Phosphorus substituted hydroxylamine and hydroxamic acid derivatives: synthesis and reactivity

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Dedicated to Prof. Julio Alvarez-Builla on the occasion of his 65th anniversary

Abstract
This review summarizes several reports concerning the synthesis and synthetic applications of hydroxylamines derived from phosphines, phosphine oxides and phosphonates, and phosphorus substituted hydroxamic acid derivatives. The first section outlines the synthesis and reactivity of phosphorus *O*-substituted and *N*-substituted hydroxylamines as well as several transformations of phosphorus substituted hydroxylamines including: rearrangement, hydrolysis, reduction and oxidation reactions. The second part of the review covers the synthesis and reactivity of phosphorus *O*-, *N*-, and *C*-substituted hydroxamic acid derivatives.

Keywords: phosphorylated hydroxylamines, phosphorylated hydroxamic acids, rearrangement, hydrolysis, reduction, oxidation, *N*-alkylation, elimination, olefination, radical reaction, cyclization

Contents

1. Introduction

Hydroxylamines have been extensively reviewed[1] and compounds with N–O linkage in their structure have been found to be an important class of chemical species due to their biological activity. Hydroxylamine derivatives have also become important as intermediates for synthesizing complex nitrogen-containing compounds, especially natural products and their analogues.[2] Such derivatives are found among iron sequestering siderophores,[3] inhibitors of 5-lipoxygenase,[4] DXP reductoisomerase,[5] and metalloproteinase.[6]

    On the other hand, the chemistry of hydroxamic acids has also been reviewed.[1] In general, hydroxamic acid derivatives have attracted considerable interest because of their activity in inhibiting medically important enzymes such as metalloproteases[7] and lipoxygenases.[8] Phosphorus compounds have also shown to exhibit biological activity in various areas by virtue of their analogy to naturally occurring compounds. However, to date there are only a few reports in the literature on the combination of the phosphorylated[9-11] and hydroxylamine and/or hydroxamic functions in a molecule.

2. Phosphorus Substituted Hydroxylamine Derivatives

2.1 Synthesis of phosphorus substituted hydroxylamine derivatives

In this section we consider phosphorus functionalized hydroxylamines derived from phosphines, phosphine oxides, phosphonates, etc. We first focus on the synthesis of phosphorus *O*-substituted hydroxylamines **I** and phosphorus *N*-substituted hydroxylamines **II** (Figure 1), after which their reactivity will be discussed.

Figure 1

2.1.1 Phosphorus *O*-substituted hydroxylamines. Several strategies have been developed for the preparation of phosphorus *O*-substituted hydroxylamines, such as phosphorus-oxygen single bond formation either by reaction of hydroxylamines and phosphorylated halides (Scheme 1, Route a_1) or by reaction of nitroso or nitroxyl derivatives and phosphorus reagents (Scheme 1, Route a_2), and by oxidation reactions where a nitrogen–oxygen single bond is formed (Scheme 1, Route b).
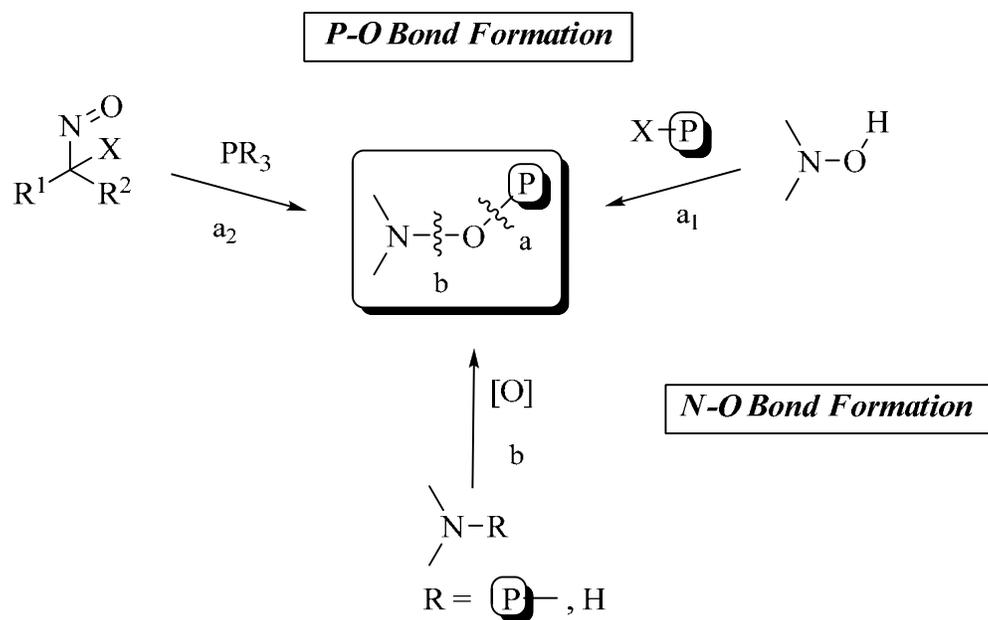
Scheme 1

2.1.1.1 Phosphorus−oxygen single bond formation reactions (Scheme 1a)

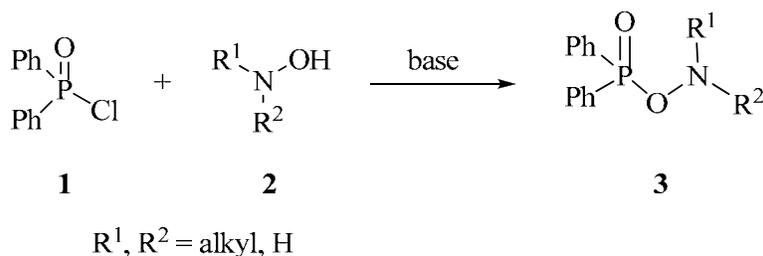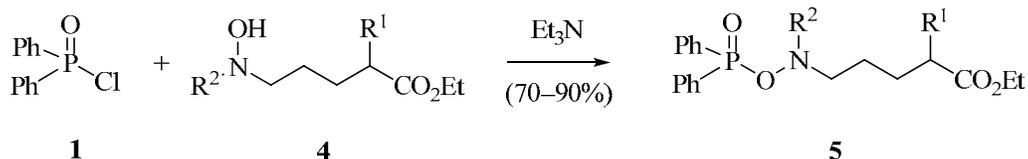### 2.1.1.1.1 Reaction of hydroxylamine derivatives with phosphorylated reagents (Scheme 1a₁).

N,N-Disubstituted and *N*-monosubstituted *O*-phosphinyl hydroxylamines **3** have been prepared by reaction of the corresponding hydroxylamines **2** and diphenylphosphinyl chloride **1** in the presence of a base (Scheme 2).[12,13]

$R^1, R^2 = alkyl, H$

Scheme 2

This process has been applied for the preparation of precursors of proline derivatives[14] involving the cyclization of 5-aminovaleric acid derivatives. The reaction of *N*-substituted hydroxylamines with 5-bromovalerate esters gave 5-(*N*-hydroxyamino) esters **4**, and the subsequent reaction with diphenylphosphinyl chloride **1** in the presence of triethylamine afforded hydroxylamine derivatives **5** in good yields (Scheme 3).[12e,13b]

Scheme 3

N-Vinylhydroxylamine **6** (X = CH₂) can be used as starting material for the preparation of phosphorus functionalized hydroxylamines, and, when it reacts with diethyl chlorophosphate **8**, *O*-phosphoryl hydroxylamine derivative **9** is obtained (Scheme 4). Similarly, the process is also extended to the preparation of the heterocyclic functionalized hydroxylamine compound **10** from pyrimidone derivative **7** (X = MeN).[15]

6 X = CH$_2$
7 X = MeN

9 X = CH$_2$
10 X = MeN
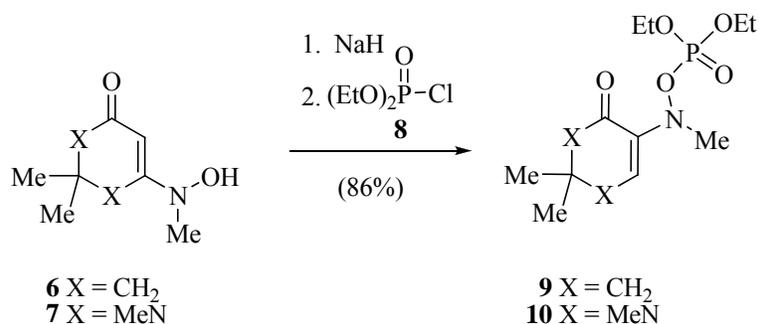
Scheme 4

Chiral aminating reagents **13** are prepared in a 'one-pot' process from ephedrine **11**, *N,N*-dimethylhydroxylamine and phosphorus oxychloride by means of nucleophilic substitution of **12** with *N,N*-dimethylhydroxylamine, with retention of configuration at the phosphorus atom (Scheme 5).[16] These compounds are used (see Section 2.2.1.4) for selective C–N bond construction.

11a   (−)-(*S,R*)-**12a**   (−)-(*S,S*)-**13a**

11b   (+)-(*S,S*)-**12b**   (+)-(*R,S*)-**13b**
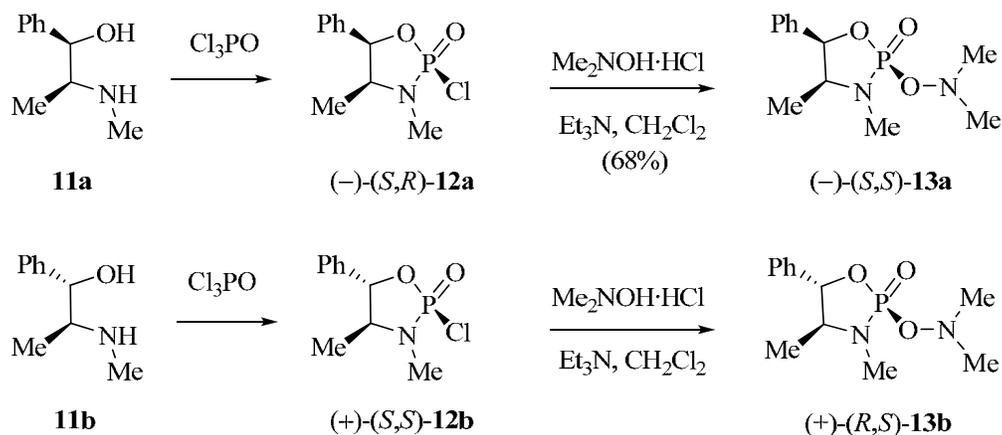
Scheme 5

Similarly, when optically active hydroxylamines **14** react with diethyl chlorophosphate **8** diethyl hydroxylamino phosphate derivatives **15** are obtained (Scheme 6).[17] By this methodology the stereochemistry of bis(*N*-phenylethyl)hydroxylamine derivatives **14** was determined.
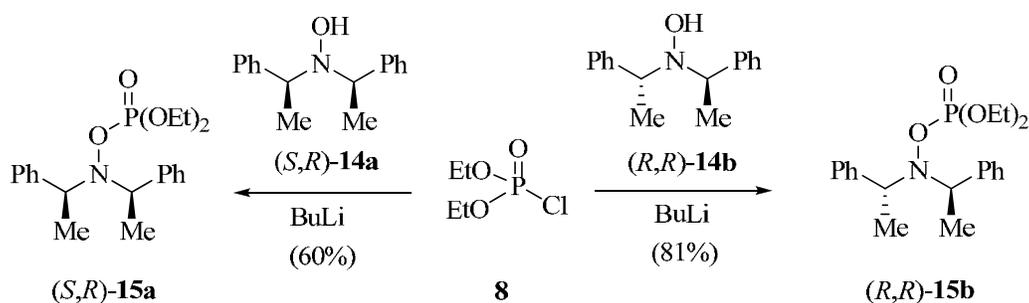
Scheme 6

