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The synthesis and characterisation of novel *o*-substituted benzyldi-*t*-butylphosphine–boranes

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ABSTRACT

The novel compounds *o*-(chloromethyl)benzyldi-*t*-butylphosphine–borane and *o*-(methoxymethyl)benzyldi-*t*-butylphosphine–borane have been synthesised in 54% and 51% yields, respectively, and have been fully characterised. An improved method for the synthesis of α-chloro-α′-methoxy-*o*-xylene is also reported.

Following the commercial success of 1,2-bis[(di-*t*-butylphosphino)methyl]benzene as an ancillary chelating ligand for the palladium-catalysed methoxycarbonylation of ethene,[1] a lot of interest has been generated in phosphine ligands containing an *o*-xylene-based backbone. A number of subsequent patents have been granted for catalytic processes that utilise 1,2-bis[(di-*t*-butylphosphino)methyl]benzene,[2] and the use of phosphine substituents other than *t*-butyl groups has also been investigated.[3] There are also recent examples wherein the two donor groups of the ligand are not identical in that the substituents on each phosphorus atom differ.[4,5]

The synthesis of these C_s-symmetric diphosphine ligands is not straightforward, as it is usually necessary to differentially substitute the two donor atom positions of a starting material with higher symmetry such as α,α′-dihydroxy-*o*-xylene or an α,α′-dihalo-*o*-xylene. At present, the synthesis of these ligands is achieved through conversion of α,α′-dihydroxy-*o*-xylene to a cyclic sulfite, followed by Ru-catalysed oxidation to the corresponding cyclic sulfate and then by two sequential nucleophilic substitution steps with different lithium phosphides[4] or lithium phosphide–boranes.[5] This synthetic methodology is limited, however, by the availability of the two nucleophilic reagents for the final synthetic steps. Herein, we report the synthesis and characterisation of the novel compounds *o*-(chloromethyl)benzyldi-*t*-butylphosphine–borane **1** and *o*-(methoxymethyl)benzyldi-*t*-butylphosphine–borane **2** (Fig. 1), as potentially versatile reagents for the synthesis of C_s-symmetric diphosphine ligands of this type.

The synthesis of **1** was achieved *via* the reaction of α,α′-dichloro-*o*-xylene with lithium di-*t*-butylphosphide–borane in diethyl ether at room temperature (Scheme 1).[6] The reaction of stoichiometric quantities of the reactants results in a statistical distribution of products, and therefore a theoretical maximum 50% yield of the desired product. However, using an excess of the xylene reagent increases the proportion of the desired product, and unreacted starting material can be removed from the crude product by sublimation (and recycled for use in subsequent reactions). The borane protecting group is key to this synthetic strategy for three reasons: most importantly it prevents cyclisation to the corresponding cyclic phosphonium ion, it also renders the product an easily handled air-stable crystalline solid and it protects the phosphorus atom from oxidation and other side reactions in any subse-

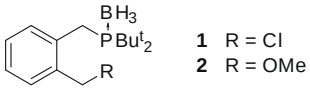
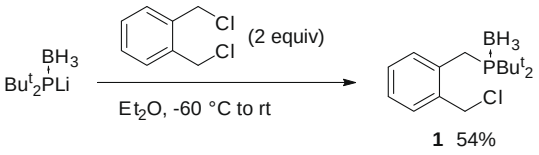


Figure 1. *o*-Substituted benzyldi-*t*-butylphosphine–boranes.



Scheme 1. Synthesis of *o*-(chloromethyl)benzyldi-*t*-butylphosphine-borane **1**.

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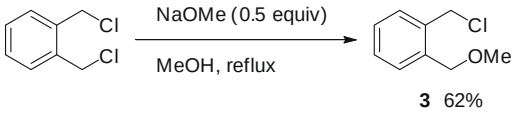
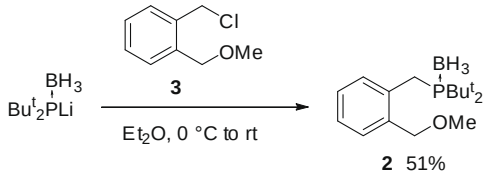


Scheme 2. Synthesis of α-chloro-α′-methoxy-*o*-xylene **3**.



