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Synthesis and Wittig Rearrangement of 3- and 4-Benzyloxyphenylphosphonamidates

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Abstract: A series of seven *O*-ethyl-*N*-butylphenylphosphonamidates with benzyl ether substituents at the *para* or *meta* position have been prepared and fully characterised. Upon treatment with *n*-butyllithium in THF at RT, these undergo Wittig rearrangement in six cases to give the novel phosphonamidate-substituted diarylmethanols in moderate to good yield.

Keywords: Wittig rearrangement; phosphonamidate; diarylmethanol; aryl benzyl ether

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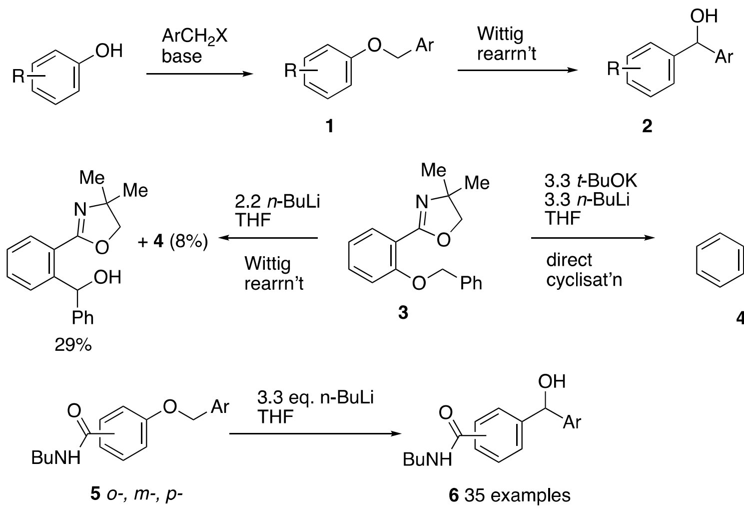
1. Introduction

The [1,2]-Wittig rearrangement of aryl benzyl ethers **1** to give diarylmethanols **2** (Scheme 1) provides a potentially valuable indirect method for C–C bond formation but, although the reaction is well known [1,2], it has not found much recent synthetic use [3], perhaps owing to the strongly basic conditions required which make it incompatible with many common functional groups. In recent studies, we have described the use of activating groups on the aryl ring to promote the Wittig rearrangement under milder conditions. The first such activating group to be discovered was the 4,4-dimethyl-2-oxazoline [4], although when this was in the ortho position to the benzyloxy group as in **3**, there was significant competition from direct cyclisation to give benzofuran products **4**, a phenomenon also later observed in benzyloxythienyloxazolines [5]. In the meantime, we developed the *N*-butylcarboxamide, CONHBu as a more effective and general activating group, facilitating Wittig rearrangement of *ortho*-, *meta*-, or *para*-disposed benzylic ethers **5** to give diarylmethanols **6** [6]. Limited success in using a chiral secondary amide group to direct asymmetric Wittig rearrangement was also reported [7].



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

In this paper, we describe the synthesis of aryl benzyl ethers bearing the phosphonamidate group, EtO-P(=O)-NHBu on the aryl ring, either *para*- or *meta*- to a benzylic ether, and their successful Wittig rearrangement to afford the corresponding phosphonamidate-functionalised diarylmethanols.

2. Materials and Methods

2.1. General Experimental Details

NMR spectra were recorded on solutions in $CDCl_3$ unless otherwise stated using Bruker instruments and chemical shifts are given in ppm to high frequency from Me_4Si with coupling constants *J* in Hz. 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 silica gel of 40–63 µm particle size and preparative TLC was carried out using 1.0 mm layers of Merck alumina 60 G containing 0.5% Woelm fluorescent green indicator on glass plates. Melting points were recorded on a Gallenkamp 50 W melting point apparatus or a Reichert hot-stage microscope.

2.2. 1-(Benzyloxy)-4-bromobenzene **7**

To a stirred solution of 4-bromophenol (10.00 g, 58.2 mmol) in MeCN (50 mL) at rt, K_2CO_3 (10.94 g, 79.2 mmol) and benzyl bromide (6.9 mL, 9.94 g, 58.2 mmol) was added and the mixture was stirred at rt overnight. The reaction was diluted with H_2O (150 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give **7** (15.61 g, quant) as a colourless solid which was used without further purification; mp 58−60 °C; (lit. [8] 60−61 °C); ^{1}H NMR (400 MHz): 7.43−7.31 (7H, m, ArH), 6.85 (2H, d, *J* = 9.0 Hz, ArH), and 5.03 (2H, s, OCH_2); ^{13}C NMR (100 MHz): 158.0 (C-O), 136.6 (C-Br), 132.4 (2CH), 128.8 (2CH), 128.2 (CH), 127.6 (2CH), 116.8 (2CH), 113.2 (C), and 70.3 (OCH_2). The ^{1}H and ^{13}C spectral data were in accordance with that previously reported [9].

2.3. Synthesis and Rearrangement of Ethyl P-(4-Benzyloxyphenyl)-N-butylphosphonamidate **10**

2.3.1. Diethyl (4-Benzyloxyphenyl)phosphonate **8**

Following a modified literature procedure [10], 1-(benzyloxy)-4-bromobenzene **7** (14.00 g, 53.2 mmol) and anhydrous $NiCl_2$ (689 mg, 5.32 mmol) were placed in a flask set up for distillation. Then, a dropping funnel containing triethyl phosphite (11.0 mL, 63.8 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 had been added. The mixture was then heated for a further 30 min and cooled to rt. The mixture was taken up in CH_2Cl_2 (100 mL) which was washed with dil. HCl (50 mL), dried, and evaporated to give, after purification via flash column chromatography (gradient elution hexane/EtOAc 9:1 to 100% ethyl acetate), **8** (13.83 g, 81%) as a slightly yellow oil; ^{1}H NMR (400 MHz): 7.75 (2H, dd, J_{HP} = 12.8, J_{HH} = 8.8 Hz, ArH), 7.45−7.37 (4H, m, ArH), 7.37−7.30 (1H, m, ArH), 7.04 (2H, dd, J_{HH} = 8.8, J_{HP} = 3.3 Hz, ArH), 5.11 (2H, s, OCH_2Ph), 4.17−4.01 (4H, m, 2 x $OC\boldsymbol{H}_2CH_3$), and 1.31 (6H, dt, J_{HH} = 7.1, J_{HP} = 0.5 Hz, 2 x $OCH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 161.8 (d, J_{CP} = 3.5 Hz, C-O), 136.1 (C), 133.6 (d, J_{CP} = 11.3 Hz, 2CH), 128.5 (2CH), 128.1 (CH), 127.3 (2CH), 119.7 (d, J_{CP} = 194.7 Hz, C-P), 114.7 (d, J_{CP} = 16.0 Hz, 2CH), 69.9 (OCH_2Ph), 61.8 (d, J_{CP} = 5.3 Hz, 2 $O\boldsymbol{C}H_2CH_3$), and 16.2 (d, J_{CP} = 6.5 Hz, 2 $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +19.6. The ^{1}H and ^{13}C spectral data were in accordance with that previously reported [11]. The ^{31}P spectral data are reported for the first time.

