University of Pécs

Doctoral School of Chemistry

Synthesis of 1,4-diazine-fused and phosphorus containing stable nitroxide free radicals

PhD thesis

Mostafa Isbera

Supervisors:

Dr. Balázs Bognár **Prof. Tamás Kálai**

Head of the Doctoral School:

Prof. Ferenc Kilár

Pécs 2022

Acknowledgment

First of all, I am grateful to Dr. Balázs Bognár and Prof. Tamás kálai for their excellent and patient supervision and also for the exciting research theme and their support and encouragement throughout the course of this work. Also I would like to thank Dr. Cecília Sár for her help and support.

I would like to thank Dr. Gergely Gulyás Fekete for NMR measurements, Dr. József Jekő (University of Nyíregyháza) for MS measurements, Dr. Attila Bényei (University of Debrecen) for the X-ray measurement, Prof. Ferenc Gallyas and his research group for the biological studies.

I would like to thank co-workers Mária Balog, Viola Csokona, Krisztina Kish, Éva Lamperth and Noémi Lazsányi for their assistance and support.

I would like to thank Hungarian Research Foundation: K137793, FK124331 and Stipendium Hungaricum Scholarship for the financial support.

Finally, I am grateful to my family and friends for the endless support.

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1. List of abbreviations

ABTS: 2,2'-Azino-bis-3-ethylbenzothiazoline-6-sulfonic acid

AcOH: acetic acid

Ac_2O: Acetic anhydride

AgOTf: silver trifluoromethanesulfonate

CDI: 1,1'-carbonyldimidazole

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEAD: diethyl azodicarboxylate

DMF: *N,N*-dimethylformamide

DMSO: Dimethyl sulfoxide

DPPA: Diphenylphosphoryl azide

DPPH: Diphenylhydrazine

EPR: Electron Paramagnetic Resonance Spectroscopy

GC-MS: Gas chromatography–mass spectrometry

$Hg(OAc)_2$: Mercury(II) acetate

HPLC: High Performance Liquid Chromatography

HWE: Horner-Wadsworth-Emmons

KHMDS: potassium hexamethyldisilazane

LiHMDS: lithium hexamethyldisilazane

m-CPBA: meta-chloroperbenzoic acid

MS: Mass Spectrometry

Nile-DiPy: 15-((9-(Ethylimino)-10-methyl-9*H*benzo[a]phenoxazin-5-yl)amino)-3,11-dioxa-7-azadispiro[5.1.58.36]hexadecan-7-yloxyl

NMO: N-Methylmorpholine N-oxide

NMR: Nuclear Magnetic Resonance Spectroscopy

OXANO: 2-Ethyl-2,5,5-trimethyl-3-oxazolidinoxyl

PARP: poly(ADP-ribose) polymerase

PBS: Phosphate-buffered saline

$Pd(PPh_3)_2Cl_2$: Dichlorobis(triphenylphosphine)palladium(II)

$Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0)

$Pd(OAc)_2$: Palladium(II) acetate

Rac-BINAP: (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene;[1,1′-Binaphthalene]-2,2′-diylbis[diphenylphosphine]

SL: Spin Labelled

SOD: Superoxide dismutase

TBAF: Tetrabutylammonium fluoride

TEAC: Trolox-Equivalent Antioxidant Capacity

TEBAC: triethyl benzyl ammonium chloride

TEMPO: 2,2,6,6-Tetramethylpiperidyl-1-oxyl

TEMPOL: 4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

TMSBr: Bromotrimethylsilane

TPAP: Tetrapropylammonium perruthenate

UV: Ultraviolet

Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

X-Phos: 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

$Yb(OTf)_3$: Ytterbium trifluoromethanesulfonate

2. Foreword

I received my Bachelor Degree in Pharmacy and Pharmaceutical Chemistry in 2012 from University of Tishreen, Lattakia, Syria. In 2016 I got my Master's Degree in Drug Design and Quality Control from the same University in the field of quality control of pharmaceutical dosage forms. During my master degree and till September 2018, I worked as university tutor and researcher resulted in 10 Publications.

In September 2018 I have joined as PhD student to Chemistry Doctoral School (chaired by Prof. Ferenc Kilár) at University of Pécs, Hungary with support from Stipendium Hungaricum. I chose my supervisors dr. Balázs Bognár and Prof. Dr. Tamás Kálai, who were dealing with organic chemistry of stable nitroxide free radicals continuing the school of late Professor Kálmán Hideg (1934-2018) and late associate professor Olga H. Hankovszky (1934-2020).

This group deals with synthesis, modification and applications of stable nitroxide free radicals almost 50 years, focusing on five- and six-membered nitroxides. Several people gained PhD-degree or „dr. Univ. degree" or „canditate of science" degree from chemistry of nitroxide free radicals topic in this group (László Lex, József Csekő, Ilona Bódi, Cecília P. Sár, Tamás Kálai, Győző Kulcsár, Balázs Bognár, Györgyi Úr).

My topics were the synthesis of P-containing stable free nitroxide radicals and 1,4-diazine condensed stable nitroxide free radicals with an estimated bigger biological potentials. In my PhD thesis after short literature review and objectives, I will continue with my own results, experimental chapter, summary and references. This thesis is based on five research papers. They will be indicated with roman numerals, while other references will be indicated with arabic numbers in the text. The published papers are attached at the end of the thesis.

3. Introduction

The study of free radicals (entity with an unpaired electron) has been occupied a significant position among the interests of researchers over the last century. Nowadays, the chemistry of free radicals could be recognized as a developing field of chemistry, studying the generation, structures, physical and chemical properties of free radicals. The biggest outbreak in free radical chemistry was the discovery of of long-lived radicals, which enabled free radicals to be isolated in a pure form. The triphenylmethyl radical **1** was the first radical to be observed by Gomberg in 1900 [1], other examples are phenalenyl radical **2,** and 1,1-diphenyl-2-picrylhydrazyl radical **3** (Figure 1).

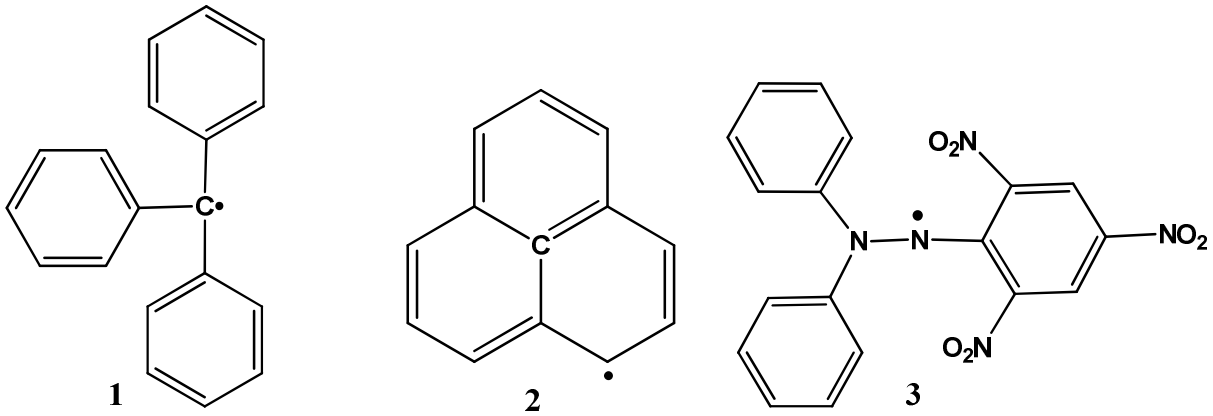


Figure 1. Some stable free radicals.

3.1. Properties of nitroxide stable free radicals

One of the most important group of free radicals, is the nitroxide free radical function. Fremy's salt **4** in 1845 was the first inorganic nitroxide to be isolated without discovering at that time the free radical nature of this salt [2], while compound **5** was the first organic nitroxide radical to be synthesized [3] (Figure 2).

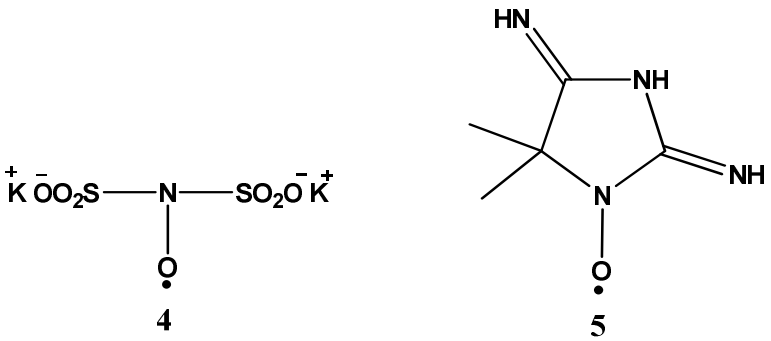


Figure 2. First isolated nitroxide radicals.

Nitroxides are a group of aliphatic, aromatic, bicyclic or heterocyclic stable radicals. The most common nitroxides are the derivatives of piperidine, pyrroline, pyrrolidine, oxazolidine, imidazoline and imidazolidine **6-16** [4] (Figure 3). These derivatives are stable due to the delocalization of free electron over N-O bond, which makes dimerization thermodynamically disfavoured [5]. Additionally the lack of hydrogen atoms at alpha carbon atom prevents the possibility of disproportionation which represents a possible nitroxide decomposition pathway [6].

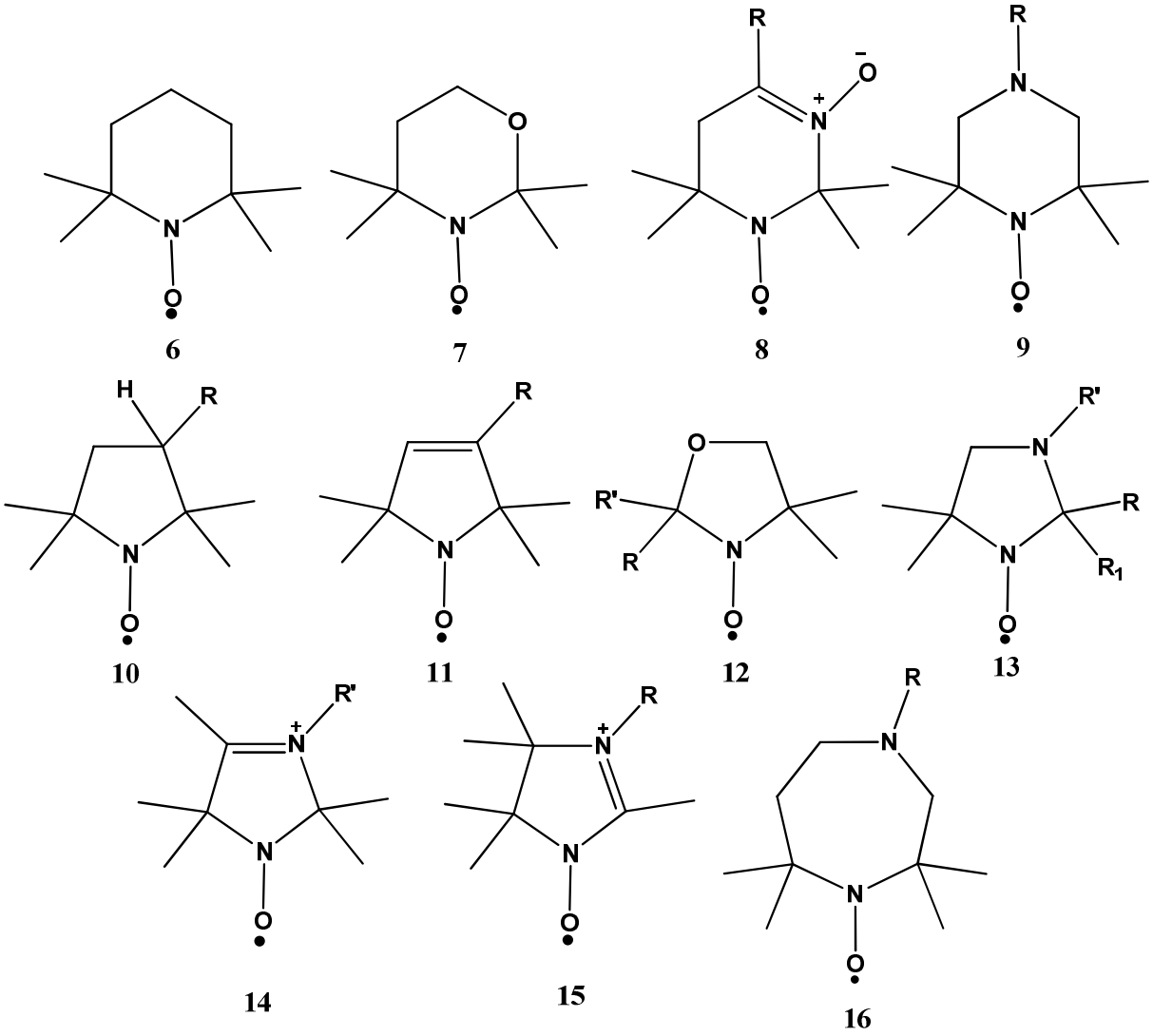
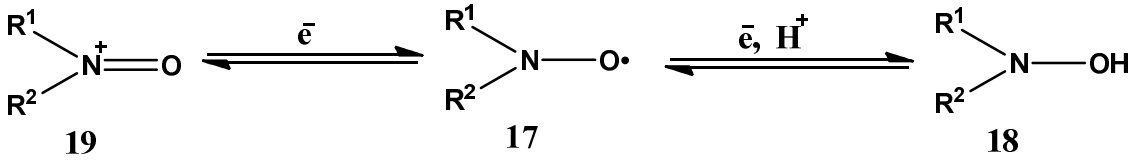


Figure 3. Most common cyclic nitroxides.

In 1960, Lebedev and Kazarnowskii [7] discovered TEMPO **6**, which is a red-orange solid at room temperature and usually prepared by the oxidation of 2,2,6,6-tetramethylpiperidine with hydrogen peroxide.

3.2. Chemistry of nitroxide radicals

In the last few decades, the attention to oxidation-reduction reactions (redox reaction) of nitroxide radicals have increased rapidly. One electron oxidation step converts nitroxide radical to the corresponding *N*-oxoammonium cation **19** (strong oxidizing agent) and, one electron reduction gives hydroxylamine **18** [8] (Scheme 1).

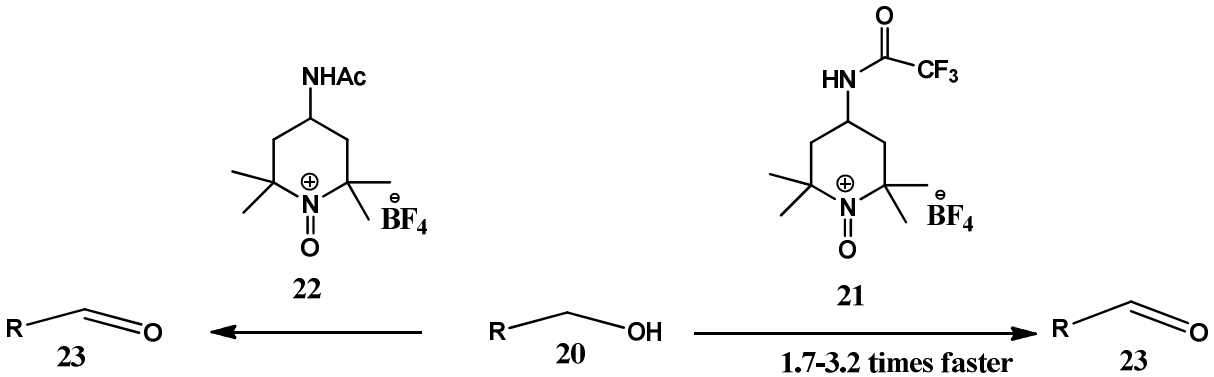


Scheme 1. Redox interconversion of nitroxide radical.

Golubev and co-workers discovered *N*-oxoammonium salt by oxidizing nitroxide radical with bromine [9, 10]. They also pioneered the studies of *N*-oxoammonium cations using them as oxidation mediators of alcohols to ketones, which led several later studies to focus on catalytic methods in which the oxoammonium species is (re)generated by a stoichiometric secondary oxidant. Nitroxide redox potential is usually used to determine the chemical activity of *N*-oxyl and N^+-oxyl moieties. Several factors cause changes in the values of nitroxide redox potentials including the change of hybridization of the nitrogen atom sp^2 to sp^3. It was noticed that the change of potentials for oxidation of cyclic nitroxyl radicals is small for six-membered rings, but increases for five-membered rings. The existence of attached aromatic rings to the nitroxide rings leads to significant increase in the redox potential [11]. In a theoretical study on 54 substituted piperidine, pyrrolidine, isoindoline, and azaphenalene nitroxides was shown that the overall ring structure has bigger effect than the inclusion of substituents (eg. COOH, NH_2, NH_3^+, OCH_3, OH, NO_2), on values of oxidation and reduction potentials. Piperidene and pyrrolidine derivatives have intermediate oxidation potentials, but on average pyrrolidine derivatives display more negative reduction potentials. Isoindoline derivatives show higher oxidation potentials and more negative reduction potentials. The effect of electron donating groups on redox potential is relatively small, while the oxidized species and electron withdrawing groups stabilize the reduced species. Azaphenalene derivatives display the lowest oxidation potentials and negative reduction potentials [8].

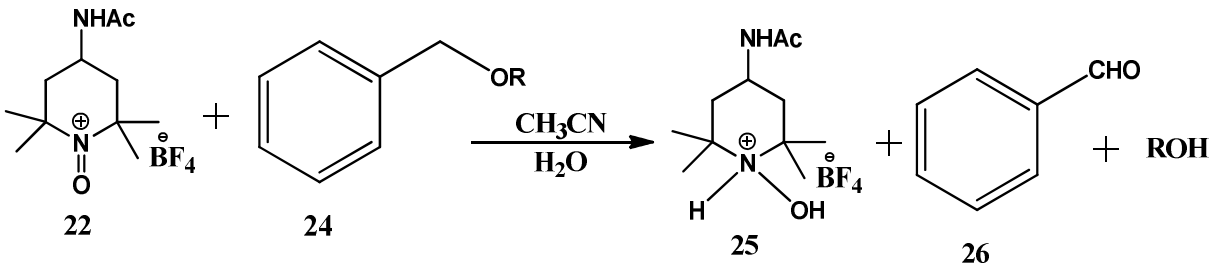
Oxoammonium species can be used as oxidizing agents in several oxidation reactions. A novel TEMPO-based oxoammonium salt **21**, and its corresponding nitroxide radical were synthesised and characterized [12]. It has been widely used in the oxidation of primary and

secondary alcohols and the oxidation reactions using compound **21** are faster than the oxoammounium salt with CH_3 moiety **22.** The presence of CF_3 group in compound **21** increases the redox potentials for the compound since it is an electron withdrawing group, making a better co-oxidant over the methyl counterpart **22**. (Scheme 2). The mechanism of oxidation premised on nucleophilic addition to the oxygen atom of the positively charged nitrogen-oxygen double bond [13].

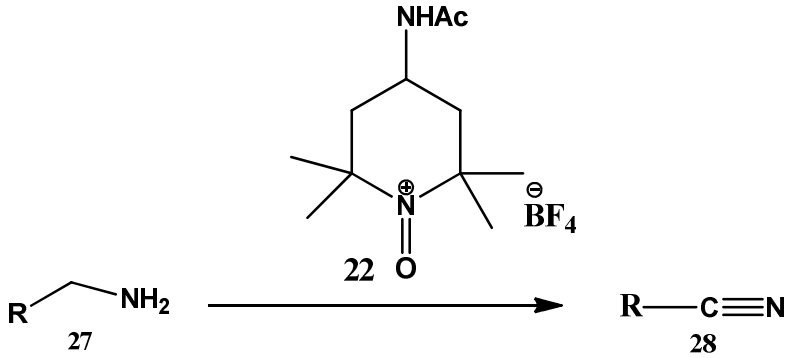


Scheme 2. Alcohol oxidation reactions using oxoammonium salt derivatives.

4-Acet amido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate **22** oxidatively cleaved benzylic ethers and related $ArCH_2OR$ substrates to give the corresponding aromatic aldehyde through hydride abstraction from the benzylic carbon [13] (Scheme 3). It was also effective in the oxidation of primary amines to nitriles [14] (Scheme 4).

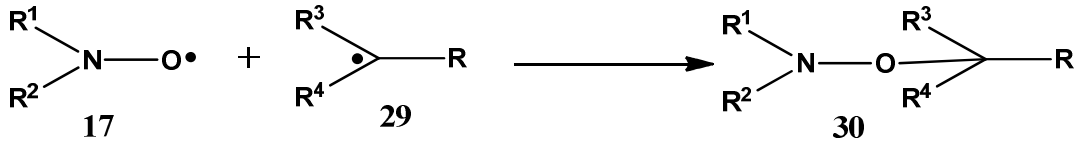


Scheme 3. Oxidative benzylic ether cleavage.



Scheme 4. Oxidation of amines using oxoammonium salt derivatives.

Nitroxide radicals are also able to recombine with organic C-centered radicals (OCCR) [15] (Scheme 5).

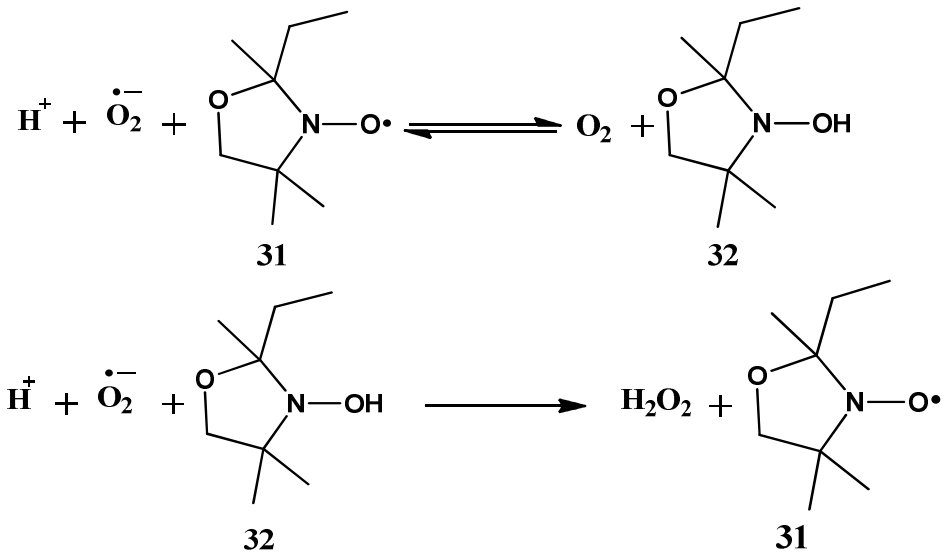


Scheme 5. Cross coupling reactions of nitroxide radicals.

Several factors affect the SOMOs of the nitroxide (SOMO π^*) and the alkyl radical, stabilization of the alkyl radical, bulkiness of the alkyl radicals and polarity.

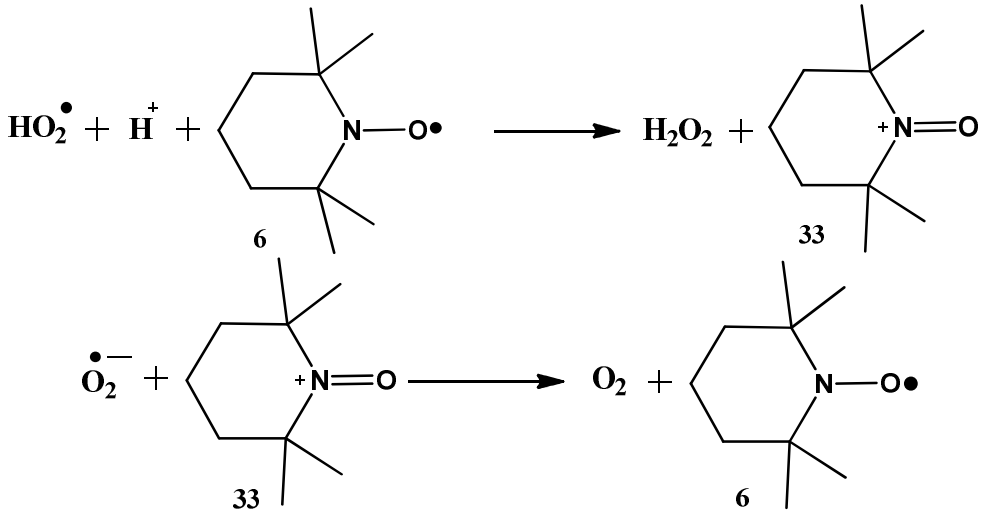
Semmelhack and co-workers found that TEMPO can act as an electrocatalyst for alcohol electrooxidation [16], and in the past decades, numerous works on electrocatalysis with nitroxides as catalysts have been performed such as electrooxidation of methanol, carbohydrates and carboxylated cellouse, racemic sec-benzylic alcohols, electrocatalytic oxidation of L-tyrosine. Immobilization of nitroxyl mediators on electrode surfaces significantly enhances the rates of alcohol oxidation and facilitate isolation of the products as comparing with methods that use dissolved nitroxide mediators [17].

Nitroxide radicals play important role in quenching the excess of reactive radicals generated in biological organisms such as superoxide radicals. They can react different ways, both the oxidation and the reduction of the nitroxide radical and the superoxide radical can take place. OXANO **31** and its corresponding hydroxylamine **32**, react with superoxide [8] allowing the dismutation of superoxide to oxygen and hydrogen peroxide [18] (Scheme 6).



Scheme 6. Reaction of OXANO with superoxide radical anion.

TEMPO **6** undergoes oxidation with superoxide radical yielding the oxoammonium salt, which then oxidizes superoxide to molecular oxygen and the oxoammonium salt is reduced back to nitroxide radical [19] (scheme 7).



Scheme 7. Reaction of TEMPO with superoxide radical.

The reaction of nitroxide radicals with antioxidant compounds occupies significant position among methods used for the evaluation of antioxidants in biological system. For example, a dual fluorophore-nitroxide probe (Nile-DiPy) **34** is used for quantitative analysis of ascorbic acid in biological liquid causing the reduction of the nitroxide by the ascorbic acid via hydrogen atom transfer [20].

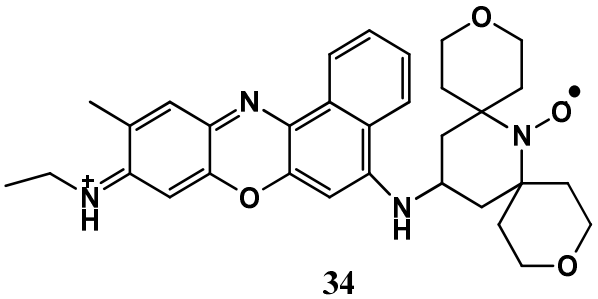


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Figure 4. Structure of Nile-DiPy.

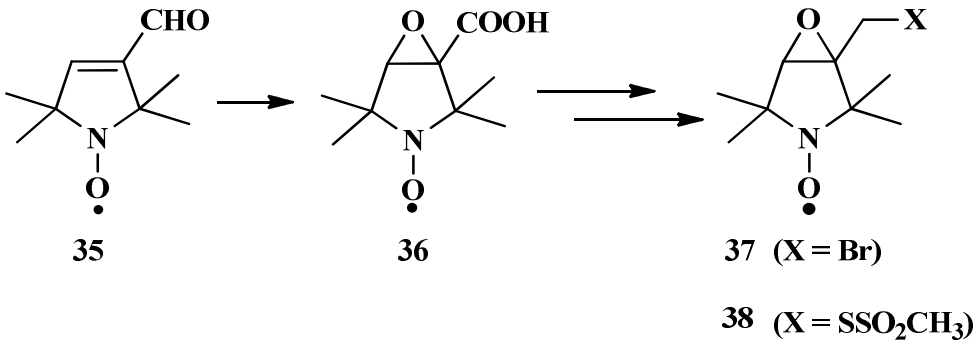
3.3. Applications of nitroxide radicals

Nowadays the importance of long lived nitroxide radicals increases rapidly due to the variety of applications and aspects they can be used in. Using their unique paramagnetic property, they can be deployed to study various biological systems and processes in living organisms through designing molecules which contain nitroxyl radical with another reactive functional group (ensuring covalent binding with the substrate) in order to get the paramagnetic spin-labelled analogues of several biogenic molecules. These compounds are called spin labels. The synthesis of spin labelled drugs enables the investigation of drugs in organisms with EPR [21, 22]. Since the nitroxide radicals affect the relaxation times T_1 and T_2 of the nuclei nearest to the nitroxyl group, they can be used as contrasting agents in the NMR tomography [23]. In this aspect, they also can be used in EPR as contrast agents as well [24]. Nitroxide radicals can participate as co-oxidants in redox reactions, due the reversible oxidation of the nitroxyl group to oxoammonium group and reduction to the hydroxylamine group. The ability of stable nitroxide radical to trap short lived free radicals allows their use as antioxidants and they also can act as superoxide dismutase (SOD) mimics affording cell protection against oxidative damage [25]. Mediating of polymerization is one of the rapidly increased application of nitroxide radicals [26]. Recently stable nitroxide radicals proved to be effective as antineoplastic compounds, and several studies proved that nitroxides are not toxic to host cells and exhibit toxicity only to tumour cells [27]. Additionally, spin labelled anticancer drugs often exhibit several times more potent effects on the tumour tissue than the unmodified drugs [28].

4. Literature review

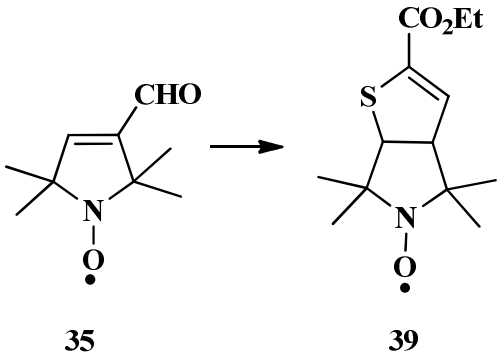
4.1. Synthesis of heterocycles fused with nitroxides

Over the past five decades, synthesis of heterocycles fused nitroxides is one of the main activities of Institute of Organic and Medicinal Chemistry, at University of Pécs. An oxirane-fused pyrrolidine nitroxide **36** was achieved by base-promoted oxidation of aldehyde **35** [29] and reported by Kálai and co-workers [30]. Fortunately, the epoxide ring of **36** was rather inert toward nucleophiles; therefore derivatives **37, 38** could also be synthesized (Scheme 8).

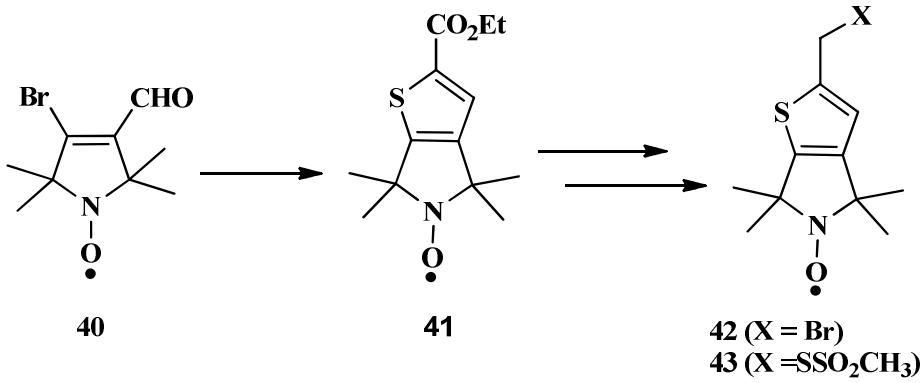


Scheme 8. Synthesis of oxirane fused pyrrolidine nitroxides.

Our institute also reported the synthesis of dihydrothiophene **39** (Scheme 9) [31] and thiophene **41** fused derivatives with Fieselmann thiophene syntheses [32], for example, the treatment of aldehydes **35** and **40** with thioglycolic acid ethyl ester. The synthesis of the SH-reactive paramagnetic thiophene derivatives **42** and **43** was also accomplished (Scheme 10).

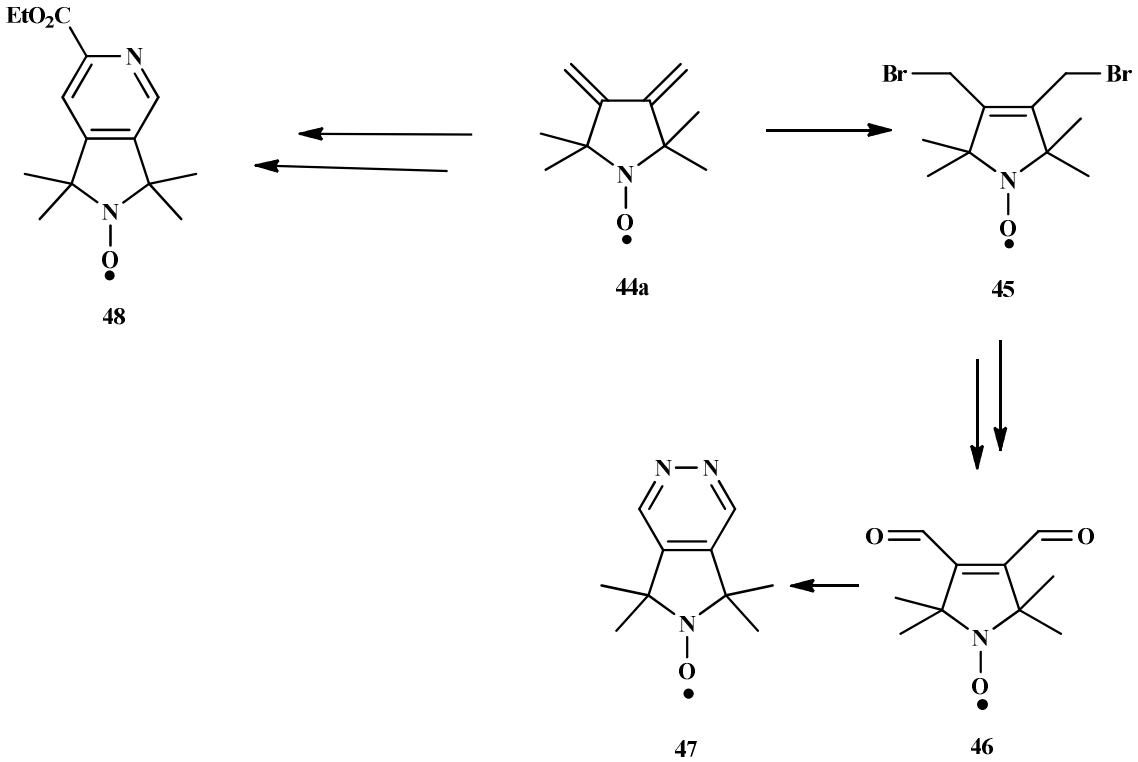


Scheme 9. Synthesis of dihydrothiophene fused pyrroline nitroxides.



Scheme 10. Synthesis of thiophene derivatives fused pyrroline nitroxides.

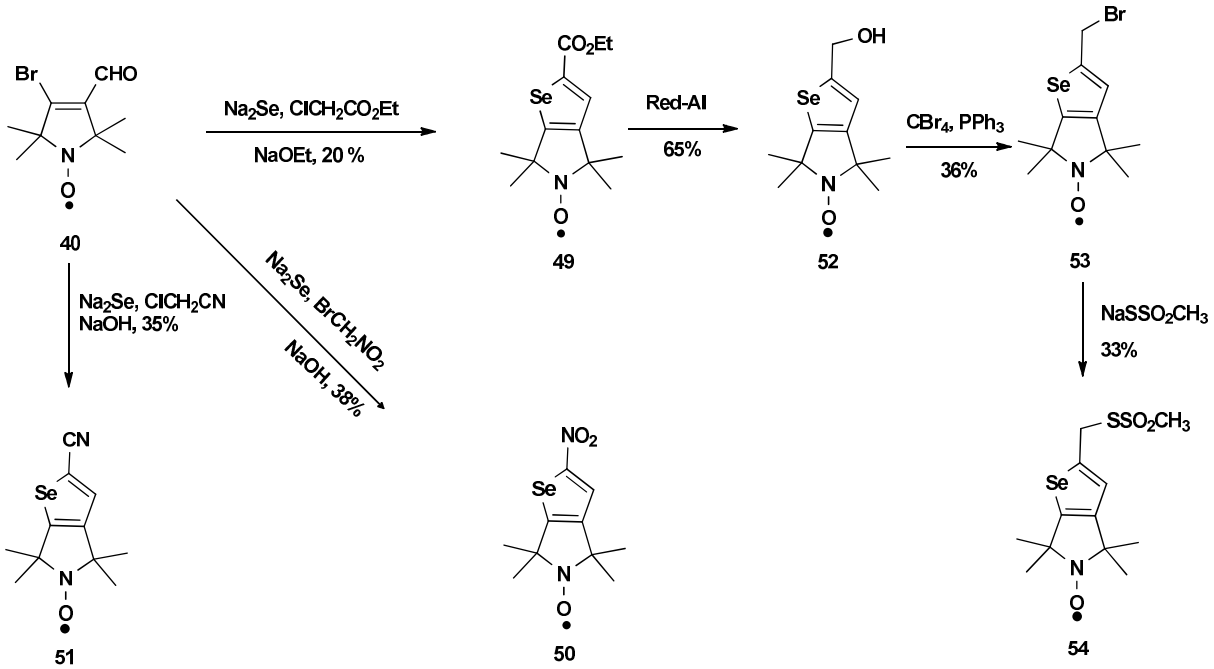
Kálai and co-workers synthesized dibromide **45** from diene **44a** of which transformation to dialdehyde **46**, followed by condensation with hydrazine offered pyridazine-annulated nitroxide **47** [33]. The hetero-Diels-Alder reaction of diene **44a** with *N*-(butoxycarbonylmethylen)-p-toluenesulfonamide after several steps offered the spin labeled picolinic acid ethyl ester **48** [34] (Scheme 11).



Scheme 11. Additional examples of six membered heterocycle fused nitroxides.

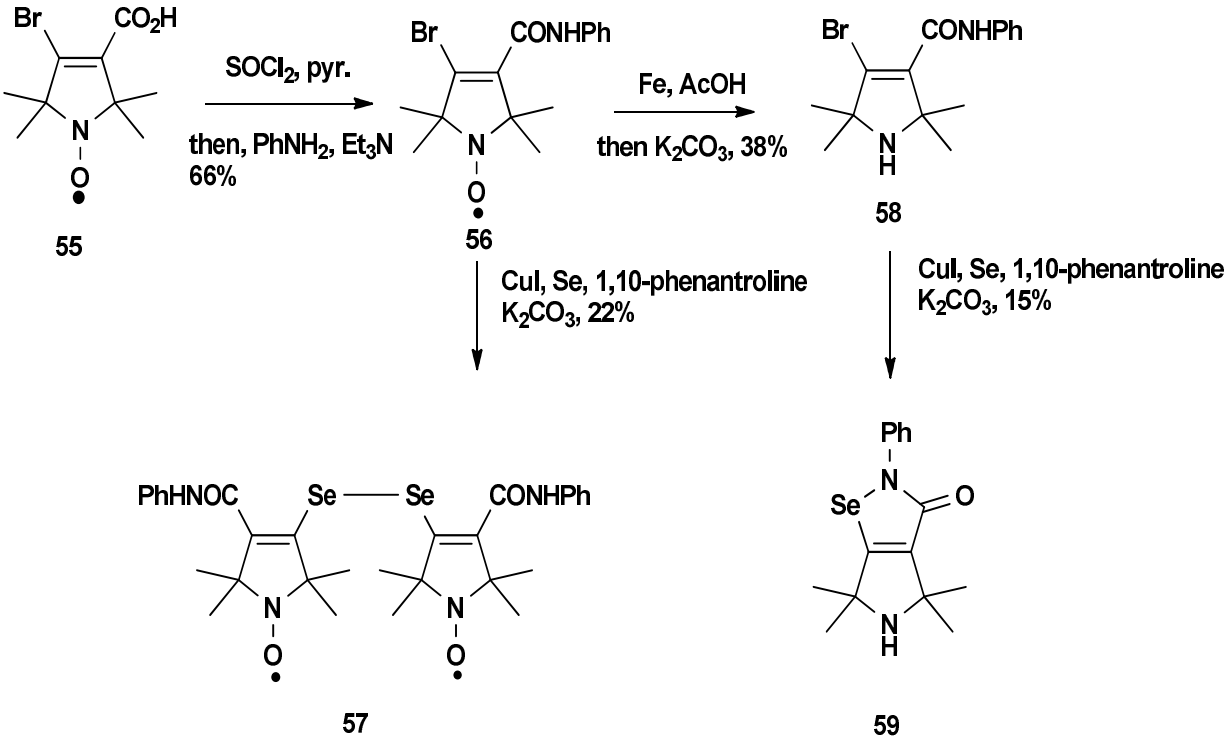
Our institute has obtained 5*H*-selenolo[2,3-c]pyrrole scaffolds **49-51** from aldehyde **40** by Na_2Se treatment followed by chloroacetic acid ester or bromonitromethane or

chloroacetonitrile, respectively in the presence of a base [35] (Scheme 12).



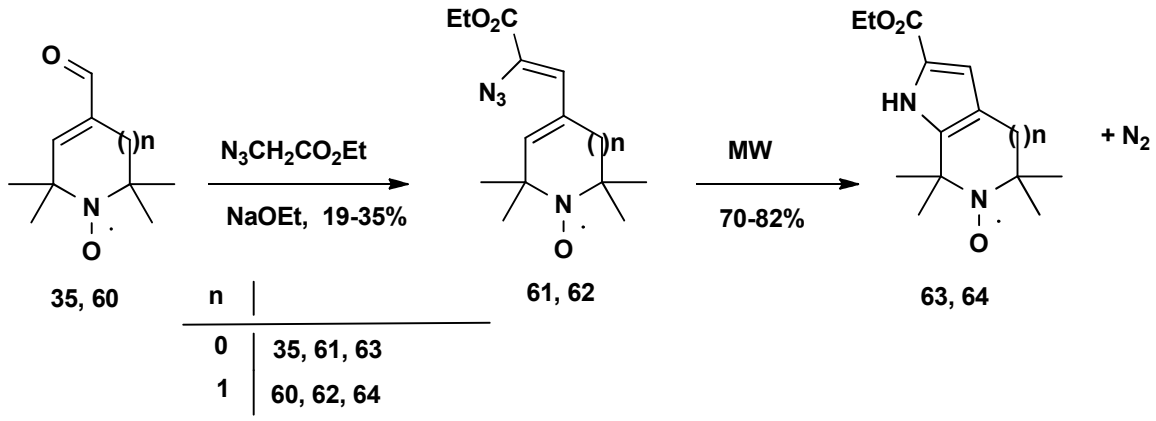
Scheme 12. Synthesis of selenophene fused nitroxides.

