

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 65th birthday

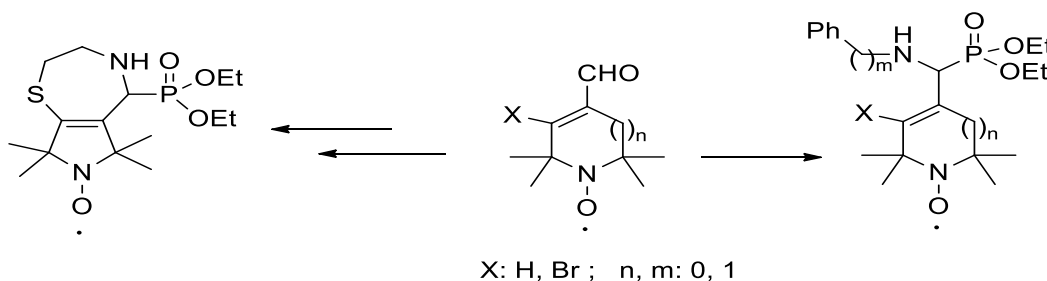
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Abstract

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



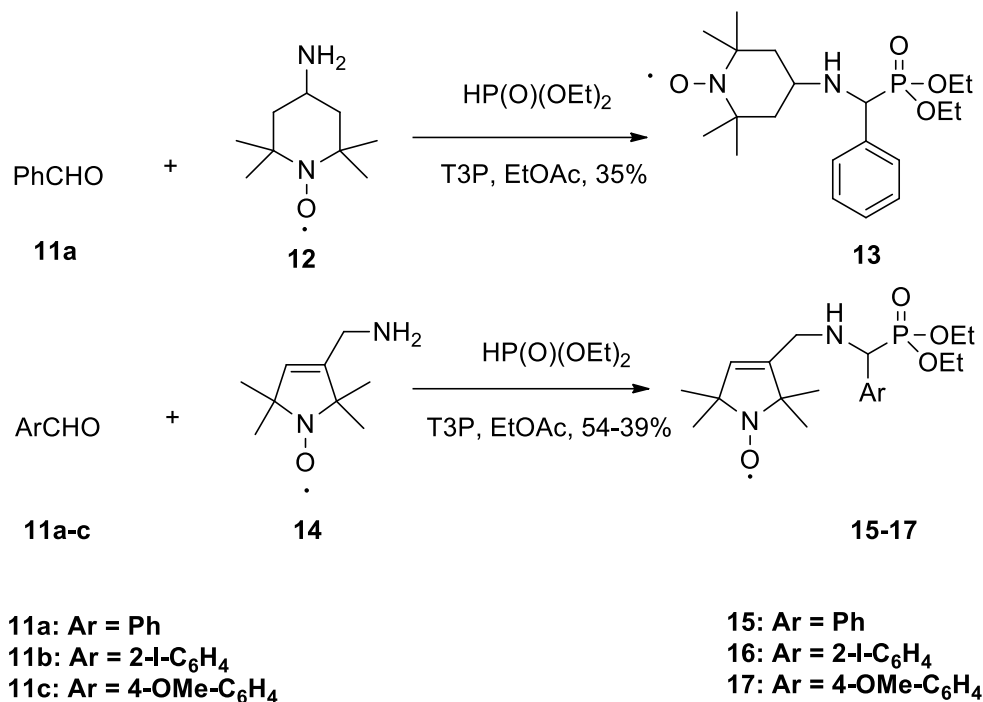
Keywords: Heterocycles, Kabachnik-Fields reaction, nitroxides, T3P®, TOAC

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.¹⁻⁴ 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).⁵ 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,⁶ Biginelli,⁷ Morita-Baylis-Hillman⁸ Mannich⁹ and Ugi¹⁰ 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,^{11,12} we decided to investigate the possibilities of the Kabachnik-Fields reaction,^{13,14} 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,^{15,16} practically in parallel with the discovery of stable nitroxide free radicals.¹⁷ A modified Kabachnik-Fields reaction was reported by Tordo’s group in the 1990s to construct β -phosphorylated pyrrolidine nitroxides by the reaction of nitrones with dialkylphosphites.¹⁸ 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 α -amino phosphonic acids and their phosphonate esters, which are analogs of α -amino carboxylic acids and amino acid esters, respectively. They exhibit various biological activities, such as enzyme inhibitory,¹⁹ antibacterial,²⁰ antiviral,²¹ and antiproliferative²² 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 α -aminophosphonates, including a phosphonate ester-substituted pyrrolo[3,4-f][1,4]thiazepine scaffold and a biradical.

