Phosphine Oxide Anions in the Synthesis of Phosphine Ligands

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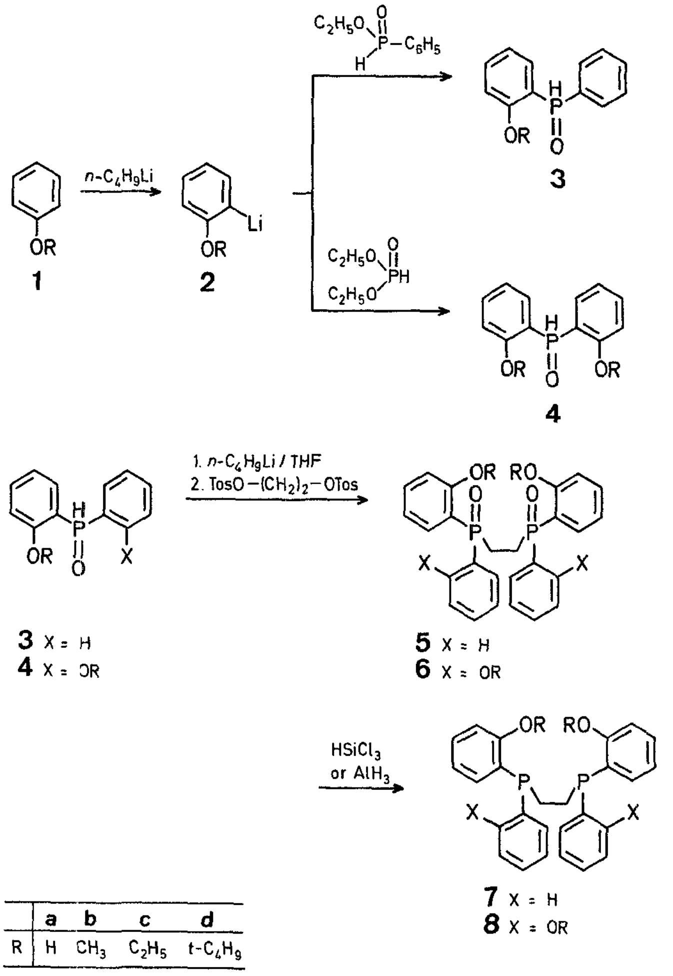
Bis-phosphines are widely employed as bidentate ligands in transition-metal-catalysed reactions[1]. In attempts to improve catalyst selectivities, a number of distinct preparative methods for bis-phosphines have enabled the incorporation of additional functionalities that exert either an electronic or a steric (notably chiral) influence in the close environment of the chelated metal centre[2-5]. In what is still the most general preparative method, that of double substitution by a (hard) phosphide anion nucleophile, a competing trivial elimination often predominates and the yield of the bis-phosphine is low (below 30%). We now describe significant improvements to literature procedures that enable the soft phosphine *oxide* anion to be used to advantage in a high-yield preparative method for a series of substituted *p,p'*-bis[diaryl]-bis-phosphines. The method is both flexible and practical, and reduces to a minimum the handling of toxic and/or air-sensitive materials.

In this series, the phosphine oxide **3** or **4** is prepared from aromatic ethers **1** by lithiation with *n*-butyllithium, which proceeds with a positional selectivity through coordinative stabilisation of the lithium cation by a hetero atom substituent. Alternatively, halogen-metal exchange can be used to generate either the same lithium salt, or a positional isomer, from the appropriately substituted aromatic halide (typically bromide)[6]. Except where lithiation is known to proceed efficiently, we would recommend the isolation of the lithium salt **2** (which can be stored conveniently in an inert atmosphere over long periods) before condensation with a phosphorus(III) ester (typically diethyl phosphite[7] or ethyl phenylphosphinate[8]) in either diethyl ether or tetrahydrofuran. The diaryl- or arylphenylphosphine oxides **4** or **3** can be reacted further or readily isolated as highly crystalline solids in yields in excess of 80%.

