β-Hydroxyimino Phosphorus Derivatives. An Efficient Tool in Organic Synthesis

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Abstract: The purpose of this review article is to illustrate synthetic aspects of functionalized phosphorus derivatives containing an oximo moiety at the beta-position. First section will be focused on the synthesis of phosphine oxides, phosphonates or phosphonium salts containing an oxime group. The synthesis of these derivatives comprises the carbon–phosphorus single bond construction by reaction of haloximes with phosphorus derivatives, nucleophilic addition of phosphorus reagents to carbonyl compounds, or nucleophilic addition of phosphorus reagents to nitro olefins. This section will also concentrate on the most practical routes for the synthesis of the target compounds, through carbon–nitrogen double bond formation, which are as follows: condensation processes of carbonyl compounds and hydroxylamine derivatives or addition of hydroxylamines to allenes or alkynes. The preparative use of beta-oximo phosphorus derivatives as synthetic intermediates will be discussed in a second section, comprising olefination reaction, oxidation of oximes to nitrile oxides by reaction at the C-N double bond of the oxime moiety, oxidation of these substrates to nitrosoalkenes, reduction to the corresponding hydroxylamines and some reactions at the hydroxyl group of the hydroxyimino moiety.

Keywords: β-Hydroxyimino phosphorus derivatives, α-haloximes, nitro olefins, nitrile oxides, nitrosoalkenes.

1. PREPARATION OF β-HYDROXYIMINO PHOSPHORUS DERIVATIVES

Some general synthetic methods exist for the preparation of β-hydroxyimino phosphorus derivatives.[#] This section will be focused on the synthesis of substituted phosphine oxide, phosphonate or phosphonium salts containing an oxime moiety at the β-position. Depending on the type of bond formed in the reaction, some strategies for the preparation of these derivatives can be highlighted (Scheme **1**). Section 1.1 outlines their preparation through carbon–phosphorus single bond construction by reaction of α-haloximes with phosphorus derivatives (route a_1), nucleophilic addition of phosphorus reagents to carbonyl compounds (route a_2) or nucleophilic addition of phosphorus reagents to nitro olefins (route a_3). Section 1.2 will concentrate on the most practical routes for the synthesis of the target compounds, through carbon-nitrogen double bond formation, which are as follows: condensation processes (route b_1) and addition of hydroxylamines to allenes or alkynes (route b_2).

1.1. Carbon-Phosphorus Single Bond Formation

1.1.1. Reaction of α-Haloximes with Phosphines and Phosphites

Alkylation of phosphines and phosphites constitutes an important entry to phosphorated oximes through C-P bond formation. Thus, reaction of oximes **2**, generated from condensation reaction of bromopyruvate **1** with *O*-methyl hydroxylamine, with triphenylphosphine (R = Ph), describes a general method through a C-P bond forming process for the preparation of oxime phosphonium salt **3a**. Similarly, β-phosphorylated oximes **3b** or **3c** can be obtained by means of Arbuzov reaction of oximes **2** with trimethylphosphite (R = OMe) (Scheme **2**) [1]. The alkylation of phosphines and phosphites with haloximes strategy has also been extended for the preparation of other substituted oximes derived from phosphonium salts [2] or phosphonates [3]. Similarly, when bromoacetophenone was used, functionalized oximes derived from phosphine oxides and phosphonates were obtained in good yields [4].

In a similar way, condensation reaction of 3-bromopyruvate **4** with hydroxylamine hydrochloride leads to α-haloxime **5**. Its protection with dihydropyrane affords *O*-THP oxime **6**, which can be converted into oxime derived from phosphonium salt **7** in very good yield on reaction with triphenylphosphine (Scheme **3**) [5].

The based-catalyzed reaction for the formation of oxime derived from phosphonium salt **9** might be explained by three paths: an attack by phosphorus atom on α-carbon in the conjugate base of the oxime (path A), an initial attack of the base on the oxime carbon followed by displacement of bromine with PPh_3 (path B), or the preliminary replacement of bromine with base followed by displacement with PPh_3 (path C), as shown in Scheme **4** [6]. Path C was ruled out by control experiments, which showed that (2-phenyl-2-oxyiminoethyl)pyridinium bromide neither reacted with PPh_3 nor catalyzed the reaction of **8** with PPh_3, whereas a catalytic amount of pyridine lead to the exclusive formation of **9** under the identical conditions. Although there is no positive evidence, the catalytic reaction may be rationalized by path A or B, which would have somewhat of an S_N1 character since the transition states are stabilized by mesomeric electron release from the nearby anionic sites.

1.1.2. Nucleophilic Addition of Phosphorus Reagents to Carbonyl Compounds

Nucleophilic addition of phosphorus reagents to carbonyl compounds represents an easy strategy for the preparation of α-hydroxy-phosphorylated compounds. This procedure has been applied to the keto-oxime **10** for the preparation of an α-hydroxy-β-oximo phospine oxide derivative **11**. In this way, addition of dimethyl phosphine oxide to keto-oxime **10** in the presence of ^{t}BuOK

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[#] These compounds could be named as β-hydroxyimino or β-oximo phosphorus derivatives if the phosphorated group is considered as the main group or α-phosphorus substituted oximes if the oximo moiety is considered as the main function. In this account we use the former β-hydroxyimino or β-oximo phosphorus derivatives.

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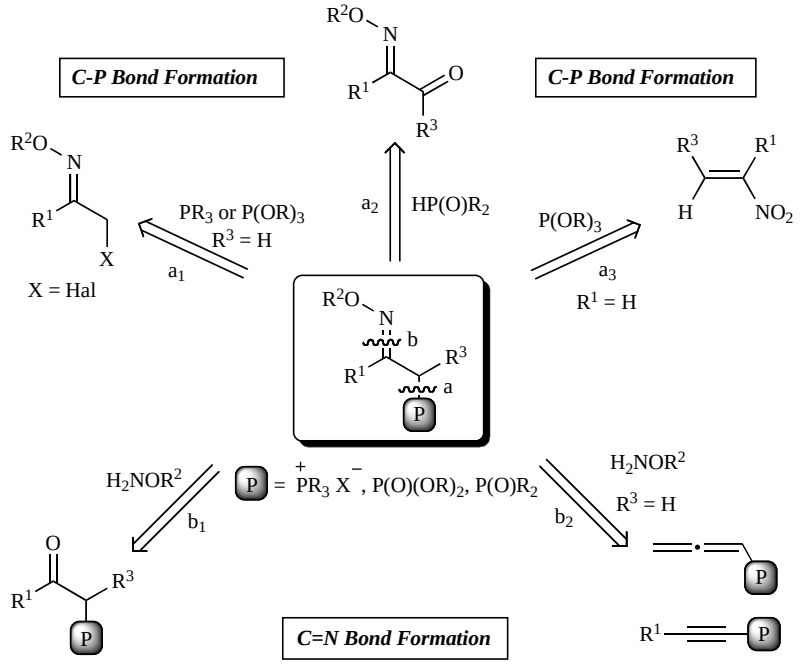
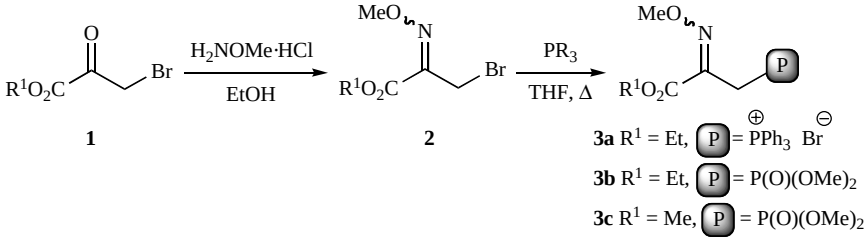
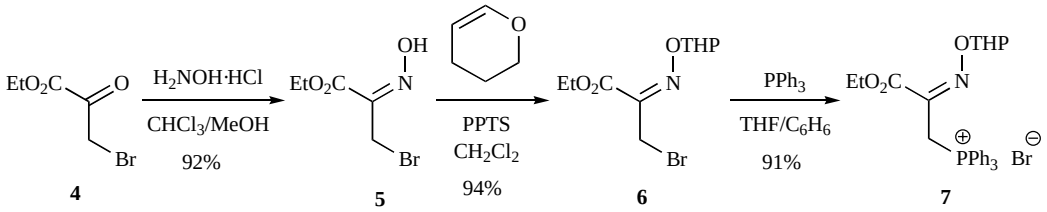


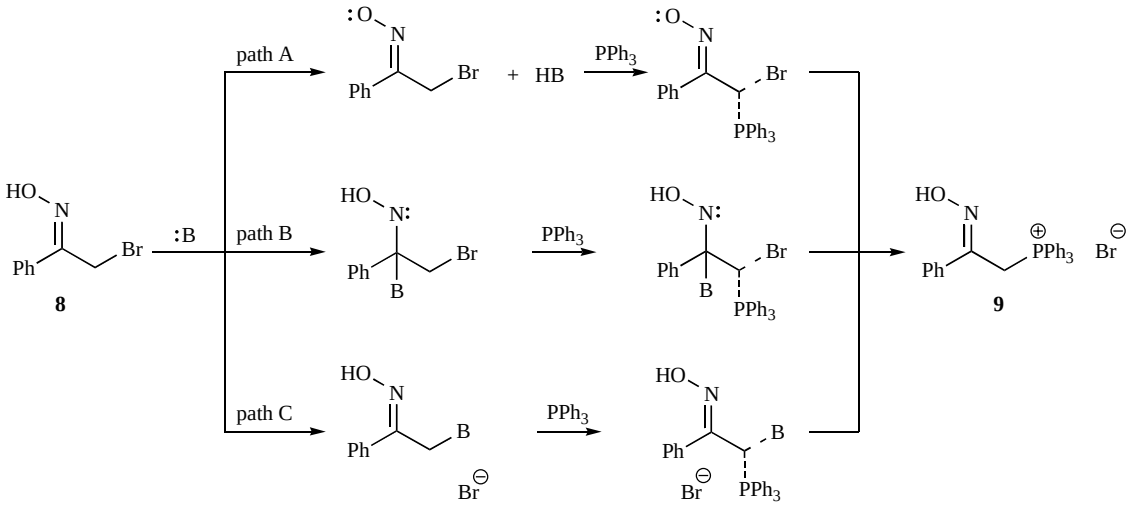
Scheme 1.



