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Phosphorus–nitrogen–phosphorus ligands: cooperative effects between nitrogen and phosphorus substituents on catalytic activity

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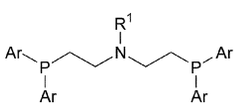
A new generation of PNP compounds bearing different diarylphosphine groups were prepared and used as ligands in palladium-catalysed Suzuki cross-coupling reactions. Rates of oxidative addition of iodobenzene to (PNP)Pd[0] complexes were measured using UV spectroscopy. Synergistic effects between the *N*- and *P*- substituents were identified and correlated in redox and catalytic chemistry.

Introduction

Previously we reported the preparation of a class of hemilabile phosphorus–nitrogen–phosphorus (PNP) ligands of the type $R–N(CH_2CH_2PPh_2)_2$, and their coordination to palladium and ruthenium complexes.[1–3] In palladium-catalysed Heck reactions, the nature of the *N*-substituent has a profound effect on the rates of turnover.[4] In the same study, electron-rich tertiary arylphosphines (PR_3) were found to promote catalytic activity and stability. This led us to speculate that the catalytic activity of the (PNP)Pd complex may be enhanced by increasing the basicity of the arylphosphine moiety. To test this hypothesis, a series of PNP ligands with different electron-rich arylphosphine groups was prepared and their performance in the Suzuki cross-coupling reactions were evaluated.

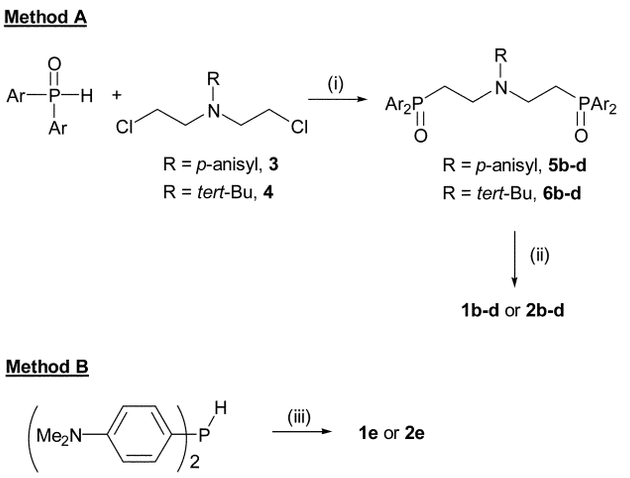


R^1 = *p*-anisole, **1**; R^1 = *tert*-butyl, **2**
Ar = Ph, **a**
Ar = *p*-$CH_3C_6H_4$, **b**
Ar = *p*-$MeOC_6H_4$, **c**
Ar = *o*-$MeOC_6H_4$, **d**
Ar = *p*-$Me_2NC_6H_4$, **e**

Results and discussion

Synthesis of diarylphosphine ligands 1 and 2

The enhanced acidity of secondary diarylphosphine oxides in DMSO[5] was exploited in the syntheses of the new PNP ligands. Diarylphosphine oxide anions may be generated using potassium hydroxide in wet DMSO. Following P–C bond formation with the appropriate nitrogen mustards **3** or **4** (Method A, Scheme 1), amino diphosphine oxides **5** and **6** may be obtained, which were reduced in a basic silane solution to give P(III) ligands **1b–d** and **2b–d**. The reactions generally proceeded in good to excellent yields, except for the electron-rich bis(4-dimethylaminophenyl)phosphine oxide. In this case, a strong base (*t*-BuLi) was used to generate the diarylphosphide nucleophile (Method B, Scheme 1).



Scheme 1 Preparation of ligands **1** and **2**. *Method A:* (i) KOH, DMSO, 50 °C; (ii) $HSiCl_3$, NEt_3, PhMe. *Method B:* (iii) a. t-BuLi, b. **3** or **4**.

Comparative catalytic activity

There have been many reports of highly active palladium catalysts for Suzuki cross-coupling reactions in recent years.[6] A quick survey revealed three main classes of phosphorus ligands that have been employed with good effect in this area: (i) cyclopalladated complexes;[7] (ii) multidentate tetraphosphine-palladium complexes;[8] and (iii) sterically bulky alkylphosphine palladium complexes.[9] With the exception of the last class of examples, elevated reaction temperatures (≥ 100 °C) are often required in the first two systems, especially for the less activated aryl bromides and chlorides. It is necessary to exercise caution with the interpretation of these results, as it has been recently suggested that certain palladacycles are unstable at high temperatures, generating colloidal/monomeric palladium species which are the true catalytic precursors.[10]

With this in mind, the lowest feasible reaction temperature was adopted in our catalytic studies, in order to preserve the integrity of the organopalladium species. Employing unactivated 4-bromotoluene and 4-methoxyphenylboronic acid as substrates in our initial studies, several reaction parameters were examined, including: metal-to-ligand ratio (1 : 1 to 1 : 2), solvent (DME, THF, dioxane, toluene), additive (K_3PO_4, CsF, Cs_2CO_3), temperature (65, 85, 100 °C) and palladium precursor [$Pd(OAc)_2$, $Pd_2(dba)_3$·$CHCl_3$], which led ultimately to the identification of the optimal reaction conditions (Scheme 2).

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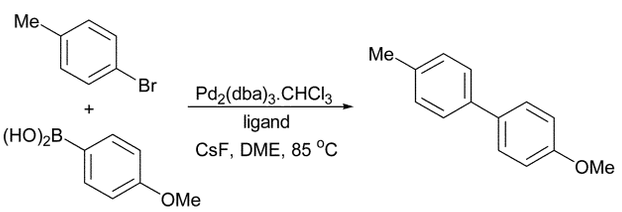
Table 1 Catalytic activity of aminodiarylphosphine ligands **1** and **2** in Suzuki-coupling reactions between 4-bromotoluene and 4-methoxyphenylboronic acid (Scheme 2)[a]

Entry	Ligand	% Conversion (2 h)	% Conversion (20 h)	Isolated yield[b] (%)
1	**1a**	12	36	28
2	**1b**	44	95	88
3	**1c**	24	83	77
4	**1d**	22	47	38
5	**1e**	56	98	91
6	**2a**	26	79	67
7	**2b**	72	93	86
8	**2c**	42	91	85
9	**2d**	21	80	78
10	**2e**	64	100	96

[a] Under optimised reaction conditions, using $Pd_2(dba)_3.CHCl_3$ (1 mol%), ligand (2.2 mol%) and CsF (2 eq.) in DME at 85 °C. Reactions were duplicated to within ±3%. [b] After 20 h, following purification by column chromatography.



Scheme 2 Suzuki coupling reaction between 4-bromotoluene and 4-methoxyphenylboronic acid.

The progress of the reactions promoted by ligands **1e**, **2c** and **2e** was monitored by GC analysis of reaction aliquots extracted during the catalytic reactions (Fig. 1). In all three cases no induction period was observed, thus supporting our belief that the (PNP)Pd[0] complexes generated *in situ* under these reaction conditions are the true catalytic precursors.

