Addition and Cycloaddition Reactions of Phosphinyl- and Phosphonyl-2H-Azirines, Nitrosoalkenes and Azoalkenes

Américo Lemos

CIQA, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus de Gambelas, 8005-137 Faro, Portugal; E-Mail: alemos@ualg.pt

Received: 25 August 2009; in revised form: 23 September 2009 / Accepted: 12 October 2009 / Published: 13 October 2009

Abstract: An overview of the use of 2H-azirines, conjugated nitrosoalkenes and conjugated azoalkenes bearing phosphorus substituents in addition and cycloaddition reactions is presented, focused on strategies for the synthesis of aminophosphonate and aminophosphine oxide derivatives.

Keywords: 2H-azirine; nitrosoalkene; azoalkene; phosphonyl; phosphinyl

1. Introduction

Over recent years we and others have investigated the use of 2H-azirines, conjugated nitrosoalkenes and conjugated azoalkenes in nucleophilic addition and cycloaddition reactions. The structures I, II and III of these three classes are outlined in Figure 1.

Figure 1. Name, structure and numbering of compounds.
A common feature of all three structures is that they possess a highly electrophilic carbon centre (C-3 in \(2H\)-azirines, C-4 in conjugated nitroso- and azo-alkenes) that allows nucleophilic addition reactions to proceed very readily. In reactions of nucleophiles with \(2H\)-azirines this often leads eventually to opening of the three membered ring. The electrophilic character of these structures also allows cycloaddition reactions, particularly those with nucleophilic olefins, to take place under very mild conditions. Such reactions have provided routes to a variety of novel heterocyclic structures which have proved to be very useful targets, not only due to their eventual biological and pharmacological properties, but especially to their wide and versatile use as synthetic intermediates or useful building blocks for the synthesis of amino acids, pyrroles, proline, indoles, pyrazines, and aza-sugars derivatives, amongst many other compounds [1-11].

Aminophosphonic and aminophosphinic acid derivatives can be considered as isosteres or surrogates of aminocarboxylic acids and they regulate various important biological functions [12-16]. In this context it is not surprising that organic chemists have been attracted to them and have paid particular attention to the synthesis of these types of compounds. The aim of this review is to illustrate the particular use of above reaction types of \(2H\)-azirines, nitrosoalkenes and azoalkenes bearing phosphinyl or phosphonyl substituents, for the construction of alkyl \(\alpha\)- and \(\beta\)-aminophosphonates and aminoalkylphosphine oxides.

2. \(2H\)-Azirines

\(2H\)-Azirines are strained and activated imines. Their high reactivity makes them very useful synthetic intermediates for the synthesis of aziridines, amino acids, indoles, pyrazines, and other biologically active compounds through cycloaddition and nucleophilic addition reactions [3,5,6,8,9,17].

2.1. Synthesis

Despite all these potential applications, \(2H\)-azirines bearing phosphorus substituents have received comparatively little attention. Photocyclization of vinyl azides [18], reaction of phosphites with \(\beta\)-nitrostyrenes [19] and carbene addition to aromatic nitriles [20,21] constituted the earlier examples of \(2H\)-azirines with a phosphinyl or phosphonyl functional group. Afterwards, a diverse methodology based on Swern oxidation of chiral aziridines 1 and 2, produced regioisomeric mixtures of azirinyl phosphonates 3-5 (Scheme 1) [22,23].

Thermolysis of vinyl azide 6 [24] allowed the isolation of diphenylphosphinyl \(2H\)-azirine 7 in good yield (Scheme 2), but this strategy was not suitable for the preparation of enantiopure azirines.

The asymmetric synthesis of \(2H\)-azirines bearing phosphinyl [24] and phosphonyl [25] substituents was disclosed by alkaloid mediated Neber reactions of \(\beta\)-keto tosylxoximes. Similarly, the use of chiral polymer-supported bases [26] led to \(2H\)-azirines 9 regioselectively and in high yields (Scheme 3).

Another approach based on the treatment of phosphorylated allenes 11 with sodium azide was the basis of a convenient methodology for the synthesis of 3-vinyl- and 3-dihydroisoxazolyl-\(2H\)-azirines 13 and 16 (Scheme 4) [27,28].
Scheme 1. Synthesis of 2H-azirines by Swern oxidation.

\[ \text{Ar} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{Ph} \]
\[ \text{O} \quad \text{OR} \quad \text{OR} \]

1 a-c

\[ \text{(R)}-3 \quad \text{a} \quad \text{R} = \text{Et}; \quad \text{Ar} = \text{Ph} \quad (62\%) \]
\[ \text{b} \quad \text{R} = \text{Me}; \quad \text{Ar} = 4-\text{MeOPh} \quad (68\%) \]
\[ \text{c} \quad \text{R} = \text{Me}; \quad \text{Ar} = \text{Ph} \quad (72\%) \]

\[ \text{(S)}-4 \quad \text{a} \quad \text{R} = \text{Et}; \quad \text{Ar} = \text{Ph} \quad (15\%) \]
\[ \text{b} \quad \text{R} = \text{Me}; \quad \text{Ar} = 4-\text{MeOPh} \quad (12\%) \]

\[ \text{N} \quad \text{H} \quad \text{Ph} \]
\[ \text{P} \quad \text{O} \quad \text{EtO} \quad \text{EtO} \]

2

\[ \text{(R)}-3 \quad \text{a} \quad \text{(40%)} \]
\[ \text{(S)}-5 \quad \text{(49%)} \]

i) DMSO, (COCl\(_2\)); then Et\(_3\)N; -78º C to r.t.

