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Palladium/Tris(*tert*-butyl)phosphine-Catalyzed Suzuki Cross-Couplings in the Presence of Water

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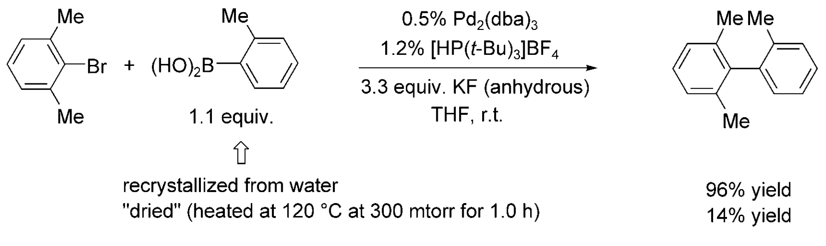
Abstract: Dipalladiumtris(dibenzylideneacetone)/tris(*tert*-butyl)phosphonium tetrafluoroborate/potassium fluoride dihydrate [$Pd_2(dba)_3$/[HP(t-Bu)$_3$]BF_4/KF·2 H_2O] serves as a mild, robust, and user-friendly method for the efficient Suzuki cross-coupling of a diverse array of aryl and heteroaryl halides with aryl- and heteroarylboronic acids.

Keywords: boron; cross-coupling; halides; palladium; water

Introduction

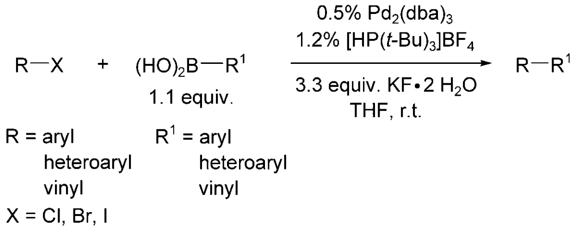
We and others have demonstrated that trialkylphosphines, including P(t-Bu)$_3$ and PCy_3, are unusually effective ligands for a range of coupling processes.[1] This generalization includes the Suzuki reaction, which is perhaps the most widely used cross-coupling method for carbon-carbon bond formation.[2–4]

We have observed that the efficiency of Pd/P(t-Bu)$_3$-catalyzed Suzuki reactions can vary significantly, depending on the batch of arylboronic acid that is used. We hypothesized that this might be due to differences in the amounts of arylboronic acid *vs.* anhydride (or water) that are present.[5,6] Indeed, we determined that, under the standard conditions that we had described earlier,[3c] an arylboronic acid that had been dried under vacuum cross-couples in considerably lower yield than an arylboronic acid that had been freshly recrystallized from water [Eq. (1)].



(1)

In view of these observations, we decided to pursue the development of a new procedure for Pd/P(t-Bu)$_3$-catalyzed Suzuki reactions that would be less dependent on the origin of the arylboronic acid. In this Update, we describe a method that we believe addresses this issue [Eq. (2)].

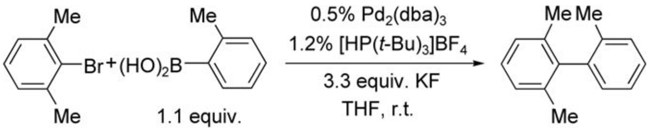


$$\underset{\substack{\text{R = aryl}\\ \text{heteroaryl}\\ \text{vinyl}\\ \text{X = Cl, Br, I}}}{R{-}X} + \underset{\substack{1.1\ \text{equiv.}\\ R^1 = \text{aryl}\\ \text{heteroaryl}\\ \text{vinyl}}}{(HO)_2B{-}R^1} \xrightarrow[\substack{3.3\ \text{equiv. KF} \bullet 2\,H_2O\\ \text{THF, r.t.}}]{\substack{0.5\%\ Pd_2(dba)_3\\ 1.2\%\ [HP(t\text{-Bu})_3]BF_4}} R{-}R^1 \qquad (2)$$

Results and Discussion

In early experiments, we determined that the addition of a small amount of water to the "dried" arylboronic acid led to a more efficient Suzuki reaction (Table 1, entries 2–5).[7,8] This suggested that, rather than employing anhydrous KF, it would be preferable to use the commercially available dihydrate (KF·2 H_2O; entry 2 *vs.* entry 6). In addition to restoring the efficiency of the Pd/P(t-Bu)$_3$-catalyzed Suzuki cross-coupling, this modification has the added advantage of a very substantial cost saving [price per mole: anhydrous KF ($450/mol); KF·2 H_2O ($19/mol)].[9] The

Table 1. Effect of reaction conditions on Pd/P(tBu)$_3$-catalyzed Suzuki cross-couplings.



