

Efficient synthesis of allylamines from a novel (*E*)-2,3-difunctionalized allyl bromide

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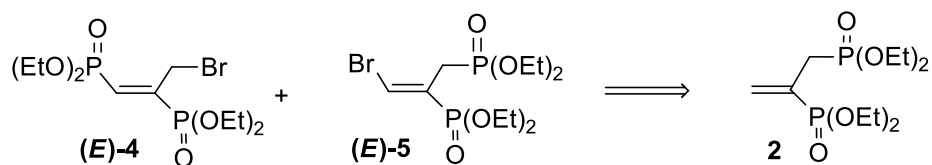
Abstract

We report a new procedure for highly stereoselective synthesis of difunctionalized allyl and vinyl bromides **E-4** and **E-5** via a tandem reaction of bromination-dehydrobromination of tetraethyl prop-2-ene-1,2-diylidiphosphonate in the presence of DBU in acetonitrile at room temperature. The coupling reaction of allyl bromide **E-4** with various primary amines in methanol at 0 °C, followed by S_N2' reaction, provides a new family of tetraethyl 1-(alkylamino)prop-2-ene-1,2-diylidiphosphonates **6** in high yields.

Keywords: Diethyl 1-(hydroxymethyl) vinylphosphonate, tetraethyl prop-2-ene-1,2-diylidiphosphonate, DBU, allyl bromide, allylamine

Introduction

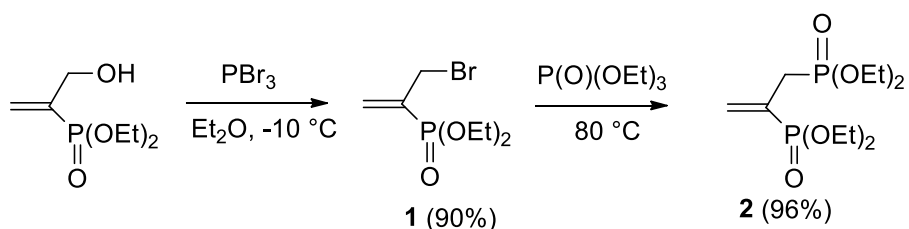
Functionalized allyl¹⁻⁶ and vinyl bromides⁷⁻¹⁰ are often used as intermediates for the synthesis of biologically active compounds¹¹⁻¹⁶ including natural products.^{17,18} Continuing with our efforts directed toward the development of new methodologies for the synthesis of functionalized brominated derivatives,¹⁹⁻²⁴ we describe in this paper an efficient alternative for the preparation of a new family of allyl bromide (**E**)-**4** and vinyl bromide (**E**)-**5** from tetraethyl prop-2-ene-1,2-diylidiphosphonate **2** (Scheme 1) with complete stereoselectivity in favour of the *E* configuration starting from inexpensive reagents. Allyl bromide (**E**)-**4** has been separated and then transformed in a one-step synthesis, to a new family of tetraethyl 1-(alkylamino)prop-2-ene-1,2-diylidiphosphonates **6**.



Scheme 1. Retrosynthetic analysis.

Results and Discussion

Our strategy began with the synthesis of functional allyl bromide **1** (90%) from diethyl 1-(hydroxymethyl) vinylphosphonate²⁵ using phosphorus tribromide as brominating agent (0.5 equiv.) in diethyl ether at $-10\text{ }^{\circ}\text{C}$, followed by nucleophilic substitution of the obtained allyl bromide **1** by triethylphosphite^{26,27} (1 equiv.) at $80\text{ }^{\circ}\text{C}$, to provide only tetraethyl prop-2-ene-1,2-diylidiphosphonate **2** in quantitative yield (Scheme 2).

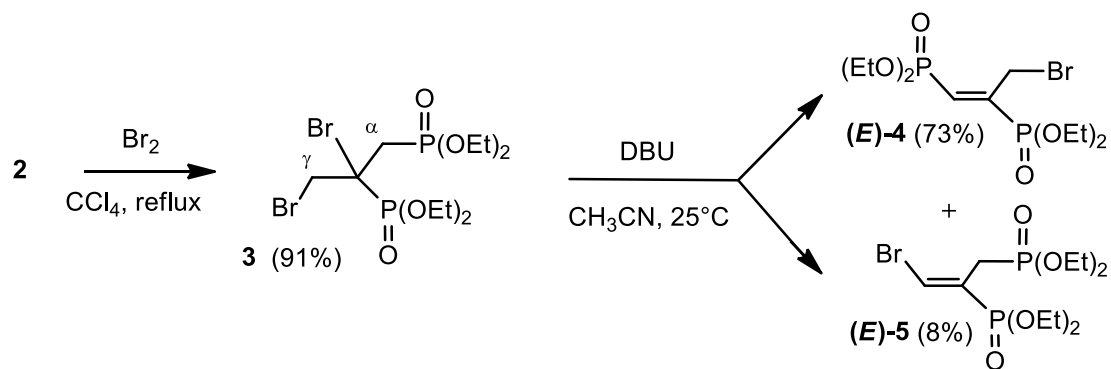


Scheme 2. Synthesis of tetraethyl prop-2-ene-1,2-diylidiphosphonate **2**.

