

Sterically Demanding, Water-Soluble Alkylphosphines as Ligands for High Activity Suzuki-Couplings in Aqueous Solvents

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General. Ligand syntheses were carried out under nitrogen using a dry box and Schlenk techniques unless noted. Coupling reactions were assembled in a drybox in screw-cap vials with a silicone/Teflon® septum or a round bottom sealed with a rubber septum. Pd(OAc)₂, TPPTS (**1**), di-*t*-butylphosphine, and dicyclohexylphosphine were purchased from Strem and stored in a drybox (M. Braun, Inc.). All boronic acids and aryl halides were purchased from Aldrich and were used without further purification. Di-*t*-phosphine-borane adduct,¹ *N*-methyl-4-piperidinyl tosylate² and ligand **5**² were prepared by literature methods. THF and diethyl ether were freshly distilled from sodium-benzophenone ketyl under nitrogen prior to use. Anhydrous grade morpholine (Aldrich) was used as received and dispensed in a drybox. Water (deionized), acetonitrile, methanol, and DMF were degassed by sparging with nitrogen and/or exposure to vacuum.

Since the yields reported in Table 3 represent the average of two independent trials, the values reported below for individual trials may not match those reported in Table 3.

(2-Di-*t*-butylphosphinoethyl)trimethylammonium chloride (3). Prepared by a modification of the synthesis of **5** reported by Grubbs.² Di(*t*-butyl)phosphine-borane (1.588 g, 9.984 mmol) adduct was dissolved in 50 mL of THF under nitrogen and cooled to $-78\text{ }^{\circ}\text{C}$. Butyl lithium (4.20 mL, 10.5 mmol) was added drop-wise to the phosphine solution. After the addition was complete, the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 minutes and then allowed to warm to room temperature and stirred for 2 hours. A second flask was charged with (2-chloroethyl)trimethylammonium chloride that had been finely ground in the drybox. The phosphine solution was cooled back to $-78\text{ }^{\circ}\text{C}$ and added *via* cannula to the solid salt, which was also cooled to $-78\text{ }^{\circ}\text{C}$. After the addition was complete, the reaction was allowed to warm to room temperature and then was refluxed for 24 hours to give a heavy white suspension. The THF was removed under reduced pressure in air and the solid residue was extracted with chloroform (3 \times 100 mL). The chloroform was removed under reduced pressure to give a colorless oil that was triturated with ether to give a slightly hygroscopic, colorless solid. The solid was dried *in vacuo* and stored in a dry box. Recovered (2.2126 g, 79 %) of the borane adduct of **3**. ¹H NMR (D₂O, 360 MHz): δ 3.70 (dt, $J = 4.47$, $J_{H-P} = 13.56$ Hz, 2H), 3.25 (s, 9H), 2.30-2.22 (m, 2H), 1.35 (d, $J_{H-P} = 13.56$ Hz, 18H), 0.39 (brq, $J_{H-B} = 83.2$ Hz, 3H). ³¹P NMR (D₂O, 202.5 MHz): δ 43.0 (brs). The phosphine-borane adduct (2.0929 g, 7.4322 mmol) was taken up in 50 mL of degassed, dry morpholine under nitrogen and heated to $110\text{ }^{\circ}\text{C}$. Upon heating, gas evolution was observed. After 3 hours, the reaction was allowed to cool to room temperature. The morpholine was removed *in vacuo*. The residue was dissolved in a minimum of degassed methanol and precipitated with ether (50 mL) to give a colorless crystalline solid, which was contaminated with morpholine-borane adduct. The crude material was placed in a sublimation apparatus and heated under vacuum (0.05 torr) at $110\text{ }^{\circ}\text{C}$ for 2 hours. The non-volatile solid (1.5892 g, 80 %) recovered was pure by NMR spectroscopy. ¹H NMR (D₂O, 360 MHz): δ 3.54 (dt, $J = 4.82$, $J_{H-P} = 14.18$ Hz, 2H), 3.21 (s, 9H), 1.95 (dt, $J = 4.86$, $J_{H-P} = 13.57$ Hz, 2H), 1.22 (d, $J_{H-P} = 12.33$ Hz, 18H). ¹³C NMR (D₂O, 90.6 MHz): δ 67.6 (d, $J_{C-P} = 43.78$ Hz),

52.5, 31.3 (d, $J_{C-P} = 11.94$ Hz), 28.8 (d, $J_{C-P} = 11.94$ Hz), 14.4 (d, $J_{C-P} = 17.25$ Hz). ^{31}P NMR (D_2O , 202.5 MHz): δ 22.3 (s). Calculated for $\text{C}_{13}\text{H}_{31}\text{ClNP}$: C, 58.30; H, 11.67; N, 5.23. Found: C, 57.55; H, 11.33; N, 5.35.

