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An alternative approach to 2-amino-phenylphosphonic acid

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Abstract: 2-Amino-phenlyphosphonic acid can easily be prepared in five steps from aniline in 38% over-all yield with a phosphoramidate-aminophosphonate rearrangement reaction as the key-step.

Keywords: 2-Amino-phenylphosphonic acid; aniline; rearrangement reaction.

Introduction

Phosphonic acids are very common structural elements in drugs, and many methods have been described for their synthesis. Phosphonoamines are of special interest in medicinal chemistry and their synthesis has been managed by a great variety of different reactions. Thus, phosphonylation of aromatic compounds has been realized by the reaction of aryl halides (or aryl triflates) either with dialkyl phosphites in the presence of palladium catalysts in Heck-type reactions [1-6] or with trialkyl phosphites [7-10] in the presence of metal catalysts in Arbuzov-type reactions. As an alternative, photochemical reactions between aryl iodides with dialkyl phosphite salts [11] or trialkyl phoshites [12] have been used, and they have been obtained from aryllithium compounds [13], from aryl diazonium salts [14, 15], by oxidation [16-18] as well as by rearrangement reactions [11, 19, 20].

During a project dealing with the synthesis of magenta colored dyes and their use in dying of human tumor cells, we became interested in the synthesis of azodyes containing a 2-aminophenylphosphonic acid moiety and derivatives thereof. Previous investigations have shown that the attachment of phosphonate-functionalised azo-dyes to oxide surfaces results for ink-jet dyes in an enhanced light and wet fastness [21]. Known syntheses for 2- aminophenylphosphonic acid (also most needed for the synthesis of potent inhibitors for the leucine aminopeptidase [22] and the synthesis of selective antagonists of human P2X1 receptors [23]) utilize 2-iodo or 2-bromo aniline in photostimulated $S_{RN}1$ reactions. Although yields are usually high for these transformations, the synthesis of larger amounts remains difficult [24, 25].

Results and Discussion

Early works by E. Zbiral [26, 27] and others [28-32] showed the potential of the phosphoramidate-aminophosphonate rearrangement reactions for the synthesis of alkyl aminophosphonates, and phosphate-phosphonate rearrangements for aryl compounds have been described by B. Dhawan and D. Redmore [33-35] several years ago as well as by F. Hammerschmidt quite recently [36]. Hence, we became interested into the rearrangement of aryl phosphoramidates into *ortho*-substituted aryl phosphonates.

Two different strategies were put to work: Reaction of aniline (**1**, Scheme 1) with diethyl chlorophosphate in the presence of triethylamine gave 91 % of the phosphoramidate **2**. Treating **2** with Boc_2O in the presence of catalytic amounts of DMAP afforded 94 % of fully protected **3.** The rearrangement reaction of **3** with *sec*-butyllithium yielded 83 % of target compound **4**. The latter is characterized by a ^{31}P NMR shift of δ =20.54 ppm (whereas the starting material showed a δ = 0.08 ppm), clearly evidencing the success of the rearrangement reaction. Deprotection of **4** was performed by its treatment either with trifluoroacetic acid or with a 3 M solution of hydrochloric acid in ethyl acetate. Compound **5** was obtained in 90 % yield, and finally deprotected by acid to afford 83% of **6**.

As an alternative, 2-bromo-aniline (**7**, Scheme 2) was transformed into the phosphoramidate **8** whose protection gave **9**. Compound **9** was reacted with *sec*- BuLi/TMEDA, and the rearranged product **4** was obtained in 94 % isolated yield. Yields dropped slightly when *sec*-BuLi/TMEDA was replaced by lithium metal/CuI, and **4** was isolated in 78 % yield.