The addition of bromine in refluxing carbon tetrachloride to the vinylidiphosphonate **2** led to the corresponding dibromo compound **3** in 91% yield. In order to find optimal conditions for the synthesis of functionalized allyl bromide **4**, we examined the dehydrobromination reaction of **3** at room temperature under various reaction conditions. As shown in Table 1, poor yields of compound **4** were obtained in the presence of Et_3N and K_2CO_3 , while the use of DABCO was completely ineffective. However, the best result was obtained when the reaction was carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.1 equiv.) in acetonitrile. It should be noted that the synthesis of allyl bromide **4** was always accompanied by the formation of its regioisomer **5**, which was easily separable from the desired product **4** by silica gel column chromatography (Scheme 3).

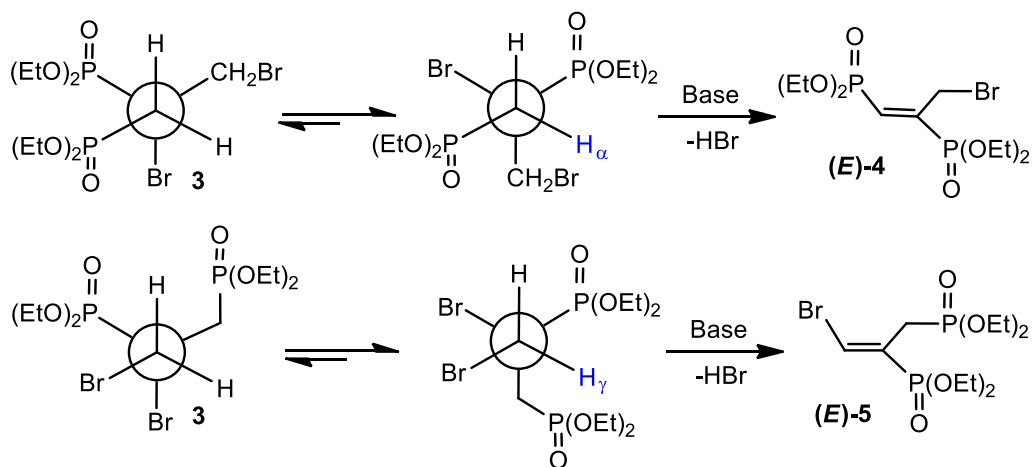
Table 1. Effect of reaction conditions on the synthesis of functionalized bromides **4** and **5**

| Entry | Base | Solvent | Time (days) | Yield (%) of (4 / 5) |
|----------|-------------------------|------------------------|-------------|--------------------------------------|
| 1 | DABCO | THF | 10 | — |
| 2 | Et_3N | CCl_4 | 15 | 16/4 |
| 3 | DBU | CH_3CN | 3 | 73/8 |
| 4 | K_2CO_3 | THF | 3 | traces |



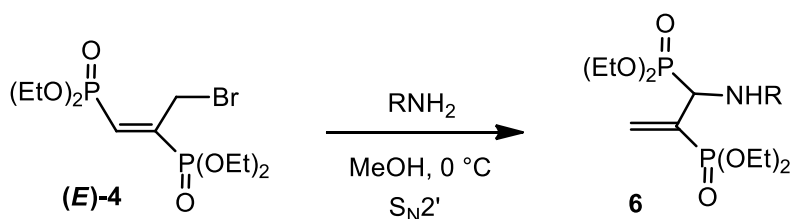
Scheme 3. Synthesis of allyl and vinyl bromides (*E*)-4, (*E*)-5.

The formation of two brominated regioisomers (*E*)-4 and (*E*)-5 can be explained on the basis of the elimination reaction of hydrogen bromide due to the mobility of hydrogen atoms H_α and H_γ , while the inherent stereochemistry of the two regioisomers can be justified on the basis of the examination of the two possible conformational equilibria of **3** and the choice of the most stable conformer in harmony with both steric bulk and electronic effects. The configuration of each of allyl- and vinylbromides (*E*)-4 and (*E*)-5 was elucidated by two-dimensional NMR (NOESY). Indeed, the absence of correlation between the vinyl proton (6.70 ppm) and the CH_2Br protons (4.6 ppm) for the allyl bromide (*E*)-4 and the ethylenic proton (7.48 ppm) and the $\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$ (3.04 ppm) in the case of vinyl bromide (*E*)-5 were in favour of the geometry (*E*) of the above regioisomers. It is also worth noting that there is good agreement between the experimental chemical shifts of vinylic protons of functionalized bromides (*E*)-4 and (*E*)-5 and those calculated by Pascual's formula^{28,29} (Scheme 4).



