



Pd/P(*i*-BuNCH₂CH₂)₃N: an efficient catalyst for Suzuki cross-coupling of aryl bromides and chlorides with arylboronic acids

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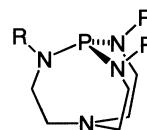
Abstract—Pd(OAc)₂ in combination with the commercially available ligand P(*i*-BuNCH₂CH₂)₃N catalyzes the Suzuki cross-coupling reaction of a wide variety of aryl bromides and chlorides with arylboronic acids, affording the desired biaryls in excellent yields. It has also been shown that P(NMe₂)₃ can be employed as a ligand, though with significantly more limited success. © 2002 Elsevier Science Ltd. All rights reserved.

The reaction of halides (or halide equivalents) with arylboronic acids to generate C–C bonds is an important transformation in organic synthesis.¹ Ever since the first report in 1981 by Suzuki and co-workers on their preparation of biaryls,² a variety of improvements in catalyst precursors have been described. These studies revealed the crucial role played by the ancillary ligands in the efficiency of this reaction. Sterically hindered, electron-rich alkyl phosphines³ and carbene⁴ ligands have received increasing interest in recent years. However, the development of new ligands or the application of existing ligands in this reaction, particularly those involving aryl chlorides as substrates, is still of considerable importance.

Although acyclic triaminophosphine ligands are well known in transition metal chemistry, they have not been used in metal-catalyzed cross-coupling reactions probably because of their diminished electron-donating capability as rationalized by Woollins⁵ recently on the basis of differences in geometries at the nitrogens. Structures of free triaminophosphines and of their transition metal complexes⁶ determined by diffraction techniques reveal that each phosphine ligand bears two nearly planar nitrogens and one pyramidal nitrogen. While the two planar nitrogens are capable of donating electron density to phosphorus, the pyramidal nitrogen

is oriented such that its lone pair is *anti* to the phosphorus lone pair, thus allowing that nitrogen to act simply as an electron withdrawing substituent on the phosphorus.

We reasoned that by making the backbone of the triaminophosphine fairly rigid but strain-free in a bicyclic framework in which all three nitrogens would be planar as in pro-azaphosphatranes **1–6**, we could potentially avoid the reduced electron donating character associated with acyclic triaminophosphines. Thus, in contrast to acyclic analogues of **1–6**, all three nitrogens in the cage structure would augment the electron-density on the phosphorus atom. As is seen in **1–6**, the electronic and steric nature of the phosphorus can be fine tuned by the substituents on each PN₃ nitrogen.⁷



- 1 R = Methyl
- 2 R = Ethyl
- 3 R = *i*-Propyl
- 4 R = *i*-Butyl
- 5 R = *neo*-Pentyl
- 6 R = 4-Pyridyl

Herein we report that bicyclic triaminophosphine **4** (commercially available from Aldrich) is an excellent ligand (and the best of the bicyclic series shown above) in palladium-catalyzed Suzuki cross-coupling reaction of aryl halides, including the less reactive aryl chlorides.⁸ We also demonstrate that the commercially available acyclic triaminophosphine P(NMe₂)₃ can also be used in the reactions involving aryl bromides and chlorides, although with much less efficiency than **4**.

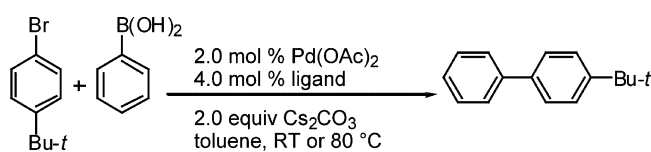
Keywords: cross-coupling reaction; ligands; bicyclic triaminophosphine.

