Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9525–9528
Tetrahedron Letters

Pyrazole-tethered arylphosphine ligands for Suzuki reactions of aryl chlorides: how important is chelation?

Anuradha Mukherjee and Amitabha Sarkar*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

Received 30 September 2004; revised 28 October 2004; accepted 2 November 2004

Abstract—Pyrazole-derived bidentate ligands (P,N-donor) with bulky substituents at the 3-position of the pyrazole, **1b–d**, were used with $Pd_2(dba)_3$ to carry out efficient Suzuki coupling reactions with both aryl bromides and chlorides. Enhanced catalytic activity on account of steric crowding in the metal complex suggested participation of a chelated structure in the intermediate catalytic steps.

Palladium catalyzed activation of the Ar–Cl bond remains a challenge in catalytic coupling reactions.[1] While aryl bromides or iodides react readily, less expensive aryl chlorides are inert with respect to most catalysts and reactions. In the pioneering studies related to catalysis of the Suzuki reaction with aryl chlorides, Buchwald and co-workers,[2] Fu and co-workers,[3a,b] and others[4] indicated that alkyl groups on the phosphine donor and the steric bulk of substituents in the ligand are crucial design elements for effective catalysis. A few representative structures are displayed in Figure 1. Buchwald showed that the alkylphosphine group improves catalytic efficiency but the presence of an amino function (as in **A**) is not essential for the ligand to be effective. On the other hand, Fu and co-workers demonstrated that tri(*tert*-butyl)phosphine, a monodentate ligand of considerable steric bulk, effected efficient catalysis of Suzuki and other reactions.[3c–e]

Exploratory experiments in our laboratory on Pd-catalyzed Suzuki coupling with a set of pyrazole-tethered triarylphosphine ligands revealed that arylphosphines could activate an aryl chloride substrate if the 3-substituent of the pyrazole was sufficiently bulky.

A set of pyrazole-tethered triarylphosphines,[5] **1a–d** were synthesized to catalyze the Suzuki reaction between phenylboronic acid and a variety of aryl halides (Scheme 1) and their effectiveness in catalysis was compared. Specifically, ligands **1b**, **1c** and **1d** were found to activate aryl chlorides for the Suzuki reaction and **1b** gave respectable turnover numbers. The complex derived from **1a** could only catalyze reactions of aryl bromides or iodides but not chlorides.[6]

Typically, 1 mol% of $Pd_2(dba)_3$ and 4 mol% of ligand (Pd:**1** = 1:2) were used in toluene at 60–80 °C in the presence of CsF.[7] The results are summarized in Scheme 2 and Tables 1–3. Yields are reported as isolated and chromatographically purified products.

We found that $Pd(OAc)_2$ can also be used as the source of palladium without compromising the efficiency of the reaction. Elevation of the temperature had a detrimental

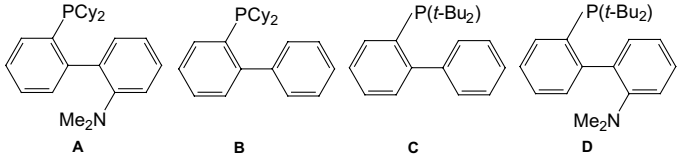
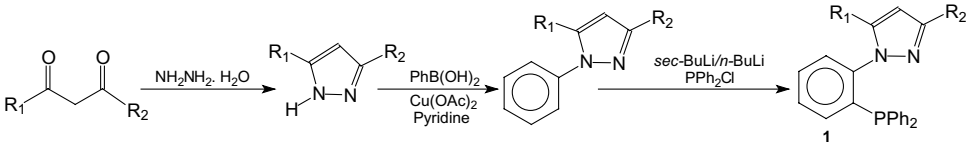


Figure 1.