Scheme 2. Thermolysis of vinyl azide 6.

\[ \text{N} \quad \text{3} \quad \text{Ph} \quad \text{O} \quad \text{Ph} \]
\[ \text{O} \quad \text{O} \]

6

(90%)

7

Scheme 3. 2H-Azirines by Neber reactions of β-keto tosyloximes.

\[ \text{R}^1 \quad \text{N} \quad \text{P} \quad \text{O} \quad \text{Ts} \]
\[ \text{Base} \]

8

\[ \text{N} \quad \text{4a, 9a} \quad \text{R}^1 = \text{Me} \quad (74-96\%) \]
\[ \text{9b} \quad \text{R}^1 = \text{Et} \]

\[ \text{10a} \quad \text{R}^1 = \text{Me} \]
\[ \text{b} \quad \text{R}^1 = \text{Et} \]

Base = Quinidine; Sparteine; Hydroquinidine;
Quinine;
Scheme 4. Synthesis of 3-vinyl- and 3-dihydroisoxazolyl-2H-azirines.

Scheme 5. Hydride addition to 2H-azirines 9 and 10.

2.2. Addition reactions

One of the earliest reported reactions of 2H-azirines bearing phosphorus substituents was hydride addition [24,25]. The treatment of azirines 9, 10 with sodium borohydride in ethanol produced cis-aziridines exclusively (Scheme 5). The stereochemical assignment was based on the large coupling constant observed for the ring protons and further established by the transformation into enantiopure cis-N-(p-toluenesulfinyl)-aziridines by treatment with (-)-(S)-menthyl p-toluenesulfinate [24].

For the synthesis of β-amino-phosphine oxide and –phosphonate derivatives 22 from tosylximes 19, a similar addition of hydride takes place with 3-fluoroalkyl-2H-azirines 20–postulated as plausible intermediates – producing regioselectively cis-aziridines 21 which then lead to compounds 22 by ring opening [29] (Scheme 6).
Scheme 6. β-Amino-phosphine oxides and –phosphonates 22 from tosyloximes 19.

\[
\begin{align*}
\text{TsO} & \quad \text{NaBH}_4 \\
\text{RF} & \quad \text{N} \\
\text{P} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{RF} & \quad \text{N} \\
\text{P} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

\[\text{THF} -30^\circ C\]

\[\begin{align*}
\text{22} & \quad \text{a} \quad \text{RF} = \text{CF}_3; \ R = \text{Ph} \quad (74\%) \\
& \quad \text{b} \quad \text{RF} = \text{CF}_3; \ R = \text{OEt} \quad (72\%) \\
& \quad \text{c} \quad \text{RF} = \text{C}_2\text{F}_5; \ R = \text{OEt} \quad (45\%)
\end{align*}\]

Nitrogen heterocycles, in the presence or absence of base, add regioselectively to the azirine nucleus following the general pattern – the attack being from the less hindered face of the azirine - yielding functionalized aziridines [29,30] (Schemes 7 and 8).

Scheme 7. Addition of nitrogen heterocycles to 2H-azirines 23.

\[
\begin{align*}
\text{23} & \quad \text{a} \quad R = \text{Ph} \\
& \quad \text{b} \quad R = \text{OEt}
\end{align*}
\]

\[
\begin{align*}
\text{24} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{25} & \quad (83\%)
\end{align*}
\]

\[
\begin{align*}
\text{27} & \quad \text{a} \quad R = \text{Ph} \quad (87\%) \\
& \quad \text{b} \quad R = \text{OEt} \quad (69%)
\end{align*}
\]

Scheme 8. Imidazole mediated generation of 2H-azirine 20a and nucleophilic addition.

\[
\begin{align*}
\text{20a} & \quad \text{TsO} \\
\text{F}_3\text{C} & \quad \text{N} \\
\text{P} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{24} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{24} & \quad (45\%)
\end{align*}
\]

Oxygen [30] (Scheme 9) and sulfur [29] (Scheme 10) nucleophiles also add in a similar and regioselective mode, to 2H-azirines bearing phosphorus substituents. In the case of the reaction with benzenethiol, if a methyl group is present in the ring of the resulting aziridines, subsequent ring opening reaction leads to α-aminophosphine oxide and –phosphonates 33.
Scheme 9. Methanol addition to 2H-azirines 20.

Methanol addition to 2H-azirines 20.

Scheme 10. Benzenethiol addition to 2H-azirines 23 and 29.

Benzenethiol addition to 2H-azirines 23 and 29.

The addition of Grignard reagents to 2-phosphinyl- and 2-phosphonyl-2H-azirines is less simple. Early reports with 2,3-diphenyl-2H-azirine revealed that the reaction followed the general pattern of addition of nucleophiles, i.e., the obtained aziridines arise from the attack at the less hindered face of the azirine [31]. These findings are in clear contrast with those obtained with alkyl 2H-azirine-2-carboxylates, in which the syn addition –to the more hindered face– is preferred (Scheme 11) [32,33]. These facts have been ascribed to a prechelating effect of the Grignard reagents with carboxylate substituents.

Scheme 11. Addition of Grignard reagents to 2H-azirine-2-carboxylates.
When the carboxylate group was replaced by a phosphoryl group, the reverse preference was observed, i.e., an exclusive attack at the least hindered side was encountered [30] (Table 1).

Table 1. Addition of Grignard reagents.

| compound | R   | R¹ | R²   | yield (%) |
|----------|-----|----|------|-----------|
| 41a      | OEt | Me | Et   | 60        |
| 41b      | OEt | Me | Bz   | 66        |
| 41c      | OEt | Ph | Allyl| 87        |
| 41d      | Ph  | Me | Et   | 57        |
| 41e      | Ph  | Me | Allyl| 68        |
| 41f      | Ph  | Me | 2-ethyl-[1,3]-dioxolanyl | 65 |
| 41g      | Ph  | Ph | Allyl| 63        |

This behaviour has been ascribed to the high exocyclic dihedral angle of the saturated carbon and to the presence of a bulky tetrahedral phosphorus group. But if a chelating substituent, such as alkylfluoromethyl or perfluoroalkylmethyl is present beside the phosphorus group, the former may play a major role in the mode of addition and in the reaction outcome, as demonstrated by the production of mixtures of cis/trans aziridines 43/44 [29] (Scheme 12).

