Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7095–7098

TETRAHEDRON
LETTERS

Palladium-catalyzed Suzuki–Miyaura reaction using aminophosphine as ligand

Jiang Cheng,[b] Feng Wang,[a] Jian-Hua Xu,[b] Yi Pan[b] and Zhaoguo Zhang[a,]*

[a] *State Key laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*
[b] *Department of Chemistry, Nanjing University, 22 Hankou Road, Nanjing 210093, China*

Received 16 May 2003; revised 17 June 2003; accepted 4 July 2003

Abstract—Suzuki–Miyaura cross-coupling reaction has been achieved under the catalysis of $Pd(OAc)_2$ in the presence of readily accessible and easily tunable aminophosphine ligands with high efficiency under mild reaction condition.

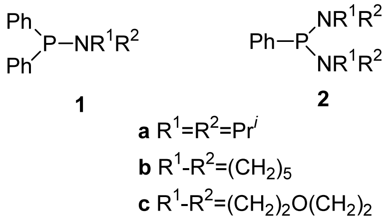
Palladium-catalyzed cross-coupling reactions between aryl (alkenyl) halides or triflates and organometallic reagents (Mg, Sn, B, Zn, Li, Zr, etc.) have been developed as a versatile and efficient method for a variety of synthetic transformations.[1] Among these reactions, palladium-catalyzed cross-coupling reaction between aryl halides and aryl boronic acids, known as Suzuki–Miyaura reaction, is highly valuable for the synthesis of symmetrical and unsymmetrical biaryls.[2–4] There have been a number of protocols to achieve an efficient Suzuki–Miyaura reaction, however, the utilization of expensive bases, solvents, scarce or difficult-handling ligands made the reaction not practical. The growing demand for a practical and efficient Suzuki–Miyaura reaction has yielded many recent achievements in ligands design and synthesis. For example, the bulky electron-rich phosphine ligands,[5] phosphites,[6] and *N*-heterocyclic carbenes[7] were used in Suzuki–Miyaura reaction.

Trivalent aminophosphines, which contained one or more P–N bonds, have not been used so widely as ligand in transition metal catalyzed cross-coupling reactions.[8] A few reports on the coordination chemistry of aminophosphine compounds revealed that the function of amino groups was more diversified than alkoxy groups in phophites:[9] In mono- and di-aminophosphines, alkyl and/or aryl amino groups served as strong electron-donating groups, making the phosphines stronger σ-donor ligands.

There are three elementary reactions involved in Suzuki–Miyaura reaction, i.e. oxidative addition, transmetallation, and reductive elimination. Oxidative addition is usually the rate-determining step in cross-coupling reactions,[10] thus, electron-rich phosphine ligands are usually needed to make the transition metal easily oxidized. Based on the above discoveries, we studied monoaminophosphines and diaminophosphines as electron rich ligands for cross-coupling reactions (Scheme 1).

Ligand **1** and **2** could be easily made from the corresponding commercially available amines and phenyl chlorophosphines according to the literature (See supporting information).[11] We first used **1a** as ligand to test the cross-coupling reaction between 4-bromoanisole (**3a**) and phenyl boronic acid (**4a**) and **5aa** was isolated in 84% yield after 24 h in refluxing THF (entry 1, Table 1).

The ligand showed good reactivity toward Suzuki–Miyaura reaction. Since bromoanisole is electron-rich



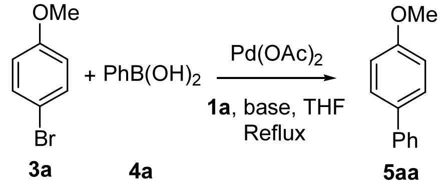
Scheme 1. Aminophosphine ligands.

---

* Corresponding author. Tel.: 86-21-64163300-3435; fax: 86-21-64166128; e-mail: zhaoguo@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01743-X

Table 1. Base effect in Suzuki–Miyaura reaction[a]



Entry	Base	Reaction time (h)	Yield (%)[b]
1	KF	24	84[c]
2	NaOAc	24	31[c]
3	Et_3N	24	32[c]
4	$K_3PO_4 \cdot 3H_2O$	24	73[c]
5	Na_2CO_3	7	85[d]
6	K_2CO_3	4	97[d]
7	$NaOBu^t$	7	85[d]
8	No base	24	24[c]

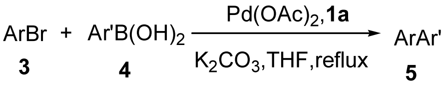
[a] Bromoanisole (1 mmol), phenyl boronic acid (1.5 mmol), base (3 mmol), $Pd(OAc)_2$ (0.025 mmol), **1a** (0.075 mmol), THF (3 mL), reflux.

[b] Isolated yield.

[c] Bromoanisole was not completely consumed.

[d] Bromoanisole was consumed.