Scheme 2.

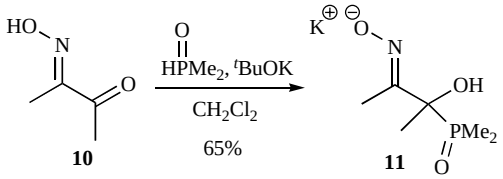


Scheme 3.



Scheme 4.

leads to the potassium salt of phosphinylated oxime **11** (Scheme **5**) [7].



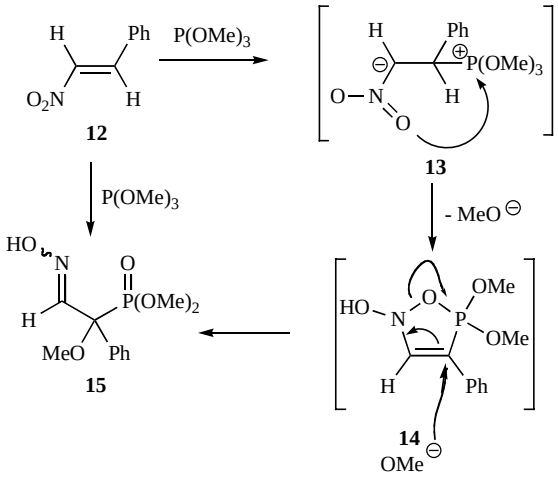
Scheme 5.

1.1.3. Nucleophilic Addition of Phosphorus Reagents to Nitro Olefins

Nitro olefins are useful intermediates in the synthesis of some biological active natural products. Due to the strong electron withdrawing properties of the nitro group, conjugated nitroalkenes are excellent Michael acceptors with a variety of nucleophiles. Several papers describe the addition of phosphorus nucleophiles to nitro olefins as Michael acceptors. Krueger *et al.* [8] reported that trimethylphosphite reacted with β-nitrostyrene **12** in *tert*-butyl alcohol to produce phosphorylated aldoxime **15** through C–P bond formation. A reaction pathway which is consistent with the experimental and spectroscopic results is proposed in Scheme **6**. The mechanism involves initial attack of trimethylphosphite at the α-carbon of β-nitrostyrene **12**, to form a zwitterion **13**, which rearranges to the proposed cyclic intermediate **14**. Methoxide ion attack on **14** affords the oxime **15**. This compound was characterized unambiguously by x-ray crystallography [8a].

The above-mentioned study was followed by other authors [9], who reported the addition reaction of triethylphosphite to β-nitrostyrene **12**. As reported in Scheme **7**, reaction of nitroalkene **12** with 3.2 equivalents of triethylphosphite leads to a mixture of diphosphonate **16**, nitrile **17** and phosphorylated oximes **18** and **19** as traces.

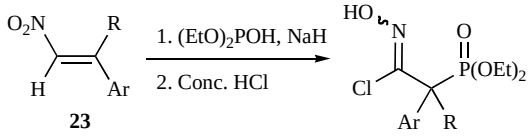
C-P Bond creation with the formation of a β-oxime phosphonate derived from sugars has also been observed in the reaction of β-nitro sugar **20** with trimethylphosphite. In this case, a mixture of



Scheme 6.

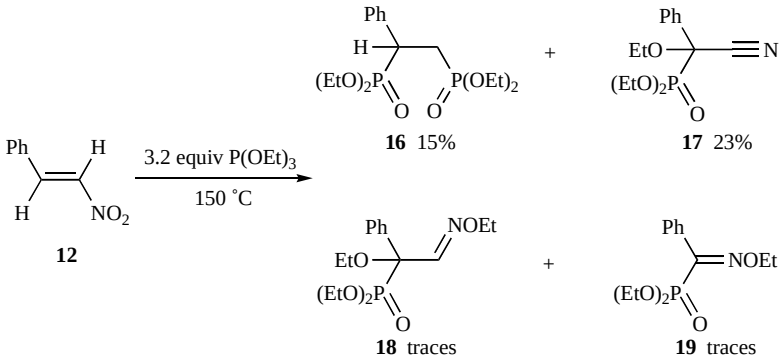
alkene **21** and phosphorylated aldoxime **22** were obtained in very low yield (Scheme **8**) [10].

Phosphorylated haloximes can be prepared from the reaction of conjugated nitroalkenes with diethyl phosphite. In such a way, treatment of conjugated nitroalkenes **23** with diethyl phosphite in the presence of a base such as sodium hydride and subsequent addition of HCl gives haloximes **24** in very good yield (Scheme **9**) [11].

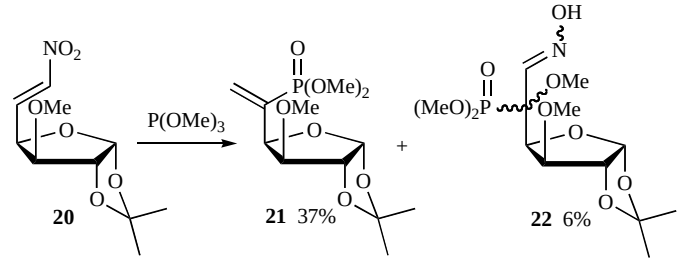


24a R = H, Ar = Ph 75%
24b R = H, Ar = *p*-MeC_6H_4 98%
24c R = Ar = Ph 95%

Scheme 9.



Scheme 7.



Scheme 8.

1.2. Carbon-Nitrogen Double Bond Formation

1.2.1. Condensation Reaction

Condensation reaction of a β-keto phosphorus substituted compounds with hydroxylamines to give aldoximes or ketoximes, represents a simple route for the preparation of β-oximo phosphorus derivatives *via* a carbon–nitrogen double bond-forming process. This is one of the most common synthetic ways for the preparation of oximes. Arbuzov reaction of bromoacetaldehyde diethyl acetal (**25**) with triethylphosphite affords phosphorylated acetal **26** with a C-P bond formation process (Scheme **10**) [12]. Deacetalization under acidic conditions and condensation with hydroxylamine hydrochloride in the presence of a base give aldoxime **28** in good yield.

Similarly, nucleophilic addition of hydroxylamine to the keto carbonyl group of diethyl β-ketopropylphosphonate (**29a**) (R = OEt, R^1 = Me) in aqueous solution around pH = 7 leads to β-oximo phosphonate **31a** (Scheme **11**) [13]. Using ^1H and ^{31}P NMR spectroscopy, during the reaction, it was possible to detect the carbinolamine **30a** resulting from addition of hydroxylamine to the keto carbonyl group, the *syn*- and *anti*-isomers of the oxime of the diester **31a** and the *syn*- and *anti*-isomers of the oxime of the monoester **32**. Under these conditions oxime **31a** undergo phosphate ester hydrolysis which appear to involve internal assistance by the OH group of the oxime, since no hydrolysis was detected for the *O*-methyloxime of **29a**. This assistance may involve nucleophilic addition to phosphorus atom by the OH oxygen to form a pentacovalent intermediate. Following this strategy, β-oximo phosphine oxides **31b** (R = Ph) have been synthesized by our group using triethylamine as the base (Scheme **11**) [14].

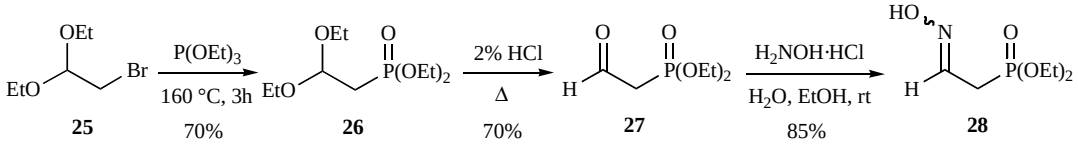
Some phosphorylated oximes have been tested as *N*-methyl-D-aspartate (NMDA) receptor antagonists. Since it appeared that the binding potency and relatively good bioavailability of **33** could be related to the β-ketophosphonic acid functionality, Whitten *et al.* [15] sought to modify the ketone with similar, less readily enolizable groups. Thus, a mixture of *syn*- and *anti*-oximes or their ethers **34** were synthesized through condensation reaction of readily available hydroxylamines with (*R*)-4-oxo-5-phosphononorvaline (**33**) by standard procedures (Scheme **12**).

Alkylation of the anion derived from diethyl methylphosphonate (**35**) with methyl iodide followed by addition of dimethylformamide affords a general method for the preparation of 1-formylalkanephosphonate **36** [16], which could be converted to the phosphorylated oxime **37** by condensation reaction of aldehyde **36** with hydroxylamine (Scheme **13**) [17]. Related phosphinyl aldoximes have been obtained in 86% yield by using the same conditions when starting from methyl diphenylphosphine oxide [18].

