Abstract: Organophosphorus compounds occupy a significant position among the plethora of organic compounds, but a limited number of paramagnetic phosphorus compounds have been reported, including paramagnetic phosphonates. This paper describes the syntheses and further transformations of pyrroline and piperidine nitroxide phosphonates by well-established methods, such as the Pudovik, Arbuzov and Horner-Wadsworth-Emmons (HWE) reactions. The reaction of paramagnetic α-bromoketone produced a vinylphosphonate in the Perkow reaction. Paramagnetic α-hydroxyphosphonates could be subjected to oxidation, elimination and substitution reactions to produce various paramagnetic phosphonates. The synthesized paramagnetic phosphonates proved to be useful synthetic building blocks for carbon-carbon bond-forming reactions in the Horner-Wadsworth-Emmons olefination reactions. The unsaturated compounds achieved could be transformed into various substituted pyrroline nitroxides, proxyl nitroxides and paramagnetic polyaromatics. The Trolox® equivalent antioxidant capacity (TEAC) of new phosphonates was also screened, and tertiary α-hydroxyphosphonatate nitroxides exhibited remarkable antioxidant activity.

Keywords: antioxidant activity; Horner-Wadsworth-Emmons olefination; nitroxides; phosphonates

1. Introduction

Functionalized phosphonates are fascinating organophosphorus compounds used in biology, pharmacology, agriculture and organic chemistry [1–3]. The main interest in preparation of these compounds originated from their application in the Horner-Wadsworth-Emmons (HWE) olefination reaction to produce various unsaturated compounds [4]. Despite the simplicity of the syntheses of phosphonates or α-hydroxyphosphonates or trialkylphosphates by the Arbuzov [5], Pudovik [6] or Perkow reactions [7], these reactions were applied limitedly to access paramagnetic phosphorus compounds, although many phosphorus containing nitroxides have been published [8–11]. Remarkable part of these materials are mainly 2-substituted β- or γ-phosphorylated five-membered nitroxides exhibiting a second notably large hyperfine splitting with the one-half spin nucleus of the phosphorus atom [12–16] (Figure 1). However, no further transformations of these paramagnetic phosphonates were reported beyond phosphonate hydrolysis [8] or transesterification [16]. In this paper, we report the syntheses of new pyrroline and piperidine nitroxide phosphonates starting from nitroxide halogenides, acetylenes, aldehydes and ketones. Our purpose was to evaluate the scope and limitations of the reactions of the newly synthesized paramagnetic phosphonates or α-hydroxyphosphonates as potential...
paramagnetic building blocks for spin labeling or construction of more complex paramagnetic scaffolds. Although paramagnetic phosphonium salts and their use in C=C bond-forming reactions have been published [17], considering the advantages of use of phosphonates [18] over phosphonium ylides (e.g., avoiding the formation of non-water-soluble triphenylphosphine oxide), paramagnetic phosphonates can be more appropriate building blocks for synthetic chemists working in this field.

![Previously reported paramagnetic phosphonates.](image)

**Figure 1.** Previously reported paramagnetic phosphonates.

### 2. Results and Discussion

#### 2.1. Use of Arbusov Reaction

Treatment of five- and six-membered allylic bromides 1a–c [19–21] with triethyl phosphite at 120 °C with stirring in an open vessel resulted in the formation of phosphonates 2a–c in 65–81% yield (monitored by thin layer chromatography). As expected in the case of compound 1b, only the more reactive allylic bromide was converted to a phosphonate, and the vinyl bromine atom was not substituted. Under these conditions, we did not observe the reduction of nitroxide function. The same reaction could be performed with dibromo compound 3 [22] to furnish bisphosphonate ester 4 (Scheme 1).

![Synthesis of paramagnetic phosphonates by the Arbusov reaction.](image)

**Scheme 1.** Synthesis of paramagnetic phosphonates by the Arbusov reaction.

#### 2.2. Use of HWE and Perkow Reaction

Because the synthesis of compound 1c is a long multistep procedure from the readily available 4-oxo-TEMPO (1-oxyl-4-oxo-2,2,6,6-tetramethylpiperidine radical) (5b) [21,23,24], we are pleased to report a simpler and more direct method that heats the sodium salt of tetraethyl
methylenediphosphonate with compound 5b in toluene at reflux temperature to produce compound 2c in a HWE reaction, although at a slightly lower 58% yield. It is well known that upon heating, α-bromoketones with trialkylphosphites furnish dialkyl vinylphosphates [7]. The same reaction was observed with 3-bromo-1-oxyl-4-oxo-2,2,6,6-tetramethylpiperidine radical 6 [25], which upon heating with triethylphosphite at 120 °C furnished the paramagnetic vinylphosphate ester 7 in 34% yield (Scheme 2).

![Scheme 2. Synthesis of paramagnetic phosphonate (2c) by a HWE reaction and phosphate 7 by a Perkow reaction from 4-oxo-TEMPO (5b).](Image)

The formation of ketophosphonate in an Arbusov reaction can be excluded because the appearance of the vinyl proton at 5.43 ppm and the 31P-NMR shift at −6.22 ppm verify the formation of diethylvinyl phosphate 7. The latter 31P-NMR data show good correlation with the reported values [26].

2.3. Pudovik Hydroxyphosphonate Synthesis and Transformations

The above results drove our decision to study the reactions of paramagnetic aldehydes and ketones with diethyl phosphite to produce α-hydroxyphosphonates because these derivatives have biological importance, i.e., herbicidal, antibacterial, antifungal and antioxidant effects, to mention but a few [27–29]. To access paramagnetic α-hydroxyphosphonates among the possible reaction conditions [30,31] tested, we choose the methodology of Kulkarni et al. [32], e.g., solvent-free conditions in the presence of 0.05 eq. K3PO4. Therefore, treatment of ketones 5a [33] or 5b [23] or five- or six-membered nitroxide aldehydes 9a [34], 9b [20], or 9c [21] with diethyl phosphite in the presence of 0.05 eq. K3PO4 offered the α-hydroxyphosphonates 8a or 8b or 10a or 10b or 10c, respectively, in 78–92% yield (Scheme 3).

The structure of these compounds is proven by the appearance of hydroxyl band of OH groups at ~3200 cm\(^{-1}\) compared with compounds 2a–c. We attributed the conversion of α-hydroxyphosphonates 8a or 8b to the corresponding vinyl phosphonate by water elimination. By treatment of compound 8a or 8b with POCl\(_3\) in anhydr. pyridine [23] after 48 h at room temperature, 11 vinylphosphonate could be isolated from 8b in 29% yield, but the expected five-membered vinylphosphonate was not formed under these conditions. The structure of vinylphosphonate 11 is proven by the split vinyl proton at 6.62 ppm with \(J = 21.5\) Hz and the upfield shift of the 31P-NMR signal at 19.3 ppm compared with that of the compound 2c 31P signal at 27.1 ppm (see Supplementary Materials). Further attempts to eliminate the water from compound 8a with sulfuric acid [35] or FeCl\(_3\)/silica gel microwave heating [36] did not
produce the required vinyl phosphonate. Our efforts to substitute the tertiary alcohols 8a or 8b with various nucleophiles via mesylate did not succeed, similar to the same experiments with the secondary alcohols 10a–c. For further possible transformations, we focused on compound 10a conversions, which could be smoothly oxidized to α-ketophosphonate 12 with 3.0 eq. Dess–Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one) [37] in CH₂Cl₂ at room temperature.

