Phenylphosphonic Acid as Efficient and Recyclable Catalyst in the Synthesis of α-Aminophosphonates under Solvent-Free Conditions

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Abstract: Phenylphosphonic acid is an efficient, friendly and reusable heterogeneous catalyst for the synthesis of α-aminophosphonates through a 'one-pot' three-component reaction of amines, carbonyl compounds and dialkyl phosphites under solvent-free conditions. This methodology illustrates a very simple procedure, with wide applicability, extending the scope to aliphatic and aromatic amines, aliphatic and aromatic aldehydes and aliphatic ketones. It also enabled the synthesis of α-aminophosphonates in large scale, clean conversion, easy workup and purification. Excellent results were obtained in each case obtaining the desire compounds in moderate to good yields.

Key words: α-aminophosphonates, phenylphosphonic acid catalyst, solvent-free conditions, heterogeneous catalysis

α-Aminophosphonates are probably the most important substitutes for the corresponding protein and nonprotein α-amino acids in biological systems, because these compounds are considered as stable mimetics of tetrahedral transition state of peptide hydrolysis,[1] and have wide applications in medicinal, bioorganic, agricultural and organic synthesis.[2–5] Many α-aminophosphonates as well as their derivatives have applications as antibacterial,[6] anticancer,[7] anti-HIV,[8] antimalarial,[9] and antifungal agents,[10] and are also carriers of hydrophilic organic molecules across phospholipid bilayer membranes.[11] Some of them show also pesticidal, insecticidal and herbicidal activity,[12] and function as plant growth regulators.[13] The inert nature of the C–P bond in α-aminophosphonates as well as physical and structural similarity to the biologically important phosphate ester and carboxylic acid functionalities contribute a great deal to these activities. Additionally, the α-aminophosphonates have been used as key synthetic intermediates for the preparation of more complex compounds and as organocatalyst.[14,15]

Due to the relevant properties exhibited by α-aminophosphonates and their derivatives, during the past decades numerous useful synthetic approaches have been developed for their preparation in both racemic and optically pure forms,[16] but certainly the Kabachnik–Fields reaction[17] is one of the most widely used methods for the synthesis of these compounds, which involves a 'one-pot' three-component reaction between aldehydes or ketones, amines and dialkyl or diaryl phosphites. For this reaction a wide spectrum of catalysts have been used including Brønsted and Lewis acids, organocatalysts, transition-metal oxides, heteropolyacids, polymer-supported catalysts, ionic liquids, nanocatalysts, and many more.[18] However, in spite of the potential utility of this reaction, the catalytic process suffers from one or more disadvantages such as the use of expensive or less available and stoichiometric amounts of catalyst, use of toxic catalysts, specialized handling techniques and tedious workup are necessary, long reaction times, vigorous reaction conditions, requirement of excess of reagents, use of flammable organic solvents, unsatisfactory yield and lack of generality. Furthermore, some of these catalysts can decompose or deactivate with the water generated during the imine formation. For these reasons, the introduction of an efficient, environmentally friendly, water-resistant and recyclable catalyst for the synthesis of α-aminophosphonates under solvent-free conditions is still a challenge.

Therefore, in connection with our program on the development of novel organic synthetic methodologies,[19] herein we report our investigation on the synthesis of α-aminophosphonates through a 'one-pot' three-component reaction between aldehydes and ketones, benzylamine and dimethyl phosphite in the presence of phosphorus acids as catalysts, which have also been used in the carbonylation of nitrobenzene,[20] three-component Ugi,[21] Biginelli,[22] and Pictet–Spengler reactions.[23] The use of these acidic catalysts displays several advantages such as operational simplicity, nontoxicity, reusability, low cost and easy isolation after completion of the reaction.

