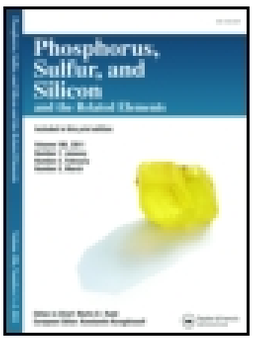

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SHORT COMMUNICATION



# Enantioselective synthesis of functionalized α-aminophosphonic acid derivatives

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**ABSTRACT**

An umpolung process for the enantioselective functionalization of α-aminophosphonates with nucleophiles has been developed. This consists in a formal oxidation of tetrasubstituted α-aminophosphonates to α-iminophosphonates followed by an organocatalyzed nucleophilic addition reaction to the imine bond. The optimal enantioselectivity has been reached by studying the effect of the size of the substituent at the phosphonate. Applications for the preparation of tetrasubstituted α-amino α-cyanophosphonates and α-amino β-nitrophosphonates enantiomerically enriched are reported.

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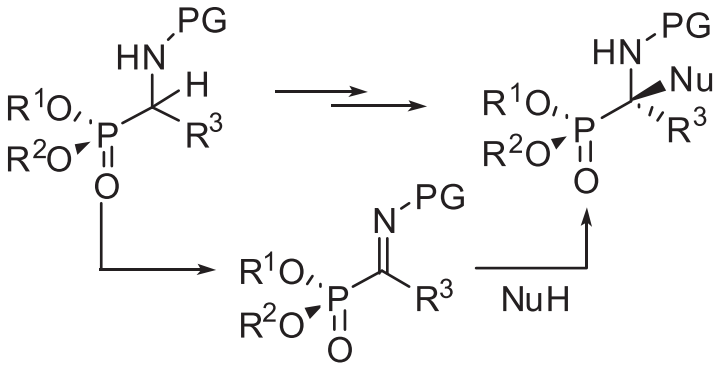
**KEYWORDS**
α-Aminophosphonates; organocatalysis; nucleophilic addition; ketimines; cyanation; aza-Henry

**GRAPHICAL ABSTRACT**




## Introduction

α-Aminophosphonic acids are the structural isosters of α-aminoacids, where the flat carboxylic group has been replaced by a phosphonic acid group, which is tetrahedral and more bulky. Due to this tetrahedral configuration of the phosphorus atom, α-aminophosphonic acid functionality is able to mimic in a stable manner the transition state for the hydrolysis of peptides, and, molecules owing this moiety are able to inhibit enzymes involved in peptide metabolism (Figure 1).[1] Consequently, α-aminophosphonic acid derivatives show important biological activities and, they have found numerous applications in medicine and agrochemistry.[2]

Moreover, the biological activity of drugs in general is known to be strongly dependent on their absolute configuration.[3] This is also true in the case of biologically active α-aminophosphonic acid derivatives. For instance, the *R* enantiomer of phospholeucine is a more potent inhibitor of leucine-peptidase than its *S* isomer[4a] and, from the four possible isomers of the phosphapeptide alaphosphaline, the one with *S*, *R* configuration, shows the more potent antibiotic activity.[4b] In consequence, the enantioselective synthesis of tetrasubstituted α-aminophosphonic acid derivatives has acquired great relevance in organic chemistry during the last few years.[5] α-Aminophosphonic acids are normally prepared from the hydrolysis of their phosphonate esters and, for this reason, a strong effort has been made during the last decades in order to develop efficient synthetic protocols for the enantioselective synthesis of quaternary α-aminophosphonates. From all the available synthetic protocols for the synthesis of enantioenriched α-aminophosphonates, the addition of nucleophile reagents to α-iminophosphonates is the less explored and most challenging route, due to the difficulty for the preparation of α-phosphorated ketimine substrates, that additionally suffer from an extreme instability. In addition, the formation of tetrasubstituted centers from ketimines is complicated by the poor electrophilic character of ketimine group and the additional steric hindrance present on the substrate. Moreover, the enantiotopic faces of ketimine derivatives are not as easily discriminated as those of aldimine derivatives when asymmetric synthesis is sought.[6]