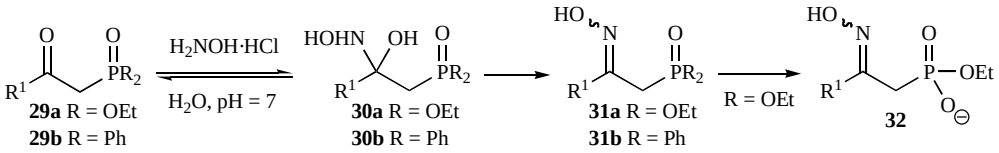
This approach has been also used for the preparation of β-oximo phosphine oxides **40a** (R = Ph) and β-oximo phosphonates **40b** (R = OEt) containing a fluoroalkyl substituent [19]. Hence, metallation of alkyl diphenylphosphine oxides **38a** or alkylphosphonates **38b** with LDA and subsequent treatment with fluorinated esters affords fluorine substituted β-ketophosphine oxides **39a** or β-ketophosphonates **39b**, respectively (Scheme **14**). The condensation of ketones **39** with hydroxylamine hydrochloride in the presence of pyridine gives fluorinated oximes **40a** or **40b**.

This method developed for the preparation of β-ketophosphonates using anions derived from alkyl phosphonates has been expanded to cyclic ketophosphonates, and thus, cyclic phosphorylated oximes by condensation reaction with hydroxylamines were reported. The diester **42** resulting from $NiCl_2$-catalyzed Arbuzov reaction of diethyl methylphosphonate and ethyl iodobenzoate **41**, reacts with 3 equivalents of potassium *tert*-butoxide in diethyl ether effecting cyclization to **43**. The corresponding phosphorylated oximes **44** resulted from oximation reaction of ketone **43** with the appropriate hydroxylamine (Scheme **15**) [20].

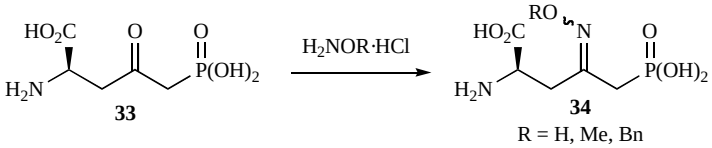
Similarly, condensation of phosphonate anions derived from **45** with diesters can be used for the preparation of 3-phosphonopyruvate



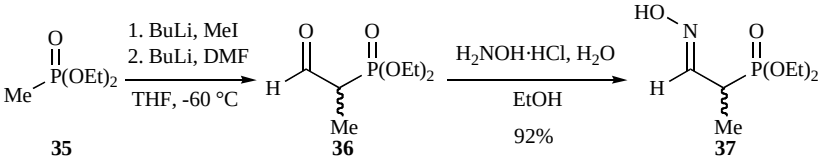
Scheme 10.



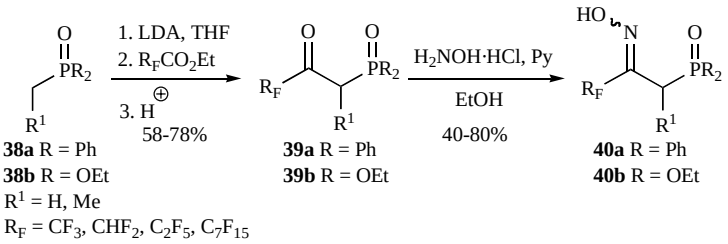
Scheme 11.



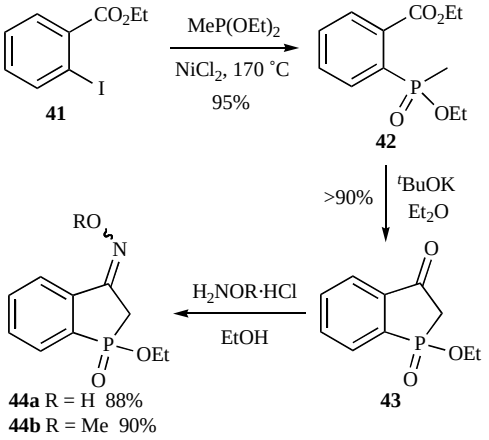
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

derivatives **46** (Scheme **16**) [21]. Oximation of these derivatives **46** affords functionalized oximes **47** in good yields.

β-Oximo phosphine oxides **50** can be obtained by C–N double bond formation through condensation reaction of hydroxylamine with β-keto phosphine oxides **49**, previously prepared on treatment of stannyloxiranes **48** with lithium diphenylphosphine (Scheme **17**) [22].

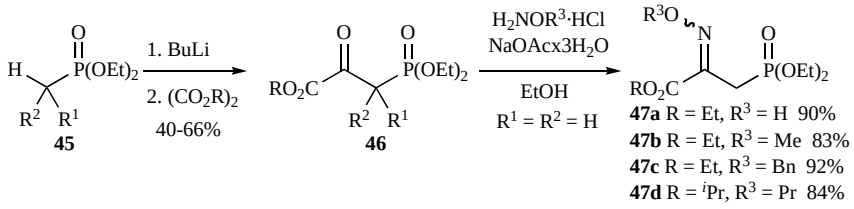
Oximes containing a phospholene ring can be prepared by quaternization reaction of trivalent *P*-bromophospholene **51**. Thus, reaction of bromophospholene **51** with α-chloroketone **52** afforded functionalized phospholene *P*-oxide **53**, which after condensation reaction with hydroxylamine hydrochloride give phosphorylated oxime **54** (Scheme **18**) [23].

Other oximes containing a phospholene ring have been prepared through a condensation reaction of ethyl formate with the anion derived from phospholene *P*-oxide **55** [24]. The corresponding aldehyde obtained **56** is condensed with hydroxylamine hydrochloride affording oxime phospholene **57** (Scheme **19**).

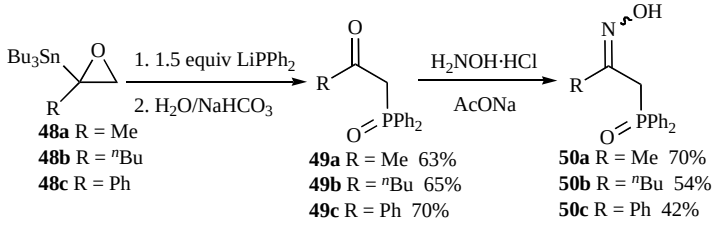
Minami *et al.* [25] have reported a synthetic methodology for the preparation of α-formylvinylphosphonates **60**, precursors of oximes **61**. Allylic alcohols **58**, prepared by trapping anions derived from vinylphosphonates with aldehydes and ketones, can react in acidic conditions to afford vinylphosphonates **60** in very good yields. This reaction probably proceeds *via* a mechanism which included attack of water on an allylic carbocation **59** stabilized by the oxygen atom. The C–N double bond formation in **61** takes place by treatment of **60** with hydroxylamine and pyridine in ethanol under reflux (Scheme **20**).

1.2.2. Nucleophilic Addition of Hydroxylamines to Allenyl or Alkynyl Derivatives

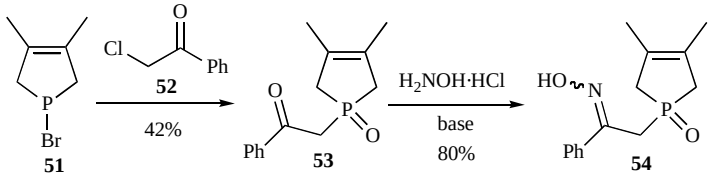
A different approach can also be applied for the preparation of phosphorylated oximes though C–N double bond formation. This strategy involves conjugative addition of hydroxylamine to the



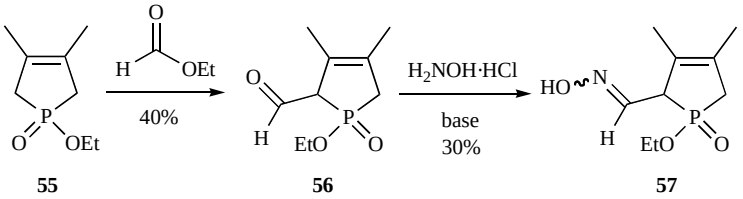
Scheme 16.



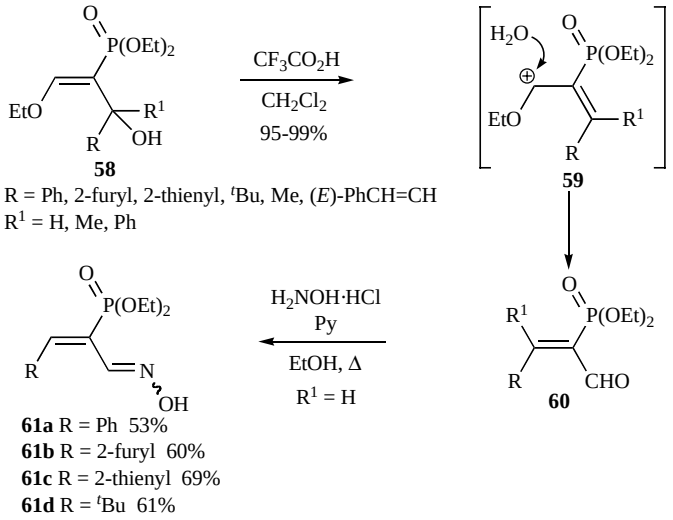
Scheme 17.



Scheme 18.

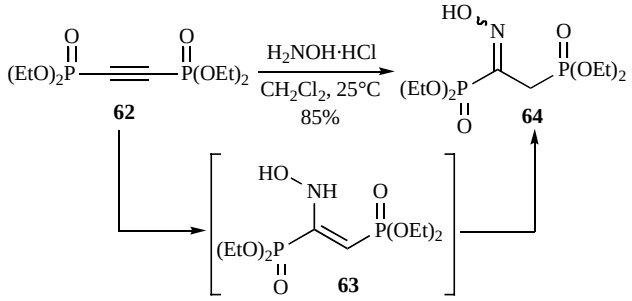


Scheme 19.



Scheme 20.

acetylenic C–C-triple bond of tetraethyl ethynyldiphosphonate **62**, and subsequent tautomerization of the *N*-hydroxyenamine **63** [26]. Through this procedure, oxime bisphosphonate **64** can be synthesized in 85% yield (Scheme **21**).