2.3.2. Ethyl (4-Benzyloxyphenyl)phosphonochloridate **9**

A solution of diethyl (4-benzyloxyphenyl)phosphonate **8** (0.50 g, 1.56 mmol) in dry toluene (10 mL) was stirred at 0 °C while PCl_5 (0.65 g, 3.12 mmol) was added. The mixture was then stirred at rt for 30 min, filtered, and evaporated to give **9** (0.42 g, 87%) as a pale-yellow oil which was used without further purification; ^{1}H NMR (400 MHz): 7.82 (2H, dd, J_{HP} = 14.7, J_{HH} = 8.9 Hz, ArH), 7.42–7.31 (5H, m, ArH), 7.06 (2H, dd, J_{HH} = 8.9, J_{HP} = 4.2 Hz, ArH), 5.13 (2H, s, OCH_2Ph), 4.48–4.30 (2H, m, $OC\boldsymbol{H}_2CH_3$), and 1.45 (3H, t, J = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 162.8 (d, J_{CP} = 3.7 Hz, ArC-O), 135.8 (C), 133.2 (d, J_{CP} = 13.5 Hz, 2CH), 128.7 (2CH), 128.3 (CH), 127.4 (2CH), 122.0 (d, J_{CP} = 188.6 Hz, C-P), 115.0 (d, J_{CP} = 18.2 Hz, 2CH), 70.1 (OCH_2Ph), 63.7 (d, J_{CP} = 7.6 Hz, $O\boldsymbol{C}H_2CH_3$), and 16.0 (d, J_{CP} = 7.4 Hz, $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +29.8.

2.3.3. Ethyl *P*-(4-Benzyloxyphenyl)-*N*-butylphosphonamidate **10**

Following a literature procedure [12], a solution of *n*-butylamine (0.14 mL, 0.10 g, 1.41 mmol) in Et_2O (5 mL) was stirred at 0 °C while a solution of ethyl (4-benzyloxyphenyl) phosphonochloridate **9** (0.20 g, 0.64 mmol) in Et_2O (5 mL) was added dropwise. The mixture was allowed to warm to rt and stirred for 18 h. Water (10 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic layers were dried and evaporated to give **10** (160 mg, 72%) as a slightly yellow oil which was used without further purification; ν_{max}/cm^{-1} 3177, 2957, 2932, 2872, 1597, 1501, 1454, 1383, 1288, 1248, 1206, 1125, 1038, 1011, 957, 752, 700, 592, and 532; ^{1}H NMR (400 MHz): 7.73 (2H, dd, J_{HP} = 12.4, J_{HH} = 8.8 Hz, ArH), 7.44–7.35 (4H, m, ArH), 7.35–7.28 (1H, m, ArH), 7.02 (2H, dd, J_{HH} = 8.8, J_{HP} = 3.0 Hz, ArH), 5.09 (2H, s, OCH_2Ph), 4.07 (2H, app quintet, J = 7.2 Hz, $OC\boldsymbol{H}_2CH_3$), 2.87–2.81 (2H, m, $NHCH_2$), 1.46–1.39 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.35–1.27 (5H, m, $NCH_2CH_2C\boldsymbol{H}_2$ and $OCH_2C\boldsymbol{H}_3$), and 0.86 (3H, t, J = 7.3 Hz, $NCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 161.3 (d, J_{CP} = 3.2 Hz, C-O), 136.2 (C), 133.3 (d, J_{CP} = 11.1 Hz, 2CH), 128.5 (2CH), 128.0 (CH), 127.3 (2CH), 122.5 (d, J_{CP} = 179.0 Hz, C-P), 114.5 (d, J_{CP} = 15.1 Hz, 2CH), 69.8 (OCH_2Ph), 60.1 (d, J_{CP} = 5.5 Hz, $O\boldsymbol{C}H_2CH_3$), 40.5 ($NHCH_2$), 33.7 (d, J_{CP} = 6.3 Hz, $NCH_2\boldsymbol{C}H_2$), 19.6 ($NCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +23.4; HRMS (ESI$^+$): found 348.1714. $C_{19}H_{27}NO_3P$ (M + H) requires 348.1729.

2.3.4. Ethyl *N*-Butyl-*P*-((4-hydroxy(phenyl)methyl)phenyl)phosphonamidate **11**

A solution of ethyl *P*-(4-benzyloxyphenyl)-*N*-butylphosphonamidate **10** (173.6 mg, 0.5 mmol) in dry THF (5 mL) was stirred at rt under N_2 while *n*-butyllithium (0.91 mL, 1.65 mmol) was added by syringe. After 10 min, the mixture was added to saturated aqueous ammonium chloride (5 mL) and the mixture was extracted with Et_2O (3 × 5 mL). Drying and evaporation of the combined extracts gave, after purification via preparative TLC (EtOAc) at R_f 0.19, **11** (122.5 mg, 71%) as a pale-yellow oil; ν_{max}/cm^{-1} 3250, 2957, 2930, 2871, 1601, 1452, 1396, 1192, 1125, 1032, 957, 700, 625, and 561; ^{1}H NMR (400 MHz): 7.69 (2H, dd, J_{HP} = 12.7, J_{HH} = 8.2 Hz, ArH), 7.45 (2H, dd, J_{HH} = 8.2, J_{HP} = 3.6 Hz, ArH), 7.37–7.24 (5H, m, ArH), 5.85 (1H, s, $C\boldsymbol{H}OH$), 4.06 (2H, app quintet, J = 7.2 Hz, OCH_2), 2.90–2.77 (2H, m, $NHC\boldsymbol{H}_2$), 1.43–1.35 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.33–1.24 (5H, m, $OCH_2C\boldsymbol{H}_3$ and $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.84 (3H, t, J = 7.2 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 147.9 (d, J_{CP} = 2.9 Hz, ***C***-CHOH), 143.6 (C), 131.5 (d, J_{CP} = 10.0 Hz, 2CH), 129.6 (d, J_{CP} = 174.6 Hz, ArC-P), 128.5 (2CH), 127.7 (CH), 126.7 (2CH), 126.4 (d, J_{CP} = 14.4 Hz, 2CH), 75.7 (CHOH), 60.4 (d, J_{CP} = 5.6 Hz, OCH_2), 40.6 ($NHCH_2$), 33.8 (d, J_{CP} = 6.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.4 (d, J_{CP} = 6.8 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +22.8; HRMS (ESI$^+$): found 348.1714. $C_{19}H_{27}NO_3P$ (M + H) requires 348.1729.

2.4. Ethyl N-Butyl-P-(4-hydroxyphenyl)phosphonamidate **12**

Following a literature procedure [13], to a solution of ethyl *P*-(4-benzyloxyphenyl)-*N*-butylphosphonamidate **10** (1.18 g, 3.4 mmol) in MeOH (20 mL) at rt was added 10% Pd/C (0.17 g) and the solution stirred under an H_2 atmosphere for 2 h. The reaction mixture was filtered through celite, and the filtrate concentrated to give **12** (0.86 g, 98%) as a slightly-yellow, viscous oil which was used without further purification; ν_{max}/cm^{-1} 3098, 2957, 2932, 2872, 1603, 1584, 1508, 1439, 1285, 1186, 1169, 1125, 1028, 955, 835, and 530;

^{1}H NMR (400 MHz): 7.59 (2H, dd, J_{HP} = 12.6, J_{HH} = 8.3 Hz, ArH), 6.94 (2H, dd, J_{HH} = 8.3, J_{HP} = 3.2 Hz, ArH), 4.10−4.02 (2H, m, OCH_2), 2.90−2.80 (2H, m, $NHCH_2$), 1.46−1.38 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.34−1.27 (5H, m, $OCH_2C\boldsymbol{H}_3$ and $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.85 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 161.3 (d, J_{CP} = 3.1 Hz, CH), 133.3 (d, J_{CP} = 11.4 Hz, 2CH), 118.9 (d, J_{CP} = 181.6 Hz, C-P), 115.8 (d, J_{CP} = 15.5 Hz, 2CH), 60.7 (d, J_{CP} = 5.6 Hz, OCH_2), 40.5 ($NHCH_2$), 33.8 (d, J_{CP} = 6.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, J_{CP} = 6.8 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (202 MHz): +25.6; HRMS (ESI^+): found 258.1248. $C_{12}H_{21}NO_3P$ (M + H) requires 258.1259.

