Phenylboronic Acid as Efficient and Eco-Friendly Catalyst for the One-Pot, Three-Component Synthesis of α-Aminophosphonates under Solvent-Free Conditions

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Abstract: A simple, mild, and efficient one-pot, three-component synthetic method has been developed for the preparation of α-aminophosphonates using phenylboronic acid as catalyst under solvent-free conditions at 50 °C. The process involves the reaction of carbonyl compounds (aldehydes or ketones) with benzylamine and dimethyl phosphite. A wide range of carbonyl compounds are compatible with this reaction, producing tertiary and quaternary α-aminophosphonates in moderated to excellent yields in short time.

Key words: α-aminophosphonates, one-pot three-component reaction, phenylboronic acid, solvent-free conditions

Multicomponent reactions (MCR) play an important role in synthetic and combinatorial chemistry because of its facility to synthesize small druglike molecules with several degrees of structural diversity. Multicomponent reactions generally involve three or more different starting materials to form a product, which contains all essential parts of them.[1] Strecker,[2] Passerini,[3,4] and the Kabachnik–Fields[5] reactions are some examples of MCR involving three reagents. The latter is one of the most important methods for the synthesis of α-aminophosphonic acids and α-aminophosphonates.

Because of its structural analogy with α-amino acids, the α-aminophosphonic acids are considered as an important class of compounds with interesting biological activities and applications,[6–8] such as peptide mimics,[9] antibiotics,[10,11] enzyme inhibitors,[12–15] antiparasitical or antitumoral agents, and many more.[16,17] Due to their low toxicity towards human beings, these compounds are attractive for use in agriculture and medicinal chemistry.[6,9] For this reason, the synthesis of α-aminophosphonates has received considerable attention, and significant progress has been made to develop more efficient methods for the preparation of these compounds.[18–20] In this context, the one-pot, three-component reaction between an aldehyde, an amine, and di- or trialkyl phosphite catalyzed by different Lewis or Brønsted acids,[21–27] is one of the most useful methods for the synthesis of α-aminophosphonates due to its versatility and high yields. In recent years, several catalysts have been designed and employed for this reaction; however, in spite of their potential utility, these procedures typically suffer from one or more disadvantages such as the use of expensive and stoichiometric amount of catalyst, specialized handling techniques and tedious workup are necessary, long reaction time, vigorous reaction conditions, requirement of excess of reagents, use of solvent, unsatisfactory yield, and lack of generality. Furthermore, some of these catalysts can decompose or deactivate with the water generated during imine formation, therefore the introduction of a new and efficient water-resistant catalyst for the synthesis of α-aminophosphonates is desirable to develop a more efficient, simple, and milder protocol.

On the other hand, phenylboronic acid [$PhB(OH)_2$] has been used as catalyst in the Biginelli reaction,[28] but to the best of our knowledge it has not yet been used in one-pot, three-component reaction for the synthesis of α-aminophosphonates. $PhB(OH)_2$ has a wide spectra of advantages as catalyst as it is commercially available, nontoxic, inexpensive, and can be regarded as a green compound because of its ultimate degradation into the environmentally friendly boric acid. Additionally, it is a water-tolerant entity that can act as Brønsted or Lewis acid in the presence of water.[29] Therefore, in connection with our program concerning to the synthesis of α-aminophosphonates,[20–33] we now report for the first time an operationally simple, expeditious solvent-free synthesis of several tertiary and quaternary α-aminophosphonates using commercially available $PhB(OH)_2$ as catalyst at 50 °C (Scheme 1). The versatility of this catalyst was exploited by us obtaining the α-aminophosphonates with moderated to excellent yields in very short reaction times.

Initially, for the reaction standardization, we carried out the reaction of benzaldehyde with benzylamine and dimethyl phosphite at 50 °C in the presence of 10 mol% of $PhB(OH)_2$ under solvent-free conditions.[34] The $PhB(OH)_2$ was found to promote the reaction efficiently, affording the corresponding α-aminophosphonate **1a** in 86% yield in only 30 minutes (Table 1, entry 1). No base or other additives were required in this process. When 2.5, 5.0, and 7.5 mol% of $PhB(OH)_2$ were used the yields were slightly lower. Additionally, the reaction of benzaldehyde with benzylamine and dimethyl phosphite at 80 °C under catalyst- and solvent-free conditions gave **1a** in no more than 37% yield after five hours.

