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Copper-Catalysed Suzuki-Miyaura Cross-Coupling of Highly Fluorinated Aryl Boronate Esters with Aryl Iodides and Bromides and Fluoroarene-arene π-Stacking Interactions in the Products

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Abstract

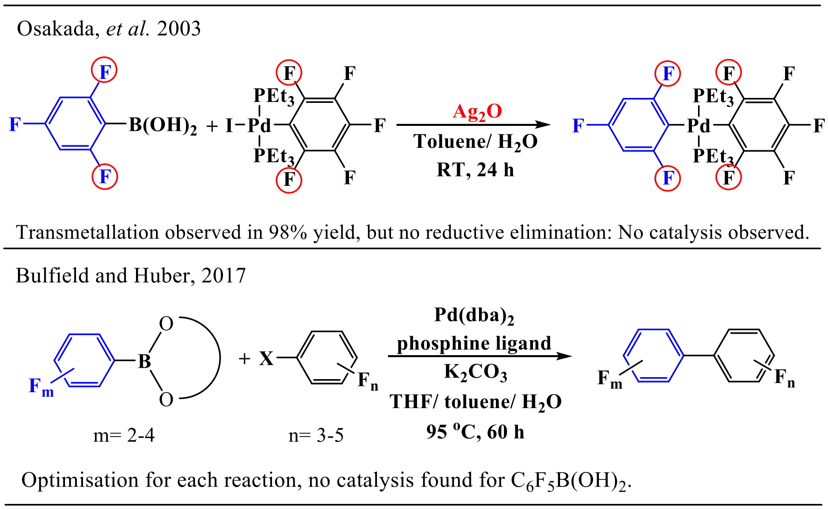
A combination of copper iodide and phenanthroline as the ligand is an efficient catalyst for Suzuki-Miyaura cross-coupling of highly fluorinated boronate esters (aryl-Bpin) with aryl iodides and bromides to generate fluorinated biaryls in good to excellent yields. This method represents a nice alternative to traditional cross-coupling methods which require palladium catalysts and stoichiometric amounts of silver oxide. We note that π···π stacking interactions dominate the molecular packing in the partly fluorinated biaryl crystals investigated herein. They are present either between the arene and perfluoroarene, or solely between arenes or perfluoroarenes, respectively.

Introduction

The conversion of highly fluorinated aromatics into fluorinated arylborononate esters is desirable as arylboronate esters are useful building blocks for organic synthesis.[1] We recently reported the successful defluoroborylation of polyfluorinated aromatics using an NHC nickel complex (NHC = *N*-Heterocyclic Carbene) as a catalyst and the diboron(4) compound B_2pin_2 (pin = pinacolato) as the boron source.[2] Having a good source of fluorinated arylboronates in hand, we were interested to explore the chemistry of these electron poor aromatics, especially in Suzuki-Miyaura cross-coupling reactions which are employed in various fields, from the synthesis of natural products to materials chemistry, including large-scale production.[3] Applications of polyfluorobiphenyls, are quite numerous including medicinal chemistry,[4] organic light emitting diodes,[5] electron-transport materials,[6] crystal engineering,[7] metal−organic frameworks (MOFs),[8] and supramolecular chemistry.[9]

However, Suzuki-Miyaura cross-coupling of highly fluorinated boronate esters, especially pentafluorophenyl boronates is highly challenging under typical palladium catalysed Suzuki-Miyaura conditions,[10] as the transfer of C_6F_5 to the palladium centre in the transmetalation step is usually inefficient.[11c] In many cases, stoichiometric amounts of costly silver oxide (Ag_2O) were added in addition to the palladium catalyst to enhance the transmetalation step and thus to obtain the desired coupling product in fair to good yield.[11] In 1987, it was initially reported by Kishi *et al*. that Ag_2O can accelerate the rate of palladium-catalysed Suzuki-Miyaura cross-coupling of alkenylboronic acids with alkenyl iodides with the relative rate being 30 times faster than that using common bases such as KOH.[12] Inspired by that, in 2002, Adonin *et al*. used 1.2 equivalents of Ag_2O to enhance the efficiency of $Pd(OAc)_2/PPh_3/K_2CO_3$ to catalyse the Suzuki-Miyaura cross-coupling of $C_6F_5B(OMe)_3Li$[11f] or $C_6F_5BF_3K$[11g] with aryl iodides in toluene. In 2005, Korenaga *et al.*[11c] reported an effective method for coupling of $C_6F_5B(OH)_2$ with aryl iodides using $Pd(PPh_3)_4/CsF$ in DMF and for coupling with aryl bromides using $Pd_2(dba)_3/P(t\text{-Bu})_3/CsF$ in DMF, in both cases requiring 1.2 equivalents of Ag_2O. In 2005, Adonin *et al*. extended their previous studies[11g] to the coupling of $C_6F_5BF_3K$ with aryl bromides instead of iodides employing $Pd(OAc)_2/P(t\text{-Bu})_3/K_2CO_3$ in toluene, but this was still only effective in the presence of 1.2 equivalents of Ag_2O.[11b] Osakada *et al*. reported that Ag_2O has the ability to replace the halide ligand of the catalyst to generate an hydroxy-palladium species, which shows higher reactivity in the transmetallation step with aryl boronates. The reaction of *trans*-$[Pd(PEt_3)_2(C_6F_5)I]$ with Ag_2O in toluene–water, for example, generates the complex *trans*-$[Pd(PEt_3)_2(C_6F_5)(OH)]$, which undergoes transmetalation with the boronic acid 4-$MeOC_6H_4B(OH)_2$.[13] In 2010, Buchwald *et al.* reported the precatalyst XPhos-Pd-G2 to solve the problem, and this works without additional Ag_2O to catalyse the coupling of $C_6F_5B(OH)_2$ with aryl chlorides, bromides, and triflates but, interestingly, did not work for aryl iodides.[11h] However, this palladium catalyst is quite expensive or at least requires a multistep synthesis.

Scheme 1. Recent challenges for Pd-catalysed Suzuki-Miyaura cross-coupling to achieve polyfluorinated biaryls


Osakada, *et al.* 2003

Transmetallation observed in 98% yield, but no reductive elimination: No catalysis observed.