Phosphorylating agents derived from 1-hydroxybenzotriazole **17** can readily be prepared by reaction with phosphorylated halides. In this way, phosphorus substituted benzotriazole derivatives **18** were prepared and subsequently used in the synthesis of activated nucleotides and their phosphorothioate and phosphorodithioate analogues (Scheme 7), useful intermediates in the preparation of *N*-methylphosphoramidates.[18]
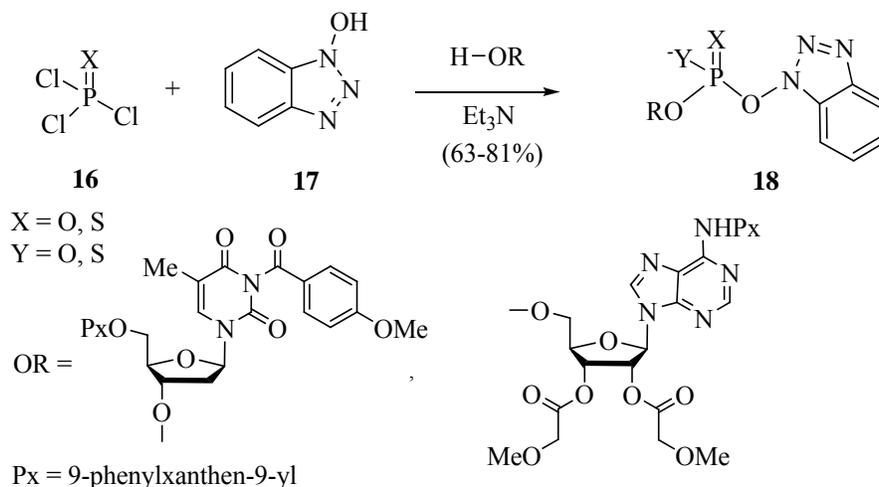

Scheme 7

Hydroxylamine can also react with phosphates, and therefore corresponding phosphorylated hydroxylamines are obtained. In this way, Nome *et al*. have reported the nucleophilic substitution reactions of methylated hydroxylamines with bis(2,4-dinitrophenyl)phosphate (BDNPP) **19**.[19] *N*-Mono- and *N,N*-dimethylation of hydroxylamine does not significantly affect rates of initial attack of MeNHOH and Me$_2$NOH on BDNPP, which is largely performed by oxygen phosphorylation (Scheme 8).

19
BDNPP

20 $R^1 = H$, $R^2 = Me$
21 $R^1 = R^2 = Me$
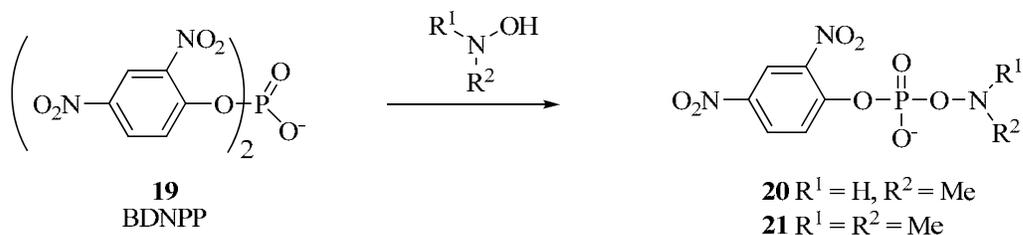
Scheme 8

2.1.1.1.2 Reaction of nitroso- and nitroxyl derivatives with phosphorus reagents (Scheme 1a$_2$). Reaction of trifluoronitrosomethane **22** with tris(trifluoromethyl)phosphine affords phosphine oxide derivative **24**,[20] whose formation is explained by an initial generation of bis(trifluoromethyl)nitroxybis(trifluoromethyl)phosphine **23**, followed by the addition of a second molecule of the nitroso compound **22** (Scheme 9).

22   **23**   **24**
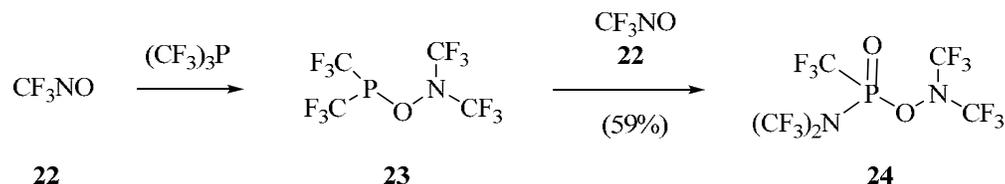
Scheme 9

Phosphine oxide **27** can be prepared by reaction of bis(trifluoromethyl)phosphinic chloride **25** with mercury (II) bis(trifluoromethyl)nitroxide **26** in excellent yield (Scheme 10).[20] Nitrosobis derivatives have also been employed in the synthesis of *O*-phosphoryl hydroxylamines.[21]

25   **26**   **27**
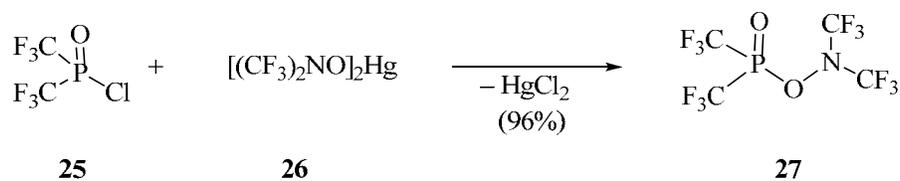
Scheme 10

Radical reactions of several phosphines with nitroxyl compounds have been studied (Scheme 11). Several *O*-phosphorus substituted compounds which contain the *N,N*-bis(trifluoromethyl)hydroxylamine moiety are prepared from phosphorus halides as PF$_3$, PBr$_3$

and PF$_2$Cl.[22] Moreover, reactions of bis(trifluoromethyl)nitroxide **28** with other phosphorus compounds are varied, and it has been reported to undergo addition-elimination reaction with phosphite (R = OMe)[22] and phosphoramide (R = NMe$_2$)[22] derivatives, affording phosphorus *O*-hydroxylamine derivatives **29**, and rather different kind of reactions with phosphine P(CF$_3$)$_3$ or halophosphines such as P(CF$_3$)$_2$X to yield compounds **23**, **30** in good to excellent yields.[23]
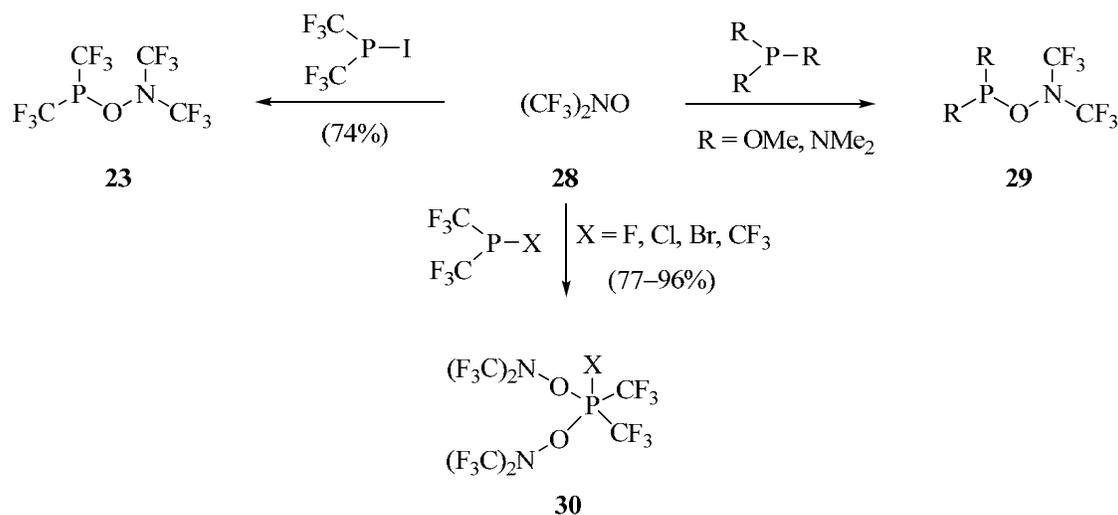
Scheme 11

2.1.1.2 Nitrogen–oxygen bond formation reactions (Scheme 1b). Oxidation of primary and secondary amines **32** with bis(diphenylphosphinyl)peroxide **31** conveniently leads to the *O*-phosphinylated hydroxylamine derivatives **3** (Scheme 12).[24] Since the peroxide **31** is easily accessible from the diphenylphosphinyl chloride and disodium peroxide, this is an appropriate method for the synthesis of *N,N*-disubstituted and *N*-monosubstituted *O*-phosphinyl hydroxylamines **3**.
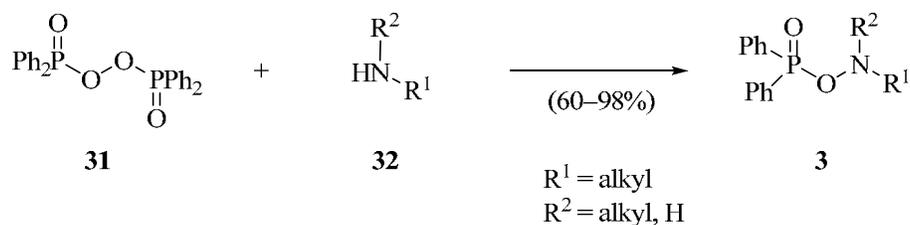
Scheme 12

When phosphoramides react with peracids phosphorus *O*-substituted hydroxylamines are obtained by a radical rearrangement reaction. Dimethyl phosphoramides **33** react with *m*-chloroperbenzoic acid (m-CPBA) to yield novel phosphorus *O*-substituted hydroxylamine derivatives **35** *via N*-oxidation to **34** followed by a radical rearrangement with *O*-insertion into the P–N bond (Scheme 13).[25]
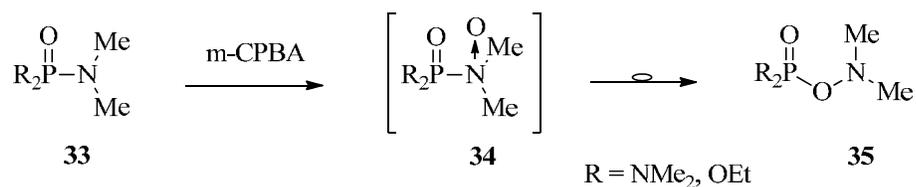
Scheme 13

Also cyclic phosphinamides react with m-CPBA, as observed for acyclic phosphoramidates.[25] The reaction of heterocyclic phosphorous derivative **36** with m-CPBA has been performed and the formation of compound **37** could be explained by the replacement of the *P*-amino by a *P-O*-amino group through an insertion of oxygen atom between the phosphorus and the nitrogen atoms of the precursor phosphinamide **36** (Scheme 14).[26]
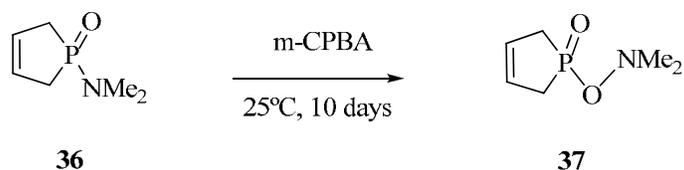
Scheme 14