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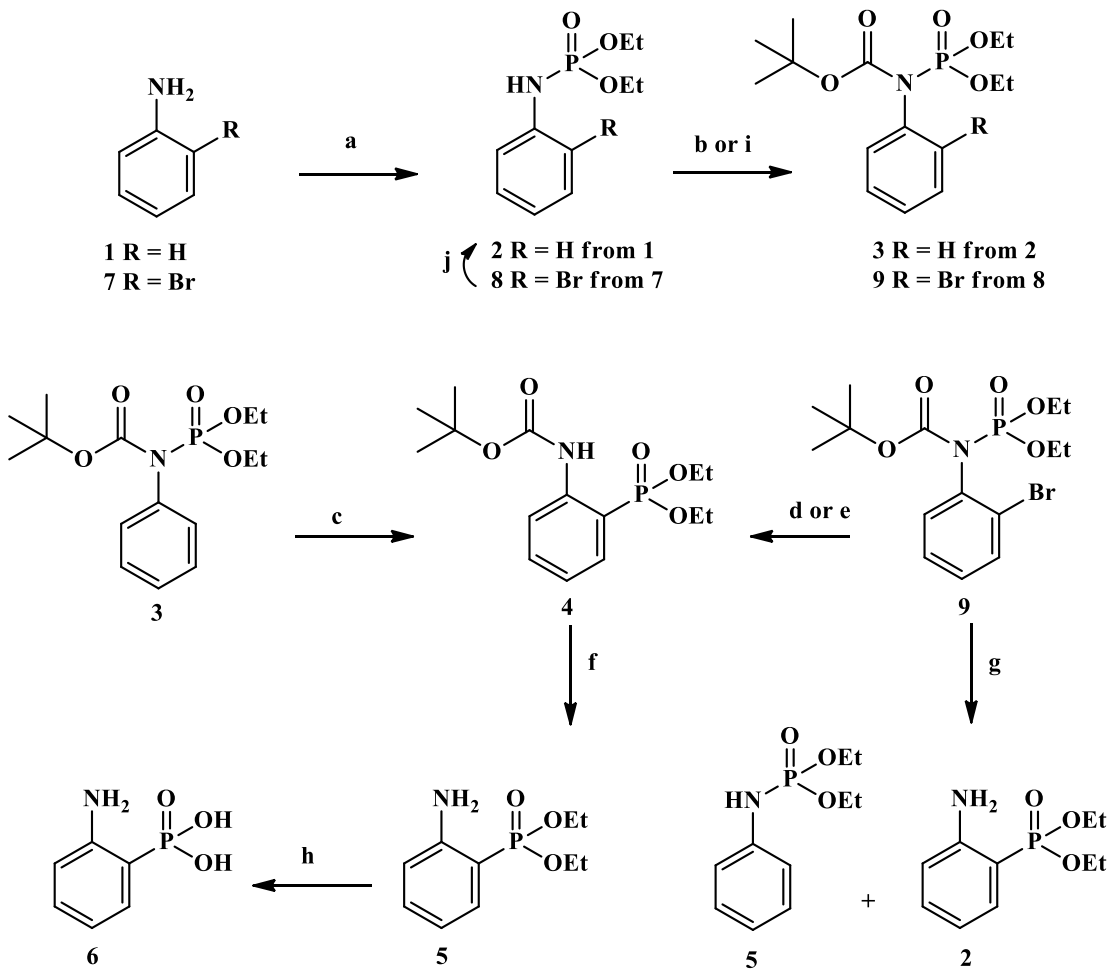
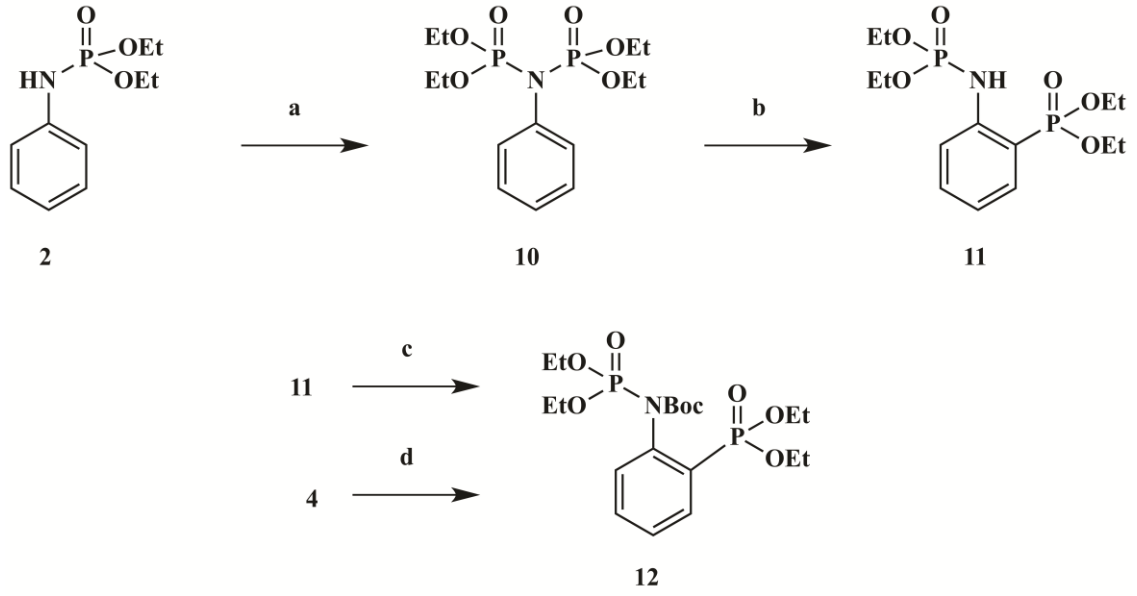


Scheme 1. Conditions: a) $ClP(=O)(OEt)_2$, NEt_3, DCM, 25 °C, 3 h, 91% (of **2**) and 53% (of **8**); b) Boc_2O, DMAP, MeCN, 25 °C, 2 h, 94%; c) *sec*-BuLi, TMEDA, Et_2O, -78 °C, 30 min, 83%; d) *sec*-BuLi, TMEDA, Et_2O, -78 °C, 30 min, 94%; e) Li, cat. CuI, THF, reflux, 3 h, 78%; f) EtOAc, aq. HCl, reflux, 3 h, 90%; g) Mg, cat. CuI, THF, reflux, 5 h, 21%; h) aq. HCl, 100 °C, 5 h, 63%; i) Boc_2O, DMAP, MeCN, 25 °C, 2 h, 89%.