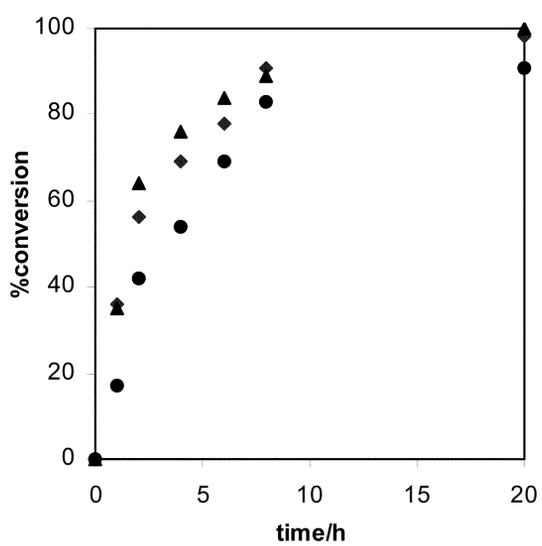
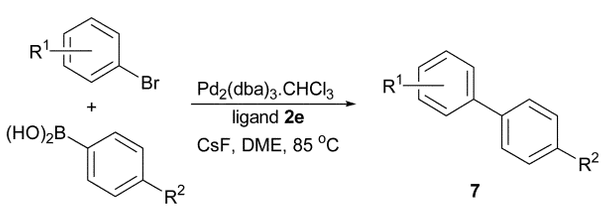


Fig. 1 Rate of 4-bromotoluene consumption *vs.* time (◆ **1e**, ● **2c**, ▲ **2e**).

Comparing the catalytic activity promoted by ligands **1** and **2**, the second generation of amino diarylphosphine ligands do indeed outperform the aminodiphenylphosphine ligands **1a** and **2a** (Table 1, entries 1 and 6). On the whole, the *tert*-butylamino ligands **2a**–**e** display higher rates of turnover than their counterparts **1a**–**e** (entries 1–5 and entries 6–10).

Examining the results within each class of ligand, it is clear that the introduction of electron-donating groups at the *para*-position of the diarylphosphine moiety improves the rate and yield of the reaction (a < b ≈ c < e). Moving the substituent to the *ortho*-position clearly imposes a detrimental effect on the catalytic activity (entries 3 and 4, and entries 8 and 9).

Combining electron-rich phosphine and nitrogen substituents, the ligand **2e** was found to afford the highest and quickest turnovers. The synthetic utility of this ligand was thus investigated in the coupling of a number of other substrates (Scheme 3, Table 2). A number of electron-rich and electron-poor aryl bromides and arylboronic acids were assessed in this study.



Scheme 3 Suzuki coupling using ligand **2e**.

Homocoupling between arylboronic acids is known to occur in certain palladium-catalysed systems, especially when the cross-coupling is very slow.[11] Thus it is important to note that even in the more difficult couplings, we did not detect any competitive homocoupling – GC analysis of the reaction mixture and the isolated material showed only the expected cross-coupled product.

Unsurprisingly, the electron poor 4-bromoacetophenone (entries 1–3) gave the highest yields of over 90% with the quickest rates of turnover. With the unactivated 4-bromotoluene, isolated yields of above 80% may also be obtained (entries 4–6). It is commonly acknowledged that electron-rich aryl halides are often the most difficult substrate to activate. In this regard, we are pleased to see that ligand **2e** was able to activate 4-bromoanisole towards the coupling reaction under these mild conditions (entries 7–9). Even the sterically demanding 2-bromoanisole gave acceptable yields (entries 10–12).

Examining the yields from different aryl boronic acids, we noticed that the electronically 'neutral' phenylboronic acid gave noticeably lower yields, compared to the electron-rich and electron-poor arylboronic acids in each of these series (entries 3, 6, 9 and 12). This unusual result is particularly interesting when compared to an earlier report of a tetraphosphine/[PdCl-(η^3-C_3H_5)]$_2$ system, where the electronic property of the arylboronic acid component was studied, and was found to be insignificant.[8]

Coordination/redox chemistry of palladium(0) precursors generated from ligands 1 and 2

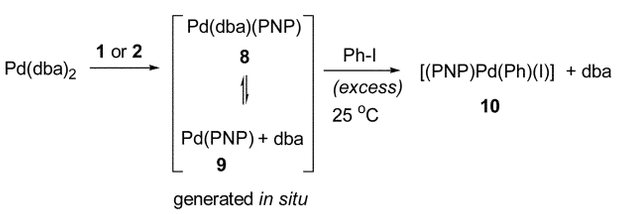
In order to understand the interplay of steric and electronic effects between the nitrogen and phosphorus donors and their influence on the resultant catalytic chemistry, the comparative reactivity of palladium(0) complexes generated from the ligands **1** and **2** towards the oxidative addition reaction with aryl halides was explored.

Table 2 Ligand **2e** in the Suzuki cross coupling between several aryl bromides and arylboronic acids (Scheme 3)[a]

Entry	R^1	R^2	Product	Time/h	Yield (%)[b]
1	4-COMe	MeO	**7a**	10	97
2	4-COMe	F	**7b**	10	95
3	4-COMe	H	**7c**	10	92
4	4-Me	MeO	**7d**	20	96
5	4-Me	F	**7e**	20	82
6	4-Me	H	**7f**	20	62
7	4-MeO	MeO	**7g**	20	63
8	4-MeO	F	**7h**	20	79
9	4-MeO	H	**7i**	20	57
10	2-MeO	MeO	**7j**	20	59
11	2-MeO	F	**7k**	20	61
12	2-MeO	H	**7l**	20	48

[a] Reaction conditions are the same as described in Table 2. [b] Purified yields after column chromatography.

As was observed previously, coordination of these ligands to $Pd(dba)_2$ generates a mixture of rapidly exchanging Pd(0) species **8** and **9** (Scheme 4), which undergo reaction with iodobenzene to furnish a single palladium(II) species, as indicated by the observation of a sharp single resonance peak in the ^{31}P NMR spectrum, corresponding to a cationic $[(PNP)Pd(Ph)]^+I^-$ complex, **10**.[1]



Scheme 4 Generation of palladium(0) precursor and oxidative addition with iodobenzene.