With the reaction of compound 10a with DEAD (diethyl azodicarboxylate) and PPh₃ in the presence of HN₃ under Mitsonubu reaction conditions [38], we created paramagnetic α-azidophosphonate 13.

Scheme 3. Synthesis of α-hydroxyphosphonates.

Under similar conditions and using methyl iodide as a source for the I⁻ nucleophile [39], we obtained iodo compound 14, which was rather inert for attempts at further nucleophilic substitution conditions (Scheme 4). The limited success of these transformations is attributed to the sterically hindered allylic position, which is surrounded by a bulky phosphonate group and a densely substituted pyrroline nitroxide ring.

Scheme 4. Further transformations of α-hydroxyphosphonates.
2.4. Phosphonate Synthesis with Lithiation

To obtain the five-membered vinylphosphonate, we attempted heating of compound 15 [40] with diethylphosphate in the presence of a catalytic amount of NiCl₂ [41], but no conversion was observed. Our efforts to construct a P-C bond with diethylphosphate via the Pd-catalyzed Hirao reaction with the conventional or microwave-assisted method [42] also failed. As a result, we finally decided to lithiate [43] the O-methyl derivative 16, as achieved via Fenton reaction in a dimethylsulfoxide/H₂O₂/Fe²⁺ system [44], followed by treatment with 1.0 eq. BuLi (buthyl lithium) and addition of diethylchlorophosphate to produce the diamagnetic vinyl phosphonate, which was not isolated but the crude product was treated with meta-chloroperoxybenzoic acid [45]. Thus we obtained compound 17, fortunately without epoxidation of the double bond. The paramagnetic acetylene phosphonate can be prepared by deprotonating acetylene 18 [46] at a terminal acetylene carbon with lithium hexamethyldisilazane (LiHMDS) followed by treatment with diethylchlorophosphate to give compound 19 (Scheme 5). The formation of acetylenephosphonate is proven by the shielded ³¹P signal at −6.4 ppm (see Supplementary Materials).

![Scheme 5. Synthesis of paramagnetic phosphonate esters by lithiation.](image)

2.5. Horner-Wadsworth-Emmons (HWE) Reactions of Synthesized Paramagnetic Phosphonates

Deprotonation of compound 2a with sodium hydride in toluene followed by treatment with aliphatic, aromatic or heteroaromatic aldehydes offered δ-paramagnetic alkenes 2a–d, as proven by the ~16 Hz coupling of the newly formed double bond protons. Saturation of compound 20a with hydrogen in a continuous flow hydrogenation system (H-Cube Mini Plus) by 10% Pd/C catalyst offered the fully saturated N-hydroxylamine, which could be oxidized back to a R,S racemic mixture of 1-oxyl-3-phenethyl-2,2,5,5-tetramethylpyrrolidine radical 21 by a catalytic amount of MnO₂. Double deprotonation of bisphosphonate withH-NaH followed by addition of an excess of benzaldehyde produced triene, which upon heating spontaneously was cyclized by 6π-electrocyclization to cis-5,6-diphenyl-2-oxyl-1,1,3,3-tetramethyl-5,6-dihydro-1H-isindolet radical, which partially oxidized to the 5,6-diphenyl-2-oxyl-1,1,3,3-tetramethylisoidindle radical. To complete the oxidation, the worked-up crude product was subjected to oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene to yield 22 isoidindle radical (Scheme 6).
3.1. General Methods and Reagents

3. Materials and Methods

Milan, Italy). The melting points were determined with a Boetius micromelting point apparatus (Franz Küstner Nachf. K. G., Dresden, Germany). The elemental analyses were obtained with a Fisons EA 1110 CHNS elemental analyzer (Fisons Instruments, Milan, Italy), a GCMS-2020 (Shimadzu, Tokyo, Japan) both operated in EI mode (70 eV) and a Thermo Q-Exactive HPLC instrument in CHCl₃ solution, and the concentrations were 1.0 × 10⁻⁴ M. All radicals gave a 3-line resonance. NMR measurement was prepared as described previously [4] and a Thermoquest Automass Multi system (ThermoQuest, CE, Waltham, MA, USA) with ESI(+) ionization. The HWE reactions of phosphonates to various alkenes and aromatic compounds including a proxyl nitroxide. The antioxidant (proton and electron donating) activities of phosphonates 2a, 2c and α-hydroxyphosphonates 8a, 8b, 10a, 10c were tested [47] in terms of trolox (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid equivalent capacity (TEAC). This method is based on reduction of the green-colored 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical (ABTS⁺), which is detected at 734 nm. Our results suggest (Table 1) that both the piperidine ring unit (2c versus 2a or 10c versus 10a) and hydroxyl group presence (compare 2a with 10a) increase the antioxidant activity. The TEAC values of tertiary α-hydroxyphosphonate nitroxides 8a (0.96) and 8b (0.93) are almost the same as the trolox activity (1.0) but do not reach the antioxididant activity of 4-hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidin radical (TEMPOL) [48].

Table 1. TEAC activity of phosphonates.

| Compound | 2a | 2c | 8a | 8b | 10a | 10c | TEMPOL |
|----------|----|----|----|----|-----|-----|--------|
| TEAC ¹   | 0.13 ± 0.01 | 0.55 ± 0.03 | 0.96 ± 0.05 | 0.93 ± 0.04 | 0.35 ± 0.01 | 0.51 ± 0.02 | 1.27 ± 0.04 |

³ Based on n = 3 parallel measurements.