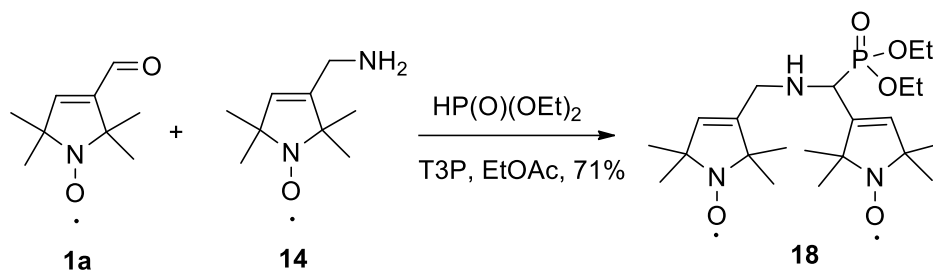
Results and Discussion

Initially, an equimolar mixture of paramagnetic aldehydes **1a**,²³ **1b**²⁴ or **1c**²⁵ and aniline **2a** in the presence of 1.0 eq. of diethyl phosphite, treated with an equimolar amount of propyl phosphonic anhydride T3P® (50% EtOAc solution) in ethyl acetate, yielded α -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).



Scheme 4. Synthesis of α -aminophosphonates from paramagnetic amines.

Recognizing the importance of biradicals,³² 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[®] 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[®]- or Yb(OTf)₃- catalyzed reactions to offer variously substituted paramagnetic α -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). ¹H NMR spectra were recorded with a Bruker Avance 3 Ascend 500 system (Bruker BioSpin Corp., Karlsruhe, Germany) operated at 500 M, and ¹³C NMR spectra were obtained at 125 M and ³¹P NMR 202 M in CDCl₃ at 298 K. The “in situ” reduction of nitroxides was achieved by adding five equivalents of hydrazobenzene (DPPH/radical). The chemical shifts (δ) 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 CHCl₃ solution, and the sample concentrations were 1.0 × 10⁻⁴ 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) GF₂₅₄. Compounds **1a**,²³ **1b**,²⁴ **1c**,²⁵ **8**,¹⁷ **12**,¹⁷ and **14**³¹ 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 α-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® (1.2 mL, 2.0 mmol, Aldrich, 50% solution in EtOAc) in EtOAc (2 mL) after 5 min. diethyl phosphite (258 μL, 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. NaHCO₃ solution (10 mL), the organic phase, was separated, dried (MgSO₄), filtered, and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc or CHCl₃/Et₂O) to afford α-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_f: 0.51 (CHCl₃/MeOH, 5/1). IR (ν) cm⁻¹: 3269, 2976, 1600, 1530. ³¹P NMR (CDCl₃ + (PhNH)₂) δ: 22.6; ¹H NMR (CDCl₃ + (PhNH)₂) δ: 1.22 (s, 3H, 1 × C(CH₃)), 1.25 (s, 6H, 1 × C(CH₃)₂), 1.34 (t, 6H, CH₂CH₃, J_{HH} 7), 1.39 (s, 3H, C(CH₃)), 3.84 (m, 1H, NH), 4.05 (d, 1H, CH, J_{HH} 8) 4.17-4.22 (m, 4H, OCH₂), 6.25 (s, 1H, HC=C), 6.75-6.84 (m, 3H, ArH), 2 aromatic protons overlap with (PhNH)₂ protons. ¹³C NMR (CDCl₃ + (PhNH)₂) δ: 16.51 (d, 1C, CH₂CH₃, J_{CP} 6), 16.54 (d, 1C, CH₂CH₃, J_{CP} 6), 24.5 (s, 1C, C(CH₃)), 25.1 (s, 1C, C(CH₃)) 25.4 (s, 