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A practical and efficient green synthesis of β -aminophosphoryl compounds via the aza-Michael reaction in water

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ABSTRACT

Biphasic systems room temperature imidazolium ionic liquid (RTIL)/water or water as a solvent significantly accelerate the addition of amines to vinylphosphoryl compounds hence opening green and effective synthesis of β -aminophosphoryl compounds in excellent yields over short reaction times. The application of water, being the cheapest and most non-toxic solvent, without any catalyst or co-solvent, is more advantageous as it provides a simple isolation procedure for products having high purity (> 95% according to the NMR data) via simple freeze-drying and does not require extraction with organic solvents. The solubility of the starting phosphorus substrate in water does not play crucial role in the reaction as it was demonstrated using water insoluble diphenylvinylphosphine oxide. In contrast to typical procedures, using a reactant ratio (vinylphosphoryl compound: amine) of 2:1 readily resulted in double phosphorylation of primary amines, including polyamines, in water.

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1. Introduction

It is well known that both natural and synthetic aminophosphonic acid derivatives, being the analogues of amino acids and competing with them for the active sites of enzymes, possess high and diverse biological activities [1]. The type of the activity and the potency of the compound depend both on the linker length and the surroundings at the phosphorus and nitrogen atoms. Among these compounds, derivatives of β -aminophosphonic acid, first isolated from *Ciliate protozoa* by Horiguchi and Kandatsu [2] in 1959, are of great importance. They demonstrate diverse biochemical properties such as antibacterial, anti-HIV and protease-inhibiting activities [3] and possess complexing properties which are advantageous for selective ionophores or membrane carrier design [3b].

One of the main approaches for C–N bond formation allowing the preparation of a variety of β -aminocarbonyl compounds and their analogues, possessing biological activity and useful as intermediates in the synthesis of β -amino alcohols, amino acids, lactams, and so on, is based on the aza-Michael reaction, namely the addition of amines to unsaturated compounds with activated double bond [4]. In the organophosphorus area, the similar approach using vinylphosphonates as the starting substrates and yielding β -aminophosphonates was firstly applied by A.N. Pudovik in 1951 [5]. The further works based on the above methodology [1,3,6] provided a wide range of β -aminophosphonates including quaternary β -amino-phosphonates which are useful as synthetic nonviral vector-mediated gene transfer agents [6c], those bearing perfluoroalkyl groups [6d], and phosphorylated analogues of putrescine and spermidine [6e], etc. Similarly, β -aminophosphine oxides exhibit coordination properties towards a variety of metals [7] and enantiopure compounds of such a type were used as ligands for ruthenium-assisted enantioselective transfer hydrogenation of

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ketones [8]. Moreover, β -aminophosphine oxides are useful building-blocks in the synthesis of the corresponding P,N-ligands bearing phosphine donor moieties [9,10].

In any case, the typical reaction conditions for the aza-Michael synthesis comprise application of amine excess (either neat or in combination with solvent), basic catalysts such as EtONa or metal sodium, require elevated temperatures and prolonged reaction times, and hence do not avoid the polymerization of the starting vinyl substrates, decreasing the yields of the desired products. The substantial acceleration of amine addition to diphenylvinylphosphine oxide was observed in MeOH as a protic solvent [10]. The authors postulated that reactions must involve charged intermediate which presumable is stabilized and the protonation step is accelerated in the presence of a proton source such as the above solvent or amine hydrochloride.

Recently, it was demonstrated that the conjugate addition of N-nucleophiles to unsaturated compounds $R-CH=CH_2$ ($R=CO_2Et$, $C(O)Me$, CN) proceeds readily at room temperature in imidazolium ionic liquids (ILs) [11], biphasic systems IL/water [12] or in water without any catalyst [13] and results in the final β -aminoderivatives in the yields close to the quantitative ones. However, in the so-called “phosphorus version,” before the beginning of our works, such attempts to optimize the synthesis of β -aminophosphoryl compounds using ILs or water as alternative solvents promoting a reaction, were still limited only by the synthesis of enantiopure β -aminophosphine oxide ligands via the reaction of diphenyl- and (*R*)-*tert*-butylphenyl-phosphine oxide with 5–10 molar excess of the (*R*)- or (*S*)-1-phenylethylamine enantiomer in water (closed ampoule, 110 °C, 7 days) [8].

Taking into account these data, it seems reasonable to estimate the possibility to use ionic liquids, their combination with water, or water as suitable solvents for the ‘green’ and effective synthesis of β -aminophosphoryl compounds. Herein, we report the results of this study and suggest an optimized, very simple and high yielding procedure for β -aminophosphonates or β -aminophosphine oxides preparation in water without any catalyst or organic co-solvent and using stoichiometrical amounts of the reactants, and describe the scopes and limitations of these reactions.