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For optimization studies, we initially screened bicyclic **1–6** and the three acyclic triaminophosphine ligands shown in Table 1 for cross-coupling of 1-bromo-4-*tert*-butylbenzene and phenylboronic acid in the presence of 2.0 equiv. of Cs₂CO₃, 2.0 mol% of Pd(OAc)₂ and 4.0 mol% of ligand in toluene. From the results summarized in Table 1, it is evident that bicyclic triaminophosphine **4** is the most effective of the triaminophosphine ligands examined, by a substantial margin, affording a 96% yield of 4-*tert*-butylbiphenyl in 6 h at 80°C (Table 1, entry 6) and a 90% yield of the same product at room temperature in 28 h (Table 1, entry 7). The other bicyclic ligands were considerably less catalytically active than **4** (Table 1, entries 1–5, 9 and 10) for reasons that are not clear at this time. It is likely that the *iso*-butyl groups on the PN₃ nitrogens provide a particularly effective steric and electronic environment at the phosphorus for stabilization of the catalytically active species. Interestingly, the acyclic triaminophosphines P(NMe₂)₃ and P(N-*i*-Bu)₂₃ also furnished the desired product in good yields (Table 1, 87% yield, entry 11 and 84% yield, entry 14, respectively) at 80°C. Although coupling for ligands **1**, **2**, **4** and P(NMe₂)₃ proceeded slowly at room temperature, the reaction proceeds significantly faster at 80°C.

We next investigated a variety of solvents and bases for the aforementioned coupling reaction catalyzed by the Pd(OAc)₂/**4** system (Table 2). Toluene was found to be the most efficacious solvent. Although dioxane and DMF gave comparable yields, the reaction times were somewhat longer (Table 2, entries 1 and 2). Employing THF as the solvent significantly decreased the yield of the desired product (Table 2, entry 3). Among the bases explored, Cs₂CO₃ gave the fastest reaction rates although CsF was also a suitable base (Table 2, entry 4). However, reactions involving KF, K₃PO₄ or K₂CO₃ as a base failed

Table 1. Effect of various triaminophosphine ligands in the Pd-catalyzed cross-coupling of 1-bromo-4-*tert*-butylbenzene with phenylboronic acid^a



Entry	Ligand	Temp. (°C)	Time (h)	Yield (%)
1	1	rt	48	52
2	1	80	18	69
3	2	rt	30	16
4	2	80	26	72
5	3	80	18	46
6	4	80	9	96
7	4	rt	28	90
8	None	80	20	45
9	5	80	24	68
10	6	80	24	14
11	P(NMe ₂) ₃	80	18	87
12	P(NMe ₂) ₃	rt	40	85
13	P(NEt ₂) ₃	80	33	31
14	P(N- <i>i</i> -Bu) ₂ ₃	80	24	84

^a Isolated yields (average of two runs).

Table 2. Effect of bases and solvents on the Pd(OAc)₂/**4**-catalyzed cross-coupling of 1-bromo-4-*tert*-butylbenzene with phenylboronic acid using the conditions given in Table 1

Entry	Base	Solvent	Time (h)	Yield (%) ^a
1	Cs ₂ CO ₃	Dioxane	13	95
2	Cs ₂ CO ₃	DMF	16	91
3	Cs ₂ CO ₃	THF	20	72
4	CsF	Toluene	10	90
5	KF	Toluene	20	78 ^b (34 ^c)
6	K ₃ PO ₄	Toluene	20	82 ^b (19 ^c)
7	K ₂ CO ₃	Toluene	13	63

^a Isolated yields (average of two runs).

^b 90% conversion based on the recovered starting material.

^c The reaction was performed at room temperature and the reaction time was 40 h.