Scheme 3. Synthesis of *o*-(methoxymethyl)benzyldi-*t*-butylphosphine-borane **2**.

quent reaction steps. The borane protecting group is easily removed at any stage with an amine base.[7]

Attempts have been made to convert **1** into **2** using various sources of methoxide, however in all cases, abstraction of the borane protecting group occurred followed by cyclisation of the starting material to the corresponding cyclic phosphonium chloride. For this reason, the synthesis of **2** requires the use of α-chloro-α′-methoxy-*o*-xylene **3**.† This compound was first synthesised by Murahashi in crude form[8] and subsequently synthesised and isolated successfully by Mann and Stewart in 1954, requiring at least three reaction steps from a commercially available material.[9] To the best of our knowledge, there have been no other published syntheses of this material. We have developed an improved method for the synthesis of **3**, requiring only one reaction step and producing yields similar to those of Mann and Stewart.

As shown in Scheme 2, α,α′-dichloro-*o*-xylene was treated with sodium methoxide in methanol at reflux.[10] Again, the reaction of stoichiometric quantities of the reactants resulted in a statistical distribution of products, and therefore a theoretical maximum 50% yield of the desired product. However, when a solution of sodium methoxide in methanol was added dropwise to a refluxing solution of excess α,α′-dichloro-*o*-xylene, the resulting yield of compound **3** increased considerably. The desired product can be isolated via two flash column chromatography steps to give an overall yield of 62%. This method is significantly more atom economic and time efficient than previously reported methods.

Compound **3** can be combined with lithium di-*t*-butylphosphide–borane in diethyl ether at 0 °C to generate the *o*-substituted benzyldi-*t*-butylphosphine–borane **2** as an air-stable white crystalline solid in a 51% yield (Scheme 3).[11]

In conclusion, we have synthesised novel *o*-substituted benzyldi-*t*-butylphosphine–boranes, which are potentially useful reagents for the synthesis of new phosphine ligands containing an *o*-xylene-based backbone. We have also developed a new method for the synthesis of α-chloro-α′-methoxy-*o*-xylene, which is more atom economic and time efficient than previously reported methods.

