

## Kabachnik–Fields reactions with stable nitroxide free radicals

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This paper is dedicated to Professor György Keglevich on the occasion of his 65<sup>th</sup> birthday

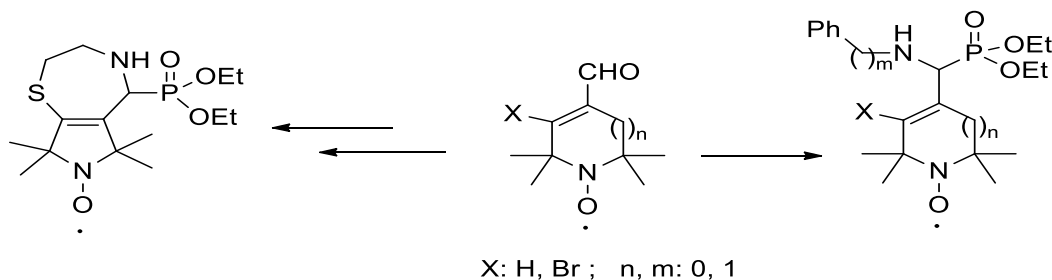
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### Abstract

The Kabachnik–Fields reaction is a multicomponent reaction that provides  $\alpha$ -aminophosphonates and phosphorus analogs of  $\alpha$ -amino acids. While paramagnetic  $\alpha$ -amino acids are well known, to the best of our knowledge, this is the first report on paramagnetic  $\alpha$ -aminophosphonate syntheses. We present examples of nitroxide-containing  $\alpha$ -aminophosphonates starting from five- and six-membered paramagnetic aldehydes, a paramagnetic ketone, and five- and six-membered paramagnetic amines. Starting from a  $\beta$ -bromo- $\alpha,\beta$  unsaturated aldehyde, we constructed a pyrroline-nitroxide-condensed heterocycle with a phosphonate ester substituent.



**Keywords:** Heterocycles, Kabachnik-Fields reaction, nitroxides, T3P<sup>®</sup>, TOAC

## Introduction

Nitroxides, as stable free radicals, have become invaluable tools for a diverse range of research fields, including biology, medicine, synthetic chemistry, materials science, and polymer chemistry.<sup>1-4</sup> These research fields require stable nitroxide free radicals with diverse substitution patterns of pyrrolidine, piperidine, pyrroline and tetrahydropyridine rings. A possible access to these multifariously substituted stable nitroxide free radicals is through the utilization of multicomponent reactions (MCRs).<sup>5</sup> In the case of stable nitroxide free radicals, only limited cases have been reported to construct complex paramagnetic structures with MCRs. Such reactions included the Hantzsch,<sup>6</sup> Biginelli,<sup>7</sup> Morita-Baylis-Hillman<sup>8</sup> Mannich<sup>9</sup> and Ugi<sup>10</sup> reactions; in addition, the latter two methodologies were used directly in spin-labeling reactions. Continuing our research interest in phosphorus-containing stable nitroxide free radicals,<sup>11,12</sup> we decided to investigate the possibilities of the Kabachnik-Fields reaction,<sup>13,14</sup> which involves the condensation of a primary or secondary amine, an aldehyde or ketone and a >P(O)H-containing reagent, which is, in most cases, a dialkyl phosphite. The classical version of the “phospha-Mannich” reactions was discovered independently by Kabachnik and Fields more than sixty years ago,<sup>15,16</sup> practically in parallel with the discovery of stable nitroxide free radicals.<sup>17</sup> A modified Kabachnik-Fields reaction was reported by Tordo’s group in the 1990s to construct  $\beta$ -phosphorylated pyrrolidine nitroxides by the reaction of nitrones with dialkylphosphites.<sup>18</sup> As far as we know, however, no other occurrence of the Kabachnik-Fields reaction with regards to nitroxide can be found in the literature. There is tremendous interest in  $\alpha$ -amino phosphonic acids and their phosphonate esters, which are analogs of  $\alpha$ -amino carboxylic acids and amino acid esters, respectively. They exhibit various biological activities, such as enzyme inhibitory,<sup>19</sup> antibacterial,<sup>20</sup> antiviral,<sup>21</sup> and antiproliferative<sup>22</sup> activities, and can be used as building blocks for peptide mimetics. These results inspired us to adopt the Kabachnik-Fields reaction for carbonyl (aldehyde or ketone)- or amino-group-containing nitroxides to give paramagnetic  $\alpha$ -aminophosphonates, including a phosphonate ester-substituted pyrrolo[3,4-f][1,4]thiazepine scaffold and a biradical.

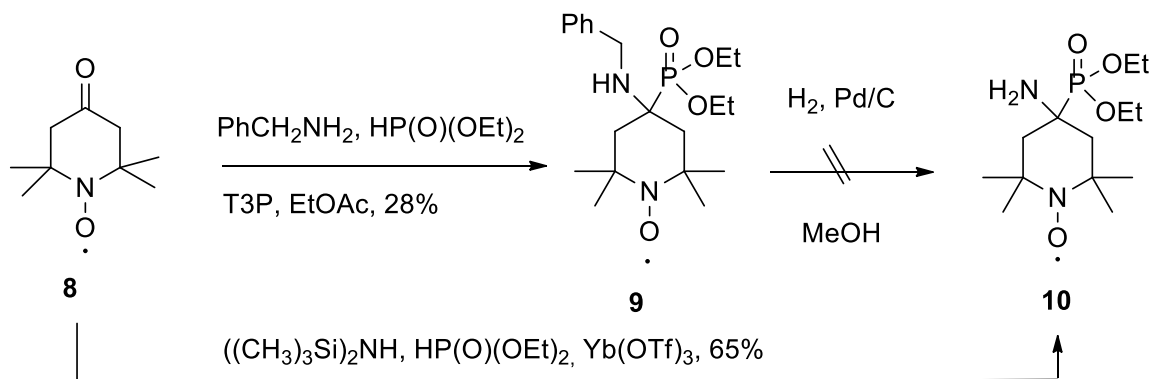
## Results and Discussion

Initially, an equimolar mixture of paramagnetic aldehydes **1a**,<sup>23</sup> **1b**<sup>24</sup> or **1c**<sup>25</sup> and aniline **2a** in the presence of 1.0 eq. of diethyl phosphite, treated with an equimolar amount of propyl phosphonic anhydride T3P<sup>®</sup> (50% EtOAc solution) in ethyl acetate, yielded  $\alpha$ -aminophosphonates **3-5** within three hours smoothly in good-to-moderate yields (72-58%) at room temperature. We also attempted the combination reaction of paramagnetic aldehyde **1a** with benzylamine **2b** and obtained the expected **6** derivative in 45% yield (Scheme 1).

