DALTON COMMUNICATION

Synthesis of bulky, electron rich hemilabile phosphines and their application in the Suzuki coupling reaction of aryl chlorides

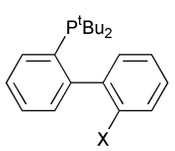
Matthew L. Clarke, David J. Cole-Hamilton and J. Derek Woollins *

School of Chemistry, University of St. Andrews, St. Andrews, Fife, UK KY16 9ST.
E-mail: jdw3@st-andrews.ac.uk; Fax: 44-1334-463384

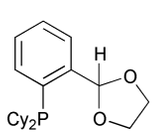
Received 27th July 2001, Accepted 5th September 2001
First published as an Advance Article on the web 17th September 2001

Novel electron rich, amine functionalised phosphines have been prepared and shown to belong to an unusual class of ligands that can activate palladium complexes to catalyse the Suzuki coupling reaction of chloroarenes.

In recent years, the use of transition metal complexes of electron rich phosphines has led to several important advances in homogeneous catalysis, and they are therefore a topic of ever growing interest.[1] One particularly high profile example has been the use of bulky electron rich ligands in the palladium catalysed Suzuki cross-coupling reaction, a reaction of considerable importance. These reactions are traditionally carried out with aryl iodides, bromides or triflates as substrates. However, in 1998 Fu and Littke showed that $^{t}Bu_3P$ and palladium(0) catalysts could, if used in a ratio of 1 : 1, be used to catalyse Suzuki coupling of cheaper and more widely available aryl chlorides (complete conversion at 80 °C using 1.5 mol% $Pd_2dba_3{\cdot}CHCl_3$, dba = dibenzylideneacetone).[2] It was proposed that the reaction proceeded through Pd complexes that only contain one phosphine ligand, and are therefore very reactive in both oxidative addition and transmetallation steps. A more active catalytic system was simultaneously developed by Buchwald and co-workers, who demonstrated that palladium complexes of ligand **1** were particularly suited to this reaction.[3] Further study revealed that the more readily synthesised ligand **2** could be used at least as effectively, even at room temperature.[4] Another publication appearing at this time showed that the P,O chelate ligand **3** could also catalyse the coupling of aryl chlorides (1 mol% $Pd_2dba_3{\cdot}CHCl_3$, 105 °C).[5] The latter three ligands have three features in common. They are electron rich, hemilabile, and bulky (ligand **2** could well form P∩arene–olefin chelate complexes). The ligands have also shown utility in Pd catalysed amination and etherifications of aryl chlorides.[6] Catalysis of the Suzuki reaction continues to be an area of intense interest as demonstrated by four recent publications appearing after the completion of this work.[10]



1 X = NMe_2
2 X = H



3

We believe that bulky electron rich hemilabile ligands will rise still further in importance as they can simultaneously activate metal complexes to oxidative addition, transmetallation/insertion and reductive elimination. There are many existing reactions that could be improved/expanded by the use of such ligands, and probably an equally large number of reactions that will not proceed with normal ligands, yet await discovery if more highly reactive metal catalysts can be discovered. We have recently proposed that the electron donating character of phosphino-amines has been underestimated as a result of only two dialkylamino groups in the parent tris(dialkylamino)-phosphines actually contributing to the basicity of the phosphine. The remaining amino group merely acts as an electron withdrawing group. Alkyl- and dialkyl-phosphino-amines are therefore especially electron rich phosphines (Fig. 1).[7]

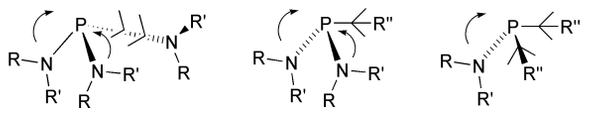
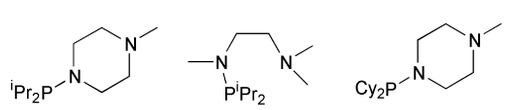


Fig. 1 Electronic contributions of amino and alkyl groups to phosphine basicity.

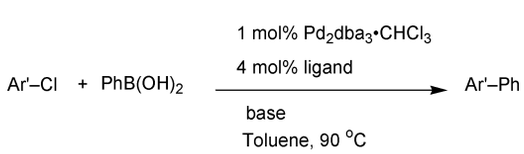
Since a huge range of amines are very readily available, and the P–N bond forming reactions are often quantitative under mild conditions, we felt that electron rich, bulky hemilabile phosphino-amines would make ideal ligand candidates for this type of catalysis. We report here our preliminary results in this area.