4-(Di-*t*-butylphosphino)-*N,N*-dimethylpiperidinium chloride (4). Prepared by a modification of the synthesis of **5** reported by Grubbs.² Di(*t*-butyl)phosphine-borane adduct (7.2062 g, 45.011 mmol) in THF (200 mL) was deprotonated with butyl lithium (19.0 mL, 47.5 mmol) as described for **3**. This solution was cooled back to -78 °C and a solution of freshly prepared *N*-methyl-4-piperidinyl tosylate (11.54 g, 42.84 mmol) in 50 mL THF was added dropwise via cannula. The resulting orange solution was allowed to warm to room temperature and then was refluxed overnight. The mixture was poured into 500 mL of saturated sodium bicarbonate and extracted with ether (3×150 mL). The crude material was flash chromatographed on a silica gel column eluting with methanol to give 1.8105 g (16 %) of (*N*-methylpiperidin-4-yl)di-*t*-butylphosphine-borane adduct. ^1H NMR (CDCl_3 , 360 MHz): δ 3.05-3.00 (brm, 2H), 2.30-2.25 (brm, 2H), 2.30 (s, 3H), 2.05-1.90 (m, 4H), 1.85-1.70 (m, 1H), 1.34 (d, $J_{H-P} = 12.33$ Hz, 18H), 0.50 (brq, $J_{H-B} = 85$ Hz, 3H). This material (1.810 g, 7.04 mmol) was dissolved in 100 mL THF and methyl iodide (1.10 mL, 17.67 mmol) was added. The reaction was refluxed overnight during which time a white precipitate formed. The precipitate was filtered off and washed with ether. The crude product was recrystallized from boiling methanol to give large, colorless, blocks (1.39 g, 50 %). ^1H NMR (CD_3OD , 360 MHz): δ 3.58-3.50 (m, 4H), 3.33 (s, 3H), 3.13 (s, 3H), 2.51-2.42 (m, 2H), 2.35-2.20 (m, 3H), 1.39 (d, $J_{H-P} = 20.35$ Hz, 18 H), 0.40 (brq, $J_{H-B} = 77.2$ Hz, 3H). ^{13}C NMR (CD_3OD , 90.6 MHz): δ 64.4 (d, $J_{C-P} = 9.25$ Hz), 57.15 (d, $J_{C-P} = 3.98$ Hz), 57.10 (d, $J_{C-P} = 3.98$ Hz), 35.2 (d, $J_{C-P} = 25.19$ Hz), 30.5 (d, $J_{C-P} = 23.88$ Hz), 29.5, 25.5. ^{31}P NMR (CD_3OD , 202.5 MHz): δ 49.3 (s). Calculated for $\text{C}_{15}\text{H}_{36}\text{BINP}$: C, 45.14; H, 9.09; N, 3.51. Found: C, 44.93; H, 8.95; N, 3.46. The recrystallized iodide was dissolved in warm methanol (50 mL) and then 50 mL of water was added followed by 35 g of Amberlite IR 400 (Cl) anion exchange resin. The mixture was stirred for 12 hours and then the resin was filtered off. The resin was again filtered off after 12 hours and fresh resin was added. After an additional 12 hours, fresh resin was added again along with 2 mL of 1M HCl. After an additional 12 hours, the resin was filtered off and the solvent was removed under reduced pressure to give a waxy solid. The solid was taken up in a small amount of methanol and precipitated by addition of ether. The solid was filtered off and washed with ether then dried *in vacuo*. Recovered 975.2 mg (91 %) of the borane adduct of **4** as a fluffy, white solid. ^1H NMR (D_2O , 360 MHz): δ 3.62 (brd, $J = 12.33$ Hz, 2H), 3.44 (brt, $J = 11.72, 13.56$ Hz, 2H), 3.22 (s, 3H), 3.15 (s, 3H), 2.60-2.51 (m, 2H), 2.44-2.25 (m, 3H), 1.40 (d, $J_{H-P} = 12.95$ Hz, 18 H) 0.40 (brq, $J_{H-B} = 84.5$ Hz, 3H). ^{13}C NMR (D_2O , 90.6 MHz): δ 63.8 (d, $J_{C-P} = 10.62$ Hz), 57.0, 47.8, 34.0 (d, $J_{C-P} = 16.54$ Hz), 29.3 (d, $J_{C-P} = 26.54$ Hz), 28.7, 24.3. The borane adduct (953 mg, 3.10 mmol) was taken up in dry, degassed morpholine under nitrogen. The suspension was heated to 100 °C and stirred for 4 hours. The reaction was then allowed to cool to room temperature to give a suspension of a white crystalline material. THF (50 mL) was added to complete the precipitation of the product. The solvent was removed *via* cannula and the solid was washed with 20 mL of THF and dried *in vacuo*. The crude material was transferred to a sublimation apparatus in a drybox and heated under vacuum (0.05 torr) at 110 °C for 3 hours. A small amount of morpholine-borane adduct sublimed during this time. The pure product was recovered as fine, colorless needles (532.3 mg, 58 %). ^1H NMR (D_2O , 360 MHz): δ 3.56 (brd, $J = 11.1$ Hz, 2H), 3.42 (brt, $J = 12.95$ Hz, 2H), 3.20 (s, 3H), 3.13 (s, 3H), 2.42-2.20 (m, 4H), 2.10-1.98 (m, 1H), 1.28 (d, $J_{H-P} = 9.87$ Hz, 18H). ^{13}C NMR (D_2O , 90.6 MHz): δ 64.3 (d, $J_{C-P} = 10.61$

Hz), 57.0, 47.6, 32.8 (d, $J_{C-P} = 15.92$ Hz), 30.4 (d, $J_{C-P} = 11.94$ Hz), 29.7 (d, $J_{C-P} = 21.23$ Hz), 26.7 (d, $J_{C-P} = 11.94$ Hz). ^{31}P NMR (D_2O , 202.5 MHz): δ 40.0 (s). Calculated for $\text{C}_{15}\text{H}_{33}\text{ClNP}$: C, 61.31; H, 11.32; N, 4.77. Found: C, 60.38; H, 11.12; N, 4.76. The amount of carbon was consistently low.

