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TiO_2 as a new and reusable catalyst for one-pot three-component syntheses of α-aminophosphonates in solvent-free conditions

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ABSTRACT

Commercially available titania (TiO_2) is reported as an extremely efficient catalyst for the synthesis of α-aminophosphonates. A three-component reaction of an amine, an aldehyde or a ketone and a dialkyl phosphite (Kabachnik–Fields reaction) took place in one-pot, under solvent-free conditions to afford the corresponding α-aminophosphonates in high yields and short times. The TiO_2 catalyzed α-aminophosphonate synthesis in the present study perhaps represents a true three-component reaction as no intermediate formation of either an imine or α-hydroxyphosphonate was observed that indicated the simultaneous involvement of the carbonyl compound, the amine and the phosphite in the transition state. Furthermore, the catalyst can be reused for several times without any significant loss of catalytic activity.

1. Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes,[1] and compounds of tetracoordinated pentavalent phosphorus are widely used as biologically active compounds. The key role of naturally occurring amino acids in the chemistry of life and as structural units in peptides, proteins and enzymes has led to intense interest in the chemistry and biological activity of synthetic analogues. For a long time the so-called 'phosphorus analogues' of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, $P(O)(OH)_2$, or phosphinic acid group, P(O)(OH)R (in which R may be H, alkyl, or aryl), as well as a phosphonate group, $P(O)(OR)_2$ (in which R may be alkyl, or aryl), have attracted particular interest in the preparation of isosteric or bioisosteric analogues of numerous natural products.[2,3] In this area, α-aminophosphonates as bioisosteric analogue of α-amino acids occupy an important place and reveal diverse and interesting biological and biochemical properties: antibacterial agents,[4] enzyme inhibitors[5] (including HIV protease),[6] antiviral agents[7] as well as their role for antibody generation.

Among the various synthetic approaches to them, nucleophilic addition of phosphites to imines is established as the most useful method to construct such significant scaffold. Generally, these transformations could be fulfilled under the catalysis of Bronsted[8] or Lewis acids.[9,10]

However, these methods are not devoid of limitations as many imines are hygroscopic and are not sufficiently stable for isolation. The first one-pot synthesis of α-aminophosphonates has been achieved by the reaction of phosphite in the presence of lanthanide triflate[11] as the catalyst with imines generated in situ from aldehydes and amines in organic solvent. Subsequently, one-pot variations in organic solvents have been improved.[12–21]

Besides, it was reported that solvent-free transformations of phosphites to α-aminophosphonates could be accomplished in the presence of acidic catalysts.[22–25] Moreover, ionic liquid, microwave assisted and ultrasonic assisted reactions proved to be a kind of promising medium for such three-component Mannich-type couplings.[26–28] However, all the existing methods displayed drawbacks, such as environmental pollution caused by utilization of organic solvents, long reaction time, unsatisfactory yields, complicated operations and do not work well with electron deficient amines such as nitro anilines. Therefore, it is necessary to further develop an efficient and convenient method to construct such significant scaffold.

The use of metal oxides catalysts has received considerable attention in organic synthesis due to their environmental compatibility, ease of handling, non-toxic nature and above all their reusability and the development of solvent-less protocol has an added advantage in the green context. In this pursuit, and during the course of my studies aimed at developing solvent-free procedures,[29] herein, for the first time, titania is reported as a new catalyst for the synthesis of α-aminophosphonates in solvent-free conditions (Scheme 1).

In order to delineate the standard operating conditions, the reaction between 4-methoxybenzaldehyde, 4-nitroaniline and

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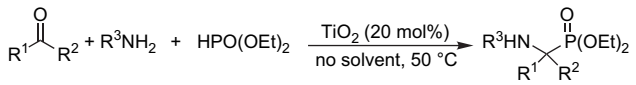


Scheme 1.

diethyl phosphite was chosen as a model. It is important to note that the presence of the methoxy group in 4-methoxybenzaldehyde reduces the electrophilicity of the carbonyl carbon through resonance and the strong electron-withdrawing property of nitro group in 4-nitroaniline decreases the nucleophilicity of the amine group. Thus, the combination of these substrates constitutes a model reaction for evaluating the efficiency of a catalyst (Table 1). Recently, TiO_2 was reported as an efficient catalyst for the Beckmann rearrangement, synthesis of bis(indolyl)methanes and Knoevenagel condensations.[29h,i,30] Herein, it was found that the use of 20 mol % of TiO_2 resulted in quantitative formation of the corresponding α-aminophosphonates in solvent-free conditions at room temperature within 7 h (entry 1). Increase in the reaction temperature led to formation of α-aminophosphonates in better yield, in 4 h. No yields were obtained when the condensation reaction was carrying out in solvents such as MeCN, THF, EtOH and PhMe (entries 3–6). Next the catalytic efficiency of other metal oxides such as ZnO, MgO and CuO was explored. However, MgO and CuO did not exhibit any significant catalytic activity and only a 60% yield was obtained in the presence of ZnO establishing that amongst the various metal oxides used, TiO_2 was the most effective in catalyzing α-aminophosphonates' formation.

To establish the generality, various aldehydes/ketones and amines were subjected to a one-pot three-component reaction catalyzed by TiO_2 (Table 2). It was found that obvious electronic and steric effects from aromatic aldehydes existed in the three-component couplings. Aromatic aldehydes with both electron-donating and withdrawing groups could be accomplished the one-pot reaction (Table 2, entries 1, 2 and 9) could be accomplished the one-pot reaction as well as that with electron-withdrawing group like *p*-nitro (Table 2, entry 9). Besides, the steric effect from the substituent positions seemed to be another remarkable impact. For *p*-chloro, *m*-chloro, *o*-chloro and 2,6-dichlorobenzaldehyde (Table 2, entries 4–6 and 10, respectively), the reaction time was prolonged while the yields of products were decreased in such a sequence. The reaction was compatible with various functional groups such as Cl, OMe, NO_2, OH, NMe_2, CN and CO_2Me that do not interfere by competitive complex formation with the catalyst. Excellent chemoselectivity was also observed for substrates containing a halogen atom and a double bond conjugated to a carbonyl group that did not experience any competitive aromatic nucleophilic substitution of the halogen atom and conjugate addition to the α,β-unsaturated carbonyl group, respectively.

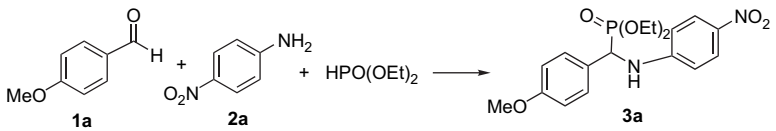
Moreover, heteroaromatic and aliphatic aldehydes were all effective substrates to successfully execute the solvent-free Mannich-type reactions by TiO_2. However, isobutyraldehyde (Table 2, entry 13) was unable to provide the expected product in yield as high as those of aromatic aldehydes. In addition to aldehydes, some ketones were also screened to carry out the three-component couplings by TiO_2 and solvent-free conditions. Due to the lower reactivity than that of aldehydes, the coupling reactions involved with ketones had to be carried out at 100 °C under solvent-free conditions. For aliphatic ketones like cyclohexanone and 3,3-dimethyl-2-butanone (Table 2, entries 14 and 15), the expected compound could be smoothly achieved in 90 and 55% yields. However, no products were gained when aromatic ketones such as acetophenone (Table 2, entry 16) was involved in such one-pot reaction under catalyst and solvent-free conditions.