3. Materials and Methods

3.1. General Methods and Reagents

Mass spectra were recorded with a Thermoquest Automass Multi system (ThermoQuest, CE, Instruments, Milan, Italy), a GCMS-2020 (Shimadzu, Tokyo, Japan) both operated in EI mode (70 eV) and a Thermo Q-Exactive HPLC/MS/MS (Thermo Scientific, Waltham, MA, USA) with ESI(+) ionization. Elemental analyses were obtained with a Fisons EA 1110 CHNS elemental analyzer (Fisons Instruments, Milan, Italy). The melting points were determined with a Boetius micromelting point apparatus.
(Franz Küstner Nachf. K. G., Dresden, Germany). The $^1$H-NMR spectra were recorded with a Bruker Avance 3 Ascend 500 system (Bruker BioSpin Corp., Karlsruhe, Germany) operated at 500 MHz, and the $^{13}$C-NMR spectra were obtained at 125 MHz and $^{31}$P-NMR 202 MHz in CDCl$_3$ or DMSO-$d_6$ at 298 K. The “in situ” reduction of the nitroxides was achieved by addition of five equivalents of hydrazobenzene ((PhNH)$_2$/radical). The O-acetyl derivative of compound 22 for NMR measurement was prepared as described previously [49]. The EPR (electron paramagnetic resonance) spectra were recorded on MiniScope MS 200 (Magnettech GMBH, Berlin, Germany) instrument in CHCl$_3$ solution, and the concentrations were 1.0 × 10$^{-4}$ M. All radicals gave a 3-line spectra characteristic of monoradicals, g$_N$ = 14.4–15.6 G, radical concentration was > 98% in each case and referred for TEMPO (1-oxyl-2,2,6,6-tetramethylpiperidine. The IR spectra were obtained using a Bruker Alpha FT-IR instrument (Bruker Optics, Ettlingen, Germany) with ATR support on a diamond plate. Spectrophotometric measurements were performed on a Specord 40 UV/VIS Spectrophotometer (Spectord, Jena, Germany) at 732 nm in a 1 × 1 cm quartz cuvette. Hydrogenation was performed with an H-Cube Mini Plus, ThalesNano, Budapest, Hungary) instrument with a 10%Pd/C cartridge at 5 bar hydrogen pressure, 35 °C, and a flow rate of 1 mL/min. Flash column chromatography was performed on a Kieselgel 60 (0.040–0.063 mm) column (Merck, Darmstadt, Germany). Qualitative TLC was performed on commercially available plates (20 cm × 20 cm × 0.02 cm) coated with Merck Kieselgel GF$_{254}$. Compounds 1a [19], 1b [20], 1c [21], 3, [22], 5a [33], 5b [26], 6 [25], 9a [34], 9b [20], 9c [21], 15 [40], 18 [46]. TEMPO [23] and TEMPOL [23] were synthesized as previously described. The reagents LiHMDS, Trolox®, m-CPBA, diethylphosphate, triphenyl-phosphine, triethylphosphosphate, DEAD, FeCl$_3$, MnO$_2$, NaH, NaN$_3$, DDQ, PCOCl$_3$, ABTS, Dess–Martin periodinane, benzaldehyde, 2-thiophencarbaldehyde, undecanal, 3-pyridinecarbaldehyde, NiCl$_2$, diethyl chlorophosphate, BuLi, DMSO-$d_6$, CDC$_3$, hydrazobenzene were purchased from Sigma Aldrich (St. Louis, MO, USA) and hexane, DCM, CHCl$_3$, methanol (MeOH), methylidide (Mel), ethyl acetate (EtOAc), tolune, benzene, THF, MgSO$_4$, FeSO$_4$, 7H$_2$O, NaCl, Na$_2$HPO$_4$, KH$_2$PO$_4$ from Molar Chemicals (Halásztelek, Hungary).

3.2. General Procedure for Arbuzov Reactions (2a–c, 4)

In a well-ventilated hood, a mixture of compound 1a or 1b or 1c or 3 (10.0 mmol) and triethylphosphite (2.5 g, 15.0 mmol, or 5.0 g, 30.0 mmol, for compound 3) was stirred in an open vessel at 120 °C in an oil bath. The ethylbromide byproduct was allowed to escape. The reaction mixture was monitored by TLC, and after consumption of the starting material (~2 h), the mixture was allowed to cool spontaneously with stirring. After cooling, the resulting mixture was purified by flash column chromatography to give the allylic phosphonates.

3.2.1. Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate Radical (2a)

Purified by flash column chromatography (eluent: hexane/EtOAc, 1:1) to produce an orange oil (1.88 g, 65%); TLC (CHCl$_3$/Et$_2$O, 2:1); R$_f$ = 0.33. $^{31}$P-NMR (CDCl$_3$ + (PhNH)$_2$): δ 26.9. $^{13}$C-NMR (CDCl$_3$ + (PhNH)$_2$): 16.6 (d, J = 6.0 Hz, 2C), 24.2 (2C), 24.3 (d, J = 143.0 Hz, 1C), 25.8 (2C), 62.2 (d, J = 6.6 Hz, 2C), 68.2 (d, J = 1.1 Hz, 1C), 71.6 (d, J = 9 Hz, 1C), 132.6 (d, J = 8.0 Hz, 1C), 134.0 (d, J = 8.0 Hz, 1C). $^1$H-NMR (CDCl$_3$ + (PhNH)$_2$): 1.32 (s, 6H), 1.36 (s, 6H), 1.39 (t, J = 6.9 Hz, 2H), 2.56 (d, J = 22 Hz, 2H), 4.19 (quint, J = 1.2 Hz, 4H), 5.86 (s, 1H). IR: 2976, 2931, 1650 cm$^{-1}$. MS (EI): m/z (%): 290 (M$^+$, 13) 260 (70), 245 (15), 138 (22), 122 (100).

3.2.2. Diethyl ((4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate Radical (2b)

Purified by flash column chromatography (eluent: hexane/EtOAc, 1:1) to afford an orange oil (2.83 g, 77%); TLC (CHCl$_3$/Et$_2$O, 2:1); R$_f$ = 0.48. $^{31}$P-NMR (CDCl$_3$ + (PhNH)$_2$): δ 26.9. $^{13}$C-NMR (CDCl$_3$ + (PhNH)$_2$): 16.5 (d, J = 6.0 Hz, 2C), 24.1 (d, J = 143.0 Hz, 1C), 24.2 (2C), 25.8 (2C), 62.1 (d, J = 6.7 Hz, 2C), 68.0 (d, J = 2.1 Hz, 1C), 71.4 (d, J = 8.8 Hz, 1C), 132.6 (d, J = 8.1 Hz, 1C), 133.9 (d, J = 11.1 Hz, 1C).
1H-NMR (CDCl₃ + (PhNH)₂) δ: 1.35 (s, 6H), 1.37 s (6H), 1.45 (bs, 6H), 2.58 (d, J = 21.5 Hz, 2H), 4.25 (bs, 4H). IR: 2979, 2932, 1644 cm⁻¹. MS (EI): m/z (%): 370/368 (M⁺, 44), 340/338 (4/4), 259(35), 121 (100).