The rate of oxidative addition of iodobenzene to the (PNP)-Pd[0] complexes was investigated at 25 °C. Palladium(0) precursors were generated by mixing equimolar quantities (1 mM) of the $Pd(dba)_2$ with the PNP ligands in THF. The solution gives rise to a single UV absorption peak at $\lambda_{max} = 395$ nm. The rate of disappearance of this absorption peak was monitored in the presence of an excess (10 equivalents) of iodobenzene (Fig. 2), and was found to be first order in [Pd]. Rate data can thus be extrapolated from the resultant logarithmic plots (Table 3). Comparison of the relative rates of the oxidative addition of iodobenzene to anisylaminodiphosphine ligands

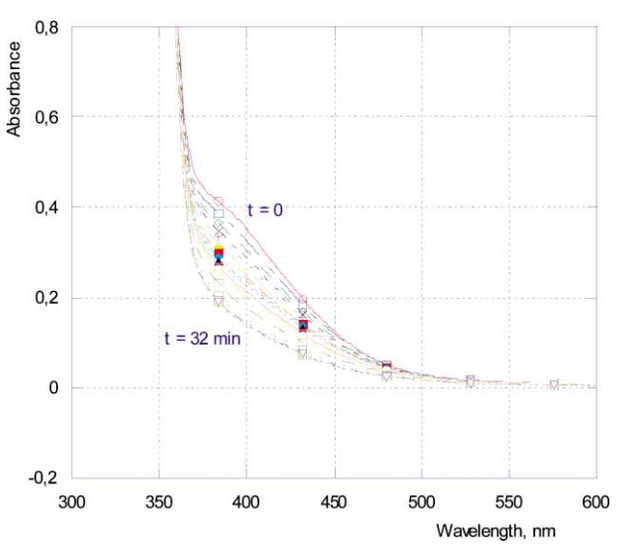


Fig. 2 Progress of oxidative addition of iodobenzene to [(**1b**)-Pd(PNP)] complex, generated *in situ* in the UV cell.

Table 3 Rate of oxidative addition of iodobenzene to [(PNP)Pd(dba)] complex[a]

Entry	PNP ligand	k ($\times 10^{-4}$ s^{-1})[b]
1	**1a**	190
2	**1b**	36
3	**1e**	25
4	**2a**	26
5	**2b**	180
6	**2e**	7.8

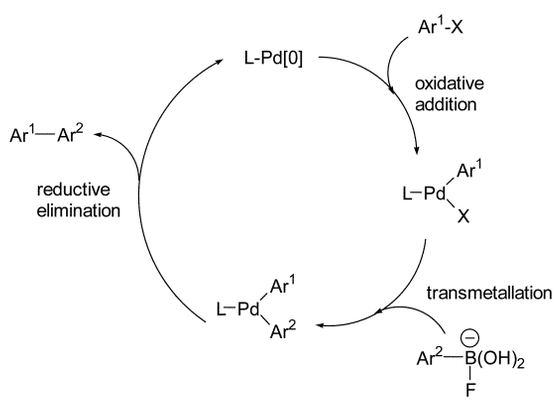
[a] Experiments were carried out at 25 °C using 1 mM of the palladium complex with 10 equivalents of PhI, and were duplicated. [b] Linear correlation constants were >0.995 in every case.

(entries 1–3) revealed that the presence of an electron-donating *P*-substituent retards the rate of the oxidative addition (**1a** >> **1b** > **1e**). This is in accordance with earlier observations, where the presence of an electron-rich *N*-substituent was found to have a similar effect.[1] However, when the reactivity of the *tert*-butylaminodiphosphine complexes was examined (entries 4–6), the *p*-tolylphosphine ligand **2b** was found to promote the fastest reaction (**2b** >> **2a** > **2e**).

In a previous study by Amatore and Jutand, oxidative addition of iodobenzene to palladium(0) precursors generated *in situ* from $Pd(dba)_2$ and triarylphosphine $P(p\text{-}Z\text{-}C_6H_4)_3$, where Z = OMe, Me, H, F and Cl, led to bell-shaped curves in subsequent Hammett plots.[12] This was attributed to the antagonistic relationship between the inherent reactivity of the $L_2Pd(0)$ complex and its effective concentration *in situ*.

The results obtained in the present system may be explained using a similar model: although complex **9** is inherently most active towards oxidative addition when it is coordinated by electron-rich aminodiphosphine ligands such as **1e** and **2e**, its effective concentration is also lower, as the coordination of dba (π-acceptor) to these complexes is also enhanced by the increased Lewis basicity of the metal centre. However, this shift in equilibrium may be offset by the *N*-substituent. From these kinetic studies, it is clear that a close synergistic relationship exists between *N*- and *P*-donor groups, where the electronic contributions are delicately balanced with the reaction conditions under which the reaction intermediates are generated.

The catalytic cycle of the Suzuki cross-coupling reaction has been generally proposed to consist of three principal steps (Scheme 5):[13] (i) oxidative addition; (ii) anion-assisted transmetalation; and (iii) reductive elimination. The reluctance of unactivated aryl chlorides and bromides to undergo oxidative addition contributes to their decreased reactivity in cross-coupling reactions (I > Br > Cl).[14] Conversely, the transfer of the aryl moiety from boron to palladium is known to decreases in the order: Cl > Br > I,[15] *i.e.* the first two steps of the catalytic cycle works counteractively under catalytic turnover conditions.



Scheme 5 Catalytic cycle of the Suzuki cross-coupling reaction.

In this case, we have shown that the ligands (**1e** and **2e**) promote the *slowest* oxidative addition (Table 3, entries 3 and 6), yet induce the *fastest* catalytic turnovers (Table 1, entries 5 and 10). However, this does not neccessarily imply that the transmetalation is rate-determining, for it is also known that the transmetalation step is promoted by the presence of electron donating substituents on arylboronic acids,[11] yet the electron-deficient 4-fluorophenyl boronic acid gave comparable, if not better, yields than the electron-rich 4-methoxyphenylboronic acid (Table 2). These two observations suggest the existence of a dynamic relationship between the oxidative addition and transmetalation steps – either can become dominant, depending on the nature of the substrate and the reaction conditions under which catalytic turnover take place.

Conclusion

A series of PNP ligands was prepared with systematic changes in the N- and P-donor substituents. Palladium complexes of these ligands were found to promote Suzuki cross-coupling under mild reaction conditions. It was found that catalysts generated from electron rich ligands are the most active and are able to activate difficult substrates such as 4-bromoanisole. During the course of the study, we observed an unusual electronic effect exerted by the arylboronic acids. In subsequent mechanistic investigations, palladium(0) precursors were generated from these ligands, and their rates of oxidative addition reactions with iodobenzene were measured using UV spectroscopy. An inverse relationship between rate of the oxidative addition and the catalytic activity was identified. The transmetalation is thus suggested to be just as important as the oxidative addition in the catalytic reactions. We demonstrated that the rate of at least one of these steps may be altered by the nature of the donor groups of the aminodiarylphosphine ligands. Therefore, the reaction outcome of catalytic reactions may be controlled by tuning these ligands.