2. Results and discussion

With regard to higher nucleophilicity of amines in ionic liquids comparing with common organic solvents [14] along with successful application of ILs as a promoting medium for the aza-Michael reaction of non-phosphorus substrates, we estimated the possibility to use such a medium in the synthesis of β -aminophosphoryl compounds. Diethyl vinylphosphonate **1** or diphenylvinylphosphine oxide **2** were used as representative starting substrates and morpholine and butylamine as N-nucleophile (Table 1). The difference in chemical shifts of the phosphorus substrate (17.2 ppm and 24.3 ppm for **1** and **2**, respectively) and the product (ca. 30–31 ppm) allows easy monitoring of the reaction course by ^{31}P NMR spectroscopy.

In the absence of catalyst, the reaction of **1** with amines does not proceed in chloroform solution (Table 1, entries

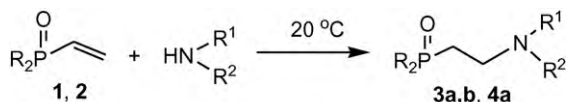
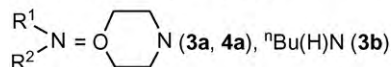
1,10). Here, ^{31}P and 1H NMR spectra of reaction mixtures revealed the presence of the starting reactants in the absence of any side products. To our surprise, in contrast to the reported data concerning the acceleration of the aza-Michael addition for non-phosphorus activated alkenes [11], the reactions at room temperature in ILs were too sluggish (Table 1, entries 5, 7, 13, 15, 17) or even do not proceed at all, as in the case of vinylphosphonate **1** in 1-hexyl-3-methylimidazolium bromide ([hmim]Br) (Table 1, entry 2). At the same time, addition of water to ionic liquid, i.e. using the mixture IL/ H_2O in 1:2 ratio (by weight), resulted in a drastic increase of the reaction rate and both counterions of the ionic liquids affected the effectivity of such systems. Thus, in the case of diethyl vinylphosphonate **1**, the reaction with morpholine completed over 45 min in the system [bmim]Br/ H_2O while the yield of the same product was only 82% upon using the system based on [hmim]Br (Table 1, entries 4 and 3, respectively). Introduction of hydrophobic counteranions in the IL structure resulted in a significant decrease of the reaction rate in the case of **1** and the yields of 2-morpholine-ethylphosphonate **3a** were 60% and 55% for biphasic systems [bmim]PF₆/ H_2O and [bmim]BF₄/ H_2O , respectively (Table 1, entries 8 and 6). Primary butylamine was less reactive and provided 81% of the corresponding β -aminophosphonate **3b** over 45 min in the best system [bmim]Br/ H_2O (Table 1, entry 11).

Under other conditions being equal, the rate of the amine addition to diphenylvinylphosphine oxide **2** possessing poor water-solubility, was lower comparing with that for the water soluble phosphonate analogue **1**. Moreover, the effect of the IL nature on the addition rate was different ([bmim]BF₄/ H_2O > [bmim]Br/ H_2O > [bmim]PF₆/ H_2O), and the reaction proceeded faster in the system [bmim]BF₄/ H_2O . As electronic factors for these compounds are close to each other (σ^P is 0.965 and 0.955 for Ph₂P(O) and (EtO)₂P(O) groups, respectively [15]) and steric factors should not interfere the reaction, one may assume that the influence of the phosphorus substrate structure on the reaction rate is apparently connected with specific solvation of the latter in the mixed solvent in use.

Despite mild reaction conditions which provided high product yields, the main drawback of such biphasic systems is connected with substantial loss of the target β -aminophosphoryl compounds over the isolation procedure, i.e., extraction with organic solvents such as diethyl ether or toluene. At the same time, in water as a sole media without any co-solvent or catalyst addition of both morpholine and butylamine to diethyl vinylphosphonate **1** proceeds with the reaction rate commensurable with that observed in the optimal biphasic system [bmim]Br/ H_2O . Moreover, after completion of the reaction, the simple lyophilization provided the final β -aminophosphonates with the yields close to the quantitative ones and of high purity (> 95% according to 1H and ^{31}P NMR data). Even in the case of diphenylvinylphosphine oxide **2**, for which the rate of the aza-Michael addition in water at room temperature is significantly lower comparing with that in the presence of ionic liquid (the system [bmim]BF₄/ H_2O), the possibility of simple isolation of the product without loss makes up the deficiency.

Table 1

Influence of the reaction media on the rate of the aza-Michael reaction for vinylphosphoryl compounds.