Scheme 2. Conditions: a) $^{i}Pr_2NH$, *sec*-BuLi, THF, -20 °C, $ClP(=O)(OEt)_2$, 25 °C, 16 h, 73%; b) *sec*-BuLi, TMEDA, Et_2O, -78 °C, 3 h, 88%; c) *sec*-BuLi, TMEDA, E2O, $ClP(=O)(OEt)_2$, 25 °C, 1 h, 54%; d) *sec*-BuLi, TMEDA, Et_2O, Boc_2O, 25 °C, 30 min, 47%.

Whereas the reaction of acid-activated Zn powder with **9** led to the formation of **2** (as a consequence of the aqueous work-up), the reaction of **9** with magnesium gave 21 % of rearranged **5** [37, 38] together with some **2**. Also, compound **2** was transformed into **10** whose re-arrangement reaction gave 88 % of **11.** Bocylation of **11** yielded fully protected **12** that was also accessed from **4** in 54 % yield. Rearrangement reactions of **11** or **12** (Li metal, LDA or *sec*-BuLi) failed to give a bis-phosphonylated product (^{31}P NMR, ESI-MS).

Conclusion

Aniline was used as a starting material for the straightforward synthesis of 2-amino-phenylphosphonic acid in five steps ion 38% over-all yield with a phosphoramidate-aminophosphonate rearrangement reaction as the key-step.

Experimental

Reagents were bought from commercial suppliers without any further purification. Melting points were measured with a Leica hot stage microscope and were not corrected. NMR spectra were recorded on Varian Gemini 2000 or Unity 500 spectrometers at 27 °C, δ are given in ppm and J in Hz. Mass spectra were taken on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. Elemental analyses were measured on a Foss-Heraeus Vario EL unit. IR spectra were recorded on a Perkin-Elmer FT- IR spectrometer Spectrum 1000 and UV/Vis spectra on a Perkin-Elmer unit, Lambda 14. TLC was performed on silica gel (Merck 5554, detection by UV absorption). Solvents were dried according to usual procedures.

Diethyl *N*-phenylphosphoramidate (2)

*From **1**:* To an ice-cold solution of aniline (**1**) (5.02 mL, 55.0 mmol) and NEt_3 (8.36 mL, 60.0 mmol) in dry DCM (50 mL) under argon within 40 min a solution of diethyl chlorophosphate (7.25 mL) in dry DCM (10 mL) was added. After stirring for 3 h at 25 °C, the reaction mixture was extracted with aq. HCl (1 N, 3 x 30 mL), and a solution of $NaHCO_3$ (satd., 3 x 30 mL), dried (Na_2SO_4), and the solvent was distilled off under reduced pressure. Re-crystallization from water furnished **2** (10.4 g, 91%) as a colorless solid.

*From **8**:* To a suspension of TMSCl-activated zinc-powder (1.50 g, 22.9 mmol) in dry THF (30 mL) a solution of **8** (1.85 g, 6.00 mmol) in dry THF (20 mL) and catal. amounts of CuI were added. Heating under reflux for 5 hours followed by chromatography (*n*-hexane/ethyl acetate, 1:1) gave **2** (1.27 g, 92%) as a colorless solid. Data for **2**: m.p. 94-95 °C (lit.: 94-96 °C) [39]; R_f = 0.37 (DCM/ethyl acetate, 8:1);
IR (KBr) ν = 3208br, 3091w, 3058w, 2984s, 2903m, 2362w, 1863w, 1605s, 1498s, 1415s, 1394m, 1371w, 1333m, 1309m, 1291s, 1245s, 1223s, 1157m, 1022s, 1002s, 973s cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (ddd, $J_{H,H}$ = 7.1, 7.1 Hz, $J_{H,P}$ = 0.8 Hz, 6 H, OCH_2CH_3), 4.01-4.12 (ddq, J = 10.1, 7.1 Hz, $J_{H,P}$ = 8.0 Hz, 2 H, OCH_2CH_3), 4.10-4.21 (ddq, $J_{H,H}$ = 10.1, 7.1 Hz, $J_{H,P}$ = 7.7 Hz, 2 H, OCH_2CH_3), 6.25-6.37 (d, $J_{H,P}$ = 9.2 Hz, 1 H, NH), 6.89-6.95 (m, l H, aryl), 6.96-7.01 (m, 2H, aryl), 7.18-7.24 (m, 2 H, aryl) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (d, $J_{C,P}$ = 7.1 Hz, OCH_2CH_3), 62.8 (d, $J_{C,P}$ = 4.9 Hz, OCH_2CH_3), 117.3 (d, $J_{C,P}$ = 7.3 Hz, aryl), 121.5 (aryl), 129.2 (aryl), 139.8 (aryl) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = 3.40 ppm;
EI-MS (70 eV): *m/z* (%) = 229 (77) $[M]^{\cdot+}$, 214 (3), 201 (27), 186 (7), 173 (100);
Analysis calcd for $C_{10}H_{16}NO_3P$ (229.21): C 52.40, H 7.04, N 6.11; found: C 52.38, H 7.11, N 6.13.

