Synthesis of biphenyl-based phosphines by Suzuki coupling

Colin Baillie, Weiping Chen and Jianliang Xiao*

Leverhulme Centre for Innovative Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK

Received 25 September 2001; accepted 19 October 2001

Abstract—A series of phosphine oxides has been synthesised by the palladium-catalysed Suzuki coupling of arylboronic acids with $OPPh_2(o\text{-}C_6H_4Br)$. On reduction with trichlorosilane, functionalised, biphenyl-based phosphine ligands were obtained in good yields. Our preliminary results indicate these ligands to be effective for palladium-catalysed C–C coupling reactions including the formation of their own oxides. © 2001 Elsevier Science Ltd. All rights reserved.

Phosphines play an extremely important role in homogeneous catalysis.[1,2] Those that possess novel electronic and steric properties and functional groups are of particular importance, as they can effect unusual activities and selectivities in metal-catalysed reactions in soluble or supported forms. Amidst such phosphines, those containing 2-biphenyl units have recently been shown to be effective ligands in a number of metal-catalysed reactions, such as asymmetric hydrogenation,[3] allylic alkylation,[4] hydroformylation[5] and C–X (X=C, N, O) bond forming reactions.[6–11] Worth noting is their outstanding performance in effecting palladium-catalysed C–X coupling reactions. In fact, bulky, biphenyl-based phosphines represent one of the most effective classes of ligands identified so far for such reactions. These phosphines are most often prepared by using Grignard and lithium reagents.[4–11] More recently, Buchwald has reported a much-simplified synthesis of alkylphosphinobiphenyl ligands on the basis of the reaction of aryl magnesium halides with benzyne, followed by the addition of a chlorodialkylphosphine.[12]

We have recently reported two simple methods for the synthesis of substituted arylphosphine ligands applicable to catalysis in solvents of widely differing solubility properties such as H_2O and supercritical CO_2.[13,14] One methodology utilises the palladium-catalysed Heck reaction of haloarylphosphine oxides $OPPh_{3-n}(p\text{-}C_6H_4Br)_n$ with olefinic substrates,[13] while the other involves the copper-mediated coupling of the same oxides with perfluoroalkyl iodides.[14] In both cases, the free phosphines are obtained in excellent yields by reduction with a chlorosilane and/or hydrogen. With biphenyl-based phosphine ligands in mind, we have extended these methodologies for the preparation of diphenylphosphinobiphenyl derivatives, employing the Suzuki coupling of $OPPh_2(o\text{-}C_6H_4Br)$ **1** with various arylboronic acids **2**, followed by reduction with trichlorosilane to give the free phosphines **4** (Scheme 1). While the Suzuki coupling is one of the most useful routes for the synthesis of biaryls, it has rarely been used for the direct preparation of phosphine ligands.[15] Our method would provide an easy entry to functionalised biphenyl-based phosphines, as the Suzuki chemistry is known to be tolerant of various functionalities. The details of the method are herein described.

Our synthesis of the phosphines **4** starts with the Suzuki coupling of **1** and **2**, which leads to the phosphine
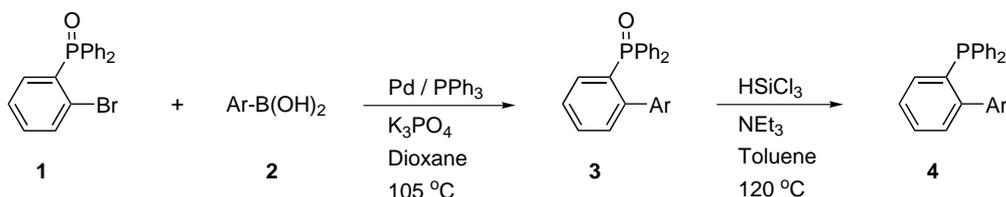
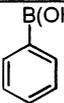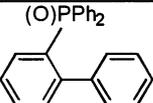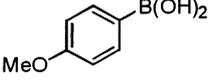**Scheme 1.** Synthesis of biphenyl-based phosphines via Suzuki coupling.
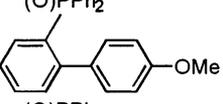
oxides **3**.[16] The coupling reaction was conducted with equimolar amounts of the aryl halide **1** and an aryl boronic acid **2** and 2 equiv. of a base (K_3PO_4) in dioxane at 105°C. The palladium catalyst was formed in situ from $Pd(dba)_2$ and 4 equiv. of PPh_3. Table 1 summarises the results obtained. The *ortho*-positioned $OPPh_2$ moiety in **1** is considerably more bulky than most other *ortho* substituents encountered in Suzuki coupling reactions, and as such one may expect the

coupling of **1** with **2** to be difficult when particularly a ligand such as PPh_3 is to be used, which is neither electron-rich nor bulky in comparison with PR_3 (R = Cy, *t*-Bu) or those based on biphenyls.[6–11,17] PPh_3 was chosen as the ligand as it is the most convenient source of phosphine due to its ready availability and ease of handling. As can be seen, **1** couples readily under the aforementioned conditions with phenylboronic acid **2a** as well as *meta* and *para* substituted aryl boronic acids

