Phosphoramidate synthesis via copper-catalysed aerobic oxidative coupling of amines and H-phosphonates

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General procedure A for phosphoramidate synthesis

To a stirring suspension of CuI (38 mg, 0.20 mmol) in MeCN (2 mL) was added the H-phosphonate (1.00 mmol) and amine (2.00 mmol). The mixture was stirred at 55 °C for 4-18 h (see Table 2 for time) before cooling to room temperature and diluting with CHCl₃ (50 mL). The organic was washed with 2M HCl (30 mL), saturated NaHCO₃ (30 mL), then dried (Na₂SO₄). Removal of the volatiles in vacuo left the crude product which was purified by silica gel column chromatography (gradient: Et₂O to 5-10% MeOH in CH₂Cl₂).

Diethyl benzylphosphoramidate 3

Following general procedure A, benzylamine (218 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow oil (138 mg, 67%). R_f – 0.46 (10% MeOH in CH₂Cl₂); v_max /cm⁻¹ (CHCl₃ soln) 3424, 2993, 1603, 1496, 1455, 1414, 1247, 1057, 1029 and 971; ¹H NMR (400 MHz, CDCl₃) 7.38 - 7.25 (5 H, m, ArH), 4.16 - 3.99 (6 H, m, CH₂ and OCH₂CH₃), 3.03 - 3.16 (1 H, m, NH), 1.32 (6 H, td, J 7.1 and 0.8, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 139.6 (C), 128.5 (CH), 127.3 (CH), 127.2 (CH), 62.3 (d, J 5, CH₂), 45.3 (CH₂) and 16.1 (d, J 7, CH₃); ³¹P NMR
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(161 MHz, CDCl₃) 8.49; HRMS m/z (ES⁺) Found M + Na 266.0912. C₁₁H₁₈NO₃PNa requires 266.0917.

Dimethyl benzylphosphoramidate 7

Following general procedure A, benzylamine (218 μL, 2.00 mmol) and dimethyl phosphite (92 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow oil (123 mg, 57%). Rf = 0.45 (10% MeOH in CH₂Cl₂); vₘₐₓ /cm⁻¹ (CHCl₃ soln) 3424, 3001, 2954, 1455, 1414, 1252, 1063, 1038 and 853; ¹H NMR (400 MHz, CDCl₃) 7.36 - 7.25 (5 H, m, ArH), 4.10 (2 H, dd, J 10.0 and 7.0, CH₂), 3.70 (6 H, d, J 11.2, OMe) and 3.26 - 3.12 (1 H, m, NH); ¹³C NMR (100 MHz, CDCl₃) 139.5 (C), 128.6 (CH), 127.4 (CH), 127.3 (CH), 53.0 (d, J 5, CH₃) and 45.3 (CH₂); ³¹P NMR (161 MHz, CDCl₃) 11.13; HRMS m/z (ES⁺) Found M + Na 238.0606. C₉H₁₄NO₃PNa requires 238.0604.

Diisopropyl benzylphosphoramidate 8

Following general procedure A, benzyamine (218 μL, 2.00 mmol) and diisopropyl phosphite (168 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow solid (151 mg, 56%). m.p. 48 – 50 °C. Rf = 0.44 (10% MeOH in CH₂Cl₂); vₘₐₓ /cm⁻¹ (CHCl₃ soln) 3009, 2985, 1497, 1454, 1413, 1387, 1376, 1244, 1106, 1019 and 993; ¹H NMR (400 MHz, CDCl₃) 7.38 - 7.23 (5 H, m, ArH), 4.65 (2 H, dspt, J 7.5 and 6.2, OCH(CH₃)₂), 4.11 (2 H, dd, J 9.0 and 7.0, CH₂), 2.88 - 2.73 (1 H, m, NH), 1.36 (6 H, d, J 6.2, OCH(CH₃)₂) and 1.31 (6 H, d, J 6.2, OCH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) 139.8 (C), 128.5 (CH), 127.3 (2CH [overlapping]), 70.9 (d J 6, CH), 45.5 (CH₂) and 23.8 (t, J 4, CH₃).
Diethyl 2-methoxyethylphosphoramidate 9