Entry	Boronic Acid	KF	Added Water	Yield [%][a]
1	recrystallized from water	dry[b]	none	96
2	dried[c]	dry[b]	none	14
3	dried[c]	dry[b]	1 equiv.	87
4	dried[c]	dry[b]	2 equiv.	88
5	dried[c]	dry[b]	4 equiv.	92
6	dried[c]	dihydrate	none	94
7	recrystallized from water	dihydrate	none	97
8	as received	dihydrate	none	97
9	recrystallized from water	dihydrate	2 equiv.	97

[a] The yield was determined by ^{1}H NMR spectroscopy *vs.* an internal standard.

[b] Anhydrous (Aldrich).

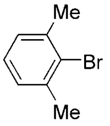
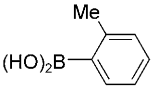
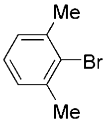
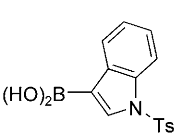
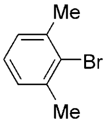
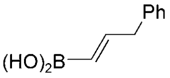
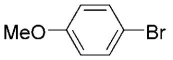
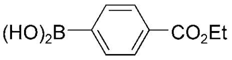
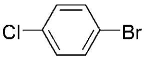
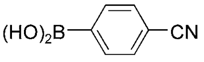
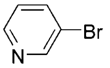
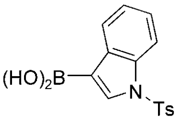
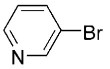
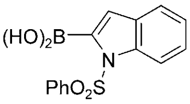
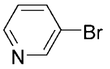
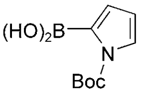
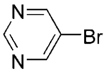
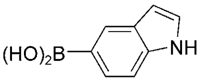
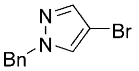
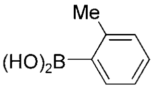
[c] Heated at 120 °C at 300 mtorr for 1.0 h.

procedure using KF·2 H$_2$O appears to be robust, providing good yields of the biaryl with a variety of boronic acid sources (entries 6–8), as well as in the presence of additional water (entry 9).

For small-scale reactions and/or for parallel synthesis, weighing small amounts of Pd$_2$(dba)$_3$ and P(t-Bu)$_3$ or [HP(t-Bu)$_3$]BF$_4$ can be tedious and inaccurate.[10] To circumvent these issues, we recommend the use of a pre-made mixture of Pd$_2$(dba)$_3$/[HP(t-Bu)$_3$]BF$_4$ [Pd:P(t-Bu)$_3$ = 1:1.2] as a convenient one-component source of palladium and P(t-Bu)$_3$ (see the Supporting Information).[11]

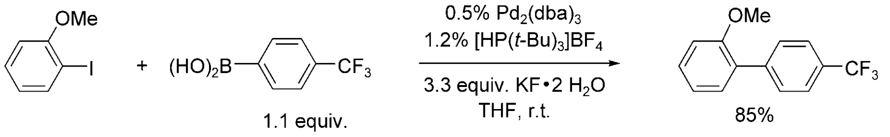
The Pd$_2$(dba)$_3$/[HP(t-Bu)$_3$]BF$_4$/KF·2 H$_2$O procedure can be applied to Suzuki cross-couplings of a wide array of substrates (Table 2).[12] Thus, a variety of aryl bromides are suitable reaction partners, including hindered (entries 1–3) and deactivated (entry 4) compounds. In addition, an aryl bromide can be cross-coupled selectively in the presence of an aryl chloride (entry 5). Furthermore, a range of nitrogen-containing heteroaryl bromides and heteroarylboronic acids are useful reaction partners (entries 6–10).