Diethyl *N*-(*tert*-butoxycarbonyl)-phenylphosphor-amidate (3)

To a solution of **2** (6.88 g, 30.0 mmol) in dry MeCN (50 mL) at 25 °C, DMAP (366 mg, 3.00 mmol) and di- *tert*-butyldicarbonate (7.20 g, 33.0 mmol) in dry MeCN (10 mL) were added, and the mixture was stirred for 2 h. Usual work-up followed by chromatography (silica gel, *n*-hexane/ethyl acetate, 2:1) furnished **3** (9.29 g, 94%) as a colorless oil; R_f = 0.46 (*n*-hexane/ethyl acetate, 1:1);
IR (film): ν = 3480br, 2982m, 2933w, 1728s, 1597w, 1492w, 1456w, 1394w, 1369w, 1301s, 1159s, 1106w, 1028s, 983m cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (ddd, $J_{H,H}$ = 7.1, 7.1 Hz, $J_{H,P}$ = 0.9 Hz, 6 H, OCH_2CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 3.99-4.10 (ddq, $J_{H,H}$ = 10.1, 7.1 Hz, $J_{H,P}$ = 8.3 Hz, 2 H, OCH_2CH_3), 4.09-4.20 (ddq, $J_{H,H}$ = 10.1, 7.1 Hz, $J_{H,P}$ = 8.2 Hz, 2 H, OCH_2CH_3), 7.18-7.22 (m, 2 H, aryl), 7.24-7.29 (m, 1 H, aryl), 7.30-7.36 (m, 2H, aryl) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (d, $J_{H,P}$ = 7.1 Hz, OCH_2CH_3), 28.1 (s, $C(CH_3)_3$), 64.0 (d, $J_{C,P}$ = 6.0 Hz, OCH_2CH_3), 82.9 (s, $C(CH_3)_3$), 127.7 (aryl), 128.9 (aryl), 129.0 (aryl), 138.4 (aryl) 153.4 (d, $J_{C,P}$ = 8.4 Hz, C=O) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = 0.08 ppm;
EI-MS (70 eV): *m/z* (%) 329 (1) $[M^+]$, 256 (9), 229 (100);
Analysis calcd for $C_{15}H_{24}NO_5P$ (329.33): C 54.71, H 7.35, N 4.25; found: C 54.58, H 7.52, N 4.03.

Diethyl-*N*-(*tert*-butoxycarbonyl)-2-aminophenyl-phosphonate (4)

*From **3**:* To a solution of **3** (1.98 g, 6.00 mmol) and TMEDA (1.36 mL, 9.00 mmol) in dry ether (35 mL) at -78 °C, a solution of *s*-BuLi (6.9 mL, 9.00 mmol, 1.3 M in cyclohexane/hexane, 92:8) was slowly added. The reaction was quenched by adding AcOH in Et_2O (2 M, 35 mL) and allowed to warm to 25 °C. The solvent was removed under diminished pressure, water (60 mL) was added, and the mixture was extracted with DCM (4 x 20 mL). The solvent was

removed, and the residue was subjected to chromatography (*n*-hexane/ethyl acetate, 1:1) to yield **4** (1.64 g, 83%) as an off-white oil.

*From **9**:* As described for the synthesis of **4** from **3**, from **9** (2.45 g, 6.00 mmol) and TMEDA (1.36 mL, 9.00 mmol) in dry ether (50 mL) and *s*-BuLi (6.9 mL, 9.00 mmol, 1.3 M in cyclohexane/hexane, 92:8) followed by chromatography (*n*-hexane/ethyl acetate, 1:1) **4** (1.86 g, 94%) was obtained as an off-white oil.

*From **9**:* To a stirred suspension of lithium (1.00 g, 0.14 mol) in dry THF (30 mL) at 25 °C, a solution of **9** (2.45 g, 6.00 mmol) in dry THF (20 mL) was added, followed by catalytic amounts of CuI. The mixture was heated under reflux for 3 hours, filtered, and usual work-up of the filtrate followed by chromatography (silica gel, *n*-hexane/ethyl acetate, 1:1) furnished 4 (1.54 g, 78%) as an off-white oil.

*From **12**:* To a solution of $^{i}Pr_2NH$ (1.12 mL, 8.0 mmol) in dry THF (20 mL) at -20 °C a solution of *s*-BuLi (6.15 mL, 8.00 mmol, 1.3 M in cyclohexane/*n*-hexane, 92:8) was slowly added, stirring was continued for another 10 min, and the mixture was cooled to -78 °C. A solution of **12** (2.00 g, 4.30 mmol) in dry THF (10 mL), was slowly added, and stirring was continued for another 4 h. Usual work-up gave **4** (1.36 g, 96%) as a colorless oil. Data for **4**: R_f = 0.71 (*n*-hexane/ethyl acetate, 1:1);
IR (film): *v* = 3247m, 3115w, 2981s, 2933m, 1731s, 1604s, 1587s, 1537s, 1478m, 1443s, 1393m, 1368s, 1305s, 1243s, 1215s, 1160s, 1094s, 1023s, 972s cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (ddd, $J_{H,H}$ = 7.1, 7.1 Hz, $J_{H,P}$ = 0.6 Hz, 6 H, OCH_2CH_3), 1.49 (s, 9 H, $C(CH_3)_3$), 3.98-4.07 (ddq, $J_{H,H}$ = 10.1, 7.1 Hz, $J_{H,P}$ = 8.0 Hz, 2 H, OCH_2CH_3), 4.08-4.17 (ddq, $J_{H,H}$ = 10.1, 7.1 Hz, $J_{H,P}$ = 7.6 Hz, 2 H, OCH_2CH_3), 6.98-7.03 (m, 1 H, aryl), 7.44-7.49 (m, 1 H, aryl), 7.49-7.55 (m, 1 H, aryl), 8.30-8.34 (m, 1 H, aryl), 9.61 (s, 1 H, NH) ppm;
^{13}C NMR (100 MHz, $CDC1_3$): δ = 16.23 (d, $J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 28.36 (s, $OC(CH_3)_3$), 62.48 (d, $J_{C,P}$ = 5.2 Hz, OCH_2CH_3), 80.36 (s, $OC(CH_3)_3$), 113.00 (d, $J_{C,P}$ = 180.0 Hz, aryl), 119.24 (d, $J_{C,P}$ = 11.4 Hz, aryl), 121.62 (d, $J_{C,P}$ =13.7 Hz, aryl), 132.52 (d, $J_{C,P}$ = 6.1 Hz, aryl), 133.82 (d, $J_{C,P}$ = 2.3 Hz, aryl), 143.30 (d, $J_{C,P}$ = 7.2 Hz, aryl), 152.90 (s, C=O) ppm;
^{31}P NMR (81 MHz, $CDC1_3$): δ = 20.54 ppm;
EI-MS (70 eV): *m/z* (%) = 329 (16) $[M]^{\cdot+}$, 256 (15), 273 (19), 229 (100);
Analysis calcd for $C_{15}H_{24}NO_5P$ (329.33): C 54.71; H 7.35, N 4.25; found: C 54.55, H 7.51, N 4.01.