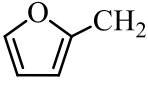
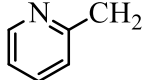
Scheme 4. Allyl and vinyl bromides (*E*)-4 and (*E*)-5 in accordance with Newman projections of **3**.

In order to establish a chemical library reserved for the various functionalized allylamines published during the last decade by our research group³⁰ and their use as basic skeletons of many biologically important substances³¹⁻³⁷ and numerous natural products³⁸⁻⁴⁷, we focused our attention on the synthesis of a new family of allylamines **6**. The best reaction conditions were obtained following the reaction of the electrophilic allyl bromide (**E**)-**4** with excess of monoalkylamines (2 equiv.) in methanol at 0 °C (entries 1-7). Due to the coexistence of the phosphoryl and bromomethyl groups on the same carbon atom, the intermediate (**E**)-**4** reacts regioselectively with amines in a clean S_N2' reaction, to provide tetraethyl 1-(alkylamino)prop-2-ene-1,2-diylidiphosphonates **6** with high purity and satisfactory yields (Scheme 5, Table 2). Furthermore, the reaction time and the overall yields have not been affected by the donor effects (entries 1-3) or withdrawing effects (entries 4-7) of the alkyl groups.



Scheme 5. Synthesis of tetraethyl 1-(alkylamino)prop-2-ene-1,2-diylidiphosphonates **6**

Table 2. Synthesis of functionalized allylamines **6a-g**

| Entry | R | Time (h) | Product | Yield (%) |
|-------|---|----------|-----------|-----------|
| 1 | C ₆ H ₅ CH ₂ | 5 | 6a | 75 |
| 2 | C ₆ H ₅ CH ₂ CH ₂ | 6 | 6b | 86 |
| 3 | <i>p</i> -MeOC ₆ H ₄ CH ₂ | 6 | 6c | 68 |
| 4 | <i>p</i> -ClC ₆ H ₄ CH ₂ | 7 | 6d | 90 |
| 5 | <i>p</i> -FC ₆ H ₄ CH ₂ | 4 | 6e | 91 |
| 6 |  | 5 | 6f | 87 |
| 7 |  | 6 | 6g | 84 |

*Yields refer to the pure isolated products characterized by ¹H, ¹³C NMR.

Conclusions

We have developed a new strategy for the synthesis of highly stereoselective 2,3-difunctionalized allyl bromide (**E**)-**4**, in addition to the family of allyl bromides we published

previously, and have shown its direct use in the synthesis of a new family of 1,2-diphosphorylated allylamines **6** in excellent yields.

Experimental Section

General. All commercially available chemicals and reagents were used without further purification. All the reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F₂₅₄). Flash column chromatography was performed with 70-230 mesh silica gel. The ¹H and ¹³C spectra were recorded in CDCl₃ at room temperature on a Bruker AMX 300 spectrometer. Some products secured by DEPT 135, NOESY, HMQC and HMBC experiments. Chemical shifts are given in δ (ppm) and coupling constants *J* (Hz) relative to TMS as internal standard. Multiplicities were recorded as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), dq (doublet of quartets), br (board) or m (multiplet). Reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. IR spectra were recorded on a Bruker Vertex 70 FT-IR spectrophotometer. High-Resolution Mass Spectrometry (HRMS) analyses were performed in Laberca laboratory at Oniris (Nantes-Atlantic National College of Veterinary Medicine, FoodScience and Engineering) on a mass spectrometer equipped with a door coupled to a linear Orbitrap (LTQ-Orbitrap of Thermo Fisher Scientific) in positive electrospray ionization.

Diethyl 3-bromoprop-1-en-2-ylphosphonate (1). To a stirred solution of diethyl 1-(hydroxymethyl) vinylphosphonate (56 mmoles) in dry ether (45 mL) was added dropwise a solution of phosphorus tribromide (28 mmoles) diluted in 5 mL of anhydrous ether at -10 °C under nitrogen atmosphere. The resulting mixture was left for one hour then hydrolyzed with water in ice bath at -10 °C and extracted with hexane (3×20 mL). The organic layer was washed with brine then dried over MgSO₄. After the solvent was evaporated, the crude product was distilled under reduced pressure to produce a colorless oil. Yield: 90%, b.p. 79 °C/0.6 mmHg; ¹H-NMR (300 MHz, CDCl₃): 6.26 (d, 1H, ³*J*_{HP} 22 Hz, =CH); 6.19 (d, 1H, ³*J*_{HP} 44 Hz, =CH); 4.17-4.07 (m, 6H, 2OCH₂, CH₂Br); 1.35 (t, 6H, *J* 7.5 Hz, 2CH₃); ¹³C-NMR (75 MHz, CDCl₃): 135.8 (d, =C, ¹*J*_{CP} 177.7 Hz); 134.4 (d, =CH₂, ²*J*_{CP} 9 Hz); 62.3 (d, 2OCH₂, ²*J*_{CP} 5.2 Hz); 29.7 (d, CH₂Br, ²*J*_{CP} 16.5 Hz); 16.3 (d, 2CH₃, ³*J*_{CP} 6 Hz); ³¹P-NMR (121 MHz, CDCl₃):15.01. C₇H₁₄BrO₃P: HRMS calculated for [M+H⁺] 256.99367, found 256.99371.