General procedure for low catalyst loading trials. Stock solutions were prepared by dissolving the appropriate amount of $\text{Pd}(\text{OAc})_2$ and **3** or **4** in degassed acetonitrile to give solutions that were $1 \times 10^{-3} - 5 \times 10^{-3}$ M in Pd. Under nitrogen, a vial was charged with sodium carbonate (1.0 mmol), phenylboronic acid (0.6 mmol), 4-bromotoluene (0.5 mmol), and mesitylene (50 μL) as internal standard. To this was added degassed 2:1 $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (1.5 mL). The reaction was allowed to equilibrate at the desired reaction temperature for 10 minutes before the catalyst solution was added *via* syringe. Aliquots were removed at regular intervals from the organic layer and analyzed by GC. Yields were calculated using response factors determined with authentic samples of 4-bromotoluene and 4-methylbiphenyl.

General procedure for coupling of water-insoluble aryl halides and arylboronic acids. In a dry box, a round bottom flask was charged with $\text{Pd}(\text{OAc})_2$ (0.02 mmol), **3** or **4** (0.02 mmol), sodium acetate (2.0 mmol), aryl halide (1.0 mmol), and arylboronic acid (1.2 mmol). The flask was sealed with a septum and removed from the drybox. Degassed 1:1 $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (5 mL) was added and the reaction stirred at room temperature until GC analysis showed no residual aryl bromide (1-2 hours). The reaction was poured into saturated sodium bicarbonate and the product extracted with ether (3×30 mL). The crude material was flash chromatographed on a short silica gel column eluting with a mixture of ethyl acetate and hexanes.

4-Methylbiphenyl. 4-Bromotoluene (122 μL , 0.997 mmol) and phenylboronic acid (144.4 mg, 1.185 mmol) were coupled as described above. The crude material was eluted with hexanes to give a colorless oil that crystallized upon standing under vacuum (156.9 mg, 94 %). ^1H and ^{13}C NMR (CDCl_3) were identical to the commercially available material (Aldrich).

4-Methoxybiphenyl. 4-Bromoanisole (125 μL , 1.00 mmol) and phenylboronic acid (147.8 mg, 1.212 mmol) were coupled by the above procedure. The crude material was eluted with 5 % ethyl acetate in hexanes to give the product as a colorless, crystalline solid (175.1 mg, 95 %). ^1H and ^{13}C NMR (CDCl_3) were identical to the commercially available material (Aldrich).

4-Acetyl-4'-methoxybiphenyl. 4-Bromoacetophenone (200.3 mg, 1.007 mmol) and 4-methoxyphenylboronic acid (186.2 mg, 1.226 mmol) were coupled by the above procedure. The crude material was flash chromatographed eluting with 75:20:5 hexanes: CH_2Cl_2 :ethyl acetate. The product was recovered as a colorless, crystalline solid (208.0 mg, 91 %). ^1H and ^{13}C NMR (CDCl_3) were identical to previously reported values.³

2-(4-Acetylphenyl)thiophene.⁴ 4-Bromoacetophenone (202.5 mg, 1.017 mmol) and 2-thienylboronic acid (157.9 mg, 1.235 mmol) were coupled by the above procedure. The crude product was flash chromatographed eluting with 75:20:5 hexanes: CH_2Cl_2 :ethyl acetate. The product was recovered as a pale yellow, crystalline solid (182.1 mg, 89 %). ^1H NMR: (CDCl_3 , 360 MHz): δ 7.97 (d, $J = 8.63$ Hz, 2H), 7.70 (d, $J = 8.63$ Hz, 2H), 7.43 (dd, $J = 1.23, 3.70$ Hz, 1H), 7.37 (dd, $J = 1.23, 4.93$ Hz, 1H), 7.12 (dd, $J = 3.70, 4.93$ Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (CDCl_3 , 90.6 MHz): δ 197.3, 143.0, 138.8, 135.8, 129.1, 128.4, 126.5, 125.7, 124.6, 26.5.

4-Methoxy-2'-methylbiphenyl. 2-Bromotoluene (120 μL , 1.00 mmol) and 4-methoxyphenylboronic acid (188.7 mg, 1.242 mmol) were coupled by the above procedure. The product was eluted using 2.5 % ethyl acetate in hexanes to give a colorless oil (185.9 mg, 94 %).