Bulfield and Huber, 2017

Optimisation for each reaction, no catalysis found for $C_6F_5B(OH)_2$.

Previously, Osakada *et al.*[13] showed that 2,4,6-trifluorophenyl-$B(OH)_2$ reacts with *trans*-$[Pd(C_6F_5)(PEt_3)_2I]$ in the presence of Ag_2O in toluene and H_2O, but the reaction stops with generation of the stable intermediate *trans*-$[Pd(C_6F_5)(2,4,6\text{-}C_6F_3H_2)(PEt_3)_2]$ as reductive elimination was not observed for this complex. Thus, for palladium complexes $[L_2Pd(Ar)(Ar')]$, if both Ar and Ar′ are highly electron deficient, the reductive elimination step becomes much more difficult, as the Pd−Ar bonds are strong.[14] Those reports show the current challenge for the palladiumcatalysed Suzuki-Miyaura cross-coupling of C_6F_5-boronates with fluorinated aryl halides (Ar_F-X), especially if the C-X bond flanked by two C-F bonds.

Polyfluorinated biaryls can be synthesised via Suzuki-Miyaura cross-coupling of polyfluorinated aryl boronic acid esters and polyfluorinated aryl iodides, as reported by Bulfield and Huber[10d] using palladium catalysts. They employed both fluoroaryl boronate and fluoroaryl halide substrates as coupling partners using a combination of palladium sources and various phosphine ligands. Although this reaction works in some cases, they had to optimise each reaction separately for the corresponding aryl boronate and aryl halide, using different types of expensive phosphine ligands. These reactions all required long reaction times (over 60 hours) and a procedure that would works for $C_6F_5B(OH)_2$ was not developed.

Recently, research to replace precious metal catalysts with cheaper and Earth-abundant metals[15] as well as metals of lower toxicity[16] has attracted much attention. Several groups have developed Cu(I) catalysts for Suzuki-Miyaura cross-coupling reactions.[17] For example, Li *et al*. have developed a copper/DABCO ligand catalyst system, but the reaction, however, does not work for sterically hindered and electron-deficient aryl boronic acids.[17c,d] Brown *et al*. reported that a combination of CuCl with xantphos can effectively catalyse Suzuki-Miyaura cross-coupling of aryl iodides with aryl boronic acid neopentylglycol ester (Bneop)[17a] and later using Cy_3PCuCl catalyst for a cross-coupling of aryl-Bpin with heteroaryl bromides.[17h] Other systems involve the use of copper nanoclusters[17e] or copper powder in polyethylene glycol solvents.[17f] Giri *et al.* reported an efficient system employing CuI and (o-(di-tert-butylphosphino)-N,N-dimethylaniline (PN) as the ligand for efficient Suzuki-Miyaura cross-coupling of aryl-Bneop with aryl iodides[17b] and extended with electron deficient aryl bromides.[17h] However, to the best of our knowledge, there are no reports of copper-catalysed Suzuki-Miyaura cross-coupling reaction of electron deficient, highly fluorinated aryl boronate esters, and only a few examples of the use of aryl bromides in Cu-catalysed Suzuki-Miyaura reactions.[17f,g,h] On the other hand, the optimised conditions for Cu-catalysed Suzuki-Miyaura cross-coupling employing aryl-Bpin and aryl iodide as coupling partners is still challenging, as Brown, *et al*.[17a] and Giri, *et al*.[17b] reported that their optimised methods to employ aryl-Bpin instead of aryl-Bneop only affording fair yields.

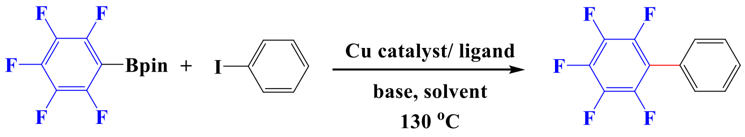
Herein, we report Suzuki-Miyaura cross-coupling of aryl iodides and bromides with highly fluorinated arylboronate esters (Ar_F-Bpin), catalysed by phenanthroline-ligated copper complexes. Notably, Cu(I)-catalysed Suzuki-Miyaura cross-coupling of C_6F_5Bpin does not require the addition of silver oxide to achieve quantitative yields.

Result and Discussion

We began our investigation using the most electron deficient compound, C_6F_5Bpin (**1a**), which was synthesised via an Ir-catalysed C-H borylation reaction.[18] Coupling of C_6F_5Bpin with phenyl iodide (**2a**) to give 2,3,4,5,6-pentafluoro biphenyl (**3a**) was chosen as a model reaction. Giri *at al*.[17g] studied the mechanism of Cu(I)-catalysed Suzuki-Miyaura cross-coupling and showed that, after the formation of $[(PN)CuI]_2$, the addition of CsF led to the formation of $[(PN)CuF]_2$, which then yielded [(PN)CuPh] after transmetallation with an aryl-Bneop reagent. Inspired by that work, we screened Cu(I) salts with different ligands, bases and solvents.

As Giri *et al*. demonstrated that the combination of CuI and (o-(di-tert-butylphosphino)-N,N-dimethylaniline (PN), CsF, in DMF/dioxane solvent at 130 °C was efficient for the Suzuki-Miyaura cross-coupling of aryl-Bneop with aryl iodide,[17b,g] we initially tried to employ these conditions to cross-couple C_6F_5Bpin with phenyl iodide, but obtained only a 5% isolated yield of the biaryl product after 18 h (Table 1, entry 1). Changing the PN-ligand to *N*-only-based chelating ligands such as 2,2′-bipyridine (bpy) and 4,4′-di-tert-butyl-2,2′-bipyridyl (dtbpy) (Table 1, entry 2 and 3) led to better yields (42% and 57%, respectively), while phenanthroline emerged as the best ligand for our purpose. The reaction of C_6F_5Bpin with 1.5 equivalents of iodobenzene in DMF at 130 °C in the presence of 10 mol% CuI, 10 mol% phenanthroline, and 2 equiv. of CsF afforded the cross-coupling product in an excellent yield of 99% after workup (Table 1**,** entry 4). The use of monodentate 4-(dimethylamino)pyridine (DMAP) instead of phenanthroline led to much poorer activity (21% yield, Table 1**,** entry 5).