R = OEt (**1**, **3a,b**), Ph (**2**, **4a**)

Entry	Phosphorus substrate	Amine	Reaction media	Reaction time	Yield (%) ^a
1	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	CHCl ₃	24 h	0
2	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[hmim]Br	45 min	0
3	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[hmim]Br/H ₂ O	45 min	82
4	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[bmim]Br/H ₂ O	45 min	100
5	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[bmim]BF ₄	45 min	9
6	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[bmim]BF ₄ /H ₂ O	45 min	55
7	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[bmim]PF ₆	45 min	2.5
8	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	[bmim]PF ₆ /H ₂ O	45 min	60
9	(EtO) ₂ P(O)CH=CH ₂ (1)	Morpholine	H ₂ O	45 min	100
10	(EtO) ₂ P(O)CH=CH ₂ (1)	BuNH ₂	CHCl ₃	24 h	0
11	(EtO) ₂ P(O)CH=CH ₂ (1)	BuNH ₂	[bmim]Br/H ₂ O	45 min	81
12	(EtO) ₂ P(O)CH=CH ₂ (1)	BuNH ₂	H ₂ O	45 min	79
13	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	[hmim]Br	45 min	4
14	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	[hmim]Br/H ₂ O	45 min	30
15	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	[bmim]BF ₄	45 min	5
16	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	[bmim]BF ₄ /H ₂ O	45 min	45
17	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	[bmim]PF ₆	45 min	4
18	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	[bmim]PF ₆ /H ₂ O	45 min	5
19	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	H ₂ O	45 min	8
20	Ph ₂ P(O)CH=CH ₂ (2)	Morpholine	H ₂ O	36 h	100

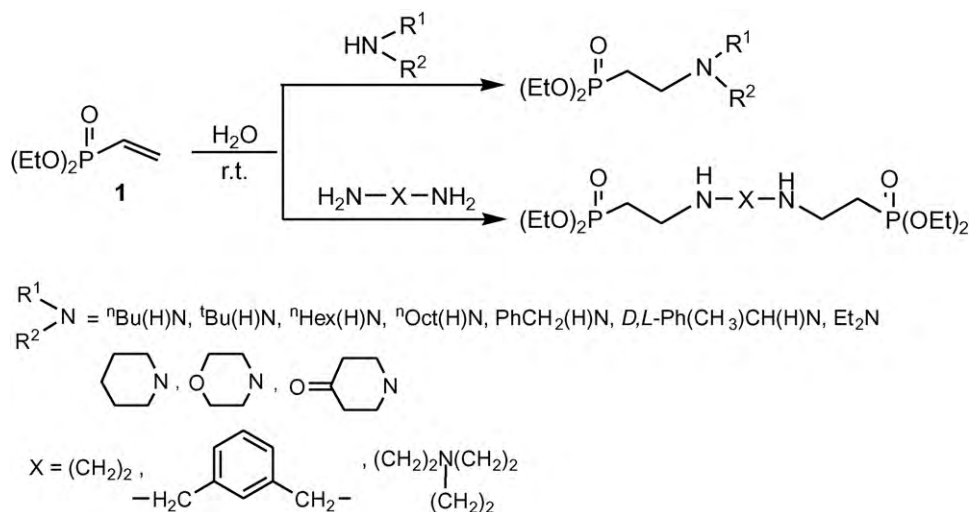
^a Yield according to ³¹P NMR spectroscopy.

Therefore, we have moved our attention to the application of water as a solvent without any additives for such transformations. It was demonstrated that various primary and secondary alkylamines add smoothly to vinylphosphoryl compounds in water at room temperature, at that the reaction proceeds rapidly in the case of diethyl vinylphosphonate **1** (generally from 45 mins to 3 h) [16] and takes more time for the corresponding unsaturated phosphine oxide **2**. Indeed, the latter is not soluble in water, i.e. in this case we use so called 'on-water' method according the definition of Sharpless et al. who demonstrated that the low miscibility or solubility of organic compounds in water is not detrimental for their high reactivity in the presence of water [17]. Hence, the higher rate of the aza-Michael reaction in the case of vinylphosphine oxide **2** in biphasic systems IL/H₂O compared with that in pure water is obviously connected with phase transfer properties of onium salts.

The detailed investigation of the aza-Michael addition has revealed that both the nucleophilic and steric properties of the amine influence on the reaction rate which decreased in the series: Alk₂NH > AlkNH₂ > ArCH₂NH₂ for both phosphorus substrates and with an increase in the bulkiness of the substituents on the nitrogen atom of the amine. Among secondary amines, cyclic piperidine was more active than morpholine whose reactivity was comparable with that of piperid-4-one. Elongation of the alkyl chain in the alkylamine resulted in a

decrease in reactivity. However, aromatic amines do not enter the reaction possibly due to a decrease in their nucleophilic properties. If more than one amine functionality was present in the starting reactant, addition to vinylphosphonate in water proceeded readily with participation of all the amine functionalities.

