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Synthesis and Butyllithium-Induced Cyclisation of 2-Benzyloxyphenylphosphonamidates Giving 2,3-Dihydrobenzo[*d*][1,3]oxaphospholes

R. Alan Aitken *, Khadija Ait Moulay, David B. Cordes, Ryan A. Inwood, Fraser G. Jamieson, Alexander J. B. Nelson and Aidan P. McKay

EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK; nelsonalexander84@yahoo.co.uk (A.J.B.N.)

* Correspondence: raa@st-and.ac.uk; Tel.: +44-1334-463865

Abstract: A series of fourteen *O*-ethyl-*N*-butylphenylphosphonamidates with benzyl ether substituents at the *ortho* position was prepared and fully characterised. Upon treatment with *n*-butyllithium in THF at RT, they underwent cyclisation in eight cases to give the novel 2,3-dihydrobenzo[*d*][1,3]oxaphospholes in moderate to low yield as a single diastereomer, for which the relative configuration was determined by X-ray diffraction in one case.

Keywords: 1,3-dihydrobenzo[*d*][1,3]oxaphosphole; 1,3-benzoxaphosphole; phosphonamidate; X-ray structure; hydrogen bonding

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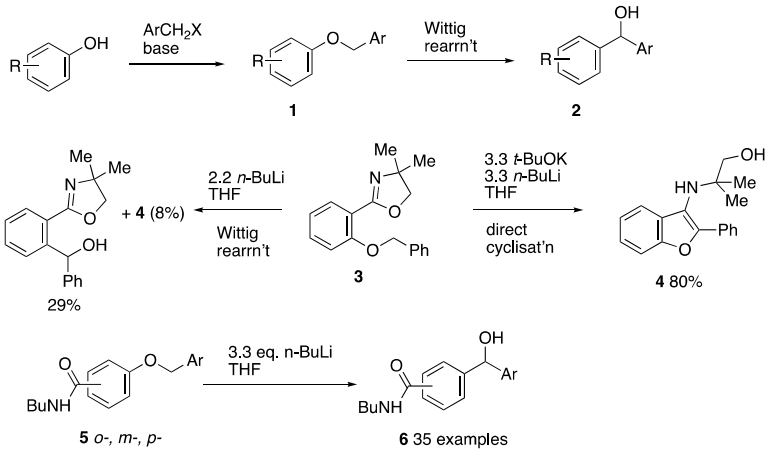
1. Introduction

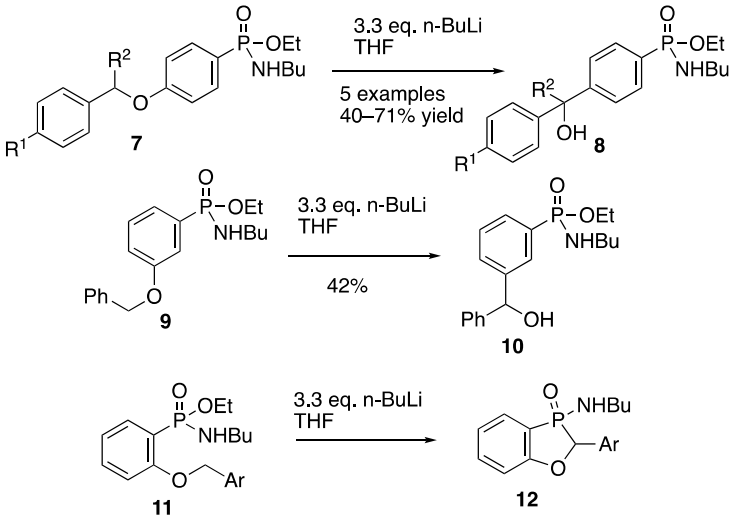
The [1,2]-Wittig rearrangement of aryl benzyl ethers **1** to give diarylmethanols **2** (Scheme 1) provides a potentially versatile indirect method for C–C bond formation, but, whilst the reaction has been known for a long time [1,2], it has not been used much recently [3]; this is most likely due to the strongly basic conditions required, which make it incompatible with many of the common functional groups. In recent studies, we reported the use of various activating groups on the aryl ring to facilitate the Wittig rearrangement under milder conditions. The first activating group for this purpose to be discovered was the 4,4-dimethyl-2-oxazoline [4], but when this was in the ortho position to the benzyloxy group, as shown in **3**, there was also significant competition from direct cyclisation to give benzofuran products **4**, a feature also observed in benzyloxythienyloxazolines [5].



Scheme 1. General strategy for indirect C–C bond formation via ether formation and Wittig rearrangement and previously reported examples [4,6].

More recently, we discovered the *N*-butylcarboxamide CONHBu as a more efficient and general activating group, allowing the Wittig rearrangement of *ortho*-, *meta*-, or *para*-oriented benzylic ethers **5** to afford diarylmethanols **6** [6]. A limited degree of success in using a chiral secondary amide group to bring about asymmetric Wittig rearrangement was also described [7]. As far as we are aware, there is only a single report of an enantioselective [1,2]-Wittig rearrangement, and this uses an external chiral bis(oxazoline) ligand [8].

In an earlier paper, we described the synthesis of aryl benzyl ethers bearing the phosphonamidate group EtO-P(=O)-NHBu on the aryl ring, either *para*- (**7**) or *meta*- (**9**) to a benzylic ether, and their successful Wittig rearrangement to afford the corresponding phosphonamidate-functionalised diarylmethanols **8** and **10**, respectively (Scheme 2) [9]. In this paper, we describe the synthesis of a series of the isomeric aryl benzyl ethers **11** bearing an *ortho*-phosphonamidate group and their reaction with butyllithium, which leads not to Wittig rearrangement but rather to cyclisation, giving 2,3-dihydrobenzo[*d*][1,3]oxaphospholes **12**. Recently, compounds of this type have been of considerable interest as chiral ligands for catalytic asymmetric synthesis, but all the previous synthetic methods involved cyclisation with the formation of the C(2)–O bond [10–13] as opposed to the method described here where the C(2)–P bond is formed.



Scheme 2. Base treatment of isomeric benzyloxyphenylphosphonamidates.

2. Materials and Methods

2.1. General Experimental Details

NMR spectra were recorded at 25 °C on solutions in $CDCl_3$, unless otherwise stated, using Bruker instruments (Bruker, Billerica, MA, USA), and the chemical shifts are given in ppm to high frequency from Me_4Si. IR spectra were recorded using the ATR technique on a Shimadzu IRAffinity 1S instrument. The ionisation method used for high-resolution mass spectra is noted in each case. Column chromatography was carried out using a silica gel of 40–63 μm particle size, and preparative TLC was carried out using 1.0 mm layers of Merck alumina 60G containing 0.5% Woelm fluorescent green indicator on glass plates. Melting points were recorded on a Gallenkamp 50W melting point apparatus or a Reichert hot-stage microscope (Reichert, Vienna, Austria).

Unless otherwise stated, all the reagents and solvents were obtained from standard suppliers and were used as received. Anhydrous nickel(II) chloride was prepared by placing the commercially available hexahydrate in a Schlenk tube under vacuum and heating with a heat-gun until no further loss of mass was observed. The final material was a fine primrose-yellow powder. Dry THF was prepared by the addition of sodium wire, and dry acetone was the commercially available analytical reagent grade.

2.2. Synthesis and Rearrangement of Ethyl P-(4-Benzyloxyphenyl)-N-butylphosphonamidate **16**

2.2.1. 1-(Benzyloxy)-2-bromobenzene **13**

To a stirred solution of 2-bromophenol (4.36 g, 25.2 mmol) in MeCN (60 mL) at rt was added K_2CO_3 (4.74 g, 34.3 mmol) and benzyl bromide (3.0 mL, 4.32 g, 25.2 mmol), and the mixture was stirred at rt overnight. The reaction was diluted with H_2O (75 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give **13** (6.35 g, 96%) as a pale-yellow oil which was used without further purification; ^{1}H NMR (400 MHz): 7.55 (1H, dd, *J* = 7.8, 1.6 Hz, ArH), 7.50–7.44 (2H, m, ArH), 7.42–7.34 (2H, m, ArH), 7.34–7.27 (1H, m, ArH), 7.22 (1H, ddd, *J* = 8.2, 7.4, 1.6 Hz, ArH), 6.92 (1H, dd, *J* = 8.2, 1.4 Hz, ArH), 6.83 (1H, ddd, *J* = 7.8, 7.4, 1.4 Hz, ArH) and 5.14 (2H, s, OCH_2); ^{13}C NMR (100 MHz) 154.9 (C-O), 136.5 (C), 133.4 (CH), 128.5 (2CH), 128.3 (CH), 127.9 (CH), 126.9 (2CH), 122.1 (CH), 113.8 (CH), 112.4 (C-Br) and 70.7 (OCH_2). The ^{1}H and ^{13}C spectral data were in accordance with those previously reported [14] (Supplementary Materials).

2.2.2. Diethyl (2-Benzyloxyphenyl)phosphonate **14**

Following a modified literature procedure [15], 1-(benzyloxy)-2-bromobenzene **13** (3.77 g, 14.2 mmol) and anhydrous $NiCl_2$ (0.92 g, 7.1 mmol) were placed in a flask set up for distillation, and a dropping funnel containing triethyl phosphite (3.0 mL, 17.2 mmol) was connected to the still head. The mixture was heated at 150 °C while the phosphite was added dropwise until the mixture was dark red. When the initial dark red colour changed to blue, more phosphite was added until the red colour returned. This was repeated until all the phosphite was added; the mixture was then heated for a further 30 min and cooled to rt. The mixture was taken up in CH_2Cl_2 (50 mL), which was washed with dil. HCl (25 mL), dried, and evaporated. Purification via flash column chromatography (gradient elution hexane/EtOAc 9:1 to 100% ethyl acetate), followed by the removal of triethyl phosphate by Kugelrohr distillation, gave **8** (2.88 g, 63%) as a pale-yellow oil; ν_{max}/cm^{-1} 1593, 1477, 1443, 1279, 1242, 1020, 959, 756, 733, 696, 573, 536, and 507; ^{1}H NMR (400 MHz): 7.87 (1H, ddd, *J* = 14.9, 7.4, 1.8 Hz, ArH), 7.55–7.50 (2H, m, ArH), 7.47 (1H, dddd, *J* = 8.3, 7.4, 1.8, 0.9 Hz, ArH), 7.41–7.35 (2H, m, ArH), 7.33–7.28 (1H, m, ArH), 7.05–6.96 (2H, m, ArH), 5.19 (2H, s, OCH_2Ph), 4.18–4.05 (4H, m, 2 $OC\boldsymbol{H}_2CH_3$) and 1.28 (6H, t, *J* = 7.1 Hz, 2 $OCH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 160.1 (d, *J* = 2.7 Hz, C-O), 136.4 (C), 135.1 (d, *J* = 7.2 Hz, CH), 134.2 (d, *J* = 2.1 Hz, CH), 128.4 (2CH), 127.7 (CH), 126.9 (2CH), 120.5 (d, *J* = 14.6 Hz, CH), 117.0 (d, *J* = 187 Hz, ArC-P), 112.3 (d, *J* = 9.3 Hz, Ar CH), 70.0 (OCH_2Ph), 62.0 (d, *J* = 5.6 Hz, 2 $O\boldsymbol{C}H_2CH_3$) and 16.2 (d, *J* = 6.5 Hz, 2 $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +17.1; HRMS (ESI^+): found 343.1058. $C_{17}H_{21}NaO_4P$ (M + Na) requires 343.1075.

2.2.3. Ethyl (2-Benzyloxyphenyl)phosphonochloridate **15**

A solution of diethyl (2-benzyloxyphenyl)phosphonate **14** (1.00 g, 3.1 mmol) in dry toluene (15 mL) was stirred at 0 °C while PCl_5 (1.30 g, 6.2 mmol) was added. The mixture was then stirred at rt for 30 min, filtered, and evaporated to give **15** (0.99 g, ~100%) as a yellow oil which was used without further purification; ^{1}H NMR (400 MHz): 7.94 (1H, ddd, *J* = 16.9, 7.7, 1.8 Hz, ArH), 7.55 (1H, tdd, *J* = 8.4, 1.8, 1.0 Hz, ArH), 7.54–7.46 (2H, m, ArH), 7.41–7.36 (2H, m, ArH), 7.35–7.32 (1H, m, ArH), 7.09–6.99 (2H, m, ArH), 5.22 (2H, s, OCH_2Ph), 4.42–4.26 (2H, m, $OC\boldsymbol{H}_2CH_3$) and 1.35 (3 H, td, *J* = 7.0, 0.5 Hz, $OCH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 159.8 (4ry, d, *J* = 2.9 Hz, ArC-O), 136.0 (C), 135.6 (d, *J* = 2.0 Hz, CH), 134.2 (d, *J* = 8.6 Hz, CH), 128.5 (2CH), 128.0 (CH), 127.0 (2CH), 120.5 (d, *J* = 16.4 Hz, CH), 118.5 (d, *J* = 179.5 Hz, C-P), 112.7 (d, *J* = 9.8 Hz, CH), 70.5 (OCH_2Ph), 63.7 (d, *J* = 7.7 Hz, $O\boldsymbol{C}H_2CH_3$) and 15.8 (d, *J* = 7.7 Hz, $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +26.5.

