Efficient Palladium-Catalyzed Synthesis of Aminopyridyl Phosphonates from Bromopyridines and Diethyl Phosphite

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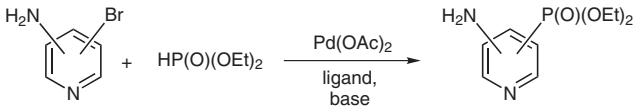
Abstract: A general method for coupling aminopyridyl bromides with diethyl phosphite is reported. This efficient route is realized through the use of a palladium catalyst and triethylamine as base.

Key words: palladium, catalysis, phosphonates, cross-coupling, pyridyl halides



Equation 1

The formation of carbon–heteroatom bonds (C–N, C–O, C–S and C–P) by transition-metal-catalyzed cross-coupling methodology has been the subject of intensive investigations in recent years and a great variety of new efficient synthetic approaches leading to key compounds have been developed.[1] Palladium-catalyzed reaction of aryl halides with dialkyl phosphite disclosed by Hirao,[2] is the most attractive route to aryl dialkylphosphonates.[3] Pyridyl and bipyridyl phosphonates can also be obtained according to this procedure.[2,4] However, the strong coordination properties of the pyridine moiety can interrupt the catalytic cycle and specific conditions have to be determined for such reactions. For example, according to Hirao's conditions, a good yield was obtained in the synthesis of pyridyl phosphonates starting from 3-bromopyridine, but 2-iodo- and 2-bromopyridines were less reactive and led to the corresponding derivatives in lower yields.[5] A large excess of triphenylphosphine (a pyridyl bromide/ligand ratio of 1:10) was necessary to run a successful synthesis of bipyridyl derivatives.[6] Aminopyridines are routinely used to prepare pharmaceuticals, hair dyes and precursors leading to new materials.[7] A survey of the literature reveals that photochemical reactions are the only efficient way with which to prepare dialkyl aminopyridylphosphonates.[5] Many attempts have clearly shown that, among the pyridine derivatives, aminopyridines are one of the most difficult coupling partners due to enhanced palladium complexation by the aminopyridine moiety.[8] In this paper, we wish to report a general method for palladium-catalyzed synthesis of aminopyridyl phosphonates from aminopyridyl bromides and diethyl phosphite (Equation 1).

5-Methyl-2-amino-3-bromopyridine was selected as a model substrate for palladium-catalyzed coupling reactions (Table 1). Initial attempts to determine the optimal reaction conditions revealed that 10 mol% of palladium precatalyst [$Pd(OAc)_2$] and 30 mol% of triphenylphosphine allowed the transformation of the bromide **1** into diethyl 5-methyl-2-aminopyridylphosphonate (**2**).

The reaction was performed using diethyl phosphite (1.2 equiv) and triethylamine (1.5 equiv) as a base with **1** (1 equiv) in refluxing solvent. The nature of the solvent is a key parameter of the reaction course. Toluene was found to be ineffective as solvent and complete transformation could not be achieved in acetonitrile (entries 1 and 2). It was surprising that ethanol, which is an inefficient solvent in the cross-coupling reaction of 3-bromopyridine with diethyl phosphite,[9] could be successfully used for the studied reaction (entry 3) as well as THF (entry 4). Decreasing the amount of palladium precatalyst to 5 mol% (entry 5) or increasing the amount of ligand (entry 6) resulted in lower conversion and yield. A slight increase in the reaction rate was observed when the precatalyst amount was increased to 12 mol% and the precatalyst/ligand ratio was decreased to 2.5 (entry 7). In ligand screening studies (entries 8–11) we found that 1,1′-bis(diphenylphosphino)ferrocene (dppf) was more active than triphenylphosphine and led to the desired product in a good yield (entry 10). Tri(cyclohexyl)phosphine, tri(2-tolyl)phosphine, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) were either less efficient or totally inefficient. Triethylamine was a suitable base in such coupling reactions. The use of inorganic bases such as Cs_2CO_3, K_2CO_3 and NaOH led to the reduced product **3** in up to 90% conversion (entries 12–14). No reaction was observed with KH_2PO_4 (entry 15).