Nitrogen-oxygen single bond formation reaction occurs also when tetraoxyspiro phosphoranes react with acetylene carboxylates.[27] The reaction mechanism could be explained by a rearrangement of oxazaspirophosphoranes **38**, **39** into the five-membered cycle **40**, and subsequent reaction with the acetylenic compound to give the major isomer **41a** (80%), which upon equilibration affords a mixture of isomers **41a/41b** (45/55%) (Scheme 15).
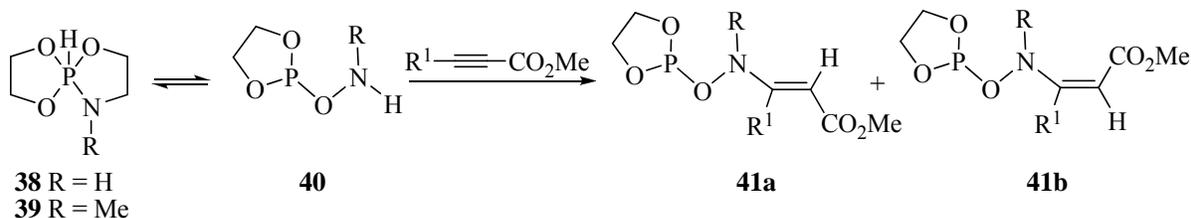
Scheme 15

2.1.2 Phosphorus *N*–substituted hydroxylamines. The synthesis of *N*-phosphorus substituted hydroxylamines can mainly be approached by two strategies: first, by phosphorus–nitrogen single bond formation reaction between hydroxylamine derivatives or nitroso compounds and phosphorus reagents (Scheme 16, Routes a$_1$ and a$_2$) or by rearrangement reactions (Scheme 16, Route a$_3$) and second, by carbon–nitrogen single bond formation reaction (Scheme 16, Route b).
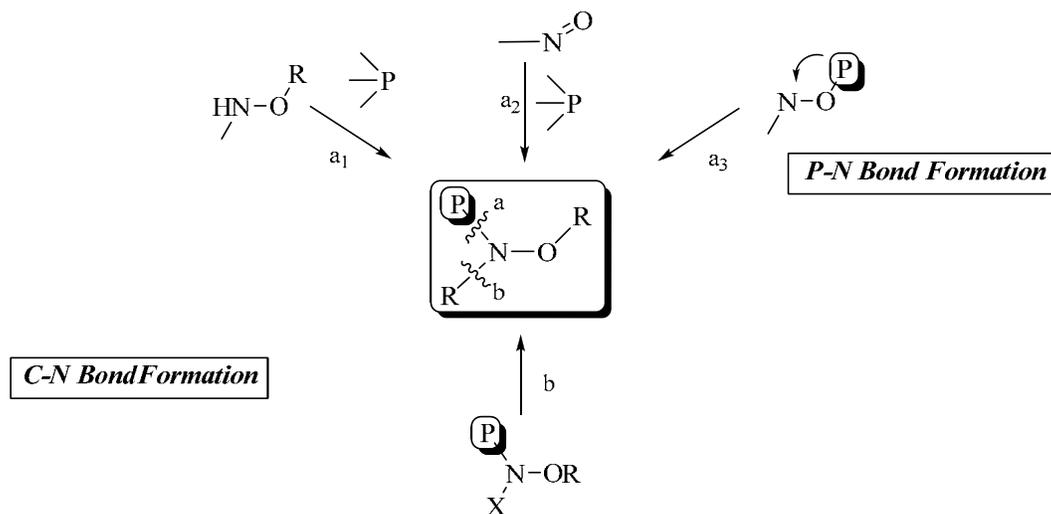
Scheme 16

2.1.2.1 Phosphorus–nitrogen single bond formation reactions (Scheme 16a)

2.1.2.1.1 Reaction of hydroxylamine derivatives with phosphorus reagents (Scheme 16a$_1$). *N*,*O*-Dimethylhydroxylamino halogenophosphines **43** have been prepared by hydroxylaminolysis reaction of halogenophosphines with *N*-methoxyhydroxylamino derivative **42** (Scheme 17).[28] It is noteworthy that a restricted P–N bond rotation of bis(*O*,*N*-dimethylhydroxylamino)halogenophosphines has been detected.[29]
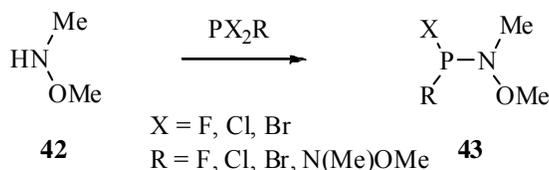
Scheme 17

Dialkyl *N*-alkoxyphosphoramidates **46** can be prepared according to the Atherton-Todd method. Diethyl *N*-methoxyphosphoramidate[30] **46** (R^1 = Et; R = Me) or diphenyl *N*-methoxyphosphoramidate[31] **46** (R^1 = Ph; R = Me) can be obtained from phosphite **44** and the

corresponding *O*-methylhydroxylamine (R = Me). However, due to the low yields obtained, a modified procedure, where the concentration of the base is increased and a catalytic amount of triethylbenzylammonium chloride (TEBAC) is used, was developed to afford the *N*-phosphorylated *O*-alkylhydroxylamines **46** (R = Me, Et, *n*-Bu, Bn, R^1 = Et) (Scheme 18) in good yields.[32]
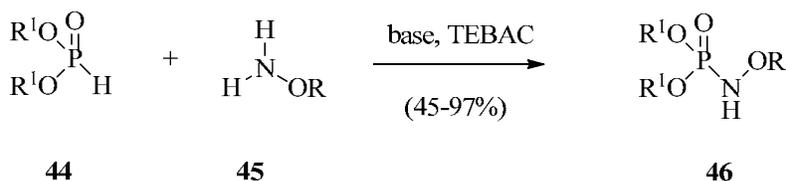
Scheme 18

Trialkyl phosphites could react with α-bromo ketones to give either Arbuzov (phosphonate formation) or Perkow pathway products (enol phosphate formation). Similarly, triethyl phosphite and 3-bromo-1,1,1-trifluoropropane-2-oxime **48** reacted in a Perkow type reaction with ene-oximophosphate formation to yield [*N*-hydroxy-*N*-(1-trifluoromethylethenyl)]amido diethylphosphate **49** (Scheme 19).[33]

Scheme 19

Hydroxylamine can also react with phosphates, and therefore the corresponding phosphorylated hydroxylamine are obtained. In this way, Nome *et al*. have reported the nucleophilic substitution reactions of methylated hydroxylamines with bis(2,4-dinitrophenyl)phosphate (BDNPP).[19] *O*-Methylation of hydroxylamine blocks the reaction and H$_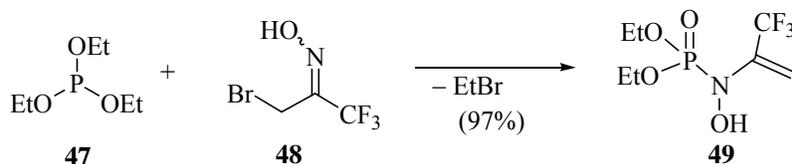2$NOMe then slowly reacts with BDNPP *via N*-attack at the phosphorus atom. This is the only example of nitrogen phosphorylation in solution reactions of hydroxylamines with BDNPP. The strong inhibition of the initial reactions by *O*-methylation when reacted with H$_2$NOMe confirms the original assumption that attack on phosphorus is preferentially by the OH group, although there is a slow reaction with H$_2$NOMe forming the *N*-phosphorylated derivative **50** (Scheme 20).

19
BDNPP

50
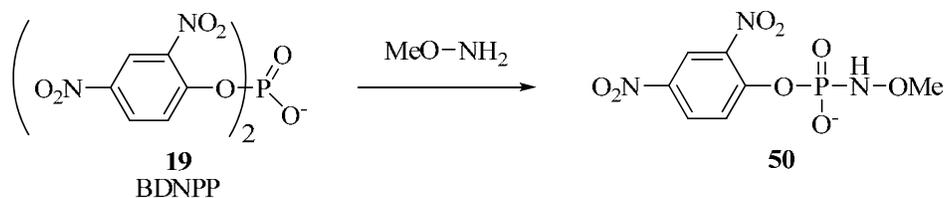
Scheme 20

2.1.2.1.2 Reaction of nitroso compounds with phosphorus reagents (Scheme 16a$_2$). Trifluoronitrosomethane **22** reacts with bis(trifluoromethyl)phosphine **51** to give the phosphoryl-substituted hydroxylamine **53**, *via* a *N*-phosphino hydroxylamine intermediate **52** (Scheme 21).[20]

51   **22**   **52**   **53**
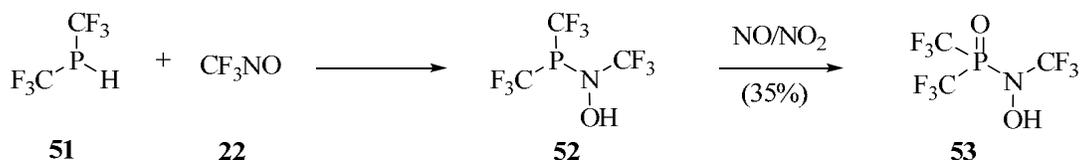
Scheme 21

Addition of *O*-silylated phosphites **54** to 2-methyl-2-nitrosopropane **55** (R^1 = *t*-Bu) or nitrosobenzene **55** (R^1 = Ph) furnished *N*-(trimethylsilyloxy)amidophosphates **57**, *via* 1,4-trimethylsilyl group shift in intermediate **56** (Scheme 22).[33b] Trifluoronitrosomethane **55** (R^1 = CF$_3$) reacts with different phosphines, among them (EtO)$_2$POSiMe$_3$ or (Me$_3$SiO)$_3$P to give the corresponding phosphinylhydroxylamine derivatives **57**.[20]

54   **55**   **57**

R^1 = *t*-Bu, Ph, CF$_3$
R^2 = Me, Et, SiMe$_3$
R^{2}R^2 = CH$_2$CH$_2$, CMe$_2$CMe$_2$

56
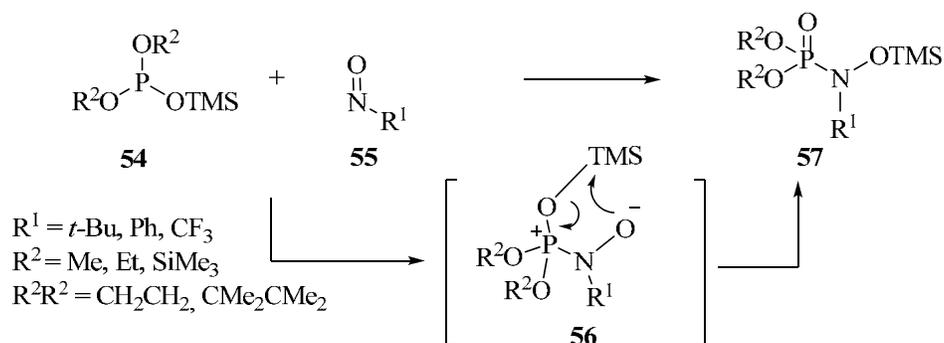
Scheme 22

2.1.2.1.3 Rearrangement reactions (Scheme 16a$_3$). *N*-Alkyl-*O*-(diphenylphosphinyl) hydroxylamines **58**, whose preparation has been outlined previously (see Section 2.1.1.1.1),

rearrange on heating, to the thermodynamically more stable *N*-phosphinylated derivatives, the *N*-alkyl-*N*-(diphenylphosphinyl)hydroxylamines **59** (Scheme 23) (see Section 2.2.1.1).[34]

R = Et, *n*-Pr, *n*-Bu, *t*-Bu, *n*-Pr$_2$CH
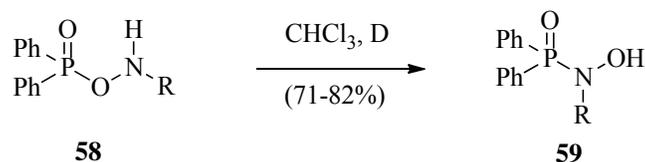
Scheme 23

2.1.2.2 Carbon−nitrogen single bond formation reactions (Scheme 16b). Easily available *N*-(diethoxyphosphoryl)benzyloxylamine **60** was shown to be a convenient protected substrate for regioselective *N*-alkylation by means of diverse halides under basic conditions (sodium hydride/tetrabutylammonium bromide (TBAB)).[35] The phosphorylated compound **60** was prepared according to the literature procedure from *N*-benzylhydroxylamine hydrochloride and diethyl phosphonate.[32] *N*-Alkylation to **61** is performed using different bases for metallation, and the best yield is obtained at room temperature when sodium hydride and catalytic amounts of TBAB are used (Scheme 24).