It was found there was no remarkable electronic and position effects on the three-component couplings from the aromatic amines, since anilines with *p*-, *o*- and *m*-substituents (Table 2, entries 17–29) resulted in the corresponding α-aminophosphonates in excellent yields, while *p*-methoxyaniline (Table 2, entry 29) and *m*-trifluromethylaniline (Table 2, entry 18) were both highly efficient substrates in this catalyst and solvent-free procedure. Apart from the above amines, aliphatic amines were also selected to carry out the three-component couplings. As for pyridine-2-methyl amine, propyl amine, ethylene diamine and 3-aminopropanol amine (Table 2, entries 30–33), they could provide the target products in reasonable yield. Secondary amines like piperidine, and morpholine (Table 2, entries 34 and 35) were ineffective partners for such a reaction. To evaluate the efficiency of this catalyst system as a general methodology the reaction of an amino acid was carried out under such reaction conditions (Table 2, entry 36). It was shown that the yield of the reaction was excellent and no competitive nucleophilic substitution of the acidic group was observed.

The ability to recycle and reuse TiO_2 and the catalytic activity of TiO_2 was studied in this system. The catalyst can be so easily separated by dispersing the reaction mixture in water that the recovery and reuse of TiO_2 could be very convenient. As shown in Table 3, the yields of **3a** only decrease a little after the reuse of TiO_2 for five times.

In conclusion, herein commercially TiO_2 has been described as a new and extremely efficient catalyst for synthesis of α-aminophosphonate by a three-component, one-pot reaction. With the increasing concern for need of green synthetic procedures, the

Table 1
Optimization of the synthesis of α-aminophosphonate **3a**

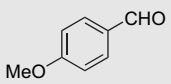
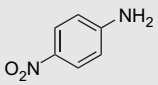
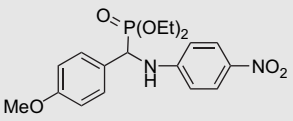
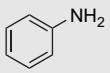
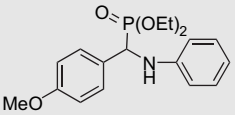
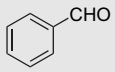
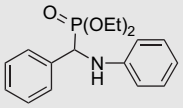
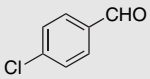
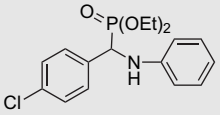
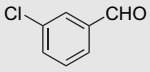
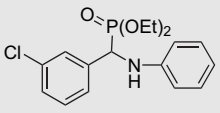
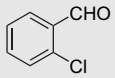
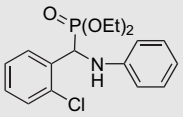
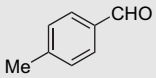
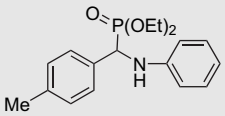
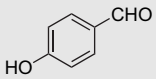
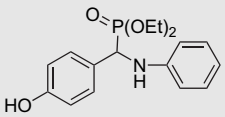
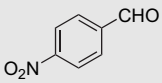
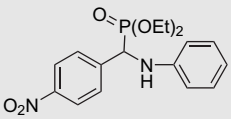
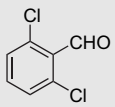
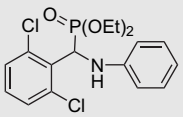
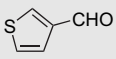
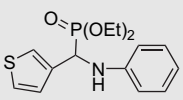
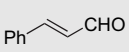
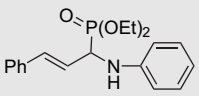
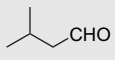
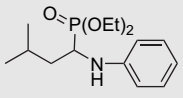
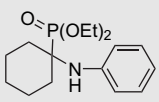


1a **2a** **3a**

Entry	Catalyst	Solvent/temp	Time (h)	Yield[a] (%)
1	TiO_2 (20 mol %)	Solvent-free/rt	7	78
2	TiO_2 (20 mol %)	Solvent-free/50 °C	4	98
3	TiO_2 (20 mol %)	MeCN/50 °C	48	0
4	TiO_2 (20 mol %)	THF/50 °C	48	0
5	TiO_2 (20 mol %)	EtOH/50 °C	48	0
6	TiO_2 (20 mol %)	PhMe/50 °C	48	0
7	ZnO (20 mol %)	Solvent-free/100 °C	24	60
8	MgO (20 mol %)	Solvent-free/100 °C	24	0
9	CuO (20 mol %)	Solvent-free/100 °C	24	0

[a] Isolated yields.

Table 2
Synthesis of α-aminophosphonates catalyzed by TiO_2

Entry	Carbonyl compounds	Amine	Product		Time (h)	Yields[a] (%)
1	 **1a**	 **2a**		**3a**	4	98
2	**1a**	 **2b**		**3b**	2.5	98
3	 **1b**	**2b**		**3c**	3.5	98
4	 **1c**	**2b**		**3d**	2	98
5	 **1d**	**2b**		**3e**	3.5	90
6	 **1e**	**2b**		**3f**	5	87
7	 **1f**	**2b**		**3g**	4.5	98
8	 **1g**	**2b**		**3h**	3	98
9	 **1h**	**2b**		**3i**	1	95
10	 **1i**	**2b**		**3j**	7	72
11	 **1j**	**2b**		**3k**	1.5	90
12	 **1k**	**2b**		**3l**	3.5	87
13	 **1l**	**2b**		**3m**	5	75
14	 **1m**	**2b**		**3n**	2	90[b]

(*continued on next page*)

Table 2 (*continued*)