Experimental

The general experimental and analytical techniques were the same as in other recent papers reported from this laboratory. Nitrogen mustards **3** and **4**,[1] secondary phosphine oxides,[16] aminodiphosphine ligands **1a** and **2a**,[1] were prepared by previously published procedures. All other chemicals were obtained from commercial sources and used without prior purification. Due to the lack of homogeneity between different batches of commerically available aryl boronic acids,[8] these were combined and recrystallised from water prior to use, to ensure reproducible results. GC analyses were performed on a Unicam 6100 system with a FID detector. A JW Scientific DB 250 column was used, with He as a carrier gas set at a flow rate of 1.0 mL min^{-1}. Oven temperature was kept isothermally at 90 °C. UV spectroscopy was performed on a DU 7400 Beckman spectrophotometer in a thermostated (25 °C) 1 mm path length cell.

Preparation of ligands

Typical procedure for the preparation of aminodiphosphine oxides. The corresponding diarylphosphine oxide (1.55 mmol) was added to a solution of KOH (115 mg, 205 mmol) in DMSO (1 cm^3) and water (0.15 cm^3), giving a light yellow suspension. After 5 minutes, the aminodichloride **3** or **4** (0.761 mmol) was added and the reaction mixture was stirred for 30 minutes, then heated at 50 °C for 1.5 hours. After cooling to room temperature, the reaction mixture was diluted with brine (8 cm^3), followed by extraction with CH_2Cl_2 (5 × 10 cm^3). The combined organic extracts were washed with brine (5 × 8 cm^3), back extracting each wash with CH_2Cl_2 (5 cm^3). The combined organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give a white foamy solid (523 mg), which was purified by flash column chromatography. Foamy solid products were dried overnight under vacuum at 45 °C.

***N,N*-bis{2-[di-(4-tolyl)phosphoryl]ethyl}-*N*-4-anisidine 5b.** Column chromatography, acetone (411 mg, 85%). Mp: 81–83 °C (Found: C, 73.9; H, 6.3; N, 2.0. $C_{39}H_{43}NO_3P_2$ requires C, 73.7; H, 6.75; N, 2.2%). ν_{max}/cm^{-1} (KBr disc) 1172 (P=O). δ_H (360 MHz, $CDCl_3$) 2.30 (12H, s, Me), 2.47 (4H, td, $^3J_{HH}$ 6.8 Hz, $^2J_{PH}$ 11.0 Hz, CH_2P), 3.37 (4H, td, $^3J_{HH}$ 6.8 Hz and $^3J_{PH}$ 14.0 Hz, NCH_2CH_2P), 3.67 (3H, s, OMe), 6.42 (2H, d, *J* 8.9 Hz, H_{ortho}), 6.66 (2H, d, *J* 8.9 Hz, H_{meta}), 7.20 (8H, dd, $^4J_{PH}$ 2.3 Hz, $^3J_{HH}$ 8.0 Hz, H_{meta}), 7.53 (8H, dd, $^3J_{HH}$ 8.0 Hz, $^3J_{PH}$ = 11.4 Hz, H_{ortho}). δ_C (90.5 MHz, $CDCl_3$) 21.9 (s, Me), 29.7 (d, $^1J_{PC}$ = 71 Hz, *C*H_2P), 38.8 (s, N*C*H_2CH_2P), 56.2 (s, OMe), 114.9 (s, C_{ortho}), 115.2 (s, C_{meta}), 129.8 (d, $^3J_{PC}$12.0 Hz, C_{meta}), 130.0 (d, $^1J_{PC}$ = 101 Hz, C_{ipso}), 131.1 (d, $^2J_{PC}$ = 10.0 Hz, C_{ortho}), 141.9 (s, C_{ipso}), 142.7 (s, C_{para}), 152.6 (s, C_{para}). δ_P (146 MHz, $CDCl_3$) +33.2. *m*/*z* (FAB) 637 (M + $2H^+$), 406, 229, 176, 154, 91.

***N,N*-bis{2-[di-(4-anisyl)phosphoryl]ethyl}-*N*-4-anisidine 5c.** Column chromatography, CH_2Cl_2/acetone, 1 : 1 (91%). Mp 68–70 °C. ν_{max}/cm^{-1} (KBr disc) 1180 (P=O). δ_H(360 MHz, $CDCl_3$) 2.27 (4H, td, $^3J_{HH}$ 11.2 Hz, $^2J_{PH}$ 16.0 Hz, CH_2P), 3.36 (4H, td, $^3J_{PH}$ 6.8 Hz, $^3J_{HH}$ 11.2 Hz, NCH_2CH_2P), 3.67 (3H, s, O*Me*), 3.75 (12H, s, O*Me*), 6.48 (2H, d, *J* 9.0 Hz, H_{ortho}), 6.66 (2H, d, *J* 9.0 Hz, H_{meta}), 6.86 (8H, dd, $^4J_{PH}$ 2.1 Hz, $^3J_{HH}$ 8.8 Hz, H_{meta}), 7.49 (8H, dd, $^3J_{HH}$ 8.8 Hz, $^3J_{PH}$ 11.1 Hz, H_{ortho}). δ_C (90.5 MHz, $CDCl_3$) 28.3 (d, $^1J_{PC}$ 69.3 Hz, *C*H_2P), 47.1 (s, N*C*H_2CH_2P), 55.8 (s, O*Me*), 56.1 (s, O*Me*), 114.5 (d, $^3J_{PC}$ 12.5 Hz, C_{meta}), 115.2 (s, C_{ortho}), 117.8 (s, C_{meta}), 124.5 (d, $^1J_{PC}$ 105 Hz, C_{ipso}), 132.8 (d, $^2J_{PC}$ 11.0 Hz, C_{ortho}), 141.1 (s, C_{ipso}), 152.3 (s, C_{para}), 162.7 (s, C_{para}). δ_P (162 MHz, $CDCl_3$) +31.6. *m*/*z* (FAB) 701 (M + $2H^+$), 439, 261, 176, 107.