R = Me, *i*-Pr, *i*-Bu, Allyl, (CH$_2$)$_3$Br, (CH$_2$)$_4$Br, Bn, Bu,
    (CH$_2$)$_3$N(OBn)P(O)(OEt)$_2$, (CH$_2$)$_3$P(O)(OEt)$_2$
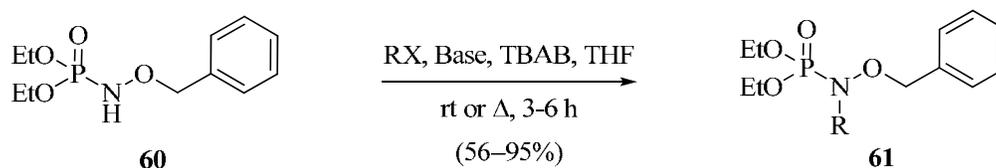
Scheme 24

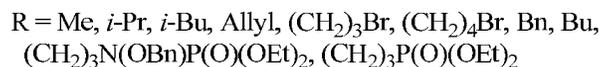Dialkyl *N*-alkoxyphosphoramidates **62** are good starting materials for the synthesis of halophosphoramides **63**, which can serve as reagents for the regiospecific functionalization of terminal C–C double bonds.[32] The method of synthesis of halophosphoramides consists of the chlorination of diethyl *N*-alkoxyphosphoramidates **62** by means of gaseous chlorine at room temperature in an aqueous buffered solution containing acetic acid and sodium acetate (Scheme 25). The compounds **62** are much more reactive towards 1-alkenes than diethyl *N,N*-dichlorophosphoramidate, undergoing addition reaction to afford two regioisomers **64a** and **64b** in a 3:1 ratio, the *anti*-Markovnikoff adduct **64a** being the main component of the mixture, apparently formed by a free-radical reaction.
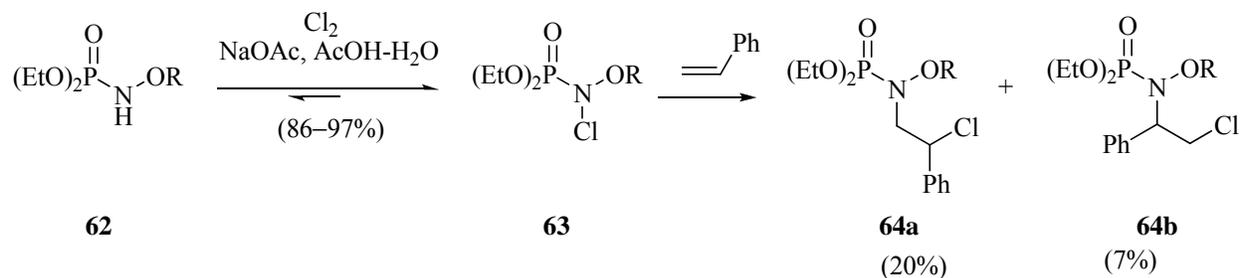
Scheme 25

2.2 Reactivity of phosphorus substituted hydroxylamine derivatives

2.2.1 Phosphorus *O*-substituted hydroxylamines

2.2.1.1 Rearrangement reactions. *N*-Alkyl-*O*-(diphenylphosphinyl)hydroxylamines rearrange on heating to the thermodynamically more stable *N*-phosphinylated derivatives and have been used for the preparation of *N*-alkyl-*N*-(diphenylphosphinyl)hydroxylamines (see Section 2.1.2.1.3).[34] When bis-*N*-(trifluoromethyl)nitroxybis(trifluoromethyl)phosphine **23**, obtained by reaction of trifluoronitrosomethane **22** with tris(trifluoromethyl)phosphine (see Section 2.1.1.1.2), is heated at 100 °C it undergoes isomerization to give the corresponding phosphine oxide **65** (Scheme 26).[20]
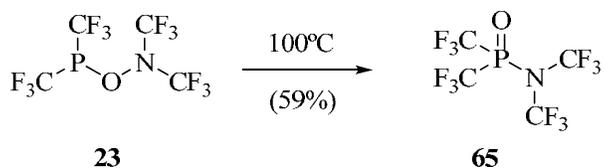
Scheme 26

Cleavage of the N–O bond has been reported by thermal treatment of *O*-phosphoryl hydroxylamines **9** (X = CH$_2$) or **10** (X = MeN) obtained by reactions between enehydroxylamines and diethyl chlorophosphate (see Section 2.1.1.1.1). Subsequent rearrangement affords functionalized enaminone **66** or 1,2-dihydropyrimidin-4-one **67**, respectively (Scheme 27).[15]

9 X = CH$_2$
10 X = MeN

66 X = CH$_2$
67 X = MeN
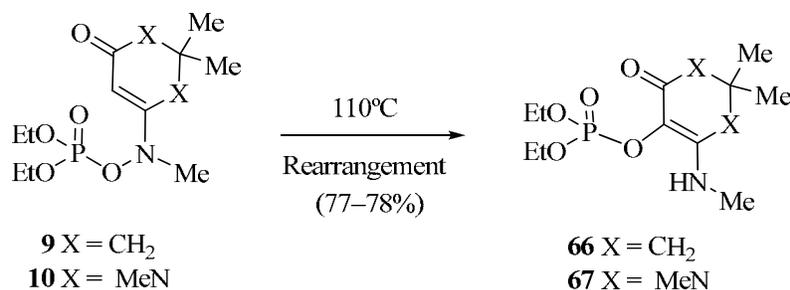
Scheme 27

However, when *N,N*-dibenzyl-*O*-(diphenylphosphinyl)hydroxylamine **68** is heated, imine **71** and diphenylphosphinic acid **70** are obtained (Scheme 28).[24,36] This mode of elimination may be rationalized by a cyclic transition state **69** involving the phosphinyl group. Thermal oxidative deamination of amines is achieved by reaction with bis(diphenylphosphinyl)peroxide (see Section 2.1.1.2) without isolation of the intermediate *N,N*-disubstituted-*O*-(diphenylphosphinyl)hydroxylamines **69**, which upon heating gives regioselectively the unstable imines **71**, isolated as benzaldehyde.
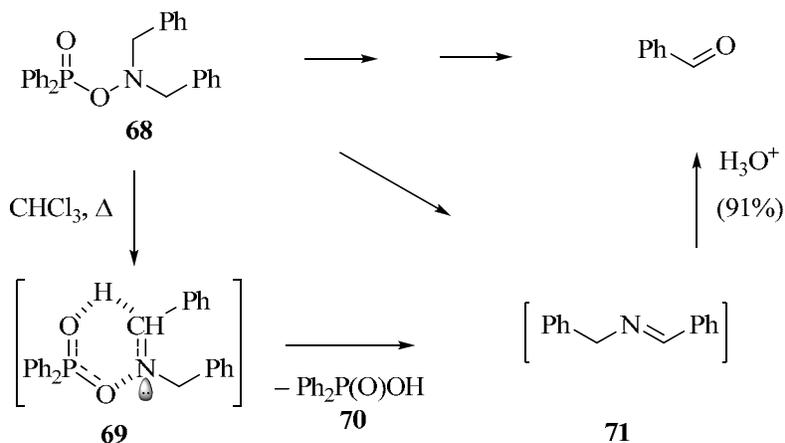
Scheme 28

2.2.1.2 Hydrolysis reactions. Acidic hydrolysis of *N*-alkyl- (R^2 = H) or *N,N*-dialkyl *O*-(diphenylphosphinyl)hydroxylamines **3** can afford hydroxylamines **2** in good yields by means of P–O bond cleavage (Scheme 29).[12a,b,g] Similarly, *N,N*-bis(trifluoromethyl)hydroxylamine **2** (R^1 = R^2 = CF$_3$) is obtained by the hydrolysis of *N,N,P,P*-tetrakis(trifluoromethyl)-*O*-phosphinylhydroxylamine[20] in the presence of hydrochloric acid.
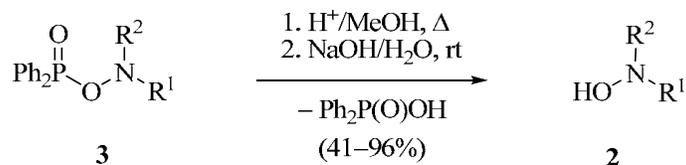
Scheme 29

Compound EM2487 **72**, a product isolated from *Streptomyces* sp. Mer-2487, has an inhibitory effect on HIV-1 replication in chronically infected cells as well as acutely infected cells.[37] EM2487 is a new class of secondary metabolites of microbial origin whose structure is completely different from that of known nucleoside antibiotics. In order to elucidate the unique structure of the title compound, hydrolysis reactions were performed. Fragments **73–77** support the presence of *O*-phosphorus substituted hydroxylamine moiety in the structure of compound EM2487 (Scheme 30).
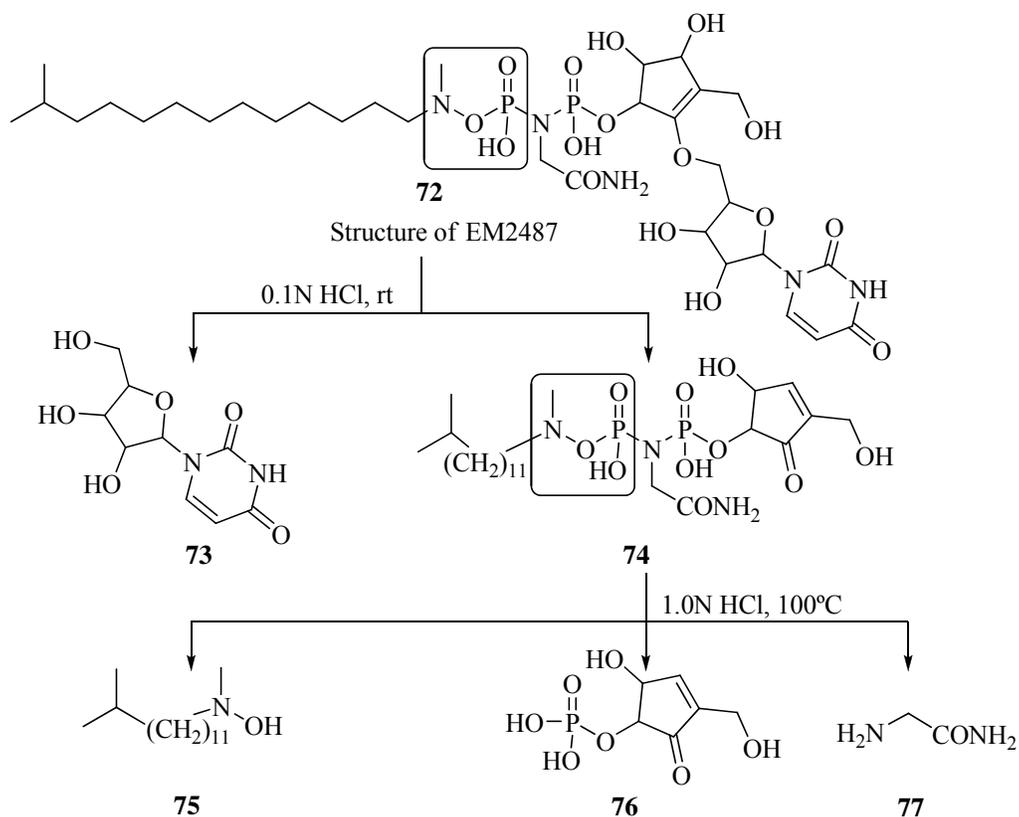
Scheme 30

