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Palladium-Catalyzed C−F Activation of Polyfluoronitrobenzene Derivatives in Suzuki−Miyaura Coupling Reactions

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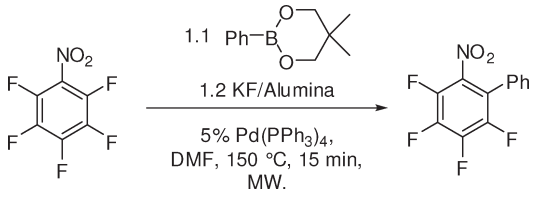

Highly fluorinated nitrobenzene derivatives are suitable substrates for palladium-catalyzed C−F bond arylation using readily available palladium catalysts under both conventional heating and microwave conditions. Arylation occurs *ortho* to the nitro group offering a synthetic route to polyfluorinated 2-arylnitrobenzene systems. The regiochemistry of the arylation reactions suggests that there is a significant directing interaction between the nitro group and the incoming nucleophilic palladium catalyst which is facilitated by the presence of several fluorine atoms attached the ring. Investigations into the regioselectivity and reactivity of several tetrafluoro- and trifluoronitrobenzene derivatives provides further evidence for the highly nucleophilic character of the oxidative addition step in contrast to the concerted mechanism of more conventional Suzuki−Miyaura coupling reactions involving aryl iodides and bromides.

Introduction

Palladium-catalyzed cross-coupling reactions have been the subject of extensive research in recent years because of the wide variety of synthetically useful carbon−carbon bond-forming reactions that may be achieved in high yield and regioselectivity under mild conditions. The application of palladium-catalyzed processes, such as Suzuki−Miyaura, Sonogashira, Heck, and Stille reactions, to natural product target synthesis, heterocyclic chemistry, and parallel syntheses in drug discovery programs are well documented and continue to increase.[1−3]

In general, the haloaromatic electrophilic species in many metal-catalyzed processes are most frequently aryl iodides or bromides because of the relative ease of oxidative addition of the catalyst into relatively weak carbon−iodine or carbon−bromine bonds. In contrast, aryl chlorides are used less often as the electrophilic coupling partners[4] due to the higher carbon−chlorine bond strength and, consequently, are much less reactive. For similar reasons, analogous reactions involving metal-catalyzed C−F activation are rarer still due to the very strong carbon−fluorine bond. However, various nickel-catalyzed functionalizations in Kumada[5−12] and Suzuki[13] couplings and hydrodefluorination[14] processes and some

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successful reactions involving cobalt,[15] platinum,[16,17] and titanium[18] species have been described and comprehensively summarized in a recent review article.[19] There remain only a few other examples of analogous palladium-catalyzed processes.[20−27]

The first examples of catalytic C−F bond activation of highly and perfluorinated heterocyclic systems were reported by Braun where vinylation of 2,3,5,6-tetrafluoropyridine by a Stille coupling reaction[21] and Suzuki−Miyaura arylation of 5-chloro-2,4,6-trifluoropyrimidine[22] were achieved by nickel catalysis. Subsequently, Radius reported the first example of catalytic C−F activation of a perfluoroaromatic system by employing an N-heterocyclic carbene stabilized nickel(0) complex as the catalyst for a Suzuki−Miyaura arylation of perfluorotoluene and perfluorobiphenyl.[26] However, catalysts based on nickel(0) systems are very air sensitive and are difficult to use in general organic synthesis. Consequently, the development of reaction conditions that allow the activation of C−F bonds in highly and perfluorinated aromatic systems by standard, commercially available palladium catalysts that may be used in typical laboratory processes are required to enable further development of C−F activation chemistry.

More recently, palladium-catalyzed C−F activation and functionalization of several monofluorinated nitrobenzene derivatives under standard Suzuki−Miyaura conditions using conventional palladium catalysts were reported by the groups of Kim and Yu[27] and Widdowson.[20] It was suggested that the nitro group, in addition to its activating electron-withdrawing properties, directs the palladium catalyst into the adjacent *ortho* C−F bond, thereby lowering the activation energy for the oxidative addition step. It was postulated that oxidative addition of the palladium catalyst into the carbon−fluorine bond occurs via a nucleophilic aromatic substitution-type process. Indeed, the nitrofluoroaromatic derivatives required the presence of a further electron-withdrawing group (CN, CHO) attached to the aromatic ring to sufficiently activate the aromatic system toward nucleophilic oxidative addition of the catalyst into the C−F bond, consistent with the suggested process.