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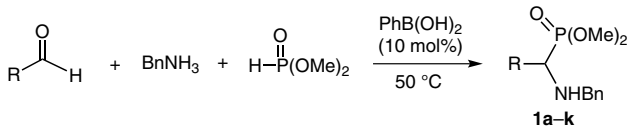
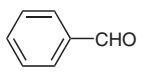
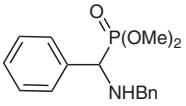
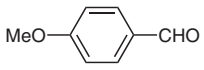
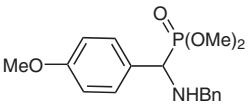
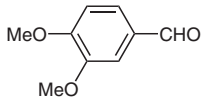
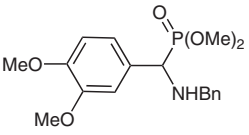
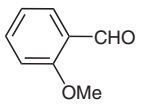
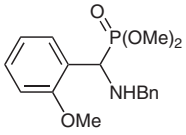
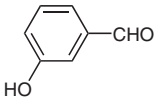
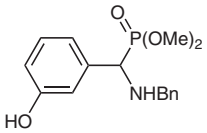
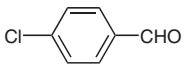
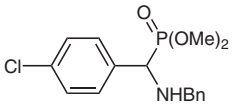
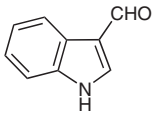
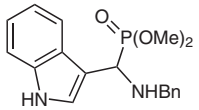
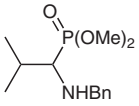
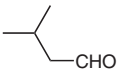
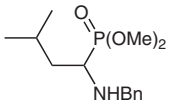
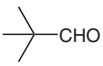
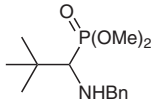
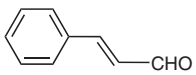
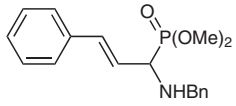


Scheme 1 Three-component, one-pot reaction catalyzed by $PhB(OH)_2$

After the optimization of the reaction conditions, the scope and limitations of this protocol were investigated by treating a diverse range of aromatic and aliphatic aldehydes with benzylamine and dimethyl phosphite in the presence of 10 mol% of $PhB(OH)_2$. The results are summarized in Table 1. Regardless of the nature of the functional groups attached to the aromatic aldehydes, all the reactions proceeded smoothly, generating the corresponding α-aminophosphonates in good yields (Table 1, entries 1–6). Even the one-pot, three-component reaction of unprotected aldehydes such as the indole-3-carboxaldehyde gave the α-aminophosphonate **1g** with 92% yield in only 15 minutes (Table 1, entry 7). The reaction was also successful with aliphatic aldehydes (Table 1, entries 8–10), but for these aldehydes the addition of benzylamine was carried out at 0 °C. However, the one-pot, three-component reaction of cinnamaldehyde afforded the α-aminophosphonate **1g** in only 62% yield (Table 1, entry 11). The formation of α-hydroxyphosphonate as a byproduct was not observed in any of the reactions.

Table 1 Three-Component Synthesis of Tertiary α-Aminophosphonates **1a**–**k** under Solvent-Free Conditions[a]

Entry	Aldehyde	Time (min)	Product **1**	Yield (%)[b]
1		30	 **1a**	86
2		60	 **1b**	93
3		20	 **1c**	91
4		45	 **1d**	83
5		30	 **1e**	85
6		30	 **1f**	73
7		15	 **1g**	92
8		30	 **1h**	74
9		45	 **1i**	69
10		30	 **1j**	79
11		30	 **1k**	62

[a] At 50 °C using 10 mol% of $PhB(OH)_2$ as catalyst.
[b] Isolated yield after chromatographic purification.

We continued our research testing the reactivity of ketones under similar conditions. The results are summarized in Table 1. The one-pot, three-component reaction with aryl ketones was sluggish to afford the corresponding α-aminophosphonates **2a**–**f** (Table 2, entries 1–6). The reaction was monitored by TLC, but the prolongation of reaction time did not show an improvement in the yield. However, aliphatic ketones were found to be more reactive and produced the corresponding α-aminophospho-

nates **2g–k** in good to excellent yields in only 30 minutes (Table 2, entries 7–11).