The ester **49** was reduced to alcohol **52** which was further substituted to bromine **53** in an Appel reaction, followed by substitution with $NaSSO_2CH_3$ to give an SH-specific methanethiosulfonate spin label **54.** Our institute intended the *N*-phenyl[1,2]selenazol ring synthesis fused to nitroxide. However, following the utilization of standard reaction conditions [36], the formation of diselenide **57** was observed from anilide **56**. Therefore, the ring closure was attempted from diamagnetic derivative **58** to give pyrrolo[3,4-d][1,2]selenazol-3(4*H*)-one scaffold **59**, although in low, 15% yield (Scheme 13) [37].



Scheme 13. Synthesis of 1,2-isoselenazole-fused pre-nitroxide.

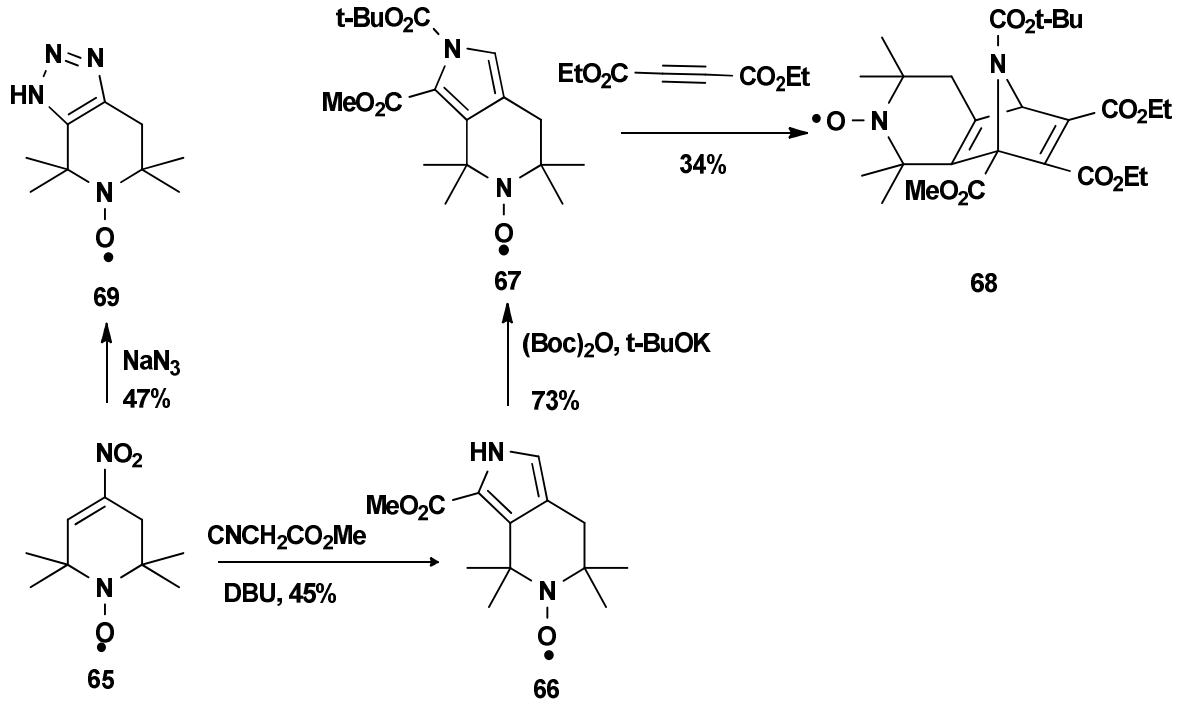
In 2015, our institute found a new approach for the synthesis of the pyrrole-fused nitroxides; aldehydes **35** and **60** condensed with ethyl 2-azidoacetate gave the vinyl azides **61**, **62**. The heating of vinyl azides in hexane under MW irradiation in a Hemetsberger–Knittel reaction offered pyrrolo[3,4-b]pyrrol **63** and pyrrolo[2,3-c]pyridine **64** scaffolds (Scheme 14).



Scheme 14. Synthesis of substituted pyrrole fused nitroxides with Hemetsberger-Knittel reactions.

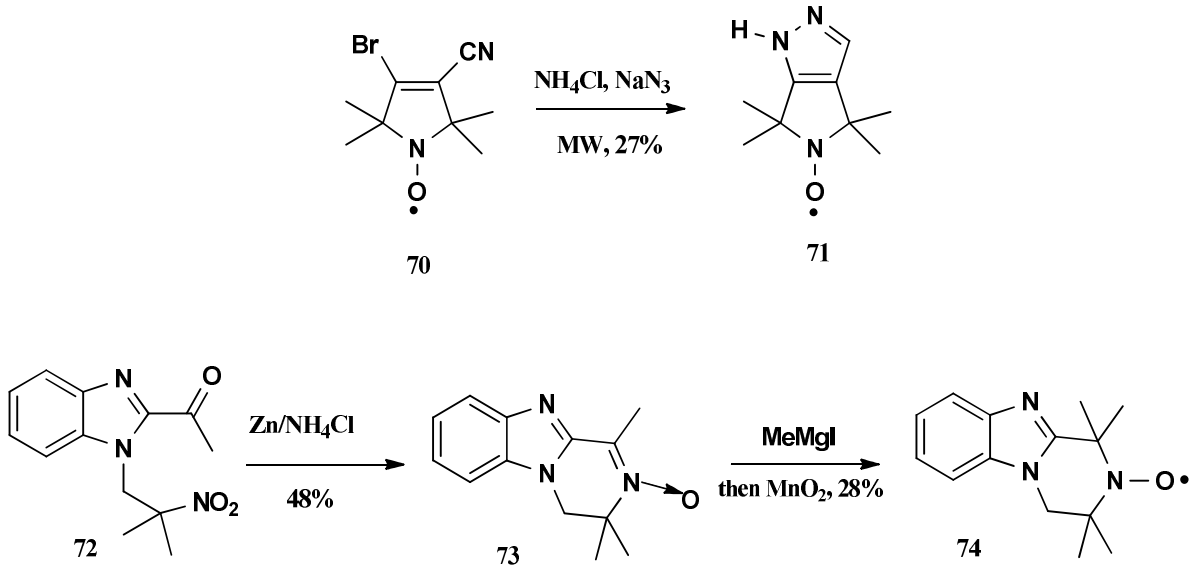
The other isomer of compound **64** was achieved by Bognár and co-workers from α,β-unsaturated nitro compound **65**, in a Barton-Zard reaction to offer compound **66**. The *N*-tert-butoxycarbonyl derivative of methyl pyrrole-2-carboxylate **67** was used in a Diels-Alder reaction to furnish polycyclic compound **68**. It is interesting to note that nitro compound **65**

with sodium azide in DMSO offered 4.4,6,6-tetramethyl-1,4,6,7-tetrahydro-5*H*-[1,2,3]triazolo[4,5-c]pyridine-5-yloxyl radical **69** [38] (Scheme 15).



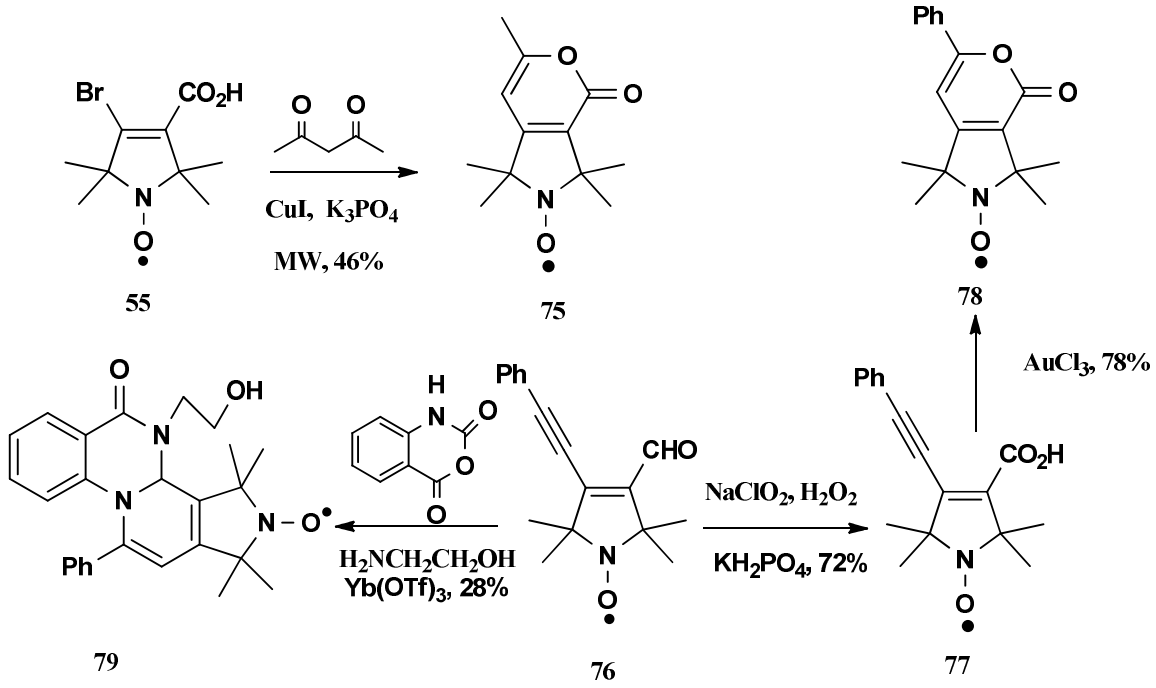
Scheme 15. Synthesis of tetrahydropiperidine fused *N*-heterocycles.

Also the synthesis of dihydropyrrolo[3,4-c]pyrazole **71** was described from nitrile **70** by $NH_4^+N_3^-$ treatment resulting in a fused pyrazole compound instead of tetrazole ring formation [38]. The benzimidazole fused nitroxide was described by Bognár and co-workers in 2008 [39]. The 2,2,6,6-tetramethylpiperazine ring was developed on the 1,3-diazole ring unit. The reduction of keto-nitro compound **72** gave nitrone **73** of which alkylation with CH_3MgI furnished nitroxide **74** (Scheme 16).



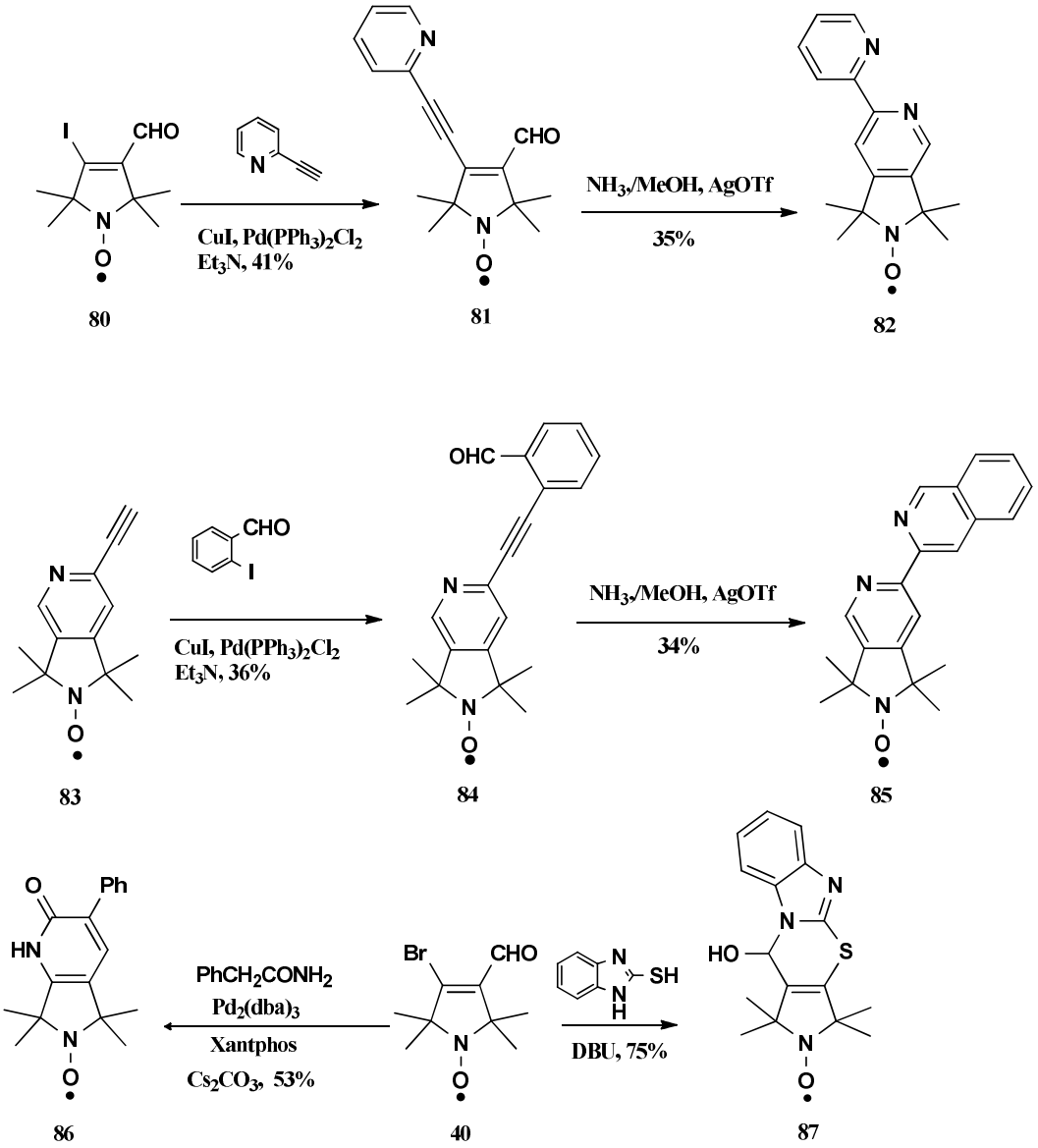
Scheme 16. Synthesis of 1,2- and 1,3- azoles fused nitroxides.

Kálai and co-workers also reported the synthesis of nitroxides fused with six-membered *O*-heterocycles. Starting from carboxylic acid **55**, its treatment with pentane-2,4-dione and CuI in the presence of base and microwave irradiation yielded lactone **75**. Its phenyl substituted analogue **78** was achieved from compound **76** [40]. The oxidation of compound **76** gave carboxylic acid **77**, which could be cyclized to **78** with $AuCl_3$. In a multicomponent reaction compound **76** with ethanolamine, isatoic anhydride and $Yb(OTf)_3$ as catalyst offered 4-(2-hydroxyethyl)-1,1,3,3-tetramethyl-5-oxo-11-phenyl-1,2,3,3b,4,5-hexahydropyrrolo[3',4':3,4] pyrido[1,2-a]quinazolin-2-yloxyl radical **79** (Scheme 17) [37].



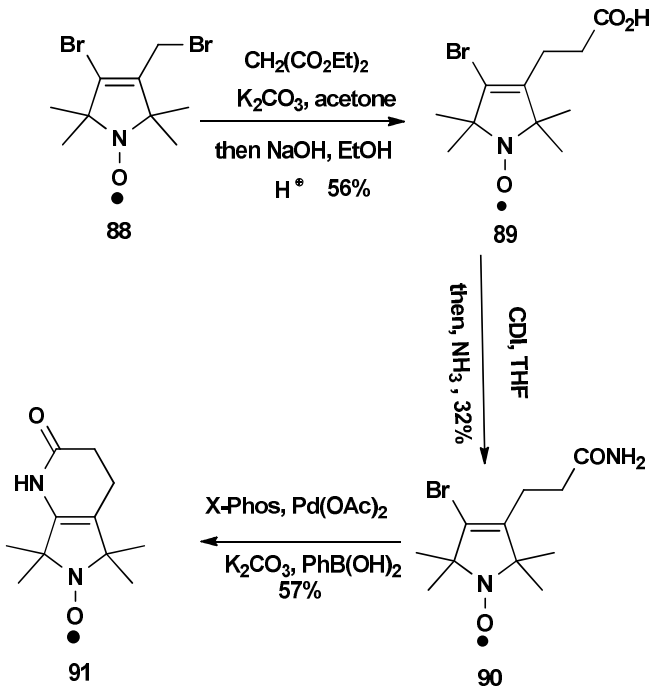
Scheme 17. Syntheis of δ-lactones and a polycycle fused nitroxide.

Úr and co-workers reported the synthesis of a pyridine-fused pyrroline nitroxide. Aldehyde **80** was coupled with 2-ethynylpyridine in Sonogashira coupling to yield compound **81**. After treating of this acetylene compound with AgOTf catalyst in methanolic ammonia solution, a paramagnetic α,α'-dipyridyl **82** was obtained, as a paramagnetic ligand [41]. The synthesis of a similar paramagnetic ligand **85** was reported in 2015 by our laboratory, starting from paramagnetic 2-ethynylpyridine **83** [42] obtained by reaction of Bestman-Ohira reagent with paramagnetic aldehyde [43]. The Sonogashira coupling with 2-iodobenzaldehyde yielded compound **84** of which ring closure with the aforementioned conditions gave compound **85**. The reaction of aldehyde **40** under Buchwald-Hartwig amidation conditions in a single step, in a one-pot procedure gave pyrrolo[3,4-b]pyridine scaffold **86**, while the reaction of aldehyde **40** with 2-mercaptobenzimidazole as a bisnucleophile furnished 11-hydroxy-1,1,3,3-tetramethyl-1,2,3,11-tetrahydro-benzimidazo[2,1-b]pyrrolo[3,4][1,3]thiazin-2-yloxyl radical **87** [44] (Scheme 18).



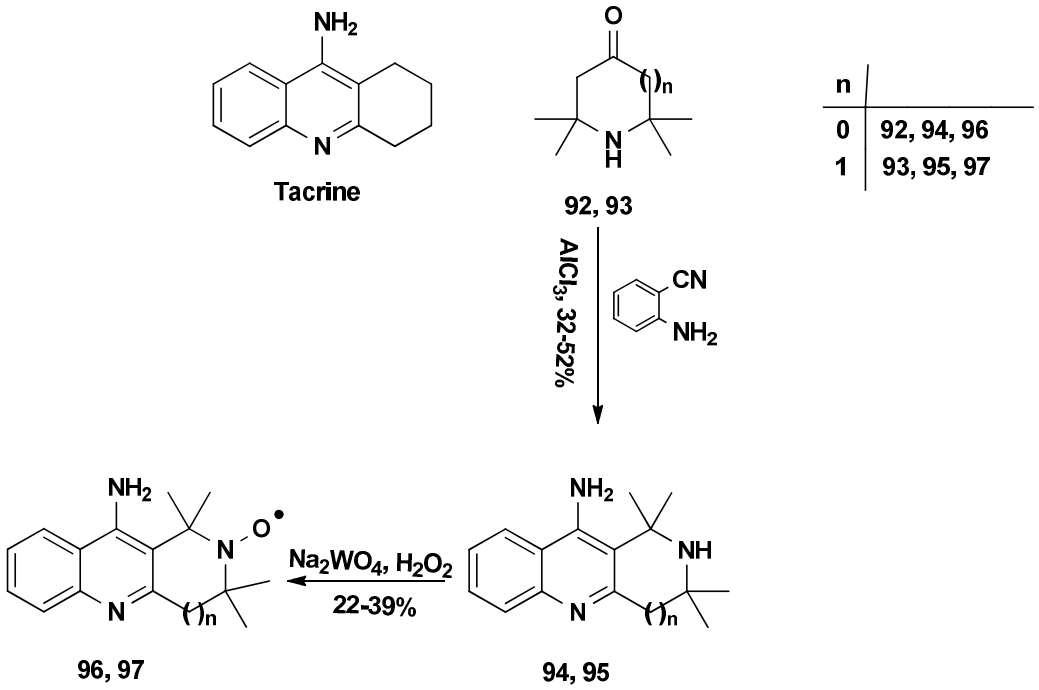
Scheme 18. Synthesis of pyridine, 1*H*-pyridin-2-one and thiazine fused pyrroline nitroxides.

The piperidin-2-one fused pyrroline nitroxide **91** was achieved by intramolecular Buchwald–Hartwig amidation reaction. Compound **88** was used as alkylating agent in a malonester synthesis and the resulted carboxylic acid **89** was converted to amide **90** followed by ring closure reaction to offer compound **91** [42] (Scheme 19).



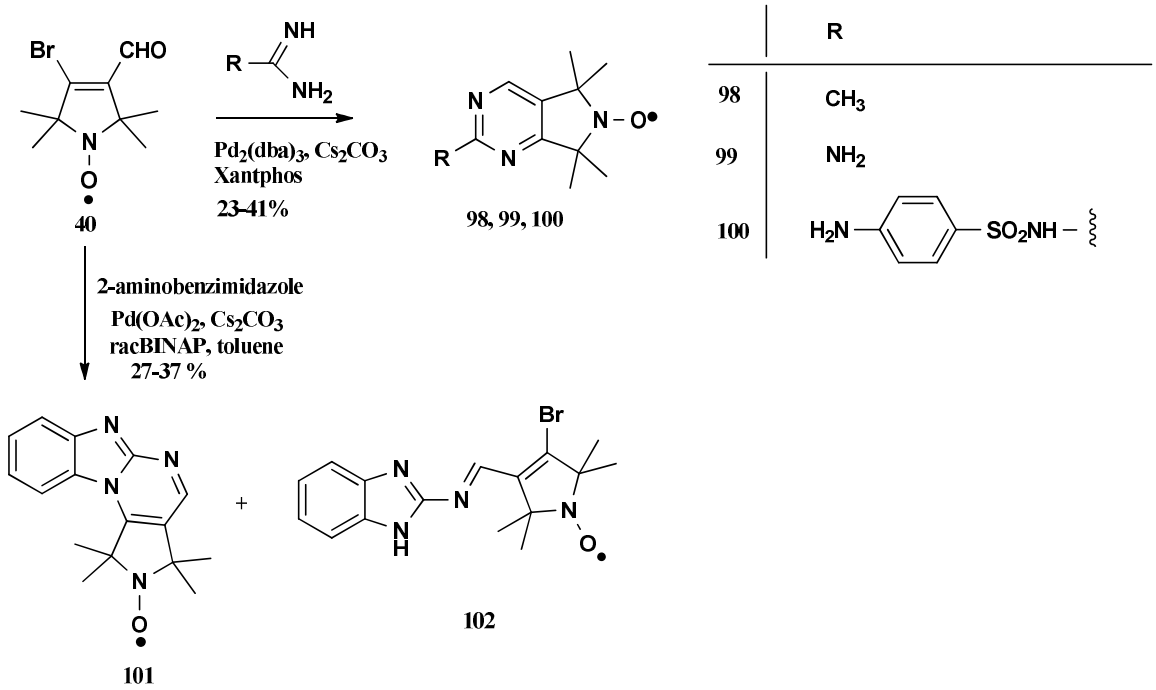
Scheme 19. Synthesis of paramagnetic piperidin-2-one.

In 2014, Kálai and co-workers reported tacrine-nitroxide hybrid experimental drugs with acetylcholinesterase inhibitory effect and antioxidant activity [45]. As a part of this study from sterically hindered ketones **92, 93** the corresponding amines **94, 95** were synthesized in a modified Friedlander synthesis with reactions of compounds **92, 93** and anthranylonitrile in the presence of Lewis acid, which was converted to nitroxides **96, 97** with Na_2WO_4/H_2O_2. Unfortunately these Tacrine chimeras lost their acetylcholinesterase inhibitory activity, but they were protecting against amyloid beta induced cytotoxicity (Scheme 20).



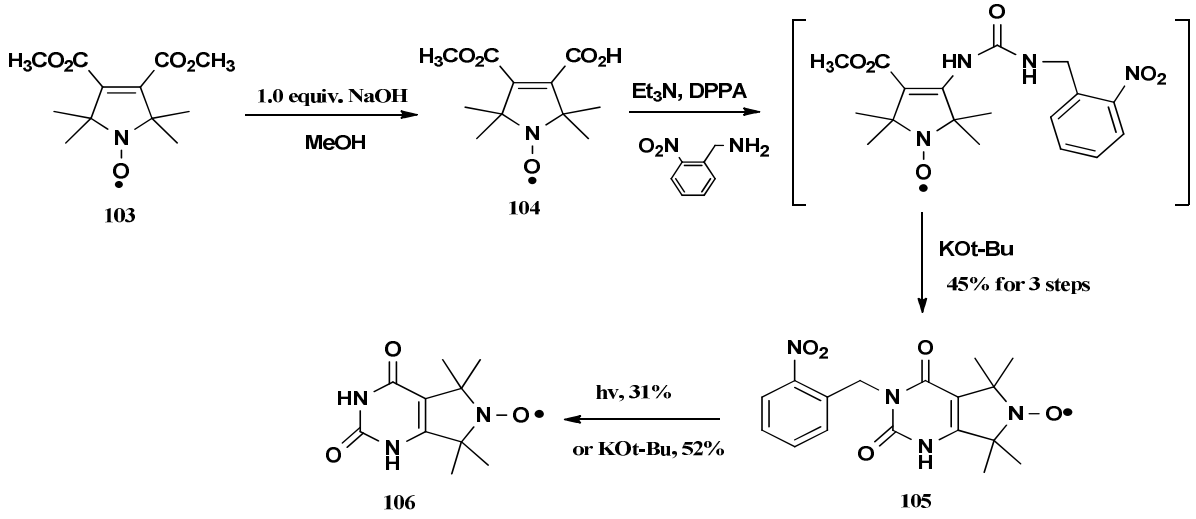
Scheme 20. Tacrine and synthesis of paramagnetic Tacrine analogs and their precursors.

In 2017, Úr and co-workers reported the synthesis of pyrroline-nitroxide fused pyrimidines **98, 99** and **100** from compound **40** [41]. The corresponding guanidines or amidines were reacted with β-bromo-α,β-unsaturated aldehyde **40** under Buchwald-Hartwig amidation conditions to give pyrimidine-fused nitroxides **98-100**. Compound **100** can be regarded as a paramagnetic analog of sulfonamide drug, sulfadiazine. The reaction of compound **40** with 2-aminobenzimidazole offered 1,1,3,3-tetramethyl-1*H*-benzimidazo[1,2]pyrrolo[3,4-e]pyrimidine-2-yloxyl radical **101**, and Schiff-base **102** [46] (Scheme 21).



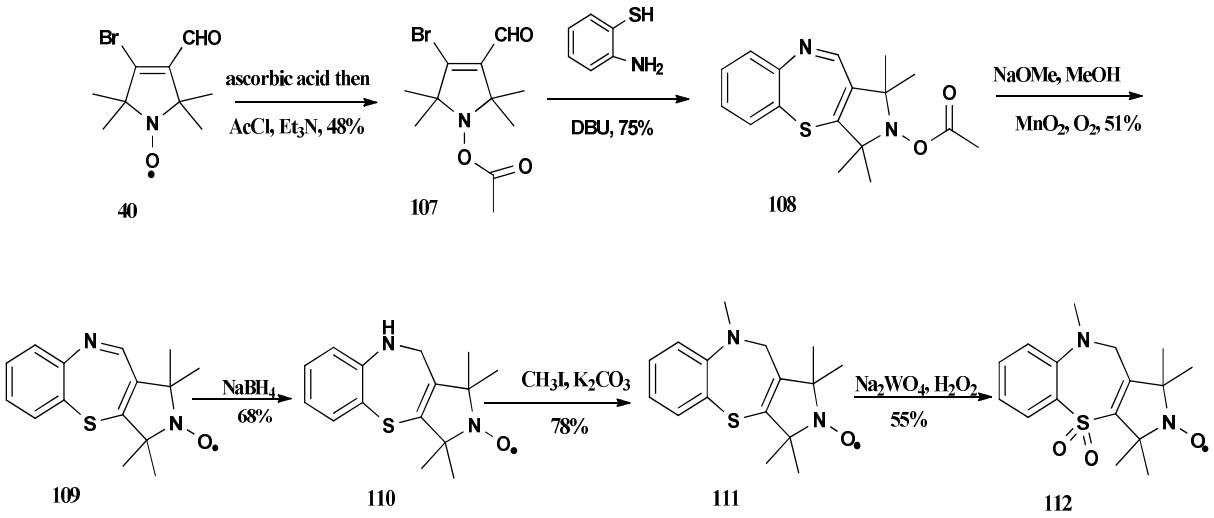
Scheme 21. Synthesis of pyrimidine-fused pyroline nitroxides.

The pyrroline nitroxide-fused uracil for nucleic acid labeling was achieved from diester **103** of which partial hydrolysis gave monoester **104**. This monoester was converted to acyl azide by diphenylphosphoryl azide (DPPA) followed by Curtius rearrangement and treatment with 2-nitrobenzylamine furnishing urethane, which has not been isolated. Cyclization of the crude urethane by KO*t*-Bu offered *N*-2-nitrobenzyl protected uracil **105** of which deprotection with UV irradiation or with excess KO*t*-Bu yielded 5,5,7,7-tetramethyl-6,7-dihydro-1*H*-pyrrolo[3,4-d]pyrimidine-2,4(3*H*,5*H*)-dione-5-yloxyl, e.g. spin labeled uracil **106** [47] (Scheme 22).



Scheme 22. Synthesis of uracil-fused pyrroline nitroxide.

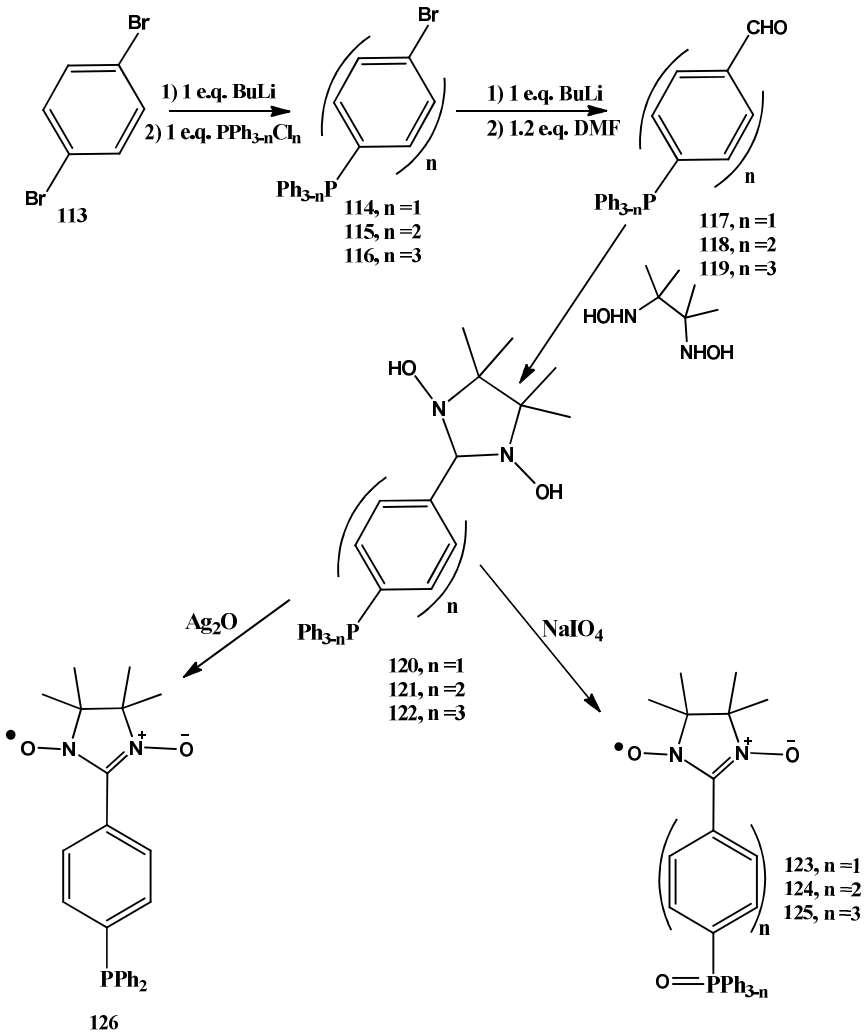
Bognár and co-workers reported nitroxides fused with seven membered heterocycles. 2-Aminothiophenol with compound **107** (the diamagnetic form of **40**) smoothly cyclized to compound **108** which was deprotected by Zemplen's deacetylation to produce compound **109** [44]**.** This benzo[1,5]thiazepine could be functionalized further by reduction, alkylation and oxidation reactions to furnish compounds **110, 111, 112** (Scheme 23).



Scheme 23. Synthesis of pyrroline-fused benzo[1,5]thiazepines.

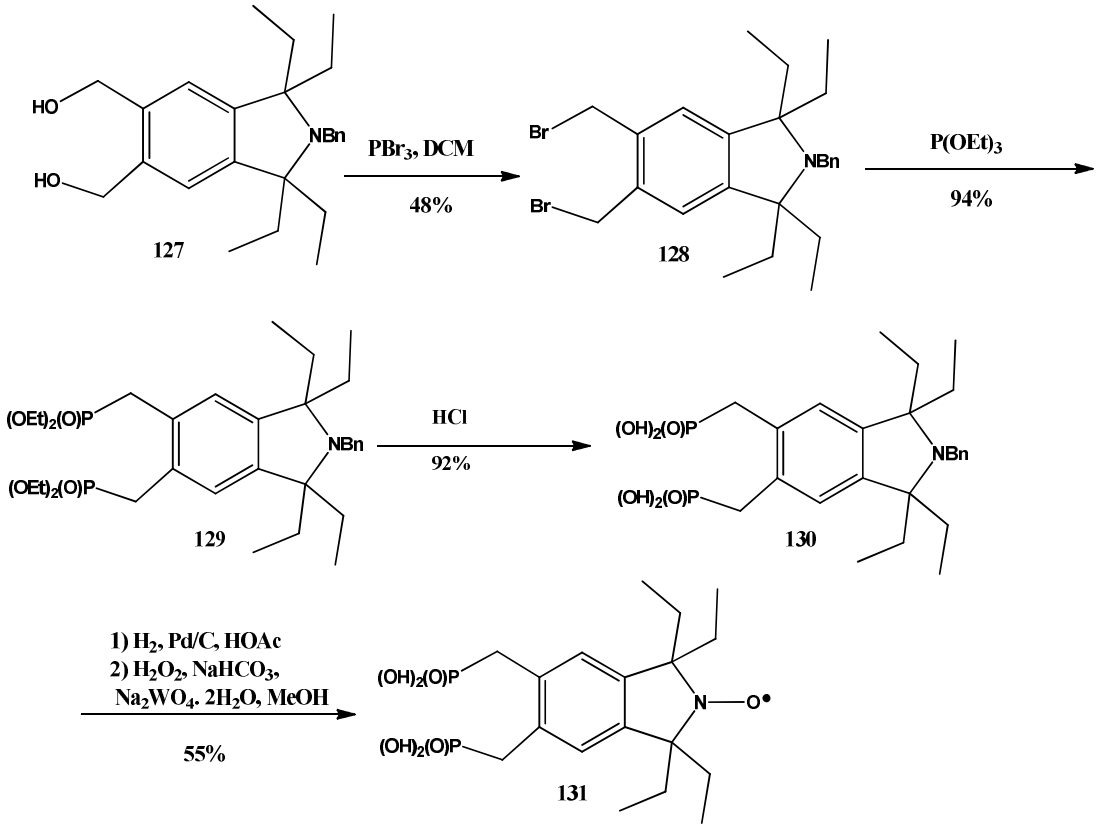
4.2. Synthesis of phosphorus containing nitroxide compounds

Organic phosphorus derivatives possess a significant position among organic compounds with a variety of applications including pharmacology, agriculture and organic synthesis [48-50]. Organophosphorus chemistry has provided many named reactions, such as the Arbuzov, Kabachnik–Fields, Perkow, Pudovik, Wittig, and Horner–Wadsworth–Emmons reactions, and has furnished many useful synthetic intermediates for C–C bond-forming reactions [51]. Despite their popularity and simplicity, application of these named reactions for the generation of stable, phosphorus-containing nitroxide (aminoxyl) free radicals has been limited, although several phosphorus-containing nitroxides have been used to investigate phosphorus hyperfine couplings or as spin labels exhibiting six bands in electron paramagnetic resonance (EPR) spectroscopy [52-57]. Rancurel and co-workers reported the synthesis of the nitronyl nitroxide-substituted phosphine and its oxide derivatives [56]. The mono-lithiation of *p*-dibromobenzene with BuLi, followed by the reaction with PCl_nPh_{3-n} (n =1 – 3) yielded the corresponding *p*-bromophenylphosphine **114, 115** and **116** [58, 59].The reactions of **114, 115** and **116** with *n*-BuLi and its subsequent formylation with DMF lead to **117, 118** and **119**. The mono-, di-, and tri-radical phosphine oxide derivatives, **123, 124** and **125**, were prepared in standard fashion [60] by condensation of the corresponding aldehyde with 2,3-dimethyl-2,3-dihydroxyaminobutane followed by oxidation with $NaIO_4$. The use of a periodate salt as oxidant results in the formation of both the radical and the phosphine oxide in a single step. For the preparation of phosphine **126**, a milder and selective oxidant is required. They have shown that a selective formation of the radical can be obtained if Ag_2O is used as oxidant [61] (Scheme 24).



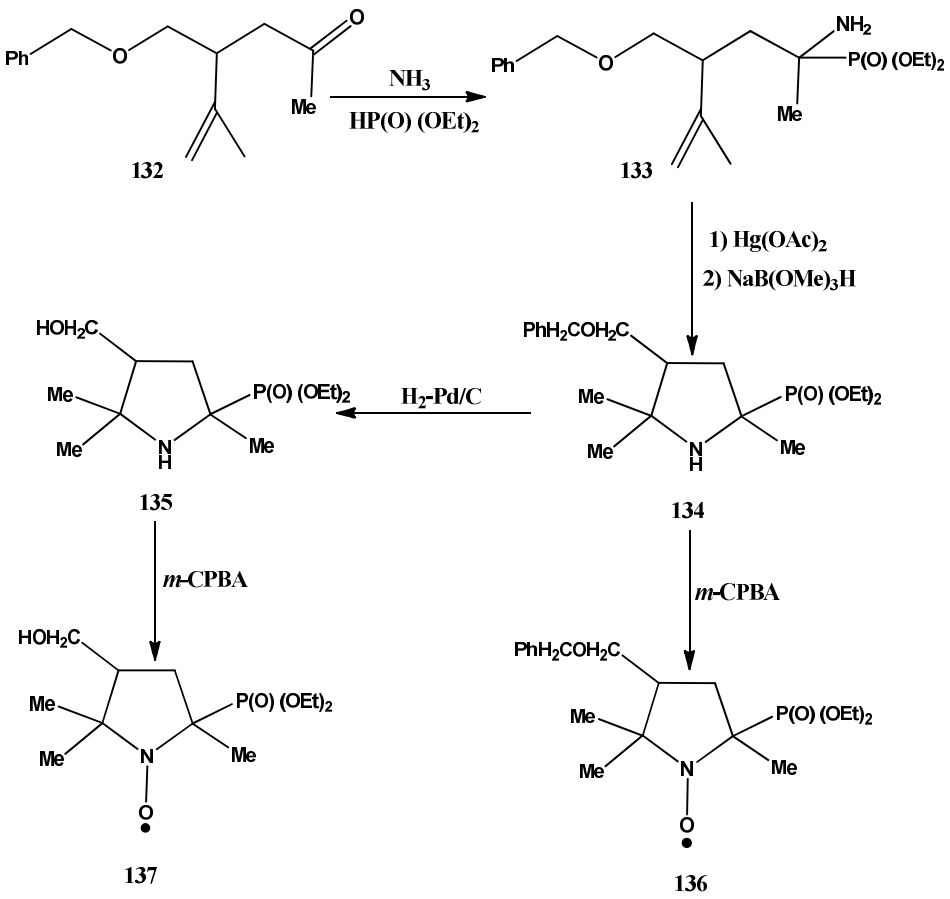
Scheme 24. Synthetic pathway for the prepartion of nitronyl nitroxide-substitued phosphine derivatives and their oxides.

In 2008, Kathryn and co-workers reported the synthesis of diphosphonic acid containing nitroxide [62]. The dibromo analogue **128** was formed by reaction of the diol **127** with phosphorus tribromide in DCM. Heating of **128** in neat triethyl phosphite in an Arbuzov reaction furnished the diphosphonate **129** in high yield (94%). Acidic hydrolysis gave the corresponding diphosphonic acid derivative **130** which underwent debenzylation by H_2-Pd/C treatment and subsequent oxidation using Na_2WO_4 to the nitroxide to afford the desired diphosphonic acid nitroxide **131** in moderate yield (55 %) (Scheme 25).



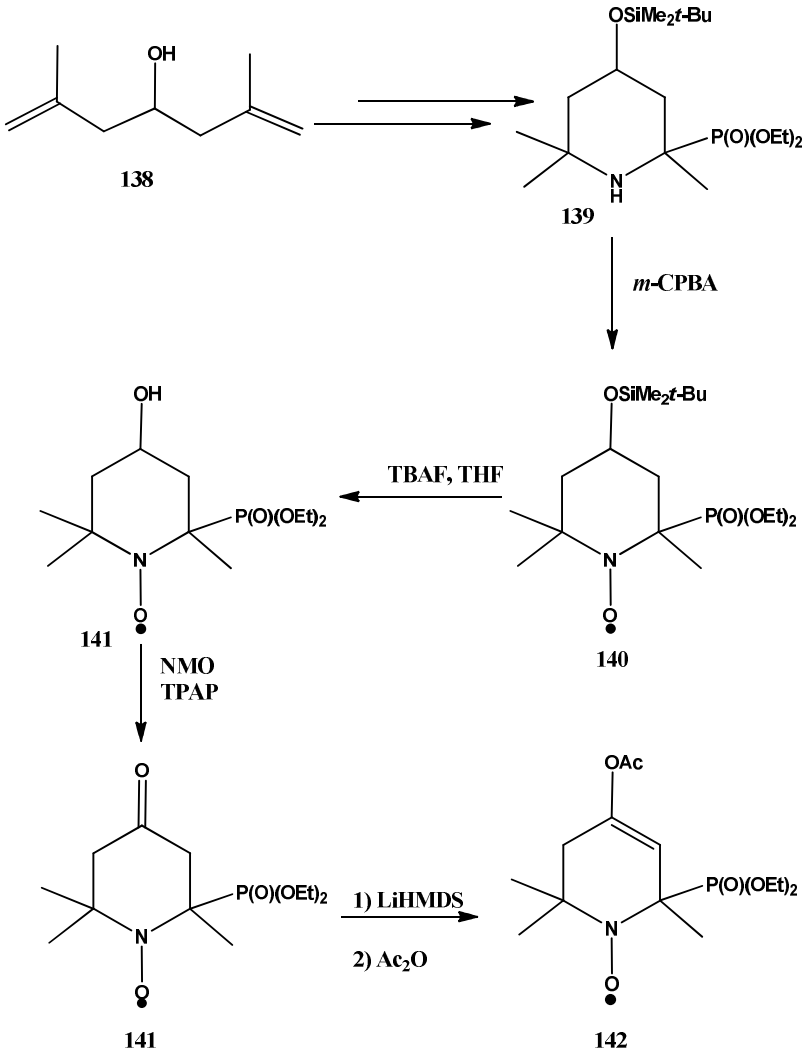
Scheme 25. Synthesis of diphosphonic acid containing nitroxide.

