

An “On-Cycle” Precatalyst Enables Room-Temperature Polyfluoroarylation Using Sensitive Boronic Acids

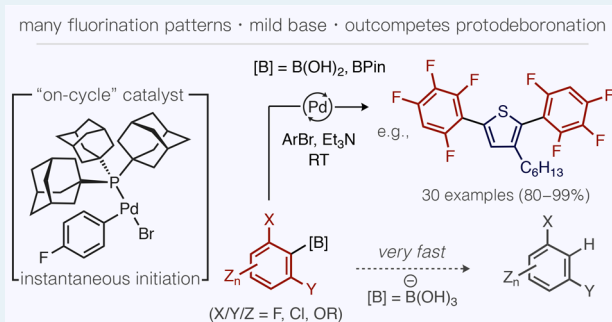
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Supporting Information

ABSTRACT: The use of fluorinated arylboronic acid building blocks in cross-coupling has remained challenging, because of their acute base sensitivity. We report a general solution to this problem using a true catalytic intermediate, $\text{Pd}(\text{PAd}_3)(p\text{-FC}_6\text{H}_4)\text{Br}$, as a uniquely effective “on-cycle” precatalyst that allows Suzuki–Miyaura coupling to occur much faster than even the most severe protodeboronation side reactions. Control of boron speciation between the active acid and dormant ester forms was also found to play a critical role in balancing the rates of catalysis versus reagent decomposition. This method is compatible with any fluorination pattern, base-labile functional groups, and a range of bromo(hetero)arenes.

KEYWORDS: cross-coupling, palladium, precatalyst, fluorine, transmetalation, boronic acid



The electronegativity of fluorine can engender distinct chemical and physical properties in fluoroaromatic compounds such as enhanced chemical stability, unique electronic structures, and solid-state packing versus their hydrocarbon analogues.¹ These effects are attractive for applications in organic electronics and catalyst design (see Figure 1),² but tailored synthetic approaches are often needed for the preparation of fluoroaromatic motifs, because of the strong influence fluorine also exerts on reactivity. A notable example of this latter effect is sensitization of (hetero)-arylboronic acids toward decomposition by base-promoted protodeboronation (PDB) with an increasing number of F

atoms, or similar inductively withdrawing substituents.³ A systematic study by Lloyd-Jones established that the rates of fluoroarylboronic acid PDB can vary dramatically over 9 orders of magnitude, depending on the substitution pattern. The most severe cases are characterized by di-*ortho*-halo substitution that shortens the boronic acid half-life to ca. 10^1 – 10^{-3} s at elevated temperature and high pH.^{3a,c} This represents a major impediment toward efficient catalysis involving these reagents.^{4,5} Low toxicity and bench stability are nevertheless attractive features of boronic acids, and they remain the only commercial organometallic sources of many polyfluoroaromatic fragments. Therefore, a Suzuki–Miyaura coupling (SMC) method compatible with *any* sensitive fluorinated boronic acid that also avoids harsh conditions or stoichiometric metal additives remains highly desirable.^{2a–c,6,7}

The problem of competing PDB in cross-coupling arises from the relatively strong bases (i.e., hydroxide, phosphate, carbonate) typically needed to drive the transmetalation (TM) step of the catalytic cycle.⁸ This base problem is the primary impediment toward general cross-coupling methods that are applicable to many sensitive substrates, including polyfluoroarylboronic acids.^{5c–e,7} In this regard, we recently reported a cationic SMC method between aryl diazonium salts and unstable boronic acids that occurs with no added base.⁶ An encouraging result in this study was the stoichiometric reaction between $\text{C}_6\text{F}_5\text{B}(\text{OH})_2$, one of the most sensitive boronic acids, and an isolated T-shaped complex $\text{Pd}(\text{PAd}_3)(p\text{-FC}_6\text{H}_4)\text{Cl}$ (1-Cl) to generate biaryl at room temperature (rt) in the absence