On the basis of these preliminary outcomes, successful reactions were generally conducted in ethanol at reflux under nitrogen atmosphere with diethyl phosphite (1.2 equiv) and palladium precursor (12 mol%) in combination with triphenylphosphine [ligand–$Pd(OAc)_2$, 2.5] in the presence of triethylamine (1.5 equiv).

Under these general reaction conditions, diethyl phosphite could be effectively coupled with a variety of bromide derivatives. As summarized in Tables 2, 2-amino-5-bromopyridine (entry 1), 2-amino-5-bromo-4-methylpyridine (entry 2), 2-amino-5-bromo-3-methylpyridine (entry 3)

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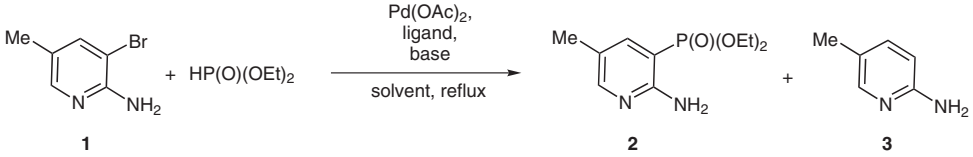
Table 1 Cross-Coupling of 5-Methyl-2-amino-3-bromopyridine (**1**) with Diethyl Phosphite[a]



1 **2** **3**

Entry	Ligand {[Pd]/[ligand] (mol%)}	Base	Solvent	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	PPh_3 (10:30)	Et_3N	Toluene	24 48	0 0	 0
2	PPh_3 (10:30)	Et_3N	MeCN	24 72	30 80	 80
3	PPh_3 (10:30)	Et_3N	EtOH	24 30 48	50 70 100[d]	 100
4	PPh_3 (10:30)	Et_3N	THF	24 48	50 100	 100
5	PPh_3 (5:15)	Et_3N	EtOH	24 30	28 45	 45
6	PPh_3 (5:30)	Et_3N	EtOH	24 30	13 29	 29
7	PPh_3 (12:30)	Et_3N	EtOH	24 36	60 100	 100
8	P(*o*-Tol)$_3$ (10:30)	Et_3N	EtOH	24 48 72	50 66 70	 70
9	P(*c*-Hex)$_3$ (10:30)	Et_3N	EtOH	24 48	13 22	13 22
10	dppf (10:15)	Et_3N	EtOH	18 36	70 100	 100[e]
11	BINAP (10:15)	Et_3N	EtOH	24 48	12 24	 24
12	PPh_3 (10:30)	Cs_2CO_3	EtOH	24	100	10
13	PPh_3 (10:30)	K_2CO_3	EtOH	24	100	30
14	PPh_3 (10:30)	NaOH	EtOH	24 48	26 100	 10
15	PPh_3 (10:30)	KH_2PO_4	EtOH	24 48	0 0	 0

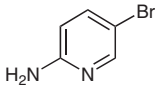
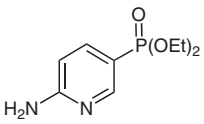
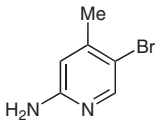
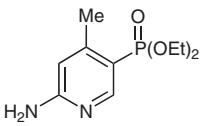
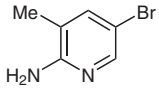
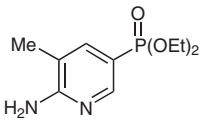
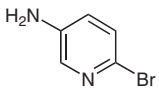
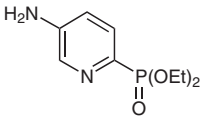
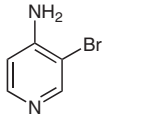
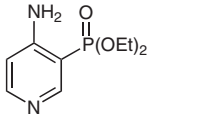
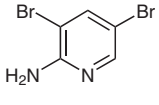
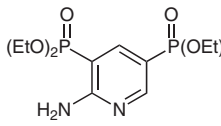
[a] Reaction conditions: bromide **1** (1 mmol), diethyl phosphite (1.2 equiv), base (1.5 equiv), $Pd(OAc)_2$ (5–12 mol%), ligand (15–30 mol%) in solvent (4 mL) at reflux under N_2.
[b] ^{1}H NMR ratio (**2**+**3**)/(**1**+**2**+**3**).
[c] ^{1}H NMR ratio **2**/(**1**+**2**+**3**).
[d] Isolated yield was 82% (colorless solid).
[e] Isolated yield was 86% (brown solid, purity >97%).

