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Palladium-Catalyzed Solid-State Polyfluoroarylation of Aryl Halides Using Mechanochemistry

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KEYWORDS

mechanochemistry, cross-coupling, polyfluoroarylation, ball mill, synthesis

ABSTRACT

The Suzuki–Miyaura cross-coupling between polyfluorinated arylboron nucleophiles and aryl halides enables the efficient construction of polyfluorinated structural motifs frequently found in organic materials and catalysts. A key challenge associated with this transformation involves the slow transmetallation with weakly nucleophilic polyfluorinated organoboron reagents, which often reduces the yield of the coupling products. Here, we show that solid-state high-temperature ball-milling conditions facilitate a palladium-catalyzed cross-coupling with polyfluorinated arylboronic acids and pinacol esters employing a simple catalytic system in the absence of any stoichiometric additives. This reaction exhibits a broad substrate scope and can be carried out in air and the use of large amounts of dry and degassed organic solvents is not required. The

successful cross-coupling of weakly nucleophilic polyfluorinated organoboron reagents was ascribed to the extremely high concentrations of the substrates and the catalyst under solid-state conditions.

INTRODUCTION

Mechanochemical synthesis using ball milling has emerged as a new tool for carrying out organic transformations under solvent-free conditions.[1–9] Due to the concerns associated with solvent waste, solvent-free solid-state organic transformations are of great interest for the development of green and sustainable synthetic methods.[1–9] In addition to these benefits, mechanochemical transformations often show much faster reaction kinetics compared to the corresponding solution-based reactions, because the solid-state conditions allow the reactions to be carried out at extremely high concentrations.[10–25] This unique advantage suggests that chemical reagents that are virtually unreactive under conventional solution-based conditions could be used more efficiently under solid-state conditions, which would provide new synthetic solutions in organic synthesis.

Polyfluorinated aromatic compounds have attracted considerable interest for the design of new organic materials and catalysts due to their unique electronic properties derived from the strong electronegativity of fluorine (Figure 1a).[26–39] The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction between polyfluorinated arylboron reagents and aryl halides represents one of the most efficient methods to construct polyfluorinated structural motifs.[40–46] This reaction proceeds through a palladium(0)-mediated oxidative addition of the aryl halide and a subsequent transmetallation with the arylboron reagent in the presence of the base, followed by a reductive elimination to form the corresponding polyfluorinated coupling compound.[40–46] Although a wide range of polyfluorinated aryl boronic acid derivatives are applicable in cross-coupling reactions in solution, the use of $C_6F_5B(OH)_2$ or $C_6F_5B(pin)$ remains challenging due to their low nucleophilicity, which decreases the reactivity of polyfluorinated arylboron nucleophiles.[40] This problem often decreases the yield of the desired coupling products, even in the presence of state-of-the-art transition-metal catalysts.

To the best of our knowledge, only two approaches for the efficient coupling between aryl halides and $C_6F_5B(OH)_2$ or $C_6F_5B(pin)$ have been reported (Figure 1b).[40,42] In 2005, Korenaga, Sakai, and co-workers reported that the use of a stoichiometric amount of Ag_2O in addition to the palladium catalyst facilitates the transmetallation with the poor nucleophile $C_6F_5B(OH)_2$ to form the desired coupling products in good yield (Figure 1b).[40] Although the acceleration effect of Ag_2O is remarkable, the requirement for a stoichiometric amount of the metal additive and long reaction times reduce the practical utility of this approach. Another solution recently reported by Carrow and co-workers allows the efficient coupling with $C_6F_5B(pin)$ using a palladium-based oxidative addition complex as a precatalyst (Figure 1b).[42] This precatalyst can instantaneously enter the catalytic cycle, thereby promoting the coupling process. However, strict control of the amount of water is still required to ensure efficient coupling under these solution-based conditions. In addition, the use of $C_6F_5B(OH)_2$ is not suitable for this protocol and thus *in situ* transformation from $C_6F_5B(OH)_2$ to $C_6F_5B(pin)$ by the addition of pinacol is necessary for successful cross-coupling. Therefore, the development of an operationally simple, general, and additive-free protocol for the fast cross-coupling of weakly nucleophilic polyfluorinated arylboron nucleophiles facilitated by a readily accessible palladium-based catalyst would be highly desirable.

