# SYNTHESIS OF HETEROCYCLIC SUBSTITUTED PHOSPHONATES, PHOSPHONIC AND PHOSPHINIC ACIDS

DOI: http://dx.medra.org/10.17374/targets.2021.24.84

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***Abstract.*** *Substituted phosphonates and phosphonic acids are well known for their diverse applications especially in medicinal chemistry and synthesis of agrochemicals. Among many structurally different phosphonates and phosphonic acids, the heterocyclic derivatives are scarcely described in literature, mostly because of the problems associated with their synthesis. Importantly those compounds are well known for their interesting physicochemical properties. In this personal account, achievements from our laboratory in the synthesis of substituted heterocyclic phosphonates and phosphonic acids are presented. The developed methods include not only the preparation of racemic mixtures but also effective protocols for asymmetric synthesis on new heterocyclic derivatives.*

**Contents**



## 1. Introduction

Functionalized phosphonic acids and their derivatives have received considerable attention due to their biological activity.[1] Especially, the α-amino- and α-hydroxyphosphonic acids are of interest to medicinal chemists because of their structural resemblance to natural α-amino- or α-hydroxy acids in which the weakly acidic, mononegative, planar, and less bulky carboxylic group is replaced by a considerably more acidic, dinegative, tetrahedral phosphonic group (Figure 1).


**Figure 1.** General structure of α-amino- and α-hydroxycarboxylic acids and their phosphorus analogues.

The physicochemical properties of the phosphonic acid group are distinct from those of the carboxylic acid group in terms of solubility, polar surface area, and binding properties to pharmacological targets.[2] Due to its tetrahedral geometry, di- or trivalent chelating properties and possible dual function as a hydrogen acceptor and donor at physiological pH, the phosphonic acid group provides unique binding interactions with biologic targets. The tetrahedral geometry of substituents around the phosphorus makes this moiety to resemble to the high-energy transition state of ester or amide bond hydrolysis and is postulated to be stabilized in enzymes active sites. Thus, the use of a phosphonic acid group in drug discovery has proven

successful in many cases. Several therapeutic candidates or lead compounds contain this moiety, with prominent examples being excellent enzyme inhibitors, potent antibacterial[3] and antiviral agents,[4] promising therapeutics for diabetes,[5] asthma,[6] inflammation,[7] heart failure,[8] malaria,[9] HIV[10] and cancer.[11] Additionally, prodrug strategies for the phosphonic acid have been developed.[12]

On the other hand, small and simple heterocycles often have surprisingly complex biological activity and belong to one of the most important classes of compounds in medicinal chemistry. They are also prevalent in many natural occurring structures of vital importance such as amino acids, neurotransmitters, nucleobases, vitamins and others.[13] Considering the aforementioned facts, the combination of phosphorus-containing moiety with the heterocyclic fragment resulted in valuable chemical and biological properties of such heterocyclic phosphonates (Figure 2). Therefore, the development of protocols enabling efficient synthesis of such compounds is especially desirable.[14]

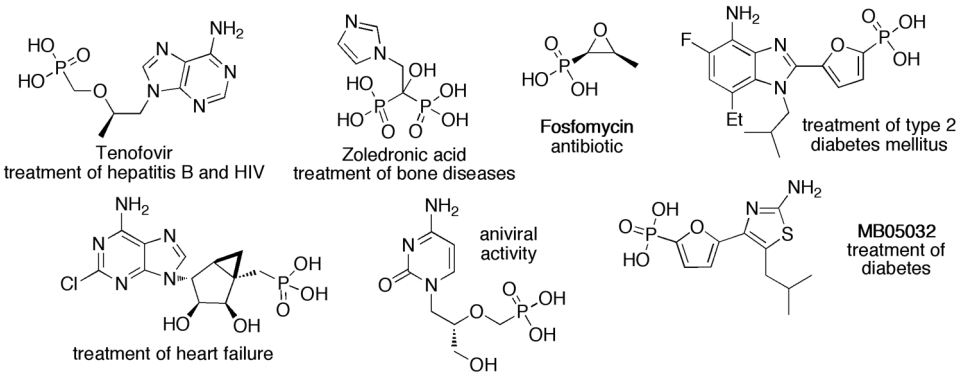



**Figure 2.** Representative examples of heterocyclic phosphonic acids with biological activity.

Owing to the significant biological importance of α-functionalized phosphonates, in particular α-amino and α-hydroxyphosphonates, substantial progress has been made over the years for developing efficient methods for the preparation of those compounds in both racemic and chiral form.[15] However, the literature describing the synthesis of heterocyclic α-functionalized phosphonates is relatively scarce. This situation can be in part justified by a difficult access to some heterocyclic carbonyl compounds, their high price and also by the instability of the C-P bond in the case of certain α-functionalized phosphonates, especially under acidic conditions or prolonged exposure to high temperatures. The first isolated examples of the synthesis of heterocyclic α-functionalized phosphonates dates back to 1970 when Lugovkin[16] described the synthesis of 2-pyridylmethyl(*N*-arylamine)phosphonates derivatives of pyridine in the reaction of pyridine aldimines with diethyl *H*-phosphonate in the presence of sodium enolate. Later on, Mastalerz *et al.*[17] reported the synthesis of aminophosphonic acids derivatives of thiophene-2 and furan-2 by means of acidic hydrolysis of corresponding α-aminophosphonates (prepared from the reaction of di(*p*-methylbenzyl) *H*-phosphonate with imines obtained from the heterocyclic aldehydes and 1-phenyl-cyclopenthylamine). In 1994, Hubert *et al.*[18] synthesised α-functionalized phosphonic acid derivatives of pyrrole-2 and furan-2 by deprotection of the α-functionalized phosphonate diesters obtained in the reaction of heterocyclic aldimines with diethyl or dibenzyl *H*-phosphonates. Finally, in the 1990s Boduszek published a facile synthesis of heterocyclic α-functionalized phosphonates and phosphonic acids derivatives of pyrrole-2, tetrazole, imidazole-4 **5** and pyridine.[19] The applied synthetic strategy involved reaction of dialkyl- or diaryl *H*-phosphonates with heterocyclic imines obtained by condensation of appropriate heterocyclic aldehydes with primary aliphatic and aromatic amines. Boduszek observed degradation of heterocyclic moieties when the reaction of the heterocyclic imines was carried out with the excess of dialkyl or diaryl *H*-phosphonates at high temperature in the absence of solvent and using an excess of *H*-phosphonates. He therefore started to use toluene as solvent at 110 °C, with an equimolar amount of *H*-phosphonates and imine, which resulted in improving the reaction outcome and allowed the preparation of desired heterocyclic α-aminophosphonates in good yields. Importantly, when trying to obtain α-aminophosphonic acids derivatives of pyridine-2 or pyridine-4 by

means of classical acidic hydrolysis of α-aminomethylphosphonate diethyl esters, Boduszek observed decomposition of the starting esters resulting from the C-P bond cleavage.[19] To avoid using acidic conditions, in 2001 he reported on the use silylated phosphorus esters as efficient nucleophiles in the reaction with heterocyclic imines at room temperature.[20] Worth mentioning are also isolated examples of catalytic methods using among others $TaCl_5.SiO_2$,[21] $AlCl_3$,[22] $InCl_3$,[23] or $SmI_2$[24] as catalysts for the preparation of some α-aminomethylphosphonates derivatives of thiophene, furan and pyridine that were reported independently in late 1990's and later on. Of special importance is the work of Jacobsen *et al.*, describing very effective catalytic asymmetric synthesis of α-aminophosphonates, also derivatives of thiophene, pyrrole, furan and pyridine in the reaction of *N*-benzyl imines with di-(2-nitrobenzyl) *H*-phosphonate in $Et_2O$ at 4 $^oC$ and catalyzed by thiourea catalysts (10 mol%) (*ee* from 81 to 99 % depending on the carbonyl substrate used in the preparation of imine).[25]

While working in Boduszek's group from year 2000, our research was focused on the development of effective synthetic methods leading to heterocyclic α-substituted phosphonates and phosphonic acids, and further optimisation and application of the method involving the use of silylated phosphorus esters and also classical addition of *H*-phosphonates to imines derivatives of *e.g.* 1-benzylimidazole-5-carboxaldehyde,[26] 2-thiazolecarboxaldehyde[27] and 2-, 3- and 4-pyridinecarboxaldehydes.[28] In this personal account, the development of effective and simple synthetic methods useful in the synthesis of heterocyclic functionalized phosphonates, phosphinates, phosphonic and phosphinic acids, not only in racemic form but also in asymmetric fashion, performed in our laboratory over the last years is summarized.

## 2. Preparation of heterocyclic substituted phosphinic acids

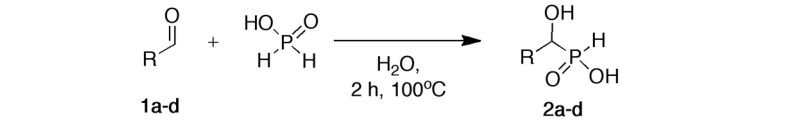
As it was mentioned earlier, due to their interesting biological properties, the synthesis of functionalized phosphonates, in particular α-amino and α-hydroxyphosphonates, was extensively developed over the years.[15] Recently, however, the syntheses of these compounds have started to be performed under eco-friendly conditions, as summarized in our recent review.[29] The described therein environmentally friendly methods are focused on reactions in water, ionic liquids or under solvent-free conditions. In the case of the synthesis of α-aminomethylphosphonates under green conditions, based on the gathered literature, there are two methods that can be considered as most straightforward: firstly, the direct condensation of a carbonyl compound, amine and phosphorus nucleophile, often called the Kabachnik-Fields reaction[30] and secondly the hydrophosphonylation of imines, known as the aza-Pudovik reaction. The advantage of the latter protocol is that the direct attack of the phosphorus nucleophile on the carbonyl compound, the common side-process in the Kabachnik-Fields reaction, is avoided. Under "green" conditions both protocols usually require the presence of additives to ensure the reactions to proceed to completion. In the case of experiments in water, it is important to mention that without any additives they are difficult to perform, because the regular substrates of both reactions are usually very poorly soluble in water. To overcome this problem, surfactants are most frequently used. Additionally, in combination with Lewis acid, they form water tolerant Lewis acid-surfactant-combined catalysts that can effectively catalyse the formation of α-aminomethylphosphonates. In turn, the use of ionic liquids appears to be a better alternative. They are either commercially available or can be easily prepared. Ionic liquids are used mainly as reaction solvents because of their ability to dissolve the reagents of both Kabachnik-Fields and aza-Pudovik reactions. Additional advantage is their reusability after completion of the reaction. Finally, the synthesis of α-aminomethylphosphonates can be performed under solvent-free conditions using the phosphorus nucleophile as solvent (usually slight excess 1.2 to 3.0 equiv) however, those reactions require elevated temperatures ranging from 50 to 100 $^oC$. The exception is the use of silylated phosphites as nucleophiles, in this case room temperature is sufficient for the reaction to proceed to completion. Importantly, the traditional heating can be effectively replaced by microwave irradiation that enables shortening the reaction time from hours to minutes and still ensure excellent yields of the desired final α-aminomethylphosphonates.

In the case of the synthesis of α-hydroxymethylphosphonates under green conditions the are also two methods that can be considered as most suitable: the direct condensation of the carbonyl substrate with dialkyl- or diaryl *H*-phosphonates (the Pudovik reaction) and reaction of carbonyl compounds with fully esterified phosphites (the Abramov reaction). There is less literature dealing with the preparation of α-hydroxymethylphosphonates under green conditions in comparison with the synthesis of

α-aminomethylphosphonates, however similar trends can be observed. The syntheses can be performed effectively in water or under solvent-free conditions, albeit the use of additives to catalyse the reaction or enable solubilisation of reacting substrates is necessary. As a contribution to the field of effective and simple methods leading to the preparation of heterocyclic α-substituted phosphinates under green conditions, we have developed a protocol for preparation of new mono- and bis(α-hydroxymethyl)phosphinic acids, derivatives of imidazole and pyridine, in aqueous media via reaction of corresponding aldehydes with aqueous hypophosphorous acid.[31]

**2.1. Synthesis of heterocyclic mono- and bis(α-hydroxymethyl)phosphinic acids**

The most convenient synthetic routes leading to α-hydroxymethylphosphinic acids include the addition of hypophosphorous acid ($H_3PO_2$) to carbonyl compounds.[32] Usually, this method requires anhydrous hypophosphorous acid in inert solvents or upon prolonged heating of the reactants in the presence of mineral acid. We have observed, however, that in the case of aldehyde derivatives of pyridine and imidazole the reaction proceeds simply by heating at 100 °C for 2 h with equimolar amounts of the corresponding aldehydes and commercially available $H_3PO_2$ (50% aqueous solution) in water (Scheme 1).[31] Under those environmentally benign conditions, the desired new heterocyclic mono-(α-hydroxymethyl)phosphinic acids **2a-d** were obtained as racemic mixtures in good yields (32-55 %) after simple crystallization from methanol.



