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A surprisingly mild and versatile method for palladium-catalyzed Suzuki cross-couplings of aryl chlorides in the presence of a tri*aryl*phosphine†

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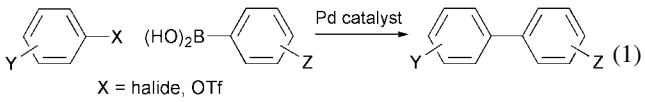
In the presence of new air-stable triarylphosphine 2, palladium-catalyzed Suzuki reactions of a wide array of aryl chlorides can be accomplished in uniformly good yield, including couplings of very sterically demanding and electronically deactivated substrates; activated aryl chlorides can be coupled at room temperature. In terms of scope and mildness, Pd–2 compares well with other catalyst systems that have been described for Suzuki reactions of aryl chlorides, thereby establishing that triarylphosphines should be regarded as fertile ground for future ligand-design efforts for palladium-catalyzed couplings of aryl chlorides.

The palladium-catalyzed cross-coupling of organic halides/triflates with organoboron reagents [Suzuki reaction; *e.g.*, eqn. (1)] is a powerful and widely used method for carbon–carbon



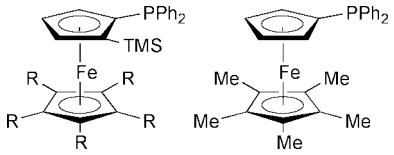
(1)

bond formation.[1] Until recently, aryl chlorides, an attractive class of substrates due to their low cost and ready availability,[2] were generally not suitable coupling partners in palladium-catalyzed Suzuki reactions.[3] However, during the past few years this deficiency has been remedied through the use of ligands such as electron-rich, sterically hindered phosphines[4] and carbenes.[5,6]

The low reactivity of aryl chlorides in palladium-catalyzed coupling reactions is often ascribed to their reluctance to oxidatively add to palladium, and the unusual effectiveness of strongly electron-donating ligands in achieving Suzuki cross-couplings of aryl chlorides is consistent with this hypothesis. Thus, at the time that we initiated our studies, there were no examples of Suzuki reactions of unactivated aryl chlorides by palladium catalysts that bear tri*aryl*phosphines,[7,8] which are generally significantly less electron-rich than tri*alkyl*phosphines.

In this communication, we describe our discovery that a wide array of palladium-catalyzed Suzuki reactions of aryl chlorides can be achieved through the use of a new ferrocene-derived triarylphosphine (**2**). In the presence of this air-stable, sterically demanding ligand, we can effect the Suzuki cross-coupling of activated aryl chlorides at rt, and we can accomplish reactions of unactivated aryl chlorides, including sterically hindered and electron-rich substrates, at 70 °C.

Phosphine **1**, previously reported by Price and Simpkins,[9] serves as a moderately efficient ligand for the palladium-catalyzed coupling of *p*-chlorotoluene with *o*-tolylboronic acid (37% yield by GC after 24 h at 70 °C; Table 1, entry 1). An increase in the steric demand of the bottom ring of the ligand (Cp → Cp*; **2**) leads to a substantial increase in reactivity (entry 2 *vs.* entry 1).[10] The TMS group is an important contributor to the unusual reactivity of **2**, as demonstrated by the slow coupling that we observe when we employ the corresponding non-silylated ligand (**3**; entry 3). Entry 4 establishes that PPh_3 is not useful under these conditions.

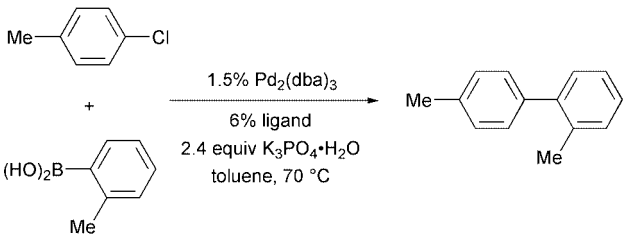


New triarylphosphine **2**, which is air- and moisture-stable both in the solid state and in solution, serves as a remarkably versatile ligand for Suzuki cross-couplings of aryl chlorides. As shown in Table 2, a variety of chlorides, including hindered (entries 2–5) and electronically deactivated (entry 6) ones, react with a range of boronic acids in very good yield. The sterically demanding coupling that is illustrated in entry 5, which furnishes a tri-*ortho*-substituted biaryl in 93% yield, is especially worthy of note.[11,12]

