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# Synthesis of P-chiral enephosphonic acid derivatives

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**Abstract**

An efficient and convenient synthesis of chiral enephosphonic acid derivatives (enephosphonates, enephosphonamides, enephosphinates) was reported by a two-step procedure involving alkylidenediphosphorylation of nucleophiles followed by a Horner–Emmons olefination. Depending on the selected strategy, the synthesis could be executed according to a one-pot or a two-step reaction sequence. Regioselectivity of Horner–Emmons reaction and $^{31}$P-NMR study of diphosphorylated anions were described.

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*Keywords:* Alkylidenediphosphorylation; Horner reaction; Diphosphorylated carbanions; $^{31}$P-NMR study; Chiral enephosphorylated derivatives

## 1. Introduction

In the last two decades, a growing interest has appeared in the synthesis of vinylphosphonates, which are compounds of great potential with numerous applications as versatile intermediates in organic synthesis [1] as well as biologically actives molecules [2].

Synthetic interest of these derivatives could be displayed regarding their wide applicability in organic chemistry and especially in carbon–carbon bond formation that could take place with introduction of a stereogenic centre at β-position, in syntheses of heterocyclic or carbocyclic compounds, and in construction of polyethylenic structures. The developed sequences to afford such transformations are mainly nucleophilic Michael metal-catalysed asymmetric addition, or Horner–Emmons olefination, but more specific methods are also described [1].

Most reported preparations of vinylphosphonates or analogues are carbonyl olefination (Wittig, Horner–Emmons or Peterson reactions), oxidative elimination of organo-sulfur or -selenyl moieties, dehydration of β-hydroxyphosphonates, transition metal-catalysed cross coupling reaction or hydrogenation of alkynylphosphonates [1a,3]. However, it is noteworthy that procedures affording vinylphosphorylated derivatives such as **1** bearing a chiral phosphorus atom had received less coverage, and are restricted to β-phosphonoacrylates ($R^1 = COOR$) and unsubstituted vinylphosphonates ($R^1 = R^2 = H$) [4]. We wish to report here the synthesis of substituted enephosphorylated derivatives **1** including a chiral phosphorus atom with a strategy based on a regioselective Horner–Emmons olefination using chiral alkylidene diphosphorylated reagents **2** (Fig. 1).

## 2. Results and discussion

### 2.1. Synthesis of alkylidene diphosphorylated reagents 2

Recently we described a convenient one-pot alkylidenediphosphorylation of nucleophiles, which allows the preparation of organophosphorus compounds **2** containing a P–C–P linkage [5]. The strategy is based on a selective phosphonomethylation of dichlorophosphorylated substrates **5a–g** using the α-lithiated diethyl methylphosphonate [3] followed by a direct substitution of the chlorine atom of intermediates [**7a–g**] with appropriate nucleophiles **8** (Scheme 1).

Most of these previous results use ethyl dichlorophosphate ($Z = OEt$) in the second step of this reaction

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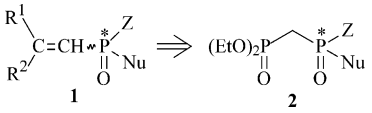


Fig. 1. P-Chiral enephosphonic acid derivative **1** and its precursor **2**.

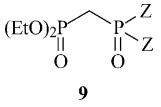
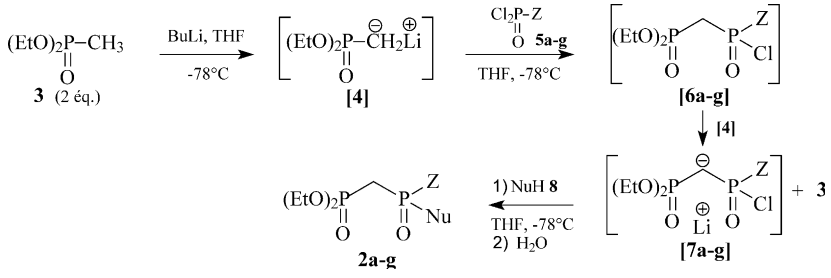


Fig. 2. By-product **2**.

sequence and the variable is the nucleophile. In these conditions, the introduction of a bulky nucleophile is difficult and the resulting yields in the preparation of the corresponding phosphoryl phosphonates **2** are poor. For example, the bulky dibenzylamine used as the nucleophile affords **2b** with a poor yield (Nu = $NBn_2$, Z = OEt, 21% yield) [5]. We found here that this disadvantage could be avoided if the bulky moiety was initially introduced via the group "Z" of the dichlorophosphorylated reagent **5** (which was easily available) and subsequently using EtOH, or $^{i}$PrOH, or EtSH as nucleophiles. In these conditions, **2b** was here obtained in 85% yield using *N*-dibenzyl dichlorophosphoramide **5b** and EtOH as the nucleophile (Z = $NBn_2$, Nu = OEt). As a consequence this strategy was led to provide derivatives **2a**–**g** in very good yields with a wide variety of dichlorophosphorylated substrates **5a**–**g** such as alkyl dichlorophosphates, phosphoramidic dichlorides and alkyl or arylphosphonic dichlorides (72–92%) (Table 1) and completed the previous procedure. In this sequence also, it could be observed that the yield decreased with the bulkiness of the nucleophile (NuH = O$^{i}$Pr, **2e**, 55%).

Another important improvement of the procedure was the possible total removal of small amounts of the by-products **9a**–**c** (Z = $NMe_2$, $NBn_2$, $N(CH_2)_5$) and **9f**–**g** (Z = OEt, O$^{i}$Pr) (Fig. 2) which were always present in the crude products **2a**–**c** and **2f**–**g** ($\sim$5%). These compounds appeared in the reaction mixture before the introduction of the nucleophile. Consequently, these products were supposed to result from a partial exchange between the corresponding intermediates **5** and **6**. That seemed to be confirmed by the fact that such an exchange occurred only in the cases where the dichlorophosphorylated substrate **5** included a good leaving group Z. Our previous study carried out with *n*-BuLi as metalling agent has shown that this base favoured the formation of by-products **9** [5]. It was now found that use of *s*-BuLi limited the formation of **9** (< 5%), whereas with *t*-BuLi it was totally suppressed. In these last conditions the crude diphosphorylated compounds **2** could be obtained practically pure with the sole necessity to eliminate the excess of the starting diethyl methylphosphonate **3** under vacuum; that was easy.

The progress of the reaction was monitored by $^{31}$P-NMR spectroscopy. The $^{31}$P-NMR spectra of the anions [**7a**–**g**] presented two doublets due to P–P coupling: diethyl phosphonate moiety exhibited a doublet as a $^{31}$P resonance signal in a restricted range of 34.4–36.9 ppm revealing that neighbouring –P(O)ZCl group had a small effect on the electronic disturb of the phosphonate moiety. On the other hand, we noted a wide range for the chemical shifts of the phosphorus atom bearing the P–Z linkage between 50.9 and 72.0 ppm (Table 2). It seemed possible to effect a direct relation between these values and the electronic density



Scheme 1.

Table 1
Alkylidenediphosphorylation of nucleophiles: preparation of **2a**–**g**

| | **2a** | **2b** | **2c** | **2d** | **2e** | **2f** | **2 g** |
|---|---|---|---|---|---|---|---|
| **Z** | $NMe_2$ | $NBn_2$ |  | Me | Ph | OEt | O$^{i}$Pr |
| **Nu** | OEt | OEt | OEt | O$^{i}$Pr | OEt | SEt | SEt |
| **Yield, %** | **88** | **85** | **92** | **55** | **75** | **75** | **72** |

Table 2
$^{31}$P-NMR data of intermediates [**7a**–**g**] [a]

| | Z | $^{31}$P-NMR ($\delta_{ppm}$, THF) | Reaction time to afford [7] |
|---|---|---|---|
| **[7a]** | $NMe_2$ | 56.3 (d, 1P, $^2J_{PP}$ = 58 Hz) ; 36.3 (d, 1P, $^2J_{PP}$ = 58 Hz) | 1h |
| **[7b]** | $NBn_2$ | 58.4 (d, 1P, $^2J_{PP}$ = 59 Hz) ; 36.9 (d, 1P, $^2J_{PP}$ = 59 Hz) | 1h |
| **[7c]** |  | 54.4 (d, 1P, $^2J_{PP}$ = 58 Hz) ; 36.5 (d, 1P, $^2J_{PP}$ = 58 Hz) | 3h |
| **[7d]** | Me | 72.0 (d, 1P, $^2J_{PP}$ = 24 Hz) ; 34.5 (d, 1P, $^2J_{PP}$ = 24 Hz) | 5h |
| **[7e]** | Ph | 62.7 (d, 1P, $^2J_{PP}$ = 32 Hz) ; 34.4 (d, 1P, $^2J_{PP}$ = 32 Hz) | 5h |
| **[7f]** | OEt | 50.9 (d, 1P, $^2J_{PP}$ = 76 Hz) ; 36.0 (d, 1P, $^2J_{PP}$ = 76 Hz) | 0.5h |
| **[7g]** | O$^i$Pr | [b] | 0.5h |

[a] Analytical samples of **[7a-g]** were cut off from the reaction mixture at -78°C, under $N_2$ atmosphere, $^{31}$P-NMR spectroscopy was performed in sweep-off mode, chemical shifts are reported in parts per million ($\delta$, ppm) downfield from $(EtO)_2P(O)CH_3$ ($\delta$ = 30.0 ppm) as an internal standard. [b] $^{31}$P-NMR spectrum showed two very broad signals in THF.

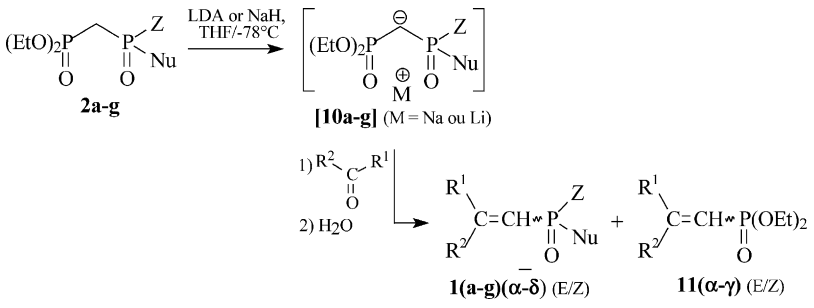
at the chiral phosphorus atom. Generally with increasing donor properties of Z bound to P $\lambda^5$ $\sigma^4$ of the phosphonyl group, the screening of the phosphorus nucleus increases and the $^{31}$P resonances show values that are shifted towards higher field strengths.