2.5. Synthesis and Rearrangement of Substituted Ethyl P-(4-Benzyloxy)phenyl)-N-butylphosphonamidates 13

2.5.1. Ethyl *N*-Butyl-*P*-(4-(4-tert-butylbenzyloxy)phenyl)phosphonamidate 13a

A solution of ethyl *N*-butyl-*P*-(4-hydroxyphenyl)phosphonamidate **12** (0.51 g, 2.0 mmol), 4-(*tert*-butyl)benzyl bromide [14] (0.45 g, 2.0 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) in DMF (10 mL) was stirred at rt for 18 h. The mixture was added to water (50 mL) and extracted with CH_2Cl_2 (20 cm^2) followed by Et_2O (3 × 20 mL). The combined organic layers were then washed with water (3 × 25 mL), brine (3 × 25 mL), dried, and evaporated. Purification of the residue via flash column chromatography (gradient elution hexane/EtOAc 1:1 to 100% EtOAc) gave **13a** (140 mg, 17%) as a colourless oil; ν_{max}/cm^{-1} 2959, 2932, 2870, 1597, 1503, 1207, 1126, 1034, 951, 827, 820, 729, and 546; ^{1}H NMR (400 MHz): 7.73 (2H, dd, J_{HP} = 12.2, J_{HH} = 8.8 Hz, ArH), 7.42 (2H, d, J = 8.4 Hz, ArH), 7.36 (2H, d, J = 8.4 Hz, ArH), 7.02 (2H, dd, J_{HH} = 8.8, J_{HP} = 3.0 Hz, ArH), 5.05 (2H, s, OCH_2Ph), 4.08 (2H, app quintet, J = 7.1 Hz, $OC\boldsymbol{H}_2CH_3$), 2.84 (2H, dtd, J = 8.9, 7.0, 1.8 Hz, $NHC\boldsymbol{H}_2$), 1.46−1.39 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.33 (9H, s, $C(CH_3)_3$), 1.31−1.24 (2H, m, $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.86 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 161.4 (d, J = 3.2 Hz, C-O), 151.1 (C), 133.2 (d, J = 11.0 Hz, 2CH), 133.1 (C), 127.3 (2CH), 125.4 (2CH), 122.4 (d, J = 179.0 Hz, C-P), 114.5 (d, J = 15.1 Hz, 2CH), 69.7 (OCH_2Ph), 60.1 (d, J = 5.5 Hz, $O\boldsymbol{C}H_2CH_3$), 40.5 ($NHCH_2$), 34.5 (C), 33.8 (d, J = 6.3 Hz, $NHCH_2\boldsymbol{C}H_2$), 31.2 ($C(\boldsymbol{C}H_3)_3$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, J = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +23.5; HRMS (ESI^+): found 404.2335. $C_{23}H_{35}NO_3P$ (M + H) requires 404.2355.

2.5.2. Ethyl *N*-Butyl-*P*-(4-(4-methoxybenzyloxy)phenyl)phosphonamidate **13b**

The same procedure as in 2.5.1 using ethyl *N*-butyl-*P*-(4-hydroxyphenyl)phosphonamidate **12** (0.51 g, 2.0 mmol), 4-methoxybenzyl bromide (0.40 g, 2.0 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) in DMF (10 mL) followed by purification of the product via flash column chromatography (EtOAc) gave **13b** (110 mg, 15%) as a colourless solid, mp 124−126 °C; ν_{max}/cm^{-1} 3215, 2957, 2936, 2866, 1612, 1597, 1516, 1389, 1253, 1213, 1036, 1024, 1001, 953, 893, 814, 783, 575, 548, 532, and 525; ^{1}H NMR (400 MHz): 7.73 (2H, dd, J_{HP} = 12.4, J_{HH} = 8.6 Hz, ArH), 7.35 (2H, d, J = 8.7 Hz, ArH), 7.01 (2H, dd, J_{HH} = 8.6, J_{HP} = 2.9 Hz, ArH), 6.91 (2H, d, J = 8.7 Hz, ArH), 5.01 (2H, s, OCH_2Ph), 4.07 (2H, app quintet, J = 7.2 Hz, $OC\boldsymbol{H}_2CH_3$), 3.81 (3H, s, OCH_3), 2.87−2.81 (2H, m, $NHC\boldsymbol{H}_2$), 1.47−1.38 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.36−1.24 (5 H, m, $OCH_2C\boldsymbol{H}_3$ and $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.86 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 161.4 (d, J_{CP} = 3.0 Hz, C-O), 159.5 ($\boldsymbol{C}$-OCH_3), 133.3 (d, J_{CP} = 11.0 Hz, 2CH), 129.2 (2CH), 128.2 (C), 122.4 (d, J_{CP} = 178.8 Hz, C-P), 114.6 (d, J_{CP} = 15.1 Hz, 2CH), 113.9 (2CH), 69.6 (OCH_2Ph), 60.2 (d, J_{CP} = 5.4 Hz, $O\boldsymbol{C}H_2CH_3$), 55.2 (OCH_3), 40.5 ($NHCH_2$), 33.8 (d, J_{CP} = 6.3 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +23.5; HRMS (ESI^+) found 378.1815. $C_{20}H_{29}NO_4P$ (M + H) requires 378.1834.

2.5.3. Ethyl *N*-Butyl-*P*-(4-(4-fluorobenzyloxy)phenyl)phosphonamidate **13c**

A solution of NaI (0.33 g, 2.2 mmol) in acetone (5 mL) was added to 4-fluorobenzyl chloride (0.26 mL, 0.32 g, 2.2 mmol) in acetone (5 mL) and the mixture was stirred until no further precipitation of NaCl was observed. The solution was then filtered, and the filtrate evaporated to give 4-fluorobenzyl iodide. This was then reacted as in 2.5.1 with ethyl *N*-butyl-*P*-(4-hydroxyphenyl)phosphonamidate **12** (0.51 g, 2.0 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) in DMF (10 mL) to give **13c** (110 mg, 15%) as a colourless solid which was used without further purification; mp 72−74 °C; ν_{max}/cm^{-1} 3200, 2957, 2930, 2872, 1599, 1512, 1225, 1209, 1126, 1034, 1009, 951, 824, 565, 538, and 525; ^{1}H NMR (400 MHz): 7.74 (2H, dd, J_{HP} = 12.4, J_{HH} = 8.8 Hz, ArH), 7.41 (2H, dd, J_{HH} = 8.6, J_{HF} = 5.6 Hz, ArH), 7.08 (2H, t, *J* = 8.6 Hz, ArH), 7.01 (2H, dd, J_{HH} = 8.8, J_{HP} = 2.9 Hz, ArH), 5.06 (2H, s, OCH_2Ph); 4.08 (2H, app quintet, *J* = 7.2 Hz, $OC\boldsymbol{H}_2CH_3$), 2.88−2.80 (2 H, m, $NHC\boldsymbol{H}_2$), 1.47−1.38 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.36−1.26 (5H, m, $OCH_2C\boldsymbol{H}_3$ and $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.86 (3H, t, *J* = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 162.5 (d, J_{CF} = 252.2 Hz, C-F), 161.2 (d, J_{CP} = 8.7 Hz, C-O), 133.4 (d, J_{CP} = 11.0 Hz, 2CH), 132.2 (d, J_{CF} = 3.1 Hz, C), 129.3 (d, J_{CF} = 8.2 Hz, 2CH), 122.7 (d, J_{CP} = 178.8 Hz, C-P), 115.5 (d, J_{CF} = 21.6 Hz, 2CH), 114.6 (d, J_{CP} = 15.1 Hz, 2CH), 69.2 (OCH_2Ph), 60.3 (d, J_{CP} = 5.4 Hz, $O\boldsymbol{C}H_2CH_3$), 40.5 ($NHCH_2$), 33.8 (d, J_{CP} = 6.3 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.4 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{19}F NMR (376 MHz): −113.8; ^{31}P NMR (162 MHz): +23.2; HRMS (ESI$^+$): found 366.1624. $C_{19}H_{26}FNO_3P$ (M + H) requires 366.1634.

