

Nuances in Fundamental Suzuki–Miyaura Cross-Couplings Employing [Pd(PPh₃)₄]: Poor Reactivity of Aryl Iodides at Lower Temperatures

Curtis C. Ho, Angus Olding, Jason A. Smith, Alex C. Bissember*

School of Natural Sciences – Chemistry, University of Tasmania, Hobart, Tasmania, Australia

email: alex.bissember@utas.edu.au

Supporting Information

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I. General

Unless otherwise specified all reactants and reagents were purchased and used as received. [Pd(PPh₃)₄] was recrystallized prior to use. *trans*-[Pd(PPh₃)₂(*p*-tol)(I)],¹ *trans*-[Pd(PPh₃)₂(*p*-tol)(Br)],² sodium phenyltrihydroxyborate,³ *trans*-[Pd(PPh₃)₂I₂],⁴ and [Pd(PPh₃)(*p*-tol)(μ -OH)]₂,⁵ Pd(PPh₃)(*p*-tol)(μ -I)]₂,⁵ *trans*-[Pd{P(2-furyl)₃}₂(*p*-tol)(I)],⁶ and PPh₃(*p*-tol)I were prepared according to literature procedures.⁷

¹H, ¹³C NMR and ³¹P spectra were recorded on a Bruker NMR spectrometer operating at 400 MHz for proton, 100 MHz for carbon, and 162 MHz for phosphorus nuclei. GC data were obtained on an Agilent 6850 Network GC System using an Agilent HP-5 ms capillary column (30 m x 0.25 mm x 0.25 mm): injection temp = 250 °C, oven temp = 45 °C (1 min) → 250 °C @ 10 °C per min. All Suzuki–Miyaura cross-coupling reactions were performed employing a Radleys parallel reactor.

II. Pd-Catalyzed Suzuki–Miyaura Cross-Couplings

General Procedure for reactions employing [Pd(PPh₃)₄] (1 mol%).

Phenylboronic acid (137.5 μ mol; 250 μ L of a 550 mM solution in *n*-PrOH), the aryl halide (125 μ mol; 1.00 mL of a 125 mM solution in *n*-PrOH),[†] Na₂CO₃ (500 μ L of a 1 M aqueous solution), and [Pd(PPh₃)₄] (1.25 μ mol; as a 750 μ L solution in *n*-PrOH), were added to Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to the specified temperature and then magnetically stirred under N₂. Aliquots were obtained from the reaction mixture at the specified times and analyzed by GC.

General Procedure for reactions employing Pd(OAc)₂ (1 mol%) and ligand.

Phenylboronic acid (137.5 μ mol; 250 μ L of a 550 mM solution in *n*-PrOH), the aryl halide (125 μ mol; 1.00 mL of a 125 mM solution in *n*-PrOH),[†] Na₂CO₃ (500 μ L of a 1 M aqueous solution), and a *n*-PrOH solution (750 μ L) containing Pd(OAc)₂ (1.25 μ mol) and ligand (μ mol as required), were added to a Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to the specified temperature and then magnetically stirred under N₂. Aliquots were obtained from the reaction mixture at the specified times and analyzed by GC.

[†] This aryl halide solution also contained 1,4-dimethoxybenzene (50 μ mol, 50 mM) as an internal standard.

Equation 1.

Phenylboronic acid (125 μmol ; 250 μL of a 550 mM solution in *n*-PrOH), a *n*-PrOH solution (1.00 mL) containing 4-bromotoluene (62.5 μmol) and 4-iodotoluene (62.5 μmol),[†] Na_2CO_3 (500 μL of a 1 M aqueous solution, and $[\text{Pd}(\text{PPh}_3)_4]$ (1.25 μmol ; as a 750 μL solution in *n*-PrOH), were added to a Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to the specified temperature and then magnetically stirred under N_2 . Aliquots were obtained from the reaction mixture at the specified intervals and were analyzed by GC.

Figure 3. Procedure for reactions employing *trans*- $[\text{Pd}(\text{PPh}_3)_2(p\text{-tol})(\text{X})]$

Phenylboronic acid (250 μmol ; 2.00 mL of a 125 mM solution in THF) was added to a mixture of *trans*- $[\text{Pd}(\text{PPh}_3)_2(p\text{-tol})(\text{X})]$ (62.5 μmol), Na_2CO_3 (1.00 mL of a 0.25 M aqueous solution), and THF (2.00 mL)[‡] in a Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to 50 °C and then magnetically stirred under N_2 . Aliquots were obtained from the reaction mixture at the specified times and analyzed by GC.

