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Sulfur-Containing Palladacycles: Efficient Phosphine-Free Catalyst Precursors for the Suzuki Cross-Coupling Reaction at Room Temperature

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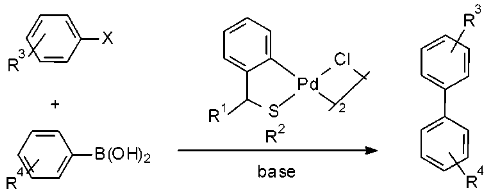
ABSTRACT



Cyclopalladated compounds derived from the ortho-metalation of benzylic *tert*-butyl thioethers are excellent catalyst precursors for the Suzuki cross-coupling reaction of aryl bromides and chlorides with phenylboronic acid under mild reaction conditions. A broad range of substrates and functional groups are tolerated in this protocol, and highly catalytic activity is attained.

The palladium-catalyzed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of $C_{aryl}-C_{aryl}$ bonds and has found widespread use in organic synthesis.[1] A plethora of palladium catalyst precursors promote the coupling of aryl halides with organoboron compounds.[2] In the case of aryl iodides and bromides containing electron-withdrawing groups, even ligandless palladium catalyst precursors are sufficient to promote this cross-coupling in high turnover.[3,4] However, in the case of less reactive aryl chlorides and electron-rich aryl bromides, the presence of added ligands is necessary to effectively promote these cross-couplings. In this respect, bulky and electron-rich[4−7] phosphine-containing Pd compounds or carbene−Pd complexes[8] are the most active catalyst precur-

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(1) (a) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(2) 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) Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487. (c) Zhang, C. M.; Huang, J. K.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (d) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596. (e) Herrmann, W. A.; Reisinger, C. P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (f) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (g) 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. (h) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830.

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sors reported to date. Indeed, since the advent of these catalyst systems, the Suzuki coupling can be conducted with "nonactivated" aryl chlorides, under mild reaction conditions and using low catalyst concentrations.[4] It is doubtless that this catalytic system represents a significant synthetic improvement for the generation of bi-aryls over existing protocols. However, the new room temperature methods require the use of relatively expensive and usually difficult-to-handle phosphine ligands.[9] We[10] and others[11] have recently reported that phosphine-free sulfur-containing palladacycles are excellent catalyst precursors for the Heck reaction.[12] We wish to report that these easily prepared air- and water-stable palladacycles also efficiently promote the Suzuki cross-coupling reactions of aryl bromides and chlorides under mild reaction conditions.

The sulfur-containing palladacycles **1**−**6** (Figure 1) have been prepared by the reaction of palladium acetate with the corresponding thioether[13] as described previously.[10,14,15]

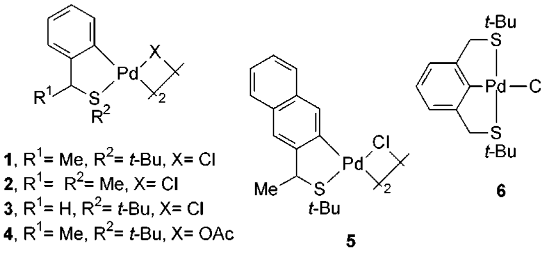
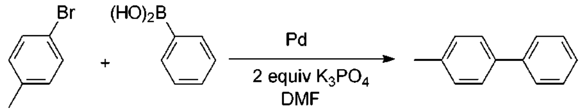


Figure 1. Sulfur-containing palladacycles **1**−**6**.

