Synthetic Methods for Azaheterocyclic Phosphonates and Their Biological Activity

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1. Introduction

Despite the importance in synthetic, agrochemical, and medicinal chemistry, to the best of our knowledge, no overview has been made on the synthetic methods and the field of application of the azaheterocyclic phosphonates.

This review on azaheterocyclic phosphonates classifies the different synthetic methods available in the scientific and the patent literature according to the type of reactions utilized. Together with the synthetic methods, the use or biological activity of the compounds is also described whenever available.

Because of the wide range of the topic, the review focuses on the monocyclic azaphosphonates not including the aromatic derivatives and describes the methods up to the end of 2003. The review is built up according to the ring size of the azaheterocycles bearing the phosphonate moiety and starting with the smallest rings. Since several methods are valuable to synthesize the phosphonate derivatives of varying ring size, these methods are treated in detail the first time they appear. Ring systems incorporating the P-atom (phosphorus heterocycles) are not included in this review.

2. Three Membered Rings—Azirines and Aziridines

2.1. Introduction

The chemistry related to the smallest azaheterocyclic ring, the aziridine, has expanded enormously in the past decades because of its mechanistic, synthetic, and biological importance. At present, the great interest in functionalized aziridines is focused on the biological activity of some derivatives. The nitrogen mustards **1** and **2**, for example, known as antitumor drugs, covalently cross-link DNA through aziridinium ion formation followed by alkylation, resulting in the inhibition of DNA replication and the breakdown of DNA strains (Figure 1).[1] Therefore, aziridines are studied intensively as reactive intermediates in biological processes.

Furthermore, it is known that phosphorus moieties regulate important biological functions by mimicking carboxylic acid groups.[2] In particular, fosfomycin (**3**, X = O) is a broad spectrum antibiotic[3] and is used in vitro[4] and clinically (Figure 2).[5] 1-Alkoxycarbonyl-2-phosphonoaziridine (**4**) also shows antibacterial activity.[6] For these reasons, functionalized azirines and aziridines containing a phosphonate group at the C-2-position are expected to play a similar role to that

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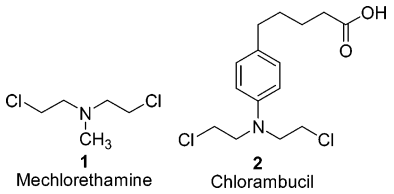


Figure 1.

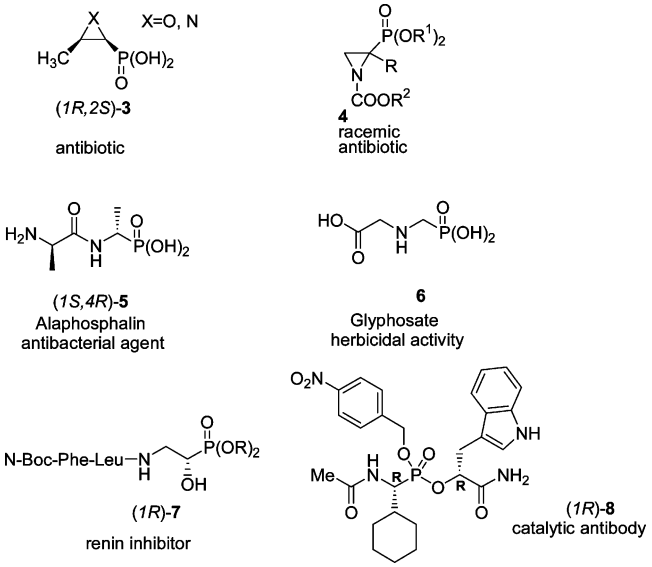


Figure 2.

observed in their isosteric analogues. They may also be used as key intermediates in the enantioselective synthesis of α- and β-aminophosphonates and their corresponding phosphonic acids. Because the phosphonic analogues of some amino acids have interesting biological properties, it is desirable to develop specific and enantioselective pathways for phosphonylated aziridines which can lead to a multitude of amino acid mimics after ring opening. These amino phosphonic acids and their derivatives can then be introduced into biologically active peptides as antibacterial agents,[7,8] enzyme inhibitors,[9] and herbicides[10] and can be used as inhibitors of renin[2,11] or HIV proteases[12] and as haptens for catalytic antibodies.[13]

2*H*-Azirines are among the most useful synthetic intermediates toward the synthesis of aziridines, amino acids, indoles, pyrazines, and other biologically active compounds. Because of their particular polarity and the strain of the three membered rings, they are not easy to synthesize but easily undergo ring opening reactions.

2.2. Ring Closure by Nucleophilic Substitution

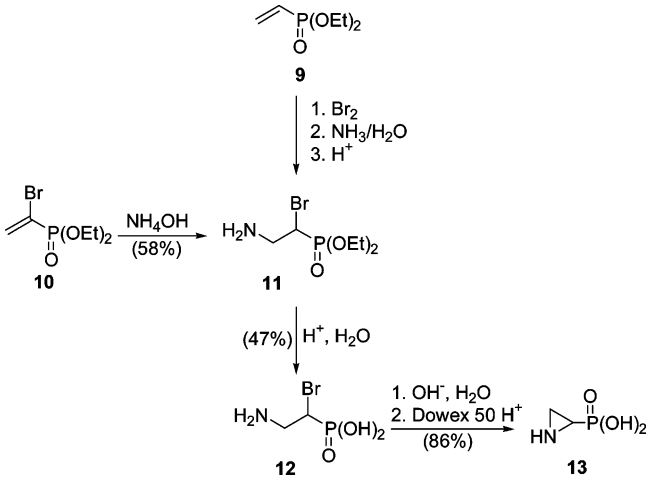
2.2.1. Racemic Syntheses

The most straightforward way to synthesize aziridinylphosphonates is by intramolecular nucleophilic substitution of a halogen or a hydroxyl function by an amino group.

Vinylphosphonates can serve as a template to introduce the necessary functionalities to perform this intramolecular nucleophilic substitution.

Fast bromination of vinylphosphonate **9** in the absence of a solvent, followed by a direct reaction with aqueous ammonia and final hydrolysis of the crude diethyl ester **11** leads in a one-pot procedure to the pure phosphonic acid **12** (yield: 47%). Cyclization in boiling aqueous sodium hydroxide forms within 5 min the disodium salt, which gives 86% of pure aziridine **13** after passage through an ion exchange column.[8,14] Treatment of 1-bromovinylphosphonate **10** with liquid ammonia under pressure also leads to intermediate **11** in 58% yield (Scheme 1).[15,16]

Scheme 1

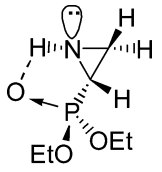


The isolation of phosphonic acid **12** was preferred instead of the corresponding ester because the free acid is more readily purified and, in addition, the ester cleavage after aziridine ring closure would be problematic.

Ring opening of 2-phosphonoaziridine (**13**) (by nucleophiles such as ROH, RSH, RNH_2) proceeds regiospecifically at the less substituted C-2-position, and no evidence was observed for the formation of isomeric products, resulting from attack of the nucleophile at the C-1-position.

N-Unsubstituted (*S*)-aziridine-2,3-dicarboxylic acid has been isolated from *Streptomyces*, and its antibacterial activity was reported.[17] The same kind of activity was established for a series of 2-phosphonoaziridines.[6,8]

The retardation of pyramidal inversion of the nitrogen atom in diethyl 2-phosphonoaziridine (**14**) is remarkable. Due to intramolecular hydrogen bonding, which is expected to be strong because it involves a five membered ring, as depicted in Figure 3, the



14

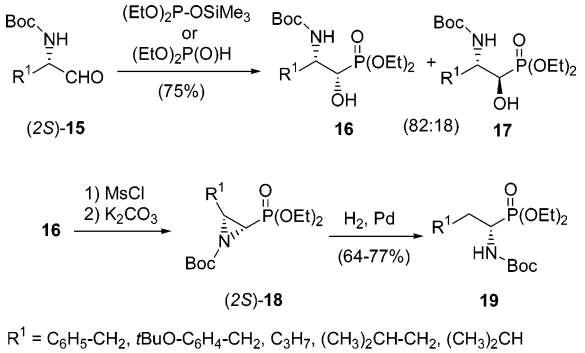
Figure 3.

rate of nitrogen inversion is measurable on the NMR time scale.[18] Evidence for the internal hydrogen bonding in **14** was obtained by IR studies. The synthesis of aziridine 14 was carried out in a similar way, as depicted in Scheme 1.

For ring closure procedures involving other functionalities in the molecule, the amino function needs to be protected (Boc, Ts) while performing the ring closure.

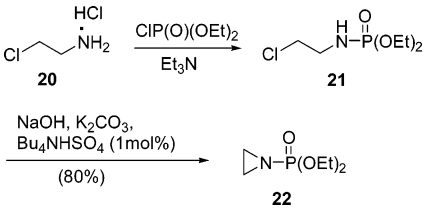
Pousset and Larchevêque[19] reported the nucleophilic addition of phosphites to α-amino aldehydes, which is one of the simplest entries to α-hydroxy aminophosphonates. However, the diastereoselectivity of this reaction is highly dependent on the nature of the protecting group. *N*-Boc protection was studied, since it is a very interesting protecting group in peptide synthesis and led to a mixture of α-hydroxy aminophosphonates **16** and **17**. This mixture of diasteroisomers was mesylated, and after separation of the minor component, **16** was cyclized in the presence of potassium carbonate in DMF to give exclusively the pure *N*-Boc-protected *cis*-aziridines **18** in excellent yields. Regioselective hydrogenation led to the formation of optically enriched α-aminophosphonates **19** (Scheme 2).

Scheme 2



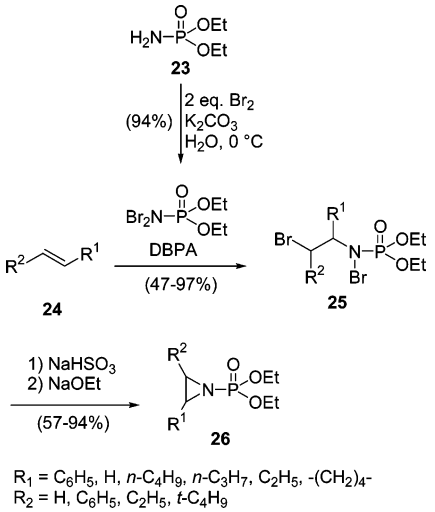
A convenient synthesis toward 1-phosphonoaziridines via nucleophilic substitution was described by Osowska-Pacewicka and Zwierzak.[20] *N*-(Diethoxyphosphoryl)aziridine (**22**) has been known since 1956, when it was prepared by phosphorylation of aziridine with diethyl chlorophosphate in the presence of triethylamine.[21] To circumvent the use of the strongly toxic and not commercially available aziridine, a new approach was developed. The readily accessible 2-chloroethylamine hydrochloride (**20**) can be phosphorylated easily with diethyl chlorophosphate. The resulting phosphoramidate **21** was then subjected to cyclization in a solid−liquid two-phase system and afforded *N*-(diethoxyphosphoryl)aziridine (**22**) in 80% yield (Scheme 3).

Scheme 3



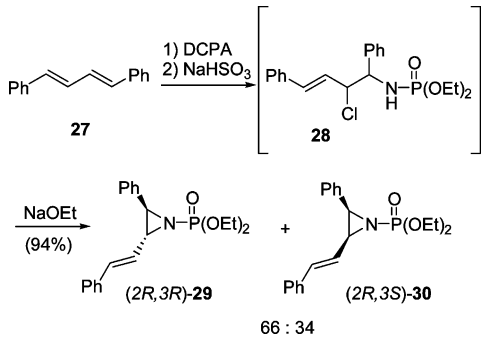
An alternative route to these 1-phosphonoaziridines is the direct synthesis from olefin precursors by addition of diethyl *N,N*-dibromophosphoramidate (DBPA) or diethyl *N,N*-dichlorophosphoramidate (DCPA). It was found that diethyl *N,N*-dibromophosphoramidate can be readily obtained in excellent yield (94%) by direct bromination of diethyl phosphoramidate (**23**). The reaction, using elemental bromine, is carried out in aqueous K_2CO_3 at 0 °C.[22] This reaction is spontaneously, photolytically, or thermally initiated depending on the structure of the substrate. Using sodium ethoxide for the cyclization, phosphorylated aziridines **26** are obtained in high yields (Scheme 4).[23−25]

Scheme 4



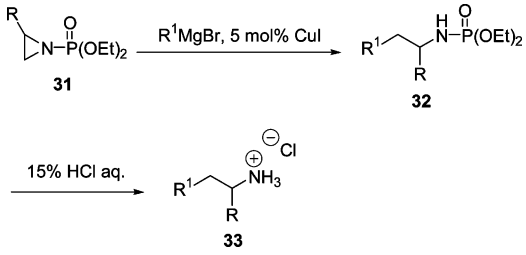
DBPA or DCPA has also been added to several conjugated 1,3-dienes.[26] In this way a mixture of *trans*- and *cis*-*N*-phosphorylated aziridines **29** and **30** was synthesized (Scheme 5).

Scheme 5



These 1-phosphonoaziridines were employed as electrophilic components for the reaction with copper-modified Grignard reagents. The resulting diethyl *N*-alkylphosphoramidates **32** could be conveniently dephosphorylated upon refluxing with 15% hydrochloric acid (Scheme 6).[20,27] They can also be used in

Scheme 6



ring expansion reactions with dianions derived from ethyl acetoacetate to give substituted pyrrolines and pyrrolidines (see section 4.5.9).

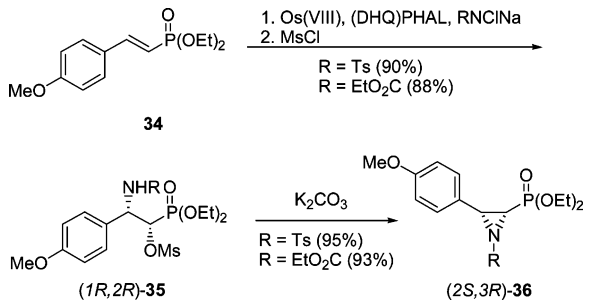
2.2.2. Asymmetric Syntheses

For the enantioselective synthesis of phosphonoaziridines, different catalytic systems have been evaluated and successfully used.

Thomas and Sharpless[28] recently discovered the asymmetric aminohydroxylation (AA), which utilizes Os(VIII) in combination with the alkaloid ligand $(DHQ)_2PHAL$, allowing the formation of β-amino-α-hydroxyphosphonates in high ee's.

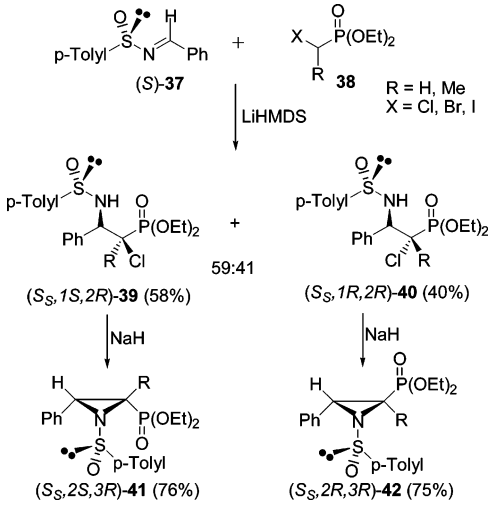
A two-step process involving aminohydroxylation and mesylation of the hydroxyphosphonates followed by treatment of the isolated mesylates **35** with K_2CO_3 in DMF resulted in the formation of the *N*-protected aziridines **36** in high yields and with high purity (>99%) (Scheme 7).

Scheme 7



Enantiopure sulfinimines have been utilized in a Darzens type synthesis of 2-methyl-2-phosphonoaziridines[29] and 3-phenyl-2-phosphonoaziridines.[30−33] The latter were transformed into the corresponding azirinylphosphonates (cf. infra). The phosphonate group was introduced by treating diethyl 1-chloroethylphosphonate or diethyl chloromethylphosphonate with LiHMDS followed by the addition of the enantiopure (*S*)-(+)-sulfinimine **37**. Other bases such as *n*-BuLi, NaHMDS, and KHMDS were also evaluated, but the results were less satisfying compared to those for LiHMDS. The diastereoisomers **39** and **40** could be separated by column chromatography in 58% and 40% yield, respectively. Ring closure was performed using NaH, resulting in the diastereoisomers **41** (76%) and **42** (75%). Afterward, the sulfinyl auxiliary was removed under acidic conditions (TFA/MeOH) or with MeMgBr (Scheme 8).

Scheme 8

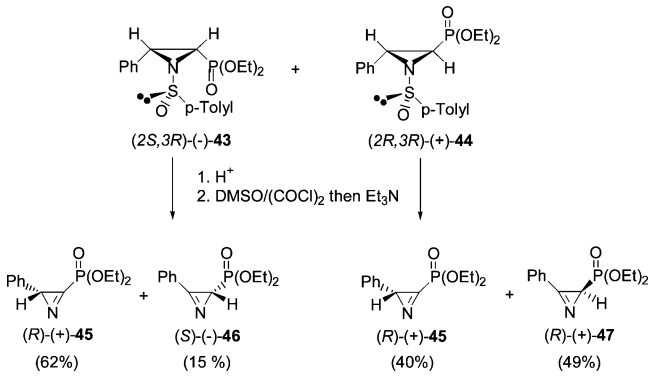


The influence or the sulfenyl auxiliary on the diastereoselectivity of the β-amino phosphonates **39** and **40** was also investigated. For this reason the sulfinimine, derived from (*S*)-(+)-*N*-*tert*-butanesulfinamide and benzaldehyde, was prepared and reacted with diethyl iodomethylphosphonate. The aziridines were formed immediately as single isomers without formation of the corresponding β-amino phosphonates. All attempts to remove the *tert*-butansulfinyl auxiliary with the use of acid or MeMgBr without concomitant ring opening failed. The *N*-(2,4,6-trimethylphenylsulfinyl) auxiliary, on the other hand, produced high diastereoselectivities in the aza-Darzens reaction while permitting selective deprotection using the Grignard protocol, leading to an improved synthesis of 2-phosphonoaziridines.[34]

Phosphonoaziridines **41** and **42** can lead to the corresponding 2*H*-azirines. However, this class of compounds has received little attention. Only a few practical syntheses of phosphorylated 2*H*-azirines have been described so far (see also section 2.7.2). In this case, initial attempts to eliminate the sulfinyl group with LDA or LDA/MeI did not lead to azirinylphosphonate formation. However, when the aziridines were subjected to Swern oxidation conditions, regioisomeric mixtures of azirinylphosphonates **45**−**47** were produced. In the case of (−)-**43**, the phosphonate ester presumably has a more pronounced

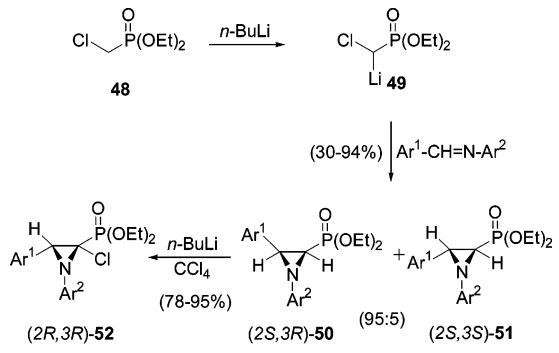
acidifying effect on the C-2 proton, leading to the major azirine product (*R*)-(+)-**45** in 62% yield. Removal of the C-3 proton gave the minor azirine product (*S*)-(−)-**46** in 15% yield. In the case of (+)-**44**, a rapidly inverting *N*-sulfonium intermediate is expected, leading to equal removal of C-2 and C-3 protons despite their acidity difference. A 1:1 mixture of azirinylphosphonates (*R*)-(+)-**45** and (*R*)-(+)-**47** was observed by ^{1}H NMR (500 MHz), and the two compounds were isolated by flash chromatography in 40% and 49% yield, respectively (Scheme 9).

Scheme 9



A similar pathway consists of the highly stereoselective synthesis of phosphonoaziridines via reaction of diethyl 1-lithio-1-chloromethylphosphonate (**49**) and aromatic imines.[35,36] The minor *trans*-aziridine could be separated from the major *cis*-aziridine by column chromatography. The resulting aziridines were then reacted with *n*-BuLi and led to the 2-lithiated aziridines, which were trapped with CCl_4 to give 2-chlorophosphonoaziridines **52** (Scheme 10). The

Scheme 10

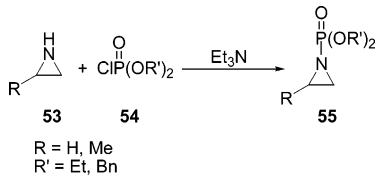


stereochemistry and reaction mechanisms of this Darzens type reaction have been studied in detail by the authors.

2.3. Electrophilic Phosphorylation

1-Phosphonoaziridines can be prepared by phosphorylation of aziridines with dialkyl chlorophosphate in the presence of triethylamine (Scheme 11).[8,21] However, the method described by Osowska-Pacewicka and Zwierzak (see section 2.2.1) to prepare these aziridines **55** is much more efficient, since it

Scheme 11

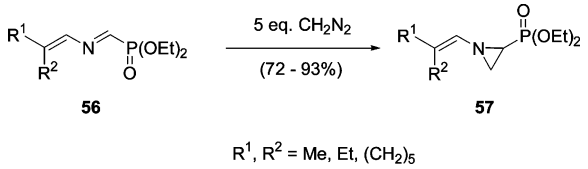


avoids the use of the strongly toxic and not commercially available aziridines **53**.

2.4. Reactions with Carbenoids

Recently, an initial study has been performed toward the reactivity of 1-phosphono-2-aza-1,3-dienes,[37] which prove to be promising substrates for the synthesis of azaheterocyclic phosphonates. Reaction of the azadienes **56** with an excess of diazomethane leads to the clean generation of 1-vinyl-2-phosphonoaziridines **57** in good yields (Scheme 12).

Scheme 12



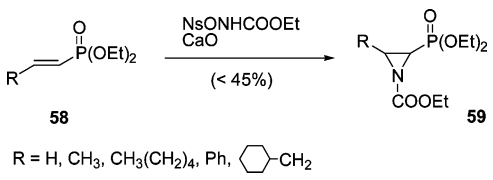
As carbenes are known to react with different kinds of olefins, no formation of the corresponding cyclopropanes could be detected.

The selectivity of the reaction was completely driven by the electron withdrawing effect of the phosphonate group and resulted in the first report on the addition of diazomethane to nonaromatic imines.

2.5. Aziridination Using Nitrenes

Aziridination of vinylphosphonates with nitrene reagents is also a commonly used strategy for the synthesis of aziridinylphosphonates. As precursor of the nitrene, *N*-{[(4-nitrobenzyl)sulfonyl]oxy}carbamate (NsONHCOOEt) has been studied for aziridination of a variety of substrates in the presence of Et_3N, showing good reactivity toward electron rich alkenes. A new strategy reported for the first time is the use of this reagent together with inorganic and insoluble bases such as CaO or K_2CO_3 to generate aziridine rings from electron deficient olefins such as vinylphosphonates **58**. However, the yield for this new kind of aziridination never exceeded 45% (Scheme 13).[38]

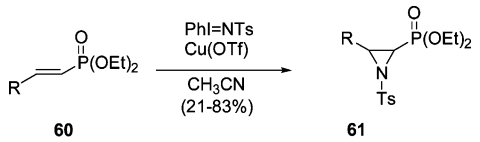
Scheme 13



The same type of aziridination via a nitrene precursor was used by Kim and Rhie.[39] In their case [*N*-(*p*-tolylsulfonyl)imino]phenyliodonane (PhI=NTs)

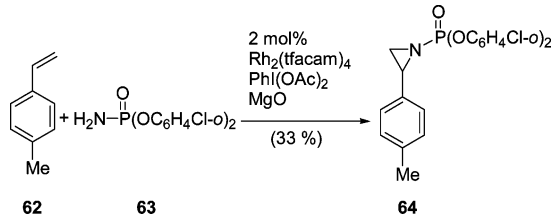
and a copper catalyst were used to form the aziridine ring from vinylphosphonates **60**. Under optimal conditions (10 mol % CuOTf, 1 equiv of PhI=NTs, 5 equiv of vinylphosphonate, CH_3CN, room temperature), the aziridination proceeded with much better yields than in the previous case (up to 83%) (Scheme 14).