Ligand **4** was prepared by the addition of $^{i}Pr_2PCl$ to an Et_2O solution of triethylamine and *N*-methylpiperazine at room temperature. Removal of Et_3NHCl gave **4** as a moisture and air sensitive liquid that is indefinitely stable under an atmosphere of dry nitrogen. Thus it is possible to convert cheap and commercially available starting materials into the pure ligand (as determined by ^{31}P, ^{1}H, ^{13}C NMR and HRMS) in about an hour.[12]



4 **5** **9**

It was found that $Pd_2dba_3{\cdot}CHCl_3$ and **4** (L : Pd = 2 : 1) catalyse the Suzuki coupling of the relatively electron poor aryl chlorides with $PhB(OH)_2$ at 90 °C to give complete conversion to the desired biaryls with no unwanted side products (Table 1, entries 1–5).[13]



Although the reactions were generally run overnight for convenience, it was found that in the case of *m*-nitrochlorobenzene the reaction was complete within six hours. Despite several attempts under various conditions, the reaction of electron rich *p*-chlorotoluene (and chlorobenzene) (using $Pd_2dba_3{\cdot}CHCl_3$/**4** catalyst) always stopped prior to complete conversion (50–70% yield). As it is known that electron rich chloroarenes are more reluctant to undergo oxidative addition to palladium(0) complexes, we presume that this is the problematic step for the **4**/Pd catalyst system. A sluggish oxidative

DOI: 10.1039/b106784b

Table 1 Palladium catalysed Suzuki coupling of phenylboronic acid with a selection of aryl chlorides

Entry	Ligand[a]	Ar′	Base	Conversion[bc] (%)
1	**4**	*p*-$F_3CC_6H_4$	K_3PO_4	100
2	**4**	*m*-$NO_2C_6H_4$[d]	K_3PO_4	100
3	**4**	*p*-NCC_6H_4	K_3PO_4	100
4	**4**	*p*-MeC_6H_4	K_3PO_4	45–60 (6 runs)
5	**4**	*p*-MeC_6H_4	CsF	*ca.* 70
6	**5**	*p*-MeC_6H_4	CsF	0
7	**8**	*p*-MeC_6H_4	CsF	0
8	**9**	*p*-MeC_6H_4	CsF	93
9	**9**	*p*-$CH_3COC_6H_4$[e]	CsF	100
10	**9**	*m*-$CHOC_6H_4$[e]	CsF	100
11	**9**	*p*-$F_3CC_6H_4$[f]	CsF	100

[a] Reactions were carried out using 1 mol% $Pd_2dba_3{\cdot}CHCl_3$, with L : Pd ratio of 2 : 1, toluene, 90 °C, 16 hours. [b] Conversions calculated by GCMS, using napthalene as an internal standard. [c] Some of the reactions contained ≈2% of biphenyl isomers. [d] Reaction time = 6 h. [e] 0.5 mol% catalyst. [f] 0.2 mol% catalyst.

addition reaction would result in the catalyst spending more time as a zerovalent palladium complex, which would reduce catalyst stability. This is somewhat surprising as Buchwald and co-workers have shown that the transmetallation is the rate determining step using their ligands.

We have also prepared ligand **5**, which has greater conformational freedom than **4**. Somewhat to our surprise, a combination of **5** and $Pd_2dba_3{\cdot}CHCl_3$ does not catalyse the Suzuki reaction of *p*-chlorotoluene at all. It is likely that a difference in co-ordination chemistry for the two ligands accounts for this lack of catalytic activity (Table 1, entry 6).