Thus, in the case of water soluble vinylphosphonate **1**, the reaction with piperidine was complete (quantitative) just in 7 min at room temperature while the yields of the corresponding β-aminophosphonates obtained using diethylamine, morpholine, *n*-butylamine and *tert*-butylamine over the same period of time were 73%, 50%, 25% and 5% [16]. After 45 min, the reaction was complete for morpholine, Et₂NH and *n*-BuNH₂, but for sterically hindered *tert*-butylamine the yield of the final addition product was 78% even after 70 h at r.t. Elongation of the alkyl chain in the alkylamine resulted in a decrease in reactivity and at room temperature long-chain aliphatic dialkylamines (> C₈) did not react with vinylphosphonate **1** in water. As mentioned above, in the absence of water even active amines such as diethylamine did not add to vinylphosphonate **1** at room temperature over long reaction times. However, more prolonged reaction time provided complete conversion under ambient conditions in all the above cases, including the reactions with ethylenediamine, *meta*-xylylenediamine and tris(2-aminoethyl)amine which resulted in bis(aminophosphonates) and tris(aminophosphonate) (Scheme 1) [16].

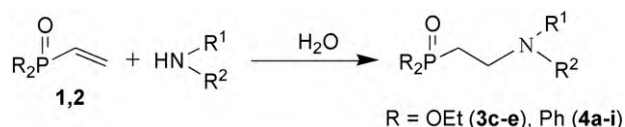


Scheme 1.

For water insoluble vinylphosphine oxide **2**, the reactions with these amines usually required the stirring of the reaction mixtures for a few days, excluding that with 40% aq. Me_2NH (without additional dilution with water) which proceeded with exothermic effect and afforded vinylphosphine oxide **4c** in quantitative yield over *ca* 15 min. Fortunately, no side reactions were observed if reactions of vinylphosphoryl compounds **1,2** with amines

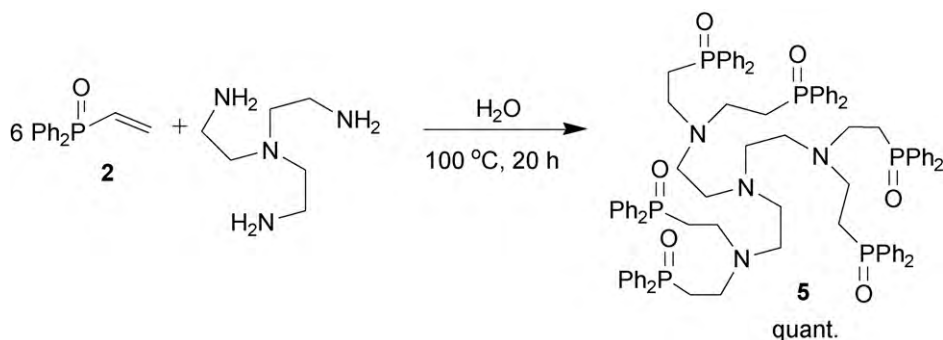
were performed at reflux. Therefore, elevated temperatures could be used to reduce the reaction time. Indeed, at 100 °C the reactions of phosphonate **1** with benzylamine and $\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)_3$ were complete in 45 min (contrast with 24 h and 20 h, respectively, at room temperature), while for less reactive ${}^t\text{BuNH}_2$ and $\text{PhCH}(\text{CH}_3)\text{NH}_2$ about 3 h were required to afford the quantitative conversion [16]. Performing reactions at reflux was especially

Table 2
Influence of reaction temperature on the rate of the aza-Michael addition in water.



Entry	R	Amine	Product	Temperature, °C	Time	Yield, % ^a
2	EtO	PhCH_2NH_2	3c	100	45 min	100 [16]
3	EtO	$L\text{-}(-)\text{-PhCH}(\text{CH}_3)\text{NH}_2$	<i>L</i> - 3d	100	3 h	100 [16]
4	EtO	$\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)_3$	3e	100	45 min	100 [16]
5	Ph		4a	100	30 min	100
6	Ph		4b	20	45 min	52
7	Ph	Me_2NH	4c	20	15 min	100
8	Ph	Et_2NH	4d	100	30 min	100
9	Ph	${}^n\text{HexNH}_2$	4e	100	5 h	100
10	Ph	${}^n\text{OctNH}_2$	4f	100	5 h	100
11	Ph	$L\text{-}(-)\text{-PhCH}(\text{CH}_3)\text{NH}_2$	<i>L</i> - 4g	100	5 h	100
12	Ph		4h	100	3 h	100
13	Ph	$\text{N}(\text{CH}_2\text{CH}_2\text{NH}_2)_3$	4i	100	45 min 3 h	75 100

^a Yield according to ${}^{31}\text{P}$ NMR spectroscopy.