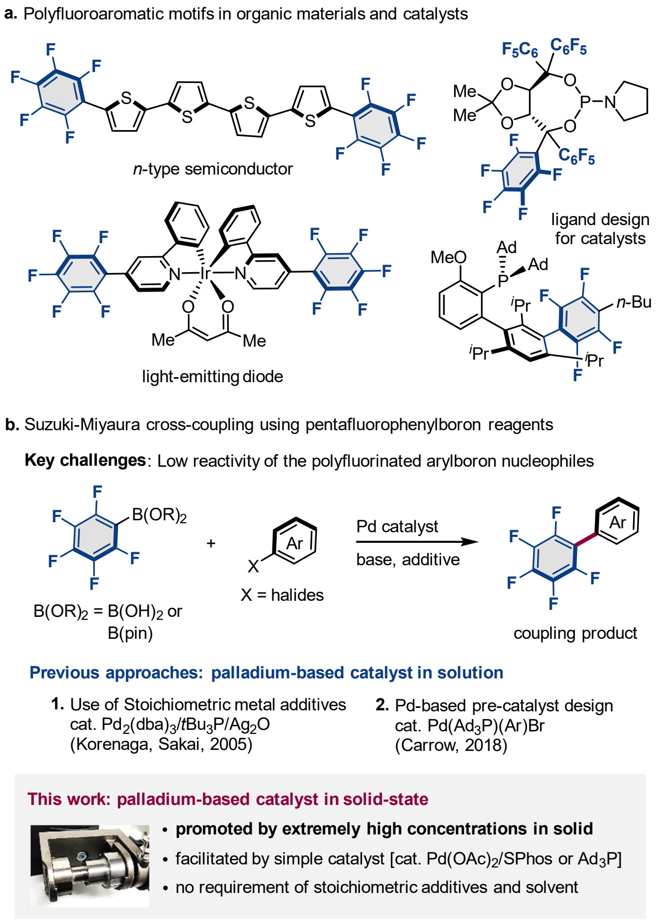


Figure 1. Palladium-catalyzed polyfluoroarylation of aryl halides with polyfluorinated arylboronic acids and pinacol esters.

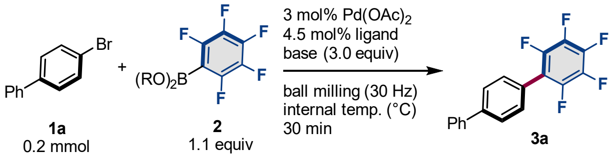
We have recently reported broadly applicable solid-state palladium-catalyzed Suzuki–Miyaura cross-coupling reactions using ball milling.[47] These reactions proceed much faster than those under conventional solution-based conditions.[47–50] This acceleration effect was attributed to the extremely high concentrations of the substrates and the catalyst under the solvent-free ball-milling conditions. Inspired by this advantage of the solid-state mechanochemical synthesis, we envisioned that a solvent-free ball milling technique would provide a general and simple solution to enable efficient coupling with weakly nucleophilic polyfluorinated arylboron reagents.

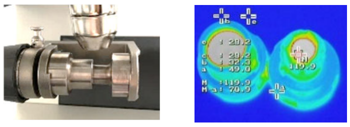
Here, we report very fast polyfluoroarylation reactions using polyfluorinated boronic acids and pinacol esters in the presence of commercially available $Pd(OAc)_2$/SPhos or $Pd(OAc)_2$/tri(1-adamantyl)phosphine (Ad_3P) catalysts under solid-state conditions in the absence of any stoichiometric additives (Figure 1b). Importantly, this solid-state protocol allows using the poor nucleophiles $C_6F_5B(OH)_2$ and C_6F_5B(pin) as efficient coupling partners. This solid-state polyfluoroarylation exhibits a broad substrate scope and can be carried out in air and without the need for large amounts of dry and degassed organic solvents. Based on preliminary mechanistic studies, we propose that the extremely high concentrations of the catalyst and the arylboron nucleophile facilitate the cross-coupling, which provides the desired polyfluorinated aromatic compounds in good to excellent yield. The present study not only provides a practical solution for the use of organoboron nucleophiles of low nucleophilicity in Suzuki-Miyaura cross-coupling reactions, but also offers a unique advantage of the solid-state reaction environment for transition-metal catalysis.