Alternatively, 4-bromoanisole (125 μ L, 1.00 mmol) and 2-tolylboronic acid (162.8 mg, 1.198 mmol) were coupled in the same manner. ^1H and ^{13}C NMR (CDCl_3) were identical to previously reported values.³

2,2'-Dimethylbiphenyl. 2-Bromotoluene (120 μ L, 1.00 mmol) and 2-tolylboronic acid (164.4 mg, 1.210 mmol) were coupled by the above method. The crude product was eluted with hexanes to give the product as a colorless oil (168.5 mg, 92 %). ^1H and ^{13}C NMR (CDCl_3) were identical to previously reported values.⁵

4-Methoxy-2',2'-dimethylbiphenyl. 2-Bromo-*m*-xylene (135 μ L, 1.01 mmol) and 4-methoxyphenylboronic acid (182.8 mg, 1.2034 mmol) were coupled as described above. The crude material was flash chromatographed eluting with 2.5 % ethyl acetate in hexanes. The product was recovered as a colorless oil that solidified upon standing (208.4 mg, 97 %). ^1H NMR (CDCl_3 , 360 MHz): 7.20-7.03 (m, 5H), 6.96 (dd, $J = 1.89, 2.47, 6.48$ Hz, 2H), 3.82 (s, 3H), 2.04 (s, 6H). ^{13}C NMR (CDCl_3 , 90.6 MHz): 158.3, 141.5, 136.5, 133.3, 130.0, 127.2, 126.7, 113.8, 55.2, 20.9.

General procedure for coupling of water-soluble aryl bromides. Reactions were assembled as described for water-insoluble aryl bromides, except that 2.5 mmol of sodium carbonate was used. After 2 hours, the reaction mixture was poured into 25 mL of 10 % aqueous HCl. The resulting suspension was extracted with ether (3×30 mL). The combined ether extracts were dried (MgSO_4) and the solvent removed under reduced pressure. The crude product was flash chromatographed.

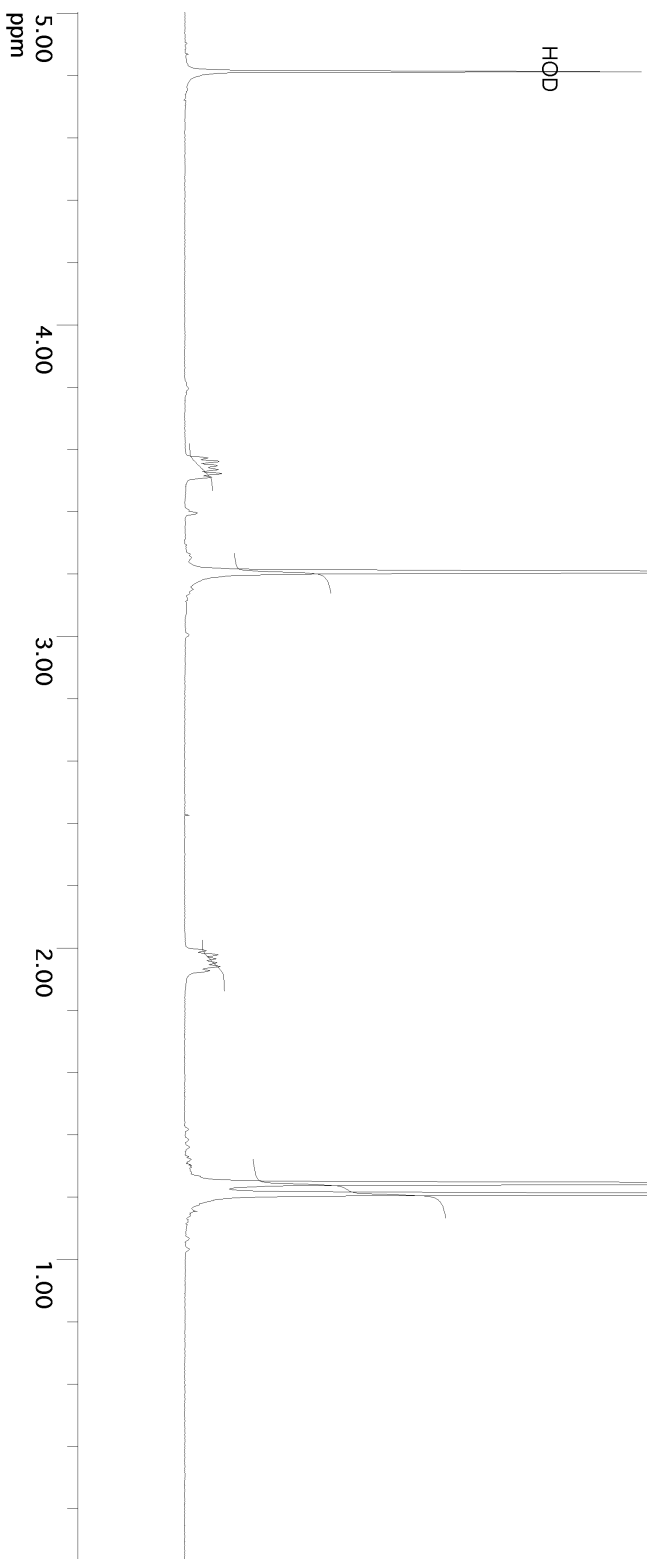
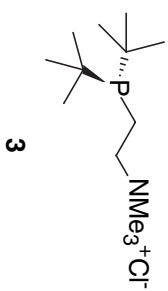
4-Hydroxybiphenyl. 4-Bromophenol (174.2 mg, 1.006 mmol) and phenylboronic acid (148.2 mg, 1.148 mmol) were coupled as described above. The crude material was flash chromatographed eluting with 15 % ethyl acetate in hexanes. The product was recovered as colorless fine needles (148.5 mg, 87 %). ^1H and ^{13}C NMR spectra (CDCl_3) were identical to the commercially available material (Aldrich).