On the other hand, the [P(O)-O-N] functionality has been rarely found in dinucleotides.[38] However, a protected-*O*-phosphorylhydroxylamine moiety occurs in the stable hapten **79**. Its

preparation has been reported by deprotection of the cyanoethyl group of **78** (Et$_3$N in pyridine) followed by removal of the two allyl-based protecting groups [Pd(PPh$_3$)$_4$, PPh$_3$, n-BuNH$_2$, and HCO$_2$H in CH$_2$Cl$_2$] to give the hapten **79** as the n-butylammonium salt (Scheme 31). The order of these deprotection steps is very important since an initial cleavage of the allyl groups from **78** could give an unidentified mixture of compounds.
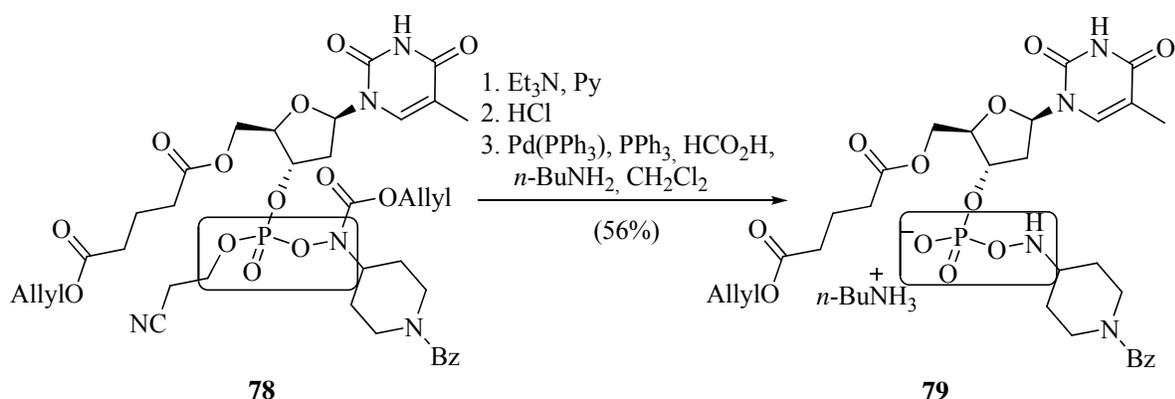
Scheme 31

2.2.1.3 Reduction reactions. Amino diethyl phosphate derivatives of *N*-phenylethylhydroxylamines were prepared (see Section 2.1.1.1.1) in order to determine the stereochemistry of precursors *N*-phenylethylhydroxylamines. For this purpose, lithium-ammonia reduction of diethyl phosphate derived hydroxylamines **15a,b** towards *N,N*-bis(α-phenylethyl)amines **80a,b** has been accomplished and the stereochemistry of obtained compounds **80a,b** determined (Scheme 32).[17]
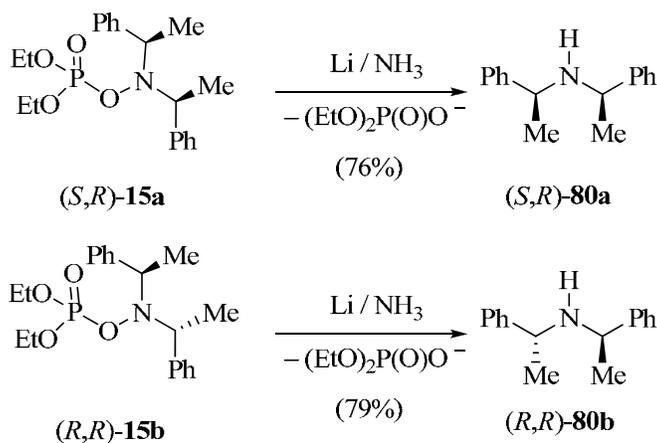
Scheme 32

2.2.1.4 Electrophilic amination. *O*-Phosphorus substituted hydroxylamines **82** have been often used as aminating reagents[39] in an electrophilic amination. In this process, reaction between organometallic compounds **81** ($R^1 = R_3C$, R_2N) and *O*-phosphorus substituted hydroxylamines **82** proceeds through carbon–nitrogen or nitrogen–nitrogen bond formation, affording the corresponding amines or hydrazines (Scheme 33).
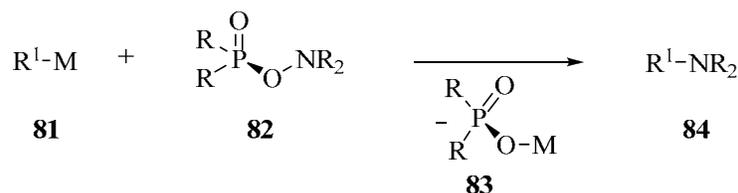
Scheme 33

When Grignard reagents derived from phenylacetylene are used with *O*-phosphinylated aminating reagents the corresponding ethinylamino (ynamine) derivatives are obtained through carbon–nitrogen bond formation reaction.[12c] Likewise, the *O*-(trimethylsilyl)aldehyde cyanohydrin anions **87** react with *O*-phosphinylated aminating reagents **88** to give amines **89**. This electrophilic amination corresponds to a mild and specific oxidation of the aldehydes **85** to the amides **90** *via* **86**–**89** (Scheme 34), which proceeds in basic medium.[12b]
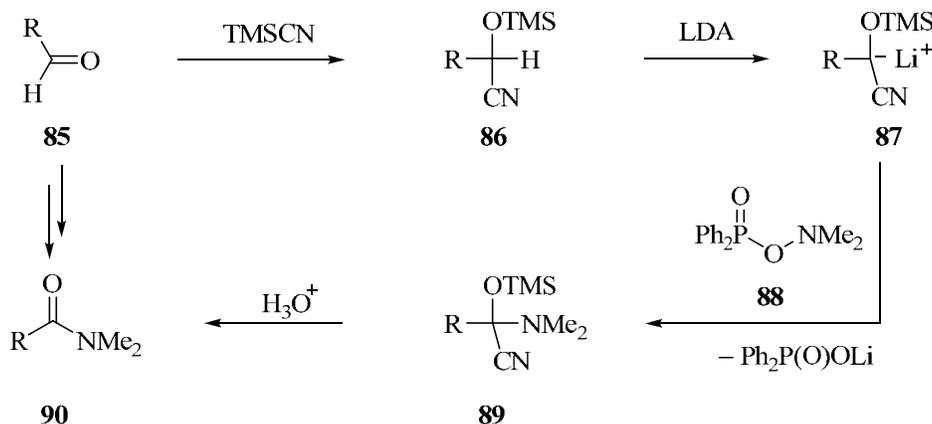
Scheme 34

By intramolecular nucleophilic substitution on the nitrogen atom, proline derivatives were prepared.[14] In this case, 5-aminovaleric acid derivatives with diphenylphosphinyloxy leaving group[12e,13b] (see Section 2.1.1.1.1) cyclizes in the presence of a base and pyrrolidines **91** are formed (Scheme 35).

Scheme 35

O-Di(*p*-methoxyphenylphosphinyl)hydroxylamine **93** reacts efficiently with stabilized sodium or potassium enolates derived from malonates, phenylacetates and phenylacetonitriles **92** and it is sufficiently soluble for its use in solution at −78 °C (Scheme 36).[40] As the pK_a of the substrate increases, amination yields to **94** decreases. Aminations using these reagents **93** are improved with respect to those using (diphenylphosphinyl)hydroxylamine **93** (Ar = Ph).[12e,13b]

Scheme 36

Boche *et al*. established that nucleophilic substitution occurs at the nitrogen of the *O*-(*N,N*-dimethylamino)diarylphosphinyl derivative **95**.[12b,16,24] Compound **95** converts into **96** on treatment with LDA followed by reaction with water, acidification and treatment with diazomethane (Scheme 37).

Scheme 37

Transfer of nitrogen from oxygen to carbanions could take place within large endocyclic rings.[41] In order to distinguish between the intermolecular and intramolecular pathways, the conversion of **97** to **99** *via* carbanion **98** is studied.[13] The results obtained show that the reaction proceeds *via* a trigonal bipyramidal transition structure and that a large bond angle is required for nucleophilic displacement at nitrogen. When a ring is of sufficient size to allow both the entering and leaving groups to be simultaneously apical in a trigonal bipyramidal transition structure, an intramolecular endocyclic reaction would be expected. This study has been carried out in a prospective 16-membered ring (Scheme 38).
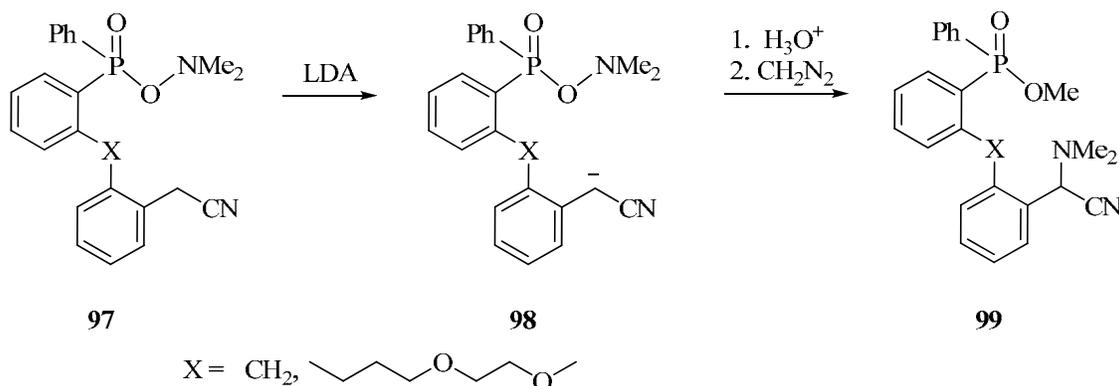
Scheme 38