In contrast to hydrocarbon aromatic systems which react with electrophilic species, highly and perfluorinated aromatic systems are very susceptible toward nucleophilic attack, and indeed, significant work[28] has been performed to exploit this unusual reactivity profile for the synthesis of, for example, macrocycles,[29−31] ring fused systems[32−34] and polyfunctional heterocyclic derivatives.[35−38] Consequently, we reasoned that carbon−fluorine bonds in highly fluorinated nitrobenzene derivatives such as pentafluoronitrobenzene should be sufficiently activated toward nucleophilic oxidative addition by palladium catalysts and that the presence of the nitro group on the aromatic ring would aid this process to provide efficient palladium-catalyzed C−F activation in perfluorinated systems. Indeed, it is established that pentafluoronitrobenzene reacts with nucleophiles to give products arising from substitution of fluorine principally at the 4-position, although some substitutions occur at the 2-position depending upon the nucleophile and reaction conditions.[28] The only direct arylation reactions of pentafluoronitrobenzene described in the literature involve reactions of pentafluorophenylmagnesium bromide[39] and pentafluorophenyllithium[40] with products arising from nucleophilic aromatic substitution of fluorine located *para* to the nitro group. In our hands, we have found that reaction of phenyllithium and phenylmagnesium bromide with pentafluoronitrobenzene does not give any useful product.

In this paper, we report the first examples of palladium-catalyzed Suzuki−Miyaura coupling reactions of perfluoroaromatic systems using standard conditions and readily available palladium catalysts for the synthesis of various highly fluorinated biphenyl systems.

Results and Discussion

In our initial studies, we chose to carry out reactions of pentafluoronitrobenzene in palladium-catalyzed Suzuki coupling reactions using the conditions analogous to those reported by Kim and Yu[41] and, in this case, reaction between pentafluoronitrobenzene **1** and phenylboronic acid with $Pd(PPh_3)_4$ as the catalyst furnished the desired biphenyl derivative **2** (Scheme 1). Microwave irradiation was employed to ensure that a rapid and reproducible heating profile was maintained.

GC−MS and ^{19}F NMR analysis of the crude reaction mixture identified the presence of a small quantity of terphenyl derivative **3**, due to reaction with the slight excess of phenylboronic acid present, and a trace amount of **5** (*m*/*z* 315) arising from nucleophilic attack of the phenylboronate anion on pentafluoronitrobenzene. 2,3,5,6-Tetrafluoro-4-nitrophenol **4**

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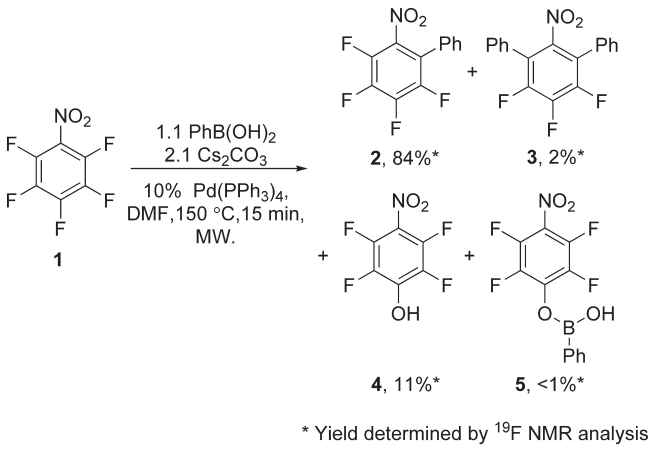
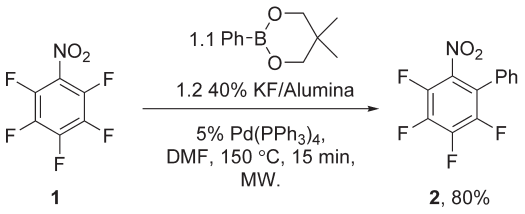
SCHEME 1. Palladium-Catalyzed Suzuki−Miyaura Reactions of Pentafluoronitrobenzene 1





was isolated and characterized by ^{19}F NMR spectroscopy and consistent with literature data,[42] and we suggest that this is formed from either the nucleophilic attack of water, which is present in small quantities due to the hygroscopic properties of the base, or the attack of cesium carbonate and its subsequent decarboxylation. In a control experiment, we found that no biaryl coupled product **2** was obtained in the absence of the palladium catalyst.