Scheme 14



Guthikonda and Du Bois[40] describe a highly effective and broadly applicable method for the preparation of aziridines using a Rh-carboxamide catalyst, an inexpensive terminal oxidant, and sulfamate esters or phosphoramidates as competent nitrogen sources. Reactions are performed with limiting amounts of alkene substrates under conditions that are considered to be optimal but found to be atypical for previously reported metal-catalyzed aziridination strategies (Scheme 15).

Scheme 15

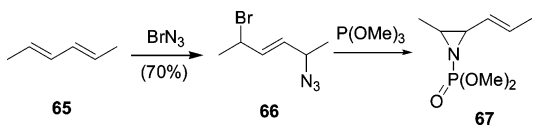


2.6. Staudinger Type Reactions

The reaction between phosphorus nucleophiles and azides (Staudinger reaction) leading to iminophosphoranes is well-known as well as their subsequent reactions with alkyl halides giving dialkylaminophosphonium salts. Incorporating both the iminophosphorane and the halide function into one molecule creates the possibility for ring closure.

Addition of halogen azides to a variety of conjugated and nonconjugated cyclic diene systems has been investigated in detail and has led to the conclusion that such systems result almost exclusively in unstable diazides. Hassner et al.[41] described the addition of halogen azides to a variety of acyclic conjugated dienes and succeeded in converting these azides to vinyl 1-phosphonoaziridines upon treatment with trimethyl phosphite (Scheme 16). The azide **66**,

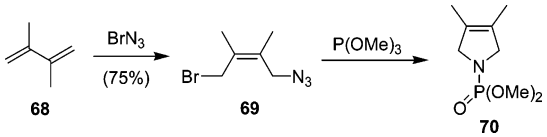
Scheme 16



derived from 1,4-addition of BrN_3 to the corresponding diene **65**, reacts with trimethyl phosphite to yield the phosphonoaziridine **67.**

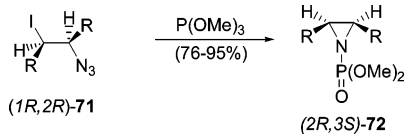
1,4-Addition of bromoazide to diene **68** yields adduct **69**, which is subsequently cyclized to 3-pyrroline (**70**) (Scheme 17).[41]

Scheme 17



2-Iodoalkyl azides react readily and stereospecifically with trivalent phosphorus nucleophiles to form 1-phosphonoaziridines (Scheme 18).[42] The (*1R*,*2R*)

Scheme 18



threo azide **71** reacts with trimethyl phosphite to yield the phosphonoaziridine **72** in the (*2R*,*3S*) *cis* configuration. Under the same conditions the *erythro* diastereoisomers lead to the *trans*-aziridines.

In Scheme 19 the proposed reaction mechanism is given. The clean stereochemical results indicate that 2-iodoalkyl azides react with trivalent phosphorus almost exclusively at the azide function. The reactions are thought to involve initial nucleophilic attack on the terminal azide nitrogen. Intermediate **74** can undergo a loss of nitrogen to ylide **75**, which cyclizes to **78** with displacement of the iodide anion. Alternatively, cyclization to **76** or **77** may precede loss of nitrogen, although the rate of nitrogen loss from azide−phosphite adducts of type **74** is generally believed to be larger than the rate of formation.

Using this methodology, it is possible to obtain a wide range of other ring sizes, starting from the corresponding iodoazides (Scheme 20).[43,44] This methodology was also used to introduce the aziridine moiety in the tetracyclic core of aziridinomitosenes **83** (Figure 4).[45−48]

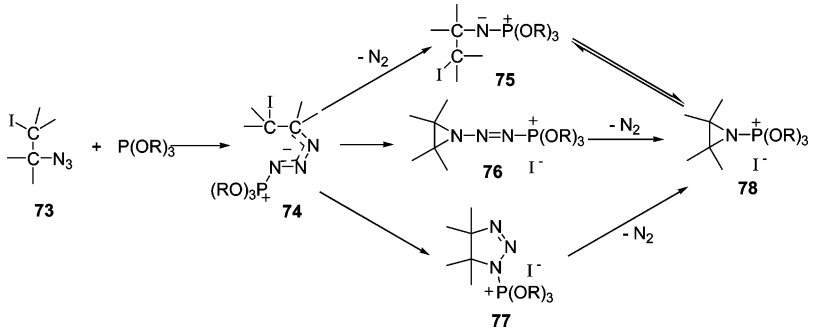
Mitomycins A (**81**) and C (**82**) are a group of *Streptomyces* metabolites having pronounced antibacterial (against Gram-positive and Gram-negative bacteria) and antitumor activity under reductive conditions.[49] The active intermediate generated by reduction of mitomycin C is believed to be mitosene **83**. Alkylation of the 2-amino group of guanine by the mitomycin results in the formation of both monoalkylated adducts and DNA cross-links. Considerable effort has been devoted to the synthesis of these clinically useful antibiotics and their bioactive degradation products, the aziridinomitosenes **83** (Figure 4). Mitomycin derivative **84** is a very reactive and biologically active compound, especially under acidic conditions.[50]

2.7. Miscellaneous

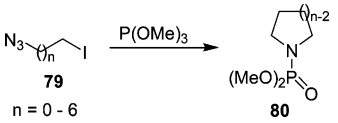
2.7.1. Reduction–Ring Closure–Addition Sequence

A special case in the synthesis of 2-phosphonoaziridines is the addition of dialkyl phosphites and trialkyl phosphites to 2,2-diphenyl-1-nitroalkenes,

Scheme 19



Scheme 20



resulting in phosphonoaziridines via an azirine intermediate. The reaction can be rationalized by a Perkow type reaction after addition of the phosphite onto the nitro function, followed by deoxygenation and elimination of diethyl phosphate (Scheme 21).[51]

2.7.2. Neber Type Reaction

Palacios et al. reported the synthesis of the phosphonoazirines **98** and azirinyl phosphinoxide **102** from tosyl oximes[52,53] and vinyl azides[53] by the Neber reaction. This latter process could also be extended to the asymmetric synthesis of 2*H*-azirines when stoichiometric amounts of chiral bases (quinidine, hydroquinidine, sparteine, quinine) were used (ee varying from 2 to 52%). The reduction of these azirines with $NaBH_4$ led to the corresponding aziridines **99** and **103** (Scheme 22).

2.7.3. Reaction of Functionalized Phosphonoallenes

Brel[54] described a convenient and efficient procedure in which phosphorylated allenes **105** were synthesized directly from the corresponding alcohols **104** by the Horner−Mark [2.3]-sigmatropic rearrangement of the unstable phosphites generated in situ by reaction with diethyl chlorophosphate in the presence of triethylamine. Treatment of allenes **105** with sodium azide resulted in 2-substituted 2-(diethylphosphono)-3-isopropenyl-2*H*-azirines **106** (Scheme 23).

2.7.4. Photocyclizations

Some antibacterial phosphonoaziridines, 2*H*-azirines, and their corresponding phosphonic acids were

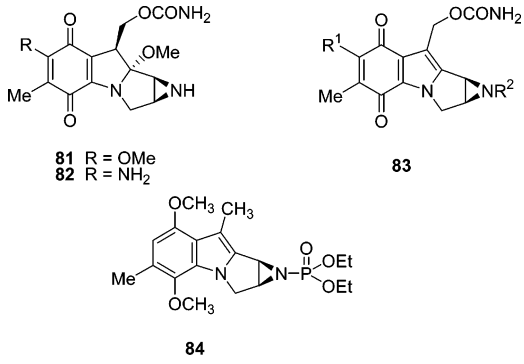
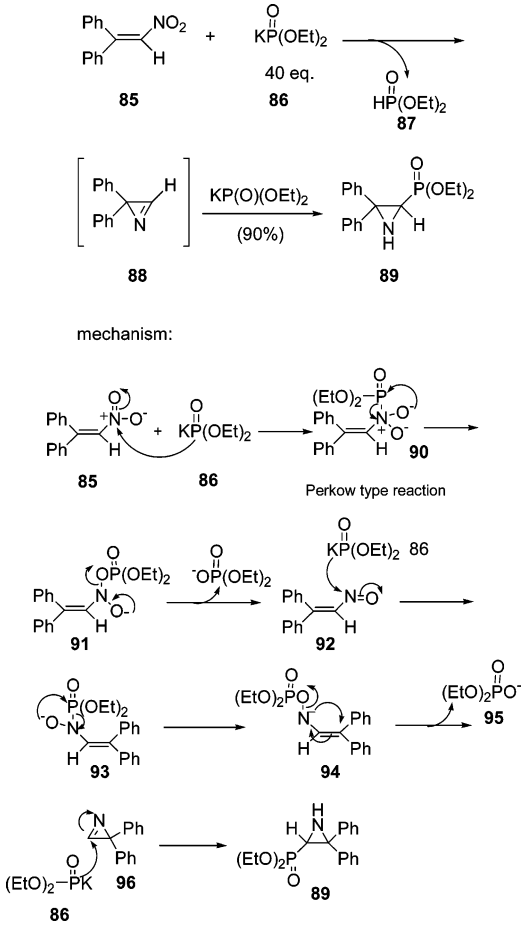


Figure 4.

Scheme 21



prepared via photocyclization reactions (Scheme 24).[8] Vinylphosphonate **107** was treated with ethyl azidoacetate, bromo azide, or sodium azide and ring closed by irradiation with UV light.

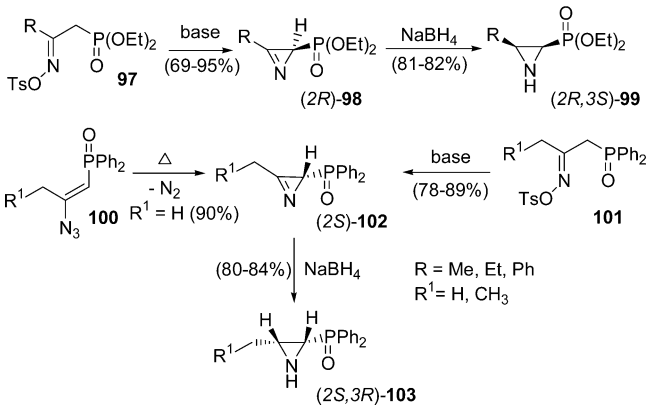
3. Four Membered Rings—Azetidines and Azetidinones

3.1. Introduction

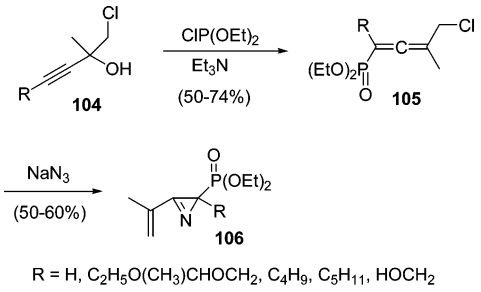
The importance of β-lactams has been revealed by the discovery and structure elucidation of penicillin. Due to the remarkable activity of the naturally occurring antibiotics, which are bicyclic azetidinones, the β-lactam heterocycle became one of the most exploited lead structures.[55]

β-Lactam antibiotics account for 50% of the world's total antibiotic market. They have high antibacterial

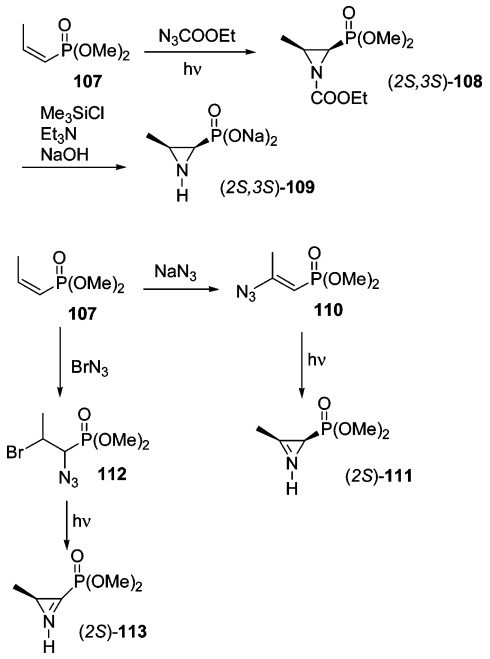
Scheme 22



Scheme 23



Scheme 24



activity and low toxicity. Synthesis of a wide range of analogues of penicillin and cephalosporin led to numerous active compounds, including penams **114**, cephems **115**, carbapenems **116**, and monobactams **118**.[56] This last class is characterized by a monocyclic β-lactam ring activated by an N-1 sulfonate group. They were isolated for the first time from a bacterial fermentation broth of *Chromobacterium violaceum* and a *Gluconobacter* species. Chemical modification led eventually to the clinically useful monobactam aztreonam (**117**), which showed an enhanced biological activity. Further research has been performed in order to change the sulfonate group into a phosphonate group. These classes of compounds are sometimes referred to as sulfams and phosphams (Figure 5).[57]

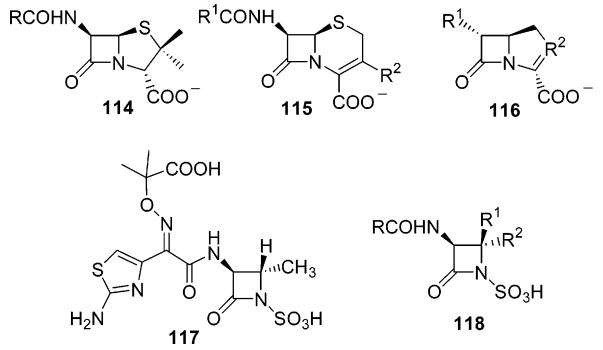


Figure 5.

β-Lactams interact with the essential serine nucleophile of the enzyme cavity of serine enzymes. Therefore, they are important as inhibitors of DD-transpeptidase and β-lactamases for antibacterial drugs, and elastases for antiinflammatory drugs.[55] β-Lactamases catalyze the hydrolysis of the β-lactam to give the ring opened and bacterially inert β-amino acid. Two main therapeutic strategies have been adopted to counteract bacterial resistance to β-lactam antibiotics. One involves the design of antibiotics which are not susceptible to β-lactamase-catalyzed hydrolysis. The other is to use an inhibitor or inactivator of the β-lactamase together with a normal β-lactam antibiotic.[56]

Unfortunately, the β-lactamase production is predominantly plasmid mediated. Consequently, bacteria are able to produce new β-lactamases, which catalyze the hydrolysis of previously poor substrates and which are no longer susceptible to previous inhibitors. Therefore, there is a continuing demand for new active compounds and new synthetic routes toward functionalized β-lactams. A few bicyclic phosphono-β-lactams have been synthesized and tested, however without promising antibacterial activity.[58−63]

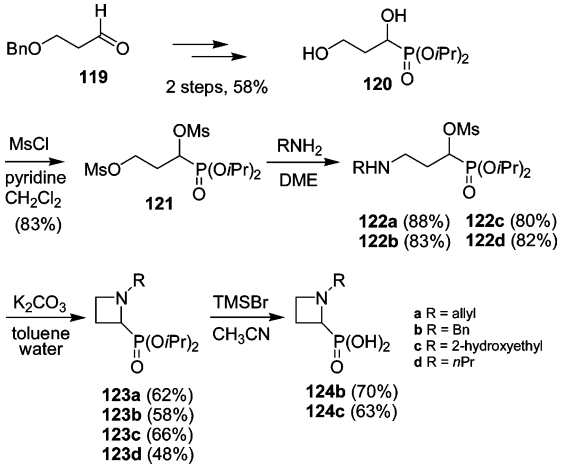
3.2. Ring Closure by Nucleophilic Substitution

Although *L*-azetidin-2-carboxylic acid is a potent proline mimetic,[64] very little is still known about the biological activity of its phosphonate analogue. Nevertheless, three syntheses can be found in the literature: two of them involve a nucleophilic ring closure, and the third example is discussed in section 3.3.

Racemic azetidinyl-2-phosphonic acid (**124**) can be prepared from 3-(benzyloxy)propanal (**119**) which is converted to the corresponding hydroxyphosphonate by a Pudovik reaction with diisopropyl phosphite. After deprotection, the 1,3-dihydroxypropylphosphonate (**120**) is converted to the corresponding dimesylate **121** followed by the selective substitution of the primary mesyl group by different amines. Ring closure is finally performed by refluxing the mesylate **122** in a toluene−water mixture in the presence of K_2CO_3 (Scheme 25).[65]

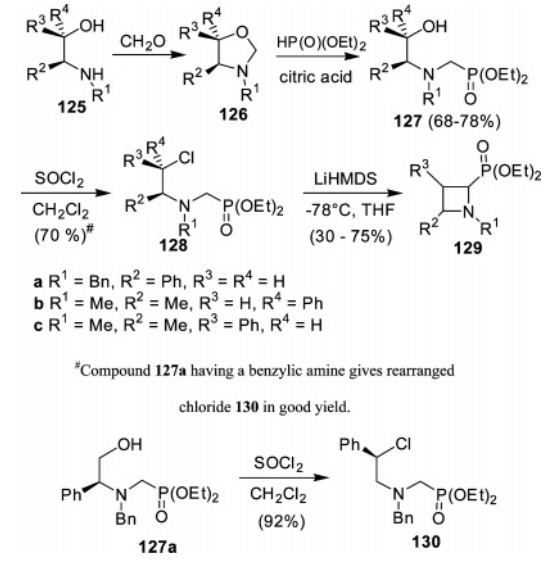
More recently, the first asymmetric synthesis of azetidinyl-2-phosphonic acids was published.[66] Start-

Scheme 25



ing from readily available β-amino alcohols, the required aminophosphonates **127a**−**c** are prepared via a two-step sequence involving (i) oxazolidine formation in the presence of formaldehyde and (ii) acid-catalyzed ring opening of the oxazolidine followed by nucleophilic addition by diethyl phosphite. Chlorination of these compounds with thionyl chloride yields the corresponding β-chloroamines **128**, which are subsequently cyclized with LiHMDS to the azetidinyl-2-phosphonates. During these transformations, there is a total retention of configuration at the stereogenic centers. Only with compound **127a**, a rearrangement occurs leading to **130** in good yield (Scheme 26).

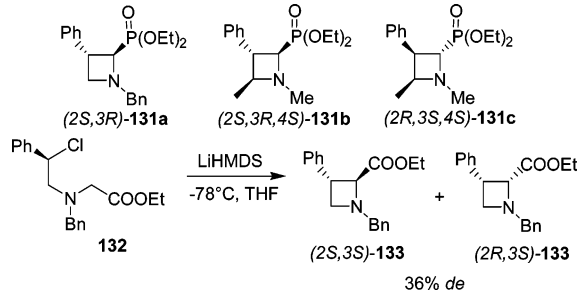
Scheme 26



During ring closure, exclusively 2,3-*trans*-azetidines **131** are formed (Scheme 27), due to the bulkiness of the lithiated phosphoenolate. Similar experiments with an ester group instead of a phosphonate group yield a mixture of 2,3-*cis*- and 2,3-*trans*-azetidines. Clearly, the steric interaction between the sp^2 ester enolate and the α-phenyl substituent is less severe in this case.

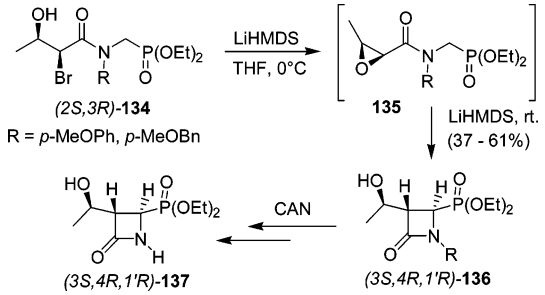
Ring closure through intramolecular nucleophilic substitution has also been applied in the synthesis of phosphono-β-lactams. The first example consists

Scheme 27



of an epoxide ring opening by intramolecular attack of a phosphorus stabilized carbanion (Scheme 28).

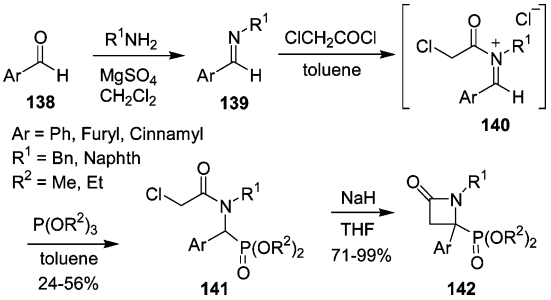
Scheme 28



The epoxide **135** is formed in situ by addition of 1 equiv of LiHMDS to amide **134**. A second equivalent was used to form the lactam **136** in a stereospecific manner: only the *trans*-β-lactams are formed. Nitrogen deprotection can then be performed using cerium ammonium nitrite (CAN), and the obtained 4-phosphono-β-lactams are potential precursors for the synthesis of carbapenems.[67−69]

A second example for the formation of phosphonylated azetidinones via nucleophilic cyclization starts from aromatic aldehydes **138** that are converted into the corresponding imines **139**. Addition of chloroacetyl chloride results in an iminium salt **140** that cannot be isolated and is reacted in situ with a trialkyl phosphite. Finally, Arbuzov-like dealkylation occurs by the liberated chloride anions. Chloroamidophosphonates **141** are then treated with NaH to invoke ring closure (Scheme 29).[70] Surprisingly,

Scheme 29

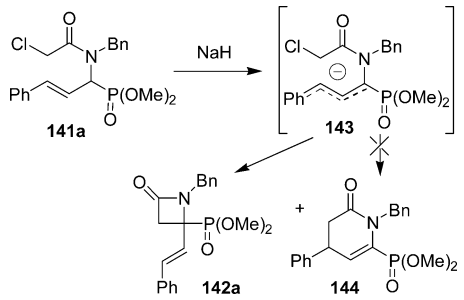


the ring closure reaction of chloroamidophosphonates **141a** exclusively leads to the azetidinone **142a**, without formation of the piperidinone **144** (Scheme 30).[70]

3.3. Nucleophilic Phosphorylation

The apparently most obvious method to synthesize phosphonylated azaheterocycles is starting from the

Scheme 30

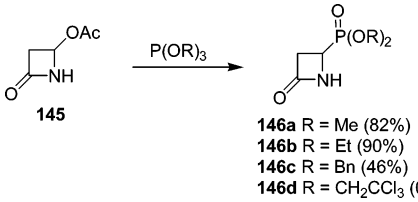


desired cyclic compound bearing a suitable leaving group which is then substituted by a phosphorus reagent. However, examples of this method are rather scarce in the literature.

4-Acetoxyazetidin-2-ones are excellent substrates in substitution reactions.[71] The C-4 carbon atom, which is connected to a nitrogen and an oxygen atom, is very reactive toward nucleophilic agents by the neighboring group effect. The substitution by trialkyl phosphite was first explored by Clauβ and co-workers[71] and further developed by Campbell and Carruthers.[72,73]

When 4-acetoxyazetidin-2-one (**145**) is treated with trialkyl phosphite, phosphonylated azetidinones **146** are formed via an atypical Michaelis−Arbuzov reaction, together with the corresponding alkyl acetate (Scheme 31). No reaction occurred with tris(2,2,2-

Scheme 31



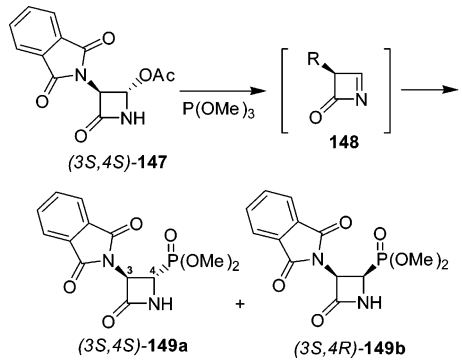
trichloroethyl) phosphite because of its reduced nucleophilicity. However, using methyl phosphonites instead of the corresponding trialkyl phosphites, the reaction proceeds faster and yields the 4-phosphinoazetidinones in 42−93% yield. Performing the reaction with dialkyl phosphite anions fails due to β-lactam cleavage because of the strongly basic nature of the reagents.