Although several other catalysts, such CeCl<sub>3</sub>·7H<sub>2</sub>O,<sup>26</sup> Mg(ClO<sub>4</sub>)<sub>2</sub><sup>27</sup> or <sup>t</sup>Bu<sub>4</sub>PcAlCl<sup>28</sup> were tested, the well-known green coupling reagent (T3P<sup>®</sup>)<sup>29</sup> with its low toxicity, low allergenic potential, easy work-up and broad functional-group tolerance was the most suitable catalyst, including the retention of the nitroxide functional group also (Table 1).

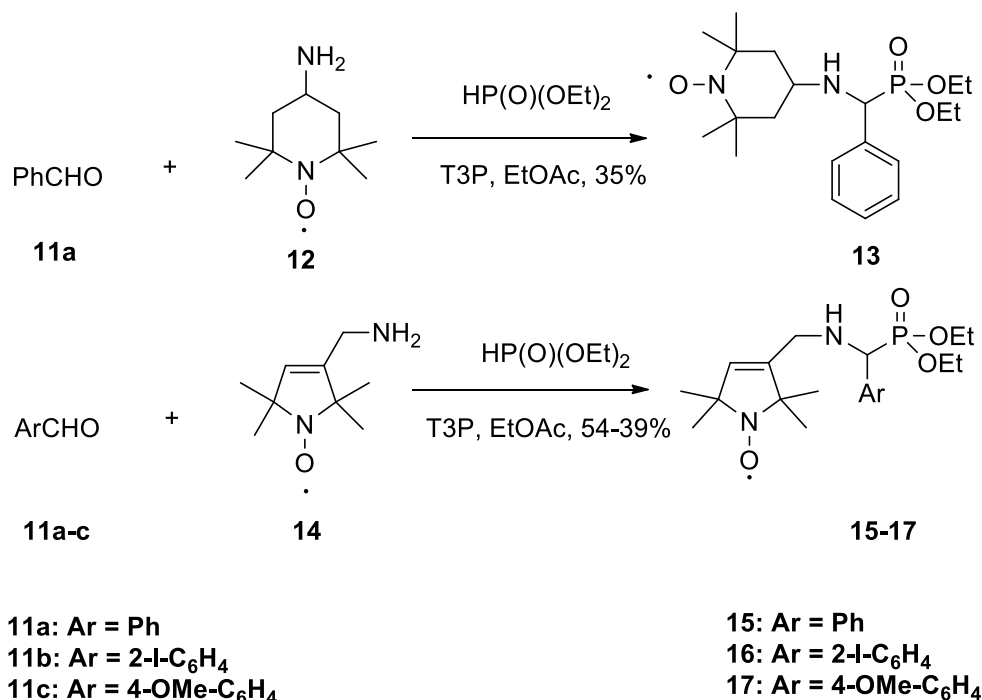


The Kabachnik-Fields reaction was also tested on ketone (TEMPONE) **8**.<sup>17</sup> Its treatment with diethyl phosphite and benzylamine in an equimolar amount of T3P<sup>®</sup> yielded aminophosphonate **9** in a 28% yield. Debenzylation of compound **9** with hydrogenation failed to form compound **10** without deterioration of the radical center (a parallel reduction to a secondary amine occurred). Therefore, we used the methodology of Sobhani et al. utilizing hexamethyldisilazane as an amine source and Yb(OTf)<sub>3</sub> as a catalyst in the Kabachnik-Fields transformation.<sup>30</sup> The resulting compound **10** can be considered a phosphorus analog of 2,2,6,6-tetramethylpiperidine-1-oxyl-4-amino-4-carboxylic acid (TOAC) (Scheme 3).



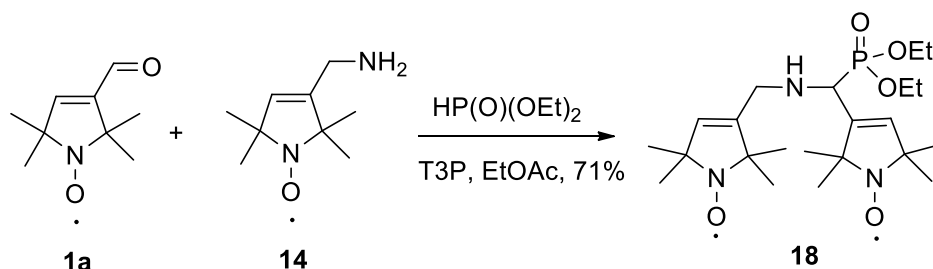
**Scheme 3.** Synthesis of the phosphorus analog of TOAC.

We wished to gauge the utility of the Kabachnik-Fields reaction on paramagnetic amines such as 4-amino-TEMPO **12**<sup>17</sup> and allyl amine **14**.<sup>31</sup> The amines mentioned above reacted with aromatic aldehydes **11a-c** and diethyl phosphite in the presence of T3P<sup>®</sup> furnishing compounds **13** and **15-17** in 35-54% yields, respectively (Scheme 4). Among the aldehydes, 2-iodobenzaldehyde **11b**, with a bulky ortho substituent, also furnished the desired  $\alpha$ -aminophosphonate **16** facily.