1C, C(CH₃)), 25.7 (s, 1C, C(CH₃)), 48.6 (d, 1C, CHP, J_{CP} 164), 62.6 (d, 1C, OCH₂, J_{CP} 7), 63.2 (d, 1C, OCH₂, J_{CP} 7), 68.0 (s, 1C, C(CH₃)₂), 71.0 (d, 1C, C(CH₃)₂, J_{CP} 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_{CP} 3), 146.5 (d, 1C, ArC, J_{CP} 3). MS (EI): m/z (%): 381 (M⁺, 4), 351 (1), 229 (23), 214 (77), 55 (100). Anal calcd. for C₁₉H₃₀N₂O₄P: 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_f: 0.41 (CHCl₃/Et₂O, 2/1), IR (ν) cm⁻¹: 3315, 2977, 1602, 1519. ³¹P NMR (CDCl₃ + (PhNH)₂) δ: 20.7; ¹H NMR (CDCl₃ + (PhNH)₂) δ: 1.22 (s, 3H, 1 × C(CH₃)), 1.34 (m, 9H, CH₂CH₃ and 1 × C(CH₃)₂), 1.37 (t, 3H, CH₂CH₃, J_{HH} 7), 1.48 (s, 3H, C(CH₃)), 4.21-4.25 (m, 4H, OCH₂), 4.58 (m, 1H, NH), 4.90 (dd, 1H, CH, ¹J_{PH} 29, ²J_{HH} 8), 6.80-7.25 (m, 3H, ArH), 2 aromatic protons overlap with (PhNH)₂

protons. ^{13}C NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 16.4 (d, 1C, CH_2CH_3 , J_{CP} 6), 16.5 (d, 1C, CH_2CH_3 , J_{CP} 6), 23.5 (s, 1C, $\text{C}(\text{CH}_3)$), 24.4 (s, 1C, $\text{C}(\text{CH}_3)$) 25.0 (s, 1C, $\text{C}(\text{CH}_3)$), 25.4 (s, 1C, $\text{C}(\text{CH}_3)$), 51.7 (d, 1C, CHP , J_{CP} 155), 62.9 (d, 1C, OCH_2 , J_{CP} 7), 63.0 (d, 1C, OCH_2 , J_{CP} 7), 70.3 (d, 1C, $\text{C}(\text{CH}_3)_2$, J_{CP} 3), 71.0 (s, 1C, $\text{C}(\text{CH}_3)_2$), 112.4 (s, 1C, $\text{BrC}=\text{C}$), 119.8 (s, 1C, ArC), 129.3 (s, 2C, ArC), 136.7 (s, 1C, $\text{BrC}=\text{C}$), 146.5 (d, 1C, ArC J_{CP} 13). A band of two aromatic carbons overlaps with carbon signal of $(\text{PhNH})_2$. MS (EI): m/z (%): 461/459 (M^+ , 7/7), 350 (13), 324/322 (20/20), 294/292 (100/100), 77 (47). Anal calcd. for $\text{C}_{19}\text{H}_{29}\text{BrN}_2\text{O}_4\text{P}$: 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_f : 0.40 ($\text{CHCl}_3/\text{Et}_2\text{O}$, 2/1). IR (ν) cm^{-1} : 3301, 2979, 1600, 1516. ^{31}P NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 22.7; ^1H NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 1.12 (s, 3H, $1 \times \text{C}(\text{CH}_3)$), 1.29 (s, 6H, $1 \times \text{C}(\text{CH}_3)_2$), 1.35 (s, 3H, $\text{C}(\text{CH}_3)$), 1.38 (t, 6H, CH_2CH_3 , J_{HH} 7), 2.26 (s, 2H, $\text{C}=\text{CCH}_2$), 4.16-4.25 (m, 4H, OCH_2), 4.54 (m, 1H, CHP), 5.66 (d, 1H, $\text{HC}=\text{C}$, J_{HH} 3), 6.79-7.28 (m, 3H, ArH), 2 aromatic protons overlap with $(\text{PhNH})_2$ protons, NH band is missing. ^{13}C NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 16.5 (t, 2C, $2 \times \text{CH}_2\text{CH}_3$, J_{CP} 7), 24.8 (s, 2C, $\text{C}(\text{CH}_3)_2$), 26.1 (s, 2C, $\text{C}(\text{CH}_3)_2$), 40.4 (s, 1C, $\text{C}=\text{CCH}_2$), 56.2 (s, 1C, $\text{C}(\text{CH}_3)_2$), 57.6 (d, 1C, $\text{C}(\text{CH}_3)_2$, J_{CP} 33), 59.8 (s, 1C, $\text{C}(\text{CH}_3)_2$), 62.7 (d, 1C, OCH_2 , J_{CP} 7), 63.3 (d, 1C, OCH_2 , J_{CP} 7), 114.1 (s, 2C, ArC), 118.6 (s, 2C, ArC), 126.1 (s, 1C, $\text{HC}=\text{C}$), 134.7 (d, 1C, $\text{HC}=\text{C}$, J_{CP} 6), 146.5 (d, ArC , 1C, J_{CP} 14). A band of an aromatic carbons overlaps with carbon signal of $(\text{PhNH})_2$. MS (EI): m/z (%): 395 (M^+ , 14), 365 (2), 309 (10), 294 (14), 258 (12), 228 (100). Anal calcd. for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_4\text{P}$: 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_f : 0.40 ($\text{CHCl}_3/\text{MeOH}$, 59/1). IR (ν) cm^{-1} : 3286, 2979, 1600. ^{31}P NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 23.3; ^1H NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 1.32 (s, 6H, $1 \times \text{C}(\text{CH}_3)_2$), 1.34 (s, 6H, $1 \times \text{C}(\text{CH}_3)_2$), 1.42 (t, 6H, $2 \times \text{CH}_2\text{CH}_3$, J_{HH} 7), 2.11 (s, 1H, NH), 3.46 (d, 1H, CHP , J_{HH} 19), 3.84 (d, 1H, CHPh , J_{HH} 13), 4.00 (d, 1H, CHPh , J_{HH} 13), 4.18-4.30 (m, 4H, OCH_2) 6.05 (s, 1H, $\text{C}=\text{CH}$), 7.32-7.39 (m, 5H, ArH). ^{13}C NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 16.5 (d, 1C, CH_2CH_3 , J_{CP} 6), 16.6 (d, 1C, CH_2CH_3 , J_{CP} 6), 24.1 (s, 1C, $\text{C}(\text{CH}_3)$), 24.2 (s, 1C, $\text{C}(\text{CH}_3)$) 25.1 (s, 1C, $\text{C}(\text{CH}_3)$), 25.2 (s, 1C, $\text{C}(\text{CH}_3)$), 51.6 (d, 1C, CH_2Ph , J_{CP} 11), 51.8 (d, 1C, CHP , J_{CP} 156), 62.8 (d, 1C, OCH_2 , J_{CP} 7), 62.9 (d, 1C, OCH_2 , J_{CP} 7), 69.1 (s, 1C, $\text{C}(\text{CH}_3)_2$), 69.2 (s, 1C, $\text{C}(\text{CH}_3)_2$), 127.2 (s, 1C, $\text{HC}=\text{C}$), 128.3 (s, 2C, ArC), 128.4 (s, 2C, ArC), 133.7 (s, 1C, ArC), 139.5 (s, 1C, ArC), 140.2 (s, 1C, $\text{C}=\text{CCHP}$). MS (EI): m/z (%): 395 (M^+ , 2), 365 (1), 258 (30), 228 (74), 91 (100). Anal calcd. for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_4\text{P}$: 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_f : 0.48 ($\text{CHCl}_3/\text{MeOH}$, 59/1). IR (ν) cm^{-1} : 3319, 2972, 2927, 1663, 1601. ^{31}P NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 27.8; ^1H NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 1.28 (s, 6H, $1 \times \text{C}(\text{CH}_3)_2$), 1.41 (t, 6H, CH_2CH_3 , J_{HH} 7), 1.58 (s, 6H, $\text{C}(\text{CH}_3)$), 1.96 (dd, 2H, CH_2 , $^1J_{\text{HH}}$ 14, $^2J_{\text{HH}}$ 2), 2.09 (dd, 2H, CH_2 , $^1J_{\text{HH}}$ 6, $^2J_{\text{HH}}$ 8), 4.11 (dd, 2H, PhCH_2 , $^1J_{\text{HH}}$ 2, $^2J_{\text{HH}}$ 4), 4.19-4.25 (q, 4H, OCH_2 J_{HH} 7), 7.29-7.42 (m, ArH , 5H), NH band is not detected. ^{13}C NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 16.7 (d, 2C, CH_2CH_3 , J_{CP} 5), 20.8 (s, 4C, $2 \times \text{C}(\text{CH}_3)_2$), 33.1 (s, 1C, CH_2), 40.8 (s, 1C, CH_2), 48.1 (s, 1C, PhCH_2), 57.2 (d, 1C, H_2NCP , J_{CP} 131), 57.9 (s, 1C, $\text{C}(\text{CH}_3)_2$), 58.1 (s, 1C, $\text{C}(\text{CH}_3)_2$), 61.9 (d, 2C, $2 \times \text{OCH}_2$, J_{CP} 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^+ , 1), 260 (14), 245 (2), 214 (13), 91 (100). Anal calcd. for $\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}_4\text{P}$: 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_f : 0.31 ($\text{CHCl}_3/\text{Et}_2\text{O}$, 2/1). IR (ν) cm^{-1} : 3311, 2974, 1601. ^{31}P NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 23.8; ^1H NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 1.00 (s, 3H, $1 \times \text{C}(\text{CH}_3)$), 1.04 (s, 3H, $1 \times \text{C}(\text{CH}_3)$), 1.17 (m, 2H, $2 \times \text{CHHCPN}$), 1.20 (s, 3H, $1 \times \text{C}(\text{CH}_3)$), 1.24 (s, 3H, $1 \times \text{C}(\text{CH}_3)$), 1.34 (t, 6H, CH_3CH_2 , J_{HH} 7), 1.67 (d, 1H, CHHCPN , J_{HH} 12), 1.90 (d, 1H, CHHCPN , J_{HH} 12), 2.82 (1H, m, CH_2CHCH_2), 3.83-4.16 (m, 4H, OCH_2), 4.20 (d, 1H, CHP , J_{PH} 21), 7.23-7.43 (m, 3H, ArH), 2 aromatic protons overlap with $(\text{PhNH})_2$ protons, NH band is not detected. ^{13}C NMR ($\text{CDCl}_3 + (\text{PhNH})_2$) δ : 16.3 (d, 1C, CH_2CH_3 , J_{CP} 5), 16.5 (d, 1C, CH_2CH_3 , J_{CP} 5), 19.9 (s, 2C, $2 \times \text{C}(\text{CH}_3)_2$), 20.1 (s, 2C, 2