2.2.4. Ethyl *P*-(2-Benzyloxyphenyl)-*N*-butylphosphonamidate **16**

Following a literature procedure [16], a solution of *n*-butylamine (0.67 mL, 0.50 g, 6.8 mmol) in Et_2O (25 mL) was stirred at 0 °C while a solution of ethyl (2-benzyloxyphenyl) phosphonochloridate **15** (1.00 g, 3.2 mmol) in Et_2O (25 mL) was added dropwise. The

mixture was allowed to warm to rt and was stirred for 18 h. Water (50 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 25 mL), and the combined organic layers were dried and evaporated. Purification by column chromatography (SiO_2, EtOAc/hexane 1:1) gave **16** (480 mg, 43%) as a slightly yellow oil; ν_{max}/cm^{-1} 2957, 2930, 2872, 1591, 1440, 1277, 1229, 1086, 1032, 951, 756, 735, 696, 571, and 534; ^{1}H NMR (400 MHz): 7.93 (1H, ddd, *J* = 14.2, 7.4, 1.8 Hz, ArH), 7.48–7.43 (3H, m, ArH), 7.42–7.32 (3H, m, ArH), 7.04 (1H, tdd, *J* = 7.4, 2.9, 0.9 Hz, ArH), 6.99 (1H, ddd, *J* = 8.4, 6.2, 0.9 Hz, ArH), 5.14 (2H, s, OCH_2Ph), 4.09–3.89 (2H, m, $OC\boldsymbol{H}_2CH_3$), 2.97–2.87 (3H, m, $N\boldsymbol{H}C\boldsymbol{H}_2$), 1.34–1.27 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.26 (3H, t, *J* = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$), 1.21–1.09 (2H, m, $NHCH_2CH_2C\boldsymbol{H}_2$) and 0.79 (3H, t, *J* = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 159.0 (d, *J* = 2.8 Hz, ArC-O), 136.1 (C), 134.4 (d, *J* = 6.4 Hz, CH), 133.3 (d, *J* = 1.6 Hz, Ar CH), 128.6 (2CH), 128.2 (CH), 127.3 (2CH), 120.8 (d, *J* = 13.5 Hz, CH), 119.8 (d, *J* = 167.0 Hz, ArC-P), 111.7 (d, *J* = 8.5 Hz, CH), 70.3 (OCH_2Ph), 60.2 (d, *J* = 5.7 Hz, $O\boldsymbol{C}H_2CH_3$) 40.3 ($NHCH_2$), 34.0 (d, *J* = 6.1 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.6 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, *J* = 6.9 Hz, $OCH_2\boldsymbol{C}H_3$) and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +21.3; HRMS (ESI$^+$): found 370.1529. $C_{19}H_{26}NNaO_3P$ (M + Na) requires 370.1548.

2.2.5. 3-Butylamino-2-phenyl-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **17**

A solution of ethyl *P*-(2-benzyloxyphenyl)-*N*-butylphosphonamidate **16** (69.5 mg, 0.2 mmol) in dry THF (2 mL) was stirred at rt under N_2 while *n*-butyllithium (0.37 mL, 0.66 mmol) was added by syringe. After 20 min, the mixture was added to saturated aqueous ammonium chloride (2 mL), and the mixture was extracted with Et_2O (3 × 2 mL). Drying and evaporation of the combined extracts gave, after purification via preparative TLC, (EtOAc/hexane 1:1) **17** (24.5 mg, 41%) as a pale-yellow oil; ν_{max}/cm^{-1}3184, 2957, 2930, 2872, 1599, 1578, 1449, 1204, 1155, 1126, 1094, 988, 916, 827, 756, 729, 696, and 515; ^{1}H NMR (400 MHz): 7.66–7.52 (2H, m, ArH), 7.42–7.38 (4H, m, ArH), 7.37–7.32 (1H, m, ArH), 7.15–7.07 (2H, m, ArH), 5.57 (1H, d, *J* = 9.9 Hz, CHP), 2.49–2.37 (1H, m, NHC***H***H), 2.30–2.21 (1H, m, N***H***CH***H***), 1.04–0.94 (4H, m, $NHCH_2C\boldsymbol{H}_2C\boldsymbol{H}_2$) and 0.70 (3H, t, *J* = 6.9 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{1}H{^{31}P} NMR (400 MHz): 5.57 (1H, s); ^{13}C NMR (100 MHz): 164.6 (d, *J* = 24.0 Hz, ArC-O), 135.5 (d, *J* = 1.7 Hz, CH), 134.7 (d, *J* = 3.4 Hz, C), 129.0 (d, *J* = 5.5 Hz, CH), 128.8 (d, *J* = 2.0 Hz, 2CH), 128.0 (d, *J* = 2.5 Hz, CH), 124.9 (d, *J* = 3.9 Hz, 2CH), 122.4 (d, *J* = 10.1 Hz, CH), 114.3 (d, *J* = 6.6 Hz, CH), 113.9 (d, *J* = 122.8 Hz, ArC-P), 79.7 (d, *J* = 87.4 Hz, CHP), 40.2 (d, *J* = 1.2 Hz, $NHCH_2$), 33.7 (d, *J* = 5.4 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.4 ($NHCH_2CH_2\boldsymbol{C}H_2$) and 13.5 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +44.6; HRMS (ESI$^+$): found 302.1295. $C_{17}H_{22}NOP$ (M + H) requires 302.1310.

2.3. Synthesis of Substituted 2-Bromophenyl Benzyl Ethers **18**

2.3.1. 2-Bromophenyl 2-Methylbenzyl Ether **18a**

To a stirred solution of 2-bromophenol (2.9 mL, 4.33 g, 25.0 mmol) and K_2CO_3 (4.70 g, 34.0 mmol) in MeCN (60 mL) at rt, 2-methylbenzyl bromide (3.4 mL, 4.63 g, 25.0 mmol) was added, and the solution was stirred for 18 h. The reaction mixture was poured into H_2O and extracted with EtOAc (2 × 50 mL), and the combined organic fractions were dried over $MgSO_4$ and concentrated to afford, after recrystallisation from hexane, **18a** (3.92 g, 57%) as colourless crystals, mp 42–44 °C; ν_{max}/cm^{-1} 3063, 3032, 2972, 2913, 2855, 1585, 1479, 1439, 1275, 1246, 1049, 1028, 737, and 665; ^{1}H NMR (300 MHz): 7.56 (1H, dd, *J* = 7.9, 1.6 Hz, ArH), 7.53–7.45 (1H, m, ArH), 7.32–7.16 (4 H, m, ArH), 6.98 (1H, dd, *J* = 8.3, 1.3 Hz, ArH), 6.85 (1 H, td, *J* = 7.5, 1.2 Hz, ArH), 5.11 (2H, s, OCH_2) and 2.40 (3H, s, $ArCH_3$); ^{13}C NMR (75 MHz): 155.1 (C), 136.3 (C), 134.3 (C), 133.5 (CH), 130.3 (CH), 128.4 (CH), 128.2 (2CH), 126.0 (CH), 122.1 (CH), 113.7 (CH), 112.5 (C), 69.4 (CH_2) and 19.0 (CH_3).

2.3.2. 2-Bromophenyl 4-Methylbenzyl Ether **18b**

A solution of sodium iodide (5.34 g, 35.6 mmol) in dry acetone (25 mL) was stirred while 4-methylbenzyl chloride (5.00 g, 35.6 mmol) was added dropwise, and the mixture

was stirred for 30 min. The mixture was added to H_2O (50 mL) and extracted with Et_2O (2 × 50 mL). Drying and evaporation of the extracts gave 4-methylbenzyl iodide 6.52 g, 79%) as a pale-yellow liquid.

To a stirred solution of 2-bromophenol (3.3 mL, 4.87 g, 28.0 mmol) and K_2CO_3 (7.16 g, 52.0 mmol) in MeCN (90 mL) at rt, 4-methylbenzyl iodide (6.52 g, 28.0 mmol) was added, and the solution was stirred for 18 h. The reaction mixture was poured into H_2O and extracted with EtOAc (2 × 50 mL), and the combined organic fractions were dried over $MgSO_4$ and concentrated to afford, after column chromatography (SiO_2, hexane/EtOAc 9:1), **18b** (6.30 g, 81%) as colourless crystals, mp 54–56 °C; ν_{max}/cm^{-1} 1479, 1454, 1441, 1292, 1285, 1275, 1246, 1213, 1180, 1158, 1055, 1028, 1020, 983, 949, 922, 808, 742, and 664; ^{1}H NMR (300 MHz): 7.55 (1H, dd, *J* = 7.8, 1.8 Hz, ArH), 7.36 (2H, d, *J* = 8.1 Hz, ArH), 7.26–7.19 (3 H, m, ArH), 6.93 (1H, dd, *J* = 8.1, 1.5 Hz, ArH), 6.83 (1H, td, *J* = 8.1, 7.5, 1.5 Hz, ArH), 5.12 (2H, s, OCH_2) and 2.36 (3H, s, CH_3); ^{13}C NMR (125 MHz): 155.0 (ArC-O), 137.6 (C), 133.5 (C), 133.4 (CH), 129.2 (2CH), 128.3 (CH), 127.1 (2CH), 122.0 (CH), 113.9 (CH), 112.5 (C-Br), 70.7 (OCH_2) and 21.2 (CH_3); HRMS (ESI$^+$): found 299.0042. $C_{14}H_{13}{}^{79}BrNaO$ (M + Na) requires 299.0047.

2.3.3. 2-Bromophenyl 4-*tert*-Butylbenzyl Ether **18c**

The same procedure as in 2.3.1 using 2-bromophenol (5.79 g, 33 mmol), K_2CO_3 (7.20 g, 52 mmol), and 4-*tert*-butylbenzyl bromide [17] (7.63 g, 33 mmol) gave **18c** (6.20 g, 55%) as a brown oil; ν_{max}/cm^{-1} 2963, 1477, 1462, 1443, 1634, 1294, 1277, 1246, 1233, 1109, 1051, 1030, 1015, 837, 818, 745, 691, 656, and 638; ^{1}H NMR (300 MHz): 7.75 (1H, dd *J* = 8.1, 1.5 Hz, ArH), 7.41 (4H, s, ArH), 7.23 (1H, m, ArH), 6.95 (1H, dd *J* = 8.4, 1.2 Hz, ArH), 6.83 (1H, ddd *J* = 8.1, 7.8, 1.5 Hz, ArH), 5.11 (2H, s, OCH_2) and 1.32 (9H, m, 3 CH_3); ^{13}C NMR (125 MHz): 155.1 (ArC-O), 150.9 (C), 133.5 (C), 133.4 (CH), 128.4 (CH), 126.8 (2CH), 125.5 (2CH), 122.0 (CH), 113.8 (CH), 112.5 (C-Br), 70.6 (CH_2O), 34.5 (***C***Me_3) and 31.3 ($3CH_3$); HRMS (ESI$^+$) found 341.0512. $C_{17}H_{19}BrNaO$ (M + Na) requires 341.0517.

2.3.4. 2-Bromophenyl 2-Methoxybenzyl Ether **18d**

The same procedure as in 2.3.1 using 2-bromophenol (6.08 g, 35 mmol), K_2CO_3 (6.64 g, 48 mmol), and 2-methoxybenzyl bromide (6.64 g, 35 mmol) gave **18d** (9.10 g, 81%) as a yellow oil; ν_{max}/cm^{-1} 1510, 1310, 1270, 1080, 1060, and 760; ^{1}H NMR (300 MHz): 7.60 (1H, m, ArH), 7.55 (1H, dd *J* = 8.0, 1.2 Hz, ArH), 7.28 (1H, m, ArH), 7.21 (1H, m, ArH), 7.01–6.95 (2H, m, ArH), 6.87 (1H, m, ArH), 6.82 (1H, ddd *J* = 8.1, 7.8, 1.5 Hz, ArH), 5.19 (2H, s, OCH_2) and 3.86 (3H, s, OCH_3); ^{13}C NMR (75 MHz): 156.3 (ArC-O), 155.1 (ArC-O), 133.3 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 124.9 (C), 121.8 (CH), 120.7 (CH), 113.7 (CH), 112.3 (C-Br), 109.9 (CH), 65.8 (OCH_2) and 55.3 (OCH_3); HRMS (ESI$^+$) found 314.9990. $C_{14}H_{13}BrNaO_2$ (M + Na) requires 314.9997.

2.3.5. 2-Bromophenyl 3-Methoxybenzyl Ether **18e**

The same procedure as in 2.3.1 using 2-bromophenol (5.99 g, 34.6 mmol), K_2CO_3 (6.50 g, 47 mmol), and 3-methoxybenzyl bromide (6.98 g, 34.6 mmol) gave **18e** (5.42 g, 54%) as a yellow oil; ν_{max}/cm^{-1} 3063, 3001, 2938, 2835, 1585, 1477, 1277, 1244, 1049, 1023, and 743; ^{1}H NMR (300 MHz): 7.53 (1H, dd, *J* = 7.9, 1.5 Hz, ArH), 7.32–7.14 (2H, m, ArH), 7.09–6.96 (2H, m, ArH), 6.92–6.74 (3H, m, ArH), 5.09 (2H, s, OCH_2) and 3.78 (3H, s, OCH_3); ^{13}C NMR (75 MHz): 159.7 (C), 154.8 (C), 138.1 (C), 133.3 (CH), 129.5 (CH), 128.3 (CH), 122.1 (CH), 118.9 (CH), 113.7 (CH), 113.4 (CH), 112.3 (C-Br), 112.2 (CH), 70.4 (CH_2) and 55.1 (CH_3); HRMS (ESI$^+$) found 314.9989. $C_{14}H_{13}{}^{79}BrNaO_2$ (M + Na) requires 314.9997.