In order to optimize the reaction conditions for the synthesis of α-aminophosphonates, different phosphorus compounds such as diphenylphosphinic acid (**1**), diphenylphosphate (**2**), phenylphosphinic acid (**3**), propylphosphonic acid (**4**), and phenylphosphonic acid (**5**) were tested as catalysts. Firstly, we carried out the reaction of benzaldehyde with benzylamine and dimethyl phosphite at 50 °C in the presence of 10 mol% of catalyst under solvent-free conditions (Table 1),[24] and found that all catalysts **1**–**5** promoted the reaction affording the α-aminophosphonate **6a** in good yield. The results in Table 1 show that the most efficient catalysts are the phenylphosphinic acid **3** and phenylphosphonic acid **5**, which in only 30 minutes afforded the desired product

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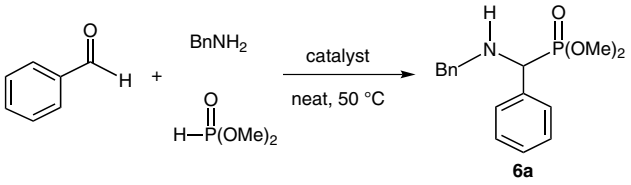
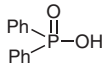
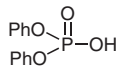
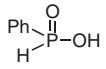
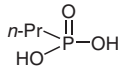
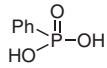
with good yield (Table 1, entries 4 and 6), and the other catalysts could only equalize this performance with longer reaction times (Table 1, entries 2, 3 and 5). These results are in agreement with the pK_a values described in the literature for these catalysts.[25] However, the reaction under catalyst- and solvent-free conditions at 80 °C gave **6a** in only 37% yield after five hours (Table 1, entry 1). Decreasing the catalyst amount of 10 mol% to 5 mol% or 2.5 mol% resulted in lower yields.

Table 1 Identification of the Most Efficient Catalyst for the 'One-Pot' Three-Component Synthesis of α-Aminophosphonate **6a**



6a

Entry	Catalyst (10 mol%)	pK_a	Time (h)	Yield (%)[a]
1	–	–	5.0	37
2	 **1**	2.30	1.0	76
3	 **2**	2.40	1.0	88
4	 **3**	1.73	0.5	93
5	 **4**	2.49	1.5	86
6	 **5**	1.86	0.5	90

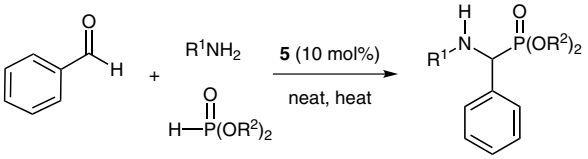
[a] Isolated yield after chromatographic purification.

With these results in hand and taking into account that phenylphosphinic acid **3** is an homogeneous catalyst, and considering that the phenylphosphonic acid (**5**) promotes the reaction as an heterogeneous catalyst, we proposed **5** as the best catalyst for the synthesis of α-aminophosphonates through 'one-pot' three-component conditions.

The ability to recycle and reuse **5** as well as its catalytic activity was studied in this system. In this context, **5** can be easily separated by filtration of the reaction mixture after dispersing in ethyl acetate. The recyclability of the heterogeneous catalytic system was also examined and can be reused for more than five successive times in new experiments without yield loss to generate **6a** with purities similar to those obtained in the first run.

In order to compare the efficiency of phenylphosphonic acid **5** as catalyst, benzaldehyde, (*S*)-α-methylbenzylamine and dimethyl phosphite were allowed to react in the presence of 10 mol% of **5** at 50 °C, yielding the α-aminophosphonates **6b** and **6c** in 64% yield (Table 2, entry 1), but when the reaction was performed at 80 °C, the mixture of (*R*,*S*)- and (*S*,*S*)-**6b** was obtained in excellent yield with predominance of the *R*,*S*-diastereoisomer (Table 2, entry 2). Similar results were obtained using diethyl phosphite, giving α-aminophosphonates (*R*,*S*)- and (*S*,*S*)-**6c** (Table 2, entry 3). The diastereoisomeric ratio was determined by ^{31}P NMR spectroscopy at 202 MHz, and the configuration was assigned by analogy with results reported in the literature.[26,27] In the next screening, benzaldehyde was reacted with aniline and dimethyl and diethyl phosphite at 50 °C for one hour, affording the α-aminophosphonates **6d** and **6e** in excellent yield (Table 2, entries 4 and 5).