2'-Methylbiphenyl-4-carboxylic acid.⁶ 4-Bromobenzoic acid (201.7 mg, 1.003 mmol) and *o*-tolylboronic acid (168.2 mg, 1.238 mmol) were coupled as described above. The crude material was flash chromatographed eluting with 5 % methanol in CH_2Cl_2 . The product was recovered as an off-white solid (201.9 mg, 95 %). ^1H NMR ($\text{DMSO-}d_6$, 360 MHz): δ 12.95 (brs, 1H), 8.0 (d, $J = 8.20$ Hz, 2H), 7.47 (d, $J = 7.29$ Hz, 2H), 7.32-7.22 (m, 4H), 2.24 (s, 3H). ^{13}C NMR ($\text{DMSO-}d_6$, 90.6 MHz): δ 167.2, 145.7, 140.3, 134.6, 130.5, 129.3, 129.24, 129.20, 129.1, 127.8, 126.0, 20.1.

4-Cyanobiphenyl. A flask was charged with $\text{Pd}(\text{OAc})_2$ (8.9 mg, 0.0396 mmol), **4** (24.2 mg, 0.0824 mmol), sodium carbonate (210.2 mg, 1.9830 mmol), 4-chlorobenzonitrile (138.8 mg, 1.009 mmol), and phenylboronic acid (147.2 mg, 1.2075 mmol) under nitrogen. Degassed 1:1 $\text{H}_2\text{O}:\text{CH}_3\text{CN}$ (5 mL) was added and the reaction was placed in an oil bath pre-heated to 80 $^\circ\text{C}$. After 3 hours, only a trace of 4-chlorobenzonitrile remained by GC. The reaction was worked up as described above. The crude material was flash chromatographed eluting with 5 % ethyl acetate in hexanes to give a white solid (166.7 mg, 92 %). ^1H and ^{13}C NMR (CDCl_3) were identical to the commercially available material (Aldrich). The reaction was repeated on a 0.2 mmol scale (chlorobenzonitrile) with ligand **3** and 50 μ L mesitylene as internal standard. The reaction was followed by GC. After 8 hours, the GC yield of 4-cyanobiphenyl was 64 % (66 % conversion).

- 1)Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244-5252.
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- 3)Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.
- 4)Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M. *Heterocycles* **1990**, *31*, 1951-1959.
- 5)Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797-6803.
- 6)Klein, S. I.; Czekaj, M.; Gardner, C. J.; Guertin, K. R.; Cheney, D. L.; Spada, A. P.; Bolton, S. A.; Brown, K.; Colussi, D.; Heran, C. L.; Morgan, S. R.; Leadley, R. J.; Dunwiddie, C. T.; Perrone, M. H.; Chu, V. *J. Med. Chem.* **1998**, *41*, 437-450.

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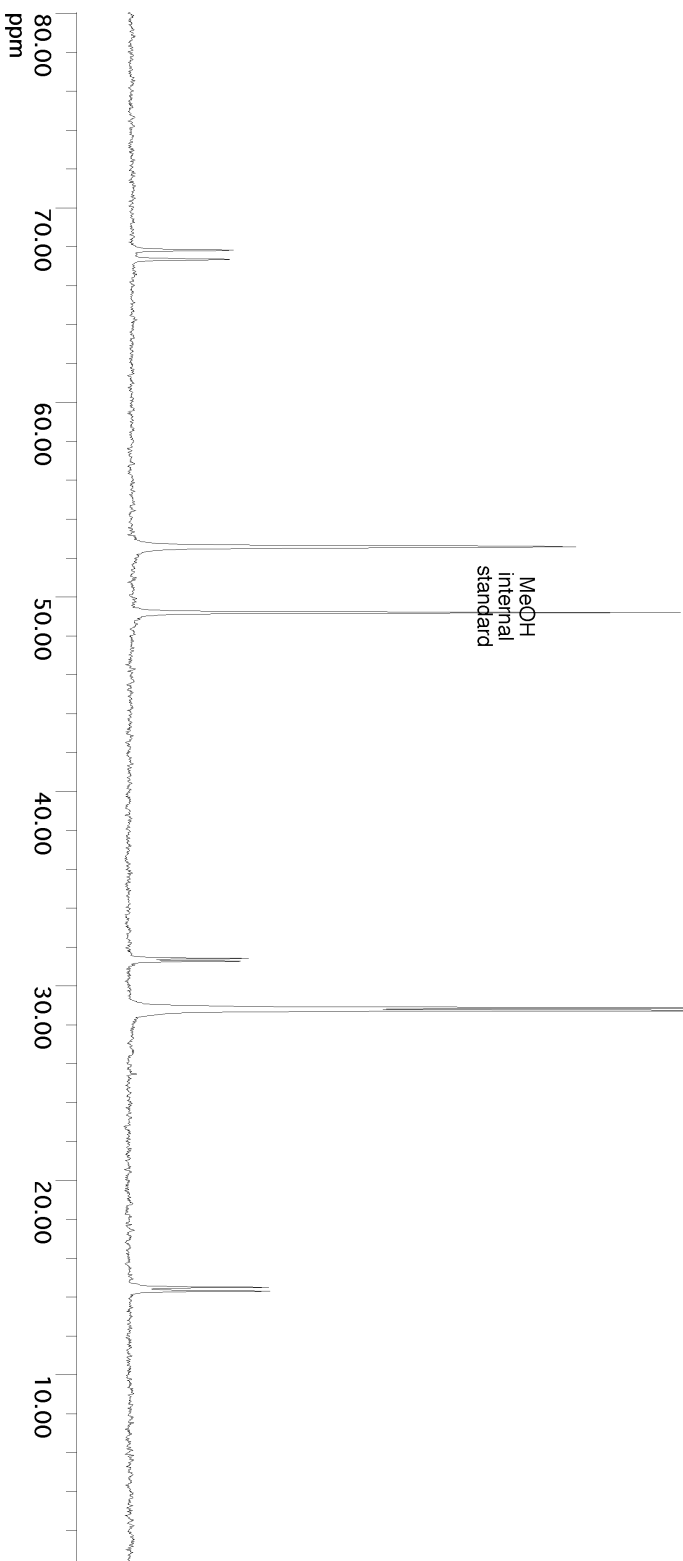
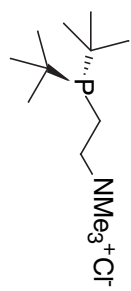