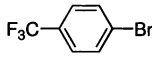
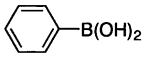
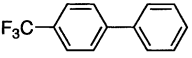
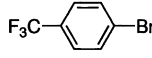
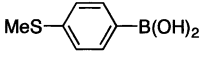
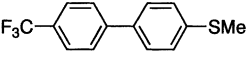
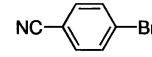
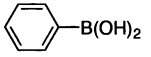
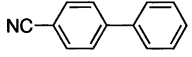
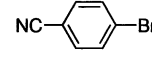
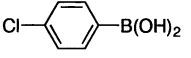
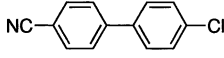
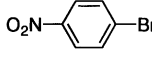
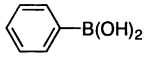
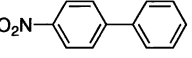
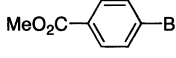
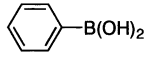
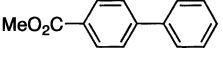
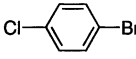
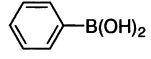
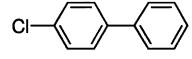
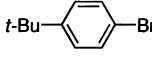
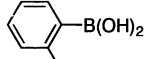
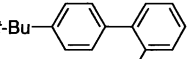
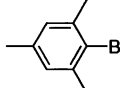
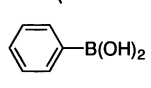
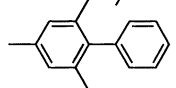
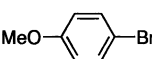
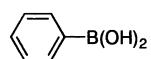
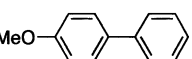
to provide complete conversion even after 20 h (Table 2, entries 5, 6 and 7).

With optimized conditions in hand, we evaluated the scope of the coupling of aryl bromides with various arylboronic acids. It is clear from Table 3 that aryl bromides containing electron-withdrawing groups such as trifluoromethyl, cyano, nitro and ester groups are coupled in excellent yields (Table 3, entries 1–5 and 6). Not surprisingly, the Pd(OAc)₂/**4** catalyst system also efficiently and highly selectively catalyzes the reaction of an aryl bromide possessing a chloride functionality (Table 3, entry 7). The use of acyclic P(NMe₂)₃ as a ligand also gave satisfactory yields with electron-deficient aryl bromides (Table 3, see yields in parenthesis for entries 1, 3 and 6). The Pd(OAc)₂/**4** catalytic system also proved to be highly efficient for electron-neutral and electron-rich aryl bromides. For example, combining 1-bromo-4-*tert*-butylbenzene with sterically hindered *o*-tolylboronic acid provided the corresponding biaryl in 96% isolated yield (Table 3, entry 8). Sterically demanding di-*ortho*-substituted-2-bromomesitylene also reacted in high yield (Table 3, entry 9). Electron-rich 4-bromoanisole was also a suitable coupling partner (Table 3, entry 10). In contrast, the Suzuki cross-coupling reactions of unactivated (electron-neutral) and deactivated (electron-rich) aryl bromides employing the acyclic triaminophosphine P(NMe₂)₃ as the ligand proceeded only in moderate to poor yields.

Although we were successful in synthesizing biaryls containing two *ortho* substituents, our attempts to synthesize *tri*- or *tetra*-*ortho* substituted biaryls were unsuccessful even with increased catalyst loading and/or longer reaction times.⁹

We next examined Suzuki reactions of usually unreactive aryl chlorides using Pd(OAc)₂/**4** as a catalyst system (Table 4). The low reactivity of such substrates has been attributed to their aversion to add oxidatively to a Pd(0) complex because of a large C–Cl bond dissociation energy (402 kJ mol⁻¹; 298 K).¹⁰ A slightly higher catalyst loading (4 mol% Pd) was required for these reactions to proceed to completion. The reaction of electron-poor (Table 4, entries 1, 2, 3 and 4) and electron-rich (Table

Table 3. Suzuki cross-coupling of aryl bromides with arylboronic acids^a

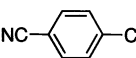
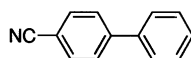
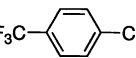
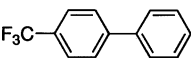
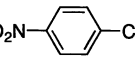
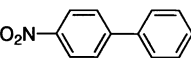
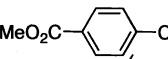
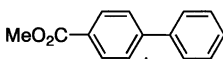