Table 2. $Pd(OAc)_2$-$Ph_2PNPr^i_2$ catalyzed Suzuki–Miyaura reaction[a]



Ar	Ar'
a: $4\text{-}MeOC_6H_4$	**a:** C_6H_5
b: C_6H_5	**b:** $2\text{-}MeC_6H_4$
c: $2\text{-}MeC_6H_4$	**c:** $3\text{-}MeC_6H_4$
d: $3,4\text{-}CH_2O_2C_6H_3$	**d:** $4\text{-}MeC_6H_4$
e: $2,6\text{-}Me_2C_6H_3$	**e:** $4\text{-}MeOC_6H_4$
f: $4\text{-}(CHO)C_6H_4$	
g: $2\text{-}(MeCO)C_6H_4$	

Entry	3	4	5	Yield (%)[b]
1	**3a**	**4a**	**5aa**	97
2	**3a**	**4b**	**5ab**	– (97)
3	**3a**	**4c**	**5ac**	89 (78)
4	**3a**	**4d**	**5ad**	80 (73)
5	**3a**	**4e**	**5ae**	95
6	**3b**	**4a**	**5ba**	94
7	**3b**	**4b**	**5bb**	86
8	**3b**	**4c**	**5bc**	– (99)
9	**3c**	**4a**	**5ca**	98 (79)
10	**3d**	**4a**	**5da**	99
11	**3e**	**4a**	**5ea**	93
12	**3e**	**4b**	**5eb**	93[c]
13	**3f**	**4a**	**5fa**	94
14	**3g**	**4a**	**5ga**	99[d]

[a] Aryl bromide (1 mmol), aryl boronic acid (1.5 mmol), K_2CO_3 (3 mmol), $Pd(OAc)_2$ (0.025 mmol), **1a** (0.075 mmol), THF (3 mL), reflux for 12 h.

[b] Isolated yield (isolated yield if the reaction was run at room temperature for 24 h.

[c] $Pd_2(dba)_3$ was used.

[d] Reaction time, 48 h.

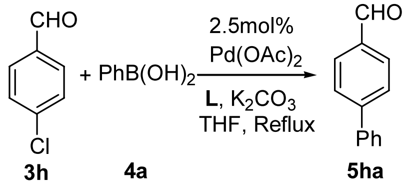
and is usually difficult to be activated in cross-coupling reactions, the ligand seems to be applicable to both electron-rich and electron-deficient aryl bromides. The choice of a base usually is important in achieving an efficient cross-coupling reaction. We therefore screened different bases and the results are summarized in Table 1. The widely used bases, such as KF, $K_3PO_4 \cdot 3H_2O$, Na_2CO_3 and K_2CO_3 had remarkable effect in the coupling reaction (entries 1, 4–6, Table 1), and K_2CO_3 was the best among the bases. Stronger base was not necessary in the reaction (entry 7, Table 1).

Screening of palladium precursors in the presence of **1a** showed that $Pd(OAc)_2$-**1a** was superior to other combinations (Table 2). Although other ligands also showed good reactivity and gave high yields (for **1b**, 86%; **1c**, 87%) when $Pd(OAc)_2$ was used as catalyst precursor, they are not so air-stable as **1a** (no significant change occurred when **1a** was exposed to air for 3 days).

As expected, both electron-rich and electron-deficient aryl bromides were applicable for this reaction. Highly electron-rich aryl bromide, such as 5-bromo-benzo-[1,3]-dioxole (**3d**), could be used as a substrate to give excellent yield (entry 10, Table 2); electron-deficient aryl bromides, such as 4-bromobenzaldehyde, worked also well (entry 13, Table 2). When 2,6-dimethyl phenyl bromide and 2-methylphenyl boronic acid were employed as substrates, the reaction could not be completed after 12 h. However, if phenyl boronic acid was used, the coupling proceeded smoothly to give the desired reaction product with excellent yield (entry 11, Table 2). This implies that the activation of bulky aryl bromides with the catalytic system was not problematic, and the rate-limiting step occurred after the oxidative addition, so that transmetallation might be the rate-determining step. Changing the catalyst to $Pd_2(dba)_3$-**1a**, we could obtain excellent yield from the reaction of 2,6-dimethyl phenyl bromide and 2-methylphenyl boronic acid (entry 12, Table 2). The catalytic system showed good reactivity and high efficiency and the reactions proceeded smoothly even at room temperature, giving biaryls **5** in good to excellent yields (entries 2–4, 8, 9, Table 2). Using less reactive aryl bromide, such as 4-bromanisole, a TON (turn over number) of 8,600 could be obtained after 24 h in refluxing THF.[13]

When aryl chloride **3h** was employed, the reaction underwent sluggishly under the catalysis of 2.5 mol% $Pd(OAc)_2$ and **1**. The yield of biaryl **5ha** did not exceed 40% after 12 h in refluxing THF (Scheme 2). This could be ascribed to the retardation of the oxidative addition, since the transmetallation rate for the species (ArPdCl) with phenyl boronic acid is decreasing in the order of Cl>Br>I[12] while the reductive elimination should be similar.