More recently,[74] the reaction was repeated with stoichiometric amounts of trimethyl phosphite in refluxing toluene, to facilitate the workup of the reaction. The desired azetidinone **146a** was obtained in 90% yield after 9 h of reflux.

Although 3-substituted 4-acetoxyazetidin-2-ones are also useful in the reaction with nucleophiles, only the phthalimido derivative **147** has been evaluated in the reaction with trialkyl phosphite. Campbell and Carruthers stated that the reaction led exclusively to the *cis* product **149b** (89% yield) (Scheme 32).[72,73] This conclusion was questioned two years later by Satoh and Tsuji.[62] They found both diastereomers in a 13:2 ratio (total yield: 80%), with the *trans* derivative **149a** predominating.

The conclusions of Satoh and Tsuji were confirmed by ^{1}H NMR studies ($J_{3,4\text{-}cis} > J_{3,4\text{-}trans}$) and are discussed in detail. They attribute the erroneous

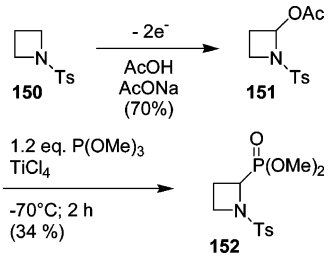
Scheme 32



stereochemical assignment of their colleagues to the lack of isolation of the other epimeric isomer. The predominating *trans* product suggested that displacement reactions of these substrates involve the 1-azetine-4-one (**148**) as an intermediate, which may undergo nucleophilic attack by phosphorus reagents preferentially from the less hindered side.

A similar methodology using an acetoxy group led to the first reported introduction of nucleophiles on the 2-position of azetidines.[75] 1-(*p*-tosyl)-2-acetoxyazetidine (**151**) was treated with 1.2 equiv of trimethyl phosphite to obtain the corresponding 2-phosphonoazetidine (**152**). Opposite to the reaction of acetoxyazetidinone (**145**) with phosphite, the presence of a Lewis acid ($TiCl_4$) as a catalyst seems to be necessary. 1-(*p*-Tosyl)-2-acetoxyazetidine (**151**) is synthesized starting from the easily available compound **150**, by anodic acetoxylation at the 2-position, while acetoxyazetidinone (**145**) is formed by a cycloaddition reaction of chlorosulfonyl isocyanate with vinyl acetate (Scheme 33).[71]

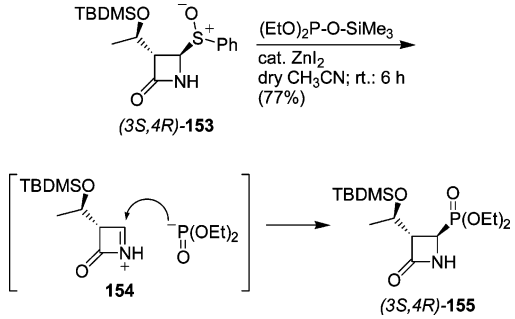
Scheme 33



4-Sulfinylazetidin-2-one (**153**) is another substrate with an appropriate leaving group for a substitution reaction with a phosphorus reagent. Treatment of **153** with silylated phosphite in the presence of ZnI_2 at room temperature for 6 h gives the 4-phosphonoazetidin-2-one (**155**) in 77% yield.[76] Actually, this reaction is not a real substitution reaction, which is indicated by the stereochemistry of the reaction. Due to the action of the Lewis acid, a reactive iminium salt **154** is formed that reacts in situ with the trivalent phosphorus nucleophile (Scheme 34).

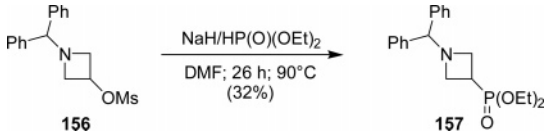
Although mesylates are well-known as substrates for substitution reactions, only one example shows their usefulness in introducing a phosphonate group in an azaheterocycle.[77] The diethyl phosphite anion is capable of performing the substitution reaction

Scheme 34



leading to azetidine **157**, phosphorylated at the 3-position. However, the yield is very low (Scheme 35).

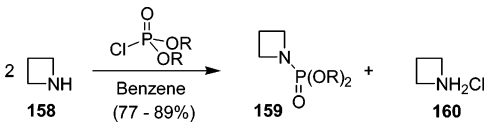
Scheme 35



3.4. Electrophilic Phosphorylation

Azetidine **158** can be utilized in the reaction with a range of chlorophosphates, although polymerization occurs at higher temperature (above 200 °C) (Scheme 36).[78] A similar methodology has been used to synthesize monophosphams, the phosphorus analogues of monosulfams (monobactams). The sulfonate moiety in monobactams activates the β-lactam ring and provides an anionic charge for binding at the active site of enzymes involved in bacterial cell wall biosynthesis. Sulfur and phosphorus have similar bound lengths and tetrahedral geometry. An N-1 phosphonate moiety should exert a smaller inductive effect on the ring compared to sulfonate. However, unlike the sulfur case, tetracoordinate phosphorus provides an extra valence for functionalization. Therefore, azetidinone-1-phosphonic acids are potential antibiotics for comparison with sulfonylated monobactams.[57,79]

Scheme 36

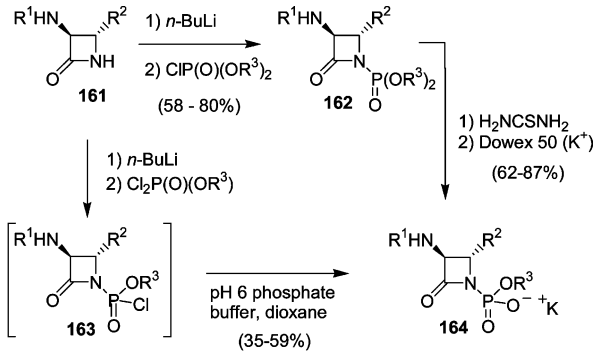


R = Me, Et, *i*Pr, *n*Pr, *i*Bu, *n*Bu, *i*Pent, Ph

To synthesize these 1-phosphonoazetidinones, β-lactams **161** are converted to the corresponding lithium salts that are reacted with either a dialkyl chlorophosphate or an alkyl dichlorophosphate. In the first case, the obtained phosphonates are partially hydrolyzed using thiourea. Complete hydrolysis can be performed using TMSBr. In the second case, the remaining chlorine atom is converted to a hydroxyl function using a phosphate buffer (Scheme 37). Racemization does not occur under the phosphorylation conditions.[79,80]

Transesterification overcomes the limited access to phosphorylating agents. Taking advantage of the nucleophilicity of tetraalkylammonium phosphonate

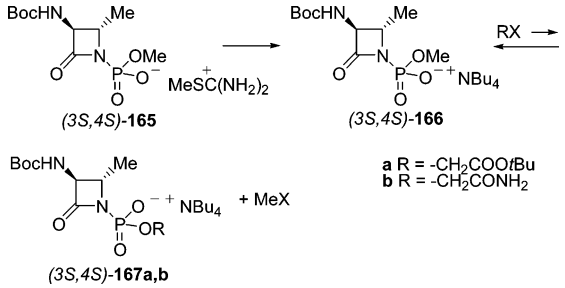
Scheme 37



R1 = Cbz, Boc, PhCH2CO-
R2 = H, Me
R3 = Me, Et, *n*Bu, CH2CF3, Ph

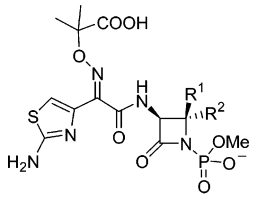
salts **166**, transesterification with more complex alkyl residues was effected by manipulating the equilibrium by changing the amount of alkylating reagent (Scheme 38).

Scheme 38



a R = -CH2COO*t*Bu
b R = -CH2CONH2

The phosphorus analogues **168** of aztreonam (**117**) have been tested toward a wide range of Gram-positive and Gram-negative microorganisms. Like aztreonam, none of the phosphonylated compounds **168** are significantly active against Gram-positive organisms. However, they are active toward Gram-negative organisms, but less active than aztreonam. The 4-β-methyl derivative **168b** was much less active whereas the 4-α-methyl derivative **168c** had almost the same activity, but the β-lactamase stability was increased compared to that of the nonsubstituted monophospham **168a** and to that of aztreonam itself (Figure 6). Nevertheless, the C-4-substituted monobactam N-1 sulfonates provide overall the most favorable combination of intrinsic microbial activity and β-lactamase stability.[57]



168a R1 = R2 = H
168b R1 = Me, R2 = H
168c R1 = H, R2 = Me

Figure 6.

3.5. Cycloaddition

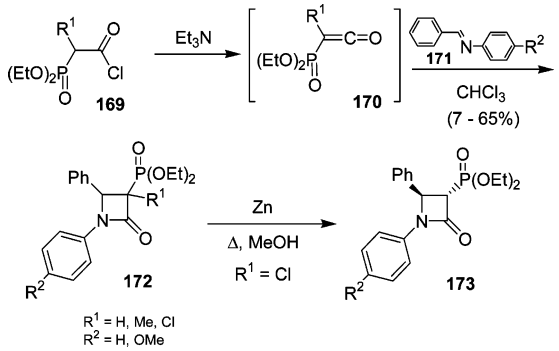
Cycloaddition is a convenient way to construct four membered ring systems. Azetidinones are often

synthesized from ketenes and imines. Ketenes bearing heteroatom substituents have been developed and successfully applied to synthesize functionalized β-lactams. However, reactions with phosphonoketenes were mostly limited to some electrophilic reactions in order to prove their generation.[81]

Cycloaddition has been used only once for the construction of a monocyclic phosphono-β-lactam.[81] In the presence of excess benzylideneaniline, ketenes **170** lead to cycloadducts **172** in 7−65% yield. Methyl- and chloro(diethylphosphono)ketenes **170** are generated in situ from the corresponding acid chlorides and triethylamine.

The stereochemistry of β-lactams **172** could not be determined. However, after the reductive removal of the chlorine atom, it could be proven that these β-lactams are *trans* isomers (Scheme 39).

Scheme 39



In conclusion, it is clear that cycloaddition can be a promising synthetic route to phosphono-β-lactams, since the reaction is stereoselective. However, the reaction is not well explored, probably due to the instability of the phosphonoketenes leading to reaction conditions that are difficult to control.

3.6. Reactions with Carbenoids

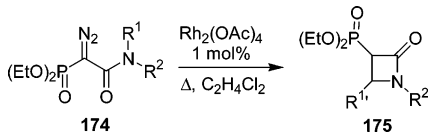
The use of carbenoids for intramolecular C−H insertion reactions is more extensively discussed in the section on five membered rings (see section 4.11). However, in some cases, β-lactam formation is favored over γ-lactam formation. In the case of **175d**, this can be explained by the electron withdrawing carboxylate group deactivating the C−H insertion into the α-methylene group.

In terms of stereoselectivity, strikingly different results are observed when β-lactam formation is considered against γ-lactam formation. While the γ-lactams are exclusively *trans*, a bulky *t*Bu group on the nitrogen atom is able to force the formation of *cis*-β-lactams (Table 1). However, during purification by flash chromatography, epimerization occurs and only the *trans*-β-lactams can be isolated (Scheme 40).[82]

Table 1. Regioselectivity in the Intramolecular C−H Insertion Reaction

	R1	R2	R1′	yield **175**	*cis/trans*
a	*i*Pr	*i*Pr	Me, Me	88%	
b	Bn	Bn	Ph	95%	5:95
c	Bn	*t*Bu	Ph	89%	88:12
d	CH_2CH_2COOMe	*t*Bu	CH_2COOMe	94%	71:29

Scheme 40



3.7. Staudinger Type Reactions

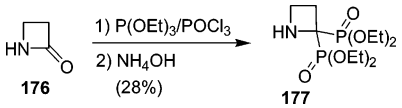
1-Phosphonoazetidines can be synthesized using a Staudinger type reaction, as described in section 2.6.

3.8. Miscellaneous

3.8.1. Phosphonylation of Lactams for the Synthesis of Bisphosphonates

β-Lactams can be phosphorylated with triethyl phosphite in the presence of phosphoroxy trichloride. Unlike the 1,1-diphosphonopyrrolidines obtained from γ-lactams (see section 4.14.1), the 1,1-diphosphonoazetidines are only obtained in low yields (28%) (Scheme 41).

Scheme 41



4. Five Membered Rings—Pyrrolidines, Pyrrolines, and Pyrrolidinones

4.1. Introduction

Five membered azaheterocycles are more widespread in organic and medicinal chemistry than the corresponding three and four membered rings. Much research has been done on the synthesis of phosphonic acid analogues of both natural and unnatural amino acids. In this section several methods will be discussed for the synthesis of the phosphonic acid analogue of proline (sometimes called phosphonoproline). Different types of activities are associated with peptides containing phosphonoproline. They are used, for instance, as antiviral agents because of their HIV protease inhibiting activity[83−85] or as inhibitors of dipeptidyl peptidase IV (see section 4.5.6).

Furthermore, phosphonoproline derivatives can be active as such. Compound **178** has bactericidal, fungicidal, and herbicidal activity.[86] Recently, 3-phosphonylated pyrrolidines were found to be Edg receptor agonists, useful for treating immune mediated diseases (Figure 7).[87,88]

1-Phosphonopyrrolidines are known as phosphyl transfer compounds. Proline derivative **184** completely and irreversibly inactivates the class C β-lactamase from *Enterobacter cloacae P99*.[89] β-Lactamases catalyze the hydrolysis of penicillins and cephalosporins and can be subdivided into three classes. Classes A and C are serine lactamases and are the most prevalent and clinically important β-lactamases. Their mechanism involves a tetrahedral acyl-enzyme intermediate while the associative

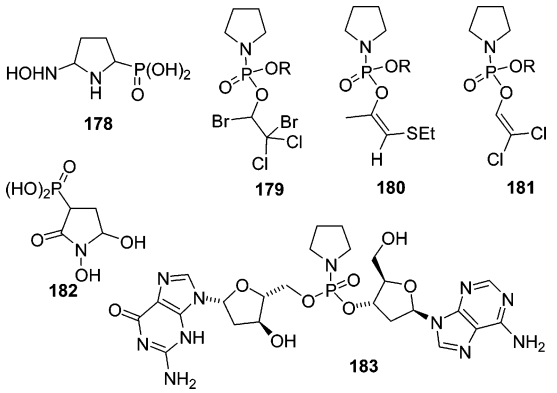
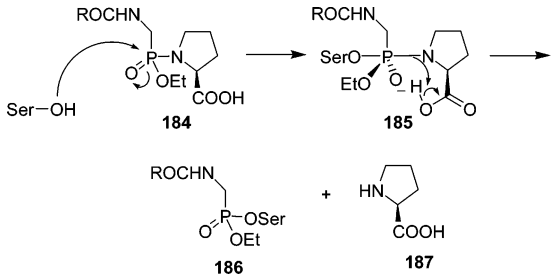


Figure 7.

mechanism for phosphyl group transfer involves a pentacoordinate intermediate with trigonal bipyramidal geometry (Scheme 42). The difference between

Scheme 42



classes A and C can be found in the amino acids that are participating in the proton transfer steps. As a consequence of this difference, the deacylation of the enzyme is the rate determining step in class C β-lactamases.

Class B lactamases are metalloproteins which require Zn(II) ions for their activity. The mechanism based inactivators which have been used against the serine enzymes are generally ineffective against this class of enzymes.[56] However, the inhibition of metalloproteins, especially those containing active-site zinc ions, arises additionally through chelation of the metal ion by the phosphoryl oxygen atoms.

Other active 1-phosphonopyrrolidines are obtained by choosing particular alkyl side chains for the phosphoramidate. With 1,2-dibromo-2,2-dichloroethyl, vinylthio, or 2,2-dichlorovinyl groups, 1-phosphonopyrrolidines **179**−**181** show acaricidal and insecticidal activity.[90−93] Nucleoside containing 1-phosphonopyrrolidines **183** are capable of treating hepatitis infections, particularly, hepatitis B viral infections.[94,95]

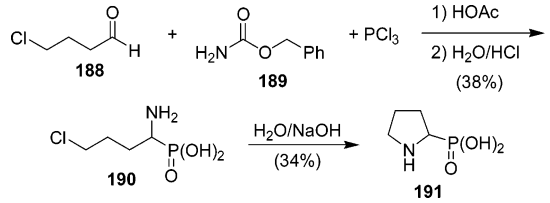
Also, 3-phosphonopyrrolidinones are of interest as lactam antibiotics. The phosphorus containing antibiotic SF-2312 (**182**), produced by *Micromonospora sp.*, is active against *Pseudomonas aeruginosa* and *Proteus vulgaris*.[96]

Further on in this section, more interesting features of five membered phosphonylated azaheterocycles will be discussed, for example, phosphorus containing spin traps and cyclic bisphosphonates as mediators in the human Ca^{2+} metabolism, together with their specific synthesis.

4.2. Ring Closure by Nucleophilic Substitution

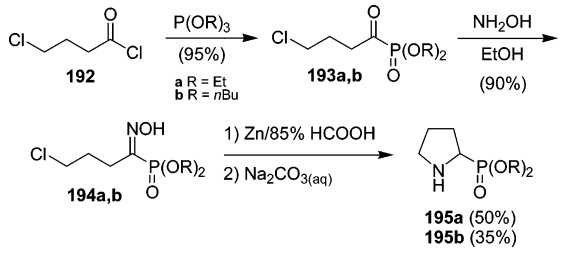
As compared to four membered rings, even less examples of formation of five membered rings by nucleophilic ring closure reactions are found in the literature. The first one is a base induced cyclization of the δ-chloro-α-aminobutanephosphonic acid (**190**), which was formed by condensation of γ-chlorobutyraldehyde (**188**) with benzyl carbamate (**189**) and PCl_3. The resulting racemic 2-phosphonopyrrolidinephosphonates **191** receive some interest as a potential structural mimetic of proline (Scheme 43).[97]

Scheme 43



The second one is a large scale preparation (easy to scale up to 1 mole) of a racemic phosphonylated analogue **195** of proline. Chlorobutyryl chloride (**192**) is allowed to react with trialkyl phosphite. Then the oxime **194** is formed and ring closure is performed after reduction of the oxime with zinc and formic acid (Scheme 44).[98]

Scheme 44



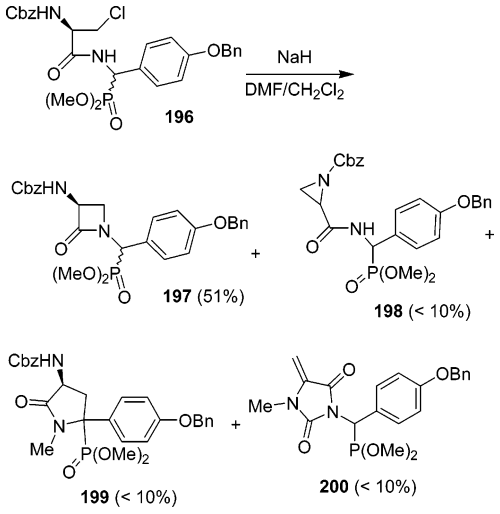
The third example is pyrrolidinone **199**, which is only formed in small amounts (<10%) as a side product of the ring closing reaction toward 3-aminocardicinic acid analogue **197**. The formation of the five membered ring **199** is due to the participation of α-phosphonate carbanions. Other side products are aziridine **198** and imidazolidine **200** (Scheme 45). These products indicate a range of competing mechanisms, which impair the usefulness of the reaction from a synthetic point of view.[99]

4.3. Nucleophilic Phosphorylation

The benzotriazole (Bt) moiety serves as a good leaving group in the α-position of a nitrogen atom and is easily eliminated in the presence of a Lewis acid to generate an iminium cation, which is subsequently attacked by a nucleophile.[100] Pyrrolidinone **202** can be prepared by reacting 2,5-dimethoxy-2,5-dihydrofuran (**201**) with benzotriazole and a primary amine. During this synthesis, benzotriazol-1-yl (Bt^1)- as well as benzotriazol-2-yl (Bt^2)-pyrrolidinone is formed. However, both Bt^1 and Bt^2 are good leaving groups and give rise to the same iminium cation.

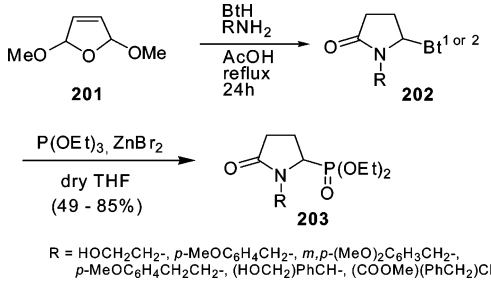
Treatment of **202** in dry THF with triethyl phosphite in the presence of 1 equiv of $ZnBr_2$ produced

Scheme 45



phosphonopyrrolidines **203** in moderate to good yields (Scheme 46).[101] Stereogenic centers at the N-1-

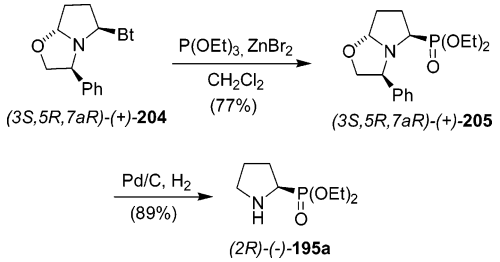
Scheme 46



position displayed poor control of the facial selectivity for phosphate addition into the iminium, resulting in little or no diastereoselectivity at C-5.

A diastereoselective version of the reaction is achieved when using the cyclic hemiaminal **204** as substrate. Treatment of **204** with triethyl phosphite in the presence of the mild Lewis acid $ZnBr_2$ yields one diastereomer in 77%. Subsequent hydrogenation gives the deprotected pyrrolidine **195a** in 63% overall yield as a single enantiomer (Scheme 47).[102] The

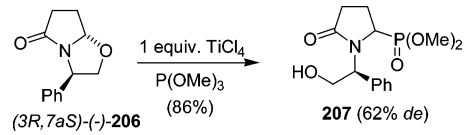
Scheme 47



same method is also applicable for the synthesis of phosphonopiperidines (see section 5.2).[103]

An asymmetric synthesis of 5-phosphonopyrrolidone is based on a similar principle. Here, the hemiaminal-like C−O bond is cleaved by the action of $TiCl_4$. The iminium ion is then trapped by trimethyl phosphite (Scheme 48) with the formation of **207** in 62% diastereomeric excess. As compared to the

Scheme 48



formation of pyrrolidine **195a** in Scheme 47, less stereocontrol is observed during the addition reaction.[104]

Despite the simplicity of the experiments and their often very satisfying results, electrochemistry is not a standard reaction in a synthetic lab. However, the methodology is also useful for the synthesis of functionalized azaheterocyclic compounds. The anodic oxidation of cyclic amides and carbamates has been shown to give α-methoxylated products.[105,106] In the presence of a Lewis acid, iminium ions are formed which are easily trapped by trialkyl phosphites.

