Synthesis of New Arylhydroxymethylphosphinic Acids and Derivatives

H.-J. Cristau,* A. Hervé, F. Loiseau, D. Virieux*

Laboratoire de Chimie Organique, UMR 5076, Ecole Nationale Supérieure de Chimie de Montpellier, 8, Rue de l'Ecole Normale, 34296 Montpellier Cedex 5, France
Fax +33(4)67144319; E-mail: cristau@cit.enscm.fr; E-mail: virieux@cit.enscm.fr
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Abstract: The synthesis of a new series of arylhydroxymethylphosphinic acid derivatives is described. The protected compounds were prepared by a palladium(0) catalysed arylation of ethyl benzyloxymethylphosphinate with aryl halides. Subsequent hydrogenolysis of the benzyl protecting group followed by acidic hydrolysis of the ester function readily afforded the target compounds. Selective removal of the ester group was achieved by basic hydrolysis whereas acidic hydrolysis directly gave the totally deprotected compounds.

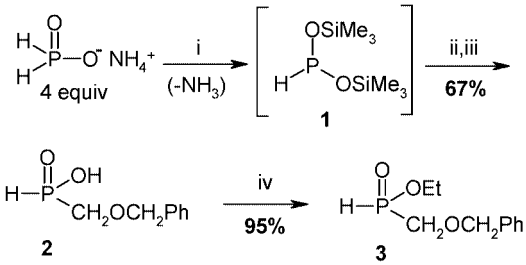
Key words: phosphorus, phosphinates, palladium, arylations, protecting groups

During the last decade, phosphonic acids aroused a growing interest due to their potential application in biomolecular chemistry.[1–4] More particularly, the synthesis of arylphosphonic acids has been extensively studied as they are valuable intermediates for the preparation of medicinal molecules.[5–11] In this context, we developed the synthesis of new arylphosphinic acids containing a hydroxymethyl group. The change of a hydroxy group of the phosphonic function by the hydroxymethyl group could improve, by the change of lipophilicity, the bioavailability and the trans-membranar transport of the molecule.[12] Indeed, some phosphonic acids derivatives are known to have a very low bio-availability due to their high ionic character in body fluids.[13]

But, although a number of arylphosphonic acids have been prepared, to date much less work has been devoted to arylphosphinic acids.[14–18] Moreover, to the best of our knowledge, there are very few papers in the literature dealing with the arylation of functionalized hydrogenophosphinic acids.[19–21] Our synthetic methodology relies on a palladium(0) catalysed arylation of a nucleophilic precursor, derived from hydroxymethylhydrogenophosphinic acid with different aryl halides.

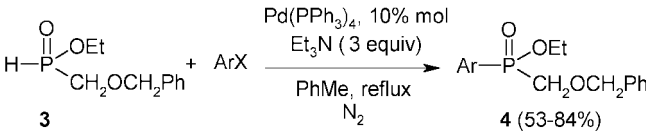
To perform this reaction, the acidic function of the phosphinic acid precursor needed to be protected. The hydroxymethyl group has also to be protected in order to avoid a retroformylation reaction in basic conditions[22,23] and also a possible competitive arylation of the oxygen atom. Thus, as the precursor of the target compounds, we selected ethyl benzyloxymethylphosphinate **3** in which the acidic function is protected as an ethyl ester and the hydroxymethyl group is converted into a benzyloxymethyl group.

Compound **3** was synthesized (63% overall yield) in two steps: first by the *pseudo*-Arbuzov reaction of the in situ generated bis(trimethylsilyl)phosphonite (BTSP) (**1**)[24–26] with benzyl chloromethyl ether to give benzyloxymethylphosphinic acid **2**, and then by esterification of the phosphinic acid group with tetraethoxysilane (Scheme 1).[27]



Scheme 1 *Reagents and conditions*: i) HMDS (4 equiv), 100 °C, N_2, 2 h; ii) $ClCH_2OCH_2Ph$ (1 equiv), 0 to 20 °C, N_2, 12 h; iii) HCl–H_2O, 15 min; iv) $Si(OEt)_4$ (1 equiv), PhMe, reflux, N_2, 12 h.

Ethyl arylbenzyloxymethylphosphinates **4a**–**g** were then prepared by the palladium catalysed arylation of **3** with the corresponding aryl halides in the presence of triethylamine (Scheme 2).