Table 2 Three-Component Synthesis of Quaternary α-Aminophosphonates **2a–k** under Solvent-Free Conditions[a]

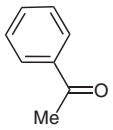
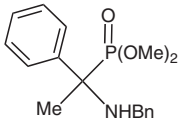
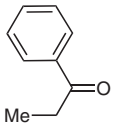
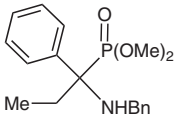
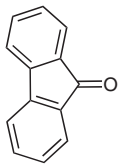
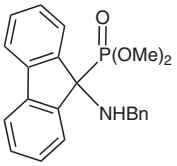
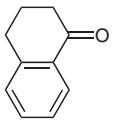
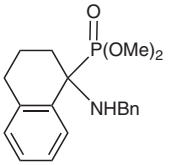
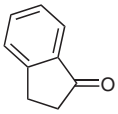
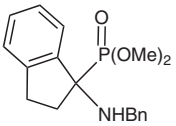
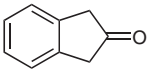
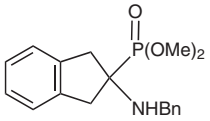
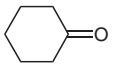
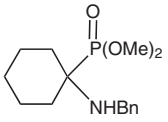
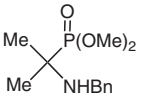
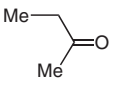
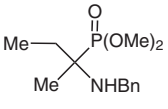
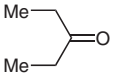
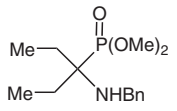
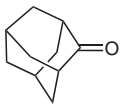
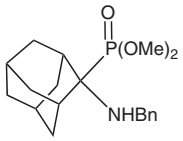
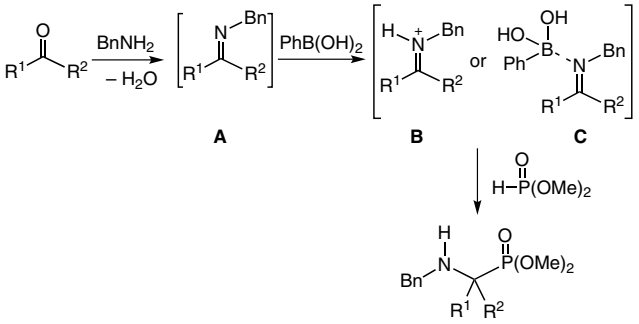
Entry	Ketone	Time (h)	Product **2**	Yield (%)[b]
1		4.0	 **2a**	37
2		8.0	 **2b**	28
3		4.0	 **2c**	-
4		4.0	 **2d**	31
5		8.0	 **2e**	50
6		8.0	 **2f**	53
7		0.5	 **2g**	93
8		0.5	 **2h**	85
9		0.5	 **2i**	76

Table 2 Three-Component Synthesis of Quaternary α-Aminophosphonates **2a–k** under Solvent-Free Conditions[a]

Entry	Ketone	Time (h)	Product **2**	Yield (%)[b]
10		0.5	 **2j**	73
11		0.5	 **2k**	68

[a] At 50 °C using 10 mol% of $PhB(OH)_2$ as catalyst.
[b] Isolated yield after chromatographic purification.

Based on the above results, we suggest a mechanism wherein the in situ formation of the imine intermediate **A**, generated from condensation reaction of aldehyde or ketone and benzylamine, is activated either by protonation giving **B** or by coordination with the boron atom to give **C**, both induced by the phenylboronic acid which acts as a Lewis or Brønsted acid.[26] In the next step, the nucleophilic attack of dimethyl phosphite to **B** or **C** afforded the corresponding α-aminophosphonates (Scheme 2).



Scheme 2 Proposed mechanism for the one-pot, three-component reaction catalyzed by $PhB(OH)_2$

In conclusion, we have developed a mild and efficient method for the synthesis of tertiary and quaternary α-aminophosphonates through a convenient one-pot, three-component reaction of aliphatic or aromatic aldehydes or ketones with benzylamine and dimethyl phosphite catalyzed by $PhB(OH)_2$ under solvent-free conditions. Some notable advantages of this method are: (a) operationally simple procedure and use of catalytic amount of $PhB(OH)_2$, (b) ability of catalyst as water-tolerant entity, (c) general applicability to aliphatic and aromatic aldehydes and ketones, (d) reaction conditions tolerant to a variety of sensitive functionalities, (e) short reaction time, and (f) excellent reaction efficiency. This method could be useful in the large-scale synthesis of α-aminophospho-

nates, for example, conpounds **1i**, **2g**,**h**,**j** have been obtained on a five-gram scale.