Moreover $^{31}$P-NMR studies revealed that carbanions [**7a**–**g**] showed a very good stability. They could be kept for 24 h, at 25 °C under nitrogen atmosphere, without degradation. The presence of the chlorine atom did not modify the high stability of these anions relatively to alkylidene diphosphonate carbanions. $^{31}$P-NMR spectra also gave information about the complete formation of lithiated anions [**7a**–**g**] and allowed these intermediates to be quenched by addition of nucleophiles **8** to obtain the expected compounds **2a**–**g** with optimum yields.

### 2.2. Olefination of alkylidene diphosphorylated reagents 2

As outlined in Scheme 2, the strategy was based on the Horner–Emmons reaction of carbanions [**10a**–**g**] with carbonyl substrates (aliphatic or aromatic aldehydes or ketones). The presence in the same molecule of two different phosphoryl groups on the same carbon can lead to two different olefins. If the leaving group is $(EtO)_2P(O)OLi$, the elimination leads to **1**, and if the leaving group is (Z)(Nu)P(O)OLi, **11** has to be obtained. The asymmetry of the diphosphorylated reagents **10** presents an interesting problem of regioselectivity.

Because the nature of the counterion of [**10a**–**g**] could influence the outcome of the Horner reaction, we performed the deprotonation step using different bases starting from model reagent **2b**: LDA in THF at −78 °C, NaH in THF at room temperature or $K_2CO_3$ in water in heterogeneous media, at room temperature [6]. As can be observed from the results of Table 3, the Horner reaction with LDA or NaH affords in all the cases the alkenylphosphorylated derivatives **1b** in good yields and with the best regioselectivity with NaH. Potassium carbonate did not lead to the expected carbanion **10b**. As a result, the reaction with other reagents **2** was generally studied with NaH as base.

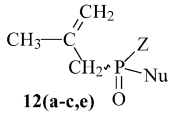



Scheme 2.

Table 3
Horner reaction: preparation of compounds **1(a–g)(α-δ)**

| | Z | Nu | $R^1$ | $R^2$ | 1/11 ratio[a,b] LDA | 1/11 ratio[a,b] NaH | 1/12[a,b] ratio | Yield (%) | [E/Z][a] |
|---|---|---|---|---|---|---|---|---|---|
| **1aα** | $NMe_2$ | OEt | Ph | H | 90/10 | - | - | **80** | [92/8] |
| **1aβ** | | | $^i$Pr | H | 89/11 | - | - | **82** | [84/16] |
| **1aγ** | | | Et | H | 95/5 | - | - | **91** | [74/26] |
| **1aδ** | | | Me | Me | 100/0 | - | 90/10[c] | **80** | |
| **1bα** | $NBn_2$ | OEt | Ph | H | 96/4 | 99/1 | - | **84**[d] | [97/3] |
| **1bβ** | | | $^i$Pr | H | 99/1 | 100/0 | - | **85**[d] | [92/8] |
| **1bγ** | | | Et | H | 97/3 | 100/0 | - | **86**[d] | [80/20] |
| **1bδ** | | | Me | Me | 100/0 | 100/0 | 92/8[d] | **78**[d] | |
| **1cα** |  | OEt | Ph | H | - | 94/6 | - | **84** | [100/0] |
| **1cβ** | | | $^i$Pr | H | - | 85/15 | - | **76** | [92/8] |
| **1cγ** | | | Et | H | - | 94/6 | - | **81** | [72/28] |
| **1cδ** | | | Me | Me | - | 100/0 | 74/26 | **63** | |
| **1d** | Me | O$i$Pr | Ph | H | - | 97/3 | - | **89** | [93/7] |
| **1dβ** | | | $^i$Pr | H | - | 63/37 | - | **57** | [93/7] |
| **1dγ** | | | Et | H | - | 100/0 | 82/18 | **71** | [86/14] |
| **1eα** | Ph | OEt | Ph | H | - | 82/18 | - | **86** | [100/0] |
| **1eβ** | | | $^i$Pr | H | - | 76/24 | - | **70** | [100/0] |
| **1eγ** | | | Et | H | - | 81/19 | - | **87** | [91/9] |
| **1eδ** | | | Me | Me | - | 100/0 | 69/31 | **62** | |
| **1fα** | OEt | SEt | Ph | H | - | 52/48 | - | **54** | [100/0] |
| **1gα** | O$i$Pr | SEt | Ph | H | - | 60/40 | - | **61** | [100/0] |

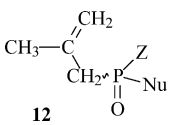
[a]Values were determined by $^{31}$P-NMR spectroscopy. [b] $^{31}$P-NMR data of **1(α–γ)** and **12(a-c, e)** are reported in experimental part.
[c] with LDA [d] with NaH.



**12(a-c,e)**

The observed results shown that:

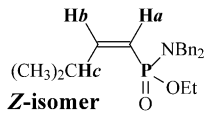
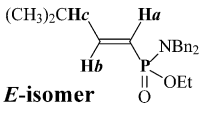
- The steric hindrance of carbonyl substrates influenced the rate of the Horner reaction, and the best results were obtained with aldehydes (61–91%). Reaction of [**10a**–**c**,**e**] with acetone was possible (62–80%), but occurred at a slow rate to give corresponding products **1(a**–**c**,**e) δ**. Consequently, the prolonged reaction time (48 h) induced a partial isomerisation of the isopropylidene of **1** into isopropenyl unit, so that the expected alkenes **1** were accompanied by phosphorylated isomers **12** (Fig. 3) in the ratio given in Table 3.
- The regioselectivity of the reaction depended on various parameters (cation, Z, Nu and nature of the carbonyl compound). It was lightly increased in favour of **1** by using sodium base instead of a lithium base, as illustrated in the case of **1b**: LDA produced a light more stable chelate [**10b**] than NaH. Sodium hydride gave a sodium counterion poorly coordinated that increased the reaction rate and consequently the more electrophilic phosphorus atom was mainly eliminated.



**12**

Fig. 3. Isomerization of compound **12**.

Table 4
$^1$H-NMR data of *E*- and *Z*-isomers of **1bβ**

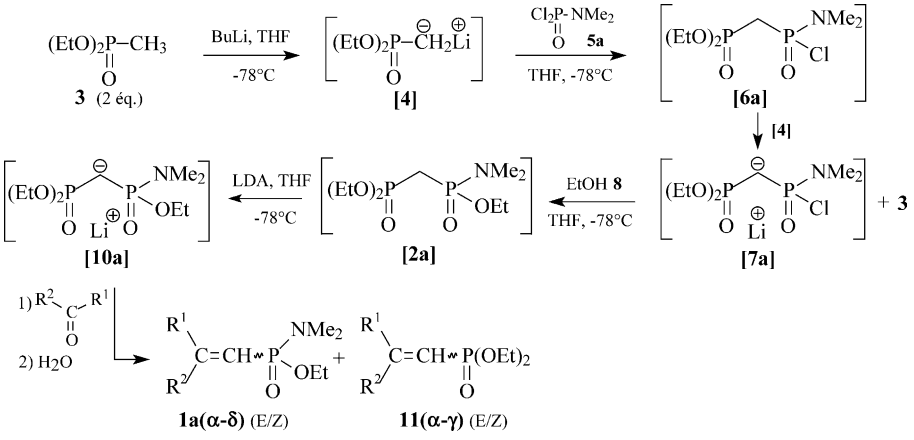
|  **Z-isomer** | |  **E-isomer** | |
|---|---|---|---|
| $H_a$ (dd, 5.58 ppm) | $H_b$ (ddd, 6.20 ppm) | $H_a$ (ddd, 5.70 ppm) | $H_b$ (ddd, 6.68 ppm) |
| $^2J(H_aP)$ = 19 Hz | **$^3J(H_bP)$ = 50Hz** | $^2J(H_aP)$ = 21 Hz | **$^3J(H_bP)$ = 21Hz** |
| **$^3J(H_aH_b)$ = 13 Hz** | **$^3J(H_bH_a)$ = 13Hz** | **$^3J(H_aH_b)$ = 17 Hz** | **$^3J(H_bH_a)$ = 17Hz** |
| - | $^3J(H_bH_c)$ = 10Hz | $^4J(H_aH_c)$ = 2 Hz | $^3J(H_bH_c)$ = 7Hz |

The regioselectivity of the reaction was also shown to be in favour of alkenes **1** when Z and Nu moieties were dialkylamino (*a*, *b* or *c* series), alkyl and bulky alkoxy (*d* series), aryl (*e* series) groups. These results for *a*, *b* and *c* series were in agreement with prior known outcomes which related the poor reactivity of phosphonamides in Horner olefination on account of the deactivating effect of two amino groups on phosphorus atom relatively to a diethylphosphono group. In the present cases of **1a**–**c**, substitution of one of both amino moieties of phosphonamides by an ethoxy unit maintained the phosphorus atom deactivation. Consequently, the diethylphosphono group was widely (**1a**, **1c**) or exclusively (**1b**) removed. Concerning the *d* series, P–C bond appeared less deactivating than P–N bond: the reaction between **1d** and *iso* butyraldehyde, displayed a ratio **1dβ/11β**: 63/37. This value showed that chiral phosphorus atom was sufficiently electrophilic to be competitive with the other phosphonyl centre in the elimination step. Nevertheless, the steric hindrance of the *iso* propoxy group on the phosphorus atom of **1d** induced a notable effect on the regioselectivity compared with results obtained in an analogue olefination (Z = Me, Nu = OEt) described in literature without any regioselectivity [3c]. In case of *f* and *g* series, a wide decrease of the regioselectivity was observed and led to conclude that one thioalkoxy group on phosphorus atom did not involve a significant deactivation of phosphorus reactivity, in contrast with the known attempts which were realised starting from *S*,*S*-dialkyl alkylphosphonodithioates.

Curiously, the regioselectivity was total with acetone whatever the Z and Nu moieties (**1a**, **1b**, **1c**, **1e**) **δ**. Any trace of corresponding diethyl enephosphonates was observed.