Acknowledgement

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References and notes

1. Tooze, R. P.; Eastham, G. R.; Whiston, K.; Wang, X. L. W. O. Patent 9619434, 1996; *Chem. Abstr.* **1996**, *125*, 145592.
2. For examples, see: (a) Bunel, E. E.; Clark, D. A. W.O. Patent 2002048094, 2002; *Chem. Abstr.* **2002**, *137*, 47592.; (b) Itsuno, S.; Ooka, K.; Sagae, T.; Inoue, T. J.P. Patent 2005247703, 2005; *Chem. Abstr.* **2005**, *143*, 307307.; (c) Keep, A. K.; Collard, S.; Hooper, M. W.; Colacot, T. J. W.O. Patent 2007029031, 2007; *Chem. Abstr.* **2007**, *146*, 329185.; (d) Eastham, G. R.; Waugh, M.; Richards, P. I. W.O. Patent 2008075108, 2008; *Chem. Abstr.* **2008**, *149*, 106861.
3. For examples, see: (a) Sesto, B.; Consiglio, G. *Chem. Commun.* **2000**, 1011–1012; (b) Gridnev, I. D.; Higashi, N.; Imamoto, T. *Organometallics* **2001**, *20*, 4542–4553; (c) Li, R.-X.; Li, X.-J.; Wong, N.-B.; Tin, K.-C.; Zhou, Z.-Y.; Mak, T. C. W. *J. Mol. Catal. A: Chem.* **2002**, *178*, 181–190; (d) Raebiger, J. W.; Miedaner, A.; Curtis, C. J.; Miller, S. M.; Anderson, O. P.; DuBois, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 5502–5514.
4. Leone, A.; Consiglio, G. *Helv. Chim. Acta* **2005**, *88*, 210–215.
5. Rucklidge, A. J.; Morris, G. E.; Slawin, A. M. Z.; Cole-Hamilton, D. J. *Helv. Chim. Acta* **2006**, *89*, 1783–1800.
6. *Preparation of o-(chloromethyl)benzyldi-t-butylphosphine-borane **1**:* A mixture of di-*t*-butylphosphine (24 mmol) and borane-dimethylsulfide complex (28 mmol) was stirred in THF (15 mL) under a nitrogen atmosphere for 2 h, and the solvent was evaporated under reduced pressure. The resulting white solid was dissolved in ether (50 mL) and cooled to 0 °C, and a solution of *n*-BuLi in hexanes (24 mmol) was added dropwise with stirring. The mixture was stirred at room temperature for 15 min, then cooled to −60 °C and a solution of α,α′-dichloro-*o*-xylene (70 mmol) in ether (50 mL) was added. After warming to room temperature, the mixture was stirred for 2 h. The resulting solution was filtered and the solvent evaporated under reduced pressure, leaving a pale yellow solid. Unreacted α,α′-dichloro-*o*-xylene was sublimed from the crude material at 50 °C and ~0.1 mmHg overnight, and the desired product **1** was recrystallised from *n*-hexane. White crystals, mp 110 °C, yield 54%. ^{1}H NMR δ (500 MHz, C_6D_6): 0.8–1.5 (br q, J = 95.0 Hz, 3H, BH_3), 1.05 (d, J = 12.3 Hz, 18H, Bu^t), 3.11 (d, J = 12.0 Hz, 2H, CH_2P), 4.72 (s, 2H, CH_2Cl), 6.89 (m, 1H, ArH), 6.98 (m, 2H, ArH), 7.57 (d, J = 7.5 Hz, 1H, ArH); ^{13}C NMR δ (125 MHz, C_6D_6): 21.91 (d, J = 22.9 Hz, CH_2P), 28.27 (d, J = 1.4 Hz, Bu^t), 32.98 (d, J = 24.3 Hz, Bu^t), 46.21 (s, CH_2Cl), 127.54 (d, J = 2.3 Hz, ArC), 128.70 (d, J = 1.4 Hz, ArC), 131.39 (d, J = 1.4 Hz, ArC), 132.29 (d, J = 3.3 Hz, ArC), 135.01 (d, J = 3.2 Hz, ArC), 137.24 (d, J = 4.1 Hz, ArC); ^{31}P NMR δ (121 MHz, C_6D_6): 47.90 (m); IR (film from CH_2Cl_2): 2377 (BH), 2969-2870 cm^{-1} (CH); HRMS calcd for $C_{16}H_{29}BClP$ $[M+Na]^+$: m/z = 321.1686; found: 321.1685; Anal. Calcd for $C_{16}H_{29}BClP$: C, 64.4; H, 9.8. Found: C, 64.1; H, 9.9.
7. Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *178-180*, 665–698.
8. Murahashi, S. *Sci. Papers Inst. Phys. Chem. (Jpn.)* **1936**, *30*, 180–194.
9. Mann, F. G.; Stewart, F. H. C. *J. Chem. Soc.* **1954**, 2819–2822.
