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ARTICLE

Palladium-catalyzed regioselective C–H bond arylations at the C3 position of *ortho*-substituted fluorobenzenes

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The influence of an *ortho*-substituent on fluorobenzene derivatives for palladium-catalyzed C–H bond arylation has been explored. In the presence of 2-bromo, 2-chloro and 2-methoxy substituents, the reaction proceeds nicely using a diphosphine-palladium catalyst and potassium acetate/dimethylacetamide (PivOK/DMA) as catalytic system. In all cases, a regioselective arylation at the the other *ortho*-position to the fluorine atom (C3) was observed. A variety of electron-withdrawing substituents on the aryl bromide coupling partner, such as formyl, nitro, nitrile, and also heteroaryl bromides was tolerated. Moreover, tri(hetero)aryl derivatives containing a fluorobenzene as central unit have been prepared from 2-bromofluorobenzene through palladium-catalyzed-successive C–H bond (hetero)arylations.

Introduction

Fluorinated biphenyl derivatives are an important class of molecules because this motif is embedded in various medicinal drugs. As examples, Flurbiprofen, which contains only one fluorine atom and Diflunisal which contains two fluorine atoms, are non-steroidal anti-inflammatory drugs (Figure 1). Tarenflurbil is investigated for its potential as a treatment for Alzheimer's disease (Figure 1). Due to the ubiquitousness of this motif, the discovery of environmentally friendly efficient synthetic routes allowing their preparation by utilizing fluorobenzene units as starting materials rather than late stage fluorination,[1] remains an important research topic.

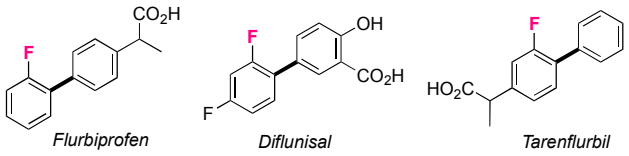

Figure 1. Pharmaceuticals containing a 2-fluorobiphenyl unit.

Palladium cross-coupling reactions (e.g., Suzuki, Negishi, Hiyama, Kumada reactions) remain a very efficient and reliable approach for the synthesis of fluorinated biphenyl motifs. However, these reactions are considered as not eco-friendly due to the generation of stoichiometric amount of metal salts as waste. Moreover, the use of an organometallic reagent as coupling partner requires its prior preparation. By contrast, transition metal-catalyzed direct C–H bond arylation allows a straightforward access to (hetero)biphenyls with a lower environmental footprint.[2] In 2006, Fagnou and co-workers reported the first example of palladium-catalyzed direct arylation of (poly)fluorobenzene derivatives using aryl halides,[3] *via* a concerted metalation–deprotonation (CMD) mechanism.[4] Since these results, number of accomplishments have been reported toward direct arylation of electron-deficient arenes,[5] including the use of alternative coupling partners to aryl halides (e.g., tosylates,[6] diaryliodonium salts,[7] boronic acids,[8] $ArSO_2Na$,[9] benzoic acids[10] or simple arenes under oxidative conditions[11]), or the use of other transition metals.[12] If poly(fluoro)benzenes [i.e., penta-,[3, 6-7, 9-13] tetra-,[6a, 6b, 14] tri-[15] or di-fluorobenzenes[16]] generally displayed good reactivities in C–H bond arylation, on the contrary fluorobenzene is almost unreactive. For example, Fagnou reported that the C2-arylation of fluorobenzene in the presence of 1-bromo-4-methylbenzene proceeded in only 8% yield (Figure 2A).[3a] To overcome the low reactivities of mono(fluoro)benzenes, one of the approaches was to introduce a functional group on the fluorobenzene ring. In this context, Daugulis and co-workers reported that the introduction of a carboxylic acid at the *meta*-position to the fluorine atom allowed the formation of C2,C5 diarylation products *via* palladium-catalyzed C–H bond activation (Figure 2 B).[17] In 2011, Larrosa and co-workers employed a similar strategy for the mono-arylation at the α position to the fluorine atom, albeit decarboxylation occurred simultaneously to afford the corresponding 2-fluorobiphenyls in high yields (Figure 2 C).[18] Our group also contributed in this field by showing that the introduction of a functional group at *meta*- or *para*-positions to the fluorine atom increased dramatically its reactivity (Figure 2 D).[19] We shown that the

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introduction of electron-withdrawing substituents (e.g., Cl, Br, CN, NO_2, CO_2R) and also an electron-donating group (e.g., OMe) enhances fluorobenzene reactivity in palladium-catalyzed direct arylation in favor of one of the *ortho*-positions of fluorine atom.[19] On the other hand, no *ortho*-substituted fluorobenzene have been employed in palladium-catalyzed C–H bond arylation (except 1,2-difluorobenzene). In the line with our previous works,[19] we decided to investigate the effect of an *ortho*-substituent on fluorobenzenes in palladium-catalyzed direct arylation using aryl bromides as coupling partners (Figure 2 E).