2.5.4. Ethyl *N*-Butyl-*P*-(4-(1-phenylethoxy)phenyl)phosphonamidate **13d**

The same procedure as in 2.5.1 using ethyl *N*-butyl-*P*-(4-hydroxyphenyl)phosphonamidate **12** (0.51 g, 2.0 mmol), (1-bromoethyl)benzene (0.27 mL, 0.37 g, 2.0 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) in DMF (10 mL) gave, after purification via flash column chromatography (hexane/EtOAc 1:1) at R_f 0.21, **13d** (150 mg, 13%) as a colourless oil; ν_{max}/cm^{-1} 2959, 2932, 2872, 1597, 1501, 1450, 1288, 1246, 1206, 1126, 1028, 953, 760, 700, 571, and 542; ^{1}H NMR (400 MHz): 7.62 (2H, dd, J_{HP} = 12.3, J_{HH} = 8.8 Hz, ArH), 7.36−7.28 (4H, m, ArH), 7.28−7.24 (1H, m, ArH), 6.89 (2H, dd, J_{HH} = 8.8, J_{HP} = 3.1 Hz, ArH), 5.36 (1H, q, *J* = 6.4 Hz, $OC\boldsymbol{H}(Ph)CH_3$), 4.07−4.00 (2H, m, OCH_2), 2.84−2.76 (2H, m, $NHC\boldsymbol{H}_2$), 2.69 (1H, br s, NH), 1.65 (3H, d, *J* = 6.4 Hz, $OCH(Ph)C\boldsymbol{H}_3$), 1.41−1.34 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.32−1.26 (5H, m, $OCH_2C\boldsymbol{H}_3$ and $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.84 (3H, t, *J* = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 160.7 (d, J_{CP} = 3.0 Hz, C-O), 142.4 (C), 133.1 (d, J_{CP} = 11.0 Hz, 2CH), 128.6 (2CH), 127.6 (CH), 125.4 (2CH), 121.9 (d, J_{CP} = 179.4 Hz, C-P), 115.5 (d, J_{CP} = 15.1 Hz, 2CH), 75.9 ($OC\boldsymbol{H}(Ph)CH_3$), 60.2 (d, J_{CP} = 5.4 Hz, OCH_2), 40.5 ($NHCH_2$), 33.8 (d, J_{CP} = 6.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 24.4 ($OCH(Ph)\boldsymbol{C}H_3$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, J_{CP} = 6.8 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +23.5; HRMS (ESI$^+$): found 362.1873. $C_{20}H_{29}NO_3P$ (M + H) requires 362.1885.

2.5.5. Ethyl *N*-Butyl-*P*-(4-(3-methylbut-2-en-1-yloxy)phenyl)phosphonamidate **13e**

The same procedure as in 2.5.1 using *N*-butyl-*P*-(4-hydroxyphenyl)phosphonamidate **12** (0.51 g, 2.0 mmol), 3-methylbut-2-en-1-yl bromide (0.30 g, 2.0 mmol), and K_2CO_3 (0.30 g, 6.0 mmol) in DMF (10 mL) but with reaction at 100 °C for 6 h gave, after purification via flash column chromatography (gradient elution hexane/EtOAc 7:3 to 100% EtOAc), **13e** (80 mg, 12%) as a yellow oil; ν_{max}/cm^{-1} 2957, 2930, 2872, 1599, 1503, 1292, 1204, 1126, 1034, 951, 829, 804, 569, and 534; ^{1}H NMR (500 MHz): 7.71 (2H, dd, J_{HP} = 12.3, J_{HH} = 8.7 Hz, ArH), 6.95 (2H, dd, J_{HH} = 8.7, J_{HP} = 3.0 Hz, ArH), 5.48 (1H, ddq, *J* = 6.8, 5.4, 1.5 Hz, $OCH_2C\boldsymbol{H}$), 4.55 (2H, d, *J* = 6.9 Hz, $OC\boldsymbol{H}_2CH$), 4.09−4.05 (2H, m, $OC\boldsymbol{H}_2CH_3$), 2.87−2.82 (2H, m, $NHC\boldsymbol{H}_2$), 1.80 (3H, s, $C(C\boldsymbol{H}_3)(CH_3)$, 1.75 (3H, s, $C(CH_3)(C\boldsymbol{H}_3)$, 1.46−1.40 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.34 (3H, t, *J* = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$), 1.31−1.27 (2H, m, $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.86 (3H, t, *J* = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 161.6 (d, J_{CP} = 3.1 Hz, C-O), 138.8 ($CH{=}\boldsymbol{C}$), 133.3 (d, J_{CP} = 11.1 Hz, 2CH), 121.8 (d, J_{CP} = 179.6 Hz, C-P), 119.0 ($\boldsymbol{C}H{=}C$), 114.5 (d, J_{CP} = 15.2 Hz, 2CH), 64.8 ($O\boldsymbol{C}H_2CH{=}C$), 60.3 (d, J_{CP} = 5.5 Hz, $O\boldsymbol{C}H_2CH_3$), 40.6 ($NHCH_2$), 33.8 (d, J_{CP} = 6.4 Hz, $NHCH_2\boldsymbol{C}H_2$), 25.8 ($CH{=}C(\boldsymbol{C}H_3)CH_3$), 19.8 ($NHCH_2CH_2\boldsymbol{C}H_2$), 18.2 ($CH{=}C(CH_3)\boldsymbol{C}H_3$), 16.4 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.7 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +23.6; HRMS (ESI$^+$): found 348.1692. $C_{17}H_{28}NaNO_3P$ (M + Na) requires *M*, 348.1704.