**Scheme 4.** Synthesis of  $\alpha$ -aminophosphonates from paramagnetic amines.

Recognizing the importance of biradicals,<sup>32</sup> we attempted to use this methodology to produce bisnitroxides. We are pleased to report, that the reaction of amine **14** with aldehyde **1a** in the presence of diethyl phosphite and T3P<sup>®</sup> gave compound **18** (Scheme 5).



**Scheme 5.** Synthesis of a biradical with the Kabachnik-Fields reaction.

## Conclusions

In conclusion, the Kabachnik–Fields reaction was successfully adapted on paramagnetic aldehydes, ketones and amines as components with diethyl phosphite in T3P<sup>®</sup>- or Yb(OTf)<sub>3</sub>- catalyzed reactions to offer variously substituted paramagnetic  $\alpha$ -aminophosphonates, including a biradical and an *N*, *S*-containing heterocycle with a phosphonate substituent. To the best of our knowledge, this is the first adaptation of the Kabachnik-Fields reaction on pyrroline, piperidine, and tetrahydropyridine nitroxides. Biological evaluations of these newly synthesized compounds are in progress.

## Experimental Section

**General.** The mass spectra were recorded with a GCMS-2020 (Shimadzu, Tokyo, Japan) operated in EI mode (70 eV) and a ThermoScientific Q-Extractive HPLC/MS/MS with ESI(+) ionization (Thermo Scientific, Waltham, MA, USA). Elemental analyses were carried out with a Fisons EA 1110 CHNS elemental analyzer (Fisons Instruments, Milan, Italy). The melting points were determined with a Boetius micro melting point apparatus (Franz Küstner Nachf. K. G., Dresden, Germany). <sup>1</sup>H NMR spectra were recorded with a Bruker Avance 3 Ascend 500 system (Bruker BioSpin Corp., Karlsruhe, Germany) operated at 500 M, and <sup>13</sup>C NMR spectra were obtained at 125 M and <sup>31</sup>P NMR 202 M in CDCl<sub>3</sub> at 298 K. The “in situ” reduction of nitroxides was achieved by adding five equivalents of hydrazobenzene (DPPH/radical). The chemical shifts ( $\delta$ ) and coupling constant (*J*) are expressed in ppm and hertz respectively. The EPR spectra were recorded using a MiniScope MS 200 (Magnettech GMBH, Berlin, Germany) in CHCl<sub>3</sub> solution, and the sample concentrations were 1.0 × 10<sup>-4</sup> M. All monoradicals gave a triplet line at  $a_{N=}$  14.4 G-15.6 G. In contrast, biradical **18** gave a quintet line  $a_{N1=}$  7.6 G,  $a_{N2=}$  14.6 G. IR spectra were obtained with a Bruker Alpha FT-IR instrument (Bruker Optics, Ettlingen, Germany) with ATR support on a diamond plate. Flash column chromatography was performed using a Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out using commercially available plates (20 × 20 × 0.02 cm) coated with Merck Kieselgel (Darmstadt, Germany) GF<sub>254</sub>. Compounds **1a**,<sup>23</sup> **1b**,<sup>24</sup> **1c**,<sup>25</sup> **8**,<sup>17</sup> **12**,<sup>17</sup> and **14**<sup>31</sup> were synthesized as previously reported. All the other reagents were purchased from Merck (Darmstadt, Germany) and Molar Chemicals (Halásztelek, Hungary).

**General procedure for synthesis of  $\alpha$ -aminophosphonates, compounds 3, 4, 5, 6, 9, 13, 15, 16, 17, 18.** To the stirred mixture of aldehyde (2.0 mmol), amine (2.0 mmol), T3P<sup>®</sup> (1.2 mL, 2.0 mmol, Aldrich, 50% solution in EtOAc) in EtOAc (2 mL) after 5 min. diethyl phosphite (258  $\mu$ L, 2.0 mmol) was added, and the mixture was stirred at 25 °C. After completion of the reaction (~ 3h) as monitored by thin layer chromatography, the mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NaHCO<sub>3</sub> solution (10 mL), the organic phase, was separated, dried (MgSO<sub>4</sub>), filtered, and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc or CHCl<sub>3</sub>/Et<sub>2</sub>O) to afford  $\alpha$ -aminophosphonates as a solid or as an oil in 72 - 28% yields.

**(Diethyl ((phenylamino)(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate-1-yl)oxydanyl (3).** 495 mg (65%), yellow powder, mp 123-125 °C, R<sub>f</sub>: 0.51 (CHCl<sub>3</sub>/MeOH, 59/1). IR ( $\nu$ ) cm<sup>-1</sup>: 3269, 2976, 1600, 1530. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 22.6; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 1.22 (s, 3H, 1  $\times$  C(CH<sub>3</sub>)), 1.25 (s, 6H, 1  $\times$  C(CH<sub>3</sub>)<sub>2</sub>), 1.34 (t, 6H, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>HH</sub> 7), 1.39 (s, 3H, C(CH<sub>3</sub>)), 3.84 (m, 1H, NH), 4.05 (d, 1H, CH, *J*<sub>HH</sub> 8) 4.17-4.22 (m, 4H, OCH<sub>2</sub>), 6.25 (s, 1H, HC=C), 6.75-6.84 (m, 3H, ArH), 2 aromatic protons overlap with (PhNH)<sub>2</sub> protons. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 16.51 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 6), 16.54 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 6), 24.5 (s, 1C, C(CH<sub>3</sub>)), 25.1 (s, 1C, C(CH<sub>3</sub>)) 25.4 (s, 1C, C(CH<sub>3</sub>)), 25.7 (s, 1C, C(CH<sub>3</sub>)), 48.6 (d, 1C, CHP, *J*<sub>CP</sub> 164), 62.6 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 63.2 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 68.0 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 71.0 (d, 1C, C(CH<sub>3</sub>)<sub>2</sub>, *J*<sub>CP</sub> 9), 113.8 (s, 2C, ArC), 118.5 (s, 2C, ArC), 129.3 (s, 1C, HC=C), 134.7 (s, 1C, ArC), 140.5 (d, 1C, C=CCHP, *J*<sub>CP</sub> 3), 146.5 (d, 1C, ArC, *J*<sub>CP</sub> 3). MS (EI): *m/z* (%): 381 (M<sup>+</sup>, 4), 351 (1), 229 (23), 214 (77), 55 (100). Anal calcd. for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>P: C, 59.83; H, 7.93; N, 7.34. Found: 59.80; H, 7.77; N, 7.32