Table 2 Synthesis of α-Aminophosphonates **6b–e**



6b–e

Entry	R^1	R^2	Conditions	Yield (%)[a]
1	**6b**: (*S*)-CH(Me)Ph	Me	50 °C, 2.0 h	64[b]
2	**6b**: (*S*)-CH(Me)Ph	Me	80 °C, 1.5 h	92[b]
3	**6c**: (*S*)-CH(Me)Ph	Et	80 °C, 3.0 h	98[c]
4	**6d**: Ph	Me	50 °C, 1.0 h	98
5	**6e**: Ph	Et	50 °C, 1.0 h	96

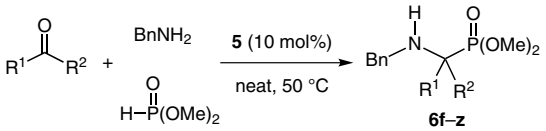
[a] Isolated yield after chromatographic purification.
[b] The *R*,*S*- and *S*,*S*-diastereoisomers were obtained with 76:24 dr.
[c] The *R*,*S*- and *S*,*S*-diastereoisomers were obtained with 80:20 dr.

Next, to ensure the efficiency and fidelity of this procedure as a general methodology, we employed a series of aldehydes and ketones, benzylamine and dimethyl phosphite to obtain the desired α-aminophosphonates under the optimized conditions using **5** as catalyst. For this study benzylamine was selected because the benzyl fragment can be easily removed by hydrogenolysis to give the corresponding α-aminophosphonates which can be used as key building blocks.

The described methodology illustrates a very simple procedure, with wide applicability, extending the scope to aliphatic and aromatic aldehydes and aliphatic ketones. Thus, the α-aminophosphonates **6f–k** were obtained in excellent yields using aromatic aldehydes bearing electron-donating groups (Table 3, entries 1–6), whereas aromatic aldehydes with electron-withdrawing groups gave the α-aminophosphonates **6l–n** in moderate yields (Table 3, entries 7–9). The electron-donating or electron-withdrawing property of the aromatic aldehydes tested, showed to have

a dramatic influence on the reaction course, which can be explained by a simple consideration of the electronic effect, whereas the heteroaromatic entities such as 3-indolecarboxaldehyde, 2-pyrrolecarboxaldehyde and furfural were also tested under this protocol, obtaining the α-aminophosphonates **6o**–**q** in good yield, thus demonstrating that the procedure is quite suitable with this kind of compounds regardless of the unprotected heteroatoms (Table 3, entries 10–12). On the other hand, the reaction of aliphatic aldehydes with benzylamine and dimethyl phosphite produced the α-aminophosphonates **6r**–**u** in good yields (Table 3, entries 13–16). Additionally, the reaction of cinnamaldehyde gave the α-aminophosphonate **6v** in 86% yield (Table 3, entry 17).

Table 3 'One-Pot' Three-Component Synthesis of α-Aminophosphonates **6f**–**z**



Entry	R^1	R^2	Time (min)	Yield (%)[a]	Product
1	3-HOC_6H_4	H	50	79	**6f**
2	3,4-$(HO)_2C_6H_3$	H	50	79	**6g**
3	3,4-$(MeO)_2C_6H_3$	H	25	98	**6h**
4	4-$MeOC_6H_4$	H	70	82	**6i**
5	2-MeO C_6H_4	H	60	88	**6j**
6	4-PhC_6H_4	H	55	65[b]	**6k**
7	4-$MeO_2CC_6H_4$	H	85	60[b]	**6l**
8	4-ClC_6H_4	H	60	63	**6m**
9	4-$F_3CC_6H_4$	H	70	47[b]	**6n**
10	3-indole	H	30	90	**6o**
11	2-pyrrole	H	60	80	**6p**
12	2-furyl	H	60	85	**6q**
13	*n*-Pr	H	60	56	**6r**
14	*i*-Bu	H	70	76	**6s**
15	*i*-Pr	H	20	63	**6t**
16	*t*-Bu	H	35	77	**6u**
17	(*E*)-PhHC=CH	H	100	86	**6v**
18	Me	Me	20	75	**6w**
19	Et	Et	20	76	**6x**
20	-$(CH_2)_5$-		40	98	**6y**

[a] Isolated yield after chromatographic purification.
[b] Yield obtained with 20 mol% of catalyst.