At this stage, we have not compared the co-ordination chemistry of **4** and **5** to any great extent. Preliminary experiments suggest that the difference between the ligands is rather subtle; ligands **4** and **5** were further characterised by conversion to *trans*-$(\eta^1\text{-L})_2PtCl_2$ complexes (**6** and **7** respectively) by reaction with $(PhCN)_2PtCl_2$ or Zeise's salt in a 2 : 1 ratio. In both compounds the ^{31}P NMR spectra are sharp and show no sign of the fluxionality which would occur if the ligand were forming a transient chelate species in solution. When one equivalent of ligand **4** was added to $(COD)PtCl_2$ (COD = cycloocta-1,5-diene), a complex mixture (containing **6** and lots of unidentified products) results. Reaction of **5** with $(COD)PtCl_2$, also does not occur cleanly. However, the major species can be identified as $[\eta^2\text{-}\mathbf{5}]PtCl_2$.[8] Thus it is possible that an excessively strong chelate may account for the lack of catalytic activity when using this ligand. Burrows and co-workers have prepared related ligand *N*-diphenylphosphino-*N*′,*N*′,*N*′-trimethylethylenediamine and shown that it readily forms chelates with platinum.[9]

To further establish the requirements for a successful ligand in this reaction, we have prepared and tested *N*-diisopropylphosphinopiperidine, **8**, which presumably shares steric and electronic properties with **4**, but lacks the auxiliary nitrogen atom. This ligand was tested in the Pd catalysed Suzuki reaction of chlorotoluene under identical conditions to those used for **4**. Ligand **8** only gives a conversion of 30% after 20 hours reaction time. This is further evidence that the potentially donating nitrogen atom in **4** plays some role in its catalytic properties.

N-Dicyclohexylphosphino-*N*-methylpiperazine, **9** could also be prepared by the same general method in excellent purity, and was tested (in combination with $Pd_2dba_3{\cdot}CHCl_3$) as a catalyst for the Suzuki coupling of phenylboronic acid and *p*-chlorotoluene. It was pleasing to find that this ligand is superior to *N*-diisopropylphosphino-*N*-methylpiperazine, **4** and that essentially complete conversion into the desired product could be achieved (Table 1, entry 8). This catalyst system could also be used to couple *p*-chloroacetophenone with phenylboronic acid using 0.5 mol% catalyst and *p*-chlorobenzotrifluoride using 0.2 mol% catalyst (Table 1, entries 9–11). However, if the reactions were run at lower temperatures (50 °C) conversions were always less than 50% which suggests that this is (at this stage) a less reactive catalytic system than that developed by Buchwald and co-workers (using ligand **2**).

In summary, we have prepared two new electron rich,[11] potentially hemilabile ligands, and shown them to belong to a rare class of ligands that catalyse the Suzuki reaction of aryl chlorides. The evidence suggests that the presence of a potentially donating amine substituent is critical to their performance, and also suggests that a cyclohexyl-substituted phosphine may be more suited than isopropyl phosphines as a ligand. This study represents the first time that phosphinoamines have been utilised in the Suzuki coupling reaction, and given that derivatives of these ligands should be easily accessible, should allow us to optimise catalytic performance of this and other reactions. An investigation into the co-ordination chemistry that is diagnostic of a successful catalyst is also underway.

Acknowledgements

The authors wish to thank the EPRSC for financial support (M. L. C.), Johnson Matthey for loan of palladium(II) chloride, the EPRSC mass spectrometry service (Swansea), and the JREI for equipment grants. The authors also wish to thank Dr D. F. Foster for performing some of the GC analysis.

Notes and references

1 (*a*) M. C. Simpson and D. J. Cole-Hamilton, *Coord. Chem. Rev.*, 1996, **155**, 163 and refs. therein; (*b*) T. Sakakura, T. Sodeyama, K. Sasaki, K. Wada and M. Tanaka, *J. Am. Chem. Soc.*, 1990, **112**, 7221 and refs. therein; (*c*) J. K. MacDougall, M. C. Simpson, M. J. Green and D. J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.*, 1996, 1161 and refs. therein; (*d*) Y. Ben-David, M. Portnoy and D. Milstein, *J. Chem. Soc., Chem. Commun.*, 1989, 1816; (*e*) M. Portnoy and D. Milstein, *Organometallics*, 1993, **12**, 1665.

2 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 1998, **37**, 3387.

3 D. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722.

4 J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchald, *J. Am. Chem. Soc.*, 1999, **121**, 9550.

5 X. Bei, H. Turner, W. H. Weinberg and A. S. Gurran, *J. Org. Chem.*, 1999, **64**, 6797.

6 (*a*) X. Bei, H. Turner, W. H. Weinberg and A. S. Gurran, *Tetrahedron Lett.*, 1999, **40**, 1237; (*b*) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 4369; (*c*) D. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722.