Anodic oxidation of methyl 1-pyrrolidine- (**208a**) and 1-piperidinecarboxylate (**208d**) proceeds smoothly at ~1.8 V vs SCE. The initiation step of the oxidation involves electron transfer from the lone pair electrons of the nitrogen atom to the anode. Next, an iminium salt is formed that can be trapped by the solvent (e.g. methanol).[105] The reaction is also applicable to sulfonamides **208b**,**e** and amidophosphates **208c**,**f** (Table 2).[107] The methoxy group can be substituted easily

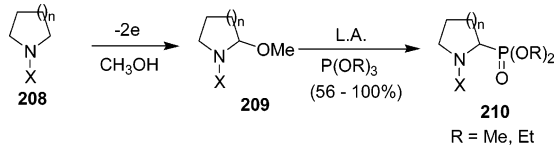
Table 2. Anodic Oxidation and Subsequent Phosphorylation of Pyrrolidine and Piperidine

208−**210**	*n*	X	yield **209**
a	1	COOMe	65%
b	1	Ts	78%
c	1	$P(O)(OEt)_2$	50%
d	2	COOMe	72%
e	2	Ts	27%[a]
f	2	$P(O)(OEt)_2$	64%

[a] Anodic oxidation of **209e** to give dimethoxylated product is faster than the oxidation of **208e**. At the stage where the double amount of electricity is passed, the dimethoxylated product is obtained in 94% yield.

with a phosphonate group because of the acetal character of the C-2 carbon atom. With $TiCl_4$ or $BF_3 \cdot OEt_2$ as a Lewis acid, an iminium ion is formed, to which trialkyl phosphites can be added (Scheme 49).[106,107]

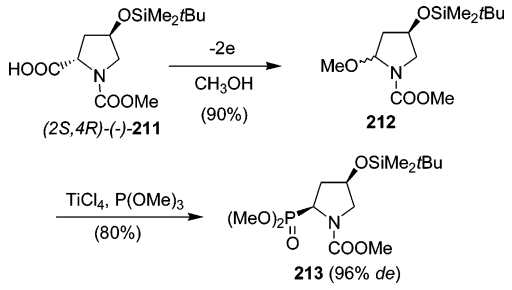
Scheme 49



With *N*-protected 4-hydroxyproline derivatives, oxidative decarboxylation occurs. In this way, amino acids are turned into *N*,*O*-acetals. The enantiomerically pure **211** is converted to a 1:1 mixture of diastereomers after anodic oxidation. Subsequent substitution in the presence of $TiCl_4$ affords the phosphonylated pyrrolidine **213** in 96% de (Scheme 50).[108]

Very similar is the conversion of cyclic α-amino acids to their phosphonate analogues through the

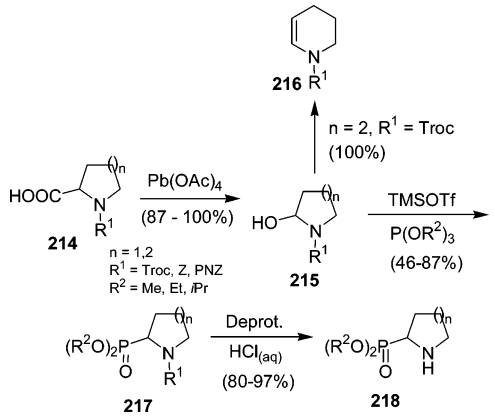
Scheme 50



corresponding 2-hydroxyamines. Decarboxylation is performed via lead tetraacetate oxidation of the *N*-protected amines **214**. The nature of the *N*-protecting group has an influence on the yield but also on the result of the reaction. Decarboxylation of **214** yields the elimination product **216** upon standing because of the very unstable nature of **215**. When the crude reaction mixture is used immediately after reaction, phosphonates **217** can be obtained.

The obtained 2-hydroxypyrrolidines **215** are then converted to the corresponding phosphonates **217** by a reaction with trialkyl phosphite in the presence of trimethylsilyl triflate as a Lewis acid. As mentioned before, an intermediate iminium ion is formed, to which the phosphite adds (Scheme 51).[109]

Scheme 51

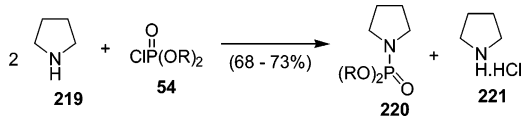


4.4. Electrophilic Phosphorylation

4.4.1. 1-Phosphonopyrrolidines

As discussed before (see section 3.4), chlorophosphates are effective substrates for a nucleophilic attack of a cyclic amine species. Similar to the reaction with azetidine, five membered heterocyclic phosphonamidates are obtained with pyrrolidine (Scheme 52).[110] These compounds were tested against

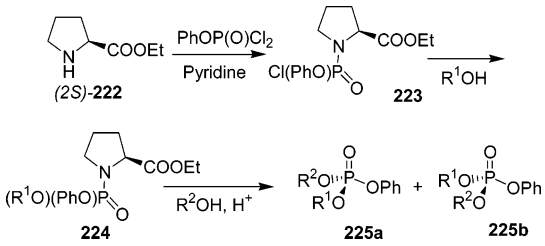
Scheme 52



four types of bacteria and two *Candida* species, but none showed antibacterial or antifungal activity.[111]

A similar methodology is applied for the synthesis of chiral phosphate triesters. Using L-proline as chiral auxiliary, phosphate triesters can be synthesized stepwise and are finally solvolyzed under acidic conditions. In Scheme 53, a dichlorophosphate is

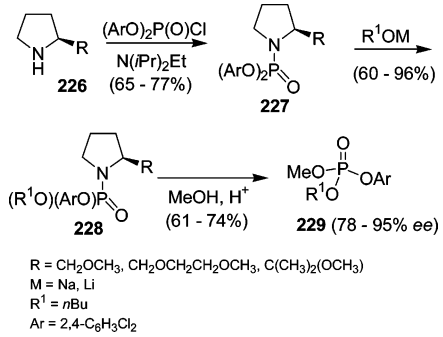
Scheme 53



used, in combination with pyridine as a base. The residual chlorine atom is then substituted by a suitable alkoxy group. The resulting diastereomers **224** can be separated by column chromatography.[112]

When pyrrolidines **226** are used as chiral auxiliary, no separation of diastereomers is necessary (Scheme 54). Because of the chelation of a metal ion between

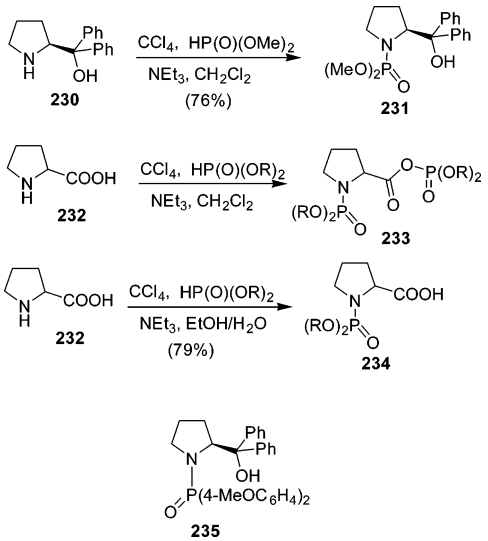
Scheme 54



the P=O moiety and the alcohol or ether function, a rigid structure is created in which an alkoxide can attack only from the less sterically hindered side of the phosphonamidate group. Therefore, only one diastereomer is formed.[113]

Another possibility to prepare the electrophilic phosphorus reagent in situ consists of the use of carbon tetrachloride and a dialkyl phosphite in the presence of triethylamine as a base (Scheme 55). In an ethanol−water mixture, only the amino group of

Scheme 55

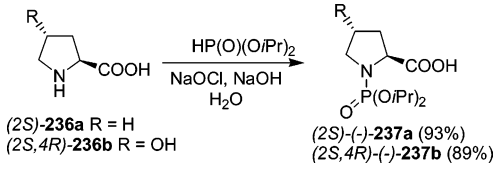


the pyrrolidine is reactive. However, when dichloromethane is used as a solvent, no reaction occurs at the hydroxyl function of **230** while the carboxylic acid **232** is converted to the corresponding mixed anhydride under the same conditions. These mixed anhydrides are being used in protein coupling reactions.[114−117] The *n*-butyl derivative of **234** (R = *n*Bu) is being used as a medicine for the treatment of schistosomiasis.[118]

1-Phosphonopyrrolidine (**231**) can be converted to **235** with an excess of *p*-anisylmagnesium bromide. The obtained phosphinamide can be used as a catalyst for the asymmetric reduction of ketones by borane.[114]

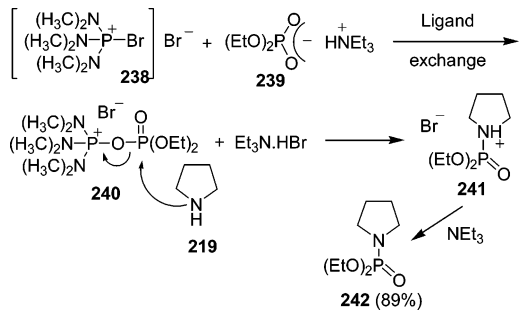
A third method also involves the in situ formation of the chlorophosphate reagent. However, to avoid the carcinogenic CCl_4, a mixture of sodium hypochlorite and sodium hydroxide in aqueous medium is used for the conversion of the diisopropyl phosphite (Scheme 56). The diisopropyl phosphoramidate group is introduced in amino acids as a nitrogen protecting group without any racemization and can be easily removed under acidic conditions. This is comparable to the Boc protecting group; however, diisopropyl phosphite is a significantly cheaper reagent.[119]

Scheme 56



The direct transformation of organophosphorus acids to the corresponding amides is a preparative challenge. This results from the pronounced tendency of organophosphorus acids to preferentially form the corresponding anhydrides under the action of various conventional dehydrating agents. Hexamethyltriamino dibromophosphorane (**238**) can be used to activate the OH group of diethyl hydrogen phosphate (**239**) by ligand exchange using triethylamine (Scheme 57). Pyrrolidine **219** then acts as a nucleophile attacking the phosphate **240** which contains now a good leaving group, so that 1-phosphonopyrrolidine (**242**) is formed in good yield (89%).[120]

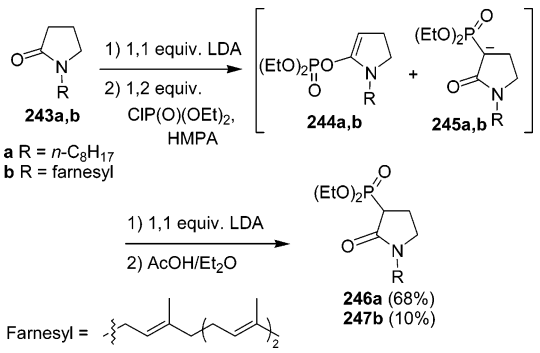
Scheme 57



4.4.2. Vinyl Phosphate–Phosphonate Rearrangement

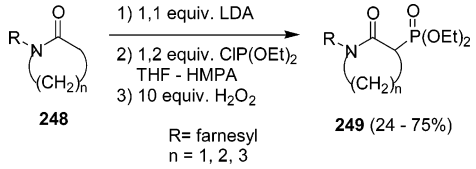
When lactone enolates are trapped with a dialkyl chlorophosphate reagent, a vinyl phosphate is obtained that can rearrange to the α-phosphonolactone upon further treatment with base.[121] An *N*-alkyllactam undergoes a similar rearrangement to afford an α-phosphonolactam (Scheme 58). The enolate is made in THF by adding LDA (1.1 equiv) followed by the chlorophosphate, together with 1 equiv of HMPA to facilitate the vinyl phosphate anion formation. After adding a second equivalent of LDA to initiate the rearrangement, the reaction is quenched with acetic acid in ether.[122] Similar results can be obtained when 2 equiv of LDA are added at once in the first step (R = Me, 65%).[123]

Scheme 58



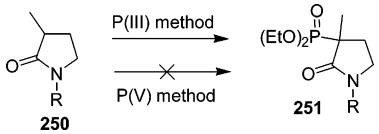
However, some side reactions occur under the strongly basic conditions with the farnesyl side chain, resulting in lower yields. Reacting dialkyl chlorophosphite with the preformed anion, however, prevents this side reaction (Scheme 59). The desired α-phosphonolactams (**249**) are then obtained by oxidation using air[124,125] or hydrogen peroxide.[122] The main advantage of this P(III) method is the use of only one equivalent of base, to form the enolate anion. No further treatment with base is necessary for the rearrangement, and the amount of side products is significantly reduced.[122]

Scheme 59



Furthermore, α-substituted α-phosphonolactams are also accessible via the P(III) reagent (Scheme 60).

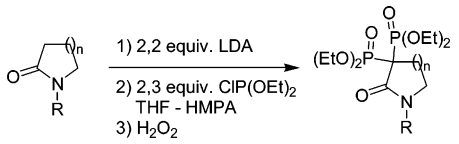
Scheme 60



The P(V) reagent fails to react, because the vinyl phosphate anion formation is required for the rearrangement, which is obviously not possible in the case of pyrrolidinone **250**.

The major drawback of the P(III) method is the formation of small amounts of bisphosphonates. This side reaction does not occur via the P(V) method, but it can be used for the synthesis of bisphosphonates when the conditions are slightly modified (Scheme

Scheme 61



61). When 2 equiv of base and chlorophosphite are used, the bisphosphonates **253** are the main products next to small amounts of monophosphorylated compounds.[126]

Geminal bisphosphonic acids have been proven to be relatively stable analogues of inorganic pyrophosphate, and many α-hydroxybisphosphonic acids bind to bone mineral and inhibit the resorption of living bone. In particular, some bisphosphonates with nitrogen-containing substituents on the geminal carbon have shown interesting biological activities, which led to the development of a number of methods for their synthesis.

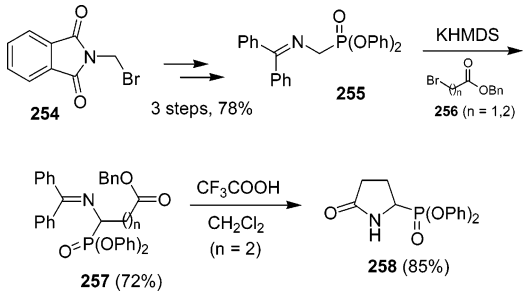
4.5. Ring Closure by Intramolecular Addition–Elimination

Ring closure with the formation of azaheterocycles can be invoked by the attack of a nucleophilic nitrogen atom onto a carbonyl group. Since both functional groups have to be present in the precursor, one of them needs to be temporarily deactivated. Most of the time, non-nucleophilic nitrogen groups are used which are then converted to a nucleophilic species to invoke the ring closure.

4.5.1. Hydrolysis of an Imine

The temporary deactivation of the amino nucleophile can be performed by the synthesis of the corresponding imine. For the synthesis of pyrrolidinone **258**, imine **255** is alkylated before the ring closure is induced by hydrolysis of the alkylated imine **257** by trifluoroacetic acid (Scheme 62). When

Scheme 62

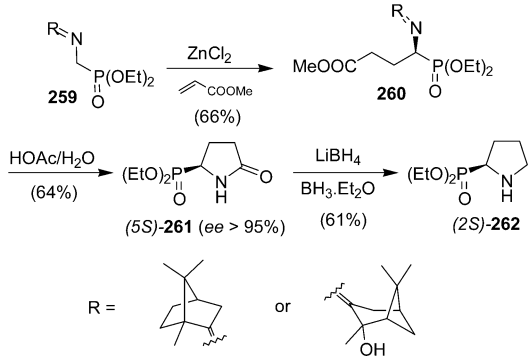


hydrochloric acid is used, no cyclization occurs and the corresponding hydrochloride salt of the acyclic amine is recovered from the reaction mixture.[127]

The same principle can be used in the asymmetric synthesis of phosphonic derivatives of proline. The stereoselectivity of the reaction is invoked by camphorlike protecting groups.

When unsubstituted acrylic esters[128,129] are used in the addition reaction, only $ZnCl_2$ generated carbanions of **259** are reactive. Iminophosphonate **260** is formed in 66% yield with 71% de. The minor diastereomer was easily removed by flash chromatography on silica gel. After hydrolysis, enantiomerically pure (*5S*)-pyroglutamic acid derivative **261** was isolated (ee ≥ 95%). The chiral auxiliary was recovered in 60% yield (Scheme 63).

Scheme 63



Reduction with $LiBH_4/BF_3{\cdot}OEt_2$ proceeds without isomerization and results in the phosphonylated analogue **262** of proline, which cannot be obtained by alkylation of **259** with diiodopropane and subsequential hydrolysis.

The diastereoselectivity is highly dependent on the substitution pattern of the acrylic esters. In the case of *trans*-substituted esters **263a**−**d**, mainly the *transoid* isomers of **264** are isolated as a mixture of enantiomers next to very little amounts of *cisoid* isomers. In the other case, with *cis* substitution of **263e**−**f**, only the (1*S*) stereoisomers are formed, but as a mixture of *cisoid*- and *transoid*-**264** (Table 3).

Table 3. Remarkable Stereochemical Results of Conjugate Addition of Phosphorus Stabilized Carbanions to Substituted Methyl Acrylates

265	R^1	R^2	R^3	1*S*,2*S*	1*S*,2*R*	1*R*,2*R*	1*R*,2*S*	yield
a	Ph	H	H	100	<2	14	<2	91%
b	Me	H	H	5	100	3	12.5	85%
c	*p*-BrPh	H	H	100	3	12	<2	86%
d	Ph	H	COOMe	100	4	4	<2	84%
e	H	Ph	H	100	16	<2	<2	89%
f	H	COOMe	H	100	49	<2	<2	88%

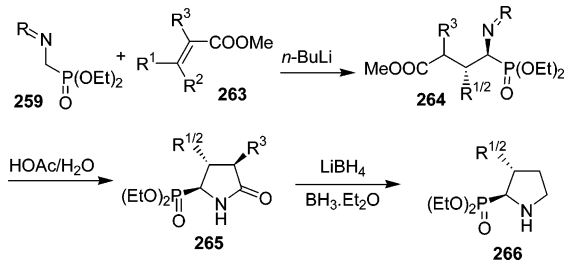
These remarkable stereochemical results are attributed to different structures of the transition states.[130]

Hydrolysis of **264** was carried out with 90% aqueous acetic acid and afforded exclusively the *trans*-substituted lactams **265**. However, after hydrolysis of the adduct **264e** (obtained from the *cis*-acrylate ester **263e**), the *cis*-substituted lactam **265e** was isolated in 10% yield besides 65% of the *trans* isomer. Both isomers could be separated by flash chromatography. Reduction of the phosphonate analogues of the pyroglutamic acids **265a**,**b**,**e** yields the diastereomerically pure pyrrolidines **5** with an enantiomeric excess of 77−95% (Scheme 64).

4.5.2. Debenzylation

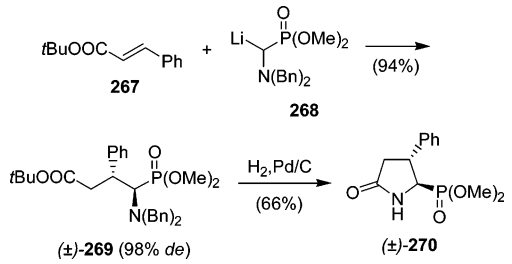
A benzyl group is often used as a nitrogen protecting group and is easily removed by hydrogenation. This technique is used in one single case for the

Scheme 64



synthesis of pyrrolidine **270**. 1,4-Addition of lithiated aminomethylphosphonate **268** proceeds in 94% yield and 98% diastereomeric excess. Reductive deprotection of **269** then leads to *trans*-phosphonopyrrolidone **270** in 66% yield (Scheme 65).[131]

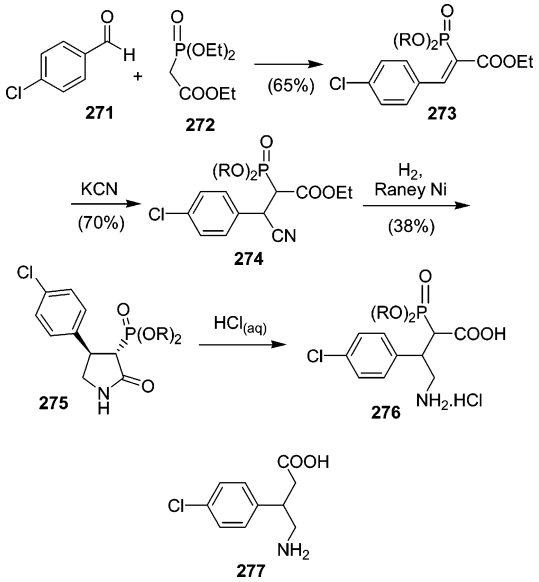
Scheme 65



4.5.3. Reduction of Cyanides

Reduction of a cyanide moiety also yields a free amine. Intramolecular attack onto the carboxyl group of **274** yields pyrrolidine **275**. Cyanide **274** is synthesized by Michael addition of cyanide to derivative **273** (Scheme 66). Pyrrolidone **275** is the cyclic

Scheme 66

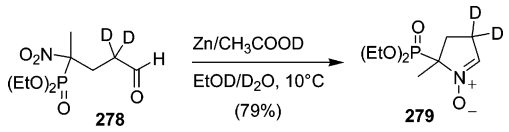


equivalent of baclofen analogue **276**, which is a potential mimetic of baclofen. Baclofen **277** is a GABA derivative and is an effective agonist of the $GABA_B$ receptor which is insensitive to biculline.[132]

4.5.4. Ring Closure of γ-Nitrocarbonyl Compounds

Upon reduction of the nitro group of a γ-nitroaldehyde, a hydroxylamine species can be formed which can cause intramolecular cyclization with the formation of a cyclic nitrone. The reduction of **278** is performed with zinc and acetic acid in an ethanol−water mixture at 10 °C (Scheme 67).[133] As compared

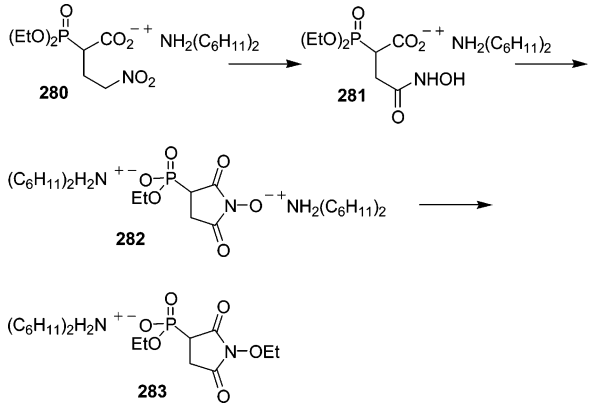
Scheme 67



to other reduction procedures, protection−deprotection of the aldehyde is not necessary under these conditions.[134] For the synthesis of deuterated 5-diethoxyphosphoryl-5-methyl-1-pyrroline *N*-oxide (DEPMPO) (**279**), which should have an enhanced signal-to-noise ratio in EPR spectra, the reaction is performed in deuterated solvents and proceeds in good yield (79%).