3.2.3. Diethyl ((1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropropidin-4-yl)methyl)phosphonate Radical (2c)

Obtained by method A: Purified by flash column chromatography (eluent: hexane/EtOAc, 1:1) to afford a red oil (2.46 g, 81%); TLC (CHCl₃/Et₂O, 2:1): Rf = 0.35. 31P-NMR (CDCl₃ + (PhNH)₂) δ: 27.1. 13C-NMR (CDCl₃ + (PhNH)₂) δ: 16.5 (d, J = 6.1 Hz, 2C), 25.0 (1C), 26.3 (bs, 1C), 34.3 (d, J = 38.1 Hz, 2C), 44.0 (d, J = 2.3 Hz, 1C), 57.7 (1C), 59.0 (d, J = 2.3 Hz, 1C), 61.9 (d, J = 6.8 Hz, 2C), 122.5 (d, J = 11.0 Hz, 1C), 134.1 (d, J = 12.0 Hz, 1C). 1H-NMR (CDCl₃ + (PhNH)₂) δ: 1.28 (s, 6H), 1.32 (s, 6H), 1.38 (t, J = 7 Hz, 6H), 2.29 (d, J = 3.5 Hz, 2H), 2.55 (d, J = 21.5 Hz, 2H), 4.13–4.20 (m, 4H), 5,43 (d, J = 5.3 Hz, 1H). IR: 2977, 2932, 1645 cm⁻¹. MS (EI): m/z (%): 304 (M⁺, 27) 274 (100), 259 (27), 152 (16), 81 (60).

3.2.4. Diethyl ((1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropropidin-4-yl)methyl)phosphonate Radical (2c)

Obtained by method B: To a stirred suspension of NaH (240 mg, 10.0 mmol) in toluene (10 mL), a solution of tetraethyl methylenediphosphonate (2.88 mg, 10.0 mmol) in toluene (10 mL) was added dropwise at 0 °C. A solution of compound 5b (1.7 g, 10.0 mmol) in toluene (10 mL) was added dropwise at 0 °C. After 30 min, the mixture was allowed to cool spontaneously with stirring. The mixture was refluxed for 3 hours. After cooling, the solvent was evaporated, and the residue was partitioned between water (30 mL) and EtOAc (50 mL). The organic phase was separated, dried (MgSO₄), filtered, and evaporated, and the residue was purified by flash column chromatography (eluent: hexane/EtOAc, 2:1) to give a brownish powder. TLC (CHCl₃/Et₂O 2:1): Rf = 0.35. IR: 2977, 2932, 1645 cm⁻¹, and all other spectral data were identical to those of one of the compounds obtained with method A.

3.2.5. Tetraethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-3,4-diyl)bis(methylene)) bisphosphonate Radical (4)

Purified by flash column chromatography (eluent: CHCl₃/Et₂O, 2:1) to give a brownish powder (3.1 g, 70%); mp 85–87 °C; TLC (CHCl₃/MeOH 29:1): Rf = 0.33. 31P-NMR (DMSO-d₆ + (PhNH)₂) δ: 27.4. 13C-NMR ((DMSO-d₆ + (PhNH)₂) δ: 16.7 (4C), 23.6 (d, J = 133.0 Hz, 2C), 24.7 (4C), 61.7 (4C), 69.4 (2C), 132.7 (2C). 1H-NMR (DMSO-d₆ + (PhNH)₂) δ: 1.11 (s, 12H), 1.23 (t, J = 6.8 Hz, 12H), 2.92 (d, J = 20.0 Hz, 4H), 4.01 (quint, J = 6.5 Hz, 8H). IR: 2982, 2933, 2920 cm⁻¹. MS (EI): m/z (%): 440 (M⁺, 10), 410 (38), 395 (28), 273 (77), 152 (8), 135 (100).

3.3. Diethyl (1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropropidin-4-yl)phosphate Radical (7)

In a well-ventilated hood, a mixture of compound 6 (2.49 g, 10.0 mmol) and triethylphosphite (2.5 g, 15.0 mmol) was stirred in an open vessel at 60 °C in an oil bath. The ethylbromide byproduct was allowed to escape. The reaction mixture was monitored by TLC, and after ~ 2 h, the temperature was increased to 100 °C for ~ 1 h. The mixture was allowed to cool spontaneously with stirring. After cooling, the resulted mixture was purified by flash column chromatography to give the Perkow product, which was purified by flash column chromatography (hexane/EtOAc, 1:1) to give a red oil (1.05 g, 34%); TLC (CHCl₃/Et₂O, 2:1): Rf = 0.50. 31P-NMR (CDCl₃ + (PhNH)₂) δ: −6.2. 13C-NMR ((CDCl₃ + (PhNH)₂) δ: 16.2 (d, J = 6.5 Hz, 2C), 25.3 (2C), 26.7 (2C), 42.1 (d, J = 3.8 Hz, 1C), 58.4 (1C), 59.1 (1C), 64.3 (d, J = 6.1 Hz, 2C), 118.0 (d, J = 5.4 Hz, 1C), 142.3 (d, J = 8.8 Hz, 1C). 1H-NMR (DMSO-d₆ + (PhNH)₂) δ: 1.30 (s, 6H), 1.35 (s, 6H), 1.43 (t, J = 7.1 Hz, 6H), 2.38 (s, 2H), 4.23 (quint, J = 7.1 Hz, 2H), 5.43 (d, J = 1.8 Hz, 1H). IR: 2980, 2935, 2911, 1696 cm⁻¹. MS (EI): m/z (%): 306 (M⁺, 8), 276(10), 155 (70) 107 (100).
3.4. General Procedure for Pudovik α-hydroxyphosphonate Synthesis from Paramagnetic Aldehydes and Ketones 8a, 8b, 10a–c

To a stirred mixture of compound 5a or 5b or 9a or 9b or 9c and diethyl phosphate (1.38 g, 10.0 mmol), K$_3$PO$_4$ (106 mg, 0.5 mmol) was added, and the stirring continued at room temperature for 1 h. Subsequently, 10% aq. Na$_2$CO$_3$ (50 mL) was added, followed by extraction with EtOAc (2 x 50 mL). The combined organic phases were dried (MgSO$_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (elucent: hexane/EtOAc, 1:1) to give the α-hydroxy-phosphonate products.

3.4.1. Diethyl (3-hydroxy-1-oxyl-2,2,5,5-tetramethylpyrrolidin-3-yl)phosphonate Radical (8a)

Purified by flash column chromatography (elucent: CHCl$_3$/Et$_2$O, 2:1) to give a yellow powder (2.7 g, 92%); mp 100–103 °C; TLC (CHCl$_3$/MeOH, 56:4): $R_f$ = 0.51. $^{31}$P-NMR (DMSO-$d_6$ (PhNH)$_2$) δ: 23.2. $^{13}$C-NMR ((DMSO-$d_6$ + (PhNH)$_2$) δ: 17.0 (d, $J = 5.2$ Hz, 2C), 20.0 (1C), 22.1 (1C), 27.0 (1C), 31.1 (1C), 46.5 (d, $J = 4.0$ Hz, 1C), 61.9 (d, $J = 8.2$ Hz, 1C), 62.6 (d, $J = 5.6$ Hz, 1C), 77.8 (1C), 79.1 (1C). $^1$H-NMR (DMSO-$d_6$ + (PhNH)$_2$) δ: 1.11–1.25 (m, 18H), 1.85 (d, $J = 13.4$ Hz, 1H), 2.35 (t, $J = 11.9$ Hz, 1H), 4.04–4.11 (m, 4H). IR: 3258, 2982, 2938, 2910 cm$^{-1}$.