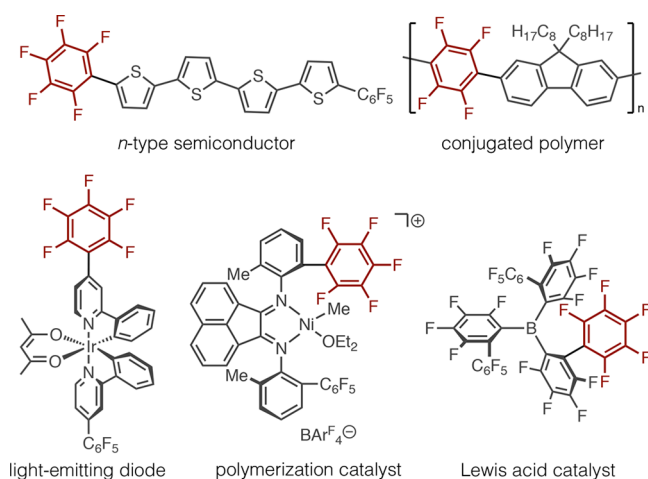


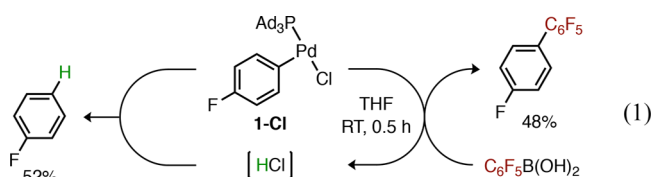
Figure 1. Illustrative examples of polyfluoroaromatic motifs in materials and catalysts.

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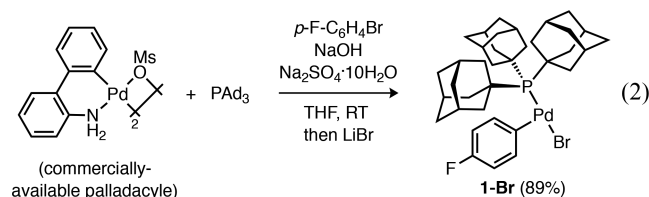
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of base (eq 1). This observation contradicts conventional wisdom about mechanisms of TM in SMC⁸ and suggested to us



that catalysis could potentially be extended to abundant haloarene electrophiles. However, a complication in the stoichiometric reaction was competing protodemetalation that limited the biaryl yield, because stoichiometric acid byproduct is formed in the absence of a base. Here, we report a solution to this problem that now allows SMC between unstable boronic acids and bromo(hetero)arenes. This was made possible by the development of a scalable, one-pot route to an “on-cycle” Pd-PAD₃ precatalyst, which enables efficient catalysis under conditions that are sufficiently mild to suppress both protodemetalation and PDB.

Coordinationally unsaturated arylpalladium halide complexes with a single dative ligand have been implicated as intermediates in several cross-coupling reactions that use state-of-the-art catalysts.⁹ The direct use of an unsaturated Pd(L)(Ar)X species as catalysts would thus be advantageous, because it would circumvent precatalyst initiation that can vary widely in time and often requires a strong base or nucleophile.¹⁰ On the other hand, the synthesis of Pd(L)(Ar)X complexes can be cumbersome or involve sensitive metal precursors.^{9a,11,12} Along these lines, **1-Cl** was initially considered as a precatalyst candidate for SMC due to its high reactivity toward base-free TM, but its reported synthesis was not scalable, because of a capricious intermediate in the multistep sequence.⁶ We have successfully identified a second-generation route to a related complex **1-Br** involving a one-pot, rt reaction between a bromoarene and a commercially available palladacycle (eq 2). The reaction proceeds via deprotonation of

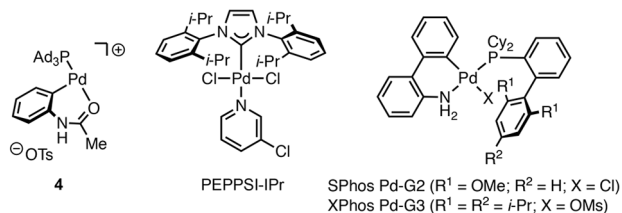


the initial PAD₃-coordinated palladacycle by sodium hydroxide, then intramolecular C–N reductive elimination to liberate carbazole and a 12-electron (PAD₃)Pd⁰ intermediate.¹³ This highly reactive Pd(0) species is trapped by oxidative addition in the presence of 1-bromo-4-fluorobenzene (**2**) to form Pd-(PAD₃)(p-FC₆H₄)Br (**1-Br**) in high isolated yield (89%) after a workup with LiBr. The inclusion of a salt hydrate (Na₂SO₄·10H₂O) was important to achieve high yield, possibly through the release of water that improves the base solubility in THF. This T-shaped complex is notably stable toward air, moisture, and even silica gel, allowing easy purification via flash chromatography and benchtop storage.

