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Miyaura Borylations of Aryl Bromides in Water at Room Temperature

Bruce H. Lipshutz*, Ralph Moser, and Karl R. Voigtritter

Department of Chemistry & Biochemistry, University of California, Santa Barbara, CA 93106 USA

Abstract

New technology for palladium-catalyzed cross-couplings between B₂pin₂ and aryl bromides leading to arylboronates is described. Micellar catalysis serves to enable borylations to take place in water as the only medium at ambient temperatures.

Keywords

borylation; micellar catalysis; cross-coupling; green chemistry

Introduction

Arylboranes play a key role in Suzuki-Miyaura couplings to form biaryl-containing targets where they serve as efficient coupling partners together with aryl halides.¹ Although numerous routes to aryl C-B bonds exist, an aryl halide precursor still serves as their primary source.² Most commonly, aryllithium or aryl Grignard reagents are used in combination with an electrophilic source of boron. However, due to the highly nucleophilic and basic nature of preformed aryl metal species in this two-step procedure, various functional groups such as nitro, cyano, ester and other carbonyl groups are not well tolerated. An alternative, one-step procedure allowing for broader functional group tolerance was first reported by Miyaura *et al.*³ involving a Pd(0)-catalyzed cross-coupling reaction of *bis*(pinacolato)diboron with haloarenes to form arylboronic esters (Table 1, conditions **A**). The combination of a weak base (KOAc), a source of palladium (PdCl₂(dppf)), and a polar solvent (DMSO) at 80 °C led to cross-couplings of aryl iodides or bromides bearing either electron-withdrawing or -donating groups. A more active Pd-catalyst (Pd(dba)₂/PCy₃) in 1,4-dioxane at 80 °C allowed for expansion of this protocol to aryl chlorides as coupling partners (conditions **B**).⁴ Additionally, reaction times of less reactive aryl bromides or triflates bearing electron-donating substituents could be significantly reduced. Fürstner exploited the inherent advantages of imidazolium salts as cheap, readily available, and fully air stable precursors to substitute ligands for phosphines (e.g., PCy₃) in couplings of aryl chlorides bearing electron-withdrawing groups in refluxing THF or under microwave irradiation (conditions **C**).⁵ Recently, Buchwald *et al.* reported the first Pd-catalyzed conversions of aryl chlorides to aryl boronates at room temperature (conditions **D**).⁶

Selected examples of sterically hindered as well as deactivated aryl chlorides were cross-coupled with Pd(OAc)₂/SPhos as catalyst, together with K₃PO₄ as base in 1,4-dioxane.

Although chloroarenes are considered among the more challenging substrates in palladium-catalyzed cross-coupling reactions, to the best of our knowledge, there has yet to be a report on aryl bromides undergoing a Pd-catalyzed Miyaura borylation at ambient temperature.⁷ We now report that Miyaura borylations can be carried out on bromoarenes under micellar conditions: in water at room temperature.

Experimental Section

Unless otherwise noted, all reactions were performed under an atmosphere of Argon. A 2% TPGS-750-M/H₂O solution was prepared by dissolving 4 g TPGS-750-M in 196 g degassed water (HPLC grade). Pd(P^tBu₃)₂ was generously supplied from Johnson Matthey (catalog # Pd-116) and handled in a glove box under Argon. Bis(pinacolato)diboron (B₂pin₂) was obtained from Frontier Scientific (catalog # D6878). KOAc was freshly ground prior use. ¹H and ¹³C spectra were recorded at 22°C on a Varian UNITY INOVA Avance 400 MHz or a Varian UNITY INOVA 500 MHz. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.23 ppm) on the δ scale. High resolution mass analyses were obtained using a VG70 double-focusing magnetic sector instrument (VG Analytical) for EI and a PE Sciex QStar Pulsar quadrupole/TOF instrument (API) for ESI.

General procedure for borylations of aryl bromides in 2% TPGS-750-M/water (GP)

A 10 mL glass vial containing a strong stir bar was charged with Pd(P^tBu₃)₂ (7.7 mg, 0.015 mmol), B₂pin₂ (140 mg, 0.55 mmol) and KOAc (147 mg, 1.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, followed by the addition of 1.0 mL of 2% TPGS-750-M/water. After 10 min of vigorous stirring, the aryl bromide (0.5 mmol) was added, followed by an additional 1.0 mL of solvent. Conversion was monitored by GC/FID and/or TLC. After the indicated time, the reaction was extracted with EtOAc (3 × 2 mL). The combined organic layers were filtered through a short plug of SiO₂ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes to afford the product.