Finally, the reaction of aliphatic ketones with benzylamine and dimethyl phosphite was tested, affording the quaternary α-aminophosphonates **6w**–**y** in good to excellent yields (Table 3, entries 18–20). Additionally, the compound **6w** was obtained on a five-gram scale, demonstrating that phenylphosphonic acid (**5**) can be used as catalyst in the large-scale synthesis of α-aminophosphonates. The formation of α-hydroxyphosphonates as a by-product was not observed in any of the reactions.

Based on the above results, we suggest a mechanism wherein the in situ formation of the imine intermediate, generated from condensation reaction of aldehyde or ketone and benzylamine, is activated by protonation giving a nine-membered transition state (Figure 1), wherein **5** could play two roles: (1) the phenylphosphonic acid hydrogen activates the imine as a Brønsted acid; and (2) the phosphoryl oxygen activates the nucleophile by coordinating with the hydrogen of the phosphite as a Brønsted base, as has been proposed for chiral phosphonic acids.[28]

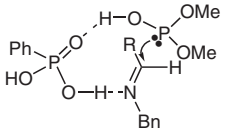


Figure 1 Proposed mechanism for the synthesis of α-aminophosphonates catalyzed by phenylphosphonic acid

In conclusion, we have developed an efficient and facile method for the synthesis of tertiary and quaternary α-aminophosphonates in moderated to excellent yields, through the 'one-pot' three-component reaction of aldehydes and ketones with benzylamine and dimethyl phosphite in the presence of catalytic amount of phenylphosphonic acid under solvent-free conditions. Utilization of mild reaction conditions, large-scale synthesis, clean conversion, easy workup, purification of reaction products and reusable phenylphosphonic acid make this process extra attractive for the synthesis of α-aminophosphonates.

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(24) In a typical experiment, to a mixture of aldehyde or ketone (2.0 mmol) and benzylamine (2.0 mmol) was added the phenylphosphonic acid (**5**; 10 mol%). The reaction mixture was stirred at r.t. for 20 min. After this time, dimethyl phosphite (2.1 mmol) was added and the reaction mixture was stirred at 50 °C for the specific period of time (see Tables 1–3), and the progress of the reaction was monitored by TLC. The crude was directly subjected to silica gel flash chromatography eluting with EtOAc, 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 **6g**: yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 [d, *J* = 10.5 Hz, 3 H, $(MeO)_2P$], 3.52 (AB system, *J* = 13.3 Hz, 1 H, Bn), 3.78 (AB system, *J* = 13.3 Hz, 1 H, Bn), 3.79 [d, *J* = 10.6 Hz, 3 H, $(MeO)_2P$], 3.89 (d, *J* = 20.1 Hz, 1 H, CHP), 6.63 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1 H, H_{Ar}), 6.77 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.11 (dd, *J* = 2.0, 2.0 Hz, 1 H, H_{Ar}), 7.20–7.31 (m, 5 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.8 (d, *J* = 17.6 Hz, Bn), 53.8 [d, *J* = 7.1 Hz, $(MeO)_2P$], 54.1 [d, *J* = 7.6 Hz, $(MeO)_2P$], 58.2 (d, *J* = 157.8 Hz, CHP), 114.7 (d, *J* = 5.0 Hz), 115.1, 121.0 (d, *J* = 8.1 Hz), 126.0, 127.2, 128.4 (2 × C), 139.0, 145.0 (2 × C). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 26.62. HRMS (FAB^+): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}NO_5P$: 338.1157; found: 338.1159.
Compound **6k**: white solid; mp 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (br s, 1 H, NH), 3.58 (AB system, *J* = 13.3 Hz, 1 H, Bn), 3.58 [d, *J* = 10.5 Hz, 3 H, $(MeO)_2P$], 3.75 [d, J_{HP} = 10.6 Hz, 3 H, $(MeO)_2P$], 3.84 (AB system, *J* = 13.3 Hz, 1 H, Bn), 4.10 (d, *J* = 20.2 Hz, 1 H, CHP), 7.22–7.36 (m, 6 H, H_{Ar}), 7.40–7.52 (m, 4 H, H_{Ar}), 7.59–7.64 (m, 4 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.3 (d, *J* = 17.4 Hz, Bn), 53.6 [d, *J* = 6.6 Hz, $(MeO)_2P$], 53.9 [d, *J* = 6.6 Hz, $(MeO)_2P$], 59.1 (d, *J* = 154.3 Hz, CHP), 127.1, 127.3, 127.4, 127.5, 128.5 (d, *J* = 6.7 Hz), 128.9, 129.1 (d, *J* = 5.5 Hz), 134.6, 139.3, 140.7, 140.9, 141.0. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 23.05. HRMS (FAB^+): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{25}NO_3P$: 382.1572; found: 382.1588.
Compound **6l**: colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (br s, 1 H, NH), 3.52 (AB system, *J* = 13.3 Hz, 1 H, Bn), 3.58 [d, *J* = 10.6 Hz, 3 H, $(MeO)_2P$], 3.74 [d, *J* = 10.6

