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A New Efficient Preparation of Polyfunctional Phosphines Using Zinc Organometallics

Falk Langer and Paul Knochel*

Fachbereich Chemie der Philipps-Universität Marburg D - 35032 Marburg, Germany

Abstract: The reaction of diorganozincs or organozinc halides with chlorophosphines $(Ph_nPCl_{3,n})$ produces polyfunctional phosphines in high yields. This method has been used to prepare several chiral phosphines in high enantiomeric purity.

Chiral phosphines are an important class of ligands for the preparation of transition metal complex catalysts of interest in asymmetric synthesis.¹ Their preparation^{1,2} is often complicated and may require tedious multi-step procedures. Both nucleophilic and electrophilic substitutions have been used to introduce the phosphorus functionality.³ Thus the reaction of chlorodiphenylphosphine with Grignard or lithium reagents leads to phosphines in moderate yields³ and does not allow the direct introduction of *functionalized* organic groups. Herein, we wish to report a new general synthesis of polyfunctional phosphines using the reaction of organozinc reagents 1 or 2 with chlorophosphine derivatives (Scheme 1). Remarkably, the reaction affords high yields of the phosphines 3 protected as the corresponding borane⁴ adducts 4 and requires only mild reaction conditions (Scheme 1 and Table 1).

Scheme 1

 $\begin{array}{cccc} (FG-R)_2Zn & 1 & Ph_2PCI, THF & BH_3 \cdot Me_2S & FG-R - PPh_2 \cdot BH_3 \\ or & 0 \circ C, 1 h & FG-R - PPh_2 & 0 \circ C & 4 : 80 - 95 \% \end{array}$

FG = CN, Cl, Br, ester, enone.

Thus, the reaction of dioctylzinc **1a** (0.5 equiv) with chlorodiphenylphosphine in THF is complete within 1h at 0 °C affording the desired diphenyloctylphosphine **3a** which was isolated as its borane adduct **4a** in 96 % yield. It should be noted that *both octyl groups* are transferred from zinc to phosphorus. By using octylzinc iodide **2a** (1 equiv), a similar reaction is observed leading to **4a** in 89 % isolated yield (entry 1 of Table 1). Starting from (1S)-(-)- β -pinene, the chiral phosphine derivative **4b** is obtained in a one-pot synthesis with 90 % overall yield via a hydroboration, boron-zinc exchange⁵ and phosphorylation with Ph₂PCl (entry 2). The use of functionalized diorganozincs furnishes an expedient method for the preparation of polyfunctional phosphines bearing a bromide, cyanide, ester or keto functionality (entries 3-5, 7 of Table 1). Benzylic secondary alkyl and alkenyl zinc derivatives can be used as well leading to the corresponding phosphine-borane adducts in 60-83 % yield (entries 6-9). Functionalized triarylphosphines such as **4j** can be obtained by react-sing arylzinc derivatives which PCl₃. Arylzinc derivatives are themselves conveniently obtained by a low tem-

perature bromine-lithium exchange⁶ of aromatic bromides, followed by transmetalation with zinc iodide (Scheme 2).



Other halogenophosphines can be used with equal success and the reaction of dichlorophenylphosphine with di-*cis*-myrtanylzinc **1b** prepared form (1S)-(-)- β -pinene and borane-methyl sulfide complex^{7,8} provides the desired chiral dimyrtanylphenylphosphine-borane adduct **5** in 85 % yield. Similarly the reaction of **1b** with PCl₃ gives the chiral C₃-symmetrical phosphine **6** in 75 % yield. Finally the chelating phosphine derivative **7** is obtained in 70 % yield by the reaction of the chiral dialkylzinc **1b** with commercially available 1,2-bis(dichlorophosphino)ethane (Scheme 3). The phosphine-borane complexes can be readily converted to the free phosphine by treatment with diethylamine (excess, 50 °C, 5h)⁹. The complexes **4a**, **4f** and **7** have been converted under these conditions to the free phosphines in >95 % yield.