A column chromatographic purification on silica gel gave pure olefins **1**. From a practical point of view, it was important to note that the components **1b**,**d**–**g** eluted faster than the corresponding diethyl enephosphonates **11**. The compound's $R_f$ **1b**,**d**–**g** were between 0.61–0.70, whereas the $R_f$ values of **11** were lowest (0.45–0.55). The difference of $R_f$ was sufficient for a preparative separation. The olefins **1a** and **1c** had a much higher affinity for the silica gel than the preceding ($R_f$ = 0.39–0.63) and the separation was possible but it was more difficult. The purity of **1a**–**g** was evaluated easily by $^{31}$P-NMR analysis.

The nature of the carbonyl compound oriented clearly the stereoselectivity of the reaction. Compounds **1(a**–**g)(α-δ)** were provided as *E*- and *Z*-isomer mixture with




Scheme 3.

Table 5
One-pot sequence of preparation of alkenylphosphonamides **1a**

| | Z | Nu | $R^1$ | $R^2$ | 1/11 ratio [a] | 1/12 [a] ratio | Yield (%) [*E*/*Z*] [a] |
|---|---|---|---|---|---|---|---|
| **1aα** | $NMe_2$ | OEt | Ph | H | 95/5 | – | **80** [92/8] |
| **1aβ** | | | $^i$Pr | H | 89/11 | – | **82** [84/16] |
| **1aδ** | | | Me | Me | 100/0 | 90/10 | **80** |

[a] Values were determined by $^{31}$P-NMR spectroscopy.

*E*- as major isomer. In all cases, the best *E*-stereoselectivity was obtained with benzaldehyde, which is typical of stabilised phosphonylated carbanions. It is noteworthy that the change of lithium ion by sodium ion induced no modification in *E*/*Z* ratio of isomers of **1**.

Assignment of the *E*-stereochemistry to the major isomer of **1** was based on analysis of $^1$H-NMR data [7]. Values of H–H double bond vicinal and H–P coupling constants were characteristic, as shown in Table 4 for compound **1bβ**.

A one-pot sequence to prepare alkenylphosphonates from diethyl methylphosphonate **3** was also explored with the *a* series (Z = $NMe_2$, Nu = OEt) as selected model (Scheme 3).

Table 6
$^{31}$P-NMR data of intermediates [**10a**–**g**] [a]

| | Z | Nu | $M^+$ | $^{31}$P-NMR ($\delta_{ppm}$, THF) |
|---|---|---|---|---|
| **10a** | $NMe_2$ | OEt | $Li^+$ | 46.7 (d, 1P, $^2J_{PP}$ = 64 Hz) ; 40.9 (d, 1P, $^2J_{PP}$ = 64 Hz) |
| | | | $Na^+$ | 43.9 (d, 1P, $^2J_{PP}$ = 64 Hz) ; 39.6 (d, 1P, $^2J_{PP}$ = 64 Hz) |
| **10b** | $NBn_2$ | OEt | $Li^+$ | 47.0 (d, 1P, $^2J_{PP}$ = 66 Hz) ; 42.8 (d, 1P, $^2J_{PP}$ = 66 Hz) |
| | | | $Na^+$ | 44.1 (d, 1P, $^2J_{PP}$ = 68 Hz) ; 40.8 (d, 1P, $^2J_{PP}$ = 68 Hz) |
| **10c** |  | OEt | $Li^+$ | 44.8 (d, 1P, $^2J_{PP}$ = 64 Hz) ; 40.2 (d, 1P, $^2J_{PP}$ = 64 Hz) |
| | | | $Na^+$ | 43.1 (d, 1P, $^2J_{PP}$ = 64 Hz) ; 40.3 (d, 1P, $^2J_{PP}$ = 64 Hz) |
| **10d** | Me | O$^i$Pr | $Li^+$ | 54.3 (d, 1P, $^2J_{PP}$ = 47 Hz) ; 39.3 (d, 1P, $^2J_{PP}$ = 47 Hz) |
| | | | $Na^+$ | 52.7 (d, 1P, $^2J_{PP}$ = 47 Hz) ; 39.6 (d, 1P, $^2J_{PP}$ = 47 Hz) |
| **10e** | Ph | OEt | $Li^+$ | 50.2 (d, 1P, $^2J_{PP}$ = 52 Hz) ; 43.6 (d, 1P, $^2J_{PP}$ = 52 Hz) |
| | | | $Na^+$ | 49.1 (d, 1P, $^2J_{PP}$ = 52 Hz) ; 43.5 (d, 1P, $^2J_{PP}$ = 52 Hz) |
| **10f** | OEt | SEt | $Li^+$ | 53.9 (d, 1P, $^2J_{PP}$ = 63 Hz) ; 36.9 (d, 1P, $^2J_{PP}$ = 63 Hz) |
| | | | $Na^+$ | 53.3 (d, 1P, $^2J_{PP}$ = 63 Hz) ; 34.8 (d, 1P, $^2J_{PP}$ = 63 Hz) |
| **10g** | O$^i$Pr | SEt | $Li^+$ | 54.8 (d, 1P, $^2J_{PP}$ = 64 Hz) ; 37.4(d, 1P, $^2J_{PP}$ = 64 Hz) |
| | | | $Na^+$ | 57.3 (d, 1P, $^2J_{PP}$ = 64 Hz) ; 36.5 (d, 1P, $^2J_{PP}$ = 64 Hz) |
| **10h** [a,b] | OEt | OEt | $Li^+$ | 40.8 (s, 2P) |
| | | | $Na^+$ | 38.9 (s, 2P) |
| **10i** [a,b] | Me | OEt | $Li^+$ | 59.8 (d, 1P, $^2J_{PP}$ = 46 Hz) ; 39.3 (d, 1P, $^2J_{PP}$ = 46 Hz) |
| | | | $Na^+$ | 57.9 (d, 1P, $^2J_{PP}$ = 46 Hz) ; 39.3 (d, 1P, $^2J_{PP}$ = 46 Hz) |

[a] Analytical samples were cut off from the reaction mixture under $N_2$ atmosphere, $^{31}$P-NMR spectroscopy was performed in sweep-off mode, in THF, chemical shifts are reported in parts per million ($\delta$, ppm) downfield from $(EtO)_2P(O)CH_3$ ($\delta$ = 30.0 ppm) as an internal standard. [b] these carbanions were derived from known precursors but were prepared in the same conditions that for **[10a-g]**


Scheme 4.

The reaction progress was monitored by $^{31}$P-NMR spectroscopy. The change was the deprotonation in situ of no-isolated [**2a**] with LDA at −78 °C, to generate the lithiated stabilised anion [**10a**] which was allowed to react directly with benzaldehyde, isobutyraldehyde or acetone to afford corresponding olefins **1a(α, β, δ)**, in very good overall yields (Table 5).

As expected, no significant variation was observed concerning the regioselectivity or the stereoselectivity. As this one-pot procedure exhibited highest yields for the preparation of **1a** (80–82% yield compared to 66–70% overall yields for the two-step procedure), it was revealed the most convenient and efficient for the synthesis of enephosphorylated compounds **1**.

As previously outlined, key-intermediates of the above described synthesis were the carbanions [**10a–g**]. $^{31}$P-NMR spectroscopic analysis was realised (Table 6). Stability of these intermediates was studied and we observed that, in anhydrous media, species [**10a–g**] underwent no degradation, even if the reaction occurred over a very long time at room temperature (e.g. addition of [**10a–c,e**] to acetone led to **1(a–c,e)δ** in good yields (62–80%) after a 48 h reaction time at 20 °C). The great stability of these new anions allowed an easy identification by $^{31}$P-NMR analysis.

An interesting comparison of the measured chemical shifts for 23 unsymmetrical diphosphorylated derivatives of general formula [**7**], **2**, and [**10**] is represented in Scheme 4. It should be noticed that replacement of Z = EtO in [**7**], **2**, or [**10**], (each of these last species where Z = OEt taken as a reference), by $NMe_2$, $NBn_2$, piperidinyl, Me, Ph, or SEt leads to a positive shift in the order: EtO ≪ Npiperidinyl < $NMe_2$ ~ $NBn_2$ ≪ Ph < SEt ≪ Me. The nature of Z linked to the chiral phosphorus atom involves a roughly constant contribution to the overall shift, whatever the structure of the compound from which the shift has been measured. To a first approximation, each group Z appears to make a given contribution to the $^{31}$P chemical shift; so that, with Z = EtO as reference, it is possible to propose empirical increments of chemical shifts associated to the nature of Z, as shown in Scheme 5.

These diphosphorylated compounds afford an interesting example of chemical shifts that are essentially governed by electronic effects of Z with a good correlation. These chemical shifts give a direct way to measure the relative electron-donating ability of various groups Z on the phosphorus atom, as they make it possible to estimate reasonably the electrophilicity of the chiral phosphorus atom.

Nevertheless, the correlations of these data with the regioselectivity of the Horner–Emmons olefination explained above only in terms of difference in the electrophilicity of the phosphonyl group are not sufficient. Other effects may be accounted for by the relative stability of the pentacoordinate intermediate with the oxaphosphetan ring in apical equatorial position of the trigonal bipyramid (TBP). This stability depends on the


Scheme 5.

apicophilicity of the substituents Z and Nu bound to the phosphorus that favours the diethoxyphosphonate group in the formation of P(V) intermediate close to the transition state. Our results appear in accordance with the relative apicophilicities of the ligands attached to phosphorus [8]. In particular, the poor regioselectivity observed in the case of the SEt group may be best accounted for by its relative apicophilicity, comparable with OEt group rather than by the difference of donating effect on the phosphorus.

## 3. Conclusion

Extension and improvement of alkylidene diphosphorylation of nucleophiles were successfully realised and allowed us to afford a large diversity of asymmetric diphosphorylated derivatives **1a**–**g**. Study of the reactivity of these compounds in Horner–Emmons reaction led us to elaborate a convenient and efficient preparation of various alkenylphosphonates and analogues including a chiral phosphorus atom. Stability of carbonion intermediates, regioselectivity and stereochemistry of olefination were studied to evaluate the reaction outline. Stereoelectronic effects and/or apicophilicity of Z explain the observed results and constitute a guide for the preparation of such P-chiral enephosphonic acid derivatives.