A similar example of the reactivity of γ-nitrocarbonyl compounds can be found with 4-nitrobutanoate **280**, which is thermally unstable and undergoes consecutive transformations while being heated in boiling nitromethane to form **281**, **282**, and **283**. A possible mechanism for the isomerization of **280** giving the hydroxamic acid **281** involves the formation of a lactone and consecutive elimination and addition of water. Dealkylation of the phosphonate ester and alkylation of the hydroxysuccinimide **282** is performed by dicyclohexylamine. After 30 h, a mixture of **282** and **283** is finally obtained in a 1:2 ratio (Scheme 68).[135]

Scheme 68

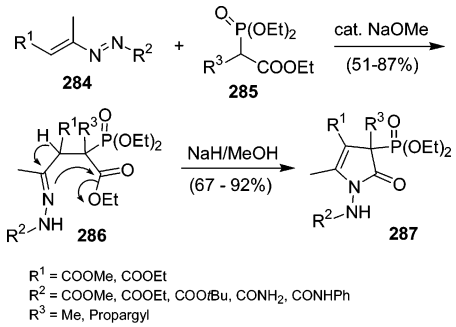


4.5.5. Michael Addition of Conjugated Azoalkanes

1,4-Addition to conjugated azoalkenes gives rise to the corresponding hydrazone. In the presence of a catalytic amount of base, **285** is deprotonated and adds to the diazo compound **284** with formation of a nucleophilic nitrogen species (R^1 is an electron withdrawing group). The reaction of azoalkenes **284** with triethyl 2-phosphonopropionate **285** readily proceeds at room temperature. Ring closure is performed in methanol with a catalytic amount of NaH (Scheme 69) but does not occur when R^3 = H, so that the corresponding starting phosphonohydrazones are recovered.[136]

The methodology was extended to the propargylic derivative of **285** (R^3 = propargyl).[137] The correspond-

Scheme 69

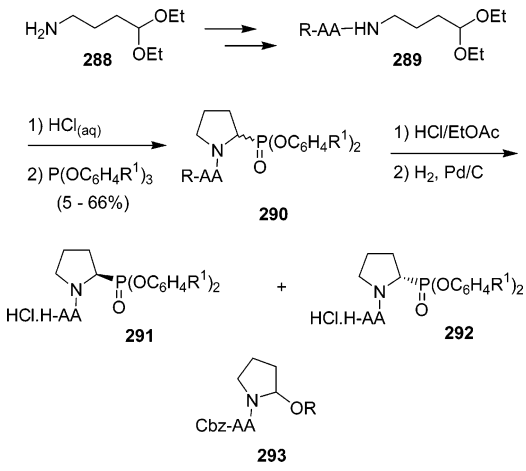


ing hydrazone is readily formed and ring closed to pyrrolinone **287**. The propargylic side chain provides an extra possibility for functionalization. A coupling reaction with triflate or halide derivatives can be performed with Pd(0) as a catalyst and Cu(I) as a cocatalyst. The reaction order of this sequence can also be changed. Starting with the coupling reaction, the obtained derivatized α-propargylphosphono acetate can be used for the 1,4-addition reaction, with a slightly improved yield.

4.5.6. Hydrolysis of an Acetal

The carbonyl group can also be protected as an acetal to avoid ring closure in an early stage. An *N*-protected amino acid is then coupled to the free amino group. The acetal **289** is hydrolyzed in acidic medium, and the resulting mixture can be treated with several triphenyl phosphite reagents in acetic acid to give diastereomeric mixtures of the protected diphenyl phosphonates **290** (Scheme 70). After depro-

Scheme 70



tection, the free diastereomers can be separated by vacuum column chromatography (with the exception of the L-Pro, L-Ala, L-Ile, and L-Arg derivatives).

The real intermediate reacting with triphenyl phosphite actually remains unknown. Hydrolysis of acetal **289** followed by heating in CCl_4 under reflux leads to the formation of the cyclic hemiaminal **293**.[138,139]

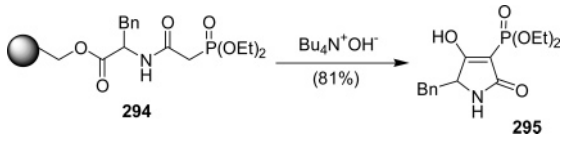
The obtained peptides, consisting of the phosphonylated analogue of proline coupled with a regular amino acid, are inhibitors of dipeptidyl peptidase IV (DPP IV). DPP IV is a post-proline cleaving enzyme that has been found in a variety of mammalian cells and tissues. An extensive review about the structural properties and clinical aspects of DPP IV has been published very recently.[140] It plays a role in glucose homeostasis, through proteolytic inactivation of the incretins, and in the imune system, by influencing T-cell activity, but DPP IV is also imlplicated in HIV-1 entry, malignant transformation, and tumor invasion. Therefore, inhibitors of DPP IV may have therapeutic utility in the modulation of the rejection of transplanted tissue by the host organism and in treatment of type 2 diabetes.[141]

Several other inhibitors of DPP IV are known, but unfortunately, most of these are unstable in aqueous solution at neutral pH. For the diphenyl phosphonates, no cytotoxicity was observed in human peripheral blood mononuclear cells and also no acute systemic or local toxicity was seen upon single intravenous injection in rabbits. The best results are obtained with proline as amino acid and with R^1 as electron withdrawing group (e.g. AA = proline, R^1 = 4-COOMe: IC_{50} = 20 nM). However, the most potent inhibitors are also the most unstable compounds.[139] Furthermore, this class of pyrrolidine phosphonates is claimed to have inhibitory effects to a wider group of serine peptidases and proteases, for example, prolyl oligopeptidase, dipeptidyl peptidase II, fibroblast activation protein a (FAPa), and elastase, and is therefore useful as antiinflammatory agents, anticoagulants, and antitumor and anti-AIDS agents, and for treating vascular and autoimmune diseases.[142−144]

4.5.7. Dieckmann Condensation

Another synthetic method to induce ring closure consists of the Dieckmann condensation. A carbanion is formed by α-deprotonation of the phosphonate **294** that attacks the carbonyl group by which it is coupled to Wang resin (Scheme 71). Pyrrolinone **295** is then

Scheme 71

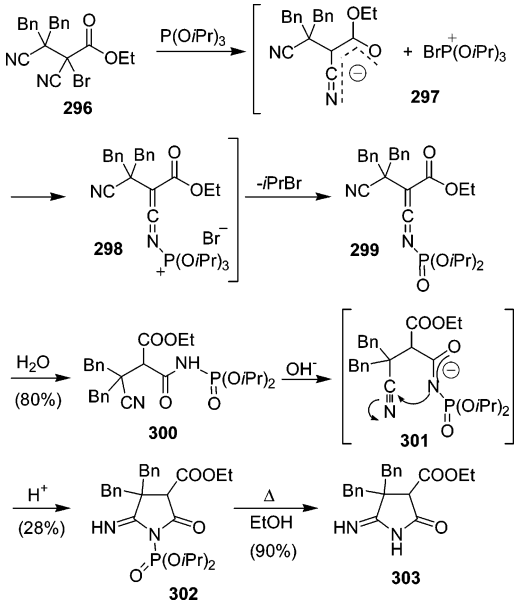


released through cyclization, leading to cleavage from the resin (81% overall yield). Tetrabutylammonium hydroxide is preferred as a base because of a more convenient work up.[145] This method also has the advantage of utilizing solid-phase chemistry.

4.5.8. α-Dehalogenation–Isomerization

Starting from bromodicyano ester **296**, the phosphorylated ketene imine **299** can be synthesized using trialkyl phosphites (Scheme 72). The reaction is initiated by a nucleophilic attack of the phosphite on the bromine atom with the formation of a stabilized anion. The electrophilic phosphorus reagent **297** on his turn attacks this anion, and the reaction is terminated by a dealkylation of the phosphonium ion **298**. A vinyl phosphate is also formed as a side product in minor amounts by the attack of the phosphite on the ester moiety in **297**.

Scheme 72

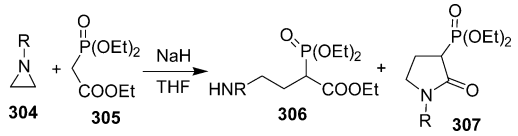


The ketene imine **299** is then easily hydrolyzed to the corresponding amide. Cyclization then occurs upon the addition of base followed by acidic work up. When the obtained 1-phosphorylated iminopyrrolidine **302** is heated in ethanol, dephosphorylation leads to the formation of iminosuccinimide **303** in 90% yield (Scheme 72).[146]

4.5.9. Ring Expansion of Aziridines

In the base induced reactions of phosphono acetate with aziridines **304**, a reactive N anion is formed that can form pyrrolidinones **307**. This cyclization seems to be strongly influenced by steric hindrance and by the actual lifetime of the anion (Scheme 73 and Table 4).[147]

Scheme 73



When *N*-phosphorylated aziridines **308** are added to a solution of dianion **309** in THF, pyrrolidine **312** is obtained in excellent yield (Scheme 74). It is obvious that ring opening of unsymmetrically substituted aziridine **308b** takes place exclusively at the least substituted carbon atom. When pyrrolidine **312** is refluxed in 20% aqueous H_2SO_4, dephosphorylation and decarboxylation occur to yield pyrroline **313**.[148]

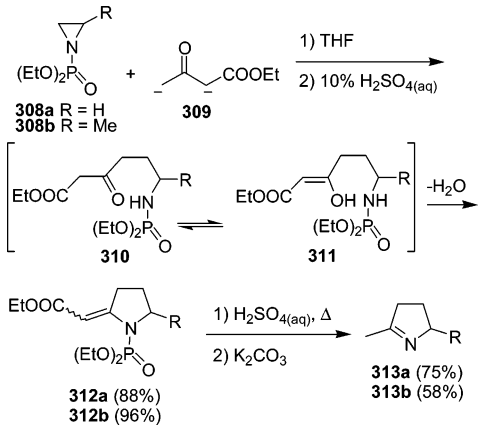
4.5.10. Intramolecular Aminomercuration

The intramolecular aminomercuration of alkenylamines is a useful approach to substituted hetero-

Table 4. Ring Expansion of Aziridines

	R	yield **306**	yield **307**
a	CO(1-adamantyl)	85%	0%
b	COPh	62%	0%
c	COOEt	0%	28%
d	$CONPh_2$	22%	41%
e	Ts	0%	53%

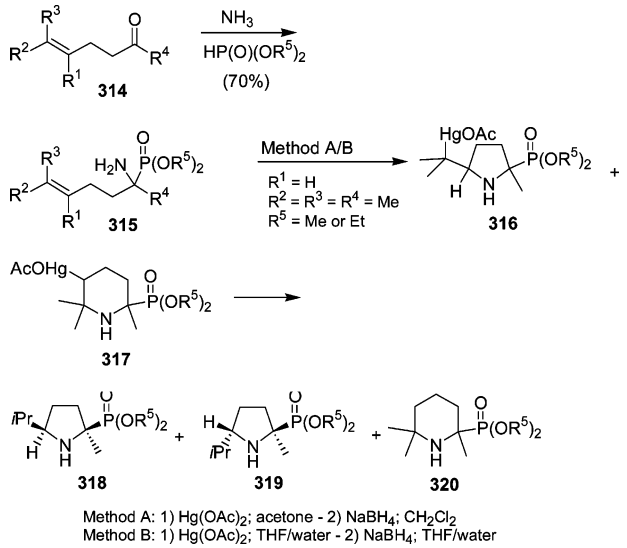
Scheme 74



cyclic amines. The starting α-amino-δ-alkenylphosphonates are synthesized by bubbling ammonia through a solution of γ-alkenyl aldehydes or ketones. Ketones are transformed in reasonable yields (50−70%); however, aldehydes give rather poor yields (15−30%).

Cyclization of the α-amino-δ-alkenylphosphonates **315** is initiated by addition of $Hg(OAc)_2$ to the double bond followed by cyclization through intramolecular nucleophilic attack of the free amine. Using α-amino-ϵ-alkenylphosphonates, it is possible to obtain the six membered analogues in similar yields (55%). The reaction is regiospecific in most cases,[149−151] although in one case (R^1 = H; R^2 = R^3 = R^4 = Me) the formation of 3−7% of the six membered ring is observed using diethyl phosphonate derivatives (Scheme 75). Demercurization is finally achieved by

Scheme 75



a reduction with $NaBH_4$. Formation of free radicals during the reduction accounts for the formation of side products such as dialkylmercury compounds or ring opening to the starting material **315**.

The stereoselectivity of the aminomercuration depends to a large extent on the reaction conditions. When the cyclization of **315** is performed in THF/H_2O, the stereoselectivity is different compared to that of the reactions performed in acetone for the

cyclization and in dichloromethane for the reduction (Table 5).[150,151]

Table 5. Ratio of the Reaction Products with Changing Reaction Conditions

entry	method	R^5	**318**	**319**	**320**
1	A	Me	12%	88%	0%
2	A	Et	10%	83%	7%
3	B	Me	88%	12%	0%
4	B	Et	80%	17%	3%

4.5.11. Addition to an Allenic Moiety

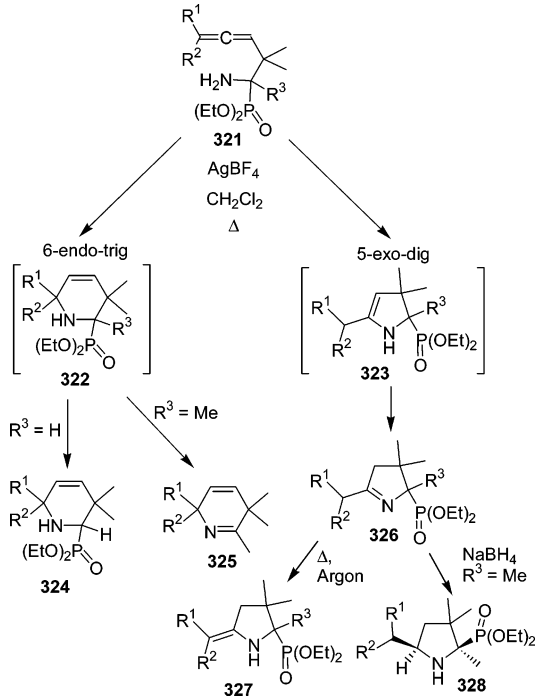
When β-allenic aminophosphonates **321** are heated in the presence of mercury or silver salts to activate the allenic moiety, a mixture of five and six membered heterocycles is obtained. The ratio of five membered to six membered rings is dependent on steric factors. When R^1 and R^2 are more sterically demanding groups, the ratio shifts toward the five membered ring. The largest effect, however, is observed when R^3 is changed from H to Me; then, only very small amounts of six membered ring **325** are formed (Table 6). When the obtained 1-pyrrolines **326**

Table 6. Ratio of Five and Six Membered Rings

entry	R^1	R^2	R^3	yield	**324**,**325**/**326** ratio
a	Me	Me	H	74%	73:27
b	Me	Et	H	72%	70:30
c	-$(CH_2)_5$-	H		73%	66:34
d	Me	Me	Me	74%	19:81
e	Me	Et	Me	80%	6:94
f	-$(CH_2)_5$-	Me		68%	12:88

are submitted to high temperatures (80 °C) under an inert atmosphere, enamines **327** are formed by tautomerization to the more thermodynamically stable compound (Scheme 76).[152,153]

Scheme 76

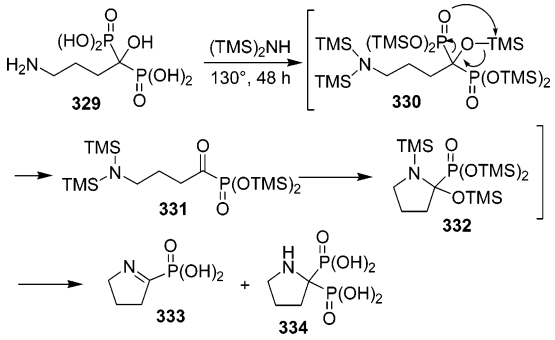


1-Pyrroline **326d**−**f** can also be reduced using $NaBH_4$ in ethanol at −20 °C. Under these conditions, no dephosphorylation occurs and only the *cis*-pyrrolidine is formed.[154]

4.5.12. Rearrangement of Bisphosphonic Acids

When bisphosphonic acid **329** is trimethylsilylated and distilled at low pressure, a rearrangement occurs in which one phosphonate group is eliminated and an intermediate α-acylphosphonate **331** is formed which is transformed in situ to the five membered heterocycle **332** by intramolecular nucleophilic addition. Finally, a mixture of pyrroline **333**, obtained by elimination, and pyrrolidine **334**, obtained by addition of the silylated phosphite, is found (Scheme 77).[155]

Scheme 77



4.6. Cycloaddition

The 1,3-dipolar cycloaddition reaction is one of the most useful methods for the construction of five membered rings in a convergent and stereocontrolled manner.[156] In particular, the [3 + 2] cycloaddition between azomethine ylids and alkenes is a direct route to substituted pyrrolidines.

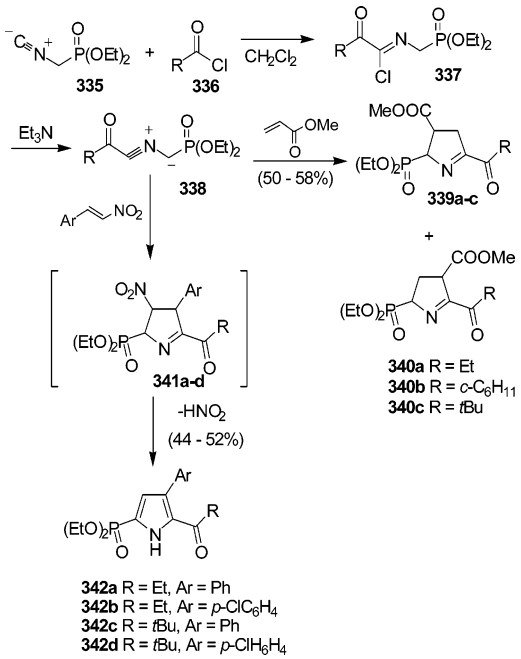
4.6.1. 1,3-Dipolar Cycloaddition to Phosphonylated Nitrile Ylids

The use of nitrile ylids **338** as 1,3-dipoles in cycloadditions has received a lot of attention as a route to a variety of five membered nitrogen containing rings. Due to the electron withdrawing effect of the phosphonate moiety, *N*-phosphonomethylimidoyl chlorides **337** are potential precursors of phosphorylated nitrile ylids by a 1,3-dehydrohalogenation process in basic medium.

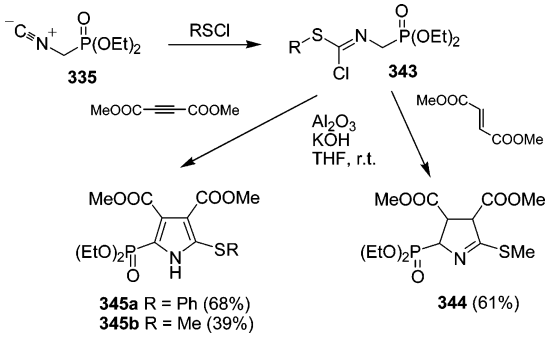
These imidoyl chlorides can be synthesized by a reaction of isocyanomethylphosphonate **335** with an acid chloride (Scheme 78). Upon treatment with triethylamine, a 1,3-dipolar species is formed, which is trapped in situ with methyl acrylates, giving a mixture of cycloadducts **339a**−**c** and **340a**−**c**. These regioisomers are difficult to separate by chromatography. When nitroalkanes are used as dipolarophiles, however, 2-phosphonopyrroles **342a**−**d** are obtained in moderate yield after elimination of nitrous acid and aromatization (Scheme 78).[157]

Another example of the formation of an imidoyl chloride concerns the reaction of isocyanomethylphosphonate **335** with sulfenyl chlorides (Scheme 79). The cycloaddition is then performed in a solid−liquid

Scheme 78



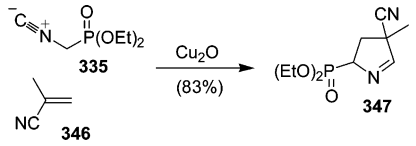
Scheme 79



medium using a KOH/Al_2O_3 mixture in THF. With dimethyl fumarate, pyrrolines **344** are formed in 61% yield. With acetylenedicarboxylate, however, aromatization occurs and 2-phosphonopyrroles **345** are isolated in moderate yields.[158]

1-Isocyanomethylphosphonate **335** can also be used immediately in a cycloaddition reaction. Reaction with methacrylonitrile and Cu_2O as a catalyst yields pyrroline **347** in 83% yield (Scheme 80).[159]

Scheme 80

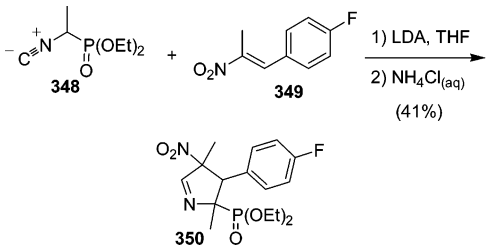


Also after deprotonation, isocyanophosphonate **348** becomes an excellent reagent to react with electron poor double bonds such as in **349** (Scheme 81). No rearrangement and elimination of nitrous acid with formation of the corresponding pyrrole are observed in this case.[160]

4.6.2. 1,3-Dipolar Cycloaddition to Phosphonoazomethine Ylids

Reaction of carbanions of *N*-phosphonomethyl imines **351** with α,β-unsaturated esters can lead to three

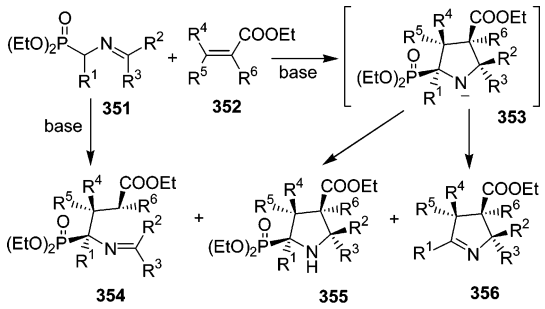
Scheme 81



different products: an acyclic adduct **354** due to Michael addition, pyrroline **356** due to cycloaddition and subsequent elimination of the diethyl phosphite anion, or pyrrolidine **355**.