3.4.2. Diethyl (4-hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl)phosphonate Radical (8b)

Purified by flash column chromatography (elucent: CHCl$_3$/Et$_2$O, 2:1) to give red crystals (2.77 g, 90%); mp 115–117 °C; TLC (CHCl$_3$/MeOH, 56:4): $R_f$ = 0.53. $^{31}$P-NMR (CDCl$_3$ (PhNH)$_2$) δ: 24.4. $^{13}$C-NMR ((CDCl$_3$ + (PhNH)$_2$) δ: 16.6 (d, $J = 5.1$ Hz, 2C), 21.0 (4 C), 33.3 (2C), 43.1 (2C), 57.9 (d, $J = 14.5$ Hz, 1C), 63.1 (d, $J = 7.5$ Hz), 71.3 (1C), 72.6 (1C). $^1$H-NMR (CDCl$_3$ + (PhNH)$_2$) δ: 1.28 (s, 6H), 1.40 (t, $J = 7$ Hz, 6H), 1.48 (s, 6H), 2.02 (d, $J = 4.01$ Hz, 4H), 3.11 (bs, 1H), 4.23 (quint, $J = 7.1$ Hz, 4H), 4.69 (bs, 1H). IR: 3198, 2993, 2973, 2929 cm$^{-1}$. MS (EI): $m/z$ (%): 294 (M$^+$, 12), 264(2), 249 (5) 180 (100), 138 (78).

3.4.3. Diethyl (hydroxy(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrro1-3-yl)methyl)phosphonate Radical (10a)

Purified by flash column chromatography (elucent: hexane/EtOAc, 1:1) to give an orange oil (2.61 g, 85%); mp 107–109 °C; TLC (CHCl$_3$/MeOH, 58:2): $R_f$ = 0.33. $^{31}$P-NMR (CDCl$_3$ (PhNH)$_2$) δ: 21.8. $^{13}$C-NMR ((CDCl$_3$ + (PhNH)$_2$) δ: 16.5 (t, $J = 5.1$ Hz, 2C), 24.5. (1C), 24.9 (1C), 25.4 (1C), 25.5 (1C), 63.1 (d, $J = 185.0$ Hz, 1C), 63.9 (d, $J = 164.0$ Hz, 2C), 68.0 (1C), 71.2 (d, $J = 9.4$ Hz, 1C), 135.1 (d, $J = 6.2$ Hz, 1C), 140.3 (1C). $^1$H-NMR (CDCl$_3$ + (PhNH)$_2$) δ: 1.34–1.42 (m, 18H), 4.26 (q, $J = 7.0$ Hz, 4H), 4.35 (d, $J = 10.8$ Hz, 1H), 6.13 (s, 1H). IR: 3286, 2977, 2931, 1645 cm$^{-1}$. MS (EI): $m/z$ (%): 306 (M$^+$, 7), 276 (9), 154 (26), 138 (100).

3.4.4. Diethyl (hydroxy(4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate Radical (10b)

Purified by flash column chromatography (elucent: hexane/EtOAc, 1:1) to give an orange powder (2.98 g, 78%); mp 107–109 °C; TLC (CHCl$_3$/MeOH, 58:2): $R_f$ = 0.34. $^{31}$P-NMR (CDCl$_3$ (PhNH)$_2$) δ: 20.7. $^{13}$C-NMR ((CDCl$_3$ + (PhNH)$_2$) δ: 16.5 (d, $J = 5.7$ Hz, 2C), 23.7 (1C), 24.5 (1C) 24.9 (1C), 25.1 (1C), 63.0 (d, $J = 7.2$ Hz, 1C), 63.6 (d, $J = 7.2$ Hz, 1C), 67.5 (d, $J = 162.1$ Hz, 1C), 70.8 (1C), 71.5 (1C), 127.1 (d, $J = 12.6$ Hz, 1C), 137.5 (1C). $^1$H-NMR (CDCl$_3$ + (PhNH)$_2$) δ: 1.33–1.47 (m, 18H), 4.18-4.30 (m, 4H), 4.94 (d, $J = 16.7$ Hz, 1H). IR: 3263, 2980, 2934, 2908, 1631 cm$^{-1}$. MS (EI): $m/z$ (%): 386/384 (M$^+$, 16/16), 356/354 (4/4), 275 (38), 138 (100).

3.4.5. Diethyl (hydroxy(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)phosphonate Radical (10c)

Purified by flash column chromatography (elucent: hexane/EtOAc, 1:1) to give a red oil (2.56 g, 80%); TLC (CHCl$_3$/MeOH, 58:2): $R_f$ = 0.38. $^{31}$P-NMR (CDCl$_3$ (PhNH)$_2$) δ: 22.0. $^{13}$C-NMR ((CDCl$_3$ +
(PhNH)_2 δ: 16.5 (d, J = 5.7 Hz, 2C), 39.8. (1 C), 57.7 (1C), 59.8 (1C), 62.8 (d, J = 7.4 Hz, 1C) 63.1 (d, J = 7 Hz, 1C), 71.3 (d, J = 158.1 Hz, 1C), 127.4 (d, J = 4.3 Hz, 1C), 132.8 (d, J = 11.5 Hz, 1C). 1H-NMR (CDCl₃ + (PhNH)_2) δ: 1.27 (s, 6H), 1.33 (s, 6H), 1.34 (s, 6H), 1.38 (t, J = 7 Hz, 3H), 2.30 (dq, J₁ = 2.5 Hz, J₂=9.9 Hz, 2H), 4.18–4.27 (m, 4H), 4.38 (d, J = 10 Hz, 1H), 5.67 (d, J = 4.6 Hz, 1H). IR: 3290, 2978, 2933, 1649 cm⁻¹. MS (EI): m/z (%): 320 (M⁺, 5), 290 (7), 272 (8), 182 (10), 152 (100).

3.5. Diethyl (1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)phosphonate Radical (11)

To a stirred solution of compound 8b (1.54 g, 5.0 mmol) in anhydrous pyridine (10 mL), POCl₃ (1.0 mL, 10.6 mmol) was added dropwise at 0 °C, and the mixture was allowed to remain at r.t for 48 h. The mixture was poured onto 100 g crushed ice, extracted with CH₂Cl₂ (20 mL), a solution of DEAD (2.09 g, 12.0 mmol in 40% toluene) diluted with benzene (5 mL) and 10% aq NaOH (15 mL) and 25 mL and 10% aq Na₂S₂O₃ (25 mL). The organic phase was washed with aq. 1N HCl (2 × 40 mL). The organic phase was dried (MgSO₄), filtered, and evaporated, and the residue was purified by flash column chromatography (eluent: hexane/EtOAc, 2:1) to give a red powder (420 mg, 29%); mp 29–31 °C.