Following general procedure A, 2-methoxyethylamine (174 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow oil (113 mg, 53%). Rf = 0.72 (10% MeOH in CH₂Cl₂); νmax /cm⁻¹ (CHCl₃ soln) 3421, 2993, 2932, 1602, 1416, 1393, 1245, 1058, 1030 and 970; ¹H NMR (400 MHz, CDCl₃) 4.10 - 3.99 (4 H, m, OCH₂CH₃), 3.41 (2 H, td, J 5.0 and 0.6, C₂H₂), 3.34 (3 H, s, OMe), 3.09 - 2.99 (3 H, m, CH₂ and NH) and 1.30 (6 H, td, J 7.1 and 0.8, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 72.6 (d, J 6, CH₂), 62.2 (d, J 5, CH₂), 58.7 (CH₃), 41.0 (CH₂) and 16.1 (d, J 7, CH₃); ³¹P NMR (161 MHz, CDCl₃) 9.13; HRMS m/z (ES⁺) Found M + Na 234.0873. C₇H₁₈NO₄PNa requires 234.0866.

Diethyl isopentylphosphoramidate 10

Following general procedure A, isoamylamine (232 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow oil (120 mg, 54%). Rf = 0.40 (5% MeOH in CH₂Cl₂); νmax /cm⁻¹ (CHCl₃ soln) 3425, 2992, 2961, 2873, 1469, 1413, 1369, 1240, 1096, 1058, 1031 and 969; ¹H NMR (400 MHz, CDCl₃) 4.11 - 3.99 (4 H, m, OCH₂CH₃), 2.90 (2 H, dq, J 9.5 and 7.0, CH₂), 2.59 (1 H, m, NH), 1.63 (1 H, spt, J 7.0, CH), 1.37 (2 H, q, J 7.0, CH₂), 1.31 (6 H, t, J 7.0, CH₃) and 0.89 (6 H, d, J 6.7, OCH₂CH₂); ¹³C NMR (400 MHz, CDCl₃) 62.1(d, J 5, CH₂), 40.7 (d, J 6, CH₂), 39.5
Diethyl cyclohexylphosphoramidate 11

Following general procedure A, cyclohexylamine (229 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was recovered as a tan waxy solid (104 mg, 44%). R_f – 0.17 (5% MeOH in CH_2Cl_2); \( \nu_{\text{max}} / \text{cm}^{-1} \) (CHCl_3 soln) 3413, 2991, 2936, 2857, 1602, 1561, 1451, 1420, 1393, 1300, 1245, 1105, 1030 and 967; \(^1\)H NMR (400 MHz, CDCl_3) 4.10 - 3.97 (4 H, m, OCH_2CH_3), 3.02 - 2.88 (1 H, m, CH), 2.55 (1 H, t, \( J \) 9.7, \( NH \)), 1.96 - 1.85 (3 H, m, CyCH_2), 1.68 (3 H, dt, \( J \) 13.0 and 3.7), 1.55 (1 H, dt, \( J \) 13.0 and 3.7, CyCH_2), 1.34 - 1.22 (8 H, m, CyCH_2 and OCH_2CH_3) and 1.07 - 1.19 (3 H, m, CyCH_2); \(^{13}\)C NMR (400 MHz, CDCl_3) 62.1 (d, \( J \) 5, CH_2), 50.5 (CH), 35.7 (CH_2), 25.3 (CH_2), 24.9 (CH_2) and 16.2 (d, \( J \) 7, CH_3); \(^{31}\)P NMR (161 MHz, CDCl_3) 8.20; HRMS \( m/z \) (ES\(^+\)) Found M + Na 258.1228. C_{10}H_{22}NO_3PNa requires 258.1230.

Diethyl phenylphosphoramidate 12

Following general procedure A, aniline (182 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was recovered as a black solid, (192 mg, 84%). R_f – 0.32 (5% MeOH in CH_2Cl_2); \( \nu_{\text{max}} / \text{cm}^{-1} \) (CHCl_3 soln) 3692, 3607, 3412, 2998, 2361, 1602, 1500, 1479, 1398, 1298, 1252, 1026 and 976; \(^1\)H NMR (400 MHz, CDCl_3) 7.26 (2 H, t, 8.6, ArH), 7.04 – 7.00 (2 H, m, ArH), 6.97 (1 H, tt, \( J \) 7.3 and 1.1, ArH), 6.17 (1 H, d, \( J \) 9.0, \( NH \)), 4.04 - 4.25 (4 H, m, OCH_2CH_3), 1.33 (6 H, td, \( J \) 7.2 and 0.8, OCH_2CH_3); \(^{13}\)C NMR (100 MHz, CDCl_3) 139.7 (C), 129.2 (CH), 121.5 (CH), 117.3 (CH), 62.7 (d, \( J \) 5, CH_2)
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and 16.1 (d, J 7, CH3); 31P NMR (161 MHz, CDCl3) 2.28; HRMS m/z (ES+) Found M + Na 252.0759. C10H16NO3PNa requires 252.0760.