× C(CH₃)₂), 32.0 (s, 1C, CH₂), 32.2 (s, 1C, CH₂), 45.6 (d, 1C, CH₂CHCH₂, *J*_{CP} 15.1), 46.2 (d, 1C, CHPNH, *J*_{CP} 112), 57.5 (s, 1C, C(CH₃)₂), 58.7 (s, 1C, C(CH₃)₂), 62.8 (d, 1C, OCH₂, *J*_{CP} 7), 63.1 (d, 1C, OCH₂, *J*_{CP} 7), 127.8 (s, 1C, ArC), 127.9 (s, 2C, ArC), 128.3 (s, 2C, ArC), 136.5 (d, 1C, ArC, *J*_{CP} 4). High-resolution MS (ESI): *m/z* [M]⁺ calc. for C₂₀H₃₅N₂O₄P⁺: 398.2334; found: 398.2328. Anal calcd. for C₂₀H₃₄N₂O₄P: 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*_f: 0.30 (CHCl₃/Et₂O, 2/1). IR (ν) cm⁻¹: 3287, 2972, 2930, 1495. ³¹P NMR (CDCl₃ + (PhNH)₂) δ: 23.6; ¹H NMR (CDCl₃ + (PhNH)₂) δ: 1.21 (t, 6H, 2 × CH₃CH₂, *J*_{HH} 7), 1.24 (s, 3H, 1 × C(CH₃)), 1.28 (s, 3H, 1 × C(CH₃)) 1.36 (s, 6H, C(CH₃)₂), 2.10 (s, 1H, NH), 3.17 (dd, 2H, CH₂NH, ¹*J*_{PH} 86, ²*J*_{HH} 14), 3.87-4.13 (m, 4H, OCH₂), 4.16 (d, 1H, CHP, *J*_{HH} 10), 5.57 (s, 1H, HC=C), 7.37-7.44 (m, 4H, ArH), 1 aromatic proton overlap with (PhNH)₂ protons. ¹³C NMR (CDCl₃ + (PhNH)₂) δ: 16.3 (d, 1C, CH₂CH₃, *J*_{CP} 5), 16.5 (d, 1C, CH₂CH₃, *J*_{CP} 5), 24.0 (s, 1C, C(CH₃)₂), 24.1 (s, 1C, C(CH₃)₂), 25.3 (s, 1C, C(CH₃)₂), 25.4 (s, 1C, C(CH₃)₂), 44.5 (d, 1C, CH₂N, *J*_{CP} 17), 60.3 (d, 1C, CHP, *J*_{CP} 153), 62.8 (d, 1C, OCH₂, *J*_{CP} 7), 63.0 (d, 1C, OCH₂, *J*_{CP} 7), 71.5 (s, 1C, C(CH₃)₂), 71.6 (s, 1C, C(CH₃)₂), 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*_{CP} 4), 142.4 (s, 1C, HC=C). MS (EI): *m/z* (%): 395 (M⁺, 13), 365 (1), 258 (55), 228 (33), 57 (100). Anal calcd. for C₂₀H₃₂N₂O₄P: 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*_f: 0.34 (CHCl₃/MeOH, 59/1). IR (ν) cm⁻¹: 3319, 2980, 2926, 1583, 1562. ³¹P NMR (CDCl₃ + (PhNH)₂) δ: 23.2; ¹H NMR (CDCl₃ + (PhNH)₂) δ: 1.19 (t, 3H, CH₃CH₂, *J*_{HH} 7), 1.27 (s, 3H, 1 × C(CH₃)), 1.29 (s, 3H, 1 × C(CH₃)), 1.34 (s, 3H, C(CH₃)₂), 1.35 (s, 3H, C(CH₃)₂), 1.42 (t, 3H, CH₃CH₂, *J*_{HH} 7), 2.09 (s, 1H, NH), 3.15 (dd, 2H, CH₂NH, ¹*J*_{PH} 75, ²*J*_{HH} 15), 3.82-4.31 (m, 4H, OCH₂), 4.67 (d, 1H, CHP, *J*_{PH} 20), 5.58 (s, 1H, HC=C), 7.05 (m, 1H, ArH), 7.45 (t, 2H, ArH, *J*_{HH} 7), 7.69 (d, 1H, ArH, *J*_{HH} 8), 7.92 (d, 1H, ArH, *J*_{HH} 8). ¹³C NMR (CDCl₃ + (PhNH)₂) δ: 16.3 (d, 1C, CH₂CH₃, *J*_{CP} 5), 16.5 (d, 1C, CH₂CH₃, *J*_{CP} 5), 24.1 (s, 1C, C(CH₃)), 24.4 (s, 1C, C(CH₃)), 25.5 (s, 1C, C(CH₃)), 25.7 (s, 1C, C(CH₃)), 44.3 (d, 1C, CH₂N, *J*_{CP} 17), 63.0 (d, 1C, OCH₂, *J*_{CP} 7), 63.1 (d, 1C, OCH₂, *J*_{CP} 7), 63.4 (d, 1C, CHP, *J*_{CP} 153), 68.3 (s, 1C, C(CH₃)₂), 70.8 (s, 1C, C(CH₃)₂), 102.1 (d, 1C, ArC, *J*_{CP} 8), 128.6 (s, 1C, HC=C), 129.5 (s, 1C, ArC), 129.6 (s, 1C, ArC), 129.7 (s, 1C, ArC), 138.9 (d, 1C, ArC, *J*_{CP} 4), 139.7 (s, 1C, HC=C), 142.2 (s, 1C, ArC). MS (EI): *m/z* (%): 521 (M⁺, 1), 491 (<1), 384 (18), 232 (35), 57 (100). Anal calcd. for C₂₀H₃₁I N₂O₄P: 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-1-yl)oxydanyl (17). 