Diethyl 2-aminophenylphosphonate (5)

*From **4***: To a solution of **4** (1.65 g, 5.00 mmol) in ethyl acetate (80 mL) 3 M aq. HCl (40 mL) was added, and the mixture was heated under reflux for 6 hours. Usual work-up furnished **5** (1.03 g, 90%) as an off-white oil.

*From **9***: To a suspension of iodine-activated magnesium powder (1.00 g, 41.1 mol) in dry THF (30 mL) a solution of **9** (1.85 g, 6.00 mmol) in dry THF (20 mL) and catal. amounts of CuI were added. Heating under reflux for 5 hours followed by usual work-up and chromatography (*n*-hexane/ethyl acetate, 1:1) furnished **5** (289 mg, 21%) as an off-white solid. Data for **5**: m.p. 116-118 °C (lit.:[25] 117-118 °C); R_f = 0.40 (*n*-hexane/ethyl acetate, 1:1);
IR (film): *v* = 3440br, 3342br, 3236br, 2983m, 2932w, 2906w, 1716w, 1601w, 1566w, 1485m, 1451s, 1392m, 1369w, 1323m, 1216m, 1163m, 1128m, 1097m, 1022s, 967s cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (dd, $J_{H,H}$ = 7.1, 7.1 Hz, 6 H, OCH_2CH_3), 3.96-4.07 (ddq, $J_{H,H}$ = 10.1, 7.1 Hz, $J_{H,P}$ = 8.0 Hz, 2 H, OCH_2CH_3), 4.05-4,16 (ddq, $J_{H,H}$ = 10.1, 7.2 Hz, $J_{H,P}$ = 7.9 Hz, 2 H, OCH_2CH_3), 4.60-5.90 (bs, 2 H, NH_2), 6.61-6.67 (m, l H, aryl), 6.66-6.72 (m, 1 H, aryl), 7.22-7.28 (m, 1 H, aryl), 7.39-7.46 (ddd, ^{3} $J_{H,H}$ = 7.7, 1.6 Hz, $J_{H,P}$ = 14.4 Hz 1 H, aryl ppm;
^{13}C NMR (100 MHz, $CDCl_3$): **δ** = 16.26 (d, $J_{C,P}$ = 6.5 Hz, OCH_2CH_3), 62.07 (d, $J_{C,P}$ = 5.0 Hz, OCH_2CH_3), 107.35-109.18 (d, $J_{C,P}$ = 183.8 Hz, aryl), 116.38 (d, $J_{C,P}$ = 12.6 Hz, aryl), 117.07 (d, $J_{C,P}$ = 14.0 Hz, aryl), 133.13 (d, $J_{C,P}$ = 7.3 Hz, aryl), 133.80 (d, $J_{C,P}$ = 2.4 Hz, aryl), 150.81 (d, $J_{C,P}$ = 8.5 Hz, aryl) ppm;
^{31}P-NMR (81 MHz, $CDCl_3$): **δ** = 22.20 ppm;
EI-MS (70 eV): *m/z* (%) = 229 (30) $[M]^{\cdot+}$, 214 (3), 201 (15), 186 (6), 173 (33), 155 (100;
Analysis calcd for $C_{10}H_{16}NO_3P$ (229.21): C 52.40, H 7.04, N 6.11; found: C 52.22, H 7.17, N 5.96.