We next turned to the catalytic SMC between C₆F₅B(OH)₂ and bromoarene **2** as a challenging model reaction. Under conditions similar to the stoichiometric TM reaction (eq 1), catalyst **1-Br** (1 mol %) produced only trace biaryl after 1 h at rt (Table 1, entry 1). We believed that some type of base

Table 1. Pentafluorophenylboronic Acid/Pinacol Ester Coupling^a

entry	[Pd]	[B]	additive(s)	3 (%) ^b
1	1-Br	B(OH) ₂		1
2	1-Br	B(OH) ₂	Et ₃ N	2
3	1-Br	BPin	Et ₃ N	2
4	1-Br	BPin	Bu ₄ NOAc	0
5	1-Br	BPin	aq NaHCO ₃	23
6	1-Br	BPin	K ₃ PO ₄	6
7	1-Br	B(OH) ₂	Et ₃ N, neopentyl glycol	12
8	1-Br	B(OH) ₂	Et ₃ N, pinacol	65
9	1-Br	BPin	Et ₃ N, H ₂ O (1.2 equiv)	91
10	1-Br	BPin	Et ₃ N, H ₂ O (2.4 equiv)	90
11 ^c	1-Br	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	93
12 ^c	PAD ₃ + Pd ₂ (dba) ₃	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	41
13 ^c	4	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	32
14 ^c	PAD ₃ + Pd(OAc) ₂	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	1
15 ^c	Pd(PAD ₃)(cinnamyl)Cl	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	1
16 ^c	[Pd(P ^t Bu ₃)(μ-Br)] ₂	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	4
17 ^c	SPhos Pd-G2	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	0
18 ^c	XPhos Pd-G3	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	0
19 ^c	Pd(IPr)(cinnamyl)Cl	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	0
20 ^c	PEPPSI-IPr	BPin	Et ₃ N, Na ₂ SO ₄ ·10H ₂ O	0



^aConditions: **2** (0.25 mmol), C₆F₅[B] (0.28 mmol), and **1-Br** (1 mol %) were stirred in toluene (2.5 mL) at room temperature (rt). A base (1.1 equiv) was added, where indicated. Pin = pinacol. ^bDetermined by ¹⁹F NMR vs 1,3-C₆F₂H₄. ^c0.12 equiv of salt hydrate.

should be an important additive to mitigate protodemetalation that might cause catalyst deactivation, but a short survey (entries 2–6) did not drastically improve the outcome and also led to significant PDB side product (Table S5 in the Supporting Information). Substitution of C₆F₅Bpin for C₆F₅B(OH)₂ also did little to improve the yield (see entries 2 and 3 in Table 1) under anhydrous conditions. On the other hand, a surprising jump in yield of biaryl **3** (65%) was observed when the ester was generated in situ from C₆F₅B(OH)₂ and pinacol (entry 7 in Table 1). The only difference between reactions in entries 3 and 8 in Table 1 is the water formed by the condensation reaction; deliberate addition of water to the SMC reaction with

isolated C_6F_5BPin recapitulated this effect and confirmed a critical role of water in this catalytic reaction.

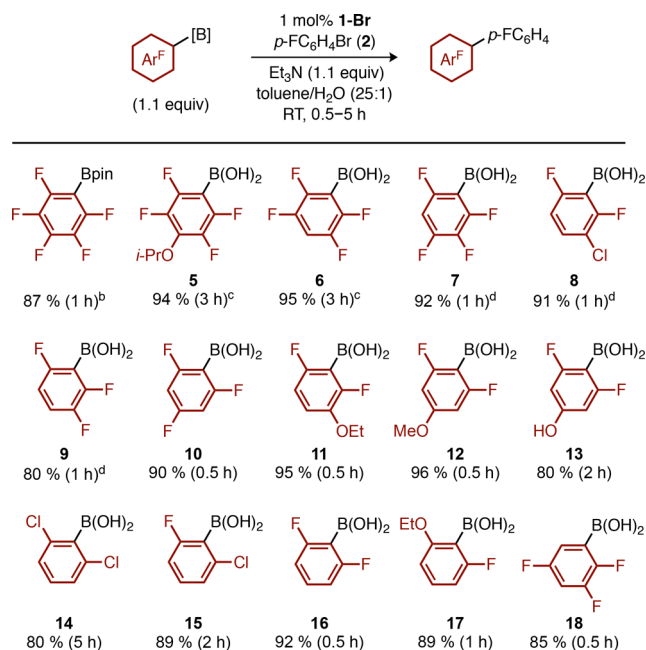
Boronic esters are known to be stable toward PDB under anhydrous conditions,^{7g} but control reactions between C_6F_5BPin and Et_3N suggest the rate of PDB approaches that of free $C_6F_5B(OH)_2$ with increasing water content (Figure S1 in the Supporting Information). Careful addition of stoichiometric water (ca. 1–2 equiv) to the SMC with isolated C_6F_5BPin is therefore important for optimal biaryl yield (entries 9 and 10 in Table 1), which may facilitate a fast equilibration between boronic acid and ester, the former being the active species in TM and the latter being stabilized toward PDB. Therefore, a favorable balance between the rates of catalysis versus PDB at low $[H_2O]$ seems critical for high yield with $C_6F_5B(OH)_2$, which is the most extreme case. In this regard, a slow release of water from an inexpensive, insoluble salt hydrate $Na_2SO_4 \cdot 10H_2O$ (entry 11 in Table 1) gave the highest biaryl yield (93%). Importantly, it is also easy to dispense and provided generally higher yields than did direct water addition, which is consistent with the established use of salt hydrates to meter water release in nonaqueous enzymatic catalysis.^{14–16}