## 4. Experimental

### 4.1. General methods

Melting points were determined on an Electrothermal IA9100 digital apparatus. Thin layer chromatography (TLC) was carried out on aluminium-backed silica gel-coated plates (Kieselgel 60-$F_{254}$, Merck or Alugram® Sil G/$UV_{254}$, Macherey-Nagel), spots were identified under an UV lamp ($\lambda = 254$ nm) or developed using iodine. Column chromatographies were performed on silica gel 60 or 70-230 mesh with the indicated eluent, dried and distilled shortly before use. Infrared spectra were obtained using a Nicolet 205 spectrometer and are given in $cm^{-1}$. NMR spectra were recorded using a Bruker AC250 spectrometer. For $^{1}H$- and $^{13}C$-NMR data, chemical shifts were reported in parts per million ($\delta$, ppm) downfield from $CHCl_3$ as an internal standard while $^{31}P$-NMR were reported with 85% $H_3PO_4$ as an external standard. NMR coupling constants ($J$ values) were listed in hertz (Hz) and spin multiplicities were reported as singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br). Mass spectra were obtained with a TRIO 1000 spectrometer. Organic solvents were purified according to the methods described by Armarego and Perrin [9]. All no aqueous reactions were performed in oven-dried glassware under nitrogen atmosphere. *n*-Butyllithium, *s*-butyllithium and *t*-butyllithium were purchased from Aldrich and were titrated in tetrahydrofuran for *n*-BuLi and benzene for *s*-BuLi according to the Watson and Eastham procedure [10]. Advancement of reactions was followed by $^{31}P$-NMR spectroscopy.

### 4.2. General procedure for the preparation of (diakylamido)phosphoric dichlorides 5a–c

A mixture of $Et_3N$ (50.0 mmol) and appropriate amine (dibenzylamine or piperidine) (50.0 mmol) in $Et_2O$ (10 ml) was added dropwise to a solution of phosphoric trichloride (50.0 mmol) in $Et_2O$ (10 ml), at 0 °C and under nitrogen. After stirring 4 h, the reaction mixture was filtered on Celite® and evaporated. The residue was dissolved in $Et_2O$ to removed trace of triethylamine hydrochloride by filtration. After evaporation of $Et_2O$, the expected (dialkylamido)phosphoric dichloride was afforded without purification.

#### 4.2.1. (Dimethylamido)phosphoric dichloride 5a

(Dimethylamido)phosphoric dichloride **5a** ($Cl_2P(O)$-$NMe_2$) was commercially available.

#### 4.2.2. (Dibenzylamido)phosphoric dichloride 5b

**5b** was obtained without purification as a solid in quantitative yield. M.p. = 58–60 °C. IR (KBr) $\nu$ ($cm^{-1}$): 1265 (P=O). $^{1}H$-NMR ($CDCl_3$) $\delta$ (ppm): 4.20 (d, 4H, $CH_2N$, $^{3}J_{HP} = 14$ Hz), 7.15–7.33 (m, 10H, $H_{arom.}$). $^{31}P$-NMR ($CDCl_3$) $\delta$ (ppm): 16.0 (s, 1P). $^{13}C$-NMR ($CDCl_3$) $\delta$ (ppm): 48.7 (d, $CH_2N$, $^{2}J_{CP} = 4$ Hz), 128.2 (s, $CH_{arom.}$), 128.5 (s, $CH_{arom.}$), 129.0 (s, $CH_{arom.}$), 134.4 (d, $C_{arom.}$, $^{3}J_{CP} = 4$ Hz).

#### 4.2.3. (Piperidinylamido)phosphoric dichloride 5c

**5c** was obtained without purification as an oil in 95% yield. IR (neat) $\nu$ ($cm^{-1}$): 1270 (P=O), 1034 (P–N). $^{1}H$-NMR ($CDCl_3$) $\delta$ (ppm): 1.59–1.72 (m, 6H, $CH_2$), 3.20–3.40 (m, 4H, $NCH_2$). $^{31}P$-NMR ($CDCl_3$) $\delta$ (ppm): 13.4 (s, 1P). $^{13}C$-NMR ($CDCl_3$) $\delta$ (ppm): 23.9 (s, $CH_2$), 25.3 (d, $CH_2$, $^{3}J_{CP} = 8$ Hz), 46.1 (s, $CH_2$).

### 4.3. Methylphosphonic dichloride 5d

Methylphosphonic dichloride **5d** ($Cl_2P(O)Me$) and phenylphosphonic dichloride **5e** ($Cl_2P(O)Ph$) were commercially available.

### 4.4. Preparation of alkyl dichlorophosphates 5f–g

#### 4.4.1. Ethyl dichlorophosphate 5f

Ethyl dichlorophosphate **5f** ($EtOP(O)Cl_2$) was commercially available.

#### 4.4.2. Isopropyl dichlorophosphate **5g**

Isopropyl dichlorophosphate **5g** was obtained according to the method described by Modro et al. [11].

### 4.5. General procedure for the preparation of diphosphorylated derivatives **2a–g**

To a dry 100 ml four-necked flask equipped with a mechanical stirrer, a thermometer and a dropping funnel, was added a solution of *s*-BuLi (10.0 ml, 13.0 mmol, solution 1.3 M in hexane) in freshly distilled THF (30 ml) at −78 °C under nitrogen atmosphere. A solution of diethyl methylphosphonate (**3**) (2.00 g, 13.0 mmol) in THF (30 ml) was added dropwise at −78 °C. After stirring at −78 °C for 45 min, a solution of appropriate derivative **5a–g** (5.9 mmol) in THF (15 ml) was added dropwise. The resulting mixture was stirred for 30 min–5 h at −78 °C, depending on derivative **5a–g**, before adding the nucleophile **8** (5.9 mmol) diluted in THF (15 ml). The mixture was allowed to stir for 5 min at −78 °C; then, slowly warmed up to room temperature (r.t.) over a period of 4 h and poured into water (30 ml). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried ($MgSO_4$), filtered and the solvent was evaporated. Evaporation of residual diethyl methylphosphonate **3** under reduced pressure ($10^{-2}$ mmHg, 40 °C) provided the expected derivative **2a–g** as oil. Yields were determined by $^{31}$P-NMR spectroscopy.

#### 4.5.1. Diethyl [(ethoxydimethylamino)phosphinyl]-methylphosphonate (**2a**)

Compound **2a** was obtained according to the general procedure in 88% yield. IR (neat) $\nu$ ($cm^{-1}$): 990 (P–N), 1266 (P=O). MS: $m/z = 287$ [M•]. $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.20–1.40 (m, 9H, $OCH_2CH_3$), 2.30–2.50 (m, 2H, $PCH_2P$), 2.72 (d, 6H, $NCH_3$, $^3J_{HP} = 9$ Hz), 3.83–4.30 (m, 6H, $OCH_2$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 18.5 (br s, 1P), 21.6 (br s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.5 (s, $OCH_2CH_3$), 15.7 (s, $OCH_2CH_3$), 15.8 (br s, $OCH_2CH_3$), 23.9 (dd, $PCH_2P$, $^1J_{CP} = 136$ Hz, $^1J_{CP} = 120$ Hz), 35.5 (d, $N(CH_3)_2$, $^2J_{CP} = 5$ Hz), 59.0 (d, $OCH_2CH_3$, $^2J_{CP} = 6$ Hz), 61.4 (d, $OCH_2CH_3$, $^2J_{CP} = 6$ Hz), 61.8 (d, $OCH_2CH_3$, $^2J_{CP} = 6$ Hz).

#### 4.5.2. Diethyl [(ethoxydibenzylamino)phosphinyl]-methylphosphonate (**2b**)

Compound **2b** was obtained according to the general procedure in 85% yield. $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 18.8 (br s, 1P), 21.8 (br s, 1P). Other spectroscopic data of **2b** are described in Ref. [5].

#### 4.5.3. Diethyl [(ethoxypiperidinyl)phosphinyl]methylphosphonate (**2c**)

Compound **2c** was obtained according to the general procedure in 92% yield. IR (neat) $\nu$ ($cm^{-1}$): 1030 (P–N), 1250 (P=O). MS: $m/z = 328$ [M+1]. $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.20–1.33 (m, 9H, $CH_3$), 1.41–1.60 (m, 6H, $CH_2$), 2.22–2.45 (m, 2H, $PCH_2P$), 2.95–3.25 (m, 4H, $NCH_2$), 3.85–4.20 (m, 6H, $OCH_2$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 18.7 (s, 1P), 21.3 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.2–15.9 (br s, $CH_3$), 23.8 (s, $CH_2$), 24.5 (dd, $PCH_2P$, $^1J_{CP} = 136$ Hz, $^1J_{CP} = 121$ Hz), 25.4 (s, $CH_2$), 25.5 (s, $CH_2$), 44.0 (s, $CH_2N$), 59.1 (d, $OCH_2CH_3$, $^2J_{CP} = 6$ Hz), 61.5 (d, $OCH_2CH_3$, $^2J_{CP} = 6$ Hz), 61.8 (d, $OCH_2CH_3$, $^2J_{CP} = 6$ Hz).

#### 4.5.4. Diethyl [(isopropyloxymethyl)phosphinyl]-methylphosphonate (**2d**)

Compound **2d** [12] was obtained according to the general procedure in 55%. IR (neat) $\nu$ ($cm^{-1}$): 1020 (P–O), 1244 (P=O). $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.30–1.39 (m, 12H, $OCH_2CH_3$, $CHCH_3$), 1.69 (d, 3H, $PCH_3$, $^2J_{HP} = 15$ Hz), 2.28–2.50 (m, 2H, $PCH_2P$), 4.06–4.27 (m, 4H, $OCH_2$), 4.64–4.87 (m, 1H, $CHCH_3$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 17.7 (s, 1P), 40.9 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.1 (d, $CH_3$, $^1J_{CP} = 100$ Hz), 16.0 (d, $OCH_2CH_3$, $^3J_{CP} = 6$ Hz), 23.8–24.2 (m, $CH(CH_3)_2$), 29.3 (dd, $PCH_2P$, $^1J_{CP} = 134$ Hz, $^1J_{CP} = 82$ Hz), 61.8–62.4 (m, $OCH_2CH_3$), 70.7–71.3 (m, $CH$).

#### 4.5.5. Diethyl [(ethoxyphenyl)phosphinyl]methylphosphonate (**2e**)

Compound **2e** was obtained according to the general procedure in 75% yield. $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 16.7 (br s, 1P), 30.8 (br s, 1P). Other spectroscopic data of **2e** are given in Ref. [13].