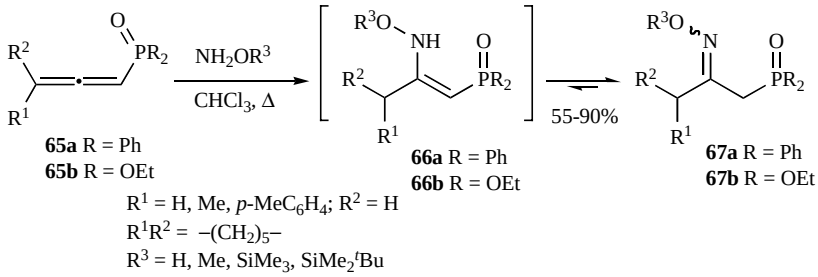


Scheme 21.

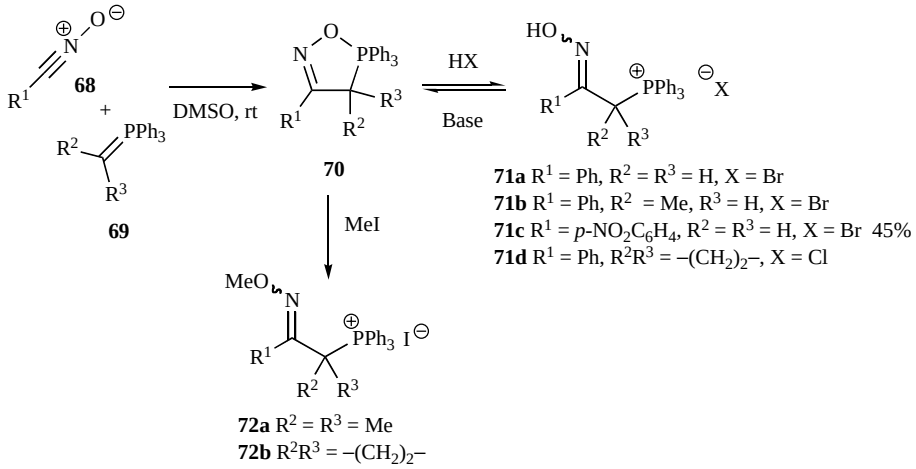
In a similar way, nucleophilic addition of unsubstituted hydroxylamine (R^3 = H), *O*-methylhydroxylamine (R^3 = Me) or *O*-silyl substituted hydroxylamines (R^3 = $SiMe_3$, $SiMe_2{}^tBu$) to allenyl phosphine oxides **65a** (R = Ph) or phosphonates **65b** (R = OEt) represents an easy procedure for the preparation of β-oximo phosphine oxides **67a** (R = Ph) or β-oximo phosphonates **67b** (R = OEt), *via* functionalized enamines **66**, in good yields (Scheme **22**) [27].

1.3. Ring Opening of 1,2,5-Oxazaphospholines

Umani-Ronchi *et al.* [2c] report the reaction between nitrile oxides **68** and phosphonium ylides **69** as a useful method for the preparation of 1,2,5-oxazaphosph(V)ol-2-ines **70**. The successful transformation of **70** into the corresponding 2-hydroxyimino phosphonium salts **71** involves the ring opening of **70** by P–O bond cleavage by the action of hydrobromic [2c] or hydrochloric acid [28] (Scheme **23**). In a similar way, oxime ethers phosphonium salts **72** can be obtained by ring opening of 1,2,5-oxazaphospholines **70** on treatment with iodomethane [28] (Scheme **23**). The use of nitrile oxides for the synthesis of such heterocycles **70**, and thus these β-oximo phosphonium salts **71** and **72**, offers a more limited route of synthesis, when compared with the Arbuzov reaction of α-haloximes and phosphines [2] (see Scheme **2**). This is because of the limited availability of nitrile oxides **68**, which usually are less easily obtained than α-haloximes. Moreover, the reaction requires the use of phosphonium ylides **69** instead of simple phosphines.



Scheme 22.



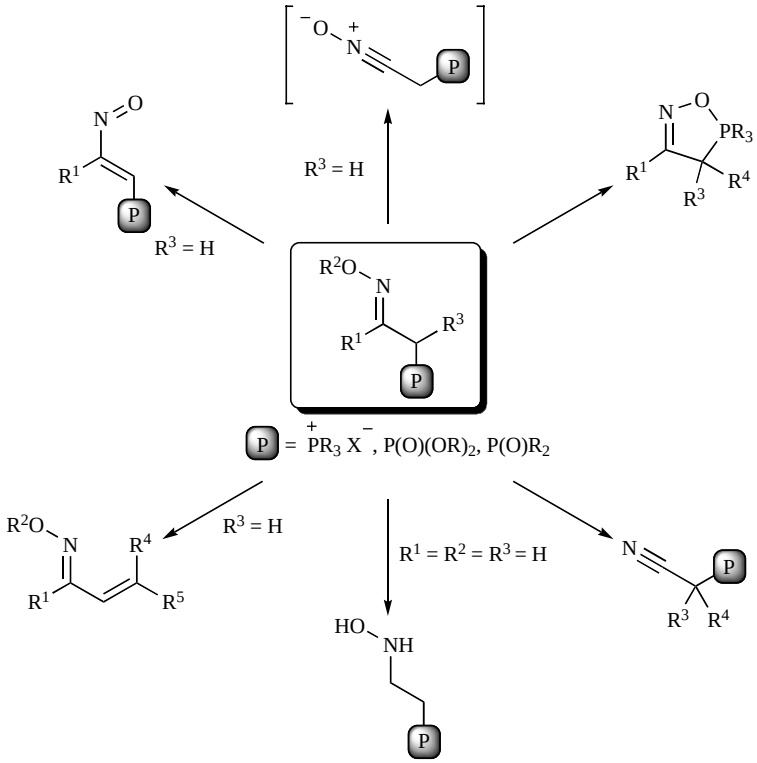
Scheme 23.

2. REACTIVITY. PREPARATIVE USE OF β-HYDROXYIMINO PHOSPHORUS DERIVATIVES AS SYNTHETIC INTERMEDIATES

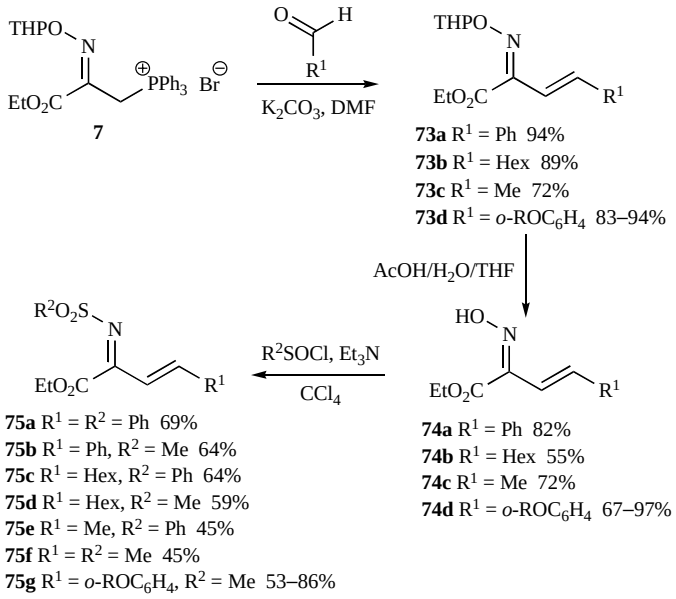
β-Hydroxyimino phosphorus derivatives are bifunctional compounds and contain an oxime moiety and a phosphorated group linked by a carbon atom. Characteristic reactions of the oxime function such as the oxidation of these substrates to nitrosoalkenes and nitrile oxides, reduction to the corresponding hydroxylamines and some reactions at the hydroxyl group of the hydroxyimino moiety has been reported, while the presence of phosphorus functional groups confers an additional preparative interest to these substrates because they can be used for the construction of selective C-C double bonds by means of the Wittig reactions or related processes [29] (Scheme **24**).

2.1. Olefination Reaction

One of the most representative examples of the reactivity of α-carbanions derived from some phosphorus derivatives entails the C–C double bond forming process, through Wittig reaction [29] or related processes with carbonyl compounds. For carbon–carbon double bond construction, not only phosphonium salts (Wittig reaction) but also phosphine oxide derivatives (Horner reaction) or phosphonates (Horner-Wadsworth-Emmons reaction) are very useful reagents. For this reason, β-oximo phosphorus compounds can be excellent starting materials for the selective preparation of α,β-unsaturated oximes. Moreover, this is a very useful method for the preparation of 1-azabuta-1,3-dienes, important building blocks for the preparation of six-membered nitrogen containing heterocycles. For example, Boger *et al*. have described the preparation of *N*-



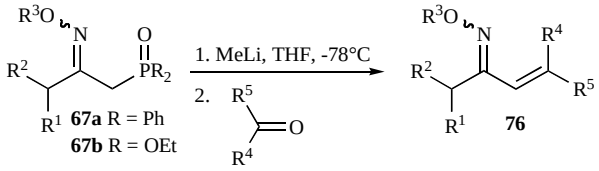
Scheme 24.



Scheme 25.

sulfonyl-1-azabuta-1,3-dienes **75**, based on the use of the stabilized Wittig reagent containing an oximo group **7**, and their 4π participation in inter [5, 30] and intramolecular [31] [4+2] cycloaddition reactions. 4-Substituted *N*-sulfonyl-1-azabuta-1,3-dienes **75** are prepared through Wittig reaction of the stabilized phosphorane generated *in situ* from the phosphonium salt **7** with aldehydes, followed by acid-catalyzed removal of the tetrahydropyranyl (THP) group, *O*-phenylsulfinyl or *O*-methylsulfinyl formation, and subsequent *in situ* homolytic rearrangement to provide **75** (Scheme **25**). 1-Azadienes, prepared through Wittig olefination reaction of β-oximo phosphonium salts, have been also used as building blocks for the preparation of indole-3-piruvic acid oxime ethers by Heck cyclization [32].