The central role of the on-cycle precatalyst **1-Br**, which requires no activation step, was subsequently validated under the optimized catalytic conditions. Four additional PA_{d_3} -coordinated catalysts were tested (entries 12–15 in Table 1), and yields of biaryl **3** were indeed significantly reduced after 1 h (1%–41%). Several other state-of-the-art Pd precatalysts were also screened (entries 16–20 in Table 1), and the resulting low yields (0–4%) indicate that the mild reactions conditions for this SMC method may indeed exacerbate typical catalyst activation pathways that typically involve a base or nucleophile stronger than a tertiary amine.^{7a,f,17} Repetition of these control experiments under the conditions previously optimized for each of the above precatalysts also led to low or no yield of **3** (see Table S6 in the Supporting Information). Complex **1-Br** should also be useful in other areas of coupling chemistry that would benefit from a fast initiating catalyst. Related oxidative addition complexes have been used with great effect in Buchwald–Hartwig amination and catalyst transfer polycondensation,^{9c,11} for example.

Upon examination of the scope of this SMC method, it was quickly apparent that a broader range of polyfluoroarylboronic acids and derivatives is tolerated (Scheme 1) than our previous cationic SMC protocol,⁶ the latter being limited to unhindered aryl groups with two inductively withdrawing *ortho*-substituents (e.g., F or OR). The addition of pinacol was beneficial when using boronic acids **5**–**9** that have particularly short PDB half-lives,^{3a} but boronic acids **10**–**18** with relatively longer half-lives afforded high yields, even in the absence of pinacol. Adjusted base loading was unnecessary for phenolic reagent **13**, thanks to the mild basicity of this medium. Also of note is that a more hindered, unstable boronic acid (**14**), which was problematic in a previous study on SMC with sensitive boron reagents,^{5d} underwent smooth coupling with this protocol. In total, high isolated yields (80%–95%) were obtained across the entire range of this challenging suite of unstable boron reagents.

Finally, the range of applicable bromo(hetero)arenes was explored (see Scheme 2). The isolated yield of biaryl appears to be relatively insensitive to substituent electronic effects at the electrophile (e.g., **20**–**22**, **24**), and several tri-*ortho*-substituted motifs were constructed in high yield. Similar to an initial report on SMC using complex **4**,^{7f} attempted synthesis of a

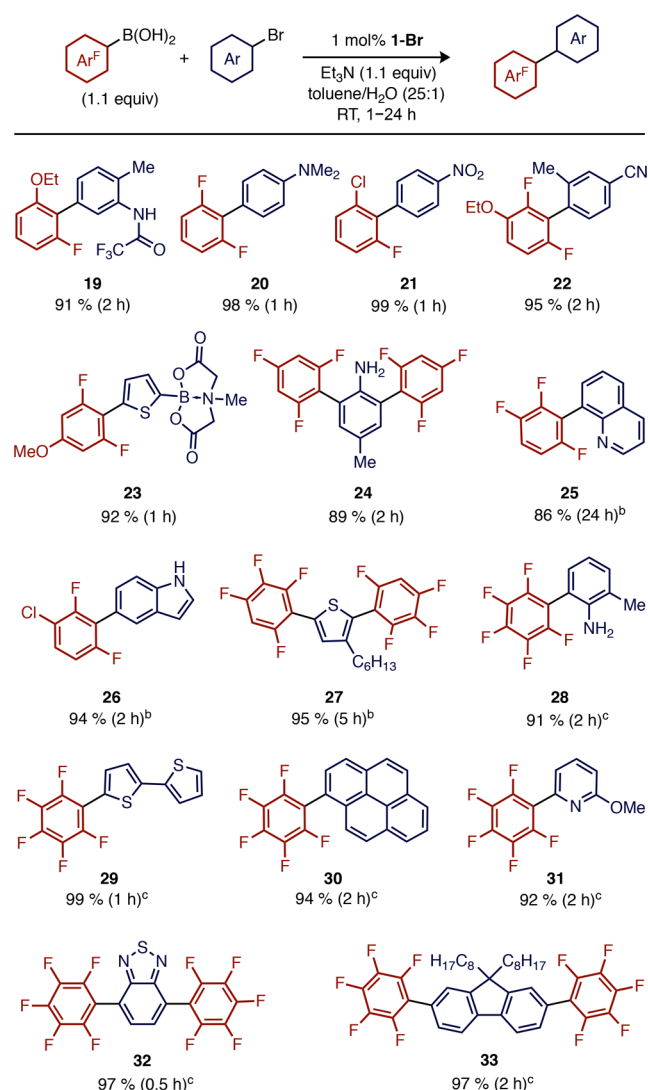
Scheme 1. Scope of SMC with Polyhaloarylboron Reagents^a