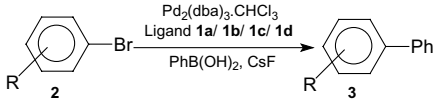
Keywords: Pyrazole; Phosphine ligand; Suzuki coupling; Palladium.
* Corresponding author. Tel.: +91 33 24734971; fax: +91 33 24732805; e-mail: ocas@iacs.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.016



Ligand	R_1	R_2	Yield
1a	CH_3	CH_3	56%
1b	CH_3	*tert*-butyl	48%
1c	CH_3	Phenyl	34%
1d	CH_3	Mesityl	26%

Scheme 1.



Scheme 2.

effect on the reaction presumably due to rapid catalyst decomposition. Although the efficiency of the reaction is high at 65 °C (for ligand **1b**) and at 80–85 °C for **1a**, no significant reaction took place at ambient temperature. The use of 0.5 mol% of $Pd_2(dba)_3$ with ligand **1a** resulted in a diminished yield of coupling product compared to the original conditions (Table 1, entry 1).

The reactivity difference between Pd(0)-complexes of ligands **1a** and **1b** is evident from the examples in Table 1. Ligand **1a** did not furnish any coupling product between 4-bromonitrobenzene and phenylboronic acid, while ligand **1b** afforded the coupling product in 81% isolated yield (Table 1, entries 9 and 10). Similarly, reaction of the sterically congested halide, 2-bromomesitylene, afforded much higher yield of coupling product in the presence of ligand **1b** than ligand **1a** (Table 1, entries 7 and 8). The catalytic efficiency remained practically unchanged when the ligand **1b** was used and the catalyst concentration was reduced by three orders of magnitude as shown by the reaction of 4-bromoacetophenone[4b,g] (Table 2). The coupling reaction between phenylboronic acid and 4-bromoacetophenone in the presence of $Pd_2(dba)_3$ (1 mol%) alone at 80 °C for 12 h gave only 15% of the cross-coupled product.

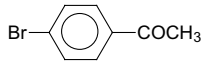
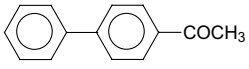
Presented in Table 3 are the results obtained from coupling reactions of aryl chlorides with phenylboronic acid. While ligand **1a** did not promote coupling of the aryl chloride with phenylboronic acid, ligands **1b**, **1c**

Table 1. Suzuki coupling reactions of aryl bromides with phenylboronic acid in the presence of $Pd_2(dba)_3$ and ligand **1a/1b/1c/1d**[a]

Entry	Substrate **2**	Ligand	Temp (°C)	Time (h)	Product **3**	Yield (%)
1	4-Bromoanisole	**1a**	85	8 (12)[a]	4-Methoxybiphenyl	80 (61%)[b]
2	4-Bromoanisole	**1b**	65	3	4-Methoxybiphenyl	97 (91%)[b]
3	4-Bromoanisole	**1c**	80	8	4-Methoxybiphenyl	61
4	4-Bromoanisole	**1d**	80	8	4-Methoxybiphenyl	61
5	2-Bromotoluene	**1a**	85	7	2-Methylbiphenyl	65
6	2-Bromotoluene	**1b**	65	3	2-Methylbiphenyl	95
7	2-Bromomesitylene	**1a**	85	10	2,4,6-Trimethylbiphenyl	31
8	2-Bromomesitylene	**1b**	70	8	2,4,6-Trimethylbiphenyl	62
9	4-Bromonitrobenzene	**1a**	80	10	4-Nitrobiphenyl	0
10	4-Bromonitrobenzene	**1b**	60	3	4-Nitrobiphenyl	81
11	4-Bromotoluene	**1a**	80	6	4-Methylbiphenyl	82 (74)[c]

[a] Reaction conditions: aryl bromide (1 mmol), phenylboronic acid (1.5 mmol), $Pd_2(dba)_3$ (1 mol%), ligand (4 mol%), Pd:**1** = 1:2, CsF (3 mmol), toluene (3 mL), temperature 65–80 °C, reaction time 2.5–10 h. Yields given here represent yields of isolated product (average of two runs).
[b] 0.5 mol% $Pd_2(dba)_3$ was used.
[c] 2 mol% of $Pd(OAc)_2$ was used.