Our group [27] reported an efficient method for the preparation of α,β-unsaturated oximes through olefination reaction, starting from oximes containing phosphorated functional groups. Consequently, β-oximo phosphine oxides **67a** (R = Ph) can be suitable precursor for the homologation of oximes into their vinylogous compounds. Oximes **67a** (R = Ph) are treated with a base such as methyl lithium, followed by addition of aromatic, heteroaromatic and aliphatic aldehydes and ketones leading to 1-azadienes **76** with high *E*-stereoselectivity of the carbon–carbon double bond, isolated as a mixture of *syn*- and *anti*-isomers, and in good yields (Scheme **26**). This olefination reaction is not restricted to β-oximo phosphine oxides **67a** (R = Ph) since oximes derived from phosphonates **67b** (R = OEt) can also be used in this approach.

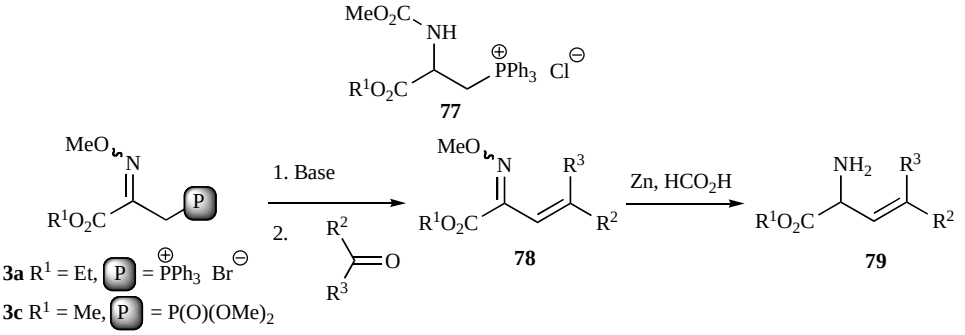


Comp.	R^1	R^2	R^3	R^4	R^5	Yield (%)
76a	H	H	H	H	^{i}Bu	81
76b	H	H	H	H	2-C_5H_4N	72
76c	H	H	H	Ph	Ph	80
76d	H	H	H	–$(CH_2)_5$–		74
76e	H	Me	H	H	*p*-MeC_6H_4	88
76f	H	Me	H	H	^{i}Bu	77
76g	H	H	$SiMe_3{}^t$Bu	H	*p*-MeC_6H_4	80
76h	H	Me	$SiMe_3{}^t$Bu	H	*p*-MeC_6H_4	71
76i	–$(CH_2)_5$–		$SiMe_3{}^t$Bu	H	*p*-MeC_6H_4	80
76j	H	H	Me	H	*p*-$MeOC_6H_4$	75
76k	H	Me	Me	H	^{i}Bu	65

Scheme 26.

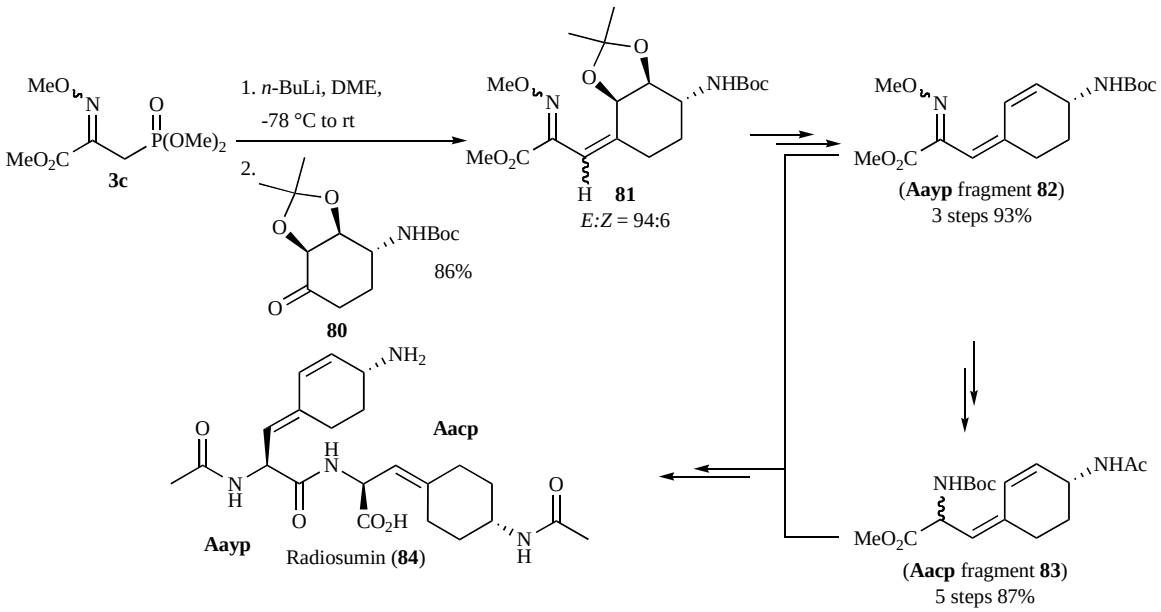
There has been considerable interest in vinyl glycines as antibiotics, enzyme inhibitors and synthetic intermediates. The β-aminophosphonium salt **77**, a vinyl glycine synthon derived from serine, is tedious to prepare and has to be used as its free acid to avoid β-elimination. Oxime phosphonium salt **3a** (P = PPh_3^+ Br^-) provide advantages as an amino acid synthon. Reaction of phosphorane derived from salt **3a**, generated from the treatment of **3a** with a base, with aldehydes gave the required 1-azabuta-1,3-dienes **78** with yields ranging from 50 to 99% (Scheme **27**). ^{n}Butyl lithium was the initial base chosen for the generation of phosphorane derived from **3a**. However, owing the partially stabilized nature of this phosphorane, it was reasoned that a weaker base would suffice. The preferred choice was potassium carbonate in DMF, which requires no special precautions and has provided excellent yields. To increase the versatility of this approach, reactions of ketones was required. Hence, Horner-Wadsworth-Emmons (H-W-E) olefination reaction of phosphorylated oxime **3c** (P = $P(O)(OMe)_2$) with sodium hydride and the corresponding ketone leads to the final azadienes **78** in 24-54% yield. Finally, the vinyl glycine derivatives **79** were obtained in good yields by reduction of α,β-unsaturated oximes **78** with zinc in formic acid (Scheme **27**) [1].

An illustration of the olefination reaction of a phosphorylated oxime as the key step in the synthesis of natural products is present in the total synthesis of radiosumin **84**, a strong trypsin inhibitor from the blue-green alga *plectonema radiosum* (Scheme **28**) [3a,33]. This structurally intriguing dipeptide **84** is composed of



3	R^1	78	R^2	R^3	Yield (%)	79	Yield (%)
3a	Et	**78a**	H	Et	50	**79a**	84
3a	Et	**78b**	H	^{i}Pr	99	**79b**	94
3a	Et	**78c**	H	Ph	98	**79c**	65
3a	Et	**78d**	H	*p*-$CF_3C_6H_4$	99		
3c	Me	**78e**	Et	Et	24	**79e**	99
3c	Me	**78f**	$-(CH_2)_5-$		36	**79f**	49
3c	Me	**78g**	$-(CH_2)_2S(CH_2)_2-$		54	**79g**	37

Scheme 27.



Scheme 28.

two unusual, novel α-amino acids: 2-amino-3-(4-amino-2-cyclohexen-1-ylidene)propionic acid (Aayp) (**82**) and 2-amino-3-(4-amino-2-cyclohexylidene)propionic acid (Aacp) (**83**). Stereoselective Horner-Wadsworth-Emmons reaction of oxime **3c** with aminocyclitol ketone **80** furnished one of the building blocks **81** for the construction of Aayp derivative **82**. The other one, Aacp derivative **83** needed for the preparation of radiosumin **84**, was prepared in five steps starting from the common intermediate **82**.

Furthermore, the high efficiency of this protocol has been also applied to the total synthesis of naturally occurring amino acid 2,6-diaminopimelic acid (DAP) (**87**) found in both bacteria and higher plants (Scheme **29**) [34]. Condensation of the aldehyde **85**, with the stabilized phosphorane three carbon synthon derived from **3a**, affords the corresponding unsaturated oxime ester **86**. This compound serve as a versatile intermediate to a variety of DAP analogues, since one can selectively reduce the oxime and the olefinic moieties.

2.2. Reactions at the C-N Double Bond

2.2.1. Oxime Reductions

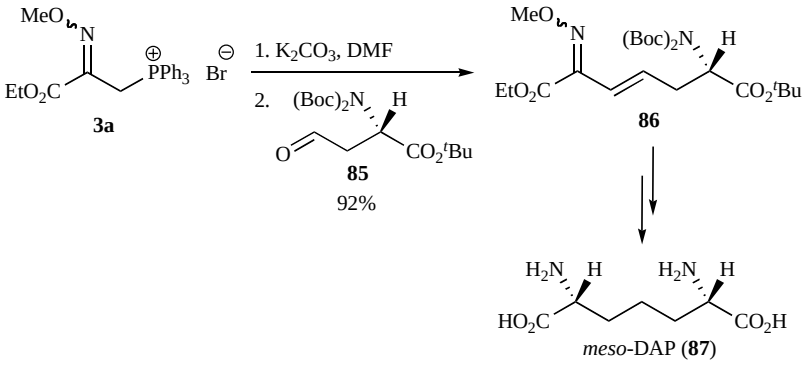
Through a simple oxime-amine reduction, fluorine containing β-amino phosphine oxides or phosphonates may be prepared in satisfactory yields [19]. For this goal, treatment of fluorine containing *p*-toluenesulfonyl oxime **88a** derived from phosphine oxides or *p*-toluenesulfonyl oxime **88b** derived from phosphonates with $NaBH_4$ at low temperature gives fluorine containing β-amino phosphine oxide **89a** or phosphonates **89b**,**c** in a regioselective fashion [19] (Scheme **30**). In a similar way, β-aminophosphonate derivatives [35] have been prepared starting from phosphorylacetaldehyde oximes, by means of an oxime-hydroxylamine reduction employing the pyridine-borane complex [36].