Table 2. Suzuki cross-couplings of aryl and heteroaryl bromides with aryl-, heteroaryl-, and alkenylboronic acids [for the reaction conditions, see Eq. (2)].

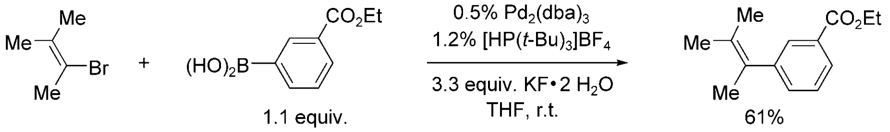
Entry	Aryl Bromide	Boronic Acid	Yield [%][a]
1			96
2			95
3			98
4			84
5			98
6			93
7			82
8			95
9			76
10			87

[a] Yield of purified product (average of two experiments).

Not only aryl bromides, but also aryl iodides [Eq. (3)] and vinyl bromides [Eq. (4)], undergo Suzuki coupling under this standard set of conditions. In ad-

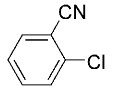
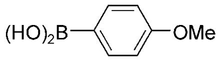
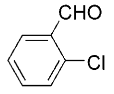
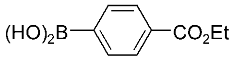
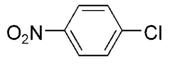
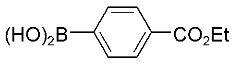
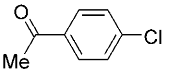
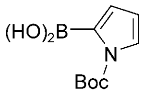
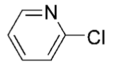
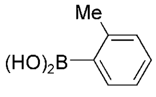
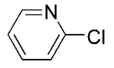
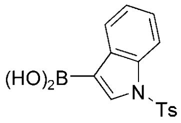
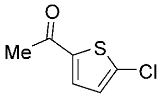
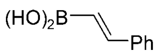


(3)



(4)

Table 3. Suzuki cross-couplings of activated aryl and heteroaryl chlorides with aryl-, heteroaryl-, and alkenylboronic acids [for the reaction conditions, see Eq. (2)].

Entry	Aryl Chloride	Boronic Acid	Yield [%][a]
1			97
2			91[b]
3			99
4			98
5			92
6			95
7			88

[a] Yield of purified product (average of two experiments).

[b] The isolated biaryl product is a 4:1 mixture of the aldehyde and its hydrate.

dition, $Pd_2(dba)_3/[HP(t\text{-}Bu)_3]BF_4/KF\cdot 2H_2O$ can achieve cross-couplings of a variety of activated aryl chlorides with an array of arylboronic acids (Table 3).[13] Both nitrogen and sulfur heterocycles are tolerated (entries 4–7), as are a wide range of substituents. Alkenylboronic acids are also suitable coupling partners (entry 7).

Conclusions

In summary, we have developed a versatile, user-friendly method for Suzuki reactions that employs a commercially available one-component source of $Pd/P(t\text{-}Bu)_3$, as well as an inexpensive activator. Thus, $Pd_2(dba)_3/[HP(t\text{-}Bu)_3]BF_4/KF\cdot 2H_2O$ accomplishes cross-couplings of a diverse set of aryl/heteroaryl halides with a range of aryl/heteroarylboronic acids at room temperature in good yield. The reaction components are air-stable, and the method is not moisture-sensitive. We anticipate that this procedure may prove useful to others.

Experimental Section

General Procedure for $Pd/P(t\text{-}Bu)_3$-Catalyzed Suzuki Cross-Couplings

$Pd_2(dba)_3/[HP(t\text{-}Bu)_3]BF_4$ [$Pd:P(t\text{-}Bu)_3 = 1:1.2$; 8.1 mg, 0.0050 mmol of $Pd_2(dba)_3$], the boronic acid (1.10 mmol), and $KF\cdot 2H_2O$ (310 mg, 3.30 mmol) were added to a 4-mL vial that contained a stir bar. The vial was purged with argon for 3 min, and then it was sealed with a septum cap. THF (2.0 mL) and the aryl halide (1.00 mmol) were added, and the reaction mixture was stirred at room temperature. Next, the mixture was diluted with Et_2O (2 mL) and filtered through a plug of silica gel [washed with Et_2O (10 mL)]. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel.