and 5-amino-2-bromopyridine (entry 4) all give the desired phosphonates in good yields. It is noteworthy that full conversion of 5-amino-2-bromopyridine and improved reaction yield were observed even with a decreased amount of catalyst [$Pd(OAc)_2$ (5 mol%) and PPh_3 (15 mol%); entry 4]. However, when 4-amino-3-bromopyridine (entry 5) was reacted with diethyl phosphite, the reaction was very slow and the desired product was isolated in low yield (31%). All attempts to improve conditions for this coupling reaction, based on the data ob-

tained in the prototypical reaction, were unsuccessful (Table 3). The use of excess triphenylphosphine or diethyl phosphite (entries 1, 2 and 3), other ligands (entries 4 and 5) or the use of THF as solvent (entry 6), did not afford higher yield. It seems that the reaction depends on the steric bulk of the pyridyl bromide. Indeed, *o*-bromo or *o*-amino-substituted pyridines were more reactive due to the decrease of the palladium complexation by the pyridine fragment. The reduction of pyridyl bromides and the formation of palladium–pyridine complexes were observed as side reactions under these conditions. When 3,5-dibromopyridine was used as a coupling partner (Table 2, entry 6), the triphenylphosphine-based system catalyzed double cross-coupling reactions with diethyl phosphite, affording the corresponding diphosphonates (60%) in a one-pot procedure.

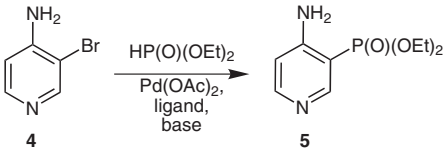
In summary, we have determined the critical conditions necessary for a general procedure for palladium-catalyzed synthesis of aminopyridyl phosphonates from aminopyridyl bromides and diethyl phosphite.

Table 2 Scope and Limitations of the Reaction Protocol[a]

Entry	Substrate	Product	Yield (%)
1			56
2			60
3			70
4			73 80[b]
5			31
6			60[c]

[a] Reaction conditions: pyridyl bromide (1–2 mmol), diethyl phosphite (1.2 equiv), Et_3N (1.5 equiv), $Pd(OAc)_2$ (12 mol%), PPh_3 (30 mol%) in EtOH (8 mL) at reflux for 48 h under N_2.
[b] $Pd(OAc)_2$ (5 mol%) and PPh_3 (15 mol%) were employed.
[c] Reaction conditions: pyridyl bromide (4 mmol), diethyl phosphite (2.4 equiv), Et_3N (3.0 equiv), $Pd(OAc)_2$ (12 mol%), PPh_3 (30 mol%) in EtOH (16 mL) at reflux for 28 h under N_2.

Table 3 Cross-Coupling of 4-Amino-3-bromopyridine with Diethyl Phosphite[a]



4 5

Entry	Ligand {[Pd]/[ligand] (mol%)}	$HP(O)(OEt)_2$ (equiv)	Solvent	Time (d)	Conversion (%)[b]
1	PPh_3 (10:60)	1.2	EtOH	5	20
2	PPh_3 (10:400)	1.2	EtOH	3	0
3	PPh_3 (10:30)	2.4	EtOH	5	50
4	Dppf (10:15)	1.2	EtOH	5	0
5	P(*o*-Tol)$_3$ (10:30)	1.2	EtOH	3	0
6	PPh_3 (5:30)	1.2	THF	5	40

[a] Reaction conditions: pyridyl bromide (1 mmol), diethyl phosphite, Et_3N (1.5 equiv), $Pd(OAc)_2$ and ligand in solvent (4 mL) at reflux for 3 d under N_2.
[b] ^1H NMR ratio **5**/(**4**+**5**).