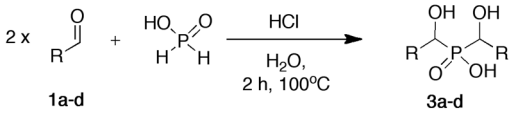

1a-d 2a-d

**2a** (32 %)[a] **2b** (54 %)[a] **2c** (45 %)[a] **2d** (55 %)[a]

[a]Yield of isolated product after crystallization from MeOH.

**Scheme 1.** Preparation of mono-(α-hydroxymethyl)phosphinic acids **2a-d**.

We have also observed that using 1 equiv. of $H_3PO_2$ (50% aqueous solution) and 2 equiv. of the corresponding heterocyclic aldehyde in the presence of 2 equiv. of HCl and heating at 100 °C for two hours leads to the corresponding new bis(α-hydroxymethyl)phosphinic acids **3a-d** (Scheme 2).




1a-d 3a-d

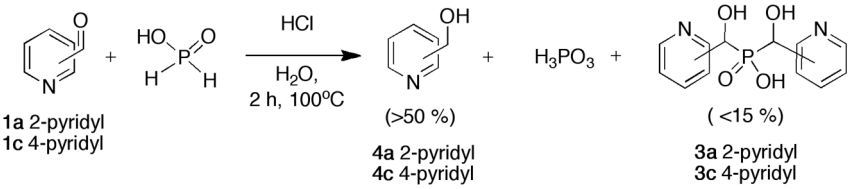
**3a** (30 %)[a] **3b** (57 %)[a] **3c** (36 %)[a] **3d** (87 %)[a]

[a]Yield of isolated product after crystallization from MeOH.

**Scheme 2.** Preparation of bis(α-hydroxymethyl)phosphinic acids **3a-d**.

Concentration of the reaction mixture and crystallization from MeOH yielded the desired products **3a-d** with good overall yields (30-87 %) (Scheme 2).

The bis(α-hydroxy)methylphosphinic acids **3a-d** were obtained as mixtures of two diastereomers (*meso* and *d,l* form) owing to the presence of two chiral carbon atoms bonded to the phosphorus atom. Interestingly, we have observed that an equimolar mixture of 2-pyridine-, or 4-pyridinecarboxaldehyde, and an aqueous solution of hypophosphorous acid in the presence of HCl heated at 100 °C leads to a mixture of the corresponding 2-pyridine- **4a**, or 4-pyridinemethanol **4c** and phosphorous acid ($H_3PO_3$). Expected [(hydroxy)(pyridyl)-methyl]phosphinic acids **2a**,**c** were not found in this case. Besides pyridinemethanols **4a**,**c**, small amounts of bis(α-hydroxymethyl)phosphinic acids **3a**,**c** were also isolated (Scheme 3).




**Scheme 3.** Reaction of $H_3PO_2$ with 2-pyridine- and 4-pyridinecarboxaldehydes in the presence of HCl.

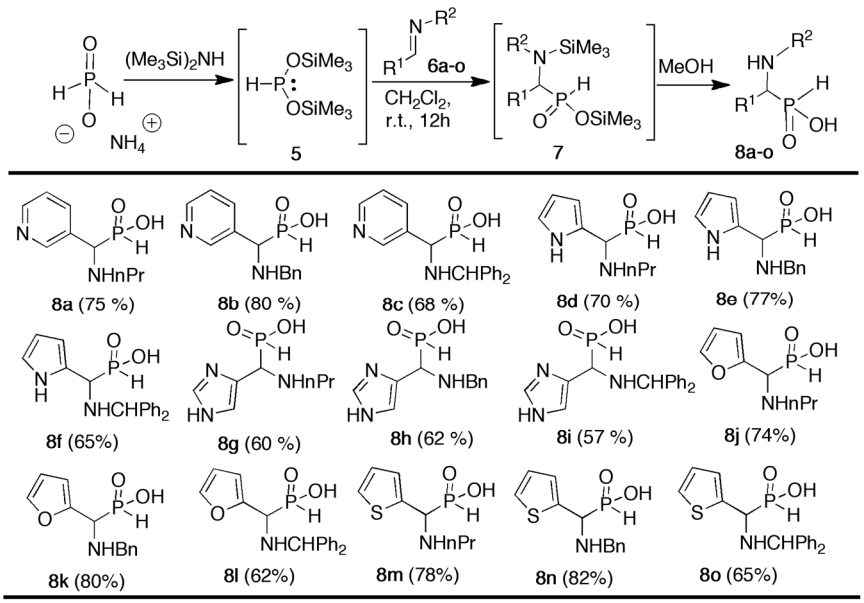
Importantly, the same reaction carried out without hydrochloric acid (Scheme 2) leads exclusively to α-hydroxymethylphosphinic acids **2a**,**c**. In the case of 3-pyridinecarboxaldehyde **1b** and imidazole-4-carboxaldehyde **1d**, the reaction proceeds in a regular way, even in the presence of hydrochloric acid, [(hydroxy)(3-pyridyl)- and (hydroxy)(4-imidazolyl)methyl]phosphinic acids **2b**,**d** were formed. The obtained results clearly indicate that **2a** and **2c** were cleaved by solutions of strong, mineral acids to form pyridinemethanols **4a**,**c** and $H_3PO_3$. The cleavage will be discussed more in detail in section 3.1 of this account.

Because of the presence of potential binding sites at nitrogen of the heterocyclic fragment and also at the oxygen of the phosphinic moiety the synthesised new mono- and bis(α-hydroxymethyl)phosphinic acids, derivatives of imidazole and pyridine, **2a-d** and **3a-d** were evaluated for their coordination properties toward Cu(II) cations.[31] During those studies it was demonstrated that the synthesised compounds had a good binding ability toward Cu(II) ions. As expected, the binding site was located on the nitrogen and phosphinic oxygen atoms. Relatively, the most effective ligand was found to be the bis(α-hydroxymethyl)phosphinic acid **3d**. Additionally, the bis(α-hydroxymethyl)phosphinic acids **3d** and **3c** served as models for surface-enhanced raman spectroscopy (SERS) studies.[33,34]

**2.2. Synthesis of heterocyclic α-aminomethylphosphinic acids**

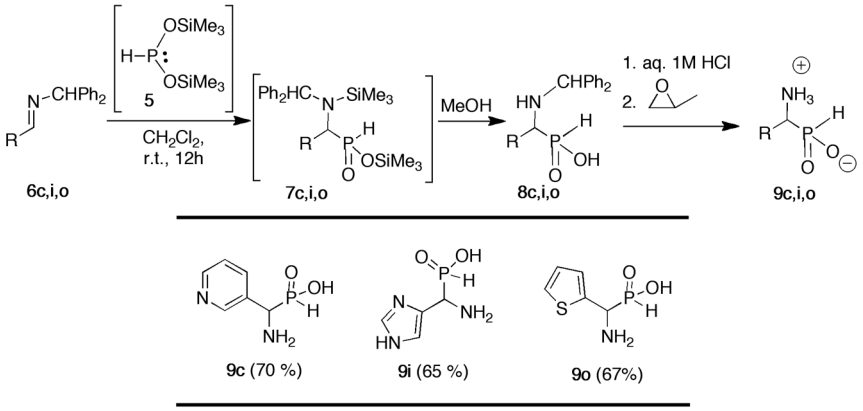
In continuation of our work on the synthesis of substituted heterocyclic phosphonic acids we have investigated the reaction of hypophosphorous acid ($H_3PO_2$) with imines[35] with the aim to obtain heterocyclic α-aminomethylphosphinic acids. Simple α-aminomethylphosphinic acids are often used as building blocks in the synthesis of more complex structures, for example, phosphinic pseudopeptides, with interesting biological activity as *e.g.* enzyme inhibitors.[36] In spite of many attempts, however, use of hypophosphorous acid in the reaction with heterocyclic imines or its primary amine salts and their subsequent reaction with heterocyclic aldehydes did not work giving either very impure products with poor yields or no products at all. Most likely, reduction of the starting imines by $H_3PO_2$ occurred as the main reaction. As a consequence, we have decided to use bis(trimethylsilyl)phosphonite **5** (BTSP) as phosphorus nucleophile.[37] This reagent was easily generated in situ by heating at 120°C, an equimolar mixture of ammonium hypophosphite and hexamethyldisilazane.[38] The presence of a bulky trimethylsilyl group in BTSP increases the power of such a nucleophile due to formation of a stable, three-coordinated phosphorus moiety with a free electron pair at phosphorus. Also, lack of the possibility of tautomerization of the three-coordinated, silylated phosphorus ester into less nucleophilic four-coordinated phosphonate-like ester additionally secured the nucleophilic character of the applied reagent. As a consequence, all reactions proceeded at room temperature and the presence of undesired side products arising from oxidation of the P-H bond and/or cleavage of the C-P bond were not detected. Nucleophilic addition of **5** to various heterocyclic imines **6a-o** derivatives of pyridine,

pyrrole, imidazole, thiophene and furan proceeded easily at room temperature during 12 hours (Scheme 4). The thus formed silylated phosphinic intermediates **7** were then treated with methanol, as a desilylating agent, to produce the desired new heterocyclic α-aminomethylphosphinic acids **8a-o** in good yields (57-82%). All compounds were isolated as crystalline solids after simple crystallization from methanol.




**Scheme 4.** Preparation of heterocyclic α-aminomethylphosphinic acids **8a-o**.

Importantly, we have found that in order to obtain α-aminomethylphosphinic acids **9c,i,o** with free amino group it was necessary, after the addition of BTSP to heterocyclic *N*-benzhydrylimines **6c,i,o**, to isolate the corresponding (benzhydrylamino)methylphosphinic acids **8c,i,o** and subsequently remove the benzhydryl group under acidic conditions (Scheme 5). The desired acids **9c,i,o** were isolated as neutral zwitterionic salts after treatment with propylene oxide as an HCl scavenger. The direct hydrolysis of silylated intermediates **7c,i,o** under acidic conditions resulted in the formation of desired acids **9c,i,o** with poor yields (<20%).

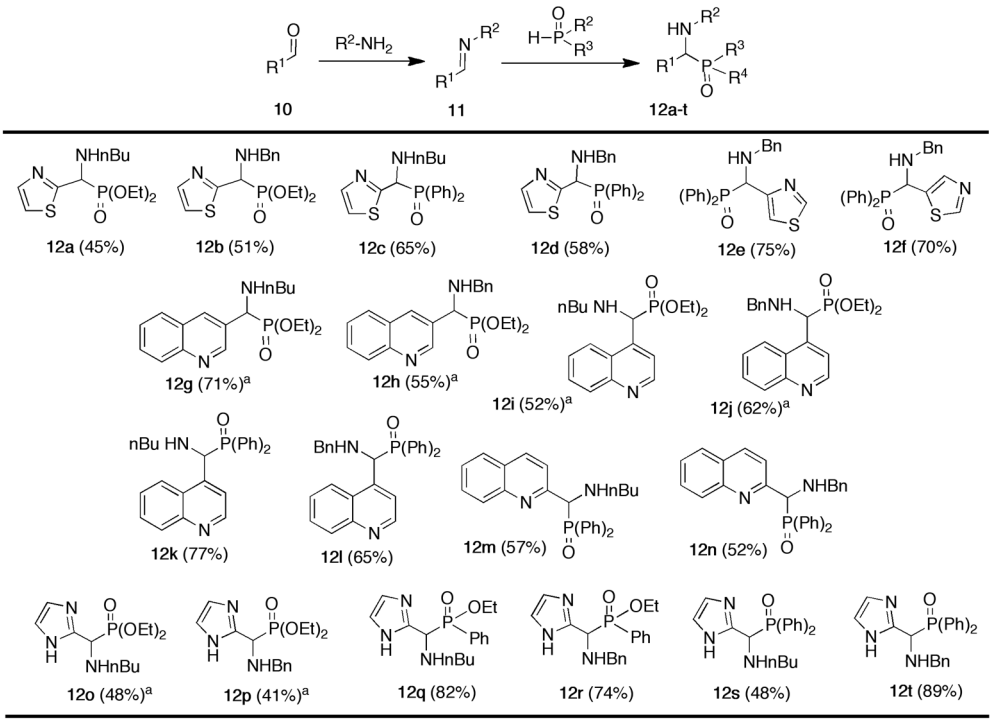



**Scheme 5.** Synthesis of heterocyclic α-aminomethylphosphinic acids **9c,i,o** with free amino group.

Additionally, isolation of the products **9c,i,o** using the latter one-pot protocol was tedious and required repeated crystallizations in order to obtain analytically pure samples.