Entry	R ₂ Zn (R)	Product 4		Yield ^a (%)
1	Oct-	Ph ₂ (Oct)P-BH ₃	4a	96 (89) ^b
2		PPh ₂ •BH ₃	4b	90
3	Br	Br PPh ₂ •BH ₃	4 c	82
4		NC PPh ₂ •BH ₃	4d	86
5	\rightarrow		4e	83
6	Ph Ph	Ph Ph PPh ₂ •BH ₃	4f	83
7	ci~~~~	CI PPh2 •BH3	4g	72¢
8	Ů,	P(O)Ph ₂	4h	60 ^d
9	\bigcirc	PPh ₂ •BH ₃	4 i	90

 Table 1. Phosphine-borane complexes 4a-i prepared by the reaction of chlorodiphenylphosphine with zinc organometallics.

^aAll yields are isolated yields of analytically pure products.

^bYield obtained by using OctZnI instead of Oct₂Zn.

^cThe organozinc reagent was prepared from the corresponding alkenyl iodide (compare with scheme 2 and see ref. 6).

The free phosphine was not protected as its borane complex, but was isolated as the phosphine oxide 4g.

In summary, we have developed a high yielding synthesis of polyfunctional phosphines starting from readily available diorganozincs or alkylzinc halides. This method also allows a convenient one-pot preparation of a range of chiral phosphines of interest for asymmetric synthesis. Further investigations are underway.

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- 8. Typical procedure: Preparation of (-)-1,2-bis(cis-dimyrtanylphosphino)ethane (8).

a) Preparation of (-)-tri-*cis*-myrtanylborane. (1S)-(-) β -pinene (13.6 g, 100 mmol) was cooled to -10 °C and borane-methyl sulfide complex (2.28 g, 30 mmol) was added. A thick precipitate was formed within 10 min. The heterogeneous reaction mixture was diluted with ether (15 mL) and was stirred 2 h at 0 °C and 8 h at rt. The solvents and excess β -pinene were removed by vacuum at rt affording tri-*cis*-myrtanylborane as a white solid (12.6 g, 29.7 mmol, 99 % yield).

b) Preparation of di-*cis*-myrtanylzinc (1b). The above prepared trialkylborane (12.5 g, 29.6 mmol) was suspended in hexanes (12 mL) and cooled to 0 °C. Diethylzinc (6 mL, 60 mmol) was added and the mixture was stirred for 30 min. The solvents and excess diethylzinc were pumped off (0.1 mm Hg, rt, 1h). To ensure the quantitative formation of 1b, diethylzinc (6 mL) was again added. The reaction mixture was stirred for 15 min and the excess diethylzinc was again evaporated as described above. The resulting clear oil was stirred at 40 °C for 4 h at 0.1 mm Hg affording analytically pure (¹H and ¹³C-NMR) di-*cis*-myrtanylzinc 1b (15.0 g, 44.1 mmol; 99 % yield). It can be stored several months at 0 °C as a THF solution.

c) Preparation of (-)-1,2-*bis*(*cis*-dimyrtanylphosphino)ethane-bisborane complex 7. A THF solution of 1b (6.61 g, 6 mmol; ca. 1M solution, 1.5 equiv) was cooled to 0 °C and 1,2-bis(dichlorophosphino)-ethane (0.46 g, 2 mmol) was slowly added with a syringe (exothermic reaction). The ice-bath was removed and the colourless reaction mixture was heated overnight to 40 °C. The reaction mixture was cooled back to 0 °C, a dichloromethane solution of borane-methyl sulfide (6 mL, 6 mmol of a 1M solution) was added and it was worked up as usually. The residue obtained after evaporation of the solvent (ether) was purified by flash chromatography (hexanes:ether:CH₂Cl₂ 17:1:2) affording the phosphine-borane complex 7 as a white solid (0.93 g, 1.4 mmol; 70 % yield, mp = 148 °C; $[\alpha]_D^{25} = -38.2$ (c = 3.35 in chloroform).

d) Preparation of (-)-1,2-bis(cis-dimyrtanylphosphino)ethane (8). The phosphine-bisborane complex 7 (333 mg, 0.5 mmol) was heated with diethylamine (731 mg, 1 mL, 10 mmol) at 50 °C for 45 min. The excess diethylamine and the formed complex (borane-diethylamine) was pumped off (0.1 mm Hg, 50 °C, 15 min). The procedure was repeated four times and the crude product was diluted with ether. After evaporation of the solvent, the pure diphosphine 8 was obtained in almost quantitative yield (315 mg) as a white solid (mp = $120 \,^{\circ}$ C; $[\alpha]_D^{25} = -24.7$ (c = 3.0 in chloroform)).

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