Hz, 3 H, $(MeO)_2P$], 3.80 (AB system, J = 13.3 Hz, 1 H, Bn), 3.93 (s, 3 H, MeO), 4.13 (d, J = 20.7 Hz, 1 H, CHP), 7.21–7.36 (m, 5 H, H_{Ar}), 7.52 (AA′BB′ system, J = 8.3, 2.2 Hz, 2 H, H_{Ar}), 8.06 (AA′BB′ system, J = 8.3 Hz, 2 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5 (d, J = 17.3 Hz, Bn), 52.3 (MeO_2C), 53.7 [d, J = 6.9 Hz, $(MeO)_2P$], 54.0 [d, J = 6.9 Hz, $(MeO)_2P$], 59.4 (d, J = 152.8 Hz, CHP), 127.5, 128.5, 128.7, 128.8 (d, J = 5.9 Hz), 130.0, 130.1, 138.9, 141.1, 166.9. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 22.15. HRMS (FAB^+): m/z $[M + H]^+$ calcd for $C_{18}H_{23}NO_5P$: 364.1314; found: 364.1322.

Compound **6n**: white solid; mp 59–62 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (br s, 1 H, NH), 3.52 (AB system, J = 13.2 Hz, 1 H, CH_2Ph), 3.61 [d, J = 10.6 Hz, 3 H, $(MeO)_2P$], 3.74 [d, J = 10.6 Hz, 3 H, $(MeO)_2P$], 3.79 (AB system, J = 13.2 Hz, 1 H, CH_2Ph), 4.12 (d, J = 20.6 Hz, 1 H, CHP), 7.21–7.35 (m, 5 H, H_{Ar}), 7.55 (AA′BB′ system, J = 8.1, 1.4 Hz, 2 H, H_{Ar}), 7.64 (AA′BB′ system, J = 8.1 Hz, 2 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.5 (d, J = 17.1 Hz, CH_2Ph), 53.7 [d, J = 6.9 Hz, $(MeO)_2P$], 54.0 [d, J = 7.0 Hz, $(MeO)_2P$], 59.3 (d, J = 153.0 Hz, CHP), 124.3 (q, J = 275.0, CF_3), 125.7 (dq, J = 3.6, 3.6 Hz), 127.6, 128.5, 128.7, 129.1 (d, J = 5.9 Hz), 130.4 (dq, J = 32.2, 2.9 Hz), 138.9, 140.1 (d, J = 3.5 Hz). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 24.78 (q, J = 2.5 Hz). HRMS (FAB^+): m/z $[M + H]^+$ calcd for $C_{17}H_{20}F_3NO_3P$: 374.1133; found: 374.1035.