### 3. Towards the synthesis of heterocyclic aminophosphonates and phosphonic acids

Our interest in the preparation of heterocyclic substituted phosphonates and phosphinates brought us to investigate the synthesis of new derivatives of thiazole,[39] quinoline[40] and imidazole.[41] We have examined the classical approach that is the addition of diethyl *H*-phosphonate, ethyl phenylphosphinate or diphenylphosphine oxide to imines prepared from corresponding heterocyclic aldehydes and primary amines. In general, reactions preceded fast (reaction time of 2 h), however, required elevated temperature (toluene at 110 °C). The desired new products were isolated in good yields ranging from 41 to 89%. In the case of α-aminomethylphosphonate diethyl esters derivatives of quinoline-3 and -4, **12g-j** and imidazole-2, **12o,p** products were isolated as oxalate salts. The α-aminomethylphosphonate diethyl esters derivatives of thiazole-2, **12a,b** ethyl phenyl α-aminomethylphosphonates derivatives of imidazole-2, **12q,r** and α-aminomethyldiphenylphosphine oxides derivatives of thiazole-2, **12c,d** thiazole-4, **12e** thiazole-5, **12f** quinoline-2, **12m,n** quinoline-4, **12k,l** and imidazole-2, **12s,t** were isolated as crystalline solids (Scheme 6).

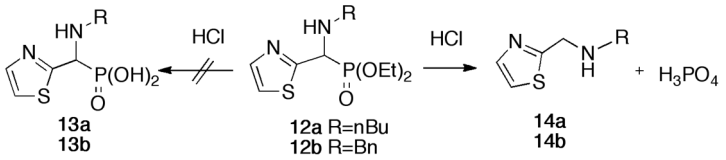



[a]Isolated as oxalate salts.

**Scheme 6.** Preparation of heterocyclic α-aminomethylphosphonates, phosphinates and phosphine oxides.

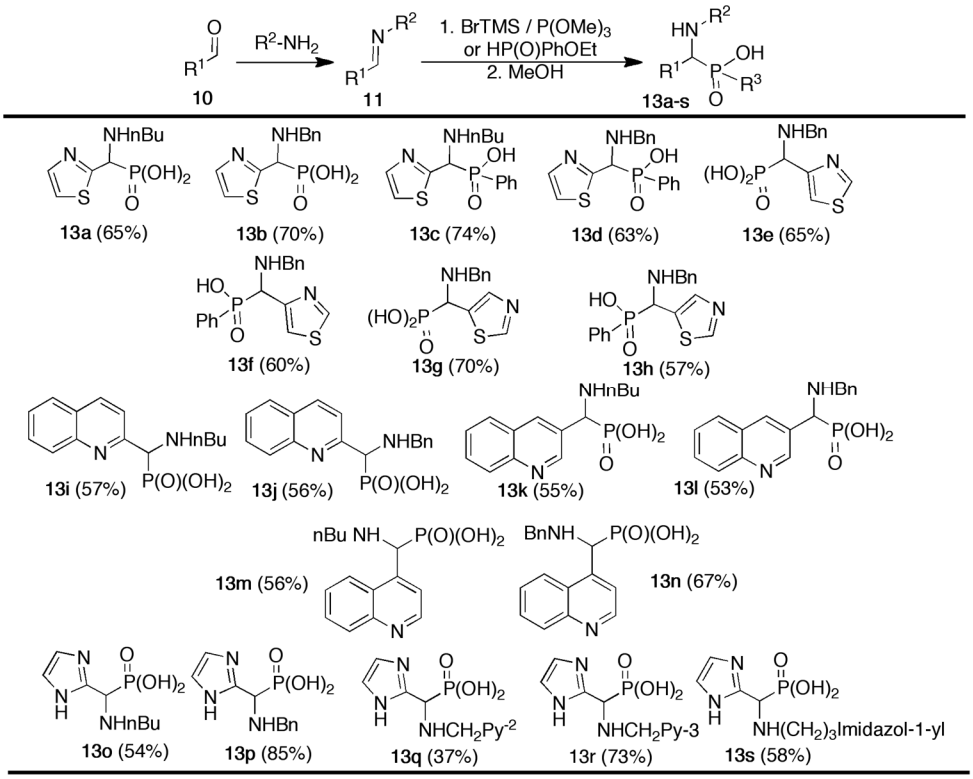
Subsequently, in order to obtain the corresponding α-aminomethylphosphonic and phosphinic acids we have performed acidic hydrolysis of the obtained α-aminomethylphosphonate diethyl esters. In the case of thiazole-2 derivatives, however, instead of the formation of the desired phosphonic acids, after concentration of the crude reaction mixture, neutralization with aqueous $Na_2CO_3$, and extraction with $CH_2Cl_2$ the secondary amines, **14a,b** were isolated. Following the hydrolysis of the esters **12a,b** by $^{31}P$ NMR, we could clearly observe the disappearance of the signal corresponding to the starting material **12a** or **12b** ($\delta_P$~23.0 ppm) and the formation of another signal at about $\delta_P$~1.2 ppm that could be assigned to the formed

phosphoric acid (Scheme 7).[39] The formation of the amines **14a**,**b** and $H_3PO_4$ was attributed to the C–P bond cleavage in α-aminomethylphosphonate diethyl esters **12a**,**b** under acidic conditions. The cleavage will be discussed in more detail in section 3.1 of this account.




**Scheme 7.** Cleavage of thiazole-2-yl-(α-aminomethyl)phosphonates **12a**,**b** in acidic conditions.

We have observed similar problems in the case of acidic hydrolysis of α-aminomethylphosphonates and phosphinates derivatives of quinoline-4 **12i,j**,[40] and imidazole-2 **12o-r**.[41] To overcome those difficulties we have applied a different strategy, namely addition of silylated phosphoesters, generated *in situ* from bromotrimethylsilane (BrTMS) and trimethyl phosphite ($P(OMe)_3$) or, in the case of phosphinic acids, ethyl phenyl phosphinate (HP(O)PhOEt), to aldimines prepared from heterocyclic aldehydes (Scheme 8).[39-41]



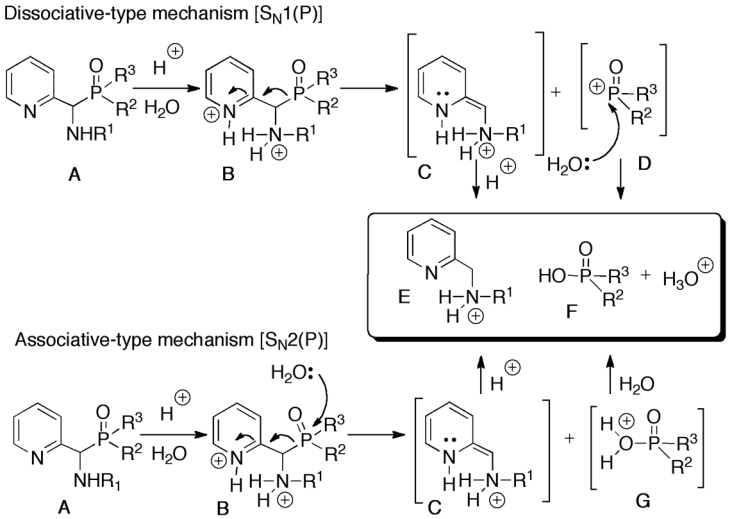

**Scheme 8.** Synthesis of α-aminomethylphosphonic and phosphinic acids **13a-s**.

The addition of silylated phosphorus esters to heterocyclic imines proceeded already at room temperature. Subsequent, treatment of the silylated intermediates with methanol resulted in formation of desired phosphinic and phosphinic acids in good yields, 37-85% as crystalline solids. Easy one-pot procedure, mild reaction conditions, relatively short reaction time (24 h usually) and easy isolation of desired

products are the main advantages of the application of the silylated phosphorus esters methodology to the synthesis of new phosphorus derivatives of thiazole, quinoline and imidazole.

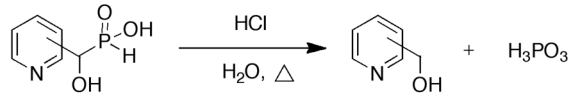
### 3.1. Cleavage of the C-P bond in derivatives of thiazole-2, quinoline-2 and -4, and imidazole-2

Organophosphorus compounds are, in general, believed to be resistant to decomposition and durable compounds under acidic and basic conditions. The carbon-phosphorus bond (C-P) present in those molecules is considered to be resistant to chemical cleavage; there are however reports in the literature describing its cleavage in some functionalized phosphonates.[42] In the case of the cleavage of the C-P bond in heterocyclic α-substituted phosphonates and phosphonic acids, Boduszek observed that α-aminomethylphosphonates derivatives of pyridine-2 undergo cleavage of C-P bond in acidic conditions.[19,43] This fact prompted him to further investigate this phenomenon in pyridine series,[43,28] 4-quinolylmethyl(*N*-butylamino)phosphonate diethyl ester,[19] and α-aminomethylphosphonic acids derivatives of chromone, coumarine and pyrone.[44] It is important to mention that the C-P bond is cleaved easily by microorganisms.[45] Therefore, in light of the agricultural and medical importance of α-substituted phosphonates and phosphonic acids the study on the chemical nature of C-P bond cleavage in heterocyclic aminophosphonates and phosphonic acids may improve the understanding of the biological C-P bond cleavage, and therefore merits further investigations. Mechanism of chemical C-P bond cleavage in heterocyclic α-substituted phosphonates and phosphonic acids under acidic conditions is complex and attempts to explain it were carried out using experimental[28,43,44,46] and theoretical studies.[46] Generally, in the case of heterocyclic α-substituted phosphonates and phosphonic acids the chemical cleavage of C-P bond in acidic conditions is postulated to proceed *via* two different mechanisms (Scheme 9). On the example of derivatives of pyridine, the first mechanism, a dissociative-type [$S_N1(P)$], assumes that after protonation of the nitrogen (intermediate **B**, Scheme 9) a cleavage of the C-P bond takes place and two intermediates are formed: an enamine-like moiety **C** and a metaphosphate-like moiety (intermediate **D**, Scheme 9). The **D**, as reactive intermediate, reacts with a nucleophile (*e.g.* water, as the reaction solvent) to form the phosphorus-containing product **F**. In turn, the enamine-like moiety **C** transforms into the amine **E**. The second mechanism, associative type mechanism [$S_N2(P)$], involve a direct nucleophilic attack of the solvent molecule ($H_2O$, in the case presented on Scheme 9) at phosphorus in the protonated aminophosphonate **B** prior to the cleavage of the C-P bond. Further reorganizations should lead to the formation of the final products, that is the secondary amine **E** and the phosphorus containing product **F**. Both mechanisms assume protonation of the starting heterocyclic α-substituted phosphonate or phosphonic acids, which can be considered as the driving force that triggers the cleavage.