#### 4.5.6. Diethyl [(ethoxyethylthio)phosphinyl]-methylphosphonate (**2f**)

Compound **2f** was obtained according to the general procedure in 75% yield. $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 15.6 (br s, 1P), 41.7 (br s, 1P). Other spectroscopic data of **2f** are described in Ref. [5].

#### 4.5.7. Diethyl[(isopropyloxyethylthio)phosphinyl]-methylphosphonate (**2g**)

Compound **2g** was obtained according to the general procedure in 72% yield. IR (neat) $\nu$ ($cm^{-1}$): 1030 (P–O), 1255 (P=O). MS: $m/z = 319$ [M+1]. $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.12–1.34 (m, 15H, $CH_3$), 2.44–2.70 (m, 2H, $PCH_2P$), 2.76–2.96 (m, 2H, $SCH_2$), 3.84–4.17 (m, 4H, $OCH_2CH_3$), 4.60–4.84 (m, 1H, $CH$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 15.6 (d, 1P, $^2J_{PP} = 9$ Hz), 39.9 (d, 1P, $^2J_{PP} = 9$ Hz). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.7 (br s, $CH_3$), 23.1 (s, $CH(CH_3)_2$), 23.5 (s, $CH(CH_3)_2$), 24.9 (s, $SCH_2$), 33.0 (dd, $PCH_2P$, $^1J_{CP} = 134$ Hz, $^1J_{CP} = 101$ Hz), 61.8 (s, $OCH_2$), 70.8 (s, $CH$).

### 4.6. General procedure for the preparation of alkenylphosphorylated derivatives *1*

#### 4.6.1. General procedure for the preparation of *1*

Compounds **1** were prepared starting from diphosphorylated derivatives **2a**–**g** which were obtained and isolated according to the general process described in Section 4.5.

The method using LDA as base was carried out as following: to a solution of LDA (6.5 mmol) in solution in THF (10 ml), was added dropwise at −78 °C a solution of **2a**–**g** (6.5 mmol) in THF (10 ml). After stirring for 1 h at −78 °C, appropriate carbonyl substrate (5.9 mmol) in THF (6 ml) was added and the mixture was stirred at −78 °C (progress of reaction was monitored by $^{31}$P-NMR spectroscopy) and then the reaction was quenched by water addition (10 ml). The organic layer was separated and aqueous layer was extracted with $CH_2Cl_2$; the combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum.

The method using NaH as base: to a suspension of freshly washed NaH (55% suspension in mineral oil, 0.50 g, 21.0 mmol) in THF (10.0 ml) was added a solution of **2a**–**g** (21.0 mmol) in THF (10.0 ml), under $N_2$ atmosphere, at r.t. After stirring for 15 min at r.t., complete metallation of **2a**–**g** was confirmed by $^{31}$P-NMR spectroscopy and appropriate carbonyl substrate (21.0 mmol) in THF (10.0 ml) was added. Mixture was stirred for 15 min at r.t. and then the reaction was quenched by water addition (10.0 ml). The aqueous layer was extracted with $CH_2Cl_2$, organic phase was dried ($MgSO_4$), filtered and solvents were removed in vacuum to leave the crude product, which was purified by column chromatography. Yields of reaction in **1**, ratio of *E*/*Z* isomers of **1** and ratio of **1/11** and **1/12** were determined by $^{31}$P-NMR spectroscopy.

#### 4.6.2. General procedure for the one-pot preparation of *1a*

Derivatives [**2a**] (5.9 mmol) were obtained in situ according to the beginning of the general procedure reported in Section 4.5. After addition of nucleophile **8** (5.9 mmol) in THF (15 ml), the mixture was allowed to stir for 5 min at −78 °C, then warmed up slowly to r.t. under $N_2$ atmosphere. Total formation of [**2a**] was confirmed by $^{31}$P-NMR spectroscopy and then, reaction mixture was cooled at −78 °C, and LDA in solution in THF (6.5 mmol) was added dropwise. After stirring for 1 h at −78 °C, appropriate carbonyl substrate (5.9 mmol) in THF (6 ml) was added and the mixture was stirred at −78 °C (progress of reaction was monitored by $^{31}$P-NMR spectroscopy) and then the reaction was quenched by water addition (10 ml). The organic layer was separated and aqueous layer was extracted with $CH_2Cl_2$; the combined organic layers were dried ($MgSO_4$), filtered and solvents were removed in vacuum. Evaporation of residual diethyl methylphosphonate **3** under reduced pressure ($10^{-2}$ mmHg, 40 °C) provided the expected alkenylphosphorylated derivatives **1**.

##### 4.6.2.1. (Dimethylamino)(ethoxy)(2-phenylethenyl)-phosphine oxide (*1aα*).

Compound **1aα** was prepared according to the general procedure described above starting from **2a** (1.50 g, 5.2 mmol) and benzaldehyde (0.55 g, 5.2 mmol). Compound **1aα** was obtained as an oil (1.00 g) in 80% yield and was afforded as a mixture of *E*/*Z* isomers in 92/8 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.37. IR (neat) $\nu$ (cm$^{-1}$): 1040 (P–O), 1239 (P=O), 1608 (C=C). MS: $m/z = 239$ [M], 240 [M+1].

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.36 (t, 3H, C$H_3$, $^3J_{HH} = 7$ Hz), 2.73 (d, 6H, NC$H_3$, $^3J_{HP} = 10$ Hz), 3.87–4.21 (m, 2H, OC$H_2$CH$_3$), 6.32 (t, 1H, P(O)C$H_{ethyl.}$, $^3J_{HH} = 18$ Hz), 7.30–7.57 (m, 6H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 22.2 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.3 (br s, $CH_3$), 35.9 (s, N$CH_3$), 59.8 (s, O$CH_2$), 115.8 (d, P(O)$C$H$_{ethyl.}$, $^1J_{CP} =$ 176 Hz), 127.5 (s, $CH_{arom.}$), 128.8 (s, $CH_{arom.}$), 129.7 (s, $CH_{arom.}$), 135.3–135.6 (m, $C_{arom.}$), 146.1 (s, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.36 (t, 3H, C$H_3$, $^3J_{HH} = 7$ Hz), 2.37 (d, 6H, NC$H_3$, $^3J_{HP} = 10$ Hz), 3.87–4.21 (m, 2H, OC$H_2$CH$_3$), 5.86 (t, 1H, P(O)C$H_{ethyl.}$, $^3J_{HH} = 14$ Hz), 7.30–7.57 (m, 6H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.3 (s, 1P).

##### 4.6.2.2. (3-Methyl-1-butenyl)(dimethylamino)(ethoxy)-phosphine oxide (*1aβ*).

Compound **1aβ** was prepared according to the general procedure described above starting from **2a** (1.50 g, 5.2 mmol) and *iso*butyraldehyde (0.31 g, 5.2 mmol). Compound **1aβ** was obtained as an oil (0.88 g) in 82% yield and was afforded as a mixture of *E*/*Z* isomers in 84/16 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.43. IR (neat) $\nu$ (cm$^{-1}$): 1034 (P–O), 1244 (P=O), 1629 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.90–1.05 (m, 6H, CH(C$H_3$)$_2$), 1.15–1.35 (m, 3H, C$H_3$), 1.40–1.65 (m, 1H, C$H$), 2.54–2.62 (m, 6H, NC$H_3$), 3.70–4.08 (m, 2H, OC$H_2$), 5.43–5.64 (m, 1H, P(O)C$H_{ethyl.}$), 6.39–6.60 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 22.7 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.3 (d, $CH_3$, $^3J_{CP} = 6$ Hz), 21.2 (s, CH($CH_3$)$_2$), 36.1 (s, N$CH_3$), 59.6–59.8 (m, O$CH_2$), 32.3 (s, $CH$), 115.5 (d, P(O)$C$H$_{ethyl.}$, $^1J_{CP} = 175$ Hz), 157.2 (s, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.90–1.05 (m, 6H, CH(C$H_3$)$_2$), 1.15–1.35 (m, 3H, C$H_3$), 1.40–1.65 (m, 1H, C$H$), 2.54–2.62 (m, 6H, NC$H_3$), 3.70–4.08 (m, 2H, OC$H_2$), 5.23–5.42 (m, 1H, P(O)C$H_{ethyl.}$), 5.92–6.24 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 20.4 (s, 1P).

##### 4.6.2.3. (1-Butenyl)(dimethylamino)(ethoxy)phosphine oxide (*1aγ*).

Compound **1aγ** was prepared according to the general procedure described above starting from **1a**

(1.50 g, 5.2 mmol) and propanal (0.30 g, 5.2 mmol). Compound **1aγ** was obtained as an oil (0.91 g) in 91% yield and was afforded as a mixture of *E*/*Z* isomers in 74/26 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.35. IR (neat) $\nu$ ($cm^{-1}$): 1038 (P–O), 1265 (P=O), 1624 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.90–1.20 (m, 3H, $CH_2CH_3$), 1.22–1.50 (m, 3H, $CH_3$), 2.15–2.30 (m, 2H, $CH_2$), 2.66 (d, 6H, $NCH_3$, $^3J_{HP} = 9$ Hz), 3.85–4.12 (m, 2H, $OCH_2$), 5.57–5.75 (m, 1H, P(O)C$H_{ethyl.}$), 6.54–6.76 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 22.2 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 11.7 (s, $CH_2CH_3$), 15.9 (d, $OCH_2CH_3$, $^3J_{CP} = 7$ Hz), 26.7 (d, $CH_2CH_3$, $^3J_{CP} = 21$ Hz), 35.7 (d, $NCH_3$, $^2J_{CP} = 5$ Hz), 58.7–59.8 (m, $OCH_2$), 116.5 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 175$ Hz), 147.9 (s, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.90–1.20 (m, 3H, $CH_2CH_3$), 1.22–1.50 (m, 3H, $CH_3$), 2.40–2.55 (m, 2H, $CH_2$), 2.65 (d, 6H, $NCH_3$, $^3J_{HP} = 9$ Hz), 3.85–4.12 (m, 2H, $OCH_2$), 5.48–5.65 (m, 1H, P(O)C$H_{ethyl.}$), 6.20–6.52 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 20.4 (s, 1P).