The reactions described above (Scheme 1) indicate that a base is required that would not lead to any apparent reaction of the perfluorinated aromatic substrate. Fluoride ion, most conveniently as either potassium fluoride or potassium fluoride adsorbed on the surface of alumina, seemed ideal for this purpose since reaction of fluoride with the perfluoroaromatic substrate would not affect the outcome of the coupling process. Of course, alumina-supported fluoride ion systems have been used as the base in many organic transformations and in various palladium-catalyzed coupling reactions.[43] Consequently, the coupling reaction of pentafluoronitrobenzene **1** with the neopentylglycol ester of phenylboronic acid using 40% KF/alumina as the base and $Pd(PPh_3)_4$ as the catalyst allowed complete consumption of **1**, as indicated by ^{19}F NMR analysis of the reaction mixture, and desired biphenyl **2** was successfully isolated in good yield (Scheme 1). 2,3,5,6-Tetrafluoro-4-nitrophenol **4** was not observed, and X-ray analysis of the purified product (Supporting Information) confirms the regiochemistry of the arylation process as being *ortho* to the nitro group.

In order to provide evidence that carbon−fluorine bond activation proceeds via the insertion of the palladium catalyst into the C−F bond *ortho* to the nitro group, the oxidative addition intermediate was synthesized in a separate experiment by reaction of a stoichiometric quantity of $Pd(PPh_3)_4$ with pentafluoronitrobenzene in dry, degassed DMF heated at 80 °C for 8 h using standard Schlenk-line techniques. Subsequent recrystallization of the crude reaction mixture from dry, degassed THF afforded the pure product, which was dissolved in toluene-d_8 and analyzed by ^{19}F NMR spectroscopy. The resulting spectrum shows four resonances (δ −110, −145, −150, −162 ppm) corresponding to the 2-nitrotetrafluoryl group and a fifth resonance (δ −311 ppm) corresponding to the metal-bound fluorine. Single crystals suitable for X-ray diffraction were obtained via the slow evaporation of diethyl ether from the recrystallized solid, and the structure clearly shows the presence of the C−Pd−F moiety (Figure 1).

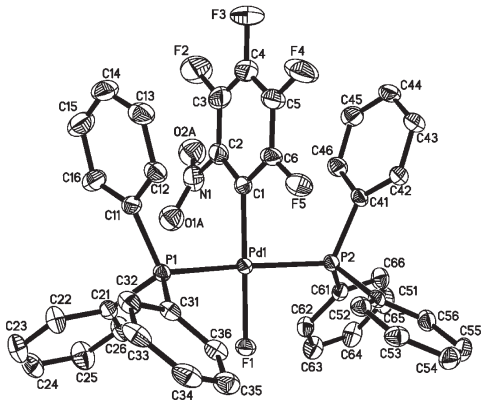
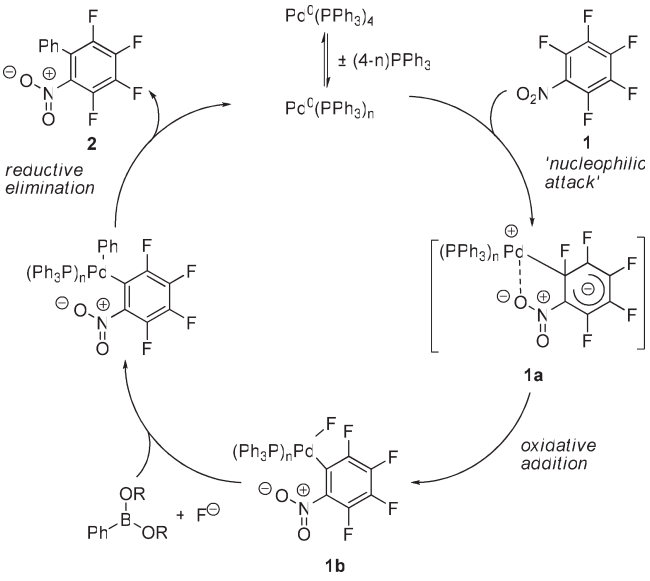


FIGURE 1. ORTEP diagram of the molecular structure of $[Pd(PPh_3)_2(F)(C_6F_4NO_2)]$ **1b** in the solid state (ellipsoids set at 40% probability level). Hydrogen atoms have been omitted for clarity. The nitro group is disordered 1:1 over two positions.

SCHEME 2. Mechanism of Pd-Catalyzed C−F Activation of Pentafluoronitrobenzene



A catalytic cycle for the C−F activation reaction can be postulated (Scheme 2) in which the nitro group directs the nucleophilic palladium center toward the adjacent C−F bond to give **1a**, which leads directly to the oxidative addition intermediate **1b**, consistent with earlier discussion.[41]

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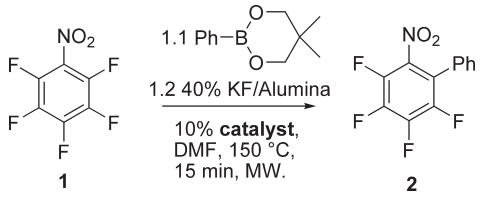
TABLE 1. Effect of Metal Catalyst



	catalyst	yield of **2**,[a] %
Pd^0	$[Pd(PPh_3)_4]$	96
	$[Pd_2(dba)_3]$, 4 $PhPCy_2$	78
	$[Pd_2(dba)_3]$, 4 P^tBu_3	0
Pd^{II}	$[Pd(OAc)_2]$	9
	$[Pd(dppf)Cl_2]$	4
Ni^{II}	$[Ni(acac)_2]$	0
	$[Ni(acac)_2]$, P^tBu_3	2

[a]NMR yield.