**(Diethyl ((phenylamino)(4-bromo-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate-1-yl)oxydanyl (4).** 662mg (72%), off-white powder, mp 177-179 °C, R<sub>f</sub>: 0.41 (CHCl<sub>3</sub>/Et<sub>2</sub>O, 2/1), IR ( $\nu$ ) cm<sup>-1</sup>: 3315, 2977, 1602, 1519. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 20.7; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 1.22 (s, 3H, 1  $\times$  C(CH<sub>3</sub>)), 1.34 (m, 9H, CH<sub>2</sub>CH<sub>3</sub> and 1  $\times$  C(CH<sub>3</sub>)<sub>2</sub>), 1.37 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>HH</sub> 7), 1.48 (s, 3H, C(CH<sub>3</sub>)), 4.21-4.25 (m, 4H, OCH<sub>2</sub>), 4.58 (m, 1H, NH), 4.90 (dd, 1H, CH, <sup>1</sup>*J*<sub>PH</sub> 29, <sup>2</sup>*J*<sub>HH</sub> 8), 6.80-7.25 (m, 3H, ArH), 2 aromatic protons overlap with (PhNH)<sub>2</sub> protons. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 16.4 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 6), 16.5 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 6), 23.5 (s, 1C, C(CH<sub>3</sub>)), 24.4 (s, 1C, C(CH<sub>3</sub>)) 25.0 (s, 1C, C(CH<sub>3</sub>)), 25.4 (s, 1C, C(CH<sub>3</sub>)), 51.7 (d, 1C, CHP, *J*<sub>CP</sub> 155), 62.9 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 63.0 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 70.3 (d, 1C, C(CH<sub>3</sub>)<sub>2</sub>, *J*<sub>CP</sub> 3), 71.0 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 112.4 (s, 1C, BrC=C), 119.8 (s, 1C, ArC), 129.3 (s, 2C, ArC), 136.7 (s, 1C, BrC=C), 146.5 (d, 1C, ArC *J*<sub>CP</sub> 13). A band of two aromatic carbons overlaps with carbon signal of (PhNH)<sub>2</sub>. MS (EI): *m/z* (%): 461/459 (M<sup>+</sup>, 7/7), 350 (13), 324/322 (20/20), 294/292 (100/100), 77 (47). Anal calcd. for C<sub>19</sub>H<sub>29</sub>BrN<sub>2</sub>O<sub>4</sub>P: C, 49.57; H, 6.35; N, 6.09. Found: C, 49.67; H, 6.10; N, 6.18.

**(Diethyl ((phenylamino)(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)phosphonate-1-yl)oxydanyl (5).** 458 mg (58%), dark yellow powder mp: 82-84 °C, R<sub>f</sub>: 0.40 (CHCl<sub>3</sub>/Et<sub>2</sub>O, 2/1). IR ( $\nu$ ) cm<sup>-1</sup>: 3301, 2979, 1600, 1516. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 22.7; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 1.12 (s, 3H, 1  $\times$  C(CH<sub>3</sub>)), 1.29 (s, 6H, 1  $\times$  C(CH<sub>3</sub>)<sub>2</sub>), 1.35 (s, 3H, C(CH<sub>3</sub>)), 1.38 (t, 6H, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>HH</sub> 7), 2.26 (s, 2H, C=CCH<sub>2</sub>), 4.16-4.25 (m, 4H, OCH<sub>2</sub>), 4.54 (m, 1H, CHP), 5.66 (d, 1H, HC=C, *J*<sub>HH</sub> 3), 6.79-7.28 (m, 3H, ArH), 2 aromatic protons overlap with (PhNH)<sub>2</sub> protons, NH band is missing. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 16.5 (t, 2C, 2  $\times$  CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 7), 24.8 (s, 2C, C(CH<sub>3</sub>)<sub>2</sub>), 26.1 (s, 2C, C(CH<sub>3</sub>)<sub>2</sub>), 40.4 (s, 1C, C=CCH<sub>2</sub>), 56.2 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>, *J*<sub>CP</sub> 33), 59.8 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 62.7 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 63.3 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 114.1 (s, 2C, ArC), 118.6 (s, 2C, ArC), 126.1 (s, 1C, HC=C), 134.7 (d, 1C, HC=C, *J*<sub>CP</sub> 6), 146.5 (d, ArC, 1C, *J*<sub>CP</sub> 14). A band of an aromatic carbons overlaps with carbon signal of (PhNH)<sub>2</sub>. MS (EI): *m/z* (%): 395 (M<sup>+</sup>, 14), 365 (2), 309 (10), 294 (14), 258 (12), 228 (100). Anal calcd. for C<sub>20</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>P: C, 60.74; H, 8.16; N, 7.08. Found: C, 60.69; H, 7.93; N, 7.08.

**(Diethyl ((benzylamino)(2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate-1-yl)oxydanyl (6).** 221 mg (28%), yellow oil, R<sub>f</sub>: 0.40 (CHCl<sub>3</sub>/MeOH, 59/1). IR ( $\nu$ ) cm<sup>-1</sup>: 3286, 2979, 1600. <sup>31</sup>P NMR (CDCl<sub>3</sub> +