2.3.6. 2-Bromophenyl 4-Methoxybenzyl Ether **18f**

The same procedure as in 2.3.1 using 2-bromophenol (6.28 g, 36.3 mmol), K_2CO_3 (6.82 g, 49.3 mmol), and 4-methoxybenzyl bromide (7.29 g, 36.3 mmol) gave **18f** (4.41 g, 81%) as red crystals, mp 84–87 °C; ν_{max}/cm^{-1} 2999, 2909, 2835, 2361, 1607, 1584, 1510, 1474, 1240, 1171, 1028, 826, 808, and 750; ^{1}H NMR (300 MHz): 7.54 (1H, dd, *J* = 7.9, 1.6 Hz, ArH),

7.38 (2H, d, *J* = 9.0 Hz, ArH), 7.26–7.16 (1H, m, ArH), 6.96–6.86 (3H, m, ArH), 6.82 (1H, td, *J* = 7.7, 1.4 Hz, ArH), 5.07 (2H, s, OCH_2) and 3.80 (3H, s, OCH_3); ^{13}C NMR (75 MHz): 159.4 (C), 155.1 (C), 133.4 (CH), 128.7 (2CH), 128.5 (C), 128.3 (CH), 122.1 (CH), 114.1 (CH), 113.9 (2CH), 112.6 (C-Br), 70.7 (CH_2) and 55.2 (CH_3); HRMS (ESI^-) found 291.0023. $C_{14}H_{12}{}^{79}BrO_2$ (M–H) requires 291.0021.

2.3.7. 2-Bromophenyl 2-Fluorobenzyl Ether **18g**

The same procedure as in 2.3.2 using 2-bromophenol (3.58 g, 21 mmol), K_2CO_3 (3.90 g, 28 mmol), and 2-fluorobenzyl iodide (4.89 g, 21 mmol) gave **18g** (4.83 g, 83%) as a yellow oil; ν_{max}/cm^{-1} 1585, 1493, 1476, 1456, 1443, 1285, 1273, 1246, 1231, 1053, 1030, 1007, 839, 743, and 665; ^{1}H NMR (300 MHz): 7.64 (1H, m, ArH), 7.56 (1H, dd *J* = 8.1, 1.8 Hz, ArH), 7.35–7.16 (3H, m, ArH), 7.08 (1H, m, ArH), 6.97 (1H, dd *J* = 8.1, 1.5 Hz, ArH), 6.86 (1H, td *J* = 8.1, 1.5 Hz, ArH) and 5.22 (2H, s, OCH_2); ^{13}C NMR (100 MHz): 160.0 (d, *J* = 244.8 Hz, ArC-F), 154.7 (ArC-O), 133.4 (CH), 129.5 (d, *J* = 8.1 Hz, CH), 129.2 (d, *J* = 4.2 Hz, CH), 128.5 (CH), 124.3 (d, *J* = 3.5 Hz, CH), 123.7 (d, *J* = 13.7 Hz, C), 123.3 (CH), 115.1 (d, *J* = 20.7 Hz, CH), 113.7 (CH), 112.5 (C-Br) and 64.4 (d, *J* = 15.0 Hz, OCH_2); ^{19}F NMR (376 MHz): –118.9; HRMS (ESI^+) found 302.9788. $C_{13}H_{10}BrFNaO$ (M + Na) requires 302.9797.

2.3.8. 2-Bromophenyl 4-Fluorobenzyl Ether **18h**

The same procedure as in 2.3.2 using 2-bromophenol (4.36 g, 25 mmol), K_2CO_3 (4.74 g, 34 mmol), and 4-fluorobenzyl iodide (5.95 g, 25 mmol) gave **18h** (6.67 g, 95%) as a yellow oil; ν_{max}/cm^{-1} 1603, 1585, 1572, 1508, 1477, 1464, 1443, 1377, 1294, 1277, 1246, 1223, 1157, 1126, 1053, 1030, 1013, 978, 937, 860, 818, 745, 664, and 600; ^{1}H NMR (300 MHz): 7.65 (1H, dd, *J* = 7.8, 1.8 Hz, ArH), 7.45 (2H, m, ArH), 7.23 (1H, m, ArH), 7.07 (2H, tt, *J* = 8.7, 2.1 Hz, ArH), 6.92 (1H, dd *J* = 8.1, 1.2 Hz, ArH), 6.85 (1H, td *J* = 7.8, 1.5 Hz, ArH) and 5.10 (2H, s, OCH_2); ^{13}C NMR (75 MHz): 162.4 (d, *J* = 246.4 Hz, ArC-F), 154.8 (ArC-O), 133.5 (CH), 132.2 (d, *J* = 3.2 Hz, C), 128.8 (d, $J_=$ 8.0 Hz, CH), 128.4 (CH), 122.3 (2CH), 115.5 (d, *J* = 21.6 Hz, 2CH), 113.9 (CH), 112.5 (C-Br) and 70.2 (OCH_2); ^{19}F NMR (376 MHz): –114.2; HRMS (ESI^+) found 205.0602. $C_{13}H_{10}NaO$ (M + Na − F − Br) requires 205.0629.

2.3.9. 2-Bromophenyl 2-Naphthylmethyl Ether **18l**

The same procedure as in 2.3.1 using 2-bromophenol (4.33 g, 25.0 mmol), K_2CO_3 (4.70 g, 34.0 mmol), and 2-(bromomethyl)naphthalene (5.53 g, 25.0 mmol) gave, after recrystallisation from hexane, **18l** (5.05 g, 65%) as light brown crystals, mp 75–77 °C; ν_{max}/cm^{-1} 3067, 3055, 2930, 2878, 1572, 1479, 1442, 1279, 1230, 1030, 1004, 814, and 737; ^{1}H NMR (300 MHz): 7.98–7.75 (4H, m, ArH), 7.66–7.40 (4H, m, ArH), 7.24–7.13 (1H, m, ArH), 6.98 (1H, dd, *J* = 8.2, 1.3 Hz, ArH), 6.85 (1H, td, *J* 7.7, 1.4 Hz, ArH) and 5.32 (2 H, s, OCH_2); ^{13}C NMR (75 MHz):155.0 (C), 134.0 (C), 133.4 (CH), 133.2 (C), 133.0 (C), 128.4 (2CH), 128.0 (CH), 127.7 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 124.8 (CH), 122.2 (CH), 114.0 (CH), 112.5 (C-Br) and 70.9 (CH_2); HRMS (ESI^+) found 335.0039. $C_{17}H_{13}{}^{79}BrNaO$ (M + Na) requires 335.0047.

2.4. Synthesis of Substituted Diethyl 2-Benzyloxyphenylphosphonates **19**

2.4.1. Diethyl 2-(4-Methylbenzyloxy)phenylphosphonate **19b**

Using the method of Section 2.2.2 with 2-bromophenyl 4-methylbenzyl ether **18b** (1.00 g, 3.6 mmol), $NiCl_2$ (0.05 g, 0.36 mmol), and triethyl phosphite (0.72 g, 4.33 mmol) gave, after column chromatography (SiO_2, hexane/EtOAc 1:1) and removal of triethyl phosphate by Kugelrohr distillation, **19b** (0.17 g, 13%) as a colourless oil; ^{1}H NMR (300 MHz): 7.86 (1H ddd, *J* = 15, 7.5, 1.8 Hz, ArH), 7.49 (1H, m, ArH), 7.40 (2H, d, *J* = 7.2 Hz, ArH), 7.18 (2H, d, *J* = 7.2 Hz, ArH), 7.07–6.93 (2H, m, ArH), 5.15 (2H, s, $ArOCH_2$), 4.22–4.02 (4H, m, 2 $OC\boldsymbol{H}_2CH_3$), 2.36 (3H, s, Ar-CH_3) and 1.28 (6H, t, *J* = 6.9 Hz, 2 $OCH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 160.3 (ArC-O), 137.5 (C), 135.2 (d, *J* = 7.1 Hz, CH), 134.2 (CH), 133.4 (C), 129.1 (2CH), 127.1 (2CH), 120.5 (d, *J* = 14.6 Hz, CH), 116.9 (d, *J* = 187 Hz, ArC-P), 112.4 (d, *J* = 9 Hz, CH), 70.1 (OCH_2Ar), 62.1 (d, *J* = 5.5 Hz, 2 $O\boldsymbol{C}H_2CH_3$), 21.2 ($ArCH_3$) and 16.3 (d, *J* = 6.4 Hz,

2 $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +17.2; HRMS (ESI^+) found 357.1219. $C_{18}H_{23}NaO_4P$ (M + Na) requires 357.1232.

2.4.2. Diethyl 2-(2-Methoxybenzyloxy)phenylphosphonate **19d**

Using the method of Section 2.2.2 with 2-bromophenyl 2-methoxybenzyl ether **18d** (4.00 g, 13.6 mmol), $NiCl_2$ (0.18 g, 1.36 mmol) and triethyl phosphite (2.80 mL, 2.72 g, 16.4 mmol) gave, after removal of triethyl phosphate by Kugelrohr distillation, **19d** (2.58 g, 54%) as a yellow oil; ν_{max}/cm^{-1} 3069, 2938, 2907, 2835, 1589, 1477, 1242, 1026, and 746.; ^{1}H NMR (300 MHz): 7.64–7.47 (2H, m, ArH), 7.32–7.18 (2H, m, ArH), 7.05–6.95 (2H, m, ArH), 6.92–6.78 (2H, m, ArH), 5.19 (2 H, s, $ArOCH_2$), 4.18–4.05 (4H, m, 2 $OC\boldsymbol{H}_2CH_3$), 3.86 (3 H, s, OCH_3) and 1.34 (6H, t, 2 $OCH_2C\boldsymbol{H}_3$); ^{31}P NMR (121 MHz): +17.4; HRMS (ESI^+) found 373.1175. $C_{18}H_{23}NaO_5P$ (M + Na) requires 373.1181.

2.4.3. Diethyl 2-(3-Methoxybenzyloxy)phenylphosphonate **19e**

Using the method of Section 2.2.2 with 2-bromophenyl 3-methoxybenzyl ether **18e** (5.16 g, 17.6 mmol), $NiCl_2$ (0.23 g, 1.76 mmol) and triethyl phosphite (3.6 mL, 3.51 g, 21.1 mmol) gave, after column chromatography (SiO_2, hexane/EtOAc 1:1) and removal of triethyl phosphate by Kugelrohr distillation, **19e** (3.17 g, 51%) as a colourless oil; ^{1}H NMR (300 MHz): 7.87 (1H, ddd, *J* = 14.9, 7.5, 1.8 Hz, ArH), 7.52–7.43 (1H, m, ArH), 7.30–7.25 (1H, m, ArH), 7.16–7.14 (1H, m, ArH), 7.11–6.91 (3H, m, ArH), 6.82 (1H, dd, *J* = 8.2, 2.2 Hz, ArH), 5.17 (2H, s, $ArOCH_2$), 4.21–4.05 (4H, m, 2 $OC\boldsymbol{H}_2CH_3$), 3.83 (3H, s, OCH_3) and 1.29 (6H, t, *J* = 7.1 Hz, 2 $OCH_2C\boldsymbol{H}_3$); ^{13}C NMR (75 MHz): 160.1 (ArC-O), 159.8 (ArC-O), 138.1 (C), 135.3 (d, *J* = 7.2 Hz, CH), 134.2 (d, *J* = 1.6 Hz, CH), 129.4 (CH), 120.6 (d, *J* = 14.6 Hz, CH), 118.9 (CH), 118.3 (d, *J* = 122.1 Hz, C-P), 113.4 (CH), 112.4 (CH), 112.3 (CH), 69.9 ($ArOCH_2$), 62.1 (d, *J* = 5.5 Hz, 2 $O\boldsymbol{C}H_2CH_3$), 55.3 (OCH_3) and 16.3 (d, *J* = 6.6 Hz, 2 $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (202 MHz): +17.1; HRMS (ESI^+) found 357.1219. $C_{18}H_{23}NaO_4P$ (M + Na) requires 357.1232.

2.5. Conversion of a Substituted Diethyl 2-Benzyloxyphenylphosphonate into the Phosphonamidate

2.5.1. Ethyl 2-(3-Methoxybenzyloxy)phenylphosphonochloridate ***20***

Using the method of Section 2.2.3 with diethyl 2-(3-methoxybenzyloxy)phenylphosphonate **19e** (2.93 g, 8.36 mmol) and PCl_5 (3.48 g, 16.7 mmol) in dry toluene (30 mL) gave **20** (2.85 g, 100%) as a yellow oil; ^{31}P NMR (121 MHz): +26.4. This was used without purification for the following stage.

2.5.2. Ethyl *N*-Butyl-*P*-(2-(3-methoxybenzyloxy)phenyl)phosphonamidate **21e**

Using the method of Section 2.2.4 with ethyl 2-(3-methoxybenzyloxy)phenylpho sphonochloridate **20** (2.85 g, 8.4 mmol) and *n*-butylamine (2.1 mL, 1.56 g, 21.4 mmol) in Et_2O (30 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21e** (1.77 g, 54%) as a yellow oil; ^{1}H NMR (300 MHz): 7.97–7.85 (1H, m, ArH), 7.55–7.42 (1H, m, ArH), 7.35–7.25 (2H, m, ArH), 7.10–6.93 (3H, m, ArH), 6.90–6.80 (1H, m, ArH), 5.25–5.10 (2H, m, $ArOCH_2$), 4.20–3.90 (2H, m, P-OCH_2), 3.82 (3H, s, OCH_3), 3.05–2.85 (3H, m, N$\boldsymbol{H}C\boldsymbol{H}_2$), 1.40–1.11 (7H, m, $NHCH_2(C\boldsymbol{H}_2)_2CH_3$ and $OCH_2C\boldsymbol{H}_3$), 0.96–0.68 (3H, t, $NCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{31}P NMR (121 MHz): +21.2; HRMS (ESI^+) found 400.1648. $C_{20}H_{28}NaNO_4P$ (M + Na) requires 400.1654.