2.2.2. Oxidation Reactions

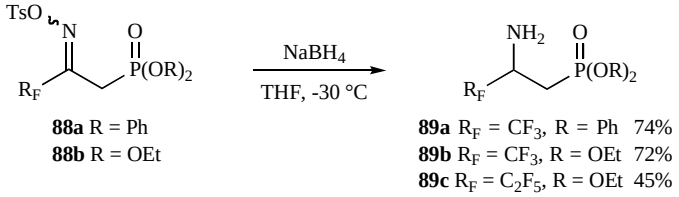
2.2.2.1. Nitrile Oxide Formation

Nitrile oxides have been much more frequently used in organic synthesis, especially in the elaboration of complex molecules, than any other 1,3-dipoles [37]. The importance of nitrile oxide is based on its high reactivity toward a wide range of olefins, both electron–poor and –rich types, forming isoxazolines which are flexible building blocks through their ability to function as masked forms of β-hydroxyketones [38] and γ-amino alcohols [39], after the N–O bond cleavage. Phosphorus functionalized nitrile oxides undergo regioselective 1,3-dipolar cycloadditions to olefins or acetylenes to furnish good yields of 2-isoxazolines or isoxazoles bearing a phosphorus substituent. For example, Tsuge *et al.* reported the first synthesis of phosphorus functionalized nitrile oxide and its cycloaddition with a variety of olefins. Nitrile oxide **91** is successfully accessible by the bromination of **28** with NBS (*N*-bromosuccinimide) followed by dehydrobromination of haloxime **90** with triethylamine. This nitrile oxide **91** has been trapped as cycloadduct with a variety of olefinic dipolarophiles giving the corresponding isoxazolines **92** as single regioisomers and in good yield (Scheme **31**) [12d,e]. Cycloaddition of phosphorus functionalized nitrile oxide **91** to acetylenic alcohols affords compounds **93**. This approach has been reported in the synthesis of *E*-isomers of furanone derivatives which are essential part of the framework of furanone natural products such as geiparvarin [40] (Scheme **31**). Other dipolarophiles such as allyl [41] and homoallyl alcohols [42] or α,β-unsaturated esters [43] have been used for the cycloaddition reaction to **91** to give terpene, pyridine or furanone derivatives, respectively. Likewise, isoxazolinephosphonates and isoxazolephosphonates substituted at 4- and 5-positions have been obtained by cycloaddition of olefins and acetylenes to **91** [12c].

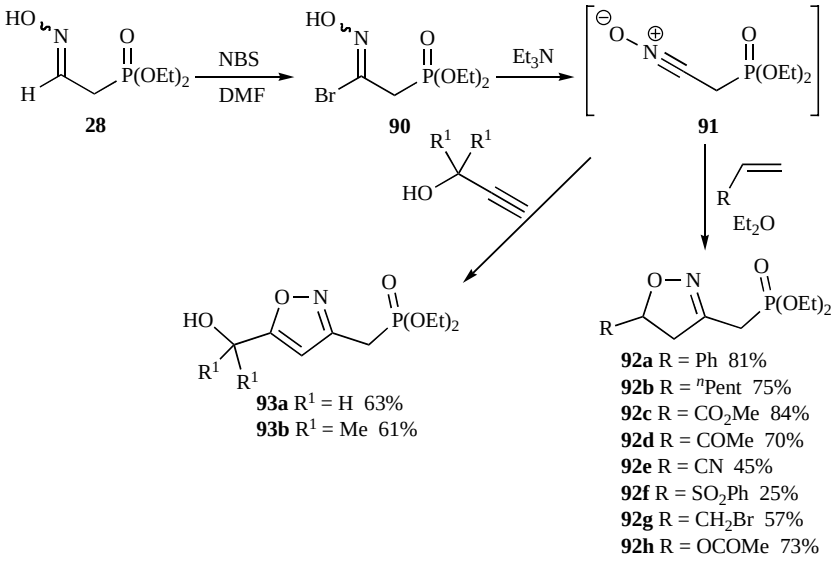
This method developed for the cycloaddition reaction of nitrile oxides with dipolarophiles was subsequently expanded to the preparation of α-alkoxycarbonyl-β-diketones by Jones *et al.* [12b]. Phosphorylated isoxazole derivative **96**, resulting from the cycloaddition of nitrile oxide **91** with enamines **95**, was used as starting material for the construction of C-C double bonds when they were treated under basic conditions with a variety of aldehydes and ketones (benzaldehyde, propanone, cyclohexanone, but-2-enal and (*E*)-2-methylbut-2-enal) to afford the 3-alkenylisoxazoles **97** (Scheme **32**). Treatment of **97** with hexacarbonylmolybdenum in moist acetonitrile gives efficient access to α-alkoxycarbonyl-β-diketones **98** in excellent yields. Early work by Warren *et al.* [18] shows the viability to performing the cycloaddition of nitrile oxide, olefination



Scheme 29.



Scheme 30.



Scheme 31.

reaction and cleavage with $Mo(CO)_6$ of isoxazole ring, for the regiospecific synthesis of derived leukotriene analogues using phosphine oxides.

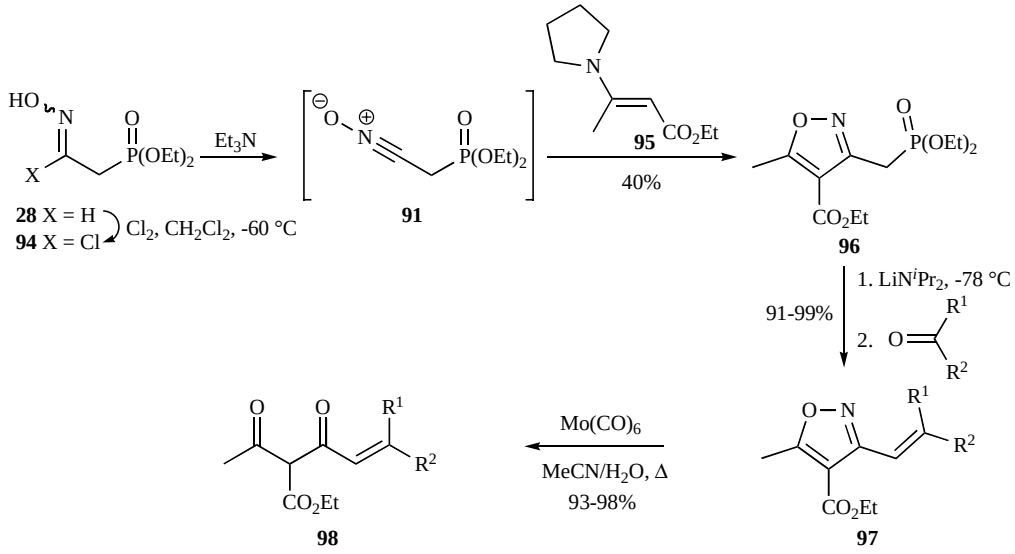
The synthetic utility of this approach has been recently demonstrated in the preparation of 1β-methylcarbapenem **100** which showed markedly antibacterial activity as well as high stability to DHP-I against *pseudomonas aeruginosa* isolates and advanced pharmacokinetic profiles in rat and dog than those of meropenem (Scheme **33**) [12a].

Recently, phosphonated dihydroisoxazole nucleosides have been prepared *via* 1,3-dipolar cycloaddition reaction of nitrile oxides with the corresponding vinyl nucleobases for antiviral studies [44]. This synthesis has been performed in a one-step process as shown in Scheme **34**. The nitrile oxide **91**, derived *in situ* from aldoxime **28** by treatment with NBS under basic conditions, was added to the vinyl nucleobases to give the racemic nucleosides **101**. This reaction showed a complete regioselectivity obtaining the 5-isomer as an exclusive product.

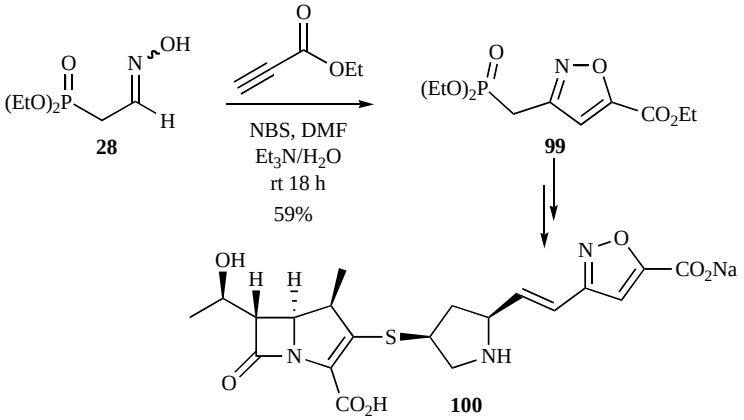
The synthetic value of nitrile oxide cycloaddition is now growing as shown in its wide applications to natural product synthesis. For example, Carreira *et al.* [17,45] reported the stereoselective syntheses of epothilones A and B *via* magnesium-mediated hydroxyl-directed nitrile oxide cycloadditions with allyl alcohols, inspired by the work of Kanemasa [46]. In this regard, the cycloadditions of the versatile oxime **37** with chiral allyl alcohols is the key to the Carreira's strategy. Oxidation of **37** to nitrile oxide **103** was followed by highly diastereoselective cycloaddition with an allyl alcohol **104**, containing and additional sterocenter, to furnish **105** as a single *syn*-diastereomer at the isoxazoline oxygen (Scheme **35**). Furthermore, these authors have applied the diastereoselective nitrile oxide cycloaddition of homoallylic alcohols in the synthesis of polyketide building blocks [47].