**Scheme 9.** Postulated mechanisms of C-P bond cleavage in acidic conditions and in protic solvent.

During the work on the synthesis of new mono- and bis(α-hydroxy)methylphosphinic acids, derivatives of imidazole and pyridine, in aqueous media *via* reaction of corresponding aldehydes with aqueous hypophosphorous acid,[31] we have observed that the [(hydroxy)(3-pyridyl)methyl]phosphinic acid **2a** and [(hydroxy)(4-pyridyl)methyl]phosphinic acid **2c** undergo cleavage of the C-P bond in the presence of HCl (Scheme 10). It is important to mention that the parent [(hydroxy)(3-pyridyl)methyl]phosphonic acid and [(hydroxy)(4-pyridyl)methyl]phosphonic acid are stable under acidic conditions.[19] Also, heterocyclic bis(hydroxy)-phosphinic acids **3a-d** proved to be resistant for cleavage in 1 M HCl, under the applied conditions. It is noteworthy that [(hydroxy)(3-pyridyl)methyl]phosphinic acid **2b** does not undergo cleavage in 1 M HCl solution. Prolonged heating of **2b** in 1 M HCl led only to a partial oxidation of **2b** by oxygen from the atmosphere to the corresponding [(hydroxy)(3-pyridyl)methyl]phosphonic acid, which is stable.[19] Also, a similar resistance for cleavage was observed for parent [(amino)(3-pyridyl)methyl]phosphonic acids.[19] The kinetic measurements that we have performed for **2a** and **2c** by means of $^{31}$P NMR spectroscopy revealed that 2-pyridyl derivative **2a** underwent cleavage much faster than corresponding 4-pyridyl derivative **2c**. The measured cleavages followed pseudo-first-order kinetics. We have found that the rate constants were strongly dependent on the concentrations of the acid. The runs, which were performed in deuterated solvents and with the use of deuterated reagents, proved that the cleavages were considerably faster in solutions of common, non-deuterated acids. Additionally, it was possible to calculate the kinetic isotope effect ($k_H/k_D$) which was equal to 6.96 and 3.24 for the 2-pyridyl and the 4-pyridyl derivatives, **2a** and **2c** respectively. The considerably high value of $k_H/k_D$ indicates that the protons are involved in a rate-determining step of the reaction. The kinetic measurements for the cleavage of **2a** were also carried out at 85 °C and 75 °C in order to calculate the activation parameters ($\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$). The low value for the energy of activation is significant and indicates the ease of splitting a C-P bond in **2a**. The calculated entropy of activation was -95.67 $Jmol^{-1}$ $K^{-1}$, and this value may reflect unease in the protonation of oxygen[47] in a phosphinic group of **2a** before splitting. It is noteworthy that the rate constants were calculated from estimated $^{31}$P NMR spectroscopic integrated signals, and therefore, these results should not be considered as exact data for mere kinetic studies. Nevertheless, they already give a general picture of the cleavage mechanism and based on those measurements and by analogy to the corresponding α-aminomethylphosphonic acids, analogous mechanisms for the C-P bond cleavage in the [(hydroxy)(3-pyridyl)methyl]phosphinic acid **2a** and [(hydroxy)(4-pyridyl)methyl]phosphinic acid **2c** could be postulated, however, leading to the corresponding pyridine methanols and phosphorus acid ($H_3PO_3$) respectively.[31]



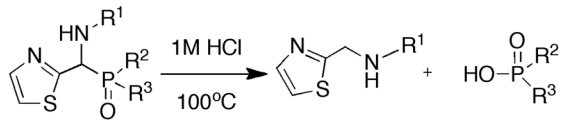

**2a** 2-pyridyl
**2c** 4-pyridyl

**4a** 2-pyridyl
**4c** 4-pyridyl

**Scheme 10.** Cleavage of C-P bond in [(hydroxy)(3-pyridyl)methyl]phosphinic acid **2a** and [(hydroxy)(4-pyridyl)methyl]phosphinic acid **2c** in acidic conditions.

The cleavage of the C-P bond in heterocyclic α-substituted phosphonates is not only limited to 2- and 4-pyridyl derivatives. We have observed this process also in the case of thiazole-2,[39] quinoline-2 and -4,[40] and imidazole-2 derived α-aminomethylphosphonates and phosphonic acids.[41] In the case of thiazole-2 derivatives, we have observed that acidic hydrolysis of the formed thiazole-2-yl-(amino)methylphosphonate diethyl esters **12a**, **b**, instead of producing desired phosphonic acids, unexpectedly leads to the decomposition of the esters **12a**,**b** and formation of secondary amines **14a**,**b** and phosphoric acid ($H_3PO_4$).[39] To overcome this problem, the desired phosphonic and phosphinic acids were obtained *via* addition of silylated phosphoesters, generated *in situ* from bromotrimethylsilane (BrTMS) and trimethyl phosphite ($P(OMe)_3$) or, in the case of phosphinic acids, ethyl phenyl phosphinate (HP(O)PhOEt), to aldimines prepared from corresponding heterocyclic aldehydes.[27] Additionally, we have prepared the thiazole-2-yl-(amino)methyldiphenylphosphine oxides in the reaction of corresponding thiazole-2 aldimines and diphenylphosphine oxide.[27] We have discovered, however, that also the synthesized

thiazole-2-yl-(α-amino)methylphosphonic and phosphinic acids **13a-d** and diphenylphosphine oxides **12c,d** were unstable under acidic conditions as the result of the cleavage of the C-P bond (Scheme 11). After heating of compounds **13a-d** and **12c,d** for up to 3 h at 100 °C in the presence of aqueous 1 M HCl, evaporation of the solvent, neutralization of the crude reaction mixture with $Na_2CO_3$, and extraction with $CH_2Cl_2$ the secondary amines **14** were isolated (Scheme 11). The remaining aqueous layer was then acidified with aqueous 0.5 M HCl and dissolved in EtOH (in the case of **13c,d** and **12c,d**) and the resulting mixture was cooled down causing precipitation of the corresponding diphenylphosphinic acid **17** (in the case of aminophosphine oxides **12c,d**) or phenylphosphinic acid **16** (in the case of aminophosphinic acids **13c,d**), that were collected by filtration. Subsequently, we have performed kinetic measurements by means of $^{31}P$ NMR spectroscopy on the cleavage of the C-P bond in thiazole-2-yl-(*N*-butylamino)methyldiphenylphosphine oxide **12c** in 50% (v/v) aqueous methanol solution (for better solubility of reagents), containing a definite quantity of HCl. The kinetics were run directly in NMR tube. The relative quantities of the phosphorus-containing product and starting material were estimated from the corresponding integrated $^{31}P$ NMR signals. In this case, the appearance of a signal assigned to diphenylphosphinic acid **17** ($\delta_P$~25 ppm), together with the subsequent decay of a signal corresponding to the starting aminophosphine oxide **12c** ($\delta_P$~31 ppm) was observed. On the basis of $^{31}P$ NMR data, the rate constants ($k_{obs}$) were calculated. The measured cleavages followed pseudo-first-order kinetics and it was found that the rate constants ($k_{obs}$) were strongly dependent on the concentration of the hydrochloric acid.[39]



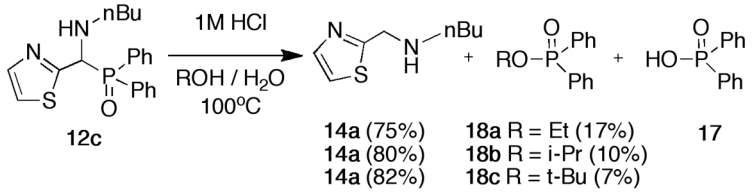

**13a** $R^1$ = nBu; $R^2$ = $R^3$ = OH — **14a** (75%) — **15** $R^2$ = $R^3$ = OH
**13b** $R^1$ = Bn; $R^2$=$R^3$ = OH — **14b** (80%) — **16** $R^2$ = OH; $R^3$ = Ph
**13c** $R^1$ = nBu; $R^2$ = OH; $R^3$ = Ph — **14a** (80%) — **17** $R^2$ = $R^3$ = Ph
**13d** $R^1$ = Bn; $R^2$ = OH; $R^3$ = Ph — **14b** (82%)
**12c** $R^1$ = nBu; $R^2$ = $R^3$ = Ph — **14a** (90%)
**12d** $R^1$ = Bn; $R^2$ = $R^3$ = Ph — **14b** (85%)

**Scheme 11.** Cleavage of the C-P bond in thiazole-2 derivatives **13a-d** and **12c,d** in acidic conditions.

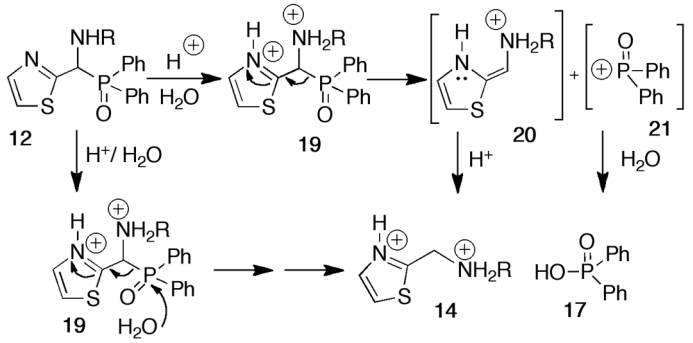
Additionally, we have conducted experiments of the cleavage of the of aminophosphine oxide **12c** in the presence of 1 M HCl and in aqueous solutions of different alcohols. The formation of the corresponding phosphoesters **18** and diphenylphosphinic acid **17** would be consistent with the both proposed mechanisms of the cleavage of the heterocyclic aminophosphonates (Scheme 9). This assumption was confirmed experimentally (Scheme 12). It was expected that if the 'protonated' metaphosphate (a phosphinylium cation)[48,49] is involved in the cleavage then the formation of phosphoesters (in this case the corresponding alkyl esters of diphenylphosphinic acid) **18** would confirm, to some extent, its presence. Since, the metaphosphate ($HOPO_2$) is considered as a strong electrophile,[50] one of the most commonly used diagnostic tests for an involvement of this intermediate is phosphorylation of alcohols, especially hindered alcohols.[50,51] It should be added that, the formation of phosphoesters **18**, can also be explained using the second, associative-type mechanism. The cleavages of **12c** were carried out in 50% aqueous solutions of various alcohols. The solutions containing ethanol, isopropanol or tert-butanol and a definite amount of 1M HCl were heated for 1h at 100 °C and the progress of the reaction was monitored by $^{31}P$ NMR spectroscopy. After that time the reaction mixtures were cooled down to room temperature and after usual work-up the corresponding *N*-(thiazole-2-ylmethyl)butan-1-amine **14a** was isolated accompanied by expected phosphinic alkyl esters **18a-c** and diphenylphosphinic acid **17**. The structures of the phosphoesters **18a-c** were confirmed by standard spectroscopic techniques. Due to the steric hindrance represented by the R substituent of the alcohol the yields of the isolated phosphoesters **18a-c** were the highest for EtOH than for *i*-PrOH and the lowest in the case of tert-butanol (Scheme 12).

Based on the aforementioned facts the cleavage of the thiazole-2-yl-(amino)methyldiphenylphosphine

oxides **12** can proceed through the two mechanism (Scheme 13).[39] The first, dissociative-type mechanistic pathway (Scheme 13) relies upon the rupture of C-P bond in protonated aminophosphine oxide **19** and formation of two intermediate products: an enamine-like **20** and a metaphosphate-like moiety **21**. The **21** as reactive intermediate can therefore react with solvent (water in this case) to form the final product, *i.e.*, diphenylphosphinic acid **17**. In turn, the enamine-like intermediate**20** transforms into the amine **14** by incorporation of a proton. In turn, the second, associative-type mechanism would involve a direct nucleophilic attack of a solvent molecule ($H_2O$ in the presented case) at phosphorus in the protonated aminophosphine oxide **19** prior to the cleavage of the C-P bond (Scheme 13). Further reorganizations would lead to the formation of the final products, *i.e.*, the secondary amine **14** and diphenylphosphinic acid **17**. A driving force that triggers the cleavage of the C-P bond in both mechanisms seems to be the presence of a positive charge on protonated nitrogen in the aminophosphonate **19**. Assuming a similar behaviour of all the other prepared thiazole-2-aminophosphonates, phosphonic and phosphinic acids **12a-d** and **13a-d** in the presence of an acid, the two alternative mechanisms (Scheme 13) may also be used to explain the cleavage of those compounds. Finally, we have also synthesised the corresponding new thiazole-4 and thiazole-5 derived α-aminomethylphosphonates and phosphonic and phosphinic acids **13e-h** (Scheme 8) to analyze their behavior in acidic conditions.[39] The obtained thiazole derivatives **13e-h** were heated at 100 °C in 1 M aqueous HCl for 3 h. In all cases, decomposition was not detected and the tested compounds were found to be stable. This fact additionally confirms the proposed mechanisms (Scheme 13). Under used acidic conditions surely protonation of nitrogen atoms in thiazole-2, -4, and -5-aminomethylphosphonates occurs. However, only in the case of thiazole-2 derivatives the existence of delocalisation (enamine-like intermediate **20**, Scheme 13), possible by the presence of a positive charge at thiazolyl nitrogen (intermediate **19**, Scheme 13), can trigger further events leading to the final secondary amine and corresponding phosphorus-containing product, respectively. In the case of thiazole-4 and -5 derivatives **13e-h** the formation of aforementioned intermediates is not possible and thus those compounds are stable under acidic conditions and no cleavage is observed.