RESULTS AND DISCUSSION

All mechanochemical reactions were conducted in a Retsch MM400 mill [stainless-steel milling jar (1.5 mL); 30 Hz; stainless-steel ball (5 mm)]. First, we investigated the coupling reactions of 4-bromobiphenyl (**1a**) with pentafluorophenylboronic acid (**2a**) in the presence of the catalyst $Pd(OAc)_2$/SPhos and the base CsF. This catalytic system was originally developed by Buchwald and co-workers for efficient Suzuki–Miyaura cross-coupling reactions in solution (Table 1).[51] Unfortunately, the solid-state cross-coupling reaction did not proceed at room temperature (30 °C) (entry 1). In our previous study, we found that the use of a high-temperature ball-milling technique employing a heat gun significantly accelerates such solid-state cross-coupling reactions.[48] In that case, external heating may help to weaken the intermolecular interactions of solid substrates, which would improve the mixing efficiency and promote cross-coupling reactions. Moreover, we expected that heating may help to overcome the activation energy required for the present solid-state polyfluoroarylation reaction to occur. Hence, we decided to conduct the reaction at higher temperature (for details, see the Supporting Information). Pleasingly, the desired coupling product (**3a**) was obtained when the internal temperature was increased to 90 °C using a heat gun at a preset temperature of 150 °C (5%, entry 2). The internal temperature was confirmed by thermography immediately after opening the milling jar. We found that the yield of **3a** significantly improved when the internal temperature was increased to 120 °C (96%, entry 3). The use of the alternative Buchwald ligands XPhos[41] and DavePhos[47] instead of SPhos resulted in lower yields (85% and 80%, respectively; entries 4 and 5). We also investigated the reaction using Ad_3P, which was originally developed by Carrow and co-workers and found to be a very effective ligand for the polyfluoroarylation of aryl halides with **2b** in solution.[42,52] However, the observed yield was only moderate (63%, entry 6). The use of a base was confirmed to be essential for this coupling reaction (entry 7). Reactions using other bases that are commonly employed in Suzuki–Miyaura cross-coupling reactions, namely, tripotassium phosphate (K_3PO_4) and sodium carbonate (Na_2CO_3), resulted in poor yields (21% and 4% yields, respectively; entries 8 and 9). We also investigated the reaction of $C_6F_5B(pin)$ (**2b**) instead of $C_6F_5B(OH)_2$ (**2a**), which resulted in an excellent yield of **3a** with both SPhos and Ad_3P (>99% and 96%, respectively; entries 10 and 11). Finally, we carried out the reaction of **2a** in dioxane (0.3 M) at 120 °C for 1 h, which resulted in a very low yield of **3a** (12%; entry 12). This result suggests that the solid-state approach is crucial for the efficient polyfluoroarylation with **2a**.

Table 1. Optimization Study of the Solid-State Polyfluoroarylation with 2.[a]





set-up with a heat gun

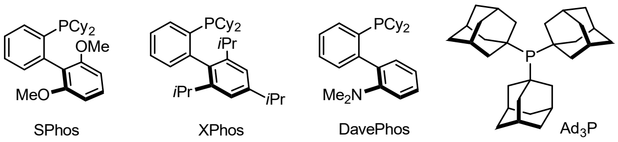
thermography image

preset temp.: 250 °C

▼

internal temp.: 119.9 °C

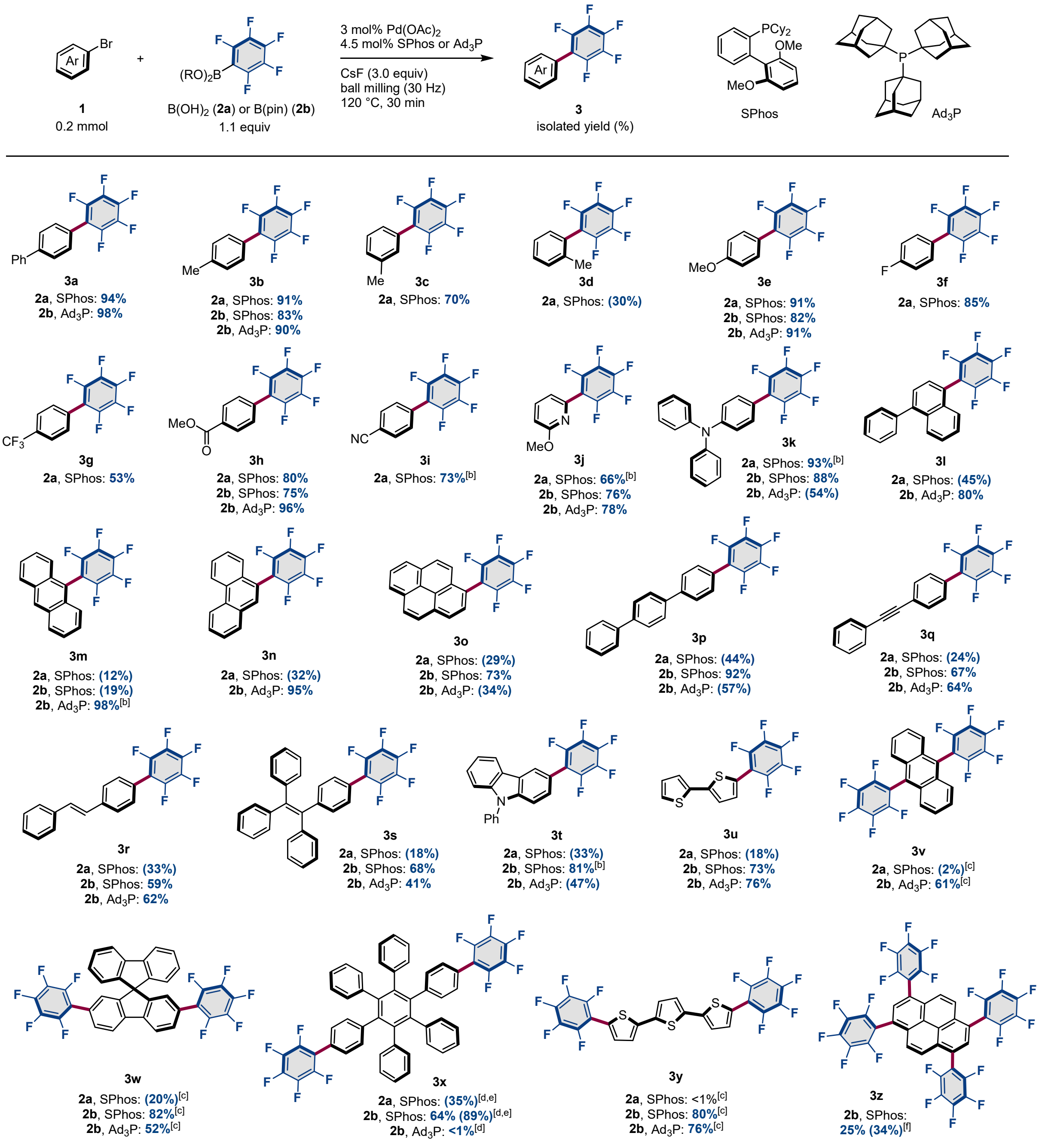
entry	B(OR)$_2$	ligand	base	temp. (°C)	yield (%)
1	B(OH)$_2$ (**2a**)	SPhos	CsF	30	<1
2	B(OH)$_2$ (**2a**)	SPhos	CsF	90	5
3	B(OH)$_2$ (**2a**)	SPhos	CsF	120	96
4	B(OH)$_2$ (**2a**)	XPhos	CsF	120	85
5	B(OH)$_2$ (**2a**)	DavePhos	CsF	120	80
6	B(OH)$_2$ (**2a**)	Ad$_3$P	CsF	120	63
7	B(OH)$_2$ (**2a**)	SPhos	None	120	3
8	B(OH)$_2$ (**2a**)	SPhos	K_3PO_4	120	21
9	B(OH)$_2$ (**2a**)	SPhos	Na_2CO_3	120	4
10	B(pin) (**2b**)	SPhos	CsF	120	>99
11	B(pin) (**2b**)	Ad$_3$P	CsF	120	96
12[b]	B(OH)$_2$ (**2a**)	SPhos	CsF	120	12