***N,N*-bis{2-[di-(2-anisyl)phosphoryl]ethyl}-*N*-4-anisidine 5d.** Column chromatography, CH_2Cl_2/MeOH, 19 : 1 increasing to 9 : 1 (495 mg, 93%). Hygroscopic white foamy solid. ν_{max}/cm^{-1} (KBr disc) 1181 (P=O). δ_H(400 MHz, $CDCl_3$) 2.69–2.78 (4H, m, CH_2P), 3.39–3.32 (4H, m, NCH_2CH_2P), 3.67 (12H, s, O*Me*), 3.72 (3H, s, O*Me*), 6.54 (2H, d, *J* 9.2 Hz, H_{ortho}), 6.73 (2H, d, *J* 9.2 Hz, H_{meta}), 6.88 (4H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{PH}$ 5.3 Hz, H-3), 6.94–7.00 (4H, m, H-5), 7.46 (4H, dddd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 7.3 Hz, $^4J_{HH}$ 1.8 Hz, $^5J_{PH}$ 0.9 Hz, H-4), 7.54 (4H, ddd, $^3J_{PH}$ 13.6 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.8 Hz, H-6). δ_C (125 MHz, $CDCl_3$) 26.7 (d, $^1J_{PC}$ 71.0 Hz, *C*H_2P), 45.0 (s, N*C*H_2CH_2P), 55.4 (s, O*Me*), 55.8 (s, O*Me*), 110.7 (d, $^3J_{PC}$ 6.4 Hz, C-3), 114.7 (C_{ortho} or C $_{meta}$), 115.0 (C_{ortho} or C $_{meta}$), 120.6 (d, $^3J_{PC}$ 11.4 Hz, C-5), 120.6 (d, $^1J_{PC}$ 101 Hz, C-1), 133.4 (d, $^4J_{PC}$ 1.8 Hz, C-4), 133.8 (d, $^2J_{PC}$ 6.8 Hz, C-6), 141.1 (s, C_{ipso}), 151.5 (s, C_{para}), 160.5 (s, C-2). δ_P (162 MHz, $CDCl_3$) +31.2. *m*/*z* (HR-ESI) 1421.4927 ($2MNa^+$, $C_{78}H_{86}N_2NaO_{14}P_4$ requires 1421.4932, 35%), 722.2424 (MNa^+, $C_{39}H_{43}NNaO_7P_2$ requires 722.2415, 100), 700.2596 (MH^+, $C_{39}H_{44}NO_7P_2$ requires 700.2595, 13), 699.2563 (M^+, $C39H_{43}NO_7P_2$ requires 699.2517, 13).

***N,N*-bis{2-[di-(4-tolyl)phosphoryl]ethyl}-*N*-*tert*-butylamine, 6b.** Column chromatography, acetone (374 mg, 84%). Mp 68–70 °C (Found: C, 74.2; H, 7.9; N, 2.15. $C_{36}H_{45}NO_2P_2$ requires C, 73.85; H, 7.7; N, 2.4%). ν_{max}/cm^{-1} (KBr disc) 1178 (P=O). δ_H (360 MHz, $CDCl_3$) 0.89 (9H, s, Me), 2.20–2.31 (4H, m, CH_2P), 2.29 (12H, s, CH_3), 2.72 (4H, td, $^3J_{PH}$ 6.0 Hz, $^3J_{HH}$ 11.8 Hz, NCH_2CH_2P), 7.16 (8H, dd, $^4J_{PH}$ 2.2 Hz and $^3J_{HH}$ 8.0 Hz, H_{meta}), 7.48 (8H, dd, $^3J_{HH}$ 8.0 Hz, $^3J_{PH}$ 11.3 Hz, H_{ortho}). δ_C (90.5 MHz, $CDCl_3$) 21.9 (s, CH_3), 27.8 (s, CH_3), 31.8 (d, $^1J_{PC}$ 67.8 Hz, *C*H_2P), 42.7 (s, N*C*H_2CH_2P), 56.0 (s, *C*Me$_3$), 127.5 (d, $^1J_{PC}$ 103 Hz, C_{ipso}), 129.7 (d, $^3J_{PC}$ 11.8 Hz, C_{meta}), 131.0 (d, $^2J_{PC}$ 9.6 Hz, C_{ortho}), 142.4 (s, C_{para}). δ_P(146 MHz, $CDCl_3$) +32.1. *m*/*z* (FAB) 586 (MH^+), 530, 356, 229, 154, 91, 77.

***N*,*N*-bis{2-[di-(4-anisyl)phosphoryl]ethyl}-*N*-*tert*-butylamine 6c.** Column chromatography, CH_2Cl_2/acetone, 1 : 1 (283 mg, 76%). Mp: 61–63 °C. ν_{max}/cm^{-1} 1174 (P=O). δ_H (360 MHz, $CDCl_3$) 0.89 (9H, s, C*Me*$_3$), 2.22 (4H, td, $^2J_{PH}$ 11.5 Hz, $^3J_{HH}$ = 15.9 Hz, C*H*$_2$P), 2.73 (4H, td, $^3J_{PH}$ 6.0 Hz, $^3J_{HH}$ 15.9 Hz, NC*H*$_2$CH$_2$P), 3.75 (12H, s, O*Me*), 6.87 (8H, dd, $^4J_{PH}$ 2.0 Hz, $^3J_{HH}$ 8.7 Hz, H$_{meta}$), 7.52 (8H, dd, $^3J_{PH}$ 11.0 Hz, $^3J_{HH}$ 8.7 Hz, H$_{ortho}$). δ_C (90.5 MHz, $CDCl_3$) 27.8 (s, Me), 32.0 (d, $^1J_{PC}$ = 69.0 Hz, *C*H$_2$P), 42.7 (s, N*C*H$_2$CH$_2$P), 55.7 (s, OMe), 56.0 (s, *C*Me$_3$), 114.5 (d, $^2J_{PC}$ 12.5 Hz, C$_{ortho}$), 125.2 (d, $^1J_{PC}$ 105 Hz, C$_{ipso}$), 132.9 (d, $^3J_{PC}$ 10.7 Hz, C$_{meta}$), 162.6 (s, C$_{para}$). δ_P(146 MHz, $CDCl_3$) +31.9. *m*/*z* (FAB) 650 (MH$^+$), 592, 388, 332, 261, 245, 154.

***N*,*N*-bis{2-[di-(2-anisyl)phosphoryl]ethyl}-*N*-*tert*-butylamine 6d.** Column chromatography, CH_2Cl_2 increasing to CH_2Cl_2/methanol, 49 : 1 (279 mg, 75%). Hygroscopic white foamy solid. δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, C*Me*$_3$), 2.83–2.64 (8H, m, C*H*$_2$C*H*$_2$P), 3.69 (12H, s, O*Me*), 6.87 (4H, dd, $^3J_{PH}$ 5.1 Hz, $^3J_{HH}$ 8.0 Hz, H-6), 7.00 (4H, tdd, $^3J_{HH}$ 7.5 Hz, $^4J_{HH}$ 2.0 Hz, $^4J_{PH}$ 1.0 Hz, H-4), 7.48–7.42 (4H, m, H-5), 7.60 (4H, ddd, $^3J_{PH}$ 13.4 Hz, $^3J_{HH}$ 7.5 Hz, $^4J_{HH}$ 2.0 Hz, H-3). δ_C (125 MHz, $CDCl_3$) 27.5 (s, Me), 30.5 (d, $^1J_{PC}$ = 70.0 Hz, *C*H$_2$P), 42.3 (s, N*C*H$_2$CH$_2$P), 55.4 (s, OMe), 55.7 (s, *C*Me$_3$), 110.8 (d, $^3J_{PC}$ 6.4 Hz, C-6), 120.5 (d, $^3J_{PC}$ 11.4 Hz, C-4), 121.0 (d, $^1J_{PC}$ 99.8 Hz, C-2), 133.3 (s, C-5), 133.8 (d, $^2J_{PC}$ 6.8 Hz, C-3), 160.5 (d, $^2J_{PC}$ 3.6 Hz, C-1). δ_P(162 MHz, $CDCl_3$) +31.3. *m*/*z* (HR-ESI) 1321.5338 (2MNa$^+$, $C_{72}H_{90}N_2NaO_{12}P_4$ requires 1321.5347, 100%), 672.2621 (MNa$^+$, $C_{36}H_{45}NNaO_6P_2$ requires 672.2623, 4), 650.2811 (MH$^+$, $C_{36}H_{46}NO_6P_2$ requires 650.2803, 4).