Spectral data for the following compounds matched previously reported data: **3**,⁸ **4**,⁹ **5**,¹⁰ **6**,⁸ **7**,⁸ **9**,⁸ **10**,⁶ **11**,⁸ **12**,⁶ **13**,¹¹ **15**,¹⁰ **16**,¹⁰ **17**.⁶

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-butan-2-one (**8**)

Following the general procedure (GP), using (*R*)-4-(4-bromophenyl)-4-((*tert*-butyldimethylsilyl)oxy)butan-2-one (179 mg, 0.5 mmol), Pd(P^tBu₃)₂ (7.7 mg, 0.015 mmol), B₂pin₂ (140 mg, 0.55 mmol), and KOAc (147 mg, 1.5 mmol) in 2 mL of 2% TPGS-750-M/H₂O, GC/FID and TLC monitoring indicated complete conversion after an overall

reaction time of 9 h. Workup according to the GP and flash column chromatography on silica (12 g, 2–10% EtOAc/hexanes) afforded **8** (165 mg, 82% yield) as a colorless oil. R_f = 0.25 (10% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.73 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.13 (dd, J = 9.0, 4.0 Hz, 1H), 2.89 (dd, J = 14.5, 9.0 Hz, 1H), 2.48 (dd, J = 14.5, 4.0 Hz, 1H), 2.11 (s, 3H), 1.31 (s, 12H), 0.81 (s, 9H), -0.03 (s, 3H), -0.22 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 207.2, 147.8, 135.0, 125.3, 83.9, 72.1, 54.4, 32.0, 25.9, 25.1, 25.0, 18.2, -4.5 , -5.1 ; HR-MS(ESI): calcd. for $\text{C}_{22}\text{H}_{37}\text{BO}_4\text{NaSi}$ ($\text{M}+\text{Na}^+$): 427.2452; found: 427.2444.

(*E*)-Ethyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acrylate (**14**)

Following the GP, using (*E*)-ethyl 3-(4-bromophenyl)acrylate (128 mg, 0.5 mmol), $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ (7.7 mg, 0.015 mmol), B_2pin_2 (140 mg, 0.55 mmol), and KOAc (147 mg, 1.5 mmol) in 2 mL of 2% TPGS-750-M/ H_2O , GC/FID and TLC monitoring indicated complete conversion after an overall reaction time of 6 h. Workup according to GP and flash column chromatography on silica (12 g, 2–10% EtOAc/hexanes) afforded **14** (116 mg, 77% yield) as a colorless oil. R_f = 0.21 (10% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.83 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 16.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 6.50 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.36 (s, 12H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.0, 144.6, 137.1, 135.4, 127.4, 119.3, 84.2, 60.7, 25.0, 14.5; HR-MS (ESI): calcd. for $\text{C}_{17}\text{H}_{23}^{10}\text{BO}_4$ (M^+): 301.1731; found: 301.1740.

((1-(4-Bromophenyl)vinyl)oxy)(*tert*-butyl) dimethylsilane (**22**)

A 250 mL round bottom flask was charged with 4-bromoacetophenone (1.99 g, 10.0 mmol), TBSCl (6.03 g, 40.0 mmol), and NaI (6.00, 40 mmol). The flask was capped with a rubber septum and placed under an atmosphere of Argon. After the addition of 200 mL MeCN, NEt_3 (6.13 mL, 44.0 mmol) was introduced and the reaction mixture was stirred for 16 h at rt until TLC monitoring indicated complete conversion. The reaction mixture was poured onto sat. NaHCO_3 solution and extracted with EtOAc (3 $\times$ 40 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and evaporated to yield a brown slurry. Hexanes was added and the obtained heterogeneous mixture was filtered through a short plug of silica using hexanes to afford **22** (3.02 g, 96% yield) as a colorless oil. R_f = 0.49 (1% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.47 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 4.88 (s, 1H), 4.44 (s, 1H), 1.00 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.2, 137.0, 131.4, 127.1, 122.4, 91.6, 26.0, 18.5, -4.4 ; HR-MS(ESI): calcd. for $\text{C}_{14}\text{H}_{21}\text{OBrSi}$ (M^+): 312.0545; found: 312.0542.

tert-Butyldimethyl((1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) vinyl)oxy) silane (**23**)