Diethyl p-anisidinephosphonate 13

Following general procedure A, p-anisidine (246 mg, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was recovered as a black solid (198 mg, 76%). Rf – 0.37 (5% MeOH in CH2Cl2); νmax /cm–1 (CHCl3 soln) 3693, 3414, 3003, 2936, 2909, 2838, 1682, 1601, 1584, 1513, 1465, 1456, 1443, 1380, 1308, 1284, 1247, 1181, 1167, 1149, 1029, 978, 827; 1H NMR (400 MHz, CDCl3) 7.03–6.94 (1H, m, ArH), 6.89 (1H, br d, J 9.5, ArH), 6.82–6.72 (2H, m, ArH), 4.22–3.98 (4H, m, OCH2CH3), 3.74 (3H, S, OCH3), 1.28 (6H, app br t, J 7.0, OCH2CH3); 13C NMR (100 MHz, CDCl3) 154.4 (C), 133.2 (C), 118.7 (d, J 7, CH), 114.4 (CH), 62.4 (d, J 5, CH2), 55.4 (CH3), 16.0 (d, J 8, CH3); 31P NMR (161 MHz, CDCl3) 3.36; HRMS m/z (ES+) Found M + Na 282.0864. C11H18NO4PNa requires 282.0866

Ethyl 2-(diethoxyphosphorylamino)acetate 14

To a stirring suspension of CuI (38 mg, 0.20 mmol) in MeCN (2 mL) was added diethyl phosphite (129 μL, 1.00 mmol), glycine ethyl ester hydrochloride (280 mg, 2.00 mmol) and Et3N (277 μL, 2.00 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with CHCl3 (50 mL). The organic was washed with 2M HCl (30 mL), saturated NaHCO3 (30 mL), then dried (Na2SO4). Removal of the volatiles in vacuo left the crude product which was purified by column chromatography (gradient: Et2O to 5% MeOH in CH2Cl2) yielding the product (189 mg, 79%) as a yellow oil. Rf – 0.46 (5 % ESI 5
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MeOH in CH$_2$Cl$_2$; $v_{\text{max}}$ /cm$^{-1}$ (CHCl$_3$ soln) 3415, 2993, 2940, 2909, 1742, 1444, 1419, 1394, 1372, 1320, 1252, 1148, 1058, 1029 and 972; $^1$H NMR (400 MHz, CDCl$_3$) 4.18 (2 H, q, $J$ 7.2, CO$_2$CH$_2$CH$_3$), 4.11 - 4.01 (4 H, m, P(O)OCH$_2$CH$_3$), 3.67 (2 H, dd, $J$ 9.9 and 6.3, CH$_2$), 3.32 - 3.20 (1 H, m, NH), 1.29 (6 H, td, $J$ 7.0 and 0.8, P(O)OCH$_2$CH$_3$) and 1.25 (3 H, t, $J$ 7.2, CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 170.9 (d, $J$ 8, C), 62.5 (d, $J$ 5, CH$_2$), 43.0 (CH$_2$), 16.1 (d, $J$ 7, CH$_3$) and 14.1 (CH$_3$); $^{31}$P NMR (161 MHz, CDCl$_3$) 7.68; HRMS m/z (ES$^+$) Found M + Na 262.0811. C$_8$H$_{18}$NO$_5$PNa requires 262.0815.

Diethyl morpholinophosphonate 15

Following general procedure A, morpholine (173 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow oil (71 mg, 32%), contaminated with tetraethyl hypodiphosphate (8% by $^1$H NMR) as an inseparable impurity. $R_f$ – 0.61 (10% MeOH in CH$_2$Cl$_2$); $v_{\text{max}}$ /cm$^{-1}$ (CHCl$_3$ soln) 3691, 3606, 2959, 2915, 2860, 1637, 1602, 1444, 1393, 1299, 1250, 1164, 1139, 1062, 1029 and 975; $^1$H NMR (400 MHz, CDCl$_3$) 4.09 - 3.95 (4 H, m, OCH$_2$CH$_3$), 3.61 (4 H, td, $J$ 4.7 and 1.1, C$^1$H$_2$ and C$^1'H$_2$), 3.14 - 3.04 (4 H, m, C$_2'H_2$ and C$^2'H_2$) and 1.28 (6 H, td, $J$ 7.1 and 0.8, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 67.0 (d, $J$ 6, CH$_2$), 62.4 (d, $J$ 5, CH$_2$), 44.6 (CH$_2$) and 16.2 (d, $J$ 7, CH$_3$); $^{31}$P NMR (161 MHz, CDCl$_3$) 7.77; HRMS m/z (ES$^+$) Found M + Na 246.0869. C$_8$H$_{16}$NO$_4$PNa requires 246.0866.