The synthesis of *β*-phosphorylated nitroxides with five membered rings were reported by Stipa and co-workers [52]. The aminophosphorylation of **132** under modified Medved–Kabachnik reaction conditions using NH_3, $HP(O)(OEt)_2$ offered compound **133**. The ring cyclization of **133** by intramolecular aminomercuration [63], followed by reduction with $NaB(OMe)_3H$ gave compound **134**. The debenzylation of **134** by palladium-catalyzed hydrogenation offered compound **135**. Oxidation of **134** and **135** with *m*-CPBA gave the corresponding nitroxides **136** and **137** (Scheme 26).



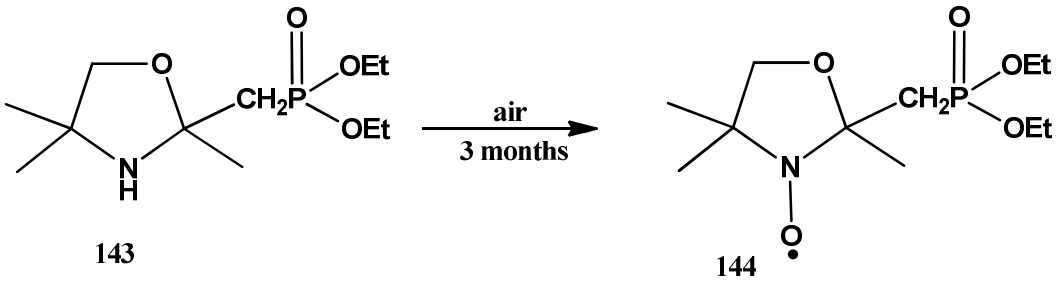
Scheme 26. Synthesis of *β*-phosphorylated five-membered ring nitroxides.

Audran and co-workers reported the synthesis of *β*-phosphorylated nitroxides with six-membered ring [64]. Diene **138** was the starting material and through 5 steps, compound **139** was obtained, followed by oxidation by *m*-CPBA to give nitroxide **140**. Desilylation of **140** offered hydroxy compound **141**, followed by oxidation to keto nitroxide **142**, which was in turn converted to nitroxide **143** after enolization, followed by treatment with Ac_2O (Scheme 27).



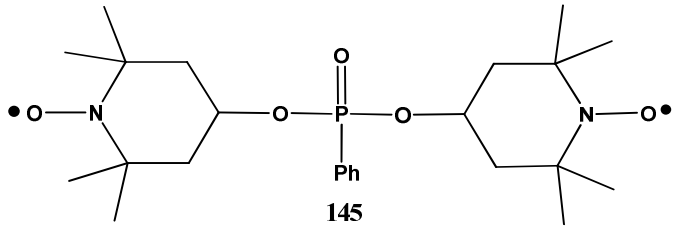
Scheme 27. Synthesis a *β*-phosphorylated six-membered ring nitroxides.

Livant and co-workers reported the synthesis of *γ*-phosphorylated nitroxides with five-membered ring [65]. Oxazolidine **143** was prepared from diethyl-β-keto-propylphosphonate and 2-amino-2-methyl-1-propanol by the method of Keana *et al.* [66]. The oxidation of **143** occurred spontaneously after three months exposure to air yielding nitroxide **144** (Scheme 28).



Scheme 28. Synthesis of *γ*-phosphorylated five-membered ring nitroxides.

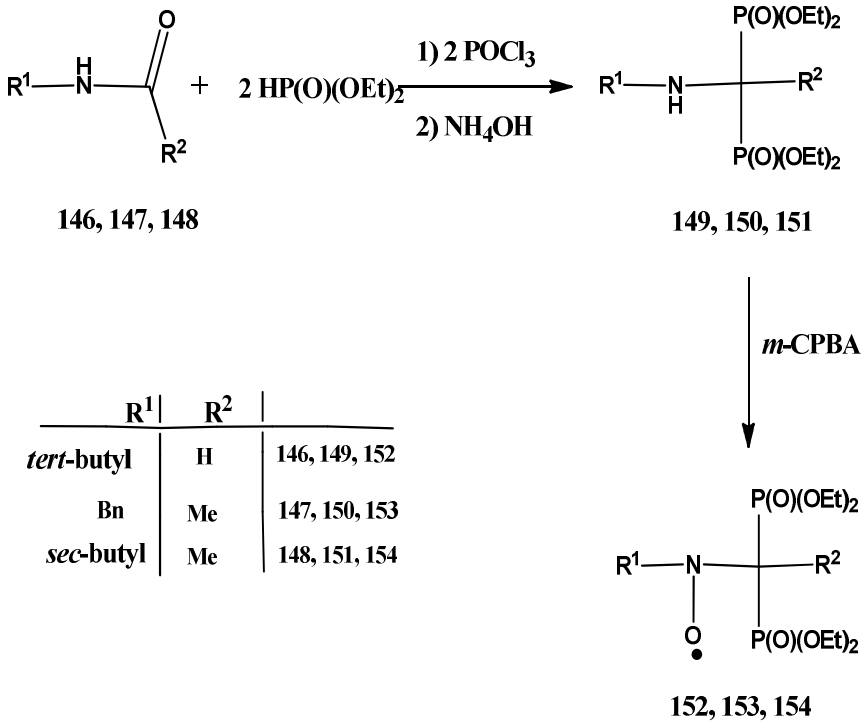
Nitroxide biradical **145** containing phosphorus atom in the bridge (Figure 5) was synthesized in 2015 by Kokorin and co-workers and have been studied by EPR and X-ray structural analysis [67].



145

Figure 5. Structure of nitroxide biradical containing phosphorus atom in the bridge.

Rockenbauer and co-workers reported the synthesis of geminal diphosphorylated linear nitroxides [68]. Compounds **149**, **150** and **151** were synthesized by method of Olive *et al* [69], followed by oxidation using *m*-CPBA to the corresponding nitroxides **152**, **153** and **154** (Scheme 29).



146, 147, 148

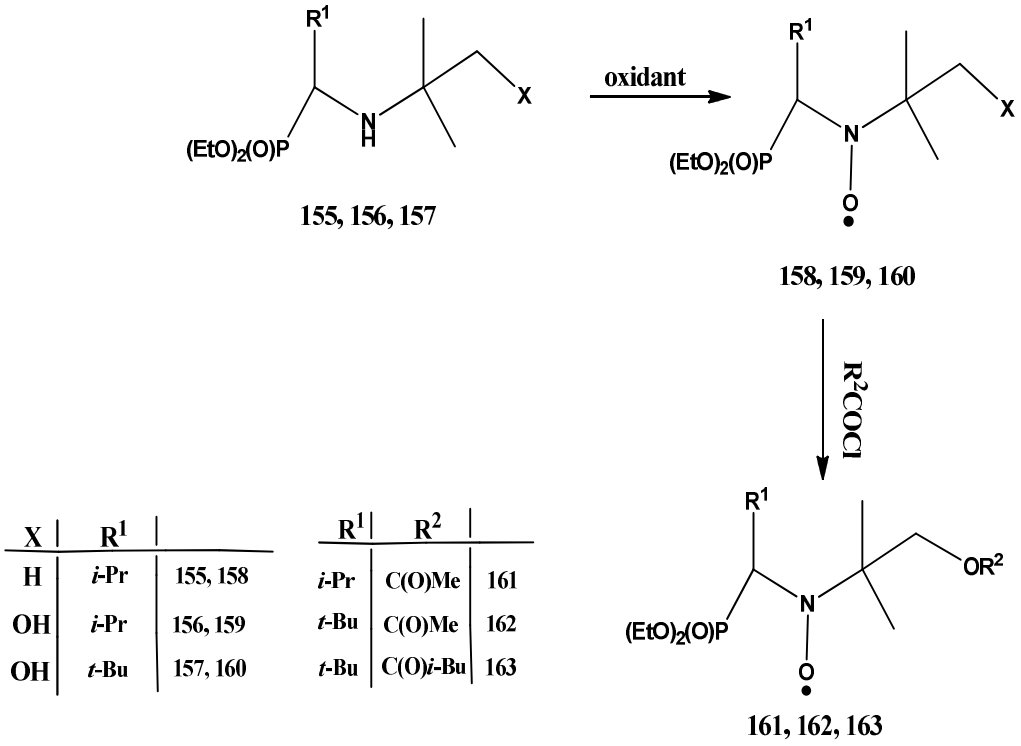
149, 150, 151

R^1	R^2	
tert-butyl	H	146, 149, 152
Bn	Me	147, 150, 153
sec-butyl	Me	148, 151, 154

152, 153, 154

Scheme 29. Synthesis of geminal diphosphorylated linear nitroxides.

β-Phosphorylated compounds in non-cyclic nitroxides were obtained by Audran and co-workers in 2016 [70]. The obtained aminophosphonates **155**, **156** and **157** were oxidized by *m*-CPBA to the corresponding nitroxides **158**, **159**, **160**. The esterification of alcohol function of **159** and **160** offered the corresponding end product nitroxides **161**, **162** and **163** (Scheme 30).



X	R^1	
H	*i*-Pr	155, 158
OH	*i*-Pr	156, 159
OH	*t*-Bu	157, 160

R^1	R^2	
i-Pr	C(O)Me	161
t-Bu	C(O)Me	162
t-Bu	C(O)*i*-Bu	163

Scheme 30. Synthesis of β-phosphorylated compounds in non-cyclic nitroxides.

5. Objectives

In my PhD thesis, we aimed at finding new methods for the synthesis of stable nitroxide radicals, which could have a variety of applications in biological studies, organic synthetic chemistry, based on following topics:

A. Syntheses of 1,4-diazine- and imidazole-fused pyrroline nitroxide.

B. Syntheses of new pyrroline and piperidine nitroxide phosphonates by the well-established methods, such as Pudovik and Arbuzov reactions and further transformations of the new products.

C. Syntheses of paramagnetic phospholene oxide, diphenylpyrroline phosphine and its phosphonum salt and investigation of its antineoplastic activity.

6. Results and discussion

6.1. Syntheses of 1,4-diazine- and imidazole-fused pyrroline nitroxides

We focused on the synthesis of pyrazine (1,4-diazine) and imidazole (1,3-diazole) fused pyrroline nitroxides. Pyrazines are important structural motifs of many biologically active molecules, such as riboflavin, and drugs, such as pyrazinamide (antituberculotics), varenicline (smoking cessation drug), flutimide & favipiravir (antiviral drugs), pyrazinediazohydroxide (potential antineoplastic), acipimox (hypolipidemic agent), sulfalene (antibacterial drug), glipizide (antidiabetic drug), bortezomib (the proteasome inhibitor for the treatment of multiple myeloma), amiloride (diuretic drug), and oltipraz (antichistosomal agent) (Figure 6) [71].

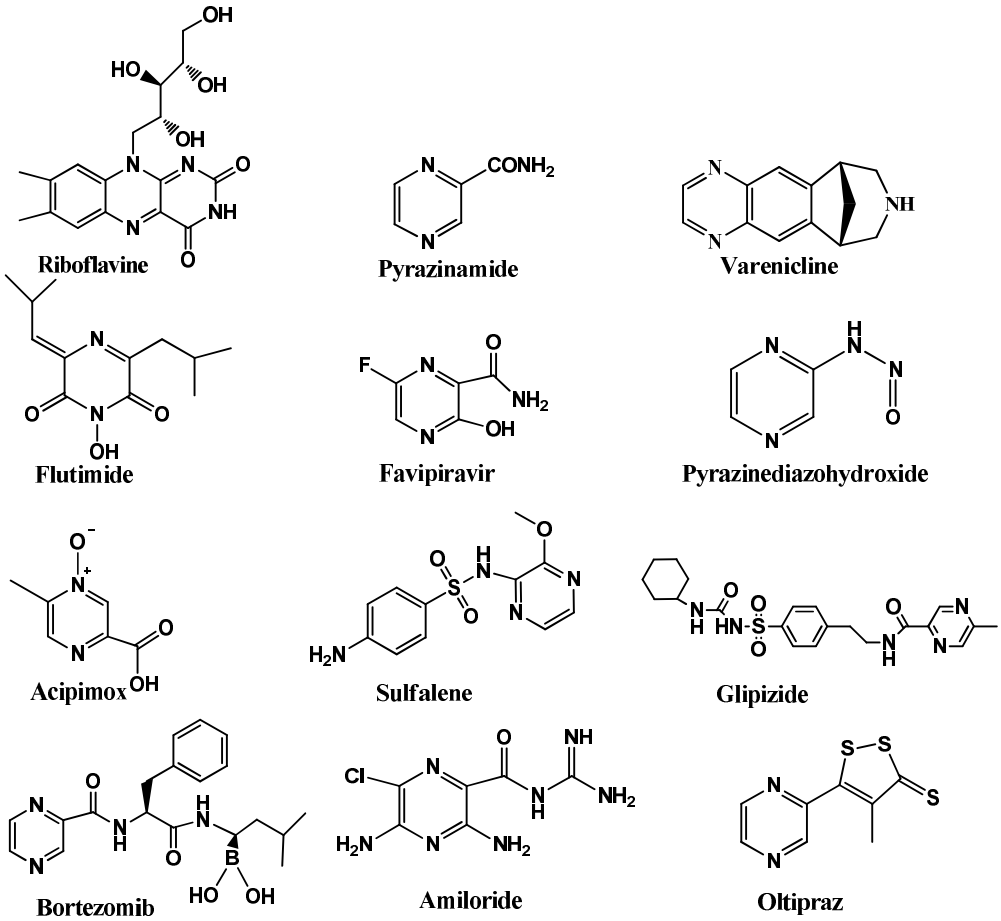


Figure 6. Bioactive molecules and drugs containing pyrazine ring.

6.1.1. Synthesis of 1,4-diazine-fused pyrroline nitroxides [V]

Obviously, the condensation of 1,2-diamine with paramagnetic 1,2-diketones suggests a synthetic route to novel paramagnetic 1,4-diazines [72, 73]. Inspired by work of Sandris and Ourisson [74], we attempted the synthesis of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3,4-dione

by SeO_2 oxidation of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3-one **164** [75]; however no reaction occurred and only starting material was recovered (Scheme 31).

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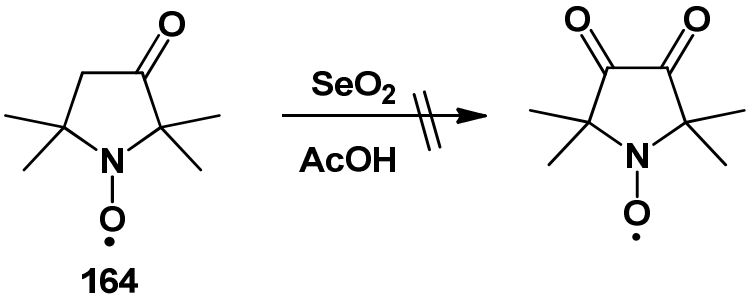
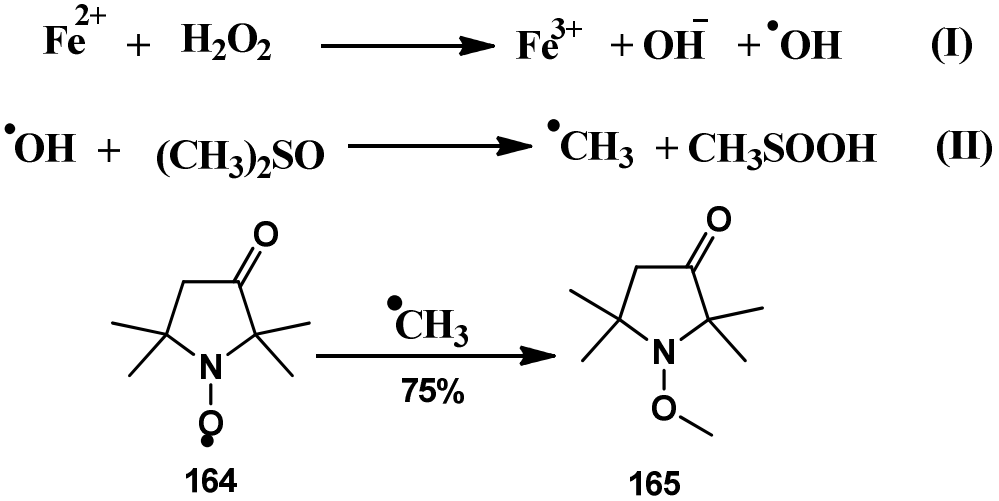


164

Scheme 31. Attempted synthesis of a paramagnetic diketone.

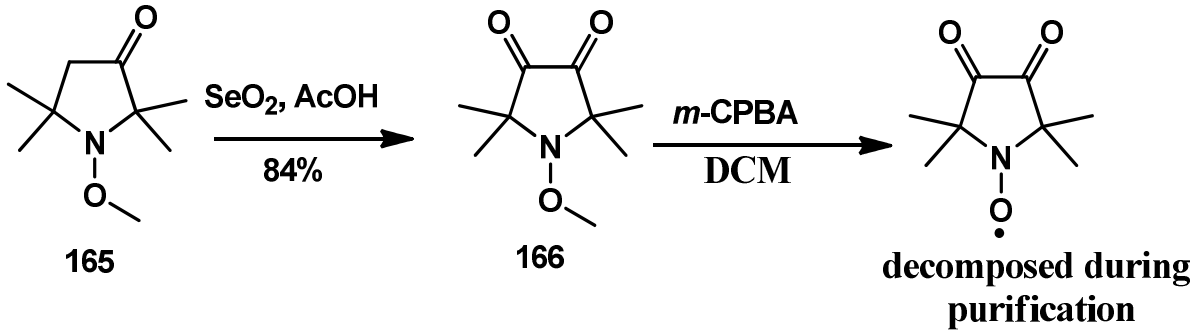
Based on our previous findings regarding sluggish reactions, we proposed that the free radical moiety must be protected; however neither the *N*-OAc protection [76] nor the hydroxylamine-HCl salt form was sufficient for camouflaging the nitroxide moiety in the oxidation reaction with SeO_2. For nitroxide protection we used the *O*-methylation technique conducted by a Fenton reaction in the presence of DMSO (**I**, **II**), which was worked out in Bottle's group. Treatment of compound **164** with a methyl radical generating system (Fe^{2+} and aq. H_2O_2 mixture in DMSO) yielded compound **165** (75%) (Scheme 32) [77a].



164 **165**

Scheme 32. Protection method of nitroxide free radical.

Oxidation of compound **165** by refluxing it with 1.5 equivalents of SeO_2 in AcOH offered compound **166** in an 84% yield. We attempted the deprotection of compound **166** with 3-chloroperbenzoic acid (*m*-CPBA) [77b], which gave an unstable five-membered 1,2-diketo nitroxide compound, which decomposed during purification (Scheme 33).



Scheme 33. Oxidation of 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3-one and attempt of deprotection.

So we decided to condense compound **166** with different aromatic and heteroaromatic 1,2-diamino compounds such as 1,2-diaminobenzene **167a**, 2,3-diaminobenzamide **168a**, [43] 1,2,4,5-tetraaminobenzene **169a**, 4,5-diaminopyrimidine **170a**, 5,6-diaminouracil **171a**, in ethanol, glacial acetic acid or aq. methanol to give the pyrazine ring condensed polycyclic compounds **167b**, **168b**, **169b**, **170b** and **171b**, respectively. Treatment of compound **167b** with *m*-CPBA in CH_2Cl_2 (DCM) yielded stable nitroxide **167c**. Deprotection of **168b** with *m*-CPBA gave the paramagnetic 5-carboxamidoquinoxaline **168c**, which can be regarded as a potential poly (ADP-ribose) polymerase (PARP) inhibitor, [78] and deprotection of compound **169b** offered the rigid biradical compound **169c** giving a quintet line in the EPR spectrum at a_N = 7.3 G (Figure 7). Deprotection of compound **170b** furnished the paramagnetic pteridine **170c**, and deprotection of compound **171b** offered the paramagnetic pteridine-2,4(3H,8H)-dione **171c**, the spin labelled (SL) lumazine (Table 1). The proposed deprotection mechanism includes forming *N*-oxide via electrophilic attack at nitrogen [77b], followed by oxygen transfer yielding a substrate that is primed for Cope elimination [79] (Scheme 34).

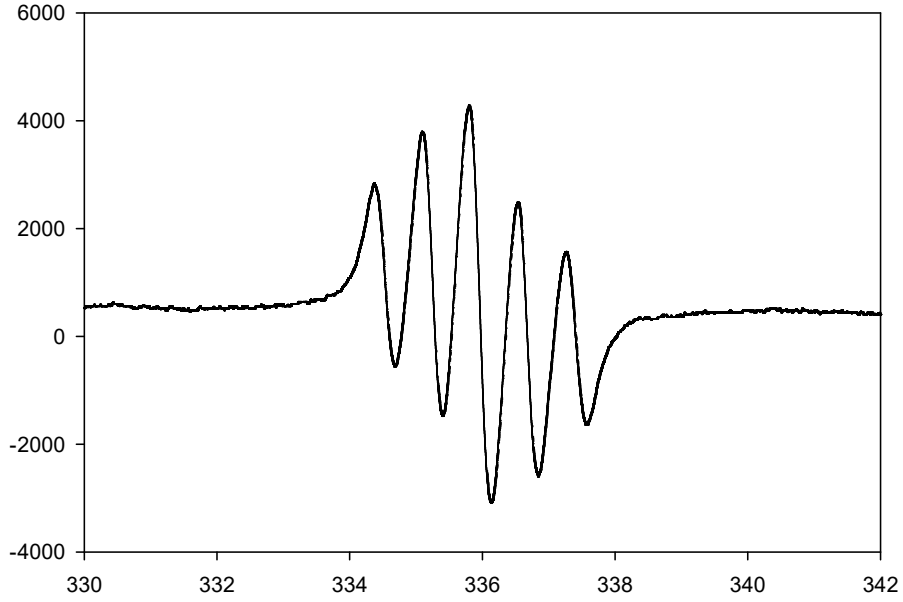
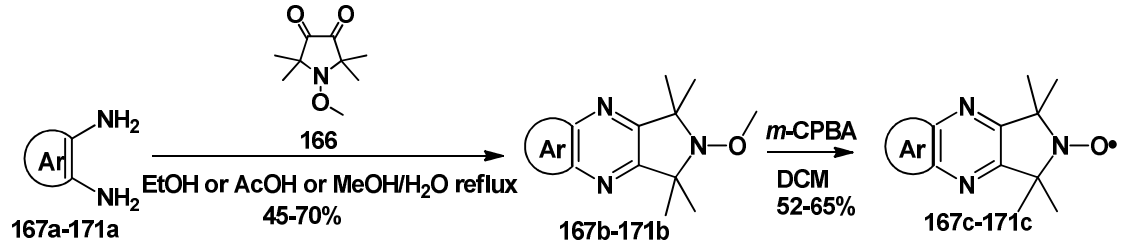
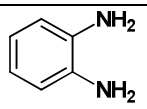
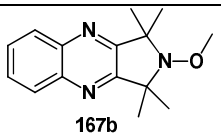
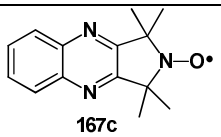
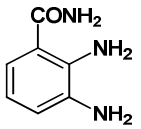
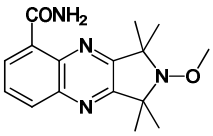
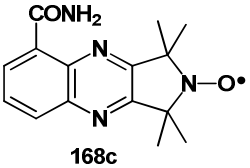
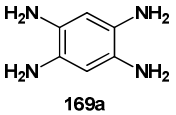
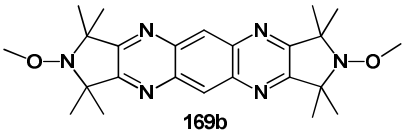
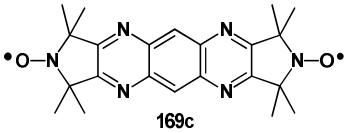
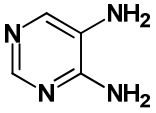
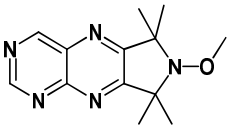
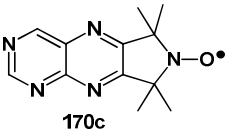
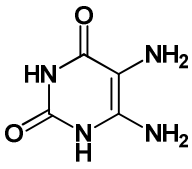
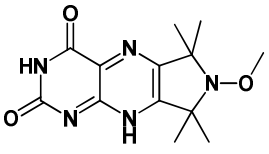
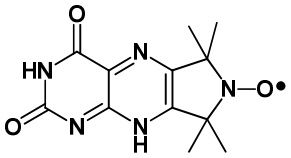


Figure 7. EPR spectra of compound **169c** (10^{-4} M) in $CHCl_3$.

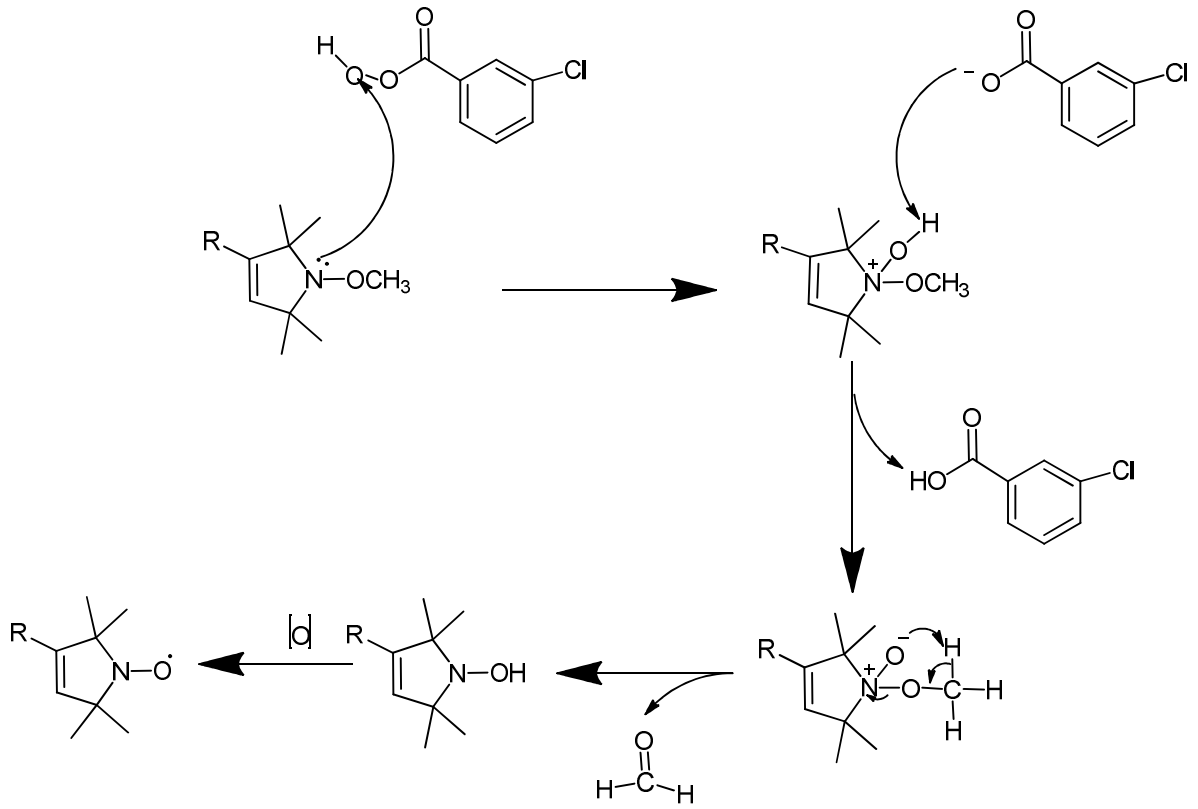
Table 1. Synthesis of pyrazine condensed paramagnetic, polycyclic compounds.



Entry	1,2-diamino compound	Diamagnetic product	Paramagnetic product
1	 167a	 167b	 167c
2	 168a	 168b	 168c
3	 169a	 169b	 169c
4	 170a	 170b*	 170c
5	 171a	 171b**	 171c

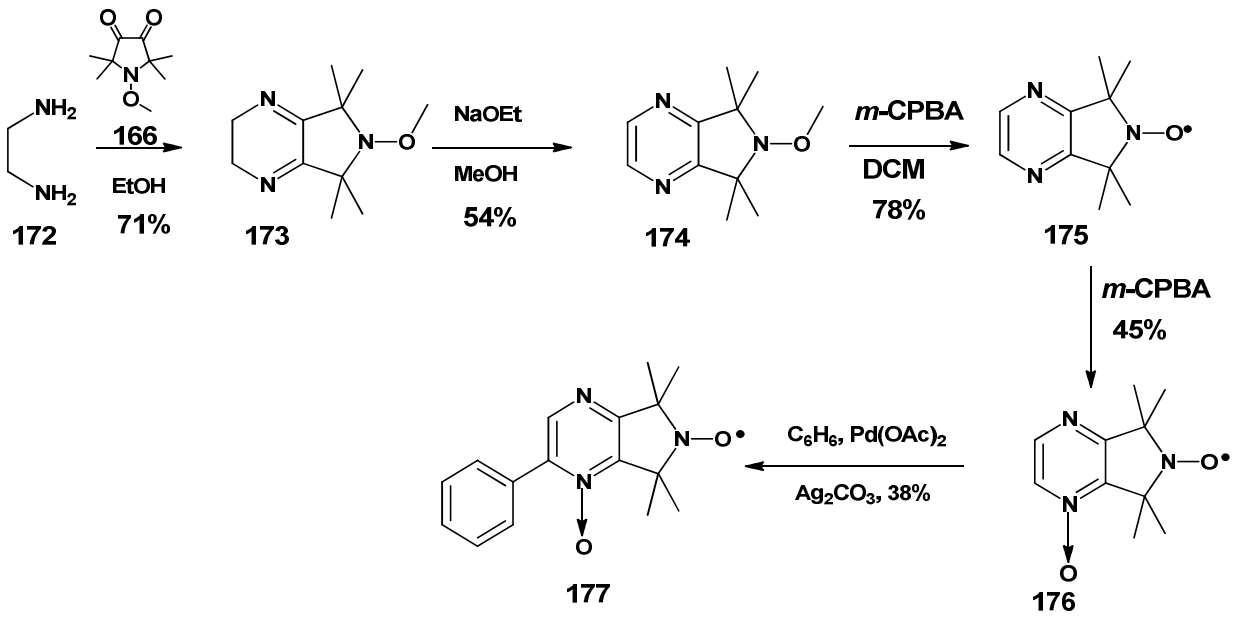
*Reflux in AcOH.

**Reflux in MeOH/H_2O



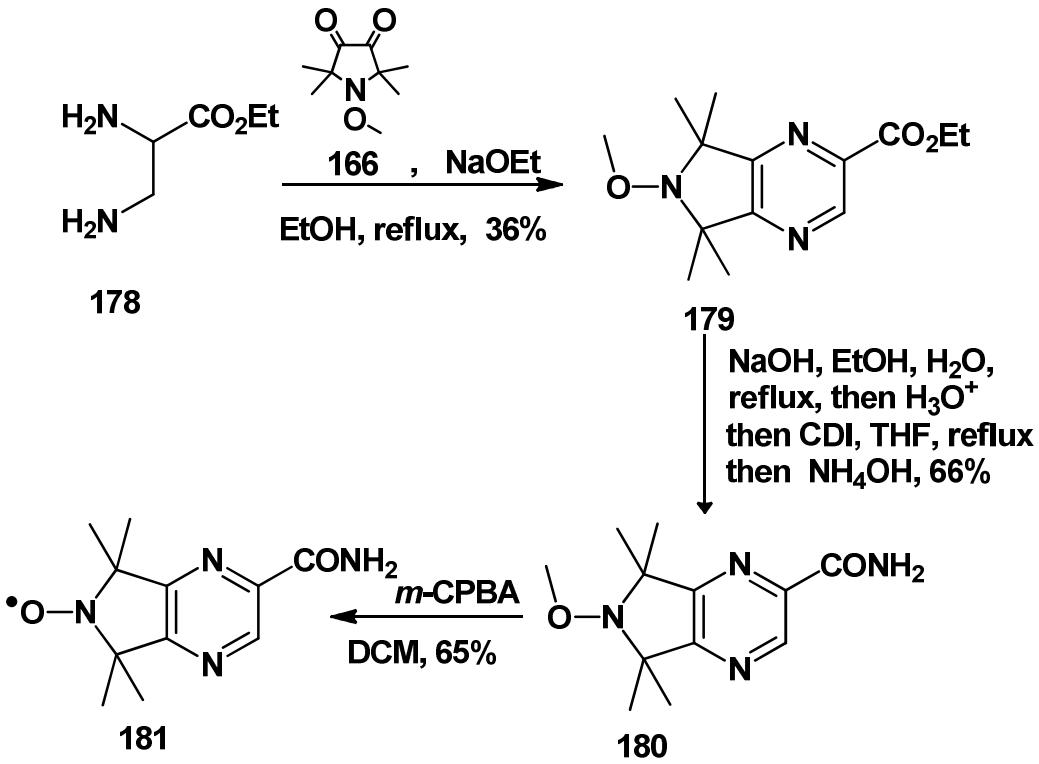
Scheme 34. The proposed deprotection mechanism of *O*-methyl hydroxylamines.

To construct the pyrrolo[3,4-b]pyrazine scaffold, compound **166** was condensed with 1,2-diaminoethane **172** yielding compound **173**. Aromatization of **173** by treatment with 2.0 equivalents of sodium ethoxide in methanol at reflux temperature [80] followed by standing overnight yielded a pyrazine-condensed precursor **174**. This was deprotected with m-CPBA to give compound **175** in a 30% overall yield in three steps. Upon prolonged reaction time and excess m-CPBA (5.0 equiv.) we observed the formation of *N*-oxide **176**, which offered the possibility of C-H functionalization with benzene at C_2 position by palladium catalysis and Ag_2CO_3 oxidation [25], to give compound **177** in a 38% yield (Scheme 35).



Scheme 35. Synthesis of diamagnetic and paramagnetic pyrrolo[3,4-b]pyrazine scaffolds and its CH functionalization.

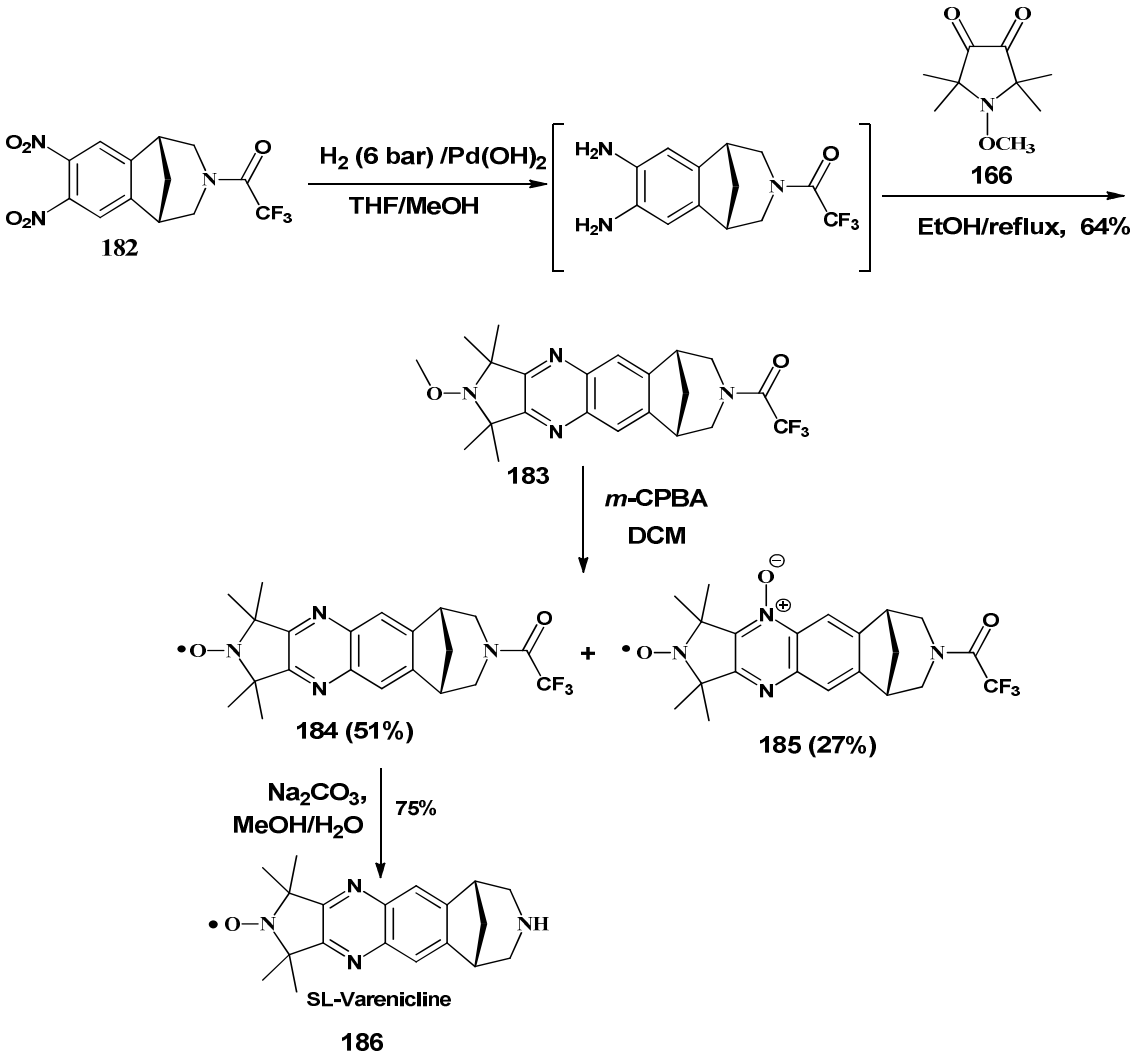
To achieve the paramagnetic analogue of the antituberculotic drug pyrazinamide, [81] a condensation reaction of compound **166** was conducted with ethyl 2,3-diaminopropanoic acid HCl salt **178** [82] in EtOH with 4.0 equivalents of sodium ethoxide to furnish compound **179**. Its hydrolysis with NaOH to the carboxylic acid, and the treatment of the crude product with 1,1'-carbonyldimidazole in THF followed by treatment with aq. 25% ammonia solution gave amide **180**. Treatment of compound **180** with *m*-CPBA furnished the spin labelled analogue of pyrazinamide **181** in an 11% overall yield via four steps (Scheme 36).



Scheme 36. Synthesis of paramagnetic pyrazinamide.

6.1.2. Synthesis of spin labelled Varenicline [III]

To obtain the spin labelled Varenicline, the commercially available **182** dinitro precursor of Varenicline was reduced in a hydrogenation flow reactor (H-cube Mini+) with a 10% $Pd(OH)_2$ cartridge at 6×10^5 Pa H_2 pressure in a THF/MeOH 50:50 (v/v%) mixture to furnish diamino compound, which was not isolated and characterized, but condensed immediately with compound **166** to give compound **183** in 64% yield. The *N*-OMe function was deprotected with 2.0 equiv. of m-CPBA in DCM to yield the mixture of **184** nitroxide and **185** pyrazine-*N*-oxide nitroxide, as a by-product. After separation of the main product, the trifluoroacetyl group was removed by treatment of compound **184** with aq. Na_2CO_3/MeOH [83] to furnish the spin labelled Varenicline **186** in 75% yield (Scheme 37).

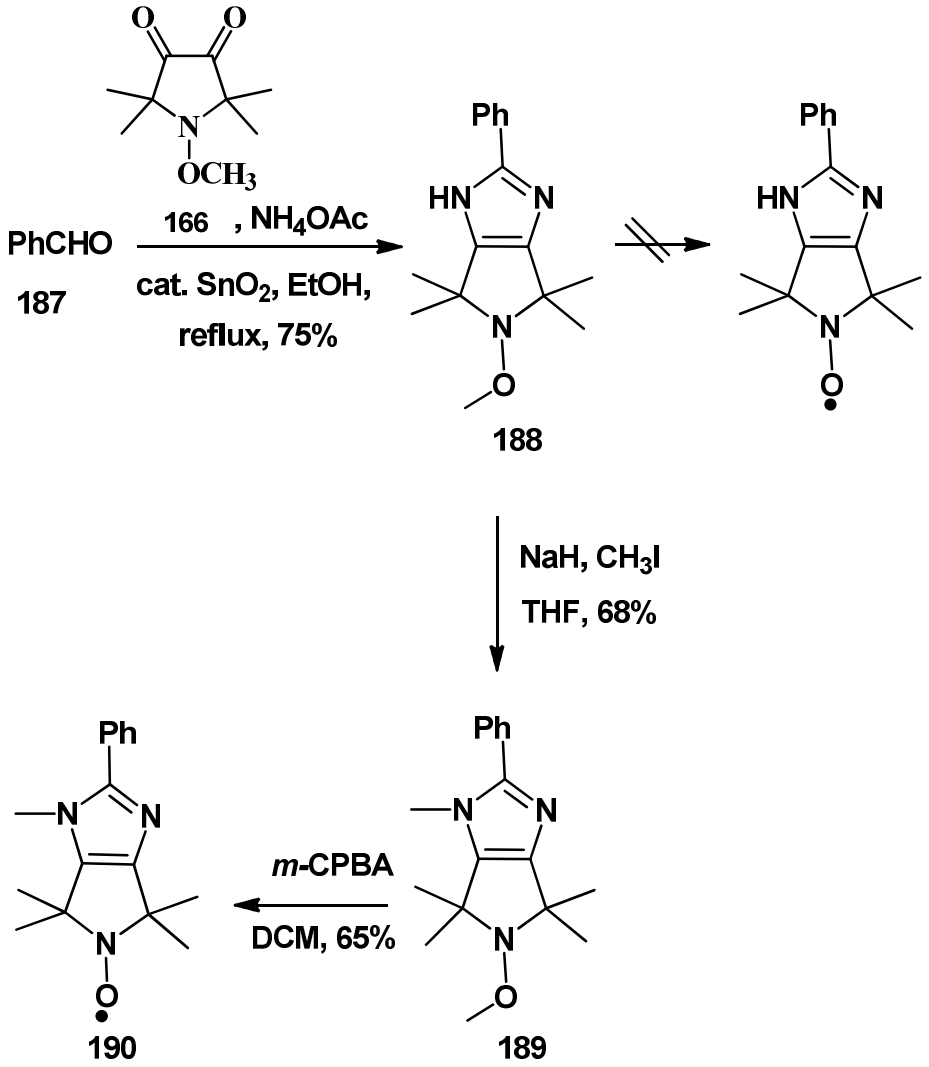


Scheme 37. Synthesis of varenicline-fused pyrroline nitroxide.