Representative procedure, tetraethyl prop-2-ene-1,2-diyldiphosphonate (2). A solution of allyl bromide **1** (20 mmol) and triethylphosphite (28 mmol) was stirred at 80 °C for 1 hour. When the reaction was completed, the mixture was evaporated under reduced pressure. The oily residue obtained was distilled under reduced pressure to obtain the allylphosphonate **2**. Colorless oil. Yield: 96%, b.p. 130 °C/0.6 mmHg; ¹H-NMR (300 MHz, CDCl₃): 6.28 (dd, 1H, ³*J*_{HP} 48 Hz, ⁴*J*_{HP} 6 Hz, =CH); 6.27(dd, 1H, ³*J*_{HP} 24 Hz, ⁴*J*_{HP} 6 Hz, =CH); 4.10 (dq, 8H, *J* 6 Hz, *J* 6 Hz, 4OCH₂); 2.77 (dd, 2H, ²*J*_{HP} 21 Hz, ³*J*_{HP} 12 Hz, CH₂P); 1.34, 1.30 (2t, 12H, *J* 6 Hz, *J* 6 Hz,

4CH₃); ¹³C-NMR (75 MHz, CDCl₃): 133.8 (t, =CH₂, ²J_{CP} 16.5 Hz, ³J_{CP} 8.2 Hz); 129.5 (dd, =CP, ¹J_{CP} 180 Hz, ²J_{CP} 30 Hz); 62.1 (2d, 4OCH₂, ²J_{CP} 9 Hz, ²J_{CP} 9 Hz); 27.6 (dd, CH₂P, ¹J_{CP} 140.2 Hz, ²J_{CP} 12 Hz); 16.3 (2d, 4CH₃, ³J_{CP} 6 Hz, ³J_{CP} 6 Hz); ³¹P-NMR (121 MHz, CDCl₃): 17.53 (d, =CP, *J* 32.6 Hz); 25.27 (d, CH₂P, *J* 32.6 Hz).

Synthesis of (*E*)-tetraethyl 3-bromoprop-1-ene-1,2-diylidiphosphonate (*E*)-4 and tetraethyl 3-bromoprop-2-ene-1,2-diylidiphosphonate (*E*)-5. A solution of bromine (74 mmol) in carbon tetrachloride (28 mL) was added dropwise to a refluxing solution of allylphosphonate **2** (71 mmol) in carbon tetrachloride (160 mL) at such a rate that the bromine color gradually disappeared. The end of the reaction is indicated by the persistence of a brownish color. Excess of bromine was removed by washing with aqueous solution of sodium thiosulfate. The organic layer was then washed with brine and dried over magnesium sulfate. Filtration and removal of the solvent gave a residue **3**. DBU (12 mmol) was added to a solution of **3** (11 mmol) in acetonitrile (60 mL). The mixture was stirred for 48 h at room temperature. After evaporation of the solvent, the residue was separated by chromatography on silica gel (CH₂Cl₂-MeOH, 97:3) affording pure compounds **4** and **5**.

Tetraethyl (*E*)-3-bromoprop-1-ene-1,2-diylidiphosphonate (4**).** Yellow liquid. Yield: 73%, IR (neat): 1643, 1240 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 6.70 (dd, 1H, ²J_{HP} 27 Hz, ³J_{HP} 18 Hz, =CH); 4.60 (d, 2H, ³J_{HP} 18 Hz, CH₂Br); 4.22-4.13 (m, 8H, 4OCH₂); 1.38, 1.36, (2t, 6H, *J* 6 Hz, *J* 6 Hz, 4CH₃); ¹³C-NMR (75 MHz, CDCl₃): 146.6 (dd, =C, ¹J_{CP} 169.5 Hz, ²J_{CP} 5.2 Hz); 133.6 (dd, =CH, ¹J_{CP} 171 Hz, ²J_{CP} 10.5 Hz); 62.6, 62.2, (2d, 4OCH₂, ²J_{CP} 6 Hz, ²J_{CP} 6 Hz); 23.2 (t, CH₂Br, ²J_{CP} ³J_{CP} 9 Hz); 16.0 (d, 2CH₃, ³J_{CP} 6 Hz); 15.9 (d, 2CH₃, ³J_{CP} 6.7 Hz); ³¹P-NMR (121 MHz, CDCl₃): 13.95 (d, =CP, *J* 91.9 Hz); 11.02 (d, CH₂P, *J* 91.9 Hz). C₁₁H₂₃BrO₆P₂ : HRMS calculated for [M+H⁺] 393.02260, found 393.02219.