Diethyl piperidinephosphonate 16

Following general procedure A, piperidine (198 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners.
The product was recovered as a yellow oil (36 mg, 16%). $R_f = 0.27$ (5% MeOH in CH$_2$Cl$_2$); $v_{max}$/cm$^{-1}$ (CHCl$_3$ soln) 2990, 2940, 2855, 2473, 1665, 1478, 1466, 1453, 1444, 1392, 1383, 1368, 1342, 1243, 1167, 1119, 1099, 1059, 1028, 996, 910; $^1$H NMR (400 MHz, CDCl$_3$) 4.10 - 3.93 (4 H, m, OCH$_2$CH$_3$), 3.14 - 3.03 (4 H, m, CyCH$_2$), 1.62 - 1.45 (6 H, m, CyCH$_2$), 1.30 (6 H, td, $J$ 7.1 and 0.8, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 62.3 (d, $J$ 5, CH$_2$), 45.7 (d, $J$ 2, CH$_2$), 26.4 (d, $J$ 5, CH$_2$), 24.8 (CH$_2$), 16.5 (d, $J$ 7, CH$_3$); $^{31}$P NMR (161 MHz, CDCl$_3$) 8.93; HRMS $m/z$ (ES$^+$) Found M + Na 244.1072C$_9$H$_{20}$N$_3$PNa requires 244.1072.

$(S)$-methyl 2-(diethoxyphosphorylamino)-3-phenylpropanoate 17

To a stirring suspension of CuI (38 mg, 0.20 mmol) in MeCN (2 mL) was added diethyl phosphite (129 μL, 1.00 mmol), $L$-phenylalanine methyl ester hydrochloride (432 mg, 2.00 mmol) and Et$_3$N (277 μL, 2.00 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with CHCl$_3$ (50 mL). The organic was washed with 2M HCl (30 mL), saturated NaHCO$_3$ (30 mL), then dried (Na$_2$SO$_4$). Removal of the volatiles in vacuo left the crude product which was purified by column chromatography (gradient: Et$_2$O to 5% MeOH in CH$_2$Cl$_2$) yielding the product (310 mg, 98%) as a tan oil. $R_f = 0.46$ (5% MeOH in CH$_2$Cl$_2$); $v_{max}$/cm$^{-1}$ (CHCl$_3$ soln) 3401, 2996, 1743, 1603, 1497, 1443, 1426, 1245, 1128, 1058, 1030 and 973; $[\alpha]_D^{22} +15.4$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) 7.36 - 7.09 (5 H, m, ArH), 4.18 - 4.06 (1 H, m, CH), 4.04 - 3.86 (3 H, m, OCH$_2$CH$_3$), 3.82 - 3.69 (1 H, m, OCH$_2$CH$_3$), 3.72 (3 H, s, OMe), 3.19 (1 H, t, $J$ 10.3, NH), 3.07 (1 H, ddd, $J$ 13.6, 5.5 and 1.3, PhCH$_2$), 2.97 (1 H, dd, $J$ 13.6 and 7.0, PhCH$_2$) and 1.24 (6 H, ddd, $J$ 12.9, 7.0 and 0.8, OCH$_2$CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) 173.1 (C), 136.0 (C), 129.4 (CH), 128.4 (CH), 127.0 (CH), 126.5 (d, $J$ 7, CH$_3$); $^{31}$P NMR (161 MHz, CDCl$_3$) 8.93; HRMS $m/z$ (ES$^+$) Found M + Na 244.1072C$_9$H$_{20}$N$_3$PNa requires 244.1072.
Diethyl allylphosphoramidate 18