10. *Preparation of α-chloro-α′-methoxy-o-xylene **3***: A solution of NaOMe (11 mmol) in methanol (30 mL) was added dropwise to a refluxing solution of α,α′-dichloro-*o*-xylene (22 mmol) in methanol (30 mL) over 30 min. Reflux was continued for 1 h, after which the cooled mixture was concentrated to half volume under reduced pressure. H_2O (40 mL) was added and the mixture was extracted with ether (2 × 40 mL). The combined organic layer was washed with brine (25 mL) and dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give a yellow liquid containing compound **3**, α,α′-dichloro-*o*-xylene and α,α′-dimethoxy-*o*-xylene. The α,α′-dimethoxy-*o*-xylene byproduct was removed by elution through a silica gel column with 5% EtOAc in *n*-hexane (R_f = 0.31). Elution through a silica gel column with 10% toluene in *n*-hexane was then used to separate the unreacted α,α′-dichloro-*o*-xylene (R_f = 0.54) and pure compound **3** (R_f = 0.17). Clear liquid, yield 62%. ^{1}H NMR δ (500 MHz, $CDCl_3$): 3.42 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2O), 4.71 (s, 2H, CH_2Cl), 7.32 (m, 2H, ArH), 7.38 (m, 2H, ArH); ^{13}C NMR δ (125 MHz, $CDCl_3$): 43.80 (s, CH_2Cl), 58.54 (s, OCH_3), 72.39 (s, CH_2O), 128.57 (s, ArC), 128.94 (s, ArC), 129.65 (s, ArC), 130.43 (s, ArC), 136.09 (s, ArC), 136.72 (s, ArC); IR (liquid film): 1088 (CO), 3068–2823 cm^{-1} (CH); Anal. Calcd for $C_9H_{11}ClO$: C, 63.4; H, 6.5. Found: C, 63.8; H, 6.6.
11. *Preparation of o-(methoxymethyl)benzyldi-t-butylphosphine-borane **2***: A mixture of di-*t*-butylphosphine (3 mmol) and borane-dimethylsulfide complex (3 mmol) was stirred in THF (4 mL) under a nitrogen atmosphere for 2 h, and the solvent was evaporated under reduced pressure. The resulting white solid was dissolved in ether (30 mL) and cooled to 0 °C, and a solution of *n*-BuLi in hexanes (3 mmol) was added dropwise with stirring. The mixture was stirred at room temperature for 30 min, then cooled to 0 °C and a solution of α-chloro-α′-methoxy-*o*-xylene **3** (3 mmol) in ether (20 mL) was added. After warming to room temperature, the mixture was stirred overnight. The resulting solution was filtered and the solvent evaporated under reduced pressure, leaving a clear liquid. The desired product **2** was recrystallised from *n*-hexane. White crystals, mp 77 °C, yield 51%. ^{1}H NMR δ (500 MHz, C_6D_6): 1.0–1.8 (br q, J = 95.0 Hz, 3H, BH_3), 1.08 (d, J = 12.5 Hz, 18H, Bu^t), 3.09 (s, 3H, OCH_3), 3.16 (d, J = 12.5 Hz, 2H, CH_2P), 4.44 (s, 2H, CH_2O), 6.99 (t, J = 8.0 Hz, 1H, ArH), 7.11 (d, J = 7.5 Hz, 2H, ArH), 8.10 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR δ (125 MHz, C_6D_6): 21.16 (d, J = 24.4 Hz, CH_2P), 28.18 (d, J = 1.0 Hz, Bu^t), 33.06 (d, J = 24.8 Hz, Bu^t), 57.54 (s, OCH_3), 74.36 (s, CH_2O), 126.75 (d, J = 1.9 Hz, ArC), 130.66 (d, J = 1.0 Hz, ArC), 131.92 (d, J = 2.9 Hz, ArC), 135.50 (d, J = 2.9 Hz, ArC), 136.55 (d, J = 5.3 Hz, ArC), (other ArC obscured by solvent peak); ^{31}P NMR δ (121 MHz, C_6D_6): 47.30 (m); IR (film from CH_2Cl_2): 1070 (CO), 2380 (BH), 2967–2871 cm^{-1} (CH); HRMS calcd for $C_{17}H_{32}BOP$ $[M+Na]^+$: m/z = 317.2182; found: 317.2180; Anal. Calcd for $C_{17}H_{32}BOP$: C, 69.4; H, 11.0. Found: C, 69.2; H, 11.1.

† **CAUTION** This compound has been reported to be strongly lachrymatory, and to cause headaches, and visual and gastric disturbance.[9]