Table 1. Suzuki-Miyaura cross-oupling of C_6F_5Bpin with PhI [a]



1a **2a** **3a**

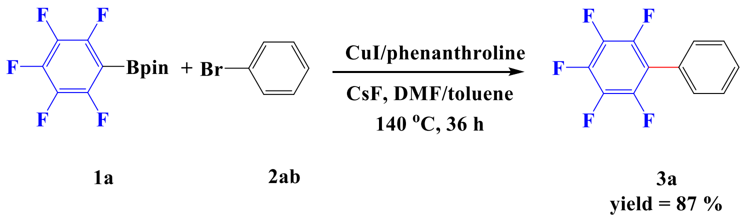
Entry	Cu catalyst	Ligand	Base	Solvent	Time	Yield (%)[b]
1	CuI	PN	CsF	DMF/dioxane	18	5
2	CuI	bpy	CsF	DMF	24	42
3	CuI	dtbpy	CsF	DMF	24	57
4	**CuI**	**phenanthroline**	**CsF**	**DMF**	**18**	**99** **99[c]** **48[d]**
5	CuI	DMAP	CsF	DMF	24	21
6	CuCl	phenanthroline	CsF	DMF	24	55
7	CuBr	phenanthroline	CsF	DMF	24	36
8	CuI	phenanthroline	KF	DMF	24	68
9	CuI	phenanthroline	NMe_4F	DMF	24	29
10	CuI	phenanthroline	K_3PO_4	DMF	24	3
11	CuI	phenanthroline	CsF	Toluene	24	0[e]
12	CuI	phenanthroline	CsF	THF	24	0[f]
13	CuI	-	CsF	DMF	24	26
14	CuI	phenanthroline	-	DMF	24	0
15	-	phenanthroline	CsF	DMF	24	0
16	**(Phen)CuI**	**-**	**CsF**	**DMF**	**18**	**94**

[a] General conditions: **1a** (0.4 mmol), **2a** (0.6 mmol), Cu catalyst (10 mol%), ligand (10 mol%), base (2 equiv.), solvent (3 mL), under argon. [b] Isolated yield after flash chromatography. [c] $C_6F_5BF_3K$ instead of C_6F_5Bpin. [d] T = 100 °C. [e] T = 110 °C. [f] T = 60 °C.

CuCl and CuBr, in place of CuI, were also tested but led to a decrease of the isolated yields to 55% and 36%, respectively (Table 1, entry 6 & 7). It is important to note that hydroxide and alkoxide bases must be avoided as the *para*-carbon atom of C_6F_6Bpin is susceptible to nucleophilic attack by these bases and they can replace the *para*-fluoro-substituent on the perfluorinated boronate substrate.[17] Thus, we examined fluorides and phosphates as bases and found that CsF gave the best results. Similarly, Korenaga *et al*.[11c] observed that CsF gave the highest yield for the Suzuki-Miyaura cross-coupling of $C_6F_5B(OH)_2$ with aryl halides using a Pd-catalyst. Using KF instead of CsF also gave a good yield of 68% (Table 1, entry 7), whereas NMe_4F afforded the product in only 29% yield (Table 1, entry 8). Non-fluoride bases such as K_3PO_4 resulted in a poor yield of 3 % (Table 1, entry 10).

Toluene and THF were ineffective solvents at temperatures close to their boiling points (Table 1**,** entry 11 and 12). It is interesting to note that without any additional ligand, the copper catalyst still gave a 26% yield (Table 1**,** entry 13**)** and was more active than the system employing PN as the ligand (Table 1, entry 1). The absence of either CsF or CuI resulted in no product formation, indicating that both base and catalyst are required. A combination of CuI and phenanthroline generates [(Phen)CuI][20] as using preformed [(Phen)CuI] gave an excellent yield (Table 1, entry 16). CsF reacts as a nucleophile and exchanges the halide ligand at Cu(I) to generate a CuF complex,[15b] which reacts more readily with the aryl boronate ester in the transmetalation step and thus accelerates the transfer of the aryl group to the metal.[10c,15b] CuI gave better result than CuBr or CuCl probably because the low bond energy[19] led to a more efficient anion exchange with CsF. It is also known that the reaction of [(phen)CuI] and CsF in DMF gives [(phen)CuF].[20] Thus a combination of 10 mol% of CuI/phenanthroline, and 2 equiv. of CsF, in DMF at 130 °C emerged as the ideal conditions for the Suzuki-Miyaura cross-coupling of C_6F_5Bpin with aryl iodide. The use of organotrifluoroborates is attractive as these are inexpensive and more stable towards air and moisture than organoboronate substrates.[21] Thus, we also employed $C_6F_5BF_3K$[11b,f] for the Suzuki-Miyaura cross-coupling and found that this also produced $C_6F_5–C_6H_5$ in an almost quantitative yield of 99% (Table 1, entry 4).

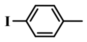
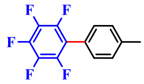
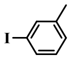
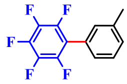
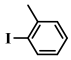
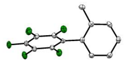
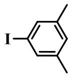
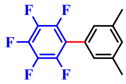
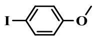
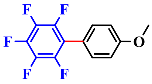
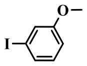
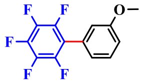
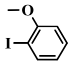
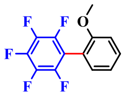
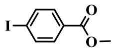
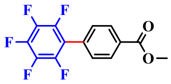
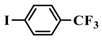
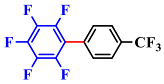
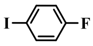
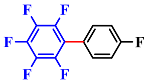
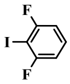
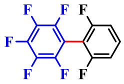
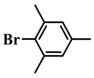
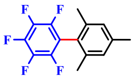
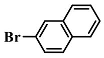
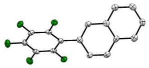
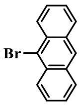
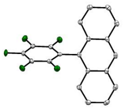
Scheme 2. Cross-coupling reaction of C_6F_5BPin with PhBr[a]



[a] Conditions: C_6F_5BPin (0.4 mmol), PhBr (0.6 mmol), CsF (2 equiv.), CuI/phenanthroline (30 mol%), DMF/toluene (1:1, 4 mL), 140 °C, 36 h, under argon, isolated yield was reported.