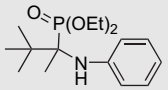
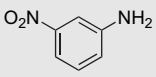
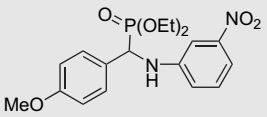
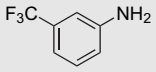
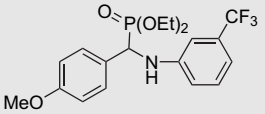
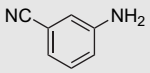
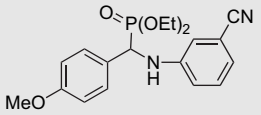
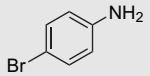
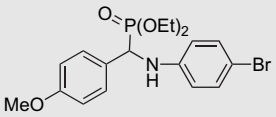
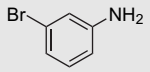
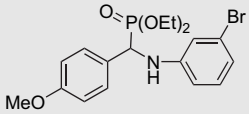
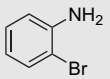
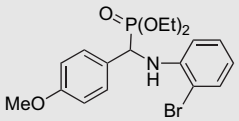
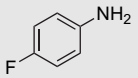
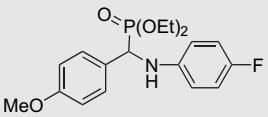
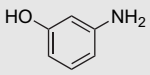
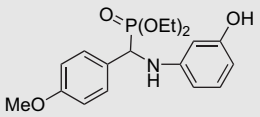
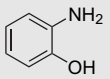
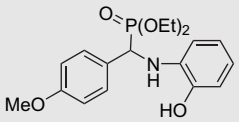
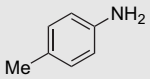
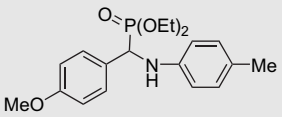
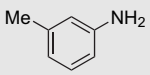
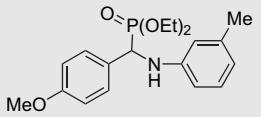
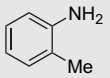
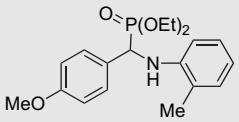
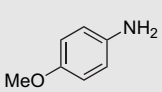
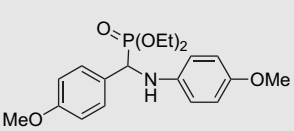
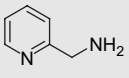
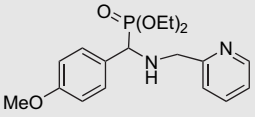
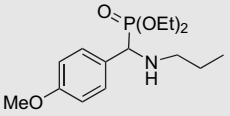
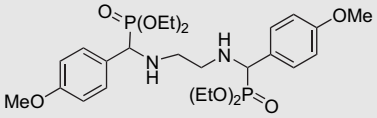
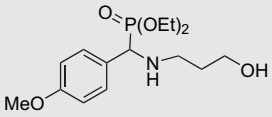
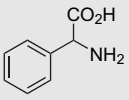
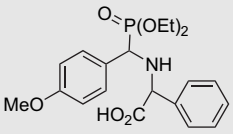
Entry	Carbonyl compounds	Amine	Product		Time (h)	Yields[a] (%)
15	 **1n**	**2b**		**3o**	5	55[b]
16	 **1o**	**2b**	No reaction			
17	**1a**	 **2c**		**3p**	4	87
18	**1a**	 **2d**		**3q**	5	93
19	**1a**	 **2e**		**3r**	6	85
20	**1a**	 **2f**		**3s**	5	80
21	**1a**	 **2g**		**3t**	1	90
22	**1a**	 **2h**		**3u**	2	80
23	**1a**	 **2i**		**3v**	6	80
24	**1a**	 **2j**		**3w**	0.5	93
25	**1a**	 **2k**		**3x**	2	95
26	**1a**	 **2l**		**3y**	6	70
27	**1a**	 **2m**		**3z**	2.5	87
28	**1a**	 **2n**		**3aa**	2	85
29	**1a**	 **2o**		**3ab**	1	98

Table 2 (*continued*)

Entry	Carbonyl compounds	Amine	Product		Time (h)	Yields[a] (%)
30	**1a**	 **2p**		**3ac**	5	76
31	**1a**	$CH_3CH_2CH_2NH_2$ **2q**		**3ad**	3	85
32	**1a**	$H_2NCH_2CH_2NH_2$ **2r**		**3ae**	2	50[c]
33	**1a**	$HOCH_2CH_2CH_2NH_2$ **2s**		**3af**	2	78
34	**1a**	 **2t**	No reaction			
35	**1a**	 **2u**	No reaction			
36	**1a**	 **2v**		**3ag**	3	90

[a] Yields are the isolated compounds.
[b] Reaction was performed at 100 °C.
[c] Conditions: diamine (1 mmol), aldehyde (2 mmol) and diethyl phosphite (2 mmol).

Table 3
Reuse of TiO_2

Number of use	Yield (%)	Recovery of TiO_2
1	98	96
2	94	95
3	92	95
4	92	95
5	90	93

advantages such as (i) solvent-free reaction, (ii) high yields, (iii) excellent chemoselectivity and (iv) ease of product isolation/purification fulfil the triple bottom line philosophy of green chemistry and make the present methodology environmentally benign.

2. Experimental

2.1. General

^1H NMR and ^{13}C NMR spectra were measured on Bruker Advance DPX FT 250 and 62.9 MHz spectrometry with TMS as an internal standard. IR spectra were obtained on a Perkin–Elmer or FTIR-800 instruments. Mass spectra were obtained on a Shimadzu GCMS0QP 1000EX at 20 and/or 70 eV. Elemental analyses were performed on Thermo Finnigan, Flash EA 1112 series microanalyzer by the head of the CHN lab.

2.2. General procedure

The required carbonyl compound (1 mmol), an amine (1 mmol) and diethyl phosphite (1 mmol) were added to TiO_2 (20 mol %, 0.016 g) and the mixture was heated in an oil bath at 50 °C. The progress of the reaction was monitored by TLC (eluent: EtOAc/*n*-hexane, 20:80). After the reaction was complete, EtOAc (2×20 mL) was added to the reaction mixture and the catalyst was separated by filtration. The organic solvent was removed under reduced pressure. After purification by chromatography on silica gel (ethyl acetate/*n*-hexane 20:80) the α-amino phosphonates were obtained. All products were characterized by NMR, IR and mass spectral data, which for known compounds were found to be identical with those described in the literature and only ^1H NMR data are shown, and for new compounds the complete spectroscopic data are described as bellow.

2.2.1. Compound ***3a***[13,28]

Yellow solid, mp 112 °C (lit. 115 °C); δ_H (250 MHz, $CDCl_3$): 0.89 (3H, t, J_{HH} 7.1 Hz, –OCH_2Me), 0.97 (3H, t, J_{HH} 7.1 Hz, –OCH_2Me), 3.42 (3H, s, PhO*Me*), 3.81–3.90 (4H, m, –OCH_2CH_3), 4.55 (1H, d, J_{HP} 23.7 Hz, –*CH*P), 6.38 (2H, d, *J* 9.1 Hz, Ar*H*), 6.55 (2H, d, *J* 8.5 Hz, Ar*H*), 6.65 (1H, br s, –N*H*), 7.13 (2H, dd, *J* 8.5, 2.1 Hz, Ar*H*), 7.96 (2H, d, *J* 9.1 Hz, Ar*H*).