Table 2. Influence of low catalyst loading on the coupling reaction[a]

Aryl halide	Product	Pd (mol%)	Yield (%)
		2	100
		1	99
		0.1	99
		0.01	98
		0.001	97

[a] Reactants were heated to 65 °C for 2 h using 1 mmol of aryl bromide, 1.5 mmol of phenylboronic acid, 3 mmol of CsF, 1 mol% $Pd_2(dba)_3$(Pd:**1b** = 1:2), and toluene (3 mL). Results are based upon isolated material (average of two runs).

Table 3. Suzuki coupling aryl chloride with ligand **1a**, **1b**, **1c** and **1d**[a]

Entry	Substrate	Ligand	Temp (°C)	Time (h)	Product	Yield (%)
1	4-Chloroacetophenone	**1a**	85	10	4-Acetylbiphenyl	0
2	4-Chloroacetophenone	**1b**	65	4	4-Acetylbiphenyl	89
3	4-Chloroacetophenone	**1c**	70–75	10	4-Acetylbiphenyl	31
4	4-Chloroacetophenone	**1d**	70–75	10	4-Acetylbiphenyl	29
5	4-Chlorotoluene	**1b**	70	4	4-Methylbiphenyl	83
6	4-Chlorobenzaldehyde	**1b**	70	5	4-Formylbiphenyl	69
7	4-Chloroanisole	**1b**	75	5	4-Methoxybiphenyl	69
8	4-Chloronitrobenzene	**1b**	70	4	4-Nitrobiphenyl	75

[a] Reaction conditions: aryl chloride (1 mmol), phenylboronic acid (1.5 mmol), CsF (3 mmol), toluene (3 mL), $Pd_2(dba)_3$ (1 mol%) and ligand (4 mol%). Results are based upon isolated material (average of two runs).

and **1d** were useful ligands for the reaction. Among **1b**–**d**, ligand **1b** with a *tert*-butyl group at the 3-position of pyrazole was the most effective (Table 3, entries 1, 2, 3 and 4).

Both electron rich and electron deficient aryl chlorides were activated by ligand **1b**, while ligands **1c** and **1d** worked only for electron deficient aryl chlorides where yields were not good. We conclude that ligand **1b** combines steric and electronic factors favorable for all the catalytic steps (oxidative addition, transmetalation and reductive elimination) of the Suzuki reaction despite being a triarylphosphine.

The similarity of the structures of ligands **1a**–**d** with Buchwald's **A**–**D** cannot be overlooked, but significant differences merit discussion. The phosphorus atom in the set of ligands, **1a**–**d**, is attached to three aryl rings unlike Buchwald's, hence the donor characteristics of the phosphine is different. Secondly, a crystal structure of Buchwald's complex reveals an unusually short contact between the metal atom and the carbon of the aromatic substituent, a feature that is said to induce the observed rate accelerating effect.[8] One can visualize a coordinating interaction with palladium via N1 of the pyrazole, in the same manner as the *ipso* carbon of a phenyl ring was shown to coordinate in Buchwald's catalyst. Alternatively, we can invoke an η^2-coordination by the N1–N2 bond of pyrazole as characterized by Winter[9] for early transition metal complexes. In both of these assumptions, a chelate structure rather than monodentate ligand behavior is implied. We believe that involvement of a chelated intermediate is also indicated by the dramatic change in catalyst activation for chloride when a 3-methyl group was changed to a 3-*tert*-butyl group on the pyrazole. For a monodentate ligand where only phosphorus is the coordinating atom, steric perturbation on pyrazole would not have made such a great difference. Chelation might stabilize a 'resting state' where coordinative unsaturation is temporarily contained by the participation of pyrazole.[10] The bulkier the pyrazole, the faster is the dissociation when the metal enters the next catalytic cycle. This can also explain the steric acceleration effect as observed.