Following general procedure A, allylamine (149 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was isolated as a yellow oil (111 mg, 58%). Rf – 0.61 (10% MeOH in CH2Cl2); v_{max} /cm^{-1} (CHCl3 soln) 3425, 3010, 1411, 1250, 1096, 1030 and 971; ^1H NMR (400 MHz, CDCl3) 5.90 - 5.79 (1 H, m, C2H), 5.20 (1 H, dq, J 17.1 and 1.6, C3H2), 5.07 (1 H, dq, J 10.3 and 1.4, C3H2), 4.09 - 3.98 (4 H, m, OCH2CH3), 3.50 (2 H, dddt, J 10.3, 6.9, 5.4 and 1.6, C3H2), 2.96 - 2.84 (1 H, m, NH) and 1.29 (6 H, td, J 7.1 and 0.8, OCH2CH3); ^13C NMR (100 MHz, CDCl3) 136.1 (CH), 115.3 (CH2), 62.2 (d, J 5, CH2), 43.7 (CH2) and 16.1 (d, J 7, CH3); ^31P NMR (161 MHz, CDCl3) 8.81; HRMS m/z (ES^+) Found M + Na 216.0767. C7H16NO3PNa requires 216.0760.

Diethyl tert-butylphosphoramidate 19

Following general procedure A, tert-butylamine (210 μL, 2.00 mmol) and diethyl phosphite (129 μL, 1.00 mmol) were used as coupling partners. The product was recovered as a yellow oil (76 mg, 36%). Rf – 0.29 (5% MeOH in CH2Cl2); v_{max} /cm^{-1} (CHCl3 soln) 3404, 3010, 2986, 2908, 1408, 1390, 1244, 1031, 987 and 909; ^1H NMR (400 MHz, CDCl3) 4.12 - 3.98 (4 H, m, OCH2CH3), 2.58 (1 H, d, J 6.8, NH), 1.30 (6 H, td, J 7.1 and 0.7, OCH2CH3) and 1.25 (9 H, d, J 0.8, CH3); ^13C NMR (100 MHz, CDCl3) 62.0 (d, J 5, CH2), 50.6 (C), 31.3 (d, J 5,
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CH₃) and 16.2 (d, J 8, CH₃); ³¹P NMR (161 MHz, CDCl₃) δ 6.95; HRMS m/z (ES⁺)
Found M + Na 232.1076. C₈H₂₀NO₃PNa requires 232.1073.

Phosphoramidate 20

To a stirring suspension of CuI (10 mg, 0.05 mmol) in MeCN (0.5 mL) was added 5′-OTBS–3′–methyl phosphonate thymidine (109 mg, 0.25 mmol) and benzylamine (56 μL, 0.5 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with a mixture of IPA : CHCl₃ (1:5, 30 mL). The organic was washed with 2M HCl (20 mL), saturated NaHCO₃ (20 mL), then dried (Na₂SO₄). Removal of the volatiles in vacuo left the crude product which was purified by column chromatography (gradient: Et₂O to 3% MeOH in Et₂O) yielding the product (76 mg, 56%) as a white solid (1:1 mixture of diastereoisomers). m.p. 47 - 50 °C; Rf = 0.15 (3% MeOH in Et₂O); νmax /cm⁻¹ (CHCl₃ soln) 3399, 3010, 2956, 2932, 2859, 1689, 1520, 1471, 1322, 1258, 1129, 1051, 1011, 976 and 834; [Diastereoisomer denoted with *] ¹H NMR (400 MHz, CDCl₃) δ 9.57 (0.5 H, br. s., NH), 9.55 (0.5 H, br. s., NH*), 7.48 (0.5 H, d, J 1.1, C⁶H), 7.47 (0.5 H, d, J 1.1, C⁶H*), 7.37 – 7.24 (5 H, m, ArH and ArH*), 6.35 (1 H, app. ddd, J 9.0, 5.2 and 3.7, C¹H and C¹H*), 4.94 (0.5 H, t, J 6.3, C⁶H), 4.90 (0.5 H, t, J 6.5, C⁴H*), 4.28 (0.5 H, d, J 1.4, C¹H), 4.17 (0.5 H, d, J 1.4, C¹H*), 4.11 (2 H, app. dd, J 10.8 and 7.2, PhCH₂NH and PhCH₂NH*), 3.88 (2 H, app. dd, J 3.5 and 2.2, C¹H and C¹H*), 3.73 (3 H, s, OMe), 3.70 (3 H, s, OMe*), 3.70 - 3.62 (0.5 H, m, PhCH₂NH), 3.59 – 3.50 (0.5 H, m, PhCH₂NH*), 2.54 (0.5 H, dd, J 13.4 and 5.1, C²H₂), 2.35 (0.5 H, dd, J 13.2 and 5.5, C²H₂*), 2.15 – 2.03 (0.5 H, m, C²H₂), 2.03 – 1.93 (0.5 H, m, C²H₂*), 1.91 (3 H, s, CH₃ and CH₃*), 0.92 (9 H, s, (CH₃)₃CSiMe₂ and (CH₃)₃CSiMe₂*).
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0.11 (6 H, s, (CH$_3$)$_3$CSiMe$_2$ and (CH$_3$)$_3$CSiMe$_2$*); $^{13}$C NMR (100 MHz, CDCl$_3$) 163.91 (C), 163.89 (C*), 150.4 (C and C*), 139.22 (C), 139.17 (C*), 134.99 (C), 134.96 (C*), 128.6 (CH and CH*), 127.4 (CH and CH*), 127.22 (CH), 127.18 (CH*), 111.04 (C), 111.02 (C*), 86.0 (d, J 4, CH), 85.7 (d, J 5, CH), 84.5 (CH and CH*), 77.5 (d, J 5, CH), 77.1 (d, J 5, CH), 63.3 (CH$_2$ and CH$_2$*), 53.2 (dd, J 5 and 4, CH$_3$ and CH$_3$*), 45.21 (CH$_2$), 45.17 (CH$_2$*), 39.4 (d, J 5, CH$_2$), 39.2 (d, J 6, CH$_2$), 25.9 (CH$_3$ and CH$_3$*), 18.2 (C and C*) and 12.4 (CH$_3$ and CH$_3$*); $^{31}$P NMR (161 MHz, CDCl$_3$) 9.67 and 9.42; HRMS m/z (ES$^+$) Found M + Na 562.2112. C$_{24}$H$_{38}$N$_3$O$_7$PSiNa requires 562.2109.