While the use of aryl bromides and aryl boronate substrates for Cu-catalysed Suzuki-Miyaura cross-coupling has been reported,[17g] the reaction of aryl bromides with electron-deficient aryl boronate substrates was found to be difficult.[17g] We found that phenyl bromide was effective in reactions with C_6F_5Bpin in a mixed solvent system such as DMF : toluene (1:1) by increasing the loading of CuI/phenanthroline to 30 mol%, generating the cross-coupling product in 87 % yield (Scheme 2).

Table 2. Cu-catalysed cross-coupling of C_6F_5Bpin with Ar-X (X = I or Br)[a]

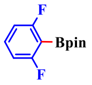
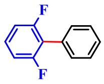
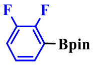
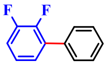
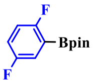
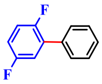
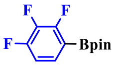
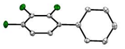
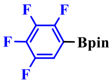
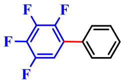
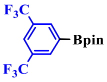
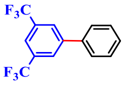
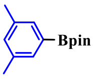
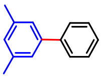
Entry	Ar-X	Product	Yield (%)[b]
1	 **2b**	 **3b**	90
2	 **2c**	 **3c**	88
3	 **2d**	 **3d**	67
4	 **2e**	 **3e**	88
5	 **2f**	 **3f**	95
6	 **2g**	 **3g**	91
7	 **2h**	 **3h**	71
8	 **2i**	 **3i**	86
9	 **2j**	 **3j**	91
10	 **2k**	 **3k**	93
11	 **2l**	 **3l**	77
12	 **2m**	 **3m**	57 (80)[c]
13	 **2n**	 **3n**	75
14	 **2o**	 **3o**	78

[a] Standard conditions: C_6F_5Bpin (0.4 mmol), Ar-X (0.6 mmol), CuI/phenanthroline (10 mol% if X = I; 30 mol% if for X = Br), CsF (0.8 mmol), DMF (3 mL, if X = I) or DMF/toluene (1:1, 4 mL, if X = Br), T (130 °C if X = I; 140 °C if X = Br), t (18 h if X = I; 36 h if X = Br), under argon. [b] Isolated yield after flash chromatography. [c] CuI/phenanthroline (50 mol%)

Having determined the optimal conditions for both phenyl iodides and bromides, we next investigated the scope of the reaction of C_6F_5Bpin with different aryl iodides and bromides (Table 2). Aryl iodides bearing electron donating groups **(2b, 2c, 2e, 2f, 2g)** at *meta* or *para* positions gave good to excellent yields (88-95%), whereas sterically more hindered substrates such as 2-methylphenyl iodide (**2d**), 2-methoxyphenyl iodide (**2h**), and mesityl bromide (**2m**) gave fair to moderate yields (57-71%). Aryl iodides bearing electron withdrawing substituents, such as methyl 4-iodobenzoate (**2i**), 4-iodotrifluorotoluene (**2j**), and 4-fluorophenyl iodide **(2k)**, gave very good to excellent yield (86-93 %). In palladium catalysis, if both Ar_F-Bpin and Ar_F-X have two *ortho*-fluoro substituents, reductive elimination has been reported to be difficult[13] (Scheme 3), but in our case, 1,3-difluoro-2-iodobenzene **(2l)** also provided a good yield (77 %). Napththalene and anthracene derivatives are interesting for application in blue organic light-emitting diodes (OLED).[22] Thus, we employed 2-bromonaphthalene **(2n)** and 9-bromoanthracene **(2o)** in our reaction, and these substrates generated 75 % and 78 % isolated yields of the corresponding perfluoro phenyl naphthalene and anthracene products, respectively.

Furthermore, we varied the number of fluoro subtituents on the aryl-Bpin reagent in coupling reactions with phenyl iodide or bromide. Thus, reaction of other fluorinated aryl-Bpin such as 2,6-difluorophenyl-Bpin (**4a**), 2,3- or 2,5-difluorophenyl-Bpin (**4b, 4c**), 2,3,4-trifluorophenyl-Bpin (**4d**), 2,3,4,5-tetrafluorophenyl-Bpin (**4e**), can be coupled with an aryl iodide affording good to excellent yields (Table 3, entries 1–5). In term of coupling with an aryl bromide, 2,6-difluorophenyl-Bpin (**4a**) proceeded nicely to give the coupling product in 85 % yield (Table 3. entry 1**)**. However, if the aryl-Bpin has one *ortho*-fluoro substituent, 50 mol% of CuI/phenanthroline is required to couple nicely with aryl bromide (Table 3, entries 2-5). Another type of electron deficient aryl boronate ester, namely 3,5-bis(trifluoromethyl)phenyl-Bpin (**4f**), also coupled nicely with phenyl iodide, but its coupling with phenyl bromide proved difficult (Table 3, entry 6). On the other hand, electron-rich 3,5-dimethylphenyl-Bpin (**4g**) coupled well with phenyl iodide, but not viable for phenyl bromide (Table 3, entry 7), indicating that in this system, aryl bromides only couple efficiently with electronic deficient aryl-Bpin compounds. However, our results show that aryl iodides can be coupled not only with electron deficient aryl-Bpin compounds but also with electron rich ones.