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after sublimation
D₂O, 360 MHz

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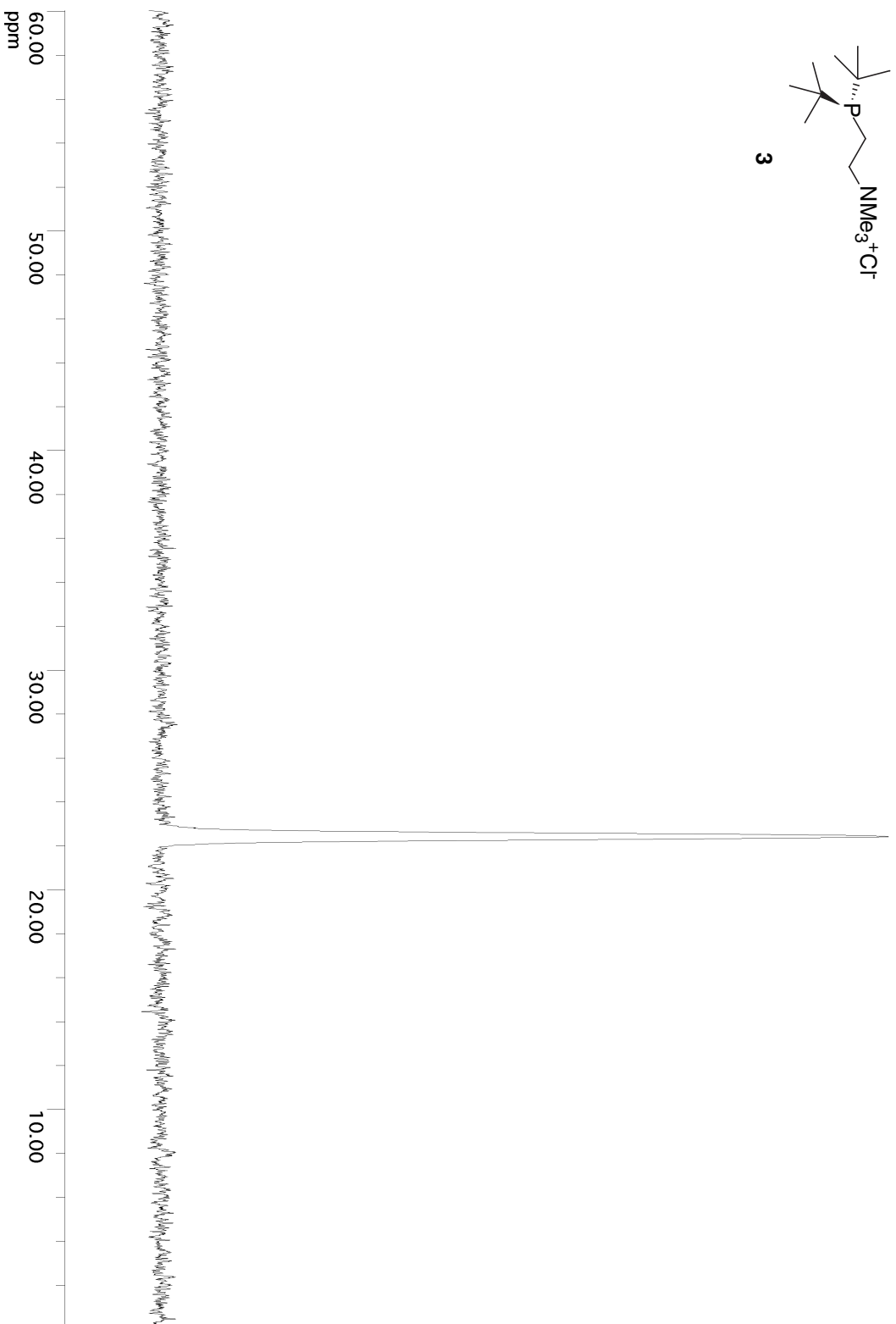
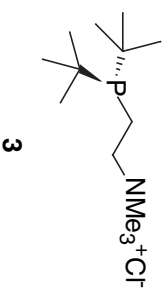
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5	31.363	2840.30	503423.25
6	31.231	2828.36	470834.06
7	28.829	2610.75	3602526.00
8	28.697	2598.81	3571260.25
9	14.456	1309.11	588818.00
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khs-2-21d
 13C NMR, internal MeOH reference
 D2O, 90.6 MHz