Scheme 12. Generation of 2H-azirines 42 by Grignard reagents and nucleophilic addition.

Carboxylic acids [26], N-protected aminoacids and peptide residues [34] also add to the carbon nitrogen double bond of phosphinyl- and phosphonyl-2H-azirines. The concomitant ring opening leads to ketamides 48 (Scheme 13).
Scheme 13. Ketamides 48 from 2H-azirines 23 and 29.

Due to their ambident character, phosphinyl- and phosphonyl-2H-azirines also react as nucleophiles with carboxylic acid derivatives, such as acid chlorides, producing exclusively trans-aziridines 50 [35]. The scope of the reaction is not limited to simple chlorides since other functionalized acyl chlorides will react similarly in good overall yields.

Scheme 14. Reactions of acyl chlorides with phosphinyl- and phosphonyl-2H-azirines.

2.3. Cycloadditions

Simple alkyl- and aryl-2H-azirines, although being more reactive than acyclic imines, participate in Diels-Alder reactions only with highly reactive dienes, such as cyclopentadienones and 1,3-diphenylisobenzofuran in refluxing toluene [36], or with acyclic dienes and cyclopentadiene under Lewis acid catalysis [37,38]. 2H-Azirines with an alkoxy-, aryl-, amino-carbonyl [8,39] or heteroaromatic [40] substituent on the C=N bond are particularly good dienophiles in Diels–Alder reactions with a great variety of dienes, as a consequence of the conjugated effect of ring strain and extra activation by the electron-withdrawing group.

Similarly enantiomerically enriched 2H-azirine-3-phosphonates 51 when stirred with 100 equiv of 2,3-dimethylbutadiene or trans-piperylene for 2-4 days at room temperature or with Danishefsky’s diene for 8 hours, afforded bicyclic aziridines 53 as single stereoisomers in good yields [23] (Scheme 15).
Scheme 15. Cycloaddition reactions of 2H-azirine 51.

The stereochemistry of cycloadducts 53 was consistent with exclusive addition of the diene to the less hindered face of the azirine 51. The longer reaction times, when compared with 2H-azirine-3-carboxylates, may suggest that 2H-azirine-3-phosphonates are less reactive than carboxylates.

Recently an azirine bearing both ethoxycarbonyl and phosphonate groups, was generated in situ and intercepted with a number of nucleophilic dienes [41]. With open chain dienes bicyclic functionalized six-membered ring fused aziridines were produced; although cyclic dienes afforded tricyclic structures. The presence of a trimethylsilyloxy group at the conjugated system, induced hydrolysis of cycloadduct 56f and 56c to 57 and 58 respectively (Scheme 16).

Scheme 16. Cycloaddition reactions of 2H-azirine 55 with nucleophilic dienes.

The products were isolated as single isomers, presumed to be formed by endo selective processes, as clearly indicated by the low field resonance of H-3 in the tricyclic structure 56d, attributed to the anisotropy of the backside double bond over H-3, due to constrain of the tricyclic structure [42]. To the poor stability of azirine 55 was ascribed the low to moderate yields of cycloadducts (Scheme 16).
3. Nitroso- and Azo-alkenes

Nitrosoalkenes and azoalkenes, used either as Michael-type acceptors in conjugate 1,4-additions, or as heterodienes in cycloaddition reactions with a range of nucleophiles, alkenes and heterocycles, have proved to be invaluable tools for the synthetic organic chemists.

3.1. Synthesis or generation

Electron-deficient nitrosoalkenes are, generally, very unstable species and for this reason, they are usually generated and intercepted \textit{in situ}. Depending on the substituents, azoalkenes are sometimes stable enough to be isolated. Anyway, being isolated or generated \textit{“in situ”}, the most common, general and broad scope method for the obtention of nitroso- and azo-alkenes is the base induced 1,4-dehydro elimination from oximes and hydrazones bearing a suitable halogen or ester leaving group at the $\alpha$-position [1,2,4,7,10,11] (Scheme 17).

\textbf{Scheme 17. General method for the obtention of nitroso- and azo-alkenes.}

3.2. Reactions with nucleophiles

Although in reactions involving nitroso- and azo-alkenes generated and intercepted \textit{in situ}, the distinction between nucleophilic substitution of the original $\alpha$-halogenated oxime or hydrazone and 1,4-conjugate (or Michael type) addition, is sometimes an intricate decision, the following reactions are thought to proceed \textit{via} this latter process.

The primary literature reference to azoalkenes bearing phosphorus substituents [43] reported their use at the synthesis of 1-aminopyrroles substituted with a phosphine oxide or phosphonate group in the 3-position.

Achiral and chiral phosphinyl- and phosphonyl-1,2-diaza-1,3-butadienes obtained from hydrazonoalkyl-phosphine oxides and –phosphonates, were reported to add ammonia, aminoesters and aminoalcohols giving functionalized $a$-amino-phosphine oxides and –phosphonates [44,45] (Scheme 18). Very low diastereoselection with optically active amines was encountered - the adducts were isolated as nonseparable diastereoisomeric mixtures. Better diastereoselection was found when the bulky (S)-\textit{tert}-leucinol substituent was used.
Scheme 18. Nucleophilic addition of ammonia, aminoesters and aminoalcohols to azoalkene 64.