All chemicals were of commercial quality (Aldrich, Acros) used from freshly opened containers. Ethanol was dried over magnesium. Preparative column chromatography was performed with SDS silica gel 60 A C.C (Chromagel, particle size 70–200 μm). Analytical TLC was carried out with silica gel 60 F_{254} plates, Merck. Melting points were measured on a Buchi B-545 apparatus and are uncorrected. Elemental analyses were obtained from EA1108 CHNS Fisons Instrument analyser. NMR spectra were taken with Bruker Avance 300 and 600 instruments with the chemical shifts reported as δ in ppm and scalar couplings expressed in Hz. Mass spectra were recorded on Thermo DSQ II apparatus (EI, 70 eV).

Diethyl Aminopyridylphosphonates; General Procedure

A 25 mL round-bottom flask equipped with a reflux condenser and a magnetic stirrer bar was charged with pyridyl bromide (1 mmol), the indicated amount of $Pd(OAc)_2$ and the ligand (Table 1 and Table 2). The reaction vessel was evacuated and purged with N_2 three times. Subsequently, solvent (4 mL), diethyl phosphite (154 μL, 1.2 mmol) and Et_3N (210 μL, 1.5 mmol) were added via syringe. The reaction mixture was stirred at reflux until conversion of the bromide was complete (^1H NMR). After cooling, the reaction mixture was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2 and the product was separated by column chromatography on silica gel.

Diethyl 2-Amino-5-methylpyridin-3-ylphosphonate (2)

Prepared from 5-methyl-2-amino-3-bromopyridine (374 mg, 2 mmol) following the general procedure and purified by column chromatography (CH_2Cl_2–MeOH, 4%).

Colorless solid; mp 80–81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.0 Hz, 6 H, CH_3), 2.19 (s, 3 H, CH_3), 4.05 (m, 4 H, CH_2), 5.68 (br s, 2 H, NH_2), 7.50 (dd, *J* = 15.2, 1.9 Hz, 1 H, H-4), 7.96 (d, *J* = 1.9 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.7 Hz), 17.2, 62.3 (d, *J* = 4.5 Hz), 103.5 (d, *J* = 185.3 Hz), 121.8 (d, *J* = 10.5 Hz), 142.9 (d, *J* = 6.8 Hz), 153.2, 158.3 (d, *J* = 10.5 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 19.16.

MS (EI, 70 eV): *m*/*z* (%) = 108.0 (60), 135.0 (15), 170.0 (32), 171.0 (46), 172.0 (58), 187.9 (100), 216.0 (68), 244.0 (100) $[M]^+$.

Diethyl 6-Aminopyridin-3-ylphosphonate (Table 2, Entry 1)
Prepared from 2-amino-5-bromopyridine (346 mg, 2 mmol) following the general procedure and purified by column chromatography (CH_2Cl_2–MeOH, 4%→5%).

Yield: 212 mg (46%); colorless solid; mp 113–114 °C.

A scale-up experiment was carried out using 2-amino-5-bromopyridine (8 g, 46.2 mmol). After cooling, the reaction mixture was evaporated under reduced pressure. The residue was taken up in toluene (150 mL), triethylammonium bromide was filtered off and the filtrate was evaporated under vacuum. The product was separated by column chromatography on silica gel (CH_2Cl_2–MeOH, 4%→5%).

Yield: 5.93 g (56%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.5 Hz, 6 H, CH_3), 4.05 (m, 4 H, CH_2), 4.50 (br s, 2 H, NH_2), 6.90 (ddd, *J* = 7.9, 5.2, 2.0 Hz, 1 H, H-4), 7.65 (dd, *J* = 7.9, 6.2 Hz, 1 H, H-3), 8.15 (d, *J* = 2.7 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.4 Hz), 62.5 (d, *J* = 5.7 Hz), 119.0 (d, *J* = 13.7 Hz), 129.4 (d, *J* = 28.1 Hz), 138.4 (d, *J* = 236.0 Hz), 139.4, 145.3 (d, *J* = 3.1 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 18.83.