*4.6.2.4. (Dimethylamino)(ethoxy)(2-methyl-1-propenyl)phosphine oxide (**1aδ**).* Compound **1aδ** was prepared according to the general procedure described above starting from **2a** (1.50 g, 5.2 mmol) and acetone (0.30 g, 5.2 mmol). Compound **1aδ** was afforded in mixture with allylic byproduct **12a** in 90/10 ratio. Derivative **1aδ** was obtained as an oil (0.80 g) in 80% yield. IR (neat) $\nu$ ($cm^{-1}$): 1029 (P–O), 1265 (P=O), 1634 (C=C). $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.80–0.90 (m, 3H, $OCH_2CH_3$), 1.40–1.50 (m, 3H, $CH_3$), 1.53–1.61 (m, 3H, $CH_3$), 2.14–2.23 (m, 6H, $NCH_3$), 3.31–3.65 (m, 2H, $OCH_2$), 4.88–5.10 (m, 1H, P(O)C$H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 20.5 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.5 (d, $OCH_2CH_3$, $^3J_{CP} = 6$ Hz), 27.3 (d, $CH_3$, $^3J_{CP} = 23$ Hz), 34.9 (d, $NCH_3$, $^2J_{CP} = 4$ Hz), 58.1 (d, $OCH_2$, $^2J_{CP} = 6$ Hz), 113.1 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 177$ Hz), 156.2 (d, $C_{ethyl.}$, $^2J_{CP} = 5$ Hz).

*4.6.2.5. (Dibenzylamino)(ethoxy)(2-phenylethenyl)-phosphine oxide (**1bα**).* Compound **1bα** was prepared according to the general procedure described above starting from **2b** (2.00 g, 4.5 mmol) and benzaldehyde (0.48 g, 4.5 mmol). Compound **1bα** was obtained as an oil (1.50 g) in 84% yield and was afforded as a mixture of *E*/*Z* isomers in 97/3 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.68. IR (neat) $\nu$ ($cm^{-1}$): 1030 (P–O), 1253 (P=O), 1613 (C=C). MS: $m/z = 348$ [M−(OEt)].

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.25 (t, 3H, $CH_3$, $^3J_{HH} = 7$ Hz), 3.90–4.15 (m, 6H, $OCH_2$, $NCH_2$), 6.26 (dd, 1H, P(O)C$H_{ethyl.}$, $^2J_{HP} = 18$ Hz, $^3J_{HH} = 17$ Hz), 7.13–7.55 (m, 16H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 20.9 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.4 (d, $CH_3$, $^3J_{CP} = 6$ Hz), 47.8 (d, $NCH_2$, $^2J_{CP} = 5$ Hz), 60.7 (d, $OCH_2$, $^2J_{CP} = 6$ Hz), 116.9 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 177$ Hz), 127.3 (s, $CH_{arom.}$), 128.8 (s, $CH_{arom.}$), 130.2 (s, $CH_{arom.}$), 135.4 (d, $C_{arom.}$, $^3J_{CP} = 22$ Hz), 137.6 (s, $C_{arom.}$), 146.6 (s, $CH_{ethyl.}$, $^2J_{CP} = 5$ Hz).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.25 (t, 3H, $CH_3$, $^3J_{HH} = 7$ Hz), 3.90–4.15 (m, 6H, $OCH_2$, $NCH_2$), 5.84–5.89 (m, 1H, P(O)C$H_{ethyl.}$), 7.23–7.55 (m, 16H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.2 (s, 1P).

*4.6.2.6. (3-Methyl-1-butenyl)(dibenzylamino)(ethoxy)-phosphine oxide (**1bβ**).* Compound **1bβ** was prepared according to the general procedure described above starting from **2b** (2.00 g, 4.5 mmol) and *iso*butyraldehyde (0.27 g, 4.5 mmol). Compound **1bβ** was obtained as an oil (1.38 g) in 85% yield and was afforded as a mixture of *E*/*Z* isomers in 92/8 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.72. IR (neat) $\nu$ ($cm^{-1}$): 1037 (P–O), 1265 (P=O), 1625 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.04 (d, 6H, $CH(CH_3)_2$, $^4J_{HP} = 7$ Hz), 1.29 (t, 3H, $OCH_2CH_3$, $^3J_{HH} = 7$ Hz), 2.35–2.50 (m, 1H, $CH$), 3.85–4.20 (m, 6H, $OCH_2$, $NCH_2$), 5.70 (ddd, 1H, P(O)C$H_{ethyl.}$, $^2J_{HP} = 21$ Hz, $^3J_{HH} = 17$ Hz, $^4J_{HH} = 2$ Hz), 6.68 (ddd, 1H, $H_{ethyl.}$, $^3J_{HP} = 21$ Hz, $^3J_{HH} = 17$ Hz, $^3J_{HH} = 7$ Hz), 7.25–7.35 (m, 10H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 21.1 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.8 (d, $OCH_2CH_3$, $^3J_{CP} = 7$ Hz), 20.6 (d, $CH(CH_3)_2$, $^4J_{CP} = 2$ Hz), 31.9 (d, $CH(CH_3)_2$, $^3J_{CP} = 20$ Hz), 47.0–47.2 (m, $NCH_2$), 59.8 (d, $OCH_2$, $^2J_{CP} = 6$ Hz), 116.0 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 174$ Hz), 126.7 (s, $CH_{arom.}$), 127.8 (s, $CH_{arom.}$), 128.0 (s, $CH_{arom.}$), 137.2 (s, $C_{arom.}$), 156.6–156.8 (m, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.04 (d, 6H, $CH(CH_3)_2$, $^4J_{HP} = 7$ Hz), 1.29 (t, 3H, $OCH_2CH_3$, $^3J_{HH} = 7$ Hz), 2.35–2.50 (m, 1H, $CH$), 3.85–4.20 (m, 6H, $OCH_2$, $NCH_2$), 5.58 (dd, 1H, P(O)C$H_{ethyl.}$, $^2J_{HP} = 19$ Hz, $^3J_{HH} = 13$ Hz), 6.20 (ddd, 1H, $H_{ethyl.}$, $^3J_{HP} = 50$ Hz, $^3J_{HH} = 13$ Hz, $^3J_{HH} = 10$ Hz), 7.25–7.35 (m, 10H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.2 (s, 1P).

*4.6.2.7. (1-Butenyl)(dibenzylamino)(ethoxy)phosphine oxide (**1bγ**).* Compound **1bγ** was prepared according to the general procedure described above starting from **2b** (2.00 g, 4.5 mmol) and propanal (0.26 g, 4.5 mmol). Compound **1bγ** was obtained as an oil (1.37 g) in 86% yield and was afforded as a mixture of *E*/*Z* isomers in 80/20 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.64. IR (neat) $\nu$ ($cm^{-1}$): 1037 (P–O), 1235 (P=O), 1627 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.96 (t, 3H, $CH_2CH_3$, $^3J_{HH} = 7$ Hz), 1.15–1.31 (m, 3H, $OCH_2CH_3$), 2.07–2.21 (m, 2H, $CH_2CH_3$), 3.77–4.13 (m, 6H, $OCH_2$, $NCH_2$), 5.57–5.77 (m, 1H, P(O)C$H_{ethyl.}$), 6.56–6.78 (m, 1H, $H_{ethyl.}$), 7.12–7.31 (m, 10H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 20.7 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$

(ppm): 12.1 (s, $CH_2CH_3$), 16.4 (d, $OCH_2CH_3$, $^3J_{CP} = 6$ Hz), 27.1 (d, $CH_2CH_3$, $^3J_{CP} = 22$ Hz), 47.6 (d, $NCH_2$, $^2J_{CP} = 5$ Hz), 60.5 (d, $OCH_2$, $^2J_{CP} = 5$ Hz), 118.3 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 175$ Hz), 127.3 (s, $CH_{arom.}$), 128.4 (s, $CH_{arom.}$), 128.7 (s, $CH_{arom.}$), 137.7 (s, $C_{arom.}$), 152.9 (d, $CH_{ethyl.}$, $^2J_{CP} = 4$ Hz).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.96 (t, 3H, $CH_2CH_3$, $^3J_{HH} = 7$ Hz), 1.15–1.31 (m, 3H, $OCH_2CH_3$), 2.07–2.21 (m, 2H, $CH_2CH_3$), 3.77–4.13 (m, 6H, $OCH_2$, $NCH_2$), 5.52–5.70 (m, 1H, P(O)$CH_{ethyl.}$), 6.17–6.56 (m, 1H, $H_{ethyl.}$), 7.12–7.31 (m, 10H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.3 (s, 1P).

*4.6.2.8. (Dibenzylamino)(ethoxy)(2-methyl-1-propenyl)phosphine oxide (**1bδ**).* Compound **1bδ** was prepared according to the general procedure described above starting from **2b** (2.00 g, 4.5 mmol) and acetone (0.26 g, 4.5 mmol). Compound **1bδ** was afforded in mixture with allylic subproduct **12b** in 91/9. Derivative **1bδ** was obtained as an oil (1.22 g) in 78% yield. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.64. IR (neat) $\nu$ ($cm^{-1}$): 1029 (P–O), 1265 (P=O), 1634 (C=C).

$^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.20–1.35 (m, 3H, $OCH_2CH_3$), 1.91 (s, 3H, $CH_3$), 2.12–2.17 (m, 3H, $CH_3$), 3.88–4.25 (m, 6H, $OCH_2$, $NCH_2$), 5.45–5.58 (m, 1H, P(O)$CH_{ethyl.}$), 7.20–7.40 (m, 10H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.9 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.4 (d, $OCH_2CH_3$, $^3J_{CP} = 7$ Hz), 28.4 (d, $CH_3$, $^3J_{CP} = 23$ Hz), 47.7 (d, $NCH_2$, $^2J_{CP} = 5$ Hz), 59.9 (d, $OCH_2$, $^2J_{CP} = 6$ Hz), 115.1 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 177$ Hz), 127.3 (s, $CH_{arom.}$), 128.4 (s, $CH_{arom.}$), 128.8 (s, $CH_{arom.}$), 137.9 (s, $C_{arom.}$), 157.6 (d, $C_{ethyl.}$, $^2J_{CP} = 6$ Hz).