Scheme 2

This reaction displays broad scope for a single set of conditions as listed in Table 1. Indeed, aromatic iodide (entry 1) and bromides (entries 2 to 5) as well as heteroaromatic bromides (entries 6 and 7) afford moderate to excellent yields (53–84%). Products **4a**–**g** were isolated by column chromatography in 27–70% yields. They were fully characterized by ^{31}P, ^{1}H, ^{13}C NMR, mass and IR spectrometries (Tables 2 and 3).

Finally, selective debenzylation[28,29] of compounds **4b**–**d** by hydrogenolysis on Pd/C readily afforded ethyl arylhydroxymethylphosphinates **7b**–**d**, respectively, in 100%, 88% and 93% yields (Scheme 3). Hydroxymethylphosphinates **7b** and **7d** were hydrolysed with concentrated hy-

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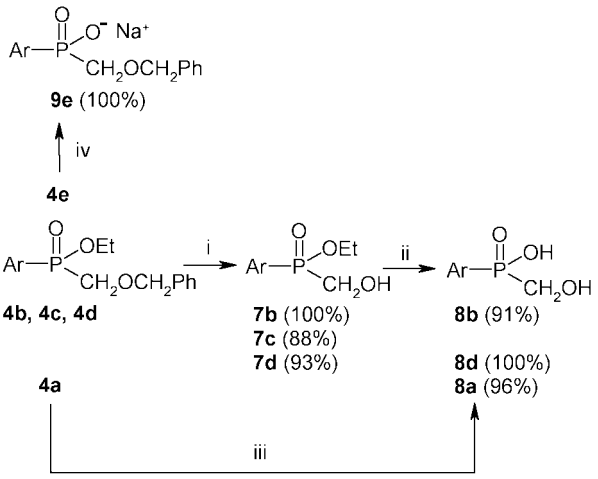
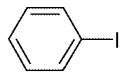
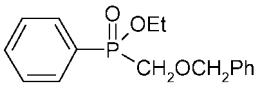
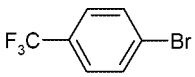
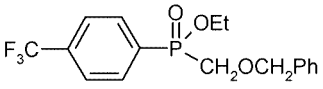
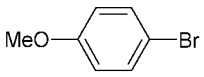
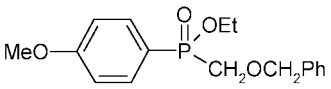
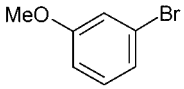
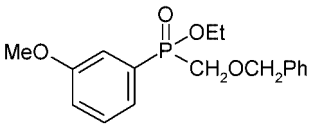
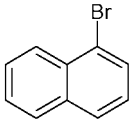
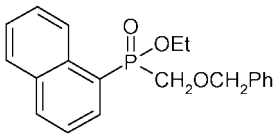
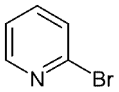
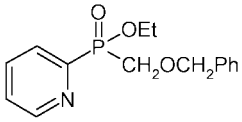
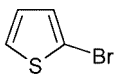
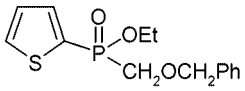
drochloric acid at 80 °C for 3 hours to give the corresponding complete deprotection products, leading to arylhydroxymethylphosphinic acids **8b** and **8d** in 91 and 100% yields.[30,31] These two steps can be combined in a one step procedure by the direct acidic hydrolysis of phosphinate **4a** which gave, after 5 hours of stirring at 80 °C, the corresponding free hydroxymethylphosphinic acid **8a** which was isolated in 96% yield. Finally, selective deprotection of the phosphinic acid function of compound **4e** was achieved by basic hydrolysis in the presence of a threefold excess of sodium hydroxide at room temperature for 5 hours.[32,33] The corresponding sodium salt **9e** was isolated in a quantitative yield.

In conclusion, several aryl- or heteroarylhydroxymethylphosphinic acid derivatives were prepared by palladium(0) catalysed arylation of ethyl benzyloxymethylphosphinate (**3**), with aromatic or heteroaromatic bromides or iodides. Finally, total or selective deprotections have been performed to confirm the com-



Scheme 3 *Reagents and conditions*: i) H_2, Pd/C, EtOH, P_{atm}, r.t.; ii) aq HCl (35%; 11 equiv), 80 °C, 3 h; iii) aq HCl (35%; 11 equiv), 80 °C, 5 h; iv) NaOH (3 equiv), EtOH, r.t., 5 h.