6.1.3. Synthesis of imidazole-fused pyrroline nitroxide

In order to extend the scope of utilization of compound **166**, we tested it in a multicomponent Debus-Radziszewski imidazole formation reaction [84] with modification of the Fallah and Mokhtary [85] method utilizing tin oxide as catalyst. Therefore, compound **166**, benzaldehyde **187**, and ammonium acetate in the presence of SnO_2 nanoparticles were suspended in EtOH and heated at reflux temperature for 3h. After the isolation of compound **188** in a 75% yield, we attempted the deprotection to nitroxide with *m*-CPBA, but the formation of (4,4,6,6-tetramethyl-2-phenyl-4,6-dihydropyrrolo[3,4-d]imidazol-5yl)oxydanyl was not observed. Considering, that Chalmers et al. reported a similar deprotection on *N*-substituted imidazole containing scaffolds, [86] we decided on the protection of the imidazole NH by alkylation. Therefore, treatment of **188** with MeI in THF in the presence of NaH gave compound **189**,

which could be deprotected to afford 1-methylimidazole-fused pyrroline nitroxide **190** in 44% overall yield in two steps (Scheme 38).



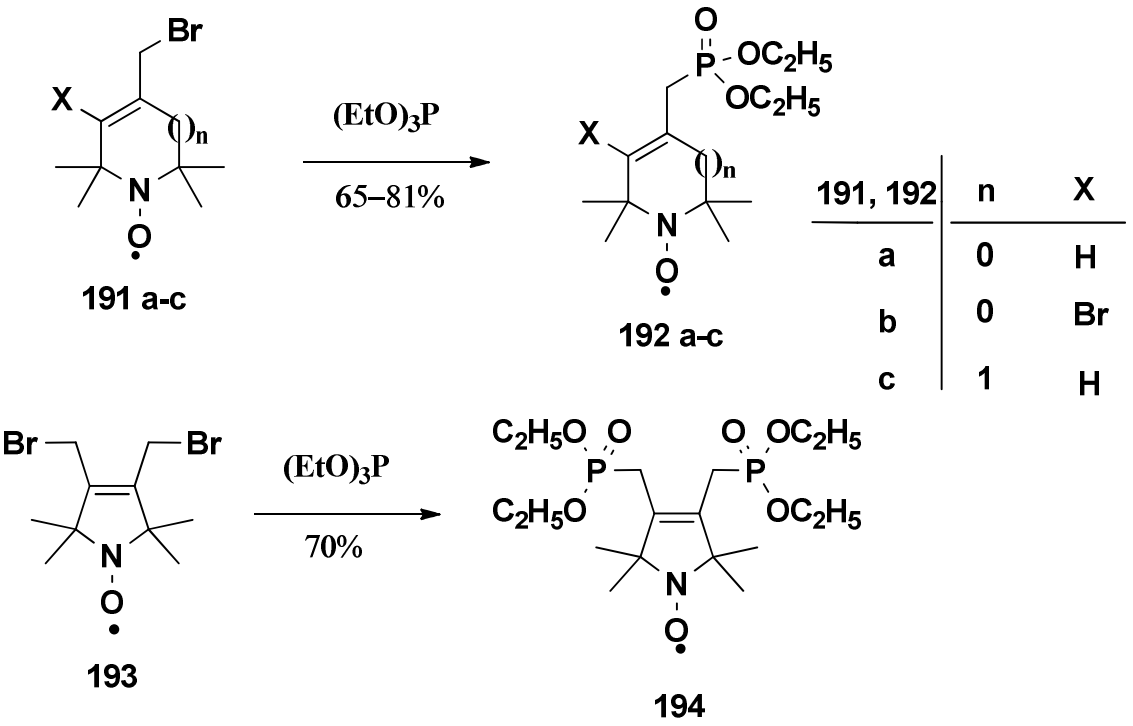
Scheme 38. Synthesis of diamagnetic and paramagnetic 1-methyl-2-phenyl-4,6-dihydropyrrolo[3,4-d]imidazole scaffolds.

6.2. Syntheses and reactions of pyrroline, piperidine nitroxide phosphonate esters [IV, II]

We aimed the syntheses of new pyrroline and piperidine nitroxide phosphonates starting from nitroxide halogenides, acetylenes, aldehydes and ketones using the well-established methods, such as Pudovik and Arbuzov reactions and further transformations.

6.2.1. Synthesis of paramagnetic allylic phosphonate, allylic bisphosphonate, and vinylphosphonate esters

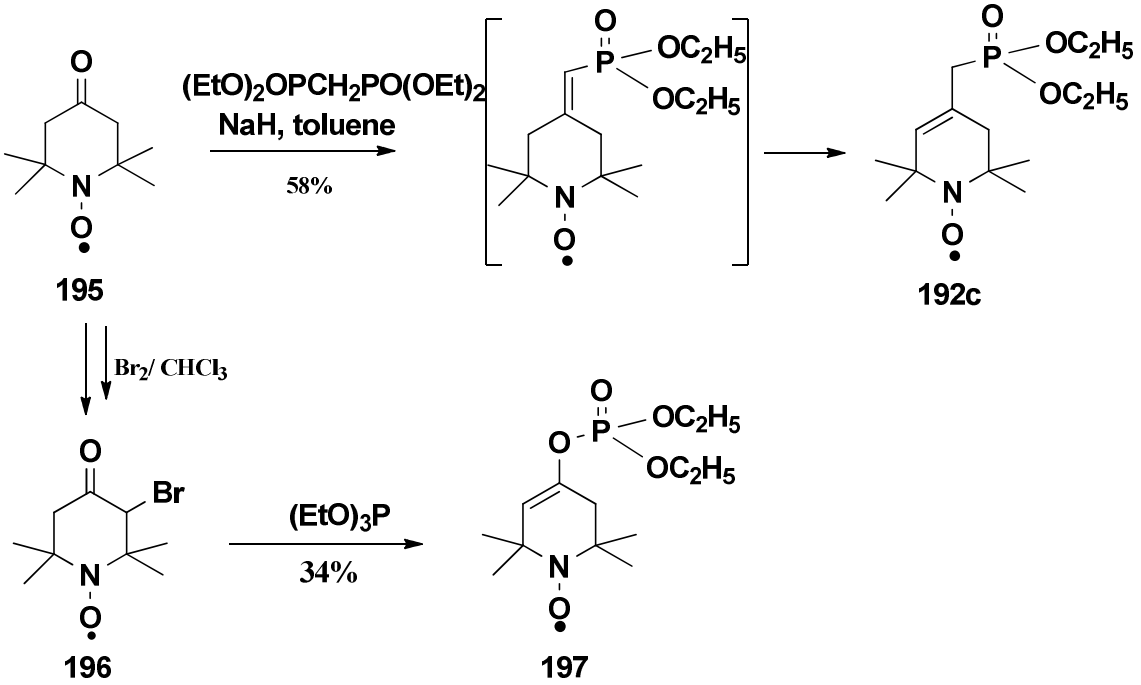
Treatment of five- and six-membered allylic bromides **191a-c** [32, 87, 88] with triethyl phosphite at 120 °C with stirring in an open vessel in an Arbuzov reaction resulted in the formation of phosphonate esters **192a-c** in 65-81% yield (monitored by TLC). As expected in case of compound **191b** only the more reactive allylic bromide was converted to phosphonate and the vinyl bromine atom was not substituted. Under these conditions, we have not observed the reduction of nitroxide function. The same reaction could be carried out with dibromo compound **193** [33] to furnish bisphosphonate ester **194** (Scheme 39).



Scheme 39. Synthesis of paramagnetic phosphonate esters by the Arbusov reaction.

As the synthesis of compound **191c** is a long multistep procedure from the readily available 4-oxo-TEMPO (1-oxyl-4-oxo-2,2,6,6-tetramethyplpiperidine radical) **195** [88,2,89], we achieved a simpler and more direct method that heats the sodium salt of tetraethyl methylenediphosphonate with compound **195** in toluene at reflux temperature to give

compound **192c** in a HWE reaction, although at a slightly lower 58% yield (first a vinylphosphonate was formed which isomerized to the corresponding allylic phosphonate **192c**) [91a]. It is well known that upon heating, α-bromoketones with trialkylphosphites furnish dialkyl vinylphosphates [90]. The same reaction was observed with 3-bromo-1-oxyl-4-oxo-2,2,6,6-tetramethylpiperidine radical **196** [91b], which upon heating with triethyl phosphite at 120 ºC furnished the paramagnetic vinylphosphate ester **197** in 34% yield in a Perkow reaction (Scheme 40).



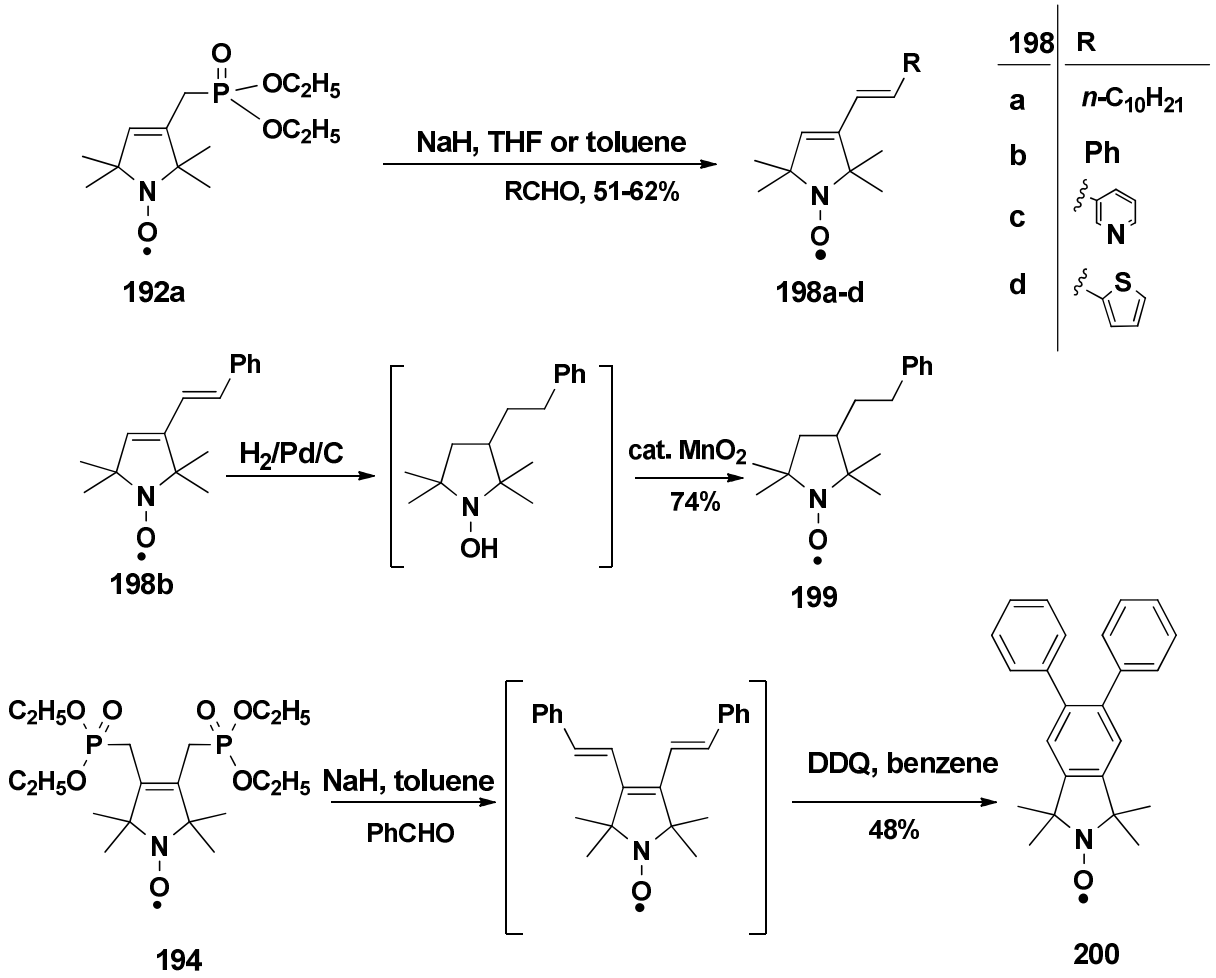
Scheme 40. Synthesis of paramagnetic phosphonate ester **192c** by a HWE reaction and phosphate **197** by a Perkow reaction from 4-oxo-TEMPO **195**.

The formation of ketophosphonate in an Arbuzov reaction can be excluded because the appearance of the vinyl proton at 5.43 ppm and the ^{31}P-NMR shift at -6.22 ppm verify the formation of diethylvinyl phosphate ester **197**. The latter ^{31}P-NMR data show good correlation with the reported values by Quin and co-workers [92].

6.2.2. Horner-Wadsworth-Emmons (HWE) reactions of synthesized paramagnetic phosphonate esters

Deprotonation of compound **192a** with sodium hydride in toluene followed by treatment with aliphatic, aromatic or heteroaromatic aldehydes offered (*E*)- paramagnetic alkenes **198a–d**, as proven by the ~16 Hz coupling of the newly formed double bond protons. Saturation of compound **198a** 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 **199** by a catalytic amount of MnO_2. Double deprotonation of bisphosphonate ester **194** with NaH followed by addition of an excess of benzaldehyde offered triene, which upon heating spontaneously was cyclized by 6π–electrocyclization to *cis* 5,6-diphenyl-2-oxyl-1,1,3,3-tetramethylisoindoline radical. Although its oxidation to isoindoline radical partially occurred spontaneously after 6π–electrocyclization, we completed the oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene to yield **200** isoindoline radical (Scheme 41).

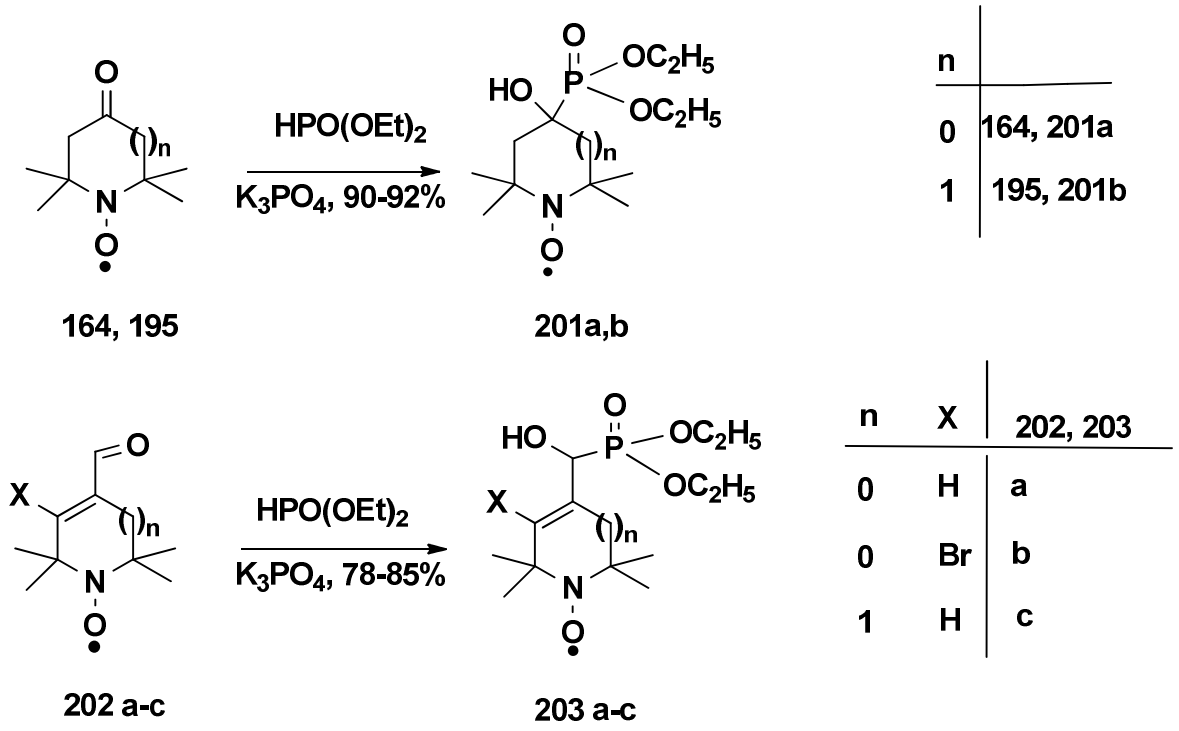


Scheme 41. HWE reactions of phosphonate esters to various alkenes and aromatic compounds

6.2.3. Synthesis of paramagnetic α-hydroxyphosphonate esters and their transformations

We decicded to study the reactions of paramagnetic aldehydes and ketones with diethyl phosphite to get paramagnetic α-hydroxyphosphonate esters because these derivatives have biological importance, i.e., herbicidal, antibacterial, antifungal and antioxidant effects, to

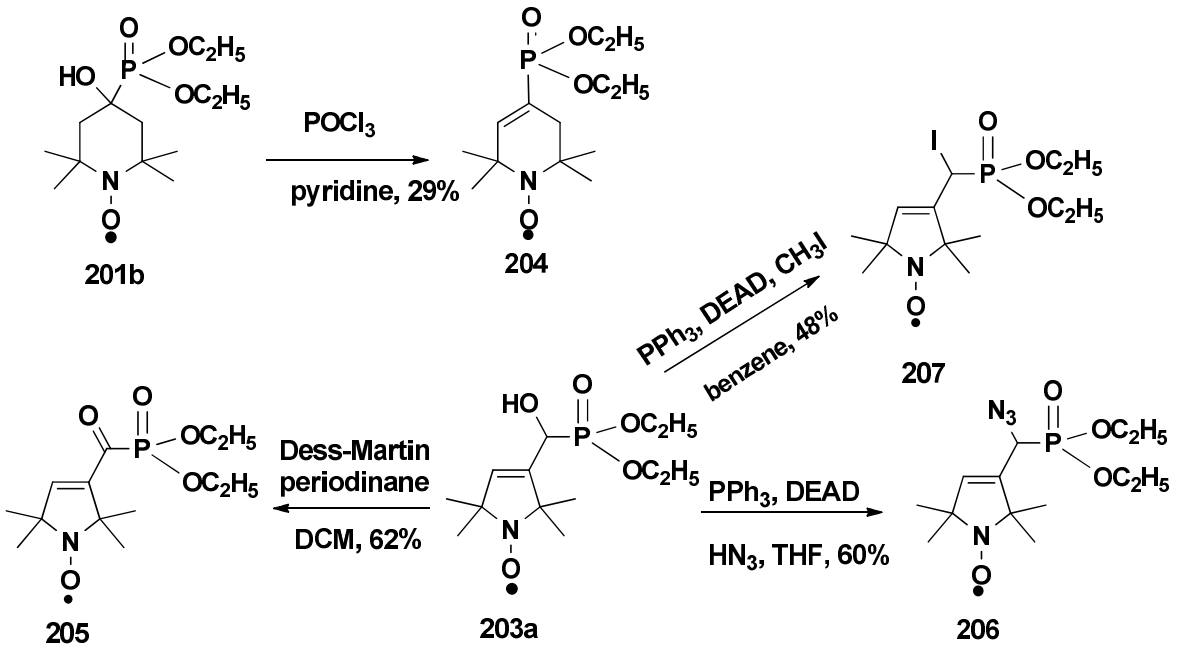
mention but a few [93–95]. To access paramagnetic α-hydroxyphosphonate esters among the possible reaction conditions [96, 97] tested, we chose the methodology of Kulkarni *et al.* [98], e.g., solvent-free conditions in the presence of 0.05 eq. K_3PO_4. Therefore, treatment of ketones **164** [32] or 1**95** [2] or five- or six-membered nitroxide aldehydes **202a** [96], **202b** [2], or **202c** [88] with diethyl phosphite in the presence of 0.05 eq. K_3PO_4 offered the α-hydroxyphosphonates **201a** or **201b** or **203a** or **203b** or **203c**, respectively, in 78–92% yield (Scheme 42).



Scheme 42. Synthesis of α-hydroxyphosphonate esters.

The structure of these compounds is proven by the appearance of hydroxyl band of OH groups at ~3200 cm^{-1} compared with compounds **192a–c**. We attributed the conversion of α-hydroxyphosphonates **201a** or **201b** to the corresponding vinyl phosphonate by water elimination. By treatment of compound **201a** or **201b** with $POCl_3$ in anhydr. pyridine [2] after 48 h at room temperature, **204** vinylphosphonate could be isolated from **201b** in 29% yield, but the expected five-membered vinylphosphonate was not formed under these conditions. The structure of vinylphosphonate **204** is proven by the split of vinyl proton at 6.62 ppm with $J = 21.5$ Hz and the upfield shift of the ^{31}P-NMR signal at 19.3 ppm compared with that of the compound **192c** ^{31}P signal at 27.1 ppm. Further attempts to eliminate the water from compound **201a** with sulfuric acid [99] or $FeCl_3$/silica gel microwave heating [100] did not give the required vinyl phosphonate. Our efforts to substitute the tertiary alcohols **201a** or

201b with various nucleophiles via mesylate did not succeed, similar to the same experiments with the secondary alcohols **203a–c**. For further possible transformations, we focused on compound **203a** conversions, which could be smoothly oxidized to α-ketophosphonate **205** with 3.0 eq. Dess–Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one) [101] in CH_2Cl_2 at room temperature in 62% yield. With the reaction of compound **203a** with DEAD (diethyl azodicarboxylate) and PPh_3 in the presence of HN_3 under Mitsonubu reaction conditions [102], we created paramagnetic α-azidophosphonate **206** in 60% yield (the structure of this compound is proven by the appearance of $-N=N^+=N^-$ band of N_3 groups at 2096 cm^{-1}). Under similar conditions and using methyl iodide as a source for the I^- nucleophile [103], we obtained iodo compound **207** (48%), which was rather inert for attempts at further nucleophilic substitution conditions (Scheme 43). 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.

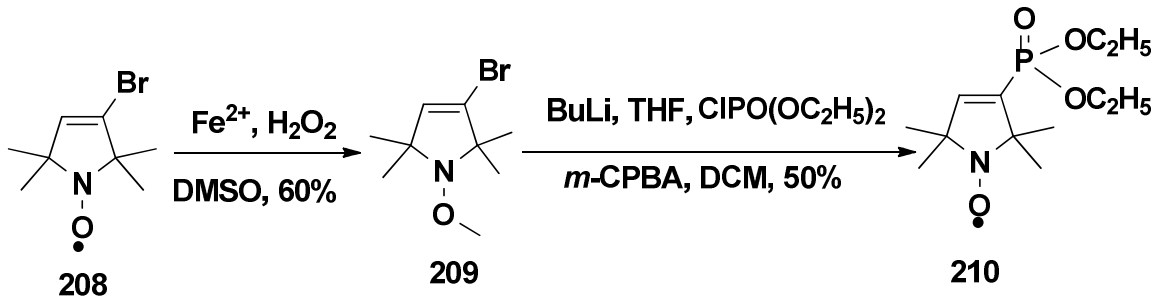


Scheme 43. Further transformations of α-hydroxyphosphonate esters.

6.2.4. Synthesis of paramagnetic five-membered vinylphosphonate ester

To obtain the five-membered vinylphosphonate, we attempted the heating of compound **208** [4] with diethyl phosphite in the presence of a catalytic amount of $NiCl_2$ [104], but no conversion was observed. Our efforts to construct a P-C bond with diethylphospite via the Pd–catalyzed Hirao reaction with the conventional or microwave-assisted method [105] also failed. As a result, we finally decided to lithiate [47] the *O*-methyl derivative **209**, as achieved via Fenton reaction in a DMSO/H_2O_2/Fe^{2+} system in 60% yield [77a], followed by treatment

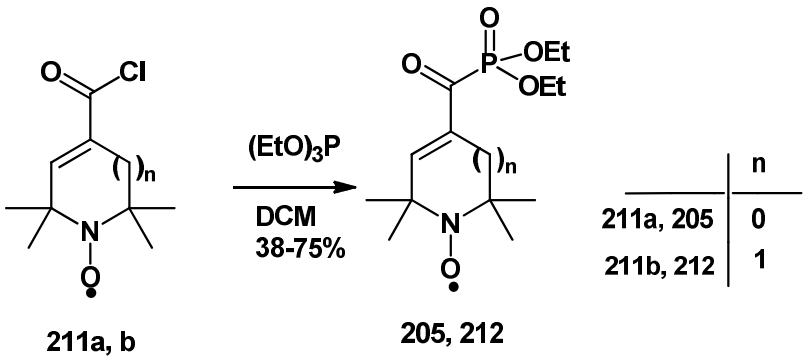
with 1.0 eq. BuLi (buthyl lithium) and addition of diethylchlorophosphate to give the diamagnetic vinyl phosphonate, which was not isolated but the crude product was treated with *m*-CPBA [77b]. Thus we obtained compound **210**, fortunately without epoxidation of the double bond in 50% yield (Scheme 44).



Scheme 44. Synthesis of paramagnetic vinylphosphonate ester by lithiation.

6.2.5. Synthesis and utilization of paramagnetic α-ketophosphonate esters

Paramagnetic five- and six-membered cyclic α-ketophosphonates (**205** and **212**) were obtained by treating freshly prepared acid chlorides **211a** [2] and **211b** [106] respectively, with a slight excess of triethyl phosphite in dry dichloromethane (DCM), with overnight stirring at 25 ºC (38-75%) (Scheme 45). Although we prepared **205** by the oxidation of an α-hydroxyphosphonate ester using Dess–Martin periodinane, this new method was cheaper and more straightforward.



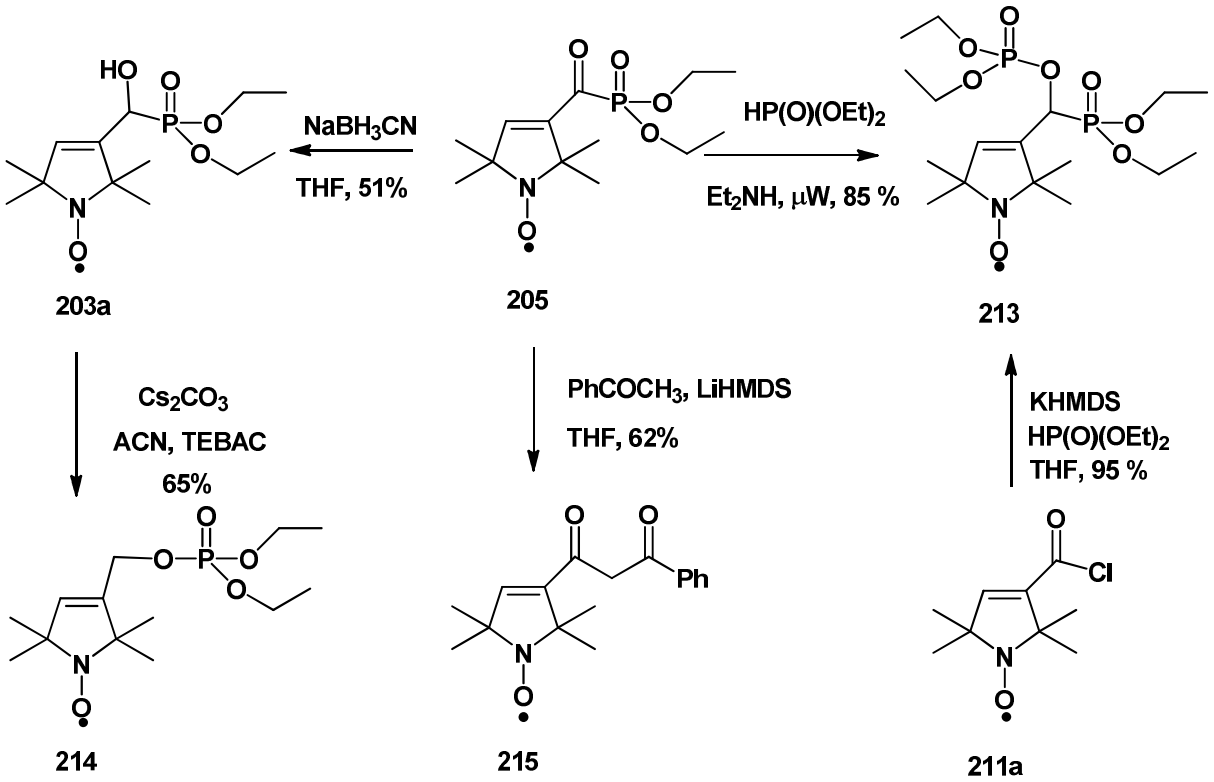
Scheme 45. Synthesis of paramagnetic α-ketophosphonate esters.

The reaction of compound **205** with diethyl phosphite in the presence of Et_2NH under microwave irradiation at 60 °C [107] did not afford the expected hydroxymethylenebisphosphonate. Only diethoxyphosphoryl(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-*1H*-pyrrol-3-yl)methyl diethyl phosphate **213** (85%) was formed, as determined from the ^{31}P NMR shifts at 16.5 and -1.4 ppm (Scheme 46). The same result was obtained in the reaction of acid chloride **211a** with a dialkyl phosphite potassium salt at low temperatures

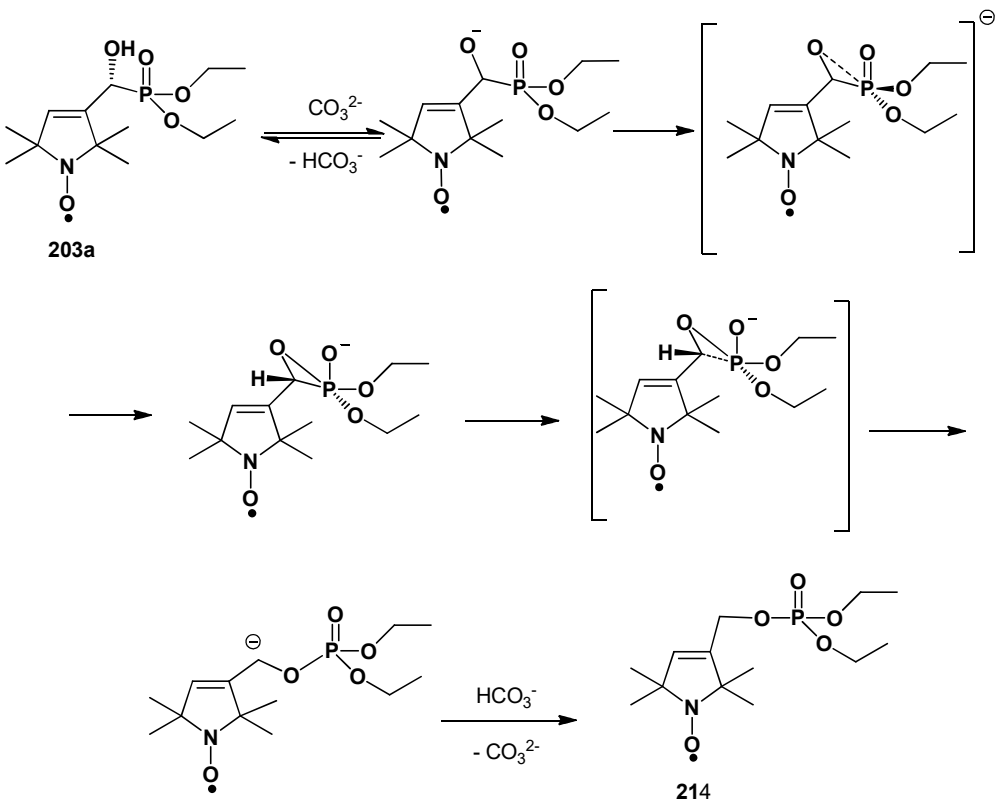
(95%), because of the bulky pyrroline ring, in accordance with the findings of Ruel and co-workers [108]. The formation of tetraethyl phosphonophosphate **213** by the rearrangement of a 1-hydroxybisphosphonate was accelerated dramatically by the presence of bulky substituents at the α-position of the acid chloride.

A similar phospha-Brook rearrangement could be achieved using compound **203a** (51%), which was prepared by reducing α-ketophosphonate ester **205** with $NaBH_3CN$ in anhydr. THF [109]. Treatment of the α-hydroxyphosphonate ester with Cs_2CO_3 in the presence of triethyl benzyl ammonium chloride (TEBAC) in acetonitrile smoothly furnished paramagnetic phosphate ester **214** (65%) and scheme 47 shows the suggested Phospha-Brook rearrangement mechanism of α-hydroxyphosphonate ester [110].

Compound **205** was successfully utilized as an acylation agent to get paramagnetic 1,3-dicarbonyl compound **215** in 62% yield using the method reported by Sekine *et al*.[111] for alkylating enolates. In this case, the enolate was generated from acetophenone upon treatment with lithium hexamethyldisilazane (LiHMDS), and was then acylated with dialkyl acylphosphonate **205**. This previously published alternative approach for the synthesis of paramagnetic 1,3-dicarbonyl compounds is a good method for C–C bond formation in the presence of a nitroxide moiety [87].



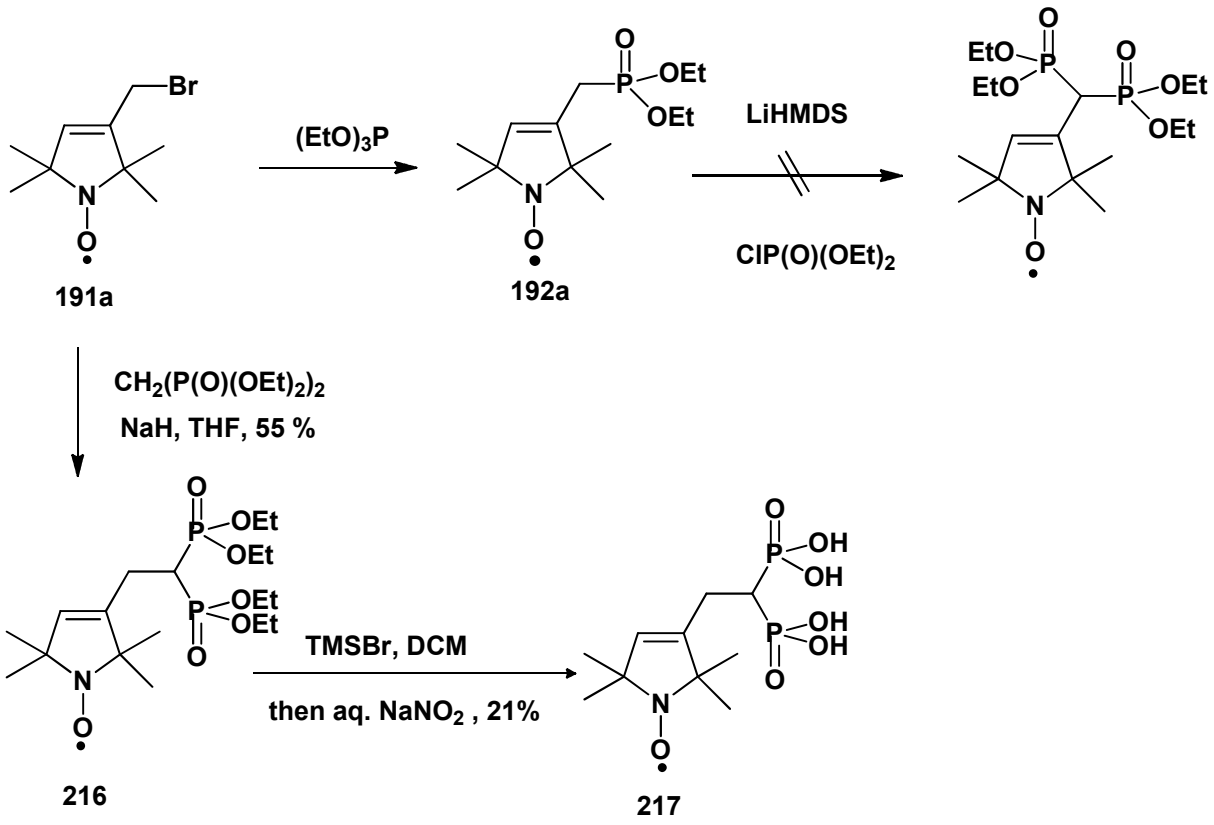
Scheme 46. Utilization of α-ketophosphonate ester **205** as an acylating agent and its transformation into paramagnetic phosphate.



Scheme 47. Suggested Phospha-Brook rearrangement mechanism of α-hydroxyphosphonate ester.

6.2.6. Synthesis of paramagnetic geminal bisphosphonic acid

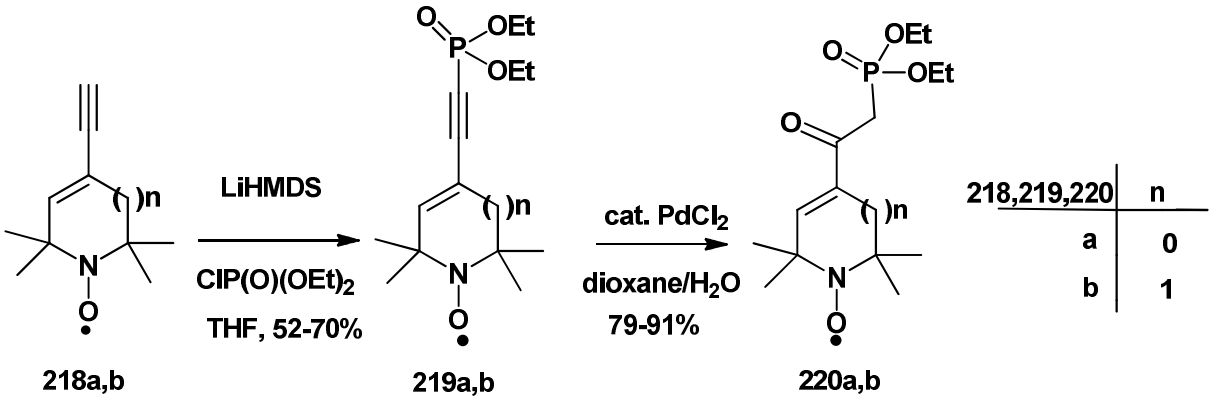
Bisphosphonate synthesis was also attempted by acylating the Li salt of allylic phosphonate ester **192a** with diethyl chlorophosphate, but the geminal bisphosphonate was not formed (Scheme 48). A homologous bisphosphonate **216** could be obtained smoothly by alkylating tetraethyl methylenebisphosphonate with compound **191a** [87] in the presence of NaH in 55% yield [112]. This was hydrolyzed by treatment with trimethylsilyl bromide [113] in DCM to obtain bisphosphonic acid **217**, followed by treatment with an aqueous solution of $NaNO_2$ to recover the stable nitroxide radical (21%) [95].



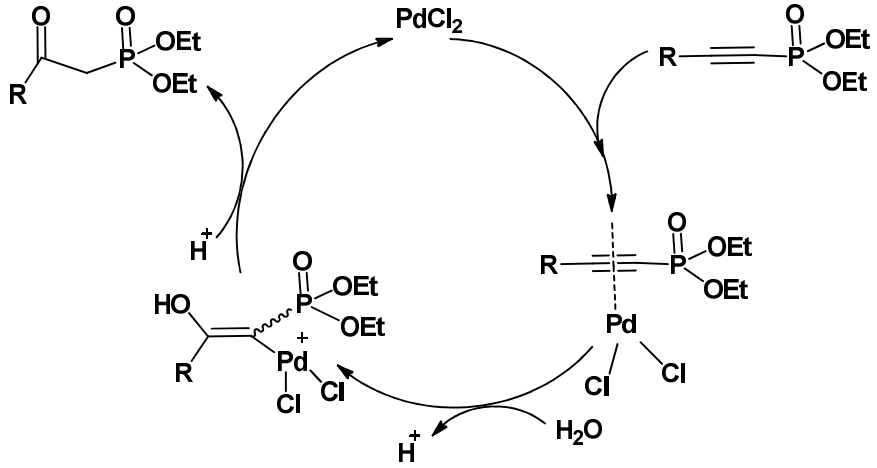
Scheme 48. Synthesis of paramagnetic geminal bisphosphonic acid.

6.2.7. Synthesis and transformations of paramagnetic β-ketophosphonate esters

To access β-ketophosphonate esters, first we needed to synthesize the paramagnetic acetylene phosphonate esters **219a** and **219b.** They could be prepared by deprotonating acetylenes **218a** and **218b** [42, 114] at terminal acetylene carbon with lithium hexamethyldisilazane (LiHMDS) followed by treatment with diethylchlorophosphate to give compounds **219a** and **219b** (52-70%) (Scheme 49). Our attempt to hydrate compound **218a** in aqueous MeOH in the presence of $AgNO_3$ failed [115]. However, hydration of phosphonates **219a** and **219b** in aqueous dioxane in the presence of 10% $PdCl_2$, as reported by Li *et al*.,[116] furnished β-ketophosphonates **220a** and **220b**, respectively, in good yields (79-91%) and scheme 50 shows the suggested mechanism for the hydration of alkynyl phosphonates [115].

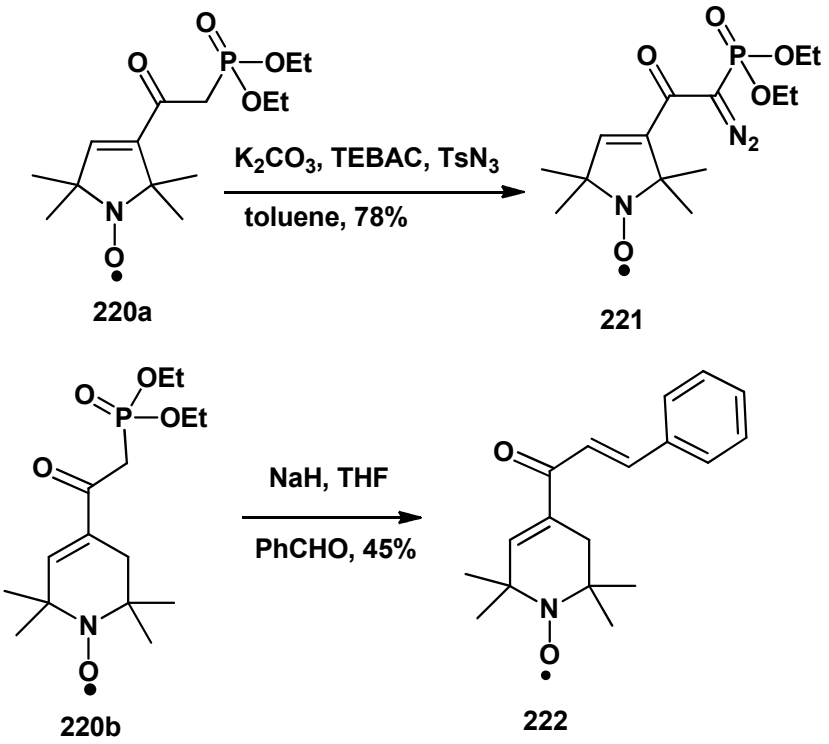


Scheme 49. Synthesis of paramagnetic β-ketophosphonate esters **220a,b**.