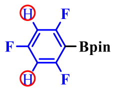
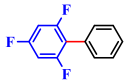
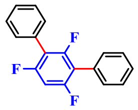
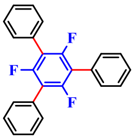
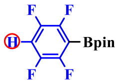
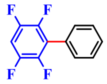
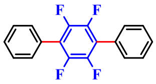
Table 3. Cu-catalysed cross-coupling of various fluorinated and nonfluorinated aryl-Bpin with Ph-X (X= I or Br)[a]

Entry	Ar-Bpin	Product and Yield (%)[b]
1	 **4a**	 **5a** X: I (99), Br (85)
2	 **4b**	 **5b** X: I (95), Br (59)(80)[c]
3	 **4c**	 **5c** X: I (94), Br (73)[c]
4	 **4d**	 **5d** X: I (93), Br (54)(70)[c]
5	 **4e**	 **5e** X: I (81), Br (42)[c]
6	 **4f**	 **5f** X: I (92), Br (35)
7	 **4g**	 **5g** X: I (95), Br (trace)

[a] Standard conditions: Ar-Bpin (0.4 mmol), Ph-X (0.6 mmol), CuI/phenanthroline (10 mol% if X = I; 30 mol% if X = Br), CsF (0.8 mmol), DMF (3 mL, if X = I) or DMF/toluene (1:1, 4 mL, if X = Br), T (130 °C if X = I; 140 °C if X = Br), t (18 h if X = I; 36 h if X = Br), under argon. [b] Isolated yield after flash chromatography. [c] CuI/phenanthroline (50 mol%).

Notably, when 2,4,6-trifluorophenyl-Bpin **(4h)** and 2,3,5,6-tetrafluorophenyl-Bpin **(4i)** were employed, besides good yields of the expected coupling products, we also observed C-H arylation byproducts generated in small (<10 %) amounts after C-Bpin arylation occured (Table 4, entries 1 and 2). It is known that the high acidity of the C-H bonds flanked by two C-F groups can be used in direct arylation.[23] However, our results show that even though both carbons are electron deficient, the C-Bpin group is more reactive than the C-H moiety as an arylation target.

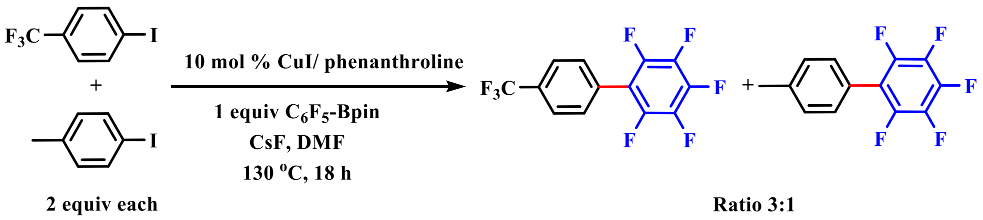
Table 4. Cross-coupling of 2,4,6-$F_3C_6H_2$Bpin and 2,3,5,6-F_4C_6HBpin with PhX (X = I or Br)[a]

Entry	Ar$_F$-Bpin	Product and Yield (%)[b]		
1	 **4h**	 **5h** X: I (75 %), Br (70 %)	 **5h′** X: I (8 %), Br (5 %)	 **5h″** X: I or Br (trace)
2	 **4i**	 **5i** X: I (74 %), Br (69%)	 **5i′** X: I (10%), Br (9%)	

[a] Standard conditions: 0.4 mmol of Ar$_F$-Bpin, 0.4 mmol of PhX, CuI/phenanthroline (10 mol% if X = I or 30 mol% if X = Br), CsF (0.8 mmol), DMF (3 mL, if X = I) or DMF/toluene (1:1, 4 mL, if X = Br), T (130 °C if X = I; 140 °C if X = Br), t (18 h if X = I; 36 h if X = Br), under argon. [b] Isolated yield after flash chromatography.

Generally, aryl halides bearing electron-withdrawing groups are more reactive and give better yields compared to aryl halides bearing electron-donating groups. We compared the reactivities of electron-poor and electron-rich aryl halides by reacting a 1:1 mixture of 4-trifluoromethyliodobenzene and 4-iodotoluene with C_6F_5Bpin (Scheme 2). Trifluoromethylphenyl iodide was more reactive, resulting in a 3 : 1 ratio of the trifluoromethyl to methyl-substrated pentafluorobiphenyl compunds.

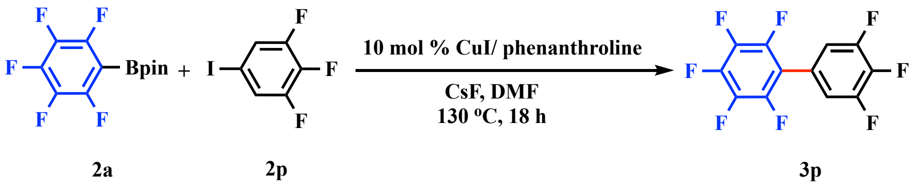
Scheme 3. Comparison of the reactivities of an electron poor and an electron rich aryl iodide[a]



[a] Conditions: C_6F_5Bpin (0.1 mmol), 4-iodotoluene (0.2 mmol), 4-iodobenzotrifluoride (0.2 mmol), CuI (0.01 mmol), 1,10-phenanthroline (0.01 mmol), CsF (0.2 mmol), and DMF (1.0 mL) at 130 °C, 18 h.

These conditions can be used to prepare polyfluorinated biaryl products on a gram scale. Thus, the coupling of C_6F_5Bpin with 1,2,3-trifluoro-5-iodobenzene **(3o)** was conducted without any difficulty using the standard conditions to provide a 98% yield of the unsymmetrical octafluoro biphenyl product (Scheme 4).

Scheme 4. Gram scale reaction[a]



2a **2p** **3p**

(1.47 g, 98 %)[b]

[a] Reaction conditions: C_6F_5Bpin (1.47 g, 5 mmol), 1,2,3-trifluoro-5-iodobenzene (1.80 g, 7 mmol), (95 mg, 0.50 mmol, 10 mol%), phenanthroline (90 mg, 0.50 mmol, 10 mol%), CsF (1.52 g, 10.0 mmol, 2 equiv), and DMF (30 mL), 130 °C, 18 h, under argon. [b] Isolated yield after column chromatography.