Table 1. Suzuki coupling of $OPPh_2(o\text{-}C_6H_4Br)$ **1** with arylboronic acids **2**[a]

Entry	Arylboronic acid	Product	Yield (%)[b]
1	**2a**	**3a**	83
2	**2b**	**3b**	72
3	**2c**	**3c**	78
4	**2d**	**3d**	76
5	**2e**	**3e**	72
6	**2f**	**3f**	66
7	**2g**	**3g**	95[c]
8	**2h**	**3h**	75[c]
9	**2i**	**3i**	74[c]
10	**2j**	**3j**	71[c]
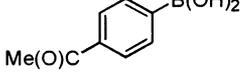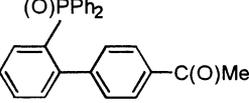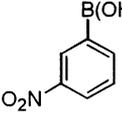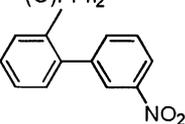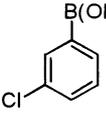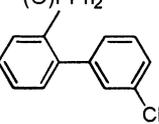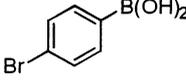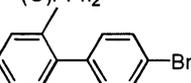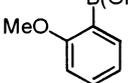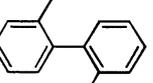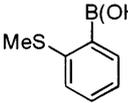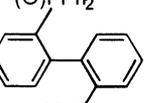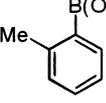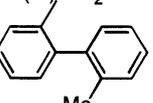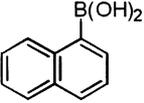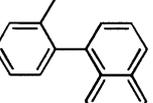
[a] For general reaction conditions, see reference 16. [b] Isolated yields; not optimised. [c] Extra equivalent of **2** added after 24 hours, and the reaction time increased from 12 to 48 h.
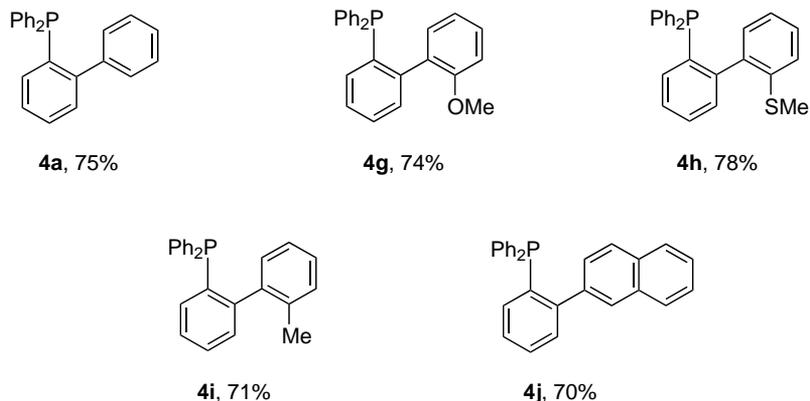
Scheme 2. Isolated biphenyl-based phosphines along with yields.[18]

2b–f to give the expected biaryls in good yields, regardless of the nature of the substituents at 2 (entries 1–4). The coupling of 1 with the halo substituted aryl boronic acids 2e or 2f was carried out by slow introduction of the latter via a dropping funnel. Directly mixing 1 and 2e or 2f resulted in lower yields, probably due to the boronic acid self-coupling and/or coupling with the product. The presence of the functional groups should make phosphines derived from these oxides easily supportable onto solid surfaces or polymers. As with other Suzuki reactions, the coupling of 1 was significantly more difficult with boronic acids containing *ortho* substituents to give di-*ortho*-substituted biaryls (entries 7–10). The yields given in Table 1 were obtained with extra addition of boronic acid during the reaction and prolonged reaction time. P(^{t}Bu)$_3$ was also examined for the reaction of 1 with 2-methoxyphenylboronic acid 2g and 2-methylthiophenylboronic acid 2h, as it had been reported to outperform PPh$_3$ in the cross-coupling of aryl chlorides and aryl boronic acids, and to be tolerant of *ortho* substitution in both substrates.[17] However, the reported conditions for our reactions gave lower yields (71% for 2g and 54% for 2h) than those obtained with PPh$_3$. This may partly be due to P(^{t}Bu)$_3$ being sterically too demanding. Fu has observed that the sterically less hindered PCy$_3$ is more effective than P(^{t}Bu)$_3$ in the Suzuki coupling of aryl chlorides that leads to tri-*ortho*-substituted biaryls.[17]

The free phosphines 4 were obtained from the oxides 3 by reduction with trichlorosilane.[18] The reaction was carried out by simply heating a mixture of 3, trichlorosilane and triethylamine in toluene at 120°C for a few hours, affording the biaryl-based phosphines 4 in crystallised forms with good yields. Some examples are shown in Scheme 2. Interestingly, 4 could also be obtained by coupling 2 with a haloarylphoshine instead of its oxide in the presence of a palladium catalyst without additional ligands. Thus, (2-bromophenyl)-diphenylphosphine PPh$_2$(o-C$_6$H$_4$Br) coupled with 2a (3% Pd(dba)$_2$, 12 h, 105°C), yielding 4a in 79% yield according to ^{31}P NMR. This method could obviate the need for reduction by trichlorosilane if proven to be generally applicable.