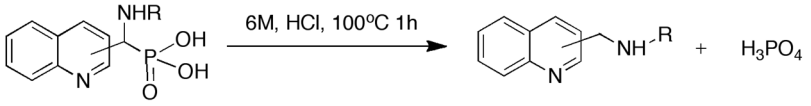

**Scheme 12.** Cleavage of diphenylphosphine oxide **12c** in acidic conditions and in 50% aqueous alcohols.




**Scheme 13.** Postulated mechanisms for the cleavage of thiazole-2-yl-(amino)methyldiphenylphosphine oxides **12**.

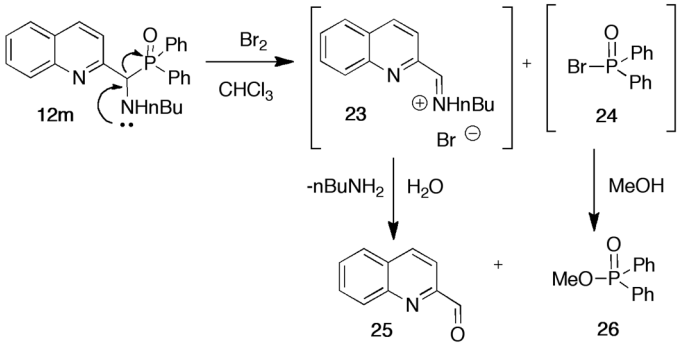
Subsequently, we have become interested in studying the behaviour of quinoline derived (amino)methylphonates and phosphonic acids in acidic conditions. During an attempt to synthesise the

4-quinolylmethyl(*N*-benzylamino)phosphonic acid *via* acidic hydrolysis of the corresponding 4-quinolylmethyl(*N*-benzylamino)phosphonate diethyl esters, instead of the corresponding aminophosphinic acid we have isolated secondary amine and on the $^{31}P$ NMR we have observed a formation of the phosphoric acid.[40] The desired quinoline derived α-aminomethylphosphonic acids **13i-n** were therefore, synthesized by the reaction of corresponding quinoline aldimines with silylated phosphoesters, generated *in situ* from bromotrimethylsilane and trimethyl phosphite. We have observed that the synthesised new quinoline-2 and quinoline-4 derived α-aminomethylphosphonic acids **13i-n** undergo decomposition involving C-P bond cleavage in acidic conditions (Scheme 14). This behaviour could be anticipated because of the structural resemblance to pyridine, however this fact was not proved experimentally before. The postulated mechanisms for the cleavage of the C-P bond in the quinoline-2 and quinoline-4 derived α-aminomethylphosphonic acids **13i,j** and **13m,n** in acidic conditions involve, by analogy to pyridine, either dissociative-type mechanistic pathway or associative-type mechanism pathway. Both mechanisms lead to similar products that is secondary amines derivatives of quinoline-2 or -4 **22a,b** or **22c,d** respectively, and phosphoric acid (for reactions in water).[40] The corresponding 3-quinolyl-(amino)methylphonates and phosphinic acids were stable in the presence of an mineral acid, and this was proved experimentally by heating the quinoline-3-yl-(*N*-benzylamino)methylphosphonic acid **13k** with 6 M HCl for 3 h and isolation of the intact starting material.



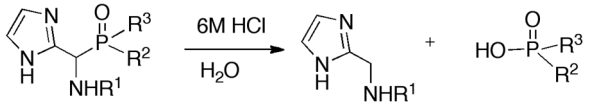

**Scheme 14.** Cleavage of the C-P bond in the quinoline derived α-aminomethylphosphonic acids.

Interestingly, we have observed for the first time that the cleavage of the quinoline-derived aminophosphonates also occur in aprotic solvent (such as chloroform) and by use of electrophilic reagents (elemental bromine $Br_2$) (Scheme 15).[40,52] Heating of aminophosphine oxide **12m** (1 mmol) in $CHCl_3$ for 3 h in the presence of $Br_2$ (3 mmol), after evaporation of the solvent, led to the mixture composed of bromide **24** and imine **23**. Subsequent treatment with MeOH (5 h at room temperature) and extraction of acidified solution with $CH_2Cl_2$ allows isolation of ester **26** (80%) and aldehyde **25** (product of decomposition of the imine **23**). In such a case the occurrence of the second postulated mechanism, the associative-type $S_N2(P)$ which assumes the nucleophilic attack of solvent molecule on phosphorus atom, that leads to the breaking of C-P bond, is questionable.




**Scheme 15.** Cleavage of the C-P bond in the presence of $Br_2$ and in aprotic solvent.

Finally, we have studied the behaviour of imidazole-2-yl-(amino)methylphosphonates, phosphine oxides and phosphonic acids under acidic conditions.[41] As in the case of thiazole-2, quinoline-2 and -4 derivatives, also in the case of imidazole-2 derivatives the acidic hydrolysis of the imidazole-2-yl-(amino)methylphosphonate diethyl esters led to the decomposition of the latter and isolation of the corresponding secondary imidazole-2 derived secondary amine **27** and phosphoric acid ($H_3PO_4$). The desired phosphonic acids were obtained *via* the silylated phosphorus esters method.[41] The thus obtained imidazole-2-yl-(amino)methylphosphonic acids, amino)methylphosphine oxides undergo decomposition as a result of the C-P bond cleavage (Scheme 16). Similar to the imidazole-2-yl-(amino)methyl phosphonate diethyl esters also imidazole-2-yl-(amino)methylphosphine oxides undergo decomposition as a result of the C-P bond cleavage. The kinetic measurements of this decomposition performed with the use of $^{31}P$ NMR showed that protons are involved in the rate-determining step (isotope effect $k_H/k_D>1$). Additionally, for compound **12t**, activation energy was calculated ($Ea$=79.15 kJmol$^{-1}$), whose low value suggested the ease of decomposition of those compounds. Two mechanisms for the cleavage of the C-P can be postulated; either dissociative-type mechanistic pathway or associative-type mechanism pathway. It is important to mention that the imidazole-4(5)-yl-(amino)methylphosphonates and phosphine oxides were found to be stable in the presence of strong mineral acid.[26] During the work on the cleavage of the imidazole-2-yl-(amino)methyl phosphonates it was discovered, the those compounds decompose also in the presence of an electrophile ($Br_2$) and in aprotic solvent ($CHCl_3$). This was experimentally confirmed on the example of imidazole-2-yl-(*N*-butylamino)-methyldiphenylphosphine oxide **13o**. The proposed mechanism, by analogy to the $Br_2$ promoted cleavage of quinoline derivatives (Scheme 15), involves the cleavage of the C-P with the subsequent formation of the bromophosphate intermediate that reacts with the MeOH to form the diphenylphosphinic acid methyl ester **26** and imidazole-2-carboxaldehyde (product of decomposition of the corresponding imidazole-2 derived aldimine).




**12r** $R^1$ = Bn, $R^2$ = Ph, $R^3$ = OEt
**12s** $R^1$ = nBu, $R^2$ = $R^3$ = Ph
**12t** $R^1$ = Bn, $R^2$ = $R^3$ = Ph
**13o** $R^1$ = nBu, $R^2$ = $R^3$ = OH
**13p** $R^1$ = Bn, $R^2$ = $R^3$ = OH

**27a** $R^1$ = Bn
**27b** $R^1$ = nBu

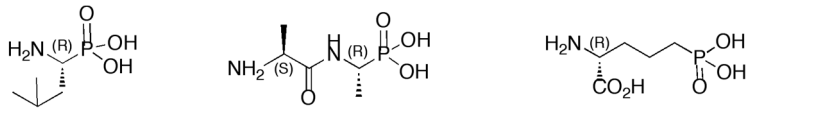
**15** $R^2$ = $R^3$ = OH
**16** $R^2$ = OH, $R^3$ = Ph
**17** $R^2$ = $R^3$ = Ph

**Scheme 16.** Decomposition of imidazole-2-yl-(amino)methylphosphinates, phosphine oxides and phosphinic acids in the presence of HCl.

**4. Asymmetric synthesis of heterocyclic substituted phosphonates and phosphonic acids**

The thus far presented syntheses described in this account were performed in non-asymmetric fashion, therefore the isolated compounds were racemic mixtures. It is well-established however, that the biological activity of *α*-substituted phosphonates, and in particular *α*-hydroxy and *α*-aminophosphonates and phosphonic acids very often strongly depends on their absolute configuration. The most prominent examples include: (*R*)-phospholeucine, which is more potent inhibitor of leucine aminopeptidase than the opposite enantiomer,[53] alafosfalin, in which the diastereoisomer with (*R)* configuration at C adjacent to phosphorus, and (*S*) configuration at carbon adjacent to $NH_2$ group, exhibits the strongest antibacterial activity out of four possible stereoisomers,[54] and (*R*)-amino-5-phosphonopentanoic acid, the *N*-methyl-D-aspartate (NMDA) antagonist, which is again more active than the opposite enantiomer (Figure 3).[55] As a consequence, the development of asymmetric methods for the enantio- and diastereoselective preparation of *α*-substituted phosphonates is of significant interest. In that respect, very often the direct condensation of phosphorus nucleophile with carbonyl substrate or imine is used to produce the desired *α*-substituted phosphonates in an asymmetric fashion. The chirality of the product can be controlled by the use of chiral substrates (chiral carbonyl compounds, chiral amines or chiral phosphorus nucleophiles) or by the employment of chiral catalysts.[15] Despite of remarkable achievements in that field, there is still a great need for further

development of simple and scalable asymmetric protocols.

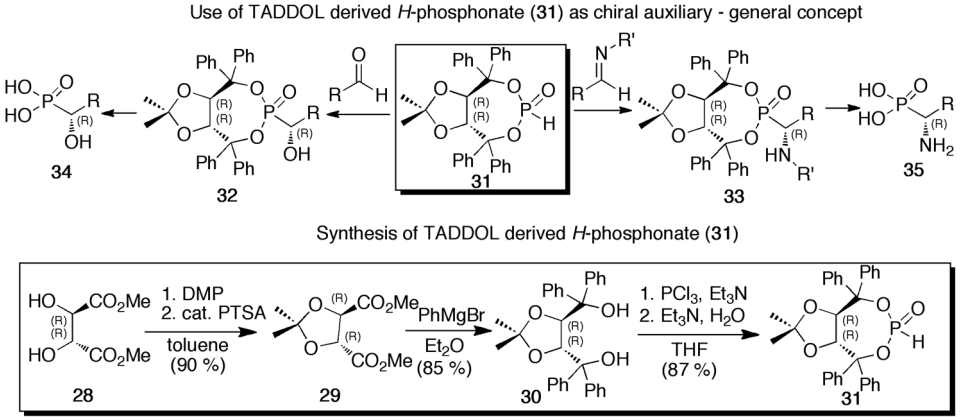


(*R*)-Phospholeucine (*S,R*)-Alafosfalin (*R*)-Amino-5-phosphonopentanoic acid

**Figure 3.** Prominent examples of biologically active (*R*)-aminophosphonic acids.

### 4.1. The use of (*R,R*)-TADDOL *H*-phosphonate as easily available chiral auxiliary

As a contribution to the field of asymmetric synthesis of heterocyclic and also aromatic and aliphatic *α*-hydroxy- and *α*-aminomethylphosphonates and phosphonic acids we have developed a diastereoselective protocol based on hydrophosphonylation of aldehydes[56,57] and chiral imines[58] with the use of nonracemic (*R,R*)-TADDOL-derived *H*-phosphonate **31**.[59] The concept of this approach is based on the use of enantiomerically pure (*R,R*)-TADDOL derived *H*-phosphonate **31** as chiral auxiliary in the hydrophosphonylation of aldehydes and chiral aldimines leading to the corresponding *α*-hydroxy- and *α*-aminomethylphosphonates, **32** and **33** respectively. Additionally, it should be noted that the $C_2$-symmetry of the chiral auxiliary **31** avoided the formation of a new stereogenic centre at the phosphorus atom and facilitated the interpretation of results of the hydrophosphonylation reaction. In each case, the diastereoselectivity of the hydrophosphonylation could be conveniently monitored by $^{31}P$ NMR of the crude product. Subsequent separation of the major diastereoisomer and cleavage of the chiral auxiliary afforded *α*-hydroxy- or *α*-aminomethylphosphonic acids **34** and **35** in enantiomerically pure form (Scheme 17).