We have determined that, in the presence of triarylphosphine **2**, Suzuki cross-couplings of activated aryl chlorides can be accomplished at rt. To date, only a few other ligands have achieved this objective.[13] For room-temperature couplings, use of $Pd(OAc)_2$ as the palladium source and an ~1:1 ratio of Pd:ligand provide the highest reactivity among the conditions that we have examined. With these conditions, we can effect Suzuki cross-couplings of a range of activated aryl chlorides, including heteroaryl (entry 2) and *ortho*-substituted (entry 3) substrates, with arylboronic acids in excellent yield (Table 3).

In summary, we have prepared a new, air-stable triarylphosphine (**2**), and we have established that it serves as an

Table 1 Suzuki reaction of an unactivated aryl chloride: triarylphosphines as ligands



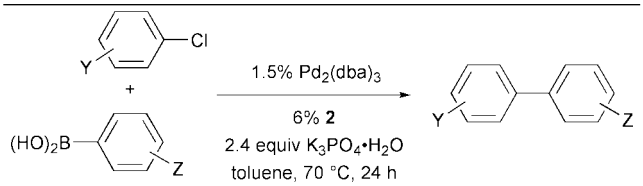
Entry	Ligand	% Yield by GC after 24 h[a]
1	**1**	37
2	**2**	87
3	**3**	8
4	PPh_3	< 2

[a] Average of two runs.

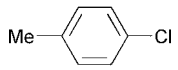
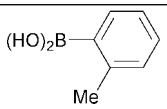
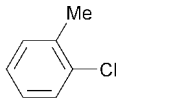
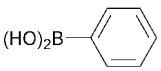
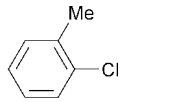
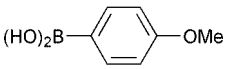
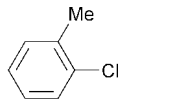
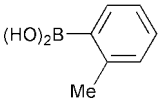
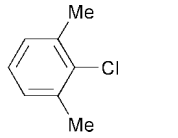
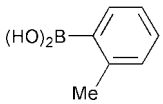
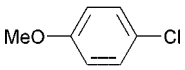
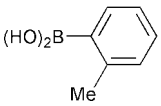
† Electronic supplementary information (ESI) available: experimental procedures and compound characterization data. See http://www.rsc.org/suppdata/cc/b1/b107888g/

 DOI: 10.1039/b107888g

Table 2 Scope of the Suzuki reaction of unactivated aryl chlorides catalyzed by Pd–triarylphosphine **2**

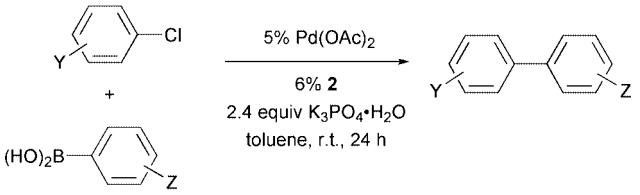


1.1 equiv

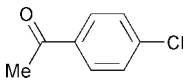
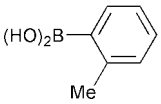
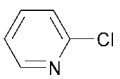
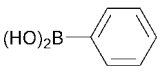
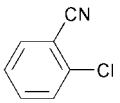
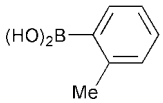
Entry	Aryl chloride	Arylboronic acid	Isolated yield[a]
1			90%
2			86%
3			82%
4			95%
5			93%
6			88%

[a] Average of two runs.

Table 3 Suzuki reaction of activated aryl chlorides at room temperature



1.1 equiv

Entry	Aryl chloride	Arylboronic acid	Isolated yield[a]
1			89%
2			93%
3			95%

[a] Average of two runs.

effective ligand in palladium-catalyzed Suzuki couplings of aryl chlorides. In the presence of Pd–**2**, a diverse array of substrates, including hindered, heteroaryl, and electronically deactivated chlorides, react in uniformly good yield. The ability of this system to achieve cross-couplings of activated aryl chlorides at rt is particularly noteworthy. Because **2** is a tri*aryl*phosphine, the high reactivity of Pd–**2** (in terms of scope and mildness, comparable to sterically demanding trialkylphosphines and greater than carbene ligands) is unexpected. In view of the ease with which the structure of **2** can be modified, we anticipate that further enhancements in reactivity will be possible, as well as the design of effective ligands for asymmetric catalysis.