Tetraethyl (*E*)-3-bromoprop-2-ene-1,2-diylidiphosphonate (5**).** Yellow liquid. Yield: 8%, ¹H-NMR (300 MHz, CDCl₃): 7.48 (dd, 1H, ³J_{HP} 14.4 Hz, ⁴J_{HP} 6 Hz, =CH); 4.16-4.08 (m, 8H, 4OCH₂); 3.04 (dd, 2H, ²J_{HP} 24 Hz, ³J_{HP} 18 Hz, CH₂P); 1.38, 1.32, (2t, 6H, *J* 6 Hz, *J* 6 Hz, 4CH₃); ¹³C-NMR (75 MHz, CDCl₃): 128.6 (dd, =C, ¹J_{CP} 174.7 Hz, ²J_{CP} 11.2 Hz); 127.0 (dd, =CH, ²J_{CP} 22.8 Hz, ³J_{CP} 12.7 Hz); 62.9, 62.7, (2d, 4OCH₂, ²J_{CP} 6 Hz, ²J_{CP} 6 Hz); 29.4 (dd, CH₂P, ¹J_{CP} 140.2 Hz, ²J_{CP} 9 Hz); 16.4 (d, 2CH₃, ³J_{CP} 6 Hz); 16.2 (d, 2CH₃, ³J_{CP} 6.7 Hz); ³¹P-NMR (121 MHz, CDCl₃): 13.64 (d, =CP, *J* 8.4 Hz); 22.29 (d, CH₂P, *J* 8.4 Hz).

Synthesis model of tetraethyl 3-(alkylamino)prop-1-ene-1,2-diylidiphosphonate **6 (a-g).** To a solution of allyl bromide (*E*)-4 (0.2g, 0.5 mmol) diluted in 3 mL of absolute methanol was added dropwise primary amine (1 mmol) at 0°C. After stirring during the time indicated in table (**1**), the mixture was concentrated and the organic residue obtained was purified by chromatography on silica gel (CH₂Cl₂-MeOH, 9.6:0.4).

Tetraethyl 1-(benzylamino)prop-2-ene-1,2-diylidiphosphonate (6a**).** Yellow liquid. Yield: 75%, IR (neat): 3392, 1649, 1246 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 7.29 (m, 5H, aromatic H); 6.46 (t, 1H, ²J_{HH} ³J_{HP} 3 Hz, =CH); 6.35 (dd, 1H, ²J_{HH} 3 Hz, ³J_{HP} 18 Hz, =CH); 4.25-4.08 (m, 8H, 4OCH₂); 3.87 (dd, 1H, ²J_{HP} 21 Hz, ³J_{HP} 15 Hz, CHP); 3.91-3.72 (AB, 2H, *J* 12 Hz, CH₂N); 2.84 (br, s, 1H, NH); 1.34, 1.32, 1.30 (3t, 12H, *J* 6 Hz, *J* 6 Hz, *J* 6 Hz, 4CH₃); ¹³C-NMR (75 MHz,

CDCl₃): 139.4 (aromatic C); 136.3 (d, =C, ¹J_{CP} 174.7 Hz); 134.0 (t, =CH₂, ²J_{CP} 8.2 Hz, ³J_{CP} 7.5 Hz); 129.0, 128.3, 128.3, 127.1, (aromatic C); 63.3, 62.7 (2d, 2OCH₂, ²J_{CP} 7.5 Hz, ²J_{CP} 7.5 Hz); 62.3, 62.1 (2d, 2OCH₂, ²J_{CP} 6 Hz, ²J_{CP} 6 Hz); 55.1 (dd, CHP, ¹J_{CP} 156.7 Hz, ²J_{CP} 12.7 Hz); 51.5 (d, CH₂N, ³J_{CP} 15 Hz); 16.5, 16.4, (2d, 4CH₃, ³J_{CP} 6 Hz, ³J_{CP} 6 Hz); ³¹P-NMR (121 MHz, CDCl₃): 16.92 (d, =CP, *J* 26.6 Hz); 22.19 (d, CHP, *J* 26.6 Hz). C₁₈H₃₁NO₆P₂: HRMS calculated for [M+H⁺] 420.16994, found 420.16956.