Table 1 Preparation of Ethyl Arylbenzyloxymethylphosphinates **4a**–**g** (Scheme 2)

Entry	ArX	Reaction time (h)	Product	Compd	Yield (%)[a]	Isolated Yield (%)
1		2.5		**4a**	84	70
2		2.5		**4b**	80	66
3		5		**4c**	73	55
4		7		**4d**	70	54
5		2		**4e**	69	50
6		12		**4f**	84	56
7		12		**4g**	53	27

[a] Yields were determined by ^{31}P NMR with 16 s as delay for relaxation time using invgate sequence.

Table 2 NMR Data of Compounds **4a**–**g** ($CDCl_3$)

Product	^{31}P NMR δ	^{1}H NMR δ, *J* (Hz)	^{13}C NMR δ, *J* (Hz)
4a	34.33	1.26 (t, 3 H, $^{3}J_{HH}$ = 7.1, CH_3), 3.75–3.93 (2 dd, ABX system, δ_{HA} = 3.80, δ_{HB} = 3.90, $^{2}J_{HAHB}$ = –13.6, $^{2}J_{PHA}$ = 5.8, $^{2}J_{PHB}$ = 8.5, CH_2), 3.92–4.12 (m, 2 H, CH_2), 4.52 (s, 2 H, CH_2), 7.13–7.24 (m, 5 H, CH), 7.42–7.47 (m, 3 H, CH), 7.79–7.83 (m, 2 H, CH).	16.24 (d, $^{3}J_{PC}$ = 6.1, CH_3), 60.12 (d, $^{2}J_{PC}$ = 6.4, CH_2), 65.80 (d, $^{1}J_{PC}$ = 168.3, CH_2), 74.54 (d, $^{3}J_{PC}$ = 11.7, CH_2), 127.51 (s, 2 C, CH), 127.57 (s, CH), 128.06 (s, 2 C, CH), 128.20 (d, $^{2}J_{PC}$ = 12.8, CH), 129.19 (d, $^{1}J_{PC}$ = 127.5, C), 131.74 (d, $^{2}J_{PC}$ = 9.7, CH), 132.34 (d, $^{4}J_{PC}$ = 2.1, CH), 136.72 (s, C).
4b	36.06	1.31–1.37 (m, 3 H, CH_3), 3.80–4.17 (m, 4 H, 2 CH_2), 4.55 (s, 2 H, CH_2), 7.16–7.18 (m, 2 H, CH), 7.25–7.28 (m, 3 H, CH), 7.71–7.73 (m, 2 H, CH), 7.79–7.83 (m, 2 H, CH).	16.23 (d, $^{3}J_{PC}$ = 6.0, CH_3), 61.42 (d, $^{2}J_{PC}$ = 6.2, CH_2), 65.76 (d, $^{1}J_{PC}$ = 120.9, CH_2), 74.79 (d, $^{3}J_{PC}$ = 12.0, CH_2), 123.58 (q, $^{1}J_{CF}$ = 272.8, CF_3), 125.28 (qd, $^{3}J_{CF}$ = 3.7, $^{3}J_{PC}$ = 12.6, CH), 127.92 (s, CH), 128.08 (s, CH), 128.42 (s, CH), 131.96 (d, $^{2}J_{PC}$ = 10.1, CH), 133.40 (d, $^{1}J_{PC}$ = 125.6, C), 134.21 (qd, $^{2}J_{CF}$ = 32.8, $^{4}J_{PC}$ = 3.0, C), 136.57 (s, C).
4c	34.33	1.24 (t, $^{3}J_{HH}$ = 7.0, 3 H, CH_3), 3.74–4.11 (m, 4 H, 2 CH_2), 3.99 (s, 3 H, CH_3), 6.93–6.97 (m, 2 H, CH), 7.18–7.27 (m, 5 H, CH), 7.73–7.80 (m, 2 H, CH).	16.49 (d, $^{3}J_{PC}$ = 6.3, CH_3), 55.22 (s, CH_3), 60.83 (d, $^{2}J_{PC}$ = 6.3, CH_2), 66.77 (d, $^{1}J_{PC}$ = 120.6, CH_2), 74.89 (d, $^{3}J_{PC}$ = 11.4, CH_2), 114.01 (d, $^{3}J_{PC}$ = 13.8, CH), 120.37 (d, $^{1}J_{PC}$ = 134.4, C), 127.79 (s, CH), 127.82 (s, CH), 128.31 (s, CH), 134.00 (d, $^{2}J_{PC}$ = 11.2, CH), 137.00 (s, C), 163.03 (d, $^{4}J_{PC}$ = 3.0, C).