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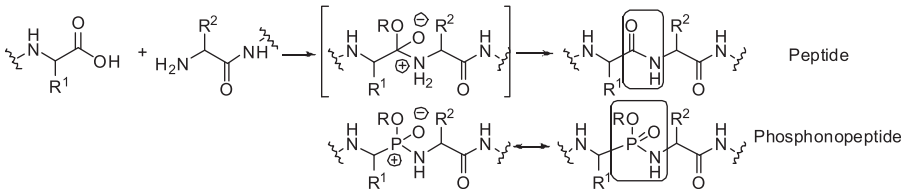
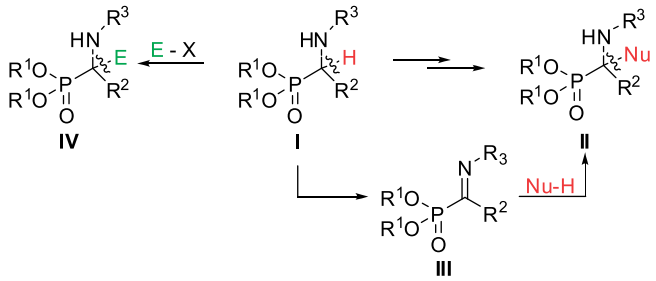



**Figure 1.** Phosphonopeptides are able to mimic the transition state for peptide cleavage.




**Scheme 1.** Global approach for the enantioselective synthesis of tetrasubstituted α-aminophosphonates.

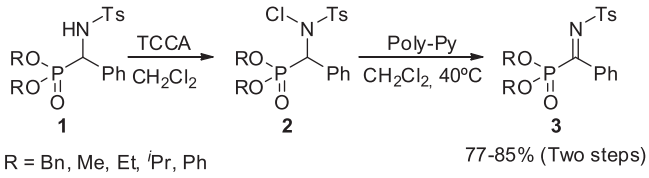
Following with the interest of our research group in the development of new strategies for the preparation of aminophosphorus compounds[7] and, in particular, in the synthesis of enantioenriched α-aminophosphonates,[8] we believed that an enantioselective addition of nucleophiles to α-ketiminophosphonates **III** would be a convenient pathway to access optically active tetrasubstituted α-amino phosphonates **II**.

The preparation of α-ketiminophosphonate substrates **III** might be feasible by oxidation of the parent α-aminophosphonates **I** and, consequently, this synthetic approach could be considered globally as an alternative route for the synthesis of tetrasubstituted α-aminophosphonates **IV** by the substitution of hydrogen in a trisubstituted α-aminophosphonate **I** by a nucleophilic reagent. This approach would be the complementary process ("umpolung reaction")[9] to the electrophilic substitution of trisubstituted α-aminophosphonates[10] (Scheme 1).

## Results and discussion

We reported an efficient synthesis of β,γ-unsaturated α-iminoesters and α-iminophosphonates through an aza-Wittig approach.[11] These imines showed a very assorted reactivity and proved to be very useful intermediates for the synthesis of several α-aminophosphonic acid derivatives.[12] Although quite general, one of the drawbacks of the aza-Wittig methodology is that only *N*-aryl and/or *N*-alkyl phosphazenes can be used for the preparation of *N*-aryl- and/or *N*-alkyl-α-iminophosphonates. Considering the moderate electrophilic character and the additional steric hindrance present in ketimine groups, we were interested in ketimine substrates bearing an electron withdrawing group at the nitrogen. This kind of protecting group would both favor nucleophilic addition to the C=N double bond and allow an easy deprotection of the nitrogen in an ultimate synthetic step.