Molecular and crystal structures: Intermolecular *π*···*π* stacking interactions

The crystal structures of the polyfluorinated biaryls **3d**, **3n**, **3o**, and **5d** were analysed using single-crystal X-ray diffraction. A comparison of the molecular geometries of these compounds in their crystal structures (Figure 1) shows a small influence of the steric demand of the hydrogenated aryl group in the vicinity of the C–C bonds joining the rings and, hence, of the repulsion between both groups of the biaryl units on their geometries. The central C–C bond is in the range 1.483(4) – 1.495(2) Å (Table 5) which is typical of biphenyl compounds.[24] It is slightly longer in compounds **3d** and **3o** than in **3n** and **5d**, although only within 1–2 su. The twist between the aryl moieties of the biaryl is slightly stronger in compounds **3d** and **3o** (61.66(5) and 64.28(5)°) than in **3n** and **5d** (51.23(15) and 49.76(7)°) (Table 5). These small differences are likely due to the substitution at the *ortho* position of the non-fluorinated phenyl ring. In **3d**, a methyl group is bonded at the *ortho* position and in **3o**, the central phenyl ring of the anthracene moiety is bonded to the fluorinated phenyl ring. This increases the bulkiness of these aryl moieties in close vicinity to the central C–C bond and, hence, to the respective fluorinated phenyl rings. Large twist angles are also reported in the bulky biaryl compounds with a pentafluorophenyl group bonded to benzo[*h*]quinoline (67°),[25a] in 9,10-bis(pentafluorophenyl)anthracene (68°),[25b] and in 5-perfluorophenyl-11-phenyltetracene (72°).[25c]

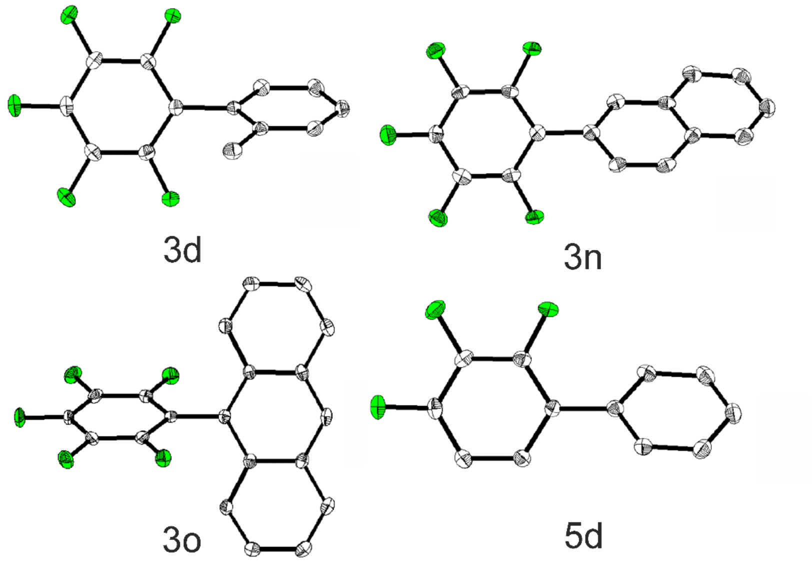


Figure 1. The solid-state molecular structures of **3d**, **3n**, **3o**, and **5d** determined by single-crystal X-ray diffraction at 100 K. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colours: white (carbon), green (fluorine).

Table 5. Selected bond lengths (Å) and angles (°) of **3d**, **3n**, **3o**, and **5d.**

	3d	**3n**	**3o**	**5d**
$C_{Aryl(H)}$–$C_{Aryl(F)}$	1.495(2)	1.484(7)	1.490(2)	1.483(4)
∠ Aryl(H)-Aryl(F)	61.66(5)	51.23(15)	64.28(5)	49.76(7)

Particularly interesting in the crystal structure analyses are the intermolecular interactions and, hence, molecular packing in these compounds. The presence of both fluorinated and nonfluorinated aryl groups leads to the formation of opposite multipoles of these moieties due to the differences in electronegativity of hydrogen and fluorine atoms with respect to the carbon atoms. This often results in attractive multipole forces between the aromatic and perfluoroaromatic groups, also called the arene-perfluoroarene interaction, and, hence, in face-to-face π-stacking with mean interplanar distances between 3.3 and 3.6 Å.[26] This type of interaction is mostly found in co-crystals of arenes and perfluoroarenes, which form highly oriented, π-stacked systems.[26c,27] However, also self-complementary compounds that contain both perfluorinated and nonfluorinated aryl groups, such as 2,3,4,5,6-pentafluorobiphenyl and 1-pentafluorophenyl-2-phenylacetylene, form arene-perfluoroarene interactions.[27d,28a] This is also the case in the polyfluorinated biaryl compounds **3n** and **5d** in which the arene-perfluoroarene interaction determines the packing of the molecules (Table 6).

Table 6. Aryl···aryl (π··· π) distances (Å) in crystals of **3d**, **3n**, **3o**, and **5d** at 100 K: centroid-centroid distance, interplanar separation, and offset shift.

Compound	Aryl···Aryl	Centroid-centroid distance	Interplanar separation	Offset shift [a]
3d	Aryl(F)···Aryl(F)	3.9121(15)	3.4489(16)	1.846(2)
3n	Aryl(F)···Aryl(H)	3.823(3) 3.767(3)	3.398(5) / 3.473(4) 3.408(4) / 3.354(5)	1.753(7) / 1.599(6) 1.605(6) / 1.714(7)
3o	Aryl(H)···Aryl(H)	3.9397(18) 4.2171(19)	3.4625(18) 3.4043(18)	1.879(2) 2.489(2)
5d	Aryl(F/H)···Aryl(H)	3.696(2)	3.380(2) / 3.336(2)	1.494(4) / 1.591(4)

[a] The offset shift, also called inter-centroid shift, is the distance within a plane of an aryl ring between the centroid of the respective aryl ring and the intersection point with the normal to the plane through the centroid of the other aryl ring.