2.2.2. Compound ***3b***[11,15]

Viscous colourless oil; δ_H (250 MHz, $CDCl_3$): 1.04 (3H, t, J_{HH} 6.9 Hz, –OCH_2Me), 1.21 (3H, t, J_{HH} 6.9 Hz, –OCH_2Me), 3.69 (3H, s,

PhO *Me*), 3.61–4.07 (4H, m, –OC*H*$_2$CH$_3$), 4.63 (1H, d, J_{HP} 23.7 Hz, C*H*P), 5.20 (1H, br s, –N*H*), 6.52 (2H, d, *J* 7.7 Hz, Ar*H*), 6.63 (1H, t, *J* 7.1 Hz, Ar*H*), 6.77 (2H, t, *J* 7.1 Hz, Ar*H*), 7.02 (2H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 7.33 (2H, d, *J* 8.5 Hz, Ar*H*).

2.2.3. Compound **3c**[11,27a]

White solid, mp 86 °C (lit. 90–91 °C); δ_H (250 MHz, $CDCl_3$): 1.15 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.32 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 3.73–3.82 (1H, m, –OC*H*$_2$CH$_3$), 3.92–3.99 (1H, m, –OC*H*$_2$CH$_3$), 4.13–4.21 (2H, m, –OC*H*$_2$CH$_3$), 4.85 (1H, d, J_{HP} 24.5 Hz, C*H*P), 6.66–6.71 (2H, m, Ar*H*), 6.90 (1H, br s, –N*H*), 7.10–7.16 (2H, m, Ar*H*), 7.27–7.56 (7H, m, Ar*H*).

2.2.4. Compound **3d**[31]

White solid, mp 57 °C (lit. 60 °C); δ_H (250 MHz, $CDCl_3$): 1.16 (3H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 1.28 (3H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 3.71–3.76 (1H, m, –OC*H*$_2$CH$_3$), 3.77–3.84 (1H, m, –OC*H*$_2$CH$_3$), 4.09–4.17 (2H, m, –OC*H*$_2$CH$_3$), 4.77 (1H, d, J_{HP} 24.4 Hz, C*H*P), 5.9 (1H, br s, –N*H*), 6.60 (2H, d, *J* 7.7 Hz, Ar*H*), 6.71 (1H, t, *J* 7.2 Hz, Ar*H*), 7.10 (2H, t, *J* 7.5 Hz, Ar*H*), 7.30 (2H, dd *J* 8.0, 2.1 Hz, Ar*H*), 7.42 (2H, d, *J* 8.0 Hz, Ar*H*).

2.2.5. Compound **3e**[31]

White solid, mp 90 °C (lit. 88–90 °C); δ_H (259 MHz, $CDCl_3$): 1.22 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.29 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 3.79–3.81 (1H, m, –OC*H*$_2$CH$_3$), 3.88–3.98 (1H, m, –OC*H*$_2$CH$_3$), 4.11–4.18 (2H, m, –OC*H*$_2$CH$_3$), 4.76 (1H, d, J_{HP} 24.5 Hz, C*H*P), 5.55 (1H, br s, –N*H*), 6.59 (2H, d, *J* 7.7 Hz, Ar*H*), 6.72 (1H, t, *J* 7.2 Hz, Ar*H*), 7.12 (2H, t, *J* 8.0 Hz, Ar*H*), 7.22–7.29 (2H, m, Ar*H*), 7.39 (1H, d, *J* 7.5 Hz, Ar*H*), 7.50 (1H, s, Ar*H*).

2.2.6. Compound **3f**[28]

White solid, mp 88 °C (lit. 88–90 °C); δ_H (250 MHz, $CDCl_3$): 0.95 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.20 (3H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 3.53–3.56 (1H, m, –OC*H*$_2$CH$_3$), 3.75–3.82 (1H, m, –OC*H*$_2$CH$_3$), 4.09–4.15 (2H, m, –OC*H*$_2$CH$_3$), 5.33 (1H, d, J_{HP} 24.8 Hz, C*H*P), 6.4 (1H, br s, –N*H*), 6.56 (2H, d, *J* 7.8 Hz, Ar*H*), 6.58 (1H, t, *J* 7.2 Hz, Ar*H*), 6.95–7.10 (6H, m, Ar*H*).

2.2.7. Compound **3g**[11,15]

White solid, mp 60 °C (lit. 62–64 °C); δ_H (250 MHz, $CDCl_3$): δ 0.97 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.10 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 2.12 (3H, s, Ph*Me*), 3.52–3.55 (1H, m, –OC*H*$_2$CH$_3$), 3.73–3.80 (1H, m, –OC*H*$_2$CH$_3$), 3.92–4.00 (2H, m, –OC*H*$_2$CH$_3$), 4.61 (1H, d, J_{HP} 24.1 Hz, C*H*P), 5.73 (1H, br s, –N*H*), 6.44–6.53 (3H, m, Ar*H*), 6.79–7.02 (4H, m, Ar*H*), 7.22 (2H, d, *J* 6.0 Hz, Ar*H*).

2.2.8. Compound **3h**[32]

Viscous colourless oil; δ_H (250 MHz, $CDCl_3$): 0.89 (3H, t, J_{HH} 7.1 Hz, –OCH$_2$ *Me*), 1.08 (3H, t, J_{HH} 7.1 Hz, –OCH$_2$*Me*), 3.48–3.54 (1H, m, –OC*H*$_2$CH$_3$), 3.70–3.76 (1H, m, –OC*H*$_2$CH$_3$), 3.84–3.91 (2H, m, –OC*H*$_2$CH$_3$), 4.55 (1H, d, J_{HP} 23.6 Hz, C*H*P), 4.96 (1H, s, –PhO*H*), 5.45 (1H, br s, –N*H*), 6.40–6.50 (3H, m, Ar*H*), 6.64 (2H, d, *J* 6.5 Hz, Ar*H*), 6.86 (2H, d, *J* 7.1 Hz, Ar*H*), 7.08 (2H, d, *J* 6.5 Hz, Ar*H*).

2.2.9. Compound **3i**[11,27a]

Bright yellow solid, mp 120 °C (lit. 124–126 °C); δ_H (250 MHz, $CDCl_3$): 1.16 (3H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 1.26 (3H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 3.86–4.17 (4H, m, –OC*H*$_2$CH$_3$), 4.90 (1H, d, J_{HP} 25.2 Hz, C*H*P), 5.21 (1H, br s, –N*H*), 6.55 (2H, d, *J* 7.7 Hz, Ar*H*), 6.67 (1H, t, *J* 7.1 Hz, Ar*H*), 7.06 (2H, t, *J* 7.1 Hz, Ar*H*), 7.66 (2H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 8.13 (2H, d, *J* 8.5 Hz, Ar*H*).

2.2.10. Compound **3j**[28,17]

Viscous colourless oil; δ_H (250 MHz, $CDCl_3$): 0.91 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.10 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 3.63–3.71 (1H, m, –OC*H*$_2$CH$_3$), 3.80–3.84 (1H, m, –OC*H*$_2$CH$_3$), 3.96–4.06 (2H, m, –OC*H*$_2$CH$_3$), 5.21 (1H, br s, –N*H*), 5.66 (1H, d, J_{HP} 25.0 Hz, C*H*P), 6.44–6.47 (3H, m, Ar*H*), 6.81–7.07 (5H, m, Ar*H*).