Construction of a carbon-nitrogen double bond from α-aminophosphonates **1** would imply the introduction of a good leaving group at the α-aminophosphonate skeleton to then promote its elimination with the proper base. According to this, the selective *N*-chlorination reaction can be achieved by treatment of trisubstituted α-aminophosphonates **1** with trichloroisocyanuric acid (TCCA) in dichloromethane (Scheme 2). *N*-Cloro α-aminophosphonates **2** are unstable species and, in order to prevent the dechlorination reaction, they are readily used without purification after elimination of the solid residue by filtration.

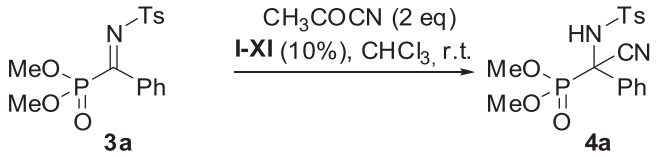



**Scheme 2.** Synthesis of starting α-aminophosphonates **3**.

β-Elimination of HCl in *N*-chloro α-aminophosphonates **2** can be performed using pyridine as a base but, unfortunately, the resulting unstable α-iminophosphonates **3** cannot be separated from pyridine hydrocloride avoiding the hydrolysis of the imine bond. The use of an insoluble base in organic solvents as the promoter of the β-elimination reaction allows the elimination of both the hydrochloride and the excess of base from the reaction solution. Therefore, refluxing overnight the resulting clear solution of *N*-chloro α-aminophosphonate **2** with an excess of poly(4-vinylpyridine) affords pure α-ketiminophosphonates **3** in very good yields after filtration and crystallization from diethyl ether (Scheme 2).

With an efficient protocol in hands for the preparation of α-ketiminophosphonates **3**, next we studied the organocatalytic asymmetric addition of nucleophiles to imines **3**. First we tested the cyanation reaction of α-iminophosphonic acid dimethyl ester **3a** in the presence of 2 equivalents of pyruvonitrile and 1,4-diazabicyclo[2.2.2]octane 5 (DABCO) (Table 1,

**Table 1.** Screening of catalysts.




| Entry | Cat. | Time (h) | %Conv. | %ee |
|---|---|---|---|---|
| 1 | DABCO | 12 | 100 | – |
| 2 | I | 48 | 100 | 17 |
| 3 | II | 48 | 100 | 24 |
| 4 | III | 48 | 100 | 20 |
| 5 | IV | 48 | 100 | 30 |
| 6 | V | 48 | 100 | 14 |
| 7 | VI | 48 | 100 | 36 |
| 8 | X | 48 | 95 | 15 |

Entry 1) and α-cyano α-aminophosphonate **4a** was obtained in full conversion.[13a]

Then, we obviously tested the asymmetric cyanation reaction in the presence of a catalytic quantity of cinchona alkaloid derivatives. Dihydroquinine (**I**) showed a modest enantioselectivity (Table 1, Entry 1) as well as other cinchona alkaloids tested such as cinchonidine (**II**) quinine (**III**), dihydroquinidine (**IV**), cinchonine (**V**) or quinidine (**VI**) (Table 1, Entries 4–7). Moreover, although bifunctional thiourea **X** catalyzed very efficiently the nucleophilic addition of cyanide, no significant enantiomeric excess was observed (Table 1, Entry 8).