3.6. Diethyl (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)phosphonate Radical (12)

To a stirred solution of compound 10a (1.53 g, 5.0 mmol) in anhydrous pyridine (10 mL), Dess–Martin periodinane (6.36 g, 15.0 mmol, 3 eq.) was added in 3 portions at 0 °C, and the mixture was allowed to remain at r.t for 48 h. The mixture was poured onto 100 g crushed ice, extracted with CH₂Cl₂ (3 × 15 mL), and the combined organic phase was washed with aq. 1N HCl (2 × 40 mL). The organic phase was dried (MgSO₄), filtered, and evaporated, and the residue was purified by flash column chromatography (eluent: hexane/EtOAc, 2:1) to give a red powder (950 mg, 62%); mp 35–37 °C.

3.7. Diethyl (azido (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl)phosphonate Radical (13)

To a stirred suspension of compound 10a (1.53 g, 5.0 mmol) in anhydrous pyridine (10 mL), POCl₃ (1.0 mL, 10.6 mmol) was added dropwise at 0 °C, and the mixture was allowed to remain at r.t for 48 h. The mixture was poured onto 100 g crushed ice, extracted with CH₂Cl₂ (3 × 15 mL), and the combined organic phase was washed with aq. 1N HCl (2 × 40 mL). The organic phase was dried (MgSO₄), filtered, and evaporated, and the residue was purified by flash column chromatography (eluent: hexane/EtOAc, 2:1) to give a red powder (420 mg, 29%); mp 29–31 °C.

3.8. Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)iodomethyl)phosphonate Radical (14)

To a stirred suspension of compound 10a (3.06 g, 10.0 mmol) and Ph₃P (3.14 g, 12.0 mmol) in benzene (20 mL), a solution of DEAD (2.09 g, 12.0 mmol in 40% toluene) diluted with benzene (5 mL)
was added dropwise at 0 °C under N₂. After 10 min to complete the addition, a solution of CH₃I (0.7 mL, 12.0 mmol) in benzene (5 mL) was added dropwise. After the addition was completed, the mixture was held for 30 min at 0 °C, and stirring was continued for 24 h at r.t. The solvent was evaporated, and the residue was partitioned between water (20 mL) and EtOAc (50 mL). The organic phase was separated, dried (MgSO₄), filtered, and evaporated, and the crude was purified by flash column chromatography (eluent: hexane/EtOAc, 1:1) to give a yellow semi-solid (2.0 g, 48%); TLC (CHCl₃/Et₂O, 2:1): Rf = 0.40, IR: 3040, 2990 1528. HRMS (ESI) m/z [M]+ calcd. for C₁₃H₂₅NO₄P: 417.0566; found: 417.1311; [M-H]+ calcd. for C₁₃H₂₄NO₄P: 289.1443; found 289.1434.

3.9. 3-Bromo-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole (16)

To a stirred solution of 15 (1.1 g, 5.0 mmol) and FeSO₄·7H₂O (6.9 g, 25.0 mmol) in DMSO (30 mL) at 0 °C, 30% aq H₂O₂ (5 mL) was added dropwise over 2 h. The reaction was monitored by TLC. Upon consumption of the starting material, distilled H₂O (50 mL) was added, and the aqueous solution was extracted with Et₂O (3 × 30 mL). The combined organic phases were dried (MgSO₄), filtered, and evaporated, and the crude product was purified by flash column chromatography (hexane–EtOAc, 1:1) to give a colorless oil (700 mg, 60%); TLC (hexane–EtOAc, 1:1) Rf = 0.42. 1H-NMR (CDCl₃) δ: 22.3 (2C) 28.6 (2C), 65.0 (1C) 68.9 (1C), 71.7 (1C), 125.6 (1C), 134.0 (1C). 13C-NMR (CDCl₃) δ: 1.27 (s, 6H), 1.29 (s, 6H), 3.69 (s, 3H), 5.69 (s, 1H). IR: 2921, 2852, 1642. MS (EI): m/z (%): 235/233 (M⁺, 3/3), 220/218 (33/33), 139 (100), 108 (25).

3.10. Diethyl (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)phosphonate Radical (17)

To a stirred solution of 16 (470 mg, 2.0 mmol) in anhydrous THF (10 mL), n-BuLi solution in hexane (0.8 mL, 2.0 mmol, 2.5 M) diluted with anhyd. THF (10 mL) was added dropwise at −78 °C under N₂. After the addition was completed, the mixture was continuously stirred for 1 h at −78 °C. A solution of diethylchlorophosphate (345 mg, 2.0 mmol) in anhydrous THF (10 mL) was added dropwise. After stirring at this temperature for 30 min, the reaction mixture was allowed to warm to r.t. with continuous stirring for 2 h. A sat. aq. NH₄Cl solution (5 mL) was added, the mixture was extracted with CH₂Cl₂ (2 × 10 mL), and the combined organic phase was dried (MgSO₄), filtered and evaporated. The crude residue (480 mg, 1.65 mmol) was dissolved in anhyd. DCM (10 mL), and 3-chloroperbenzoic acid (~60%, 1.18 g, 4.1 mmol, 2.5 eq) was added in 2–3 portions at −78 °C over a period of 10 min. Stirring was continued for an additional 1 h at ambient temperature. The solution was washed with 10% aq. Na₂CO₃ solution (2 × 20 mL), and the organic phase was separated, dried (MgSO₄), filtered and evaporated. The residue was purified by flash column chromatography (eluent: hexane/EtOAc, 1:1) to give a yellow powder (140 mg, 50%); mp 60–62°C. 1H-NMR (CDCl₃) δ: 14.6. 13C-NMR ((CDCl₃ (PhNH)₂) δ: 16.3 (d, J = 6.3 Hz, 2C), 25.0 (2C), 25.3 (2C), 61.9 (d, J = 5.6 Hz, 2C), 68.7 (d, J = 15.6 Hz, 1C), 71.3 (d, J = 15.6 Hz, 1C), 133.8 (d, J = 4.0 Hz, 1C), 150.6 (d, J = 8.1 Hz, 1C). 19F-NMR (CDCl₃ (PhNH)₂): 1.33 (s, 6H), 1.40 (t, J = 7.5 Hz, 6H), 1.44 (s, 6H) 4.13–4.21 (m, 4H), 6.57 (d, J = 13.5 Hz, 1H). IR: 3079, 2977, 2931, 2866, 1609 cm⁻¹. MS (EI): m/z (%): 276 (M⁺, 15), 246 (65), 231 (100), 203 (5), 175 (44), 107 (78).