The chiral aminating reagents (−)-**13a** and (+)-**13b** have been prepared in a 'one-pot' reaction from (−)-ephedrine and (+)-ephedrine[16] (see Section 2.1.1.1.1). These compounds react with carbon nucleophiles **100** to yield **101** and the optically active amines **102** with moderate conversion and up to 44% ee (Scheme 39).
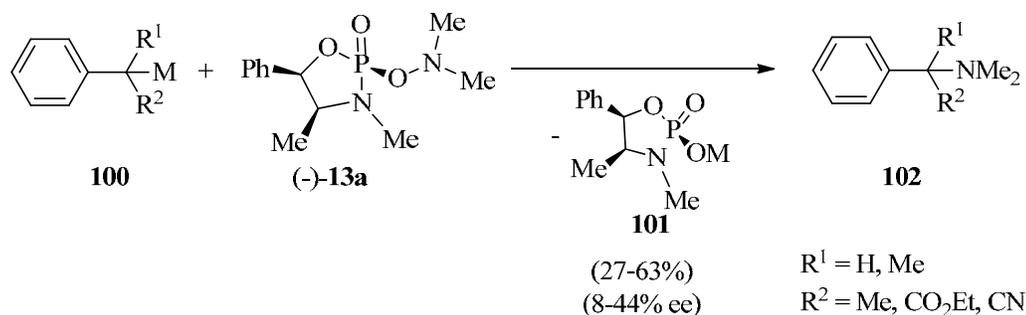
Scheme 39

Nitrogen–nitrogen bond formation can be performed by electrophilic aminating reagents as O-(diphenylphosphinyl)hydroxylamines.[42]   The   reactions   of   the O-(diphenylphosphinyl)hydroxylamines **103** with the amines **104** lead to the hydrazines **105** *via* electrophilic amination, and to the symmetrical azo compounds **107**.[43] The behaviour of the acceptor substituted O-(diphenylphosphinyl)hydroxylamines **103** towards N-methylaniline ($R^1 = R^2 = n$-Pr), morpholine ($R^1R^2 = CH_2CH_2OCH_2CH_2$) and di-$n$-propyl amine ($R^1 = Me, R^2 = Ph$) has been studied. It can be concluded that, the acceptor qualities of substituents increase in the order COMe < CN < SO$_2$Me < NO$_2$ (Scheme 40). On the other hand, it was seen that there is a competition between the nucleophilic attack of the amines **104** on the electrophilic nitrogen atoms of **103** to give hydrazines **105**, and a reaction starting with deprotonation which leads to symmetrical azo compounds **107** through the corresponding ammonium salts **106**.
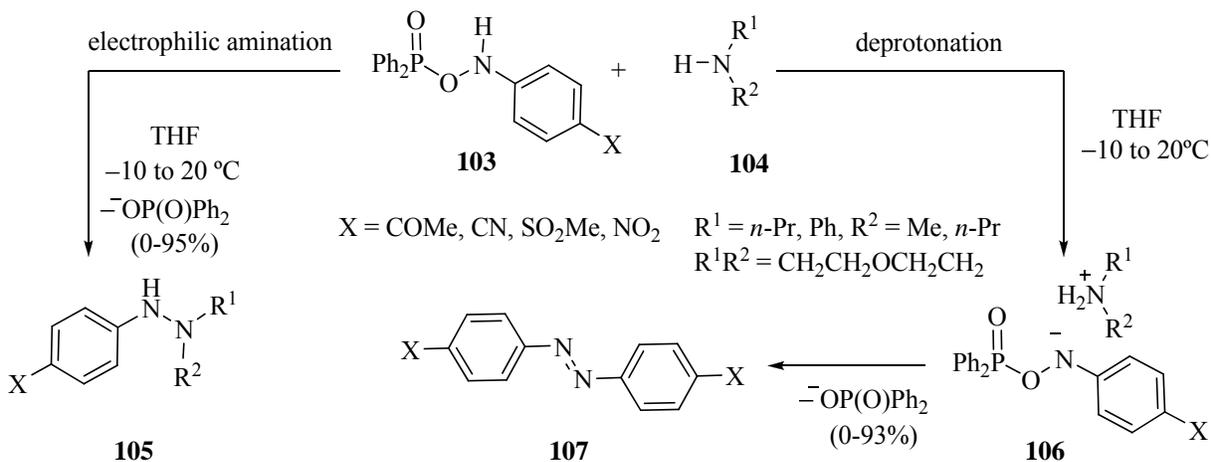
Scheme 40

2.2.1.5 Oxidation reactions. Derivatives **35** under oxidative conditions afford the corresponding phosphinic acid derivatives **110**, *via* N-oxide intermediate **109**, or the corresponding phosphinic

anhydride **111** by reaction of the *N*-methylhydroxylamine derivative **108** with the aromatic carboxylic acid (Scheme 41).[25]
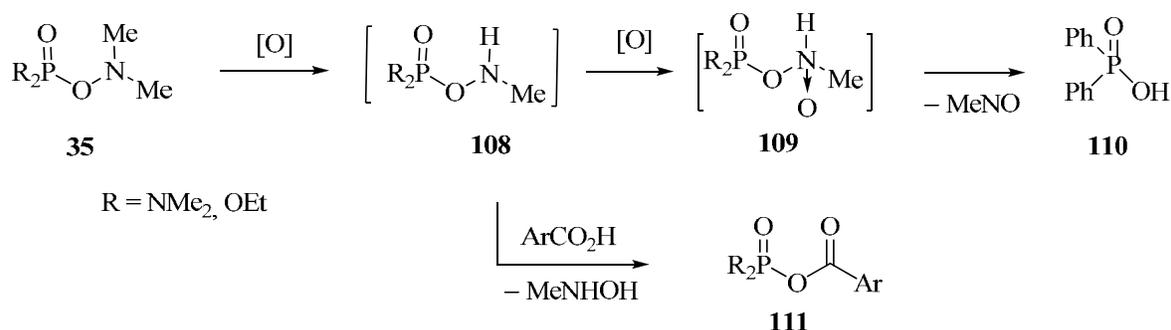
Scheme 41

2.2.2 Phosphorus *N*-substituted hydroxylamines

2.2.2.1 Rearrangement reactions. Among studies of amine oxidation with bis(diphenylphosphinyl)peroxide, a general method for the preparation and isolation of *N*-alkyl-*N*-(diphenylphosphinyl)hydroxylamines **112** (R = *n*-Bu) or *N*-alkyl-*O*-(diphenylphosphinyl)hydroxylamine **115** through intermediates **113** and **114** has been reported (see Section 2.1.2.1.3).[34] In methanolic solution, **115** reacts with sodium methoxide at room temperature to give nearly equal amounts of diphenylphosphinic acid derivative **116** and methyl diphenylphosphinate **118** together with imine **117** and hydroxylamine **119**, by competing attack of methoxide at the O-NH moiety or at the phosphorus atom of **115**, respectively (Scheme 42). Similar rearrangements have been reported previously (R = H).[44]
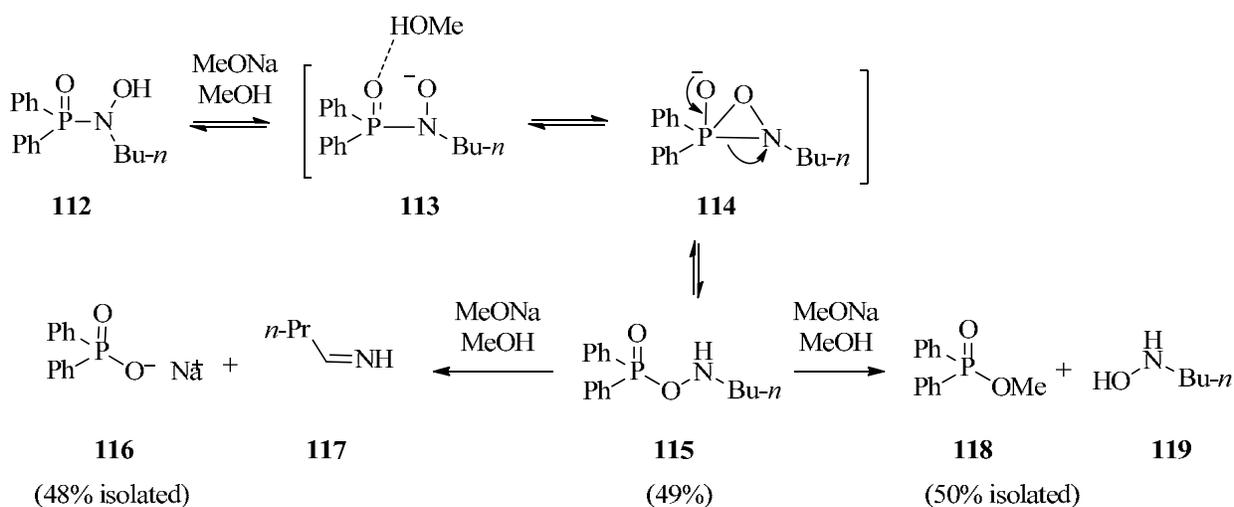
Scheme 42

2.2.2.2 Hydrolysis reactions. Taking into account the lability of the P–N bond, dephosphorylation of *N*-substituted-*O*-benzylhydroxylamines **61** (see Section 2.1.2.2) has been carried out by treatment with 4M HCl in ethanol at reflux, and the corresponding dephosphorylated compounds **120** were obtained as crystalline hydrochlorides, as oxalate hemiacetals or as free amines (Scheme 43).[35] Therefore, phosphoryl groups can be regarded as convenient protecting groups for hydroxylamines.

R = Me, *i*-Pr, *i*-Bu, Allyl, $(CH_2)_3Br$, $(CH_2)_4Br$, Bn, Bu,
$(CH_2)_3N(OBn)P(O)(OEt)_2$, $(CH_2)_3P(O)(OEt)_2$
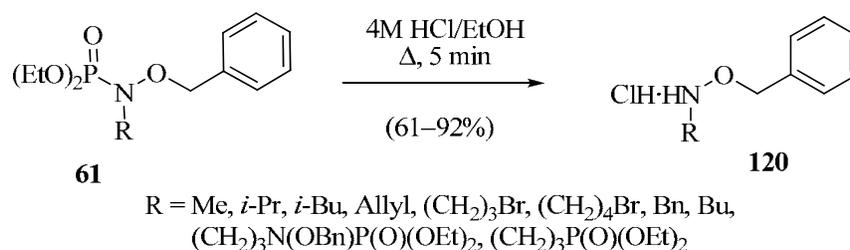
Scheme 43

2.2.2.3 *N*-Alkylation reactions. *N*-Phosphorylated *O*-alkylhydroxylamines are good starting materials for the synthesis of halophosphoramides, which can serve as reagents for the regiospecific functionalization of terminal C–C double bonds,[32] as has been reported by the reaction of diethyl *N*-alkoxyphosphoramidates with alkenes (see Section 2.1.2.2).