Tetraethyl 1-(phenethylamino)prop-2-ene-1,2-diylidiphosphonate (6b). Green liquid. Yield: 86%, IR (neat): 3421, 1651, 1233 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 7.23 (m, 5H, aromatic H); 6.35 (dd, 1H, ²J_{HH} 3 Hz, ³J_{HP} 15 Hz, =CH); 6.23 (dd, 1H, ²J_{HH} 3 Hz, ³J_{HP} 39 Hz, =CH); 4.16-4.03 (m, 8H, 4OCH₂); 3.83 (dd, 1H, ²J_{HP} 21 Hz, ³J_{HP} 12 Hz, CHP); 2.99-2.72 (m, 4H, 2CH₂); 1.99 (br, s, 1H, NH); 1.34, 1.32, (2t, 12H, *J* 6 Hz, *J* 6 Hz, 4CH₃); ¹³C-NMR (75 MHz, CDCl₃): 139.8 (aromatic C); 136.3 (d, =C, ¹J_{CP} 174.7 Hz); 133.6 (t, =CH₂, ²J_{CP} 8.2 Hz, ³J_{CP} 7.5 Hz); 128.7, 128.3, 126.1, (aromatic C); 63.2, 62.6 (2d, 2OCH₂, ²J_{CP} 7.5 Hz, ²J_{CP} 7.5 Hz); 62.2, 62.0 (2d, 2OCH₂, ²J_{CP} 6 Hz, ²J_{CP} 6 Hz); 55.4 (dd, CHP, ¹J_{CP} 156.7 Hz, ²J_{CP} 12.7 Hz); 48.9 (d, CH₂N, ³J_{CP} 13.5 Hz); 36.3 (s, CH₂); 16.4 (d, 2CH₃, ³J_{CP} 5.2 Hz); 16.3 (d, 2CH₃, ³J_{CP} 6 Hz); ³¹P-NMR (121 MHz, CDCl₃): 17.16 (d, =CP, *J* 29.0 Hz); 22.31 (d, CHP, *J* 29.0 Hz). C₁₉H₃₃NO₆P₂: HRMS calculated for [M+H⁺] 434.18559, found 434.18504.

Tetraethyl 1-(4-methoxybenzylamino)prop-2-ene-1,2-diylidiphosphonate (6c). Yellow liquid. Yield: 68%, IR (neat): 3368, 1642, 1238 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 7.24 (d, 2H, *J*_{HH} 9 Hz, aromatic H); 6.83 (d, 2H, *J*_{HH} 9 Hz, aromatic H); 6.44 (t, 1H, ²J_{HH} ³J_{HP} 3 Hz, =CH); 6.33 (dd, 1H, ²J_{HH} 3 Hz, ³J_{HP} 21 Hz, =CH); 4.21-4.08 (m, 8H, 4OCH₂); 3.85 (dd, 1H, ²J_{HP} 21 Hz, ³J_{HP} 15 Hz, CHP); 3.79 (s, 3H, CH₃); 3.83-3.65 (AB, 2H, *J* 12 Hz, CH₂N); 2.58 (br, s, 1H, NH); 1.34, 1.28, (2t, 12H, *J* 6 Hz, *J* 6 Hz, 4CH₃); ¹³C-NMR (75 MHz, CDCl₃): 158.7 (aromatic C); 136.3 (d, =C, ¹J_{CP} 175.7 Hz); 133.9 (t, =CH₂, ²J_{CP} 8.2 Hz, ³J_{CP} 7.5 Hz); 131.5, 129.4, 113.6, (aromatic C); 63.1, 62.5 (2d, 2OCH₂, ²J_{CP} 6.7 Hz, ²J_{CP} 6.7 Hz); 62.1, 62.0 (2d, 2OCH₂, ²J_{CP} 6 Hz, ²J_{CP} 6 Hz); 54.9 (dd, CHP, ¹J_{CP} 156.7 Hz, ²J_{CP} 12.7 Hz); 55.1 (OCH₃); 50.8 (d, CH₂N, ³J_{CP} 15 Hz); 16.4, 16.2 (2d, 4CH₃, ³J_{CP} 6 Hz, ³J_{CP} 6 Hz); ³¹P-NMR (121 MHz, CDCl₃): 16.95 (d, =CP, *J* 25.4 Hz); 22.17 (d, CHP, *J* 25.4 Hz) C₁₉H₃₃NO₇P₂: HRMS calculated for [M+H⁺] 450.18050, found 450.17976.