MS (EI, 70 eV): *m*/*z* (%) = 94.0 (75), 121.0 (48), 139.0 (24), 140.0 (26), 156.0 (48), 157.0 (42), 158.0 (42), 174.0 (56), 201.1 (45), 202.1 (52), 229.1 (30), 230.1 (100) $[M]^+$.

Anal. Calcd for $C_9H_{15}N_2O_3P$: C, 46.96; H, 6.57; N, 12.17. Found: C, 47.24; H, 6.60; N, 11.86.

Diethyl 6-Amino-4-methylpyridin-3-ylphosphonate (Table 2, Entry 2)
Prepared from 2-amino-5-bromo-4-methylpyridine (374 mg, 2 mmol) following the general procedure and purified by column chromatography (CH_2Cl_2–MeOH, 4%→5%).

Colorless solid; mp 126–127 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 6.9 Hz, 6 H, CH_3), 2.33 (s, 3 H, CH_3), 4.05 (m, 4 H, CH_2), 5.06 (br s, 2 H, NH_2), 6.28 (d, *J* = 3.9 Hz, 1 H, H-5), 8.37 (d, *J* = 7.8 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.7 Hz), 20.8 (d, *J* = 3.0 Hz), 61.7 (d, *J* = 5.3 Hz), 109.6 (d, *J* = 12.8 Hz), 130.1 (d, *J* = 186.6 Hz), 151.7 (d, *J* = 10.5 Hz), 154.2 (d, *J* = 15.3 Hz), 161.6 (d, *J* = 1.5 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 19.63.

MS (EI, 70 eV): *m*/*z* (%) = 108.0 (60), 135.0 (15), 170.0 (32), 171.0 (46), 172.0 (58), 187.9 (100), 216.0 (68), 244.0 (100) $[M]^+$.

Anal. Calcd for $C_{10}H_{17}N_2O_3P{\cdot}0.5H_2O$: C, 45.19; H, 6.74; N, 11.71. Found: C, 44.97; H, 6.68; N, 11.13.

Diethyl 6-Amino-5-methylpyridin-3-ylphosphonate (Table 2, Entry 3)
Prepared from 2-amino-5-bromo-3-methylpyridine (374 mg, 2 mmol) following the general procedure and purified by column chromatography (CH_2Cl_2–MeOH, 4%→5%).

Colorless solid; mp 82–83 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 6.0 Hz, 6 H, CH_3), 2.08 (s, 3 H, CH_3), 4.04 (m, 4 H, CH_2), 4.92 (br s, 2 H, NH_2), 7.54 (ddd, *J* = 12.1, 1.6, 0.9 Hz, 1 H, H-4), 8.25 (dd, *J* = 6.6, 1.6 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.5 Hz), 16.9, 61.9 (d, *J* = 5.3 Hz), 112.6 (d, *J* = 198.6 Hz), 116.0 (d, *J* = 12.3 Hz), 140.2 (d, *J* = 9.8 Hz), 150.2 (d, *J* = 13.8 Hz), 159.9.

^{31}P NMR (121 MHz, $CDCl_3$): δ = 19.12.

MS (EI, 70 eV): *m*/*z* (%) = 108.0 (55), 135.0 (18), 170.0 (48), 171.0 (46), 172.0 (46), 188.0 (64), 216.0 (74), 244.0 (100) $[M]^+$.

Anal. Calcd for $C_{10}H_{17}N_2O_3P$: C, 49.18; H, 7.02; N, 11.47. Found: C, 49.66; H, 7.20; N, 11.38.

Diethyl 5-Aminopyridin-2-ylphosphonate (Table 2, Entry 4)
Prepared from 5-amino-2-bromopyridine (173 mg, 1 mmol) following the general procedure and purified by column chromatography (CH_2Cl_2–MeOH, 5%).