The coupling reaction of the relatively unactivated 4-bromotoluene with phenylboronic acid, catalyzed by palladacycle **1**, was selected as a model reaction. DMF was found to be the most effective solvent although DMA and toluene can be also used, giving slightly lower yields. In opposition, very low conversion was achieved using DMSO as solvent. Among the bases evaluated, K_3PO_4 was the base of choice. K_2CO_3 could be used, affording slightly lower yields while reactions using CsF and NaOAc gave moderate yields of cross-coupled product, and very low conversion was obtained when triethylamine was employed as a base. The reaction proceeds to completion at 25 °C (entry 11, Table 1), using DMF and K_3PO_4, and the biphenyl product is isolated in 94% yield.[16]

Table 1. Palladacycles Catalyzed Suzuki Cross-Coupling of *p*-Bromotoluene



entry	Pd	% Pd	*t* (h)	*T* (°C)	Bu_4NBr (%)	yield (%)[a]
1	**1**	1	1	130		100
2	**2**	1	1	130		82
3	**3**	1	1	130		99
4	**4**	1	1	130		96
5	**5**	1	1	130		97
6	**6**	1	1	130		69
7	**1**	0.02	1	130		54
8	**1**	0.02	1	130	20	73
9	**1**	0.002	13	130	20	74
10	**1**	0.2	4	130	20	100 (96)[b]
11	**1**	0.5	16	25	20	100 (96)[b]

[a] GC yield. [b] Isolated yield.

All the palladacycles studied promote the Suzuki cross-coupling of 4-bromotoluene (Table 1). The catalytic activity depends on the palladacycle structure. The most efficient catalyst precursors present one *t*-BuS moiety bonded to the palladium atom (**1**, **3**, **4**, and **5**). Lower activities were observed with a MeS (**2**) or with two *t*-BuS groups (**6**) ligated to the palladium atom. Moreover, no discernible influence was observed when changing from chloro (**1**) to acetate (**4**) bridges, from methyl to hydrogen (**3**) in the R^1 position, and from a phenyl (**1**) to a naphthyl group (**5**) in the palladacycle. Only biphenyl and 4,4′-dimethylbiphenyl were detected as side products in the crude solutions (<1% by GC-MS). Lower concentrations of palladium can be employed leading to TON up to 37 000 (entries 7−9, Table 1). As previously observed for the Heck reaction,[10] the use of $N(n\text{-}Bu)_4Br$[17] as promoter increases the reaction rate (entry 8, Table 1).

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[9] Although tri-*tert*-butylphosphine is commercially available, it should usually be handled in an inert atmosphere and in dry conditions.

[10] Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287.

[11] Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531.

[12] For nitrogen- and phosphorous-containing palladacycle catalysts, see: (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.

[13] The thioethers are easily prepared in high yields from the reaction of the corresponding benzylic alcohols with *tert*-butylmercaptan in the presence of zinc iodide. Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357.

[14] Cyclopalladated compounds are one of the most popular and investigated families in organometallic chemistry, and their synthesis is usually straightforward. See, for example: Pfeffer, M.; Goel, A. B. *Inorg. Synth.* **1989**, 211.

[15] Dupont, J.; Beydon, N.; Pfeffer, M. *J. Chem. Soc., Dalton Trans.* **1989**, 1715.

[16] In a typical experiment an oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with K_3PO_4 (424 mg, 2.0 mmol). The flask was evacuated and back-filled with argon, and then 4-bromotoluene (171 mg, 1.0 mmol), phenylboronic acid (182.9 mg, 1.5 mmol), $N(t\text{-}Bu)_4Br$ (64.5 mg, 0.2 mmol), and a solution of **1** (1.68 mg, 0.005 mmol), in 5 mL of dimethylformamide was added. The reaction mixture was stirred at room temperature for 16 h. 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 4-methylbiphenyl (161 mg, 96% yield) as a white solid in >95% purity as determined by GC and ^1H NMR (see Supporting Information for characterization data). Similar yields have been obtained when the reaction was performed in air and using commercial dimethylformamide (Acros) without purification.

[17] The role of the salt additive is not yet clear, but it is probably involved in the stabilization of anionic palladium intermediate species. For a discussion on the role of anionic Pd(0) and Pd(II) intermediates in cross-coupling reactions, see, for example: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

To evaluate the scope and limitations of this procedure, the reaction of a wide variety of aryl halides with phenylboronic acid was examined using palladacycle **1** in DMF and K_3PO_4 as a base (Table 2).