(PhNH)<sub>2</sub> δ: 23.3; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 1.32 (s, 6H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.34 (s, 6H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.42 (t, 6H, 2 × CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>HH</sub> 7), 2.11 (s, 1H, NH), 3.46 (d, 1H, CHP, *J*<sub>HH</sub> 19), 3.84 (d, 1H, CHPh, *J*<sub>HH</sub> 13), 4.00 (d, 1H, CHPh, *J*<sub>HH</sub> 13), 4.18-4.30 (m, 4H, OCH<sub>2</sub>) 6.05 (s, 1H, C=CH), 7.32-7.39 (m, 5H, ArH). <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 16.5 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 6), 16.6 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 6), 24.1 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 24.2 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 25.1 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 25.2 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 51.6 (d, 1C, CH<sub>2</sub>Ph, *J*<sub>CP</sub> 11), 51.8 (d, 1C, CHP, *J*<sub>CP</sub> 156), 62.8 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 62.9 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 69.1 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 69.2 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 127.2 (s, 1C, HC=C), 128.3 (s, 2C, ArC), 128.4 (s, 2C, ArC), 133.7 (s, 1C, ArC), 139.5 (s, 1C, ArC), 140.2 (s, 1C, C=CCHP). MS (EI): *m/z* (%): 395 (M<sup>+</sup>, 2), 365 (1), 258 (30), 228 (74), 91 (100). Anal calcd. for C<sub>20</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>P: C, 60.74; H, 8.16; N, 7.08. Found: C, 60.79; H, 7.96; N, 7.09

**(Diethyl (4-(benzylamino)-2,2,6,6-tetramethylpiperidin-4-yl)phosphonate-1-yl)oxydanyl (9)**. 246 mg (31%, orange oil, R<sub>f</sub>: 0.48 (CHCl<sub>3</sub>/MeOH, 59/1). IR (ν) cm<sup>-1</sup>: 3319, 2972, 2927, 1663, 1601. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 27.8; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 1.28 (s, 6H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.41 (t, 6H, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>HH</sub> 7), 1.58 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.96 (dd, 2H, CH<sub>2</sub>, <sup>1</sup>*J*<sub>HH</sub> 14, <sup>2</sup>*J*<sub>HH</sub> 2), 2.09 (dd, 2H, CH<sub>2</sub>, <sup>1</sup>*J*<sub>HH</sub> 6, <sup>2</sup>*J*<sub>HH</sub> 8), 4.11 (dd, 2H, PhCH<sub>2</sub>, <sup>1</sup>*J*<sub>HH</sub> 2, <sup>2</sup>*J*<sub>HH</sub> 4), 4.19-4.25 (q, 4H, OCH<sub>2</sub>, *J*<sub>HH</sub> 7), 7.29-7.42 (m, ArH, 5H), NH band is not detected. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 16.7 (d, 2C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 5), 20.8 (s, 4C, 2 × C(CH<sub>3</sub>)<sub>2</sub>), 33.1 (s, 1C, CH<sub>2</sub>), 40.8 (s, 1C, CH<sub>2</sub>), 48.1 (s, 1C, PhCH<sub>2</sub>), 57.2 (d, 1C, H<sub>2</sub>NCP, *J*<sub>CP</sub> 131), 57.9 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 58.1 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 61.9 (d, 2C, 2 × OCH<sub>2</sub>, *J*<sub>CP</sub> 8), 126.9 (s, 1C, ArC), 128.1 (s, 2C, ArC), 128.5 (s, 2C, ArC), 140.7 (s, 1C, ArC). MS (EI): *m/z* (%): 397 (M<sup>+</sup>, 1), 260 (14), 245 (2), 214 (13), 91 (100). Anal calcd. for C<sub>20</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>P: C, 60.44; H, 8.62; N, 7.05. Found: C, 60.22; H, 8.49; N, 6.85.

**(Diethyl (((2,2,6,6-tetramethylpiperidin-4-yl)amino)(phenyl)methyl)phosphonate-1-yl)oxydanyl (13)**. 278 mg (35%), pink solid, mp: 81-83 °C, R<sub>f</sub>: 0.31 (CHCl<sub>3</sub>/Et<sub>2</sub>O, 2/1). IR (ν) cm<sup>-1</sup>: 3311, 2974, 1601. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 23.8; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 1.00 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.04 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.17 (m, 2H, 2 × CHHCP), 1.20 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.24 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.34 (t, 6H, CH<sub>3</sub>CH<sub>2</sub>, *J*<sub>HH</sub> 7), 1.67 (d, 1H, CHHCPN, *J*<sub>HH</sub> 12), 1.90 (d, 1H, CHHCPN, *J*<sub>HH</sub> 12), 2.82 (1H, m, CH<sub>2</sub>CHCH<sub>2</sub>), 3.83-4.16 (m, 4H, OCH<sub>2</sub>), 4.20 (d, 1H, CHP, *J*<sub>PH</sub> 21), 7.23-7.43 (m, 3H, ArH), 2 aromatic protons overlap with (PhNH)<sub>2</sub> protons, NH band is not detected. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 16.3 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 5), 16.5 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 5), 19.9 (s, 2C, 2 × C(CH<sub>3</sub>)<sub>2</sub>), 20.1 (s, 2C, 2 × C(CH<sub>3</sub>)<sub>2</sub>), 32.0 (s, 1C, CH<sub>2</sub>), 32.2 (s, 1C, CH<sub>2</sub>), 45.6 (d, 1C, CH<sub>2</sub>CHCH<sub>2</sub>, *J*<sub>CP</sub> 15.1), 46.2 (d, 1C, CHPNH, *J*<sub>CP</sub> 112), 57.5 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 58.7 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 62.8 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 63.1 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 127.8 (s, 1C, ArC), 127.9 (s, 2C, ArC), 128.3 (s, 2C, ArC), 136.5 (d, 1C, ArC, *J*<sub>CP</sub> 4). High-resolution MS (ESI): *m/z* [M]<sup>+</sup> calc. for C<sub>20</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>P<sup>+</sup>: 398.2334; found: 398.2328. Anal calcd. for C<sub>20</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>P: C, 60.44; H, 8.62; N, 7.05. Found: C, 60.13; H, 8.57; N, 6.95.