\[
\begin{align*}
\text{CO}_2\text{R}^1 & \quad \text{NH}_3 \\
\text{N} & \quad \text{PR}_2 \\
\text{O} & \quad \text{CO}_2\text{R}^1 \\
\hline
\text{N} & \quad \text{PR}_2 \\
\text{O} & \quad \text{CO}_2\text{R}^1 \\
\hline
\text{N} & \quad \text{NH} \\
\hline
\end{align*}
\]

\[\text{H}_2\text{N} \quad \text{R}^2 \quad \text{R}^3\]

\[\text{R}^1 = \text{Et}; \text{R} = \text{Ph} \quad (68\%)\]

\[\text{R} = \text{OEt}; \text{Ph}; \text{R}^1 = \text{Et}; \text{(-)-Ment} \]
\[\text{R}^2 = \text{Me}; \text{CH}_2\text{OH}; \text{CHMeOH} \]
\[\text{R}^3 = \text{H}; \text{iBu}; \text{Ph} \]

(43-99\%) (\text{<10-70 de\%})

The diastereoselective addition of optically active amino esters gave slightly improved results when an optically active group was introduced at position 3 of the azoalkene. Thus the azovinylphosphonate 68 produced hydrazono derivatives 70 in good yields but moderate diastereoselectivity [46] (Scheme 19).

Scheme 19. Addition of amino esters to optically active azoalkene 68.

\[
\begin{align*}
\text{CO}_2\text{Bn} & \quad \text{H}_2\text{N} \quad \text{R}^2 \\
\text{N} & \quad \text{PR}_2 \\
\text{O} & \quad \text{CO}_2\text{Bn} \\
\hline
\text{N} & \quad \text{PR}_2 \\
\text{O} & \quad \text{CO}_2\text{Bn} \\
\hline
\text{N} & \quad \text{NH} \\
\hline
\end{align*}
\]

\[\text{R}^1 = \text{Bn}; \text{R}^2 = \text{H} \quad 40 \quad 75\]
\[\text{R}^2 = \text{H} \quad 30 \quad 64\]
\[\text{R}^1 = \text{CH}_2\text{CH}_2\text{CO}_2\text{Et}; \text{R}^2 = \text{H} \quad 70 \quad 83\]
\[\text{R}^1 = \text{p}-\text{OMeC}-\text{C}_6\text{H}_4; \text{R}^2 = \text{H} \quad 84 \quad 77\]
\[\text{R}^1 = \text{p}-\text{EtO}_2\text{C}-\text{C}_6\text{H}_4; \text{R}^2 = \text{H} \quad 84 \quad 77\]
\[\text{R}^1 = \text{iPr}; \text{R}^2 = \text{CO}_2\text{Me} \quad 40 \quad 87\]
\[\text{R}^1 = \text{Bn}; \text{R}^2 = \text{CO}_2\text{Me} \quad 50 \quad 81\]
\[\text{R}^1 = \text{CO}_2\text{Me}; \text{R}^2 = \text{iPr} \quad 65 \quad 57\]

Amino- and alkoxy-carbonyl 1,2-diaza-1,3-dienes underwent 1,4-addition with sulfur nucleophiles such as 1,2-aminothiols [47] (Scheme 20), thiourea [48] (Scheme 21) and 3-mercapto-2-ketones [49] (Scheme 22) producing either functionalized hydrazones or ensuing cyclised heterocycles.
**Scheme 20.** 1,4-Addition of 1,2-aminothiols 72 to nitrosoalkenes 71.

Similarly, hydrazones 78a,b arised from the 1,4-addition of oxygen nucleophiles to 1,2-diaza-1,3-dienes [48] (Scheme 21).

**Scheme 21.** Addition of thiourea and methanol to 1,2-diaza-1,3-butadienes 75.

**Scheme 22.** Addition of 3-mercapto-2-ketones 80 to azoalkenes 79.

Under solvent free or solid-phase conditions, a Michael type addition of 1,2-diamines to phosphinyl- and phosphonyl-azoalkenes was observed, furnishing substituted hydrazones which subsequently were cyclised into pyridazines [50] (Scheme 23).
Scheme 23. Addition of 1,2-diamines to phosphinyl- and phosphonyl-azoalkenes 83.

\[
\begin{align*}
\text{N} & \text{OEt} \\
\text{P} & \text{R}
\end{align*}
\]

The nitrogen heteroaromatic \(N\)-methylimidazole was reported to promote dehydrohalogenation of hydrazone 87 and to add regioselectively to the azo-alkene 89, conducting to functionalized \(\alpha\)-hydrazonophosphonate 91 [51] (Scheme 24).

Scheme 24. \(N\)-methylimidazole generation of azoalkene 89 and nucleophilic addition.

Several examples of nucleophilic conjugate addition to nitrosoalkenes are reported in the literature [4,10,52-54], whereas reports of related reactions of phosphinyl- and phosphonyl-nitrosoalkenes are scarcely described. Nitrosoalkenes 92, generated “in situ” from the corresponding \(\alpha\)-bromooxime, were reported to act as Michael acceptors towards ammonia, amines and optically active amino esters, affording \(\alpha\)-amino phosphine oxides and \(\alpha\)-amino phosphonates [55] (Scheme 25). The reactions, although being regioselective, lacked stereoselectivity with optically active compounds.

Scheme 25. Nitrosoalkenes 92 as Michael acceptors.
There are various works reporting reactions of conjugated nitrosoalkenes with enamines \[52,56-60\] affording 1,2-oxazines in good to excellent yields via postulated Diels-Alder reactions with inverse electron demand. A more recent work \[61\] using density functional theory (DFT) studies, showed a polar character of the Diels–Alder reaction of nitrosoalkenes with enamines, being the two σ bonds formed in these polar cycloaddition reactions in a highly asynchronous concerted process. On the other hand reactions of azoalkenes with enamines are solvent and structure – of enamine and azoalkene dependent \[1,62-69\], proceeding either via \[4+2\] cycloaddition or conjugate addition.