2.6. Formation and O-Benzylation of Ethyl N-Butyl-P-(2-hydroxyphenyl)phosphonamidate

2.6.1. Ethyl *N*-Butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22**

Using a literature procedure [18], a solution of ethyl *P*-(2-benzyloxyphenyl)-*N*-butylph osphonamidate **16** (2.20 g, 6.3 mmol) in MeOH (40 mL) and 5% Pd/C (0.34 g) was stirred under a hydrogen atmosphere at rt for 2 h. The reaction mixture was filtered and concentrated to afford **22** (1.57 g. 96%); ^{1}H NMR (300 MHz): 10.77 (1H, br s, OH), 7.45–7.28 (2H, m, ArH), 6.98–6.85 (2H, m, ArH), 4.10–3.85 (2H, m, $OC\boldsymbol{H}_2CH_3$), 3.00–2.78 (3H, m, N$\boldsymbol{H}C\boldsymbol{H}_2$), 1.50–1.20 (4 H, m, $NHCH_2(C\boldsymbol{H}_2)_2CH_3$), 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$) and 0.87 (3H, t, *J* = 7.3 Hz, $NH(CH_2)_3C\boldsymbol{H}_3$); ^{13}C NMR (75 MHz): 162.2 (d, *J* = 6.5 Hz, ArCOH), 134.4

(d, *J* = 2.1 Hz, CH), 131.4 (d, *J* = 7.1 Hz, CH), 119.2 (d, *J* = 13.2 Hz, CH), 117.5 (d, *J* = 10.9 Hz, CH), 111.1 (d, *J* = 162.8 Hz, ArC-P), 61.6 (d, *J* = 4.5 Hz, O***C***H_2CH_3), 40.2 ($NHCH_2$), 33.8 (d, *J* = 6.1 Hz, $NHCH_2$***C***H_2), 19.6 ($NHCH_2CH_2$***C***H_2), 16.2 (d, *J* = 6.7 Hz, OCH_2***C***H_3) and 13.6 ($NHCH_2CH_2CH_2$***C***H_3); ^{31}P NMR (121 MHz): +28.2; HRMS (ESI^+): found 280.1073. $C_{12}H_{20}NaNO_3P$ (M + Na) requires 280.1078.

2.6.2. Ethyl *N*-Butyl-*P*-(2-(2-methylbenzyloxy)phenyl)phosphonamidate **21a**

To a stirred solution of ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **16** (0.25 g, 0.97 mmol) and K_2CO_3 (0.40 g, 2.92 mmol) in DMF (10 mL) at rt, 2-methylbenzyl bromide (0.13 mL, 0.18 g, 0.97 mmol) was added, and the solution was stirred for 18 h. The reaction mixture was poured into H_2O (40 mL) and extracted with CH_2Cl_2 (20 mL) and EtOAc (3 × 20 mL). The combined organic fractions were washed with H_2O (6 × 50 mL), dried over $MgSO_4$, and concentrated to afford, after purification via column chromatography (SiO_2, EtOAc/hexane 1:1), **21a** (0.20 g, 57%) as a yellow oil; ^{1}H NMR (300 MHz): 7.94 (1H, ddd, *J* = 14.3, 7.5, 1.8 Hz, ArH), 7.54–7.39 (2H, m, ArH), 7.33–7.20 (3H, m, ArH), 7.14–6.94 (2H, m, ArH), 5.14 and 5.08 (2H, AB pattern, *J* = 11.1 Hz, OCH_2), 4.05–3.85 (2H, m, OC***H***$_2CH_3$), 3.00–2.80 (3H, m, N***H***C***H***$_2$), 2.41 (3H, s, $ArCH_3$), 1.28–1.05 (4H, m, $NHCH_2$(C***H***$_2$)$_2CH_3$), 1.22 (3H, t, *J* = 7.0 Hz, OCH_2C***H***$_3$) and 0.78 (3 H, t, *J* = 7.2 Hz, $NHCH_2(CH_2)_2$C***H***$_3$); ^{13}C NMR (75 MHz): 159.2 (d, *J* = 2.8 Hz, ArCO), 136.4 (C), 134.5 (d, *J* = 6.5 Hz, CH), 134.0 (C), 133.4 (CH), 130.4 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 120.8 (d, *J* = 13.5 Hz, CH), 119.8 (d, *J* = 166.8 Hz, ArC-P), 111.5 (d, *J* = 8.6 Hz, CH), 68.7 (ArO***C***H_2), 60.2 (d, *J* = 5.8 Hz, O***C***H_2CH_3), 40.2 ($NHCH_2$), 34.0 (d, *J* = 6.2 Hz, $NHCH_2$***C***H_2), 19.6 ($NHCH_2CH_2$***C***H_2), 18.8 ($ArCH_3$), 16.3 (d, *J* = 6.9 Hz, OCH_2***C***H_3) and 13.6 ($NHCH_2CH_2CH_2$***C***H_3); ^{31}P NMR (121 MHz): +21.3; HRMS (ESI^+): found 384.1699. $C_{20}H_{28}NaNO_3P$ (M + Na) requires 384.1705.

2.6.3. Ethyl *N*-Butyl-*P*-(2-(4-methylbenzyloxy)phenyl)phosphonamidate **21b**

To a stirred solution of NaI (0.16 g, 1.07 mmol) in acetone (1.5 mL), 4-methylbenzyl chloride (0.14 mL, 0.15 g, 1.07 mmol) was added, and the solution was stirred at rt until no further precipitation was observed. The solution was filtered and concentrated to afford 4-methylbenzyl iodide, which was used without further purification.

The 4-methylbenzyl iodide (1.07 mmol) was added to a stirred solution of ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.25 g, 0.97 mmol) and K_2CO_3 (0.40 g, 2.92 mmol) in DMF (10 mL), and the mixture was stirred for 18 h at rt. The reaction mixture was poured into H_2O (40 mL) and extracted with CH_2Cl_2 (20 mL) and EtOAc (3 × 20 mL). The combined organic fractions were washed with H_2O (6 × 50 mL), dried over $MgSO_4$, and concentrated to afford the product **20** (0.21 g, 60%) as an orange oil; ^{1}H NMR (400 MHz): 7.93 (1H, ddd, *J* = 14.3, 7.5, 1.8 Hz, ArH), 7.50–7.42 (1H, m, ArH), 7.35 (2H, d, *J* = 8.0 Hz, ArH), 7.21 (2H, d, *J* = 8.0 Hz, ArH), 7.16–7.00 (1H, m, ArH), 7.00–6.95 (1H, m, ArH), 5.09 (2H, s, $ArOCH_2$), 4.05–3.90 (2H, m, OC***H***$_2CH_3$), 3.01–2.82 (3H, m, N***H***C***H***$_2$), 2.38 (3H, s, $ArCH_3$), 1.34–1.21 (4H, m, $NHCH_2$(C***H***$_2$)$_2CH_3$), 1.25 (3H, t, *J* = 7.2 Hz, OCH_2C***H***$_3$) and 0.79 (3H, t, *J* = 7.2 Hz, $NHCH_2(CH_2)_2$C***H***$_3$); ^{13}C NMR (100 MHz): 159.2 (d, *J* = 2.8 Hz, ArCO), 138.1 (C), 134.5 (d, *J* = 6.5 Hz, CH), 133.3 (CH), 133.2 (C), 129.4 (2CH), 127.5 (2CH), 120.8 (d, *J* = 13.1 Hz, CH), 120.0 (d, *J* = 170.2 Hz, ArC-P), 111.8 (d, *J* = 8.6 Hz, CH), 70.4 ($ArOCH_2$), 60.3 (d, *J* = 5.7 Hz, O***C***H_2CH_3), 40.3 ($NHCH_2$), 34.1 (d, *J* = 6.2 Hz, $NHCH_2$***C***H_2), 21.2 ($ArCH_3$), 19.7 ($NHCH_2CH_2$***C***H_2), 16.4 (d, *J* = 6.8 Hz, OCH_2***C***H_3) and 13.7 ($NHCH_2CH_2CH_2$***C***H_3); ^{31}P NMR (121 MHz): +21.3.

2.6.4. Ethyl *N*-Butyl-*P*-(2-(4-*tert*-butylbenzyloxy)phenyl)phosphonamidate **21c**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 4-*tert*-butylbenzyl bromide [17] (0.56 g, 2.5 mmol) and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21c** (0.33 g, 33%) as a pale-yellow oil; ν_{max}/cm^{-1} 2959, 2930, 2870, 2423, 1591, 1475, 1443, 1165, 1018, 955, 762, and 550; ^{1}H NMR (400 MHz): 7.96–7.90 (1H, m, ArH),

7.48–7.42 (1H, m, ArH), 7.43 and 7.39 (2H, AB pattern, J = 8.5 Hz, ArH), 7.06–6.98 (2H, m, ArH), 5.10 (2H, s, OC***H***$_2$Ar), 4.08–3.93 (2H, m, OC***H***$_2$CH$_3$), 2.95–2.86 (3H, m, N***H***C***H***$_2$), 1.34 (9H, s, C(C***H***$_3$)$_3$), 1.32–1.20 (2H, m, NHCH$_2$C***H***$_2$), 1.25 (3H, t, J = 7.2 Hz, OCH$_2$C***H***$_3$), 1.16 (2H, sextet, J = 7.2 Hz, NHCH$_2$CH$_2$C***H***$_2$) and 0.79 (3H, t, J = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H***$_3$); ^{13}C NMR (100 MHz): 159.2 (d, J = 2.9 Hz, ArC-O), 151.4 (C), 134.5 (d, J = 6.3 Hz, ArCH), 133.4 (d, J = 1.6 Hz, ArCH), 133.2 (C), 127.3 (2CH), 125.6 (2CH), 120.8 (d, J = 13.6 Hz, ArCH), 119.8 (d, J = 165.5 Hz, ArC-P), 111.8 (d, J = 8.6 Hz, ArCH), 70.3 (OCH$_2$Ar), 60.3 (d, J = 5.7 Hz, O***C***H$_2$CH$_3$), 40.3 (NHCH$_2$), 34.6 (***C***Me$_3$), 34.1 (d, J = 6.4 Hz, NHCH$_2$***C***H$_2$), 31.3 (C(***C***H$_3$)$_3$), 19.6 (NHCH$_2$CH$_2$***C***H$_2$), 16.3 (d, J = 6.6 Hz, OCH$_2$***C***H$_3$) and 13.7 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +21.3; HRMS (ESI$^+$): found 404.2336. $C_{23}H_{35}NO_3P$ (M + H) requires 404.2355.

2.6.5. Ethyl *N*-Butyl-*P*-(2-(2-methoxybenzyloxy)phenyl)phosphonamidate **21d**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 2-methoxybenzyl bromide (0.50 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21d** (0.24 g, 28%) as a pale-yellow oil; ν_{max}/cm^{-1} 2957, 2932, 1591, 1441, 1240, 1028, 953, 752, and 571; ^{1}H NMR (400 MHz): 7.93 (1H, ddd, J = 14.4, 7.6, 2.0 Hz, ArH), 7.51–7.29 (3H, m, ArH), 7.06–6.92 (4H, m, ArH), 5.21 and 5.15 (2H, AB pattern, J = 12.0 Hz, ArOC***H$_2$***), 4.06–3.90 (2H, m, OC***H$_2$***CH$_3$), 3.87 (3H, s, OCH$_3$), 3.15–3.05 (1H, br m, NH), 3.01–2.90 (2H, m, NHC***H$_2$***), 1.36–1.29 (2H, m, NHCH$_2$C***H$_2$***), 1.23–1.16 (2H, m, NHCH$_2$CH$_2$C***H$_2$***), 1.21 (3H, t, J = 7.2 Hz, OCH$_2$C***H$_3$***) and 0.80 (3H, t, J = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H$_3$***); ^{13}C NMR (100 MHz): 159.2 (d, J = 2.9 Hz, ArC-O), 156.8 (C), 134.3 (d, J = 6.5 Hz, CH), 133.3 (d, J = 2.1 Hz, CH), 129.3 (CH), 128.8 (CH), 124.4 (C), 120.6 (CH), 120.5 (d, J = 11.2 Hz, CH), 119.6 (d, J = 162.9 Hz, ArC-P), 111.6 (d, J = 8.6 Hz, CH), 110.3 (CH), 65.5 (OCH$_2$Ar), 60.2 (d, J = 5.6 Hz, O***C***H$_2$CH$_3$), 55.3 (OCH$_3$), 40.3 (NHCH$_2$), 34.2 (d, J = 6.8 Hz, NHCH$_2$***C***H$_2$), 19.6 (NHCH$_2$CH$_2$***C***H$_2$), 16.2 (d, J = 6.8 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +21.5; HRMS (ESI$^+$): found 400.1637. $C_{20}H_{28}NaNO_4P$ (M + Na) requires 400.1654.