Scheme 50. Suggested mechanism for the hydration of alkynyl phosphonates.

The pyrroline β-ketophosphonate ester **220a** was deprotonated under phase-transfer conditions using K_2CO_3 in the presence of TEBAC in toluene and then treated with tosyl azide, furnishing diazo compound **221** via Regitz diazo transfer in 78% yield (the structure of this compound is proven by the appearance of $=N^+=N^-$ band of N_2 group at 2116 cm^{-1}) (Scheme 51) [117, 118]. Deprotonation of compound **220b** using NaH in THF, followed by reaction with benzaldehyde, furnished the *E* isomer of *α,β*-unsaturated ketone **222**, as indicated by the coupling of the vinyl protons (J = 16 Hz) via Horner-Wadsworth-Emmons in 45% yield.



Scheme 51. Transformations of β-ketophosphonate esters.

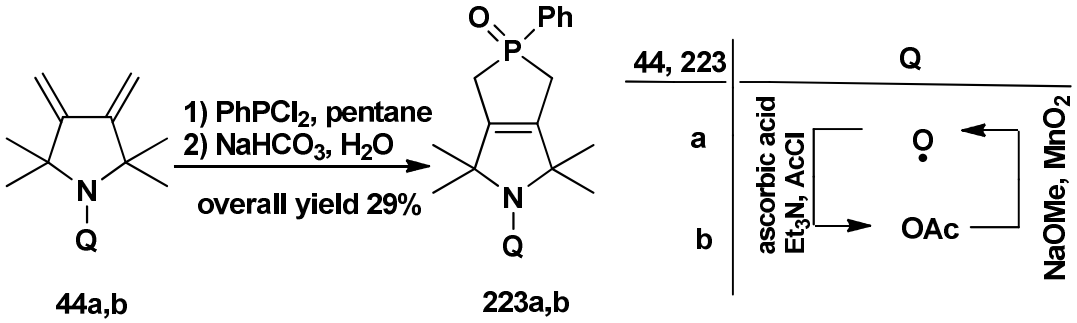
6.3. Syntheses and study of a pyrroline nitroxide condensed phospholene oxide and a pyrroline nitroxide attached diphenylphosphine [I]

We have promoted the synthesis of phosphorus-containing heterocycles condensed with pyrroline nitroxide and pyrroline nitroxide-diphenylphosphine and pyrroline nitroxide-diphenylphosphine oxide compounds, and this might open a new route for synthesizing such novel types of paramagnetic phosphorus-containing compounds.

6.3.1. Synthesis of paramagnetic phospholene oxide

A standard procedure to form phospholene oxide is McCormac cycloaddition attempted from compound **44a** [119] and dichlorophenylphosphine [120,121]. However, this addition did not give the expected, isolable product. Proposing the disruption of the nitroxide under the reaction conditions applied, we protected nitroxide as an *O*-acetyl derivative **44b** [76]. Treatment of compound **44b** with dichlorophenylphosphine in a three week-long reaction time in pentane at 37 °C enabled us to obtain compound **223b** after hydrolysis with a modest 36% yield. Deprotection of the *O*-acetyl group by a catalytic amount of NaOMe, followed by oxidation of the *N*-hydroxylamine with MnO_2 offered 1,1,3,3-tetramethyl-5-phenyl-1,2,3,4,5,6-hexahydrophospholo[3,4-c]pyrrole-5-oxide-2-oxyl **223a** as the first pyrroline nitroxide condensed phospholene oxide (Scheme 52). Compound **223a** was reduced to its hydroxylamine derivative in situ in the NMR tube and in the resulted ^{31}P-NMR we found a

single peak at 61.8 ppm and methylene protons as multiplets 2.68–2.73 and 2.79–2.85 ppm with 2H–2H integrals, suggesting that compound **223a** contains an endocyclic double bond. Our attempts to reduce phospholene oxide to phosphine failed.



Scheme 52. Synthesis of a paramagnetic phospholene oxide via the McCormack reaction.

6.3.2. Synthesis of pyrroline nitroxide diphenylphosphine and its phosphonium salt

As triphenylphosphine is an essential building block of mitochondria-targeted antioxidants and neoplastic agents [122,123], e.g. it is necessary for the formation of lipophilic triphenylphosphonium cations. Therefore, we aimed to synthesize the paramagnetic analog of triphenylphosphine. We intended to determine whether or not we can synthesize different types of nitroxide-containing mitochondrially targeted molecules compared to MITO-CP **224** (Figure 8) [124]. In our case, nitroxide would function as a superoxide dismutase (SOD) mimic at the cationic "warhead".

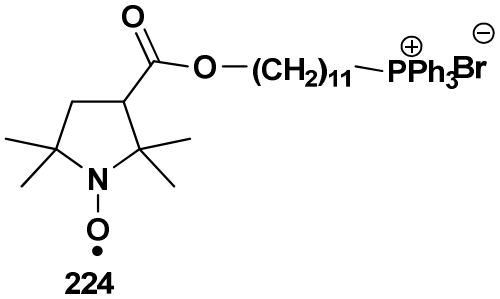
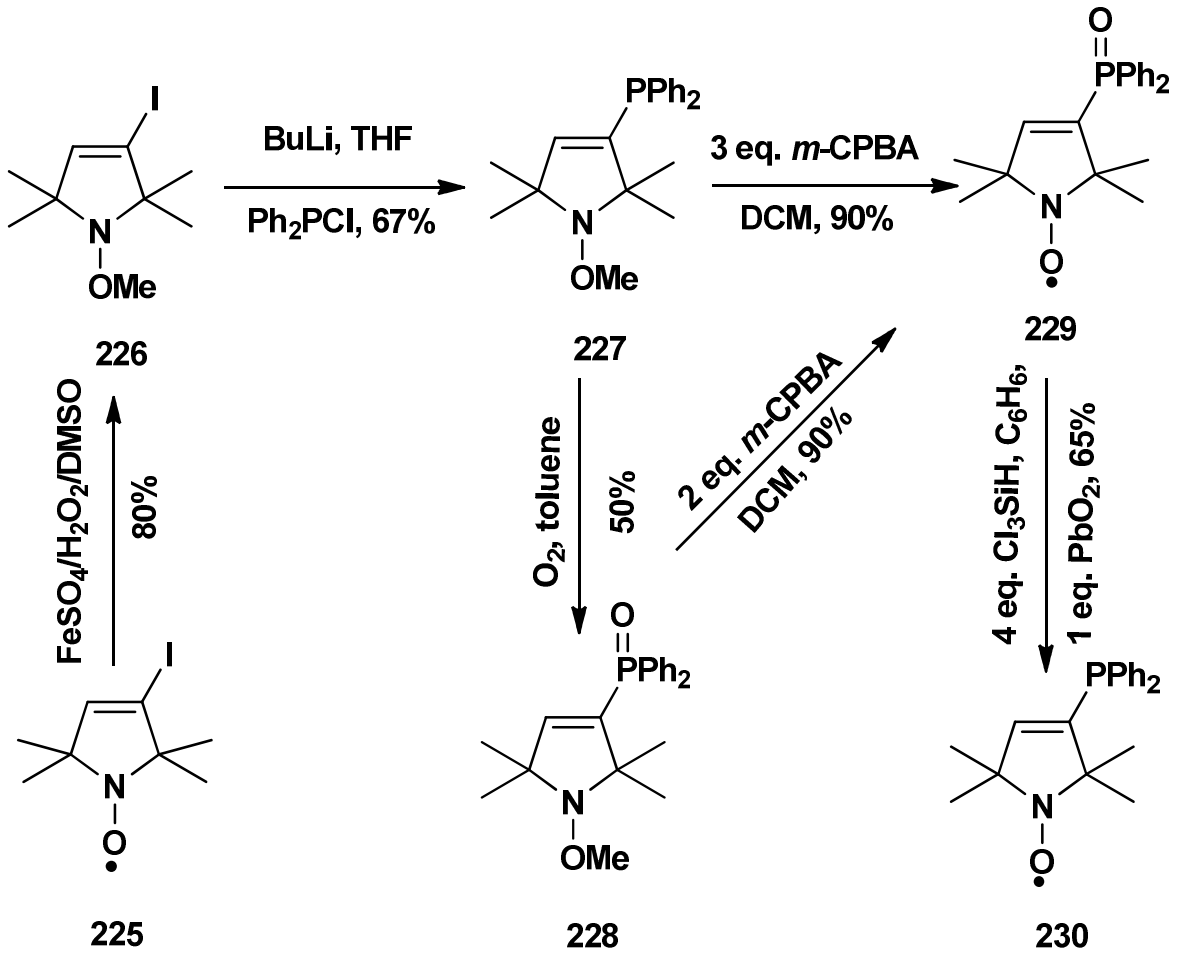


Figure 8. Structure of MITO-CP.

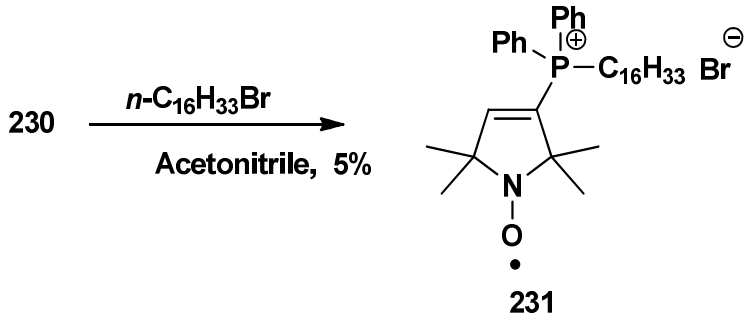
Compound **225** [125] was converted to the corresponding **226** *O*-methyl derivative (80%) in a coupled Fenton reaction. This protected pyrroline nitroxide **226** was treated with 1.1 eq. BuLi followed by the addition of diphenylchlorophosphine to furnish compound **227** in 67% yield. Phosphine **227** proved to be rather stable during the flash chromatography purification process and could be stored for weeks under an Ar atmosphere at −18 °C without oxidation

(e.g., appearance of compound **228**). However, by refluxing it in toluene in air oxidized it to phosphine **228** oxide in 50% yield. Treatment of compounds **227** and **228** with *m*-CPBA to remove the protecting methyl group from the oxygen atom furnished paramagnetic phosphine oxide **229** in 90% yield. Compound **229** could be reduced to paramagnetic pyrroline nitroxide diphenylphospine by heating it with 4 eq. trichlorosilane in toluene at 80 °C to reduce the phosphinoxide function [126,127] to phosphine and reduce nitroxide to hydroxylamine. The latter could be selectively oxidized to nitroxide **230** by PbO_2 (Scheme 53) without oxidation of phosphorus in 65% yield.



Scheme 53. Synthesis of paramagnetic pyrroline nitroxide diphenylphosphine and diphenylphosphine oxide.

Compound **230** was heated with hexadecylbromide for 5 days in acetonitrile at 90°C in a closed vial to afford compound **231** in a low 5% yield in a sluggish reaction, presumably because of sterical hindrance due to the pyrroline nitroxide ring [128] (Scheme 54).



Scheme 54. Synthesis of paramagnetic phosphonium salt **231**.

6.3.3. X-ray crystallographic study of pyrroline nitroxide-diphenylphosphine

The molecular structure of **230** as the targeted nitroxide derivative of the diphenylphosphinopyrrole derivative is fully supported by the X-ray diffraction study. Both the N-O distance and the double bond between C3 and C4 (Figure 9) were proven. A search of the Cambridge Structural Database (version 5.41 Updates March 2020) [129] revealed 73 hits for similar 2,2,5,5-tetramethylpyrrole nitroxide compounds, with an average N-O distance of 1.278(33) Å. We observed a similar value of 1.271(3) Å. However, no phosphorous derivative at C3 or C4 could be found, showing the uniqueness of our compound. The compound crystallized in the monoclinic space group $P2_1$. Moreover, the Flack parameter is very close to 0 (Table 2) indicating that we have a chiral lattice for our achiral molecule. The packing diagram shows a very small portion of the unit cell as a void (Figure 10).

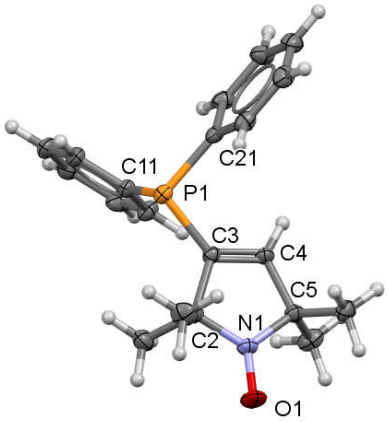


Figure 9. Ortep style view of 8 with a partial numbering scheme showing thermal displacement ellipsoids drawn at the 50% probability level. Key bond lengths [Å] and angles [°] are P1-C3 1.827(2), P1-C21 1.835(2),P1-C11 1.827(2), N1-O1 1.271(3), C3-C4 1.322(3), N1-C2 1.480(3), N1-C5 1.476(3); O1-N1-C5 122.2(2),C5-N1-C2 114.94(18), C4-C3-P1 129.02(18), C2-C3-P1 119.46(17).

Table 2. Crystal data for compound **230**.

Chemical formula	$C_{20}H_{23}NOP$
M_r	324.36
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	200
a, b, c (Å)	8.3032 (3), 12.1786 (4), 9.3477 (3)
β (°)	108.792 (2)
V (Å^3)	894.86 (5)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.16
Crystal size (mm)	0.45 × 0.44 × 0.28
Data collection	
Diffractometer	Bruker D8 VENTURE
Absorption correction	Multiscan *SADABS2016*/2 - Bruker AXS area detector scaling and absorption correction
T_{min}, T_{max}	0.85, 0.96
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	13054, 3528, 3427
R_{int}	0.037
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.619
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.031, 0.096, 1.21
No. of reflections	3528
No. of parameters	213
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.51, -0.50
Absolute structure	Flack x determined using 1581 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.05 (3)

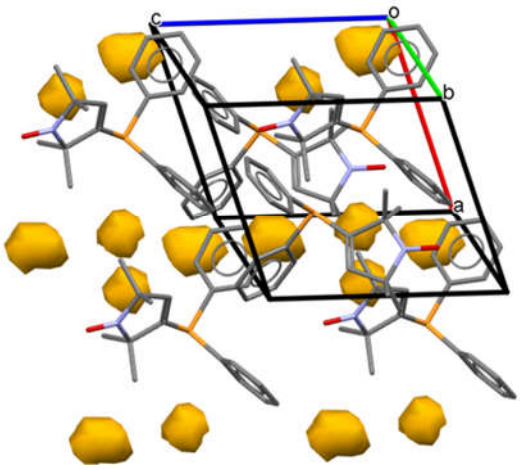


Figure 10. Packing diagram of **230**. Hydrogen atoms are omitted for clarity.

6.4. Antioxidant activity of nitroxide phosphonate esters

The antioxidant (proton and electron donating) activities of phosphonates **192a**, **192c** and α-hydroxyphosphonates **201a**, **201b**, **203a**, **203c** were tested [130] in terms of trolox equivalent capacity (TEAC). This method is based on reduction of the green-colored 2,2´-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical ($ABTS^{\bullet+}$), which is detected at 734 nm. Our results suggest (Table 3) that both the piperidine ring unit (**192c** versus **192a** or **203c** versus **203a**) and hydroxyl group presence (compare **192a** with **203a**) increase the antioxidant activity. The TEAC values of tertiary α-hydroxyphosphonate nitroxides **201a** (0.96) and **201b** (0.93) are almost the same as the trolox activity (1.0) but do not reach the antioxidant activity of 4-hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidin radical (TEMPOL) [131].

Table 3. TEAC activity of phosphonates

Compound	192a	192c	201a	201b	203a	203c	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

[1] based on n = 3 parallel measurements.

6.5. Antiproliferative studies of paramagnetic phosphonium salts

Mitochondria-targeted nitroxide, MITO-CP **224**, has previously been reported to suppress the proliferation and survival of various cancer cells in vitro and in vivo [132, 133]. Based on the similarity between compound **231** and MITO-CP **224** in terms of composition and structural elements, we studied the cytostatic effect of compound **231** in comparison with MITO-CP **224** on MDA-MB-231 (Figure 11) and MCF-7 human breast cancer lines (Figure 12).

Compound **231** had more pronounced cytotoxicity than MITO-CP at all studied concentrations. Even compound **231** achieved maximal cytostatic effects in both cell lines at a concentration of 10 μM, while MITO-CP did so only at a concentration of 50 μM. These results indicate a potential for compound **231** in cancer therapy that has to be further evaluated.

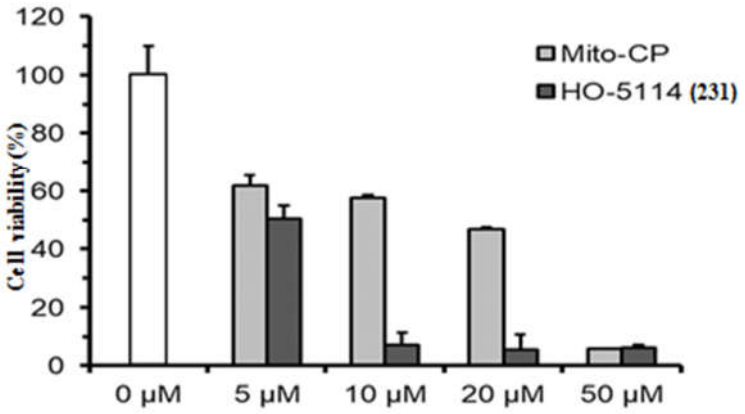


Figure 11. Cytostatic effect of compound **231** on MDA-MB-231 human breast cancer lines.

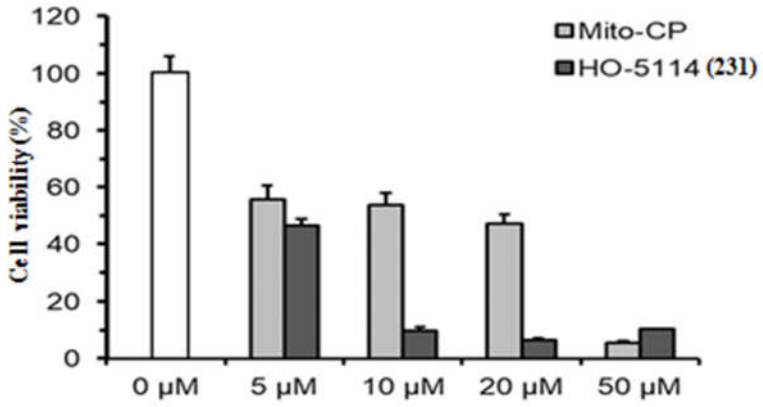


Figure 12. Cytostatic effect of compound **231** on MCF7 human breast cancer lines.

7. Experimental work

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., Karslruhe, Germany) operated at 500 MHz, and the ^{13}C NMR spectra were obtained at 125 MHz and ^{31}P NMR 202 MHz in $CDCl_3$, CD_3OD or DMSO-d_6 at 298 K. The "in situ" reduction of the nitroxides was achieved by addition of five equivalents of hydrazobenzene (DPPH/radical). 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. 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 (Specord, Jena, Germany) at 732 nm in a 1 × 1 cm quartz cuvette. Hydrogenations were performed with a ThalesNano H-CubeVR Mini Plus reactor with 20% $Pd(OH)_2/C$ cartridge (Pearlman's catalyst, Thalesnano, cat. no. THS-01115). 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 GF254. Solvents and reagents were purchased from Sigma Aldrich, Molar Chemicals, Merck, Alfa Aesar, TCI, and Toronto Research Chemicals

General procedure for synthesising compounds 165, 209, and 226:

To a stirred solution of compound **164** or **225** (10.0 mmol) **208** (5.0 mmol) and $FeSO_4 \cdot 7H_2O$ (6.9 g, 25.0 mmol) in DMSO (30 mL) at 0 °C was added 30% aq H_2O_2 (5 mL) dropwise over 2 h. The reaction was monitored by TLC. Upon consumption of the starting material, H_2O (50 mL) (and 25 mL of 10% aq. Na_2SO_3 in case of compound **226**), were added to the reaction mixture and the aqueous solution was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by flash column chromatography to give the *O*-methyl derivative.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3-one (165):

Purified by flash column chromatography (hexane/EtOAc, 2:1) to give colourless oil (1.28 g, 75%); R_f = 0.58 (Hexane/EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26 (s, 6H, C(C*H*$_3$)$_2$), 1.29 (s, 6H, C(C*H*$_3$)$_2$), 2.34 (s, 2H, C*H*$_2$), 3.72 (s, 3H, OC*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.65 (2C), 31.59 (2C), 49.76 (1C), 61.2 (1C), 65.2 (1C), 67.2 (1C), 216.3 (1C). IR (neat) $\overline{\nu}$ = 2972, 2940, 1751 cm^{-1}. MS (EI): m/z (%) = 171 (M^+, 3), 156 (25), 70 (48), 42 (100). Anal. calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.06; H, 9.81; N, 8.02.

3-Bromo-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole (209):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give a colourless oil (700 mg, 60%); TLC (hexane/Et_2O, 9:1): R_f = 0.42. ^{1}H NMR ($CDCl_3$) δ = 1.27 (s, 6H, C(C*H*$_3$)$_2$), 1.29 (s, 6H, C(C*H*$_3$)$_2$), 3.69 (s, 3H, OC*H*$_3$), 5.69 (s, 1H, *H*C=C). ^{13}C NMR ($CDCl_3$) δ = 22.3 (2C) 28.6 (2C), 65.0 (1C) 68.9 (1C), 71.7 (1C), 125.6 (1C), 134.0 (1C). IR (neat) $\overline{\nu}$ = 2921, 2852, 1642 cm^{-1}. MS (EI): m/z (%) = 235/233 (M^+, 3/3), 220/218 (33/33), 139 (100), 108 (25). Anal. calcd for $C_9H_{16}BrNO$: C, 46.17; H, 6.89; N, 5.98. Found: C, 46.11; H, 6.85; N, 5.94.

3-Iodo-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole (226):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give a colourless oil (2.24 g, 80%); TLC (hexane/Et_2O, 58:2): R_f = 0.52. ^{1}H NMR ($CDCl_3$) δ = 1.24 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.67 (s, 3H, OC*H*$_3$), 5.94 (s, 1H, *H*C=C). ^{13}C NMR ($CDCl_3$) δ = 22.2 (2C), 29.5 (2C), 64.9 (1C), 70.7 (1C), 72.9 (1C), 101.6 (1C) 142.8 (1C). IR (neat) $\overline{\nu}$ = 2973, 2894, 1610 cm^{-1}. MS (EI): m/z (%): 281 (M^+, 5), 266 (97), 139 (100), 108 (33), 83 (43). Anal. calcd for $C_9H_{16}INO$: C, 38.45; H, 5.74; N, 4.98. Found: C, 38.36; H, 5.56; N, 4.99.

1-Methoxy-2,2,5,5-tetramethylpyrrolidin-3,4-dione (166):

To a solution of compound **165** (7.0 mmol) in glacial AcOH (10 mL), SeO_2 (1.16 g, 10.5 mmol) and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with distilled H_2O (10 mL), and filtered through a Celite pad. The pad was then washed with EtOAc (10 mL). The filtrate was basified using solid $NaHCO_3$, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **166** as a yellow solid (1.08 g, 84%); mp 41–42 °C; TLC (hexane/EtOAc, 2:1): R_f = 0.51, visualized by I_2 vapor. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.39 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.76 (s, 3H. OC*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.7 (2C), 25.3 (2C), 65.7 (C), 67.3 (2C), 202.6 (2C). IR (neat) $\overline{\nu}$ = 2986, 2940, 1754 cm^{-1}. MS (EI): m/z (%) = 186 ([M + H]$^+$, 33), 185 (7), 144 (23), 98

(100), 88 (60), 43 (27). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.48; H, 8.11; N, 7.36.

General procedure for the preparation compounds (167b, 168b, and 169b):

To a solution of compound **166** (5.0 mmol) in anhydr. ethanol (20 mL) was added compound **167a** (5.0 mmol), or **168a** (5.0 mmol), or **169a** (the latter was previously released from its 2 HCl salt with 2.0 equiv. of NaOEt) (2.5 mmol) and the mixture was refluxed for 3 h and allowed to stay in air overnight. The solvent was evaporated, and the residue was purified by flash column chromatography to give compounds **167b** or **168b** or **169b**.

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-b]quinoxaline (167b):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give a white powder (900 mg, 70%); mp 131-134 °C; TLC (hexane/Et_2O, 2:1): R_f = 0.63. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.62 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.88 (s, 3H, OC*H*$_3$), 7.73 (dd, ^1J =7.0 Hz, ^2J = 7.0 Hz, 2H, Ar*H*), 8.13 (dd, ^1J =7.0 Hz, ^2J = 7.0 Hz, 2H, Ar*H*).^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.2 (2C), 27.2 (2C), 65.7 (1C), 65.8 (2C), 128.9 (2C), 129.1 (2C), 142.9 (2C), 160.2 (2C). IR (neat) $\overline{\nu}$ = 3087, 3045, 2976, 1668 cm^{-1}. MS (EI): *m*/z (%) = 257 (M^+, 31), 242 (100), 196 (38) 42 (31). Anal. calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.12; H, 7.58; N, 16.37.

2-Methoxy-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoxalin-5-carboxamide (168b):

Purified by flash column chromatography ($CHCl_3$/Et_2O, 2:1) to give a white powder (690 mg, 46%); mp 225-228 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.42. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.55 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.82 (s, 3H, OC*H*$_3$), 7.93 (t, *J* = 8.5 Hz, 1H, Ar*H*), 7.95 (s, 1H, N*H*), 8.29 (d, *J* = 8.5 Hz, 1H, Ar*H*), 8.49 (d, *J* = 7 Hz, 1H, Ar*H*), 9.24 (s, 1H, N*H*). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 24,0 (2C), 28.0 (2C), 65.9 (1C), 66.0 (2C), 129.6 (1C), 131.6 (1C), 132.3(1C), 132.9 (1C), 139.8 (1C), 142.8 (1C), 159.5 (1C), 160.2 (1C), 166.4 (1C). IR (neat) $\overline{\nu}$ = 3332, 3148, 2978, 2936 1681, 1576 cm^{-1}. MS (EI): *m*/z (%) = 300 (M^+, 18), 285 (100), 268 (10), 42 (13). Anal. calcd. for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.85; H, 6.68; N, 18.58.

2,8-Dimethoxy-1,1,3,3,7,7,9,9-octamethyl-1,2,3,7,8,9-hexahydropyrrolo[3,4-*b*]pyrrolo [3′,4′:5,6]pyrazino[2,3-*g*]quinoxaline (169b):

Purified by flash column chromatography (hexane/EtOAc, 2:1) to give a beige powder (588 mg, 45%); mp: 246-250°C; TLC (hexane/EtOAc, 2:1): R_f = 0.51. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.68 (s, 24H, 4 × C(C*H*$_3$)$_2$), 3.91 (s, 6H, 2 × OC*H*$_3$), 8.86 (s, 2H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.6 (4C), 27.8 (4C), 65.8 (2C), 66.0 (4C), 128.5 (2C), 141.3 (4C),

162.3 (4C). IR (neat) $\overline{\nu}$ = 2977, 2918, 1636 cm^{-1}. MS (EI): *m*/z (%) = 436 (M^+, 21), 421 (100), 375 (20). 329 (10), 43(2). Anal. calcd. for $C_{24}H_{32}N_6O_2$: C, 66.03; H, 7.39; N, 19.25. Found: C, 66.06; H, 7.26; N, 19.18.

7-Methoxy-6,6,8,8-tetramethyl-7,8-dihydro-6*H*-pyrrolo[3,4-g]pteridine (170b):

To a solution of compound **166** (555 mg, 3.0 mmol) in glacial AcOH (10 mL), compound **170a** (330 mg, 3.0 mmol) was added and the mixture was refluxed for 3 h. After cooling, the solvent was evaporated, and the residue was treated with distilled H_2O (20 mL) and sat. aq K_2CO_3 (20 mL). The mixture was extracted with $CHCl_3$ (3 × 30 mL), the combined organic phases were dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give compound **170b** as a beige powder (385 mg, 50%); mp 115-117 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.57. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.63 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.86 (s, 3H, OC*H*$_3$), 9.51 (s, 1H, Ar*H*), 9.67 (s, 1H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.02 (2C), 28.13 (2C), 65.8 (1C), 66.0 (1C), 66.4 (1C), 134.6 (1C), 154.6 (1C), 158.0 (1C), 162.4 (1C), 163.9 (1C), 169.2 (1C). IR (neat) $\overline{\nu}$ = 3068, 2980, 1616, 1573 cm^{-1}. MS (EI): *m*/z (%) = 259 (M^+, 14), 244 (100), 213 (33), 198 (22), 42 (8). Anal. calcd. for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.15; H, 6.42; N, 26.91.

7-Methoxy-6,6,8,8-tetramethyl-6,7,8,9-tetrahydro-2*H*-pyrrolo[3,4-g]pteridine-2,4(3*H*)-dione (171b):

To a suspension of compound **171a** sulfate (476 mg, 2.0 mmol) in distilled H_2O (25 mL), was added powdered $NaHCO_3$ (336mg, 4.0 mmol), and the mixture was stirred at r.t. for 15 min. Then a solution of compound **166** (370 mg, 2.0 mmol) in MeOH (20 mL) was added to the mixture. The resulting mixture was refluxed for 3 h. After cooling, the mixture was filtered on a sintered glass funnel to remove inorganic salts. The solvents were evaporated, and the residue was partitioned between distilled H_2O (15 mL), MeOH (5 mL) and $CHCl_3$ (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography ($CHCl_3$/Et_2O, 2:1) to give compound **171b** as an orange powder (350 mg, 60%); mp 163-166 °C; TLC ($CHCl_3$/MeOH, 24:1): R_f = 0.33. ^{1}H NMR (500 MHz, CD_3OD) δ = 1.52 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.82 (s, 3H, OC*H*$_3$). ^{13}C NMR (125 MHz, CD_3OD) δ = 22.2 (2C), 27.0 (2C), 64.7 (1C), 65.6 (1C), 65.9 (1C) 126.3(1C), 150,0 (1C), 150.2 (1C), 154.9 (1C), 162.0 (1C), 164.1 (1C). IR (neat) $\overline{\nu}$ = 3187, 3072, 2983, 1691, 1575, 1527 cm^{-1}. MS (EI): *m*/z (%) = 291 (M^+, 14), 276 (100), 245 (25), 230 (23), 42 (23). Anal. calcd. for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.59; H, 5.65; N, 23.96.

2,2,2-Trifluoro-1-(2-methoxy-1,1,3,3-tetramethyl-2,3,6,7,9,10-hexahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxalin-8(1*H*)-yl)ethanone (183):

A solution of compound **182** (345 mg, 1.0 mmol) in a mixture of anhydr. THF/MeOH (1:1 v/v, 80 mL) was reduced by hydrogenation using a H-Cube® Mini Plus flow reactor equipped with a 20% $Pd(OH)_2/C$ cartridge at a pressure of 6×10^5 Pa H_2 and a flow rate of 0.7 mL min^{-1}. After consumption of the starting material (monitored by TLC), the solvents were evaporated. The residue was dissolved in anhydr. EtOH (10 mL), and a solution of compound **166** (185 mg, 1.0 mmol) in anhydr. EtOH (10 mL) was added. The mixture was refluxed for 3 h and allowed to stand in air overnight. The solvent was evaporated, and the residue was purified by flash column chromatography (hexane/Et_2O 2:1) to give an off-white powder (278 mg, 64%); mp 200-202 °C; TLC (hexane/EtOAc, 2:1): R_f = 0.32. ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 1.49 (s, 12H, 2 × C(C*H*$_3$)$_2$), 2.18 (d, *J* = 11 Hz, 1H,CC*H*HC), 2.28 (m, 1H, CCH*H*C), 3.35 (s, 2H, NC*H*$_2$), 3.56 (s, 2H, NC*H*$_2$), 3.78 (s, 3H, OC*H*$_3$), 3.89 (d, *J* = 12 Hz, 1H, ArCC*H*), 4.37 (d, *J* = 12 Hz, 1H, ArCC*H*), 7.94 (s, 1H, Ar*H*), 7.96 (s, 1H, Ar*H*). ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 23.2 (2C), 28.9 (2C), 41.3 (2C), 48.6 (2C), 50.7 (1C), 65.7 (1C), 65.8 (2C), 122.4 (1C), 122.6 (1C), 142.8 (2C), 147.1 (2C), 147.6 (2C), 158.9 (d, *J* = 9 Hz, 1C) (CF_3 signal is missing). IR (neat) $\overline{\nu}$ = 2980, 2932, 1685 cm^{-1}. MS (EI): m/z (%) = 434 (M^+, 3), 419 (100), 373 (22), 69 (7), 57(11), 43 (13). Anal calcd. for $C_{22}H_{25}F_3N_4O_2$: C, 60.82; H, 5.80; N, 12.90; found: C, 60.78; H, 5.82; N, 12.72.

General procedure for the deprotection of methoxyamines (167c, 168c, 169c, 170c, 171c, 175, 181, 190):

Methoxyamine **167b** or **168**b or **169b** or **170b** or **171b** or **174** or **180** or **189** (2.0 mmol) was stirred in DCM (20 mL) at r.t. Solid *m*-CPBA (~60%, 1.43 g, 5.0 mmol, 2.86 g and 10,0 mmol for **169b**) was added portion wise over a period of 10 min. The reaction was monitored by TLC and upon the consumption of the starting material (10-30 min), DCM (10 mL) was added. The organic layer was washed with aq. 10% Na_2CO_3 (2 × 15 mL) and then H_2O (10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated, and the residue was purified flash column chromatography.

2-Oxyl-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-b]quinoxaline radical (167c):

Purified by flash column chromatography (hexan/Et_2O, 2:1) to give a yellow solid (266 mg, 55%); mp 169-171 °C; TLC (hexane-Et_2O, 2:1): R_f = 0.41. ^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.47 (s, 12H, 2 × C(C*H*$_3$)$_2$), 7.80 (dd, ^1J = 7Hz, ^2J = 7Hz, 2H, Ar*H*), 8.12 (dd, ^1J = 7Hz, ^2J = 7Hz, 2H, Ar*H*). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 25.30 (4C), 65.2 (2C), 129.2 (2C), 129.3 (2C), 142.6 (2C), 160.9 (2C). Anal. calcd. for $C_{14}H_{16}N_3O$: C, 69.34;

H, 6.66; N, 17.34. Found: C, 69.30; H, 6.60; N, 17.29. (IR (neat) $\overline{\nu}$ = 3064, 2976, 2930, 1639, 1619, 1501 cm^{-1}. MS (EI): *m*/z (%) = 242 (M^+, 100), 211 (32), 197 (71), 42 (47). Anal. Calcd. for $C_{14}H_{16}N_3O$: C, 69.34; H, 6.66; N, 17.34. Found: C, 69.30; H, 6.60; N, 17.29.

2-Oxyl-1,1,3,3-tetramethyl-2,3-dihydro-1*H*-pyrrolo[3,4-b]quinoxaline-5-carboxamide radical (168c):

Purified by flash column chromatography (hexane/EtOAc, 2:1) to obtain an orange powder (348 mg, 61%); mp 249-252 °C; TLC ($CHCl_3/Et_2O$, 2:1) R_f = 0.30. ^1H NMR (500 MHz, DMSO-d_6) δ = 1.48 (s, 12H, 2 × C(CH_3)$_2$), 8.01 (m, 2H, Ar*H* and *H*NH), 8.29 (dd, *J* = 8 Hz, 1H, Ar*H*), 8.56 (dd, *J* = 7.5 Hz, 1H, Ar*H*), 9.42 (s, 1H, HN*H*). ^{13}C NMR (125 MHz, DMSO) δ = 25.1 (2C), 25.2 (2C), 65.3 (2C), 129.3 (1C), 131.2 (1C), 132.3 (1C), 133.0 (1C), 139.3 (1C), 142.7 (1C), 160.3 (1C), 161.0 (1C), 166.4 (1C). IR (neat): $\overline{\nu}$ = 3357, 3180, 2984, 1672, 1575 cm^{-1}. MS (EI): *m*/z (%) = 285 (M^+, 100), 255 (12), 238 (48) 42 (20). Anal. calcd. for $C_{15}H_{17}N_4O_2$: C, 63.14; H, 6.01; N, 19.64. Found: C, 63.24; H, 5.88; N, 19.55.

2,8-Dioxyl-1,1,3,3,7,7,9,9-octamethyl-7,9-dihydropyrrolo[3,4-b]pyrrolo[3',4':5,6] pyrazino[2,3-g]quinoxaline radical (169c):

Purified by flash column chromatography (Hexane/EtOAc, 2:1) to obtain a brown powder (422 mg, 52%); mp 235-238 °C; TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.44. ^1H NMR and ^{13}C NMR spectra cannot be recorded because of precipitation of compound **169c** in DMSO-d_6 in the presence of 10.0 equiv. $(PhNH)_2$. IR (neat) $\overline{\nu}$ = 2990, 2933, 1548 cm^{-1}. MS (EI): *m*/z (%) = 406 (M^+, 100) 391 (63), 361 (48), 346 (43), 331 (27), 158(29). Anal. calcd. for $C_{22}H_{26}N_6O_2$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.04; H, 6.35; N, 20.76.

7-Oxyl-6,6,8,8-tetramethyl-6*H*-pyrrolo[3,4-g]pteridine radical (170c):

Purified by flash column chromatography (hexane/EtOAc, 2:1) to obtain a bordeaux colored powder (317 mg, 65%); mp 202-205 °C; TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.41. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.67 (s, 6H, C(CH_3)$_2$), 1.71 (s, 6H, C(CH_3)$_2$), 9.60 (s, 1H, Ar*H*), 9.74 (s, 1H, Ar*H*). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 24.8 (2C), 24.9 (2C), 66.1(1C), 66.5 (1C), 134.70 (1C), 154.7(1C), 158.0 (1C), 162.3 (1C), 163.9 (1C), 169.2 (1C). IR (neat) $\overline{\nu}$ = 3063, 3023, 2979, 2931, 1615, 1572, 1556 cm^{-1}. MS (EI): *m*/z (%) = 244 (M^+, 77), 214 (28), 213 (33), 199 (100). 184 (38). Anal. calcd. for $C_{12}H_{14}N_5O$: C, 59.00; H, 5.78; N, 28.67. Found: C, 58.80; H, 5.63; N, 28.51.

7-Oxyl-6,6,8,8-tetramethyl-6,7,8,9-tetrahydro-2*H*-pyrrolo[3,4-g]pteridine-2,4(3*H*)-dione-radical (171c):

Purified by flash column chromatography ($CHCl_3/Et_2O$, 2:1) to obtain an orange powder (342 mg, 62%); mp 250-252 °C (recrystallized from MeOH/Et_2O); TLC ($CHCl_3$/MeOH, 24:1): R_f

= 0.30. ^{1}H NMR [500 MHz,DMSO-d_6 + $(PhNH)_2$] δ = 1.37 (s, 12H, 2 × C(CH_3)$_2$). ^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$]: δ = 25.0 (2C), 25.3 (2C), 65.0 (1C), 66.5 (1C), 127.1 (1C), 150.4 (1C), 150.5 (1C), 154.6 (1C), 161.4 (1C), 163.4 (1C). IR (neat) $\overline{\nu}$ = 3509, 3181, 3044, 2979, 1730, 1702, 1673, 1537 cm^{-1}. MS (EI): *m*/z (%) = 276 (M^+, 65), 246 (100), 231 (89), 42 (76). Anal. calcd. for $C_{12}H_{14}N_5O_3$: C, 52.17; H, 5.11; N, 25.35. Found: C, 52.02; H, 5.07; N, 25.20.

6-Oxyl-5,5,7,7-tetramethyl-5*H*-pyrrolo[3,4-b]pyrazine radical (175):

Purified by flash column chromatography (hexane/EtOAc, 2:1) to afford a yellow powder (300 mg, 78%); mp 118-121 °C; (TLC (hexane-EtOAc, 2:1): R_f = 0.43. ^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.36 (s,12H, 2 × C(CH_3)$_2$), 8.47 (s, 2H, Ar*H*). ^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 25.30 (4C), 65.3 (2C), 144.2 (2C), 159.0 (2C). IR (neat) $\overline{\nu}$ = 2973, 2929, 1541 cm^{-1}. MS (EI): *m*/z (%) = 192 (M^+, 50) 162 (41), 147 (100), 132(30), 42 (37). Anal. calcd. for $C_{10}H_{14}N_3O$: C, 62.48; H, 7.34; N, 21.86. Found: C, 62.37; H, 7.70; N, 21.78.

6-Oxyl-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazine-2-carboxamide radical (181):

Purified by flash column chromatography ($CHCl_3$/Et_2O, 2:1) to obtain a yellow powder (305 mg, 65%); mp 220-223 °C; TLC ($CHCl_3$/MeOH, 24:1): R_f = 0.51. ^{1}H NMR [500 MHz, DMSO–d_6 + $(PhNH)_2$] δ = 1.39 (s, 6H, C(CH_3)$_2$), 1.41 (s, 6H, C(CH_3)$_2$), 9.08 (s, 1H, Ar*H*). ^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 25.18(4C), 65.2 (1C), 65.5 (1C), 143.1 (1C), 145.0 (1C), 157.7 (1C), 161.9 (1C), 165.6 (1C). IR (neat) $\overline{\nu}$ = 3475, 3268, 2981, 1692, 1572 cm^{-1}. MS (EI): *m*/z (%) = 235 (M^+, 57), 205 (34), 190 (44). 42 (100). Anal. calcd. for $C_{11}H_{15}N_4O_2$: C, 56.16; H, 6.43; N, 23.81. Found: C, 56.24; H, 6.18; N, 23.76.

