: 89%; orange oil; R_f = 0.56 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.35 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 3.17 (m, 2 H, CH_2), 4.10 (m, 4 H, OCH_2), 4.29 (m, 2 H, OCH_2), 5.59 (dd, $^3J_{H,H}$ = 9.6 Hz, $^4J_{H,P}$ = 5.5 Hz, 1 H, CH), 5.88 (br d, $^3J_{H,P}$ = 45.9 Hz, 1 H, $=CH_2$), 6.12 (br d, $^3J_{H,P}$ = 21.7 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.9 (s, CH_3), 16.3 (d, $^3J_{P,C}$ = 6.3 Hz, CH_3), 33.9 (d, $^2J_{P,C}$ = 11.5 Hz, CH_2), 62.4 (2 d, $^2J_{P,C}$ = 5.7 Hz, OCH_2), 63.3 (s, OCH_2), 86.5 (s, CH), 132.7 (d, $^1J_{P,C}$ = 177.3 Hz, PC=), 134.1 (d, $^2J_{P,C}$ = 8.6 Hz, $=CH_2$), 163.8 (s, CO_2).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 16.8.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{11}H_{20}NO_7P$: 310.1050; found: 310.1052.

Diethyl 4,4-Bis(phenylsulfonyl)but-1-en-2-ylphosphonate (14)
Yield: 99%; colorless oil; R_f = 0.40 (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 3.18 (dd, $^3J_{H,P}$ = 16.8 Hz, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2), 3.95 (m, 4 H, OCH_2), 5.63 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, CH), 5.84 (br d, $^3J_{H,P}$ = 45.3 Hz, 1 H, $=CH_2$), 5.91 (br d, $^3J_{H,P}$ = 21.3 Hz, 1 H, $=CH_2$), 7.47 (m, 4 H_{arom}), 7.59 (m, 2 H_{arom}), 7.84 (m, 4 H_{arom}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.1 (d, $^3J_{P,C}$ = 6.6 Hz, CH_3), 29.4 (d, $^2J_{P,C}$ = 13.2 Hz, CH_2), 62.2 (d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 79.8 (d, $^3J_{P,C}$ = 1.6 Hz, CH), 128.8 (s, CH_{arom}), 129.1 (s, CH_{arom}), 132.6 (d, $^1J_{P,C}$ = 178.4 Hz, PC=), 133.0 (d, $^2J_{P,C}$ = 8.2 Hz, $=CH_2$), 134.2 (s, CH_{arom}), 138.2 (s, C_{arom}).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 17.1.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{20}H_{25}O_7PS_2$: 473.0852; found: 473.0854.

Ethyl 2,4-Bis(diethoxyphosphoryl)pent-4-enoate (15)
Yield: 63%; yellow oil; R_f = 0.43 (EtOAc–MeOH, 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.29 (m, 12 H, CH_3), 2.75 (m, 2 H, CH_2), 3.36 (ddd, $^2J_{H,P}$ = 23.2 Hz, $^3J_{H,H}$ = 11.9 Hz, $^4J_{H,P}$ = 3.0 Hz, 1 H, CH), 4.04 (m, 2 H, OCH_2), 4.13 (m, 8 H, OCH_2), 5.79 (dq, $^3J_{H,P}$ = 47.4 Hz, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, $=CH_2$), 6.04 (br d, $^3J_{H,P}$ = 22.5 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.9 (s, CH_3), 16.1 (d, $^3J_{P,C}$ = 6.0 Hz, CH_3), 16.1 (d, $^3J_{P,C}$ = 6.0 Hz, CH_3), 29.6 (dd, $^2J_{P,C}$ = 11.8 Hz, $^2J_{P,C}$ = 3.6 Hz, CH_2), 43.9 (dd, $^1J_{P,C}$ = 129.0 Hz, $^3J_{P,C}$ = 4.4 Hz, CH), 61.3 (s, OCH_2), 61.8 (2 d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 62.7 (2 d, $^2J_{P,C}$ = 6.6 Hz, OCH_2), 131.3 (d, $^2J_{P,C}$ = 9.3 Hz, $=CH_2$), 135.9 (dd, $^1J_{P,C}$ = 174.5 Hz, $^3J_{P,C}$ = 17.0 Hz, PC=), 168.0 (s, CO_2).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 18.4, 21.8.

HRMS (EI): *m*/*z* calcd [M + H$^+$] for $C_{15}H_{30}O_8P_2$: 401.1489; found: 401.1491.

Tetraethyl 1-Cyanobut-3-ene-1,3-diyldiphosphonate (16)
Yield: 79%; yellow oil; R_f = 0.35 (EtOAc–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 1.38 (m, 6 H, CH_3), 2.65 (m, 1 H, CH_2), 2.89 (m, 1 H, CH_2), 3.49 (ddd, $^2J_{H,P}$ = 23.2 Hz, $^3J_{H,H}$ = 11.9 Hz, $^4J_{H,P}$ = 3.8 Hz, 1 H, CH), 4.10 (m, 4 H, OCH_2), 4.25 (m, 4 H, CH_2), 6.00 (br d, $^3J_{H,P}$ = 46.1 Hz, 1 H, $=CH_2$), 6.19 (br d, $^3J_{H,P}$ = 21.5 Hz, 1 H, $=CH_2$).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.2 (m, CH_3), 29.6 (dd, $^1J_{C,P}$ = 142.4 Hz, $^3J_{C,P}$ = 2.5 Hz, CH), 30.9 (dd, $^2J_{C,P}$ = 12.1 Hz, $^2J_{C,P}$ = 3.3 Hz, CH_2), 62.3 (2 d, $^2J_{P,C}$ = 6.0 Hz, OCH_2), 64.0 (2 d, $^2J_{P,C}$ = 6.6 Hz, OCH_2), 133.4 (d, $^2J_{P,C}$ = 9.3 Hz, $=CH_2$), 133.9 (dd,

$^{1}J_{P,C}$ = 177.0 Hz, $^{3}J_{P,C}$ = 15.1 Hz, PC=), 115.4 (d, $^{2}J_{P,C}$ = 9.3 Hz, C≡N).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 17.2, 17.3.

HRMS (EI): *m/z* calcd [M + H$^+$] for $C_{13}H_{25}NO_6P_2$: 354.1230; found: 354.1229.

Diethyl α-[2-(Diethoxyphosphoryl)allyloxymethyl]vinylphosphonate (17)

This compound was obtained following the general procedure except that no pronucleophile was added; yield: 85%; colorless oil; R_f = 0.49 (EtOAc–MeOH, 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, $^{3}J_{H,H}$ = 7.0 Hz, 12 H, CH_3), 4.06 (m, 8 H, OCH_2), 4.14 (br d, $^{3}J_{H,P}$ = 7.5 Hz, 4 H, CH_2), 6.09 (br d, $^{3}J_{H,P}$ = 46.7 Hz, 2 H, =CH_2), 6.14 (br d, $^{3}J_{H,P}$ = 22.8 Hz, 2 H, =CH_2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.3 (d, $^{3}J_{P,C}$ = 6.9Hz, CH_3), 62.0 (d, $^{2}J_{P,C}$ = 5.7 Hz, CH_2), 69.2 (d, $^{2}J_{P,C}$ = 17.8 Hz, OCH_2), 129.7 (d, $^{2}J_{P,C}$ = 6.3 Hz, =CH_2), 136.1 (d, $^{1}J_{P,C}$ = 175.5 Hz, PC=).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 16.8.

HRMS (EI): *m/z* calcd [M + H$^+$] for $C_{15}H_{31}O_7P_2$: 371.1383; found: 371.1378.

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