When sodium hydride is used as a base at room temperature, pyrrolidines **355** are formed exclusively in good yields (77−90%) due to the stereospecificity of the reaction related to the concerted mechanism. However, when a lithium base is used such as butyllithium or LDA, pyrroline **356** is formed as a side product depending on the temperature profile of the reaction. In the case of the lithium bases, an acyclic derivative is formed first that is then cyclized to a mixture of isomers. However, the yield is low due to the disfavored 5-*endo-trig* mechanism (Scheme 82).[161−163]

Scheme 82

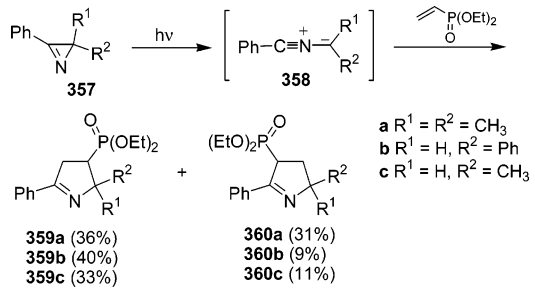


4.6.3. 1,3-Dipolar Cycloaddition to Vinylphosphonates

When phenylazirines **357** are irradiated with UV light, nitrile ylids **358** are formed which can react in situ with activated C=C or C=X (X = N, O, S) bonds. The P=O bond of phosphonates, however, is not active in this kind of reaction, although the phosphonate group is able to activate a C=C bond. Reaction of irradiated azirines **357** in the presence of vinylphosphonate yields two regioisomers **359** and **360**, which can be separated by preparative GC (Scheme 83). Each regioisomer is isolated as a mixture of the *cis* and *trans* isomers.[164]

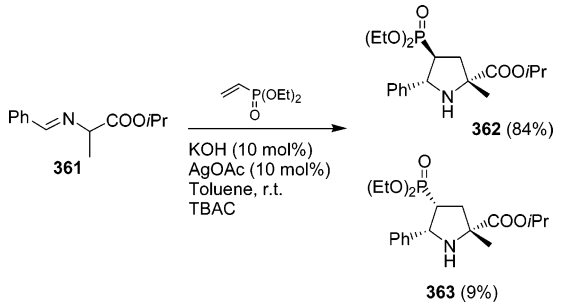
Cycloaddition of vinylphosphonate with azomethine ylids instead of nitrile ylids **358** appeared to be impossible under thermal conditions. However, in the presence of a catalytic amount of AgOAc as a Lewis acid, the reactions proceed in good yields (90%). Tetrabutylammonium chloride (TBAC) has to be added as a phase transfer catalyst in the solid−liquid system, resulting in long reaction times. However, in this case, the cycloaddition reaction is regioselec-

Scheme 83



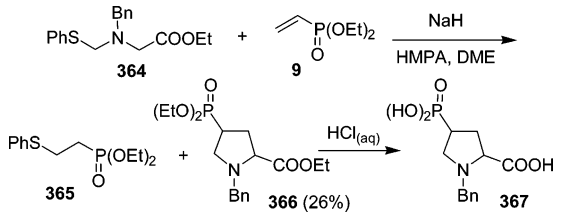
tive with the *trans*-pyrrolidine **362** predominating (Scheme 84).[165]

Scheme 84



Treatment of phenylthioglycinate **364** with NaH yields an intermediate azomethine ylid that can react with vinylphosphonate with the formation of ethyl 4-phosphonoprolinate **366**. However, the major drawback of this approach is the formation of large amounts of 1,4-adduct **365** that causes the yield to drop to 26% (Scheme 85).[166]

Scheme 85

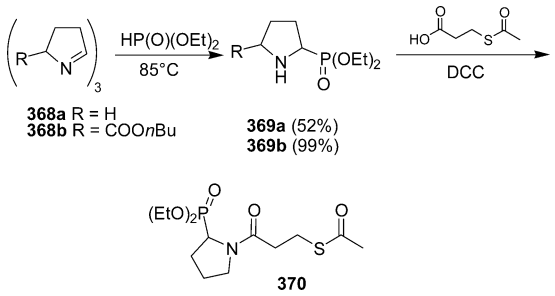


4.7. Addition to Cyclic Imines

Nucleophilic addition of a dialkyl phosphite to an 1,2-unsaturated azaheterocycle is one of the most direct ways to synthesize cyclic α-aminophosphonates. For the synthesis of the phosphonate analogue of proline, pyrroline **372** would be an interesting starting product. However, pyrroline is unstable, and trimers are rapidly formed upon standing. Nevertheless, when dialkyl phosphite is added to these trimers, the desired phosphonylated pyrrolidines **369** are obtained in good yields by thermal depolymerization of the trimer (Scheme 86).[141,167−170] The obtained pyrrolidine **369a** can then easily be converted to amide **370**, which has angiotensin enzyme inhibitory activity.[171]

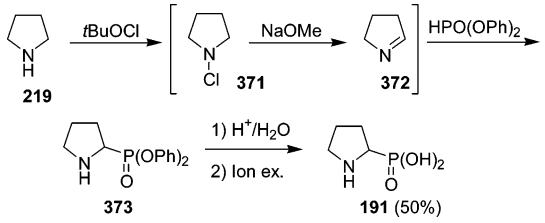
Another possibility is to synthesize the pyrroline derivative from a readily available starting material and allow it to react with dialkyl phosphite in situ. Starting from pyrrolidine, pyrroline can be formed by chlorination with tertiary butyl hypochlorite and

Scheme 86



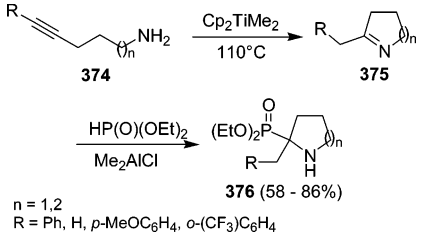
subsequent elimination. In this way, phosphonylated pyrrolidine **191** is formed in 50% overall yield (Scheme 87).[172,173]

Scheme 87



In the presence of a Lewis acid, an intermediate iminium salt is formed, which is more easily attacked by the phosphite. In a one-pot synthesis of 2-phosphonopyrrolidines **376**, an unsaturated 1-azaheterocycle **375** is formed by intramolecular hydroamination of aminoalkynes **374** in the presence of catalytic amounts of Cp_2TiMe_2 at 110 °C (Scheme 88). After addition of

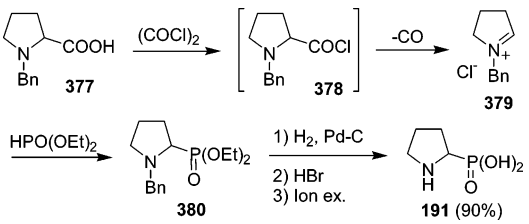
Scheme 88



diethyl phosphite together with 5 mol % Me_2AlCl, the phosphonylated azaheterocycles **376** were obtained in good overall yields (58−86%). The application of inter- and intramolecular hydroamination reactions leads to the formation of both cyclic and acyclic α-aminophosphonates.[174]

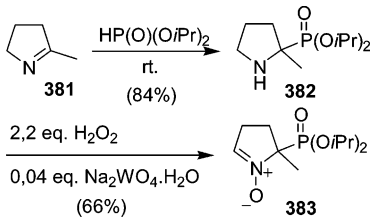
When 1-benzylproline (**377**) is treated with oxalyl chloride, decarboxylation occurs with formation of the iminium salt **3** (Scheme 89). 2-Phosphonopyrrolidine **191** is then obtained by addition of diethyl phosphite, followed by debenzylation and dealkylation in 90% overall yield.[172]

Scheme 89



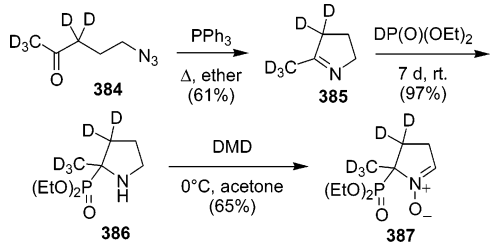
Finally, addition of diisopropyl phosphite to the commercially available 2-methyl-1-pyrroline (**381**) yields **382** in 84% yield. The phosphorylated nitrone **383** is then obtained by oxidation with sodium tungstate (Scheme 90).[175]

Scheme 90



The deuterated equivalent of this nitrone is synthesized using a modified procedure. The starting pyrroline **385** is formed by an aza-Wittig reaction from azide **384** followed by addition of diethyl phosphite, yielding **386** in 97% (Scheme 91).[133]

Scheme 91

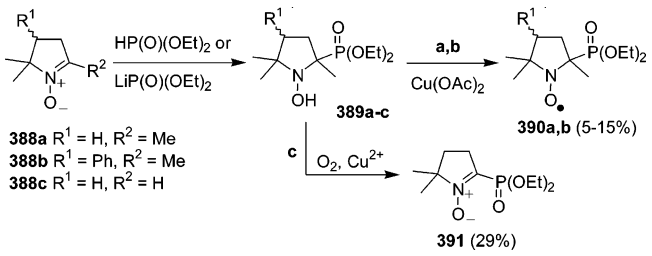


4.8. Addition to Nitrones

Nitrones have attracted the interest of many chemists because of their versatile reactivity. Similar to imines and iminium salts, nitrones are suitable for addition of a phosphorus nucleophile, giving rise to hydroxylamines.

The hydroxylamines **389a**,**b** can be obtained using dialkyl phosphites or their corresponding lithium salts and are further oxidized to β-phosphorylated nitroxides (Scheme 92). These represent a new class

Scheme 92



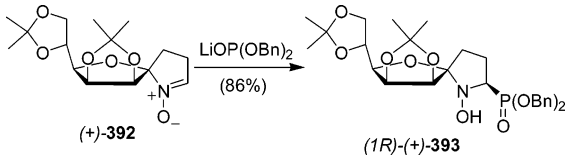
of stable organic free radicals. However, the overall synthesis yield remains rather low (5−29%).[176,177]

Compound **391** is an alternative for 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), which is one of the most widely used spin traps. DMPO rapidly scavenges free radicals, generating secondary radicals, so-called spin adducts. The nonzero nuclear spin of the β-H on the aminoxyl spin adduct provides remarkably suitable EPR information useful for the diagnosis of the structure of the free radical addend. However, the same hydrogen atom is also responsible for the instability of the spin adducts. This can be overcome by substituting the β-H by a phosphorus atom, which also has a nonzero nuclear spin and a high natural abundance. The result is a spin trap, 1-diethoxyphosphoryl-5,5-dimethyl-1-pyrroline *N*-oxide (DEP-DMPO), which is useful in both aqueous and organic solutions, which is more sensitive and which yields more persistent spin adducts with hydroxyl, alkoxyl, acyl, and C-centered radicals.[177]

Recently, nitroxide **390a** was shown to exert a cardioprotective action that was attributed to its antioxidant action, through reduction of the hydroxyl radical formation and the tissue lipid peroxidation (Scheme 92).[178]

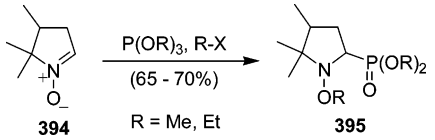
Starting from the enantiopure **392**, the addition reaction can also be performed diastereoselectively. Using lithium dibenzyl phosphite, *N*-hydroxyaminophosphonate **393** is obtained as a single diastereomer in 86% yield (Scheme 93).[179]

Scheme 93



The use of trialkyl phosphite as a nucleophile instead of dialkyl phosphites is restricted to a three component reaction of a nitrone, a phosphite, and an alkyl halide. Upon heating in an anhydrous solvent, the phosphonopyrrolidines **395** are formed in 65−70% yield (Scheme 94). A push pull mechanism

Scheme 94

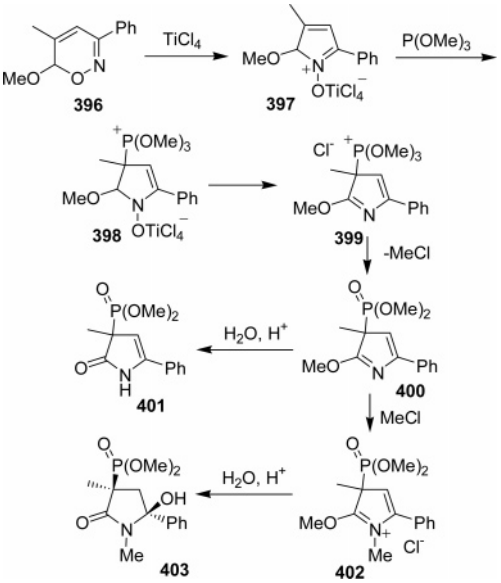


is suggested, since no reaction was observed in the absence of one of the reactants. A catalytic amount of alkyl halide is sufficient for the reaction to occur, since additional alkyl halide is liberated during the phosphite addition (Arbuzov type dealkylation). As a matter of fact, when the added alkyl halide is different from the halide formed during the reaction, a mixture of the two corresponding phosphonopyrrolidines is obtained.[180]

One example of 1,4-addition was described under modified conditions. In the presence of a Lewis acid, ring contraction of 6*H*-1,2-oxazine **396** occurs with the formation of an α,β-unsaturated nitrone **397**. Upon treatment with trimethyl phosphite, two phosphonylated lactams **401** and **403** are formed in a 6:21 ratio. The mechanism of the reaction is depicted in Scheme 95. The occurrence of 1,4-addition of the phosphite reagent in this case can be explained from a sterical point of view, since addition of the much smaller cyanide nucleophile exclusively yields 1,2-addition.[181]

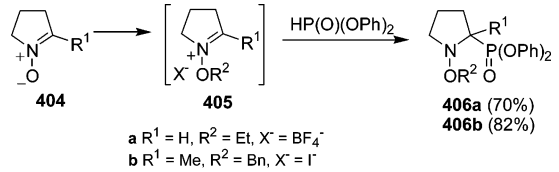
Finally, nitrones can also be converted to alkoxyiminium salts before the reaction with dialkyl phos-

Scheme 95



phite. Alkylation of pyrroline *N*-oxide **404** with triethyloxonium tetrafluoroborate (Meerwein's salt) or benzyl iodide followed by reaction with diphenyl phosphite leads to phosphonates **406a**,**b** in 70% and 82% yield, respectively (Scheme 96). The same meth-

Scheme 96



odology is also applicable to six membered rings (see section 5.7).[182]

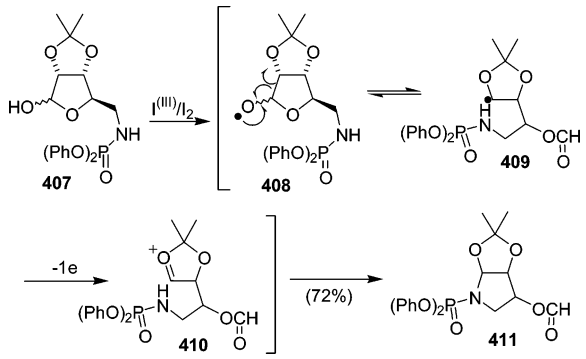
4.9. Radical Addition Induced Cyclization

A radical initiated ring opening−ring closing methodology is used for the synthesis of polyhydroxylated pyrrolidines and piperidines, the so-called azasugars. Because the ring oxygen has been replaced by a basic nitrogen atom, these azasugars can bind to the active site of glycosidase enzymes, mimicking the corresponding carbohydrate. Since glycosidases are involved in many types of important biological processes, some of these compounds have promising antiviral or anticancer activity or can be used in the treatment of diabetes.

The method of synthesis relies on the initial formation of an alkoxy anomeric radical by the action of a hypervalent iodine species, for example, iodosylbenzene, in the presence of iodine (Scheme 97). This alkoxy radical **408** undergoes fragmentation to a C2 radical **409**, which is subsequently oxidized by an excess of reagent to the oxonium ion **410**. The intramolecular nucleophilic cyclization of the amine derivative affords the required azasugar derivative.[183,184]

The halogen atom transfer radical cyclization (HATRC) of *N*-allyl α-perchloroamides is also a valuable technique for the preparation of pyrrolidi-

Scheme 97



nones. One of the main advantages of this rearrangement is the preservation of all carbon−halogen functions on the final skeleton, which remain available for further functionalization.

The reaction was also exploited for 2-phosphonoallyl derivatives **412**, yielding 4-phosphonopyrrolidinones **415** in quite reasonable yields (44−71%).[185] The cyclization reaction is initiated by halogen abstraction by the Cu(I)Cl catalyst. The resulting radical invokes ring closure via a *5-endo-trig* mechanism. The reaction is terminated by recombination of a chlorine atom of the catalyst with the radical **414**. The phosphonolactams could then be rearranged to the unsaturated lactams **416** upon treatment with alkoxides (Scheme 98).

4.10. Electrochemical Methods

1-Phosphonopyrrolidines can also be synthesized by an electrochemical reaction of dialkyl phosphites with amines. Yields are generally high when iodide salts are added to the medium together with the supporting electrolyte. The use of other halides, however, results in low yields. The oxidation of the system is considered to proceed by a discharge of iodide on the anode (Scheme 99).[186,187]

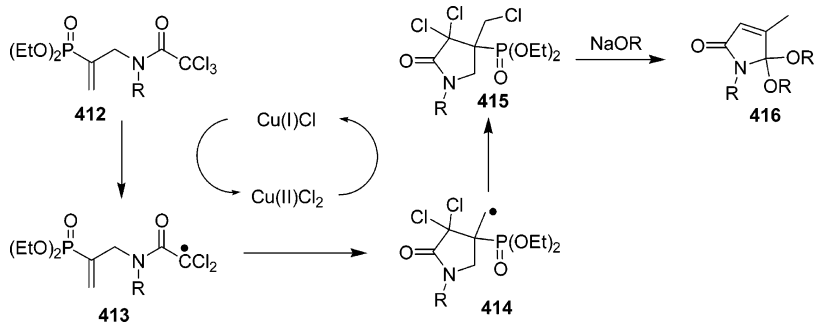
4.11. Reactions with Carbenoids

The use of dirhodium(II) acetate as a catalyst for the formation of metal carbenes from diazocarbonyl compounds affords a route to heterocycles via intramolecular C−H insertion. The utility of this approach is directly related to the level of regio- and stereoselectivity of the C−H insertion process. This selectivity not only depends on the type of α-diazocarbonyl compound and rhodium catalyst being utilized but also is governed by steric, conformational, and electronic factors.

The $[Rh_2(OAc)_4]$-catalyzed cyclization of α-diazo-α-diethoxyphosphorylacetamides **174** affords α-phosphonolactams **175** and **420** in high yield (Table 7). The regioselectivity of the reaction is strongly determined by electronic effects, and in several cases, mixtures are obtained.

Not only does the phosphonate moiety have a stabilizing effect on the carbenoid carbon atom, it also has a profound influence on the stereoselectivity. The bulky phosphonate group appears to induce a remarkable preference for the formation of the five membered ring with stereocontrol in favor of the

Scheme 98



Scheme 99

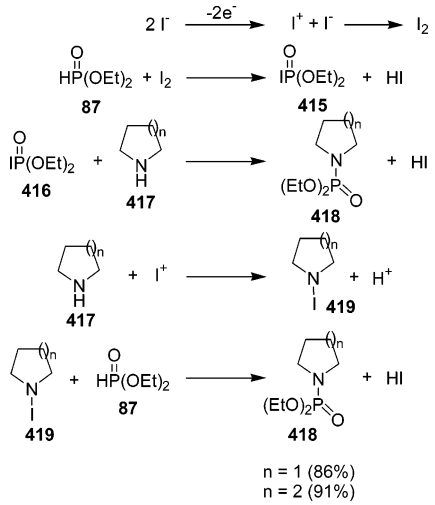
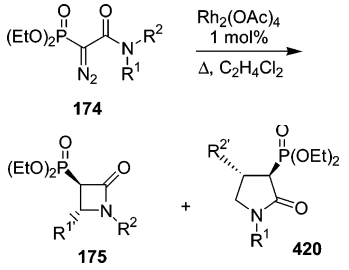


Table 7. Regioselectivity in the Intramolecular C−H Insertion Reaction

	R^1	R^2	$R^{1'}$	$R^{2'}$	yield **175**	yield **420**
a	*n*Bu	*n*Bu	Pr	Et	0%	87%
b	*t*Bu	CH_2CH_2Ph		Ph	0%	81%
c	CH_2CH_2OMe	CH_2CH_2OMe		OMe	0%	89%
d	CHMePh	*n*Bu	Me, Ph	Et	18%	76%
e	Et	Et	Me	H	18%	50%

trans diastereomer. In the case of the four membered rings, however, stereochemistry is highly dependent on the nitrogen substituents (Scheme 100) (see section 3.6).[82]

Scheme 100

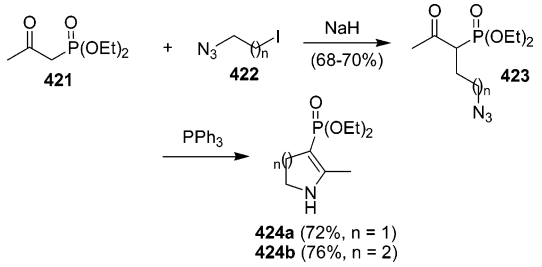


The same C−H insertion reaction was also evaluated in room temperature ionic liquids (RTILs). These have been recognized as an alternative to environmentally unattractive organic solvents, notably chlorinated hydrocarbons. The main advantage in the dirhodium-catalyzed C−H insertion reaction is the possibility to recover the catalyst by simple extraction of the RTIL with TBME, and the yields of the reaction are comparable to those in dichloroethane. The catalyst can be reused up to six times without major drop of the reaction yield.[188]

4.12. Aza-Wittig Reaction

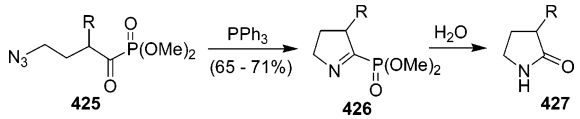
Azides are generally reduced with phosphines to the corresponding amines by hydrolysis of the corresponding iminophosphoranes (Staudinger reaction). However, in the presence of a carbonyl group and in the absence of H_2O (no hydrolysis can then occur), the iminophosphorane leads to cyclic imines via an intramolecular aza-Wittig reaction. Alkylation of phosphonate **421** with iodoazide **422** results in a suitable starting material for the ring closure to the phosphono-2-pyrroline and piperidine **424** (Scheme 101).[189]

Scheme 101



The same methodology is also applicable to similar azidoacylphosphonates **425**. Upon reaction with triphenylphosphine in anhydrous ether, the ring closed 1-pyrrolines **426** are obtained in 65−71% yield (Scheme 102). Upon hydrolysis, the cyclic imine can

Scheme 102



further be transformed to lactam **427** and dimethyl phosphite (see also section 5.9). [190]

4.13. Staudinger Type Reactions

1-Phosphonopyrrolidines can be synthesized using a Staudinger type reaction, as described in 2.6.

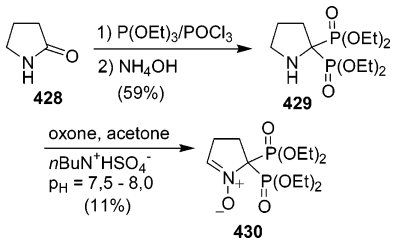
4.14. Miscellaneous

4.14.1. Phosphonylation of Lactams for the Synthesis of Bisphosphonates

When 2 equiv of $POCl_3$ is added to a mixture of pyrrolidinone **428** and 2 equiv of trialkyl phosphite,

the carbonyl group is transformed into a diphosphonate moiety by consecutive addition and elimination of the phosphorus oxychloride reagents (Scheme 103).