Figure 3. Procedure for reactions employing *trans*- $[\text{Pd}(\text{PPh}_3)_2(p\text{-tol})(\text{X})]$ + PPh_3

Phenylboronic acid (250 μmol ; 2.00 mL of a 125 mM solution in THF) was added to a mixture of *trans*- $[\text{Pd}(\text{PPh}_3)_2(p\text{-tol})(\text{X})]$ (62.5 μmol), PPh_3 (375 μmol ; 2.00 mL of a 187.5 mM solution in THF),[‡] and Na_2CO_3 (1.00 mL of a 0.25 M aqueous solution) in a Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to 50 °C and then magnetically stirred under N_2 . Aliquots were obtained from the reaction mixture at the specified times and analyzed by GC.

Figure 3. Procedure for reactions employing $[\text{Pd}(\text{PPh}_3)(p\text{-tol})(\mu\text{-OH})]_2$

Phenylboronic acid (250 μmol ; 2.00 mL of a 125 mM solution in THF) was added to a mixture of $[\text{Pd}(\text{PPh}_3)(p\text{-tol})(\mu\text{-OH})]_2$ (31.3 μmol), H_2O (1.00 mL), and THF (2.00 mL)[‡] in a Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to 50 °C and then magnetically stirred under N_2 . Aliquots were obtained from the reaction mixture at the specified times and analyzed by GC.

Figure 3. Procedure for reactions employing $[\text{Pd}(\text{PPh}_3)(p\text{-tol})(\mu\text{-OH})]_2$ + PPh_3

Phenylboronic acid (250 μmol ; 2.00 mL of a 125 mM solution in THF) was added to a mixture of $[\text{Pd}(\text{PPh}_3)(p\text{-tol})(\mu\text{-OH})]_2$ (31.3 μmol), PPh_3 (375 μmol ; 2.00 mL of a 187.5 mM solution in THF),[‡] and H_2O (1.00 mL) in a Radleys reactor tube (containing a stir bar). This tube was then placed in a Radleys parallel reactor that had been preheated to 50 °C and then magnetically stirred under N_2 . Aliquots were obtained from the reaction mixture at the specified times and analyzed by GC.

III. Additional Experiments

Table S1. Respective reactions of *p*-iodo- and *p*-bromotoluene with phenylboronic acid in Suzuki–Miyaura couplings: effect of increasing $[\text{Pd}(\text{PPh}_3)_4]$ loading.

entry	$[\text{Pd}(\text{PPh}_3)_4]$ (%)	yield (%) ^a
1	2.5	5 (5)
2	5	4 (4)

^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments); yields after 0.25 h are given in parentheses.

[‡] This THF solution also contained 1,4-dimethoxybenzene (25 μmol , 12.5 mM) as an internal standard.

Table S2. Respective reactions of *p*-iodo- and *p*-bromotoluene with phenylboronic acid in Suzuki–Miyaura couplings: effect of added PPh₃.
$$p\text{-tol-X} + \text{Ph-B(OH)}_2 \xrightarrow[\substack{\text{4:1 } n\text{-PrOH/ H}_2\text{O} \\ \text{50 } ^\circ\text{C, 0.5 h}}]{\substack{1\% [\text{Pd}], \text{X}\% \text{PPh}_3 \\ \text{4 equiv Na}_2\text{CO}_3}} p\text{-tol-Ph}$$

1: X = I
2: X = Br

Ph-B(OH)₂ 1.1 equiv

entry	[Pd]	PPh ₃ (%)	yield (%) ^a	
			using 1	using 2
1	[Pd(PPh ₃) ₄]	2	4 (3)	62 (35)
2	Pd(OAc) ₂	6	3(3)	51 (27)

^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments); yields after 0.25 h are given in parentheses.

Table S3. Reactions of *p*-iodotoluene with phenylboronic acid in Suzuki–Miyaura couplings: effect of base loading.
$$p\text{-tol-I} + \text{Ph-B(OH)}_2 \xrightarrow[\substack{\text{4:1 } n\text{-PrOH/ H}_2\text{O} \\ \text{70 } ^\circ\text{C, 0.5 h}}]{\substack{1\% [\text{Pd}(\text{PPh}_3)_4] \\ \text{X equiv Na}_2\text{CO}_3}} p\text{-tol-Ph}$$

1: *p*-tol-I
3: *p*-tol-Ph

Ph-B(OH)₂ 1.1 equiv

entry	Na ₂ CO ₃ (equiv)	yield (%) ^a
1	1	21 (18)
2	2	28 (23)
3	3	24 (19)
4	4	26 (20)
5	5	25 (18)

^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments); yields after 0.25 h are given in parentheses.

