



PdCl₂(SEt₂)₂ and Pd(OAc)₂: simple and efficient catalyst precursors for the Suzuki cross-coupling reaction

Danilo Zim, Adriano L. Monteiro and Jairton Dupont*

Laboratory of Molecular Catalysis, Instituto de Química, UFRGS. Av. Bento Gonçalves, 9500, Porto Alegre 91501-970 RS, Brazil

Received 17 August 2000; revised 1 September 2000; accepted 5 September 2000

Abstract

PdCl₂(SEt₂)₂ and Pd(OAc)₂ efficiently promote the cross-coupling of aryl bromides and chlorides with arylboronic acids under mild reaction conditions. These methods tolerate a variety of functional groups and represent, from a synthetic point of view, two of the simplest catalyst precursors that mediate the Suzuki cross-coupling reaction at room temperature. © 2000 Elsevier Science Ltd. All rights reserved.

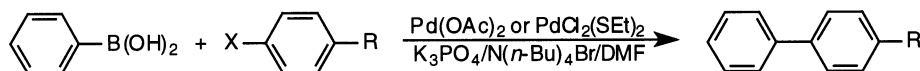
Keywords: coupling reactions; palladium catalysts; Suzuki; boronic acids; aryl halides.

The palladium-catalysed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of carbon–carbon (*sp*²–*sp*²) bonds.¹ Almost any Pd(II) or Pd(0) derivative, usually associated with phosphine ligands, promotes this coupling reaction involving aryl iodides or aryl bromides, substituted with electron-withdrawing groups, in high turnover numbers.² However, in the case of the less reactive aryl chlorides and electron-rich aryl bromides, the presence of added ligands is necessary to effectively promote these reactions. In this respect Pd(II) and/or Pd(0) associated with electron-rich and sterically-demanding phosphines,³ imidazole carbenes⁴ and palladacycles,⁵ are amongst the most active catalyst precursors that operate under relatively mild reaction conditions. While investigating the use of sulfur-containing palladacycles⁶ as catalyst precursors for Suzuki^{5e} coupling we have observed, in control experiments, that simple complexes such as Pd(OAc)₂ and PdCl₂(SEt₂)₂ also generate catalytic active species for this coupling reaction. We wish to report that commercially available palladium acetate and the simple sulfur-containing palladium complex PdCl₂(SEt₂)₂, which is easy to make, thermally stable and insensitive to air and moisture, can be used in the Suzuki coupling reaction of various aryl halides at room temperature.

PdCl₂(SEt₂)₂ is easily and quantitatively prepared by simply adding 2.5 molar excess of SEt₂ to a solution of sodium tetrachloropalladate at room temperature, using a procedure similar to that described for the analogous platinum(II) complex.⁷

* Corresponding author. E-mail: dupont@iq.ufrgs.br

Based on our recent success with sulfur-containing palladacycles as catalyst precursors in Suzuki coupling reactions of aryl halides, we employed the same experimental protocol.^{5c} In initial experiments, DMF was chosen as the solvent and potassium phosphate as the base for the reaction of 4-bromotoluene with phenylboronic acid (Scheme 1) at 130°C using PdCl₂(SEt₂)₂ or Pd(OAc)₂ as catalyst precursors (entries 1–4, Table 1).



Scheme 1. Suzuki cross-coupling reaction

It is clear from entries 1–4 (Table 1) that the salt additive N(*n*-Bu)₄Br has a beneficial effect in the case of Pd(OAc)₂ and no significant effect when using PdCl₂(SEt₂)₂. The role of this additive in these systems is not well understood but it is believed that it is involved in the stabilisation of anionic palladium species such as [Br–Pd–ligand][−].⁸ At the moment we cannot offer a definitive explanation for the different effect of the salt in each case and investigations in this direction are currently underway in our laboratory.

Table 1
Suzuki reaction between phenylboronic acid and aryl halides (Scheme 1^a)