2.2.11. Compound **3k**[20b]

White solid, mp 70 °C (lit. 70 °C); δ_H (250 MHz, $CDCl_3$): 1.03 (3H, t, J_{HH} 7.1 Hz, –OCH$_2$*Me*), 1.23 (3H, t, J_{HH} 7.1 Hz, –OCH$_2$*Me*), 3.78–3.84 (1H, m, –OC*H*$_2$CH$_3$), 3.97–4.15 (3H, m, –OC*H*$_2$CH$_3$), 4.94 (1H, d, J_{HP} 23.4 Hz, C*H*P), 5.90 (1H, br s, –N*H*), 6.63–6.72 (3H, m, Ar*H*), 7.07–7.33 (4H, m, Ar*H*), 7.59 (1H, s, Ar*H*).

2.2.12. Compound **3l**[11,19c]

White solid, mp 104 °C (lit. 105–106 °C); δ_H (250 MHz, $CDCl_3$): 1.09 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$ *Me*), 1.21 (3H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 3.53–3.56 (1H, m, –OC*H*$_2$CH$_3$), 3.72–3.74 (1H, m, –OC*H*$_2$CH$_3$), 3.92–3.99 (2H, m, –OC*H*$_2$CH$_3$), 5.33 (1H, d, J_{HP} 24.8 Hz, C*H*P), 5.52 (1H, m, Ph–CH=C*H*–), 5.84 (1H, br s, –N*H*), 6.43 (1H, m, Ph–C*H*=CH–), 6.56–7.99 (10H, m, Ar*H*).

2.2.13. Compound **3m**[31]

Viscous colourless oil; δ_H (250 MHz, $CDCl_3$): 0.65–0.98 (15H, m), 3.71–3.83 (4H, m, –OC*H*$_2$CH$_3$), 5.24 (1H, d, J_{HP} 25.0 Hz, C*H*P), 5.87 (1H, br s, –N*H*), 6.37 (2H, d, *J* 8.1 Hz, Ar*H*), 6.62 (1H, t, *J* 8.8 Hz, Ar*H*), 6.88 (2H, d, *J* 8.1 Hz, Ar*H*).

2.2.14. Compound **3n**[28,33]

White solid, mp 104 °C (lit. 93–95 °C); δ_H (250 MHz, $CDCl_3$): 1.07 (6H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.33–1.46 (6H, m), 1.59–2.10 (4H, m), 3.86–3.93 (4H, m, –OC*H*$_2$CH$_3$), 5.38 (1H, br s, –N*H*), 6.63 (1H, t, *J* 7.1 Hz, Ar*H*), 6.86 (2H, d, *J* 8.1 Hz, Ar*H*), 6.99 (2H, t, *J* 8.1 Hz, Ar*H*).

2.2.15. Compound **3o**

Viscous colourless oil. Found: C, 61.28; H, 9.00. $C_{16}H_{28}NO_3P$ requires: C, 61.32; H, 9.01%. R_f (AcOEt/hexane 20:80) 0.37; ν_{max} (KBr): 3339 (–NH), 1238 (P=O), 1100 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.15 (9H, s, –C*Me*$_3$), 1.33 (6H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.78 (3H, d, *J* 10 Hz, –PC*Me*), 4.15–4.27 (4H, m, –OC*H*$_2$CH$_3$), 5.21 (1H, br s, –N*H*), 6.32 (2H, d, *J* 7.7 Hz, Ar*H*), 6.54 (1H, t, *J* 7.1 Hz, Ar*H*), 7.10 (2H, d, *J* 7.1 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.4, 16.6 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 16.7 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 17.2, 31.2, 28.0, 63.9 (d, $^2J_{CP}$ 6.8 Hz, O*C*H$_2$CH$_3$), 64.2 (d, $^2J_{CP}$ 6.8 Hz, O*C*H$_2$CH$_3$), 71.1 (d, J_{CP} 155.0 Hz, *C*HP), 113.7, 117.6, 131.4, 151.1; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 20.20; *m*/*z* 313 (M^+).

2.2.16. Compound **3p**[13]

Yellow solid, mp 148 °C (lit. 152 °C); δ_H (250 MHz, $CDCl_3$): 1.04 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.15 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 3.68 (3H, s, PhO*Me*), 3.73–3.77 (1H, m, –OC*H*$_2$CH$_3$), 3.86–3.90 (1H, m, –OC*H*$_2$CH$_3$), 3.99–4.05 (2H, m, –OC*H*$_2$CH$_3$), 5.11 (1H, d, J_{HP} 23.1 Hz, C*H*P), 5.60 (1H, br s, –N*H*), 6.87 (2H, d, *J* 8.2 Hz, Ar*H*), 7.09 (1H, t, *J* 6.7 Hz, Ar*H*), 7.17–7.34 (2H, m, Ar*H*), 7.45 (2H, d, *J* 8.5 Hz, Ar*H*), 7.65 (1H, s, Ar*H*).

2.2.17. Compound **3q**[28]

Viscous colourless oil; δ_H (250 MHz, $CDCl_3$): 1.10 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.25 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 3.68 (3H, s, PhO*Me*), 3.73–3.77 (1H, m, –OC*H*$_2$CH$_3$), 3.86–3.90 (1H, m, –OC*H*$_2$CH$_3$), 3.99–4.05 (2H, m, –OC*H*$_2$CH$_3$), 5.11 (1H, d, J_{HP} 23.1 Hz, C*H*P), 5.60 (1H, br s, –N*H*), 6.87 (2H, d, *J* 8.2 Hz, Ar*H*), 7.09 (1H, t, *J* 6.7 Hz, Ar*H*), 7.17–7.34 (2H, m, Ar*H*), 7.45 (2H, d, *J* 8.5 Hz, Ar*H*), 7.65 (1H, s, Ar*H*).

2.2.18. Compound **3r**

White solid, mp 117 °C. Found: C, 60.95; H, 6.15. $C_{19}H_{23}N_2O_4P$ requires: C, 60.96; H, 6.19%. R_f (AcOEt/hexane 20:80) 0.29; ν_{max} (KBr): 3330 (–NH), 2270 (–CN), 1238 (P=O), 1103 (P–O–Et); δ_H

(250 MHz, $CDCl_3$): 1.13 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.27 (3H, t, J_{HH} 6.9 Hz, –OCH_2Me), 3.77 (3H, s, PhO*Me*), 3.73–3.77 (1H, m, –O*CH*$_2$$CH_3$), 3.78–3.87 (1H, m, –O*CH*$_2$$CH_3$), 4.07–4.13 (2H, m, –O*CH*$_2$$CH_3$), 6.65 (1H, d, J_{HP} 25 Hz, *CH*P), 5.33 (1H, br s, –N*H*), 6.80–6.93 (5H, m, Ar*H*), 7.13 (1H, t, *J* 7.4 Hz, Ar*H*), 7.36 (2H, d, *J* 7.1 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.2 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 54.9 (d, $^1J_{CP}$ 153 Hz, *C*HP), 55.2, 63.2 (d, $^2J_{CP}$ 7.4 Hz, O*CH*$_2$$CH_3$), 63.6 (d, $^2J_{CP}$ 7.1 Hz, O*CH*$_2$$CH_3$), 112.7, 114.2, 116.2, 118.2, 119.2, 126.4, 128.9, 130.0, 146.8, 159.5; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 19.62; *m*/*z* 374 (M^+).