Colorless solid; mp 102–103 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.0 Hz, 6 H, CH_3), 4.10 (m, 4 H, CH_2), 5.12 (br s, 2 H, NH_2), 6.53 (dd, *J* = 8.5, 2.0 Hz, 1 H, H-5), 7.76 (ddd, *J* = 11.8, 8.8, 2.2 Hz, 1 H, H-2), 8.44 (dd, *J* = 7.1, 2.0 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.7 Hz), 62.0 (d, *J* = 5.3 Hz), 107.9 (d, *J* = 12.9 Hz), 112.3 (d, *J* = 199.8 Hz), 140.8 (d, *J* = 10.0 Hz), 152.7 (d, *J* = 14.7 Hz), 160.9.

^{31}P NMR (121 MHz, $CDCl_3$): δ = 18.87.

MS (EI, 70 eV): *m*/*z* (%) = 93.7 (74), 120.7 (20), 155.8 (28), 156.8 (59), 157.8 (53), 173.7 (100), 201.6 (60), 229.7 (38) $[M]^+$.

Anal. Calcd for $C_9H_{15}N_2O_3P$: C, 46.96; H, 6.57; N, 12.17. Found: C, 47.07; H, 6.91; N, 11.89.

Diethyl 4-Aminopyridin-3-ylphosphonate (Table 2, Entry 5)
Prepared from 4-amino-3-bromopyridine (173 mg, 1 mmol) following the general procedure and purified by column chromatography (CH_2Cl_2–MeOH, 5%).

Purity >97% (traces of PPh_3O); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 6 H, CH_3), 3.95 (m, 4 H, CH_2), 5.81 (br s, 2 H, NH_2), 6.33 (d, *J* = 6.0 Hz, 1 H, H-5), 7.98 (dd, *J* = 6.0, 1.4 Hz, 1 H, H-2), 8.21 (d, *J* = 8.2 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.7 Hz), 62.2 (d, *J* = 5.3 Hz), 104.6 (d, *J* = 183.8 Hz), 110.3 (d, *J* = 9 Hz), 152.1, 153.7 (d, *J* = 9.7 Hz), 156.6 (d, *J* = 7.5 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 18.88.

MS (EI, 70 eV): *m*/*z* (%) = 94.0 (37), 120.0 (36), 139.9 (22), 155.9 (41), 157.0 (36), 158.0 (36), 173.9 (46), 202.0 (48), 230.0 (100) $[M]^+$.

Tetraethyl 2-Aminopyridin-3,5-diyldiphosphonate (Table 2, Entry 6)
Prepared from 2-amino-3,5-dibromopyridine (1.008 g, 4 mmol) following the general procedure. The reaction mixture was purified by chromatography (CH_2Cl_2–MeOH, 4%).

Colorless solid; mp 63–64 °C.

A scale-up experiment was carried out using 2-amino-3,5-dibromopyridine (10 g, 39.7 mmol). After cooling, the reaction mixture was evaporated under reduced pressure. The residue was taken up in toluene (150 mL), triethylammonium bromide was filtered off and the filtrate was evaporated under vacuum. The product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 4%). Yield: 11.26 g (79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.9 Hz, 6 H, CH_3), 1.27 (t, *J* = 6.9 Hz, 6 H, CH_3), 4.03 (m, 8 H, CH_2), 6.75 (br s, 2 H, NH_2), 8.00 (ddd, *J* = 15.2, 12.6, 2.2 Hz, 1 H, H-4), 8.43 (ddd, *J* = 6.2, 2.3, 2.3 Hz, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.7 Hz), 62.4 (d, *J* = 5.3 Hz), 103.9 (d, *J* = 185.3 Hz), 112.8 (d, *J* = 10.5 Hz), 142.6 (d, *J* = 4.5 Hz), 153.0, 160.21 (d, *J* = 5.6 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 17.19 (d, *J* = 3.6 Hz), 17.40 (d, *J* = 3.6 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 155.9 (17), 173.9 (23), 202.0 (40), 218.9 (32), 229.0 (46), 230.0 (64), 257.0 (56), 258.1 (40), 338.0 (32), 366.0 (100) $[M]^+$.

Anal. Calcd for $C_{13}H_{24}N_2O_6P_2 \cdot 0.5H_2O$: C, 41.61; H, 6.71; N, 7.46. Found: C, 41.99; H, 6.75; N, 7.46.

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