In this context, Palacios and co-workers \[70\] found that the reactions of nitrosoalkenes, bearing a phosphinyl or phosphonyl substituent at the terminal carbon, with enamines \(99\) did not proceed by \[4+2\] cycloaddition reactions producing the expected 1,2-oxazines, but \(N\)-hydroxypyrroles were instead isolated, presumably by a mechanism involving an initial conjugate addition of the enamine followed by a formal \[3+2\] dipolar cycloaddition (Scheme 26).

**Scheme 26. Reaction of nitrosoalkenes \(92\) with enamines \(99\).**

3.3. Cycloadditions

Cycloaddition reactions of nitroso- and azo-alkenes with electron rich carbon-carbon double bonds and heterocycles are important and powerful synthetic tools, as demonstrated by the enormous impetus of the chemistry of these compounds over the last decades.

Azoalkenes with a phosphinyl or phosphonyl substituent at the 4-position were generated by triethylamine induced dehydrohalogenation of chlorohydrzones \[71\]. Its interception with acyclic—styrene and cyclic—cyclopentadiene and norbornadiene alkenes and di-hydrofuran gave regio- and stereo-selectively endo cycloadducts, except in the case of the strained norbornadiene, which produced an exo cycloadduct (Scheme 27).
Attempts to bring about some degree of diastereoselectivity to the reaction, induced by the use of an optically active (-)-menthyl ester, were unsuccessful, since a diasteroisomeric ratio of 1:1 was found.

Cycloadducts were also obtained in regioselective fashion in reactions of azoalkenes bearing a phosphonate substituent at the 3-position with electron rich olefins [51] (Scheme 28).

Reactions with electron rich heterocycles such furan and dihydrofuran gave rise to the formation of the corresponding cycloadducts. With pyrrole and indole open chain hydrazones were isolated (Table 2), assumed to be the result of rearomatization of the primarily formed cycloadducts [72]. The yields were, in general, lower than those obtained in similar reactions with azoalkenes bearing the same alkoxy carbonylazo substituent, but having an ethoxycarbonyl group at the 3-position [73], pointing out that eventually the ethoxycarbonyl group may play a more effective role than the phosphonate moiety.
Table 2. Reactions of azoalkene 89 with electron-rich heterocycles.

| Azoalkene | Heterocycle | Product | Yield (%) |
|-----------|-------------|---------|-----------|
| 120       | 111         | 121     | 44        |
| 123       | 124         | 125     | 33        |
| 126       |             |         |           |

Nitrosovinylphosphonates generated from the corresponding chlorooximes were intercepted by electron-rich alkenes and heterocycles [74]. The yields, although not optimised, were fair and the reactions were found to be completely regioselective: no other isomers were detected or isolated from the reaction medium (Scheme 29).

Scheme 29. Cycloaddition reactions of nitrosovinylphosphonates 128.
4. Concluding Remarks

Synthetic applications of 2H-azirines, nitroso- and azo-alkenes bearing phosphinyl or phosphonyl substituents, emphasised towards the synthesis of $\alpha$- and $\beta$-amino-phosphonates and –phosphine oxides have been addressed in this review. Established methods of aziridine ring opening [17,75] and reductive transformations at the C=N bond [76-78] will further broaden the scope and importance of these strategies that surely will be further developed and attract the attention and interest of synthetic chemists.

Acknowledgements

Special thanks are due to T. L. Gilchrist for helpful suggestions and discussions.

References and Notes

1. Attanasi, O.A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F.R.; Santeusanio, S. Cultivating the passion to build heterocycles from 1,2-diaza-1,3-dienes: The force of imagination. Eur. J. Org. Chem. 2009, 3109–3127.
2. Rai, K.M.L. Heterocycles via Oxime Cycloadditions. Top. Heterocycl. Chem. 2008, 13, 1–69.
3. Palacios, F.; Ochoa de Retana, A.M.; Marigorta, E.M.; de los Santos, J.M. Addition Reactions to the Imine Bond of 2H-Azirines. Synthesis of Heterocyclic Compounds. In Recent Developments in Heterocyclic Chemistry; Pinho e Melo, T.M.V.D., Rocha-Gonsalves, A.M.A., Eds.; Research Signpost: Trivandrum, India, 2007; pp. 27–58.
4. Reissig, H.U.; Zimmer, R. 1-Nitrosoalkenes. In Science of Synthesis; Molander, G.A., Ed.; Thieme: Stuttgart, Germany, 2006; Vol. 33; pp. 371–389.
5. Pinho e Melo, T.M.V.D.; Rocha Gonsalves, A.M.A. Exploiting 2-halo-2H-Azirine chemistry. Curr. Org. Synth. 2004, 1, 275–292.
6. Palacios, F.; Ochoa de Retana, A.M.; Marigorta, E.M.; de los Santos, J.M. Preparation, properties and synthetic applications of 2H-Azirines. A review. Org. Prep. Proced. Int. 2002, 34, 219–269.
7. Attanasi, O.A.; De Crescentini, L.; Filippone, P.; Mantelilini, F.; Santeusanio, S. 1,2-Diaza-1,3-butadienes; just a nice class of compounds, or powerful tools in organic chemistry? Reviewing an experience. ARKIVOC 2002, 274–292.
8. Gilchrist, T.L. Activated 2H-Azirines as Dienophiles and Electrophiles. Aldrichim. Acta 2001, 34, 51–55.
9. Palacios, F.; Ochoa de Retana, A.M.; Marigorta, E.M.; de los Santos, J.M. 2H-Azirines as synthetic tools in organic chemistry. Eur. J. Org. Chem. 2001, 2401–2414.
10. Lyapkalo, I.M.; Ioffe, S.L. Conjugated Nitrosoalkenes. Russ. Chem. Rev. 1998, 67, 467–484.
11. Attanasi, O.A.; Filippone, P. Working twenty years on conjugated azo-alkenes (and environs) to find new entries in organic synthesis. Synlett 1997, 1128–1140.
12. Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. An overview of stereoselective synthesis of $\alpha$-aminophosphonic acids and derivatives. Tetrahedron 2009, 65, 17–49.
13. Palacios, F.; Alonso, C.; de los Santos, J.M. Synthesis of $\beta$-Aminophosphonates and -Phosphinates. Chem. Rev. 2005, 105, 899–931.
14. Moonen, K.; Laureyn, I.; Stevens, C.V. Synthetic methods for aza-azaheterocyclic phosphonates and their biological activity. *Chem. Rev.* **2004**, *104*, 6177–6215.