2.2.19. Compound **3s**[12]

White solid, mp 105 °C (lit. 108–109 °C); δ_H (250 MHz, $CDCl_3$): 0.93 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.02 (3H, t, J_{HH} 7.1 Hz, –OCH_2Me), 3.54 (3H, s, PhO*Me*), 3.51–3.54 (1H, m, –O*CH*$_2$$CH_3$), 3.58–3.69 (1H, m, –O*CH*$_2$$CH_3$), 3.88–3.93 (2H, m, –O*CH*$_2$$CH_3$), 4.45 (1H, d, J_{HP} 23.8 Hz, *CH*P), 4.96 (1H, br s, –N*H*), 6.28 (2H, d, *J* 8.5 Hz, Ar*H*), 6.66 (2H, d, *J* 8.3 Hz, Ar*H*), 6.95 (2H, d, *J* 8.8 Hz, Ar*H*), 7.13 (2H, d, *J* 8.8 Hz, Ar*H*).

2.2.20. Compound **3t**

White solid, mp 98 °C. Found: C, 50.45; H, 5.40. $C_{18}H_{23}BrNO_4P$ requires: C, 50.48; H, 5.41%. R_f (AcOEt/hexane 20:80) 0.31; ν_{max} (KBr): 3323 (–NH), 1236 (P═O), 1100 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.03 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.15 (3H, t, J_{HH} 6.8 Hz, –OCH_2Me), 3.64 (s, 3H, PhO*Me*), 3.56–3.61 (1H, m, –O*CH*$_2$$CH_3$), 3.82–3.86 (1H, m, –O*CH*$_2$$CH_3$), 3.98–4.07 (2H, m, –O*CH*$_2$$CH_3$), 4.59 (1H, d, J_{HP} 23.9 Hz, *CH*P), 5.20 (1H, br s, –N*H*), 6.43 (1H, s, Ar*H*), 6.64–6.81 (5H, m, Ar*H*), 7.29 (2H, d, *J* 8.7 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.2 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 16.5 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 54.9 (d, J_{CP} 153 Hz, *C*HP), 55.3, 63.2, (d, $^2J_{CP}$ 7.1 Hz, O*CH*$_2$$CH_3$), 64.4 (d, $^2J_{CP}$ 7.0 Hz, O*CH*$_2$$CH_3$), 112.1, 114.0, 116.7, 120.7, 122.9, 127.2, 129.0, 130.3, 147.9, 159.3; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 20.52; *m*/*z* 428 (M^+).

2.2.21. Compound **3u**

White solid, mp 51 °C. Found: C, 50.45; H, 5.40. $C_{18}H_{23}BrNO_4P$ requires: C, 50.48; H, 5.41%. R_f (AcOEt/hexane 20:80) 0.32; ν_{max} (KBr): 3320 (–NH), 1231 (P═O), 1106 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.11 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.22 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 3.64 (3H, s, PhO*Me*), 3.66–3.67 (1H, m, –O*CH*$_2$$CH_3$), 3.75–3.77 (1H, m, –O*CH*$_2$$CH_3$), 3.94–4.07 (2H, m, –O*CH*$_2$$CH_3$), 4.70 (1H, d, J_{HP} 23.8 Hz, *CH*P), 5.40 (1H, br s, –N*H*), 6.41 (1H, d, *J* 7.0 Hz, Ar*H*), 6.49 (1H, t, *J* 7.6 Hz, Ar*H*), 7.82 (2H, d, *J* 8.6 Hz, Ar*H*), 6.94 (1H, t, *J* 7.8 Hz, Ar*H*), 7.28–7.36 (3H, m, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.2 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 55.1, 55.3 (d, J_{CP} 152.7 Hz, *C*HP), 63.5 (d, $^2J_{CP}$ 7.1 Hz, O*CH*$_2$$CH_3$), 63.7 (d, $^2J_{CP}$ 7.1 Hz, O*CH*$_2$$CH_3$), 110.5, 112.7, 113.6, 118.8, 126.7, 128.3, 128.8, 132.4, 143.1, 159.4; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 19.73; *m*/*z* 428 (M^+).

2.2.22. Compound **3v**[33a,b]

White solid, mp 52 °C (lit. 54–55 °C); δ_H (250 MHz, $CDCl_3$): 1.07 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.22 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 3.68 (3H, s, PhO*Me*), 3.63–3.64 (1H, m, –O*CH*$_2$$CH_3$), 3.70–3.90 (1H, m, –O*CH*$_2$$CH_3$), 4.03–4.10 (2H, m, –O*CH*$_2$$CH_3$), 5.70 (1H, br s, –N*H*), 6.51 (2H, d, *J* 8.8 Hz, Ar*H*), 6.76 (2H, d, *J* 8.8 Hz, Ar*H*), 6.82 (2H, d, *J* 8.3 Hz, Ar*H*), 7.34 (2H, d, *J* 8.5 Hz, Ar*H*).

2.2.23. Compound **3w**

White solid, mp 96 °C. Found: C, 59.15; H, 6.60. $C_{18}H_{24}NO_5P$ requires: C, 59.17; H, 6.62%. R_f (AcOEt/hexane 20:80) 0.28; ν_{max} (KBr): 3354 (–OH), 3334 (–NH), 1234 (P═O), 1101 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 0.97 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.06 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 3.42 (3H, s, PhO*Me*), 3.44–3.87 (4H, m, –O*CH*$_2$$CH_3$), 4.44 (1H, d, J_{HP} 25.0 Hz, *CH*P), 5.12 (1H, br s, –N*H*), 5.91 (1H, s, –O*H*), 6.51–6.62 (6H, m, Ar*H*), 7.05 (2H, d, *J* 8.8 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.1 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 16.3 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 55.0, 55.1 (J_{CP} 152.9 Hz, *C*HP), 61.9 (d, $^2J_{CP}$ 6.9 Hz, OCH_2CH_3), 63.4 (d, $^2J_{CP}$ 6.9 Hz, O*CH*$_2$$CH_3$), 101.2, 105.8, 106.4, 113.2, 127.5, 128.9, 129.9, 147.7, 157.5, 159.1; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 20.42; *m*/*z* 365 (M^+).