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References and Notes

(1) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
(2) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 15118.
(3) Brioche, J.; Masson, G.; Zhu, J. *Org. Lett.* **2010**, *12*, 1432.
(4) Soeta, T.; Kojima, Y.; Ukaji, Y.; Inomata, K. *Org. Lett.* **2010**, *12*, 4280.
(5) Kabachnik, M. I.; Medved, T. *Dokl. Acad. Nauk. SSSR* **1952**, *83*, 689.
(6) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17*, 264.
(7) Naydenova, E. D.; Todorov, P. T.; Troev, K. D. *Amino Acids* **2010**, *38*, 23.
(8) Lejczak, B.; Kafarski, P. *Top. Heterocycl. Chem.* **2009**, *20*, 31.
(9) *Aminophosphinic and Aminophosphonic Acids: Chemistry and Biological Activity*; Kukhar, V. P.; Hudson, H. R., Eds.; John Wiley and Sons: Chichester, **2000**.
(10) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J. P.; Ringrose, S. *Nature (London)* **1978**, *272*, 56.
(11) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29.
(12) Rozenfeld, R.; Iturrioz, X.; Okada, M.; Maigret, B.; Llorents-Cortes, C. *Biochemistry* **2003**, *42*, 14785.
(13) Hirschmann, R.; Smith, A. B. III.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *26*, 5234.
(14) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652.
(15) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603.
(16) Kafarski, P.; Lejczak, B. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 301.
(17) Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, C.; Cudennec, C.; Pierré, A. *J. Med. Chem.* **1991**, *34*, 1998.
(18) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17.
(19) Kudzin, Z. H.; Kudzin, M. H.; Drabowicz, J.; Stevens, C. V. *Curr. Org. Chem.* **2011**, *15*, 2015.
(20) Ordóñez, M.; Viveros-Ceballos, J. L.; Cativiela, C.; Arizpe, A. *Curr. Org. Synth.* **2012**, *9*, 310.
(21) Hou, J. T.; Gao, J. W.; Zhang, Z. H. *Appl. Organomet. Chem.* **2011**, *25*, 47; and references cited therein.
(22) Reddy, M. V.; Dindulkar, S. D.; Jeong, Y. T. *Tetrahedron Lett.* **2011**, *52*, 4764; and references cited therein.
(23) Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. *Ultrason. Sonochem.* **2010**, *17*, 760; and references cited therein.
(24) Boroujeni, K. P.; Shirazi, A. N. *Heteroat. Chem.* **2010**, *21*, 418; and references cited therein.
(25) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 6029.
(26) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263.
(27) Zhan, Z.-P.; Yang, R.-F.; Li, J.-P. *Chem. Lett.* **2005**, *34*, 1042.
(28) Debache, A.; Boumoud, B.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2006**, *47*, 5697.
(29) *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2005**.
(30) Tibhe, G. D.; Lagunas-Rivera, S.; Vargas-Díaz, E.; García-Barradas, O.; Ordoñez, M. *Eur. J. Org. Chem.* **2010**, 6573.
(31) Viveros-Ceballos, J. L.; Cativiela, C.; Ordoñez, M. *Tetrahedron: Asymmetry* **2011**, *22*, 1479.
(32) Arizpe, A.; Sayago, F. J.; Jiménez, A. I.; Ordóñez, M.; Cativiela, C. *Eur. J. Org. Chem.* **2011**, 6732.
(33) Arizpe, A.; Sayago, F. J.; Jiménez, A. I.; Ordóñez, M.; Cativiela, C. *Eur. J. Org. Chem.* **2011**, 3074.