2.2.2.4 Oxidation reactions. Trifluoronitrosomethane **22** reacts with bis(trifluoromethyl) phosphine **51** to give the phosphinyl substituted hydroxylamine, **52**[45] probably *via* a *N*-phosphino-hydroxylamine followed by oxidation (see Section 2.1.2.1.2, Scheme 21).[20] Similarly, previous reactions with diethyl phosphite affording hydroxamic acid derivatives have been reported.[46]

2.2.2.5 Elimination reactions. [*N*-Hydroxy-*N*-(1-trifluoromethylethenyl)]amido diethylphosphate **49** is obtained by reaction of triethyl phosphite and 3-bromo-1,1,1-trifluoropropane-2-oxime **48** (see Section 2.1.2.1.1). Compound **49** adds water in a Markovnikov manner across the C–C double bond to form [*N*-hydroxy-*N*-(1-trifluoromethyl-1-hydroxyethyl)]amido diethyl phosphate **121**.[33] Subsequently, water may be abstracted using dicyclohexylcarbodiimide (DCC) to give the corresponding *N*-phosphorylated 3-methyl-3-trifluomethyloxaziridine **122** (Scheme 44).
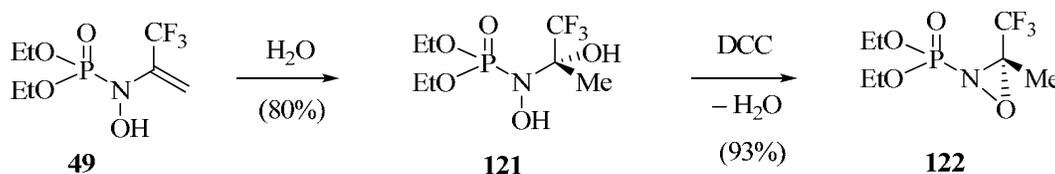
Scheme 44

Addition of nitrosoalkanes to *O*-silylated phosphites furnished colourless *N*-trimethylsiloxyamidophosphates (see Section 2.1.2.1.2).[33b] *N*-Phosphorylated-*O*-silylhydroxylamines **123**, prepared by addition of nitrosotrifluoromethane to *O*-silylated phosphites, such as $(EtO)_2POSiMe_3$, or to phosphines, as $(Me_3SiO)_3P$, lead to the formation of *N*-phosphorus substituted imines **124** by fluorine elimination (Scheme 45).
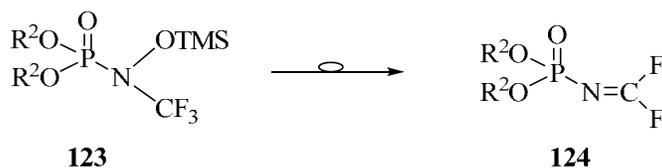
Scheme 45

3. Synthesis and Reactivity of Phosphorus Substituted Hydroxamic Acid Derivatives

Few reports have been found in the literature mentioning the combination of the phosphonic and hydroxamic functions in one molecule. We illustrate here several aspects of the synthesis and the reactivity of phosphorus *O*-substituted (**III**) and *N*-substituted (**IV**) hydroxamic acid derivatives. The phosphorus *C*-substituted derivatives (**V**) are also included due to their structural similarity (Figure 2).
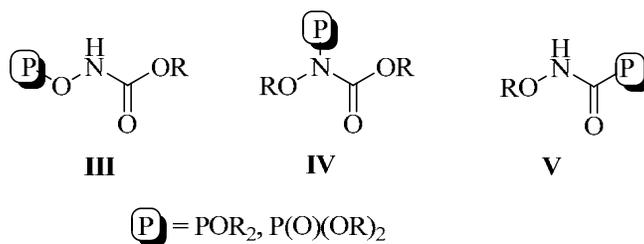
Figure 2

3.1 Phosphorus *O*-substituted hydroxamic acid derivatives
The most common approaches to synthesize phosphorus substituted hydroxamic acids comprise the phosphorus−oxygen single bond formation between the corresponding hydroxamic acid derivatives and phosphorylated halides.

O-Phosphoryl hydroxamates can be prepared by P−O bond formation reaction between the corresponding hydroxamic acid derivatives and phosphorylated halides. The synthesis of intermediate *O*-phosphodichloridate **126** is performed *in situ* from *N*-hydroxyurethane **125** and

phosphorus oxychloride (Scheme 46).[47] *O*-Phosphodichloridate **126** is an appropriate substrate for the synthesis of bis(aziridinyl)phosphinyl-*N*-hydroxyurethane derivatives **127**, useful as antineoplastic agents.
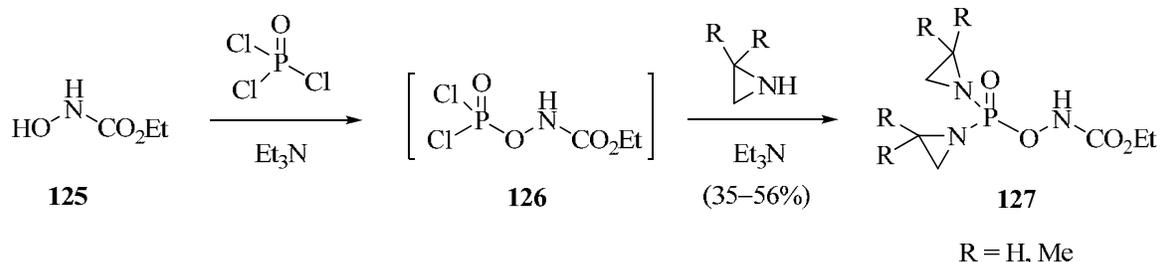
Scheme 46

Phosphorus substituted compounds derived from hydroxamic acid are prepared by dropwise addition of diphenylphosphinyl chloride **1** to stoichiometric amounts of the hydroxamic acid **128** and triethylamine (Scheme 47).[48] Some *O*-diphenylphosphinyl derivatives **129** (R = Ph, Bn) have been tested as potential inhibitors of neuropathy target esterase, although little activity of these compounds is observed against studied targets. *O*-(Diphenylphosphinyl)hydroxamate **129** (R = *t*-Bu), whose X-ray structure has been reported,[49] can be applied as electrophilic aminating agent,[34,50-52] or in Schmidt reactions.[43]

Scheme 47

The reaction between *N*-methylbenzohydroxamic acid and various chlorides of tervalent phosphorous has been studied.[53] *N*-Methyl-*p*-(methylphenyl)hydroxamic acid **130** reacts rapidly with phosphorus compounds XYPCl **131** (X = Ph, Y = OEt and XY = OCH₂CH₂O) in the presence of pyridine to give 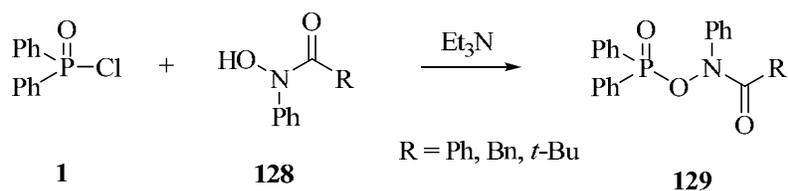P(III) intermediates **132** (Scheme 48). They decompose at room temperature with homolysis of the N–O bond to give isomeric *N*-phosphine oxides **134**, accompanied by varying amounts of *O*-hydroxamic acids **135**, *N*-methyl-4-methylbenzamide **133**, and phosphoryl-radical related products. The origin of *O*-phosphinylhydroxamic acids **135** is not known, but presumably involves the combination of phosphinyl and acylnitroxyl radicals.

Compounds **137** are also synthesized by treatment of hydroxamic acid **130** with the appropriate chlorophosphine oxide **136** in the presence of one equivalent of base (Scheme 48).

133 R = H
134 R = P(O)XY
135 R = OP(O)XY

X = Ph, Y = OEt
XY = OCH$_2$CH$_2$O
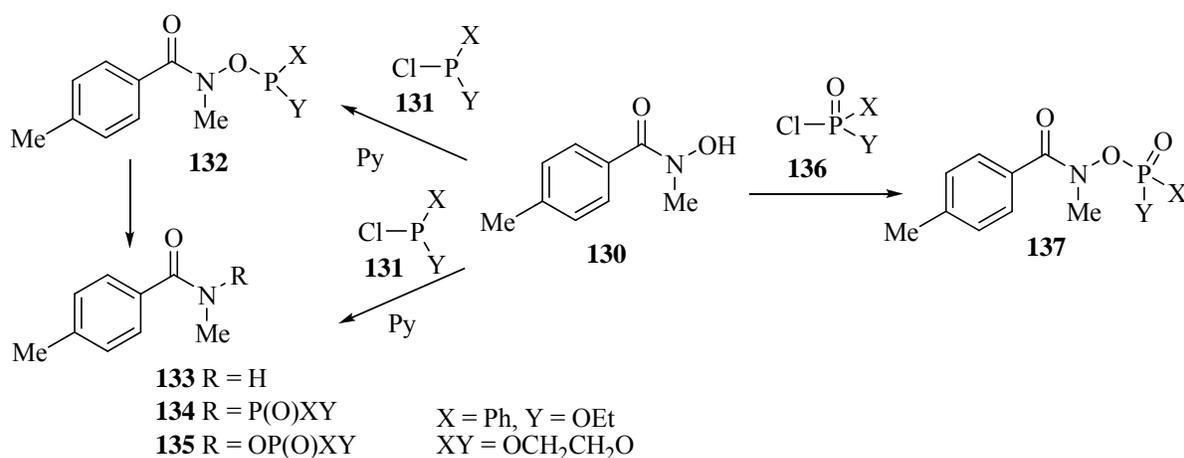
Scheme 48

The synthesis of a new class of aryl adenylate analogs with potent inhibitory activity against enterobactin biosynthesis enzyme (EntE), an enzyme that catalyzes the synthesis of 2,3-dihydrobenzoyl adenylate (DHB-AMP) during the early stages of enterobactin biosynthesis, has been reported.[54] The authors design a stable mimic of DBH-AMP as a potential inhibitor, which contains an *N*-acyl hydroxamoylphosphate group in place of the labile carboxylic-phosphoric anhydride linkage. Compounds **140** are obtained by combining hydroxamic acids **138** with imidazole-activated adenosine 5'-phosphate (AMP-Im) **139** (Scheme 49).

138   139   140

A =

R = 2,3-(HO)$_2$C$_6$H$_3$, *o*-HOC$_6$H$_4$, Ph, Me
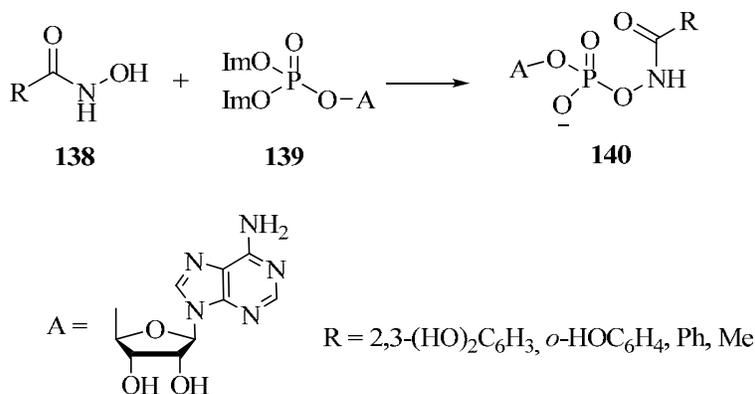
Scheme 49

O-Phosphorus substituted hydroxamates can also be prepared by P−O bond formation reaction between the corresponding hydroxamic acid derivatives and phosphorus derivatives as phosphonates or phosphinothioyloxy disulfanes. Direct thionation of hydroxamic acids with Lawesson´s reagent (LR) **142** can be very useful in the synthesis of thio analogues of natural

hydroxamates and *N*-hydroxythiopeptides.[55,56] Treatment of hydroxamic acids with LR gives a mixture of different phosphorus-containing products, such as *O*-thiophosphonylated **146** (R = H), pyrothiophosphonate **145** (R = H), and (4-methoxyphenyl)phosphothioic acid **144** (R = H, Scheme 50). The formation of these compounds **144–146** is explained by the electrophilic attack of metadithiophosphonate **142** (AnPSS) on the oxygen atom of the hydroxy group in the hydroxamic acid **141** to give the primary intermediate *O*-dithiophosphonylated hydroxamic thioacid **143** (detected by ^{31}P NMR). To confirm the formation of compound **146** the reaction mixture is treated with TBDMSCl in the presence of triethylamine, or with diazomethane or methyl iodide in the presence of triethylamine, and compound **146** is transformed *in situ* to a mixture of *O*- and *S*-methyl esters.[55]