Tetraethyl 1-(4-chlorobenzylamino)prop-2-ene-1,2-diylidiphosphonate (6d). Yellow liquid. Yield: 90%, IR (neat): 3336, 1646, 1260 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃): 7.28 (m, 4H, aromatic H); 6.44 (d, 1H, ³J_{HP} 3 Hz, =CH); 6.33 (dd, 1H, ²J_{HH} 3 Hz, ³J_{HP} 21 Hz, =CH); 4.21-4.08 (m, 8H, 4OCH₂); 3.82 (dd, 1H, ²J_{HP} 21 Hz, ³J_{HP} 15 Hz, CHP); 3.87-3.69 (AB, 2H, *J* 12 Hz, CH₂N); 2.26 (br, s, 1H, NH); 1.34, 1.32, 1.28 (3t, 12H, *J* 6 Hz, *J* 6 Hz, *J* 6 Hz, 4CH₃); ¹³C-NMR (75 MHz, CDCl₃): 138.0 (aromatic C); 136.3 (d, =C, ¹J_{CP} 173.2 Hz); 133.9 (t, =CH₂, ²J_{CP} 8.2 Hz, ³J_{CP} 7.5 Hz); 132.8, 129.6, 128.4, (aromatic C); 63.2, 62.7 (2d, 2OCH₂, ²J_{CP} 7.5 Hz, ²J_{CP} 7.5 Hz); 62.3, 62.1 (2d, 2OCH₂, ²J_{CP} 6 Hz, ²J_{CP} 6 Hz); 55.0 (dd, CHP, ¹J_{CP} 157.5 Hz, ²J_{CP} 13.5 Hz); 50.6 (d, CH₂N, ³J_{CP} 15 Hz); 16.5, 16.3 (2d, 4CH₃, ³J_{CP} 6.7 Hz, ³J_{CP} 6.7 Hz); ³¹P-NMR (121 MHz, CDCl₃): 16.80 (d, =CP, *J* 25.4 Hz); 22.17 (d, CHP, *J* 25.4 Hz). C₁₈H₃₀ClNO₆P₂: HRMS calculated for [M+H⁺] 454.13096, found 454.13043.

Tetraethyl 1-(4-fluorobenzylamino)prop-2-ene-1,2-diylidiphosphonate (6e). Orange liquid. Yield: 91%, IR (neat): 3389, 1647, 1245 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.3 (dd, 2H, $^3J_{\text{HF}}$ 9 Hz, $^3J_{\text{HP}}$ 6 Hz, aromatic H); 6.98 (t, 2H, $^3J_{\text{HH}}$ $^4J_{\text{HF}}$ 9 Hz, aromatic H); 6.45 (t, 1H, $^2J_{\text{HH}}$ $^3J_{\text{HP}}$ 3 Hz, =CH); 6.33 (dd, 1H, $^2J_{\text{HH}}$ 3 Hz, $^3J_{\text{HP}}$ 21 Hz, =CH); 4.19-4.08 (m, 8H, 4OCH₂); 3.83 (dd, 1H, $^2J_{\text{HP}}$ 21 Hz, $^3J_{\text{HP}}$ 12 Hz, CHP); 3.87-3.69 (AB, 2H, J 12 Hz, CH₂N); 2.53 (br, s, 1H, NH); 1.34, 1.30 (2t, 12H, J 6 Hz, J 6 Hz, 4CH₃); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 161.9 (d, aromatic C, $^1J_{\text{CF}}$ 243.7 Hz); 137.5 (aromatic C); 134.4 (dd, =C, $^1J_{\text{CP}}$ 111 Hz, $^2J_{\text{CP}}$ 8.2 Hz); 133.8 (t, =CH₂, $^2J_{\text{CP}}$ 8.2 Hz, $^3J_{\text{CP}}$ 7.5 Hz); 129.8, 129.7, 115.1, 114.88, (aromatic C); 63.1, 62.6 (2d, 2OCH₂, $^2J_{\text{CP}}$ 6.7 Hz, $^2J_{\text{CP}}$ 6.7 Hz); 62.2, 62.0 (2d, 2OCH₂, $^2J_{\text{CP}}$ 6 Hz, $^2J_{\text{CP}}$ 6 Hz); 54.9 (dd, CHP, $^1J_{\text{CP}}$ 156.7 Hz, $^2J_{\text{CP}}$ 12.7 Hz); 50.6 (d, CH₂N, $^3J_{\text{CP}}$ 15 Hz); 16.4, 16.2, (2d, 4CH₃, $^3J_{\text{CP}}$ 6 Hz, $^3J_{\text{CP}}$ 6 Hz); $^{31}\text{P-NMR}$ (121 MHz, CDCl_3): 16.86 (d, =CP, J 25.4 Hz); 22.22 (d, CHP, J 25.4 Hz); $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -115.85. $\text{C}_{18}\text{H}_{30}\text{FNO}_6\text{P}_2$: HRMS calculated for $[\text{M}+\text{H}^+]$ 438.16052, found 438.16003.