In compound **3n** the biaryls form columns of offset face-to-face π-stacked naphthalene and perfluorophenyl moieties along the *b* axis. Due to the large twist angle of ca. 51° of the biaryl, the columnar stacks are cross-like formed (Figure 2). Similar cross-like columnar stacks are observed in 2,3,4,5,6-pentafluorobiphenyl, 1,2,4,5-tetrafluoro-3-phenyl-6(trifluoromethyl)benzene, and 4′-bromo-2,3,5,6-tetrafluorobiphenyl-4-carbonitrile, which show biphenyl twist angles of 52, 50, and 41°, respectively.[28] In compound **5d** only part of one phenyl ring is fluorinated. Still, the arene-perfluoroarene interaction leads to π-stacking between phenyl and 2,3,4-trifluoro phenyl rings. However, the phenyl and partly fluorinated phenyl rings are π-stacked with different neighboring molecules. Hence, they do not form a columnar arrangement but instead, zig-zag like chains along the *c* axis (Figure 3). The packing of the molecules in compound **3d** follows a similar pattern as in **5d** (Figure 4). However, the type of π···π interactions is different as there is no arene-perfluoroarene interaction present. Instead, neighboring perfluorophenyl moieties are π-stacked via perfluoroarene-perfluoroarene interactions and neighboring tolyl moieties are offset-stacked forming zig-zag chains along the *a* axis.

10.1002/cctc.201901220

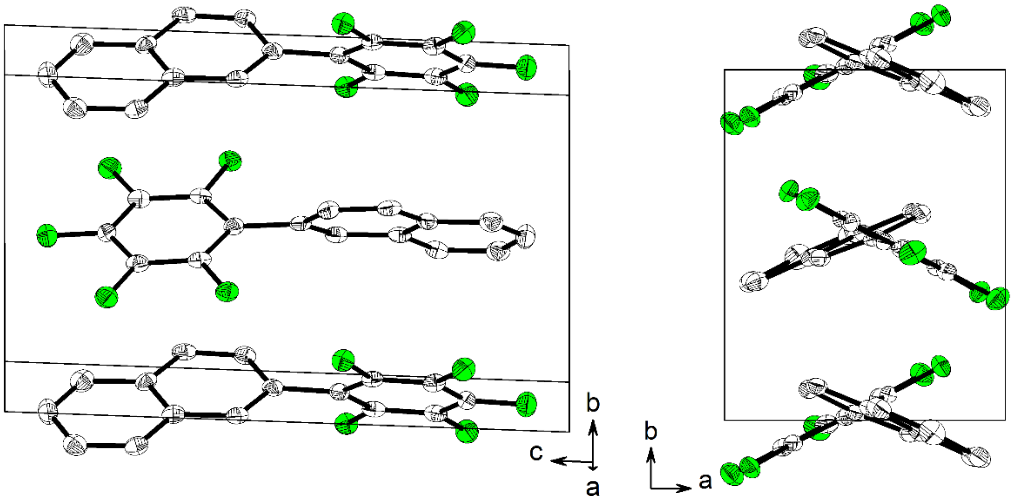


Figure 2. Crystal structure of **3n** projected along (left) an axis close to the *a* axis and (right) along the *b* axis, at 100 K. Perfluorophenyl and naphthalene moieties are π-stacked along the *b* axis via arene-perfluoroarene interactions. The intramolecular angle between the planes of the perfluorophenyl and naphthalene moieties is 51° leading to the formation of cross-like stacks (right). All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colours: white (carbon), green (fluorine).

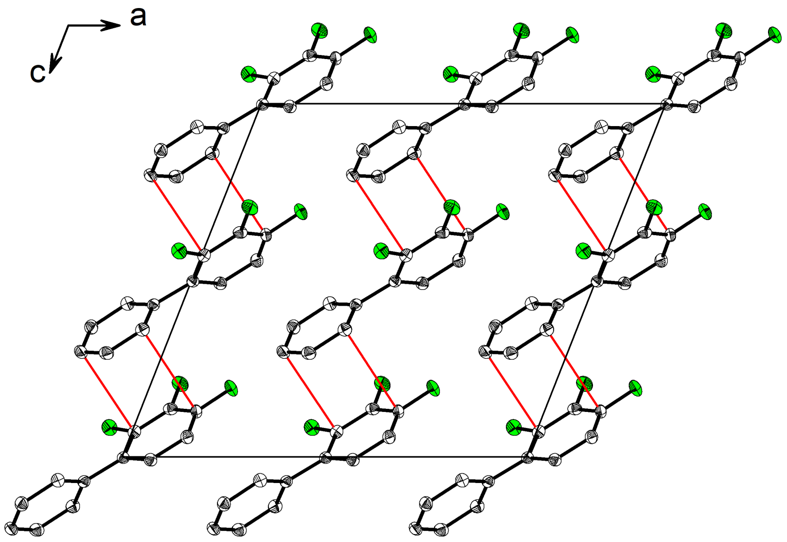


Figure 3. Crystal structure of **5d** projected along the *b* axis, at 100 K. Phenyl and partly fluorinated phenyl rings are π-stacked with different neighboring molecules via the arene-perfluoroarene interaction. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colours: white (carbon), green (fluorine). Close C···C contacts are shown in red.

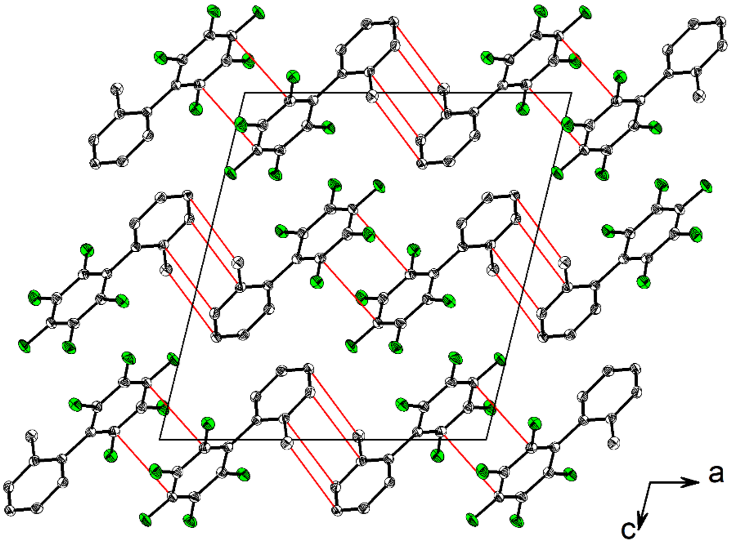


Figure 4. Crystal structure of **3d** projected along the *b* axis, at 100 K. Neighboring perfluorophenyl moieties are π-stacked, while tolyl moieties are offset-stacked. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colours: white (carbon), green (fluorine). Close C···C contacts are shown in red.