[a] Conditions: **1a** (0.2 mmol), **2** (0.22 mmol), Pd(OAc)$_2$ (0.006 mmol), ligand (0.009 mmol), and base (0.6 mmol) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (diameter: 5 mm). Yields were determined using GC with tridecane as an internal standard. A heat gun was used to control the internal temperature in the milling jar. [b] The reaction was carried out in dioxane (0.3 M) at 120 °C for 1 h.

With the optimized conditions in hand, the substrate scope of aryl bromides was studied (Table 2). First, we focused on reactions with **2a** in the presence of the $Pd(OAc)_2$/SPhos catalyst. Various substrates bearing electron-donating and -withdrawing groups reacted efficiently to afford the desired products (**3a**–**3i**) in moderate to high yield (30–96%). Unfortunately, this reaction was sensitive to steric effects, as the reaction of a substrate bearing an *o*-methyl group afforded the corresponding product (**3d**) in low yield (30%). Furthermore, we investigated aryl bromides that contain a variety of substituents (e.g., ethyl, methoxy, and methyl ester) at the ortho-position, which afforded the desired products in low to moderate yield (for details, see the Supporting Information). Cross-coupling with heteroaryl bromides provided the desired products (**3j** and **3k**) in good to high yield (66% and 96%, respectively). These reactions also proceeded smoothly with **2b** instead of **2a** using both SPhos and Ad_3P as a ligand. This solid-state reaction allows the synthesis of large polycyclic hydrocarbon compounds that contain a polyfluorophenyl group, which are potentially attractive organic-materials scaffolds.[53–55] For these substrates, the use of **2b** as a coupling partner was crucial in order to obtain high product yields (**3l**–**3z**). For example, 1-bromonaphthalene derivatives and 9-bromoanthracene efficiently provided the corresponding coupling products (**3l**–**3o**) in high yield (73–98%). We found that the use of Ad_3P was more effective for the reaction with 9-bromoanthracene than the use of SPhos. The present conditions were also applied to other aromatic cores, namely, terphenyl, internal alkyne, stilbene, and tetraphenylethylene compounds, to afford the desired products (**3p**–**3s**) in good to high yield (62–92%). Carbazole- and bithiophene-containing coupling products (**3t** and **3u**) were also obtained in good yield (73–81%). Moreover, double pentafluorophenylations were successful for various di-bromoarenes (**3v**–**3y**). Finally, tetrapentafluorophenylpyrene (**3z**) was successfully synthesized via the solid-state cross-coupling with **2b**.