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Notes and references

1 For reviews, see: N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147; N. Miyaura, in *Advances in Metal-Organic Chemistry*, ed. L. S. Liebeskind, JAI, London, 1998, Vol. 6, pp. 187–243; A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich, P. J. Stang, Wiley-VCH, New York, 1998, Chapter 2.

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4 For early work, see: (*a*) D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722; J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550; (*b*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 1998, **37**, 3387, ref. 3; (*c*) X. Bei, H. W. Turner, W. H. Weinberg, A. S. Guram and J. L. Petersen, *J. Org. Chem.*, 1999, **64**, 6797.

5 For early work, see: W. A. Herrmann, C.-P. Reisinger and M. Spiegler, *J. Organomet. Chem.*, 1998, **557**, 93; T. Weskamp, V. P. W. Bohm and W. A. Herrmann, *J. Organomet. Chem.*, 1999, **585**, 348; C. Zhang, J. Huang, M. L. Trudell and S. P. Nolan, *J. Org. Chem.*, 1999, **64**, 3804.

6 For other early work, see: F. Firooznia, C. Gude, K. Chan and Y. Satoh, *Tetrahedron Lett.*, 1998, **39**, 3985. See also: G. Y. Li, *Angew. Chem., Int. Ed.*, 2001, **40**, 1513.

7 For a single example of a Suzuki coupling of an *activated* aryl chloride by a Pd–triarylphosphine catalyst, see: P. Kocovsky, S. Vyskocil, I. Cisarova, J. Sejbal, I. Tislerova, M. Smrcina, G. C. Lloyd-Jones, S. C. Stephen, C. P. Butts, M. Murray and V. Langer, *J. Am. Chem. Soc.*, 1999, **121**, 7714.

8 As our investigation was nearing completion, Richards described one Suzuki coupling of an unactivated aryl chloride (*p*-chlorotoluene) and one reaction of an activated aryl chloride (*p*-chloronitrobenzene) that proceed in good yield by GC at 60 °C, using a Pd–tris(2-methylferrocenyl)phosphine catalyst: T. E. Pickett and C. J. Richards, *Tetrahedron Lett.*, 2001, **42**, 3767. This catalyst furnishes modest yields in couplings of deactivated and *ortho*-substituted aryl chlorides (< 50% by GC).

9 D. Price and N. S. Simpkins, *Tetrahedron Lett.*, 1995, **36**, 6135.

10 For a related observation of a change in reactivity upon conversion of a remote Cp group to a C_5Ph_5 group, see: Q. Shelby, N. Kataoka, G. Mann and J. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 10 718.

11 Suzuki cross-couplings that efficiently generate tri-*ortho*-substituted biaryls are very uncommon, especially with aryl chlorides as substrates. For a discussion, see ref. 3.

12 This catalyst system is also very active for Suzuki reactions of aryl bromides. For example, in the presence of 0.25% Pd_2dba_3–0.5% **2**, the cross-coupling of 2-bromo-*m*-xylene with *o*-tolylboronic acid proceeds in 99% isolated yield after 24 h at rt. To the best of our knowledge, only P(*t*-Bu)$_3$ has been shown to effect a room-temperature Suzuki reaction of an unactivated aryl bromide to generate a tri-*ortho*-substituted biaryl (ref. 3).

13 Only Buchwald's aryldialkylphosphines are effective for room-temperature couplings of unactivated aryl chlorides: ref. 4*a*. See also: ref. 4*b* (six examples); D. Zim, A. L. Monteiro and J. Dupont, *Tetrahedron Lett.*, 2000, **41**, 819 (two examples); P. Kocovsky, S. Vyskocil, I. Cisarova, J. Sejbal, I. Tislerova, M. Smrcina, G. C. Lloyd-Jones, S. C. Stephen, C. P. Butts, M. Murray and V. Langer, *J. Am. Chem. Soc.*, 1999, **121**, 7714 (one example).