Typical procedures for the reduction of aminodiphosphine oxides (Method A). At −78 °C, trichlorosilane (0.52 cm^3, 5.15 mmol) was added dropwise to a mixture of the corresponding amino phosphine oxide **5** or **6** (0.84 mmol) and triethylamine (6 cm^3) in toluene (25 cm^3). The mixture was allowed to warm to room temperature, then refluxed for 4 hours. After cooling with an ice bath, the suspension was diluted with degassed diethyl ether (20 cm^3) and excess reducing agent destroyed with saturated aqueous sodium carbonate (0.25 cm^3). The suspension was filtered, washing the precipitate with further portions of diethyl ether. The filtrate was concentrated *in vacuo* to give an oil which was dissolved in degassed ethyl acetate (25 cm^3) and washed with degassed saturated brine (2 × 15 cm^3), dried over Na_2SO_4 and concentrated *in vacuo* to give the product either as a colourless oil (which may be precipated as the HCl salt by the addition of 2M aq. HCl) or a solid white foam.

***N*,*N*-bis{2-[di-(4-tolyl)phosphino]ethyl}-*N*-4-anisidine hydrochloride salt 1b·HCl.** 489 mg, 91%. Mp: 101–103 °C. δ_H (360 MHz, $CDCl_3$, free amine) 2.09 (4H, td, $^3J_{HH}$ 5.6 Hz, $^2J_{PH}$ = 8.0 Hz, C*H*$_2$P), 2.26 (12H, s, Me), 3.17 (4H, td, $^3J_{HH}$ 5.6 Hz $^3J_{PH}$ 11.1 Hz, NC*H*$_2$CH$_2$P), 3.66 (3H, s, OMe), 6.32 (2H, d, *J* 9.1 Hz, H$_{ortho}$), 6.62 (2H, d, *J* 9.1 Hz, H$_{meta}$), 7.04 (8H, dd, $^4J_{PH}$ 2.6 Hz, $^3J_{HH}$ 7.5 Hz, H$_{meta}$), 7.19 (8H, d, $^3J_{PH}$ 6.9 Hz, $^3J_{HH}$ 7.5 Hz, H$_{ortho}$). δ_C (90.5 MHz, $CDCl_3$, free amine) 20.3 (s, Me), 24.9 (d, $^1J_{PC}$ 13.4 Hz, *C*H$_2$P), 47.5 (d, $^2J_{PC}$ = 25.4 Hz, N*C*H$_2$CH$_2$P), 54.7 (s, OMe), 113.7 (s, C$_{ortho}$), 114.3 (s, C$_{meta}$), 128.2 (d, $^3J_{PC}$ 7.0 Hz, C$_{meta}$), 131.6 (d, $^2J_{PC}$ 18.7 Hz, C$_{ortho}$), 133.6 (d, $^1J_{PC}$10.8 Hz, C$_{ipso}$), 137.6 (s, C$_{ipso}$), 140.7 (s, C$_{para}$), 150.6 (s, C$_{para}$). δ_P (146 MHz, $CDCl_3$, free amine) −21.9. *m*/*z* (FAB) 604.2910 (M$^+$ − Cl, $C_{39}H_{44}NOP_2$ requires 604.2898).

***N*,*N*-bis{2-[di-(4-anisyl)phosphino]ethyl}-*N*-4-anisidine hydrochloride salt, 1c·HCl.** 555 mg, 94%. Mp: 86–88 °C (Found: C, 66.5; H, 6.25; N, 2.0. $C_{39}H_{42}NO_5P_2$.HCl requires: C, 66.5; H, 6.25; N, 2.0%). δ_H (400 MHz, $CDCl_3$) 1.89 (2H, br s, C*H*$_2$P), 2.94 (2H, br s, NCH$_2$C*H*$_2$P), 3.18 (2H, br s, NC*H*$_2$CH$_2$P), 3.54 (2H, br s, NC*H*$_2$CH$_2$P), 3.81 (6H, s, OMe), 3.84 (6H, s, OMe), 3.89 (3H, s, OMe), 6.87 (4H, d, *J* 8.0 Hz, H$_{meta}$), 6.93 (4H, d, *J* 8.0 Hz, H$_{meta}$), 6.98 (2H, d, *J* 8.9 Hz, H$_{ortho}$), 7.27 (4H, t, *J* 8.0 Hz, H$_{ortho}$), 7.42 (4H, t, *J* 8.0 Hz, H$_{ortho}$), 7.56 (d, 2H, *J* 8.9 Hz, H$_{meta}$), 11.4 (1H, br s, N–*H*). δ_C (free amine, 90.5 MHz, $CDCl_3$) 26.7 (d, $^1J_{PC}$13.0 Hz, *C*H$_2$P), 49.0 (d, $^2J_{PC}$ 25.5 Hz, N*C*H$_2$CH$_2$P), 55.6 (s, OMe), 56.1 (s, OMe), 114.5 (d, $^3J_{PC}$ 7.5 Hz, C$_{meta}$), 115.1 (s, C$_{ortho}$), 115.8 (s, C$_{meta}$), 129.5 (d, $^1J_{PC}$ = 9.5 Hz, C$_{ipso}$), 134.5 (d, $^2J_{PC}$ = 20.0 Hz, C$_{ortho}$), 142.1 (s, C$_{ipso}$), 152.1 (s, C$_{para}$), 160.5 (s, C$_{para}$). δ_P (free amine, 146 MHz, $CDCl_3$) −22.3. *m*/*z* (free amine, FAB) 668 (MH$^+$), 560, 422, 245, 107.