(34) In a typical experiment, to a mixture of aldehyde or ketone (2.5 mmol) and benzylamine (2.5 mmol) was added $PhB(OH)_2$ (10 mol%). The reaction mixture was stirred at r.t. for 15 min. After this time, dimethyl phosphite (2.6 mmol) was added, and the reaction mixture was stirred at 50 °C for a specific period of time (see Tables 1 and 2), and the progress of the reaction was monitored by TLC. The crude was purified by flash chromatography with EtOAc–hexane (70:30), obtaining the pure α-aminophosphonates. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and HRMS data for some newly obtained α-aminophosphonates are as follows.
Compound **1c**: white solid; mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (br s, 1 H, NH), 3.55 [d, J_{HP} = 10.8 Hz, 3 H, $(CH_3O)_2P$]. 3.74 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.80 (AB system, J = 13.2 Hz, 2 H, CH_2Ph), 3.89 (s, 3 H, CH_3O), 3.90 (s, 3 H, CH_3O), 3.98 (d, J_{HP} = 19.6 Hz, 1 H, CHP), 6.86–7.00 (m, 3 H, HAr), 7.23–7.33 (m, 5 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.3 (d, J_{CP} = 16.7 Hz, CH_2Ph), 53.5 [d, J_{CP} = 6.1 Hz $(CH_3O)_2P$], 53.8 [d, J_{CP} = 7.5 Hz $(CH_3O)_2P$], 56.1 (CH_3O), 56.2 (CH_3O), 59.1 (d, J_{CP} = 154.7 Hz, CHP), 111.5, 111.9, 121.4 (d, J_{CP} = 7.6 Hz), 127.3, 128.0, 128.5, 128.6, 139.5, 149.2, 149.5. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 27.03. HRMS (FAB^+): *m/z* calcd for $C_{18}H_{25}NO_5P$: 366.1470; found: 366.1467.
Compound **1d**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (br s, 1 H, NH), 3.51 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.56 (AB system, J = 13.2 Hz, 1 H, CH_2Ph), 3.74 (AB system, J = 13.2 Hz, 1 H, CH_2Ph), 3.78 [d, J_{HP} = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.80 (s, 3 H, OCH_3), 4.68 (d, J_{HP} = 21.1 Hz, 1 H, CHP), 6.90 (d, J_{HH} = 8.4 Hz, 1 H, HAr), 7.01 (t, J_{HH} = 7.2 Hz, 1 H, HAr), 7.20–7.31 (m, 6 H, HAr), 7.53–7.56 (m, 1 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.6 (d, J = 16.8 Hz, CH_2Ph), 51.7 (d, J_{CP} = 156.6 Hz, CHP), 53.4 [d, J_{CP} = 6.5 Hz $(CH_3O)_2P$], 53.9 [d, J_{CP} = 6.6 Hz $(CH_3O)_2P$], 55.8 (CH_3O), 111.0 (d, J_{CP} = 2.2 Hz), 121.2 (d, J_{CP} = 3.0 Hz), 124.4, 127.2, 128.4, 128.6, 129.0 (d, J_{CP} = 5.6 Hz), 129.1 (d, J_{CP} = 3.0 Hz), 139.8, 158.0 (d, J_{CP} = 7.3 Hz). ^{31}P NMR (80 MHz, $CDCl_3$): δ = 27.66. HRMS (FAB^+): *m/z* calcd for $C_{17}H_{23}NO_4P$: 336.1365; found: 336.1378.
Compound **1e**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.47 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.53 (AB system, J = 13.2 Hz, 1 H, CH_2Ph), 3.78 (AB system, J = 12.8 Hz, 1 H, CH_2Ph), 3.79 [d, J_{HP} = 10.4 Hz, 3H, $(CH_3O)_2P$], 3.96 (d, J_{HP} = 20.8 Hz, 1 H, CHP), 6.75–6.86 (m, 2 H, HAr), 7.16–7.25 (m, 3 H, HAr), 7.26–7.33 (m, 4 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.0 (d, J_{CP} = 18.0 Hz, CH_2Ph), 53.7 [d, J_{CP} = 6.7 Hz, $(CH_3O)_2P$], 54.1 [d, J_{CP} = 6.9 Hz $(CH_3O)_2P$], 58.8 (d, J_{CP} = 155.0 Hz, CHP), 114.9 (d, J_{CP} = 5.1 Hz), 115.8