Table 2. Scope of Aryl Halides in the Solid-State Coupling with Pentafluorophenyl Boronic Acid 2a and Pinacol Ester 2b.[a]



3a
2a, SPhos: **94%**
2b, Ad_3P: **98%**

3b
2a, SPhos: **91%**
2b, SPhos: **83%**
2b, Ad_3P: **90%**

3c
2a, SPhos: **70%**

3d
2a, SPhos: **(30%)**

3e
2a, SPhos: **91%**
2b, SPhos: **82%**
2b, Ad_3P: **91%**

3f
2a, SPhos: **85%**

3g
2a, SPhos: **53%**

3h
2a, SPhos: **80%**
2b, SPhos: **75%**
2b, Ad_3P: **96%**

3i
2a, SPhos: **73%**[b]

3j
2a, SPhos: **66%**[b]
2b, SPhos: **76%**
2b, Ad_3P: **78%**

3k
2a, SPhos: **93%**[b]
2b, SPhos: **88%**
2b, Ad_3P: **(54%)**

3l
2a, SPhos: **(45%)**
2b, Ad_3P: **80%**

3m
2a, SPhos: **(12%)**
2b, SPhos: **(19%)**
2b, Ad_3P: **98%**[b]

3n
2a, SPhos: **(32%)**
2b, Ad_3P: **95%**

3o
2a, SPhos: **(29%)**
2b, SPhos: **73%**
2b, Ad_3P: **(34%)**

3p
2a, SPhos: **(44%)**
2b, SPhos: **92%**
2b, Ad_3P: **(57%)**

3q
2a, SPhos: **(24%)**
2b, SPhos: **67%**
2b, Ad_3P: **64%**

3r
2a, SPhos: **(33%)**
2b, SPhos: **59%**
2b, Ad_3P: **62%**

3s
2a, SPhos: **(18%)**
2b, SPhos: **68%**
2b, Ad_3P: **41%**

3t
2a, SPhos: **(33%)**
2b, SPhos: **81%**[b]
2b, Ad_3P: **(47%)**

3u
2a, SPhos: **(18%)**
2b, SPhos: **73%**
2b, Ad_3P: **76%**

3v
2a, SPhos: **(2%)**[c]
2b, Ad_3P: **61%**[c]

3w
2a, SPhos: **(20%)**[c]
2b, SPhos: **82%**[c]
2b, Ad_3P: **52%**[c]

3x
2a, SPhos: **(35%)**[d,e]
2b, SPhos: **64% (89%)**[d,e]
2b, Ad_3P: **<1%**[d]

3y
2a, SPhos: <1%[c]
2b, SPhos: **80%**[c]
2b, Ad_3P: **76%**[c]

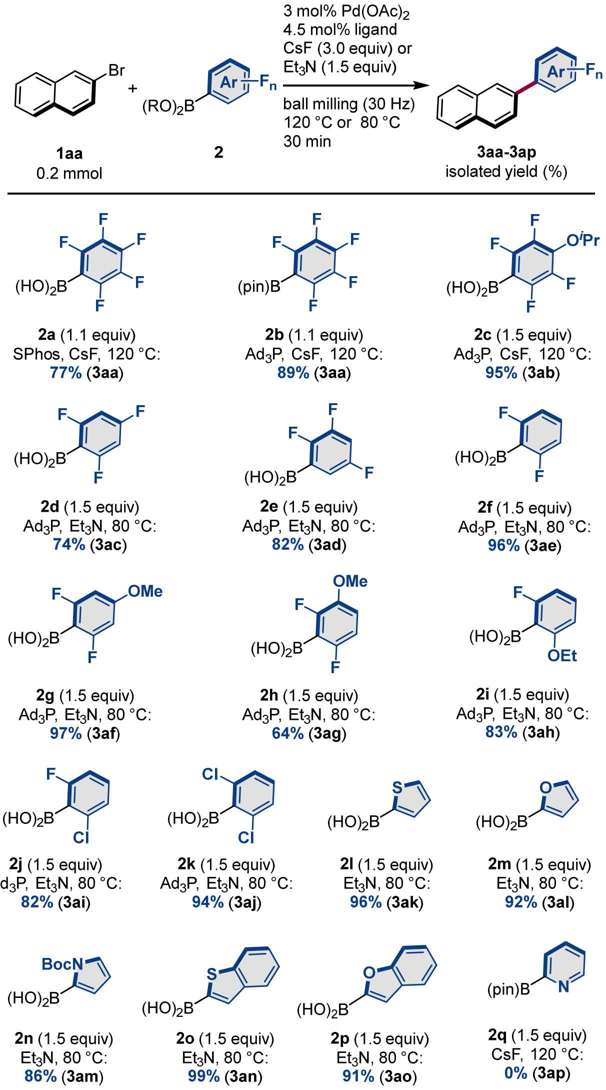
3z
2b, SPhos:
25% (34%)[f]

[a] Conditions: **1** (0.2 mmol), **2** (0.22 mmol), $Pd(OAc)_2$ (0.006 mmol), ligand (0.009 mmol), and CsF (0.6 mmol) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (diameter: 5 mm).