Table 2. Palladacycle **1** Catalyzed Suzuki Cross-Coupling of Aryl Halides and Phenylboronic Acid[a]

entry	ArX	**1** (%)	T (°C)	t (h)	yield (%)[b]
1	2,5-$Me_2C_6H_4Br$	0.2	25	38	94
2	4-$MeOC_6H_4Br$	0.5	130	4	90
3	4-$MeOC_6H_4Br$	0.5	25	38	95
4	4-PhC_6H_4Br	0.2	130	2	99
5	1-naphthylBr	0.2	130	4	97
6	2-naphthylBr	0.5	25	38	95
7	4-$CF_3C_6H_4Br$	0.2	130	2	98
8	3-$CF_3C_6H_4Br$	0.2	130	2	97
9	2-$CF_3C_6H_4Br$	0.2	130	2	93
10	4-$O_2NC_6H_4Br$	0.2	130	2	92
11	4-$O_2NC_6H_4Br$	0.5	25	16	98
12	4-AcC_6H_4Br	0.2	130	2	97
13	4-$MeOC_6H_4I$	0.5	25	38	93
14	4-AcC_6H_4Cl	0.5	130	4	92
15	4-NCC_6H_4Cl	0.5	130	4	90
16	4-NCC_6H_4Cl	0.5	25	16	92
17	4-$O_2NC_6H_4Cl$	0.5	130	4	93
18	4-$O_2NC_6H_4Cl$	0.5	25	16	95
19	PhCl	0.5	130	22	46[c]
20	1-naphthylCl	2	130	18	40
21	4-MeC_6H_4Cl	2	130	21	29[c]
22	4-$MeOC_6H_4Cl$	2	130	21	13[c]

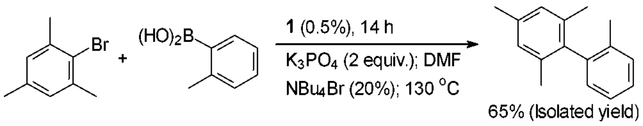
[a] Reaction conditions: 1 mmol of ArX, 1.5 equiv of $PhB(OH)_2$, 2 equiv of K_3PO_4, 0.2 equiv of NBu_4Br, 5 mL of DMF. [b] Isolated yields average of two runs. [c] GC yield.

It is clear from Table 2 that both electron-rich and -poor aryl bromides are efficiently coupled in the presence of **1** to provide the corresponding biaryl products in excellent isolated yields (>90%), and a wide variety of functional groups are tolerated (nitro, acetyl, cyano, etc.). Moreover, palladacycle **1** promotes the Suzuki coupling even at room temperature although longer reactions times were necessary (compare, for example, entries 2 and 3, Table 2). Only with reactions involving electron-neutral and -rich aryl chlorides are low conversions achieved even at higher reaction temperatures (entries 19−22, Table 2). Lower reaction times were necessary in the case of electron-poor aryl bromides (∼2 h) compared with electron-rich aryl bromides (∼4 h). An ortho-CF_3-substitued aryl bromide (entry 9, Table 2) gave slightly lower yields compared with its meta- and para-substituted analogues (entries 8 and 7, Table 2). Cross-couplings of electron-poor aryl chlorides also gave excellent yields in the corresponding biaryl products (entries 13−18, Table 2).

Note that except for electron-neutral and -rich aryl chlorides the reaction proceeds to completion at room temperature, producing the bis-aryls in >90% isolated yields. Palladacycle **1** is, therefore, the most efficient phosphine-free palladium catalyst precursor for the Suzuki coupling at room temperature reported to date.[18] Moreover, these reactions can be performed in air without the need of any special experimental precautions, rendering this method highly attractive for synthetic purposes.

Palladacycle **1** also efficiently promotes the cross-coupling of sterically demanding substrates.[19] Thus, the reaction of 2-bromomesitylene with 2-tolylboronic acid over 14 h at 130 °C affords 2,2′,4,6-tetramethylbiphenyl in 65% isolated yield (Scheme 1).