Transmetalation and reductive elimination proceed following established literature pathways to give the biphenyl product **2**.

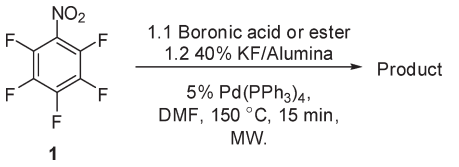
Several catalyst and ligand combinations have been screened in order to establish the most active catalytic system for the palladium-catalyzed cross-coupling procedure (Table 1). In general, palladium(0) catalysts are observed to be much more effective than palladium(II) systems, whereas nickel(II) derivatives are very inefficient. In a typical reaction procedure, all solids were charged into the reaction vessel, which was repeatedly purged under vacuum and backfilled with argon, before the solvent and liquid reagents were added and heated under microwave irradiation. Quantitative data was obtained via ^{19}F NMR analysis of the crude reaction mixtures relative to a known quantity of 1,4-difluorobenzene, which was added after the reactions had been cooled to room temperature.

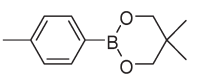
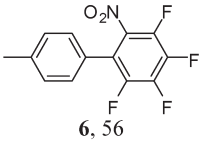
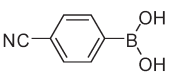
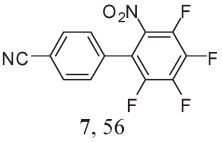
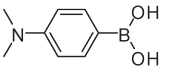
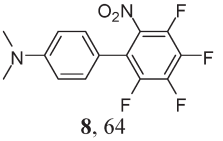
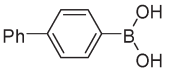
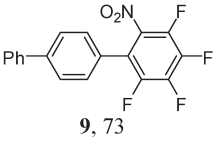
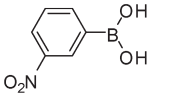
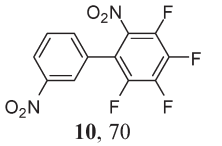
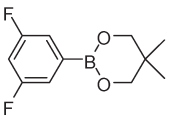
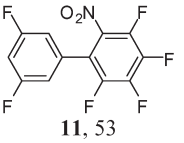
The results in Table 1 show that palladium(0) catalysts are highly effective species for initiating the coupling procedure. Subsequently, a second reaction optimization process was carried out by varying the phosphine ligand system, and these results are contained in the Supporting Information (Table S1). While PPh_2Cy is observed to offer the highest conversion of pentafluoronitrobenzene to **2**, there is no significant difference in the performance of either PPh_3 or $PPhCy_2$ as ligands, and so, because of its commercial availability and relative stability toward atmospheric decomposition, $Pd(PPh_3)_4$ remains our catalyst of choice.

In addition, several aprotic solvents of differing polarity were screened in an attempt to further improve the efficiency of the cross-coupling reaction (Table S2, Supporting Information), and we found that the more polar solvents are generally the most effective reaction media for the arylation of pentafluoronitrobenzene and that both DMF and DMSO offer the highest conversions of starting material to product. As DMF is marginally easier to remove during the purification procedure, it was selected as solvent for further coupling reactions in the first instance.

Using our preferred conditions, several boronic acids and esters bearing electron-releasing and -withdrawing groups were successfully coupled to pentafluoronitrobenzene in moderate to good yield (Table 2), demonstrating the applicability of this carbon−fluorine bond activation process to some functionalized aromatic substrates.

TABLE 2. Palladium-Catalyzed Suzuki−Miyaura Reactions of Pentafluoronitrobenzene



Boronic Acid or Ester	Product, Yield /%
	 **6**, 56
	 **7**, 56
	 **8**, 64
	 **9**, 73
	 **10**, 70
	 **11**, 53

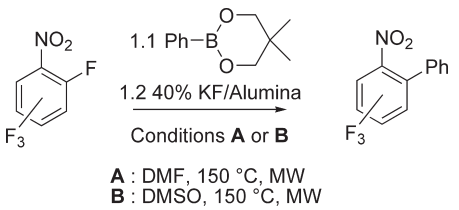
Regiospecific arylation *ortho* to the nitro group is observed in all cases, and the structures of biphenyl derivatives **2** and **9** were confirmed by X-ray crystallography. The presence of four signals in the ^{19}F NMR spectrum of each product, all of which have chemical shifts similar to those of **2** and **9** and show the appropriate $^3J_{FF}$ coupling constants (~20 Hz), confirm the structures of the remaining biphenyl derivatives **6**−**8**, **10**, and **11**.