2.2.24. Compound **3x**

White solid, mp 75 °C. Found: C, 59.16; H, 6.62. $C_{18}H_{24}NO_5P$ requires: C, 59.17; H, 6.62%. R_f (AcOEt/hexane 20:80) 0.25; ν_{max} (KBr): 3352 (–OH), 3303 (–NH), 1231 (P═O), 1100 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.18 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.28 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 3.65 (3H, s, PhO*Me*), 3.70–3.73 (1H, m, –O*CH*$_2$$CH_3$), 3.84–3.95 (1H, m, –O*CH*$_2$$CH_3$), 4.19–4.25 (2H, m, –O*CH*$_2$$CH_3$), 4.83 (1H, d, J_{HP} 24.6 Hz, *CH*P), 5.12 (1H, br s, –N*H*), 6.48–6.56 (3H, m, Ar*H*), 6.64 (2H, d, *J* 8.6 Hz, Ar*H*), 6.79 (1H, d, *J* 7.4 Hz, Ar*H*), 7.34 (2H, d, *J* 8.6 Hz, Ar*H*), 7.52 (1H, br s, O*H*); δ_C (62.9 MHz, $CDCl_3$): 16.1 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 16.3 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 55.2 (d, J_{CP} 155.5 Hz, *C*HP), 55.4, 63.6 (d, $^2J_{CP}$ 6.9 Hz, O*CH*$_2$$CH_3$), 64.0 (d, $^2J_{CP}$ 6.9 Hz, O*CH*$_2$$CH_3$), 112.0, 113.5, 114.3, 118.2, 119.8, 127.3, 129.2, 134.8, 145.2, 159.1; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 21.0; *m*/*z* 365 (M^+).

2.2.25. Compound **3y**[27a]

White solid, mp 95 °C (lit. 100–102 °C); δ_H (250 MHz, $CDCl_3$): 0.97 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.11 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.99 (3H, s, Ph*Me*), 3.51 (3H, s, PhO*Me*), 3.52–3.57 (1H, m, –O*CH*$_2$$CH_3$), 3.77–3.80 (1H, m, –O*CH*$_2$$CH_3$), 3.92–3.99 (1H, m, 2H, –O*CH*$_2$$CH_3$), 4.58 (d, 1H, J_{HP} 23.8 Hz, *CH*P), 5.35 (br s, –N*H*), 6.41 (2H, d, *J* 7.5 Hz, Ar*H*), 7.67 (2H, d, *J* 7.2 Hz, Ar*H*), 6.74 (2H, d, *J* 8.2 Hz, Ar*H*), 7.26 (2H, d, *J* 8.5 Hz, Ar*H*).

2.2.26. Compound **3z**

White solid, mp 86 °C. Found: C, 62.79; H, 7.20. $C_{19}H_{26}NO_4P$ requires: C, 62.80; H, 7.21%. R_f (AcOEt/hexane 20:80) 0.33; ν_{max} (KBr): 3321 (–NH), 1230 (P═O), 1100 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.01 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.13 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 2.1 (3H, s, Ph*Me*), 3.61 (3H, s, PhO*Me*), 3.51–3.58 (1H, m, –O*CH*$_2$$CH_3$), 3.78–3.85 (1H, m, –O*CH*$_2$$CH_3$), 3.95–4.04 (2H, m, –O*CH*$_2$$CH_3$), 4.63 (1H, d, J_{HP} 23.9 Hz, *CH*P), 5.75 (1H, br s, –N*H*), 6.28–6.40 (3H, m, Ar*H*), 6.75 (2H, d, *J* 8.4 Hz, Ar*H*), 6.86 (1H, t, *J* 7.7 Hz, Ar*H*), 7.30 (2H, d, *J* 8.4 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 15.2 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 15.4 (d, $^3J_{CP}$ 5.7 Hz, OCH_2CH_3), 54.0, 54.1 (d, J_{CP} 152.9 Hz, *C*HP), 62.0 (d, $^2J_{CP}$ 7.0 Hz, O*CH*$_2$$CH_3$), 62.2 (d, $^2J_{CP}$ 6.9 Hz, O*CH*$_2$$CH_3$), 109.8, 112.6, 112.9, 118.1, 126.7, 127.9, 128.0, 137.7, 145.5, 158.2; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 22.82; *m*/*z* 363 (M^+).

2.2.27. Compound **3aa**[34,35]

White solid, mp 65 °C (lit. 67–69 °C); δ_H (259 MHz, $CDCl_3$): 0.96 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.13 (3H, t, J_{HH} 7.1 Hz, –OCH_2Me), 2.43 (3H, s, Ph*Me*), 3.57 (3H, s, PhO*Me*), 3.59–3.66 (1H, m, –O*CH*$_2$$CH_3$), 3.70–3.79 (1H, m, –O*CH*$_2$$CH_3$), 3.86–3.92 (2H, m, –O*CH*$_2$$CH_3$), 4.58 (1H, d, J_{HP} 23.7 Hz, *CH*P), 4.85 (1H, br s, –N*H*), 6.24 (1H, d, *J* 8.0 Hz, Ar*H*), 6.52 (1H, t, *J* 7.3 Hz, Ar*H*), 6.69 (2H, d, *J* 8.5 Hz, Ar*H*), 6.77 (1H, t, *J* 7.5 Hz, Ar*H*), 6.89 (1H, d, *J* 7.1 Hz, Ar*H*), 7.18 (2H, d, *J* 8.5 Hz, Ar*H*).

2.2.28. Compound **3ab**[14,28]

White solid, mp 118 °C (lit. 119 °C); δ_H (250 MHz, $CDCl_3$): 1.09 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 1.27 (3H, t, J_{HH} 7.0 Hz, –OCH_2Me), 3.40 (6H, s, PhO*Me*), 3.62–3.70 (1H, m, –O*CH*$_2$$CH_3$), 3.87–3.92 (1H, m, –O*CH*$_2$$CH_3$), 4.03–4.12 (2H, m, –O*CH*$_2$$CH_3$), 4.62 (1H, d, J_{HP} 24.2 Hz, *CH*P), 5.45 (1H, br s, –N*H*), 6.51 (2H, d, *J* 7.5 Hz, Ar*H*), 6.67 (2H, d, *J* 7.2 Hz, Ar*H*), 6.96 (2H, d, *J* 8.5 Hz, Ar*H*), 7.20 (2H, d, *J* 8.5 Hz, Ar*H*).