3.11. Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)ethynyl)phosphonate Radical (19)

To a stirred solution of compound 18 (492 mg, 3.0 mmol) in anhyd. THF (10 mL), LiHMDS (3.0 mL 3.0 mmol, 1 M THF solution) was added dropwise at −78 °C under N₂. After the addition was completed, the mixture was stirred for 1 h at −78 °C. A solution of diethylchlorophosphate (517 mg, 3.0 mmol) in anhyd. THF (10 mL) was added dropwise, and the temperature was allowed to warm to r.t. spontaneously with stirring for 2 h. The reaction mixture was quenched with sat. NH₄Cl solution (5 mL). The mixture was diluted with EtOAc (20 mL), the organic phase was separated, the aq. phase was extracted with EtOAc (10 mL), and the combined phases were dried (MgSO₄), filtered and evaporated. The residue was subjected to flash column chromatography purification (eluent: hexane/EtOAc, 1:1) to offer a yellow solid (470 mg, 52%); mp 50–52 °C; TLC (CHCl₃/Et₂O, 2:1): Rf = 0.43.
31P-NMR (CDCl3 (PhNH)2) δ: −6.4. 13C-NMR ((CDCl3 + (PhNH)2) δ: 16.1 (d, J = 6.9 Hz, 2C), 24.9 (2C), 25.2 (2C), 63.2 (d, J = 5.5 Hz, 2C), 69.2 (1C), 71.3 (1C), 81.7 (d, J = 297.8 Hz, 1C), 93.8 (d, J = 52.7 Hz, 1C), 125.6 (d, J = 3.6 Hz, 1C), 146.2 (d, J = 3.0 Hz, 1C). 1H-NMR (CDCl3 + (PhNH)2) δ: 1.32 (s, 6H), 1.38 (s, 6H) 1.45 (t, J = 7.1 Hz, 6H), 4.22–4.28 (m, 4H), 6.22 (d, J = 0.7 Hz, 1H). IR: 3073, 2976, 2931, 2908, 2866, 2171, 1612 cm⁻¹. MS (EI): m/z (%): 300 (M⁺, 14), 285 (33), 270 (20), 241 (7), 132 (100), 117 (52).

3.12. General Procedure for HWE Olefination with 2a Nitroxide Phosphonate: Compounds 20a–d

To a stirred suspension of oil-free NaH (120 mg, 5.0 mmol) in anhydr. toluene (10 mL), a solution of compound 2a (1.45 g, 5.0 mmol) in anhydr. toluene (5 mL) was added dropwise at 0 °C under N2. After 30 min, a solution of the appropriate aldehyde (5.0 mmol) in anhydr. toluene (10 mL) was added dropwise at 0 °C. The mixture was refluxed for 3 h and allowed to stand overnight at r.t. The solvent was evaporated, and the residue was partitioned between sat. aq. NH₄Cl solution (25 mL) and EtOAc (50 mL). The organic phase was separated, dried (MgSO₄), filtered, and evaporated, and the crude product was purified by flash column chromatography to yield the olefinated nitrooxides.

3.12.1. (E)-3-(Dodec-1-en-1-yl)-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole Radical (20a)

Purified by flash column chromatography (eluent: hexane/Et₂O, 2:1) to give a brown oil (950 mg, 62%); TLC (hexane/Et₂O, 5:1): Rf = 0.56. 13C-NMR ((CDCl3 + (PhNH)2) δ: 24.9 (2C), 25.0 (2C) 25.7 (1C), 29.0 (1C), 29.1 (1C), 29.2 (1C), 29.3 (1C)29.4 (1C), 29.5 (1C), 33.3 (1C), 33.8 (1C), 65.4 (1C), 67.4 (1C), 114.2 (1C), 130.8 (1C), 131.25 (1C), 139.1 (1C). 139.2 (1C). 1H-NMR (CDCl3 + (PhNH)2) δ: 1.33–1.37 (m, 33H), 2.13 (d, J = 6.1 Hz, 2H) 5.02 (d, J = 10.0 Hz, 1H), 5.08 (d, J = 17 Hz, 1H), 5.88–5.95 (m, 1H). IR: 3075, 2975, 2924, 2853, 1640 cm⁻¹. MS (EI): m/z (%): 306 (M⁺, 2), 281 (7), 207 (28), 149 (25), 55 (100).

3.12.2. (E)-1-Oxyl-3-styryl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole Radical (20b)

Purified by flash column chromatography (eluent: hexane/Et₂O, 2:1) to give a to give an orange powder; mp 67–70 °C (730 mg, 60%); TLC (hexane/Et₂O, 2:1): Rf = 0.53. 13C-NMR ((CDCl3 + (PhNH)2) δ: 25.4 (2C), 26.0 (2C), 67.6 (1C), 70.3 (1C), 122.4 (1C), 126.4 (2C), 127.7 (1C), 128.8 (2C), 129.9 (1C), 131.9 (1C), 137.4 (1C), 142.7 (1C). 1H-NMR (CDCl3 + (PhNH)2) δ: 1.45 (s, 6H), 1.56 (s, 6H) 5.86 (s, 1H), 6.7 (d, J = 16.5 Hz, 1H), 7.36–7.47 (m, 3H). 3H are overlapped with peaks of diphenyl hydrazine. IR: 3023, 2972, 2927, 2865, 1634, 1596 cm⁻¹. MS (EI): m/z (%): 242 (M⁺, 12), 227 (22), 212 (100), 197 (71), 91 (28).

3.12.3. (E)-1-Oxyl-3-(2-(pyridin-3-yl)vinyl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrole Radical (20c)

Purified by flash column chromatography (eluent: hexane/Et₂O, 2:1) to give an orange powder; mp 90–93 °C (680 mg, 56%); TLC (CHCl₃/Et₂O, 2:1): Rf = 0.33. 13C-NMR ((CDCl3 + (PhNH)2) δ: 25.2 (2C), 25.7 (2C), 67.5 (1C), 70.0 (1C), 123.5 (1C), 124.5 (1C), 126.0 (1C), 132.5 (1C), 133.0 (1C), 133.3 (1C), 142.4 (1C), 148.4 (1C), 148.5 (1C). 1H-NMR (CDCl3 + (PhNH)2) δ: 1.37 (s, 6H), 1.48 (s, 6H) 5.86 (s, 1H), 6.68 (d, J = 16.5 Hz, 1H), 6.82 (d, J = 16.5 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 8.54 (d, J = 4.4 Hz, 1H), 8.71 (s, 1H). 1H is overlapped with diphenyl hydrazine peaks. IR: 3042, 3017, 2974, 2928, 2868, 1633, 1566 cm⁻¹. MS (EI): m/z (%): 243 (M⁺, 20), 228 (42), 213 (100), 198 (75), 125 (37), 93 (61).