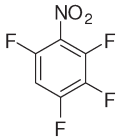
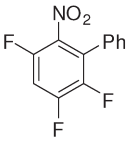
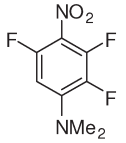
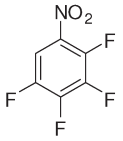
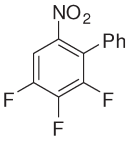
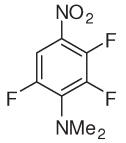
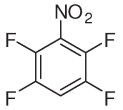
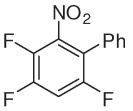
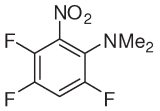
In order to probe the factors that affect the mechanism of this C−F activation process, we studied arylation reactions of the three tetrafluoronitrobenzenes (Table 3) under similar reaction conditions, although extended heating was required to achieve complete conversion of the starting materials.

Arylation *ortho* to the nitro group is observed in all cases, and the structures of **15** and **17** were confirmed by X-ray crystallography (see the Supporting Information).

The tetrafluoronitrobenzene derivatives are significantly less reactive toward Pd-catalyzed arylation than pentafluoronitrobenzene, reflecting the one less activating fluorine substituent present in these substrates. While the reaction

TABLE 3. Palladium-Catalyzed Suzuki−Miyaura Reactions of Tetrafluoronitrobenzene Derivatives



Substrate	Time / min	Conditions A or B	Product, Yield /%	Major by-product, Yield /%
				
12	30	**A**	**13**, 54	**13a**, 18
12	30	**B**	**13**, 81	**13a**, 0
				
14	120	**A**	**15**, 27	**15a**, 6
14	120	**B**	**15**, 65	**15a**, 0
				
16	120	**A**	**17**, 48	**17a**, 6
	120	**B**	**17**, 54	**17a**. 0

mixtures of all three reactions predominantly consist of the desired arylated material, significant quantities of byproduct **13a**, **15a**, and **17a** were observed. In each case, the major byproduct was isolated and characterized as the corresponding dimethylamino-substituted trifluoronitrobenzene derivative. In order to verify the identity of several of the byproduct arising from the decomposition of DMF during the arylation of tetrafluoronitrobenzene systems (Table 3), we carried out separate amination reactions of **12**, **14**, and **16** by reacting excess dimethylamine with each of the tetrafluoronitrobenzene starting materials, and these results are collated in the Supporting Information (Scheme S1).

It is evident, therefore, that DMF is not stable under the relatively forcing reaction conditions employed in these arylation procedures and that decomposition to dimethylamine becomes problematic. Indeed, repeating the reactions in the absence of boronic acid and catalyst results in a complex mixture of products, from which a small quantity of dimethylamino-substituted derivatives are readily identifiable by GC−MS and ^{19}F NMR analysis. For less activated systems such as the tetrafluoronitrobenzene substrates, because higher reaction temperatures are required to achieve significant yields of arylated product, there is a competing nucleophilic aromatic substitution amination process due to the decomposition of solvent DMF under the relatively harsh reaction conditions required.

Consequently, to avoid the problems associated with using DMF as the arylation reaction medium, we carried out the Suzuki−Miyaura reactions in DMSO (Table 3), which is stable under the reaction conditions and, from solvent screening studies (Table S2, Supporting Information), offers conversions of starting materials similar to those using DMF. Gratifyingly, complete conversion of starting materials was achieved in each case, and overall competing processes were significantly reduced, as reflected by the increased isolated yields of **13**, **15**, and **17**.

These experiments allow us to assess the relative effects of the fluorine atoms that are *ortho*, *meta*, and *para* to the site of arylation and provide insight into whether the oxidative addition of palladium to the C−F bond is a nucleophilic-type process. It is well-known, for nucleophilic aromatic substitution reactions of perfluorinated aromatic systems, that fluorine located at positions *ortho* to the site of nucleophilic attack is strongly activating, *meta* fluorine is activating, and *para* fluorine is slightly deactivating with respect to hydrogen, as determined by a series of competitive kinetics experiments.[28] Consequently, it was established that, for the majority of cases, nucleophilic aromatic substitution

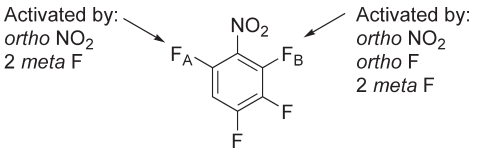


FIGURE 2. C−F bonds activated in tetrafluoronitrobenzene **12**.

reactions of perfluoroaromatic systems occur to give products arising from maximizing the number of fluorine atoms *ortho* and *meta* to the site of nucleophilic attack.