***N*,*N*-bis{2-[di-(2-anisyl)phosphino]ethyl}-*N*-4-anisidine 1d.** Foamy solid. 405 mg, 72%. δ_H (400 MHz, $CDCl_3$) 2.29–2.35 (4H, m, C*H*$_2$P), 3.33–3.40 (4H, m, NC*H*$_2$CH$_2$P), 3.73 (3H, s, OMe), 3.74 (12H, s, OMe), 6.54 (2H, *J* 9.2 Hz, H$_{ortho}$), 6.74 (2H, d, *J* 9.2 Hz, H$_{meta}$), 6.84 (4H, dd, $^3J_{HH}$ 8.3, $^4J_{PH}$4.3 Hz, 3-H), 6.85–6.91 (4H, m, 5-H), 7.09 (4H, ddd, $^3J_{HH}$ 7.5 Hz, $^3J_{PH}$ 5.5 Hz, $^4J_{HH}$ 1.7 Hz, 6-H), 7.28–7.33 (4H, m, 4-H). δ_C (125 MHz, $CDCl_3$) 22.6 (d, $^1J_{PC}$14.2 Hz, *C*H$_2$P), 49.1 (d, $^2J_{PC}$ 28.3 Hz, N*C*H$_2$CH$_2$P), 55.4 (s, OMe), 55.8 (s, OMe), 110.2 (3-C), 114.7 (s, C$_{ortho}$), 120.8 (s, C$_{meta}$), 120.8 (s, 5-C), 125.1 (d, $^1J_{PC}$15.1 Hz, 1-C), 130.0 (s, 4-C), 132.8 (d, $^2J_{PC}$ 6.4 Hz, 6-C), 142.0 (s, C$_{ipso}$), 151.2 (s, C$_{para}$), 161.3 (d, $^2J_{PC}$ 13.3 Hz, 2-C). δ_P (162 MHz, $CDCl_3$) −38.9. *m*/*z* (FAB) 668.2715 (MH$^+$, $C_{39}H_{44}NO_5P_2$ requires 668.2695), 422, 245.

***N*,*N*-bis{2-[di-(4-tolyl)phosphino]ethyl}-*N*-*tert*-butylamine hydrochloride salt 2b·HCl.** 426 mg, 92%. Mp: 82–84 °C. δ_H (360 MHz, $CDCl_3$) 1.31 (9H, s, Me), 2.26 (6H, s, CH$_3$), 2.29 (6H, s, CH$_3$), 2.70 (2H, m, C*H*$_2$P), 3.01 (2H, m, NCH$_2$C*H*$_2$P), 3.25 (2H, m, NC*H*$_2$CH$_2$P), 3.43 (m, 2H, NC*H*$_2$CH$_2$P), 7.10 (4H, d, *J* 7.1 Hz, H$_{meta}$), 7.18 (4H, d, *J* 7.1 Hz, H$_{meta}$), 7.37 (4H, m, H$_{ortho}$), 7.47 (4H, m, H$_{ortho}$), 11.68 (1H, br s, N–*H*). δ_C (free amine, 90.5 MHz, $CDCl_3$) 21.7 (s, CH$_3$), 27.8 (s, CH$_3$), 30.3 (d, $^1J_{PC}$ 11.6 Hz, *C*H$_2$P), 46.9 (d, $^2J_{PC}$ 26.4 Hz, N*C*H$_2$CH$_2$P), 55.7 (s, *C*Me$_3$), 129.6 (d, $^2J_{PC}$ 7.1 Hz, C$_{ortho}$), 132.0 (d, $^3J_{PC}$ 18.6 Hz, C$_{meta}$), 135.6 (d, $^1J_{PC}$11.1 Hz, C$_{ipso}$), 138.7 (s, C$_{para}$). δ_P(146 MHz, $CDCl_3$) −13.8. *m*/*z* (FAB, free amine) 553 (MH$^+$), 462, 340, 283, 213, 182, 91.

***N*,*N*-bis{2-[di-(4-anisyl)phosphino]ethyl}-*N*-*tert*-butylamine hydrochloride salt, 2c·HCl.** 521 mg, 95%. Mp: 81–83 °C (Found: C, 66.0; H, 7.1; N, 2.05%. $C_{36}H_{46}NO_4P_2Cl$ requires C, 66.1; H, 7.1; N, 2.15%). δ_H (free amine, 360 MHz, $CDCl_3$) 0.89 (9H, s, Me), 2.00 (4H, td, $^2J_{PH}$ 4.6 Hz, $^3J_{HH}$ 8.7 Hz, C*H*$_2$P), 2.48 (4H, td, $^3J_{PH}$ 5.2 Hz, $^3J_{HH}$ 8.7 Hz, NC*H*$_2$CH$_2$P), 3.70 (12H, s, OMe), 6.76 (8H, dd, $^4J_{PH}$2.4 Hz, $^3J_{HH}$ 8.4 Hz, H$_{meta}$), 7.23 (8H, dd, $^3J_{PH}$ 7.0 Hz, $^3J_{HH}$ 8.4 Hz, H$_{ortho}$). δ_C (free amine, 90.5 MHz, $CDCl_3$) 29.6 (s, *C*H$_3$), 32.6 (d, $^1J_{PC}$ 12.8 Hz, *C*H$_2$P), 48.7 (d, $^2J_{PC}$ 26.9 Hz, N*C*H$_2$CH$_2$P), 57.3 (s, OMe), 57.5 (s, *C*Me$_3$), 116.2 (d, $^3J_{PC}$ 7.7 Hz, C$_{meta}$), 131.9 (d, $^1J_{PC}$ = 9.3 Hz, C$_{ipso}$), 136.2 (d, $^2J_{PC}$ = 19.9 Hz, C$_{ortho}$), 162.2 (s, C$_{para}$). δ_P (free amine, 146 MHz, $CDCl_3$) −22.7. *m*/*z* (free amine, FAB) 618 (MH$^+$), 510, 372, 315, 245, 214.

***N*,*N*-bis{2-[di-(2-anisyl)phosphino]ethyl}-*N*-*tert*-butylamine 2d.** Foamy solid. 425 mg, 82%. δ_H (360 MHz, $CDCl_3$) 1.00 (9H, s, C*Me*$_3$), 2.27–2.21 (4H, m, C*H*$_2$P), 2.69–2.63 (4H, m, NC*H*$_2$-CH$_2$P), 3.70 (12H, s, OMe), 6.81 (4H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{PH}$ 4.2 Hz, 6-C), 6.85 (4H, t, $^3J_{HH}$ 7.4 Hz, 4-C), 7.09 (4H, ddd, $^3J_{HH}$ 7.4 Hz, $^3J_{PH}$ 5.3 Hz, $^4J_{HH}$ 1.7 Hz, 3-C), 7.30–7.25 (4H, m, 5-C). δ_C (90.5 MHz, $CDCl_3$) 26.6 (d, $^1J_{PC}$ 14.7 Hz, *C*H$_2$P), 27.4 (s, Me), 47.3 (d, $^2J_{CP}$ 28.5 Hz, N*C*H$_2$CH$_2$), 55.5 (s, OMe), 110.1 (s, 6-C), 120.8 (s, 4-C), 125.6 (d, $^1J_{PC}$ 16.7 Hz, 2-C), 129.8 (s, 5-C), 132.7 (s, 3-C), 161.4 (d, $^2J_{PH}$ 11.7 Hz, 1-C) – *C*Me$_3$ signal is obscured. δ_P (146 MHz, $CDCl_3$) −39.1. *m*/*z* (FAB) 618.2926 (MH$^+$. $C_{36}H_{46}NO_4P$ requires 618.2902).