3.12.4. (E)-1-Oxyl-2,2,5,5-tetramethyl-3-(2-(thiophen-2-yl)vinyl)-2,5-dihydro-1H-pyrrol Radical (20d)

Purified by flash column chromatography (eluent: hexane/Et₂O, 2:1) to give brown crystals; mp 75–77 °C (635 mg, 51%); TLC (CHCl₃/Et₂O, 2:1): Rf = 0.5. 13C-NMR ((CDCl3 + (PhNH)2) δ: 25.3 (2C), 25.9 (2C), 67.5 (1C), 70.0 (1C), 122.1 (1C), 124.4 (1C), 125.9 (1C), 127.6 (1C), 132.1 (1C), 142.4 (1C), 143.0 (1C). 1H-NMR (CDCl3 + (PhNH)2) δ: 1.40 (s, 6H), 1.51 (s, 6H) 5.81 (s, 1H), 6.52 (d, J = 16.2 Hz, 1H), 7.03 (d, J = 16.2 Hz, 1H), 7.08–7.26 (m, 3H). IR: 3101, 3059, 3037, 2979, 2930, 2862. 1624 cm⁻¹. MS (EI): m/z (%): 248 (M⁺, 16), 233 (24), 218 (100), 203 (59), 175 (48), 44 (73).
3.13. (R,S)-1-Oxyl-3-phenethyl-2,2,5,5-tetramethylpyrrolidine Radical (21)

A solution of compound 20b (485 mg, 2.0 mmol) in anhydr. EtOH (75 mL) was subjected to continuous flow hydrogenation by a H-Cube Mini Plus apparatus with a 10% Pd/C catalyst cartridge. After consumption of the starting material (monitored by TLC and the content of the receiving flask), the solvent was evaporated, the residue was dissolved in CHCl$_3$ (25 mL), MnO$_2$ (17.4 mg, 0.2 mmol) was added, and the mixture was bubbled with O$_2$ for 30 min., followed by filtration through a Celite pad. After rinsing the pad with CHCl$_3$ (10 mL), the filtrate was evaporated and the crude product was purified by flash column chromatography (eluent: hexane/Et$_2$O, 2:1) to give an orange powder; mp 60–62 °C (367 mg, 74%); TLC (hexane/Et$_2$O, 2:1): R$_f$ = 0.35. $^{13}$C-NMR ((CDCl$_3$ + (PhNH)$_2$)$_2$): δ: 17.2 (1C), 26.6 (1C), 27.2 (1C), 29.9 (1C), 32.4(1C), 34.7(1C), 40.0 (1C), 43.0 (1C), 61.4 (1C), 66.5(1C), 125.9 (1C), 128.4 (2C), 128.5 (2C), 142.6 (1C). $^1$H-NMR (CDCl$_3$ + (PhNH)$_2$): δ: 1.10 (s, 3H), 1.29 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.54–1.59 (m, 2H), 1.86–1.89 m (2H), 1.98–2.02 (m 1H), 2.61–2.67 (m, 1H), 2.77–2.82 (m, 1H), 7.42–7.45 (m, 3H). 2H are overlapped with peaks of with diphenyl hydrazine. IR: 3066, 3025, 2965, 2917, 2879, 2857, 1602 cm$^{-1}$. MS (EI): m/z (%): 246 (M$^+$, 43), 216 (26), 117 (19), 91 (100).

3.14. 6-Diphenyl-2-Oxyl-1,1,3,3-tetramethylisoindoline Radical (22)

To a suspension of oil-free NaH (144 mg, 6.0 mmol) in anhydrous toluene (10 mL), a solution of compound 4 (1.32 g, 3.0 mmol) in anhydrous toluene (10 mL) was added dropwise at 0 °C under N$_2$. After 30 min, a solution of freshly distilled benzaldehyde (848 mg, 8.0 mmol) in toluene (10 mL) was added at 0 °C. The mixture was refluxed with stirring for 2 h. After cooling, sat. aq. NH$_4$Cl solution (5 mL) and Et$_2$O (30 mL) were added to the mixture and stirred for 10 min. The organic phase was separated, dried (MgSO$_4$), filtered, and evaporated. The residue was dissolved in toluene (20 mL), followed by the addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 681 mg, 3.0 mmol), and the mixture was refluxed for 3 h. After cooling, sat. aq. NH$_4$Cl solution (20 mL), MnO$_3$ (17.4 mg, 0.136 M NaCl, 0.0027 M KCl, 0.01 M Na$_2$HPO$_4$, 0.00176 M KH$_2$PO$_4$) to a 7.0 mM concentration. ABTS solution in final concentrations of 12.5, 10, 7.5, and 2.5 µM. After addition, the mixtures were incubated for 6 min at 37 °C before measuring their absorbance at 734 nm. All determinations were repeated three times. The percentage inhibition of absorbance at 734 nm is calculated with the usual formula: $(A_0-A_{\text{Antioxidant}})/A_0$, where $A_0$ is the absorbance of the diluted ABTS$^*$ solution. The concentration–response curves of new compounds were compared with the curve of Trolox.

3.15. ABTS Scavenging Assay

The measurements were collected on a Specord 40 instrument. ABTS was dissolved in PBS buffer (0.136 M NaCl, 0.0027 M KCl, 0.01 M Na$_2$HPO$_4$, 0.00176 M KH$_2$PO$_4$) to a 7.0 mM concentration. ABTS radical cations (ABTS$^{•+}$) were produced by reacting the ABTS stock solution with potassium persulfate at a final concentration of 2.45 mM and allowing the mixture to stand in the dark at room temperature for 16 h before use. For study of the compounds, the ABTS$^{•+}$ solution was diluted with water to an absorbance of 0.70 (±0.02) at 734 nm and equilibrated at 37 °C. Stock solutions of new compounds and Trolox in dimethylsulfoxide (DMSO) were added to the diluted ABTS$^{•+}$solution in final concentrations of 12.5, 10, 7.5, and 2.5 µM. After addition, the mixtures were incubated for 6 min at 37 °C before measuring their absorbance at 734 nm. All determinations were repeated three times. The percentage inhibition of absorbance at 734 nm is calculated with the usual formula: $(A_0-A_{\text{Antioxidant}})/A_0$, where $A_0$ is the absorbance of the diluted ABTS$^{•+}$ solution. The concentration–response curves of new compounds were compared with the curve of Trolox.
4. Conclusions

In conclusion, the Arbusov, Pudovik, Perkow and HWE reactions were adopted to access paramagnetic allylic-, vinyl-, acetylene- and α-hydroxyphosphonates or vinyl phosphates, giving the desired products with moderate to good yields. α-hydroxyphosphonates could be further transformed by oxidation, substitution or elimination reactions. We demonstrated that allylic phosphonates are good building blocks in olefination reactions for the introduction of pyrroline nitroxide rings in various scaffolds. Additionally, paramagnetic saturated α-hydroxyphosphonates exhibited remarkable antioxidant (proton and electron donor) activity against the ABTS•+ radical. Further synthetic, biological and biophysical applications of the newly synthesized nitroxide phosphonates are in progress.

Supplementary Materials: The following are available online, 31P-NMR, 1H-NMR and 13C-NMR spectra of reduced in situ compounds 2a, 2b, 2c, 4, 7, 8a, 8b, 8c, 10a, 10b, 10c, 11, 12, 13, 16, 17, 19, 20a, 20b, 20c, 20d, 21, 22 and structure of tempol and trolox.

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Sample Availability: Samples of the compounds. 1a, 1c, 3, 8a, 8b, 10a, 10b, 10c are available from the authors.

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