2.6.6. Ethyl *N*-Butyl-*P*-(2-(4-methoxybenzyloxy)phenyl)phosphonamidate **21f**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 4-methoxybenzyl bromide (0.50 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21f** (0.38 g, 44%) as a pale-yellow oil; ν_{max}/cm^{-1} 2957, 2932, 2872, 1591, 1514, 1236, 1030, 951, 820, 756, and 567; ^{1}H NMR (400 MHz): 7.92 (1H, ddd, J = 14.0, 7.2, 1.6 Hz, ArH), 7.48–7.43 (1H, m, ArH), 7.39 (2H, d, J = 8.4 Hz, ArCH), 7.06–6.97 (2H, m, ArH), 6.93 (2H, d, J = 8.4 Hz, ArCH), 5.06 (2H, s, ArOC***H$_2$***), 4.06–3.90 (2H, m, OC***H$_2$***CH$_3$), 3.83 (3H, s, OCH$_3$), 2.95–2.85 (3H, m, N***H***C***H$_2$***), 1.34–1.20 (2H, m, NHCH$_2$C***H$_2$***), 1.25 (3H, t, J = 7.2 Hz, OCH$_2$C***H$_3$***), 1.20–1.10 (2H, m, NHCH$_2$CH$_2$C***H$_2$***) and 0.79 (3H, t, J = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H$_3$***); ^{13}C NMR (100 MHz): 159.6 (C), 159.2 (d, J = 2.9 Hz, ArC-O), 134.4 (d, J = 6.2 Hz, CH), 133.4 (d, J = 2.0 Hz, CH), 129.2 (2CH), 128.2 (C), 120.8 (d, J = 13.2 Hz, CH), 119.7 (d, J = 166.1 Hz, ArC-P), 114.0 (2CH), 111.8 (d, J = 8.5 Hz, CH), 70.2 (OCH$_2$Ar), 60.3 (d, J = 5.7 Hz, O***C***H$_2$CH$_3$), 55.3 (OCH$_3$), 40.3 (NHCH$_2$), 34.0 (d, J = 6.4 Hz, NHCH$_2$***C***H$_2$), 19.6 (NHCH$_2$CH$_2$***C***H$_2$), 16.3 (d, J = 6.8 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +21.3; HRMS (ESI$^+$): found 400.1631. $C_{20}H_{28}NaNO_4P$ (M + Na) requires 400.1654.

2.6.7. Ethyl *N*-Butyl-*P*-(2-(2-fluorobenzyloxy)phenyl)phosphonamidate **21g**

Using the method of Section 2.6.3 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.64 g, 2.5 mmol), 2-fluorobenzyl iodide (0.59 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21g** (0.16 g, 19%) as a pale-yellow oil; ν_{max}/cm^{-1} 2949, 2932, 2370, 1620, 1491, 1231, 1105, 1036, 1007, 945, 833, 559 and 509; ^{1}H NMR (400 MHz): 7.93 (1H, ddd,

J = 14.4, 7.6, 1.6 Hz, ArH), 7.57 (1H, td, *J* = 5.8, 1.7 Hz, ArH), 7.50–7.45 (1H, m, ArH), 7.38–7.33 (1H, m, ArH), 7.19 (1H, td, *J* = 7.6, 1.2 Hz, ArH), 7.14–7.09 (1H, m, ArH), 7.06 (1H, tdd, *J* = 7.4, 2.8, 0.9 Hz, ArH), 7.04–7.01 (1H, m, ArH), 5.23 and 5.19 (2H, AB pattern, *J* = 12.0 Hz, ArOC***H*****$_2$**), 4.06–3.90 (2H, m, OC***H*****$_2$**CH$_3$), 3.01–2.85 (3H, m, N***H***C***H*****$_2$**), 1.36–1.29 (2H, m, NHCH$_2$C***H*****$_2$**), 1.23–1.14 (2H, m, NHCH$_2$CH$_2$C***H*****$_2$**), 1.23 (3H, t, *J* = 7.2 Hz, OCH$_2$C***H*****$_3$**) and 0.81 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 160.5 (d, *J* = 245.7 Hz, ArC-F), 158.9 (d, *J* = 2.9 Hz, ArC-O), 134.6 (d, *J* = 6.1 Hz, CH), 133.4 (d, *J* = 2.1 Hz, CH), 130.2 (d, *J* = 8.0 Hz, CH), 129.9 (d, *J* = 3.8 Hz, CH), 124.4 (d, *J* = 3.6 Hz, CH), 123.4 (d, *J* = 14.2 Hz, C), 121.0 (d, *J* = 13.2 Hz, CH), 119.9 (d, *J* = 165.9 Hz, ArC-P), 115.5 (d, *J* = 21.0 Hz, CH), 111.6 (d, *J* = 8.5 Hz, CH), 64.2 (d, *J* = 4.3 Hz, OCH$_2$Ar), 60.3 (d, *J* = 5.6 Hz, O***C***H$_2$CH$_3$), 40.4 (NHCH$_2$), 34.1 (d, *J* = 6.1 Hz, NHCH$_2$***C***H$_2$), 19.7 (NHCH$_2$CH$_2$***C***H$_2$), 16.3 (d, *J* = 6.7 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{19}F NMR (376 MHz): –118.5; ^{31}P NMR (162 MHz): +21.0; HRMS (ESI$^+$): found 388.1437. C$_{19}$H$_{25}$FNaNO$_3$P (M + Na) requires 388.1454.

2.6.8. Ethyl *N*-Butyl-*P*-(2-(4-fluorobenzyloxy)phenyl)phosphonamidate **21h**

Using the method of Section 2.6.3 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphona midate **22** (0.64 g, 2.5 mmol), 4-fluorobenzyl iodide (0.59 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21h** (0.22 g, 26%) as a pale-yellow oil; ν_{max}/cm^{-1} 2959, 2930, 2872, 1603, 1512, 1443, 1223, 1157, 1030, 951, 756 and 563; ^{1}H NMR (400 MHz): 7.92 (1H, ddd, *J* = 14.4, 7.6, 2.0 Hz, ArH), 7.48–7.44 (3H, m, ArH), 7.10 (2H, t, *J* = 8.8, Hz, ArH), 7.09–7.04 (1H, m, ArH), 6.97 (1H, dd, *J* = 8.0, 6.0 Hz, ArH), 5.10 (2H, s, ArOC***H*****$_2$**), 4.07–3.94 (2H, m, OC***H*****$_2$**CH$_3$), 3.00–2.75 (3H, m, N***H***C***H*****$_2$**), 1.33–1.23 (2H, m, NHCH$_2$C***H*****$_2$**), 1.26 (3H, t, *J* = 7.2 Hz, OCH$_2$C***H*****$_3$**), 1.22–1.12 (2H, m, NHCH$_2$CH$_2$C***H*****$_2$**) and 0.80 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 162.6 (d, *J* = 245.4 Hz, ArC-F), 159.0 (d, *J* = 2.9 Hz, ArC-O), 134.4 (d, *J* = 6.5 Hz, CH), 133.4 (d, *J* = 2.1 Hz, CH), 132.0 (d, *J* = 3.5 Hz, C), 129.3 (d, *J* = 8.1 Hz, 2CH), 121.0 (d, *J* = 13.4 Hz, CH), 119.9 (d, *J* = 167.0 Hz, ArC-P), 115.6 (d, *J* = 21.3 Hz, 2CH), 111.8 (d, *J* = 8.4 Hz, CH), 69.7 (OCH$_2$Ar), 60.2 (d, *J* = 5.7 Hz, O***C***H$_2$CH$_3$), 40.3 (NHCH$_2$), 34.0 (d, *J* = 5.9 Hz, NHCH$_2$***C***H$_2$), 19.6 (NHCH$_2$CH$_2$***C***H$_2$), 16.4 (d, *J* = 6.9 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{19}F NMR (376 MHz): –113.6; ^{31}P NMR (162 MHz): +21.0; HRMS (ESI$^+$): found 388.1436. C$_{19}$H$_{25}$FNaNO$_3$P (M + Na) requires 388.1454.

2.6.9. Ethyl *N*-Butyl-*P*-(2-(4-chlorobenzyloxy)phenyl)phosphonamidate **21i**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphona midate **22** (0.60 g, 2.5 mmol), 4-chlorobenzyl bromide (0.40 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave, after purification by column chromatography (SiO_2, hexane/EtOAc 1:1), **21i** (0.67 g, 70%) as colourless crystals, mp 75–77 °C; ν_{max}/cm^{-1} 2957, 2932, 2872, 1591, 1443, 1221, 1092, 1030, 955, 760, and 563; ^{1}H NMR (400 MHz): 7.92 (1H, ddd, *J* = 14.4, 7.6, 2.0 Hz, ArH), 7.48–7.40 (1H, m, ArH), 7.43 and 7.38 (4H, A_2B_2 pattern, *J* = 8.8 Hz, ArCH), 7.06 (1H, tdd, *J* = 7.6, 2.8, 0.8 Hz, ArCH), 6.98–6.94 (1H, m, ArH), 5.11 (2H, s, ArOC***H*****$_2$**), 4.08–3.94 (2H, m, OC***H*****$_2$**CH$_3$), 2.96–2.78 (3H, m, N***H***C***H*****$_2$**), 1.34–1.20 (2H, m, NHCH$_2$C***H*****$_2$**), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C***H*****$_3$**), 1.20–1.10 (2H, m, NHCH$_2$CH$_2$C***H*****$_2$**) and 0.80 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 158.9 (d, *J* = 2.9 Hz, ArC-O), 134.7 (C), 134.5 (d, *J* = 6.4 Hz, CH), 134.1 (C), 133.4 (d, *J* = 2.0 Hz, CH), 128.9 (2CH), 128.7 (2CH), 121.1 (d, *J* = 13.6 Hz, CH), 119.9 (d, *J* = 166.6 Hz, ArC-P), 111.8 (d, *J* = 8.6 Hz, CH), 69.6 (OCH$_2$Ar), 60.2 (d, *J* = 5.6 Hz, O***C***H$_2$CH$_3$), 40.4 (NHCH$_2$), 34.1 (d, *J* = 6.2 Hz, NHCH$_2$***C***H$_2$), 19.6 (NHCH$_2$CH$_2$***C***H$_2$), 16.4 (d, *J* = 6.9 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +20.9; HRMS (ESI$^+$): found 404.1138. C$_{19}$H$_{25}$ClNaNO$_3$P (M + Na) requires 404.1158.

2.6.10. Ethyl *P*-(2-(4-Bromobenzyloxy)phenyl)-*N*-butylphosphonamidate **21j**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 4-methoxybenzyl bromide (0.62 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave **21j** (0.86 g, 81%) as colourless crystals, mp 80–82 °C; ν_{max}/cm^{-1} 3177, 2953, 2928, 1591,1474, 1445, 1219,1030, 943, 760, 692, and 557; ^{1}H NMR (400 MHz): 7.92 (1H, ddd, *J* = 14.0, 7.6, 1.6 Hz, ArH), 7.54 (2H, d, *J* = 8.4 Hz, ArCH), 7.49–7.43 (1H, m, ArH), 7.37 (2H, d, *J* = 8.4 Hz, ArCH), 7.06 (1H, tdd, *J* = 7.6, 2.8, 0.8 Hz, ArCH), 6.98–6.93 (1H, m, ArH), 5.10 (2H, s, ArOC***H*****$_2$**), 4.10–3.95 (2H, m, OC***H*****$_2$**CH$_3$), 2.95–2.80 (3H, m, N***H*****C*H*****$_2$**), 1.34–1.28 (2H, m, NHCH$_2$C***H*****$_2$**), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C***H*****$_3$**), 1.22–1.12 (2H, m, NHCH$_2$CH$_2$C***H*****$_2$**) and 0.80 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 158.9 (d, *J* = 2.8 Hz, ArC-O), 135.3 (C), 134.5 (d, *J* = 6.3 Hz, CH), 133.4 (d, *J* = 1.8 Hz, CH), 131.9 (2CH), 129.0 (2CH), 122.2 (C-Br), 121.1 (d, *J* = 13.2 Hz, CH), 120.1 (d, *J* = 166.0 Hz, ArC-P), 111.8 (d, *J* = 8.6 Hz, CH), 69.7 (OCH$_2$Ar), 60.3 (d, *J* = 5.5 Hz, O***C***H$_2$CH$_3$), 40.4 (NHCH$_2$), 34.1 (d, *J* = 6.3 Hz, NHCH$_2$***C***H$_2$), 19.7 (NHCH$_2$CH$_2$***C***H$_2$), 16.4 (d, *J* = 7.0 Hz, OCH$_2$***C***H$_3$) and 13.7 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +20.9; HRMS (ESI$^+$): found 426.0814. $C_{19}H_{26}{}^{79}BrNO_3P$ (M + H) requires 426.0834.