2-Aminophenylphosphonic acid (6)

A solution of **5** (1.00 g, 4.36 mmol) in 6 M aq. HCl (50 mL) was heated at 100 °C for 5 hours. Usual work-up followed by crystallization from cyclohexane furnished **6** (0.48 g, 63%) a colorless solid; m.p. 197-200 °C; lit.:[40] 199-200 °C; R_f = 0.26 (^{i}PrOH/H_2O/NH_3, 6:3:1);
IR (KBr): *v* = 3427br, 2923s, 2906w, 2362m,1594m, 1533m, 1484w, 1448m, 1313w, 1278m, 1216m, 1170m, 1150s, 1077s, 1015s, 905s cm^{-1};
^{1}H NMR (400 MHz, DMSO): δ = 4.00-4.60 (bs, NH_2, 2 x OH), 6.49-6.56 (m, 1 H, aryl), 6.60-6.65 (m, 1 H, aryl), 7.10-7.16 (m, 1 H, aryl), 7.28-7.36 (ddd, $J_{H,H}$ = 7.6 Hz, 1.5 Hz, $J_{H,P}$ = 14.4 Hz 1 H, aryl) ppm;
^{13}C NMR (100 MHz, DMSO): δ = 113.35 (d, $J_{C,P}$ = 178.7 Hz, aryl), 114.98 (d, $J_{C,P}$ = 13.6 Hz, aryl), 115.25 (d, $J_{C,P}$ = 11.8 Hz, aryl), 131.94 (d, $J_{C,P}$ = 2.2 Hz, aryl), 132.35 (d, $J_{C,P}$ = 7.7 Hz, aryl), 150.26 (d, $J_{C,P}$ = 8.2 Hz, aryl) ppm;
^{31}P NMR (81 MHz, DMSO): δ = 16.17 ppm;
EI-MS (70 eV): *m/z* (%) = 173 (3) $[M]^{\cdot+}$, 155 (5), 93 (100);
Analysis calcd for $C_6H_8NO_3P$ (173.11): C 41.63, H 4.66, N 8.09; found: C 41.49, H 5.01, N 7.87

Diethyl *N*-(2-bromophenyl)-phosphoramidate (8)
Following the procedure given for the synthesis of **2**, from 2-bromo-aniline (**7**, 6.00 g, 34.8 mmol) and NEt_3 (5.5 mL, 39.5 mmol) in dry DCM (40 mL) and diethyl chlorophosphate (6.00 mL, 41.4 mmol) in dry DCM (10 mL) followed by chromatographic purification (silica gel, *n*-hexane/ethyl acetate, 1:1) **8** (5.7 g, 53%) was obtained as a colorless solid; m.p. 55-57 °C; R_f = 0.45 (*n*-hexane/ethyl acetate, 1:1);
IR (KBr): ν = 3184br, 2986m, 2903w, 1931w, 1590m, 1489s, 1458m, 1411m, 1297m, 1278m, 1255m, 1228m, 1018s, 976s, 767m cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (ddd, $J_{H,H}$ = 7.1 Hz, 7.1 Hz, $J_{H,P}$ = 0.8 Hz, 6 H, OCH_2CH3), 4.03-4.14 (ddq, $J_{H,H}$ = 10.1 Hz, 7.1 Hz, $J_{H,P}$ = 8.1 Hz, 2 H, OCH_2CH_3), 4.12-4.23 (ddq, $J_{H,H}$ = 10.1 Hz, 7.1 Hz, $J_{H,P}$ = 8.0 Hz, 2 H, OCH_2CH_3), 5.61 (d, $J_{H,P}$ = 8.3 Hz, 1 H, NH), 6.81 (ddd, $J_{H,H}$ = 7.4, 8.0, 1.5 Hz, 1 H, aryl), 7.20 (ddd, $J_{H,H}$ = 7.5 Hz, 8.2 Hz, 1.5 Hz, 1 H, aryl), 7.31 (dd, $J_{H,H}$ = 8.2, 1.5 Hz, 1 H, aryl), 7.47 (ddd, $J_{H,H}$ = 8.0 Hz, 1.5 Hz, $J_{H,P}$ = 1.5 Hz, 1 H, aryl) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.09 (d, $J_{C,P}$ = 6.9 Hz, OCH_2CH_3), 63.17 (d, $J_{C,P}$ = 5.1 Hz, OCH_2CH_3), 112.41 (aryl), 117.71 (aryl), 122.67 (aryl), 128.43 (aryl), 132.53 (aryl), 137.58 (aryl) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = 2.03 ppm;
EI-MS (70 eV): *m/z* (%) = 309/307 (5) $[M]^{\cdot +}$, 228 (7), 200 (14), 172 (100);
Analysis calcd for $C_{10}H_{15}BrNO_3P$ (308.11): C 38.98, H 4.91, N 4.55; found: C 39.10, H 5.18, N 4.49.