5-Oxyl-1,4,4,6,6-pentamethyl-2-phenyl-4,6-dihydropyrrolo[3,4-d]imidazole radical (190):

Purified by flash column chromatography (hexane/EtOAc, 2:1) to obtain yellow crystals (351 mg, 65%); mp 133-135 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.47. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.58 (s, 6H, C(CH_3)$_2$), 1.59 (s, 6H, C(CH_3)$_2$), 3.69 (s, 3H, NCH_3), 7.47-7.44 (m, 1H, Ar*H*), (2 aromatic H is overlaps with $(PhNH)_2$ bands) 7.69 (d, *J* =7.5 Hz, 2H, Ar*H*). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 25.2 (2C), 25.4 (2C), 32.4 (1C), 64.1 (1C), 64.7(1C), 128.5 (2C), 129.0 (2C), 130.7 (1C), 134.8 (1C), 145.8 (1C), 148.9 (1C), 150.2 (1C). IR (neat) $\overline{\nu}$ = 2973, 2927, 1577 cm^{-1}. MS (EI): *m*/z (%) = 270 (M^+, 2), 240 (100), 225 (89), 211 (20). 77 (15), 43(16). Anal. calcd. for $C_{16}H_{20}N_3O$: C, 71.08; H, 7.46; N, 15.54. Found: C, 71.02; H, 7.35; N, 15.67.

2,2,2-Trifluoro-1-(2-oxyl-1,1,3,3-tetramethyl-2,3,6,7,9,10-hexahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxalin-8(1*H*)-yl))ethanone radical (184) and (6R(S),10R(S))-2-oxyl-1,1,3,3-tetramethyl-8-(2,2,2-trifluoroacetyl)-1,2,3,6,7,8,9,10-octahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxaline 4-oxide radical (185):

To a stirred solution of compound **183** (220 mg, 0.506 mmol) in anhydr. DCM (20 mL), *m*-CPBA (~60%, 290 mg, 1.01 mmol, 2.0 eq) was added in 2-3 portions at 0 °C over a period of 10 min and stirring was continued at r.t. with continuous monitoring by TLC. Consumption of the starting material (after ~30 min) resulted in the formation of deprotected nitroxide **184** together with pyrazine-*N*-oxide nitroxide **185** as a side product. The solution was washed with 10% aq. Na_2CO_3 solution (2 × 20 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **184** as a yellow powder (108 mg, 51%); mp 212–215 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.44. ^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.43 (s, 6H, C(C*H*$_3$)$_2$), 1.44 (s, 6H, C(C*H*$_3$)$_2$), 2.13 (d, *J* = 11 Hz, 1H, CC*H*HC), 2.26 (m, 1H, CCH*H*C), 3.25 (d, *J* = 12 Hz, 1H, NCH*H*), 3.72 (d, *J* = 12 Hz, 1H, NC*H*H), 3.87 (d, *J* = 12 Hz, 1H, ArCC*H*), 4.25 (d, *J* = 12 Hz, 1H, ArCC*H*), 7.64 (s, 1H, Ar*H*), 8.09 (s, 1H Ar*H*). ^{13}C NMR (125 MHz, DMSO-d_6] δ = 25.1 (1C), 25.2 (1C), 25.4 (1C), 25.5 (1C), 41.4 (1C), 48.6 (2C), 50.7 (2C), 65.2 (2C), 116.5 (q, *J* = 287 Hz, 1C), 122.4 (1C), 122.6 (1C), 142.8 (2C), 146.7 (2C), 147.2 (2C), 159.7 (d, *J* = 8 Hz, 1C). IR (neat) $\overline{\nu}$ = 2985, 2879, 1685 cm^{-1}. MS (EI): m/z (%) = 419 (M+, 70), 389 (100), 374 (36), 262 (58), 139 (26). Anal. calcd. for $C_{21}H_{22}F_3N_4O_2$: C, 60.14; H, 5.29; N, 13.36; found: C, 60.02; H, 5.31; N, 13.25.

Compound **185** was obtained as a yellow powder (60 mg, 27%); mp 228–230 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.37. ^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.40 (s, 3H, CC*H*$_3$), 1.42 (s, 3H, CC*H*$_3$), 1.45 (s, 3H, CC*H*$_3$), 1.54 (s, 3H, CC*H*$_3$), 2.16 (d, *J* = 11 Hz, 1H, CCH*H*C), 2.27 (m, 1H, CC*H*HC), 3.34 (d, *J* = 12 Hz, 1H, NCH*H*), 3.53-3.58 (m, 2H, NC*H*$_2$), 3.75 (d, *J* = 12 Hz, 1H, NC*H*H), 3.89 (d, *J* = 12 Hz, 1H, ArCC*H*), 4.24 (d, *J* = 12 Hz, 1H, ArCC*H*), 7.98 (d, *J* = 13 Hz, 1H, Ar*H*), 8.38 (d, *J* = 15Hz, 1H, Ar*H*). ^{13}C NMR (125 MHz, DMSO-d_6]: δ = 21.9-22.3 (2C), 25.0-25.2 (2C), 44.3 (1C), 48.4 (2C), 50.6 (2C), 65.1 (1C), 66.4 (1C), 112.0 (1C), 122.7 (1C), 137.0 (1C), 141.0 (1C), 145.7 (1C), 147.1 (1C), 147.6 (1C), 148.7 (1C), 149.2 (1C), 162.1 (d, *J* = 8 Hz, 1C). IR (neat) $\overline{\nu}$ = 3012, 2871, 1688, 1583 cm^{-1}. MS (EI): m/z (%) = 435 (M+4), 405 (39), 388 (100), 98 (52). Anal. calcd. for $C_{21}H_{22}F_3N_4O_3$: C, 57.93; H, 5.09; N, 12.87; found C, 58.02; H, 5.13; N, 12.70.

6-Methoxy-5,5,7,7-tetramethyl-3,5,6,7-tetrahydro-2*H*-pyrrolo[3,4-b]pyrazine (173):

A solution of compound **166** (740 mg, 4.0 mmol) and 1,2-diaminoethane (240 mg, 4.0 mmol) in anhydr. EtOH (20 mL) was refluxed for 1 h under N_2 then left to stand overnight. The solvent was evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to obtain a colorless oil (593 mg, 71%); TLC ($CHCl_3$/Et_2O, 2:1) R_f = 0.33. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.34 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.54 (s, 4H, 2 × C*H*$_2$), 3.73 (s, 3H, OC*H*$_3$). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 166.1 (2C), 65.6 (1C) , 64.3 (2C), 44.9 (2C), 27.0 (2C), 21.0 (2C). MS (EI): *m*/z (%) = 209 (M^+, 31), 194 (100), 162 (62), 42 (34). IR (neat) $\bar{\nu}$ = 2978, 2940, 2900, 1641 cm^{-1}. Anal. calcd. for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.05; H, 9.10; N, 20.03.

6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazine (174):

To a stirred solution of compound **173** (418 mg, 2.0 mmol) in anhydr. MeOH (10 mL), a solution of NaOEt [freshly prepared from Na (92 mg, 4.0 mmol) and anhydr. EtOH (20 mL)] was added and then, the resulting mixture was refluxed for 4 h under N_2. After cooling, the solvents were evaporated, and the residue was partitioned between sat. aq. NH_4Cl (20 mL) and $CHCl_3$ (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/Et_2O, 2:1) to give compound **174** as a colorless oil (223 mg, 54%); TLC (hexane/EtOAc, 2:1): R_f = 0.56 ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.51 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.82 (s, 3H, OC*H*$_3$), 8.38 (s, 2H, Ar*H*). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 23.5 (2C), 28.2 (2C), 65.6 (2C), 65.8 (1C), 143.7 (2C), 158.8 (2C). IR (neat): $\bar{\nu}$ = 3049, 2980, 2934 1545 cm^{-1}. MS (EI): *m*/z (%) = 207 (M^+, 15), 192 (100), 160 (23), 146 (46), 42 (42). Anal. calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.65; H, 8.18; N, 20.10.

1,6-Dioxyl-5,5,7,7-tetramethyl-5*H*-pyrrolo[3,4-b]pyrazine radical (176):

To a stirred solution of compound **175** (768 mg, 4.0 mmol) in anhydr. DCM (40 mL), solid *m*-CPBA (~60%, 5.73 g, 20.0 mmol) was added over a period of 1 h. The reaction was monitored by TLC, and upon the consumption of the starting material (24 h), the precipitated 3-chlorobenzoic acid was filtered out on a sintered glass funnel. DCM (40 mL) was added and the organic layer was washed with aq. 10% Na_2CO_3 (2 × 20 mL) followed by H_2O (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated, and the residue was purified flash column chromatography (hexane/EtOAc, 2:1 then $CHCl_3$/Et_2O, 4:1)to give compound **176** as yellow powder (374 mg,45%); mp 103-106 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.33. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.67 (s, 6H, C(C*H*$_3$)$_2$), 1.83 (s ,6H, C(C*H*$_3$)$_2$), 8.18 (d, *J* = 4.5 Hz, 1H, Ar*H*), 8.36 (d, *J* = 4.5 Hz, 1H, Ar*H*). ^{13}C NMR [125 MHz,

$CDCl_3$ + $(PhNH)_2$] δ = 21.3 (2C), 24.1 (2C), 68.1 (1C), 69.0 (1C), 134.1 (1C), 134.5 (1C), 143.1 (1C), 147.0 (1C). IR (neat) $\bar{\nu}$ = 3086, 2979, 2968, 1691, 1588 cm^{-1}. MS (EI): *m*/z (%) = 208 (M^+, 16), 178 (64), 161 (100). 42 (33). Anal. calcd. for $C_{10}H_{14}N_3O_2$: C, 57.68; H, 6.78; N, 20.18. Found: C, 57.84; H, 6.61; N, 20.06.

1,6-Dioxyl-2-phenyl-5,5,7,7-tetramethyl-5*H*-pyrrolo[3,4-b]pyrazine radical (177):

A degassed mixture of $Pd(OAc)_2$ (22.0 mg, 0.1 mmol), Ag_2CO_3 (605 mg, 2.2 mmol), and compound **176** (208 mg, 1.0 mmol) in benzene (5 mL) in a screw-capped vial was stirred at 130 °C for 16 hours. After cooling, the mixture was filtered through a plug of celite, and then washed with EtOAc (40 mL). The solvents were evaporated and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **177** as yellow crystals (108 mg, 38%); mp 121-124 °C; TLC (hexane/EtOAc, 2:1): R_f = 0.33. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.63 (s, 6H, C(CH_3)$_2$), 1.78 (s, 6H, C(CH_3)$_2$), 7.87 (d, *J* = 9.5 Hz, 2H, Ar*H*), [3 aromatic H is overlaps with $(PhNH)_2$ bands], 8.55 (s, 1H, Ar*H*). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 22.0 (2C), 24.8 (2C), 66.6 (1C), 67.1 (1C), 128.6 (2C), 129.3 (1C), 129.5 (2C), 130.1 (1C), 144.1 (1C), 144.3 (1C), 147.0 (1C), 161.4 (1C). IR (neat) $\bar{\nu}$ = 3060, 2978, 2932, 1585 cm^{-1}. MS (EI): *m*/z (%) = 284 (M^+, 14), 254 (52), 239 (100), 195 (75), 77 (57), 42 (85). Anal. calcd. for $C_{16}H_{18}N_3O_2$: C, 67.58; H, 6.38; N, 14.08. Found: C, 67.38; H, 6.43; N, 14.08.

Ethyl-6-methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazine-2-carboxylate (179):

To a stirred suspension of compound **178** HCl salt (1.03 g, 5.0 mmol) in EtOH (30 ml) freshly made NaOEt [from Na (230 mg, 10.0 mmol) and anhydr. EtOH (20 mL)] was added. The precipitated NaCl was filtered, and to the filtrate compound **166** (925 mg, 5.0 mmol) was added in one portion, followed by heating at reflux temperature for 1 h under N_2. A second portion of sodium ethoxide (made from 230 mg, 10.0 mmol of Na in 20 mL of EtOH) was added, and the reaction mixture was refluxed for 4 hours under N_2. After standing overnight at ambient temperature in air, solvents were evaporated and the residue was partitioned between sat. aq NH_4Cl (20 mL) and $CHCl_3$ (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **179** as a yellow oil (502 mg, 36%); TLC (hexane/EtOAc, 2:1): R_f = 0.55. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.46 (t, *J* =7.5 Hz, 3H, OCH_2CH_3), 1.55 (s, 12H, 2 × C(CH_3)$_2$), 3.81 (s, 3H, OCH_3), 4.52 (q, *J* = 7.5 Hz, 2H, OCH_2CH_3), 9.09 (s, 1H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.3 (1C), 22.9 (2C), 28.0 (2C), 62.0 (OCH_2), 65.7 (1C), 66.0 (2C), 143.0 (1C), 145.4 (1C), 158.9 (1C), 162.3 (1C),

164.4 (1C). IR (neat) $\overline{\nu}$ = 2979, 2936, 1720, 1573, 1559 cm^{-1}. MS (EI): *m*/z (%) = 279 (M^+, 12) 264 (100), 218 (6). Anal. calcd. for $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58; N, 15.04. Found: C, 60.26; H, 7.49; N, 14.96.

6-Methoxy-5,5,7,7-tetramethyl-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazine-2-carboxamide (180):

To a solution of compound **179** (558 mg, 2.0 mmol) in EtOH (20 mL), aq. 10% NaOH (2 mL) was added and the mixture was heated for 1 h. After standing overnight r.t., the EtOH was evaporated off. The residue was diluted with H_2O (10 mL) and the mixture was acidified with aq. 5% sulfuric acid (pH 2). The aqueous phase was extracted with $CHCl_3$ (2 × 30 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was dissolved in anhydr. THF (25 mL), and carbonyl diimidazole (CDI, 405 mg, 2.5 mmol) was added to the resulting solution. The mixture was heated for 15 min., and then, 25% aq. NH_4OH solution (5 mL) was added, followed by an additional 10 min. of heating. After cooling, the mixture was extracted with $CHCl_3$ (2 × 30 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **180** as a beige solid (330 mg, 66%); mp 158-160 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.36. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.45 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.77 (s, 3H, OC*H*$_3$), 7.84 (s, 1H, Ar*H*), 8.18 (s, 1H, HN*H*), 9.03 (s, 1H, *H*NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.3 (2C), 27.7 (2C), 65.7 (1C), 65.8 (1C), 66.1 (1C), 143.4 (1C), 145.3 (1C), 156.8 (1C), 160.9 (1C), 165.4 (1C). IR (neat) $\overline{\nu}$ = 3440, 3197, 2977, 2948, 1685, 1575 cm^{-1}. MS (EI): *m*/z (%) = 250 (M^+, 14), 235 (100), 189 (20), 42 (43). Anal. calcd. for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.57; H, 7.20; N, 22.28.

5-Methoxy-2-phenyl-4,4,6,6-tetramethyl-1,4,5,6-tetrahydropyrrolo[3,4-d]imidazole (188):

To a stirred solution of compound **166** (740 mg, 4.0 mmol) in anhydr. EtOH (20 mL), NH_4OAc (616 mg, 8.0 mmol), SnO_2 nanoparticles (151 mg, 1.0 mmol) and benzaldehyde **187** (424 mg, 4.0 mmol) were added. The resulting mixture was refluxed for 3 h, and after cooling, the mixture was filtered through plug of celite, followed by evaporation of the filtrate. The residue was partitioned between DCM (50 mL) and distilled H_2O (30 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **188** as a white powder (813 mg, 75%); mp 250-253 °C; TLC (hexane/EtOAc, 2:1): R_f = 0.42. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.39 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.75 (s, 3H, OC*H*$_3$), 7.35-7.29 (m, 3H,

Ar*H*), 7.95 (d, *J* = 7 Hz, 2H, ArH), ^{13}C NMR (125 MHz, $CDCl_3$) δ = 30.92 (4C), 64.2 (2C), 65.6 (1C), 125.3 (2C), 128.6 (1C), 128.8 (2C), 130.2 (1C), 140.0 (1C), 148.7 (1C). IR (neat) $\overline{\nu}$ = 3065, 3032, 2971, 1600 cm^{-1}. MS (EI): m/z (%) = 271 (M^+, 8), 256 (42), 227 (43), 43 (100). Anal. calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.75; H, 7.72; N, 15.64.

5-Methoxy-1,4,4,6,6-pentamethyl-2-phenyl-1,4,5,6-tetrahydropyrrolo[3,4-d]imidazole (189):

To a stirred suspension of NaH (48 mg, 2.0 mmol) in anhydr. THF (10 mL) was added a solution of compound **188** (542 mg, 2.0 mmol) in THF (20 mL) dropwise at 0 °C under N_2. After 30 min., MeI (426 mg, 3.0 mmol) was added dropwise at 0 °C. After stirring the mixture for 3 hours at r.t., the solvent was evaporated, and the residue was partitioned between EtOAc (40 mL) and distilled H_2O (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give compound **189** as a white solid (387 mg, 68%); mp 71-73°C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.57. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.53 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.66 (s, 3H, NC*H*$_3$), 3.82 (s, 3H, OC*H*$_3$), 7.47-7.38 (m, 3H, Ar*H*), 7.62 (d, *J* = 8.5 Hz, 2H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.5 (2C), 28.5 (2C), 32.2 (1C), 63.8 (1C), 64.3 (1C), 65.8 (1C), 128.3 (2C), 128.4 (1C), 128.9 (2C), 130.8 (1C), 134.6 (1C), 145.7(1C), 150.0 (1C). IR (neat) $\overline{\nu}$ = 3060, 2971, 1691, 1580 cm^{-1}. MS (EI): *m*/z (%) = 285 (M^+, 32), 270 (54), 238 (100), 43 (28). Anal. calcd. for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.42; H, 8.06; N, 14.58.

2-Oxyl-1,1,3,3-tetramethyl-3,6,7,8,9,10-hexahydro-6,10-methanoazepino[4,5-g]pyrrolo[3,4-b]quinoxaline radical (186):

To a solution of compound **184** (100 mg, 0.23 mmol) in MeOH (2.0 mL) was added a solution of Na_2CO_3 (48.7 mg, 0.46 mmol, 2.0 eq) in distilled H_2O (2.0 mL). The mixture was warmed to 70 °C for 2 h, then the solvents were evaporated. The residue was treated with H_2O (20 mL) and extracted with DCM (3 × 10 mL). The organic phase was separated, dried ($MgSO_4$), filtered, evaporated, and the crude reaction mixture was purified by flash column chromatography (hexane/EtOAc 2:1, then $CHCl_3$/MeOH, 9:1) to give an orange powder (56 mg, 75%); mp 205–207 °C; TLC ($CHCl_3$/MeOH, 5:1): R_f = 0.33. ^{1}HNMR (500 MHz, DMSO-d_6) δ = 1.46 (s, 12H, 2 × C(C*H*$_3$)$_2$), 1.89 (s, 1H, CCH*H*C), 1.95 (d, *J* = 10 Hz, 1H, CC*H*HC), 2.31 (bs, 1H, N*H*), 2.74 (d, *J* = 11 Hz, 2H, NC*H*$_2$), 2.95 (d, *J* = 12Hz, 2H, NC*H*$_2$) 3.11 (s, 2H, 2 × ArCC*H*), 7.80 (s, 2H, Ar*H*). ^{13}CNMR (125 MHz, DMSO-d_6) δ = 25.3 (2C), 25.4 (2C), 42.1 (1C), 43.4 (2C), 50.2 (2C), 65.2 (2C), 122.6 (2C), 143.0 (2C), 149.2 (2C), 158.9 (2C). IR (neat) $\overline{\nu}$ = 3321, 3076, 2974, 1574 cm^{-1}. MS (EI): m/z (%) = 323 (M^+, 45), 293 (11), 280 (13),

250 (100), 98 (49), 57 (61). EPR triplet line, a_N = 15.3 G, radical content > 98% (in 0.15 M glycine buffer, pH=3.1). Anal. calc. for $C_{19}H_{23}N_4O$: C, 70.56; H, 7.17; N, 17.32; found: C, 70.48; H, 7.09; N, 17.18.

General procedure for Arbuzov reactions (192a–c, 194):

In a well-ventilated hood, a mixture of compound **191a** or **191b** or **191c** or **193** (10.0 mmol) and $(EtO)_3P$ (2.5 g, 15.0 mmol, or 5.0 g, 30.0 mmol, for compound **193**) 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.

Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-*1H*-pyrrol-3-yl)methyl)phosphonate radical (192a)

Purified by flash column chromatography (hexane/EtOAc, 1:1) to afford an orange oil (1.88 g, 65%); TLC ($CHCl_3$/Et_2O, 2:1): R_f =*0.*33. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 26.9. ^{1}H NMR [500, $CDCl_3$ + $(PhNH)_2$] δ = 1.32 (s, 6H, C(C*H*$_3$)$_2$), 1.36 (s, 6H, C(C*H*$_3$)$_2$), 1.39 (t, *J* = 6.9 Hz, 6H, 2 × OCH$_2$C*H*$_3$)., 2.56 (d, *J* = 22 Hz, 2H, C*H*$_2$), 4.19 (quint, *J* = 1.2 Hz, 4H, 2 × OC*H*$_2$CH$_3$), 5.86 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 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 Hz, 1C). IR (neat) $\overline{\nu}$ = 2976, 2931, 1650 cm^{-1}. MS (EI): m/z (%): 290 (M^+, 13) 260 (70), 245 (15), 138 (22), 122 (100). Anal. calcd. for $C_{13}H_{25}NO_4P$: C, 53.78; H, 8.68; N, 4.82. Found: C, 53.75; H, 8.65; N, 4.79.

Diethyl ((4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl)phosphonate radical (192b)

Purified by flash column chromatography (hexane/EtOAc, 1:1) to produce an orange oil (2.83 g, 77%); TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.48. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 26.9. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.35 (s, 6H, C(C*H*$_3$)$_2$), 1.37(s, 6H, C(C*H*$_3$)$_2$), 1.45 (bs, 6H, 2 × OCH$_2$C*H*$_3$)., 2.58 (d, *J* = 21.5 Hz, 2H, C*H*$_2$), 4.25 (bs, 4H, 2 × OC*H*$_2$CH$_3$).^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 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). IR (neat) $\overline{\nu}$ = 2979, 2932, 1644 cm^{-1}. MS (EI): m/z (%): 370/368 (M^+, 44), 340/338 (4/4), 259 (35), 121 (100). Anal. calcd for $C_{13}H_{24}BrNO_4P$: C, 42.29; H, 6.55; N, 3.79. Found: C, 42.21; H, 6.53; N, 3.76.

Diethyl ((1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)phosphonate radical (192c):

Obtained by method **A**: Purified by flash column chromatography (hexane/EtOAc, 1:1) to afford a red oil (2.46 g, 81%); TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.35. ^{31}PNMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 27.1. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.28 (s, 6H, C(C*H*$_3$)$_2$), 1.32 (s, 6H, C(*CH*$_3$)$_2$), 1.38 (t, *J* = 7 Hz, 6H, 2 × OCH$_2$C*H*$_3$), 2.29 (d, *J* = 3.5 Hz, 2H, C*H*$_2$), 2.55 (d, *J* = 21.5 Hz, 2H, C*H*$_2$PO), 4.13–4.20 (m, 4H, 2 × OC*H*$_2$CH$_3$), 5,43 (d, *J* = 5.3 Hz, 1H, *H*C=C). ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.5 (d, *J* = 6.1 Hz, 2C), 25.0 (2C), 26.3 (2C), 34.3 (d, *J* = 38.1 Hz, 1C), 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). IR (neat) $\overline{\nu}$ = 2977, 2932, 1645 cm^{-1}. MS (EI): m/z (%): 304 (M+, 27) 274 (100), 259 (27), 152 (16), 81 (60). Anal. calcd. for $C_{14}H_{26}NO_4P$: C, 55.25, H, 8.94, N, 4.60. Found: C, 55.15; H, 8.91, N, 4.55.

Obtained by method B: to a stirred suspension of NaH (240 mg, 10.0 mmol) in toluene (10 mL), a solution of $(EtO)_2OPCH_2PO(OEt)_2$ (2.88 mg, 10.0 mmol) in toluene (10 mL) was added dropwise at 0 °C under N_2. After 30 min., a solution of compound **195** (1.7 g, 10.0 mmol) in toluene (10 mL) was added dropwise at 0 °C. Then the mixture was refluxed for 3 hours. After cooling, the solvent was evaporated, and the residue was partitioned between H_2O (30 mL) and EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give a red oil; (1.77 g, 58%); TLC ($CHCl_3/Et_2O$ 2:1): R_f = 0.35. IR (neat) $\overline{\nu}$ =: 2977, 2932, 1645 cm^{-1}, and all other spectral data were identical to those of one of the compounds obtained with method A.

Tetraethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3,4-diyl)bis(methylene))bisphosphonate radical (194):

Purified by flash column chromatography ($CHCl_3/Et_2O$, 2:1) to give a brownish powder (3.1 g, 70%); mp 85–87 °C; TLC ($CHCl_3$/MeOH 29:1): R_f = 0.33. ^{31}P NMR [202 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 27.4. ^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.11 (s, 12H, 2 × C(C*H*$_3$)$_2$), 1.23 (t, *J* = 6.8 Hz, 12H, 4 × OCH$_2$C*H*$_3$), 2.92 (d, *J* = 20.0 Hz, 4H, 2 × C*H*$_2$PO), 4.01 (quint, *J* = 6.5 Hz, 8H, 4 × OC*H*$_2$CH$_3$). ^{13}C NMR [125 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 16.7 (4C), 23.6 (d, *J* = 133.0 Hz, 2C), 24.7 (4C), 61.7 (4C), 69.4 (2C), 132.7 (2C). IR (neat) $\overline{\nu}$ = 2982, 2933, 2920 cm^{-1}. MS (EI): m/z (%): 440 (M$^+$, 10), 410 (38), 395 (28), 273 (77), 152 (8), 135 (100). Anal. calcd. for $C_{18}H_{36}NO_7P_2$: C, 49.09; H, 8.24; N, 3.18. Found: C, 49.11; H, 8.19; N, 3.15.

Diethyl (1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)phosphate radical (197):

In a well-ventilated hood, a mixture of compound **196** (2.49 g, 10.0 mmol) and $(EtO)_3P$ (2.5 g, 15.0 mmol) was stirred in an open vessel at 60 ºC 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 ºC 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; (1.04 g, 34%); TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.50. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = -6.2. ^1H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.30 (s, 6H, C(C*H*$_3$)$_2$), 1.35 (s, 6H, C(C*H*$_3$)$_2$), 1.43 (t, *J* = 7.1 Hz, 6H, 2 × OCH_2CH_3), 2.38 (s, 2H, C*H*$_2$), 4.23 (quint, *J* = 7.1 Hz, 4H, 2 × OCH_2CH_3), 5.43 (d, *J* = 1.8 Hz, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ = 2980, 2935, 2911, 1696 cm^{-1}. MS (EI): m/z (%): 306 (M+, 8), 276(10), 155 (70) 107 (100). Anal. calcd. for $C_{13}H_{25}NO_5P$: C, 50.97; H, 8.23; N, 4.57. Found: C, 50.94; H, 8.22; N, 4.51.

General procedure for HWE olefination with 192a nitroxide phosphonate (198a-d):

To a stirred suspension of oil-free NaH (120 mg, 5.0 mmol) in anhydr. toluene (10 mL), a solution of compound **192a** (1.45 g, 5.0 mmol) in anhydr. toluene (5 mL) was added dropwise at 0°C under N_2. 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 hours and allowed to stand overnight at r.t. The solvent was evaporated, and the residue was partitioned between sat. aq. NH_4Cl solution (25 mL) and EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by flash column chromatography to yield the olefinated nitroxides.

(*E*)-3-(Dodec-1-en-1-yl)-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole radical (198a):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give a brown oil; (950 mg, 62%); TLC (hexane/Et_2O, 5:1): R_f = 0.56. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.33-1.37 (m, 33H, 2 × $C(CH_3)_2$ + $C_{10}H_{21}$), 2.13 (d, *J* = 6.1 Hz, 2H, HC=CHC*H*$_2$) 5.02 (d, *J* =10.0 Hz, 1H, HC=C*H*CH_2), 5.08 (d, *J* = 17 Hz, 1H, *H*C=C), 5.88-5.95 (m, 1H, C=C-C*H*=$CHCH_2$). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ =: 3075, 2975, 2924, 2853, 1640 cm^{-1}. MS (EI): m/z (%): 306 (M^+, 2), 281 (7), 207 (28), 149 (25), 55 (100). Anal. calcd. for $C_{20}H_{36}NO$: C, 78.37; H, 11.84; N, 4.57. Found: C, 78.32; H, 11.81; N, 4.59.

(*E*)-1-Oxyl-3-styryl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole radical (198b):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give an orange powder (730 mg, 60%); mp 67-70 °C TLC (hexane/Et_2O, 2:1): R_f = 0.53. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$) δ = 1.45 (s, 6H, C(C*H*$_3$)$_2$), 1.56 (s, 6H, C(C*H*$_3$)$_2$) 5.86 (s, 1H, *H*C=C), 6.7 (d, *J* =16.5 Hz, 1H, C=C-C*H*=CH), 7.36-7.47 (m, 3H, Ar*H* + =CHC*H*-Ph). 3H are overlapped with peaks of diphenylhydrazine.^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ = 3023, 2972, 2927, 2865, 1634, 1596 cm^{-1}. MS (EI): m/z (%): 242 (M^+, 12), 227 (22), 212 (100), 197 (71), 91 (28). Anal. calcd. for $C_{16}H_{20}NO$: C, 79.30; H, 8.32; N, 5.78. Found: C, 79.25; H, 8.31; N, 5.74.

(*E*)-1-Oxyl-3-(2-(pyridin-3-yl)vinyl)-2,2,5,5-tetramethyl--2,5-dihydro-1*H*-pyrrole radical (198c):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give an orange powder (680 mg, 56%); mp 90-93°C TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.33. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.37 (s, 6H, C(C*H*$_3$)$_2$), 1.48 (s, 6H, C(C*H*$_3$)$_2$) 5.86 (s, 1H, *H*C=C), 6.68 (d, *J* = 16.5 Hz, 1H, HC=C*H*-C_5H_4N), 6.82 (d, *J* = 16.5 Hz, 1H, *H*C=CH-C_5H_4N), 7.76 (d, *J* = 7.8 Hz, 1H, Ar*H*), 8.54 (d, *J* = 4.4 Hz, 1H, Ar*H*), 8.71 (s, 1H, Ar*H*). 1H is overlapped with diphenyl hydrazine peaks.^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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) . IR (neat) $\overline{\nu}$ = 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). Anal. calcd. for $C_{15}H_{19}N_2O$: C, 74.04; H, 7.87; N, 11.51. Found: C, 74.01; H, 7.89; N, 11.49.

(E)-(1-oxyl-2,2,5,5-tetramethyl-3-(2-(thiophen-2-yl)vinyl)-2,5-dihydro-1*H*-pyrrol Radical (198d):

Purified by flash column chromatography (hexane/Et_2O, 2:1) to give brown crystals (635 mg, 51%); mp 75-77°C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.5. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.40 (s, 6H, C(C*H*$_3$)$_2$), 1.51 (s, 6H, C(C*H*$_3$)$_2$) 5.81 (s, 1H, *H*C=C), 6.52 (d, *J* = 16.2 Hz, 1H, HC=C*H*-C_4H_3S), 7.03 (d, *J* = 16.2 Hz, 1H, *H*C=CH-C_4H_3S), 7.08-7.26 (m, 3H, Ar*H*). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ =

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). Anal. calcd. for $C_{14}H_{18}NOS$: C, 67.70; H, 7.30; N, 5.64. Found: C, 67.72; H, 7.27; N, 5.62.

(*R,S*)-1-Oxyl-3-phenethyl-2,2,5,5-tetramethylpyrrolidine radical (199):

A solution of compound **198b** (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 (hexane/Et_2O, 2:1) to give an orange powder (367 mg, 74%); mp 60-62°C; TLC (hexane/Et_2O, 2:1): R_f=0.35. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.10 (s, 3H, CC*H*$_3$), 1.29 (s, 3H, CC*H*$_3$), 1.33 (s, 3H, CC*H*$_3$), 1.36 (s, 3H, CC*H*$_3$), 1.54-1.59 (m, 1H, CC*H*CH_2), 1.86-1.89 (m, 2H, CC*H*$_2$CH), 1.98-2.02 (m 2H, CHC*H*$_2$$CH_2$Ph), 2.61-2.67 (m, 1H, CH*H*Ph), 2.77-2.82 (m, 1H, C*H*HPh), 7.42-7.45 (m, 3H, Ar*H*). 2H are overlapped with peaks of with diphenyl hydrazine. ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 17.2 (1C), 26.6 (1C), 27.2 (1C), 29.9 (1C), 32.4(1C), 34.7(1C), 43.0 (1C), 43.1 (1C), 61.4 (1C), 66.5(1C), 125.9 (1C), 128.4 (2C), 128.5 (2C), 142.6 (1C). IR (neat) $\overline{\nu}$ = 3066, 3025, 2965, 2917, 2879, 2857, 1602 cm^{-1}. MS (EI): m/z (%): 246 (M^+, 43), 216 (26), 117 (19), 91 (100). Anal. calcd. for $C_{16}H_{24}NO$: C, 78.00; H, 9.82; N, 5.69. Found: C, 77.96; H, 9.84; N, 5.64.

5,6-Diphenyl-2-oxyl-1,1,3,3-tetramethylisoindoline radical (200):

To a suspension of oil-free NaH (144 mg, 6.0 mmol) in anhydr. toluene (10 mL), a solution of compound **194** (1.32 g, 3.0 mmol) in anhydr. 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 dropwise at 0°C. The mixture was refluxed for 3 hours. After cooling, sat. aq. NH_4Cl solution (5 mL) and Et_2O (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 benzene (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 with stirring for 2 h. After cooling, the solvent was evaporated, and the residue was partitioned between 10% aq. Na_2CO_3 solution (25 mL) and EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the crude product was purified by flash column chromatography (hexane/Et_2O, 2:1) to give a beige powder (500 mg, 48%); mp

213-216°C; TLC (hexane/Et_2O, 2:1): R_f = 0.40. ^{1}H NMR of *O*-acetyl (500 MHz, $CDCl_3$) δ = 1.53 (s, 6H, C(C*H*$_3$)$_2$), 1.59 (s, 6H, C(C*H*$_3$)$_2$) 2.28 (s, 3H, COC*H*$_3$), 7.17-7.28 (m, 12H, Ar*H*). ^{13}C NMR of *O*-acetyl (125 MHz, $CDCl_3$) δ = 19.3 (1C), 25.3 (1C), 28.9 (4C), 68.3 (2C), 123.7 (2C), 126.5 (2C) 127.8 (4C), 129.9 (2C), 140.4 (2C), 141.6 (2C), 143.3 (2C), 171.7 (2C). IR (neat) $\overline{\nu}$ = 3057, 3026, 2979, 2925, 2853, 1601 cm^{-1}. MS (EI): m/z (%): 342 (M^+, 1), 312 (100), 297 (21), 141 (10). Anal. calcd. for $C_{24}H_{24}NO$: C, 84.17; H, 7.06; N, 4.09. Found: C, 84.12; H, 7.04; N, 4.10.

General procedure for Pudovik α-hydroxyphosphonate synthesis from paramagnetic aldehydes and ketones 201a, 201b, 203a–c:

To a stirred mixture of compound **164** or **195** or **202a** or **202b** or **202c** and diethyl phosphite (1.38 g, 10.0 mmol) K_3PO_4 (106 mg, 0.5 mmol) was added and the stirring continued at r.t. for 1 h. Subsequently, 10% aq. Na_2CO_3 (50 mL) was added, followed by extraction with EtOAc (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give the α-hydroxyphosphonate products.

Diethyl (3-hydroxy-1-oxyl-2,2,5,5-tetramethylpyrrolidin-3-yl)phosphonate radical (201a):

Purified by flash column chromatography ($CHCl_3$/Et_2O, 2:1) to give a yellow powder (2.7 g, 92%); mp 100–103 ºC; TLC ($CHCl_3$/MeOH, 56:4): R_f = 0.51. ^{31}P NMR [DMSO-d_6 + $(PhNH)_2$] δ = 23.2. ^{1}H NMR [500 MHz, DMSO-d_6 + $(PhNH)_2$] δ = 1.11–1.25 (m, 18H, 2 × C(C*H*$_3$)$_2$ + 2 × OCH$_2$C*H*$_3$), 1.85 (d, *J* = 13.4 Hz, 1H, C*H*H), 2.35 (t, *J* = 11.9 Hz, 1H, CH*H*), 4.04–4.11 (m, 4H, 2 × OC*H*$_2$CH$_3$). ^{13}C NMR [125 MHz, 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). IR (neat) $\overline{\nu}$ = 3258, 2982, 2938, 2910 cm^{-1}. MS (EI): m/z (%): 294 (M+, 12), 264(2), 249 (5) 180 (100), 138 (78). Anal. calcd. for $C_{12}H_{25}NO_5P$: C, 48.97; H, 8.56; N, 4.76. Found: C, 48.93; H, 8.57; N, 4.72.

Diethyl (4-hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl)phosphonate radical (201b):

Purified by flash column chromatography ($CHCl_3$/Et_2O, 2:1) to give red crystals (2.77 g, 90%); mp 115–117 ºC; TLC ($CHCl_3$/MeOH, 56:4): R_f = 0.53. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 24.4. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.28 (s, 6H, C(C*H*$_3$)$_2$), 1.40 (t, *J* = 7 Hz, 6H, 2 × OCH$_2$C*H*$_3$), 1.48 (s, 6H, C(C*H*$_3$)$_2$), 2.02 (d, *J* = 4.01 Hz, 4H, 2 × C*H*$_2$), 3.11 (bs, 1H, O*H*), 4.23 (quint, *J* = 7.1 Hz, 4H, 2 × OC*H*$_2$CH$_3$).^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.6 (d, *J* = 5.1 Hz, 2C), 21.0 (4C), 33.3 (2C), 43.1 (2C), 57.9 (d, *J* = 14.5 Hz, 1C), 63.1 (d, *J* = 7.5 Hz, 1C), 71.3 (1C), 72.6 (1C). IR (neat) $\overline{\nu}$ = 3198, 2993, 2973, 2929 cm^{-}

[1]. MS (EI): m/z (%): 308 (M^+, 13), 259 (10), 222 (38), 194 (16), 156 (18), 138 (100). Anal. calcd. for $C_{13}H_{27}NO_5P$: C, 50.64; H, 8.83; N, 4.54. Found: C, 50.59; H, 8.81; N, 4.55.

Diethyl (hydroxy(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl)phosphonate radical (203a):

Purified by flash column chromatography (hexane/EtOAc, 1:1) to give an orange oil (2.61 g, 85%); TLC ($CHCl_3$/MeOH, 58:2): R_f = 0.33. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 21.8. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.34–1.42 (m, 18H, 2 × $C(CH_3)_2$ + 2 × OCH_2CH_3), 4.26 (q, *J* = 7.0 Hz, 4H, 2 × OCH_2CH_3), 4.35 (d, *J* = 10.8 Hz, 1H, C*H*PO), 6.13 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ = 3286, 2977, 2931, 1645 cm^{-1}. MS (EI): m/z (%): 306 (M^+, 7), 276 (9), 154 (26), 138 (100). Anal. calcd. for $C_{13}H_{25}NO_5P$: C, 50.97; H, 8.23; N, 4.57. Found: C, 50.94; H, 8.25; N, 4.51.

Method B: To a stirred solution of compound **205** (608 mg, 2.0 mmol) in anhydr. THF (10 mL), $NaBH_3CN$ (494 mg, 6.11 mmol) was added. The mixture was stirred at 25 °C overnight, and then 20 mL of distilled H_2O was added, followed by acetic acid for neutralization. The aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), treated with MnO_2 (17.4 mg, 0.2 mmol), bubbled with O_2 for 30 min, filtered, and evaporated. The residue was subjected to flash column chromatography purification (hexane/EtOAc, 1:9) to afford an orange oil; (312 mg, 51%). IR (neat) $\overline{\nu}$ = 3286, 2977, 2931, 1645 cm^{-1}. MS (EI): m/z (%): 306 (M+, 7), 276 (9), 154 (26), 138 (100). All other spectral data were identical to those of one of the compounds obtained with method A.

Diethyl (hydroxy(4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl) phosphonate radical (203b):

Purified by flash column chromatography (hexane/EtOAc, 1:1) to give an orange powder (2.98 g, 78%); mp 107–109 ºC; TLC ($CHCl_3$/MeOH, 58:2): R_f = 0.34. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 20.7. ^1H NMR [$CDCl_3$ + $(PhNH)_2$] δ = 1.33–1.47 (m, 18H, 2 × $C(CH_3)_2$ + 2 × OCH_2CH_3), 4.18-4.30 (m, 4H, 2 × OCH_2CH_3), 4.94 (d, *J* = 16.7 Hz, 1H, C*H*PO).^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ = 3263, 2980, 2934, 2908, 1631 cm^{-1}. MS (EI): m/z (%): 386/384 (M^+, 16/16), 356/354 (4/4), 275 (38), 138 (100). Anal. calcd. for $C_{13}H_{24}BrNO_5P$: C, 40.53; H, 6.28; N, 3.64. Found: C, 40.57; H, 6.25; N, 3.60.

Diethyl (hydroxy(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)-phosphonate radical (203c):

Purified by flash column chromatography (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 [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 22.0. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.27-1.42 (m, 18H, 2 × $C(CH_3)_2$ + 2 × OCH_2CH_3), 2.30 (dq, J_1 = 2.5 Hz, J_2 = 9.9 Hz, 2H, CH_2), 4.18–4.27 (m, 4H, 2 × OCH_2CH_3), 4.38 (d, J = 10 Hz, 1H, CHPO), 5.67 (d, J = 4.6 Hz, 1H, HC=). ^{13}C NMR [125 MHz, $CDCl_3$ +$(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ =: 3290, 2978, 2933, 1649 cm^{-1}. MS (EI): m/z (%): 320 (M^+, 5), 290 (7), 272 (8), 182 (10), 152 (100). Anal. calcd. for $C_{14}H_{27}NO_5P$: C, 52.49; H, 8.50; N, 4.37. Found: C, 52.44; H, 8.46; N, 4.31.