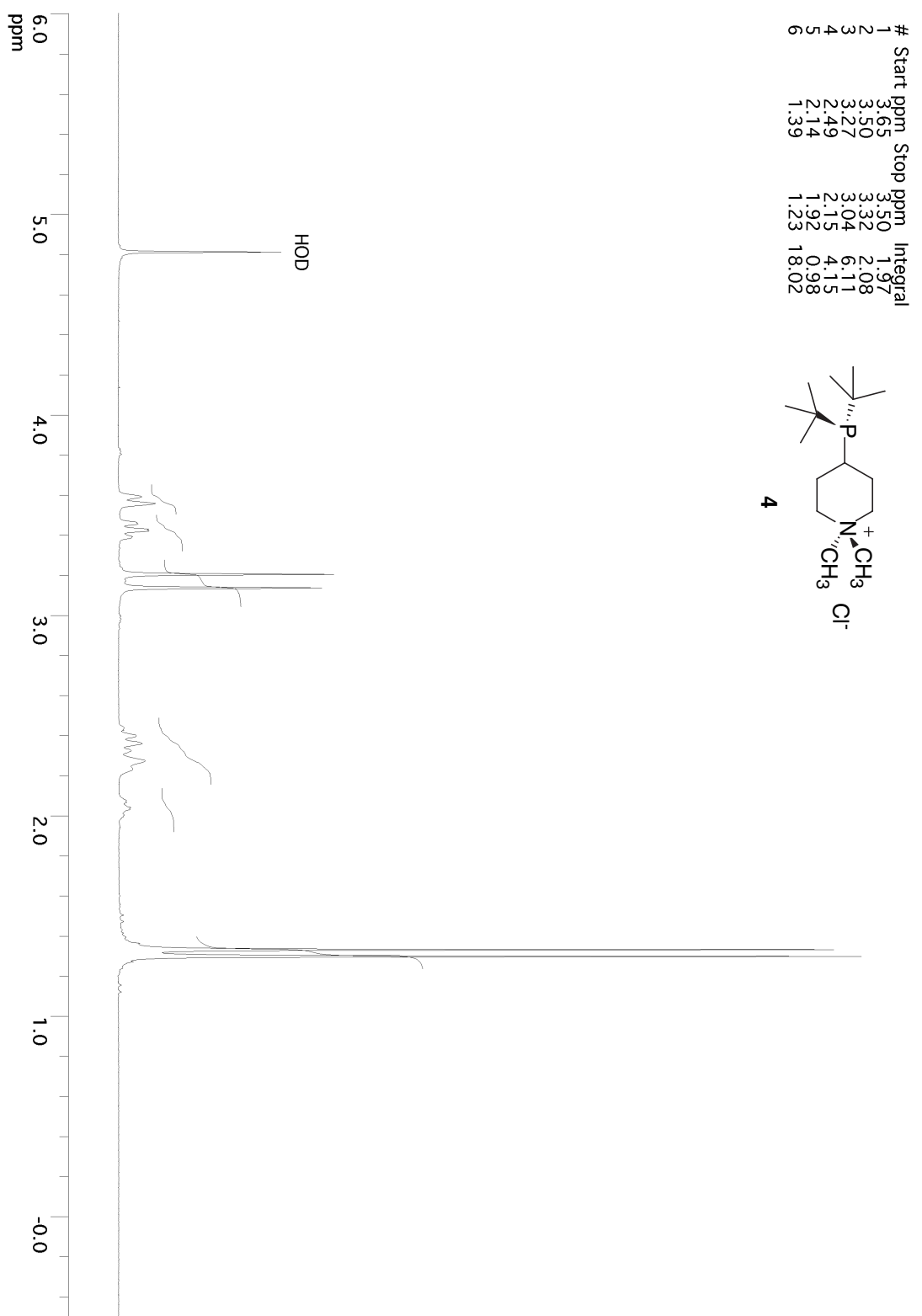
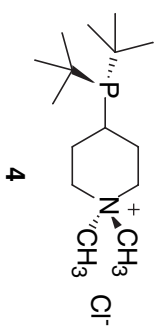
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khs-2-21d
after sublimation
31P NMR, external H3PO4 reference
D2O, 202.5 MHz

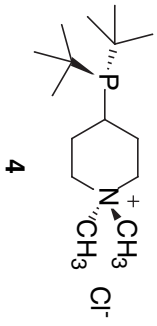
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5	2.14	1.23	0.98
6	1.39		18.02