4d	37.32	1.25–1.35 (m, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.81–4.15 (m, 4 H, 2 CH_2), 4.56 (s, 2 H, CH_2), 7.07–7.40 (m, 9 H, CH).	16.53 (d, $^{3}J_{PC}$ = 6.3, CH_3), 55.36 (s, CH_3), 61.21 (d, $^{2}J_{PC}$ = 6.7, CH_2), 66.66 (d, $^{1}J_{PC}$ = 120.2, CH_2), 75.02 (d, $^{3}J_{PC}$ = 11.5, CH_2), 116.49 (d, $^{2}J_{PC}$ = 11.2, CH), 119.17 (d, $^{4}J_{PC}$ = 2.6, CH), 124.17 (d, $^{2}J_{PC}$ = 9.3, CH), 127.88 (CH), 127.92 (CH), 128.37 (CH), 129.75 (d, $^{3}J_{PC}$ = 14.9, CH), 130.59 (d, $^{1}J_{PC}$ = 126.4, C), 136.94 (C), 159.61 (d, $^{3}J_{PC}$ = 15.6, C).
4e	38.10	1.35–1.39 (m, 3 H, CH_3), 4.02–4.24 (m, 4 H, 2 CH_2), 4.53 (s, 2 H, CH_2), 7.08–7.09 (m, 2 H, CH), 7.10–7.20 (m, 3 H, CH), 7.52–7.59 (m, 2 H, CH), 7.56 (ddd, 1 H, J_{HH} = 8.2, $^{3}J_{HH}$ = 7.1, $^{4}J_{PH}$ = 2.6, CH), 7.89–7,94 (m, 1 H, CH), 8.07 (ddd, 1 H, $^{3}J_{HH}$ = 8.2, $^{4}J_{HH}$ = 1.2, $^{5}J_{PH}$ = 1.2, CH), 8.25 (ddd, 1 H, $^{3}J_{HH}$ = 7.1, $^{4}J_{HH}$ = 1.2, $^{3}J_{PH}$ = 14.4, CH).	16.55 (d, $^{3}J_{PC}$ = 6.3, CH_3), 31.35 (d, $^{2}J_{PC}$ = 6.3, CH_2), 67.38 (d, $^{1}J_{PC}$ = 118.7, CH_2), 74.89 (d, $^{3}J_{PC}$ = 11.2, CH_2), 124.73 (d, $^{3}J_{PC}$ = 13.4, CH), 126.25 (d, $^{3}J_{PC}$ = 11.2, CH), 125.90 (d, $^{1}J_{PC}$ = 122.1, C), 127.79 (s, CH), 127.81 (s, CH), 128.24 (s, CH), 133.11 (d, $^{2}J_{PC}$ = 11.2, C), 133.61 (d, $^{3}J_{PC}$ = 10.8, C), 136.84 (s, C),126.14 (CH), 126.21 (CH), 126.35 (CH), 126.97 (CH), 127.50 (CH), 128.97 (CH), 129.00 (CH), 133.82 (CH), 133.88 (CH), 134.83 (CH), 135.00 (CH).
4f	33.62	1.33–1.36 (m, 3 H, CH_3), 3.97–4.18 (2 dd, ABX system, δ_{HA} = 4.02, δ_{HB} = 4.13, $^{2}J_{HAHB}$ = –13.6, $^{2}J_{PHA}$ = 8.2, $^{2}J_{PHB}$ = 5.7), 4.01–4.24 (m, 2 H, CH_2), 4.52–4.63 (2 d, 2 H, AB system, δ_{HA} = 4.55, δ_{HB} = 4.59, $^{2}J_{HAHB}$ = –12.4, CH_2), 7.19–7.29 (m, 5 H, CH), 7.41 (m, 1 H, CH), 7.80–7.83 (m, 1 H, CH), 8.04–8.09 (m, 1 H, CH), 8.74 (m, 1 H, CH).	16.38 (d, $^{3}J_{PC}$ = 6.0, CH_3), 60.97 (d, $^{2}J_{PC}$ = 6.7, CH_2), 64.69 (d, $^{1}J_{PC}$ = 121.7, CH_2), 74.93 (d, $^{3}J_{PC}$ = 10.8, CH_2), 126.33 (d, $^{4}J_{PC}$ = 3.4, CH), 127.86 (s, CH), 127.90 (s, CH), 128.31 (s, CH), 128.84 (d, $^{3}J_{PC}$ = 21.7, CH), 136.28 (d, $^{2}J_{PC}$ = 6.7, CH), 136.82 (C), 150.40 (d, $^{3}J_{PC}$ = 20.5, CH), 152.30 (d, $^{1}J_{PC}$ = 158.6, C).
4g	31.96	1.21–1.36 (m, 3 H, CH_3), 3.80–4.18 (m, 4 H, 2 CH_2), 4.60 (s, 2 H, CH_2), 7.19–7.32 (m, 6 H, CH), 7.69–7.73 (m, 2 H, CH).	16.38 (d, $^{3}J_{PC}$ = 6.2, CH_3), 61.40 (d, $^{2}J_{PC}$ = 6.7, CH_2), 67.00 (d, $^{1}J_{PC}$ = 128.8, CH_2), 75.06 (d, $^{3}J_{PC}$ = 11.9, CH_2), 127.87 (d, J_{PC} = 15.0, CH), 127.93 (s, CH), 128.11 (s, CH), 128.42 (s, CH), 128.92 (d, $^{1}J_{PC}$ = 139.9, C), 134.37 (d, J_{PC} = 5.6, CH), 136.30 (s, C), 137.20 (d, $^{2}J_{PC}$ = 10.8, CH).