(d, J_{CP} = 2.9 Hz), 120.4 (d, J_{CP} = 7.9 Hz), 127.1, 128.3, 128.4, 129.6 (d, J_{CP} = 1.8 Hz), 136.3 (d, J_{CP} = 2.8 Hz), 139.1, 157.6 (d, J_{CP} = 2.8 Hz). ^{31}P NMR (80 MHz, $CDCl_3$): δ = 27.19. HRMS (FAB^+): *m/z* calcd for $C_{16}H_{21}NO_4P$: 322.1208; found: 322.1219.

Compound **1f**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (br s, 1 H, NH), 3.52 (AB system, *J* = 13.6 Hz, 1 H, CH_2Ph), 3.59 [d, J_{HP} = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.73 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.79 (AB system, *J* = 13.6 Hz, 1 H, CH_2Ph), 4.03 (d, J_{HP} = 20.0 Hz, 1 H, CHP), 7.22–7.38 (m, 9 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.3 (d, *J* = 16.7 Hz, CH_2Ph), 53.7 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 54.0 [d, J_{CP} = 6.0 Hz, $(CH_3O)_2P$], 58.7 (d, J_{CP} = 154.7 Hz, CHP), 127.5, 128.5, 128.7, 129.0, 130.1 (d, J_{CP} = 6.1 Hz), 134.0 (d, J_{CP} = 4.5 Hz), 134.2 (d, J_{CP} = 4.5 Hz), 139.0. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 26.20. HRMS (FAB^+): *m/z* calcd for $C_{16}H_{20}ClNO_3P$: 340.0869; found: 340.0872.

Compound **1g**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (br s, 1 H, NH), 3.51 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.66 (AB system, *J* = 13.2 Hz, 1 H, CH_2Ph), 3.78 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.86 (AB system, *J* = 13.2 Hz, 1 H, CH_2Ph), 4.40 (d, J_{HP} = 18.4 Hz, 1 H, CHP), 7.09–7.38 (m, 9 H, HAr), 7.66 (d, J_{HH} = 2.0 Hz 1 H, HAr), 9.10 (br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5 (d, J_{CP} = 16.7 Hz, CH_2Ph), 51.6 (d, J_{CP} = 162.3 Hz, CHP), 53.6 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 53.9 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 109.7, 111.7, 119.5, 119.9, 122.3, 124.7 (d, J_{CP} = 7.6 Hz), 127.0, 127.3, 128.5, 128.6, 136.5, 139.7. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 27.89. HRMS (FAB^+): *m/z* calcd for $C_{18}H_{22}N_2O_3P$: 345.1368; found: 345.1369.

Compound **1i**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, J_{HH} = 6.4 Hz, 3 H, CH_3), 0.91 (d, J_{HH} = 7.2 Hz, 3 H, CH_3), 1.48–1.55 (m, 2 H, CH_2), 1.60 (br s, 1 H, NH), 1.84–1.88 (m, 1 H, CH), 2.93–2.99 (m, 1 H, CHP), 3.79 [d, J_{HP} = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.80 [d, J_{HP} = 10.0 Hz, 3 H, $(CH_3O)_2P$], 3.86 (AB system, *J* = 13.2 Hz, 1 H, CH_2Ph), 4.00 (AB system, *J* = 13.2 Hz, 1 H, CH_2Ph), 7.23–7.35 (m, 5 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH_3), 23.6 (CH_3), 24.6 (d, J_{CP} = 11.7 Hz, CH), 39.4 (d, J_{CP} = 2.2 Hz, CH_2), 52.1 (d, J_{CP} = 147.9 Hz, CHP), 52.5 (d, J_{CP} = 3.7 Hz, CH_2Ph), 52.9 [d, J_{CP} = 6.5 Hz, $(CH_3O)_2P$], 53.0 [d, J_{CP} = 7.3 Hz, $(CH_3O)_2P$], 127.3, 128.5, 128.6, 140.3. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 32.58. HRMS (FAB^+): *m/z* calcd for $C_{14}H_{25}NO_3P$: 286.1572 found: 286.1570.

Compound **1j**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 [s, 9 H, $(CH_3)_3C$], 1.7 (br s, 1 H, NH), 2.57 (d, J_{HP} = 15.6 Hz, 1 H, CHP), 3.76 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.78 (AB system, *J* = 12.4 Hz, 1 H, CH_2Ph), 3.79 [d, J_{HP} = 10.8 Hz, 3H, $(CH_3O)_2P$], 4.05 (AB system, *J* = 12.4 Hz, 1 H, CH_2Ph), 7.23–7.38 (m, 5 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7 [d, J_{CP} = 6.5 Hz, $(CH_3)_3C$], 35.4 [d, J_{CP} = 7.3 Hz, $C(CH_3)_3$], 52.1 [d, J_{CP} = 6.6 Hz, $(CH_3O)_2P$], 52.8 [d, J_{CP} = 7.3 Hz, $(CH_3O)_2P$], 55.4 (d, J_{CP} = 2.2 Hz, CH_2Ph), 64.5 (d, J_{CP} = 138.5 Hz, CHP), 127.3, 128.5, 128.6, 140.4. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 31.99. HRMS (FAB^+): *m/z* calcd for $C_{14}H_{25}NO_5P$: 286.1572; found: 286.1565.