**(Diethyl (((2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)amino)(phenyl)methyl)phosphonate-1-yl)oxydanyl (15)**. 426 mg (54%), yellow oil, R<sub>f</sub>: 0.30 (CHCl<sub>3</sub>/Et<sub>2</sub>O, 2/1). IR (ν) cm<sup>-1</sup>: 3287, 2972, 2930, 1495. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 23.6; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 1.21 (t, 6H, 2 × CH<sub>3</sub>CH<sub>2</sub>, *J*<sub>HH</sub> 7), 1.24 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.28 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.36 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 2.10 (s, 1H, NH), 3.17 (dd, 2H, CH<sub>2</sub>NH, <sup>1</sup>*J*<sub>PH</sub> 86, <sup>2</sup>*J*<sub>HH</sub> 14), 3.87-4.13 (m, 4H, OCH<sub>2</sub>), 4.16 (d, 1H, CHP, *J*<sub>HH</sub> 10), 5.57 (s, 1H, HC=C), 7.37-7.44 (m, 4H, ArH), 1 aromatic proton overlap with (PhNH)<sub>2</sub> protons. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 16.3 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 5), 16.5 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>, *J*<sub>CP</sub> 5), 24.0 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 24.1 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 25.3 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 25.4 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 44.5 (d, 1C, CH<sub>2</sub>N, *J*<sub>CP</sub> 17), 60.3 (d, 1C, CHP, *J*<sub>CP</sub> 153), 62.8 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 63.0 (d, 1C, OCH<sub>2</sub>, *J*<sub>CP</sub> 7), 71.5 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 71.6 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 123.1 (s, 1C, HC=C), 128.0 (s, 1C, ArC), 128.1 (s, 2C, ArC), 128.6 (s, 2C, ArC), 135.6 (d, 1C, ArC, *J*<sub>CP</sub> 4), 142.4 (s, 1C, HC=C). MS (EI): *m/z* (%): 395 (M<sup>+</sup>, 13), 365 (1), 258 (55), 228 (33), 57 (100). Anal calcd. for C<sub>20</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>P: C, 60.74; H, 8.16; N, 7.08. Found: C, 60.66; H, 8.12; N, 6.92

**(Diethyl (((2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)amino)(2-iodophenyl)methyl)phosphonate-1-yl)oxydanyl (16)**. 427 mg (41%), yellow solid, mp: 93-95 °C, R<sub>f</sub>: 0.34 (CHCl<sub>3</sub>/MeOH, 59/1). IR (ν) cm<sup>-1</sup>: 3319, 2980, 2926, 1583, 1562. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 23.2; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>) δ: 1.19 (t, 3H, CH<sub>3</sub>CH<sub>2</sub>, *J*<sub>HH</sub> 7), 1.27 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.29 (s, 3H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.34 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.35 (s, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.42

(t, 3H,  $\text{CH}_3\text{CH}_2$ ,  $J_{\text{HH}}$  7), 2.09 (s, 1H, NH), 3.15 (dd, 2H,  $\text{CH}_2\text{NH}$ ,  $^1J_{\text{PH}}$  75,  $^2J_{\text{HH}}$  15), 3.82-4.31 (m, 4H,  $\text{OCH}_2$ ), 4.67 (d, 1H,  $\text{CHP}$ ,  $J_{\text{PH}}$  20), 5.58 (s, 1H,  $\text{HC}=\text{C}$ ), 7.05 (m, 1H, ArH), 7.45 (t, 2H, ArH,  $J_{\text{HH}}$  7), 7.69 (d, 1H, ArH,  $J_{\text{HH}}$  8), 7.92 (d, 1H, ArH,  $J_{\text{HH}}$  8).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 16.3 (d, 1C,  $\text{CH}_2\text{CH}_3$ ,  $J_{\text{CP}}$  5), 16.5 (d, 1C,  $\text{CH}_2\text{CH}_3$ ,  $J_{\text{CP}}$  5), 24.1 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 24.4 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 25.5 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 25.7 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 44.3 (d, 1C,  $\text{CH}_2\text{N}$ ,  $J_{\text{CP}}$  17), 63.0 (d, 1C,  $\text{OCH}_2$ ,  $J_{\text{CP}}$  7), 63.1 (d, 1C,  $\text{OCH}_2$ ,  $J_{\text{CP}}$  7), 63.4 (d, 1C,  $\text{CHP}$ ,  $J_{\text{CP}}$  153), 68.3 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 70.8 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 102.1 (d, 1C, ArC,  $J_{\text{CP}}$  8), 128.6 (s, 1C,  $\text{HC}=\text{C}$ ), 129.5 (s, 1C, ArC), 129.6 (s, 1C, ArC), 129.7 (s, 1C, ArC), 138.9 (d, 1C, ArC,  $J_{\text{CP}}$  4), 139.7 (s, 1C,  $\text{HC}=\text{C}$ ), 142.2 (s, 1C, ArC). MS (EI):  $m/z$  (%): 521 ( $\text{M}^+$ , 1), 491 (<1), 384 (18), 232 (35), 57 (100). Anal. calcd. for  $\text{C}_{20}\text{H}_{31}\text{N}_2\text{O}_4\text{P}$ : C, 46.08; H, 5.99; N, 5.37. Found: C, 45.85; H, 5.77; N, 5.23