patibility and the complementarity of the protecting groups on the phosphorus atom and on the hydroxymethyl group. The synthetic sequence affords a reliable and general access to this class of phosphinic acids.

All reactions involving air or moisture sensitive reagents or intermediates were carried out under dry nitrogen in flame-dried glassware. Reagents and solvents were purified before use and stored under a nitrogen atmosphere. All reactions were monitored by TLC (Merck, SIL, G/UV_{254}) or ^{31}P NMR. Merck silica gel (70–200 m) was used for column chromatography. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AC 200 (^{1}H at 200.13 MHz, ^{13}C at 50.32 MHz and ^{31}P at 81.01 MHz) and on Bruker AC 250 spectrometers (^{1}H at 250.13 MHz, ^{13}C at 62.89 MHz and ^{31}P at 101.25 MHz). Chemical shifts are expressed in ppm and coupling constants in Hz. IR spectra were obtained with Perkin–Elmer 377 and Nicolet FT-IR 210 spectrometers. Mass spectra were measured with a Jeol JMS DX-300 spectrometer (positive FAB ionisation and high resolution, glycerol-thioglycerol or *p*-nitrobenzyl alcohol).

Preparation of Phosphinates 4a–g; General Procedure
In a typical procedure, a mixture of ethyl benzyloxymethylphosphinate (1 equiv) and aryl halide (1 equiv) in dry toluene was placed in a two-necked flask under a nitrogen atmosphere. Tetrakis[triphenylphosphine]palladium (0.1 equiv) and Et_3N (3 equiv) were added and the reaction mixture was heated in an oil bath at 100–110 °C for 2–12 h. After the mixture had been cooled, EtOAc was added and the solid filtered off. The oily residue was purified by column chromatography [silica gel; petroleum ether (bp 60–90 °C)–EtOAc].