Scheme 2.

advantageous in the case of vinylphosphine oxide **2** and under these conditions addition of more reactive secondary amines such as piperidine, morpholine and diethylamine completed at the most of 30 min or over a few hours for other N-nucleophiles. The difference in reactivity of phosphorus unsaturated compounds **1** and **2** was evident even at reflux. Thus, at 100 °C, the reaction of phosphine oxide **2** with *L*(-)-phenylethylamine and N(CH₂CH₂NH₂)₃ completed over 5 h and 3 h, respectively (vs. 3 h and 45 mins for compound **1** [16]) (Table 2).

When the starting reactants were used in the ratio 1:1, only mono adducts were formed in the case of primary amines and no traces of the corresponding bis-addition products were observed. However, use of the reactants in the ratio R₂P(O)CH=CH₂/amine = 2:1 allowed double phosphonoethylation of primary amines in water. It should be emphasized that for non-phosphorylated activated alkenes, double addition to primary amines was not observed in water as a reaction media [13]. To the best of our knowledge, no examples of such double phosphonoethylation have been observed previously under common reaction conditions for diethylvinylphosphonate **1**. For diphenylvinylphosphine oxide **2**, double addition to primary amines was performed previously under severe conditions in the reaction with methylamine (as step-by-step synthesis, i.e. 10 mol eq. of aq.MeNH₂, 1 h, 20–25 °C, followed by distillation, 76% yield; then addition of **2** (1 eq.), DMSO/H₂O, 100 °C, 3 h, 81%) [7], octylamine (neat, catalyst octylamine hydrochloride, 180 °C, 3 h) [18] or a series of C3–C6-alkyl amines (R = ⁿPr, ⁱPr, ⁿBu, ^sBu, ^tBu; sealed tube, MeOH, 80 °C, 8–24 h, or without solvent in the presence of amine hydrochloride as a catalyst, 140 °C, 4 h) [10].

At the same time, in water we succeeded in obtaining the corresponding oligo-phosphonates in excellent yields using *n*-butylamine, ethylenediamine, *m*-xylylenediamine, and tris(2-aminoethyl)amine either under ambient conditions or at reflux [16]. Despite the lower reactivity of phosphine oxide **2** compared with phosphonate **1** in water, the double addition products with phosphine oxide groups can be also obtained in the yields close to the quantitative ones as it was illustrated for the reaction with *tris*-amine as a representative example (Scheme 2). According to ³¹P NMR monitoring, the reaction proceeded via a stepwise process giving firstly the compound **4i** bearing three phosphine oxide groups. Over 5 h phosphine oxide **5** was

formed in ca.80% yield, but for complete conversion 20 h were necessary.

Although the rate of the aza-Michael addition in water for vinylphosphoryl compounds is a little lower than that for α,β-unsaturated carbocyclic acid esters, nitriles or amides [13], it proceeds much faster comparing with the known procedures for the synthesis of β-aminophosphoryl compounds and provide higher yields of the desired products. Double phosphorylation of primary amines also proceeds much faster in water compared with MeOH [10] and does not require application of an additional catalyst such as amine hydrochloride.

It seems reasonable that acceleration of the aza-Michael addition in ionic liquids in the presence of water or in water alone is promoted by both hydrogen bond formation between the H-atom of water with the oxygen atom of the phosphoryl moiety increasing the electrophilic character of the β-carbon atom and that between the H-atom of the amine with the oxygen atom of water resulting in increased amine nucleophilic properties.

3. Conclusion

To conclude the results presented, water being the cheapest and most non-toxic solvent known also as a 'nature solvent' significantly accelerates the aza-Michael reaction for vinylphosphoryl compounds, even those which are insoluble in water. The synthetic and isolation procedures are extremely simple and reaction rates are very high compared with typical toxic or flammable organic solvents. The reactions can be performed either under ambient conditions or at reflux. Elevated temperatures do not cause any detrimental effect on the purity of the final product. The reactions in water allow one to introduce either one or two phosphorylethyl moieties to the nitrogen atom in the case of primary amines and to use all reactive NH-functions in polyamine matrices. Such an effective, cheap and green approach opens wide possibilities to prepare a variety of biologically active substances, complexing agents or molecular sensors. In general, the reported approach to β-aminophosphoryl compounds being wide in scope, resulted in high yields without any by-products, proceeded in a benign solvent under simple reaction conditions with readily available starting materials, satisfies the stringent criteria for classification it as a click reaction [19].