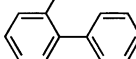
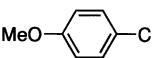
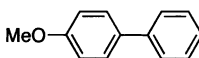
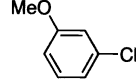
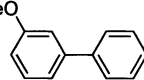
Entry	Aryl Bromide	Arylboronic Acid	Product	Yield (%) ^b
1				99 (57) ^c
2				98
3				99 (90) ^c
4				95
5				96
6				90 (85) ^c
7				90
8				96
9				99 (76) ^c
10				93 (82) ^c

^a Reaction conditions: 1.0 mmol of aryl bromide, 1.5 mmol of arylboronic acid, 2.0 mmol of Cs₂CO₃, 2.0 mol % Pd(OAc)₂, 4.0 mol % ligand 4, 5 mL of toluene, 80 °C, 4–12 h, reaction times have not been minimized.

^b Isolated yields (average of two runs).

^c Yields in parenthesis refer to reactions in which P(NMe₂)₃ was employed as a ligand.

Table 4. Suzuki cross-coupling of aryl chlorides with phenylboronic acid^a

Entry	Aryl Chloride	Product	Yield (%) ^b
1			95 (84) ^c
2			90 (80) ^c
3			99
4			98
5			92
6			90
7			88

^a Reaction conditions: 1.0 mmol of aryl chloride, 1.5 mmol of phenylboronic acid, 2.0 mmol of Cs₂CO₃, 4.0 mmol Pd(OAc)₂, 8.0 mol % ligand 4, 5 mL of toluene, 80 °C, 18 h.

^b Isolated yields (average of two runs).

^c Yields in parenthesis refer to reaction in which 10 mol % Pd(OAc)₂ and 20 mol % P(NMe₂)₃ were employed.

4, entries 6 and 7) aryl chlorides with phenylboronic acid provided very good yields of the biaryl product. Sterically hindered 2-chlorotoluene was equally reactive and the desired product was isolated in 92% yield (Table 4, entry 5). In contrast, cross-coupling of aryl chlorides with phenylboronic acid in the presence of $\text{P}(\text{NMe}_2)_3$ resulted in no detectable product formation even over 36 h when 4 mol% $\text{Pd}(\text{OAc})_2$ was employed. However, the use of 10 mol% $\text{Pd}(\text{OAc})_2$ and 20 mol% $\text{P}(\text{NMe}_2)_3$ did allow cross-coupling of electron-poor aryl chlorides with phenylboronic acid and the desired biaryls were obtained in acceptable yields (Table 4, parenthesized yields for entries 2 and 4). The lower yields obtained with the $\text{Pd}(\text{OAc})_2/\text{P}(\text{NMe}_2)_3$ catalyst system were due largely to the formation of hydrodehalogenation products. Since triaminophosphines are apparently less electron-rich than trialkylphosphines, their effectiveness in the activation of C–Cl bond under our conditions is quite remarkable.

In summary, we have shown that the new, cheap and readily accessible catalyst system $\text{Pd}(\text{OAc})_2/4$ is effective for the convenient and efficient synthesis of unsymmetrical biaryls from aryl bromides or chlorides. While the catalyst system $\text{Pd}(\text{OAc})_2/\text{P}(\text{NMe}_2)_3$ is also effective for aryl bromides, it is not very efficient with aryl chlorides.

Acknowledgements

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- For a recent review of the chemistry of pro-azaphosphatranes, see: Verkade, J. G. *Top. Curr. Chem.*, in press.
- General procedure:** An oven-dried Schlenk flask, equipped with a magnetic stir bar, septum, and a condenser with an argon inlet–outlet was charged with aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), base (1.5 mmol), $\text{Pd}(\text{OAc})_2$ (2 mol% for aryl bromide and 4 mol% for aryl chloride), ligand (4 mol% for aryl bromide and 8 mol% for aryl chloride) and 5 mL of solvent. The flask was immersed in an oil bath at the temperature indicated in the tables. Upon complete consumption of starting material as determined by TLC analysis, the reaction mixture was adsorbed onto silica and the biaryl product was isolated by column chromatography (hexanes/EtOAc). All the biphenyl products are known compounds.
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