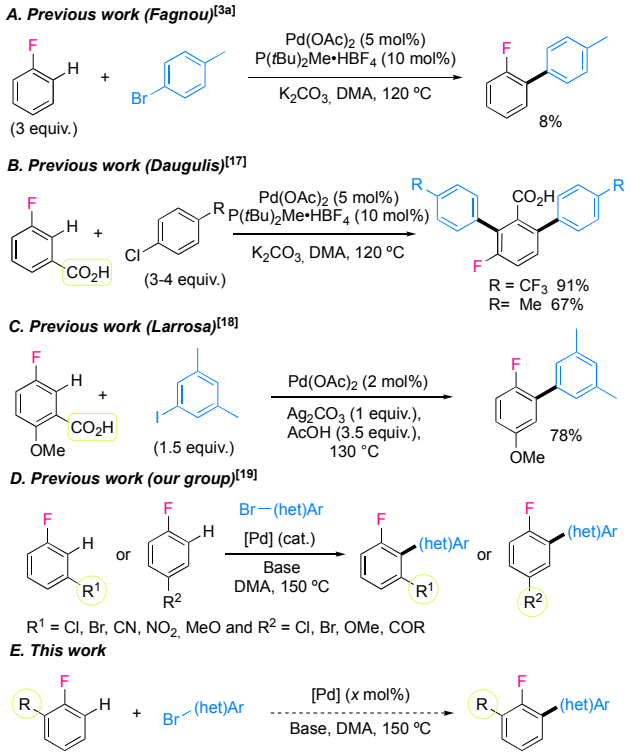
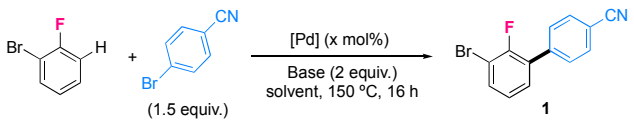


Figure 2. Previous palladium-catalyzed intermolecular direct arylations of fluorobenzenes.

Results

In our previous work, we demonstrated that a bromo substituent at *para*- or *meta*-position of the fluorine atom on benzene ring exhibits a positive impact on their reactivity in palladium-catalyzed C–H bond arylation of mono-fluorobenzenes. Therefore, we decided to investigate the reactivity of 1-bromo-2-fluorobenzene in palladium catalyzed C–H bond arylation. We selected 4-bromobenzonitrile as coupling partner –as its oxidative addition to palladium is faster than that of 1-bromo-2-fluorobenzene as it is more electron-deficient–[20] and investigated different parameters on the reaction outcome (Table 1). In the presence of 1 mol% $Pd(OAc)_2$ associated to 2 equivalents of KOAc in DMA at 150 ºC, we were pleased to find that the arylation of 1-bromo-2-fluorobenzene occurred regioselectively at *ortho*-position of the fluorine atom, albeit in poor yield, but without the cleavage of the C–Br bond of the fluorobenzene unit (Table 1, entry 1). $PdCl_2$ used as catalyst allowed the formation of **1** in higher 29% yield (Table 1, entry 2). The use of 1 mol% a diphosphine palladium catalyst, namely $PdCl(C_3H_5)$dppb gave the fluorobiphenyl **1** in 65%; moreover employing 2 mol% of this catalyst, a better yield of 73% was obtained (Table 1, entries 3 and 4). However, a full conversion of 1-bromo-2-fluorobenzene was observed due to the formation of 2,2'-difluoro-1,1'-biphenyl and fluorobenzene as side-products. The use of other bases such as PivOK, K_2CO_3 or Cs_2CO_3 did not allowed the formation of **1** in higher yields due to the formation of other cross-coupling products (Table 1, entries 5-7). No reaction occurred in DMSO, xylene, diethylcarbonate (DEC), or pentan-1-ol (Table 1, entries 8-11). When the reaction is performed in absence of 4-bromobenzonitrile, no homocoupling reaction occurred (i.e., 3-bromo-2,2'-difluoro-1,1'-biphenyl was not detected) (Table 1, entry 12). This result suggested that under these conditions only electron-deficient aryl bromides can be used as coupling partners to allow the C–H bond activation of the fluorobenzene unit.