4. Experimental part

4.1. General remarks

NMR spectra were recorded with a Bruker AMX-400 spectrometer (^1H , 400, ^{31}P , 121 and ^{13}C , 101 MHz) using residual proton signals of deuterated solvent as an internal standard (^1H , ^{13}C) and H_3PO_4 (^{31}P) as an external standard. The ^{13}C NMR spectra were registered using the JMODECHO mode; the signals for the C atom bearing odd and even numbers of protons have opposite polarities. IR spectra were recorded in KBr pellets on a Fourier-spectrometer “Magna-IR750” (Nicolet), resolution 2 cm^{-1} , 128 scans. Melting points were uncorrected.

The starting diphenylvinylphosphine oxide **2** was obtained by the known procedure including interaction of 2-(diphenylphosphinyl)ethanol with phosphoric trichloride in the presence of triethylamine as reported in ref. [19]. Other reactants were purchased from Aldrich and used without further purification.

Physicochemical constants and spectral data of the known compounds **3a,b** [6b], **3c–e** [16], **4a,b** [20], **4c** [21], and **L-4 g** [22] fit well the literature data.

4.1.1. The aza-Michael reaction in ionic liquids and ionic liquid/water systems

In a typical experiment, to a solution of the amine (1 mmol) (Table 1) in ionic liquid (0.5 g) or biphasic system ionic liquid (0.5 g)/water (1 ml) was added 1 mmol of diethyl vinylphosphonate or diphenylvinylphosphine oxide. The mixture was stirred at room temperature over the time mentioned in the Table 1. The aliquots were taken off and analyzed by ^{31}P NMR. For isolation, the reaction solutions were extracted twice with CH_2Cl_2 . Combine extract was dried over Na_2SO_4 . After evaporation of the solvent under reduced pressure, the product was separated from the residual amount of the corresponding ionic liquid (in the case of [hmim]Br and [bmim]Br) by column chromatography (SiO_2 , CHCl_3 : methanol, 100:2). The yields of β -aminophosphoryl compounds after workup range from 65 to 72%.

4.1.2. General procedure for β -aminophosphoryl compounds synthesis via the aza-Michael reaction in water

To a solution of the amine (1 mmol) in water (2 ml) at room temperature was added the appropriate stoichiometric amount of diethyl vinylphosphonate **1** or diphenylvinylphosphine oxide **2**. The mixture was stirred over the time mentioned in the Table 2 either at room temperature or at reflux. Lyophilisation of the reaction mixture afforded the crude final product with purity > 95% according to NMR data. If desired, further purification could be performed via recrystallization from EtOAc for 2-(amino)ethylphosphine oxides **4a–i**, **5**. For the experimental details for the synthesis of β -aminophosphonates see [16].

4.1.2.1. *N*-[2-(Diphenylphosphinyl)ethyl]diethylamine

(**4d**). Yield 96% (after freeze-drying), off-white solid, m.p. 55°C [$55\text{--}56^\circ\text{C}$ (cyclohexane)]. ^{31}P NMR (CDCl_3): δ 31.35. Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{NOP}$: C, 71.33; H, 8.03; N, 4.65; P, 9.83. Found: C, 71.33; H, 7.95; N, 4.61; P, 10.28%.

4.1.2.2. *N*-[2-(Diphenylphosphinyl)ethyl]hexylamine

(**4e**). Yield 95% (after freeze-drying), off-white solid, m.p. 69°C . ^{31}P NMR (CDCl_3): δ 31.35. ^1H NMR (CDCl_3): δ 0.83 (t, $^3J_{\text{HH}} = 6.5\text{ Hz}$, 3H, CH_3), 1.21 (br. s, 6H, 3CH_2), 1.34–1.39 (m, 2H, CH_2), 2.06 (br. s, 1H, NH), 2.47–2.53 (m, 4H, P- CH_2 and NH- $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 2.92 (dt, $^3J_{\text{PH}} = 10.8\text{ Hz}$, $^3J_{\text{HH}} = 7.6\text{ Hz}$, 2H, P $\text{CH}_2\text{CH}_2\text{N}$), 7.41–7.50, 7.65–7.73 (all m, 6H + 4H, C_6H_5). ^{13}C NMR (CDCl_3): δ 13.74 (s, CH_3), 22.24 (s, CH_2CH_3), 26.60 (s, $\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 29.53 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 29.97 (d, $^1J_{\text{PC}} = 70.8\text{ Hz}$, P- CH_2), 31.38 (s, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 42.56 (s, NH- $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 49.39 (s, NH- $\text{CH}_2\text{--CH}_2\text{--P}$), 128.37 (d, $^3J_{\text{PC}} = 11.6$, *meta*- $\text{C}_6\text{H}_5\text{--P}$), 130.36 (d, $^2J_{\text{PC}} = 9.4\text{ Hz}$, *ortho*- $\text{C}_6\text{H}_5\text{--P}$), 131.47 (d, $^4J_{\text{PC}} = 2.6\text{ Hz}$, *para*- $\text{C}_6\text{H}_5\text{--P}$), 132.66 (d, $^1J_{\text{PC}} = 98.9\text{ Hz}$, *ipso*-C). IR (KBr; ν , cm^{-1}): 1176 (P=O). Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{NOP}$: C, 72.92; H, 8.57; N, 4.25. Found: C, 72.88; H, 8.69; N, 4.17%.