Tetraethyl 1-(furfurylamino)prop-2-ene-1,2-diylidiphosphonate (6f). Yellow liquid. Yield: 87%, IR (neat): 3417, 1644, 1250 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.34 (m, 1H, =CH); 6.46 (dd, 1H, $^2J_{\text{HH}}$ 3 Hz, $^3J_{\text{HP}}$ 9 Hz, =CH); 6.34 (dd, 1H, $^2J_{\text{HH}}$ 3 Hz, $^3J_{\text{HP}}$ 12 Hz, =CH); 6.29 (t, 1H, J 3 Hz, =CH); 6.21 (d, 1H, J 3 Hz, =CH); 4.23-4.08 (m, 8H, 4OCH₂); 3.87 (dd, 1H, $^2J_{\text{HP}}$ 21 Hz, $^3J_{\text{HP}}$ 12 Hz, CHP); 3.88-3.72 (AB, 2H, J 12 Hz, CH₂N); 2.35 (br, s, 1H, NH); 1.34, 1.28 (2t, 12H, J 6 Hz, J 6 Hz, 4CH₃); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 153.0, 141.8, (=C); 136.0 (d, =C, $^1J_{\text{CP}}$ 175.5 Hz); 134.2 (t, =CH₂, $^2J_{\text{CP}}$ 8.2 Hz, $^3J_{\text{CP}}$ 7.5 Hz); 110.1, 107.4, (=C); 63.3, 62.8 (2d, 2OCH₂, $^2J_{\text{CP}}$ 6.7 Hz, $^2J_{\text{CP}}$ 6.7 Hz); 62.3, 62.2 (2d, 2OCH₂, $^2J_{\text{CP}}$ 6 Hz, $^2J_{\text{CP}}$ 6 Hz); 54.4 (dd, CHP, $^1J_{\text{CP}}$ 156.7 Hz, $^2J_{\text{CP}}$ 13.5 Hz); 44.0 (d, CH₂N, $^3J_{\text{CP}}$ 15 Hz); 16.4, 16.3 (2d, 4CH₃, $^3J_{\text{CP}}$ 6 Hz, $^3J_{\text{CP}}$ 6 Hz); $^{31}\text{P-NMR}$ (121 MHz, CDCl_3): 22.05 (d, =CP, J 29.0 Hz); 17 (d, CHP, J 29.0 Hz). $\text{C}_{16}\text{H}_{29}\text{NO}_7\text{P}_2$: HRMS calculated for $[\text{M}+\text{H}^+]$ 410.14920, found 410.14865.

Tetraethyl 1-(2-picolylamino)prop-2-ene-1,2-diylidiphosphonate (6g). Yellow liquid. Yield: 84%, IR (neat): 3422, 1646, 1230 cm^{-1} . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.52 (dd, 1H, J 4.8 Hz, J 1.8 Hz, =CHN); 7.64 (td, 1H, J 1.8 Hz, J 7.8 Hz, =CH); 7.38 (d, 1H, J 7.8 Hz, =CH); 7.16 (dd, 1H, J 4.8 Hz, J 7 Hz, =CH); 6.44 (dd, 1H, $^2J_{\text{HH}}$ 4.2 Hz, $^3J_{\text{HP}}$ 20.4 Hz, =CH); 6.37 (t, 1H, $^2J_{\text{HH}}$ $^3J_{\text{HP}}$ 3 Hz, =CH); 4.27-4.07 (m, 8H, 4OCH₂); 4.03-3.87 (AB, 2H, J 12 Hz, CH₂N); 3.90 (dd, 1H, $^2J_{\text{HP}}$ 21 Hz, $^3J_{\text{HP}}$ 12 Hz, CHP); 2.49 (br, s, 1H, NH); 1.36, 1.32, (2t, 12H, J 6 Hz, J 6 Hz, 4CH₃); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 159.1 (=C); 149.0 (=C); 136.5 (=C); 135.8 (d, =CP, $^1J_{\text{CP}}$ 175.5 Hz); 134.1 (t, =CH₂, $^2J_{\text{CP}}$ 8.2 Hz, $^3J_{\text{CP}}$ 7.5 Hz); 122.2, 122.0, (=C); 63.2, 62.8 (2d, 2OCH₂, $^2J_{\text{CP}}$ 7.5 Hz, $^2J_{\text{CP}}$ 7.5 Hz); 62.3, 62.2 (2d, 2OCH₂, $^2J_{\text{CP}}$ 6.7 Hz, $^2J_{\text{CP}}$ 6.7 Hz); 55.3 (dd, CHP, $^1J_{\text{CP}}$ 156.7 Hz, $^2J_{\text{CP}}$ 13.5 Hz); 52.7 (d, CH₂N, $^3J_{\text{CP}}$ 14.2 Hz); 16.5, 16.3 (2d, 4CH₃, $^3J_{\text{CP}}$ 6 Hz, $^3J_{\text{CP}}$ 6 Hz); $^{31}\text{P-NMR}$ (121 MHz, CDCl_3): 16.51 (d, =CP, J 25.4 Hz); 22.24 (d, CHP, J 25.4 Hz). $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}_6\text{P}_2$: HRMS calculated for $[\text{M}+\text{H}^+]$ 421.16519, found 421.16476.

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