Compound **1k**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (br s, 1 H, NH), 3.67–3.82 [m, 8 H, $(CH_3O)_2P$, CHP, and CH_2Ph], 3.97 (AB system, *J* = 13.4 Hz, 1 H, CH_2Ph), 6.12–6.17 (m, 1 H, CH), 6.62 (d, J_{HH} = 16.0 Hz, 1 H, CH), 7.26–7.41 (m, 10 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5 (d, J_{CP} = 16.1 Hz, CH_2Ph), 53.7 [d, J_{CP} = 6.6 Hz, $(CH_3O)_2P$], 53.9 [d, J_{CP} = 7.3 Hz, $(CH_3O)_2P$], 57.7 (d, J_{CP} = 155.1 Hz, CHP), 124.1 (d, J_{CP} = 6.6 Hz, CH), 126.8, 127.4, 128.2, 128.5, 128.7, 128.8, 134.9 (d, J_{CP} = 14.0 Hz, CH), 136.5, 139.5. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 27.06. HRMS (FAB^+): *m/z* calcd for $C_{18}H_{23}NO_3P$: 332.1416; found: 332.1420.

Compound **2b**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, J_{HH} = 7.2 Hz, 3 H, CH_3), 2.07–2.21 (m, 2 H, CH_2CH_3 and NH), 2.40–2.50 (m, 1 H, CH_2CH_3), 3.51 [d, J_{HP} = 10.0 Hz, 3 H, $(CH_3O)_2P$], 3.70 (AB system, *J* = 13.2 Hz, 1 H, CH_2Ph), 3.72 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.76 (AB system, *J* = 12.8 Hz, 1 H, CH_2Ph), 7.24–7.45 (m, 8 H, HAr), 7.70–7.73 (m, 2 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.9 (d, J_{CP} = 6.1 Hz, CH_3), 27.3 (CH_2), 46.7 (d, J_{CP} = 9.1 Hz, CH_2Ph), 53.2 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 53.5 [d, J_{CP} = 6.0 Hz, $(CH_3O)_2P$], 64.4 (d, J_{CP} = 142.6 Hz, CHP), 127.1, 127.3 (d, J_{CP} = 3.1 Hz), 128.1, 128.2, 128.3, 128.5, 139.0, 140.8. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 29.92. HRMS (FAB^+): *m/z* calcd for $C_{18}H_{25}NO_3P$: 334.1572; found: 334.1581.

Compound **2d**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.87 (m, 1 H, CH_2), 2.09–2.25 (m, 2 H, CH_2), 2.32–2.43 (m, 1 H, CH_2), 2.78–2.85 (m, 2 H, CH_2), 3.45 [d, J_{HP} = 10.0 Hz, 3 H, $(CH_3O)_2P$], 3.51 (AB system, *J* = 12.0 Hz, 1 H, CH_2Ph), 3.70 (AB system, *J* = 12.4 Hz, 1 H, CH_2Ph), 3.75 [d, J_{HH} = 10.8 Hz, 3H, $(CH_3O)_2P$], 7.13–7.33 (m, 8 H, HAr), 7.76–7.80 (m, 1 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (d, J_{CP} = 3.1 Hz, CH_2), 30.2 (CH_2), 30.4 (CH_2), 47.0 (d, J_{CP} = 12.1 Hz, CH_2Ph), 53.7 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 54.1 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 60.2 (d, J_{CP} = 148.7 Hz, CHP), 126.2 (d, J_{CP} = 3.0 Hz), 127.1, 127.7 (d, J_{CP} = 3.0 Hz), 128.4, 128.5, 128.8 (d, J_{CP} = 4.6 Hz), 128.9, 129.6, 139.8 (d, J_{CP} = 6.1 Hz), 140.6. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 30.52. HRMS (FAB^+): *m/z* calcd for $C_{19}H_{25}NO_3P$: 346.1572; found: 346.1568.