Scheme 103



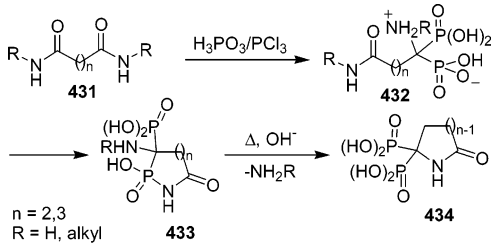
More recently, the reaction has been optimized and the bisphosphonate **429** was obtained in 59% yield. It can be further oxidized to nitrone **430**, which can be used in spin trap experiments.[191−194] Furthermore, bisphosphonate **429** is used to monitor the intracellular pH in vivo via noninvasive ^{31}P NMR spectroscopy and displays a 4-fold higher sensitivity than inorganic phosphate or other commonly used phosphonates.[195−197] The preparation method has also been extended to four and six membered rings, however resulting in lower yields (respectively 28% and 19%).[194]

When pyrrolidinone **428** is treated with a mixture of H_3PO_3 and PCl_3, the free phosphonic acid analogue of pyrrolidine **429** is obtained together with small amounts of side products.[198] This bisphosphonic acid is useful for treating or preventing disorders of calcium and phosphate metabolism.[199] Furthermore, it is claimed to have a synergistic effect on certain neoplasm inhibitors and is therefore useful for the treatment of bone-metastasizing tumors.[200] Due to its Ca^{2+} complexing abilities, it is also used as a hardening retardant for gypsum[201] and as a component in anticalculus or antiplaque compositions in oral care products.[202] Finally, it has proven to reduce the calcification of the rat aorta.[201]

4.14.2. Phosphonylation of Diamides

The outcome of the phosphonylation reaction of diamides **431** with H_3PO_3/PCl_3 depends on their chain length. With $n > 3$, a mixture of bis- and tetraphosphonic acids is obtained. However, with $n = 2$ or 3, only cyclic bisphosphonic acids are obtained. A possible reaction mechanism is outlined in Scheme 104.[198] The obtained diphosphonopyrrolidone **434** (n = 2) can be used in a mouth rinse to inhibit the formation of dental plaque.[203]

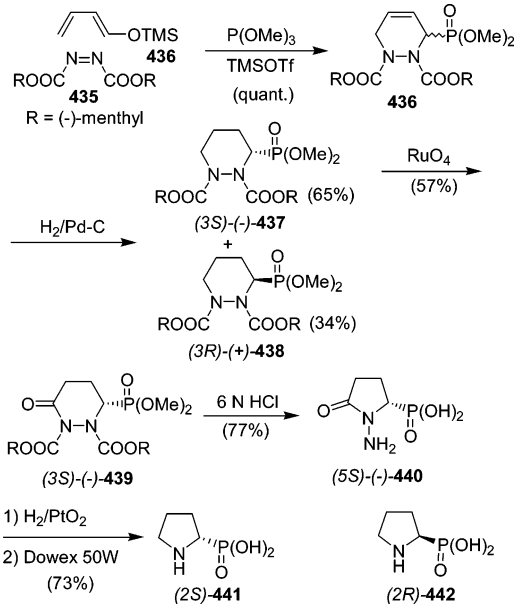
Scheme 104



4.14.3. Ring Contraction of Piperidazines

Piperidazine **436** can be synthesized via a Diels−Alder reaction of di-(−)-menthylazodicarboxylate and 1-trimethylsilyloxybutadiene in the presence of trimethyl phosphite and a Lewis acid, as an inseparable mixture of diastereomers (Scheme 105). However,

Scheme 105

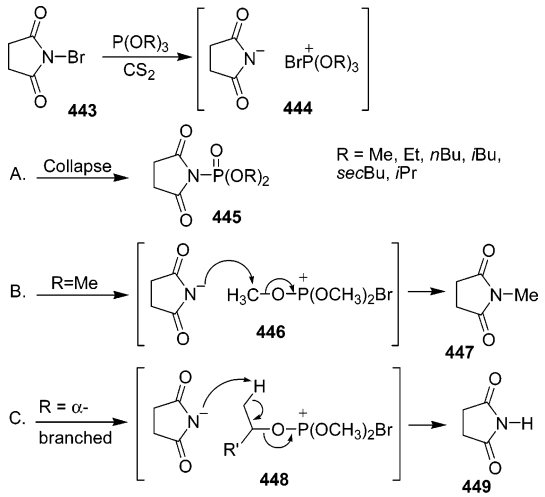


after hydrogenation of **436**, the piperidazines **437** and **438** can easily be separated by column chromatography. Oxidation of **437** with RuO_4 then yields the corresponding piperidazin-6-one **439** as a single product. Hydrolysis does not afford the ring opened product but the ring contracted five membered enantiomerically pure lactam **440** in 77% yield. The other enantiomer can be obtained by repeating the reaction sequence starting from piperidazine **438**. After a PtO_2-catalyzed hydrogenation, both (*R*)- and (*S*)-2-phosphonopyrrolidine can be obtained in enantiomerically pure form.[204]

4.14.4. Phosphorylation of Succinimides

When *N*-bromosuccinimide is treated with trialkyl phosphites, the *N*-(dialkylphosphonyl)succinimides **445** are obtained in good yields (91−95%) when R is not methyl or an α-branched alkyl substituent (Scheme 106). In the latter case, yields drop below

Scheme 106

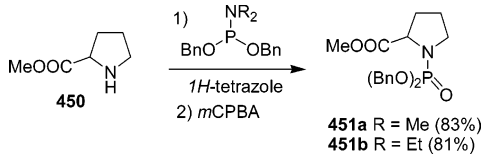


50% due to two major side reactions. When trimethyl phosphite is used, sterically unencumbered attack occurs on the methyl group by the nucleophilic succinimidyl anion instead of attack on phosphorus (reaction B). In the case of an α-branched alkyl group, the succinimidyl anion primarily acts as a base (reaction C). In both cases, the formation of a P−O double bond is the driving force.[205] Phosphorylated succinimide **445** (R = Et) can be used in batteries to interfere with flame propagation.[206]

4.14.5. Phosphoramidite Amine Exchange

Solid-phase amine exchange chemistry is often used for the synthetic development of nucleoside phosphoramidites. However, the exchange reaction is also useful for the phosphonylation of amino acids. The amine exchange reaction of proline ester **450** is performed with dibenzyl *N,N*-dialkylphosphoramidite in the presence of 1*H*-tetrazole, which facilitates the displacement of a dialkylamino ligand on the phosphorylating reagent by an incoming amine (Scheme 107). The 1*H*-tetrazole is always used in large excess,

Scheme 107

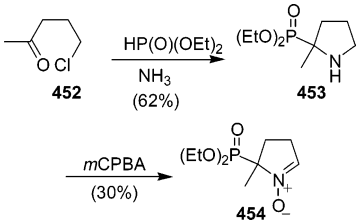


but its exact role has not yet been fully understood. The second step involves an oxidation to the phosphoramidate **451** with *m*CPBA.[207]

4.14.6. Multicomponent Reactions

2-(Diethylphosphono)-2-methylpyrrolidine (**453**) is obtained in a one-pot reaction by bubbling ammonia into an ethanolic solution of 5-chloropentan-2-one (**452**) and diethyl phosphite (Kabachnik Fields' reaction). Further oxidation with *m*CPBA leads to the hydroscopic nitrone **454** (Scheme 108).[208,209]

Scheme 108



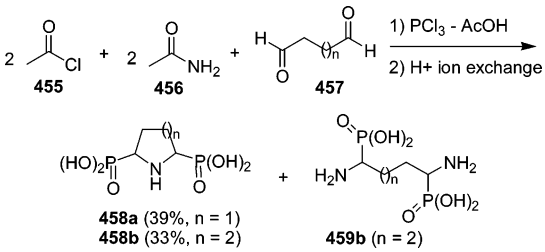
Reaction of butanedial, acetamide, and acetyl chloride with PCl_3 in acetic acid exclusively yields the bisphosphonate **458a** in 39% yield (Scheme 109). When the reaction is performed with pentanedial, the corresponding piperidine **458b** is formed (33%) in a 1:1 mixture with the acyclic bis(aminophosphonate) **459b**.[210]

5. Six Membered Rings—Piperidines and Piperidinones

5.1. Introduction

Six membered heterocyclic phosphonates have also shown great promise on several fronts. A series of

Scheme 109



dipeptides which contain phosphonate analogues **460** of proline and piperidinyl-2-carboxylic acid (homoproline) have been reported recently as potential therapeutic agents to prevent the rejection of transplanted tissues.[141] Further, fosmidomycin (**461**), an acyclic aminohydroxyphosphonate, is an inhibitor of 1-deoxy-D-xylulose 5-phosphate reductoisomerase, a key enzyme localized in the metabolic pathway inside the apicoplast of the malaria parasite. Fosmidomycin was originally isolated as a natural antibiotic from *Streptomyces lavendulae* in the 1970s. Its molecular target and the antimalarial activity have only been known since 1998.[211] Oral treatment with fosmidomycin of patients infected with malaria showed already promising results.[212] The fosmidomycin derivative FR900098 **462** is approximately twice as active in vitro and in infected mice (Figure 8).[211]

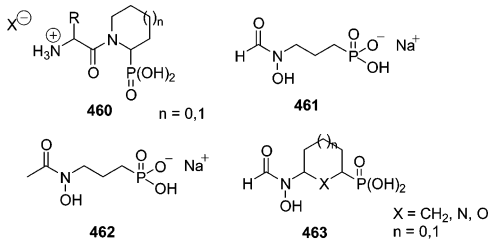


Figure 8.

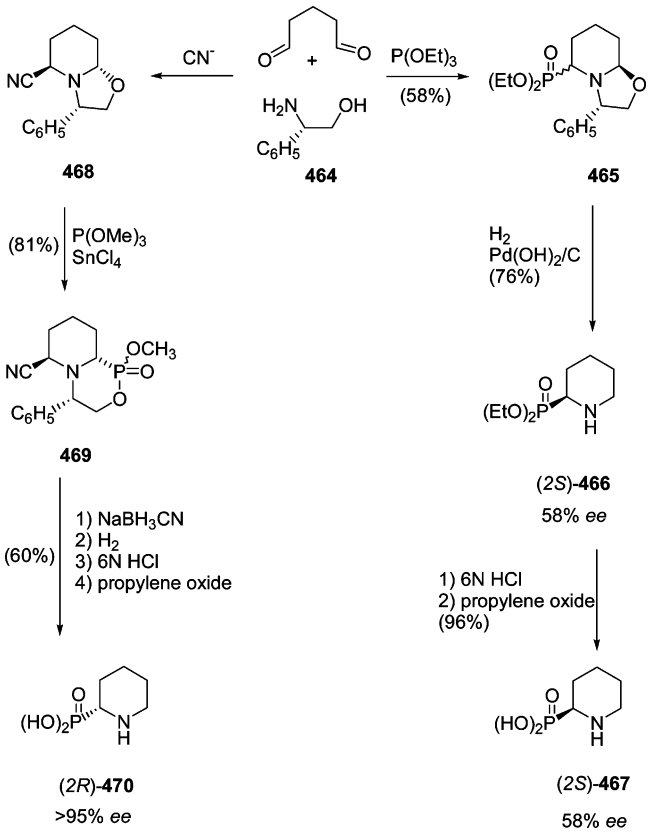
Therefore, a search for azaheterocyclic analogues resulted in the phosphonates **463**, which show bactericidal, fungicidal, and herbicidal properties.[213]

5.2. Nucleophilic Phosphorylation

Royer et al.[214] have developed two strategies to synthesize both enantiomers of piperidin-2-ylphosphonic acid. The first one uses the double condensation of gluteraldehyde with (*R*)-(−)-phenylglycinol and triethyl phosphite to give 2-(diethylphosphono)-6-oxazolopiperidine (**465**), which furnishes in a few steps (*S*)-(+)-piperidin-2-ylphosphonic acid (**467**) in 58% ee. The second strategy utilizes the 2-cyano-6-oxazolopiperidine **468**, which upon treatment with trimethyl phosphite gave 2-cyano-6-oxazaphosphorinane **469**, which lead to pure (*R*)-(−)-piperidin-2-ylphosphonic acid (**470**) in good overall yield after reduction and hydrogenolysis (Scheme 110).

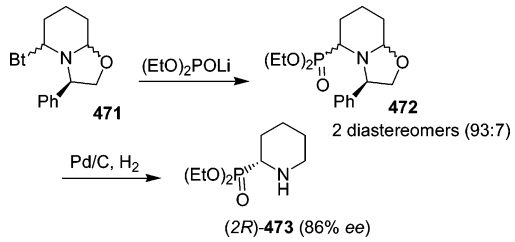
Although the use of the 2-cyano-6-oxazolopiperidine synthon was demonstrated in the chiral synthesis of 2-phosphonopiperidines, this methodology required the use of KCN as reagent. Katritzky et al.[103] were able to synthesize 2-phosphonopiperidines via the benzotriazole methodology. Intermediate **471** was prepared in a similar way as the 2-cyano-6-oxazolopiperidine synthon of Royer, that is, starting

Scheme 110



from (*S*)-2-phenylglycinol, gluteraldehyde, and benzotriazole in 95% yield. The Bt group, known as a good leaving group, was displaced by the phosphonate function through substitution with a phosphorus nucleophile. However, unlike with a five membered ring (see section 4.3), piperidine **471** does not react with a trialkyl phosphite in the presence of $ZnBr_2$. Lithium diethyl phosphite needs to be used to obtain a mixture of two diastereoisomers **472** (93:7, 68% overall yield), which can be hydrogenated to the corresponding 2-phosphonopiperidine in 86% ee (Scheme 111).

Scheme 111



Using Lewis acids, it is also possible to substitute a methoxy or hydroxy function by trialkyl phosphite (see section 4.3).[105−107,109]

The attachment of an amino acid or small peptide to a weakly active substance is a well-established method for enhancing its transport through cell membranes[7,215] or into tissues[216] and, consequently, improving its activity. Phosphono peptides may display their activity in the intact form, or alternatively, they may serve as carriers of active aminophosphonates into plant tissues. This approach has been used to synthesize phosphononylated peptides **474** (Figure 9) and to evaluate their influence on the

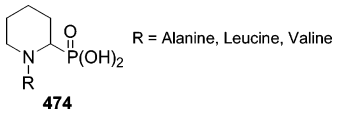


Figure 9.

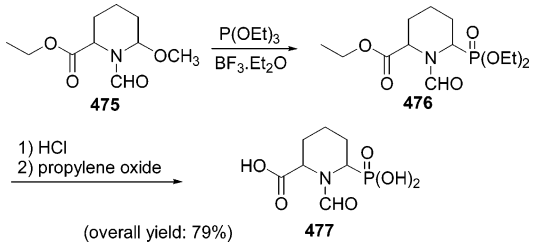
growth characteristics of *Lepidum sativum* and *Cucumis sativus*.[217]

In general, it could be concluded that the peptides containing valine and leucine strongly inhibit the growth of *Lepidium sativum*.

It was also mentioned before (see section 4.5.6) that dipeptide phosphonates of this type can act as inhibitors of dipeptidyl peptidase IV.[141] It could be concluded that a series of dipeptide phosphonates which contain a proline or a homoproline analogue at the P_1 site are specific irreversible inhibitors of DPP IV. Due to their high specificity and stability, these dipeptide phosphonates should be useful in establishing the biological roles of DPP IV and may have therapeutic utility.

As mentioned before (see section 4.3), the phosphonate moiety can easily be introduced onto methoxylated piperidines such as **475** in the presence of a Lewis acid by trapping the iminium ion with triethyl phosphite.[106] This methodology was used to synthezise phosphonopiperidine **477** (Scheme 112).

Scheme 112



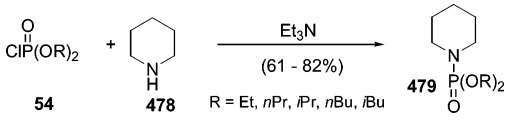
Although it contains the structural part of glyphosate HOOC−C−N−C−P(O)(OH)$_2$, no activity could be detected toward weeds at a concentration of 4 kg/ha.[77]

5.3. Electrophilic Phosphorylation

5.3.1. 1-Phosphonopiperidines

Nucleophilic substitution between heterocyclic starting compounds such as piperidines and dialkyl chlorophosphates, which serve as phosphorylating agents, lead to 1-phosphonopiperidines **479** (Scheme 113).[111]

Scheme 113



The chlorophosphate reagent can also be synthesized in situ from dialkyl phosphite, CCl_4, and Et_3N (see section 4.4.1). These 1-phosphonopiperidines **479** can also be synthesized according to the method introduced by Hassner and Galle (see section 2.6).

Much of the biochemistry and toxicology associated with organophosphorus compounds such as 1-phosphonopiperidines **479** is oriented toward their acetylcholinesterase properties. Therefore, Ozmen et al.[218] studied the in vitro and in vivo acetylcholinesterase-inhibiting effect in *Rana ridibunda* tadpoles of different phosphonates **479** (Figure 10). The *n*-propyl

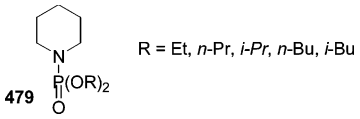


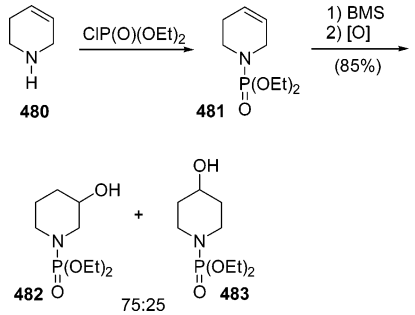
Figure 10.

ester significantly suppressed the AchE activity without causing any lethal effect, whereas the *n*-butyl ester caused death in 100 ppm concentration. These results support the finding of previous studies[219] that branched-chain alkyl groups decrease the Ache activity, probably due to steric hindrance.

Sener and Mete[110,111] investigated the same azaheterocyclic phosphonates (Figure 10) on their antimicrobial activities against different bacteria and fungi. The compounds tested generally were ineffective against bacteria. On the other hand, all compounds tested were found to be effective against yeast-like fungi such as *Candida albicans* and *Candida tropicalis*. Particularly, the *i*Pr, *n*Bu, and *i*Bu esters showed more inhibition, with MIC values between 100 and 400 μg/mL.

Dicko and Montury[220] investigated the efficiency of the trimethylsilyl group and the phophonate group to protect the N−H bond of unsaturated amines in the hydroboration reaction with BMS (borane−methyl sulfide complex). 1-Phosphono-3-piperine (**481**) can undergo addition of BMS in a 1/1 molar ratio at 0 °C, without any complexation between the nitrogen and the boron atoms. The deprotection can be achieved by refluxing in hydrochloric acid after oxidation of the borane derivative to the corresponding alcohols **482** and **483** (Scheme 114).

Scheme 114



5.3.2. Vinyl Phosphate–Phosphonate Rearrangement

The replacement of a phosphate P−O bond by a P−C bond is considered to increase the metabolic stability while maintaining a geometrical structure similar to that of the phosphate ester. Therefore, α-phosphonoacetates have been prepared and tested as inhibitors of a variety of enzymes, including farnesyl transferase protein (FTPase),[221] biotin carboxylase,[222] aspartate carbamoyltransferase,[223] DNA polymerase,[224] and squalene synthase.[225] Ring systems are often incorporated as templates to restrict the possible conformations and/or to serve as a platform to incorporate other functional groups.

For this reason, Wiemer et al.[226] reported the synthesis of several α-phosphono lactones, incorporating a farnesyl chain, in search of FTPase inhibitors. An α-phosphono lactone such as **484** is used as mimic for the pyrophosphate moiety (Figure 11).

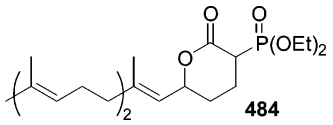
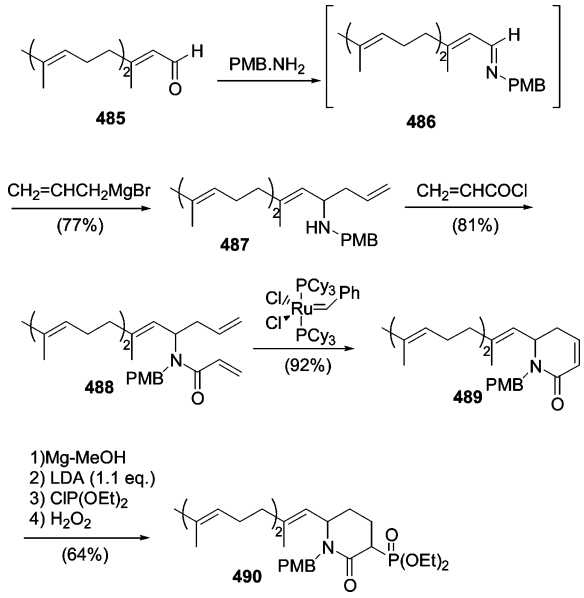


Figure 11.

Not only are structural similarity and polarity important for potential activity, but possibly also the potential to act as leaving group during enzyme-catalyzed nucleophilic displacement. The carbon chain of the lactone ring would then serve as a tether to keep the leaving group connected. Compounds that could function in this manner might serve as useful probes in revealing the FTPase mechanism and for the attachment of modified farnesyl groups to various proteins.

An α-phosphono lactam analogous to compound **484** can also be viewed as a farnesyl pyrophosphate analogue. For the synthesis of such an α-phosphono lactam **490**, condensation of farnesal **2** with *p*-methoxybenzylamine afforded the desired imine **486**, and this intermediate was treated with allylmagnesium bromide without isolation to give the secondary amine **487**. After a sequence of reactions, including reaction with acryloyl chloride to give the amide **488** and subsequent ring closing metathesis with Grubbs catalyst, the conjugated δ-lactam **489** was obtained. Reduction with Mg-MeOH at room temperature provided the saturated lactam, which was phosphorylated through formation of the enolate as described in section 4.4.2 (Scheme 115).

Scheme 115



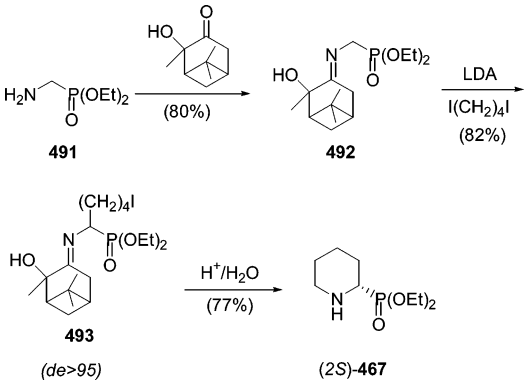
A pathway for the synthesis of mono- and bisphosphorylated *N*-farnesyl lactams has been described in section 4.4.2.

5.4. Ring Closure by Nucleophilic Addition–Elimination

5.4.1. Hydrolysis of an Imine

Enantiomerically pure 2-phosphonopiperidine ester **467** could be prepared using the method of Jacquier et al.[128] The efficient asymmetric synthesis was achieved by alkylation of the Schiff base **492**, prepared from (1*R*,2*R*,5*R*)-(+)- or (1*S*,2*S*,5*S*)-(−)-2-hydroxy-3-pinanone and diethyl α-aminomethylphosphonate (**491**). The diastereoisomeric alkylated Schiff bases were separated by column chromatography and afforded the enantiomerically pure compounds **467** after hydrolytic cleavage (Scheme 116).

Scheme 116



5.4.2. Debenzylation

Recently,[227] a practical synthesis of nojirimycin C-glycosides and related compounds was described. This synthesis of nojirimycin **1**, the first azasugar analogue of glucose, was extended with its reaction with a P-nucleophile resulting in the first synthesis of an iminosugarphosphonate **495** (Figure 12).

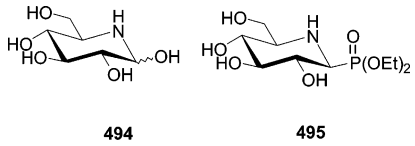
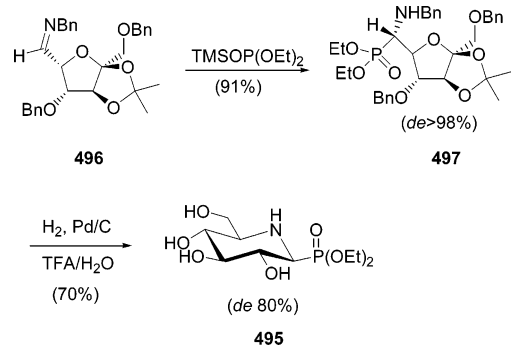


Figure 12.

These iminosugars are a new generation of potential medicines with a wide range of applications for diseases such as diabetes, viral infections, and tumor metastasis.

Imine **496** was prepared from commercially available 2,3,4,6-di-*O*-isopropylidene-α-L-sorbofuranose in high yields and was treated with silylated diethyl phosphite and submitted to a hydrogenolysis−reductive amination, resulting in the piperidinylphosphonate **495** (Scheme 117). This phosphonate was designed to have a strong affinity toward certain carbohydrate-processing enzymes, since iminosugars are known to become easily protonated in biological medium and to form a cation which can strongly interact with a negatively charged group at the

Scheme 117



enzyme active site. In addition, glycosyl phosphate mimetics that consist of a phosphonate directly bound to the pseudoanomeric carbon were found to have a polarity similar to that of the natural sugar 1-phosphates.[228]

5.4.3. Intramolecular Aminomercuration

In the search for new and stable nitroxides, Tordo et al. synthesized interesting phosphonylated pyrrolidines and piperidines by intramolecular aminomercuration (see section 4.5.10).

5.4.4. Addition to an Allenic Moiety

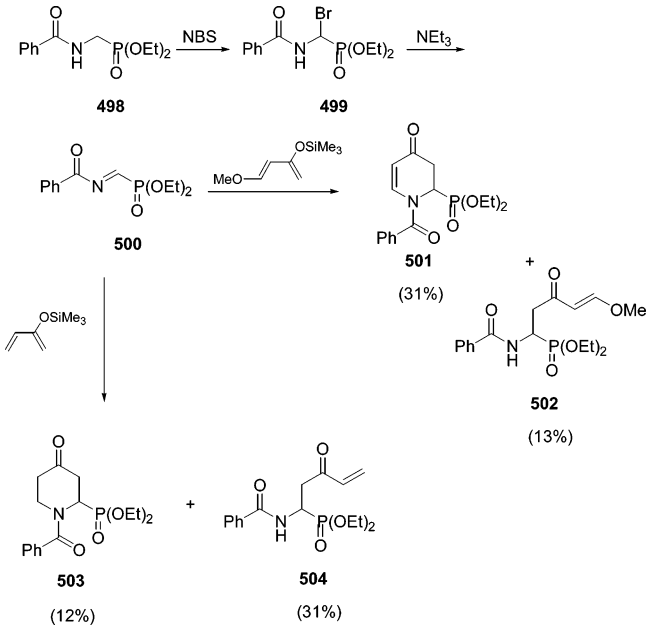
When β-allenic aminophosphonates **321** are heated in the presence of mercury or silver salts to activate the allenic moiety, a mixture of five and six membered heterocycles is obtained (see section 4.5.11).