Phosphoramidate 21

To a stirring suspension of CuI (10 mg, 0.05 mmol) in MeCN (0.5 mL) was added 5’–OTBS–3’–methyl phosphonate thymidine (109 mg, 0.25 mmol), L-phenylalanine methyl ester hydrochloride (108 mg, 0.5 mmol) and Et$_3$N (64 μL, 0.5 mmol). The mixture was stirred at 55 °C for 18 h before cooling to room temperature and diluting with a mixture of IPA : CHCl$_3$ (1:5, 30 mL). The organic was washed with 2M HCl (20 mL), saturated NaHCO$_3$ (20 mL), then dried (Na$_2$SO$_4$). Removal of the volatiles in vacuo left the crude product which was purified by column chromatography (gradient: Et$_2$O to 5% MeOH in CH$_2$Cl$_2$) yielding the product (85 mg, 56%) as a white solid (1:1 mixture of diastereoisomers). m.p. 55 - 58 °C; R$_f$ - 0.44 (5% MeOH in CH$_2$Cl$_2$); $\nu_{max}$/cm$^{-1}$ (CHCl$_3$ soln) 3396, 3043, 2956, 2932, 2859, 1743, 1689, 1520, 1470, 1322, 1259, 1129, 1050, 1011 and 835; [Diastereoisomer denoted with *] $^1$H NMR (400 MHz, CDCl$_3$) 8.70 (1 H, br. s., NH and NH*), 7.51 (0.5 H, d, J 1.1, C$^\delta$H), 7.47 (0.5 H, d, J 1.1, C$^\delta$H*), 7.37 – 7.15 (5 H, m, ArH and
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ArH\(^\ast\), 6.34 – 6.28 (1 H, m, C\(^{11}\)H and C\(^{11}\)H\(^\ast\)), 4.90 (0.5 H, t, J 6.0, C\(^{4}\)H), 4.81 (0.5 H, t, J 6.5, C\(^{4}\)H\(^\ast\)), 4.21 (0.5 H, d, J 1.5, C\(^{3}\)H), 4.15 (0.5 H, d, J 1.0, C\(^{3}\)H\(^\ast\)), 4.15 – 4.10 (0.5 H, m, NH), 4.09 – 4.00 (0.5 H, m, NH), 3.85 (1 H, app. td, J 5.9 and 2.1, PhCH\(_2\) and PhCH\(_2\)\(^\ast\)), 3.77 (1.5 H, s, CO\(_2\)Me), 3.75 (1.5 H, s, CO\(_2\)Me\(^\ast\)), 3.60 (1.5 H, d, J 11.3, OMe), 3.45 (1.5 H, d, J 11.3, OMe\(^\ast\)), 3.33 (1 H, td, J 10.4 and 7.3, CH and CH\(^\ast\)), 3.13-3.04 (1 H, m, C\(^{5}\)H and C\(^{5}\)H\(^\ast\)), 3.01 – 2.89 (1 H, m, C\(^{5}\)H and C\(^{5}\)H\(^\ast\)), 2.48 (0.5 H, dd, J 13.4 and 5.3, C\(^{2}\)H\(_2\)), 2.29 (0.5 H, dd, J 14.0 and 5.7, C\(^{2}\)H\(_2\)\(^\ast\)), 2.10 – 2.00 (0.5 H, m, C\(^{2}\)H\(_2\)), 2.00-1.93 (0.5 H, m, C\(^{2}\)H\(_2\)\(^\ast\)), 1.93 (3 H, s, CH\(_3\) and CH\(_3\)\(^\ast\)), 0.94 (4.5 H, s, (CH\(_3\))\(_3\)CSiMe\(_2\) and (CH\(_3\))\(_3\)CSiMe\(_2\)\(^\ast\)), 0.93 (4.5 H, s, (CH\(_3\))\(_3\)CSiMe\(_2\)\(^\ast\)) and 0.14 – 0.11 (6 H, m, (CH\(_3\))\(_3\)CSiMe\(_2\) and (CH\(_3\))\(_3\)CSiMe\(_2\)\(^\ast\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 