Isolated yields are shown. ^{19}F NMR yields determined with fluorobenzene or benzotrifluoride as an internal standard are shown in parentheses. A heat gun was used to control the internal temperature in the milling jar. ^{b}**2** (1.5 equiv) was used. ^{c}**1** (0.15 mmol), **2** (2.5 equiv), Pd(OAc)$_2$ (0.009 mmol), ligand (0.0135 mmol), and CsF (6.0 equiv) were used. ^{d}**1** (0.10 mmol), **2** (3.0 equiv), Pd(OAc)$_2$ (0.01 mmol), ligand (0.015 mmol), CsF (6.0 equiv) were used. Reaction time: 60 min. ^{e}1.5-cod (0.2 μL/mg) was used. ^{f}**1** (0.05 mmol), **2** (6.0 equiv), Pd(OAc)$_2$ (0.006 mmol), SPhos (0.009 mmol), CsF (12.0 equiv), and 1.5-cod (0.2 μL/mg) were used.

We expected that the present solid-state approach might allow the use of other less-nucleophilic boronic acids and pinacol esters for a polyfluoroarylation in the solid state (Table 3).[40–46] Although the reactions of 2-bromonaphthalene (**1aa**) with polyfluorinated arylboron reagents (**2a**–**2c**) proceeded smoothly under the optimized conditions, other less-fluorinated boronic acids (**2d**–**2k**) did not provide the corresponding products (**3ac**–**3aj**) in good yield. However, we found that the reactions using boronic acids **2d**–**2k** were successful when Et$_3$N was used as the base instead of CsF. In addition, base-sensitive heteroaryl boronic acids (**2l**–**2p**) efficiently provided the desired products (**3ak**–**3ao**) in excellent yield (86–99%). Unfortunately, 2-pyridyl boronic acid pinacol ester (**2q**), which is highly sensitive to protodeboration[56–61], did not react under the applied solid-state conditions.

Table 3. Scope of Polyfluorinated Boronic Acids and Pinacol Esters.[a]



1aa
0.2 mmol

2

3aa-3ap
isolated yield (%)

2a (1.1 equiv)
SPhos, CsF, 120 °C:
77% (**3aa**)

2b (1.1 equiv)
Ad$_3$P, CsF, 120 °C:
89% (**3aa**)

2c (1.5 equiv)
Ad$_3$P, CsF, 120 °C:
95% (**3ab**)

2d (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
74% (**3ac**)

2e (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
82% (**3ad**)

2f (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
96% (**3ae**)

2g (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
97% (**3af**)

2h (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
64% (**3ag**)

2i (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
83% (**3ah**)

2j (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
82% (**3ai**)

2k (1.5 equiv)
Ad$_3$P, Et$_3$N, 80 °C:
94% (**3aj**)

2l (1.5 equiv)
Et$_3$N, 80 °C:
96% (**3ak**)

2m (1.5 equiv)
Et$_3$N, 80 °C:
92% (**3al**)

2n (1.5 equiv)
Et$_3$N, 80 °C:
86% (**3am**)

2o (1.5 equiv)
Et$_3$N, 80 °C:
99% (**3an**)

2p (1.5 equiv)
Et$_3$N, 80 °C:
91% (**3ao**)

2q (1.5 equiv)
CsF, 120 °C:
0% (**3ap**)

[a] Conditions: **1aa** (0.20 mmol), **2** (0.22 or 0.30 mmol), Pd(OAc)$_2$ (0.006 mmol), ligand (0.009 mmol), and base (CsF: 0.60 mmol or Et$_3$N: 0.30 mmol) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (diameter: 5 mm), using a heat-gun, 30 min.

To gain insight into the mechanism of the acceleration effect in the polyfluoroarylation reactions in the solid state, we carried out preliminary mechanistic studies (Figure 2). First, we evaluated the kinetics of the reaction of **1a** with **2a** under both solid-state conditions and solution-based conditions (Figure 2a). Each data point was obtained from an individual reaction, because the mechanochemical reactions require stopping the mill and opening the jar; the solution-based reactions were carried out under reflux at 120 °C. Under the conventional solution-based conditions, the reaction rate increased slightly with increasing concentration of the substrates and the catalyst (0.1 M to 1.5 M), albeit that the yield of **3a** remained below 20% in all cases. In contrast, using the developed solid-state conditions, the reaction completed rapidly (within 30 min) and **3a** was obtained in quantitative yield (Figure 2a, red line). As CsF is not fully dissolved in the solvent at high concentrations (1.0 and 1.5 M), the acceleration effect by increasing concentrations seems not to be remarkable. Subsequently, we investigated the kinetics of the reaction using the unstable boronic acid **2f** (Figure 2b). We again observed an increasing reaction rate upon increasing the concentration from 0.3 M to 1.0 M under the solution-based conditions. In contrast to the reaction using CsF, we noticed that the solution-based reactions using Et_3N appear homogeneous. Therefore, we could confirm the acceleration effect more clearly by increasing the concentrations. Under our solid-state conditions, the cross-coupling was very fast (complete within 10 min) to form **3ae** in quantitative yield (>99%) (Figure 2b, red line). Based on these results, we propose that the extremely high concentrations of the catalyst and the arylboron nucleophile under solid-state conditions facilitates the polyfluoroarylation reactions.