Bis[*o*-*t*-butoxyphenyl]phosphine oxide (**4d**; R=t-C_4H_9; prepared from *t*-butyl phenyl ether[9] by lithiation in cyclohexane[10], followed by addition of diethyl phosphite) on treatment with trifluoroacetic acid in chloroform gives the corresponding bis-phenol **4a**, R = H, which can be obtained more directly, but in very poor yield (17%), by lithiation of *o*-bromophenol[11]. The bis-phenol **4a** can be selectively alkylated using a weak base such as potassium carbonate and an alkyl bromide (use of stronger bases such as sodium hydride result in alkylation at the phosphorus centre), and is therefore useful as a versatile intermediate for the attachment of different functional groups.



	a	b	c	d
R	H	CH_3	C_2H_5	t-C_4H_9

Addition of one equivalent of *n*-butyllithium to the diarylphosphine oxide **3** or **4** dissolved in tetrahydrofuran affords a homogeneous orange solution of the anion, which at 0 °C is reacted with added (solid) 1,2-ethanediyl bis-tosylate. After discharge of the colour, the mixture is heated at the reflux temperature for two hours and the bis-substitution product, the 1,2-ethanediylbis[diarylphosphine oxide] **5** or **6**, is isolated in yields between 85 and 95%. (Alkyl substituents on the bridging ethane fragment appear to have no adverse effect on the nucleophilic substitution.)[12]

Reduction of the bis-phosphine oxides that contain two or less *o*-substituted aryl rings (Type **5**) can be achieved using the system chlorosilane/tri-*n*-butylamine/acetonitrile as described in a published procedure[2], without further modification. Additional *o*-substituents (Type **6**) confer only partial

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solubility in this reducing system and these oxides are best reduced by the commercially available aluminium hydride (as a diethyl ether complex, from Ventron Company) in warm tetrahydrofuran. In the only literature precedent, the reduction of triphenylphosphine oxide[13], the reaction was worked up by the addition of aqueous sodium hydroxide. It is easier and cleaner to add methanol when reduction is complete (as judged by thin layer chromatograms on the reaction mixture) and to remove in the filtrate the bis-phosphine **7** or **8**. Indeed, because of the extreme convenience of this reduction method, we would recommend it generally for small-scale work with both types of bis-phosphines **7** and **8**.

In the preparation of these ligands, and more complex macrocycles, we have found the phosphine oxide anion to be a pow-