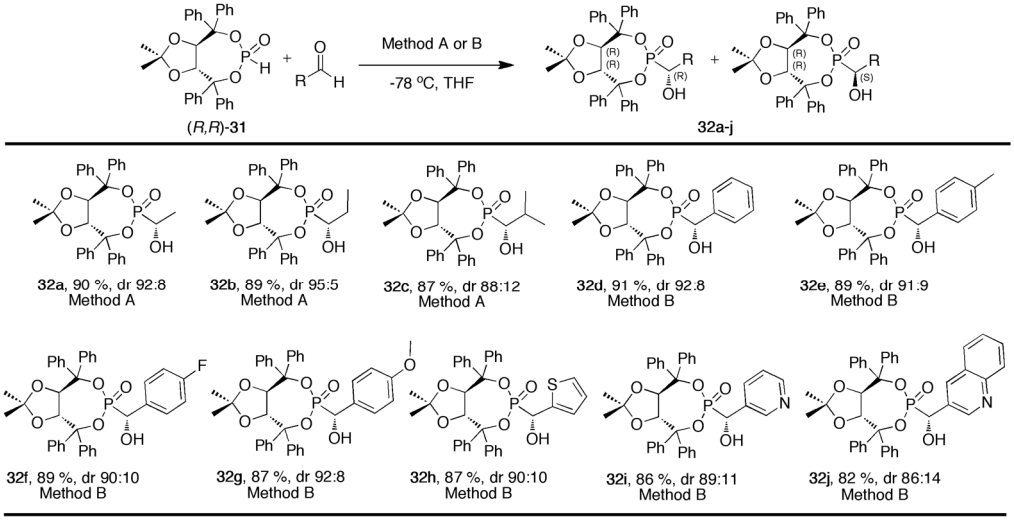



**Scheme 17.** Synthesis of (*R,R*)-TADDOL derived *H*-phosphonate **31** and its use as chiral auxiliary in the asymmetric synthesis of substitutedphosphonic acids, **34** and **35** respectively.
DMP 2,2-dimethoxypropane; PTSA *p*-toluenesulfonic acid.

The **31** could be prepared on a multigram scale from easily available (*R,R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxolane **30** (*R,R*)-(TADDOL) and the latter from commercially available and affordable (*2R,3R*)-tartaric acid dimethyl ester **28**. It needs to be added that the concept of the asymmetric synthesis of *α*-hydroxy- and *α*-aminomethylphosphonic acids based on the addition of chiral *H*-phosphonates and phosphites to carbonyl substrates or imines is scarcely described in the literature. The known examples include the application of di- or trialkylphosphites, derivatives of (1*R*,2*S*,5*R*)-(-)-menthol, endo-(1*S*)-(-)-borneol or (-)-1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose in the hydrophosphonylation of aldehydes[60] and aldimines.[60,61] Usage of chiral phosphorus acid diamides in the reaction with aldehydes,[62] application of P-H spirophosphoranes in the reaction with long chain aldimines,[63] use of BINOL *H*-phosphonate in the reaction with achiral 3-thiazolines[64] and finally the reaction of chiral

silylphosphites derivatives of ephedrine,[65] dimethyl tartrate,[66] and BINOL[67] with carbonyl compounds are also described. Thus, the application of (*R,R*)-TADDOL **31** as chiral phosphorus nucleophile represents an original contribution to the field of asymmetric synthesis of *α*-hydroxy and *α*-aminomethylphosphonates and phosphonic acids. This approach involves the use of easy available (even on multi-gram scale), stable and inexpensive chiral auxiliary, broad substrate scope and good to excellent diastereoselectivity of the hydrophosphonylation process, as well as easy procedure for removal of the chiral auxiliary (Scheme 17).

Examining the usefulness of the (*R,R*)-TADDOL **31** in the diastereoselective synthesis of *α*-hydroxymethylphosphonates **32** (Scheme 18) we have observed a strong influence of the additives used in the hydrophosphonylation reaction on the diastereoselectivity of the process.[56] During the preliminary experiments priopionaldehyde and benzaldehyde were used as model substrates. For aliphatic aldehyde when the reaction was performed in the presence of $Et_3N$ and, to enhance the diastereoselectivity, at low temperature (-78 °C) with LDA, n-BuLi and also with NaH and LiHMDS the observed diastereoselectivity was not acceptable (ratio of diasteroisomers, *dr* 69:31, in the best case). A breakthrough came with the use of diethylzinc ($Et_2Zn$), and the desired *α*-hydroxymethylphosphonate **32b** was formed in very good yield and with high diastereoselectivity (*dr* 95:5). As reported earlier in the literature, the reaction of $Et_2Zn$ with phosphonates leads to the formation organozinc–phosphorus adducts, which are very reactive albeit very insoluble hence the presence of tetramethylethylenediamine (TMEDA) to improve the solubility at low temperature is necessary.[68] In turn, for benzaldehyde, after testing a similar set of conditions it was discovered that the best diastereoselectivity could be obtained with the use of LDA. During further optimization of the reaction it was found that THF was the solvent of choice ensuring excellent solubility of reagents at low temperature and giving best possible diastereoselectivity of the reaction.[56] The optimized reaction conditions were extended to other aliphatic, aromatic and heteroaromatic aldehydes to examine the scope and limitations of the protocol (Scheme 18).[56] In the case of aliphatic aldehydes, the *dr* observed in the final *α*-hydroxymethylphosphonates **32a-c** was up to 95:5. The size of the R group in the aliphatic aldehyde slightly influenced the *dr*; for branched *α*-hydroxymethylphosphonate **32c** the *dr* was found to be slightly lower than for linear **33a** and **32b**. In turn, for aromatic aldehydes the measured *dr* in the formed aromatic *α*-hydroxymethylphosphonates **32d-g** was in the range from 90:10 to 92:8. Small variations of the *dr* were caused by the presence of electron donating or electron withdrawing groups on the aromatic ring.



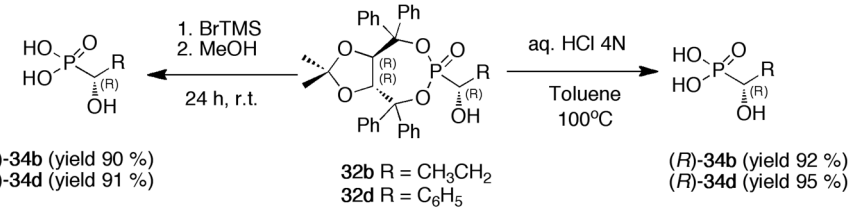

Method A: (*R,R*)-**31** (1.0 equiv.), $Et_2Zn$ (1.1 M in Toluene) (1. equiv.), TMEDA (1.2 equiv.), aldehyde (1 equiv.), -78 °C, THF, 12 h; Method B: (*R,R*)-**31** (1.0 equiv.), LDA (1. equiv.), aldehyde (1 equiv.), -78 °C, THF, 12 h; dr based on $^{31}P$ NMR of the crude reaction product.

**Scheme 18.** Diastereoselective hydrophsphonylation of aldehydes with (*R,R*)-TADDOL **31**, reaction scope.

Importantly, heteroaromatic aldehyde derivatives of 3-pyridine, 3-quinoline and 2-thiophene were also

tested in the presented reaction and afforded the desired heteroaromatic α-hydroxyphosphonates **32h-j** with *dr* up to 90:10. Thus, it can be concluded that this methodology is general and affords the desired α-hydroxymethylphosphonates in good yields and diastereoselectivities. Importantly, in each case the major diastereoisomer could be separated by simple recrystallization of the product from diethyl ether.

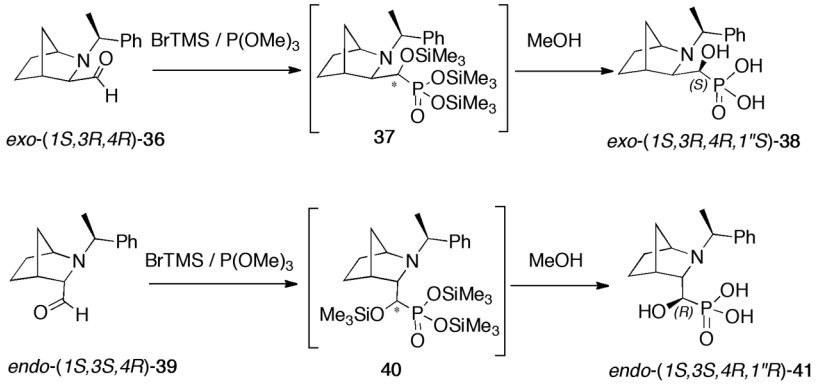
In order to complete the reaction sequence and to obtain the free α-hydroxymethylphosphonic acids **34** and additionally, to verify their absolute configuration, the chiral auxiliary was removed (Scheme 19). For this purpose, the isolated pure major diastereoisomers derived from α-hydroxymethylphosphonates **32b** and **32d** were used. Two different procedures were applied (Scheme 19). The first method was based on dissolving the α-hydroxymethylphosphonates **32b** or **32d** in toluene, adding aqueous 4 M HCl and stirring the resulting reaction mixture at 100 °C for 2 h. After separation of layers the aqueous phase was evaporated to dryness and the resulting crude product was recrystallized from EtOH to yield the desired enantiomerically pure α-hydroxymethylphosphonic acids **34b** and **34d**, respectively (Scheme 19). Alternatively, milder reaction conditions could be applied by using bromotrimethylsilane (BrTMS). In that case, the reaction was carried out in $CH_2Cl_2$ at room temperature for 24 h. Subsequent removal of the formed silylated esters by the addition of MeOH and recrystallization of the crude product from EtOH yielded pure enantiomers of α-hydroxymethylphosphonic acids **34b** and **34d** (Scheme 19). To elucidate the absolute configuration in the obtained acids **34**, the α-hydroxymethylphosphonic acids **34b** and **34d** were transformed into their dimethyl phosphonate esters by employing trimethylsilyldiazomethane ($TMSCHN_2$) as a reagent of choice for racemization free esterification of the phosphonic acids. The measured specific rotation values obtained for thus obtained α-hydroxymethylphosphonate dimethyl esters were consistent with the values reported in the literature for the opposite (*S*)-enantiomers, but had the opposite sign which suggested an (*R*)-configuration at the α-carbon atom in the obtained esters and therefore in their parent α-hydroxymethylphosphonic acids **34b,d** as well. Additionally, α-hydroxymethylphosphonic acid **34d** was converted into its salt with cyclohexylamine and the comparison of specific rotation values with those reported in the literature additionally confirmed the (*R*)-configuration at the stereogenic α-carbon in **34d**.[56]




**Scheme 19.** Removal of the chiral auxiliary and the preparation of α-hydroxymethylphosphonic acids.

Continuing our interest in the asymmetric synthesis of heterocyclic α-hydroxymethylphosphonates and phosphonic acids, we have prepared new α-hydroxymethylphosphonic acids derivatives of 2-azanorbornane.[57] Derivatives of 2-azanorbornane (2-azabicyclo[2.1.1]heptane) are endowed with biological activity and have found numerous applications as ligands in asymmetric catalysis,[69] thus it could be expected that the union of the 2-azanorbornane scaffold with the α-hydroxymethylphosphonic acid moiety would result in valuable chemical and biological properties of such heterocyclic phosphonic acids. The desired α-hydroxymethylphosphonic acids *exo*-**38** and *endo*-**41** were obtained via the hydrophosphonylation of the corresponding 2-azanorbornane aldehydes *exo*-**36** and *endo*-**39**. Aldehyde *exo*-**38** was used for preliminary tests during which we have quickly realized, that the configurationally stable, rigid, bicyclic chiral framework of 2-azanorbornane scaffold was not readily prone to hydrophosphonylation. The reaction at room temperature with diethyl *H*-phosphonate [$HP(O)(OEt)_2$] in the presence of triethylamine gave only trace amounts (>5%) of the desired α-hydroxymethylphosphonate diethyl ester. Heating the reaction mixture for 5 days in toluene at 110 °C afforded 50% conversion to a α-hydroxymethylphosphonate diethyl ester with *dr* 74:26. Under the same conditions, use of anhydrous $K_2CO_3$ as a base resulted in a significantly lower conversion (30%, *dr* not determined). Exchanging the $HP(O)(OEt)_2$ with the sterically less bulky and thus more reactive $HP(O)(OMe)_2$ resulted in the formation of the corresponding α-hydroxymethylphosphonate dimethyl ester, with improved conversion (60%, *dr* 75:25).