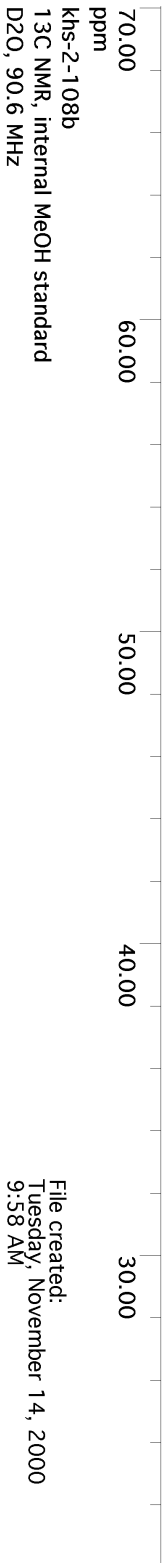
Khs-1-108b
 after sublimation
 D2O, 360 MHz

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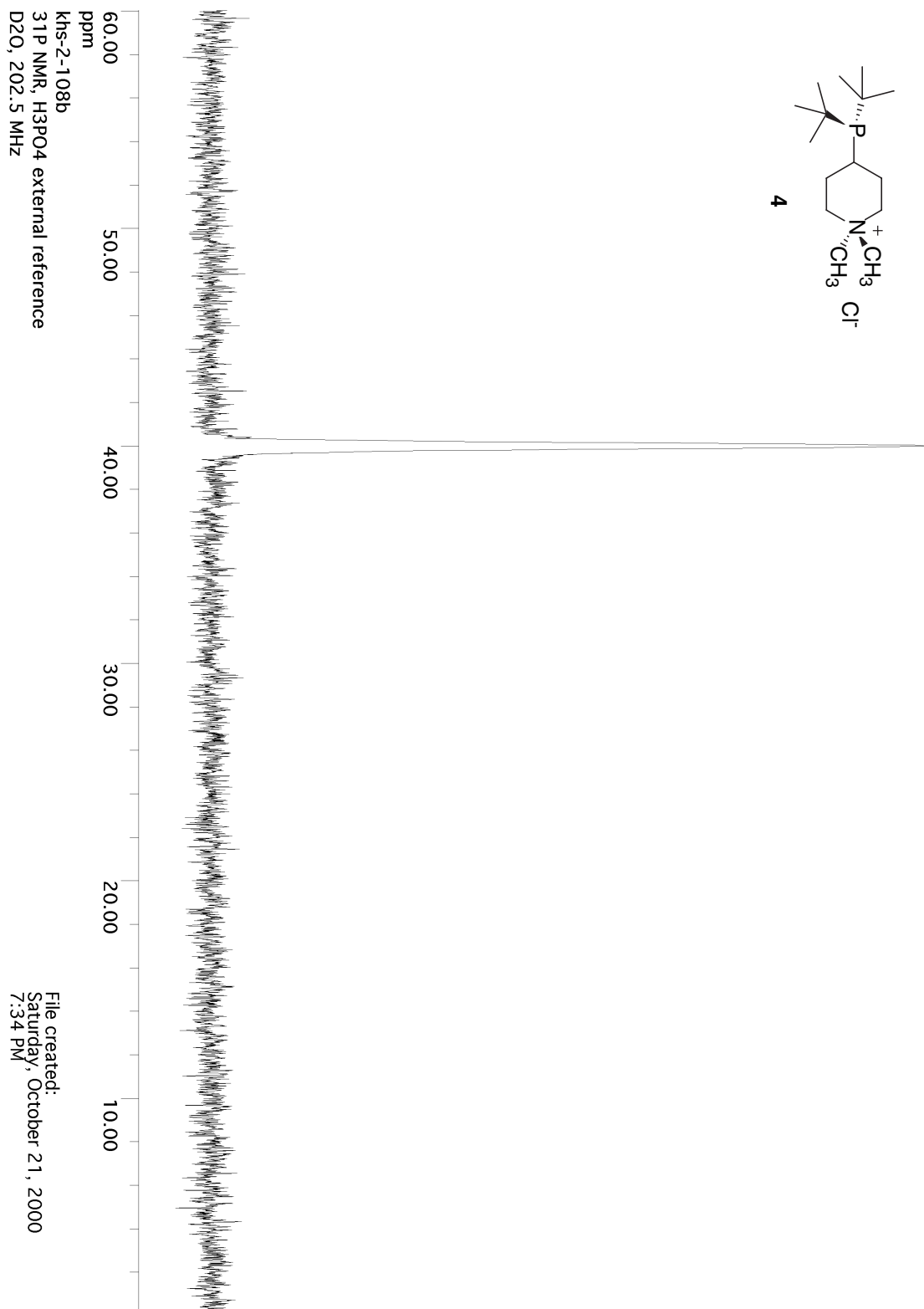
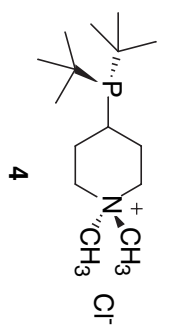


13 peaks found in khs-2-108b-c.lmport

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5	47.610	4311.10	613357.00
6	32.883	2977.61	590936.00
7	32.708	2961.69	566520.00
8	30.524	2763.99	3516253.00
9	30.392	2752.05	3326929.00
10	29.850	2702.95	479719.00
11	29.616	2681.72	548679.00
12	26.788	2425.64	1078410.00
13	26.656	2413.70	1011026.00



File created:
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