Table S4. Reactions of electrophiles with phenylboronic acid in Suzuki–Miyaura couplings: effect of solvent and halide additives (reactions at at 70 °C).
$$p\text{-tol-I} + \text{Ph-B(OH)}_2 \xrightarrow[\substack{\text{4:1 co-solvent/ H}_2\text{O} \\ \text{70 } ^\circ\text{C, 0.5 h}}]{\substack{1\% [\text{Pd}(\text{PPh}_3)_4] \\ \text{4 equiv Na}_2\text{CO}_3 \\ \text{20\% additive}}} p\text{-tol-Ph}$$

1: *p*-tol-I
3: *p*-tol-Ph

Ph-B(OH)₂ 1.1 equiv

entry	co-solvent	additive	yield (%) ^a	
			using 1	using 2
1	PhMe	–	<2(<2)	
2	THF	–	11 (8)	
3	<i>n</i> -PrOH	–	26 (20)	67 (65)
4	<i>n</i> -PrOH	NH ₄ I	8 (5)	3 (<2)
5	<i>n</i> -PrOH	NH ₄ Br	5 (5)	13 (8)
6	<i>n</i> -PrOH	NH ₄ F	7(6)	17 (10)
7	acetone	–	34 (23)	
8	DMF	–	73 (47)	

^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments); yields after 0.25 h are given in parentheses.

Table S5. Reactions of *p*-iodotoluene with phenylboronic acid in Suzuki–Miyaura couplings: effect of additives.
$$\begin{array}{c}
 \textit{p}\text{-tol-I} \\
 \mathbf{1}
 \end{array}
 +
 \begin{array}{c}
 \text{Ph-B(OH)}_2 \\
 \text{1.1 equiv}
 \end{array}
 \xrightarrow[4:1 \textit{n}\text{-PrOH/ H}_2\text{O}]{\begin{array}{c} 1\% [\text{Pd}(\text{PPh}_3)_4] \\ 4 \text{ equiv Na}_2\text{CO}_3 \\ \mathbf{20\% \text{ additive}} \end{array}}
 \begin{array}{c}
 \textit{p}\text{-tol-Ph} \\
 \mathbf{3}
 \end{array}$$

50 °C, 0.5 h

entry	additive	yield (%) ^a
1	LiCl	6 (5)
2	LiBr	3 (3)
3	KCl	5 (5)
4	KBr	5 (5)
5	CsCl	6 (5)
6	CsBr	5 (3)
7	NMe ₄ Cl	7 (6)
8	NMe ₄ Br	5 (4)
9	NMe ₄ I	<2 (<2)

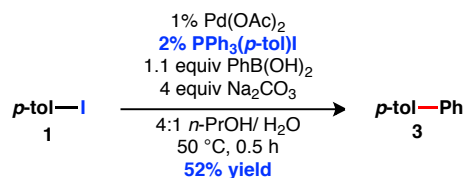
^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments); yields after 0.25 h are given in parentheses.

Table S6. Reactions of *p*-iodotoluene with phenylboronic acid in Suzuki–Miyaura couplings: effect of bases.
$$\begin{array}{c}
 \textit{p}\text{-tol-I} \\
 \mathbf{1}
 \end{array}
 +
 \begin{array}{c}
 \text{Ph-B(OH)}_2 \\
 \text{1.1 equiv}
 \end{array}
 \xrightarrow[4:1 \textit{n}\text{-PrOH/ H}_2\text{O}]{\begin{array}{c} 1\% [\text{Pd}(\text{PPh}_3)_4] \\ \mathbf{4 \text{ equiv base}} \end{array}}
 \begin{array}{c}
 \textit{p}\text{-tol-Ph} \\
 \mathbf{3}
 \end{array}$$

50 °C, 0.5 h

entry	base	yield (%) ^a
1	Cs ₂ CO ₃	14 (12)
2	NMe ₄ OH	10 (8)

^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments); yields after 0.25 h are given in parentheses.

Equation S1. Reactions of *p*-iodotoluene with phenylboronic acid in Suzuki–Miyaura couplings: effect of PPh₃(*p*-tol)I.⁸

^aDetermined via GC with the aid of a calibrated internal standard (average of 2 experiments).

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