2.6. Rearrangement of Substituted Ethyl N-Butyl-P-(4-benzyloxyphenyl)phosphonamidates

2.6.1. Ethyl *N*-Butyl-*P*-(4-(4-(tert-butylphenyl(hydroxy)methyl)phenyl)phosphonamidate **14a**

Following the method of 2.3.4 using ethyl *N*-butyl-*P*-(4-(4-*tert*-butylbenzyloxy)phenyl) phosphonamidate **13a** (80.7 mg, 0.2 mmol) and *n*-butyllithium (0.37 mL, 0.66 mmol) in THF (2 mL) at rt for 1 h gave, after purification via preparative TLC (EtOAc) at R_f 0.28, **14a** (50.9 mg, 63%) as a yellow oil; ν_{max}/cm^{-1} 3250, 2959, 2932, 2870, 1603, 1460, 1395, 1198, 1125, 1105, 1034, 957, 685, 581, and 534; ^{1}H NMR (400 MHz): 7.69 (2H, dd, J_{HP} = 12.6, J_{HH} = 8.1 Hz, ArH), 7.46 (2H, dd, J_{HH} = 8.1, J_{HP} = 3.6 Hz, ArH), 7.34 (2H, d, J = 8.4 Hz, ArH), 7.26 (2H, d, J = 8.4 Hz, ArH), 5.82 (1H, s, C***H***OH), 4.10−4.01 (2H, m, OCH_2), 2.86−2.77 (2H, m, $NHC\boldsymbol{H}_2$), 1.42−1.36 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.34−1.27 (14H, m, $OCH_2C\boldsymbol{H}_3$, $NHCH_2CH_2C\boldsymbol{H}_2$ and $C(CH_3)_3$), and 0.84 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 150.6 (C), 148.0 (d, J_{CP} = 2.9 Hz, C), 140.5 (C), 131.4 (d, J_{CP} = 10.1 Hz, 2CH), 129.3 (d, J_{CP} = 174.3 Hz, C-P), 126.5 (2CH), 126.4 (d, J_{CP} = 14.3 Hz, 2CH), 125.4 (2CH), 75.5 (CHOH), 60.4 (d, J_{CP} = 5.6 Hz, $O\boldsymbol{C}H_2CH_3$), 40.6 ($NHCH_2$), 34.5 (C), 33.8 (d, J_{CP} = 6.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 31.3 ($C(\boldsymbol{C}H_3)_3$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.4 (d, J_{CP} = 6.8 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.7 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +22.9; HRMS (ESI$^+$): found 404.2347. $C_{23}H_{35}NO_3P$ (M + H) requires 404.2355.

2.6.2. Ethyl *N*-Butyl-*P*-(4-(Hydroxy(4-methoxyphenyl)methyl)phenyl)phosphonamidate **14b**

Following the method of 2.3.4 using Ethyl *N*-butyl-*P*-(4-(4-methoxybenzyloxy)phenyl) phosphonamidate **13b** (75.5 mg, 0.2 mmol) and *n*-butyllithium (0.37 mL, 0.66 mmol) in THF (2 mL) at rt for 2 h gave, after purification via preparative TLC (EtOAc) at R_f 0.15, **14b** (36.7 mg, 49%) as a yellow oil; ν_{max}/cm^{-1} 3270, 2957, 2932, 2872, 1068, 1510, 1246, 1171, 1125, 1030, 959, 766, 590, 571, and 565; ^{1}H NMR (400 MHz): 7.70 (2H, dd, J_{HP} = 12.7, J_{HH} = 8.2 Hz, ArH), 7.43 (2H, dd, J_{HH} = 8.2, J_{HP} = 3.5 Hz, ArH), 7.25 (2H, d, J = 8.7 Hz, ArH), 6.85 (2H, d, J = 8.7 Hz, ArH), 5.81 (1H, s, C***H***OH), 4.13−4.01 (2H, m, $OC\boldsymbol{H}_2CH_3$), 3.78 (3H, s, OCH_3), 2.84−2.77 (2H, m, $NHC\boldsymbol{H}_2$), 1.42−1.36 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.32 (3H, t, J = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$), 1.29−1.23 (2H, m, $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.84 (3H, t, J = 7.3 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (100 MHz): 159.1 (C-O), 148.0 (d, J_{CP} = 2.9 Hz, C), 135.8 (C), 131.5 (d, J_{CP} = 10.1 Hz, 2CH), 129.4 (d, J_{CP} = 174.7 Hz, C-P), 128.0 (2CH), 126.3 (d, J_{CP} = 14.5 Hz, 2CH), 113.9 (2CH), 75.3 (CHOH), 60.4 ($O\boldsymbol{C}H_2CH_3$), 55.2 (OCH_3), 40.6 ($NHCH_2$), 33.8 (d, J_{CP} = 6.1 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2C\boldsymbol{H}_2$), 16.4 (d, J_{CP} = 6.8 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.7 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +22.8; HRMS (ESI$^+$): found 400.1646. $C_{20}H_{28}NaNO_4P$ (M + Na) requires 400.1654.

2.6.3. Ethyl *N*-Butyl-*P*-(4-(4-fluorophenyl(hydroxy)methyl)phenyl)phosphonamidate **14c**

Following the method of 2.3.4 using ethyl *N*-butyl-*P*-(4-(4-fluorobenzyloxy)phenyl) phosphonamidate **13c** (73.1 mg, 0.2 mmol) and *n*-butyllithium (0.27 mL, 0.66 mmol) in THF (2 mL) at rt for 2 h gave, after purification via preparative TLC (hexane/EtOAc 1:1) at R_f 0.27, **14c** (49.3 mg, 67%) as a pale-yellow oil; ν_{max}/cm^{-1} 3258, 2957, 2932, 2872, 1603, 1506, 1396, 1219, 1120, 1125, 1030, 957, 767, 588, and 569; ^{1}H NMR (400 MHz): 7.69 (2H, dd, J_{HP} = 12.7, J_{HH} = 8.2 Hz, ArH), 7.44 (2H, dd, J_{HH} = 8.2, J_{HP} = 3.6 Hz, ArH), 7.34 (2H dd, J_{HH} = 8.4, J_{HF} = 5.4 Hz, ArH), 7.00 (2H, t, J = 8.5 Hz, ArH), 5.82 (1H, s, C***H***OH), 4.11−4.06 (2H, m, OCH_2), 2.85−2.80 (2H, m, $NHC\boldsymbol{H}_2$), 1.44−1.39 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.36−1.33 (5H, m, $OCH_2C\boldsymbol{H}_3$ and $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.84 (3H, t, J = 7.2 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 162.1 (d, J_{CF} = 246.0 Hz, C-F), 147.9 (d, J_{CP} = 2.6 Hz, C), 139.4 (d, J_{CF} = 2.9 Hz, C), 131.5 (d, J_{CP} = 10.1 Hz, 2CH), 129.7 (d, J_{CP} = 174.5 Hz, C-P), 128.4 (d, J_{CF} = 8.1 Hz, 2CH), 126.4 (d, J_{CP} = 14.5 Hz, 2CH), 115.3 (d, J_{CF} = 21.4 Hz, 2CH), 74.9 (CHOH), 60.5 (d, J_{CP} = 5.6 Hz, OCH_2), 40.6 ($NHCH_2$), 33.8 (d, J_{CP} = 6.1 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.4 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{19}F NMR (376 MHz): −114.8; ^{31}P NMR (162 MHz): +22.7; HRMS (ESI$^+$): found 366.1620. $C_{19}H_{26}FNO_3P$ (M + H) requires 366.1634.