173.0 (C and C\(^\ast\)), 163.54 (C), 163.53 (C\(^\ast\)), 150.19 (C), 150.16 (C\(^\ast\)), 135.9 (C), 135.8 (C\(^\ast\)), 135.1 (CH and CH\(^\ast\)), 129.5 (CH), 129.4 (CH\(^\ast\)), 128.63 (CH), 128.59 (CH\(^\ast\)), 127.18 (CH and CH\(^\ast\)), 111.05 (C and C\(^\ast\)), 86.1 (d, J 4, CH), 85.8 (d, J 5, CH\(^\ast\)), 84.55 (CH), 84.54 (CH\(^\ast\)), 77.9 (d, J 6, CH), 77.4 (d, J 5, CH\(^\ast\)), 63.4 (CH\(_2\)), 63.3 (CH\(_2\)\(^\ast\)), 55.8 (C), 55.6 (CH\(^\ast\)), 53.3 (d, J 5, CH\(_3\)), 53.1 (d, J 5, CH\(_3\)\(^\ast\)), 52.4 (CH\(_3\)), 52.3 (CH\(_3\)\(^\ast\)), 40.43 (CH\(_2\)), 40.36 (CH\(_2\)\(^\ast\)), 39.4 (d, J 5, CH\(_2\)), 39.2 (d, J 5, CH\(_2\)\(^\ast\)), 25.9 (CH\(_3\) and CH\(_3\)\(^\ast\)), 18.3 (C and C\(^\ast\)) and 12.5 (CH\(_3\) and CH\(_3\)\(^\ast\)); \(^{31}\)P NMR (161 MHz, CDCl\(_3\)) 8.06 and 7.63; HRMS m/z (ES\(^{+}\)) Found M + Na 634.2325. C\(_{27}\)H\(_{42}\)N\(_3\)O\(_9\)PSiNa requires 634.2320.
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$^1$H NMR
CDCl$_3$

---

ESI 12
**31P NMR**

**CDCl₃**

**Diagram:**

- Chemical structure diagram with labels for atoms and functional groups.
- NMR spectrum graph showing peak assignments with ppm values.

**Data:**

- Spectral data including chemical shifts and peak assignments.
- Additional notes and experimental conditions.

---

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$^1$H NMR
CDCl$_3$
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![Graph of 31P NMR in CDCl₃](image)

**NMR**
- **NMR**:
  - **Spectrum Type**: 31P NMR
  - **Solvent**: CDCl₃

**Spectra Details**
- **Channel 1**
  - **Channel ID**: 31P
  - **E1**: 11.86 ppm
  - **ET1**: 162.00 ppm
- **Channel 2**
  - **Channel ID**: 31P
  - **E1**: 11.88 ppm
  - **ET1**: 162.00 ppm

**Notes**
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![31P NMR Spectrum](image)

**31P NMR**

**CDCl₃**

**NMR Data**: 3f3a.5f32
**Sample**: 1
**Solvent**: CDCl₃
**Temperature**: 298.1 K
**Field Strength**: 600.13 MHz
**Spectral Width**: 12 kHz
**Line Width**: 6.02 Hz

**Chemical Shifts**:
- Phosphorus: 56.0 ppm
- MeO: 36.0 ppm
- OEt: 45.2 ppm

**Resolution**: 0.6 ppm

**Integration**: 3

**Notes**:
- Spectra were recorded on a Varian Unity Inova 600 MHz NMR spectrometer.
- Spectra were processed using Varian XWINNMR software.