Taking the advantage of our new protocol for the preparation of α-ketiminophosphonates **3**, we implemented the analysis of the influence of the phosphorus substituent on the enantioselectivity of the cyanation reaction using *cinchona* alkaloids **II** and **VI** as organocatalysts (Table 2).[13a]

A significant dependence of the enantioselectivity of the reaction was observed for acyclic aliphatic substituents at the phosphonate moiety. The lowest enantiomeric excesses were obtained for dibenzyl phosphonates **3b** (Table 2, Entries 1–2), while slightly higher enantioselectivity was obtained for dimethyl or diethyl phosphonates **3a** and **3c** (Table 2, Entries 3–5). The best results were observed for di-*iso*-propyl phosphonate **3d** (Table 2, Entries 6–7). A special case is the use of diphenyl phosphonates. Curiously, very low asymmetric induction is observed in the cyanation reaction of diphenyl phosphonate **3e** (Table 2, Entry 8). This result may be due to the ability of phenyl ring to adopt a parallel conformation, decreasing the steric crowding at the iminic carbon. The best enantioselectivity was obtained when the cyanation reaction of di-*iso*-propyl phosphonate **3d** was performed using cinchonidine (**II**) as organocatalyst. (Table 2, Entry 6) and this result could be improved to a 92% ee by performing the reaction at lower temperature (Table 2, Entry 9). It should be noted that this reaction can be extended to other aromatic α-iminophosphonates bearing electron donating or electron withdrawing groups with almost equal enantioselectivities.[13a]

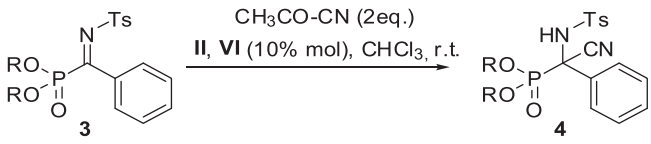
In our pursuit of new synthesis of enantioenriched tetrasubstituted α-aminophosphonic acid derivatives, next we studied the enantioselective aza-Henry reaction of α-iminophosphonate substrates **3.** Initially, the treatment of α-iminophosphonate **3a** with nitromethane, without solvent, in the presence of a catalytic amount of a *Cinchona* alkaloids **I-V** led to a fast formation of α-amino *β*-nitrophosphonates **5a** but, unfortunately, with poor enantioselectivity (Table 3, Entries 1–5).[13b]

However, the use of bifunctional thioureas **VII-X** (Figure 2, *vide supra*) as organocatalysts in the aza-Henry reaction of α-iminophosphonate **3a** α-amino *β*-nitrophosphonate **5a** with increased enantioselectivities (Table 3, Entries 7–10).[13b]

Encouraged by these results, we again implemented the analysis of the influence of the phosphorus substituent in α-iminophosphonate substrates **3** on the enantioselectivity of the aza-Henry reaction using thiourea **IX** (Figure 2). In this reaction an increased enantiomeric excess was observed towards dimethyl phosphonate **3a** when diethyphosphonate **3c** (Table 4, Entry 2) or di-*iso*-propylphosphonate **3d** (Table 4, Entry 3) were used.[13b]

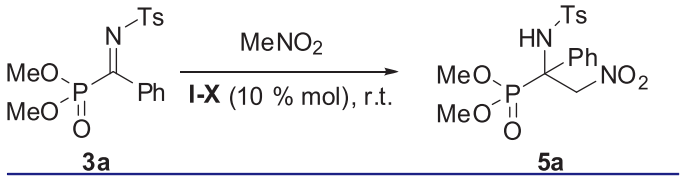
Bearing these results in mind, we thought that better results could be obtained if the aza-Henry reaction was per-

**Table 2.** Influence of the phosphorus substituent in the cyanation reaction of α-iminophosphonates **3**.




| Entry | Comp. | Cat. | R | Temp (°C) | %ee |
|---|---|---|---|---|---|
| 1 | **4b** | **II** | Bn | 25 | 16 |
| 2 | **4b** | **VI** | Bn | 25 | 22 |
| 3 | **4a** | **II** | Me | 25 | 24 |
| 4 | **4a** | **VI** | Me | 25 | 36 |
| 5 | **4c** | **VI** | Et | 25 | 38 |
| 6 | **4d** | **II** | $^{i}$Pr | 25 | 80 |
| 7 | **4d** | **VI** | $^{i}$Pr | 25 | 60 |
| 8 | **4e** | **II** | Ph | 25 | 6 |
| 9 | **4d** | **II** | $^{i}$Pr | −30 | 92 |