An = *p*-MeOC$_6$H$_4$
Ar = *p*-NO$_2$C$_6$H$_4$, Ph
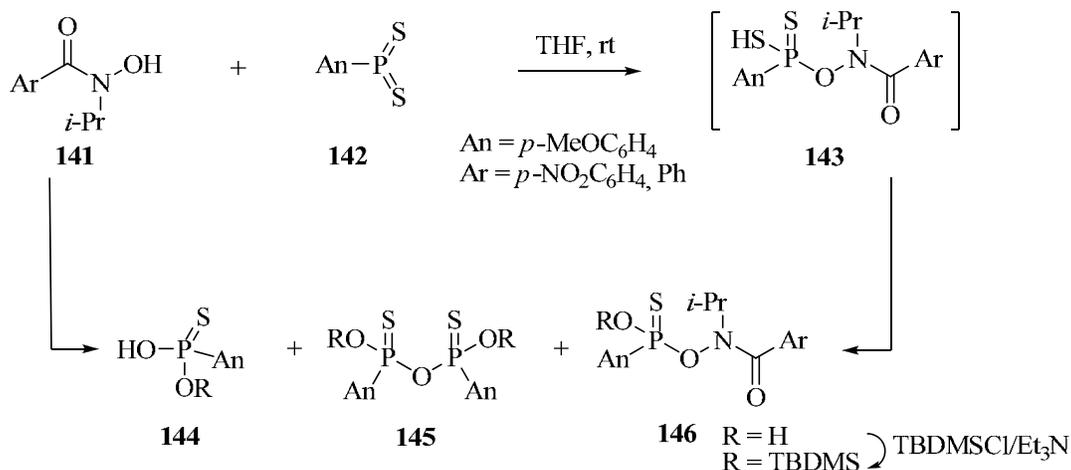
Scheme 50

Reaction of various disulfanes **147** with *N*-alkylbenzohydroxamates **148** has been investigated (Scheme 51).[57] Disulfanes **147** are treated with benzohydroxamate salts **148** to give *O*-phosphothioylated hydroxamic acids **149** (Scheme 51). The reaction has also been studied using optically pure disulfane. X-Ray analysis shows that the product is formed with a complete inversion of configuration. Therefore, the reaction has an ionic character and proceeds *via* an S$_N$2P mechanism at the phosphorus atom.

Ar = *p*-ClC$_6$H$_4$
R^3 = Me, *i*-Pr, *t*-Bu
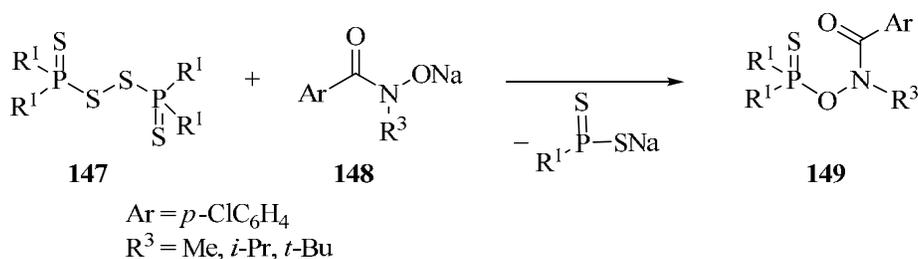
Scheme 51

N-Functionalization of phosphinylhydroxylamines can be achieved when *O*-(diarylphosphinyl)hydroxylamines **150** react with acetic anhydride to give the corresponding *N*-acetyl derivatives **151** (Scheme 52).[12f,50]
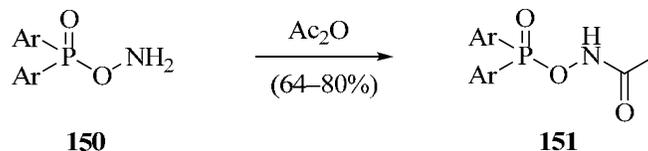
Scheme 52

N-Acyl phosphoramides have been reported to be quite nucleophilic at nitrogen in the Mitsunobu reaction. Intramolecular nucleophilic transfer reaction by treatment of *N*-benzyl phosphoramide **154** with two equivalents of DIEA in acetonitrile resulted in only a small amount (5%) of desired product **155** (Scheme 53)[58] and purification was difficult due to the highly polar nature of product. However, by changing to the more electron withdrawing phenyl groups of compound **154** (R = Ph) (Scheme 53), the acidification of the N-H bond of the *N*-acyl phosphoramide is possible allowing a more effective nucleophile transfer reaction to afford compound **156** in 33% yield.
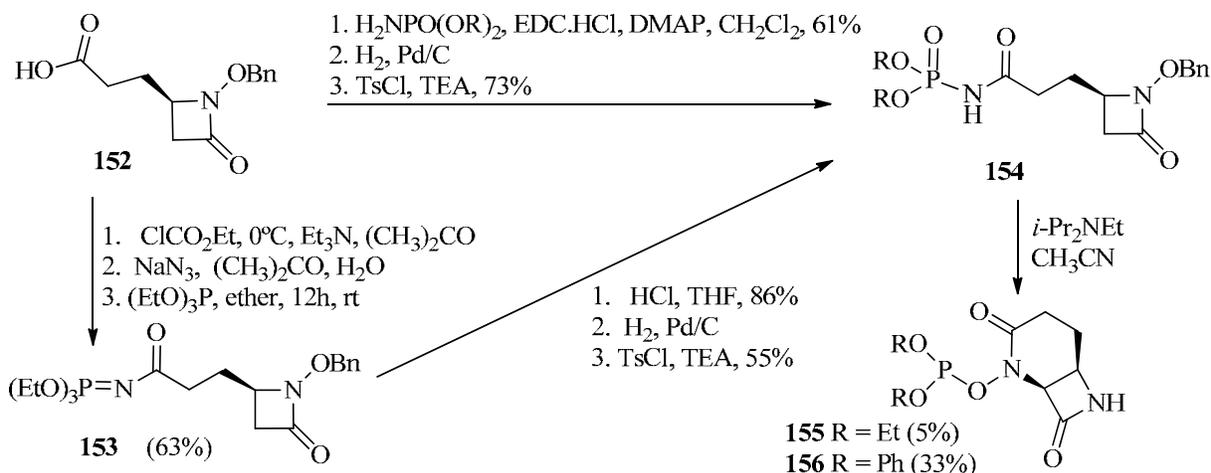
Scheme 53

3.2 Phosphorus *N*-substituted hydroxamic acid derivatives

Few examples of *N*-phosphoramidate hydroxamic acid derivatives have been reported, one of them being the synthesis of new "dual antagonists" in which the 2,2-dimethylaziridine phosphinyl function is linked to the *N*-hydroxyurethane rather than to the urethane moiety.[59] *O*-

Benzyl-*N*-hydrourethane **157** is used as the starting material and reacts with phosphorus oxychloride to give the corresponding compound **158** by P–N bond formation. Subsequent reaction with 2,2-dimethylaziridine gives *O*-benzyl-*N*-phosphinyl derivative **159** (Scheme 54).

Scheme 54

3.3 Phosphorus *C*-substituted hydroxamic acid derivatives
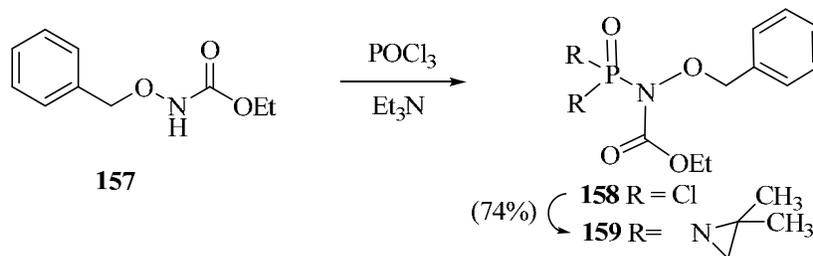
Phosphonates have also been shown to exhibit biological activity in various areas by virtue of their analogy to naturally occurring phosphates and carboxylic acids. *N*-Hydroxyphosphonoformamide **161** ($R^3 = R^4 = H$) can be prepared from bis(trimethylsilyl) [(methylthio)carbonyl]phosphonate **160** ($R^1 = $ OTMS, $R^2 = $ Me) (Scheme 55).[60,61] The hydroxamic acid derivative **161** ($R^1 = $ ONa) is formed by adding a solution of *O*-(trimethylsilyl)hydroxylamine to a solution of phosphonate **160** in ethyl ether. The authors report this compound as an inhibitor of recombinant HIV-1 RT P-66 from the yeast, *Saccharomyces cerevisiae*[60] and as a powerful binding inhibitor of enolase.[62] Analogously, several (phosphonoformyl)hydroxamates **161** ($R^1 = $ *i*-Pr) can be prepared. In these cases, thioester **160** is allowed to react with hydroxylamine and its *N*-methyl and *O*-methyl derivatives in the presence of pyridine and triethylamine.[63] The derivative obtained by reaction with hydroxylamine ($R^3 = R^4 = H$) suffers Lossen rearrangement[64] which involves the cleavage of the carbon–phosphorus bond in order to make a new phosphorus–nitrogen single bond of derivative **162**, whose hydrolysis yields the corresponding compound **163** (Scheme 55).
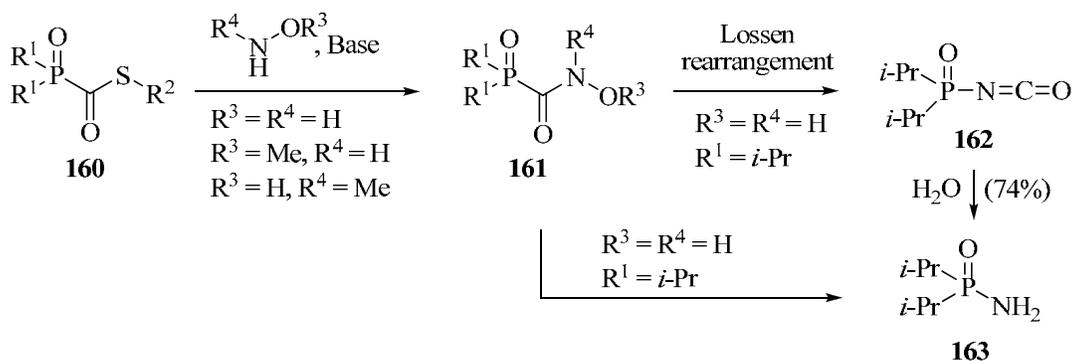
Scheme 55

In summary, this review presents the literature concerning the synthesis and reactivity of phosphorus substituted hydroxylamine and hydroxamic acid derivatives. It is noteworthy that not much examples regarding this type of compounds have been published, however, it is hoped that it will further stimulate the use of these compounds as versatile building blocks for the synthesis of acyclic and heterocyclic compounds which may have industrial, biological or pharmacological interest.

4. Acknowledgements

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