In summary, we have established that steric modulation of the structure of a set of pyrazole-based bidentate ligands for Pd(0) can provide efficient catalysts for the Suzuki reaction between aryl chlorides and arylboronic acids. Exploration of other pyrazole-based ligand structures as well as mechanistic details of this reaction are being studied.

Acknowledgments

One of us (A.M) would like to thank CSIR, India, for a research fellowship.

References and notes

1. (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062; (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
2. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723; (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416; (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561; (d) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052; (e) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.
3. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388; (b) Adam, F. L.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731; (d) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724; (e) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.
4. (a) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555–1557; (b) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077–1080; (c) Navarro, O.; Kelly, R. A.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195; (d) Hu, Q.-S.; Lu, -Y.; Tang, Z.-Y.; Yu, H.-B. *J. Am. Chem. Soc.* **2003**, *125*, 2856–2857; (e) LeBlond, C. R.; Andrews, A. T.; Sowa, J. R., Jr.; Sun, Y. *Org. Lett.* **2001**, *3*, 1555–1557; (f) Jensen, J. F.; Johannsen, M. *Org. Lett.* **2003**, *5*, 3025–3028; (g) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095–2096.
5. Typical procedure:
Ligand **1b**: *n*-BuLi (2.3 mL of 1.6 M, 2.55 mmol) was added dropwise to *N*-phenyl-3-*t*-butyl-5-methylpyrazole (0.53 g, 2.48 mmol) in 3 mL THF at 0 °C. The ice bath was removed after addition of *n*-buLi. The color of the reaction mixture gradually changed into yellow then brown and stirring was continued for 6 h. PPh_2Cl (0.56 mL, 2.55 mmol) was added at 0 °C and stirring was continued for another 4 h. After the usual work up a semi-solid product was obtained which was purified by column chromatography on silica gel (eluting with acetone/pet

ether, 1:10). Yield: 0.47 g (48%). mp: 99.5 °C. IR (Neat): 1552 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.46–7.29 (m, 14H, PhH), 6.04 (s, 1H, PzH), 2.21 (s, 3H, CH_3), 1.22 (s, 9H, $C(CH)_3$). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 161.3, 144.1, 143.6, 139.3, 137.9, 137.6, 136.9, 134.7, 134.2, 133.7, 129.3, 128.5, 128.2, 127.8, 102.2, 31.8, 30.3, 11.9. ^{31}P NMR ($CDCl_3$, 81.02 MHz): δ: −13.23 ppm. Anal. Calcd for $C_{26}H_{27}N_2P$ (398) Cal: C, 78.39%; H, 6.78%; N, 7.03%. Found: C, 78.32%; H, 6.67%; N, 6.98%.

Spectral and analytical data for ligands **1a**, **1c** *and* **1d**:

Ligand **1a**: mp: 110 °C. IR (Nujol): 1552 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31 (br s, 14H, PhH), 5.86 (s, 1H, PzH) 2.19 (s, 3H, CH_3), 2.00 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 147.7, 143.2, 142.8, 139.9, 137.8, 137.4, 136.1, 135.9, 134.0, 133.9, 133.5, 129.1, 128.4, 128.1, 127.9, 127.7, 105.1, 13.2, 11.4 ppm. ^{31}P NMR ($CDCl_3$, 81.02 MHz): δ −23.89 ppm. Anal. Calcd for $C_{23}H_{21}N_2P$ (356): C, 77.52%; H, 5.89%; N, 7.86%. Found: C, 77.29%; H, 5.64%; N, 7.24%. Ligand **1c**: mp: 103 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.54–7.15 (m, 19H, PhH), 6.36 (s, 1H, PzH), 2.22 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ: 150.8, 141.6, 135.6, 135.5, 132.9, 132.0, 131.8, 131.7, 131.5, 131.4, 131.3, 131.1, 129.2, 129.1, 129.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 125.4, 103.5, 11.6. ^{31}P NMR ($CDCl_3$, 81.02 MHz): δ −18.14 ppm. Anal. Calcd for $C_{28}H_{23}N_2P$ (418) Cal: C, 80.38%; H, 5.50%; N, 6.69%. Found: C, 80.21%; H, 5.57%; N, 6.91%.