2.6.4. Ethyl *N*-Butyl-*P*-(4-(1-hydroxy-1-phenylethyl)phenyl)phosphonamidate **14d**

Following the method of 2.3.4 using Ethyl *N*-butyl-*P*-(4-(1-phenylethoxy)phenyl) phosphonamidate **13d** (72.2 mg, 0.2 mmol), *n*-butyllithium (0.26 mL, 0.66 mmol) and THF (2 mL) gave, after purification via preparative TLC (hexane/EtOAc 1:1) at R_f 0.09, **14d** (28.6 mg, 40%) as a pale-yellow oil; ν_{max}/cm^{-1} 3250, 2957, 2932, 2872, 1599, 1447, 1394, 1198, 1126, 1098, 1030, 959, 764, 731, 698, 656, 594, and 569; ^{1}H NMR (300 MHz): 7.73 (2H, dd, J_{HP} = 12.5, J_{HH} = 8.3 Hz, ArH), 7.51 (2H, dd, J_{HH} = 8.3, J_{HP} = 3.5 Hz, ArH), 7.45−7.39 (2H, m, ArH), 7.37−7.31 (2H, m, ArH), 7.29−7.23 (1H, m, ArH), 4.08 (2H, app quintet, *J* = 7.3 Hz, OCH_2), 2.87−2.75 (3H, m, N***H***CH_2), 1.95 (3H, s, O(C)CH_3), 1.48−1.39 (2H, m, $NHCH_2C\boldsymbol{H_2}$), 1.40−1.31 (5H, m, $OCH_2C\boldsymbol{H_3}$ and $NHCH_2CH_2C\boldsymbol{H_2}$), and 0.85 (3H, t, *J* = 7.2 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H_3}$); ^{13}C NMR (100 MHz): 151.9 (d, J_{CP} = 2.8 Hz, ***C***-C-OH), 147.4 (C), 131.3 (d, J_{CP} = 10.1 Hz, 2CH), 129.2 (d, J_{CP} = 174.7 Hz, C-P), 128.2 (2CH), 127.2 (CH), 125.83 (2CH), 125.82 (d, J_{CP} = 14.4 Hz, 2CH), 76.0 (C-OH), 60.4 (d, J_{CP} = 5.6 Hz, OCH_2), 40.6 ($NHCH_2$), 33.8 (d, J_{CP} = 6.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 30.6 (C-***C***H_3), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.4 (d, J_{CP} = 6.8 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.7 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +22.7; HRMS (ESI$^+$): found 362.1878. $C_{20}H_{29}NO_3P$ (M + H) requires 362.1885.

2.7. 1-(Benzyloxy)-3-bromobenzene **15**

To a stirred solution of 3-bromophenol (10.0 g, 58.2 mmol) in MeCN (150 mL) at rt was added K_2CO_3 (10.94 g, 79.2 mmol) and benzyl bromide (6.9 mL, 9.94 g, 58.2 mmol) and the mixture stirred at rt overnight. The reaction was diluted with H_2O (150 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give **15** (15.61 g, quant) as a colourless solid which was used without further purification; mp 58−60 °C; (lit. [e5] 61–62 °C); ^{1}H NMR (400 MHz): 7.42–7.36 (4H, m, ArH), 7.36−7.30 (1H, m, ArH), 7.15−7.10 (2H, m, ArH), 7.08 (1H, dt, *J* = 7.9, 1.4 Hz, ArH), 6.89 (1H, ddd, *J* = 7.9, 2.5, 1.4 Hz, ArH), and 5.02 (2H, s, OCH_2); ^{13}C NMR (100 MHz): 159.6 (C-O), 136.5 (C-Br), 130.7 (CH), 128.8 (2CH), 128.3 (CH), 127.6 (2CH), 124.2 (CH), 122.9 (C), 118.3 (CH), 113.9 (CH), and 70.3 (OCH_2). The ^{1}H and ^{13}C spectral data were in accordance with that previously reported [15].

2.8. Synthesis and Rearrangement of Ethyl P-(3-Benzyloxy)phenyl)-N-butylphosphonamidate **18**

2.8.1. Diethyl (3-(Benzyloxy)phenyl)phosphonate **16**

Following the method of 2.3.1 using 1-(benzyloxy)-3-bromobenzene **15** (14.00 g, 53.2 mmol), $P(OEt)_3$ (11.0 mL, 63.8 mmol), and $NiCl_2$ (689 mg, 5.32 mmol) gave, after purification via flash column chromatography (gradient elution hexane/EtOAc 9:1 to 100% ethyl acetate), **16** (15.43 g, 91%) as a yellow oil; ν_{max}/cm^{-1} 1591, 1576, 1483, 1420, 1391, 1244, 1016, 959, 785, 743, 693, and 561; ^{1}H NMR (400 MHz): 7.48−7.31 (8H, m, ArH), 7.20−7.14 (1H, m, ArH), 5.10 (2H, s, OCH_2Ph), 4.18−4.05 (4H, m, 2 x $OC\boldsymbol{H_2}CH_3$), and 1.31 (6H, t, *J* = 7.1 Hz, 2 x $OCH_2C\boldsymbol{H_3}$); ^{13}C NMR (125 MHz): 158.5 (d, J_{CP} = 18.9 Hz, C-O), 136.3 (C), 129.7 (d, J_{CP} = 17.5 Hz, CH), 129.5 (d, J_{CP} = 186.6 Hz, C-P), 128.5 (2CH), 128.0 (CH), 127.4 (2CH), 124.1 (d, J_{CP} = 9.1 Hz, CH), 119.4 (d, J_{CP} = 3.2 Hz, CH), 117.3 (d, J_{CP} = 11.3 Hz, CH), 70.0 (OCH_2Ph), 62.1 (d, J_{CP} = 5.4 Hz, 2 x $O\boldsymbol{C}H_2CH_3$), and 16.2 (d, J_{CP} = 6.5 Hz, 2 x $OCH_2\boldsymbol{C}H_3$); ^{31}P NMR (162 MHz): +18.5; HRMS (ESI$^+$): found 343.1059. $C_{17}H_{21}NaO_4P$ (M + Na) requires 343.1075.

2.8.2. Ethyl (3-Benzyloxy)phenyl)phosphonochloridate **17**

Following the method of 2.3.2 using diethyl (3-benzyloxylphenyl)phosphonate **16** (2.00 g, 6.2 mmol) and PCl_5 (2.60 g, 12.5 mmol) in toluene (40 mL) gave **17** (1.77 g, 91%) as a yellow oil which was used without further purification; ^{1}H NMR (400 MHz): 7.54−7.50 (1H, m, ArH), 7.47−7.34 (7H, m, ArH), 7.25−7.19 (1H, m, ArH), 5.11 (2H, s, OCH_2Ph), 4.49−4.33 (2H, m, $OC\boldsymbol{H_2}CH_3$), and 1.46 (3H, dt, *J* = 7.1, 1.5 Hz, $OCH_2C\boldsymbol{H_3}$); ^{13}C NMR (100 MHz): 158.6 (d, J_{CP} = 21.6 Hz, C-O), 136.1 (C), 131.7 (d, J_{CP} = 179.2 Hz, C-O), 130.1 (d, J_{CP} = 20.0 Hz, CH), 128.7 (2CH), 128.2 (CH), 127.6 (2CH), 123.4 (d, J_{CP} = 11.0 Hz, CH), 120.6

(d, J_{CP} = 3.6 Hz, CH), 116.6 (d, J_{CP} = 13.7 Hz, CH), 70.3 (OCH_2Ph), 63.9 (d, J_{CP} = 7.6 Hz, $OC\boldsymbol{H}_2CH_3$), and 16.0 (d, J_{CP} = 7.5 Hz, $OCH_2C\boldsymbol{H}_3$); ^{31}P NMR (162 MHz): +28.9.