2.2.29. Compound **3ac**

White solid, mp 125 °C. Found: C, 59.32; H, 6.90. $C_{18}H_{25}N_2O_4P$ requires: C, 59.33; H, 6.92%. R_f (AcOEt/hexane 20:80) 0.29; ν_{max}

(KBr): 3320 (–NH), 1234 (P═O), 1100 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 0.98 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.21 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 2.71–2.88 (2H, m, –NHC*H*$_2$), 3.56 (3H, s, PhO*Me*), 3.50–3.59 (1H, m, –OC*H*$_2$CH$_3$), 3.63–3.75 (1H, m, –OC*H*$_2$CH$_3$), 3.85–3.90 (2H, m, –OC*H*$_2$CH$_3$), 4.73 (1H, d, J_{HP} 24 Hz, C*H*P), 6.80 (1H, br s, –N*H*), 7.2–7.46 (7H, m, Ar*H*), 8.65 (1H, d, *J* 4.8 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.6 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 16.8 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 54.8, 55.2, 58.1 (d, J_{CP} 157.0 Hz, –*C*HP), 62.5 (d, $^2J_{CP}$ 7.2 Hz, O*C*H$_2$CH$_3$), 63.3 (d, $^2J_{CP}$ 7.1 Hz, O*C*H$_2$CH$_3$), 114.1, 122.1, 124.9, 125.8, 130.5, 135.2, 148.1, 160.4, 160.6; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 20.21; *m*/*z* 364 (M^+).

2.2.30. Compound ***3ad***[28,17]

Viscous colourless oil; δ_H (250 MHz, $CDCl_3$): 0.74 (3H, t, J_{HH} 7.2 Hz, –OCH$_2$*Me*), 0.88 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.16 (3H, t, *J* 6.9 Hz, –CH$_2$CH$_2$C*H*$_3$), 1.59–1.68 (2H, m, –CH$_2$C*H*$_2$CH$_3$), 2.70–2.76 (2H, m, –C*H*$_2$CH$_2$CH$_3$), 3.71 (3H, s, PhO*Me*), 3.75–3.98 (4H, m, –OC*H*$_2$CH$_3$), 5.26 (1H, d, J_{HP} 24.0 Hz, C*H*P), 6.81 (2H, d, *J* 8.4 Hz, Ar*H*), 6.98 (1H, br s, –N*H*), 7.30 (2H, d, *J* 8.4 Hz, Ar*H*).

2.2.31. Compound ***3ae***

White solid, mp 118 °C. Found: C, 54.53; H, 7.37. $C_{26}H_{42}N_2O_8P_2$ requires: C, 54.54; H, 7.39%. R_f (AcOEt/hexane 40:60) 0.34; ν_{max} (KBr): 3303 (–NH), 1232 (P═O), 1023 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 0.78 (6H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 0.85 (6H, t, J_{HH} 6.9 Hz, –OCH$_2$*Me*), 2.67 (4H, m, –NHC*H*$_2$C*H*$_2$NH–), 3.37 (6H, s, PhO*Me*), 3.38–3.70 (8H, m, –OC*H*$_2$CH$_3$), 4.93 (2H, d, J_{HP} 24.0 Hz, C*H*P), 5.14 (2H, br s, –N*H*), 6.48 (4H, d, *J* 8.5 Hz, Ar*H*), 6.92 (4H, d, *J* 8.5 Hz, Ar*H*); δ_C (62.9 MHz, $CDCl_3$): 16.1 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 16.3 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 46.6, 59.8 (d, J_{CP} 154.6 Hz, *C*HP), 62.5 (d, $^2J_{CP}$ 6.8 Hz, O*C*H$_2$CH$_3$), 62.8 (d, $^2J_{CP}$ 6.8 Hz, O*C*H$_2$CH$_3$), 113.6, 127.3, 129.4, 159.1; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 20.81; *m*/*z* 572 (M^+).

2.2.32. Compound ***3af***

White solid, mp 113 °C (lit. 108–109 °C). Found: C, 54.36; H, 7.90. $C_{15}H_{26}NO_5P$ requires: C, 54.37; H, 7.91%. R_f (AcOEt/hexane 20:80) 0.30; ν_{max} (KBr): 3371 (–OH), 3331 (–NH), 1237 (P═O), 998 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.01 (3H, t, J_{HH} 7.3 Hz, –OCH$_2$*Me*), 1.06 (3H, t, J_{HH} 7.0 Hz, –OCH$_2$*Me*), 1.39–1.60 (2H, m, –NHCH$_2$C*H*$_2$CH$_2$OH), 2.33–2.56 (2H, m, –NHCH$_2$CH$_2$C*H*$_2$OH), 3.48–3.59 (2H, m, –NHC*H*$_2$CH$_2$CH$_2$OH), 3.60 (3H, s, PhO*Me*), 3.73–3.88 (4H, m, –OC*H*$_2$CH$_3$), 4.77 (1H, d, J_{HP} 24.0 Hz, C*H*P), 5.35 (1H, br s, –N*H*), 6.67 (2H, d, *J* 6.5 Hz, Ar*H*), 7.12 (2H, d, *J* 6.1 Hz, Ar*H*), 7.99 (1H, br s, –O*H*); δ_C (62.9 MHz, $CDCl_3$): 16.2 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 16.4 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 30.4, 46.2, 55.0, 59.7 (d, J_{CP} 155.0 Hz, –*C*HP), 61.8, 62.5 (d, $^2J_{CP}$ 6.9 Hz, O*C*H$_2$CH$_3$), 63.7 (d, $^2J_{CP}$ 6.9 Hz, O*C*H$_2$CH$_3$), 113.7, 127.1, 131.3, 159.1; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 22.44; *m*/*z* 331 (M^+).

2.2.33. Compound ***3ag***

White solid, mp 127 °C. Found: C, 58.94; H, 6.40. $C_{20}H_{26}NO_6P$ requires: C, 58.96; H, 6.43%. R_f (AcOEt/hexane 20:80) 0.19; ν_{max} (KBr): 3381 (–OH), 3331 (–NH), 1701 (C═O), 1232 (P═O), 1100 (P–O–Et); δ_H (250 MHz, $CDCl_3$): 1.05–1.22 (6H, m, –OCH$_2$*Me*), 3.70 (3H, s, PhO*Me*), 3.71–3.96 (4H, m, –OC*H*$_2$CH$_3$), 4.97 (1H, d, J_{HP} 24.0 Hz, C*H*P), 5.50 (1H, s, –NC*H*CO$_2$H), 6.84 (2H, d, *J* 8.5 Hz, Ar*H*), 6.82–7.45 (7H, m, Ar*H*), 8.56 (2H, br s, –N*H*, –O*H*); δ_C (62.9 MHz, $CDCl_3$): 16.2 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 16.5 (d, $^3J_{CP}$ 5.7 Hz, OCH$_2$*C*H$_3$), 40.7, 55.1, 58.4 (d, J_{CP} 153.7 Hz, *C*HP), 62.9 (d, $^2J_{CP}$ 6.9 Hz, O*C*H$_2$CH$_3$), 63.1 (d, $^2J_{CP}$ 6.9 Hz, O*C*H$_2$CH$_3$), 113.9, 126.1, 128.2, 129.7, 130.3, 137.2, 159.3, 175.9; ^{31}P NMR (202 MHz, $CDCl_3/H_3PO_4$): δ 20.32; *m*/*z* 407 (M^+).

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