**Table 3.** Screening of the catalyst for the aza-Henry reaction of α-iminophosphonate **3a**.




| Entry | Cat. | t (h) | %Conv. | %ee |
|---|---|---|---|---|
| 1 | **I** | 22 | 60 | 12 |
| 2 | **II** | 3 | 95 | 10 |
| 3 | **III** | 3 | 95 | 13 |
| 4 | **IV** | 3 | 100 | 6 |
| 5 | **V** | 3 | 75 | 10 |
| 6 | **VII** | 3 | 95 | 29 |
| 7 | **VIII** | 6 | 100 | 22 |
| 8 | **IX** | 6 | 95 | 27 |
| 90 | **X** | 6 | 95 | 23 |

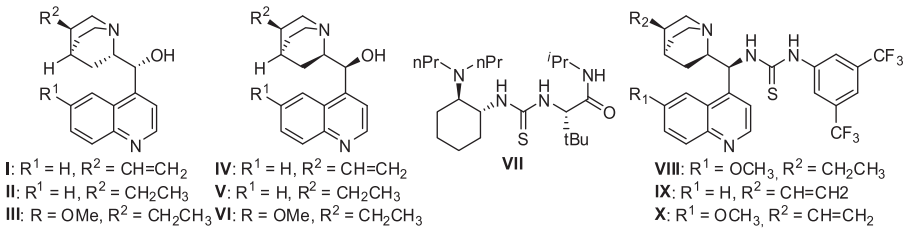
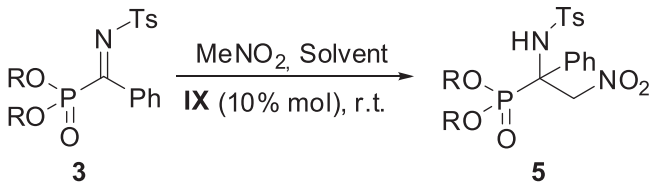



**Figure 2.** Organocatalysts tested in this study.

**Table 4.** Screening of the phosphorus substituent for the aza-Henry reaction of α-iminophosphonates **3**.




| Entry | Comp | R | Solvent | t (h) | %Conv. | %ee |
|---|---|---|---|---|---|---|
| 1 | **5a** | **Me** | **No** | 24 | 95 | 27 |
| 2 | **5c** | **Et** | **No** | 6 | 100 | 30 |
| 3 | **5d** | **$^{i}$Pr** | **No** | 24 | 95 | 45 |
| 4 | **5d** | **$^{i}$Pr** | **$CH_2Cl_2$** | 24 | 90 | 68 |
| 5 | **5d** | **$^{i}$Pr** | **$CHCl_3$** | 36 | 95 | 67 |
| 6 | **5d** | **$^{i}$Pr** | **Toluene** | 36 | 100 | 80 |

formed under solvation conditions. An inverse dependence of the enantioselectivity into the polarity of the solvent is observed if non coordinating solvents are used (Table 4, Entries 4-5). This dependence probably arises from a diminishing in the difference of the energy of activation for the formation of the two enantiomers due to a stabilization of both possible diastereomeric transition states in a polar solvent, rational for reactions with ionic transition states. An optimal enantiomeric excess of 80% was obtained when the reaction was performed at room temperature in toluene. As in the case of the cyanation reaction this process can be extended to other aromatic α-iminophosphonates bearing electron donating or electron withdrawing groups with almost equal enantioselectivities.[13b]

## Conclusions

The enantioselective functionalization of α-aminophosphonates with nucleophiles has been achieved through an umpolung process consisting in the oxidation of tetrasubstituted α-aminophosphonates to α-iminophosphonates followed by the organocatalyzed addition of nucleophile reagents such as cyanide and nitromethane.

## Acknowledgments

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