Diethyl (1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)phosphonate radical (204):

To a solution of compound **201b** (1.54 g, 5.0 mmol) in anhydr. pyridine (10 mL), $POCl_3$ (1.0 mL, 10.6 mmol) was added dropwise at 0 ºC, and the mixture was allowed to remain at r.t for 48 h. The mixture was poured onto 100 g crushed ice, extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phase was washed with aq. 1N HCl (2 × 40 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated, and the residue was purified by flash column chromatography (eluent: hexane/EtOAc, 2:1) to give a red powder (420 mg, 29%); mp 53–55 ºC; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.44. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 19.3. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.27 (s, 6H, $C(CH_3)_2$), 1.38–1.41 (m, 12H, 2 × OCH_2CH_3 + $C(CH_3)_2$), 2.31 (d, J = 6.1 Hz, 2H, CH_2), 4.10-4.2 (m, 4H, 2 × OCH_2CH_3), 6.6 (d, J = 21.5 Hz, 1H, HC=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.4 (d, J = 6.1 Hz, 2C), 24.6 (2C), 25.5 (2C), 39.1 (d, J = 7.3 Hz, 1C), 57.3 (d, J = 4.9 Hz, 1C), 60.5 (d, J = 17.8 Hz, 1C), 61.7 (d, J = 5.4 Hz, 1C), 120.5 (d, J = 182.6 Hz, 1C), 149.3 (d, J = 7.6 Hz, 1C). IR (neat) $\overline{\nu}$ = 2979, 2932, 2903, 1658 cm^{-1}. MS (EI): m/z (%): 320 (M^+, 5), 290 (7), 272 (8), 182 (10), 152 (100). Anal. calcd. for $C_{13}H_{25}NO_4P$: C, 53.78; H, 8.68; N, 4.82. Found: C, 53.72; H, 8.63 N, 4.83.

Diethyl (azido (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl)phosphonate radical (206):

To a stirred suspension of Ph_3P (3.14 g, 12.0 mmol) in anhydr. DCM (10 mL), a solution of DEAD 5.2 mL (2.09 g, 12.0 mmol in 40% toluene) in anhydr. DCM (5 mL) was added

dropwise at -78°C under N_2. A 1.85 M solution of HN_3 (6.7 ml, 12.5 mmol) in benzene was added dropwise, and the stirring was continued for 5 min at 0°C followed by dropwise addition of a solution of compound **203a** (3.06 g, 10.0 mmol) in anhydr. DCM (10 mL). 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 resulted mixture was filtered on a sintered glass funnel, and solvents were evaporated. The residue was purified by flash column chromatography (eluent: hexane/EtOAc, 2:1) to give a yellow powder (1.97 g, 60%); mp 50-52°C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.60. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 15.6. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.38-1.43 (m, 18H, 2 × C(CH_3)$_2$ + 2 × OCH_2CH_3), 4.12-4.28 (m, 4H, 2 × OCH_2CH_3), 4.98 (s, 1H, C*H*PO), 5.81 (d, *J* = 13.1 Hz, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.4 (t, *J* = 5.7 Hz, 2C), 19.7 (1C), 22.4 (1C) 25.0 (1C), 30.9 (1C), 61.7 (d, *J* = 5.6 Hz, 1C), 62.0 (d, *J* = 5.6 Hz, 1C), 66.1 (1C), 66.3 (1C), 66.5 (d, *J* = 6.4 Hz, 1C), 114.1 (d, *J* = 191 Hz, 1C), 167.0 (d, *J* = 5.4 Hz, 1C). IR (neat) $\overline{\nu}$ = 2981, 2935, 2096, 1635 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calc. for $C_{13}H_{25}N_4O_4P$: 332.1613; found: 332.1609. Anal. calcd. for $C_{13}H_{24}N_4O_4P$: C, 47.13; H, 7.30; N, 16.91. Found: C, 47.09; H, 7.28; N, 16.93.

Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)iodomethyl)phosphonate radical (207):

To a stirred suspension of compound **203a** (3.06 g, 10.0 mmol) and Ph_3P (3.14 g, 12.0 mmol) in benzene (20 mL), a solution of DEAD (2.09 g, 12.0 mmol in 40% toluene) in benzene (5 mL) was added dropwise at 0°C under N_2. After 10 min of the complete addition, a solution of CH_3I (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 H_2O (20 mL) and EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), 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 ($CHCl_3$/Et_2O, 2:1): R_f = 0.40. IR (neat) $\overline{\nu}$ = 3040, 2990 1528. HRMS (ESI) m/z $[M]^+$ calc. for $C_{13}H_{25}INO_4P$: 417.0566; found: 417.1311; $[M-HI]^+$ calc. for $C_{13}H_{24}NO_4P$: 289.1443; found 289.1434. Anal. calcd. for $C_{13}H_{24}INO_4P$: C, 37.51; H, 5.81; N, 3.37. Found: C, 37.48; H, 5.79; N, 3.39.

Diethyl (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate radical (210):

To a stirred solution of compound **209** (470 mg, 2.0 mmol) in anhydr. THF (10 mL), *n*-BuLi solution in hexane (0.8 mL, 2.0 mmol, 2.5 M) diluted with anhydr. THF (10 mL) was added dropwise at -78°C under N_2. After the addition was completed, the mixture was continuously

stirred for 1 h at -78°C. A solution of $ClPO(OC_2H_5)_2$ (345 mg, 2.0 mmol) in anhydr. 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. NH_4Cl solution (5 mL) was added, the mixture was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic phase was dried ($MgSO_4$), filtered and evaporated. The crude residue (480 mg, 1.65 mmol) was dissolved in anhydr. DCM (10 mL), *m*-CPBA (~60%, 1.18 g, 4.1 mmol, 2.5 eq) was added in 2-3 portions at 0°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. Na_2CO_3 solution (2 × 20 mL), and the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column (hexane/EtOAc, 1:1) to give a yellow powder (227 mg, 50%); mp 60-62°C; TLC ($CHCl_3$/MeOH, 2:1): R_f =0.50. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 14.6. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.33 (s, 6H, $C(CH_3)_2$), 1.40 (t, *J* = 7.5 Hz, 6H, 2 × OCH_2CH_3), 1.44 (s, 6H, $C(CH_3)_2$) 4.13-4.21 (m, 4H, 2 × OCH_2CH_3), 6.57 (d, *J* = 13.5 Hz, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ = 3079, 2977, 2931, 2866, 1609 cm^{-1}. MS (EI): m/z (%): 276 (M^+, 15), 246 (65), 231 (100), 203 (5), 175 (44), 107 (78). Anal. calcd. for $C_{12}H_{23}NO_4P$: C, 52.17; H, 8.39; N, 5.07. Found: C, 52.15; H, 8.40; N, 5.02.

General procedure for synthesis of α-ketophosphonates (205, 212):

To a stirred solution of triethyl phosphite (1.827 g, 11.0 mmol) in anhydr. DCM (10 mL), freshly prepared acid chloride **211a** or **211b** (10.0 mmol), dissolved in anhydr. DCM (20 mL), was added dropwise at 0 °C and the mixture was stirred overnight at 25 °C. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (20 mL). The organic phase was separated, dried on anhydrous $MgSO_4$, filtered, and evaporated; the residue was purified using flash column chromatography (hexane/EtOAc, 1:1) to obtain α-ketophosphonate **205** or **212**.

Diethyl (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-carbonyl)phosphonate radical (205):

Red solid (2.28 g, 75%); mp 35–37 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.56. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = -2.9. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.42-1.46 (m, 18H, 2 × $C(CH_3)_2$ + 2 × OCH_2CH_3), 4.28 (quint, *J* = 7.24 Hz, 4H, 2 × OCH_2CH_3). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.4 (d, *J* = 5.7 Hz, 2C), 24.3. (2 C), 24.7 (2C) 63.9 (d, *J* = 7.3 Hz, 2C), 69.0 (1C), 70.3 (d, *J* =10.8 Hz, 1C), 143.2 (d, *J* = 64.0 Hz, 1C), 155.2 (1C), 196 (d, *J* = 174.0 Hz, 1C). IR (neat) $\overline{\nu}$ = 3067, 2976, 2931, 1637, 1601 cm^{-1}. MS (EI): m/z (%):

304 (M^+, 4), 274 (6), 246 (3), 137 (49), 109 (100). Anal. calcd. for $C_{13}H_{23}NO_5P$: C, 51.31; H, 7.62; N, 4.60. Found: C, 51.29; H, 7.64; N, 4.55.

Method B: to a stirred solution of compound **203a** (1.53 g, 5.0 mmol) in anhydr. DCM (10 mL), Dess–Martin periodinane (6.36 g, 15.0 mmol, 3 eq.) was added in 3 portions at 0°C over a period of 10 min. The stirring was continued for 1 h at r.t. The resulting mixture was filtered on a sintered glass funnel. The filtrate was diluted with DCM (25 mL) and washed with 10% aq $NaHCO_3$ solution (25 mL) and 10% aq $Na_2S_2O_3$ (25 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give a red powder (950 mg, 62%); mp 35-37 °C TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.56. IR (neat) $\overline{\nu}$ = 3067, 2976, 2931, 1637, 1601 cm^{-1}. MS (EI): m/z (%): 304 (M^+, 4), 274 (6), 246 (3), 137 (49), 109 (100). All other spectroscopy data were identical to those one of the first method.

Diethyl (1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-carbonyl)phosphonate radical (212):

Orange solid (1.21 g, 38%); mp 80–83 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.45. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = −1.6. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.24 (s, 6H, C(C*H*$_3$)$_2$), 1.43 (s, 3H, C(C*H*$_3$)), 1.44 (t, *J* = 14 Hz, 6H, 2 × OCH_2CH_3), 1.46 (s, 3H, C(C*H*$_3$)), 2.40 (s, 2H, C*H*$_2$), 4.24–4.32 (m, 4H, 2 × OCH_2CH_3), 6.90 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.44 (d, *J* = 5.7 Hz, 2C), 24.64 (2C), 25.45 (2C), 36.66 (1C), 57.51 (1C), 60.56 (1C), 63.85 (d, *J* = 7.3 Hz, 2C), 132.75 (d, *J* = 62.0 Hz. 1C), 154.67 (1C), 199.01 (d, *J* = 169.0 Hz, 1C). IR (neat) $\overline{\nu}$ = 2978, 2940, 1692, 1662, 1593 cm^{-1}. MS (EI): m/z (%): 318 (M^+, 5), 288 (20), 150 (92), 135 (27), 107 (100). Anal. calcd. for $C_{14}H_{25}NO_5P$: C, 52.82; H, 7.9; N, 4.39. Found: C, 52.85; H, 8.06; N, 4.39.

Diethoxyphosphoryl-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl diethyl phosphate radical (213):

Method A: In a pressure-proof tube, a mixture of compound **205** (304 mg, 1.0 mmol), $HP(O)(OEt)_2$ (138 mg, 1.0 mmol), and Et_2NH (5 mg, 0.06 mmol) was irradiated by microwave at 60 °C for 30 min. The resulting mixture was subjected to flash column chromatography purification (hexane/EtOAc, 1:9) to afford a yellow oil (376 mg, 85%); TLC ($CHCl_3$/MeOH, 59:1): R_f = 0.31. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.5 (d, *J* = 28 Hz), −1.3 (d, *J* = 28 Hz). ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.31 (m, 24H, 4 × OCH_2CH_3 + 2 × C(C*H*$_3$)$_2$), 4.09–4.15 (m, 2H, OCH_2CH_3), 4.19–4.31 (m, 6H, 3 × OCH_2CH_3), 5.08 (dd, ^1J = 11 Hz, ^2J = 11 Hz, 1H, OC*H*P), 6.15 (d, *J* = 3.5 Hz, 1H, *H*C=).^{13}C NMR [125

MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.05 (1C), 16.13 (1C), 16.48 (1C), 16.53 (1C), 24.31 (1C), 24.89 (1C), 25.10 (1C), 25.80 (1C), 63.42 (d, *J* = 6.5 Hz, 1C), 63.50 (d, *J* = 7.2 Hz, 1C), 64.02 (d, *J* = 6.1 Hz, 1C), 64.16 (d, *J* = 5.8 Hz, 1C), 67.67 (d, *J* = 8.2 Hz, 1C), 68.10 (1C), 70.07 (d, *J* = 246 Hz, 1C), 137.67 (d, *J* = 7.6 Hz, 1C), 138.01 (1C). IR (neat) $\overline{\nu}$ = 2979, 2933, 1723, 1636 cm^{-1}. MS (EI): m/z (%): 442 (M^+, 10), 427 (7), 412 (2), 258 (100), 243 (30), 120 (80). Anal. calcd. for $C_{17}H_{34}NO_8P_2$: C, 46.15; H, 7.75; N, 3.17. Found: C, 45.97; H, 7.74; N, 3.16.

Method B: To a stirred solution of $HP(O)(OEt)_2$ (690 mg, 5.0 mmol) in anhydr. THF (30 mL), KHMDS (10.0 mL, 5.0 mmol, 0.5 M toluene solution) was added dropwise at −78 °C under N_2. After it was stirred for 30 min, the reaction mixture was cooled to −100 °C and then freshly prepared compound **211a** (506 mg, 5.0 mmol) in anhyd THF (10 mL) was added. The mixture was stirred at −100 °C for 10 s and then quenched with a saturated aq. NH_4Cl solution (10 mL). After it had warmed to 25 °C, the mixture was diluted with EtOAc (20 mL); the organic phase was separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was subjected to flash column chromatography purification (eluent: hexane/EtOAc, 1:9) to afford a yellow oil; (2.1 g, 95%); TLC ($CHCl_3$/MeOH, 59:1): R_f = 0.31; IR (neat) $\overline{\nu}$ = 2979, 2933, 1723, 1636 cm^{-1}. All other spectral data were identical to those of the compound obtained with method A.

Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl) phosphate radical (214):

To a stirred solution of compound **203a** (612 mg, 2.0 mmol) in anhydr. acetonitrile (10 mL), Cs_2CO_3 (650 mg, 2.0 mmol) and TEBAC (45 mg, 0.2 mmol) were added and the mixture was refluxed for 15 min. After it had cooled, the mixture was filtered on a sintered glass funnel and the solvent was evaporated under vacuum. The residue was subjected to flash column chromatography purification (hexane/EtOAc, 1:9) to afford an orange oil (398 mg, 65%). TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.30. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = −0.7. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 1.33 (s, 6H, $C(CH_3)_2$), 1.37 (s, 6H, $C(CH_3)_2$), 1.41 (t, *J* = 7 Hz, 6H, 2 × OCH_2CH_3), 4.17–4.23 (m, 4H, 2 × OCH_2CH_3), 4.62 (d, *J* = 7 Hz, 2H, CH_2), vinyl H is not observed; ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 16.24 (d, *J* = 6.5 Hz, 2C), 24.56 (2C), 25.46 (2C), 63.54 (d, *J* = 5.2 Hz, 1C), 63.99 (d, *J* = 5.0 Hz, 2C), 68.38 (1C), 70.33 (1C), 132.32 (1C), 139.60 (d, *J* = 7.6 Hz, 1C). IR (neat) $\overline{\nu}$ = 2977, 2931, 1655 cm^{-1}. MS (EI): m/z (%): 306 (M^+, 5), 276 (2), 155 (40), 107 (100). Anal. calcd. for $C_{13}H_{25}NO_5P$: C, 50.97; H, 8.23; N, 4.57. Found: C, 50.84; H, 8.11; N, 4.45.

1-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-3-phenylpropan-1,3-dione radical (215):

To a stirred solution of acetophenone (600 mg, 5.0 mmol) in anhydr. THF (10 mL), LiHMDS (5.0 mL, 5.0 mmol, 1 M THF solution) was added dropwise at −78 °C under N_2. After the addition was completed, the mixture was stirred for 1h at −78 °C. A solution of compound **205** (1.52 g, 5.0 mmol) in anhydr. THF (10 mL) was added dropwise, and the temperature was allowed to increase to 25 °C spontaneously with stirring for 2 h. The reaction mixture was quenched with a saturated NH_4Cl solution (5 mL). The mixture was diluted with EtOAc (20 mL); the organic phase was separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was subjected to flash column chromatography purification (hexane/EtOAc, 1:1) to afford a yellow solid (887 mg, 62%); mp 78–80 °C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.45. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$]: δ = 1.40 (s, 6H, C(C*H*$_3$)$_2$), 1.58 (s, 6H, C(C*H*$_3$)$_2$), 6.54 (s, 1H, *H*C=C), 6.58 (s, 1H, *H*C=C-CO), 7.98 (d, *J* = 7 Hz, 2H, Ar*H*), the other aromatic proton signals (3H) overlap with diphenylhydrazine signals and compound exists in enol form (1H) in the presence of diphenylhydrazine. ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 25.08 (2C), 25.26 (2C), 67.88 (1C), 70.27 (1C), 94.53 (1C), 127.03 (2C), 128.72 (2C), 132.33 (1C), 135.35 (1C), 142.73 (1C), 183.56 (1C), 184.37 (1C). One aromatic C is not observed or overlaps with $(PhNH)_2$ signals. IR (neat) $\bar{\nu}$ = 3056, 2978, 2932, 2851, 1728, 1599, 1554 cm^{-1}. MS (EI): m/z (%): 286 (M^+, 16), 256 (36), 241 (59), 151 (47), 105 (100). Anal. calcd. for $C_{17}H_{20}NO_3$: C, 71.31; H, 7.04; N, 4.89. Found: C, 71.45; H, 7.01; N, 4.75.

Tetraethyl (2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)ethane-1,1-diyl)bis(phosphonate) radical (216):

To a stirred suspension of NaH (120 mg, 5.0 mmol) in anhydr. THF (10 mL), a solution of $CH_2(P(O)(OEt)_2)_2$ (1.44 g, 5.0 mmol) in anhydr. THF (10 mL) was added dropwise at 0 °C under N_2. After 30 min of stirring, a solution of compound **191a** (1.17 g, 5.0 mmol) in anhydr. THF (10 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for three days. The solvent was evaporated, and the residue was partitioned between water (30 mL) and EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified using flash column chromatography (hexane/EtOAc, 1:1) to afford a yellow oil (1.21 g, 55%); TLC ($CHCl_3$/MeOH, 58:2): R_f = 0.52. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 23.4. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.33 (s, 6H, C(C*H*$_3$)$_2$), 1.35 (s, 6H, C(C*H*$_3$)$_2$), 1.44 (t, *J* = 7 Hz, 12H, 4 × OCH_2C*H*_3), 2.40 (d, *J* = 283 Hz,

1H, PC*H*P), 2.64-2.75 (m, 2H, =CCH_2), 4.23–4.29 (m, 8H, 4 × OCH_2CH$_3$), 5.47 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.51 (4C), 23.02 (1C), 24.10 (2C), 25.58 (2C), 34.73 (t, *J* = 133 Hz, 1C), 62.76 (d, *J* = 7 Hz, 2C), 62.91 (d, *J* = 7 Hz, 2C), 68.40 (1C), 71.88 (d, *J* = 4 Hz, 1C), 128.31 (1C), 141.50 (t, *J* = 7 Hz, 1C). IR (neat) $\overline{\nu}$ = 2977, 2932, 1648 cm^{-1}. MS (EI): m/z (%): 440 (M^+, 5), 410 (9), 288 (23), 273 (100). Anal. calcd. for $C_{18}H_{36}NO_7P_2$: C, 49.09; H, 8.24; N, 3.18. Found: C, 48.99; H, 8.32; N, 3.05.

(2-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)ethane-1,1-diyl)diphosphonic acid radical (217):

To a stirred solution of compound **216** (440 mg, 1.0 mmol) in anhydr. DCM (10 mL) in a sealed vial, TMSBr (1.84 g, 12.0 mmol) was added at 0 °C and the resulting mixture was stirred under Ar at 25 °C for 18 h. The mixture was concentrated under reduced pressure, and then $CHCl_3$ (5 mL) and a solution of $NaNO_2$ (69 mg, 1.0 mmol dissolved in 10 mL of H_2O) were added. The resulting mixture was stirred vigorously for 4 h at 25 °C, and then DCM (20 mL) was added. The aqueous phase was separated and evaporated, and the crude residue was dissolved in methanol (10 mL); this mixture was filtered on a sintered glass funnel and evaporated to give a brownish solid (69 mg, 21%); mp 120–122 °C. ^{31}P NMR [202 MHz, CD_3OD + $(PhNH)_2$] δ = 20.4. ^{1}H and ^{13}C NMR data were not obtained because of the low solubility of the title compound. IR (neat) $\overline{\nu}$ = 3406, 2976, 1614 cm^{-1}. HRMS (ESI): m/z $[M]^+$ calc. for $C_{10}H_{20}NO_7P_2$: 328.0715; found: 328.0719. Anal. calcd. for $C_{10}H_{20}NO_7P_2$: C, 36.59; H, 6.14; N, 4.27. Found: C, 36.47; H, 6.02; N, 4.15.

General procedure for synthesis of ethynylphosphonates (219a, 219b):

To a stirred solution of compound **218a** or **218b** (5.0 mmol) in anhydr. THF (10 mL), LiHMDS (5.0 mL, 5.0 mmol, 1 M THF solution) was added dropwise at −78 °C under N_2. After the addition was completed, the mixture was stirred for 1h at −78 °C. A solution of $ClP(O)(OEt)_2$ (863 mg, 5.0 mmol) in anhydr. THF (10 mL) was added dropwise, and the temperature was allowed to increase to r.t. spontaneously with stirring for 2 h. The reaction mixture was quenched with a saturated NH_4Cl solution (10 mL). The mixture was diluted with EtOAc (20 mL); the organic phase was separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was subjected to flash column chromatography purification (hexane/EtOAc, 1:1).

Diethyl ((1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)ethynyl)phosphonate radical (219a):

yellow solid (780 mg, 52%); mp 50–52 °C; TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.43. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = -6.4. ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.32 (s, 6H, C(C*H*$_3$)$_2$), 1.38 (s, 6H, C(C*H*$_3$)$_2$), 1.45 (t, *J* = 7.1 Hz, 6H, 2 × OCH_2CH_3), 4.22-4.28 (m, 4H, 2 × OCH_2CH_3), 6.22 (d, *J* = 0.7 Hz, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] 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). IR (neat) $\overline{\nu}$ = 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). Anal. calcd. for $C_{14}H_{23}NO_4P$: C, 55.99; H, 7.72; N, 4.66. Found: C, 55.96; H, 7.73; N, 4.62.

Diethyl ((1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)ethynyl)phosphonate radical (219b):

red solid (1.1 g, 70%); mp 45–47 °C; TLC ($CHCl_3/Et_2O$, 2:1): R_f = 0.48. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = −5.6; ^1H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.24 (s, 6H, C(C*H*$_3$)$_2$), 1.32 (s, 6H, C(C*H*$_3$)$_2$), 1.44 (t, *J* = 7 Hz, 6H, 2 × OCH_2CH_3), 2.30 (s, 2H, =CCH_2), 4.21–4.27 (m, 4H, 2 × OCH_2CH_3), 6.20 (s, 1H, *H*C=C).^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.22 (d, *J* = 7.1 Hz, 2C), 24.73 (2C), 25.62 (2C), 42.30 (1C), 57.40 (1C), 60.39 (1C), 63.19 (d, *J* = 5.5 Hz, 2C), 99.60 (1C), 100.02 (1C), 112.53 (d, *J* = 5.6 Hz, 1C), 147.52 (d, *J* = 3.0 Hz, 1C). IR (neat) $\overline{\nu}$ = 2980, 2934, 2168, 1635 cm^{-1}. MS (EI): m/z (%): 314 (M^+, 12), 284 (56), 256 (8), 185 (17), 145 (100). $C_{15}H_{25}NO_4P$: C, 57.31; H, 8.02; N, 4.46. Found: C, 57.40; H, 8.14; N, 4.56.

General procedure for hydration of ethynyl phosphonates (220a, 220b):

To a solution of compound **219a** or **219b** (1.0 mmol) in 1,4-dioxane (1.2 mL), distilled H_2O (0.2 mL) and $PdCl_2$ (20 mg, 0.11 mmol) were added, and the mixture was stirred at 80 °C. The reaction mixture was monitored using TLC, and after complete consumption of the starting material (~3 h), the mixture was allowed to cool, diluted with DCM (10 mL), and filtered through a Celite pad. The pad was rinsed with DCM (10 mL), and the filtrate was evaporated; the residue was partitioned between H_2O (5 mL) and DCM (20 mL). The organic phase was separated, dried on anhydrous $MgSO_4$, filtered, and evaporated, and the residue was purified using flash column chromatography (hexane/EtOAc, 1:9).

Diethyl (2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-2-oxoethyl)phosphonate radical (220a):

orange oil (251 mg, 79%); TLC ($CHCl_3$/MeOH, 59:1): R_f = 0.38. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 20.3. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.38 (t, *J* = 7 Hz, 6H, 2 × OCH_2CH_3), 1.39 (s, 6H, $C(CH_3)_2$), 1.47 (s, 6H, $C(CH_3)_2$), 3.36 (d, *J* = 10 Hz, 2H, $COCH_2P$), 4.18–4.24 (m, 4H, 2 × OCH_2CH_3), 6.69 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.42 (d, *J* = 6.5 Hz, 2C), 24.56 (2C), 24.98 (2C), 39.27 (d, *J* = 129 Hz, 1C), 62.66 (d, *J* = 6.5, Hz, 2C), 68.09 (1C), 70.23 (1C), 144.12 (1C), 149.26 (1C), 188.77 (d, *J* = 7 Hz, 1C). IR (neat) $\overline{\nu}$ = 2925, 2852, 1684 cm^{-1}. MS (EI): m/z (%): 318 (M^+, 19), 288 (4), 256 (8), 270 (92), 132 (100). $C_{14}H_{25}NO_5P$: C, 52.82; H, 7.92; N, 4.40. Found: C, 52.66; H, 8.10; N, 4.29.

Diethyl (2-(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-oxoethyl)phosphonate radical (220b):

orange oil (302 mg, 91%); TLC ($CHCl_3$/MeOH, 59:1): R_f = 0.41. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 20.7. ^{1}H NMR [500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.23 (s, 6H, $C(CH_3)_2$), 1.38 (t, *J* = 7 Hz, 6H, 2 × OCH_2CH_3), 1.42 (s, 6H, $C(CH_3)_2$), 2.43 (s, 2H), 3.42 (d, *J* = 23 Hz, 2H, CH_2), 4.18–4.24 (m, 4H, 2 × OCH_2CH_3), 6.74 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.45 (d, *J* = 6.5 Hz, 2C), 25.00 (2C), 25.75 (2C), 37.24 (d, *J* = 129 Hz, 1C), 37.67 (1C), 57.23 (1C), 59.90 (1C), 62.64 (d, *J* = 6.5 Hz, 2C), 132.52 (1C), 148.83 (d, *J* = 3 Hz, 1C), 192.23 (d, *J* = 8 Hz, 1C). IR (neat) $\overline{\nu}$ = 2978, 2932, 1667 cm^{-1}. MS (EI): m/z (%): 332 (M^+, 7), 302 (53), 284 (10), 179 (13), 258 (33), 123 (100). Anal. calcd. for $C_{15}H_{27}NO_5P$: C, 55.21; H, 8.19; N, 4.21. Found: C, 55.28; H, 8.23; N, 4.06.

Diethyl (1-diazo-2-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-2-oxoethyl)phosphonate radical (221):

To a stirred solution of compound **220a** (636 mg, 2.0 mmol) in toluene (5 mL), TEBAC (45 mg, 0.2 mmol) and anhydr. K_2CO_3 (1.1 g, 8.0 mmol) were added, and the resulting suspension was heated to 60 °C; then, TsN_3 (395 mg, 2.0 mmol) in toluene (5 mL) was added. The reaction mixture was stirred at this temperature and monitored using TLC. After the reaction was complete (~1 h), the mixture was filtered on a sintered glass funnel. The filtrate was washed with 0.5 M aqueous NaOH (2 × 10 mL) and H_2O (2 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated, and the residue was purified using flash column chromatography (hexane/EtOAc, 1:1) to afford a yellow oil (537 mg, 78%); TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.50. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 10.6. ^{1}H NMR

[500 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 1.35–1.46 (m, 18H, 2 × OCH_2CH_3 + 4 × $C(CH_3)_2$), 4.21–4.28 (m, 4H, 2 × OCH_2CH_3), 6.40 (s, 1H, *H*C=C). ^{13}C NMR [125 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 16.23 (d, *J* = 6.5 Hz, 2C), 24.68 (2C), 24.91 (2C), 63.84 (d, *J* = 6 Hz, 2C), 68.74 (1C), 71.83 (1C), 141.27 (1C), 148.96 (1C), 183.38 (d, *J* = 10 Hz, 1C), diazo carbon not observed. IR (neat) $\overline{\nu}$ = 2979, 2932, 2869, 2116, 1640, 1610 cm^{-1}. MS (EI): m/z (%): 344 (M^+, 26), 314 (2), 301 (14), 286 (27), 258 (33), 230 (45), 215 (100). Anal. calcd. for $C_{14}H_{23}N_3O_5P$: C, 48.33; H, 6.73; N, 12.20. Found: C, 48.29; H, 6.89; N, 12.22.

(*E*)-1-(1-Oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)-3-phenylprop-2-en-1-one radical (222):

To a stirred suspension of NaH (48 mg, 2.0 mmol) in anhydr. THF (10 mL), a solution of compound **220b** (664 mg, 2.0 mmol) in anhydr. THF (10 mL) was added dropwise at 0 °C under N_2. After 30 min, a solution of benzaldehyde (213 mg, 2.0 mmol) in anhydr. DMF (5 mL) was added dropwise at 0 °C. Then, the mixture was warmed to 25 °C and stirred for 5 h at this temperature. The solvent was evaporated, and the residue was partitioned between water (30 mL) and EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified using flash column chromatography (hexane/Et_2O, 2:1) to afford a red solid; mp 88–90 °C (256 mg, 45%); TLC (hexane/Et_2O, 2:1): R_f = 0.40. ^1H NMR of NOAc ($C_{20}H_{25}NO_3$) derivative (500 MHz, $CDCl_3$) δ = 1.18 (s, 3H, CC*H*$_3$), 1.24 (s, 3H, CC*H*$_3$), 1.33 (s, 3H, CC*H*$_3$), 1.40 (s, 3H, CC*H*$_3$), 2.15 (s, 3H, C*H*$_3$CO), 2.59 (q, *J* = 18 Hz, 2H, C=CC*H*$_2$), 6.64 (s, 1H, *H*C=C─CO), 7.28 (d, *J* = 16 Hz, 1H, =C*H*─CO), 7.41 (s, 3H, Ar*H*), 7.61(s, 2H, Ar*H*), 7.68 (d, *J* = 16 Hz, 1H, C*H*=CH─CO). ^{13}C NMR of NOAc ($C_{20}H_{25}NO_3$) derivative (125 MHz,$CDCl_3$) δ = 19.08 (1C), 21.56 (1C), 22.79 (1C), 29.16 (1C), 30.22 (1C), 37.57 (1C), 58.47 (1C), 60.65 (1C), 120.68 (1C), 128.33 (2C), 128.93 (2C), 130.37 (1C), 133.75 (1C), 134.93 (1C), 143.49 (1C), 143.66 (1C), 170.86 (1C), 189.97 (1C). IR (neat) $\overline{\nu}$ = 2970, 2929, 2871, 1726, 1658, 1595, 1573 cm^{-1}. MS (EI): m/z (%): 284 (M^+, 11), 254 (100), 239 (59), 131 (95), 103 (72). Anal. calcd. for $C_{18}H_{22}NO_2$: C, 76.02; H, 7.80; N, 4.93. Found: C, 76.02; H, 7.82; N, 4.88.

Synthesis of 2,2,5,5-tetramethyl-3,4-dimethylenepyrrolidin-1-yl acetate (44b):

A solution of ascorbic acid (8.80 g, 50.0 mmol) in H_2O (10 mL) was added to a solution of radical **44a** (1.66 g, 10.0 mmol) in dioxane (30 mL), and the mixture was stirred at 40°C for 15 min under N_2. The pale yellow solution was extracted with $CHCl_3$ (2 × 20 mL) and dried on $MgSO_4$ under N_2. Acetyl chloride (860 mg, 10.0 mmol) was added at 0°C, followed by slow addition of Et_3N (1.10 g, 11.0 mmol) at this temperature. Stirring was continued for 1 h at room temperature, and after adding EtOH (1 mL), the reaction mixture was filtered, and the

filtrate was evaporated to dryness. The residue was partitioned between brine (15 mL) and EtOAc (20 mL). The organic phase was separated, and the aqueous phase was washed with EtOAc (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated, and after flash chromatography purification, we obtained compound **44b** as a white solid **(**1.79 g, 86%); mp 35-37°C*;* TLC (hexane/Et_2O, 5:1): R_f = 0.43. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.30 (s, 12H, 2 × C(C*H*$_3$)$_2$), 2.16 (s, 3H, C*H*$_3$CO), 4.89 (s, 2H, C*H*$_2$), 5.44 (s, 2H, C*H*$_2$), ^{13}C NMR ($CDCl_3$) δ = 19.1 (1C), 29.6 (4C), 66.4 (2C), 104.2 (2C), 151.1 (2C), 171.2 (1C). IR (neat) $\overline{\nu}$ = 2974, 2933, 1766, 1618 cm^{-1}. MS (EI): m/z (%): 209 (M^+, 1), 194 (11), 167 (14), 152 (100), 120 (16), 43 (9). Anal. calcd. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.75; H, 8.95; N, 6.59.

Synthesis of 1,1,3,3-tetramethyl-5-oxido-5-phenyl-5,6-dihydrophospholo[3,4-c]pyrrol-2(1*H*,3*H*,4*H*)-yl acetate (223b):

Compound **44b (**1.88 g, 9.0 mmol), Cu(II) stearate (100 mg, 0.15 mmol as polymerization inhibitor), pentane (10 mL) were added together with $PhPCl_2$ (3.22 g, 18.0 mmol) dropwise into a pressure-proof tube equipped with a magnetic stirrer, with stirring at 0°C. After addition, the tube was capped and stirred at room temperature for 4 days followed by stirring for 17 days at 37°C. After cooling, the solution was poured into a 250 mL beaker containing a mixture of ice (40 g) and sat. $NaHCO_3$ solution (40 mL). The tube was rinsed with $NaHCO_3$ solution (10 mL), $CHCl_3$ (10 mL) was poured into the beaker, $CHCl_3$ (80 mL) was added, and the two-phase system was stirred for 15 min. After separation of the organic phase, the aqueous phase was washed with $CHCl_3$ (2 x 10 mL), and the combined organic phases were dried ($MgSO_4$)*,* filtered and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc followed by $CHCl_3$/Et_2O) to give compound **223b** as a white solid (1.07 g, 36%); mp 150-152°C; TLC ($CHCl_3$/MeOH, 58:2): R_f =0.41. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 61.7. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.29 (s, 12H, 2 × C(C*H*$_3$)$_2$), 2.18 (s, 3H, C*H*$_3$CO), 2.68-2.73 (m, 2H, C*H*$_2$), 2.79-2.85 (m, 2H, C*H*$_2$), 7.50-7.74 (m, 5H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.2. (1C), 21.7 (2C), 27.1 (2C), 31.2 (d, *J* = 65.5 Hz, 2C), 128.9 (d, *J* = 11 Hz, 2C), 129.2. (d, *J* = 10.0 Hz, 2C) 132.3 (1C), 134.4 (d, *J* = 94 Hz, 1C), 139.4 (*J* = 11 Hz, 2C), 170.9 (1C). IR (neat) $\overline{\nu}$ = 2974, 2927, 1767 cm^{-1}.; MS (EI): m/z (%): 333 (M^+, 1), 318 (19), 291 (54), 276 (100), 259 (38). Anal. calcd. for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.65; H, 7.15; N, 4.17.

Synthesis of 1,1,3,3-tetramethyl-5-phenyl-5-oxido-1,2,3,4,5,6-hexahydrophospholo[3,4-c]pyrrole-2-yloxyl radical (223a):

Freshly prepared NaOMe (from 12 mg, 0.52 mmol Na dissolved in 5 mL MeOH) was added to a solution of compound **223b** (999 mg, 3.0 mmol) in MeOH (20 mL), and the mixture was allowed to remain for 2 h at 25°C. The solvent was evaporated off, the residue was dissolved in sat. aq. NH_4Cl solution (10 mL) and extracted with $CHCl_3$ (2 x 20 mL). The combined organic phase was dried ($MgSO_4$), MnO_2 (86 mg, 1.0 mmol) was added, and O_2 was bubbled through for 10 min. After filtration, the reaction mixture was evaporated and purified by flash column chromatography ($CHCl_3$/Et_2O) to furnish the title compound as a yellow solid (826 mg, 95%); mp 194-197°C; TLC ($CHCl_3$/MeOH, 58:2): R_f = 0.37. ^{31}P NMR [202 MHz, $CDCl_3$ + $(PhNH)_2$] δ = 61.8. ^{1}H NMR [500 MHz, $CDCl_3$+$(PhNH)_2$]: δ = 1.34 (s, 12H, 2 × C(C*H*$_3$)$_2$), 2.70 (dd, J^1 = 7.0 Hz, J^2 = 7.0 Hz, 2H, C*H*$_2$), 2.88 (t, *J* = 16 Hz, 2H, C*H*$_2$), ,aromatic protons overlap with $(PhNH)_2$ protons. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.7 (2C), 24.5 (2C), 31.2 (d, *J* = 67 Hz, 2C), 68.4 (d, *J* = 9 Hz, 2C), 128.9 (d, *J* =11 Hz, 2C), 129.3 (2C) 132.2 (1C), 134.3 (d, *J* = 88 Hz, 1C), 139.8 (d, *J* = 11 Hz, 2C). IR (neat) $\overline{\nu}$ = 2974, 2827 cm^{-1}. MS (EI): m/z (%): 290 (M^+, 13), 275 (31), 260 (73), 245 (100). Anal. calcd. For $C_{16}H_{21}NO_2P$: C, 66.19; H, 7.29; N, 4.82. Found: C, 66.05; H, 7.15; N, 4.84.

Synthesis of 3-(diphenylphosphino)-1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole (227):

n-BuLi solution in hexane (2.8 mL, 7.0 mmol, 2.5 M) diluted with anhydr. THF (10 mL) was added dropwise to a stirred solution of compound **226** (1.97 g, 7.0 mmol) in anhydr. THF (10 mL) at -78°C under N_2. After the addition was completed, the mixture was continuously stirred for 1 h at -78°C. Then, a solution of Ph_2PCl (1.55 g, 7.0 mmol) in anhydr. 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. NH_4Cl solution (5 mL) was added, the mixture was extracted with EtOAc (2 x 20 mL), the combined organic phase was dried ($MgSO_4$), filtered and evaporated, and the crude product was purified by flash column chromatography (hexane/Et_2O, 4:1) to give a white powder (1.6 g, 67%); mp 95-97°C; TLC (hexane/Et_2O, 58:2): R_f = 0.31. ^{31}P NMR (202 MHz, $CDCl_3$) δ = -27.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (s, 12H, 2 × C(C*H*$_3$)$_2$), 3.70 (s, 3H, OC*H*$_3$), 5.28 (s, 1H, *H*C=C), 7.37 (bs, 10H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.0 (2C), 29.6 (2C), 65.0 (1C), 68.5 (1C), 73.1 (d, *J* =24 Hz, 1C), 128.35 (d, *J* = 7 Hz, 4C), 128.7 (2C), 133.9 (d, *J* =20 Hz, 4C), 135.8 (d, *J* = 16 Hz, 2C) 143.2 (d, *J* = 18 Hz, 1C), 143.5 (d, *J* = 2.6 Hz, 1C). IR (neat) $\overline{\nu}$ =

3056, 2971, 1620, 1572 cm^{-1}. MS (EI): m/z (%): 339 (M^+, 5), 324 (100), 293 (78), 201 (12), 108 (44). Anal. calcd. for $C_{21}H_{26}NOP$: C, 74.31; H, 7.72; N, 4.13. Found: C, 74.21; H, 7.66; N, 4.11.

Synthesis of 1-methoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)diphenylphosphine oxide (228):

A solution of compound **227** (679 mg, 2.0 mmol) in toluene (15 mL) was heated at the reflux temperature for 12 h. The solvent was evaporated, and the crude material was subjected to flash column chromatography (hexane/EtOAc, 2:1) to give a yellow powder (355 mg, 50%); mp 128-130°C; TLC ($CHCl_3$/Et_2O, 2:1): R_f = 0.46. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 23.5. ^1H NMR (500MHz, $CDCl_3$): δ = 1.28 (s, 6H, C(C*H*$_3$)$_2$), 1.36 (s, 6H, C(C*H*$_3$)$_2$), 3.65 (s, 3H, OC*H*$_3$), 5.68 (d, *J* = 11.5 Hz, 1H, *H*C=C), 7.48-7.72 (m, 10H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.7 (2C), 29.7 (2C), 65.1 (1C), 68.8 (d, *J* = 13 Hz, 1C), 73.2 (d, , *J* =11 Hz, 1C), 128.4 (d, *J*=12 Hz, 4C), 131.75 (2C), 131.79 (d, *J* = 4 Hz, 4C), 132.3 (d, *J* = 124 Hz, 2C), 138.6 (d, *J* = 101 Hz, 1C), 150.1 (d, *J* = 8 Hz, 1C). IR (neat) $\overline{\nu}$ = 2973, 2674, 1606 cm^{-1}. MS (EI): m/z (%): 355 (M^+, 2), 340 (90), 310 (10), 308 (45), 201 (100), 108 (25). Anal. calcd. for $C_21H_{26}NO_2P$: C, 70.97; H, 7.37; N, 3.94. Found: C, 71.07; H, 7.41; N, 3.87.

Synthesis of 3-(diphenylphosphinoxido)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radical (229):

First, *m*-CPBA (3.0 eq. for compound **227**, 2.0 eq. for compound **228**) was added in 2-3 portions at 0°C to a stirred solution of compound **227** or **228** (2.0 mmol) in anhydr. CH_2Cl_2 (5 mL) for 10 min. The solution was stirred for an additional 30 min at r.t. Then, the solution was washed with 10% aq. Na_2CO_3 (2 × 10 mL), and the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The residue was subjected to flash column chromatography (hexan/EtAOAc, 1:9) to give a yellow powder (612 mg, 90%); mp 135-137°C; TLC ($CHCl_3$/MeOH, 58:2): R_f = 0.56. ^{31}P NMR [202 MHz, $CDCl_3$+$(PhNH)_2$] δ = 23.4. ^1H NMR [500 MHz, $CDCl_3$+$(PhNH)_2$] δ = 1.32 (s, 6H, C(C*H*$_3$)$_2$), 1.42 (s, 6H, C(C*H*$_3$)$_2$), 5.82 (d, *J* = 11.5 Hz, 1H, *H*C=C), aromatic protons overlap with $(PhNH)_2$ signals. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.1 (2C), 25.8 (2C), 69.1 (d, *J* = 12 Hz, 1C), 73.4 (d, *J* =11 Hz, 1C), 128.5 (d, *J* = 12 Hz, 4C), 131.8 (d, *J* = 10 Hz, 4C), 131.90 (s, 2C), 132.6 (d, *J* = 4 Hz, 2C), 138.9 (d, *J* = 101 Hz, 1C), 149.8 (d, *J* = 8 Hz, 1C). IR (neat) $\overline{\nu}$ = 2973, 2925, 1596 cm^{-1}. MS (EI): m/z (%): 340 (M^+, 90), 310 (10), 308 (47), 201 (100), 108 (21). Anal. calcd. for $C_{20}H_{23}NO_2P$: C, 70.57; H, 6.81; N, 4.12. Found: C, 70.71; H, 6.77; N, 4.01.