7 (*a*) M. L. Clarke, D. J. Cole-Hamilton, A. M. Z. Slawin and J. D. Woollins, *Chem. Commun.*, 2000, 2065; (*b*) M. L. Clarke, A. M. Z. Slawin and J. D. Woollins, unpublished work.

8 The structure of this chelate complex, $[\eta^2\text{-}P,N\text{-}\mathbf{5}]PtCl_2$, has been recently verified by an X-ray crystal structure determination; M. L. Clarke, A. M. Z. Slawin and J. Derek Woollins, unpublished work. Analytical data for $[\eta^2\text{-}P,N\text{-}\mathbf{5}]PtCl_2$: Found: C, 27.63; H, 5.63; N, 5.60. $C_{11}H_{27}N_2P_1Pt_1Cl_2$ requires C, 27.28; H, 5.62; N, 5.78%.

9 A. D. Burrows, M. F. Mahon and M. T. Palmer, *J. Chem. Soc., Dalton Trans.*, 2000, 3615.

10 (*a*) G. Y. Li, *Angew. Chem., Int. Ed.*, 2001, **40**, 1513; (*b*) S. Gibson, G. R. Eastham, D. F. Foster, R. P. Tooze and D. J. Cole-Hamilton, *Chem. Commun.*, 2001, 779; (*c*) T. E. Pickett and C. J. Richards, *Tetrahedron Lett.*, 2001, **42**, 3767; (*d*) A. Furstner and A. Leitner, *Synlett*, 2001, 290.

11 We have additionally prepared [*trans*-$L_2Rh(CO)Cl$] complexes from ligands **4** and **9**. We were surprised to find the position of $\nu(CO)$ for these compounds to be at 1960 cm^{-1} [for *trans*-$(\mathbf{4})_2Rh(CO)Cl$] and 1964 cm^{-1} [for *trans*-$(\mathbf{9})_2Rh(CO)Cl$]. This suggests that these two ligands are not especially strong donor ligands.[7] Our more recent work suggests that bulky alkyl groups can diminish the N⟶P donation, and reduce phosphine basicity.[7b].

12 All ligands were characterised by multinuclear NMR, IR and (high resolution) mass spectroscopies. Their structure was further confirmed by the preparation of the platinum and rhodium complexes described, which gave satisfactory chemical analyses. Selected ^{31}P NMR and analytical data ($CDCl_3$; chemical shift in ppm relative to external phosphoric acid) for compounds discussed here. **4** δ_P 82.8; **5** δ_P 86.3; **6** δ_P 77.3 ($^1J_{P\text{–}Pt}$ = 2676 Hz). Found: C, 38.05;

H, 7.16; N, 7.86; $C_{22}H_{50}N_4P_2Pt_1Cl_2$ requires C, 37.82; H, 7.21; N, 8.02%. **7** δ_P 82.2 ($^1J_{P-Pt}$ = 2641 Hz). Found: C, 38.20; H, 8.29; N, 7.80; $C_{22}H_{54}N_4P_2Pt_1Cl_2$ requires C, 37.61; H, 7.75; N, 7.97%. **8** δ_P 84.5. **9** δ_P 75.8. *trans*-(**4**)$_2$Rh(CO)Cl: δ_P 102.1 ($^1J_{P-Rh}$ = 133 Hz). Found: C, 46.12; H, 8.41; N, 9.35. $C_{23}H_{50}P_2N_4O_1Rh_1Cl_1$ requires C, 46.37; H, 8.76; N, 9.36%.

13 Representative procedure for Suzuki coupling reactions: To a Schlenk flask containing ligand **9** (36 mg, 0.121 mmol, 4 mol%) under a nitrogen atmosphere was added dry toluene (10 mL). This was then degassed by two freeze–thaw cycles. This was then added to a second Schlenk flask containing Pd_2dba_3·$CHCl_3$ (31 mg, 0.030 mmol, **1** mol%), napthalene internal standard and CsF (1.39 g, 9.12 mmol, 3 equiv.). Chlorotoluene was then added by syringe (0.385 g, 3.04 mmol). A sample for GC analysis was taken at this time before introduction of phenylboronic acid (0.556 g, 4.55 mmol, 1.5 equiv.). The reactions were sampled periodically by removing 0.05 mL by syringe, and analysing by GC. The GC was set at a ramp program from 60 to 250 °C. Products can be readily separated from the more volatile aryl chlorides with retention times between 4 and 20 minutes.