**(Diethyl (((2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)amino)(4-methoxyphenyl)methyl)phosphonate-1yl)oxydanyl (17)**. 663 mg (39%), yellow oil,  $R_f$ : 0.37 ( $\text{CHCl}_3/\text{MeOH}$ , 59/1). IR ( $\nu$ )  $\text{cm}^{-1}$ : 3286, 1609, 1510.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 23.8;  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 1.22 (t, 3H,  $\text{CH}_3\text{CH}_2$ ,  $J_{\text{HH}}$  7), 1.25 (s, 3H,  $1 \times \text{C}(\text{CH}_3)$ ), 1.28 (s, 3H,  $1 \times \text{C}(\text{CH}_3)$ ), 1.33 (s, 3H,  $1 \times \text{C}(\text{CH}_3)$ ), 1.34 (s, 3H,  $1 \times \text{C}(\text{CH}_3)$ ), 1.36 (t, 3H,  $\text{CH}_3\text{CH}_2$ ,  $J_{\text{HH}}$  7), 2.09 (s, 1H, NH), 3.16 (dd, 2H,  $\text{CH}_2\text{NH}$ ,  $^1J_{\text{PH}}$  87,  $^2J_{\text{HH}}$  15), 3.86 (s, 3H,  $\text{OCH}_3$ ), 3.89-4.19 (m, 4H,  $\text{OCH}_2$ ), 4.12 (d, 1H,  $\text{CHP}$ ,  $J_{\text{PH}}$  20), 5.56 (s, 1H,  $\text{HC}=\text{C}$ ), 6.96 (d, 2H, ArH,  $J_{\text{HH}}$  8), 7.39 (d, 2H, ArH,  $J_{\text{HH}}$  7).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 16.3 (d, 1C,  $\text{CH}_2\text{CH}_3$ ,  $J_{\text{CP}}$  5), 16.5 (d, 1C,  $\text{CH}_2\text{CH}_3$ ,  $J_{\text{CP}}$  5), 24.1 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 24.3 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 25.4 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 25.5 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 44.4 (d, 1C,  $\text{CH}_2\text{N}$ ,  $J_{\text{CP}}$  17), 55.3 (s, 1C,  $\text{OCH}_3$ ), 59.5 (d, 1C,  $\text{CHP}$ ,  $J_{\text{CP}}$  154), 62.8 (d, 1C,  $\text{OCH}_2$ ,  $J_{\text{CP}}$  7), 62.9 (d, 1C,  $\text{OCH}_2$ ,  $J_{\text{CP}}$  7), 68.6 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 71.1 (s, 1C,  $\text{C}(\text{CH}_3)_2$ ), 114.0 (s, 2C, ArC), 127.5 (s, 1C,  $\text{HC}=\text{C}$ ), 129.71 (s, 2C, ArC), 129.76 (s, 1C, ArC), 142.4 (s, 1C,  $\text{HC}=\text{C}$ ), 159.4 (s, 1C, ArC). MS (EI):  $m/z$  (%): 425 ( $\text{M}^+$ , 4), 395 (1), 288 (87), 258 (47), 136 (100). Anal. calcd for:  $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_5\text{P}$ : C, 59.28; H, 8.05; N, 6.58. Found: C, 59.16; H, 8.02; N, 6.51.

**(Diethyl ((2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl) (((2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)amino)methyl)phosphonate)-1,1-diyl)dioxydanyl (18)**. 648 mg, (71%), red oil,  $R_f$ : 0.34 ( $\text{CHCl}_3/\text{MeOH}$ , 59/1). IR ( $\nu$ )  $\text{cm}^{-1}$ : 3466, 2975, 2930, 1647.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 23.6;  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 1.35 (s, 12H,  $2 \times \text{C}(\text{CH}_3)_2$ ), 1.37 (s, 9H,  $1.5 \times \text{C}(\text{CH}_3)_2$ ), 1.41 (s, 3H,  $\text{C}(\text{CH}_3)$ ), 1.43 (t, 6H,  $\text{CH}_3\text{CH}_2$ ,  $J_{\text{HH}}$  7), 3.36 (dd, 2H,  $^1J_{\text{PH}}$  105,  $^2J_{\text{HH}}$  15), 3.48 (d, 1H,  $J_{\text{HH}}$  15), 4.22-4.31 (m, 4H,  $\text{OCH}_2$ ), 5.68 (s, 1H,  $4'\text{-HC}=\text{C}$ ), 6.02 (d, 1H,  $4\text{-HC}=\text{C}$ ,  $J_{\text{HP}}$  2.5), NH is signal is missing.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 16.6 (d, 2C,  $\text{CH}_2\text{CH}_3$ ,  $J_{\text{CP}}$  6), 24.7 (s, 2C,  $\text{C}(\text{CH}_3)_2$ ), 24.8 (s, 2C,  $\text{C}(\text{CH}_3)_2$ ), 25.0 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 25.82 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 25.87 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 26.0 (s, 1C,  $\text{C}(\text{CH}_3)$ ), 45.0 (d, 1C,  $6'\text{-CH}_2\text{N}$ ,  $J_{\text{CP}}$  13), 52.9 (d, 1C,  $6\text{-CHP}$ ,  $J_{\text{CP}}$  155), 62.7 (d, 1C,  $\text{OCH}_2$ ,  $J_{\text{CP}}$  7), 62.9 (d, 1C,  $\text{OCH}_2$ ,  $J_{\text{CP}}$  7), 67.9 (s, 2C,  $2'\text{-C}(\text{CH}_3)_2$  and  $5'\text{-C}(\text{CH}_3)_2$ ), 70.5 (s, 1C,  $5\text{-C}(\text{CH}_3)_2$ ), 71.1 (d, 1C,  $2\text{-C}(\text{CH}_3)_2$ ,  $J_{\text{CP}}$  7), 128.9 (s, 1C,  $4\text{-HC}=\text{C}$ ), 134.5 (d, 1C,  $3\text{-HC}=\text{C}$ ,  $J_{\text{CP}}$  7), 139.9 (s, 1C,  $4'\text{-HC}=\text{C}$ ), 143.1 (s, 1C,  $3'\text{-HC}=\text{C}$ ). See numbering in SM. MS (EI):  $m/z$  (%): 457 ( $\text{M}^+$ , 8), 427 (2), 320 (30), 290 (81), 260 (59), 138 (100). Anal. calcd. for  $\text{C}_{22}\text{H}_{40}\text{N}_3\text{O}_5\text{P}$ : C, 57.75; H, 8.81; N, 9.18. Found: C, 57.50; H, 8.56; N, 8.98.

**(Diethyl (6,6,8,8-tetramethyl-3,4,5,6,7,8-hexahydro-2H-pyrrolo[3,4-f][1,4]thiazepin-5-yl)phosphonate-7yl)oxydanyl (7)**.