Thus, for **12** there are two sites at which arylation may occur, but the reaction is completely regioselective. If the oxidative addition of palladium into the C−F bond is assumed to be the overall rate-determining step and the palladium catalyst can be considered to have significant nucleophilic character, as described above and suggested elsewhere,[41,44] then it is possible to consider the regiochemistry of this C−F activation process in a manner similar to that for nucleophilic aromatic substitution processes in perfluoroaromatic systems (Figure 2). For tetrafluoronitrobenzene **12**, there are two sites (F_A and F_B) which are *ortho* to the nitro group and, therefore, sites of possible arylation. Both F_A and F_B are activated by two *meta* fluorine atoms, but F_B is further activated by an *ortho* fluorine. Consequently, F_B is postulated to be more activated toward nucleophilic attack by the palladium catalyst, and this is confirmed by experiment.

Of course, for tetrafluoronitrobenzenes **14** and **16** there is only one possible site that is *ortho* to the nitro group at which arylation may occur. However, as both **14** and **16** are only activated by one, rather than two, *meta* fluorine atoms they are noticeably less reactive than **12**, and this is reflected in the longer reaction times required to effect complete conversions of **14** and **16** relative to **12**.

In order to establish the relative reactivities of each of the tetrafluoronitrobenzene systems toward arylation, a competition reaction was performed in which 10 mol % of **12**, **14**, and **16** and 5 mol % of $Pd(PPh_3)_4$ were dissolved in degassed DMSO (2 mL) and heated to 100 °C, under microwave irradiation, for 30 min. Quantitative reactivity data was obtained by ^{19}F NMR signal intensities, with reference to a known quantity of 1,4-difluorobenzene (Table 4).

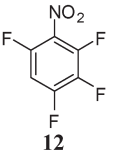
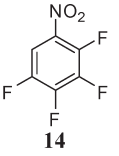
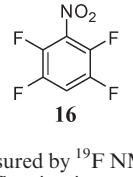
There appears to be a reasonable correlation between the relative rates of palladium-catalyzed C−F activated arylation and those concerning analogous methoxydefluorination processes of **12**, **14**, and **16**,[45] offering further evidence for the nucleophilic character and rate-determining nature of the oxidative addition step.

Subsequently, palladium-catalyzed coupling reactions of several trifluoronitrobenzene derivatives were investigated (Table 5). These processes require a higher catalyst loading (10 mol %) and extended heating in order to effect complete conversion of starting material to products, and DMSO is preferred as the solvent for these transformations due to the aforementioned instability of DMF.

Ortho arylation is observed in each case, but it was not possible to gather reliable kinetic data on the relative reactivities of **18**, **20** ,and **22** because a number of side products are formed in the coupling process due to the harsh reaction conditions, and consequentially, ^{19}F NMR analysis of the product mixture is not particularly reliable in this case. However, the low conversion and poor isolated yield of **23** indicates that **22** is the least activated of the trifluoronitrobenzene derivatives screened, and this can be attributed to the fact that the site of arylation is only significantly activated by a single *meta* fluorine atom.

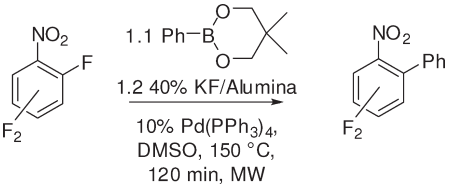
(44) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578–579.

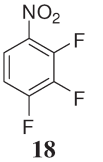
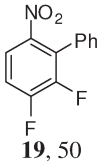
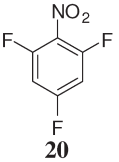
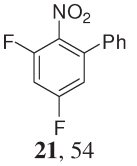
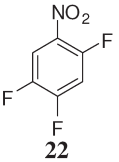
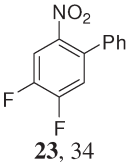
TABLE 4. Competition Experiment

Substrate	Relative Reactivity[a]	Calculated Reactivity[b]
 **12**	6.8	6.8
 **14**	4.6	4.3
 **16**	1.0	0.3

[a]As measured by ^{19}F NMR analysis. [b]Calibrated literature values for methoxydefluorination processes.[45]

TABLE 5. Palladium-Catalyzed Suzuki−Miyaura Reactions of Trifluoronitrobenzene Derivatives



Substrate	Product, Yield /%
 **18**	 **19**, 50
 **20**	 **21**, 54
 **22**	 **23**, 34

(45) Bolton, R.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1978**, 141–144.