Following the GP, using ((1-(4-bromophenyl)vinyl)oxy)(*tert*-butyl) dimethylsilane; **22**) (157 mg, 0.5 mmol), $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ (7.7 mg, 0.015 mmol), B_2pin_2 (140 mg, 0.55 mmol), and KOAc (147 mg, 1.5 mmol) in 2 mL of 2% TPGS-750-M/ H_2O , GC/FID and TLC monitoring indicated complete conversion after an overall reaction time of 2.5 h. Workup according to GP and flash column chromatography on silica (12 g, 3% EtOAc/hexanes) afforded **23** (153 mg, 77 % yield) as a colorless oil. R_f = 0.51 (10% EtOAc/hexanes); ^1H NMR (500 MHz,

CDCl₃) δ 7.77 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 4.95 (s, 1H), 4.47 (s, 1H), 1.35 (s, 12H), 1.00 (s, 9H), 0.20 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ = 156.1, 140.6, 134.8, 124.7, 84.0, 60.6, 26.0, 25.1, 18.5, -4.4; HR-MS (ESI): calcd. for C₂₀H₃₃¹⁰BO₃Si (M⁺): 359.2328; found: 359.2333.

4'-Methoxy-2-methyl-1,1'-biphenyl (26)

Tandem 1-pot borylation-Suzuki-Miyaura cross-coupling in water: A 10 mL glass vial containing a strong stir bar was charged with Pd(P^{*i*}Bu₃)₂ (5.7 mg, 0.011 mmol), B₂pin₂ (100 mg, 0.40 mmol), and KOAc (100 mg, 1.13 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, followed by the addition of 1.0 mL of 2% TPGS-750-M/water. After 10 min of vigorous stirring, 2-bromo-toluene (46 μ L, 0.38 mmol) was added, followed by an additional 0.5 mL of solvent. After 3 h, GC/FID confirmed the successful borylation. 4-Bromoanisole (34 μ L, 0.25 mmol) and KOH (42 mg, 0.75 mmol) were added followed by 0.5 mL of solvent. The reaction was stirred for an additional 3 h and extracted with EtOAc (3 $\times$ 2 mL). The combined organic layers were filtered through a short plug of SiO₂ and the solvent was removed under reduced pressure. The obtained residue was purified by flash chromatography eluting with 5% Et₂O/hexanes to afford the biaryl compound **26** (40 mg, 80% yield). Spectral data match previously reported data.¹²

Results & Discussion

Optimization studies using *p*-bromoanisole (**1**) led to limited success even after extended reaction times (Table 2). Both cremophore¹³ and the new surfactant TPGS-750-M¹⁴ appeared to be the leading candidates for these couplings. Further screening of a variety of preformed catalysts revealed the superiority of *t*-Bu₃P-ligated palladium(0) in promoting borylation at room temperature. With stronger bases than acetate; e.g., K₂CO₃ or NEt₃, significant biaryl formation was observed. By reducing the amount of cremophore, or by switching to newly designed surfactant TPGS-750-M,¹³ high isolated yields of the pinacolboronate **2** were obtained after only three hours at room temperature (0.25 M). A control experiment run in water only (i.e., “on-water”)¹⁵ confirmed the essential role of the micelle-forming surfactant in generating nanoreactors, where the inner lipophilic core serves as the reaction medium.¹⁶ Surprisingly, polar organic solvents oftentimes used in Miyaura borylations, such as THF, 1,4-dioxane, or DMSO,^{3–6} led to either low conversion or significant byproduct formation under otherwise identical conditions.

Substrate scope was next investigated (Table 3). A variety of aryl bromides bearing electron-donating groups could be successfully cross-coupled in either 1% cremophore or 2% TPGS-750-M in water at room temperature to provide the corresponding arylpinacol esters in high isolated yields. In the cases of *p*-bromo-*N,N*-dimethylaniline and *p*-bromoaniline, the latter amphiphile led to significantly reduced reaction times as well as a noteworthy increase in terms of product yields (products **6**, **7**). Sterically hindered substrates displayed a similar trend and led to full conversion of the aryl bromide in less than nine hours at room temperature with 2 wt % TPGS-750-M (products **9**, **10**). Several functional groups, including thioethers, amines, esters, enoates and ketones, were tolerated under these very mild conditions. Assorted aryl bromides bearing electron-withdrawing groups can also

be used under these optimized conditions. However, aryl ketones afforded significant amounts of biaryl formation and, therefore, lower isolated yields (products **16** and **17**).