15. Kafarski, P.; Lejczak, B. The Biological Activity of Phosphono- and Phosphino-peptides. In *Aminophosphinic and Aminophosphoric Acids. Chemistry and Biological Activity*; Kukhar, V.P., Hudson, H.R., Eds.; John Wiley & Sons Ltd: Chichester, UK, 2000; pp. 173–203, 407–442.

16. Kafarski, P.; Lejczak, B. Biological activity of aminophosphonic acids. *Phosphor. Sulfur Silicon* **1991**, *63*, 193–215.

17. Singh, G.S.; D’hooghe, M.; De Kimpe, N. Synthesis and reactivity of C-heteroatom-substituted aziridines. *Chem. Rev.* **2007**, *107*, 2080–2135.

18. Christensen, B.G.; Beattie, T.R. Herstellung von Phosphonsäuren. *Ger. Offen.* 2,011,092, 1970; [Chem. Abstr. **1971**, *74*, 42491].

19. Russel, G.A.; Yao, C.F. Reactions of ethyl phosphites with β-nitrostyrenes. The role of nitrosoalkenes as intermediates. *J. Org. Chem.* **1992**, *57*, 6508–6513.

20. Alcaraz, G.; Wecker, U.; Baceiredo, A.; Dahan, F.; Bertrand, G. Synthesis of a 2H-Azirine by [1+2] cycloaddition of a phosphinocarbene with a nitrile and its ring-expansion to a 1,2 $\lambda^5$-Azaphosphete. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1246–1248.

21. Piquet, V.; Baceiredo, A.; Gornitzka, H.; Dahan, F.; Bertrand, G. The Stable (phosphino)silyl)carbene as a useful building block: Synthesis and reactivity of 2-phosphorus-substituted 2H-Azirines. *Chem. Eur. J.* **1997**, *3*, 1757–1264.

22. Davis, F.A.; McCoull, W. Asymmetric synthesis of aziridine 2-phosphonates and azirinyl PHOSPHONATES from enantiopure sulfinimines. *Tetrahedron Lett.* **1999**, *40*, 249–252.

23. Davis, F.A.; Wu, Y.; Yan, H.; Prasad, K.R.; McCoull, W. 2H-Azirine 3-phosphonates: A new class of chiral iminodienophiles. asymmetric synthesis of quaternary piperidine phosphonates. *Org. Lett.* **2002**, *4*, 655–658.

24. Palacios, F.; Ochoa de Retana, A.M.; Gil, J.I.; Ezpeleta, J.M. Simple asymmetric synthesis of 2H-Azirines derived from phosphine oxides. *J. Org. Chem.* **2000**, *65*, 3213–3217.

25. Palacios, F.; Ochoa de Retana, A.M.; Gil, J.I. Easy and efficient synthesis of enantiomerically enriched 2H-azirines derived from phosphonates. *Tetrahedron Lett.* **2000**, *41*, 5363–5366.

26. Palacios, F.; Aparicio, D.; Ochoa de Retana, A.M.; de los Santos, J.M.; Gil, J.I.; Alonso, J.M. Asymmetric synthesis of 2H-Azirines derived from phosphine oxides using solid-supported amines. Ring opening of azirines with carboxylic acids. *J. Org. Chem.* **2002**, *67*, 7283–7288.

27. Brel, V.K. New synthetic route to 2-(Diethylphosphono)-2H-Azirines. *Synthesis* **2002**, *1829–1832.*

28. Brel, V.K. Synthesis of 3-azido-4-(diethoxyphosphoryl)alka-1,3-dienes and their transformation to derivatives of 2H-azirine. *Synthesis* **2007**, 2674–2680.

29. Palacios, F.; Ochoa de Retana, A.M.; Alonso, J.M. Regioselective synthesis of fluoroalkylated β-aminophosphorus derivatives and aziridines from phosphorylated oximes and nucleophilic reagents. *J. Org. Chem.* **2006**, *71*, 6141–6148.

30. Palacios, F.; Ochoa de Retana, A.M.; Alonso, J.M. Reaction of 2H-Azirine phosphine oxide and - phosphonates with nucleophiles. Stereo-selective synthesis of functionalized aziridines and α- and β-aminophosphorus derivatives. *J. Org. Chem.* **2005**, *70*, 8895–8901.
31. Carlson, R.M.; Lee, S.Y. Olefin synthesis via the stereospecific deamination of aziridines. *Tetrahedron Lett.* **1969**, *10*, 4001–4004.

32. Davis, F.A.; Liang, C.H.; Liu, H. Asymmetric synthesis of β-substituted α-amino acids using 2H-azirine-2-carboxylate esters. Synthesis of 3,3-disubstituted aziridine-2-carboxylate esters. *J. Org. Chem.* **1997**, *62*, 3796–3797.

33. Davis, F.A.; Deng, J.; Zhang, Y.; Haltiwanger, R.C. Aziridine-mediated asymmetric synthesis of quaternary β-amino acids using 2H-azirine 2-carboxylate esters. *Tetrahedron* **2002**, *58*, 7135–7143.