2.8.3. Ethyl *P*-(3-Benzyloxyphenyl)-*N*-butylphosphonamidate **18**

Following the method of 2.3.3 using ethyl (3-benzyloxyphenyl)phosphonochloridate **17** (1.77 g, 5.7 mmol) in Et_2O (50 mL) and *n*-butylamine (1.20 mL, 0.89 g, 12.5 mmol) in Et_2O (50 mL) gave, after purification via flash column chromatography (EtOAc/hexane 7:3) at R_f 0.29, **18** (600 mg, 30%) as a colourless solid, mp 62−65 °C; ν_{max}/cm^{-1} 2955, 2930, 2864, 1589, 1454, 1418, 1250, 1207, 1126, 1026, 947, 731, 692, and 555; ^{1}H NMR (400 MHz): 7.45−7.29 (8H, m, ArH), 7.12−7.07 (1H, m, ArH), 5.07 (2H, s, OCH_2Ph), 4.08 (2H, app quintet, *J* = 7.2 Hz, $OC\boldsymbol{H}_2CH_3$); 3.02 (1H, br s, NH), 2.87−2.79 (2H, m, $NHC\boldsymbol{H}_2$), 1.46−1.36 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.33 (3H, t, *J* = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$), 1.31−1.23 (2H, m, $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.85 (3H, t, *J* = 7.4 Hz, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 158.3 (d, J_{CP} = 17.8 Hz, C-O), 136.4 (C), 132.4 (d, J_{CP} = 171.2 Hz, C-O), 129.4 (d, J_{CP} = 16.6 Hz, CH), 128.4 (2CH), 127.8 (CH), 127.3 (2CH), 123.6 (d, J_{CP} = 9.1 Hz, CH), 118.4 (d, J_{CP} = 2.4 Hz, CH), 117.0 (d, J_{CP} = 10.9 Hz, CH), 69.9 (OCH_2Ph), 60.2 (d, J_{CP} = 5.5 Hz, $O\boldsymbol{C}H_2CH_3$), 40.4 ($NHCH_2$), 33.7 (d, *J* = 6.1 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.6 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.2 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.5 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (202 MHz): +22.5; HRMS (ESI$^+$): found 348.1713. $C_{19}H_{27}NO_3P$ (M + H) requires 348.1729.

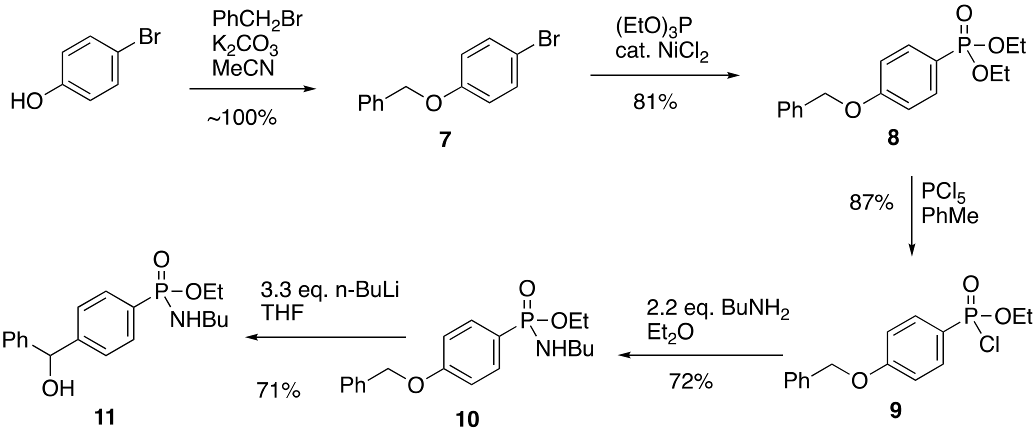
2.8.4. Ethyl *N*-Butyl-*P*-(3-(hydroxy(phenyl)methyl)phenyl)phosphonamidate **19**

Following the method of 2.3.4 using ethyl *P*-(3-benzyloxyphenyl)-*N*-butylphosphonamidate **18** (173.7 mg, 0.5 mmol) and *n*-butyllithium (0.91 mL, 1.65 mmol) in THF (5 mL) at rt for 20 min gave, after purification via preparative TLC (EtOAc) **19** (73.7 mg, 42%) as a yellow oil as an inseparable 1:1 mixture of diastereomers; ν_{max}/cm^{-1} 3234, 2959, 2932, 2872, 1452, 1420, 1188, 1117, 1032, 957, 908, 729, 698, 556, and 525; ^{1}H NMR (500 MHz): 7.86−7.79 (1H, m, ArH), 7.65−7.59 (1H, m, ArH), 7.54−7.46 (1H, m, ArH), 7.39−7.33 (3H, m, ArH), 7.31−7.27 (2H, m, ArH), 7.25−7.22 (1H, m, ArH), 5.824 and 5.816 (2 × 1 H, s, C$\boldsymbol{H}$OH diastereomer 1 and 2), 4.06−3.98 (2H, m, OCH_2), 2.81−2.74 (2H, m, $NHC\boldsymbol{H}_2$), 1.36−1.32 (2H, m, $NHCH_2C\boldsymbol{H}_2$), 1.31−1.27 (3H, m, $OCH_2C\boldsymbol{H}_3$), 1.25−1.20 (2H, m, $NHCH_2CH_2C\boldsymbol{H}_2$), and 0.84−0.80 (3H, m, $NHCH_2CH_2CH_2C\boldsymbol{H}_3$); ^{13}C NMR (125 MHz): 144.7 (d, J_{CP} = 13.7 Hz, C), 143.8 (d, J_{CP} = 5.2 Hz, C), 130.71 and 130.64 (2 x d, J_{CP} = 179.8 Hz, P–C), 130.20 and 130.17 (2 x d, J_{CP} = 9.5 Hz, CH), 130.01 and 129.99 (2 x d, J_{CP} = 16.4 Hz, CH), 129.46 and 129.43 (2 x d, J_{CP} = 10.6 Hz, CH), 128.39 and 128.38 (2 x d, J_{CP} = 13.6 Hz, CH), 128.4 (2CH), 127.4 (CH), 126.60 and 126.56 (2CH), 75.5 (CHOH), 60.4 (d, J_{CP} = 5.7 Hz, OCH_2), 40.5 ($NHCH_2$), 33.7 (d, J_{CP} = 6.2 Hz, $NHCH_2\boldsymbol{C}H_2$), 19.7 ($NHCH_2CH_2\boldsymbol{C}H_2$), 16.3 (d, J_{CP} = 6.7 Hz, $OCH_2\boldsymbol{C}H_3$), and 13.6 ($NHCH_2CH_2CH_2\boldsymbol{C}H_3$); ^{31}P NMR (202 MHz): +22.9; HRMS (ESI$^+$): found 348.1713. $C_{19}H_{27}NO_3P$ (M + H) requires 348.1729.

3. Results and Discussion

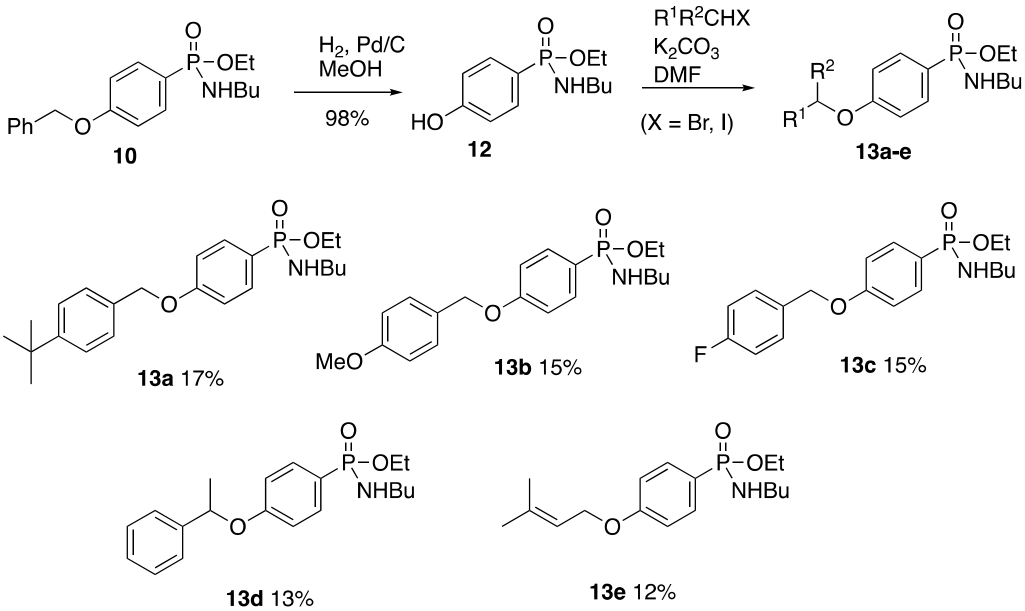
Starting from 4-bromophenol, the known benzyl ether **7** was prepared in essentially quantitative yield (Scheme 2). The phosphonate functionality was installed by the nickel-catalysed Michaelis–Arbuzov-type reaction with triethyl phosphite introduced by Tavs [10]. We found that to obtain a good yield of product **8,** it was essential to use anhydrous nickel(II) chloride. The diethyl phosphonate **8** was treated with phosphorus pentachloride in toluene to afford **9** which reacted directly with two equivalents of butylamine giving phosphonamidate **10**.