2.2.2.2. Nitrosoalkene Formation

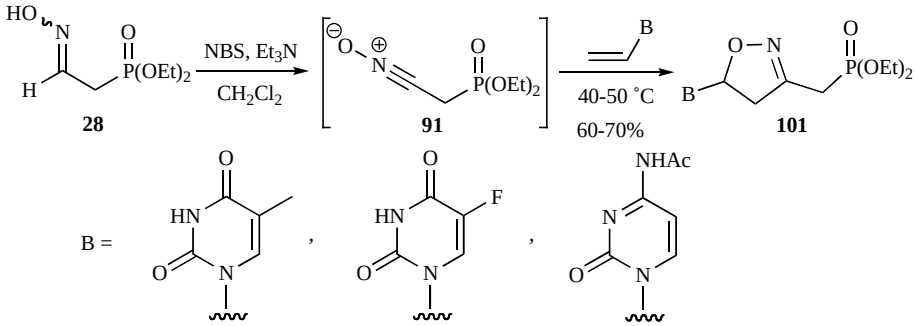
Nitrosoalkenes are functionalized nitroso derivatives, and the presence of an adjacent double bond in conjugation with the nitroso moiety introduces new reactivity centers in these substrates and



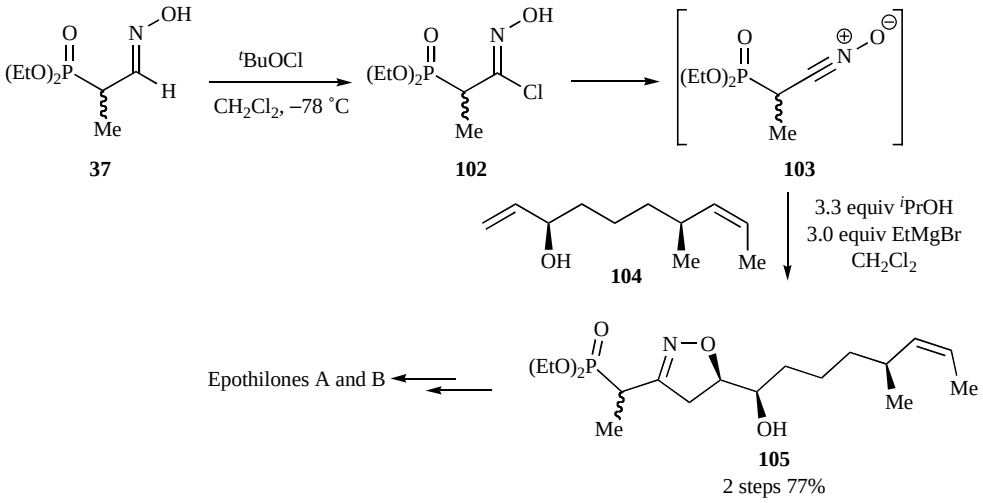
Scheme 32.



Scheme 33.



Scheme 34.



Scheme 35.

then increases the synthetic value of these compounds. Therefore, the usefulness of nitrosoalkenes [48] as conjugate addition acceptors [49], coupled with the easy conversion of the nitroso group into other functionalities, such as oximes and ketones [50], or their ability to act as dienes in hetero-Diels-Alder reactions for the preparation of 1,2-oxazine derivatives [51], have been reported. The synthesis of nitrosoalkenes containing a phosphorus substituent at *C*–4 has been scarcely explored. Only one example of the preparation of these systems has been recently reported by our group [52]. As outlined in Scheme **36**, for the preparation of phosphorylated nitrosoalkenes **108** the required bromooximes **107** are easily accessible from reaction of functionalized oximes **106** with an excess of base and subsequent addition of bromine. Nitrosoalkenes **108** have been prepared in almost quantitative yield through base-mediated dehydrohalogenation of α-bromooximes **107**. These functionalized nitrosoalkenes are useful Michael acceptors and thus, conjugate addition of nucleophilic reagents such as ammonia, primary and secondary amines or optically active amino esters furnish α-aminophosphine oxides (R = Ph) and phosphonates (R = OEt) **109** in a highly regioselective fashion (Scheme **36**) [52]. More recently, these nitrosoalkenes **108** have been used for the preparation of five-membered nitrogen containing heterocycles such as *N*-hydroxypyrrole derivatives **110**, through conjugate addition of enamines at the terminal carbon atom of the heterodiene **108**, ring closure (formally a [3+2] dipolar cycloaddition), and elimination of the pyrrolidine residue (Scheme **36**) [53]. The synthesis of similar *N*-hydroxypyrroles is also reported by other authors *via* conjugate

addition of enolates derived from ketones to phosphorylated α-chlorooximes [54].

2.3. Reactions at the OH Group of the Oxime Moiety

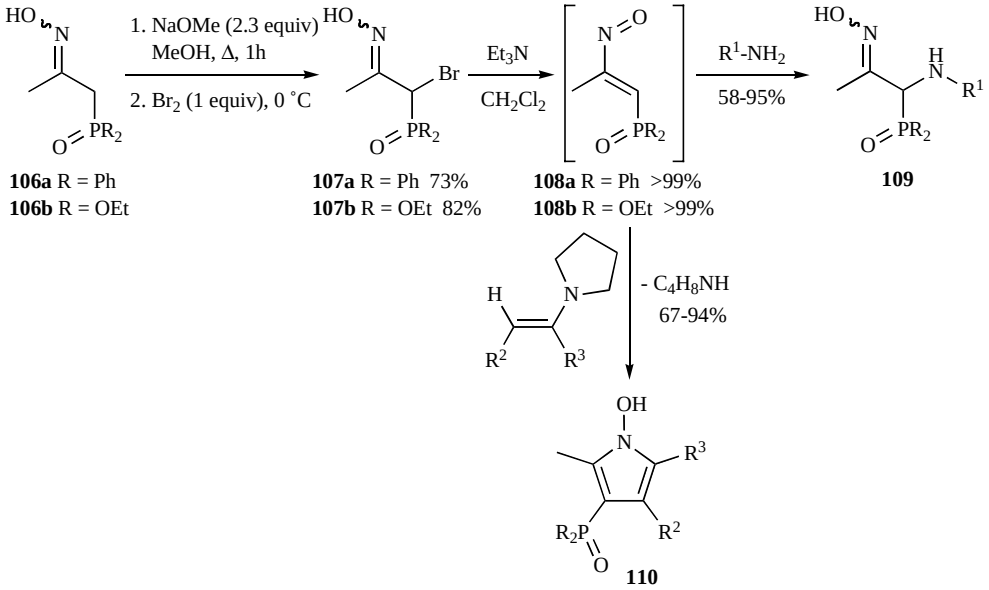
2.3.1. Cyclization Reactions

Some reports [2b,c,28a] describes the preparation of oxazaphospholine intermediates **70** by treatment of oxime phosphonium salts **71** with a base. These oxazaphospholines are readily converted, on pyrolysis at 100–150 ºC, into 2*H*-azirines **111** by an initial P–C bond cleavage [55], subsequent loss of triphenylphosphine oxide and ring-contraction (Scheme **37**).

A convenient synthesis of phosphono-substituted heterocyclic compounds has been recently reported through vinylphosphonates *via* condensation-intramolecular 1,4-addition sequence [25]. α-Formylvinylphosphonates **60** are treated with hydroxylamine hydrochloride and pyridine in ethanol under reflux to afford 4-phosphono isoxazoles **112**. Treatment of the independently prepared oxime **113** with pyridine in ethanol under reflux afforded the isoxazole **112a** in quantitative yield (Scheme **38**). This result demonstrates that the oxime **113** clearly underwent the 5-endo-trigonal cyclization to give the isoxazole **112a**.

2.3.2. Dehydratation of Oximes

Acetic anhydride-mediated dehydration of oximes can be applied to aldoxime **15** for the preparation of substituted phosphonate carbonitrile **115a**. The formation of nitrile **115a** apparently preceded by acylation of the starting aldoxime **15** with formation of the intermediate acetate **114**, and subsequent elimination of acetic acid (Scheme **39**) [8c]. A similar behaviour has been observed by our group starting from *O*-tosyl aldoximes and diethyl cyanomethylphosphonate **115b** was obtained [56].



106a R = Ph
106b R = OEt

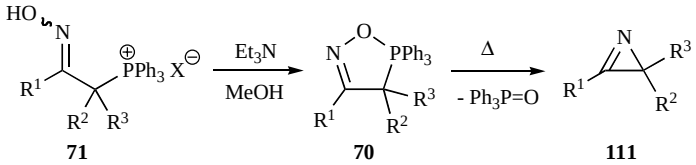
107a R = Ph 73%
107b R = OEt 82%

108a R = Ph >99%
108b R = OEt >99%

109

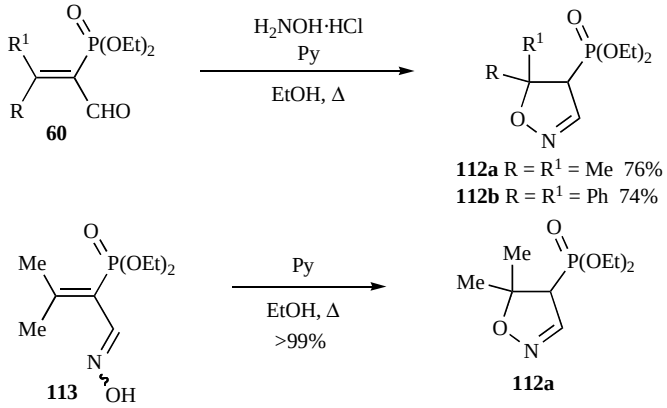
110

Scheme 36.