663 mg (39%), yellow oil, *R*_f: 0.37 (CHCl₃/MeOH, 59/1). IR (ν) cm⁻¹: 3286, 1609, 1510. ³¹P NMR (CDCl₃ + (PhNH)₂) δ: 23.8; ¹H NMR (CDCl₃ + (PhNH)₂) δ: 1.22 (t, 3H, CH₃CH₂, *J*_{HH} 7), 1.25 (s, 3H, 1 × C(CH₃)) 1.28 (s, 3H, 1 × C(CH₃)), 1.33 (s, 3H, 1 × C(CH₃)), 1.34 (s, 3H, 1 × C(CH₃)), 1.36 (t, 3H, CH₃CH₂, *J*_{HH} 7) 2.09 (s, 1H, NH), 3.16 (dd, 2H, CH₂NH, ¹*J*_{PH} 87 ²*J*_{HH} 15), 3.86 (s, 3H, OCH₃), 3.89-4.19 (m, 4H, OCH₂), 4.12 (d, 1H, CHP, *J*_{PH} 20), 5.56 (s, 1H, HC=C), 6.96 (d, 2H, ArH, *J*_{HH} 8), 7.39 (d, 2H, ArH, *J*_{HH} 7). ¹³C NMR (CDCl₃ + (PhNH)₂) δ: 16.3 (d, 1C, CH₂CH₃, *J*_{CP} 5), 16.5 (d, 1C, CH₂CH₃, *J*_{CP} 5), 24.1 (s, 1C, C(CH₃)₂), 24.3 (s, 1C, C(CH₃)₂), 25.4 (s, 1C, C(CH₃)₂), 25.5 (s, 1C, C(CH₃)₂), 44.4 (d, 1C, CH₂N, *J*_{CP} 17), 55.3 (s, 1C, OCH₃), 59.5 (d, 1C, CHP, *J*_{CP} 154), 62.8 (d, 1C, OCH₂, *J*_{CP} 7), 62.9 (d, 1C, OCH₂, *J*_{CP} 7), 68.6 (s, 1C, C(CH₃)₂), 71.1 (s, 1C, C(CH₃)₂), 114.0 (s, 2C, ArC), 127.5 (s, 1C, HC=C), 129.71 (s, 2C, ArC), 129.76 (s, 1C, ArC), 142.4 (s, 1C, HC=C), 159.4 (s, 1C, ArC). MS (EI): *m/z* (%): 425 (M⁺, 4), 395 (1), 288 (87), 258 (47), 136 (100). Anal. calcd for: C₂₁H₃₄N₂O₅P: 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 (CHCl₃/MeOH, 59/1). IR (ν) cm⁻¹: 3466, 2975, 2930, 1647. ³¹P NMR (CDCl₃ + (PhNH)₂) δ: 23.6; ¹H NMR (CDCl₃ + (PhNH)₂) δ: 1.35 (s, 12H, 2 × C(CH₃)₂), 1.37 (s, 9H, 1.5 × C(CH₃)₂), 1.41 (s, 3H, C(CH₃)), 1.43 (t, 6H, CH₃CH₂, *J*_{HH} 7),

3.36 (dd, 2H, $^1J_{PH}$ 105, $^2J_{HH}$ 15), 3.48 (d, 1H, J_{HH} 15), 4.22-4.31 (m, 4H, OCH₂), 5.68 (s, 1H, 4'-HC=C), 6.02 (d, 1H, 4-HC=C, J_{HP} 2.5), NH is signal is missing. ^{13}C NMR (CDCl₃ + (PhNH)₂) δ : 16.6 (d, 2C, CH₂CH₃, J_{CP} 6), 24.7 (s, 2C, C(CH₃)₂), 24.8 (s, 2C, C(CH₃)₂), 25.0 (s, 1C, C(CH₃)), 25.82 (s, 1C, C(CH₃)), 25.87 (s, 1C, C(CH₃)), 26.0 (s, 1C, C(CH₃)), 45.0 (d, 1C, 6'-CH₂N, J_{CP} 13), 52.9 (d, 1C, 6-CHP, J_{CP} 155), 62.7 (d, 1C, OCH₂, J_{CP} 7), 62.9 (d, 1C, OCH₂, J_{CP} 7), 67.9 (s, 2C, 2'-C(CH₃)₂ and 5'-C(CH₃)₂), 70.5 (s, 1C, 5-C(CH₃)₂), 71.1 (d, 1C, 2-C(CH₃)₂, J_{CP} 7), 128.9 (s, 1C, 4-HC=C), 134.5 (d, 1C, 3-HC=C, J_{CP} 7), 139.9 (s, 1C, 4'-HC=C), 143.1 (s, 1C, 3'-HC=C). See numbering in SM. MS (EI): m/z (%): 457 (M⁺, 8), 427 (2), 320 (30), 290 (81), 260 (59), 138 (100). Anal calcd. for C₂₂H₄₀N₃O₅P: 