2.6.11. Ethyl *N*-Butyl-*P*-(2-(1-naphthylmethoxy)phenyl)phosphonamidate **21k**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 1-bromomethylnaphthalene (0.55 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave **21k** (0.81 g, 82%) as a pale-yellow oil; ν_{max}/cm^{-1} 3393, 2957, 2930, 2870, 1591, 1472, 1441, 1227, 1084, 1032, 997, 951, 758, and 542; ^{1}H NMR (400 MHz): 8.13–8.03 (1H, m, ArH), 7.95 (1H, ddd, *J* = 14.4, 7.6, 2.0 Hz, ArH), 7.94–7.78 (2H, m, ArH), 7.63–7.41 (5H, m, ArH), 7.15 (1H, dd, *J* = 8.0, 6.0 Hz, ArCH), 7.08 (1H, tdd, *J* = 7.6, 3.2, 0.8 Hz, ArCH), 5.57 and 5.51 (2H, AB pattern, *J* = 11.0 Hz, ArOC***H*****$_2$**), 3.85–3.75 (2H, m, OC***H*****$_2$**CH$_3$), 2.82–2.64 (3H, m, N***H*****C*H*****$_2$**), 1.10–1.00 (2H, m, NHCH$_2$C***H*****$_2$**), 1.08 (3H, t, *J* = 7.2 Hz, OCH$_2$C***H*****$_3$**), 1.00–0.90 (2H, m, NHCH$_2$CH$_2$C***H*****$_2$**) and 0.69 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 159.1 (d, *J* = 2.9 Hz, ArC-O), 134.6 (d, *J* = 6.5 Hz, CH), 133.8 (C), 133.4 (d, *J* = 2.1 Hz, CH), 131.5 (C), 131.3 (C), 129.4 (CH), 128.8 (CH), 126.9 (CH), 126.7 (CH), 126.0 (CH), 125.3 (CH), 123.3 (CH), 120.9 (d, *J* = 13.2 Hz, CH), 120.0 (d, *J* = 168.0 Hz, ArC-P), 111.4 (d, *J* = 8.3 Hz, CH), 68.8 (OCH$_2$Ar), 60.1 (d, *J* = 5.8 Hz, O***C***H$_2$CH$_3$), 40.2 (NHCH$_2$), 33.9 (d, *J* = 5.9 Hz, NHCH$_2$***C***H$_2$), 19.5 (NHCH$_2$CH$_2$***C***H$_2$), 16.2 (d, *J* = 6.9 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +20.9; HRMS (ESI$^+$): found 420.1688. $C_{23}H_{28}NaNO_3P$ (M + Na) requires 420.1705.

2.6.12. Ethyl *N*-Butyl-*P*-(2-(2-naphthylmethoxy)phenyl)phosphonamidate **21l**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 2-bromomethylnaphthalene (0.55 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave **21l** (0.81 g, 82%) as a pale-yellow oil; ν_{max}/cm^{-1} 2957, 2930, 2870, 1591, 1441, 1227, 1086, 1030, 951, 813, 756, 565, and 475; ^{1}H NMR (400 MHz): 7.96 (1H, ddd, *J* = 15.2, 7.2, 1.6 Hz, ArH), 7.93–7.72 (4H, m, ArH), 7.60–7.44 (4H, m, ArH), 7.08–7.01 (2H, m, ArCH), 5.31 and 5.29 (2H, AB pattern, *J* = 11.4 Hz, ArOC***H*****$_2$**), 4.10–3.93 (2H, m, OC***H*****$_2$**CH$_3$), 3.00–2.82 (3H, m, N***H*****C*H*****$_2$**), 1.30–1.20 (2H, m, NHCH$_2$C***H*****$_2$**), 1.28 (3H, t, *J* = 7.2 Hz, OCH$_2$C***H*****$_3$**), 1.12–1.02 (2H, m, NHCH$_2$CH$_2$C***H*****$_2$**) and 0.71 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$CH$_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 159.1 (d, *J* = 2.9 Hz, ArC-O), 134.6 (d, *J* = 6.5 Hz, CH), 133.8 (C), 133.4 (d, *J* = 2.1 Hz, CH), 131.5 (C), 131.3 (C), 129.4 (CH), 128.9 (CH), 126.9 (CH), 126.7 (CH), 126.0 (CH), 125.3 (CH), 123.3 (CH), 120.9 (d, *J* = 13.3 Hz, CH), 120.0 (d, *J* = 165.7 Hz, ArC-P), 111.4 (d, *J* = 8.5 Hz, CH), 68.8 (OCH$_2$Ar), 60.1 (d, *J* = 5.8 Hz, O***C***H$_2$CH$_3$), 40.2 (NHCH$_2$), 33.9 (d, *J* = 5.9 Hz, NHCH$_2$***C***H$_2$), 19.5 (NHCH$_2$CH$_2$***C***H$_2$), 16.2 (d, *J* = 6.9 Hz, OCH$_2$***C***H$_3$) and 13.6 (NHCH$_2$CH$_2$CH$_2$***C***H$_3$); ^{31}P NMR (162 MHz): +21.2; HRMS (ESI$^+$): found 420.1686. $C_{23}H_{28}NaNO_3P$ (M + Na) requires 420.1705.

2.6.13. Ethyl *N*-Butyl-*P*-(2-(2-thienylmethoxy)phenyl)phosphonamidate **21m**

Using the method of Section 2.6.2 with ethyl *N*-butyl-*P*-(2-hydroxyphenyl)phosphonamidate **22** (0.60 g, 2.5 mmol), 2-bromomethylthiophene (0.44 g, 2.5 mmol), and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (4 mL) gave **21m** (0.88 g, >95%) as a dark-orange oil; ν_{max}/cm^{-1} 3401, 2957, 2930, 2872, 1591, 1441, 1232, 1032, 953, 700, 577, and 540; ^{1}H NMR (400 MHz): 7.94 (1H, ddd, *J* = 14.0, 7.2, 1.6 Hz, ArH), 7.50–7.45 (1H, m, ArH), 7.36 (1H, dd, *J* = 4.8, 1.2 Hz, ArCH), 7.14 (1H, dd, *J* = 3.6, 1.2 Hz, ArCH), 7.07 (1H, tdd, *J* = 7.6, 3.2, 0.6, ArH), 7.04–6.99 (2H, m, ArCH), 5.31 and 5.28 (2H, AB pattern, *J* = 11.8 Hz, ArOC***H*****$_2$**), 4.07–3.90 (2H, m, OC***H*****$_2$**CH_3), 3.00–2.85 (3H, m, N***H*****C*H*****$_2$**), 1.35–1.25 (2H, m, $NHCH_2$C***H*****$_2$**), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2C***H*****$_3$**), 1.25–1.15 (2H, m, $NHCH_2CH_2$C***H*****$_2$**) and 0.81 (3H, t, *J* = 7.2 Hz, $NHCH_2CH_2CH_2$C***H*****$_3$**); ^{13}C NMR (100 MHz): 158.6 (d, *J* = 2.9 Hz, ArC-O), 138.2 (C), 134.6 (d, *J* = 6.4 Hz, CH), 133.3 (d, *J* = 2.1 Hz, CH), 127.1 (CH), 126.9 (CH), 126.5 (CH), 121.2 (d, *J* = 13.2 Hz, CH), 120.2 (d, *J* = 165.4 Hz, ArC-P), 111.7 (d, *J* = 8.6 Hz, CH), 65.3 (OCH_2Ar), 60.3 (d, *J* = 5.8 Hz, O***C***H_2CH_3), 40.4 ($NHCH_2$), 34.1 (d, *J* = 6.0 Hz, $NHCH_2$***C***H_2), 19.7 ($NHCH_2CH_2$***C***H_2), 16.3 (d, *J* = 7.0 Hz, OCH_2***C***H_3) and 13.7 ($NHCH_2CH_2CH_2$***C***H_3); ^{31}P NMR (162 MHz): +20.8; HRMS (ESI$^+$): found 376.1097. $C_{17}H_{24}NaNO_3PS$ (M + Na) requires 376.1112.

2.7. Base Treatment of Substituted Ethyl P-(2-Benzyloxyphenyl)-N-butylphosphonamidates

2.7.1. 3-Butylamino-2-(4-tert-butylphenyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23c**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(4-*tert*-butylbenzyloxy)phenyl) phosphonamidate **21c** (100 mg, 0.25 mmol) and *n*-butyllithium (0.33 mL, 0.83 mmol) in THF (2 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23c** (9.5 mg, 11%) as a pale-yellow oil; ^{1}H NMR (400 MHz): 7.64–7.53 (2H, m, ArH), 7.42–7.40 (2H, m, ArH), 7.36–7.30 (2H, m, ArH), 7.15–7.07 (2H, m, ArH), 5.54 (1H, d, *J* = 10.0 Hz, CHP), 2.46–2.40 (1H, m, NHC***H***H), 2.32–2.27 (1H, m, NHCH***H***), 2.16–2.10 (1H, br m, NH), 1.32 (9H, s, $C(CH_3)_3$), 1.01–0.85 (4H, m, $NHCH_2CH_2$C***H*****$_2$**) and 0.69 (3H, t, *J* = 7.2 Hz, $NHCH_2CH_2CH_2$C***H*****$_3$**); ^{13}C NMR (176 MHz): 164.6 (d, *J* = 23.9 Hz, ArC-O), 151.1 (d, *J* = 2.5 Hz, C), 135.4 (d, *J* = 1.7 Hz, CH), 131.5 (C), 129.0 (d, *J* = 5.1 Hz, CH), 125.6 (2CH), 124.7 (2CH), 122.3 (d, *J* = 10.2 Hz, CH), 114.3 (d, *J* = 7.0 Hz, CH), 114.0 (d, *J* = 122.0 Hz, ArC-P), 79.7 (d, *J* = 87.8 Hz, CHP), 40.2 ($NHCH_2$), 34.5 (***C***$(CH_3)_3$), 33.5 (d, *J* = 5.4 Hz, $NHCH_2$***C***H_2), 31.2 (C(***C***$H)_3)_3$), 19.4 ($NHCH_2CH_2$***C***H_2) and 13.4 ($NHCH_2CH_2CH_2$***C***H_3); ^{31}P NMR (162 MHz): +44.6; HRMS (ESI$^+$): found 380.1746. $C_{21}H_{28}NaNO_2P$ (M + Na) requires 380.1755.

2.7.2. 3-Butylamino-2-(2-methoxyphenyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23d**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(2-methoxybenzyloxy)phenyl) phosphonamidate **21d** (100 mg, 0.26 mmol) and *n*-butyllithium (0.34 mL, 0.86 mmol) in THF (5 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23d** (3.1 mg, 4%) as colourless crystals; ^{1}H NMR (400 MHz): 7.61–7.51 (2H, m, ArH), 7.32–7.22 (2H, m, ArH), 7.14–7.05 (2H, m, ArH), 6.97–6.92 (2H, m, ArH), 5.82 (1H, d, *J* = 12.4 Hz, CHP), 3.90 (3H, s, OMe), 2.41–2.35 (1H, m, NHC***H*****$_2$**), 2.15–2.08 (1H, br m, NH), 1.08–0.98 (4H, m, $NHCH_2$C***H*****$_2$C*H*****$_2$**) and 0.72 (3H, t, *J* = 6.8 Hz, $NHCH_2CH_2CH_2$C***H*****$_3$**); ^{31}P NMR (162 MHz): +45.6; HRMS (ESI$^+$): found 354.1217. $C_{18}H_{22}NaNO_3P$ (M + Na) requires 354.1235.

2.7.3. 3-Butylamino-2-(3-methoxyphenyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23e**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(3-methoxybenzyloxy)phenyl) phosphonamidate **21e** (100 mg, 0.26 mmol) and *n*-butyllithium (0.34 mL, 0.86 mmol) in THF (5 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23c** (6.7 mg, 8%) as a pale-yellow oil; ^{1}H NMR (400 MHz): 7.64–7.51 (2H, m, ArH), 7.31 (1H, t, *J* = 8.0 Hz, ArH), 7.15–7.10 (2H, m, ArH), 7.00–6.85 (3H, m, ArH), 5.54 (1H, d, *J* = 10.4 Hz, CHP), 3.82 (3H, s, OMe), 2.53–2.47 (1H, m, NHC***H***H), 2.35–2.28 (1H, m, NHCH***H***), 2.15–2.10 (1H, br m, NH), 1.05–0.98 (4H, m, $NHCH_2$C***H*****$_2$C*H*****$_2$**) and 0.72 (3H, t,

J = 6.8 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{31}P NMR (162 MHz): +44.5; HRMS (ESI^+): found 354.1221. $C_{18}H_{22}NaNO_3P$ (M + Na) requires 354.1235.

2.7.4. 3-Butylamino-2-(2-fluorophenyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23g**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(2-fluorobenzyloxy)phenyl) phosphonamidate **21g** (100 mg, 0.27 mmol) and *n*-butyllithium (0.36 mL, 0.89 mmol) in THF (5 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23c** (6.9 mg, 8%) as a pale-yellow oil; ^1H NMR (400 MHz): 7.65–7.52 (2H, m, ArH), 7.35–7.26 (2H, m, ArH), 7.18–7.09 (4H, m, ArH), 5.74 (1H, d, *J* = 11.6 Hz, CHP), 2.52–2.39 (2H, m, $NHC\boldsymbol{H}_2$), 2.28–2.20 (1H, br m, NH), 1.10–1.00 (4H, m, $NHCH_2C\boldsymbol{H}_2C\boldsymbol{H}_2$) and 0.72 (3H, t, *J* = 6.8 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{19}F NMR (376 MHz): –114.3; ^{31}P NMR (162 MHz): +44.6; HRMS (ESI^+): found 342.1019. $C_{17}H_{19}FNaNO_2P$ (M + Na) requires 342.1035.