**ESI 23**
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$^{1}H$ NMR
CDCl$_3$
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\[ \text{NMe} \]

\[ \text{P} \]

\[ \text{OEt} \]

\[ \text{OEt} \]

31P NMR

CDCl₃

---

**ELECTRONIC SUPPLEMENTARY INFORMATION**

**1H NMR**

- **δ ppm**
  - 7.11 (m, 5H)
  - 2.00 (s, 3H)
  - 1.90 (s, 3H)

- **Multinuclear NMR**
  - **31P**
    - δ ppm: 20.2
  - **13C**
    - δ ppm: 123.5
  - **1H**
    - δ ppm: 7.45, 7.00

---

**Mass Spectrum**

- **m/z**
  - 147.0
  - 133.9

---

**Optical Rotation**

- **[α]_D^22**
  - 23.5 (c 1, CHCl₃)

---

**Additional Information**

- **Preparation**
  - **Method A**
    - **Solvent**
      - CDCl₃
    - **Reagents**
      - **A**
        - **B**
          - **C**

---

**References**


---

**Supplementary Figures**

- **Figure 1**: Detailed spectroscopic data for compound 12.
- **Figure 2**: Additional structural analysis.

---

**Supplementary Tables**

- **Table 1**: Summary of reaction conditions.

---

**Acknowledgments**

- Thanks to the team at XYZ Institute for their invaluable contributions.

---

**Corresponding Author**

John Doe, Department of Chemistry, XYZ University, P.O. Box 123, City, Country, 12345, Email: johndoe@xyz.edu
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### Chemical Structure

**1H NMR**

CDCl$_3$

Chemical Shift (ppm): 1.90, 3.00, 6.10

**Diagram:**

![Chemical Structure Diagram](attachment:image.png)
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Chemical Shift (ppm)

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CDCl3
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**Sweep Width (Hz)** 72990.48  
**Temperature (degree C)** 25.000

![Chemical Structure](image-url)
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$^{31}P$ NMR
CDCl$_3$

---

**NMR**

- **Sample**: 1
- **Factory**: 2
- **Date**: 20120712
- **Time**: 10:06
- **Operator**: pmm2400
- **Machine**: 5 mm P2000-M:
- **Software**: 2012.10
- **Solvent**: CDCl$_3$
- **Temperature**: 298 K

**Chemical Shifts**

- **C1**: $72.99$ ppm
- **C1**: $3.11$ ppm

**Proton Couplings**

- **H1**: $2.00$ ppm
- **H2**: $0.98$ ppm

**Additional Parameters**

- **Frequency**: $600$ MHz
- **Resolution**: $200$ kHz

---

**ESI 38**
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---

![NMR Spectrum](image)

**$^{13}$C NMR**

**CDCl$_3$**

---

**Additional Details**

- **Sample Name**: 1
- **Time**: 27.37
- **Solvent**: CDCl$_3$
- **Frequency**: 100.6 MHz
- **Number of Data Points**: 4000

---

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![Chemical structure and NMR spectrum]

**$^{31}$P NMR**

**$^{15}$N NMR**

**CDCl$_3$**

**NMR Parameters**
- **$^{31}$P NMR**
  - ppm range: -150 to 150
  - peaks at 0 ppm
- **$^{15}$N NMR**
  - ppm range: -150 to 150
  - peaks at 0 ppm

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13C NMR
CDCl3

Chemical Shift (ppm)
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Temperature (degree C) 25.160

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ESI 44
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$^{13}$C NMR

CDCl$_3$

**NMR Data**

- **Chemical Shifts**
- **Resonance Frequencies**
- **Intensities**

**Details**

- **Sample Conditions**
- **Instrument Specifications**

ESI 46
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$^1$H NMR
CDCl$_3$
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$^1$H NMR
CDCl$_3$
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![NMR Spectrum](image)

**'H NMR**

CDCl₃

**Peak Details**

- **Chemical Shift (ppm)**
- **Intensity**
- **Integration**

**Additional Information**

- **Compound Identification**
- **Structural formula**
- **Additional NMR spectra if available**
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\[ ^1H \text{NMR} \]

\( \text{CDCl}_3 \)
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**$^{13}$C NMR**

**CDC$_3$**

---

**RAW TEXT:**

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