Conclusions

Highly fluorinated nitrobenzene derivatives undergo regioselective Suzuki−Miyaura cross-coupling reactions via the insertion of palladium(0) catalysts into a C−F bond located *ortho* to the nitro group. The arylation of pentafluoronitrobenzene offers a synthetic route to previously unreported 2,3,4,5-tetrafluoro-6-nitrobiphenyl derivatives, and these processes represent the first examples of palladium-catalyzed Suzuki−Miyaura cross-coupling reactions of a perfluorinated aromatic system. Tetrafluoronitrobenzene and trifluoronitrobenzene systems are less reactive than pentafluoronitrobenzene, as expected due to the corresponding reduction in electrophilicity of the aromatic ring. A reactivity study of the arylation of the three tetrafluoronitrobenzenes parallels that of typical nucleophilic aromatic substitution processes and provides evidence for the nucleophilic character and rate-limiting nature of the oxidative addition step.

Experimental Section

General Method for Suzuki−Miyaura Reactions of Highly Fluorinated Nitrobenzene Substrates. The boronic acid or boronic ester (1.1 equiv), 40% KF/alumina (1.2 equiv), and $Pd(PPh_3)_4$ (0.05 equiv) were charged to a microwave vial (0.5−2.0 mL) and sealed. The microwave vial was evacuated under high vacuum and backfilled with argon three times to create an inert atmosphere. Dry, degassed DMF or DMSO (2 mL) and the relevant polyfluoronitrobenzene (1.0 equiv) were added to the vial and heated (150 °C, 20−120 min) with stirring. The vial and its contents were cooled and filtered through silica gel and volatile material was evaporated. Purification by column chromatography on silica gel using hexanes and DCM (4:1) as the eluent and recrystallization from hexanes afforded the pure product.

2,3,4,5-Tetrafluoro-6-nitrobiphenyl. Reaction of pentafluoronitrobenzene (0.248 g, 1.16 mmol) with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (0.263 g, 1.39 mmol) afforded 2,3,4,5-tetrafluoro-6-nitrobiphenyl as an off-white solid (0.251 g, 80%): mp 70−71 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 (2H, m), 7.46−7.52 (3H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.2 (ddd, $^2J_{CF}$ = 18.9 Hz, $^3J_{CF}$ = 4.3 Hz, $^{3/4}J_{CF}$ = 1.1 Hz), 127.0 (s), 129.3 (s), 129.5 (s), 130.5 (s), 135.8 (m), 141.2 (dddd, $^1J_{CF}$ = 259 Hz, $^2J_{CF}$ = 14.7 Hz, $^2J_{CF}$ = 13.5 Hz, $^3J_{CF}$ = 3.4 Hz), 141.1 (dddd, $^1J_{CF}$ = 260 Hz, $^2J_{CF}$ = 11.6 Hz, $^3J_{CF}$ = 4.8 Hz, $^4J_{CF}$ = 2.7 Hz), 142.8 (dddd, $^1J_{CF}$ = 261 Hz, $^2J_{CF}$ = 17.5 Hz, $^2J_{CF}$ = 12.3 Hz, $^3J_{CF}$ = 3.2 Hz), 143.9 (dddd, $^1J_{CF}$ = 253 Hz, $^2J_{CF}$ = 11.0 Hz, $^3J_{CF}$ = 3.8 Hz, $^4J_{CF}$ = 1.8 Hz); ^{19}F NMR (658 MHz, $CDCl_3$, $CFCl_3$) δ −138.17 (1F, ddd, $^3J_{FF}$ = 22.4 Hz, $^4J_{FF}$ = 3.5 Hz, $^5J_{FF}$ = 10.7 Hz), −147.82 (1F, ddd, $^3J_{FF}$ = 21.2 Hz, $^4J_{FF}$ = 5.1 Hz, $^5J_{FF}$ = 10.7 Hz), −149.95 (1F, ddd, $^3J_{FF}$ = 22.4 Hz, $^3J_{FF}$ = 20.7 Hz, $^4J_{FF}$ = 5.1 Hz), −152.87 (1F, ddd, $^3J_{FF}$ = 21.2 Hz, $^3J_{FF}$ = 20.7 Hz, $^4J_{FF}$ = 3.5 Hz); FT-IR (cm^{-1}) 1365, 1546; *m*/*z* (EI$^+$) 272 (M$^+$, 1), 271 (M$^+$, 8), 243 (65), 224 (73), 187 (100), 175 (30), 51 (14), 30 (13). Anal. Calcd for $C_{12}H_5F_4NO_2$: C, 53.15; H, 1.86; N, 5.17. Found: C, 53.20; H, 1.89; N, 5.17.