We have also tested chiral, sterically bulky (*R*, *R*)-TADDOL *H*-phosphonate **31** as phosphorus nucleophile. Performing the reaction in toluene at 110 °C for 5 days we have obtained good diastereoselectivity of the reaction (*dr* 90:10), however low conversion was observed (55 %) due to the thermal instability of the (*R*, *R*)-TADDOL *H*-phosphonate **31** and its decomposition to the TADDOL under the reaction conditions. Finally, we have used the silylated esters, generated in situ by reacting trimethylphosphite $P(OMe_3)_3$ with bromotrimethylsilane (BrTMS), as the phosphorus nucleophile (Scheme 20). The desired *α*-hydroxymethylphosphonic acids *exo*-**38** and *endo*-**41** were obtained, after dealkylation of the formed silylated esters **37** and **40** with methanol, in very good yields and under mild reaction conditions (room temperature, 12 h). Very high levels of chiral induction were observed during this process. As seen from the $^{31}P$ NMR spectra, a single diastereoisomer of *α*-hydroxymethylphosphonic acid *exo*-**38** ($\delta_P$ 14.56 ppm, $D_2O$) and a single diastereoisomer of the *α*-hydroxymethylphosphonic acid *endo*-**41** ($\delta_P$ 17.11 ppm, $D_2O$) were isolated after simple recrystallization of the crude product from EtOH/$Et_2O$ mixture. In order to elucidate the diastereochemical outcome of hydrophosphonylation reaction of the 2-azanorbornane aldehydes with silylated phosphorus esters, molecular orbital studies on the substrates and products of the reaction on the DFT level of theory were used. For the reaction of aldehydes *exo*-**36** and *endo*-**39** with mixture BrTMS/$P(OMe)_3$, the thermodynamically stable products **37**, **40** with either (*R*)- or (*S*)-configurations for the newly created stereogenic center were found (Scheme 20). The energy values of the optimized structures pointed to (1''*S*)-**37** and (1''*R*)-**40** as being the favourable products of the reaction. The dealkylation of (1''*S*)-**37** and (1''*R*)-**40** with methanol should therefore lead to the corresponding *α*-hydroxymethylphosphonic acids *exo*-**38** and *endo*-**41**, respectively, with a conserved stereochemistry of the carbon stereogenic center adjacent to the phosphorus atom. The observed stereochemical outcome of the reaction can be accounted for by the preferential approach of the phosphorus reagent from the less hindered face of the formyl group of *exo*-**36** or *endo*-**39**.




**Scheme 20.** Preparation of *α*-hydroxymethylphosphonic acids *exo*-**38** and *endo*-**41**.

DFT calculations showed the favoured orientation of this fragment of the substrate. The access to the carbonyl carbon atom was hindered from one side by the *N*-*α*-methylbenzyl substituent. The approach from the unhindered face leads to the observed (*S*)-product in the case of the *exo*-**36,** and (*R*) when the *endo*-**39** is used (Figure 4). A similar explanation for the stereodifferentiation was given for the reaction of aldehyde *exo*-**36** with Grignard reagents leading to secondary alcohols described by Brandt et al.[70] The stereochemical outcome of our reaction was unambiguously confirmed by X-ray data collected for compound *exo*-**38**. The compound *exo*-**38** had (*S*)-configuration on the carbon adjacent to the phosphorus atom (Figure 5). Interestingly, compound *exo*-**38** crystallizes as two crystallographic ally independent molecules in the asymmetric unit differing by protonation of the phosphonate group. Both molecules bear positively charged protonated tertiary nitrogen atoms. One of these charges is balanced by the proton removal from the phosphonate hydroxyl group and one molecule is thus zwitterionic. Such an intramolecular proton transfer was observed in the X-ray structures of various phosphonic acids bearing nitrogen functions. At the same

time, both hydroxyl groups of phosphonic acid remained protonated in second molecule and its charge was balanced with bromide anion, so it could be described as a salt (hydrobromide).

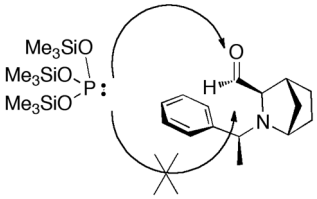



**Figure 4.** Preferential approach of the silylated phosphorus ester.

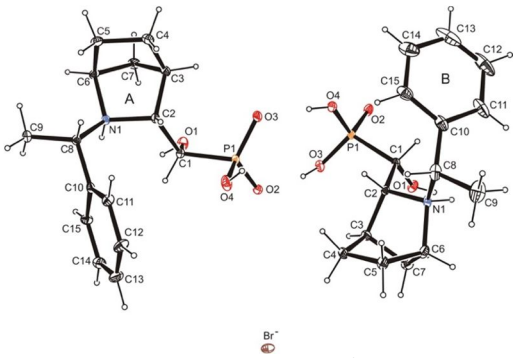
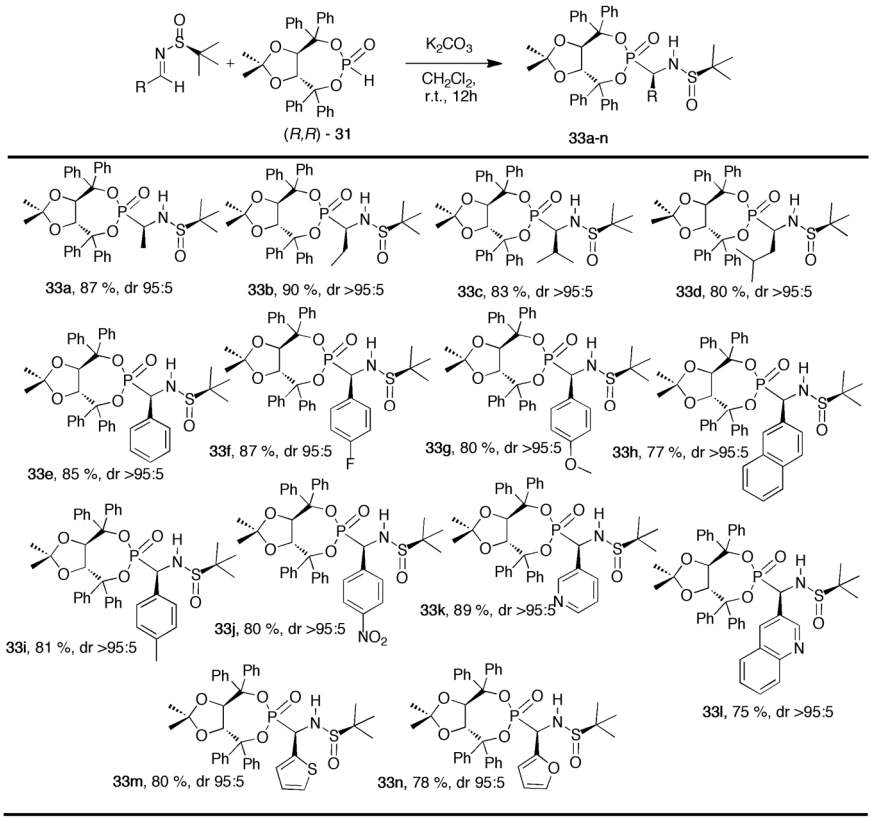



**Figure 5.** X-ray structure of *exo*-**38.**

Finally, we have focused on the asymmetric synthesis of heterocyclic, aromatic and aliphatic *α*-aminomethylphosphonates and phosphonic acids. For that purpose we have applied the mentioned earlier strategy based on diastereoselective hydrophoshonylation of chiral imines with (*R,R*)-TADDOL **31** (Scheme 17).[58] After extensive preliminary experiments it was discovered that very good diastereoselectivity of the hydrophosphonylation process can be obtained when using (*S*)-*N*-tert-butylsulfinyl aldimines and (*R,R*)-TADDOL **31** as chiral phosphorus nucleophile.[71] During optimization of that reaction with the (*S*)-*N*-benzylidene-2-methylpropane-2-sulfinamide, as a model substrate, we have established that reaction performed at room temperature during 12h with the use of $K_2CO_3$ as a base and $CH_2Cl_2$ as solvent gives the best diastereoselectivity and yield of final *α*-aminomethylphosphonate **33e**. Use of other amines such as $Et_3N$, $Cs_2CO_3$, $RbCO_3$ or solvents as THF or $Et_2O$ led to decrease in diastereoselectivy and/or yield of the reaction. Importantly the reaction under the optimized conditions using the (*R*)-enantiomer of *N*-benzylidene-2-methylpropane-2-sulfinamide gave a mixture of diastereoisomers with *dr* 22:78. The $^{31}P$ NMR of that crude reaction mixture showed two signals, which corresponded to the mixture of diastereoisomers with the major signal being shifted upfield contrary to the $^{31}P$ NMR of the reaction with the use of the (*S*)-enantiomer, where the signal of the major diastereoisomer was shifted downfield. With the optimized conditions in hand, a selected range of (*S*)-*N*-tert-butylsulfinyl imines was examined in order to test the scope of the protocol (Scheme 21). For aliphatic aldehydes, the observed diastereoselectivity of the reaction was not influenced by the size of the aliphatic chain. Yields however were slightly lower for branched (S)-*N*-tert-butylsulfinyl imines **33c,d** probably because of the steric hindrance around the reaction centre and the difficulty of the (*R,R*)-**31** to access the C=N bond. Similar conclusions were drawn from the hydrophosphonylation of aromatic (*S*)-*N*-tert-butylsulfinyl imines **33e-j**, in which the diastereoselectivity of the process was only slightly influenced by the substituents present in the aromatic ring. The lowest yield (77%) was observed in the case of (*S*)-2-methyl-*N*-(naphthalen-2-ylmethylene)propane-2-sulfinamide **33h,** the most sterically encumbered substrate. Finally, heterocyclic (*S*)-*N*-tert-butylsulfinyl imines were reacted under optimized reaction conditions with (*R,R*)-**31** and the desired *α*-aminomethylphosphonates **33k-n** were obtained with very good diastereoselectivity and good yields. The presented approach represented the first

application of double asymmetric induction in the synthesis of α-aminomethylphosphonates and phosphonic acids involving the use of enantiomerically pure *N*-tert-butylsulfinyl aldimines and chiral phosphorus nucleophile. Finally, in order to synthesise α-aminomethylphosphonic acids and to establish the absolute configuration of the stereogenic carbon atom, both chiral auxiliaries were simultaneously removed. For that purpose pure diastereomers of α-aminophosphonates **33c,e,f,m** (isolated by simple crystallization) were dissolved in toluene, treated with aqueous 4 M HCl and heated at 100 °C for 6h. After separation of the layers, the aqueous layer containing the desired α-aminomethylphosphonic acids, was concentrated to dryness and the products was crystallized from absolute EtOH/propylene oxide mixture. The specific rotation values obtained for the pure α-aminophosphonic acids **5a-d** were in agreement with the values reported in the literature and indicated in all four cases an (*R*)-configuration at the stereogenic α-carbon attached to the phosphorus (Scheme 22).