4.1.2.3. *N*-[2-(Diphenylphosphinyl)ethyl]octylamine

(**4f**). Yield 96% (after freeze-drying), off-white solid, m.p. 35°C . ^{31}P NMR (CDCl_3): δ 31.33. ^1H NMR (CDCl_3): δ 0.84 (t, $^3J_{\text{HH}} = 6.2\text{ Hz}$, 3H, CH_3), 1.21 (br. s, 10H, 5CH_2), 1.78 (br. s, 2H, CH_2), 2.48–2.54 (m, 4H, P- CH_2 and NH- $\text{CH}_2(\text{CH}_2)_6\text{CH}_3$), 2.89–2.96 (m, P $\text{CH}_2\text{CH}_2\text{N}$), 7.43–7.49, 7.66–7.74 (all m, 6H + 4H, C_6H_5). ^{13}C NMR (CDCl_3): δ 13.88 (s, CH_3), 22.44 (s, CH_2CH_3), 27.06 (s, $\text{CH}_2(\text{CH}_2)_5\text{CH}_3$), 29.01 (s, $\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 29.26 (s, $\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 29.66 (s, $\text{CH}_2(\text{CH}_2)_4\text{CH}_3$), 30.08 (d, $^1J_{\text{PC}} = 71.1\text{ Hz}$, P- CH_2), 31.61 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 42.69 (s, NH- $\text{CH}_2(\text{CH}_2)_6\text{CH}_3$), 49.50 (s, NH- $\text{CH}_2\text{--CH}_2\text{--P}$), 128.50 (d, $^3J_{\text{PC}} = 11.7$, *meta*- $\text{C}_6\text{H}_5\text{--P}$), 130.52 (d, $^2J_{\text{PC}} = 9.2\text{ Hz}$, *ortho*- $\text{C}_6\text{H}_5\text{--P}$), 131.61 (d, $^4J_{\text{PC}} = 2.6\text{ Hz}$, *para*- $\text{C}_6\text{H}_5\text{--P}$), 132.81 (d, $^1J_{\text{PC}} = 99.0\text{ Hz}$, *ipso*-C). IR (KBr; ν , cm^{-1}): 1179 (P=O). Anal. Calcd for $\text{C}_{22}\text{H}_{32}\text{NOP} \cdot 0.3\text{H}_2\text{O}$: C, 72.70; H, 9.06; N, 3.85. Found: C, 72.50; H, 8.98; N, 3.54%.

4.1.2.4. *N*-[2-(Diphenylphosphinyl)ethyl]benzenemethanamine

(**4h**). Yield 98% (after freeze-drying), pale yellow oil. ^{31}P NMR (CDCl_3): δ 31.18. ^1H NMR (CDCl_3): δ 2.52 (dt, $^2J_{\text{PH}} = 10.8\text{ Hz}$, $^3J_{\text{HH}} = 7.4\text{ Hz}$, 2H, P CH_2), 2.95 (dt, $^3J_{\text{PH}} = 8.2\text{ Hz}$, $^3J_{\text{HH}} = 7.4\text{ Hz}$, 2H, N $\text{CH}_2\text{CH}_2\text{P}$), 3.81 (2H, $\text{C}_5\text{H}_4\text{N--CH}_2\text{N}$), 7.05–7.08, 7.17–7.21 (both m, 1H + 1H, $\text{C}_5\text{H}_4\text{N}$), 7.40–7.47 (m, 6H, C_6H_5), 7.51–7.55 (m, 1H, $\text{C}_5\text{H}_4\text{N}$), 7.66–7.70 (m, 4H, C_6H_5), 8.45 (br. s, 1H, $\text{C}_5\text{H}_4\text{N}$). ^{13}C NMR (CDCl_3): δ 29.70 (d, $^1J_{\text{PC}} = 71.0\text{ Hz}$, P CH_2), 41.86 (s, N $\text{CH}_2\text{CH}_2\text{P}$), 54.08 (s, $\text{C}_5\text{H}_4\text{NCH}_2\text{N}$), 121.28 (s, C^2), 121.49 (s, C^4), 128.03 (d, $^3J_{\text{PC}} = 11.7\text{ Hz}$, *meta*- $\text{C}_6\text{H}_5\text{P}$), 130.01 (d, $^2J_{\text{PC}} = 9.5\text{ Hz}$, *ortho*- $\text{C}_6\text{H}_5\text{P}$), 132.32 (d, $^4J_{\text{PC}} = 2.6\text{ Hz}$, *para*- $\text{C}_6\text{H}_5\text{P}$), 135.79 (s, C^3), 148.49 (s, C^5), 158.59 (s, C^1). Sample for elemental analysis was obtained by solvent removing from ^{13}C NMR sample. Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{OP} \cdot 1\text{H}_2\text{O} \cdot 0.1\text{CDCl}_3$: C, 64.11; H, 6.13; P, 8.18. Found: C, 63.81; H, 6.08; P, 8.12%.