2.7.5. 3-Butylamino-2-(4-fluorophenyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23h**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(4-fluorobenzyloxy)phenyl) phosphonamidate **21h** (100 mg, 0.27 mmol) and *n*-butyllithium (0.36 mL, 0.89 mmol) in THF (5 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23c** (7.0 mg, 8%) as a pale-yellow oil; ^1H NMR (400 MHz): 7.66–7.54 (2H, m, ArH), 7.41–7.36 (2H, m, ArH), 7.16–7.08 (4H, m, ArH), 5.53 (1H, d, *J* = 9.6 Hz, CHP), 2.50–2.42 (1H, m, $NHC\boldsymbol{H}H$), 2.31–2.22 (1H, m, $NHCH\boldsymbol{H}$), 2.20–2.10 (1H, br m, NH), 1.08–0.98 (4H, m, $NHCH_2C\boldsymbol{H}_2C\boldsymbol{H}_2$) and 0.72 (3H, t, *J* = 7.0 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 135.6 (d, *J* = 1.8 Hz, CH), 129.1 (d, *J* = 5.5 Hz, CH), 126.7 (dd, *J* = 8.2, 4.0 Hz, 2CH), 122.6 (d, *J* = 10.1 Hz, CH), 115.8 (dd, *J* = 21.7, 2.2 Hz, 2CH), 114.3 (d, *J* = 6.5 Hz, CH), 79.3 (d, *J* = 87.9 Hz, CHP), 40.2 ($NHCH_2$), 33.8 (d, *J* = 5.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.4 ($NHCH_2CH_2\boldsymbol{C}H_2$) and 13.5 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$) [only non-quaternary signals observed due to small amount of material]; ^{19}F NMR (376 MHz): –113.9; ^{31}P NMR (162 MHz): +44.1; HRMS (ESI^+): found 342.1018. $C_{17}H_{19}FNaNO_2P$ (M + Na) requires 342.1035.

2.7.6. 3-Butylamino-2-(1-naphthyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23k**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(1-naphthylmethoxy)phenyl) phosphonamidate **21k** (100 mg, 0.25 mmol) and *n*-butyllithium (0.33 mL, 0.83 mmol) in THF (2 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23c** (6.6 mg, 7%) as a pale-yellow oil; ^{31}P NMR (162 MHz): +45.6; HRMS (ESI^+): found 352.1456. $C_{21}H_{23}NO_2P$ (M + H) requires 352.1456.

2.7.7. 3-Butylamino-2-(2-naphthyl)-2*H*-benzo[*d*][1,3]oxaphosphole 3-Oxide **23l**

Using the method of Section 2.2.5 with ethyl *N*-butyl-*P*-(2-(2-naphthylmethoxy)phenyl) phosphonamidate **21l** (100 mg, 0.25 mmol) and *n*-butyllithium (0.33 mL, 0.83 mmol) in THF (2 mL) at rt for 20 min gave, after purification via preparative TLC (hexane/EtOAc 1:3), **23l** (8.1 mg, 9%) as a pale-yellow oil; ^1H NMR (400 MHz): 7.90–7.80 (4H, m, ArH), 7.68–7.46 (5H, m, ArH), 7.19–7.10 (2H, m, ArH), 5.73 (1H, d, *J* = 10.0 Hz, CHP), 2.46–2.37 (1H, m, $NHC\boldsymbol{H}H$), 2.28–2.19 (1H, m, $NHCH\boldsymbol{H}$), 2.18–2.08 (1H, br m, NH), 0.90–0.80 (4H, m, $NHCH_2C\boldsymbol{H}_2C\boldsymbol{H}_2$) and 0.50 (3H, t, *J* = 7.0 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (176 MHz): 164.6 (d, *J* = 23.7 Hz, ArC-O), 135.6 (d, *J* = 1.2 Hz, CH), 133.3 (d, *J* = 2.0 Hz, C), 132.10 (C), 132.07 (C), 129.1 (d, *J* = 5.6 Hz, CH), 128.6 (d, *J* = 1.9 Hz, CH), 127.82 (CH), 127.80 (CH), 126.6 (CH), 126.2 (CH), 123.7 (d, *J* = 5.1 Hz, CH), 122.8 (d, *J* = 2.9 Hz, CH), 122.5 (d, *J* = 10.2 Hz, CH), 114.4 (d, *J* = 6.5 Hz, CH), 114.1 (d, *J* = 121.9 Hz, ArC-P), 80.0 (d, *J* = 86.7 Hz, CHP), 40.3 ($NHCH_2$), 33.7 (d, *J* = 5.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.3 ($NHCH_2CH_2\boldsymbol{C}H_2$) and 13.3 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +44.5; HRMS (ESI^+): found 374.1271. $C_{21}H_{22}NaNO_2P$ (M + Na) requires 374.1286.

2.8. X-ray Structure Determination of **23d**

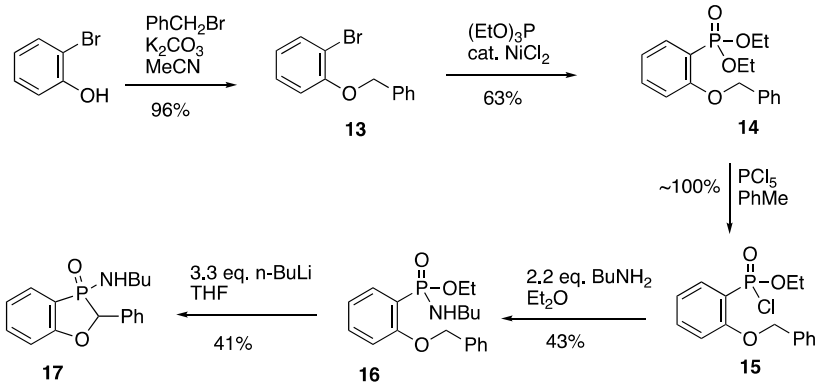
The X-ray diffraction data for compound **23d** were collected at 173 K using a Rigaku MM-007HF High Brilliance RA generator/confocal optics with an XtaLAB P200 diffrac-

tometer [Cu Kα radiation (λ = 1.54187 Å), Tokyo, Japan]. The data were collected and processed (including correction for Lorentz, polarisation, and absorption) using CrysAlisPro [19]. The structures were solved by dual-space methods (SHELXT) [20] and refined by full-matrix least squares against F^2 (SHELXL-2019/3) [21]. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model, except for the hydrogen atoms on N3 and N23 which were located using the difference Fourier map and refined isotropically, subject to a distance restraint. All the calculations were performed using the Olex2 interface [22].

Crystal data for $C_{18}H_{22}NO_3P$: M = 331.33 g mol^{-1}, colourless prism, crystal dimensions 0.06 × 0.06 × 0.04 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 11.01041(14), b = 16.9371(2), c = 18.6444(2) Å, β = 100.5651(12)°, V = 3417.95(7) Å^3, Z = 8, D_{calc} = 1.288 g cm^{-3}, T = 173 K, R_1 = 0.0409 wR_2 = 0.1143 for 6052 reflections with $I > 2\sigma(I)$ and 494 variables, R_{int} 0.0451, and goodness of fit on F^2 1.076. The data were deposited at the Cambridge Crystallographic Data Centre as CCDC 2299148. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures (accessed on 16 October 2023).

3. Results and Discussion

Starting from 2-bromophenol, the known benzyl ether **13** was prepared in excellent yield (Scheme 3). To prepare **14** the phosphonate functionality was installed by the nickel-catalysed Michaelis–Arbuzov-type reaction, with triethyl phosphite introduced by Tavs [15]. We found that to obtain a good yield of product **14**, it was essential to use anhydrous nickel(II) chloride. The diethyl phosphonate **14** was treated with phosphorus pentachloride in toluene to afford **15**, which reacted directly with two equivalents of butylamine, giving phosphonamidate **16**. As previously observed in the *para* and *meta* series [9], the reaction sequence was accompanied by distinctive changes in the ^{31}P NMR shift: from +17.1 ppm for **14** to +26.5 ppm for **15** to +21.3 ppm for **16**. Compound **16** showed an interesting and highly informative pattern of phosphorus couplings in the ^{13}C NMR spectrum (Figure 1), with coupling observed to all carbons of the phosphorus-bearing benzene ring and both carbons of the *O*-ethyl group, but only to C-2 of the *N*-butyl group.



Scheme 3. Stepwise synthesis and cyclisation of compound **16**.

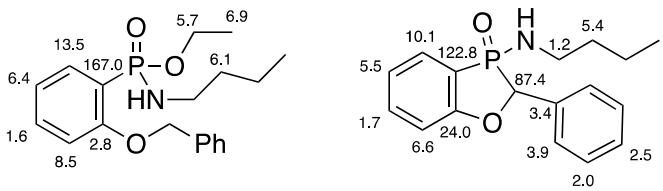


Figure 1. Magnitude of J_{P-C} (Hz) for carbon atoms in compounds **16** and **17**.

When a solution of compound **16** in dry THF was treated with 3.3 equiv. of n-butyllithium at RT, there was a rapid reaction to afford, after aqueous work-up and chro-

matographic purification, a new product identified as the 1,3-benzoxaphosphole **17**. The ^{31}P NMR shift had moved dramatically from +21.3 to +44.6 ppm and both the ^{1}H and the ^{13}C NMR spectra showed the absence of the OEt group. Most significantly, the signals for the benzylic CH_2 group of **16** had been replaced in the proton NMR spectrum by a 1H doublet at 5.57 ppm ($^{2}J_{H–P}$ 9.9 Hz), which collapsed to a singlet upon ^{31}P decoupling, and a corresponding carbon signal at 79.7 ppm ($^{1}J_{C–P}$ 87.4 Hz), which was consistent with P–CH(Ph)–O. The pattern of phosphorus coupling throughout the structure (Figure 1) showed interesting differences from that of **16**, with a drop in the value at ArC–P from J = 167.0 to 122.8 Hz and a corresponding increase in the value at the oxygen-bearing benzene ring position from 2.8 to 24.0 Hz. It was also clear from the spectra that the product had been formed as a single diastereomer with complete control of the relative configuration of the two adjacent newly formed stereocentres. It was not possible to determine which isomer had been formed at this stage since the material was obtained as an oil. This aspect is addressed below for a crystalline analogue.

As far as we are aware, this method, in which there is cyclisation with formation of the C(2)–P bond, represents a new synthetic approach to the dihydrobenzo[*d*][1,3]oxaphosphole ring system. As noted in a recent review [23], previous approaches involved either cyclisation with the formation of the C(2)–O bond [10–13] or the introduction of a C-1 unit to an *ortho*-hydroxyarylphosphine (Figure 2).

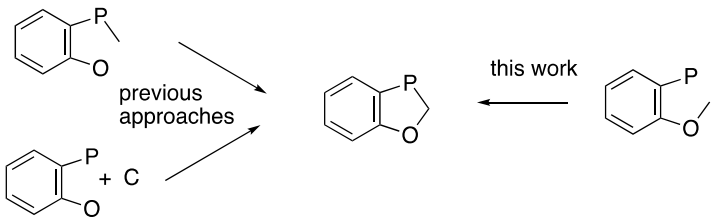
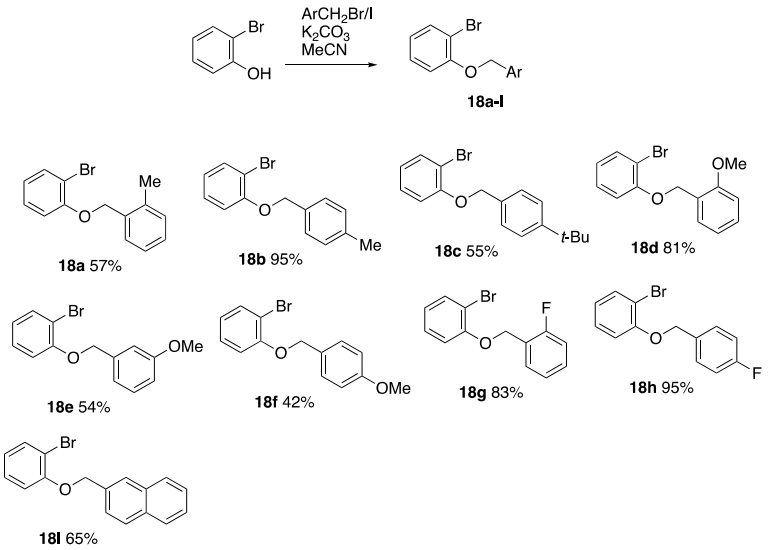


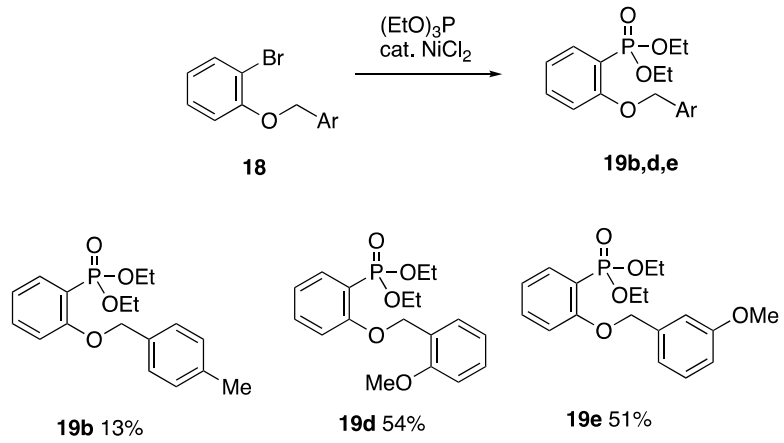
Figure 2. Synthetic approaches to the dihydrobenzo[*d*][1,3]oxaphosphole ring system.