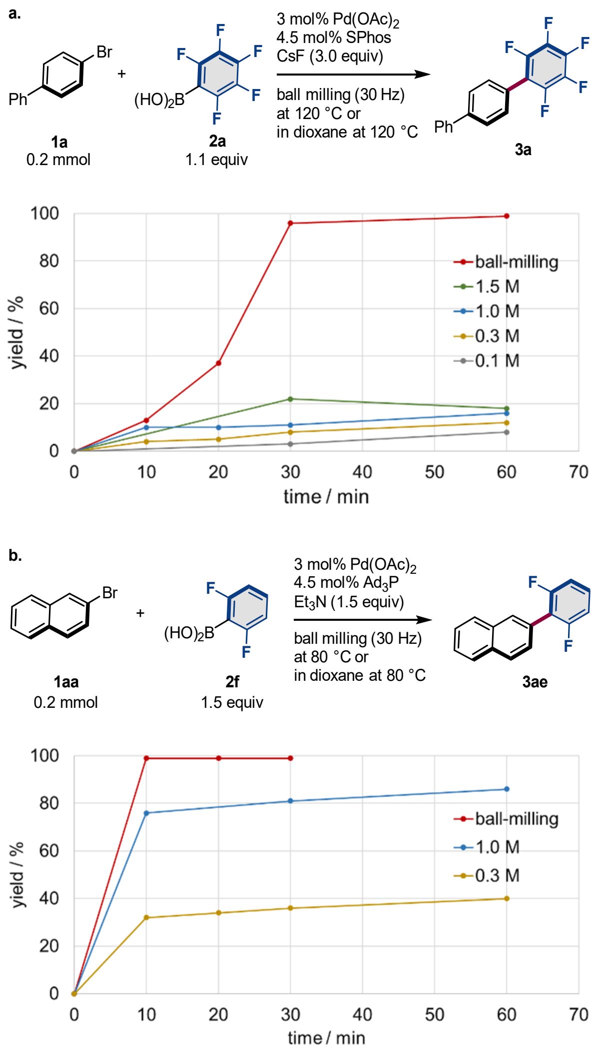
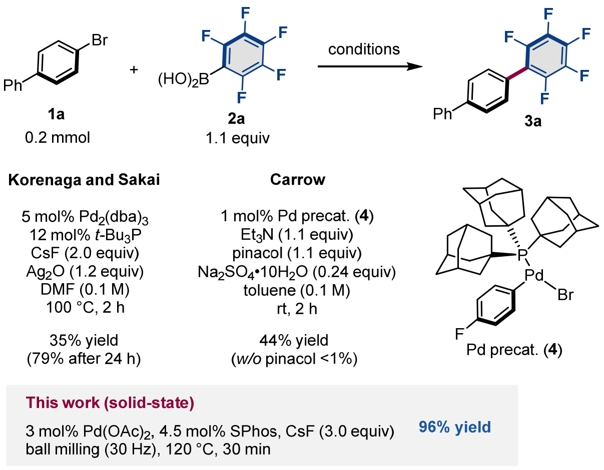


Figure 2. Kinetic studies at different concentrations in the polyfluoroarylation using **2a** and **2f**.

We also found that the reaction of pentafluorobenzene (**2'**) with **1a** under the optimized solid-state conditions furnished the desired product (**3a**) in high yield (95%; for details, please see the Supporting Information). We also carried out the C–H arylation of pentafluorobenzene (**2'**) with **1x** under the optimized solid-state conditions, albeit that the yield of **3x** was decreased (68%) compared to the reaction of pentafluorophenyl boronic acid (**1b**) with **1x** (89%). The ^{1}H NMR analysis of the crude reaction mixtures of all polyfluorinated arylboron reagents used in this study confirmed that no regioisomers and no multiple arylation products were produced. These results suggest that the polyfluoroarylation products should be obtained via the Suzuki-Miyaura coupling as the major pathway, while a protodeboration/C–H arylation[62] may proceed simultaneously to form the corresponding products as the minor pathway.