*4.6.2.9. (Ethoxy)(2-phenylethenyl)(piperidinyl)-phosphine oxide (**1cα**).* Compound **1cα** was prepared according to the general procedure described above starting from **1c** (2.00 g, 6.1 mmol) and benzaldehyde (0.65 g, 6.1 mmol). Compound **1cα** was obtained as an oil (1.43 g) in 84% yield (100% *E* isomer). $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.48. IR (neat) $\nu$ ($cm^{-1}$): 1034 (P–O), 1259 (P=O), 1607 (C=C). MS: $m/z = 279$ [M], 280 [M+1].

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.30–1.45 (m, 3H, $CH_3$), 1.46–1.65 (m, 6H, $CH_2$), 3.05–3.10 (m, 4H, $NCH_2$), 3.90–4.20 (m, 2H, $OCH_2$), 6.31 (dd, 1H, P(O)$CH_{ethyl.}$, $^2J_{HP} = 18$ Hz, $^3J_{HH} = 18$ Hz), 7.34–7.51 (m, 6H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.6 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.1 (br s, $OCH_2CH_3$), 24.5 (s, $CH_2$), 26.1 (d, $CH_2$, $^3J_{CP} = 5$ Hz), 44.5–44.6 (m, $NCH_2$), 59.6 (d, $OCH_2$, $^2J_{CP} = 5$ Hz), 116.5 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 176$ Hz), 127.3 (s, $CH_{arom.}$), 128.8 (s, $CH_{arom.}$), 129.5 (s, $CH_{arom.}$), 134.2 (s, $C_{arom.}$), 145.4 (d, $CH_{ethyl.}$, $^2J_{CP} = 5$ Hz).

*4.6.2.10. (3-Methyl-1-butenyl)(ethoxy)(piperidinyl)-phosphine oxide (**1cβ**).* Compound **1cβ** was prepared according to the general procedure described above starting from **1c** (2.00 g, 6.1 mmol) and *iso*butyraldehyde (0.37 g, 6.1 mmol). Compound **1cβ** was obtained as an oil (1.14 g) in 76% yield and was afforded as a mixture of *E*/*Z* isomers in 92/8 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.63. IR (neat) $\nu$ ($cm^{-1}$): 1040 (P–O), 1260 (P=O), 1623 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.05 (d, 6H, $CH(CH_3)_2$, $^4J_{HP} = 7$ Hz), 1.28–1.34 (m, 3H, $OCH_2CH_3$), 1.40–1.65 (m, 6H, $CH_2$), 2.35–2.50 (m, 1H, $CH(CH_3)_2$), 2.95–3.15 (m, 4H, $NCH_2$), 3.93–4.07 (m, 2H, $OCH_2$), 5.61 (ddd, 1H, P(O)$CH_{ethyl.}$, $^2J_{HP} = 21$ Hz, $^3J_{HH} = 17$ Hz, $^4J_{HH} = 2$ Hz), 6.57 (ddd, 1H, $H_{ethyl.}$, $^3J_{HP} = 21$ Hz, $^3J_{HH} = 17$ Hz, $^3J_{HH} = 6$ Hz). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 20.2 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.8 (d, $OCH_2CH_3$, $^3J_{CP} = 7$ Hz), 20.6 (d, $CH(CH_3)_2$, $^4J_{CP} = 2$ Hz), 24.2 (s, $CH_2$), 25.8 (s, $CH_2$), 32.0 (d, $CH(CH_3)_2$, $^3J_{CP} = 21$ Hz), 44.2 (s, $NCH_2$), 58.9–59.2 (m, $OCH_2$), 115.0 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 175$ Hz), 156.1 (s, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.05 (d, 6H, $CH(CH_3)_2$, $^4J_{HP} = 7$ Hz), 1.28–1.34 (m, 3H, $OCH_2CH_3$), 1.40–1.65 (m, 6H, $CH_2$), 2.35–2.50 (m, 1H, $CH(CH_3)_2$), 2.95–3.15 (m, 4H, $NCH_2$), 3.93–4.07 (m, 2H, $OCH_2$), 5.40–5.60 (m, 1H, P(O)$CH_{ethyl.}$), 6.12 (ddd, 1H, $H_{ethyl.}$, $^3J_{HP} = 49$ Hz, $^3J_{HH} = 13$ Hz, $^3J_{HH} = 10$ Hz). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 17.8 (s, 1P).

*4.6.2.11. (1-Butenyl)(ethoxy)(piperidinyl)phosphine oxide (**1cγ**).* Compound **1cγ** was prepared according to the general procedure described above starting from **1c** (2.00 g, 6.1 mmol) and propanal (0.35 g, 6.1 mmol). Compound **1cγ** was obtained as an oil (1.14 g) in 81% yield and was afforded as a mixture of *E*/*Z* isomers in 72/28 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.59. IR (neat) $\nu$ ($cm^{-1}$): 1040 (P–O), 1265 (P=O), 1619 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.07–1.10 (m, 3H, $CH_2CH_3$), 1.20–1.34 (m, 3H, $OCH_2CH_3$), 1.40–1.64 (m, 6H, $CH_2$), 2.18–2.25 (m, 2H, $CH_2CH_3$), 2.95–3.15 (m, 4H, $NCH_2$), 3.80–4.15 (m, 2H, $OCH_2$), 5.57–5.76 (m, 1H, P(O)$CH_{ethyl.}$), 6.54–6.76 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 19.8 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 12.0 (s, $CH_2CH_3$), 16.2 (s, $OCH_2CH_3$), 24.7 (s, $CH_2$), 26.1 (s, $CH_2$), 27.1 (d, $CH_2CH_3$, $^3J_{CP} = 21$ Hz), 44.7 (s, $NCH_2$), 59.3 (d, $OCH_2$, $^2J_{CP} = 5$ Hz), 117.4 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 176$ Hz), 151.6 (d, $CH_{ethyl.}$, $^2J_{CP} = 4$ Hz).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.07–1.10 (m, 3H, $CH_2CH_3$), 1.20–1.34 (m, 3H, $OCH_2CH_3$), 1.40–1.64 (m, 6H, $CH_2$), 2.18–2.25 (m, 2H, $CH_2CH_3$), 2.95–3.15 (m, 4H, $NCH_2$), 3.80–4.15 (m, 2H, $OCH_2$), 5.46–5.69 (m, 1H, P(O)$CH_{ethyl.}$), 6.17–6.49 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 17.8 (s, 1P).

*4.6.2.12. (Ethoxy)(2-methyl-1-propenyl)(piperidinyl)-phosphine oxide (**1cδ**).* Compound **1cδ** was prepared according to the general procedure described above starting from **1c** (2.00 g, 6.1 mmol) and acetone (0.35 g, 6.1 mmol). Compound **1cδ** was afforded in mixture with allylic subproduct **12c** in 74/26. Derivative **1cδ** was obtained as an oil (0.89 g) in 63% yield. IR (neat) $\nu$ ($cm^{-1}$): 1029 (P–O), 1255 (P=O), 1634 (C=C).

$^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.25–1.40 (m, 3H, $OCH_2CH_3$), 1.43–1.62 (m, 6H, $CH_2$), 1.89 (s, 3H, $CH_3$), 2.00–2.07 (m, 3H, $CH_3$), 2.94–3.15 (m, 4H, $NCH_2$), 3.82–4.14 (m, 2H, $OCH_2$), 5.33–5.47 (m, 1H, $P(O)CH_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 18.6 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.4 (s, $OCH_2CH_3$), 24.4 (s, $CH_2$), 26.0 (s, $CH_2$), 28.0 (d, $CH_3$, $^3J_{CP} = 23$ Hz), 44.3 (s, $NCH_2$), 61.9 (d, $OCH_2$, $^2J_{CP} = 5$ Hz), 114.4 (d, $P(O)CH_{ethyl.}$, $^1J_{CP} = 177$ Hz), 156.8 (d, $C_{ethyl.}$, $^2J_{CP} = 6$ Hz).

*4.6.2.13. (Methyl)(2-phenylethenyl)(isopropyloxy)-phosphine oxide (**1dα**).* Compound **1dα** was prepared according to the general procedure described above starting from **2d** (2.00 g, 7.3 mmol) and benzaldehyde (0.78 g, 7.3 mmol). Compound **1dα** was obtained as an oil (1.46 g) in 89% yield and was afforded as a mixture of *E*/*Z* isomers in 93/7 ratio. For spectroscopic data see Ref. [14].

*4.6.2.14. (3-Methyl-1-butenyl)(isopropyloxy)(methyl)-phosphine oxide (**1dβ**).* Compound **1dβ** was prepared according to the general procedure described above starting from **2d** (2.00 g, 7.3 mmol) and *iso* butyraldehyde (0.44 g, 7.3 mmol). Compound **1dβ** was obtained as an oil (0.79 g) in 57% yield and was afforded as a mixture of *E*/*Z* isomers in 93/7 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.63. IR (neat) $\nu$ ($cm^{-1}$): 1034 (P–O), 1254 (P=O), 1628 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.90–1.05 (m, 6H, $CH(CH_3)_2$), 1.10–1.30 (m, 6H, $OCH(CH_3)_2$), 1.29–1.47 (m, 3H, $P(O)CH_3$), 3.87–4.00 (m, 1H, CH), 4.35–4.60 (m, 1H, OCH), 5.35–5.65 (m, 1H, $P(O)CH_{ethyl.}$), 6.50–6.75 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 37.5 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 20.1–20.6 (m, $CH(CH_3)_2$), 21.9 (d, $P(O)CH_3$, $^1J_{CP} = 184$ Hz), 31.3–32.1 (m, $CH(CH_3)_2$), 69.1–69.8 (m, $OCH(CH_3)_2$), 118.1 (d, $P(O)CH_{ethyl.}$, $^1J_{CP} = 127$ Hz), 157.5–157.8 (m, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 0.90–1.05 (m, 6H, $CH(CH_3)_2$), 1.10–1.30 (m, 6H, $OCH(CH_3)_2$), 1.29–1.47 (m, 3H, $P(O)CH_3$), 3.87–4.00 (m, 1H, CH), 4.35–4.60 (m, 1H, OCH), 5.35–5.65 (m, 1H, $P(O)CH_{ethyl.}$), 6.50–6.75 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 36.5 (s, 1P).