Diethyl *N*-(*tert*-butoxycarbonyl)-2-bromophenyl-phosphoramidate (9)
Following the procedure given for **3**, from **8** (6.50 g, 21.1 mmol), DMAP (258 mg, 2.11 mmol) and di-*tert*- butyldicarbonate (5.50 g, 31.9 mmol) followed by usual work-up and chromatography (silica gel, DCM/ethyl acetate, 8:1) **9** (7.66 g, 89%) was obtained as an off-white solid; m.p. 43-45 °C; R_f = 0.60 (DCM/ethyl acetate); IR (film): ν = 3478br, 3388w, 3065w, 2981s, 2932m, 2910m, 1732s, 1634w, 1592m, 1475s, 1456m, 1443m, 1394s, 1369s, 1303s, 1159s, 1098s, 1029s cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (ddd, $J_{H,H}$ = 7.1, 7.1 Hz, $_{JH,P}$ = 0.9 Hz, 3 H, OCH_2CH_3), 1.30 (ddd, $J_{H,H}$ = 7.1, 7.1 Hz, $J_{H,P}$ = 0.8 Hz, 3 H, OCH_2CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 4.11-4.31 (m, 4 H, OCH_2CH_3)g), 7.12-7.17 (m, l H, aryl), 7.28-7.30 (m, 1 H, aryl), 7.30-7.31 (m, 1 H, aryl), 7.56-7.60 (m, 1 H, aryl) ppm;
^{13}C NMR (100 MHz): δ = 16.24 (d, $J_{C,P}$ = 7.1 Hz, OCH_2CH_3), 28.05 (s, $C(CH_3)_3$), 64.30 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 64.42 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 83.04 (s, $C(CH_3)_3$), 124.25 (aryl), 127.98 (aryl), 129.11 (aryl), 130.87 (aryl), 133.06 (aryl), 137.78 (aryl), 152.06 (d, $J_{C,P}$ = 8.5 Hz, C=O) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = -0.91 ppm;
EI-MS (70 eV): *m/z (%)* = 352/354 (3) $[M]^{\cdot +}$, 334/336 (14), 328 (47), 307/309 (100);
Analysis calcd for $C_{15}H_{23}BrNO_5P$ (408.22): C 44.13, H 5.68, N 3.43; found: C 44.00, H 5.83, N 3.32.

Diethyl *N*-(diethoxyphosphinyl)-phenylphosphor-amidate (10)
To a solution of ^{i}Pr$_2$NH (1.12 mL, 8.0 mmol) in dry THF (20 mL) under argon at -20 °C, a solution of *s*-BuLi (6.15 mL, 8.00 mmol, 1.3 M in cyclohexane/*n*-hexane, 92:8) was added, and the mixture was stirred for 10 min. A solution of **2** (1.50 g, 6.54 mmol) in dry THF (10 mL) was added at -78 °C and diethyl chlorophosphate (1.50 mL, 10.35 mmol) in dry THF (10 mL) was slowly added. After warming to 25 °C, stirring was continued for another 16 h. The solvent was removed under diminished pressure. Usual aqueous work-up followed by chromatographic purification (silica gel, *n*-hexane/ethyl acetate, 1:1) furnished **10** (1.75 g, 73%) as a yellowish oil; R_f = 0.31 (DCM/ethyl acetate, 1:8);
IR (film): ν = 3455br, 2985m, 2933w, 1644w, 1594w, 1491w, 1445w, 1393w, 1370w, 1270s, 1165w, 1024 s cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (dd, $J_{H,H}$ = 7.1, 7.1 Hz, 12 H, OCH_2CH_3), 4.04-4.20 (m, 8 H, OCH_2CH_3), 7.22-7.35 (m, 5 H, aryl) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.00 (d, $J_{C,P}$ = 3.5 Hz, OCH_2CH_3), 16.04 (d, $J_{C,P}$ = 3.5 Hz, OCH_2CH_3), 63.94 (d, $J_{C,P}$ = 2.9 Hz, OCH_2CH_3), 63.98 (d, $J_{C,P}$ = 2.9 Hz, OCH_2CH_3), 127.55 (d, $J_{C,P}$ = 1.5 Hz, aryl), 129.01 (d, $J_{C,P}$ = 1.3 Hz, aryl), 129.17 (d, $J_{C,P}$ = 2.7 Hz, aryl), 137.86 (aryl) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = 1.05 ppm;
EI-MS (70 eV): *m/z* (%) = 365 (37) $[M]^{\cdot +}$, 337 (6), 320 (5), 262 (22), 245 (25), 236 (47), 229 (69), 216 (44), 201 (53), 173 (100);
Analysis calcd for $C_{14}H_{25}NO_6P_2$ (365.30): C 46.03, H 6.90, N 3.83; found: C 45.86, H 7.04.

Diethyl *N*-(diethoxyphosphinyl)-2-ammophenyl-phosphonate (11)
To a solution of **10** (2.19 g, 6.00 mmol) and TMEDA (1.36 mL, 9.00 mmol) in dry ether (35 mL) at -78 °C a solution of *s*-BuLi (6.9 mL, 9.00 mmol, 1.3 M in cyclohexane/hexane, 92:8) was slowly added, and the mixture was stirred for 3 hours. Usual work-up followed by re-crystallization (from *n*-hexane) furnished **11** (1.93 g, 88%) as a colorless solid; m.p. 91-92 °C; R_f = 0.63 (DCM/ethyl acetate, 1:8);
IR (film): *ν* = 3442br, 3204m, 2987m, 2907m, 1601m, 1581m, 1503m, 1461m, 1431m, 1393w, 1370w, 1309m, 1241s, 1205m, 1149m, 1045s, 977s, 802m, 778m cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (dd, $J_{H,H}$ = 7.1 Hz, 7.1 Hz, 6 H, OCH_2CH_3), 1.30 (dd, $J_{H,H}$ = 7.1 Hz, 7.1 Hz, 6 H, OCH_2CH_3), 3.96-4.20 (m, 8 H, OCH_2CH_3), 6.91-6.97 (m, 1 H, aryl), 7.36-7.52 (m, 3 H, aryl), 8.43 (d, $J_{H,P}$ = 9,1 Hz, 1 H, NH) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.16 (d, $J_{C,P}$ = 7.1 Hz, OCH_2CH_3), 16.23 (d, $J_{C,P}$ = 6.8 Hz, OCH_2CH_3), 62.45 (d, $J_{C,P}$ = 5.1 Hz, OCH_2CH_3),