Entry	ArX	[Pd] (%)	N(<i>n</i> -Bu) ₄ Br %	T/°C	Time/h	Yield/% ^b
1	4-MeC ₆ H ₄ Br	PdCl ₂ (SEt) ₂ (0.02)	0.2	130	1	41
2	4-MeC ₆ H ₄ Br	Pd(OAc) ₂ (0.02)	0.2	130	1	76
3	4-MeC ₆ H ₄ Br	PdCl ₂ (SEt) ₂ (0.02)		130	1	63
4	4-MeC ₆ H ₄ Br	Pd(OAc) ₂ (0.02)		130	1	51
5	4-MeOC ₆ H ₄ Br	PdCl ₂ (SEt) ₂ (0.2)		130	62	100 (87) ^c
6	4-MeOC ₆ H ₄ Br	PdCl ₂ (SEt) ₂ (0.2)		25	96	100 (91) ^c
7	4-MeC ₆ H ₄ Br	PdCl ₂ (SEt) ₂ (0.2)		25	62	100 (92) ^c
8	2,4-Me ₂ C ₆ H ₃ Br	PdCl ₂ (SEt) ₂ (0.2)		25	62	72
9	4-CNC ₆ H ₄ Cl	PdCl ₂ (SEt) ₂ (0.2)		130	96	100 (48) ^c
10	2,4-Me ₂ C ₆ H ₃ Br ^d	PdCl ₂ (SEt) ₂ (0.2)		130	62	68
11	4-MeOC ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	25	87	100 (94) ^c
12	4-MeOC ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	130	2	94
13	4-MeC ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	25	87	100 (92) ^c
14	4-MeC ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	130	2	100
15	1-BrC ₁₀ H ₇	Pd(OAc) ₂ (0.5)	0.2	25	87	100
16	1-BrC ₁₀ H ₇	Pd(OAc) ₂ (0.5)	0.2	130	2	100
17	4-NO ₂ C ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	25	87	100 (93) ^c
18	4-NO ₂ C ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	130	2	100 (95) ^c
19	3-CF ₃ C ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	130	2	100
20	4-PhC ₆ H ₄ Br	Pd(OAc) ₂ (0.5)	0.2	130	2	100
21	4-NCC ₆ H ₄ Cl	Pd(OAc) ₂ (0.5)	0.2	25	87	94
22	4-NCC ₆ H ₄ Cl	Pd(OAc) ₂ (0.5)	0.2	130	2	85
23	4-NO ₂ C ₆ H ₄ Cl	Pd(OAc) ₂ (0.5)	0.2	25	87	100 (92) ^c
24	4-NO ₂ C ₆ H ₄ Cl	Pd(OAc) ₂ (0.5)	0.2	130	2	100

^a Reaction conditions: DMF, K₃PO₄ (2.0 equivalents).

^b GC yield using undecane as internal standard.

^c Isolated yield.

^d Using 2-tolylboronic acid instead of phenylboronic acid.

Under this experimental protocol (DMF, K_3PO_4), $PdCl_2(SEt_2)_2$ (0.2%) efficiently promotes the coupling of aryl bromides (containing electron withdrawing or donating groups) and electron poor aryl chlorides with phenyl boronic acid leading to biaryls in high yields (>90%). Note that this cross-coupling reaction can be performed at room temperature, although longer reaction times are required compared to those at 130°C (see entries 5–10, Table 1). However, in the case of electron-rich or electron-neutral aryl chlorides this catalytic system failed under these reaction conditions.

More interestingly, palladium acetate can be also used in these coupling reactions giving biaryls in high isolated yields (see entries 11–24). It is noteworthy that aryl iodides and activated aryl bromides have been coupled with arylboronic acids at room temperature using $Pd(OAc)_2$ in aqueous media.⁹ In addition, we found that $Pd(OAc)_2$ in DMF is active in the Suzuki coupling of neutral and electron-rich arylbromides and even activated aryl chlorides. The reaction can be performed at room temperature and various functional groups in the aryl halide can be tolerated.

From an experimental point of view this method is extremely simple: an oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with K_3PO_4 (424 mg, 2.0 mmol), boronic acid (183 mg, 1.5 mmol), and additive $N(n-Bu)_4Br$ (64.5 mg, 0.2 mmol). The flask was evacuated and back-filled with argon and then the aryl halide (1.0 mmol) and a solution of $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in 5 mL of dimethylformamide were added. The reaction mixture was stirred at room temperature until the starting aryl halide had been completely consumed, as judged by GC analysis. Palladium black was only observed visually in the reactions performed using more than 0.5% on palladium. The solution was then taken up in ether (20 mL) and washed with aqueous NaOH (1 M, 5 mL) and brine (2×5 mL), and then dried over $MgSO_4$. After filtration, the solvent was evaporated to give the respective product, which was characterised by GCMS, 1H and ^{13}C NMR.

In summary we have shown that under the appropriate reaction conditions, commercially available palladium acetate effectively promotes the Suzuki cross-coupling reaction of arylboronic acids with various aryl halides (except for electron neutral and rich aryl chlorides). This is the simplest palladium catalyst system for the generation of biaryls reported to date. Moreover, these results suggest that only electron neutral and rich aryl chlorides should be used as benchmarks for testing new palladium catalysts for Suzuki coupling.

Acknowledgements

This work was supported by grants from the PADCT-CNPq and FAPERGS. Help from Dr. J. Spencer (TRI, England) in the proof reading of the manuscript is greatly appreciated.

References

1. For reviews see for example: (a) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 49–97. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
2. See for example: (a) Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487. (b) Zhang, C. M.; Huang, J. K.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (c) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596. (d) Herrmann, W. A.; Reisinger, C. P.; Spiegler, M. J.

- Organomet. Chem.* **1998**, *557*, 93. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (f) Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smreina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714. (g) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830. (h) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885. (i) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (j) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170. (k) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.
3. (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797.
4. Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595.
5. (a) Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901. (b) Herrmann, W. A.; Bohm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141. (c) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095. (d) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848. (e) Zinn, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881.
6. (a) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (b) For another example of the application of sulfur-containing palladacycles in coupling reactions see: Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531.
7. Kauffman, G. B.; Cowan, D. O. *Inorg. Synth.* **1960**, *6*, 211.
8. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
9. For ligandless Pd(OAc)₂ catalysed Suzuki reactions see: (a) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (b) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395 and references cited therein.