To a suspension of compound **1b** (494 mg, 2.0 mmol) and cysteamine hydrochloride (227 mg, 2.0 mmol) in acetonitrile (10 mL) DBU (638 mg, 4.2 mmol) was added in one portion, and the mixture was stirred overnight at 25 °C. The solvent was evaporated off, the residue was dissolved in EtOAc (20 mL), the organic phase washed with water (10 mL), separated, dried, filtered, and then T3P® (1.2 mL, 2.0 mmol, Aldrich, 50% solution in EtOAc) was added followed by addition of diethyl phosphite (258  $\mu\text{L}$ , 2.0 mmol). The reaction mixture was heated at reflux temperature for 8h. After cooling, the solution was washed with sat. aq.  $\text{NaHCO}_3$  solution (10 mL), the organic phase, was separated, dried ( $\text{MgSO}_4$ ), filtered, and evaporated. The residue was purified by flash column chromatography to give the title compound as a thick yellow oil of 138 mg (19%),  $R_f$ : 0.39 ( $\text{CHCl}_3/\text{MeOH}$ , 59/1). IR ( $\nu$ )  $\text{cm}^{-1}$ : 3636, 2976, 2928, 1635.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 23.4;  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $(\text{PhNH})_2$ )  $\delta$ : 1.30 (s, 3H,  $1 \times \text{C}(\text{CH}_3)$ ), 1.32 (s, 3H,  $1 \times \text{C}(\text{CH}_3)$ ), 1.37 (s, 6H,  $1 \times \text{C}(\text{CH}_3)_2$ ), 1.40 (t, 6H,  $\text{CH}_3\text{CH}_2$ ,  $J_{\text{HH}}$  7),



2.75 (m, 1H, SCHH), 3.10 (m, 1H, SCHH), 3.29 (m, 1H, CHHNH), 3.74 (m, 1H, CHHNH), 4.01 (d, 1H, CHP,  $J_{HP}$  26), 4.21-4.23 (q, 4H, OCH<sub>2</sub>,  $J_{HH}$  7), NH band is not detected. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 16.4 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>,  $J_{CP}$  5), 16.6 (d, 1C, CH<sub>2</sub>CH<sub>3</sub>,  $J_{CP}$  5), 23.8 (s, 1C, C(CH<sub>3</sub>)), 23.9 (s, 1C, C(CH<sub>3</sub>)), 24.4 (s, 1C, C(CH<sub>3</sub>)), 24.7 (s, 1C, C(CH<sub>3</sub>)), 35.2 (d, 1C, CH<sub>2</sub>S,  $J_{CP}$  4), 48.7 (d, 1C, CH<sub>2</sub>NH  $J_{CP}$  5), 54.4 (d, 1C, CHP,  $J_{CP}$  141), 62.1 (d, 1C, OCH<sub>2</sub>,  $J_{CP}$  7), 62.4 (d, 1C, OCH<sub>2</sub>,  $J_{CP}$  7), 70.96 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 70.98 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 138.5 (s, 1C, SC=C), 141.0 (d, 1C, SC=C,  $J_{CP}$  7.5). MS (EI):  $m/z$  (%): 363 (M<sup>+</sup>, 4), 333 (<1), 226 (34), 21 (100). Anal calcd. for C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>PS: C, 49.57; H, 7.77; N, 7.71; S, 8.82. Found: C, 49.47; H, 7.65; N, 7.49; S, 8.74.

#### (Diethyl (4-amino-2,2,6,6-tetramethylpiperidin-4-yl)phosphonate-1-yl)oxydanyl (10).

A mixture of TEMPONE **8** (1.7 g, 10.0 mmol), hexamethyldisilazane (1.67 mL, 8.0 mmol), diethyl phosphite (1.03 mL, 8.0 mmol), and ytterbium triflate (100 mg, 0.16 mmol) was stirred in an oil bath at 80 °C for 2h. The reaction mixture was cooled, and 1.0 M aq. HCl (30 mL) was added and extracted with EtOAc (2 × 10 mL), and the organic phase was discarded. The aqueous phase was transferred to a 500 mL beaker and basified by adding solid K<sub>2</sub>CO<sub>3</sub> to pH=9 (**caution: vigorous foaming!**), and the product was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried over MgSO<sub>4</sub>, filtered, and evaporated, and the residue was purified by flash column chromatography to afford a pink solid of 1.59 g (65%), mp: 80-82 °C, R<sub>f</sub>: 0.41 (CHCl<sub>3</sub>/MeOH, 59/1). IR ( $\nu$ ) cm<sup>-1</sup>: 3514, 3423, 3370, 2976, 2929. <sup>31</sup>P NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 28.8; <sup>1</sup>H NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 1.27 (s, 6H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.39 (t, 6H, CH<sub>2</sub>CH<sub>3</sub>,  $J_{HH}$  7), 1.56 (s, 6H, 1 × C(CH<sub>3</sub>)<sub>2</sub>), 1.73 (d, 2H, CH<sub>2</sub>,  $J_{HH}$  13), 2.04 (m, 2H, CH<sub>2</sub>), 4.15-4.21 (m, 4H, OCH<sub>2</sub>), NH<sub>2</sub> band is not detected. <sup>13</sup>C NMR (CDCl<sub>3</sub> + (PhNH)<sub>2</sub>)  $\delta$ : 16.6 (d, 2C, CH<sub>2</sub>CH<sub>3</sub>,  $J_{CP}$  6), 21.6 (s, 4C, 2 × C(CH<sub>3</sub>)<sub>2</sub>), 33.4 (s, 1C, CH<sub>2</sub>), 42.4 52.3 (d, 1C, H<sub>2</sub>NCP,  $J_{CP}$  142), 58.0 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 58.2 (s, 1C, C(CH<sub>3</sub>)<sub>2</sub>), 62.4 (d, 2C, 2 × OCH<sub>2</sub>,  $J_{CP}$  =8). MS (EI):  $m/z$  (%): 307 (M<sup>+</sup>, 7), 275 (3), 221 (13), 170 (35), 138 (33), 97 (100). Anal calcd. for C<sub>13</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 50.80; H, 9.18; N, 9.11. Found: C, 50.69; H, 8.98; N, 9.01.

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## Supplementary Material

<sup>1</sup>H and <sup>13</sup>C NMR spectra and EPR of the biradical are provided in the supplementary material associated with this manuscript.

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