5.5. Cycloaddition

Acylimines are known to participate in cycloadditions and are particularly interesting because they incorporate both diene and dienophile properties. Schrader and Steglich[229] described the [4 + 2] cycloaddition reaction of (*N*-acyliminomethyl)phosphonates **500** with electron rich dienes either as dienophiles or as diene components, resulting in phosphonylated 1,3-oxazin derivatives, azabicyclo[2.2.1]heptenes, piperidin-4-ones such as **501**, and phosphono-2,3-dihydro-4-pyridinones **503.** The cycloadditions proceed regioselectively in all cases: the most nucleophilic carbon atom of the silylated enolether attacks the α-carbon atom of the acylimine. As a side product the aminophosphonates **502** and **504** are formed in 13% and 31% yield, respectively, which is the result of an inverse electron demand Diels−Alder reaction between the reagents followed by hydrolysis (Scheme 118).

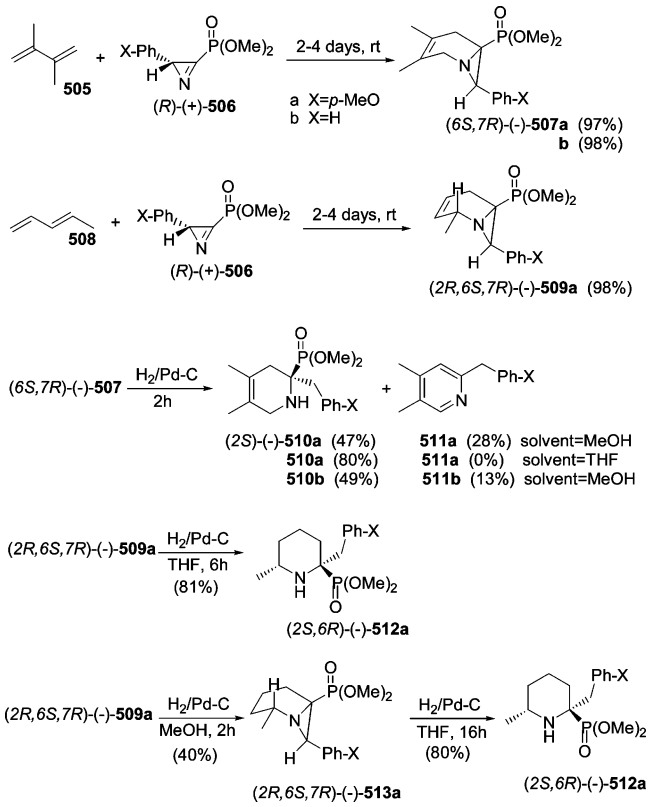
Davis and co-workers[33] described [4 + 2] cycloadditions between 2,3-dimethylbutadiene (**505)** or *trans*-piperylene **508** and azirinylphosphonates **506** (as prepared in section 2.2.2). The diene (100 equiv) is reacted with the phosphonoazirine for 2−4 days at room temperature. Bicyclic aziridines **507**−**509** are isolated as single stereoisomers by flash chromatography in 89−98% yield. Catalytic hydrogenation of **507** results in two products. The major products, isolated in 47−4 9% yield, are identified as quaternary piperidinephosphonates (2*S*)-(−)-**510**, which result from the expected cleavage of the C-7−N bond in **507**. The minor products, obtained in 28% yield

Scheme 118



and 13% yield, respectively, were identified as pyridines **511**. Controlling the conditions for the hydrogenation of **509** leads to the reduction of the C−C double bond, affording the bicyclic aziridine (2*S*,7*R*)-(−)-**513** and the phosphonopiperidine **512** (Scheme 119).

Scheme 119



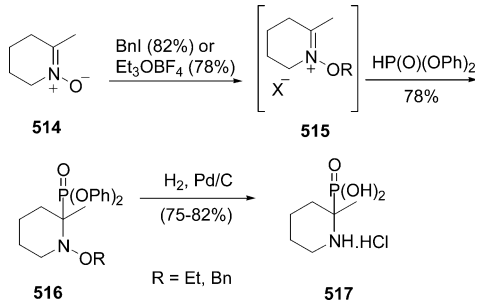
5.6. Addition to Cyclic Imines

The synthesis of 2-phosphonopiperidines by intramolecular hydroamination and addition of diethyl phosphite has already been discussed before (see section 4.7).

5.7. Addition to Nitrones

Another pathway leading to phosphonylated piperidines consists of the addition of phosphite to cyclic nitrones.[182] Ethylation of nitrone **514** afforded the oxoiminium salt **515**, which reacted with diphenyl phosphite to yield the corresponding α-methyl-*N*-alkoxyphosphonopiperidine **516** in 78%. Hydrogenolysis of the N−O bond was accompanied by ester hydrolysis, which furnished the phosphonopiperidine **517** in 82% yield (Scheme 120).

Scheme 120



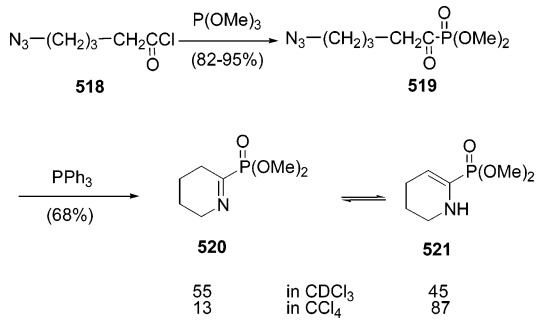
5.8. Electrochemical Methods

A remarkable synthesis of piperidinephosphonates is the direct phosphorylation of piperidine by an iodonium ion-promoted electrolytic procedure (yield: 91%).[186] This methodology has been described in section 4.10.

5.9. Aza-Wittig Reaction

Azidoesters and their corresponding acid chlorides are known to be interesting reagents for nucleophilic and electrophilic aminoalkylation. The corresponding α-acylphosphonates can be synthesized via reaction with trimethyl phosphite. Further treatment with PPh_3 then leads to cyclic iminophosphonates via an intramolecular aza-Wittig reaction (see also section 4.12).[190] The iminophosphonate **520** showed an interesting behavior in solution. A solvent dependent tautomeric imine−enamine equilibrium was observed in the ^{1}H NMR spectrum (Scheme 121).

Scheme 121



Another preparation of azidoacylphosphonates has been described in section 4.12 which also leads to six membered azaheterocyclic phosphonates.

5.10. Miscellaneous

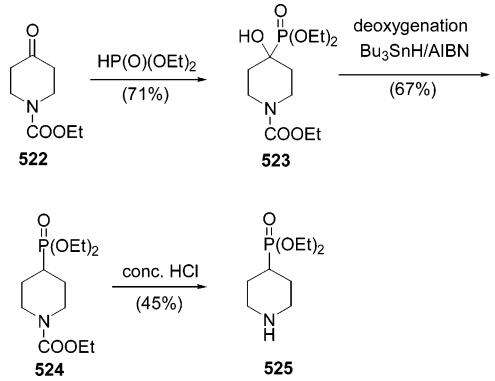
5.10.1. Phosphonylation of Lactams for the Synthesis of Bisphosphonates

Phosphonylation of lactams with trialkyl phosphite and phosphoroxy trichloride has been used for the synthesis of gem-bisphosphonic pyrrolidines (see section 4.14.1). This method has been extended to piperidines, however with a lower yield (19%).[194]

5.10.2. Addition to a Carbonyl Moiety

A mild and efficient procedure for the synthesis of 4-phosphonopiperidine analogues of the $GABA_A$ agonist 4-carboxypiperidine was described by Kehler et al.[230] Base-catalyzed Pudovik addition of diethyl phosphite to ethyl 4-oxopiperidine-1-carboxylate (**522**) gave the corresponding hydroxyphosphonate **523**. Radical deoxygenation followed by acidic hydrolysis finally resulted in the $GABA_A$ analogue **525** (Scheme 122).

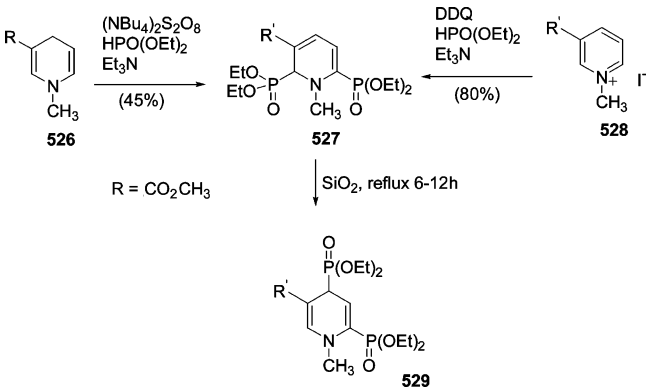
Scheme 122



5.10.3. Addition to Dihydropyridines and Pyridinium Salts

An oxidative double phosphonylation of dihydropyridines **526** and pyridinium salts **528** was achieved through the use of dialkyl phosphite, triethylamine, and tetrabutylammonium peroxydisulfate or DDQ, respectively. 2,6-Diphosphonylated 1,2-dihydropyridines **527** were obtained in a one-pot reaction involving tandem nucleophilic addition−oxidation processes. Isomerization of **527** to the more stable 2,4-diphosphonylated 1,4-dihydropyridine **529** was observed after flash chromatography. This reaction could also be induced by refluxing the dihydropyridine **527** for 6−12 h in ethanol (Scheme 123).[231]

Scheme 123



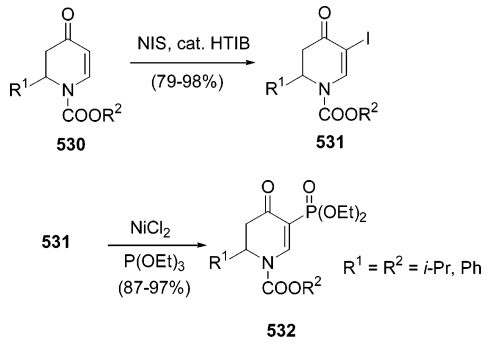
5.10.4. Phosphonylation of Diamides

The synthesis of diphosphonopiperidinones has already been discussed in the part about the five membered rings (see section 4.14.2).

5.10.5. Arbuzov Type Reaction

Comins and Olliger[232] synthesized several phosphonylated dihydropyridones **532** as building blocks for the preparation of C-5 alkylidene derivatives. The phosphorus moiety is introduced via a $NiCl_2$-catalyzed Arbuzov reaction of the corresponding iodine derivative **531**.[233,234] By reduction or addition, these dihydropyridones **532** can provide piperidinones, which can be used in olefinations via a Horner−Wadsworth−Emmons reaction (Scheme 124).

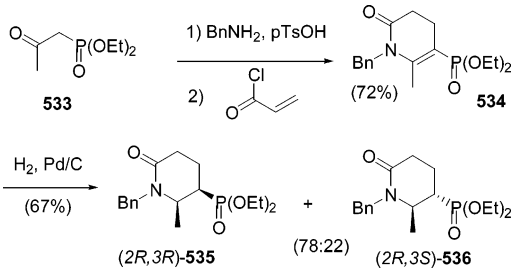
Scheme 124



5.10.6. Enamine Condensation–Aza-annulation

The introduction of an electron withdrawing group, such as a phosphonate, in the β-position to a ketimine has several key advantages in the aza-annulation reaction. The tautomeric equilibrium shifts from the ketimine to the β-enamino functionality and increases in this way significantly the reaction yield and the selectivity. Using this strategy, Paulvannan and Stille[235] synthesized the phosphonylated piperidinones **535** and **536** in a two-step process by hydrogenation, leading to a 78:22 ratio of diastereomers (Scheme 125).

Scheme 125

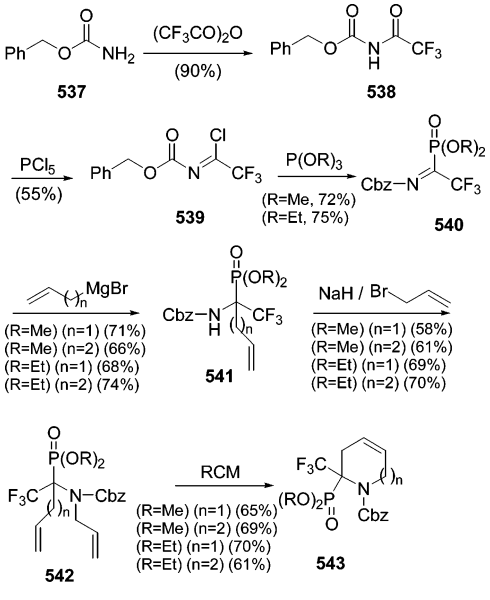


5.10.7. Ring Closing Metathesis

Ring closing metathesis (RCM) of α-aminophosphonates, bearing two terminal alkene chains, is a convenient strategy to synthesize azaheterocyclic phosphonates. Osipov et al.[236] succeeded in the synthesis of the cyclic aminophosphonate **543** in a three-step sequence: acylation of the benzylcarbamate **537**, formation of the corresponding imidoyl chloride using PCl_5, and finally an Arbuzov reaction

leading to the imines **540**. These imines are very electrophilic and react easily with Grignard reagents, leading to the new unsaturated α-aminophosphonates **541**. Allylation of the nitrogen atom gives rise to 1,7-dienes which can be ring closed to the 3-piperidines using a Ru catalyst (Scheme 126).

Scheme 126



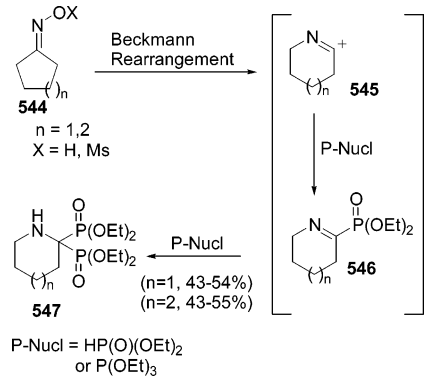
5.10.8. Beckmann Type Rearrangement

Methylenebisphosphonic acids, carbon analogues of inorganic pyrophosphate, exhibit unique physical and chemical properties in the interaction with the alkaline earth cations or heavy metal cations.[237] Thus, these compounds are known to possess a number of useful biological properties including antiviral, antiamoebic, herbicidal, and bone-resorption activities which appear to be related to their ability to chelate metal ions.[238]

Simple and efficient methods for the synthesis of cyclic analogues of aminomethylene-*gem*-diphosphonates are scarce. Shibuya et al.[239] reported diphosphonylation reactions of oximes via a Beckmann rearrangement to give these azaheterocyclic *gem*-diphosphonates efficiently.

Iminocarbocations **545** produced by Beckmann rearrangement from oxime **544** can react with a variety of C-nucleophiles under the appropriate conditions to give nitrogen heterocycles. Similarly, the Beckmann rearrangement of an oxime in the presence of a suitable phosphorus nucleophile constitutes a facile method for generation of aminomethylene-*gem*-diphosphonates **547**. Phosphorus nucleophiles such as $P(OEt)_3$ and $H(O)P(OEt)_2$ were evaluated. However, these reactions gave the expected diphosphonates in modest yields. Diethyl phosphite was found to be the better phosphorus reagent (yield: 54−55%). When $P(OEt)_3$ was used, a large amount of the corresponding lactams was produced and the yields were lower (43%) (Scheme 127).

Scheme 127

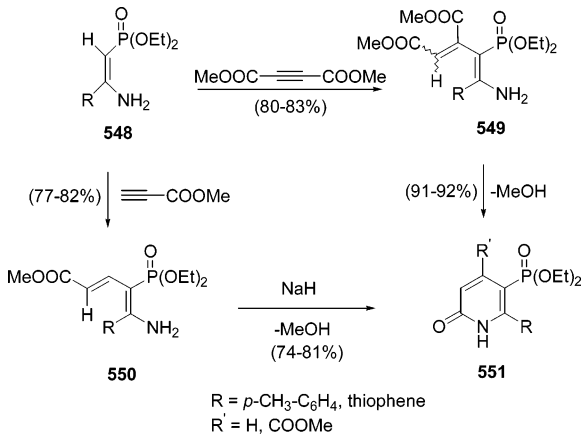


5.10.9. Intramolecular Cyclization of β-Phosphono Enamines

The (1*H*)-pyridone moiety is a prominent structural feature in a variety of natural products, as well as in other compounds of medicinal interest, and has therefore attracted considerable attention.[240] It constitutes[22] the skeleton of elfamycin antibiotics[241] and the antifungal compound ikicocilin.[242] On the other hand, aminophosphonates are gaining interest in medicinal chemistry, since they are mimetics of amino acids. Combining these two structural moieties could lead to compounds with promising activities.

Palacios et al.[243] described the synthesis of primary β-phosphono enamines **548** obtained by alkylation of diethyl methylphosphonate with nitriles, followed by addition of acetylenic esters such as methyl propiolate and dimethyl acetylenedicarboxylate, resulting in the corresponding 5-phosphonyl-2(1*H*)-pyridones **551** in 92% yield (Scheme 128). In this way, an

Scheme 128



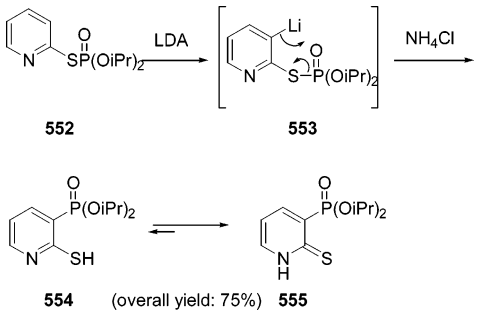
efficient and easy access is provided to 2(1*H*)-pyridones bearing a phosphonate moiety at the 5-position, utilizing readily available starting materials.

5.10.10. Phosphonate Migration in 2-Mercaptopyridines

Masson and co-workers reported the first example of phosphonyl S → C migration from the ortholithiated derivative **553** of *O,O*-diisopropyl (*S*)-(2-pyridyl)thiophoshate (**552**).[244] Due to the electron withdrawing properties of the phosphonyl substituent, a quasi complete shift of the equilibrium between

the 2-mercaptopyridine **554** and the pyrid-2-thione **555** has been observed (Scheme 129).

Scheme 129



5.10.11. Multicomponent Reactions

A multicomponent reaction of acetyl chloride, acetamide, pentanedial, and phosphorus trichloride leads to the synthesis of 2,6-diphosphonopiperidine (**458b**), as described in section 4.14.6.

6. Seven Membered and Larger Rings

6.1. Introduction

Only a few papers have been published in the field of seven membered and larger azaheterocyclic phosphonates. Nevertheless, some of these large azaheterocyclic phosphonates, more specifically the bisphosphonates, show interesting biological activities.

Recently, bone-resorption inhibitory activity of disodium azacycloheptane-2,2-diphosphonic acids **556** was demonstrated (Figure 13).[245]

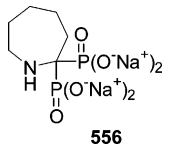
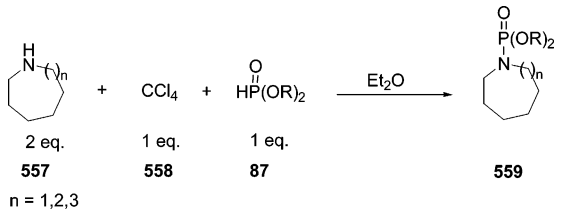


Figure 13.

6.2. Electrophilic Phosphorylation

As mentioned before for the five and six membered rings (see sections 4.4.1 and 5.3.1), the phosphonylated amines of ring size seven and larger can be prepared by adding equimolar amounts of dialkyl phosphite and CCl_4 to 2 equiv of the amine in ether (Scheme 130).[44]

Scheme 130



6.3. Staudinger Type Reaction

Seven membered ring phosphonates can also be prepared by reaction of 2-iodoalkyl azides with trialkyl phosphites, as described in section 2.6.[43]

6.4. Miscellaneous

6.4.1. Ring Closing Metathesis

The methodology introduced by Osipov et al.[235] (see section 5.10.7) for the preparation of phosphonopiperidines can also be utilized to form the corresponding phosphonylated seven membered azaheterocycles.

6.4.2. Beckmann Type Rearrangement

As mentioned in section 5.10.8, conformationally constrained aminomethylene-*gem*-diphosphonate derivatives can be prepared via a Beckmann rearrangement. The seven membered azaheterocycles are obtained in rather good yields (43−55%).

7. Conclusion

Aminophosphonates and aminophosphonic acids prove to be of interest for a variety of socially relevant fields: the medicinal and pharmaceutical field, the agrochemical and biochemical field, the field of metal complexation, and so forth.

Because of these well-known biological properties of aminophosphonates, also the azaheterocyclic phosphonates have attracted and are still attracting the attention of many research groups. Their efforts resulted in a vast diversity of synthetic pathways and a better understanding of the reactivities of this class of compounds. During the preparation of this review, we have been trying to sort the different pathways into general subdivisions based on the reaction type. However, this classification is rather artificial, since each ring size has its own identity and its own special features.

From all the reactions, those leading to enantiopure heterocyclic phosphonates are of major importance and interest, given their potential biological activity. Numerous examples of biologically active compounds have already been presented in this article, and from our point of view, more research in this exciting field will result in even more active examples upon further biotesting.

8. Acknowledgment

Kristof Moonen wishes to thank the Fund for Scientific Research Flanders (FWO Vlaanderen) for the financial support.

9. Abbreviations

$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
AchE	acetylcholine esterase
AIBN	azoisobutyronitrile
Ala	alanine
Arg	arginine
BMS	borane−methyl sulfide complex
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bt	benzotriazole
CAN	cerium ammonium nitrite
Cbz	phenylmethoxycarbonyl
Cp	cyclopentadiene
Cy	cyclohexyl
DBPA	*N*,*N*-dibromophosphoramidate

DBT	dibenzoyl-L-(+)-tartaric acid
DCC	dicyclohexyl carbodiimide
DCPA	*N*,*N*-dichlorophosphoramidate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEP-DMPO	1-diethoxyphosphoryl-5,5-dimethyl-1-pyrroline-*N*-oxide
DEPMPO	5-diethoxyphosphoryl-5-methyl-1-pyrroline *N*-oxide
DMD	dimethyl dioxirane
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMPO	5,5-dimethyl-1-pyrroline *N*-oxide
DPP IV	dipeptidyl peptidase IV
EPR	electron paramagnetic resonance
FAPa	fibroblast activation protein a
FTPase	farnesyl protein transferase
GABA	γ-aminobutyric acid
Gly	glycine
HATRC	halogen atom transfer radical cyclization
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HTIB	[hydroxyl(tosyloxy)iodo]benzene
Ile	isoleusine
LDA	lithium diisopropylamide
LiHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazane
*m*CPBA	*m*-chloroperoxybenzoic acid
MIC	minimum inhibition concentration
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NsONHCOOEt	*N*-{[(4-nitrobenzyl)sulfonyl]oxy}-carbamate
PhI=NTs	[*N*-(*p*-tolylsulfonyl)imino]phenyliodonane
PMB	*p*-methoxybenzyl
PNZ	*p*-nitrobenzyloxycarbonyl
Pro	proline
RCM	ring closing metathesis
RTIL	room-temperature ionic liquid
SCE	standard calomel electrode
TBAC	tetrabutylammonium chloride
TBME	*tert*-butyl methyl ether
Tf	triflate
TFA	trifluoroacetic acid
tfacam	2,2,2-trifluoroacetamide
THF	tetrahydrofuran
TMS	trimethylsilyl
Troc	trichloroethoxycarbonyl
Trt	trityl
Z	phenylmethoxycarbonyl

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