34. Palacios, F.; Ochoa de Retana, A.M.; Gil, J.I.; Alonso, J.M. Synthesis of optically active oxazoles and N-protected amino acids or peptides. *Tetrahedron Asymmetry* **2002**, *13*, 2541–2552.

35. Palacios, F.; Ochoa de Retana, A.M.; Gil, J.I.; Alonso, J.M. Regioselective synthesis of 4- and 5-oxazole-phosphate oxides and –phosphonates from 2H-azirines and acyl chlorides. *Tetrahedron* **2004**, *60*, 8937–8947.

36. Anderson D.J.; Hassner, A. Synthesis of heterocycles via cycloadditions to 1-azirines. *Synthesis* **1975**, 483–495.

37. Ray, C.A.; Risberg, E.; Somfai, P. Lewis acid-catalyzed hetero Diels–Alder cycloadditions of 3-alkyl, 3-phenyl and 3-carboxylated 2H-azirine. *Tetrahedron Lett.* **2001**, *42*, 9289–9291.

38. Ray, C.A.; Risberg, E.; Somfai, P. Diastereoselective Lewis acid-catalysed [4+2] cycloadditions of 3-alkyl-, 3-aryl- and 3-carboxyl-2H-azirines: A route to aziridine containing azabicyclo[4.1.0]heptanes and azatricyclo[2.2.1.0]nonanes. *Tetrahedron* **2002**, *58*, 5983–5987.

39. Gilchrist, T.L.; Mendonça, R. Synthesis and diels–alder reactions of 2H-azirine-3-carboxamides. *ARKIVOC* **2000**, 769–778.

40. Alves, M.J.; Fortes, A.G.; Lemos, A.; Martins, C. Ethyl 3-(2-pyridyl)-2H-azirine-2-carboxylate: synthesis and reaction with dienes. *Synthesis* **2005**, 555–558.

41. Alves, M.J.; Lemos, A.; Rodriguez-Borges, J.E.; García-Mera, X.; Fortes, A.G. Ethyl 2-(diisopropoxyphosphoryl)-2H-azirine-3-carboxylate: Reactions with nucleophilic 1,3-dienes. *Synthesis* **2009**, 3263–3266.

42. Alves, M.J.; Gilchrist, T.L. Methyl 2-aryl-2H-azirine-3-carboxylates as dienophiles. *J. Chem. Soc. Perkin 1* **1998**, 299–303.

43. Palacios, F.; Aparicio, D.; de los Santos, J.M. An efficient strategy for the regioselective synthesis of 3-phosphorylated-1-aminopyrroles from β-hydrazono phosphine oxides and phosphonates. *Tetrahedron* **1999**, *55*, 13767–13778.

44. Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J.M. Addition of amine derivatives to phosphorylated 1,2-diaza-1,3-butadienes. Synthesis of α-aminophosphonates. *Tetrahedron Lett.* **2004**, *45*, 4345–4348.

45. Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J.M.; Ignacio, R. An efficient synthesis of functionalized α-amino-phosphate oxides and -phosphonates by addition of aminoalcohols to 4-phosphorylated-1,2-diaza-1,3-butadienes. *Arkivoc* **2005**, 153–161.

46. Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J.M. Synthesis of functionalized α-amino-phosphate oxides and -phosphonates by addition of amines and aminoesters to 4-phosphinyl- and 4-phosphonyl-1,2-diaza-1,3-butadienes. *Tetrahedron* **2005**, *61*, 2815–2830.
47. Attanasi, O.A.; Filippone, P.; Lillini, S.; Mantellini, F.; Nicolini, S.; de los Santos, J.M.; Ignacio, R.; Aparicio, D.; Palacios, F. Reactions of 1,2-diaza-1,3-dienes with thiol derivatives: A versatile construction of nitrogen/sulfur heterocycles. *Tetrahedron* **2008**, *64*, 9264–9274.

48. Attanasi, O.A.; Baccolini, G.; Boga, C.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F. Carbon-phosphorus bond formation and transformation in the reaction of 1,2-diaza-1,3-butadienes with alkyl phenylphosphonites. *Tetrahedron* **2008**, *64*, 6724–6732.

49. Attanasi, O.A.; Filippone, P.; Lillini, S.; Mantellini, F.; de los Santos, J.M.; Ignacio, R.; Palacios, F. Domino reaction for the construction of new 2-Oxo[1,2,4]triazolo[5,1-c]thiazines. *Synlett* **2009**, 735–738.

50. Aparicio, D.; Attanasi, O.A.; Filippone, P.; Ignacio, R.; Lillini, S.; Mantellini, F.; Palacios, F.; de los Santos, J.M. Straightforward access to pyrazines, piperazinones, and quinoxalines by reactions of 1,2-diaza-1,3-butadienes with 1,2-diamines under solution, solvent-free, or solid-phase conditions. *J. Org. Chem.* **2006**, *71*, 5897–5905.

51. Lemos, A.; Lopes, M. Reactions of azovinylphosphonates with nucleophilic alkenes and heterocycles: Synthesis of tetrahydropyridazine-3-phosphonate and 2-substituted-1-hydrazonoethylphosphonate derivatives. *Phosphor. Sulfur Silicon* **2008**, *183*, 2882–2890.

52. Gilchrist, T.L.; Lingham, D.A.; Roberts, T.G. Ethyl 3-bromo-2-hydroxyiminopropanoate, a reagent for the preparation of ethyl esters of α-amino acids. *J. Chem. Soc. Chem. Commun.* **1979**, 1089–1090.

53. Gilchrist, T.L.; Stretch, W.; Chrystal, E.J.T. Reaction of azoles with ethyl bromopyruvate oxime: Alkylation by substitution and by elimination-addition. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2235–2239.