To improve the reactivity for the activation of aryl chloride, one easy way is to increase the electron density of the phoshpine ligand to make the oxidative step more favorable. As reported in the literature,[8a,d] a second amino group also serves as an electron donating



L=1a (2a) 30% (23%)
L=1b (2b) 35% (67%)
L=1c (2c) 29% (88%)

Scheme 2. Suzuki–Miyaura reaction with activated aryl chloride.

functional group. The introduction of the second amino group might therefore improve the electron density of the phosphorus atom of the phosphine ligand. In light of this argument, bis(dialkylamino)phenyl phosphine **2a–c** were made to test the reactivity.

Unexpectedly, when **2a** was used as the ligand to perform the coupling reaction outlined in Scheme 2, the reactivity decreased, the conversion of the substrate was not complete after 12 h of refluxing in THF, and the product was isolated in 23% yield with unreacted 4-chlorobenzaldehyde. However, under the same reaction conditions, when **2b** and **2c** were used as ligands, the reactivity was greatly improved, giving the product **5ha** with yields of 67 and 88%, respectively.

In summary, we have developed a new type of easily-prepared aminophosphine ligands in the Suzuki–Miyaura coupling reaction. The air-stable, easy-to-handle and efficient ligands combine to make the coupling reaction practical.

In view of the steric effect and electronic effect, the research on more efficient ligands to activate the more challenging C–Cl bond is under progress in our laboratory.

Acknowledgements

We thank the National Natural Science Foundation of China, Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality for financial support.

References

1. (a) *Cross-coupling reactions: A practical guide (Topics in Current Chemistry, Vol. 219)*; Miyaura, N., Ed.; Springer: Berlin, 2002 and references cited therein; (b) Grushin, V. V.; Alper, H. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer: New York, 1999; Vol. 3, pp. 193–226; (c) Suzuki A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2; (d) Beller, M.; Riermeier, T. H. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, pp. 184–193; (e) Negishi, E.-I.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 1–48; (f) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
2. Szmant, H. H. *Organic Building Blocks for the Chemical Industry*; John Wiley & Sons: New York, 1989.
3. (a) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152; (b) Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4883–4884; (c) Siddiqui, M. A.; Sneieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523–1525; (d) Kelly, T. R.; Garcia, A.; Lang, F.; Walsh, J. J.; Bhasker, K. V.; Boyd, M. R.; Götz, R.; Keller, P. A.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994**, *35*, 8747–8750.
4. (a) Hird, M.; Gray, G. W.; Toyne, K. J. *Mol. Cryst. Liq. Cryst.* **1991**, *206*, 187–204; (b) Kim, Y. H.; Webster, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4592–4593; (c) Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1991**, *113*, 7411–7412; (d) Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723–11736.
5. (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416; (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561; (c) Bei, X.; Curam, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855–3858; (d) Bei, X.; Turner, H. W.; Weinberg, W. H.; Curam, A. S. *J. Org. Chem.* **1999**, *64*, 6797–6803; (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388; (f) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (g) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370; (h) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481–483; (i) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 6667–6670.
6. (a) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095–2096; (b) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830–1833; (c) Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487–2490.
7. (a) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873; (b) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363–1365; (c) Loch, J. A.; Albrecht, M.; Peris, E.; Mata, J.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 700–706; (d) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761–3764; (e) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93–96.
8. (a) Clarke, M. L.; Cole-Hamilton, D. J.; Woolins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721–2723; (b) Schareina, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 1521–1523; (c) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921–8924; (d) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woolins, J. D. *Chem. Commun.* **2000**, 2065–2066.
9. (a) Rømming, C.; Songstad, J. *Acta Chem. Scand. Ser. A.* **1978**, *32*, 689–699; (b) Rømming, C.; Songstad, J. *Acta Chem. Scand. Ser. A.* **1979**, *33*, 187–197; (c) Rømming, C.; Songstad, J. *Acta Chem. Scand. Ser. A.* **1982**, *36*, 665–671; (d) Moloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696–7710; (e) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 88–94.

10. Farina, V.; Krishnamurihy, V.; Scott, W. J. *The Stille Reaction in Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. 50.

11. (a) Frank, A. W. *J. Org. Chem.* **1961**, *26*, 850–852; (b) Gallagher, M. J.; Jenkins, I. D. *J. Chem. Soc. C* **1966**, 2176–2181; (c) Contreras, R.; Grevy, J. M.; Garcia-Hernandez, Z.; Gueizado-Rodriguez, M.; Wrackmeyer, B. *Heteroatom. Chem.* **2001**, *12*, 542–550.

12. (a) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151; (b) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

13. A general procedure was as follows: A degassed Schlenk reaction tube was charged successively with THF (3 mL), K_2CO_3 (414 mg, 3 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), **1a** (21.4 mg, 0.075 mmol), aryl bromide (1 mmol) and aryl boronic acid (1.5 mmol) under a nitrogen atmosphere. The reaction mixture was refluxed for 12 h or stirred at room temperature (20–24°C) for 24 h. After the removal of the solvent, 20 mL of ether and 10 mL of water were added, the organic layer was separated and the water phase was extracted twice with ether (2×10 ml). The combined organic extract was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by flash chromatography (hexane or hexane–ethyl acetate) to afford the pure desired product.