Synthesis of ligands 1e and 2e (Method B). *tert*-Butyllithium (4.4 cm^3, 1.5*M* solution in pentane, 6.6 mmol) was added

dropwise to a solution of di-(4-*N,N*-dimethylaminophenyl)-phosphine (1.63 g, 6.0 mmol) in dry Et_2O (20 cm^3) at 0 °C. After stirring for 30 minutes, it was warmed gradually to room temperature, where it developed an intense red colour over a period of 1 h. It was cooled down to 0 °C, where a solution of the aminodichloride **4** (0.59 g, 3.0 mmol) in Et_2O (5.0 cm^3) was added. The reaction mixture was then left to stir overnight at room temperature. After dilution with toluene (10 cm^3), the reaction mixture was carefully quenched by the addition of distilled water (5.0 cm^3) at 0 °C. The suspension was filtered and the combined filtrates were evaporated under vacuum to furnish a pale yellow residue, which was recrystallised from methanol to afford the product as a white solid.

***N,N*-bis{2-[di-(4-dimethylaminophenyl)phosphino]ethyl}-*N*-*p*-anisidine, 1e.** 1.72 g, 80%. Mp 129–131 °C (Found: C, 71.35; H, 7.3; N, 9.3. $C_{43}H_{55}N_5P_2O$ requires C, 71.75; H, 7.65; N, 9.7%). δ_H (400 MHz, $CDCl_3$) 2.20 (4H, m, CH_2P), 2.99 (24H, s, N*Me*), 3.20 (4H, td, $^3J_{PH}$ 5.3 Hz, $^3J_{HH}$ 8.1 Hz, NCH_2CH_2P), 3.77 (3H, s, O*Me*), 6.42 (2H, d, *J* 9.0 Hz, H_{ortho}), 6.72 (8H, dd, $^4J_{PH}$ 2.9 Hz, $^3J_{HH}$ 8.3 Hz, H_{meta}), 7.30–7.37 (10H, m, Ar-H). $^{13}C\{^1H\}$ NMR δ_C (100 MHz, $CDCl_3$) 26.8 (d, $^1J_{PC}$12.5 Hz, CH_2P), 40.7 (s, N*Me*), 48.9 (d, $^2J_{PC}$ 27.0 Hz, NCH_2CH_2P), 56.2 (s, O*Me*), 112.7 (d, $^3J_{PC}$ 7.5 Hz, C_{meta}), 115.3 (s, C_{ortho}), 115.1 (s, C_{meta}), 124.3 (d, $^1J_{PC}$ 7.0 Hz, C_{ipso}), 134.1 (d, $^2J_{PC}$ = 20.0 Hz, C_{ortho}), 142.5 (s, C_{ipso}), 151.0 (s, P–C_{para}), 151.6 (s, C_{para}). δ_P (146 MHz, $CDCl_3$) −24.9. *m*/*z* (FAB) 720.3956 (MH^+. $C_{43}H_{56}N_5OP_2$ requires 720.3960).

***N,N*-bis{2-[di-(4-dimethylaminophenyl)phosphino]ethyl}-*N*-*tert*-butylamine, 2e.** 1.31 g, 65%. Mp: 86–88 °C. Found: C, 71.9; H, 8.4; N, 10.0. $C_{40}H_{57}N_5P_2$ requires C, 71.75; H, 8.5; N, 10.4 %. δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, CMe_3), 2.03 (4H, td, $^2J_{PH}$ 4.5 Hz, $^3J_{HH}$ 8.5 Hz, NCH_2CH_2P), 2.49 (4H, td, $^3J_{PH}$ 4.01 Hz, $^3J_{HH}$ 8.5 Hz, NCH_2CH_2P), 2.84 (24H, s, N*Me*), 6.57 (8H, dd, $^4J_{PH}$ 2.0 Hz, $^3J_{HH}$ 8.6 Hz, H_{meta}), 7.19 (8H, dd, $^3J_{PH}$ 7.0 Hz, $^3J_{HH}$ 8.6 Hz, H_{ortho}). δ_C(100 MHz, $CDCl_3$) 27.9 (s, CH_3), 30.7 (d, $^1J_{PC}$ 10.4 Hz, NCH_2CH_2P), 40.7 (s, N*Me*), 47.1 (d, $^2J_{PC}$ 27 Hz, NCH_2-CH_2P), 55.7 (s, CMe_3), 112.8 (d, $^3J_{PC}$ 7.5 Hz, P–C_{meta}), 125.0 (d, $^1J_{PC}$ 7 Hz, C_{ipso}), 134.1 (d, $^2J_{PC}$ 20 Hz, C_{ortho}), 150.9 (s, C_{para}). δ_P (162 MHz, $CDCl_3$) −23.8. *m*/*z* (FAB) 670.4163 (MH^+. $C_{40}H_{56}N_5P_2$ requires 670.4167).

Kinetic studies

UV spectroscopy. The solution cell was carefully purged with argon prior to the experiment. The Pd(0) complex was generated by mixing stock solutions of $Pd(dba)_2$ (1.0 mM) and appropriate PNP ligands (1.0 mM) in dry THF at room temperature. After stirring for 10 minutes, the colour of the reaction mixture changes from red–purple to yellow–brown, indicating the formation of Pd(0) precursors. These solutions were then transferred *via* a cannula into the UV cell, to which 10.0 eq. of phenyl iodide were injected *via* a microlitre syringe. The decay of the UV absorption band due to the Pd(dba)(PNP) precursor at 395 nm was followed.

Suzuki cross-coupling reactions

Catalytic runs were performed in parallel using a Radley's 12-placed reaction carousel under an Ar or N_2 atmosphere. $[Pd_2(dba)_3.CHCl_3]$ (1.0 mol%) and the appropriate PNP ligand (2.2 mol%) were weighed into a small vial which was flushed with argon. 1.0 cm^3 of DME was added into the vial and the reaction mixture was stirred at 40 °C. After 10 minutes, the initial purple–black colour of the solution was discharged, giving a yellow–brown solution indicating the formation of the complex. 4-Methoxyphenyl boronic acid (228 mg, 1.5 mmol) and CsF (2.2 equivalents) were introduced into a Radley's reaction tube, which was placed in the carousel and purged with argon. 2.0 cm^3 of DME was introduced *via* the septum along with 4-bromotoluene (0.12 cm^3, 1.0 mmol) and 0.19 cm^3 of decane (GC internal standard). The solution containing the catalyst precursor was introduced into the Radley's tube, along with an additional volume of DME (1.0 cm^3). The reaction temperature was adjusted to 85 °C and maintained at the specific temperature (± 0.1 °C) with the aid of a thermostat. The progress of the reaction was monitored by periodically extracting aliquots of the reaction mixtures, which were analysed by GC. At the end of the reaction, the products were purified by column chromatography (EtOAc–hexane) and isolated as white solids.

Characterisation data for biaryl compounds **7a**–**l** listed in Table 2 agree with previously reported values.[17–28]

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