Table. Compounds **3-8** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	M.S.[b] *m/e* (rel. int. %)	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$)[c] δ [ppm]
3a	84	188-191°	$C_{12}H_{11}O_2P$ (218.2)	219 (M^+ + H, 100)	8.20 (d, 1 H, J_{HP} = 510 Hz); 7.9-7.7 (m, 3 H); 7.7-7.4 (m, 4 H); 7.2-6.7 (m, 2 H)[d]
3b	85	105-106°	$C_{13}H_{13}O_2P$ (232.2)	233 (M^+ + H, 100)	8.12 (d, 1 H, J_{HP} = 500 Hz); 7.9-7.5 (m, 3 H); 7.5-7.4 (m, 4 H); 7.2-6.7 (m, 2 H); 3.72 (s, 3 H)
3c	78	69°	$C_{14}H_{15}O_2P$ (246.2)	247 (M^+ + H, 100)	8.12 (d, 1 H, J_{HP} = 500 Hz); 8.0-7.5 (m, 3 H); 7.5-7.3 (m, 4 H); 7.2-6.7 (m, 2 H); 3.94 (q, 2 H, J = 7 Hz); 1.16 (t, 3 H, J = 7 Hz)
3d	86	84°	$C_{16}H_{19}O_2P$ (274.3)	275 (M^+ + H, 24); 219 (M^+ + H − C_4H_8, 100)	8.11 (d, 1 H, J_{HP} = 499 Hz); 8.0-7.6 (m, 3 H); 7.6-7.3 (m, 4 H); 7.2-7.0 (m, 2 H); 1.35 (s, 9 H)
4a	99	193-196°	$C_{12}H_{11}O_3P$ (234.2)	235 (M^+ + H, 100)	8.26 (d, 1 H, J_{HP} = 518 Hz); 7.7-7.4 (m, 4 H); 7.1-6.8 (m, 4 H)[d]
4b	81	135-136°	136[7]	263 (M^+ + H, 100)	8.26 (d, 1 H, J_{HP} = 515 Hz); 7.8-7.4 (m, 4 H); 7.1-6.7 (m, 4 H); 3.75 (s, 6 H)
4d	76	92-93°	$C_{20}H_{27}O_3P$ (346.4)	347 (M^+ + H, 48); 291 (M^+ + H − C_4H_8, 21); 235 (M^+ + H − 2 C_4H_8, 100)	8.19 (d, 1 H, J_{HP} = 517 Hz); 7.8-7.3 (m, 4 H); 7.1-6.9 (m, 4 H); 1.34 (s, 18 H)
5a	98	342-344°	344°[14]	463 (M^+ + H, 100)	8.0-7.3 (m, 14 H); 7.2-6.8 (m, 4 H); 3.2-2.3 (m, 4 H)[e]
5b[f]	86	205-207°	207°[2]	491 (M^+ + H, 100)	8.1-7.5 (m, 6 H); 7.5-7.3 (m, 8 H); 7.2-6.7 (m, 4 H); 3.70 (s, 6 H); 2.8-2.5 (m, 4 H) 8.1-7.6 (m, 6 H); 7.5-7.3 (m, 8 H); 7.2-6.7 (m, 4 H); 3.60 (s, 6 H); 2.8-2.6 (m, 4 H)
5c[g]	75	190-195°	$C_{30}H_{32}O_4P_2$ (518.5)	519 (M^+ + H, 100); 441 (M^+ + H − C_6H_6, 25); 397 (M^+ + H − $C_6H_5OC_2H_5$, 17)	8.2-7.5 (m, 6 H); 7.5-7.2 (m, 9 H); 7.2-6.6 (m, 4 H); 4.02-3.48 (2q, 4 H); 2.8-2.6 (m, 4 H); 1.16-0.76 (2t, 6 H)
5d[g]	81	260-264°	$C_{34}H_{40}O_4P_2$ (574.7)	575 (M^+ + H, 100) 519 (M^+ + H − C_4H_8, 34); 463 (M^+ + H − 2 C_4H_8, 80)	8.2-7.5 (m, 6 H); 7.5-7.2 (m, 8 H); 7.1-6.8 (m, 4 H); 2.8-2.5 (m, 4 H); 1.12 (s, 9 H); 0.96 (s, 9 H)
6b	91	205-206°	$C_{30}H_{32}O_6P_2$ (550.5)	551 (M^+ + H, 65); 443 (M^+ + H − $C_6H_5OCH_3$, 34); 289 [M^+ + H − $PO(C_6H_4OCH_3)_2$, 34); 263 [M^+ + H − $(CH_2)_2$—$PO(C_6H_4OCH_3)_2$, 74]	7.8-7.3 (m, 8 H); 7.1-6.7 (m, 8 H); 3.58 (s, 12 H); 2.7 (m, 4 H)
7c[g]	72	decomp.	$C_{30}H_{32}O_2P_2$ (486.5)	487 (M^+ + H)	7.6-7.2 (m, 14 H); 7.2-6.7 (m, 4 H); 4.10-3.75 (2q, 4 H); 2.5-2.0 (m, 4 H); 1.30-1.00 (tt, 6 H)
7d[g]	78	decomp.	$C_{34}H_{40}O_2P_2$ (542.6)	543 (M^+ + H, 48); 259 ($C_4H_9OC_6H_4PH_2C_6H_5^+$, 26); 231 [$HOC_6H_4PH(C_2H_5^+$, 24]; 203 ($HOC_6H_4PH_2C_6H_5^+$, 100)	7.4-7.0 (m, 14 H); 7.0-6.8 (m, 4 H); 2.2-1.8 (m, 4 H); 1.28 (s, 9 H); 1.22 (s, 9 H)
8b	85	decomp.	$C_{30}H_{32}O_4P_2$ (518.5)	519 (M^+ + H, 7); 411 (M^+ + H − $CH_3OC_6H_5$, 2); 247 [$(CH_3OC_6H_5)_2PH_2^+$, 100]	7.3-7.2 (m, 4 H); 7.1-6.9 (m, 4 H); 6.9-6.7 (m, 8 H); 3.71 (s, 12 H); 2.2-2.1 (m, 4 H)

[a] Satisfactory microanalyses obtained for new compounds **3-6** (C ±0.28, H ±0.16); exceptions: **3c**, C −0.53; **4d**, H −0.96. Compound **3c** was analysed as the phosphinic acid following aerial oxidation; compound **4d** was characterised as the bis-phenol **4a**. Compounds **7** and **8** were characterised by mass, ^{1}H-N.M.R., and ^{31}P-N.M.R. spectrometry and by reoxidation to the corresponding phosphine oxides **5** and **6**.

[b] Measured on Finnigan 4000 and TSQ spectrometers using Methane Chemical Ionisation Mass Spectrometry.

[c] The ^{1}H-N.M.R. spectra were recorded with a Bruker 90 MHz spectrometer.