Table 3 IR and Mass Data of Compounds **4a–g**

Product	IR (cm^{-1})	Pos FAB MS (NBA) *m/z* (%)
4a	1400 (C=C), 1250 (P=O), 1225 (P=O), 1175 [(O)–O–C], 1130 [(O)-O-C].	291 (42, $[M + H]^+$), 91 (100, $C_7H_7^+$).
4b	1410 (C=C), 1340 (C-F), 1260 (P=O), 1240 (P=O), 1180 [(C)O–C], 1145 [(C)O–C].	359 (10, $[M + H]^+$), 91 (100, $C_7H_7^+$), 77 (18, Ph^+).
4c	1410 (C=C), 1380 (C=C), 1330 [(Ph)O–C], 1315 [(Ph)O–C], 1260 (P=O), 1230 (P=O), 1140 [(C)O–C], 1130 [(C)O–C], 1050 [(P)O–C].	321 (39, $[M + H]^+$), 91 (100, $C_7H_7^+$).
4d	1400 (C=C), 1380 (C=C), 1340 [(C)O–C], 1300 [(C)O–C], 1260 (P=O), 1230 (P=O), 1140 [(P)O–C], 1120 [(P)O–C], 1100 [(P)O–C].	321 (47, $[M + H]^+$), 91 (100, $C_7H_7^+$), 77 (12, Ph^+).
4e	1400 (C=C), 1230 (P=O), 1220 (P=O), 1160 [(P)O–C], 1120 [(P)O–C], 1050 [(C)O–C].	341 (98, $[M + H]^+$), 91 (100, $C_7H_7^+$).
4f	1400 (C=C), 1250 (P=O), 1230 (P=O), 1180 [(P)O–C], 1050 [(C)O–C].	292 (65, $[M + H]^+$), 91 (100, $C_7H_7^+$).
4g	1260 (P=O), 1230 (P=O), 1130 [(P)O–C].	297 (98, $[M + H]^+$), 91 (100, $C_7H_7^+$).

Preparation of Phosphinates 7b–d; General Procedure
In a typical procedure, Pd/C (10%; 0.2 equiv) was added to a solution of phosphinates **4b–d** (ca. 1 mmol) in absolute EtOH (10 mL). The mixture was placed under hydrogen at atmospheric pressure and r.t. After consumption of the required volume of hydrogen, the mixture was filtered on Celite, and the filtrate was concentrated under reduced pressure to afford the corresponding phosphinates **7b–d** as oils.

Ethyl Hydroxymethyl-(4-trifluoromethylphenyl)phosphinate (7b)
Yield: 100%; yellow oil.

IR (NaCl): 1320 (CF), 1220 (P=O), 1170 [(P)O–C], 1130 [(P)O–C], 1100 [(P)O–C], 1060 [(P)O–C] cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.24 (t, $^3J_{HH}$ = 6.9, 3 H, CH_3), 3.87–4.09 (m, 4 H, 2 CH_2), 5.09 (br s, OH), 7.64–7.67 (m, 2 H, CH), 7.85–7.94 (m, 2 H, CH).

^{13}C NMR ($CDCl_3$): δ = 16.32 (d, $^3J_{PC}$ = 6.0, CH_3), 59.50 (d, $^1J_{PC}$ = 116.7, CH_2), 61.93 (d, $^2J_{PC}$ = 7.1, CH_2), 125.34 (qd, $^3J_{CF}$ = 3.7, $^3J_{PC}$ = 7.4, CH), 131.73 (d, $^2J_{PC}$ = 10.1, CH), 133.08 (d, $^1J_{PC}$ = 120.9, C), 134.30 (qd, $^4J_{PC}$ = 3.0, $^2J_{CF}$ = 32.9, C), 136.60 (q, $^1J_{CF}$ = 272.8, CF_3).

^{31}P NMR ($CDCl_3$): δ = 39.16.

Pos FAB MS (NBA): *m/z* = 269 (100, $[M + H]^+$).

HRMS: *m/z* calcd for $C_{10}H_{13}F_3O_3P$: 269.0554; found: 269.0551.

Ethyl Hydroxymethyl-(4-methoxyphenyl)phosphinate (7c)
Yield: 88%. Yellow oil.

IR (NaCl): 3370 (OH), 1260 (P=O), 1070 [(P)O–C] cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.06 (t, $^3J_{HH}$ = 7.2, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 3.83–4.18 (m, 4 H, 2 CH_2), 5.04 (br s, OH), 6.97 (dd, $^4J_{PH}$ = 2.27, $^3J_{HH}$ = 8.6, 2 H, CH), 7.73 (dd, $^3J_{PH}$ = 10.7, $^3J_{HH}$ = 8.6, 2 H, CH).