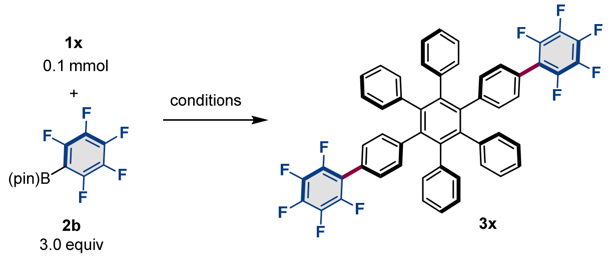
To demonstrate its synthetic utility, we compared the reactivity of the present solid-state conditions with previously reported solution-based catalytic systems (Scheme 1). When $C_6F_5B(OH)_2$ (**2a**) was used, the reaction under our solid-state conditions was fast (complete within 30 min) to provide **3a** in quantitative yield (96%). The solution-based reaction reported by Korenaga, Sakai, and co-workers[40] using stoichiometric Ag_2O as an additive proceeded, albeit that a lower yield was obtained even upon prolonging the reaction time (2 h: 35%; 24 h: 79%; Scheme 1). The reaction using the palladium-based precatalyst bearing Ad_3P (**4**) developed by Carrow and co-workers[42] provided **3a** in moderate yield (44%; Scheme 1). The reaction without pinacol under Carrow's conditions did not furnish any **3a** (<1%; Scheme 1), which is consistent with a reported that $C_6F_5B(OH)_2$ (**2a**) is not suitable for this protocol and thus *in situ* transformation from **2a** to $C_6F_5B(pin)$ (**2b**) by the addition of pinacol is necessary in Carrow's method.[42]

Scheme 1. Comparison of Previously Reported Catalytic Systems for the Reaction with 2a.



Moreover, we found that this solid-state polyfluoroarylation is particularly useful for poorly soluble aryl halides (Scheme 2). For example, **1x** is poorly soluble due to strong intermolecular interactions and exhibits solubility comparable to that of fullerene, which is one of the most iconic poorly soluble molecules.[63] While reactions between **1x** and **2a** under the reported solution-based conditions[40,42] provided very low or moderate yields of **3x** (5% and 51%), our solid-state cross-coupling protocol furnished **3x** in 89% yield within 60 min.

Scheme 2. Polyfluoroarylation of poorly soluble aryl halide 1x.



Korenaga and Sakai	**Carrow**	**This work (solid-state)**
5 mol% $Pd_2(dba)_3$ 12 mol% t-Bu_3P CsF (4.0 equiv) Ag_2O (1.2 equiv) DMF (0.1 M), 100 °C, 2 h	10 mol% Pd precat. (**4**) Et_3N (3.0 equiv) Na_2SO_4•$10H_2O$ (0.24 equiv) toluene (0.1 M) rt, 2 h	10 mol% $Pd(OAc)_2$ 15 mol% SPhos CsF (6.0 equiv) 1,5-cod (0.2 μL/mg) ball milling (30 Hz) 120 °C, 60 min
5% yield	51% yield	**89% yield**

CONCLUSION

In summary, we have developed the first practical and general protocol for the Suzuki–Miyaura cross-coupling of polyfluorinated arylboronic acids and pinacol esters using commercially available, simple palladium-based catalysts without the need for any stoichiometric pinacol and $Na_2SO_4 \cdot 10H_2O$ additives. The key to the success of this challenging transformation is the extremely high concentration of the substrates and the catalyst under solid-state conditions, which efficiently facilitates the desired cross-coupling, even when the weak nucleophiles

$C_6F_5B(OH)_2$ and $C_6F_5B(pin)$, which are difficult to use as substrates under conventional solution-based conditions, are used as coupling partners. Compared to previously reported solution-based methods,[40,42] our solid-state approach using ball milling presents the following advantages: (1) Commercially available, simple palladium-based catalyst such as $Pd(OAc)_2$/SPhos or $Pd(OAc)_2/Ad_3P$ can be used under these solid-state conditions, whereas the preparation of the precatalyst is necessary when using Carrow's method; (2) in order to stabilize boronic acid and control the water stoichiometry, the careful addition of additives such as pinacol and $Na_2SO_4 \cdot 10H_2O$ is essential when applying Carrow's conditions, while our solid-state conditions do not require any additives; (3) solid-state coupling reactions are particularly effective for poorly soluble aryl halides. In fact, as shown in Scheme 2, we have demonstrated that our solid-state coupling of poorly soluble aryl halide **1x**, which exhibits solubility comparable to that of fullerene, provided much higher yield compared to that of the solution-based conditions; (4) solvent waste is greatly reduced.[64] The present study illustrates the great potential of this solid-state cross-coupling approach for the preparation of valuable polyfluorinated molecules that are difficult to access by other means.

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ASSOCIATED CONTENT

Supporting Information.

Methods and materials, supplementary graphics, characterization data, and references.

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(64) Based on the E-factor, the present solid-state approach can be regarded as a much more sustainable polyfluoroarylation method than that reported by Carrow (ref. 42); for details, see the Supporting Information.