The Wittig rearrangement of compound **10** occurred readily on treatment with 3.3 equiv. of n-butyllithium in THF at RT to afford the benzhydrol-4-phosphonamidate **11** in good yield. The process creates a new stereogenic centre but the C and P centres are too far apart to affect one another and only a single set of NMR signals was observed for what is almost inevitably an equal mixture of all four possible diastereomers. The rearrangement was most obvious from the change from $PhCH_2O$ [δ_H 5.09 (2H, s), δ_C 69.8] to PhCH(OH) [δ_H 5.85 (1H, s), δ_C 75.7] (see Supplementary Materials).



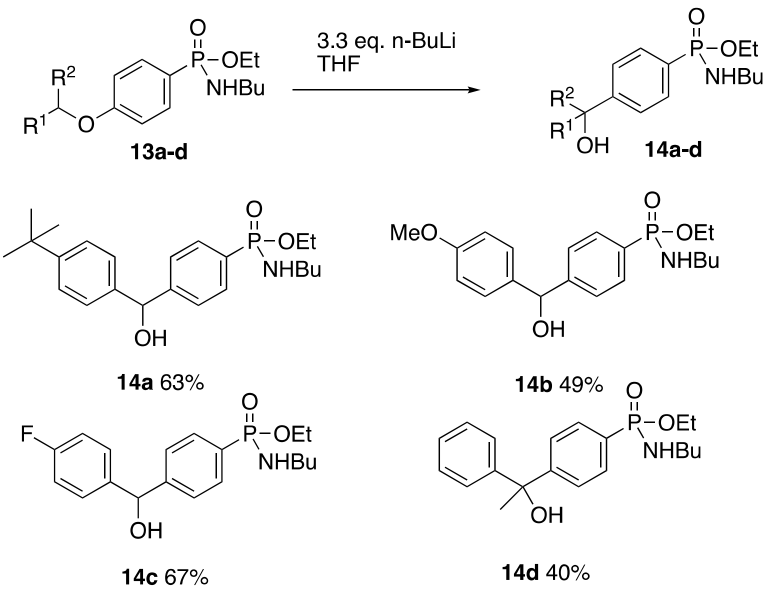
Scheme 2. Stepwise synthesis and Wittig rearrangement of *para* compound **10**.

We now wished to explore the scope of the process for substituted benzyl and other analogous groups and, rather than repeat the four-step synthetic sequence used for **10** with different benzyl halides, we were able to remove the *O*-benzyl group from **10** in excellent yield using catalytic hydrogenation to give the hydroxyphenylphosphonamidate **12**. This was then *O*-alkylated to give a range of derivatives **13a–e** (Scheme 3). The low yield of these after chromatographic purification was disappointing and compound **12** seems to be deactivated towards *O*-alkylation. In each case, there was a significant amount of unreacted **12** remaining even after overnight reaction and the products partly decomposed during chromatography, resulting in a poor recovery. Despite this, the products were obtained in sufficient quantity for full characterisation and a study of their reactivity. All the phosphonamidates in this paper show ^{31}P signals in the narrow range δ_P +22.5–25.6, and the expected phosphorus coupling is observed in the ^{13}C NMR spectra for all signals of the phosphorus-bearing benzene ring, both carbons of OEt but interestingly only C–2 of NHBu.



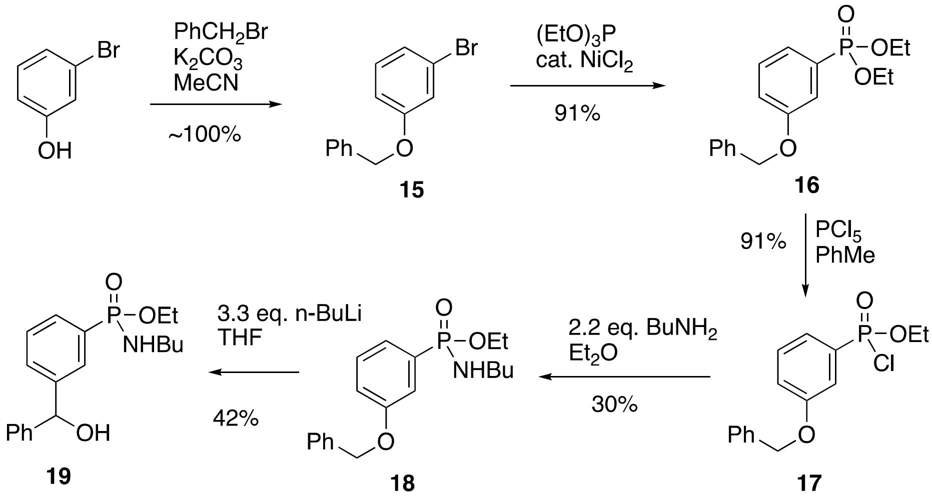
Scheme 3. Synthesis of phenylphosphonamidates with different substituents at the 4-position.

When compounds **13a–d** were subjected to treatment with butyllithium under the same conditions as for **10**, the Wittig rearrangement was again observed and the products **14a–d** were obtained in moderate to good yield (Scheme 4). The 3-methylbut-2-enyl ("prenyl") ether **13e** did give some indication of forming the rearranged product but this was accompanied by a myriad of other byproducts from which it could not be separated, so we conclude that the process is not likely to be useful for such non-benzylic allyl ethers. This is consistent with the corresponding *N*-butyl carboxamides **5** where the prenyl ether did rearrange in the *para*-position, but in low yield [7].



Scheme 4. Wittig rearrangement of substituted examples.

We now turned to the isomeric *meta*-substituted system and starting from 3-bromophenol, the same four-step sequence as for **10** gave the desired product **18** by way of intermediates **15**, **16**, and **17** (Scheme 5). Only the final stage was rather low yielding.



Scheme 5. Stepwise synthesis and Wittig rearrangement of *meta* compound **18**.

When compound **18** was subjected to the usual rearrangement conditions, the expected product **19** was obtained in moderate yield. Now for the first time, the two stereogenic centres were close enough to affect one another and this compound showed doubling of the ^{13}C NMR signals for the phosphorus-bearing benzene ring carbons and the *ortho*-CHs of the other benzene ring, indicating a 1:1 mixture of diastereomers for the (racemic) compound.

In conclusion, the phosphonamidate group EtO-P(=O)-NHBu is effective in promoting the Wittig rearrangement of *meta*- or *para*-disposed aryl benzyl ethers, allowing access to novel phosphonamidate-substituted diarylmethanols. We have also investigated the synthesis and base-treatment of the corresponding *ortho*-benzyloxyphenylphosphonamidates but this takes a quite different course as will be reported shortly.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org4010005/s1, Figures S1–S57: ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra of all new compounds.

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Conflicts of Interest: The authors declare no conflict of interest.

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