^{13}C NMR ($CDCl_3$): δ = 16.49 (d, $^3J_{PC}$ = 6.0, CH_3), 55.31 (s, CH_3), 60.19 (d, $^1J_{PC}$ = 116.5, CH_2), 61.18 (d, $^2J_{PC}$ = 6.7, CH_3), 114.24 (d, $^2J_{PC}$ = 13.4, CH), 118.85 (d, $^1J_{PC}$ = 130.2, C), 133.95 (d, $^3J_{PC}$ = 11.2, CH), 163.08 (s, C).

^{31}P NMR ($CDCl_3$): δ = 40.87.

Pos FAB MS (NBA): *m/z* = 231 (100, $[M + H]^+$), 203 (30, $[M + H – Et]^+$), 77 (38, Ph^+).

HRMS: *m/z* calcd for $C_{10}H_{16}O_4P$: 231.0786; found: 231.0788.

Ethyl Hydroxymethyl-(3-methoxyphenyl)phosphinate (7d)
Yield: 93%; yellow oil.

IR (NaCl): 3390 (OH), 1250 (P=O), 1190 [(P)O–C], 1050 [(P)O–C] cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.24 (t, $^3J_{HH}$ = 7.0, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 3.89–4.13 (m, 4 H, 2 CH_2), 5.02 (br s, OH), 7.00–7.05 (m, 1 H, CH), 7.25–7.35 (m, 3 H, CH).

^{13}C NMR ($CDCl_3$): δ = 16.46 (d, $^3J_{PC}$ = 5.9, CH_3), 55.34 (s, CH_3), 59.89 (d, $^1J_{PC}$ = 116.1, CH_2), 61.44 (d, $^2J_{PC}$ = 7.1, CH_2), 116.61 (d, $^2J_{PC}$ = 10.8, CH), 118.88 ($^4J_{PC}$ = 2.6, CH), 123.98 (d, $^2J_{PC}$ = 9.6, CH), 129.86 (d, $^3J_{PC}$ = 14.5, CH), 130.08 (d, $^1J_{PC}$ = 122.1, C), 159.54 ($^3J_{PC}$ = 15.2, C).

^{31}P NMR ($CDCl_3$): δ = 40.80.

Pos FAB MS (NBA): *m/z* = 231 (100, $[M + H]^+$), 91 (9, $C_7H_7^+$).

HRMS: *m/z* calcd for $C_{10}H_{16}O_4P$: 231.0786; found: 231.0782.

Preparation of Phosphinic Acids 8b and 8d; General Procedure
In a typical procedure, phosphinates **7b** and **7d** (ca. 1 mmol) were stirred with aq HCl (35%; 11 equiv) at 80 °C for 3 h. Evaporation of the solvent and drying (P_4O_{10}) afforded the corresponding acids **8b** and **8d** as oils.

Hydroxymethyl-(4-trifluoromethylphenyl)phosphinic Acid (8b)
Yield: 91%; yellow oil.

IR (NaCl): 3300 (OH), 1330 (CF), 1270 (P=O) cm^{-1}.

^{1}H NMR (CD_3OD): δ = 3.99 (d, $^2J_{PH}$ = 5.6, 2 H, CH_2), 5.78 (br s, OH), 7.80–7.83 (m, 2 H, CH), 8.00–8.09 (m, 2 H, CH).

^{13}C NMR (CD_3OD): δ = 60.78 (d, $^1J_{PC}$ = 119.5, CH_2), 125.23 (q, $^1J_{CF}$ = 272.0 Hz, CF_3), 126.39 (qd, $^3J_{PC}$ = 8.2, $^3J_{CF}$ = 3.7, CH), 134.30 (d, $^2J_{PC}$ = 10.0, CH), 135.05 (q, $^2J_{CF}$ = 32.0, C), 136.63 (d, $^1J_{PC}$ = 125.8, C).

^{31}P NMR (CD_3OD): δ = 35.72.

Pos FAB MS (NBA): *m/z* = 241 (100, $[M + H]^+$).