54. Zimmer, R.; Reissig, H.U. Efficient synthesis of trifluoromethyl-substituted 5,6-dihydro-4H-1,2-oxazines by the hetero-diels-aldor reaction of 1,1,1-trifluoro-2-nitroso-2-propene and electron-rich olefins. *J. Org. Chem.* **1992**, *57*, 339–347.

55. De los Santos, J.M.; Ignacio, R.; Aparicio, D.; Palacios, F. Michael addition of amine derivatives to conjugate phosphinyl and phosphonyl nitrosoalkenes. Preparation of α-amino phosphine oxide and phosphate derivatives. *J. Org. Chem.* **2007**, *72*, 5202–5206.

56. Henning, R.; Lerch, U.; Urbach, H. Synthesis of esters of lipophilic proline analogs by reduction of ethyl 5,6-dihydro-4H-1,2-oxazine-3-carboxylates. *Synthesis* **1989**, 265–268.

57. Paulini, K.; Reissig, H.U.; Rademacher, P. On the reactivity of N,N-bis(trimethyl)silylated enamines: Model studies on hetero Diels-Alder reactions and other cycloadditions. *J. Prakt. Chem.* **1995**, *337*, 209–215.

58. Gallos, J.K.; Sarli, V.C.; Var vogli, A.C; Papadoyanni, C.Z.; Papaspyrou, S.D.; Argyropoulos, N.G. The hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to electron-rich alkenes as a route to unnatural α-amino acids. *Tetrahedron Lett.* **2003**, *44*, 3905–3909.

59. Wabnitz, T.C.; Saaby, S.; Jorgensen, K.A. The first catalytic inverse-electron demand hetero-Diels–Alder reaction of nitroso alkenes using pyrrolidine as an organocatalyst. *Org. Biomol. Chem.* **2004**, *2*, 828–834.

60. Gallos, J.K.; Sarli, V.C.; Massen, Z.S.; Varvogli, A.C.; Papadoyanni, C.Z.; Papaspyrou, S.D.; Argyropoulos, N.G. A new strategy for the stereoselective synthesis of unnatural α-amino acids. *Tetrahedron* **2005**, *61*, 565–574.
61. Domingo, L.R.; Picher, M.T.; Arroyo, P. Towards an understanding of the polar Diels–Alder reactions of nitrosoalkenes with enamines: A theoretical study. *Eur. J. Org. Chem.* **2006**, *6*, 2570–2580.

62. Rossi, E.; Abbiati, G.; Attanasi, O.A.; Rizzato, S.; Santeusanio, S. Divergent and solvent dependent reactions of 4-ethoxycarbonyl-3-methyl-1-tert-butoxycarbonyl-1,2-diaza-1,3-diene with enamines. *Tetrahedron* **2007**, *63*, 11055–11065.

63. Attanasi, O.A.; Favi, G.; Filippone, P.; Forzato, C.; Giorgi, G.; Morganti, S.; Nitti, P.; Pitacco, G.; Rizzato, E.; Spinelli, S.; Valentin, E. On the reactivity of some 2-methyleneindolines with β-nitroenamines, α-nitroalkenes, and 1,2-diaza-1,3-butadienes. *Tetrahedron* **2006**, *62*, 6420–6434.

64. South, M.S. Novel cyclization reactions of mono- and dichloroazodienes. A new synthesis of substituted pyridazines. *J. Heterocycl. Chem.* **1999**, *36*, 301–319.

65. South, M.S.; Jakuboski, T.L.; Westmeyer, M.D.; Dukesherer, D.R. Synthesis and reactions of haloazodienes. A new and general synthesis of substituted pyridazines. *J. Org. Chem.* **1996**, *61*, 8921–8934.

66. South, M.S.; Jakuboski, T.L.; Westmeyer, M.D.; Dukesherer, D.R. Novel cyclization reactions of dichloroazodienes. *Tetrahedron Lett.* **1996**, *37*, 1351–1354.

67. South, M.S.; Jakuboski, T.L. Synthesis and reactions of chloroazodienes. A new and general synthesis of pyridazines. *Tetrahedron Lett.* **1995**, *36*, 5703–5706.

68. Clarke, S.J.; Davies, D.E.; Gilchrist, T.L. Competing [4+2] and [3+2] cycloaddition in the reactions of nucleophilic olefins with ethyl 3-(toluene-p-sulphonylazo)but-2-enoate. *J. Chem. Soc. Perkin Trans. 1* **1993**, *1*, 1391–1395.

69. Clarke, S.J.; Gilchrist, T.L.; Lemos, A. Reactions of azoalkenes derived from hydrazones of ethyl bromopyruvate with electron rich alkenes and heterocycles. *Tetrahedron* **1991**, *47*, 5615–5624.

70. Gilchrist, T.L.; Lemos, A.; Roberts, T.G. Reactions of nitrosoalkenes derived from hydrazones of ethyl bromopyruvate with electron rich alkenes and heterocycles. *Phosphor. Sulfur Silicon* **2007**, *182*, 2149–2155.

71. Hu, E.X. Nucleophilic ring opening of aziridines. *Tetrahedron* **2004**, *60*, 2701–2743.

72. Rogers, R.S.; Stern, M.K. An improved synthesis of the phosphonic acid analog of tryptophan. *Synlett* **1992**, *708–708*. 
77. Burk, M.J.; Martinez, J.P.; Feaster, J.E.; Cosford, N. Catalytic asymmetric reductive amination of ketones via highly enantioselective hydrogenation of the C=N double bond. *Tetrahedron* **1994**, *50*, 4399–4428.

78. Demir, A.S.; Tanyeli, C.; Sesenoglu, O.; Demiç, S. A simple synthesis of 1-aminophosphonic acids from 1-hydroxyiminophosphonates with NaBH₄ in the presence of transition metal compounds. *Tetrahedron Lett.* **1996**, *37*, 407–410.

*Sample Availability:* Not applicable.

© 2009 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).