Compound **6p**: yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.56 (br s, 1 H, NH), 3.43 [d, J = 10.4 Hz, 3 H, $(MeO)_2P$], 3.60 (AB system, J = 13.4 Hz, 1 H, CH_2Ph), 3.74 [d, J = 10.5 Hz, 3 H, $(MeO)_2P$], 3.82 (AB system, J = 13.4 Hz, 1 H, CH_2Ph), 4.09 (d, J = 20.2 Hz, 1 H, CHP), 6.10–6.17 (m, 2 H, H_{Ar}), 6.78 (ddd, J = 4.3, 2.6, 1.8 Hz, 1 H, H_{Ar}), 7.18–7.35 (m, 5 H, H_{Ar}), 9.71 (br s, 1 H, NH-pyrrole). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.2 (d, J = 16.9 Hz, CH_2Ph), 52.5 (d, J = 160.4 Hz, CHP), 53.5 [d, J = 6.9 Hz, $(MeO)_2P$], 53.9 [d, J = 7.0 Hz, $(MeO)_2P$], 108.1, 109.5 (d, J = 9.4 Hz), 119.0, 124.8 (d, J = 5.4 Hz), 127.2, 128.4, 128.5, 139.5. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 22.70. HRMS (FAB^+): m/z $[M + H]^+$ calcd for $C_{14}H_{20}N_2O_3P$: 295.1212; found: 295.1224.

Compound **6q**: yellow liquid. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.94 (br s, 1 H, NH), 3.60 (AB system, J = 13.3 Hz, 1 H, Bn), 3.64 [d, J = 10.6 Hz, 3 H, $(MeO)_2P$], 3.81 [d, J = 10.6 Hz, 3 H, $(MeO)_2P$], 3.87 (AB system, J = 13.3 Hz, 1 H, Bn), 4.12 (d, J = 22.2 Hz, 1 H, CHP), 6.36–6.42 (m, 2 H, H_{Ar}), 7.22–7.35 (m, 5 H, H_{Ar}), 7.46 (ddd, J = 2.5, 1.8, 0.8 Hz, 1 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.3 (d, J = 16.4 Hz, CH_2Ph), 52.7 (d, J = 162.5 Hz, CHP), 53.4 [d, J = 6.9 Hz, $(MeO)_2P$], 53.9 [d, J = 6.8 Hz, $(MeO)_2P$], 109.5 (d, J = 7.5 Hz), 110.6, 127.2, 128.4 (2 × C), 138.8, 142.7 (2 × C). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 23.36. HRMS (FAB^+): m/z $[M + H]^+$ calcd for $C_{14}H_{19}NO_4P$: 296.1052; found: 296.1039.

Compound **6r**: colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.3 Hz, 3 H, Me), 1.31–1.43 (m, 1 H, CH_2), 1.49–1.64 (m, 3 H, NH, CH_2), 1.68–1.81 (m, 1 H, CH_2), 2.91 (ddd, J = 12.2, 8.5, 4.6 Hz, 1 H, CHP), 3.77 [d, J = 9.9 Hz, 3 H, $(MeO)_2P$], 3.80 [d, J = 9.9 Hz, 3 H, $(MeO)_2P$], 3.87 (AB system, J = 13.1, 1.8 Hz, 1 H, Bn), 3.96 (AB system, J = 13.1 Hz, 1 H, Bn), 7.20–7.37 (m, 5 H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (Me), 19.4 (d, J = 10.9 Hz, CH_2), 32.1 (CH_2), 52.3 (d, J = 5.0 Hz, CH_2Ph), 52.8 [d, J = 7.6 Hz, $(MeO)_2P$], 53.0 [d, J = 6.4 Hz, $(MeO)_2P$], 53.7 (d, J = 149.4 Hz, CHP), 127.2, 128.5 (2 × C), 140.1. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 28.35. HRMS (FAB^+): m/z $[M + H]^+$ calcd for $C_{13}H_{23}NO_3P$: 272.1416; found: 272.1415.

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