71 **70** **111**

Scheme 37.



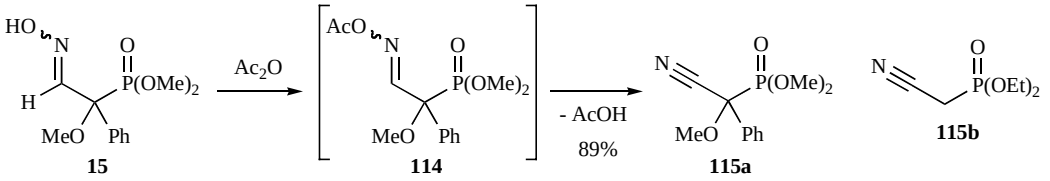
60

112a R = R^1 = Me 76%
112b R = R^1 = Ph 74%

113

112a

Scheme 38.



Scheme 39.

2.3.3. O-Functionalization Reactions

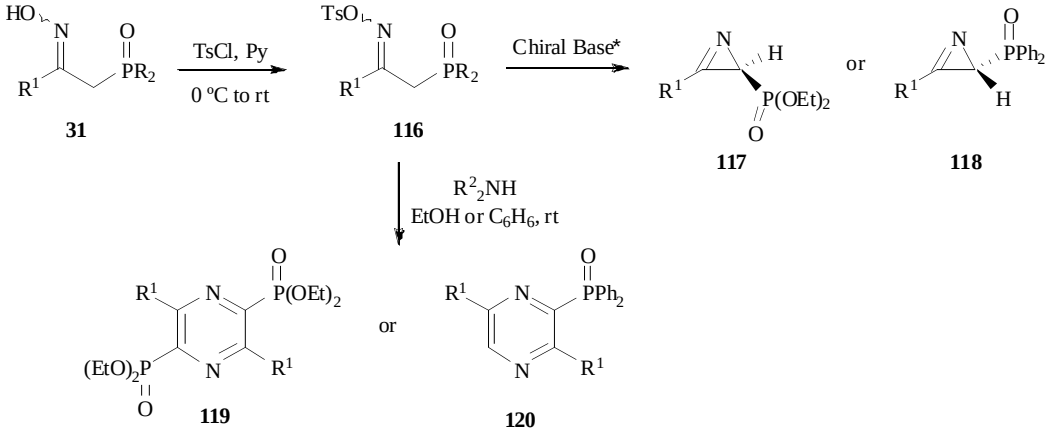
Functionalized *O*-tosyloximes **116**, can be easily accomplished by simple reaction of phosphorated oximes derived from phosphonate **31** (R = OEt) or phosphine oxide **31** (R = Ph) with tosyl chloride in pyridine (Scheme **40**). The synthesis of these phosphorylated tosyl ketoximes **116** has been applied to the asymmetric preparation of phosphorylated 2*H*-azirines **117** and **118** through the modified Neber reaction [57,58]. The same approach has been applied to the synthesis of 2*H*-azirines **117** as building blocks for the preparation of oxazoles [59], and α- and β-aminophosphonates [14,35]. *p*-Tosyloximes **116** derived from phosphonates and phosphine oxides can also be used as synthons for the preparation of phosphorus substituted pyrazines **119** and **120** [60]. Treatment of *p*-tosyloximes derived from phosphonates **116** (R = OEt) with primary or secondary amines (α-methylbenzylamine, diethylamine or piperidine) at room temperature give pyrazines **119**. Similarly, pyrazines **120** can be obtained from *p*-tosyloximes derived from phosphine oxides **116** (R = Ph) in the presence of piperidine (Scheme **40**). The formation of these pyrazines suggests the dimerization of vinyl nitrene intermediates or unstable nitrile ylide dipoles, generated from oximes **116**, followed by oxidation. In the case of pyrazines **120**, loss of diphenyl phosphine oxide ($HPOPh_2$) takes place.

O-Functionalization reaction of fluoroalkyl ketoximes **121** for the preparation of fluoroalkyl *p*-toluenesulfonyl ketoximes **122** have been recently reported by our group [19]. For this purpose, *p*-toluenesulfonyl chloride in the presence of a base such as sodium hydride was necessary for the tosylation of oximes **121** (Scheme **41**). *O*-Functionalized oximes **122** have been applied to the stereoselective synthesis of fluoroalkyl substituted aziridine-2-phosphine oxides and phosphonates **123**–**125** by diastereoselective addition of methoxide, imidazole, benzenethiol, and Grignard reagents (Scheme **41**).

3. CONCLUSIONS

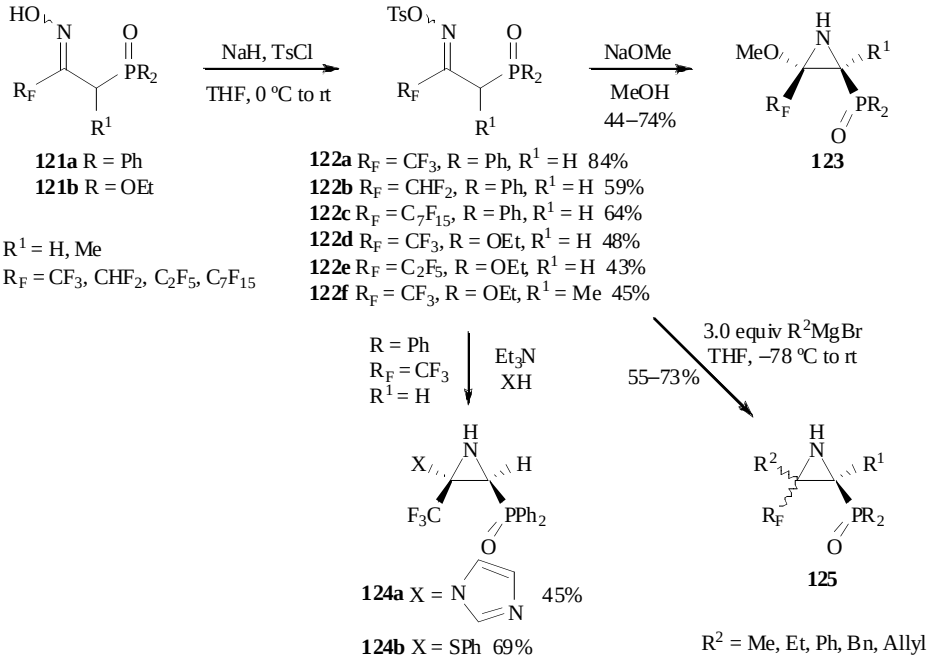
The versatility and synthetic interest of functionalized β-hydroxyimino phosphorus derivatives are outlined. Most of the published strategies in the preparation of phosphine oxides, phosphonates or phosphonium salts containing an oxime moiety at the beta-position, refer to the carbon–nitrogen double bond construction or the carbon–phosphorus single bond formation reactions.

Condensation reaction of β-keto phosphorus substituted compounds with hydroxylamines has been so far the most employed strategy to the preparation of phosphorated oximes through carbon–nitrogen double bond formation, while alkylation of phosphines and phosphites can be considered a remarkable synthetic procedure to achieve β-oximo phosphorus derivatives *via* a carbon–phosphorus single bond-forming process. Although the application of the hydrophosphinylation of *N*-protected α-amino aldehydes has become a useful and versatile method for the synthesis of the very interesting α-hydroxy-β-amino phosphonic acid derivatives, only a report has reported the nucleophilic addition of phosphorus reagents to



31	R	R^1	116	Yield (%)	2*H*-Azirine	Yield (%)	Pyrazine	Yield (%)
31a	OEt	Me	**116a**	73	**117a**	90	**119a**	97
31b	OEt	Et	**116b**	70	**117b**	95	**119b**	98
31c	OEt	Ph	**116c**	35	**117c**	69		
31d	Ph	Me	**116d**	61	**118a**	96	**120a**	70
31e	Ph	Et	**116e**	58	**118b**	95	**120b**	68

Scheme 40.



Scheme 41.

keto-oximes for the synthesis of α-hydroxy-β-oximo phosphine oxides in moderate yield. The use of the enantioselective metal-catalysed version of this reaction could offer a very efficient method for the preparation of optically pure α-hydroxy-β-oximo phosphonic acid derivatives.

Characteristic reactions of the oxime function such as the oxidation or the reduction of these substrates have been reported. Therefore, these polyfunctional compounds can be used in the elaboration of complex molecules such as natural products epothilones A and B, phosphonated dihydroisoxazole nucleosides, 1β-methylcarbapenem antibiotics and β-amino phosphorus derivatives. Moreover, the presence of phosphorus functional groups confers an additional preparative interest to these substrates because they can be used for the construction of selective C–C double bonds by means of the Wittig reaction or related processes. These bifunctional β-hydroxyimino phosphorus derivatives are excellent synthetic intermediates in preparative organic chemistry and in medicinal chemistry for the synthesis of a wide number of acyclic and heterocyclic compounds, some of them presenting biological activity. The use of enantioselective processes could use the synergy of both moieties (oximo and phosphorated groups) and open a new and efficient way for the preparation of optically pure functionalized organophosphorus derivatives and biologically active compounds.

ACKNOWLEDGEMENT

The present work was financially supported by the Dirección General de Investigación del Ministerio de Ciencia e Innovación (DGI, CTQ2009-12156 BQU), the Departamento de Educación, Universidades e Investigación del Gobierno Vasco (GV, Vitoria, IT-422-10) and by the Universidad del País Vasco (UPV/EHU) (GIU 09/57). Vicario, J. thanks the Ministerio de Ciencia e Innovación (Madrid) for a Ramón y Cajal contract.

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