Scheme 1. Suzuki Cross-Coupling of Sterically Demanding Substrates



To gain some insight into the reaction mechanism, a preliminary competitive experiment was performed. A mixture of 0.002 mmol of **1**, 0.2 mmol of each aryl bromide (4-bromoanisol, 4-bromotoluene, bromobenzene, 4-bromobiphenyl, and 4-acetylbromobenzene), 5 mmol of $PhB(OH)_2$, and 2 mmol of K_3PO_4 in 4 mL of DMF was heated at 80 °C for 1 h. The biaryls 4-methoxybiphenyl, biphenyl, triphenyl, and 4-acetylbiphenyl were obtained in the ratio of 1:1.6:8.7:10:50.6, respectively. This behavior, i.e., electron-withdrawing substituents on the aryl bromide increasing the reaction rate, is analogous to those already reported for other palladium[12a] and nickel[20] catalyst precursors. A detailed study on the mechanism of this reaction is underway in our laboratory and will published in due course.

In summary, these results clearly demonstrate that for a wide range of aryl halides the Suzuki coupling, at room temperature, can be readily promoted by palladacycle **1**. Moreover, these results illustrate the high versatility of cyclopalladated compounds (in particular, sulfur-containing palladacycles)[21] as catalyst precursors for C−C bond-forming reactions.[22]

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(18) Until now only palladium complexes associated with electron-rich and bulky phosphine efficiently promote the cross-coupling at room temperature (for unactivated aryl chlorides see refs 4 and 5; for activated aryl chlorides see ref 6). For the coupling of aryl iodides and aryl bromides at room temperature, see: (a) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naesland, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (b) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123. (c) Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756. (d) Johnson, C. R.; Johns, B. A. *Synlett* **1997**, *53*, 15123. (e) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (f) Katamani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743. (h) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384. (g) Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965.

(19) For the cross-coupling of sterically hindered halo-arenes, see for example ref 2b.

(20) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024.

(21) For the synthesis and applications of sulfur-containing palladacycles, see, for example: (a) Spencer, J.; Pfeffer, M.; Kyritsakas, N.; Fischer, J. *Organometallics* **1995**, *14*, 2214. (b) Dupont, J.; Basso, N. R.; Meneghetti, M. R.; Konrath, R. A.; Burrow, R.; Horner, M. *Organometallics* **1997**, *16*, 2386. (c) Dupont, J.; Basso, N. R.; Meneghetti, M. R. *Polyhedron* **1996**, *15*, 2299. (d) Albéniz, A. C.; Espinet, P.; Kin, Y.-S. *Organometallics* **1996**, *15*, 5010.

It is expected that due to their facility of synthesis,[23] high thermal stability, and the possibility of modulating their electronic and steric properties (by simply changing the donor group, metalated carbon, size of the ring, etc.) palladacycles will no doubt progress as an important alternative family of organometallic catalyst precursors.[24]

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Supporting Information Available: Detailed experimental procedure and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) It is interesting to note that nitrogen- and phosphorus-containing palladacycles, apparently, only promote the cross-coupling at elevated temperatures (see refs 3).

(23) See, for example: (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567. (c) Pfeffer, M *Pure Appl. Chem*. **1992**, *64*, 335. (c) Spencer, J.; Pfeffer, M. *Adv. Met. Org. Chem.* **1998**, *6*, 103.

(24) For other catalytic reactions catalyzed by palladacycles, see, for example: (a) Camargo, M.; Dani, P.; Dupont, J.; de Souza R. F.; Pfeffer, M.; Tkatchenko, I. *J. Mol. Catal. A* **1996**, *109*, 127. (b) Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837. (c) Dani, P.; Dupont, J.; Monteiro, A. L. *J. Braz. Chem. Soc*. **1996**, *7*, 15. (d) Lewis, L. N. J. *Am. Chem. Soc.* **1986**, *108*, 743.