[d] Recorded in CD_3OD; P—H protons exchange rapidly.

[e] Recorded in $CDCl_3$—CF_3COOH solution.

[f] The two diastereoisomeric forms were separated by crystallisation (chloroform/ether) and measured separately.

[g] Measurements made on diastereoisomeric pairs without separation.

erful but soft nucleophile that accomplishes 1,2-bis-substitution *without elimination*. The oxide functionality further serves as a protecting group for the phosphine moiety, making possible a number of transformations on stable intermediates; yet it can be conveniently removed in this synthetic method for the preparation of known or entirely new bis-phosphine ligands.

The experiments described are representative of the General Method; significant departures from the procedures are mentioned in the text. All reactions were conducted in an atmosphere of dry argon, in solvents freshly distilled from sodium. *n*-Butyllithium was used as supplied (hexane solution, 1.6 molar; Merck). All compounds prepared had structures confirmed by mass (methane-chemical ionisation technique), ^{1}H-N.M.R. (Table 1), and ^{31}P-N.M.R. spectrometry; microanalyses for new compounds were satisfactory.

Bis[*o*-methoxyphenyl]phosphine Oxide (4b):
To a solution of *o*-bromoanisole (100.8 g, 0.54 mol) in pentane (150 ml), *n*-butyllithium solution (337 ml, 0.54 mol) is added slowly with efficient stirring. The mixture is stirred overnight and the resulting suspension is allowed to settle. In a dry box in a nitrogen atmosphere, the liquor is decanted, the solid residue of *o*-anisyllithium is washed well with pentane, and dried under high vacuum to give a powder; yield: 56.5 g (92%); which is stored for later use, or used as follows.

o-Anisyllithium (34.2 g, 0.30 mol) is dissolved in diethyl ether (400 ml) and cooled to −20 °C. Diethyl phosphite (13.8 g, 0.1 mol) is slowly added with efficient stirring, and the solution is then allowed to reach 25 °C, before being warmed at reflux temperature for 2 h. After cooling, 0.1 molar hydrochloric acid (300 ml) is added, and the product is extracted with dichloromethane (3 x 50 ml), and the combined organic layers are dried with magnesium sulphate. The solvents are removed to give an oil and excess anisole is removed by warming (70 °C) under vacuum. The last traces of anisole are removed by washing the resultant white powder with diethyl ether, and following crystallisation from chloroform/diethyl ether the product is obtained, identical to that prepared previously[7]; yield: 21.32 g (81%); m.p. 135–136 °C (Ref.[7], m.p. 136 °C).

1,2-Ethanediylbis[di-*o*-methoxyphenylphosphine Oxide] (6b):
Bis[*o*-methoxyphenyl]phosphine oxide (**4b**; 10.48 g, 40 mmol) in tetrahydrofuran (600 ml) is treated with *n*-butyllithium solution (25 ml, 40 mmol) at 0 °C. The orange homogeneous solution of the lithium salt is stirred for 1 h at room temperature and then cooled to 0 °C when solid 1,2-ethanediyl bis-tosylate (7.4 g, 20 mmol) is added. The colour of the solution fades upon warming to room temperature, and a white slurry formed as the mixture is heated at reflux temperature (overnight). The mixture is then cooled and quenched by the addition of water (150 ml); extraction of the product into dichloromethane (3 x 100 ml), followed by drying with magnesium sulphate and concentration of the solution affords the product as a white crystalline solid; yield: 10.0 g (91%); m.p. 205–206 °C.

$C_{30}H_{32}O_6P_2 \cdot H_2O$	calc.	C 63.38	H 6.03
(568.6)	found	63.55	5.99

1,2-Ethanediylbis[di-*o*-methoxyphenylphosphine] (8b):
Aluminium hydride [$AlH_3 \cdot 1/3\,(C_2H_5)_2O$; Ventron Co., 1.1 g, 20 mmol] is added in portions to a solution of the bis-phosphine oxide **6b** (1.1 g; 2 mmol) in tetrahydrofuran (250 ml). The mixture is warmed at reflux temperature and the reaction monitored by thin layer chromatography until judged to be complete (generally after one night). The reaction is quenched by the addition of methanol (10 ml), followed by separation of the floccular precipitate (aluminium salts) by filtration, and concentration of the filtrate. Addition of methanol affords the crystalline bis-phosphine; yield: 0.88 g (85%); m.p. not measureable (decomposition).

$C_{30}H_{32}O_4P_2$ (518.5)

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