*4.6.2.15. (1-Butenyl)(isopropyloxy)(methyl)phosphine oxide (**1dγ**).* Compound **1dγ** was prepared according to the general procedure described above starting from **1d** (2.00 g, 7.3 mmol) and propanal (0.43 g, 7.3 mmol). Compound **1dγ** was obtained as an oil (0.92 g) in 71% yield and was afforded as a mixture of *E*/*Z* isomers in 86/14 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.70. IR (neat) $\nu$ ($cm^{-1}$): 1029 (P–O), 1265 (P=O), 1634 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.02–1.11 (m, 3H, $CH_2CH_3$), 1.28–1.38 (m, 6H, $C(CH_3)_2$), 1.50 (d, 3H, $P(O)CH_3$, $^2J_{HP} = 14$ Hz), 2.18–2.30 (m, 2H, $CH_2CH_3$), 4.50–4.75 (m, 1H, CH), 5.50–5.81 (m, 1H, $P(O)CH_{ethyl.}$), 6.71–7.02 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 37.3 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 11.7 (s, $CH_2CH_3$), 13.2 (d, $P(O)CH_3$, $^1J_{CP} = 184$ Hz), 23.8 (d, $C(CH_3)_2$, $^3J_{CP} = 4$ Hz), 24.2 (d, $C(CH_3)_2$, $^3J_{CP} = 4$ Hz), 27.4 (s, $CH_2CH_3$), 68.4–68.6 (m, $OCH(CH_3)_2$), 120.4 (d, $P(O)CH_{ethyl.}$, $^1J_{CP} = 137$ Hz), 153.4–153.9 (m, $CH_{ethyl.}$).

Isomer *Z*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.02–1.11 (m, 3H, $CH_2CH_3$), 1.28–1.38 (m, 6H, $C(CH_3)_2$), 1.50 (d, 3H, $P(O)CH_3$, $^2J_{HP} = 14$ Hz), 2.18–2.30 (m, 2H, $CH_2CH_3$), 4.50–4.75 (m, 1H, CH), 5.50–5.60 (m, 1H, $P(O)CH_{ethyl.}$), 6.26–6.57 (m, 1H, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 36.8 (s, 1P).

*4.6.2.16. (Phenyl)(2-phenylethenyl)(ethoxy)-phosphine oxide (**1eα**).* Compound **1eα** was prepared according to the general procedure described above starting from **2e** (2.00 g, 6.2 mmol) and benzaldehyde (0.66 g, 6.2 mmol). Compound **1eα** was obtained as an oil (1.46 g) in 86% yield (100% *E* isomer). $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.68. For spectroscopic data see Ref. [15].

*4.6.2.17. (3-Methyl-1-butenyl)(ethoxy)(phenyl)-phosphine oxide (**1eβ**).* Compound **1eβ** was prepared according to the general procedure described above starting from **2e** (2.00 g, 6.2 mmol) and *iso* butyraldehyde (0.38 g, 6.2 mmol). Compound **1eβ** was obtained as an oil (1.04 g) in 70% yield (100% *E* isomer). $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.67. IR (neat) $\nu$ ($cm^{-1}$): 1034 (P–O), 1265 (P=O), 1623 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.00–1.07 (m, 6H, $CH(CH_3)_2$), 1.25–1.40 (m, 3H, $OCH_2CH_3$), 2.35–2.55 (m, 1H, CH), 3.85–4.15 (m, 2H, $OCH_2$), 5.75–5.91 (m, 1H, $P(O)CH_{ethyl.}$), 6.67–6.85 (m, 1H, $H_{ethyl.}$), 7.43–7.83 (m, 5H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 28.6 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.1 (d, $OCH_2CH_3$, $^3J_{CP} = 6$ Hz), 20.7 (s, $CH(CH_3)_2$), 32.5 (d, $CH(CH_3)_2$, $^3J_{CP} = 18$ Hz), 60.3 (d, $OCH_2$, $^2J_{CP} = 6$ Hz), 117.5 (d, $P(O)CH_{ethyl.}$, $^1J_{CP} = 137$ Hz), 128.0 (s, $CH_{arom.}$), 131.1 (s, $CH_{arom.}$), 132.0 (s, $CH_{arom.}$), 133.0 (s, $C_{arom.}$), 158.7 (d, $CH_{ethyl.}$), $^2J_{CP} = 3$ Hz).

*4.6.2.18. (1-Butenyl)(ethoxy)(phenyl)phosphine oxide (**1eγ**).* Compound **1eγ** was prepared according to the general procedure described above starting from **2e** (2.00

g, 6.2 mmol) and propanal (0.35 g, 6.2 mmol). Compound **1eγ** was obtained as an oil (1.21 g) in 87% yield and was afforded as a mixture of *E*/*Z* isomers in 91/9 ratio. $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.61. For spectroscopic data see Ref. [16].

*4.6.2.19. (Ethoxy)(phenyl)(2-methyl-1-propenyl)-phosphine oxide (**1eδ**).* Compound **1eδ** was prepared according to the general procedure described above starting from diphosphorylated derivative **2e** (2.00 g, 6.2 mmol) and acetone (0.36 g, 6.2 mmol). Compound **1eδ** was afforded in mixture with allylic subproduct **12e** in 69/31 ratio. Derivative **1eδ** was obtained as an oil (0.87 g) in 62% yield. IR (neat) $\nu$ ($cm^{-1}$): 1030 (P–O), 1203 (P=O), 1633 (C=C).

$^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.22–1.40 (m, 3H, $OCH_2CH_3$), 1.91 (s, 3H, $CH_3$), 2.01–2.11 (m, 3H, $CH_3$), 3.97–4.09 (m, 2H, $OCH_2$), 5.60–5.72 (m, 1H, P(O)$CH_{ethyl.}$), 7.45–7.76 (m, 5H, $H_{arom.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 27.6 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 16.4 (d, $OCH_2CH_3$, $^3J_{CP} = 7$ Hz), 28.4 (d, $CH_3$, $^3J_{CP} = 21$ Hz), 60.0–60.1 (m, $OCH_2$), 116.2 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 142$ Hz), 128.2 (s, $CH_{arom.}$), 131.1 (s, $CH_{arom.}$), 131.8 (s, $CH_{arom.}$), 134.3 (s, $C_{arom.}$), 159.0 (d, $C_{ethyl.}$, $^2J_{CP} = 6$ Hz).

*4.6.2.20. (Ethoxy)(ethylthio)(2-phenylethenyl)-phosphine oxide (**1fα**).* Compound **1fα** was prepared according to the general procedure described above starting from **2f** (2.00 g, 6.6 mmol) and benzaldehyde (0.70 g, 6.6 mmol). Compound **1fα** was obtained as an oil (0.85 g) in 54% yield (100% *E* isomer). $R_f$ (acetone–AcOEt–hexane: 1/1/1): 0.68. IR (neat) $\nu$ ($cm^{-1}$): 1039 (P–O), 1249 (P=O), 1607 (C=C). MS: $m/z = 256$ [M], 258 [M+2].

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.23–1.43 (m, 6H, $CH_3$), 2.68–2.87 (m, 2H, $SCH_2$), 3.91–4.28 (m, 2H, $OCH_2CH_3$), 6.36 (dd, 1H, P(O)$CH_{ethyl.}$, $^2J_{HP} = 23$ Hz, $^3J_{HH} = 17$ Hz), 7.14–7.64 (m, 6H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 40.2 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 20.3–21.3 (m, $CH_3$), 24.4 (s, $SCH_2$), 61.3 (s, $OCH_2$), 114.3 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 190$ Hz), 127.3 (s, $CH_{arom.}$), 128.4 (s, $CH_{arom.}$), 129.8 (s, $CH_{arom.}$), 134.3–134.8 (m, $C_{arom.}$), 148.0 (s, $CH_{ethyl.}$).

*4.6.2.21. (Ethylthio)(isopropyloxy)(2-phenylethenyl)-phosphine oxide (**1gα**).* Compound **1gα** was prepared according to the general procedure described above starting from **2g** (2.00 g, 6.3 mmol) and benzaldehyde (0.67 g, 6.3 mmol). Compound **1gα** was obtained as an oil (0.97 g) in 61% yield (100% *E* isomer). IR (neat) $\nu$ ($cm^{-1}$): 1024 (P–O), 1259 (P=O), 1618 (C=C).

Isomer *E*: $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.30–1.45 (m, 9H, $CH_3$), 2.80–2.95 (m, 2H, $SCH_2$), 4.80–5.00 (m, 1H, $CH$), 6.42 (dd, 1H, P(O)$CH_{ethyl.}$, $^2J_{HP} = 23$ Hz, $^3J_{HH} = 17$ Hz), 7.35–7.60 (m, 6H, $H_{arom.}$, $H_{ethyl.}$). $^{31}$P-NMR ($CDCl_3$) $\delta$ (ppm): 39.7 (s, 1P). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 15.8 (d, $CH_2CH_3$, $^3J_{CP} = 6$ Hz), 23.7 (d, $CH_3$, $^3J_{CP} = 4$ Hz), 29.1 (s, $SCH_2$), 71.0 (d, $OCH(CH_3)_2$, $^2J_{CP} = 7$ Hz), 119.1 (d, P(O)$CH_{ethyl.}$, $^1J_{CP} = 153$ Hz), 127.5 (s, $CH_{arom.}$), 128.5 (s, $CH_{arom.}$), 129.9 (s, $CH_{arom.}$), 146.5 (d, $C_{ethyl.}$, $^2J_{CP} = 6$ Hz), 162.0 (s, $CH_{arom.}$).

### 4.7. $^{31}$P-NMR data and $R_f$ of 11(α-γ) and 12(a–c, e)

| | $R_1$ | $R_2$ | $\delta_{(ppm,\ CDCl_3)}$ | *R*f |
|---|---|---|---|---|
| **11α** | Ph | H | 17.1 (s, 1P) | 0.55 |
| **11β** | $^i$Pr | H | 17.3 (s, 1P) | 0.47 |
| **11γ** | Et | H | 16.8 (s, 1P) | 0.45 |

| | Z | Nu | $\delta_{(ppm,\ CDCl3)}$ |
|---|---|---|---|
| **12a** | $NMe_2$ | OEt | 28.9 (s, 1P) |
| **12b** | $NBn_2$ | OEt | 28.7 (s, 1P) |
| **12c** |  | OEt | 27.3 (s, 1P) |
| **12e** | Ph | OEt | 38.2 (s, 1P) |

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