Table 1. Reactivity of 1-bromo-2-fluorobenzene in palladium-catalyzed direct arylation with 4-bromobenzonitrile



Entry	[Pd] (x mol%)	Base	Solvent	Conv. (%) [a]	1 (%)
1	$Pd(OAc)_2$ (1)	KOAc	DMA	32	12
2	$PdCl_2$ (1)	KOAc	DMA	54	29
3	$PdCl(C_3H_5)$(dppb) (1)	KOAc	DMA	85	65
4	$PdCl(C_3H_5)$(dppb) (2)	KOAc	DMA	100	73
5	$PdCl(C_3H_5)$(dppb) (2)	PivOK	DMA	95	68
6	$PdCl(C_3H_5)$(dppb) (2)	K_2CO_3	DMA	100	12
7	$PdCl(C_3H_5)$(dppb) (2)	Cs_2CO_3	DMA	100	0
8	$PdCl(C_3H_5)$(dppb) (2)	KOAc	DMSO	100	0
9	$PdCl(C_3H_5)$(dppb) (2)	KOAc	xylene	0	0
10	$PdCl(C_3H_5)$(dppb) (2)	KOAc	DEC	0	0
11	$PdCl(C_3H_5)$(dppb) (2)	KOAc	pentan-1-ol	0	0
12[b]	$PdCl(C_3H_5)$(dppb) (2)	KOAc	DMA	<5	0

[a] Determined by GC-MS analysis using *n*-dodecane as internal standard (Conv. = conversion based on 1-bromo-2-fluorobenzene, DEC = diethyl carbonate). [b] Reaction performed without 4-bromobenzonitrile.

Then, we studied the scope of the aryl bromides in Pd-catalyzed regioselective arylation of 1-bromo-2-fluorobenzene using 2 mol% of $PdCl(C_3H_5)$dppb catalyst associated to 2 equivalents of KOAc as base in DMA at 150 ºC over 16 h (Scheme 1). Aryl bromides substituted at *para*-position by an electron-withdrawing group, such as nitro, benzoyl, or formyl allowed the formation of desired C3-arylated 1-bromo-2-fluorobenzenes **2-4** in 57-69% yields. It is important to note that in all case the C–Br bonds on the fluorobenzene ring remained untouched. By contrast, no desired 2-fluorobiphenyls were obtained when electron-donating aryl bromides such as 4-bromoanisole were used. A *meta*-

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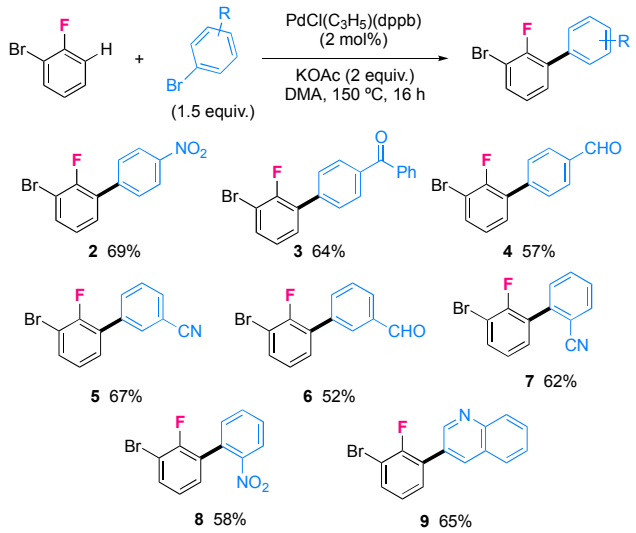
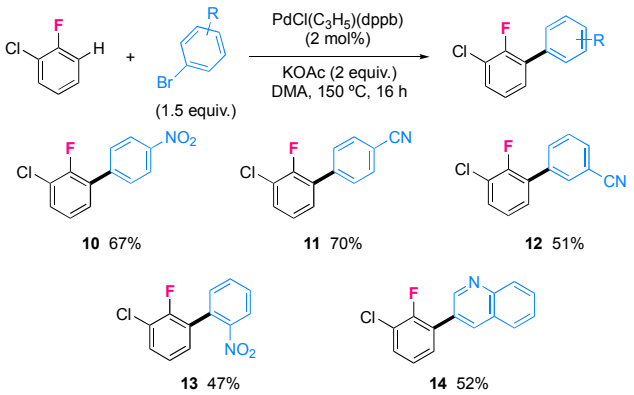
substituent on aryl bromide has no influence on the yield, as the coupling products **5** and **6** were isolated in 67% and 52% yields, respectively from 3-bromobenzonitrile and 3-bromobenzaldehyde. The reaction appears to be not very sensitive to the steric hindrance, as the reactions between 2-bromobenzonitrile or 2-bromonitrobenzene and 1-bromo-2-fluorobenzene afforded the biphenyls **7** and **8** in 62% and 58% yields, respectively. Heteroaryl bromides could also be used as coupling partners. For example, 3-bromoquinoline was regioselectively coupled with 1-bromo-2-fluorobenzene to give the desired compound **9** in 65% yield.