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 μ L, 2.0 mmol). The reaction mixture was heated at reflux temperature for 8h. After cooling, the solution was washed with sat. aq. NaHCO₃ solution (10 mL), the organic phase, was separated, dried (MgSO₄), 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 (CHCl₃/MeOH, 59/1). IR (ν) cm⁻¹: 3636, 2976, 2928, 1635. ^{31}P NMR (CDCl₃ + (PhNH)₂) δ : 23.4; 1H NMR (CDCl₃ + (PhNH)₂) δ : 1.30 (s, 3H, 1 \times C(CH₃)), 1.32 (s, 3H, 1 \times C(CH₃)), 1.37 (s, 6H, 1 \times C(CH₃)₂), 1.40 (t, 6H, CH₃CH₂, J_{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, OCH₂, J_{HH} 7), NH band is not detected. ^{13}C NMR (CDCl₃ + (PhNH)₂) δ : 16.4 (d, 1C, CH₂CH₃, J_{CP} 5), 16.6 (d, 1C, CH₂CH₃, J_{CP} 5), 23.8 (s, 1C, C(CH₃)), 23.9 (s, 1C, C(CH₃)), 24.4 (s, 1C, C(CH₃)), 24.7 (s, 1C, C(CH₃)), 35.2 (d, 1C, CH₂S, J_{CP} 4), 48.7 (d, 1C, CH₂NH J_{CP} 5), 54.4 (d, 1C, CHP, J_{CP} 141), 62.1 (d, 1C, OCH₂, J_{CP} 7), 62.4 (d, 1C, OCH₂, J_{CP} 7), 70.96 (s, 1C, C(CH₃)₂), 70.98 (s, 1C, C(CH₃)₂), 138.5 (s, 1C, SC=C), 141.0 (d, 1C, SC=C, J_{CP} 7.5). MS (EI): m/z (%): 363 (M⁺, 4), 333 (<1), 226 (34), 21 (100). Anal calcd. for C₁₅H₂₈N₂O₄PS: 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 \times 10 mL), and the organic phase was discarded. The aqueous phase was transferred to a 500 mL beaker and basified by adding solid K₂CO₃ to pH=9 (**caution: vigorous foaming!**), and the product was extracted with EtOAc (2 \times 20 mL). The combined organic phase was dried over MgSO₄, 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_f: 0.41 (CHCl₃/MeOH, 59/1). IR (ν) cm⁻¹: 3514, 3423, 3370, 2976, 2929. ^{31}P NMR (CDCl₃ + (PhNH)₂) δ : 28.8; 1H NMR (CDCl₃ + (PhNH)₂) δ : 1.27 (s, 6H, 1 \times C(CH₃)₂), 1.39 (t, 6H, CH₂CH₃, J_{HH} 7), 1.56 (s, 6H, 1 \times C(CH₃)₂), 1.73 (d, 2H, CH₂, J_{HH} 13), 2.04 (m, 2H, CH₂), 4.15-4.21 (m, 4H, OCH₂), NH₂ band is not detected. ^{13}C NMR (CDCl₃ + (PhNH)₂) δ : 16.6 (d, 2C, CH₂CH₃, J_{CP} 6), 21.6 (s, 4C, 2 \times C(CH₃)₂), 33.4 (s, 1C, CH₂), 42.4 52.3 (d, 1C, H₂NCP, J_{CP} 142), 58.0 (s, 1C, C(CH₃)₂), 58.2 (s, 1C, C(CH₃)₂), 62.4 (d, 2C, 2 \times OCH₂, J_{CP} =8). MS (EI): m/z (%): 307 (M⁺, 7), 275 (3), 221 (13), 170 (35), 138 (33), 97 (100). Anal calcd. for C₁₃H₂₈N₂O₄: 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

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

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