Our initial results suggest that these phosphines are effective ligands for Suzuki coupling reactions. Thus,

replacing PPh$_3$ with 4a in the coupling of OPPh$_2$(o-C$_6$H$_4$Br) 1 and phenylboronic acid 2a afforded an 84% conversion of 1 to 3a, the oxide of 4a, in a 6 h reaction time under the conditions described for PPh$_3$. When the sterically more demanding 2-methoxyphenylboronic acid 2g was coupled to 1 in the presence of Pd-4a, an 84% conversion of 1 to 3g was observed after 24 h. More interestingly, Pd-4i [0.1 mol% Pd(dba)$_2$, 4 equiv. of 4i] is effective in catalysing the coupling of the electron-rich 4-bromotoluene with phenylboronic acid, furnishing 4-methylbiphenyl in 92% isolated yield at 60°C in a 24 h reaction time.

We have previously shown that the Heck and related reactions can provide a powerful route to arylphosphines with special solubility properties.[13,14,19] The work presented here shows that functionalised biphenyl-based phosphine ligands can readily be accessed by another class of catalytic C–C bond formation reactions, namely Suzuki coupling reactions. Research is underway to test the applicability of these ligands in catalysis.

Acknowledgements

References

1. *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A., Eds.; VCH: Weinheim, Germany, 1996.
2. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000.
3. Mikami, K.; Aikawa, K.; Korenaga, T. *Org. Lett.* **2001**, *3*, 243.
4. Tsuruta, H.; Imamoto, T. *Synlett* **2001**, *SI*, 999.
5. Kadyrov, R.; Heinicke, J.; Kindermann, M. K.; Heller, D.; Fischer, C.; Selke, R.; Fischer, A. K.; Jones, P. G. *Chem. Ber.* **1997**, *130*, 1663.

6. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

7. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

8. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

9. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

10. Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

11. Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

12. Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

13. Chen, W.; Xu, L.; Xiao, J. *Org. Lett.* **2000**, *2*, 2675.

14. Chen, W.; Xiao, J. *Tetrahedron Lett.* **2000**, *41*, 3697.

15. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

16. A typical procedure is given for **3a**. To a Schlenk tube were charged $OPPh_2(o\text{-}C_6H_4Br)$ **1** (0.500 g, 1.40 mmol) and phenylboronic acid **2a** (0.171 g, 1.40 mmol) together with $Pd(dba)_2$ (0.024 g, 0.04 mmol), PPh_3 (0.044 g, 0.17 mmol) and K_3PO_4 (0.594 g, 2.80 mmol) in 5 ml of dioxane under an atmosphere of argon. The Schlenk tube was stirred at 105°C overnight. After cooling to room temperature, the mixture was diluted with water and extracted with $CHCl_3$ (3×20 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash chromatography (2:1 EtOAc/hexane) and crystallised in EtOAc/hexane to yield **3a** as white crystals in 83% yield (0.410 g, 1.16 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.03 (m); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 28.9 (s); anal. calcd for $C_{24}H_{19}PO$: C, 81.33; H, 5.41; found: C, 81.23; H, 5.39; mp 148–150°C. Compounds **3b**–**j** have all been similarly characterised.

17. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

18. Conditions for the reduction of **3a** to **4a**. A 10 ml toluene solution of **3a** (0.400 g, 1.12 mmol) was frozen in liquid nitrogen, to which were added trichlorosilane (0.57 ml, 5.7 mmol) and triethylamine (0.86 ml, 6.2 mmol). The mixture was stirred at 120°C under argon for 6 h. After cooling to room temperature, a saturated $NaHCO_3$ aqueous solution (1 ml) was added. The mixture was stirred for a further 5 min, filtered through a pad of alumina maintaining an argon atmosphere, washed with degassed toluene (3×10 ml) and evaporated in vacuo to give a crude oily product. This was purified by crystallisation with ethanol to yield the desired product as fine white needles in 75% yield (0.284 g, 0.84 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.19 (m); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −12.3 (s); anal. calcd for $C_{24}H_{19}P$: C, 85.20; H, 5.65; found: C, 84.91; H, 5.65; mp 80–82°C. All the compounds in Scheme 2 have been similarly characterised.

19. Hu, Y.; Banet-Osana, A. M.; Chen, W.; Xiao, J. *Organometallics* **2001**, *14*, 3206.