63.15 (d, $J_{C,P}$ = 5.5 Hz, OCH_2CH_3), 112.63 (d, $J_{C,P}$ = 182.5 Hz, aryl), 118.12 (aryl), 120.64 (aryl), 132.83 (aryl), 133.98 (aryl), 144.92 (aryl) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = 2.08 (d, $J_{P,P}$ = 2.5 Hz, 1 P, N-P(O)(OEt)), 21.16 (d, $J_{P,P}$ = 2.5 Hz, 1 P, Ar-P(O)(OEt));
EI-MS (70 eV): *m/z (%)* = 365 (23) $[M]^{\cdot+}$, 264 (5), 256 (45), 246 (47), 229 (58), 201 (50), 173 (38), 155 (100); Analysis calcd for $C_{14}H_{25}NO_6P_2$ (365.30): C 46.03, H 6.90, N 3.83; found: C 45.86, H 7.04, N 3.59.

Diethyl-*N*-(*tert*-butoxycarbonyl)-*N*-(diethoxyphosphinyl)-2-aminophenyl phosphonate (12)

*From **4**:* To a -78 °C cold solution of **4** (3.00 g, 9.11 mmol) and TMEDA (2.8 mL, 18.5 mmol) in dry ether (50 mL) a solution of *s*-BuLi (14.2 mL, 18.5 mmol, 1.3 M in cyclohexane/hexane, 92:8) was added, and stirring was continued for another 10 min. A solution of diethyl chlorophosphate (2.75 mL, 19.0 mmol) in dry ether (15 mL) was slowly added, stirring continued for another hour, and the mixture was allowed to warm to 25 °C. Usual work-up followed by chromatography (silica gel, *n*-hexane/ethyl acetate, 2:1) furnished **12** (2.29 g, 54%) as a colorless oil.

*From **11**:* To a solution of **11** (3.30 g, 9.3 mmol) and TMEDA (2.8 mL, 18.5 mmol) in dry ether (50 mL) at -78 °C a solution of *s*-BuLi (14.2 mL, 18.5 mmol, 1.3 M in cyclohexane/*n*-hexane, 92:8) was added) as described above followed by the addition of di-*tert*-butyldicarbonate (2.75 mL, 19.0 mmL). After warming to 25 °C, usual work-up and chromatography (silica gel, *n*-hexane/ethyl acetate, 2.1), **12** (1.98 g, 47%) was obtained as a colorless oil. Data for **12**: R_f = 0.35 (*n*-hexane/ethyl acetate);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (dd, $J_{H,H}$ = 7.2, 7.2 Hz, 6 H, OCH_2CH_3), 1.30 (dd, JH,H = 7.2 Hz, 7.2 Hz, 6 H, OCH_2CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 3.96-4.28 (m, 8 H, OCH_2CH_3), 7.25-7.31 (m, 1 H, aryl), 7.34-7.41 (m, 1 H, aryl), 7.49-7.55 (m, 1 H, aryl), 7.84-7.92 (ddd, $J_{H,H}$ = 7.7, 1.4 Hz, $J_{H,P}$ = 14.3 Hz, 1 H, aryl) ppm;
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.21 (d, $J_{C,P}$ = 8.0 Hz, OCH_2CH_3), 16.30 (d, $J_{C,P}$ = 8.0 Hz, OCH_2CH_3), 16.39 (d, $J_{C,P}$ = 6.4 Hz, OCH_2CH_3), 16.42 (d, $J_{C,P}$ = 6.0 Hz, OCH_2CH_3), 28.14 (s, $OC(CH_3)_3$), 62.28 (d, $J_{C,P}$ = 5.4 Hz, OCH_2CH_3), 62.34 (d, $J_{C,P}$ = 5.4 Hz, OCH_2CH_3), 63.97 (d, $J_{C,P}$ = 6.3 Hz, OCH_2CH_3), 64.32 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 82.73 (s, $OC(CH_3)_3$), 127.56 (aryl), 127.87 (d, $J_{C,P}$ = 181.8 Hz, aryl), 130.87 (aryl), 133.10 (aryl), 134.55 (aryl), 141.29 (aryl), 153.02 (d, $J_{C,P}$ = 7.2 Hz, C=0) ppm;
^{31}P NMR (81 MHz, $CDCl_3$): δ = -0.72 (d, $J_{P,P}$ = 1.5 Hz, 1 P, N-P(O)(OEt)), 16.53 (d, $J_{P,P}$ = 1.5 Hz, 1 P, Ar-P) ppm;
ESI-MS (MeOH): *m/z* 466.1 (48) $[M+H]^+$, 488.1 (100) $[M+Na]^+$, 952.9 (55) $[2M+Na]^+$;
Analysis calcd for $C_{19}H_{33}NO_8P_2$ (465.41): C 52.53, H 7.66, N 3.22; found: C 52.37, H 7.91, N 3.01.

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