^aIsolated yields. ^bConditions described in Table 1, entry 11. ^cAr^FB(OH)₂ (1.3 equiv), pinacol (1.3 equiv), MgSO₄ (1.5 equiv), no added H₂O. ^dAr^FB(OH)₂ (1.1 equiv), pinacol (1.1 equiv), Na₂SO₄·10H₂O (1 equiv), no added H₂O.

tetra-*ortho*-substituted biaryl (e.g., **S1**) failed using **1-Br**, presumably due to the significant space filling of PA_{d_3} within the catalyst coordination sphere. Compatibility with coordinating heteroarenes was very good (e.g., **25**, **31**, and **32**) and base-sensitive functional groups, such as trifluoroacetamide (**19**) or *N*-methyliminodiacetic acid boronate (**23**) persisted under the mild conditions. Protic amines or *N*-heterocycles (e.g., **24**, **26**, and **28**) also did not poison the catalyst, which can be problematic under more basic coupling conditions that generate covalent metal–nitrogen bonds.¹⁸ The polyfluoroaromatic anilines **24** and **28** (89%–91%) are building blocks for α -diimine ligands used in late transition-metal-catalyzed insertion polymerization;^{2f,19} the reported synthesis of the former occurred with poor regioselectivity and low yield (3%). Also note that competing methods to generate polyfluoroaromatics analogous to **27** and **29**, such as by direct arylation or oxidative cross-coupling,^{4a–c} have been developed but have a tendency to generate product mixtures, occur under harsher conditions, and/or require stoichiometric metal additives. Lastly, compounds representative of privileged motifs in organic electronic materials, such as (oligo)thiophene, pyrene, benzothiadiazole, and 9,9-dioctylfluorene fragments (**29**–**33**),²⁰ successfully underwent polyhaloarylation with excellent isolated yields (92%–99%).

In summary, the first general SMC of unstable polyfluoroaryl boronic acids and pinacol esters with bromo(hetero)arenes has been developed. The bench-stable and easily accessible “on-cycle” precatalyst $Pd(PAd_3)(p-FC_6H_4)Br$ (**1-Br**), which can instantaneously enter the catalytic cycle, even in the absence of strong base or nucleophile, is central to the success of this method. Control of boron speciation was also critical to tame the relative rate of base-promoted protodeboronation versus cross-coupling with sensitive boronic acids. The fast rt reactions that we observe using the boronic acid pinacol esters also

Scheme 2. Polyfluoroarylation of Brom(hetero)arenes^a

^aIsolated yields. ^bpinacol (1.1–1.3 equiv) added. ^cAr^FBPIn (2.2 equiv), Na₂SO₄·10H₂O (0.24 equiv), no added H₂O.

contrast the generally sluggish reactivity of this reagent class in most coupling methods, which highlights the excellent reactivity of PAd₃-coordinated complexes. The synthesis of diverse polyfluoro(hetero)aromatic motifs common in organic electronics was also demonstrated in consistently high yield. This work further substantiates the notion that efficient catalytic SMC is possible even under nonbasic or weakly basic conditions by exploiting catalysts that are more reactive toward transmetalation.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b00341.

Experimental procedures and spectral data for new compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): A patent was filed by Princeton University: Carrow, B. P.; Chen, L. WO2017/075581 A1, May 4, 2017.

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