We now wished to explore the scope of the process for substituted benzyl groups and prepared a range of ethers **18** from 2-bromophenol (Scheme 4). Where the relevant benzylic bromide was available, this was used directly, but the benzylic chlorides were first activated towards substitution by Finkelstein conversion into the corresponding benzyl iodide (examples b, g and h). It should be noted that the isomeric fluorobenzyl iodides are severely lachrymatory and care is required in handling them. The resulting products **18**, all previously unknown, gave the expected spectroscopic and analytical data.



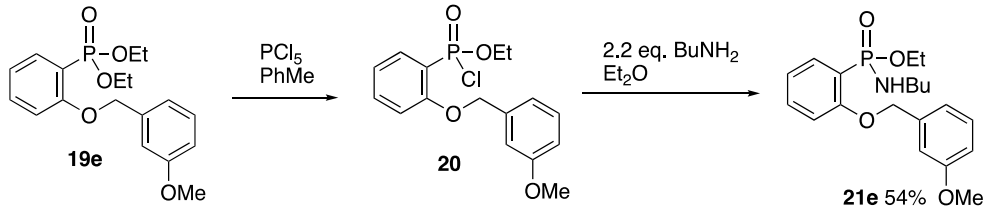
Scheme 4. Preparation of substituted benzyl 2-bromophenyl ethers **18**.

When we attempted to introduce the diethyl phosphonate group in these substituted examples using the previously described nickel catalysed reaction with triethyl phosphite, it quickly became apparent that the reaction was unreliable. In some cases, it worked well and gave the products in reasonable yield, but in most cases, it failed. Three new phosphonates were obtained by this method (Scheme 5) and gave analytical and spectroscopic data that were consistent with **14**.



Scheme 5. Direct synthesis of substituted diethyl 2-benzyloxyphenylphosphonates.

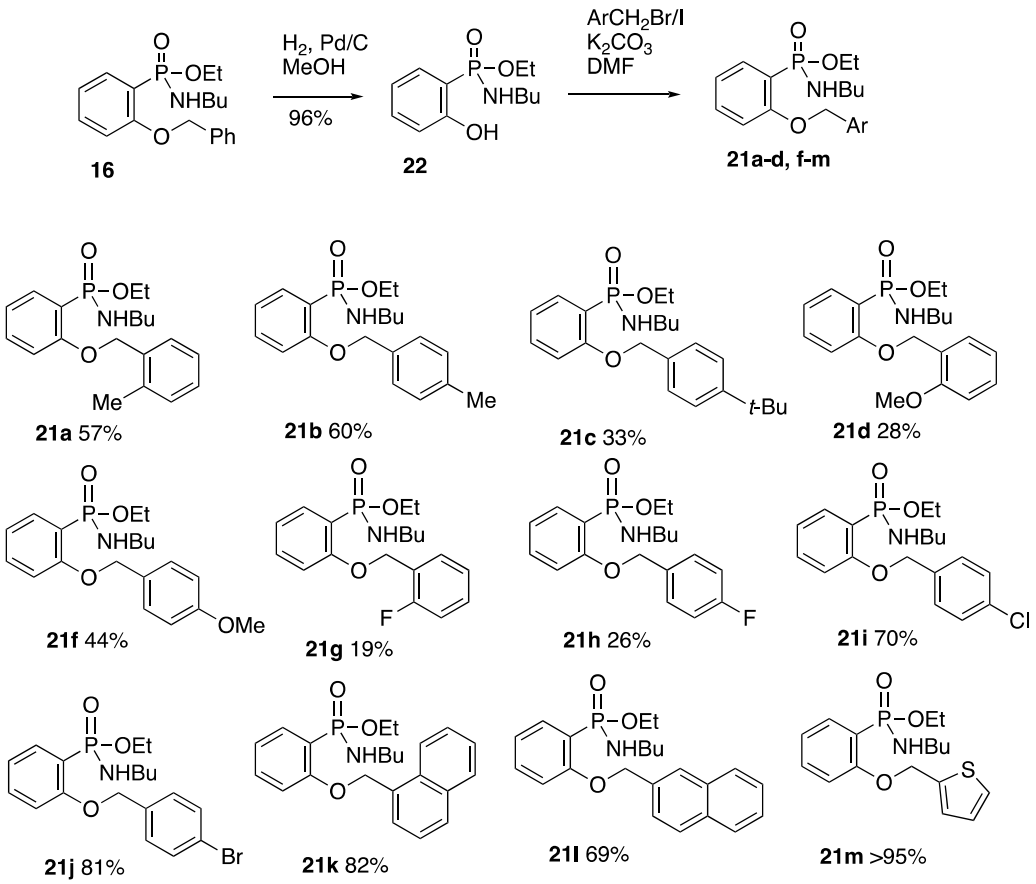
As compound **19e** was available in the greatest quantity, it was subjected to reaction with phosphorus pentachloride to give the phosphonochloridate **20**, followed by treatment with *n*-butylamine to give the first substituted phosphonamidate **21e** in satisfactory overall yield (Scheme 6).



Scheme 6. Stepwise synthesis of phosphonamidate **21e**.

However, it was clear that this approach to accessing a wider range of substituted phosphonamidates was unsatisfactory. Instead, we were able to remove the *O*-benzyl group from **16** in excellent yield using catalytic hydrogenation to give the hydroxyphenylphosphonamidate **22**. This was then *O*-alkylated to give a range of derivatives, **21a–d** and **f–m**, in varying yields (Scheme 7).

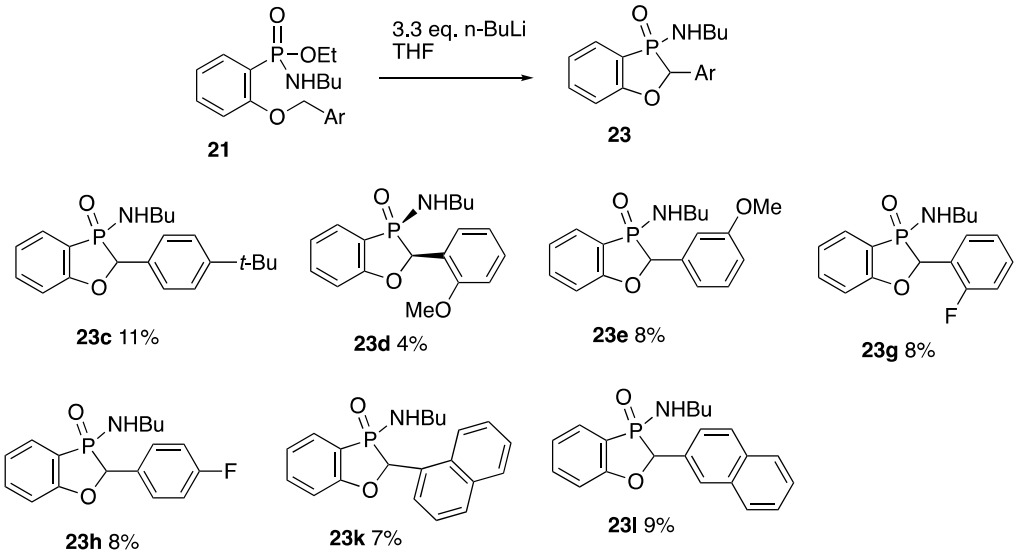
All the phosphonamidates in this paper show ^{31}P signals in the narrow range of δ_P +20.8–21.5, and the expected phosphorus coupling is observed in the ^{13}C NMR spectra for all the signals of the phosphorus-bearing benzene ring and both carbons of OEt but, interestingly, only C–2 of NHBu. The magnitude of the values was consistent with that shown for **16** in Figure 1. In the substituted examples, the benzylic CH_2 protons were magnetically non-equivalent only in the more sterically hindered examples, leading to the observation of an AB pattern in the ^{1}H NMR spectra for **21a, d, g, k, l**, and **m**.



Scheme 7. Synthesis of substituted phenylphosphonamidates by alkylation of **22**.

When compounds **21a–m** were subjected to treatment with butyllithium under the same conditions as for **16**, a varying pattern of reactivity was observed. In each case, a complex mixture of products was obtained, but by using preparative TLC, the cyclised products **23** could be obtained in seven cases (Scheme 8). The final isolated yields were low in all cases, but the spectroscopic data were in good agreement with those already established for **17**. The main competing reaction seemed to be *O*-debenzylation to regenerate compound **22**, which was observed in all cases. The reaction was complete within 20 min, and leaving it for longer resulted in reduced yields of **23**. The failure of the cyclisation for **21i** and **21j** was not surprising as the lithium–halogen exchange was expected to occur. Significantly, each benzophosphole product was obtained as a single diastereomer with consistent values of $^{2}J_{H–P}$ 9.6–12.4 Hz for the 2-CH signal observed at 5.53–5.82 ppm in the ^{1}H NMR spectra and $^{1}J_{C–P}$ 86.7–87.9 Hz for the corresponding 2-C signal observed at 79.3–80.0 ppm in the ^{13}C NMR spectra. The two N–CH_2 protons were also magnetically non-equivalent in each case, leading to two separate multiplets in the ^{1}H NMR spectrum in each case.

In the case of the *ortho*-methoxyphenyl compound **23d**, crystals suitable for X-ray diffraction were obtained, and the resulting structure (Figure 3) showed two independent but closely similar molecules linked in an $R^{2}_{2}(8)$ [24] dimer by N–H···O=P hydrogen bonding. Not unexpectedly, there was significant disorder within the flexible N-butyl groups.



Scheme 8. Base-induced cyclisation to give substituted benzophosphole products **23**.

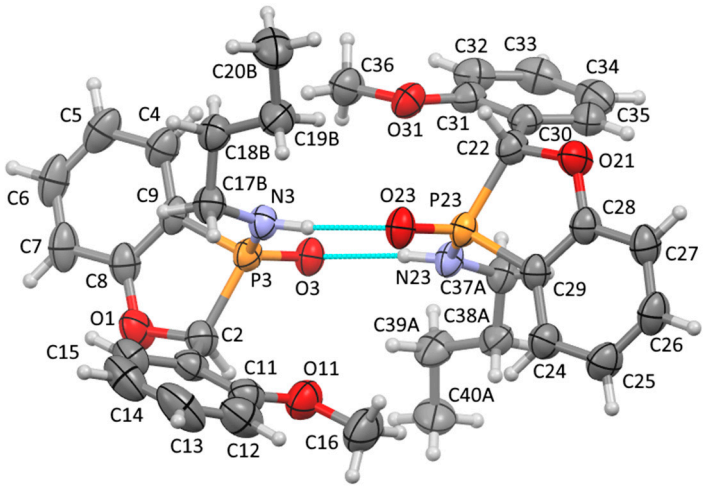


Figure 3. The two independent molecules in the crystal structure of **23d** showing the numbering system used, probability ellipsoids at the 50% level, and hydrogen bonding.

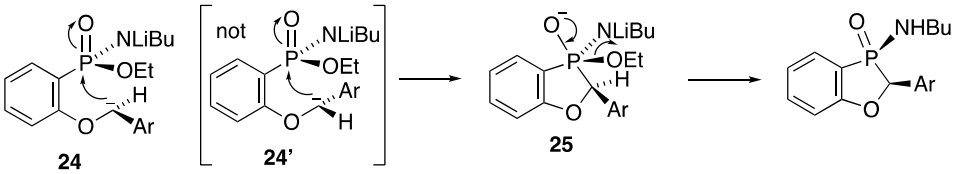
The structure clearly shows a *cis* arrangement of the 2-CH and P=O groups with the 2-aryl group *cis* to the NHBu, as depicted in Scheme 8. Based on the consistency of the NMR data, we assume all the cyclic products **17** and **23** obtained have this relative configuration. The hydrogen bonding parameters (Table 1) fall within normal ranges.

Table 1. Hydrogen bonding parameters for **23d** (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N(3)–H(3)···O(23)	0.922(14)	1.984(15)	2.9006(16)	172.4(18)
N(23)–H(23)···O(3)	0.935(15)	2.007(15)	2.9392(16)	174.3(19)

A mechanistic explanation for the high stereoselectivity of the ring closure process is complicated by the fact that such substitutions at phosphorus are well known to involve a trigonal bipyramidal intermediate with the associated possibility of pseudo-rotation. Despite this complication, such substitutions usually proceed with net inversion of the configuration at P. With this in mind, we suggest that the ring closure of carbanion **24** in preference to the isomer **24′** is favoured on steric grounds, with the aryl group preferring to

be cis to OEt rather than N(Li)Bu. Loss of ethoxide from the resulting intermediate **25** is then expected to afford the product with the observed relative configuration (Scheme 9).



Scheme 9. Proposed mechanism to explain stereospecific ring closure.

In conclusion, when the phosphonamidate group EtO-P(=O)-NHBu, which is effective in promoting the Wittig rearrangement of *meta*- or *para*-disposed aryl benzyl ethers, is placed in the *ortho*-position, a quite different process is observed upon treatment with butyllithium, resulting in cyclisation with the loss of ethanol to give access to the novel 2-aryl-3-butylamino-2*H*-benzo[*d*][1,3]oxaphosphole 3-oxides in moderate to low yield. These are all formed as a single diastereomer, which was shown to have the *cis* arrangement of aryl and NH-butyl groups by an X-ray structure determination in one case.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org5010002/s1, Figures S1–S103: ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra of all new compounds.

Author Contributions: K.A.M., R.A.I., F.G.J. and A.J.B.N. carried out the experimental work and analysed the data; D.B.C. and A.P.M. collected the X-ray diffraction data and solved the structure; R.A.A. designed the experiments and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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