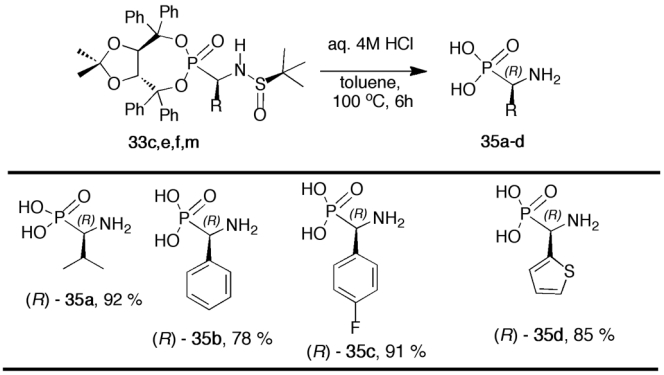



**Scheme 21.** Preparation of α-aminomethylphosphonates **33a-h**.

### 4.2. Asymmetric synthesis of phosphonates and phosphonic acids derivatives of hexahydroquinoxalin-2(1*H*)-one

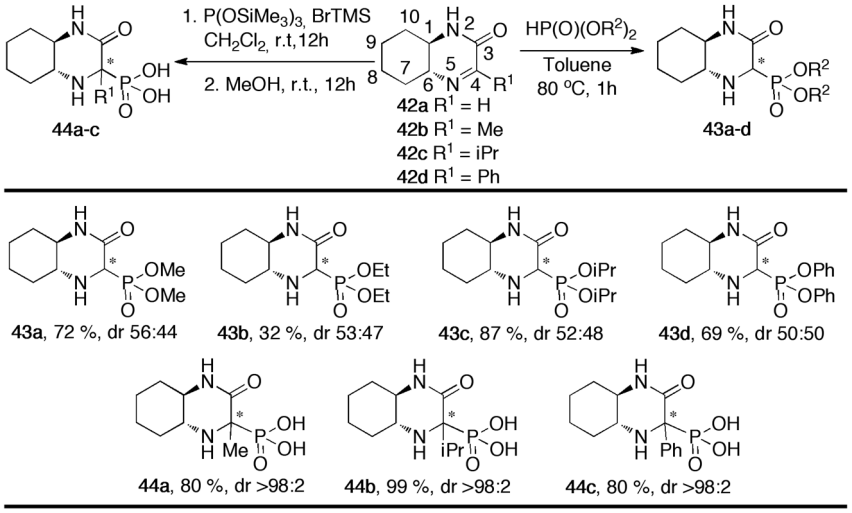
Very recently, we have focused on the preparation of azaheterocyclic phosphonates and phosphonic acids and in particular derivatives of hexahydroquinoxalin-2(1*H*)-one. Those compounds are direct, chiral analogues of quinoxalin-2(1*H*)-ones, well known for their broad pharmacological properties.[71] In our approach we used the classical protocol namely the addition of phosphorus nucleophiles to hexahydroquinoxalin-2(1*H*)-one derived imines **42a-d** (Scheme 23). The imines were conveniently prepared in the reaction of enantiopure (1*R*,2*R*)-1,2-diaminocyclohexane with ethyl glyoxalate (in the case of imine **42a**) or appropriate α-ketoesters (for imines **42b-d**) (Scheme 23). In the case of imine **42a** under optimised

reaction conditions the desired phosphonates **43a-d** (Scheme 23) were obtained in good overall yields albeit with low diastereoselectivity.[72]




**Scheme 22.** Removal of the chiral auxiliaries - synthesis of (*R*)-*α*-aminomethylphosphonic acids **35a-d**.[58]

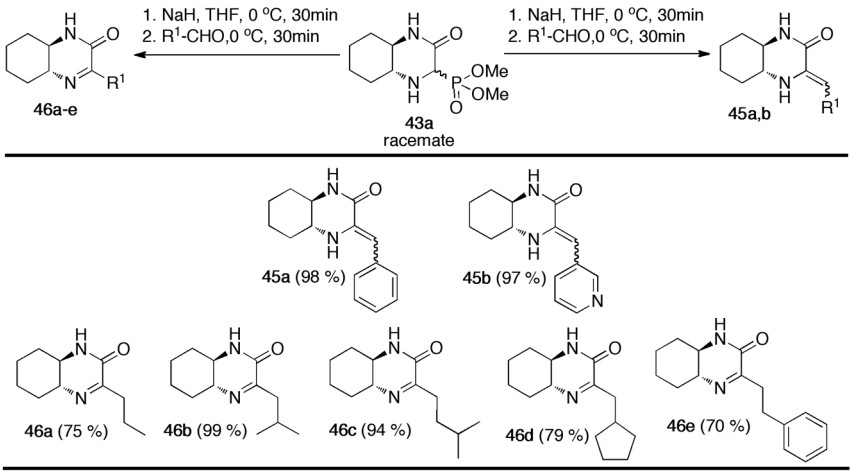
This was assigned to the fact that under the optimized reaction conditions ($Et_3N$, Toluene, 80 °C) the presence of both carbonyl and phosphonate functions rendered the 4-H proton prone to dissociation which led to epimerisation on 4-C in phosphonates **43a-d**. This was confirmed by DFT calculations performed for the reaction of imine **42a** with $HP(O)(OMe)_2$ where the energies of two epimers of **43a** were essentially the same which was in agreement with the observed diastereomeric ratio (*dr* 56:44). It seemed very likely therefore, that the two phosphonate epimers readily interconverted under the reaction conditions and this precluded their formation in high dastereoselectivity via our methodology.[72] To our satisfaction, changing the bicyclic imine **42a** to ketimines **42b-d** and suitable optimization of the reaction conditions resulted in significant improvement of diastereoselectivity of the reaction and allowed us to prepare desired aminophosphonic acids **44a-c**, with tetrasubstituted sterogenic carbon, derivatives of substituted hexahydroquinoxalin-2(1*H*)-ones (Scheme 23).[73]




**Scheme 23.** Synthesis of hexahydroquinoxalin-2(1*H*)-one derived phosphonates **44a-d** and phosphonic acids **45a-c** selected examples.

The aminophosphonic acids **44a-c** were obtained in the reaction of ketimines **42b-d** with tris(trimethylsilyl) phosphite $P(OSiMe_3)_3$, commercially available reagent, performed in $CH_2Cl_2$ at room temperature during 12 h. The silylated esters thus obtained were treated in situ with methanol, as dealkylating agent, at room temperature for additional 12h producing the desired aminophosphonic acids, that were obtained in the form of pure diasteromers after simple recrystallization from methanol. It has to be noted that the reaction required activation of the imines to achieve high yields of the final products. This was done by the use of bromotrimethylsilane (BrTMS) that reacted with the imine forming an iminium cation that was found to be more reactive towards tris(trimethylsilyl) phosphite.[74] The X-ray diffraction analysis of the isolated major epimer of **44a** revealed the *R* configuration on the newly created tetrasubstituted chiral carbon center. It should also be noted that the synthesis of optically active quaternary substituted phosphonic acids attract considerable attention[75] since they can act as scaffolds widely present in pharmaceuticals and biologically active compounds, especially in enzyme inhibitors. In that aspect, addition of phosphorus nucleophiles to ketimines is a classical approach for construction of tetrasubstituted stereogenic centers however, performing this reaction is asymmetric fashion remains problematic. This is due to lower reactivity of ketimines when compared to aldimines and difficulty in enantiofacial discrimination.[76] Thus, our approach to hexahydroquinoxalin-2(1*H*)-one derived phosphonic acids represents and interesting approach to the synthesis of this class of compounds. Additionally, we have demonstrated that such optically pure acids can be easily converted to their phosphonate esters by simple and racemisation free reaction with trimethylsilyldiazomethane ($TMSCHN_2$)[73] thus showing the utility of those compounds for the preparation other useful molecules (Scheme 23).

In the search for further applications of our azaheterocyclic phosphonates **43** we have discovered that **43a** can serve as an excellent source of phosphonate carbanion in the Horner-Wadsworth-Emmons (HWE) reaction allowing for the selective preparation of new bicyclic substituted imines, enamines and amines difficult to obtain by alternative methods (Scheme 24).[72,77]




**Scheme 24.** Application of the heteroclic aminophosphonate **43a** in HWE reaction selected examples.

Our protocol with the use of simple aromatic and heterocyclic aldehydes afforded corresponding enamines **45a,b**. In turn for aliphatic, cyclic and aromatic aldehydes where the carbonyl group is placed on the alkyl chain corresponding imines **46a-e** were formed. In some cases, where a non-separable mixture enamine/imine was formed the crude product was submitted for direct reduction of the double bond with *e.g.* $NaBH_4$ to cleanly produce hexahydroquinoxalin-2(1*H*)-one derived amines.[77] This is especially in the case of use of ketones where non-separable mixture of products was usually obtained and treatment with $NaBH_4$ was necessary to obtain pure nonracemic amines. In summary, our HWE protocol is especially useful in the case of preparation of substituted imines. Other known protocols for the preparation of this class of

hexahydroquinoxalin-2(1*H*)-one derivatives include condensation of cyclohexane-1,2-diamine with pyruvates (the Hinsberg reaction),[78] a methodology using immobilized oxazolones in combination with difunctional nucleophiles,[79] or palladium-catalyzed aminocarbonylation/cyclization synthetic strategy based on the use of carbon monoxide, cyclohexane-1,2-diamine and iodoindoles.[80] Those methods however are limited by not always easy access to wide range of pyruvates,[78] need for preparation in each case of new substituted oxazolone fragment and its subsequent introduction onto the resin,[79] or the need of using metal catalyst and narrow substrates scope.[80] Our protocol therefore represents an interesting alternative to the known methods. The possibility for easy introduction of structural diversity by using simple, inexpensive and commercially available aldehydes can be considered as the key advantage of this approach (Scheme 24).[72,77]

## 5. Conclusion

In this personal account, a plethora of new heterocyclic substituted phosphonates, phosphonic and phosphinic acids synthesised in our laboratory was described. The list includes derivatives of pyridine, thiazole, imidazole, quinoline and bicyclic 2-azanorbornane or hexahydroquinoxalin-2(1*H*)-one derivatives. The leading approach was based on the addition of different phosphorus nucleophiles to the carbon heteroatom bond (usually C=N or C=O bond) present in the heterocyclic fragment. In the case of the preparation of phosphonic acids we observed that heterocyclic derivatives of pyridine-2 and -4, thiazole-2, quinoline-2 and -4 and imidazole-2 were prone to decomposition resulting from C-P bond cleavage under acidic conditions, that are typically used in the synthesis of phosphonic acids from their phosphonate esters. The mechanism of that cleavage was studied in detail. We have circumvented the problems of C-P bond cleavage under acidic conditions by using silylated phosphonate esters as phosphorus nucleophiles. This approach did not require the presence of strong mineral acid and resulted in formation of the desired heterocyclic substituted phosphonic acids in high yields. In order to prepare the heterocyclic phosphonates and phosphonic acids in asymmetric fashion we have developed highly diastereoselective and general protocol based on the use chiral auxiliaries. In the case of asymmetric synthesis of $\alpha$-hydroxy- and $\alpha$-aminomethylphosphonates and phosphonic acids the optically pure (*R,R*)-TADDOL derived *H*-phosphonate was used as chiral auxiliary in the hydrophosphonylation of aldehydes and chiral aldimines. Easy preparation of (*R,R*)-TADDOL derived *H*-phosphonate, high level of asymmetric induction and racemisation free protocol for the removal of the chiral auxiliary are among the advantages of our methodology. Currently, we continue to work in the exciting field of preparation of new heterocyclic phosphonates and phosphonic acids

## Acknowledgements

I wish to thank my teacher and mentor Prof. Bogdan Boduszek for many years of fruitful collaboration and many good advices not only concerning chemistry but also regarding life in general.

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