Compound **2e**: dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (br s, 1 H, NH), 2.30–2.43 (m, 1 H, CH_2), 2.59–2.70 (m, 1 H, CH_2), 3.00–3.05 (m, 2 H, CH_2), 3.52 (AB system, *J* = 12.8 Hz, 1 H, CH_2Ph), 3.60 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.70 (AB system, *J* = 12.4 Hz, 1 H, CH_2Ph), 3.72 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 7.20–7.33 (m, 8 H, HAr), 7.49–7.52 (m, 1 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6 (d, J_{CP} = 3.0 Hz, CH_2), 32.2 (CH_2), 46.9 (d, J_{CP} = 12.1 Hz, CH_2Ph), 53.6 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 54.3 [d, J_{CP} = 6.0 Hz, $(CH_3O)_2P$], 69.7 (d, J_{CP} = 154.7 Hz, CHP), 125.1, 125.7 (d, J_{CP} = 3.0 Hz), 126.7, 127.1, 128.3, 128.5, 128.7, 140.2, 140.5, 145.0 (d, J_{CP} = 7.6 Hz). ^{31}P NMR (80 MHz, $CDCl_3$): δ = 29.41. HRMS (FAB^+): *m/z* calcd for $C_{18}H_{23}NO_3P$: 332.1416; found: 332.1431.

Compound **2f**: brown solid; mp 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (br s, 1 H, NH), 3.12 (dd, *J* = 16.4, 7.2 Hz, 2 H, CH_2), 3.53 (dd, *J* = 16.4, 13.2 Hz, 2 H, CH_2), 3.77 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.78 [d, J_{HP} = 10.4 Hz, 3H, $(CH_3O)_2P$], 3.84 (s, 2 H, CH_2Ph), 7.16–7.25 (m, 9 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0 (d, J_{CP} = 6.1 Hz, CH_2), 48.4 (d, J_{CP} = 6.1 Hz, CH_2Ph), 53.4 [d, J_{CP} = 6.0 Hz, $(CH_3O)_2P$], 64.3 (d, J_{CP} = 156.3 Hz, CHP), 124.6, 127.0, 128.2, 128.4, 140.5, 140.6, 140.8. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 32.42. HRMS (FAB^+): *m/z* calcd for $C_{18}H_{23}NO_3P$: 332.1416; found: 332.1431.

Compound **2i**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J_{HH} = 7.2 Hz, 3 H, CH_3CH_2), 1.31, (d, J_{HP} = 16.0 Hz, 3 H, CH_3), 1.65–1.78 (m, 2 H, CH_2CH_3 and NH), 1.81–1.91 (m, 1 H, CH_2CH_3), 3.80 [d, J_{HP} = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.82 [d, J_{HP} = 10.4 Hz, 3H, $(CH_3O)_2P$], 3.83 (AB system, *J* = 12.4 Hz, 1 H, CH_2Ph), 3.90 (AB system, *J* = 12.4 Hz, 1 H, CH_2Ph), 7.21–7.38 (m, 5 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.2 (d, J_{CP} = 7.6 Hz, CH_3), 20.6 (CH_3), 27.4 (CH_2), 47.6 (CH_2Ph), 52.9 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 53.2 [d, J_{CP} = 7.6 Hz, $(CH_3O)_2P$], 57.1 (d, J_{CP} = 141.1 Hz, CP), 127.1, 128.4, 128.6, 141.2. ^{31}P NMR (80 MHz, $CDCl_3$):

δ = 34.32. HRMS (FAB$^+$): *m/z* calcd for $C_{13}H_{23}NO_3P$: 272.1416; found: 272.1417.

Compound **2j**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J_{HH} = 8.0 Hz, 6 H, CH_3CH_2), 1.71–1.85 (m, 5 H, CH_2CH_3 and NH), 3.80 [d, J_{HP} = 10.8 Hz, 6 H, $(CH_3O)_2P$], 3.85 (s, 2 H, CH_2Ph), 7.22–7.38 (m, 5 H, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7 (d, J_{CP} = 6.1 Hz, CH_3), 25.8 (d, J_{CP} = 4.5 Hz, CH_2), 47.3 [d, J_{CP} = 3.0 Hz, $(CH_3O)_2P$], 52.7 (d, J_{CP} = 9.1 Hz, CH_2Ph), 60.6 (d, J_{CP} = 136.5 Hz, CHP), 127.0, 128.3, 128.5, 141.2. ^{31}P NMR (80 MHz, $CDCl_3$): δ = 30.61. HRMS (FAB$^+$): *m/z* calcd for $C_{14}H_{25}NO_3P$: 286.1572; found: 286.1575.