2,3,4-Trifluoro-6-nitrobiphenyl. Reaction of 2,3,4,5-tetrafluoronitrobenzene (0.243 g, 1.25 mmol) with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (0.283 g, 1.41 mmol) afforded 2,3,4-trifluoro-6-nitrobiphenyl as a yellow solid (0.085 g, 27%): mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, m), 7.48 (3H, m), 7.68 (1H, ddd, $^3J_{HF}$ = 9.0 Hz, $^4J_{HF}$ = 6.6 Hz, $^5J_{HF}$ = 2.3 Hz); ^{13}C NMR (176 MHz, $CDCl_3$) δ 109.5 (dd, $^2J_{CF}$ = 22.0 Hz, $^3J_{CF}$ = 3.9 Hz), 123.9 (dd, $^2J_{CF}$ = 17.7 Hz, $^3J_{CF}$ = 4.3 Hz), 128.8 (s), 129.1 (s), 129.1 (s), 129.6 (s), 143.2 (ddd, $^1J_{CF}$ = 262 Hz, $^2J_{CF}$ = 16.5 Hz, $^2J_{CF}$ = 14.9 Hz), 144.1 (m), 149.2 (ddd, $^1J_{CF}$ = 253 Hz, $^2J_{CF}$ = 10.8 Hz, $^3J_{CF}$ = 3.7 Hz), 149.7 (ddd, $^1J_{CF}$ = 255 Hz, $^2J_{CF}$ = 10.9 Hz, $^3J_{CF}$ = 4.2 Hz); ^{19}F NMR (658 MHz, $CDCl_3$, $CFCl_3$) δ −130.06 (1F, dd, $^3J_{FF}$ = 21.4 Hz, $^4J_{FF}$ = 7.7 Hz), −131.08 (1F, ddd, $^3J_{FF}$ = 20.9 Hz, $^3J_{FH}$ = 9.0 Hz, $^4J_{FF}$ = 7.7 Hz), −150.14 (1F, ddd, $^3J_{FF}$ = 21.5 Hz, $^3J_{FF}$ = 21.3 Hz, $^4J_{FH}$ = 6.6 Hz); FT-IR (cm^{-1}) 1359, 1530; *m*/*z* (EI$^+$) 253 (M$^+$, 3), 225 (22), 169 (44), 51 (31), 30 (100). Anal. Calcd for $C_{12}H_6F_3NO_2$: C, 56.93; H, 2.39; N, 5.53. Found: C, 56.67; H, 2.43; N, 5.58.

3,5-Difluoro-6-nitrobiphenyl. Reaction of 2,4,6-trifluoronitrobenzene (0.262 g, 1.50 mmol) with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (0.323 g, 1.58 mmol) afforded 3,5-difluoro-6-nitrobiphenyl as a yellow solid (0.188 g, 54%): mp 52−53 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.00 (2H, m), 7.35 (3H, m), 7.45 (2H, m); ^{13}C NMR (176 MHz, $CDCl_3$) δ 105.5 (dd, $^2J_{CF}$ = 23.1 Hz, $^2J_{CF}$ = 26.8 Hz), 113.9 (dd, $^2J_{CF}$ = 23.4 Hz, $^4J_{CF}$ = 3.6 Hz), 127.92 (s), 129.37 (s), 129.8 (s), 134.7 (s), 136.0 (m), 139.0 (d, $^{2/3}J_{CF}$ = 10.1 Hz), 154.9 (dd, $^1J_{CF}$ = 260 Hz, $^3J_{CF}$ = 13.5 Hz), 162.8 (dd, $^1J_{CF}$ = 256 Hz, $^3J_{CF}$ = 12.1 Hz); ^{19}F NMR (658 MHz, $CDCl_3$, $CFCl_3$) δ −103.75 (1F, m), −118.96 (1F, m); FT-IR (cm^{-1}) 1350, 1530; *m*/*z* (EI$^+$) 235 (M$^+$, 18), 207 (76), 188 (99), 151 (100), 51 (16). Anal. Calcd for $C_{12}H_7F_2NO_2$: C, 61.28; H, 3.00; N, 5.96. Found: C, 61.27; H, 3.01; N, 5.90.

Acknowledgment. We thank EPSRC and the SONY Corp. for funding (studentships to A.J.T. and M.R.C.).

Supporting Information Available: Tables S1 and S2, Scheme S1, representative NMR spectra of all new compounds, and X-ray files for **1b**, **2**, **9**, **13a**, **15**, and **17** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.