Synthesis of 3-(diphenylphosphino)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radical (230):

Cl_3SiH (0.8 mL, 4 eq, 8 mmol) was added to a stirred solution of compound **229** (680 mg, 2.0 mmol) in anhydr. benzene (10 mL), at 0°C under N_2. The resulting mixture was stirred at 78°C for 4 h under N_2, cooled to room temperature and then poured into a 250 mL beaker containing ice (40 g) and 5% aq. NaOH solution (10 mL). The organic phase was extracted with EtOAc (2 × 15 mL), dried ($MgSO_4$), oxidized by adding PbO_2 (478 mg, 2.0 mmol), filtered and then evaporated. The residue was purified by flash column chromatography (hexane/Et_2O) to give a yellow powder (421 mg, 65%); mp 120-122°C; TLC (hexane/Et_2O, 2:1): R_f = 0.42. ^{31}P NMR [202 MHz, $CDCl_3$+$(PhNH)_2$] δ = -26.6. ^1H NMR [500 MHz, $CDCl_3$+$(PhNH)_2$] δ = 1.32 (s, 6H, C(C*H*$_3$)$_2$), 1.34 (s, 6H, C(C*H*$_3$)$_2$), 5.45 (d, *J* = 4 Hz, 1H, *H*C=C), aromatic protons overlap with $(PhNH)_2$ signals. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.1 (2C), 25.8 (2C), 69.1 (d, *J* = 12 Hz, 1C) 73.4 (d, *J* =11 Hz, 1C), 128.4 (d, *J* = 7 Hz, 4C), 128.9 (2C), 131.8 (d, *J* =10 Hz, 2C), 134.0 (d, *J* = 20 Hz, 4C), 135.7 (d, *J* = 8 Hz, 1C), 143.3 (d, *J* = 2 Hz, 1C). IR (neat) $\overline{\nu}$ = 3054, 2974, 2855, 1598, 1582 cm^{-1}. MS (EI): m/z (%): 324 (M^+, 17), 294 (99), 279 (100), 183 (62), 108 (84). Anal. calcd. For $C_{20}H_{23}NOP$: C, 74.05; H, 7.15; N, 4.32. Found: C, 74.21; H, 6.94; N, 4.46.

Synthesis of hexadecyl (1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)diphenylphosphonium bromide radical (231):

A mixture of compound **230** (324 mg, 1.0 mmol) and *n*-$C_{16}H_{33}Br$ (305 mg, 1.0 mmol) in acetonitrile (10 mL) in a pressure-proof closed vial was stirred and heated at 90°C for 5 days. After cooling to room temperature, the solvent was evaporated, and the crude material was purified by flash column chromatography ($CHCl_3$/MeOH, 9:1) to furnish the title compound as a beige solid (31 mg, 5%); mp 118-120°C; TLC ($CHCl_3$/MeOH, 9:1): R_f = 0.40. ^1H and ^{13}C NMR data were not obtained because of the low solubility of the title compound. IR (neat) $\overline{\nu}$ = 2923, 2852, 1598 cm^{-1}. HRMS (ESI): m/z $[M]^+$ calc. for $C_{36}H_{56}NOP^+$: 549.4094; found: 549.4099. Anal. calcd. for $C_{36}H_{56}BrNOP$: C, 68.66; H, 8.96; N, 2.22. Found: C, 68.47; H, 8.89; N, 2.13.

X-ray Crystallographic Study of Pyrroline Nitroxide-Diphenylphosphine:

X-ray-quality crystals of **230** were grown by slow crystallization from pentane/Et_2O (2:1) solution by spontaneous evaporation of the solvent. A suitable crystal was fixed under a microscope onto a Mitegen loop using high-density oil. Diffraction intensity data were collected at 200 K using a Bruker-D8 Venture diffractometer (Bruker AXS GmbH, Karlsruhe,

Germany) equipped with INCOATEC IμS 3.0 (Incoatec GmbH, Geesthacht, Germany) dual (Cu and Mo) sealed tube micro sources and a Photon II Charge-Integrating Pixel Array detector (Bruker AXS GmbH, Karlsruhe, Germany) using Mo Kα (λ = 0.71073 Å) radiation. High multiplicity data collection and integration were performed using APEX3 (version 2017.3-0, Bruker AXS Inc., 2017, Madison, WI, USA) software. Data reduction and multiscan absorption correction were performed using SAINT (version 8.38A, Bruker AXS Inc., 2017, Madison, WI, USA). The structure was solved using direct methods and refined on F2 using the SHELXL program [134] incorporated into the APEX3 suite. Refinement was performed anisotropically for all nonhydrogen atoms. Hydrogen atoms were placed into geometric positions. The CIF file was manually edited using Publcif software [135], while graphics were prepared using the Mercury program [136]. The results for the X-ray diffraction structure determinations were very good according to the Checkcif functionality of PLATON software (Utrecht University, Utrecht, The Netherlands) [137], and structural parameters such as bond length and angle data were in the expected range. The crystallographic and refinement details are given in Table 2. CCDC contains the supplementary crystallographic data for **230** with deposition number 2082286. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, accessed on 21 May 2021.

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_2HPO_4, 0.00176 M KH_2PO_4) to a 7.0 mM concentration. ABTS radical cations ($ABTS^{\bullet+}$) 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 $ABTS^{\bullet+}$ 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 $ABTS^{\bullet+}$ 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: (A0−Aantioxidant)/A0, where A0 is the absorbance of the diluted $ABTS^{\bullet+}$ solution. The concentration–response curves of new compounds were compared with the curve of Trolox.

Cell survival assay:

MDA-MB-231 (ATCC® HTB-26™) and MCF-7 (ATCC® HTB-22™) human breast cancer lines were purchased from the American Type Culture Collection (Lomianki, Poland) and maintained at 37°C in a humidified atmosphere containing 5% CO_2 in 10% fetal calf serum supplemented with Dulbecco′s modified Eagle′s medium (DMEM) and Roswell Park Memorial Institute (RPMI) medium, respectively. The cell survival rates were assessed by using the sulforhodamine B (SRB) assay. This assay is based on the measurement of cellular protein content and is the most reliable assay for toxicity screening of compounds on adherent cells when the compounds affect mitochondrial function [138]. Briefly, the cells were seeded at the starting density of 5000 cells/well into 96-well plates a day before exposing them to 0 μM, 5 μM, 10 μM, 20 μM or 50 μM of MITO-CP **224**, compound **231** for 24 h. Then, the medium was removed, the wells were rinsed with phosphate buffered saline solution pH=7.4, 100 μl/well cold 10% trichloroacetic acid solution was added, and the plates were incubated at 4 °C for 30 min. The medium was replaced with 70 μl/well of 0.1% w/v SRB in 1% acetic acid solution for 20 min. at room temperature. The SRB solution was removed, and the plates were rinsed five times with 1% acetic acid before air drying. Bound SRB was solubilized with 200 μl/well 10 mM tris(hydroxymethyl)aminomethane base solution by shaking for at least 10 min. The absorbance was read using a 96-well plate reader at wavelengths of 492 nm and 620 nm. Optical density $(OD)_{492}$-OD_{620} values were used to calculate the viability expressed in % of untreated cells, mean + SEM from three independent experiments each running in at least four parallels (n=12).

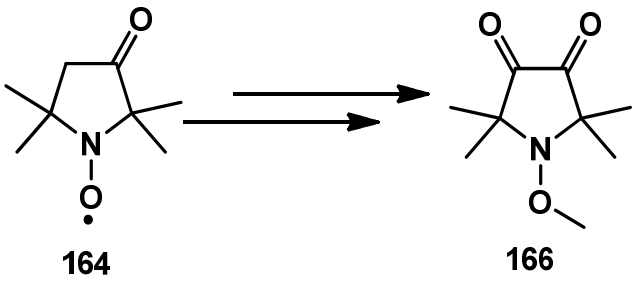
8. Summary

The aim of my PhD-work at the University of Pécs, Institute of Organic and Medicinal Chemistry was to develop new selective syntheses and methods to access new nitroxide derivatives, suitable for biological applications. The results were published in 5 peer-reviewed papers on the synthesis and characterization of new stable nitroxide compounds and are summarised in the following main topics:

1. Syntheses of 1,4-diazine- and an imidazole-fused pyrroline nitroxide.
2. Syntheses of new pyrroline and piperidine nitroxide phosphonate esters by the well-established methods and further transformations of the new products.
3. Syntheses of paramagnetic phospholene oxide, diphenyl-pyrroline nitroxide phosphine and its phosphonum salt

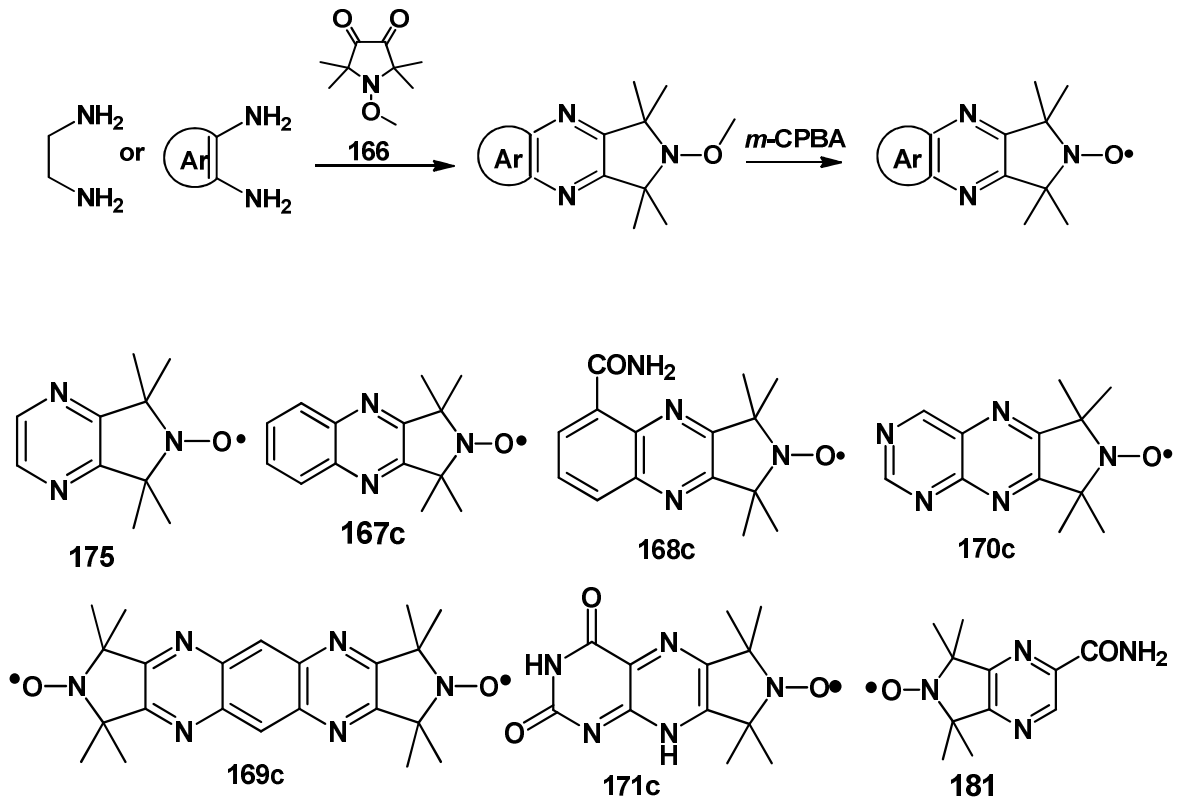
1. Syntheses of 1,4-diazine- and imidazole-fused pyrroline nitroxides

We developed a new diamagnetic synthon, 1-methoxy-2,2,5,5-tetramethylpyrrolidine-3,4-dione **166 (**Scheme 55**)** which was condensed with different aliphatic, aromatic or heteroaromatic 1,2-diamines followed by deprotection of the nitroxide function with *m*-CPBA, yielded pyrroline nitroxide fused pyrazines **175**, **181**, pteridines **170c**, **171c** or quinoxalines **167c**, **168c**, **169c** (Scheme 56).



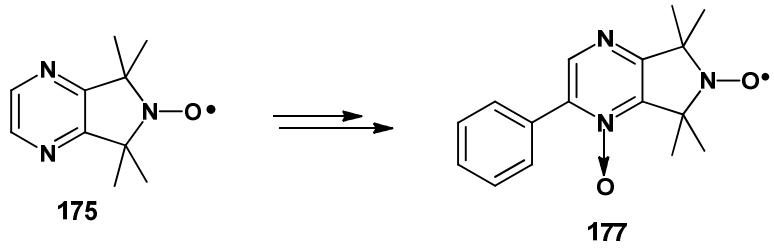
164 **166**

Scheme 55. Synthesis of diamagnetic synthon.



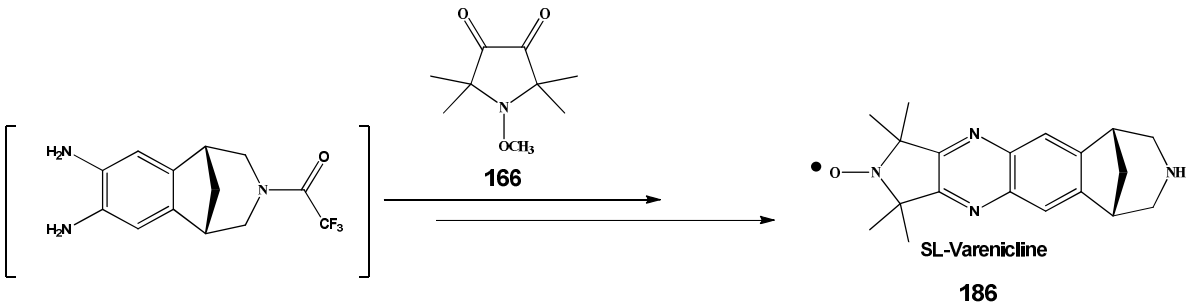
Scheme 56. Synthesis and structures of 1,4-diazine-fused paramagnetic, polycyclic compounds.

The oxidation of **175** resulted in the formation of *N*-oxide, which offered the possibility of C-H functionalization with benzene as a solvent at C2 position by palladium catalysis and Ag_2CO_3 oxidation to give compound **177** (Scheme 57).



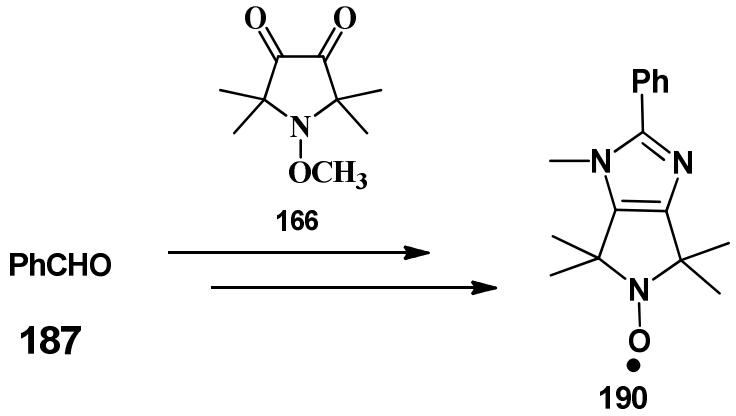
Scheme 57. Synthesis of functionalized paramagnetic pyraizne *N*-oxide.

Reaction of the diamagnetic 1,2-diketone with the diamino precursor of Varenicline followed by the deprotection of *N*-OMe by *m*-CPBA, and the removal of the trifluoroacetyl group by Na_2CO_3/MeOH furnished the spin labelled Varenicline **186** (Scheme 58).



Scheme 58. Synthesis of spin labeled Varenicline.

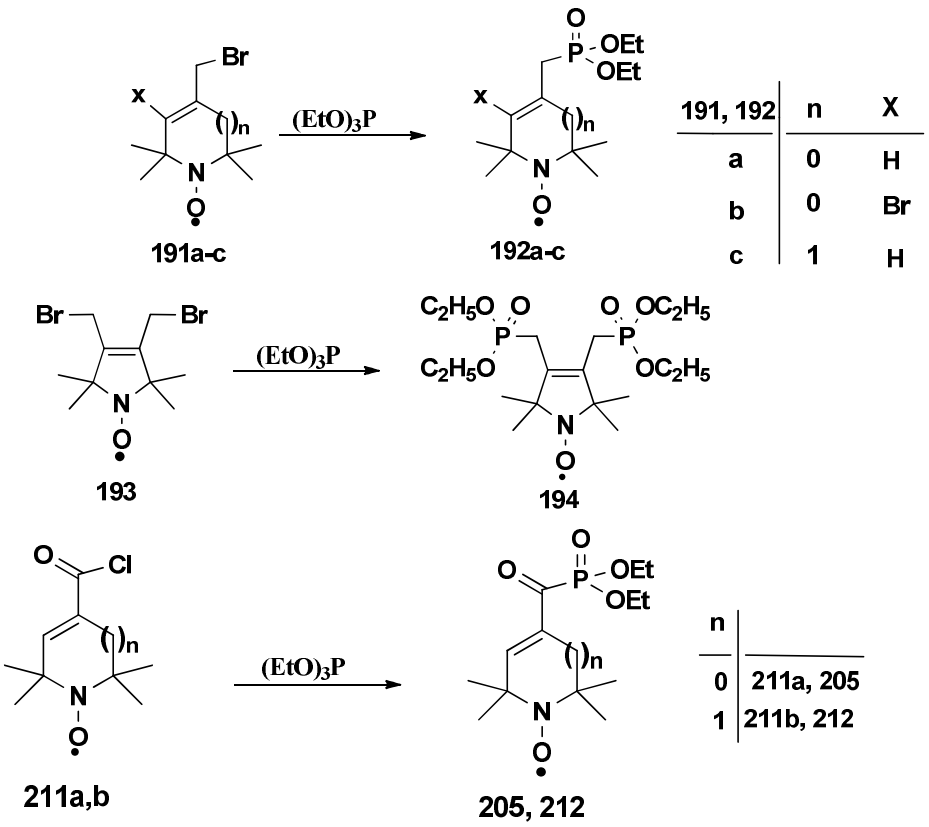
Reaction of the diamagnetic 1,2-diketone with benzaldehyde and ammonium acetate yielded a pyrrolo[3,4-d]imidazole scaffold (**190**) in the Debus-Radziszewski reaction. The *O*-methyl group deprotection required the protection (alkylation) of NH function of the imidazole (Scheme 59).



Scheme 59. Syntheses of imidazole-fused pyrroline nitroxides.

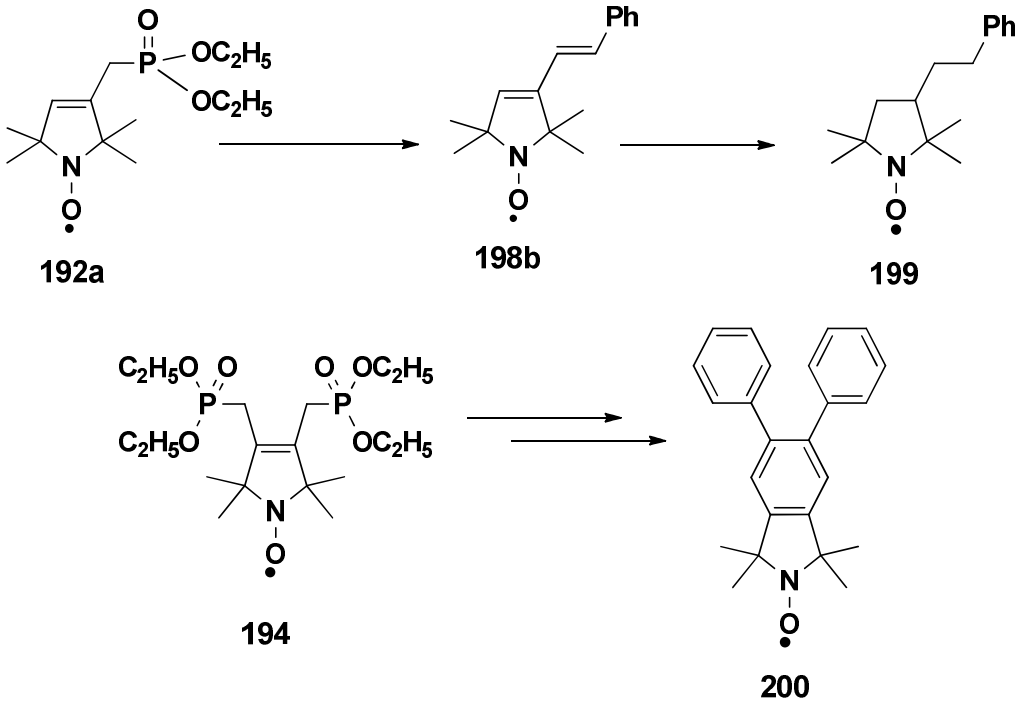
2. Syntheses of new pyrroline and piperidine nitroxide phosphonates by the well-established methods and further transformations of the new products

Treatment of five- and six-membered allylic bromides **191a-c**, dibromo compound **193,** acyl chlorides **211a,b** respectively with triethyl phosphite in an Arbuzov reaction resulted in formation of allylic phosphonate esters **192a-c**, bisphosphonate ester **194,** α-ketophosphonate esters **205**, **212** (Scheme 60).



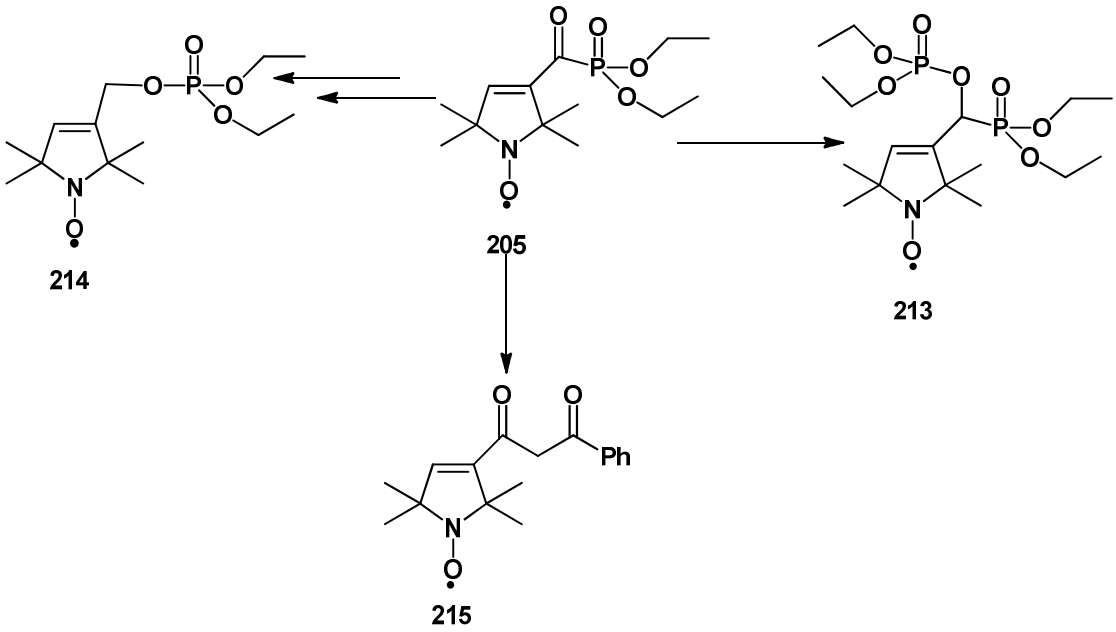
Scheme 60. Apllications of Arbuzov reactions.

We utilized the allylic phosphonate ester **192a** in Horner-Wadsworth-Emmons (HWE) reactions through deprotonation and treatment with benzaldehyde yielding *E*-alkenes**198b**. The reduction of the resulted C=C bond could be achieved using continuous flow hydrogenation system. The bisphosphonate ester **194** was deprotonatied followed by benzaldehyde treatment offered a triene of which spontaneous electrocyclization, followed by oxidation with DDQ resulted in formation of **200** isoindoline radical (Scheme 61).



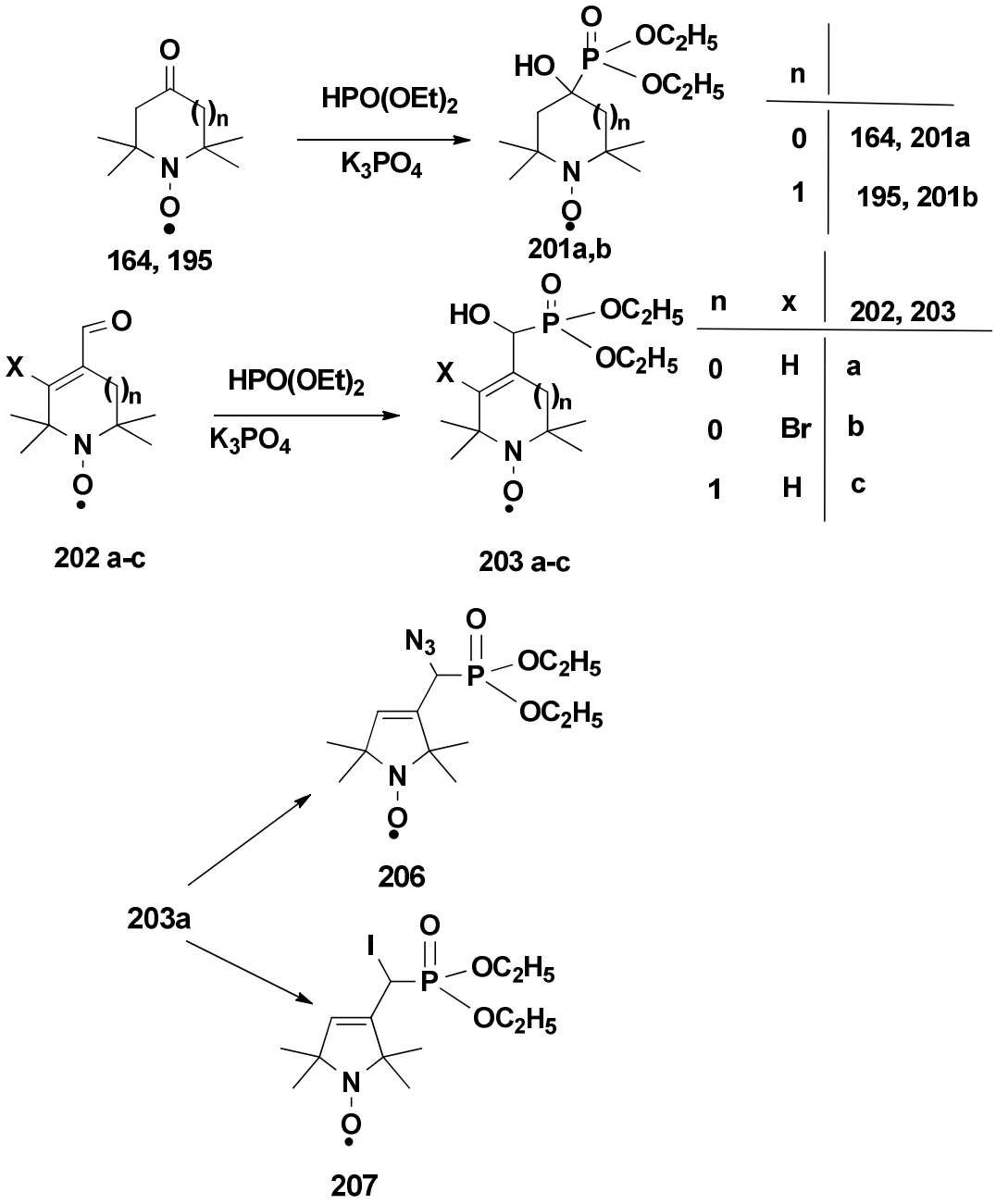
Scheme 61. HWE reactions of phosphonate esters to various alkenes and aromatic compounds.

Compound **205** was utilized as an acylating agent to give paramagnetic 1,3-dicarbonyl compound **215**. The reduction of **205** to α-hydroxyphosphonate ester followed by a phospha-Brook rearrangement furnished paramagnetic phosphate ester **214.** The nucleophilic addition of diethylphosphite to compound **205** gave phosphate phosphonate ester **213** (Scheme 62).



Scheme 62. Transformations of compound **205**.

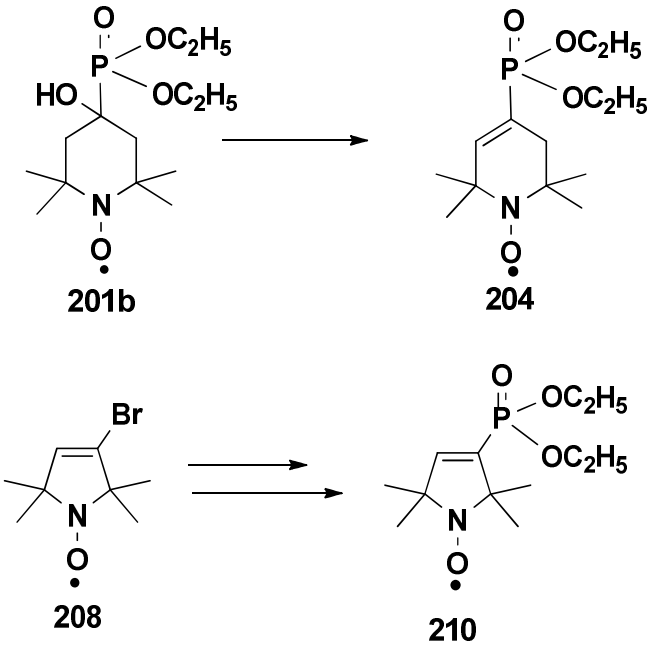
We synthesized paramagnetic five- and six- membered ring containing α-hydroxyphosphonate esters **201a,b** and **203a-c** starting from paramagnetic five- and six- ring membered aldehydes **202a-c** and ketones **164**, **195** by Pudovic reaction under solvent-free conditions. Compound **203a** was functionalized further in Mitsonubu reaction yielding compounds **206** and **207** (Scheme 63).



Scheme 63. Synthesis and transformations of paramagnetic *α*-hydroxyphoshonate esters.

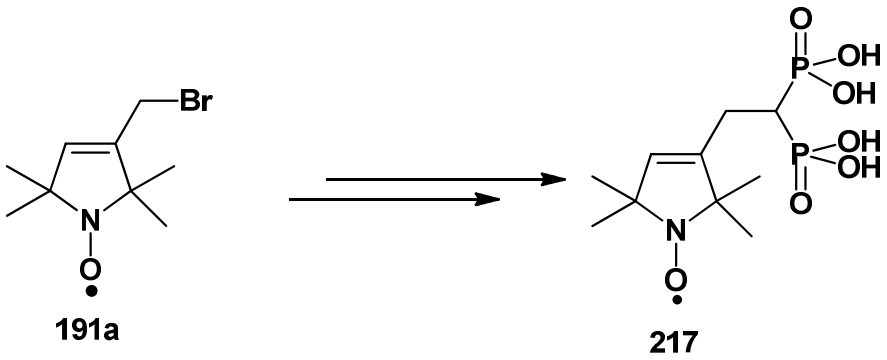
Water elimination of compound **201b** yielded paramagnetic six-membered vinyl phosphonate ester **204**. Paramagnetic five-membered vinylphosphonate ester **210** was obtained from compound **208** through a process including protection of nitroxide moiety as *O*-methyl by

Fenton reaction, followed by lithiation, addition of diethylchlorophosphate to give the diamagnetic vinyl phosphonate, and finally restoring of nitroxide moiety by *m*-CPBA treatment (scheme 64).



Scheme 64. Synthesis and paramagnetic five and six membered vinyl phosphonate esters.

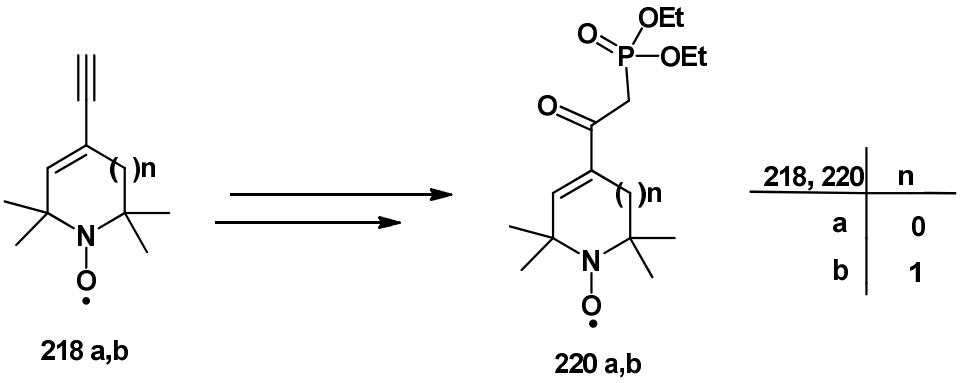
Geminal bisphosphonic acid **217** was accessed by alkylating tetraethyl methylenebisphosphonate with compound **191a**, followed by hydrolysis and oxidation (Scheme 65).



Scheme 65. Synthesis of geminal bisphosphonic acid.

We utilized paramagnetic acetylenes **218a** and **218b** to get β-ketophosphonates **220a**, **b**, through a process including deprotonation and treatment with diethylchlorophosphate. The

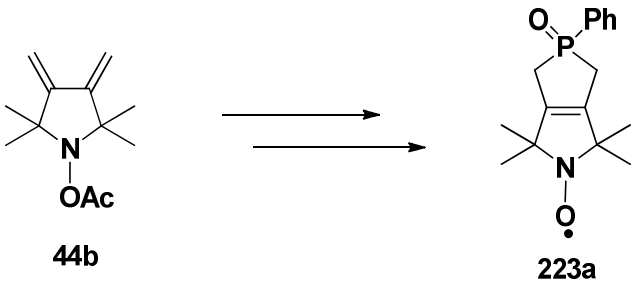
ethynylphosphonate esters were hydrated in aqueous dioxane in the presence of 10% $PdCl_2$ (Scheme 66).



Scheme 66. Synthesis of paramagnetic *β*-ketophosphonate esters.

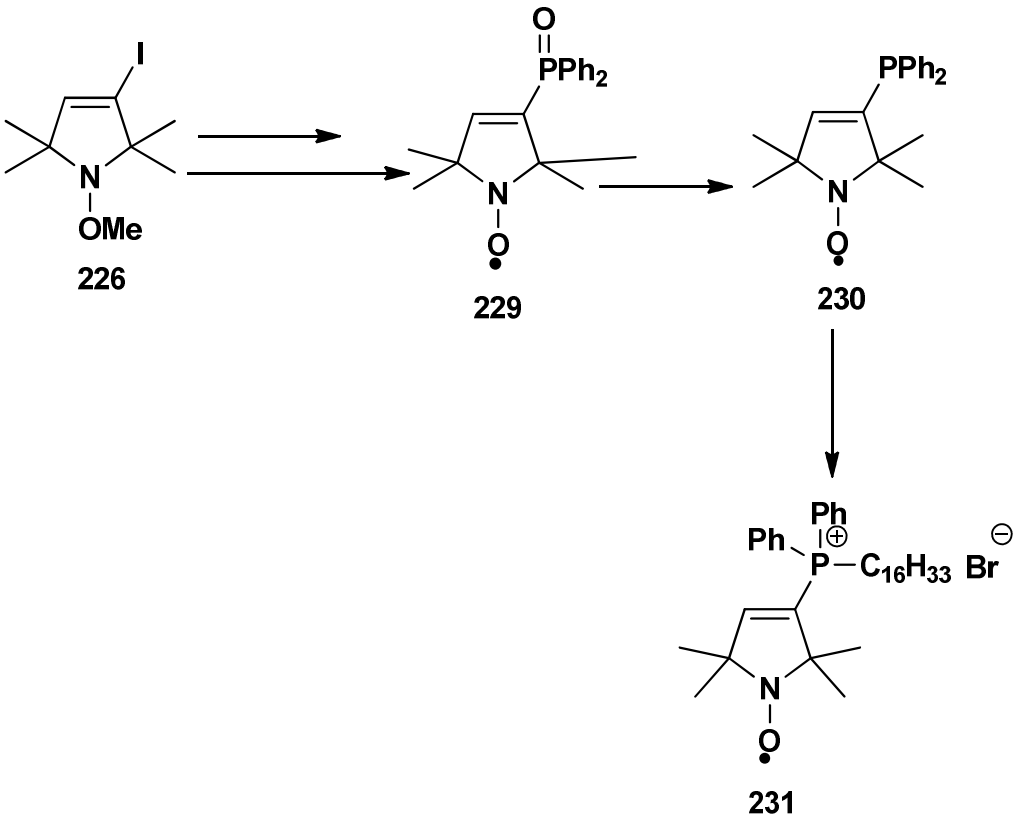
3. Syntheses of paramagnetic phospholene oxide, diphenyl-pyrroline phosphine and its phosphonum salt.

The reaction of a diene nitroxide precursor **44b** with dichlorophenyl phosphine in a McCormac procedure offered 2-oxyl-1,1,3,3-tetramethyl-5-phenyl-1,2,3,4,5,6-hexahydrophospholo[3,4-c]pyrrole-5-oxide **223a** after deacetylation (Scheme 67).



Scheme 67. Synthesis of a paramagnetic phospholene oxide.

We achieved the paramagnetic phosphine derivative **230**, starting from a protected pyrroline nitroxide, **226** which was lithiated, followed by treatment with diphenylchlorophosphine, and *m*-CPBA deprotection to give compound **229**. The reduction with Cl_3SiH and selective oxidation of **229** by PbO_2 offered compound **230**. The heating of compound **230** with hexadecyl bromide in acetonitrile offered the phosphonium salt **231** (Scheme 68). The latter was tested in vitro on on MDA-MB-231 and MCF-7 human breast cancer lines and pronounced remarkably antineoplastic effect.



Scheme 68. Synthesis of paramagnetic pyrroline nitroxide diphenylphosphine and its phosphonium salt.

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10. Publications

Publications related to the PhD thesis

I. Syntheses and Study of a Pyrroline Nitroxide Condensed Phospholene Oxide and a Pyrroline Nitroxide Attached Diphenylphosphine**.**
Isbera, M.; Bognár, B.; Gallyas, F.; Bényei, A.; Jekő, J.; Kálai, T.
Molecules **2021**, *26*, 4366. (IF 2020: 4.411, Q2)

II. Syntheses and utilizations of pyrroline-nitroxide and tetrahydropyridine-nitroxide-based α- ketophosphonates, β-ketophosphonates, and a bisphosphonate.
Isbera, M.; Bognár, B.; Sár, C.; Jekő, J.; Kálai, T.
Synthetic Communications **2021**, *51*, 1353–1362. (IF 2020: 1.796, Q3)

III. Synthesis of a Nitroxide Spin-labeled Varenicline (Chantix) Derivative.
Bognár, B.; Isbera, M.; Kálai, T.
Organic Preparations and Procedures International **2021**, *53*, 311–315. (IF 2020: 1.628, Q4)

IV. Syntheses and Reactions of Pyrroline, Piperidine Nitroxide Phosphonates.
Isbera, M.; Bognár, B.; Sár, C.; Jekő, J.; Hideg, k.; Kálai, T.
Molecules **2020**, *25*, 2430. (IF: 4.411, Q2)

V. Syntheses of Pyrazine-, Quinoxaline-, and Imidazole-Fused Pyrroline Nitroxides.
Isbera, M.; Bognár, B.; Gulyás Fekete, G.; Kish, K.; Kálai, T.
Synthesis **2019**, 51, 4463-4472. (IF: 2.675, Q1)

Other publications

VI. Cytostatic Effect of a Novel Mitochondria-Targeted Pyrroline Nitroxide in Human Breast Cancer Lines**.**
Andreidesz, K.; Szabó, A.; Kovács, D.; Kőszegi, B.; Bagóné Vántus, V.; Vamos, E.; Isbera, M.; Kálai, T.; Bognár, Z.; Kovács, K.; Gallyas, F.
International Journal of Molecular Sciences **2021***, 22,* 9016*.* (IF 2020: 5.923, Q1)

11. Conference presentations

Oral presentations

I. *Syntheses and Studies of Phosphorus Containing Stable Nitroxide Radicals*. Mostafa Isbera, Attila Bényei, Ferenc Gallyas, Balázs Bognár, Cecília P. Sár, Kálmán Hideg, József Jekő, Tamás Kálai. Az MTA Heterociklusos és Elemorganikus Kémiai Munkabizottságának a Patonay Tamás-díj átadásával egybekötött nyílt ülésére. Budapest, Hungary. 3rd September, 2021.

II. *Synthesis of pyrazine-, quinoxaline- and imidazole-fused pyrroline nitroxides*. Mostafa Isbera, Balázs Bognár, Gergely Gulyás Fekete, Krisztina Kish, Tamás Kálai. Hterociklusos és Elemorganikus Munkabizottság előadóülése. Microsoft Teams Meeting. 31st May, 2021.

Poster presentations

III. *Syntheses and study of a pyrroline nitroxide condensed phospholene oxide and a pyrroline nitroxide attached diphenylphosphine.* Mostafa Isbera, Attila Bényei, Ferenc Gallyas, Balázs Bognár, József Jekő, Tamás Kálai. 23rd International Conference on Phosphorus Chemistry. Częstochowa, Poland. 5-9th July, 2021 (online).

IV. *Syntheses and utilizations of pyrroline-nitroxide- and tetrahydropyridine-nitroxide-based phosphonates, α-ketophosphonates, β-ketophosphonates, and a bisphosphonate.* Tamás Kálai, Mostafa Isbera, Balázs Bognár, Cecília Sár, József Jekő, Kálmán Hideg. 23rd International Conference on Phosphorus Chemistry. Częstochowa, Poland. 5-9th July, 2021 (online).

V. *Syntheses of pyrazine, quinoxaline and imidazole fused pyrroline nitroxides.* Mostafa Isbera, Balázs Bognár, Gergely Gulyás-Fekete, Krisztina Kish, Tamás Kálai. A Magyar Szabadgyök-Kutató Társaság X. Kongresszusa. Szeged, Hungary. 29-30th August, 2019.