Ligand **1d**: mp: 107 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.52–7.10 (14H, m, PhH),6.85 (2H, s, PhH), 6.04 (1H, s, PzH), 2.28 (3H, s, CH_3), 2.13 (3H, s, CH_3), 2.02 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ: 150.9, 149.2, 141.4, 140.2, 139.9, 138.7, 138.3, 137.3, 137.0, 130.8, 129.3, 128.8, 128.5, 128.4, 128.2, 127.9, 126.9, 126.0, 125.9, 124.4, 122.3, 108.1, 20.9, 20.5, 12.6. ^{31}P NMR ($CDCl_3$, 81.02 MHz) δ: −20.70 ppm. Anal. Calcd for $C_{31}H_{29}N_2P$ (460) Cal: C, 80.86%; H, 6.30%; N, 6.08%. Found: C, 80.53%; H, 5.97%; N, 6.23%.

6. Mukherjee, A.; Sarkar, A. *Arkivoc* **2003**, 87–95.
7. (a) We found that CsF was a more effective base than Cs_2CO_3 and K_3PO_4. Toluene was a better solvent than THF or dioxane.

(b) *General procedure for Suzuki coupling*: An oven dried round bottomed flask was evacuated and flushed with argon and charged with $Pd_2(dba)_3$. $CHCl_3$ (1 mol%), ligand **1** (4 mol%), phenylboronic acid (1.5 mmol) and base (3 mmol). The flask was evacuated and flushed with argon. Aryl halide (1 mmol) and toluene (3–5 mL) were added to the reaction mixture by a syringe. The reaction mixture was heated (65–85 °C) with stirring for 2–10 h and the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature, filtered through Celite and washed with dichloromethane. The crude material was purified by flash column chromatography. The identity of each product was confirmed by comparison with literature spectroscopic data: 4-methoxybiphenyl,[11a] 2-methylbiphenyl,[11b] 2,4,6-trimethylbiphenyl,[11c] 4-nitrobiphenyl,[11d] 4-methylbiphenyl,[2a] 4-acetylbiphenyl,[11e] and 4-formylbiphenyl.[11f]

8. Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714–7715.
9. (a) Guzei, I. A.; Baboul, A. G.; Yap, G. P. A.; Rheingold, A. L.; Schlegel, H. B.; Winter, C. H. *J. Am. Chem. Soc.* **1997**, *119*, 3387–3388; (b) Guzei, I. A.; Winter, C. H. *Inorg. Chem.* **1997**, *36*, 4415–4420; (c) Yelamos, C.; Heeg, M. J.; Winter, C. H. *Inorg. Chem.* **1999**, *38*, 1871–1878.
10. Ligand **1a** has been used for making complexes with other late transition metals such as, Ni(II) [CCDC No 250554] and Cu(I) [CCDC No 250553]. In both cases the pyrazole nitrogen and phosphine act as bidentate ligands as proved by their crystal structure. A manuscript is under preparation.
11. (a) Rao, M. S. C.; Rao, G. S. K. *Synthesis* **1987**, 231; (b) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Peterson, J. L. *J. Org. Chem.* **1999**, *64*, 6797–6803; (c) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123–15134; (d) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830–1833; (e) Barba, I.; Chinchilla, R.; Gomez, C. *Tetrahedron* **1990**, *46*, 7813–7822; (f) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523–6526.