Supporting Information

General information and compound characterization data are available as Supporting Information.

Acknowledgements

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[1] For leading references, see: G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564.

[2] For reviews, see: a) *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, New York, **2004**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E.-i. Negishi), Wiley-Interscience, New York, **2002**.

[3] For the development of methods for $Pd/P(t\text{-}Bu)_3$- and Pd/PCy_3-catalyzed Suzuki reactions, see: a) A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586–3587; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388; b) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; c) M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295–4298; d) N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1304–1306; *Angew. Chem. Int. Ed.* **2006**, *45*, 1282–1284.

[4] For a few recent examples of applications of $Pd/P(t\text{-}Bu)_3$-catalyzed Suzuki reactions, see: a) T. Amaya, T. Nakata, T. Hirao, *J. Am. Chem. Soc.* **2009**, *131*, 10810–10811; b) W. Huang, L. Su, Z. Bo, *J. Am. Chem. Soc.* **2009**, *131*, 10348–10349; c) H. Ihara, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 7502–7503.

[5] For an example of related, independent observations by others, see: A. Antoft-Finch, T. Blackburn, V. Snieckus, *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752.

[6] For an overview of boronic acids, see: *Boronic Acids*, (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**.

[7] We have previously described the use of dioxane/water as a solvent for Pd/PCy_3-catalyzed Suzuki reactions (ref.[3d]).

[8] For examples of reports of the beneficial effect of water on Pd/P(t-Bu)$_3$-catalyzed Suzuki reactions, see: a) R. T. Lewis, W. P. Blackaby, T. Blackburn, A. S. R. Jennings, A. Pike, R. A. Wilson, D. J. Hallett, S. M. Cook, P. Ferris, G. R. Marshall, D. S. Reynolds, W. F. A. Sheppard, A. J. Smith, B. Sohal, J. Stanley, S. J. Tye, K. A. Wafford, J. R. Atack, *J. Med. Chem.* **2006**, *49*, 2600–2610; b) S. T. Handy, D. Mayi, *Tetrahedron Lett.* **2007**, *48*, 8108–8110; c) M. J. Fray, A. T. Gillmore, M. S. Glossop, D. J. McManus, I. B. Moses, C. F. B. Praquin, K. A. Reeves, L. R. Thompson, *Org. Process Res. Dev.* **2010**, *14*, 263–271.

[9] Aldrich (online prices on 31 March 2010): anhydrous KF ($196/25 g); $KF{\cdot}2H_2O$ ($100/500 g).

[10] The Pd:P(t-Bu)$_3$ ratio has an impact on the rate of cross-coupling. For a discussion, see ref.[3b]

[11] $Pd_2(dba)_3$/[HP(t-Bu)$_3$]BF_4 [Pd:P(t-Bu)$_3$ = 1:1.2] is available from Strem Chemicals (catalog number 46-3015). We have observed that $Pd_2(dba)_3$/[HP(t-Bu)$_3$]BF_4 can be exposed to air for seven months without a change in its activity as a Suzuki cross-coupling catalyst.

[12] a) Under our standard conditions: aryltrifluoroborates and pinacolboronate esters are not suitable cross-coupling partners; replacement of HP(t-Bu)$_3$]BF_4 with [$HPCy_3$]BF_4 results in a slower reaction. b) A gram-scale reaction (entry 1 of Table 2) proceeded in 97% yield (1.14 g). c) According to ^{1}H NMR spectroscopy, the addition of water to the “dried” arylboronic acid in THF at room temperature led to rapid formation of the arylboronic acid.

[13] For *unactivated* aryl chlorides, the catalyst system described in ref.[3d] is more effective than the method provided in Eq. (2).