4.1.2.5. *N*¹-[2-(Diphenylphosphinyl)ethyl]-*N*²,*N*²-bis[2-[(2-(diphenylphosphinyl)ethyl)amino]ethyl]-1,2-ethanediamine

(**4i**). Yield 95% (after freeze-drying), pale yellow hygroscopic solid, m.p. 45°C . ^{31}P NMR (CDCl_3): δ 31.84. ^1H NMR (CDCl_3): δ 2.39–2.46 (m, 6H, P CH_2), 2.49–2.59 (m, 12H, N $\text{CH}_2\text{CH}_2\text{N}$), 2.84–2.92 (m, 6H, N $\text{CH}_2\text{CH}_2\text{P}$), 7.34–7.51, 7.60–7.78 (all m, 18H + 12H, C_6H_5). ^{13}C NMR (CDCl_3): δ 29.62 (d, $^1J_{\text{PC}} = 70.9\text{ Hz}$, P- CH_2), 42.74 (N- $\text{CH}_2\text{--CH}_2\text{--P}$), 46.86 (s, N- $\text{CH}_2\text{--CH}_2\text{--NH}$), 53.99 (s, N- $\text{CH}_2\text{--CH}_2\text{--NH}$),

128.50 (d, $^3J_{PC} = 11.7$ Hz, *meta*-C₆H₅-P), 130.52 (d, $^2J_{PC} = 9.2$ Hz, *ortho*-C₆H₅-P), 131.61 (d, $^4J_{PC} = 2.6$ Hz, *para*-C₆H₅-P), 132.81 (d, $^1J_{PC} = 99.0$, *ipso*-C). IR (KBr, ν , cm⁻¹): 1175 br. (P=O). Anal. Calcd for C₄₈H₅₇N₄O₃P₃·2H₂O: C, 66.50; H, 7.09; N, 6.46. Found: C, 66.43; H, 6.97; N, 6.39%.

4.1.2.6. *N*¹,*N*¹-Bis[2-[bis[2-(diphenylphosphinyl)ethyl]amino]ethyl]-*N*²,*N*²-bis[2-(diphenylphosphinyl)ethyl]-1,2-ethanediamine (5). Yield 96% (after freeze-drying), pale yellow hygroscopic solid, m.p. 67 °C. ^{31}P NMR (CDCl₃): δ 30.83 (br. s). ^1H NMR (CDCl₃): δ 2.16–2.18 (m, 6H, NCH₂CH₂N), 2.26–2.33 (m, 18H, PCH₂ and NCH₂CH₂N), 2.69–2.74 (m, 12H, NCH₂CH₂P), 7.38–7.43, 7.67–7.72 (all m, 36H + 24H, C₆H₅). ^{13}C NMR (CDCl₃): δ 26.56 (d, $^1J_{PC} = 69.0$ Hz, PCH₂), 45.71 (s, NCH₂CH₂P), 46.61 (s, NCH₂CH₂N), 52.85 (s, NCH₂CH₂N), 128.54 (d, $^3J_{PC} = 11.7$ Hz, *meta*-C₆H₅P), 130.54 (d, $^2J_{PC} = 9.5$, *ortho*-C₆H₅P), 131.56 (d, $^4J_{PC} = 2.2$ Hz, *para*-C₆H₅P), 133.06 (d, $^1J_{PC} = 98.3$, *ipso*-C). IR (KBr, ν , cm⁻¹): 1174 br. (P=O). Anal. Calcd for C₉₀H₉₆N₄O₆P₆·3H₂O: C, 68.87; H, 6.55; N, 3.57. Found: C, 68.89; H, 6.51; N, 3.40%.

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