Remarkably, although **18** did not undergo borylation, the isothiocyanate group was left unaffected (Figure 1). Other selected aryl bromides, *e.g.* *N*-Boc-protected hydrazone **19**, trimethoxy-substituted *ortho*-bromobenzaldehyde **20**, or *ortho*-bromobiaryl **21** each led to low levels of conversion under optimized conditions.

For comparison purposes, silyl enol ether **22** was prepared and treated as previously described herein (Table 1, conditions **A-E**). Miyaura's first protocol (**A**) using PdCl₂(dppf) in warm DMSO³ led to complete deprotection to form borylated acetophenone **24b** (Table 4, entry 1). The more active catalyst system (**B**) led to full conversion within two hours without deprotection,⁴ albeit still requiring 80 °C (entry 2). Low conversion and chemoselectivity in refluxing THF were observed on this aryl bromide employing Fürstner's conditions (entry 3).⁵ Buchwald's procedure,⁶ applied also to bromide **22**, could be run at room temperature; however, long reaction times are needed and the yield is modest (entry 4). Under our optimized conditions using 2% TPGS-750-M in water, this Miyaura borylation is complete within 2.5 hours at room temperature with high conversion and no observed deprotection (entry 5).

Prospects for reducing catalyst loading were tested on model compound **1**. Dropping the amount of (*t*-Bu₃P)₂Pd to 0.1 mole percent gave a good yield (90%) of the anticipated product in only four hours at room temperature (Scheme 1).

Very recently, commercially available (*t*-Bu₃P)₂Pd was shown to also serve as a very active cross-coupling catalyst for Suzuki-Miyaura reactions of aryl/heteroaryl halides (bromides or chlorides) with aryl-, heteroaryl-, and alkenylboronic acids.¹⁷ Through the careful choice of bases, a one-pot tandem borylation-Suzuki coupling could be accomplished, providing the biaryl product in good yield (Scheme 2). The presence of KOAc in the first step minimizes homocoupling of *o*-bromotoluene (**25**), whereas introduction of KOH in the second step activates boron and leads to subsequent coupling to give biaryl **26**.

Conclusions

In summary, an exceptionally mild method for Miyaura borylations of aryl bromides has been developed. Applying micellar catalysis, reactions can be run in water at room temperature, with reaction times shorter than those normally required using traditional organic solvents. In addition, highly chemoselective transformations can be achieved, leading to more efficient couplings. Through the judicious choice of base, the potential for 1-pot, 3-component couplings involving an initial Miyaura borylation followed by a Suzuki-Miyaura coupling has also been documented.

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Figure 1.
Examples of educts that did not undergo borylation.

Scheme 1.

Borylation with 0.1 mol % catalyst.

Scheme 2.

Tandem 1-pot borylation-Suzuki-Miyaura cross-coupling in water at rt.

Table 1

Literature reports on borylations of aryl halides.

- A:** PdCl₂(dppf)/KOAc/DMSO Miyaura *et al.* **1995** ³
B: Pd(dba)₃/2PCy₃/KOAc/dioxane Miyaura *et al.* **2001** ⁴
C: Pd(OAc)₂/IPr/KOAc/THF F Yrstner *et al.* **2002** ⁵
D: Pd(OAc)₂ or Pd₂dba₃/XPhos or SPhos/K₃PO₄/dioxane Buchwald *et al.* **2007** ⁶

ArX (Ar =)	ArX (X =)	conditions	T [°C]	time [h]	yield [%]
<i>p</i> -MeOC ₆ H ₄	Br	A	80	24	69
<i>p</i> -MeOC ₆ H ₄	Br	B	80	7	81
<i>p</i> -MeOC ₆ H ₄		B	80	48	78
<i>p</i> -MeOC ₆ H ₄		D	<i>rt</i>	24	97
<i>p</i> -Me ₂ NC ₆ H ₄	Br	A	80	24	23
<i>p</i> -Me ₂ NC ₆ H ₄	Br	B	80	6	81
<i>p</i> -Me ₂ NC ₆ H ₄		B	80	48	73
2,4,6-Me ₃ C ₆ H ₂	I	A	80	24	71
2,6-Me ₂ C ₆ H ₃		D	<i>rt</i>	48	86
EWG-C ₆ H ₅		C	66	4-6	90