Finally, in compound **3o** the intermolecular packing is dominated by π-stacking arene-arene interactions between the anthracene moieties, which form stacks along the *a* axis (Table 6). Similarly, offset π···π stacking is observed between the tetracene moieties of the compound 5-perfluorophenyl-11-phenyltetracene.[25c] 9,10-bis(pentafluorophenyl)anthracene was reported as a host system with benzene or 1,4-dioxane guest molecules.[25b] In these structures, no π···π interactions are observed, but C–F···π interactions are dominant for the molecular arrangement in the crystal structures. In contrast, the bulky 5-pentafluorophenyl-benzo[*h*]quinoline exhibits both arene-perfluoroarene and arene-arene π-stacking interactions in the crystal structure.[25a]

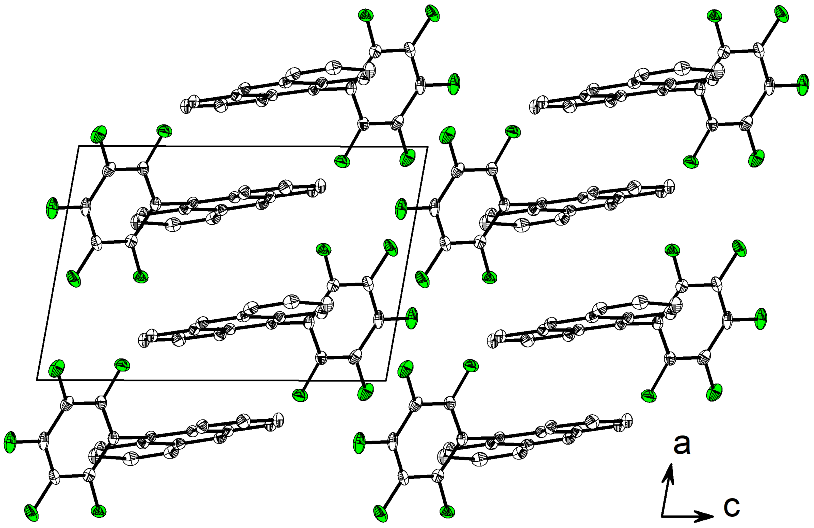


Figure 5. Crystal structure of **3o** projected along the *b* axis, at 100 K. Anthracene moieties are π-stacked along the *a* axis. All ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colours: white (carbon), green (fluorine).

Conclusion

In summary, a combination of copper (I) iodide with phenanthroline as the ligand is an efficient catalyst for Suzuki-Miyaura cross-coupling reactions of electron deficient C_6F_5Bpin with aryl iodides and bromides in up to quantitative yield. Thus, the reaction proceeds using a non-toxic and inexpensive Earth-abundant metal catalyst, replacing the traditional palladium catalysts which require large amounts of silver oxide as an additive. This reaction is also viable for cross-coupling a wide range of fluorinated phenyl boronic acid pinacol esters with aryl iodides or bromides. Notably, for aryl iodides, it can be used not only for coupling with electron deficient fluoroaryl boronates, but also for electron rich aryl boronates giving excellent yields.

A diverse range of $\pi\cdots\pi$ stacking interactions is observed in the partly perfluorinated biaryl compounds investigated herein, ranging from arene-perfluoroarene interactions (**3n**, **5d**) to arene-arene (**3o**) and perfluoroarene-perfluoroarene (**3d**) interactions. Other applications of highly fluorinated aryl boronate substrates are under investigation in our laboratory.

Experimental Section

General procedure for the coupling reactions: unless otherwise noted, inside a glovebox, fluorinated phenyl boronic acid pinacol ester (0.4 mmol), the arylhalide (Ar-X) (0.6 mmol), CuI (10 mol% if X = iodide; 30–50 mol% if X = bromide), phenanthroline (10 mol% if X = iodide; 30–50 mol% if X = bromide), CsF (0.8 mmol, 2 equiv), were added to a Schlenk flask that equipped with a stirring bar. The flask was capped and taken out of the glovebox. Solvent (DMF 3 mL if X = iodide; 1/1 mixture of DMF and toluene, 4 mL if X = bromide) were added under an argon atmosphere using a Schlenk vacuum line. The reaction was heated and stirred at 130 °C for 18 h if X = iodide or at 140 °C for 36 h if X = bromide. After cooling to room temperature, the resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over $MgSO_4$, filtred, and concentrated *in vacuo*. The residue was finally purified by flash column chromatography on silica gel (hexane). After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield the pure product. Full experimental details as well as characterization data and spectra of the products are provided in the Supporting Information.

Crystallographic details

Crystal data collection and processing parameters are given in the Supporting Information. CCDC-1917134 (**3d**), 1917135 (**3n**), 1917136 (**3o**), and 1917137 (**5d**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: homogeneous catalysis; boron; boronate; fluorine; fluoroarene

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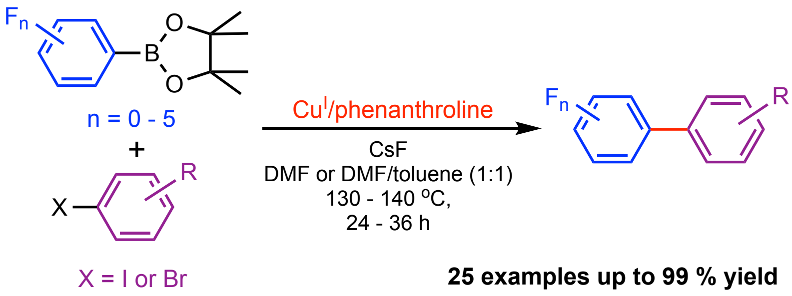
Graphics and Entry for TOC



Moving to a cheap, Earth-abundant, and less toxic metal catalyst. We introduce an alternative for Suzuki-Miyaura cross-coupling reactions of challenging substrates, namely highly fluorinated aryl-boronate esters, with aryl iodides or bromides using Cu^I/phenanthroline as the catalyst precursor to generate fluorinated biaryls in good to excellent yields. Crystals of the products show a diverse range of interesting π-stacking interactions.