HRMS: *m/z* calcd for $C_8H_9F_3O_3P$: 241.0241; found: 241.0238.

Hydroxymethyl-(3-methoxyphenyl)phosphinic Acid (8d)
Yield: 100%; yellow oil.

IR (NaCl): 3300 (OH), 1220 (P=O) cm^{-1}.

^{1}H NMR (CD_3OD): δ = 3.82 (s, 3 H, CH_3), 3.96 (d, $^2J_{PH}$ = 5.2, 2 H, CH_2), 5.69 (br s, OH), 7.13–7.46 (m, 4 H, CH).

^{13}C NMR (CD_3OD): δ = 54.06 (s, CH_3), 58.91 (d, $^1J_{PC}$ = 118.7, CH_2), 115.81 (d, $^2J_{PC}$ = 11.2, CH), 117.63 (d, $^4J_{PC}$ = 2.6, CH), 122.88 (d, $^2J_{PC}$ = 10.0, CH), 129.08 (d, $^3J_{PC}$ = 14.5, CH), 130.09 (d, $^1J_{PC}$ = 122.4, C), 159.03 (d, $^3J_{PC}$ = 16.0, C).

^{31}P NMR (CD_3OD): δ = 37.83.

Pos FAB MS (NBA): *m*/*z* = 203 (100, $[M + H]^+$).

HRMS: *m*/*z* calcd for $C_8H_{12}O_4P$: 203.0473; found: 203.0466.

Hydroxymethyl(phenyl)phosphinic acid (8a)

Phosphinate **4a** (140 mg, 0.48 mmol, 1 equiv) was stirred with aq HCl (35%; 0.5 mL, 15 equiv) at 80 °C for 5 h. Evaporation of the solvent and drying (P_4O_{10}) afforded the corresponding acid **8a**.

Yield: 79 mg, 0.46 mmol (96%); yellow oil.

IR (NaCl): 3310 (OH), 1275 (P=O) cm^{-1}.

^{1}H NMR (CD_3OD): δ = 3.93 (d, $^2J_{PH}$ = 5.5, 2 H, CH_2), 5.05 (br s, OH), 7.52–7.91 (m, 5 H, CH).

^{13}C NMR (CD_3OD): δ = 59.30 (d, $^1J_{PC}$ = 117.2, CH_2), 121.9 (d, $^2J_{PC}$ = 11.5, CH), 122.98 (d, $^3J_{PC}$ = 15.1, CH), 122.13 (d, $^4J_{PC}$ = 2.5, CH), 129.26 (d, $^1J_{PC}$ = 128.9, C).

^{31}P NMR (CD_3OD): δ = 37.00.

Pos FAB MS (NBA): *m*/*z* = 173 (100, $[M + H]^+$).

HRMS: *m*/*z* calcd for $C_7H_{10}O_3P$: 173.2322; found: 173. 2563.

Sodium Benzyloxymethyl(phenyl)phosphinate (9e)

Phosphinate **4e** (200 mg, 0.59 mmol, 1 equiv) in EtOH (5 mL) was stirred with 3 equiv of aq NaOH (1 M) at r.t. for 5 h. The reaction mixture was concentrated under reduced pressure to yield compound **9e**.

Yield: quantitative; white solid.

IR (NaCl): 1225 (P=O), 1105 [(P)O–C] cm^{-1}.

^{1}H NMR (CD_3OD): δ = 3.99 (d, $^2J_{PH}$ = 5.7, 2 H, CH_2), 4.45 (s, 2 H, CH_2), 7.08–7.10 (m, 2 H, CH), 7.12–7.21 (m, 3 H, CH), 7.55–8,26 (m, CH).

^{13}C NMR (CD_3OD): δ = 69.37 (d, $^1J_{PC}$ = 115.2, CH_2), 74.19 (d, $^3J_{PC}$ = 10.5, CH_2), 127.83 (s, CH), 127.92 (s, CH), 128.30 (s, CH), 137.61 (s, C), 133.16 (d, $^2J_{PC}$ = 8.6, C), 133.62 (d, $^3J_{PC}$ = 10.5, CH), 125.17, 125.36, 126.20, 128.99, 131.12, 132.40, 132.44, 133.35, 133.44, 133.56.

^{31}P NMR (CD_3OD): δ = 39.06.

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