Table 2Optimization studies. ^[a]

catalyst	solvent	time [h]	yield ^[b] [%]
PdCl ₂ (dppf)	2% cremophore/H ₂ O	20	13
Pd ₂ (dba) ₃ /2 PCy ₃	2% cremophore/H ₂ O	20	< 5
Pd(OAc) ₂ /XPhos	2% cremophore/H ₂ O	20	16
[PdBr(P ^t Bu ₃) ₂] ₂	2% cremophore/H ₂ O	3	79
Pd(P ^t Bu ₃) ₂	2% cremophore/H ₂ O	3	78
Pd(P ^t Bu ₃) ₂	2% cremophore/H ₂ O	3	50 ^[c]
Pd(P ^t Bu ₃) ₂	1% cremophore/H ₂ O (A)	3	86 ^[d]
Pd(P ^t Bu ₃) ₂	2% TPGS-750-M/H ₂ O (B)	3	85 ^[d]
Pd(P ^t Bu ₃) ₂	1% TPGS-750-M/H ₂ O	3	64
Pd(P ^t Bu ₃) ₂	H ₂ O	3	41
Pd(P ^t Bu ₃) ₂	THF	3	20
Pd(P ^t Bu ₃) ₂	1,4-dioxane	3	16
Pd(P ^t Bu ₃) ₂	DMSO	3	6

^[a] Optimization reactions performed on 0.5 mmol scale using 2 mL of solvent.^[b] Determined by GC/FID using tridecane as internal standard.^[c] Using 3 equiv K₂CO₃ as base.^[d] Isolated yield after column chromatography.

Table 3

Representative examples of borylations.^[a]

$\text{Ar}-\text{Br} \xrightarrow[\text{surfactant A or B/H}_2\text{O}]{\begin{array}{c} 3 \text{ mol } \% \text{ Pd(P}^t\text{Bu}_3)_2 \\ 1.1 \text{ equiv B}_2\text{pin}_2 \\ 3 \text{ equiv KOAc} \\ \text{room temp} \end{array}} \text{Ar}-\text{B} \begin{array}{c} \diagup \text{O} \diagdown \\ \diagdown \text{O} \diagup \end{array} \begin{array}{c} \diagup \text{C} \diagdown \\ \diagdown \text{C} \diagup \end{array}$		
conditions A = 1% cremophore B = 2% TPGS-750-M
<p>A: 86% (3 h) B: 59% (4 h)</p>	<p>A: <i>n.d.</i>^[b] B: 79% (6 h)</p>	<p>A: <i>n.d.</i> B: 80% (3 h)</p>
<p>A: 60% (24 h) B: 80% (8 h) A + B: 84% (18 h)</p>	<p>A: 70% (48 h) B: 85% (24 h)</p>	<p>A: <i>n.d.</i> B: 82% (9 h)</p>
<p>A: 90% (20 h) B: 93% (9 h)</p>	<p>A: 90% (20 h) B: 86% (9 h)</p>	<p>A: 79% (20 h) B: 83% (3 h)</p>
<p>A: <i>n.d.</i> B: 88% (8 h)</p>	<p>A: <i>n.d.</i> B: 90% (24 h)</p>	<p>A: <i>n.d.</i> B: 77% (6 h)</p>
<p>A: <i>n.d.</i> B: 87% (3 h)</p>	<p>A: <i>n.d.</i> B: 71%^[c] (6 h)</p>	<p>A: <i>n.d.</i> B: 39%^[c] (6 h)</p>

^[a]Reactions performed on 0.5 mmol scale using 2 mL of solvent. Isolated yields after column chromatography.^[b]Not determined.

^[c]Significant biaryl formation.

Table 4

Comparison between literature methods for borylation and this work on bromide **22**.^[a]

entry	conditions	temp [°C]	time[h]	yield 23 ^[b] [%]	yield 24a/24b ^[b] [%]
1	Miyaura 1995 (A) ³	80	3	0	0/77
2	Miyaura 2001 (B) ⁴	80	2	97	0/0
3	Fürstner 2002 (C) ⁵	66	10	41 ^[c]	11/9
4	Buchwald 2007 (D) ⁶	rt	24	58	0/0
5	2% TPGS-750/H ₂ O (E) ⁷	rt	2.5	85	0/0

^[a] Reactions were performed on 0.5 mmol scale and monitored through GC/FID analysis until full conversion.

^[b] NMR yield using Ph₃CH as internal standard.

^[c] Low conversion.