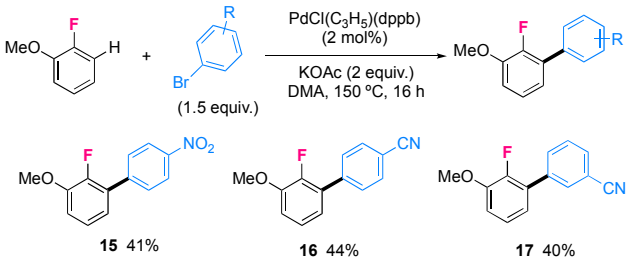
Scheme 1. Scope of (hetero)aryl bromides in Pd-catalyzed *ortho*-C–H bond arylation of 1-bromo-2-fluorobenzene.

As a bromo substituent at *ortho* position of fluorine was found to dramatically enhance the reactivity of fluorobenzene in palladium-catalyzed C–H bond arylation, we turned our attention to the reactivity of 1-chloro-2-fluorobenzene (Scheme 2). A chloro-substituent seems to display a similar influence on the reactivity. From electron-deficient aryl bromides such as 4-bromonitrobenzene and 4-bromobenzonitrile, 1-chloro-2-fluorobenzene was regioselectively arylated at the C3 position to afford the fluorinated biphenyls **10** and **11** in 67% and 70% yields, respectively. Again, *meta*- or *ortho*-substituents on the aryl bromides were tolerated, as from 3-bromobenzonitrile and 2-bromonitrobenzene the desired products **12** and **13** were isolated in 51% and 47% yields, respectively. The reaction between 3-bromoquinoline and 1-chloro-2-fluorobenzene also allowed the synthesis of target compound 3-(3-chloro-2-fluorophenyl)quinoline (**14**) in 52% yield.



Scheme 2. Scope of (hetero)aryl bromides in Pd-Catalyzed *ortho*-C–H bond arylation of 1-chloro-2-fluorobenzene.

Next, we investigated the reactivity of 2-fluoroanisole, in which methoxy group has a low electron-withdrawing character (σ_{meta}* = 0.12) at the *meta*-position (Scheme 3). Using the same reaction conditions, the arylation of 2-fluoroanisole with 4-bromonitrobenzene or 4-bromobenzonitrile allowed the formation of C3-arylated fluorobenzene derivatives **15** and **16** in 41% and 44% yields, respectively. The reaction between 3-bromobenzonitrile and 2-fluoroanisole also afforded the desired fluorinated biphenyl **17** in 40% yield.



Scheme 3. Scope of aryl bromides in Pd-catalyzed *ortho*-C–H bond arylation of 2-fluoroanisole.

We also investigated the reactivity of other *ortho*-substituted fluorobenzene derivatives, which proved to be unreactive under our optimized reaction conditions, namely, PdCl(C_3H_5)dppb (2 mol%) in the presence of KOAc (2 equiv.) as base in DMA at 150 ºC (Scheme 4). Indeed, fluorobenzene bearing a strong electron-withdrawing group such as NO_2 (σ_{meta}* = 0.71) or CN (σ_{meta}* = 0.56) were completely unreactive. Under our optimized reaction conditions, there was also no C–H bond activation using 2-fluoroacetophenone and 2-fluorobenzaldehyde in the presence of 4-bromobenzaldehyde as aryl source, albeit their electronic properties are similar to a chloro or bromo substituents [i.e., Hammett constants: formyl (σ_{meta}* = 0.35), acetyl (σ_{meta}* = 0.38), bromo (σ_{meta}* = 0.39) and chloro (σ_{meta}* = 0.37)].[19a] On the other hand, 2-fluoroaniline and 2-fluorotoluene which bear electron-donating groups [i.e., NH_2 (σ_{meta}* = -0.16) or Me (σ_{meta}* = -0.07)] were also unreactive under these reaction conditions. Overall, the reactivity for C–H bond cleavage/functionalization at *ortho*-position of fluorine atom

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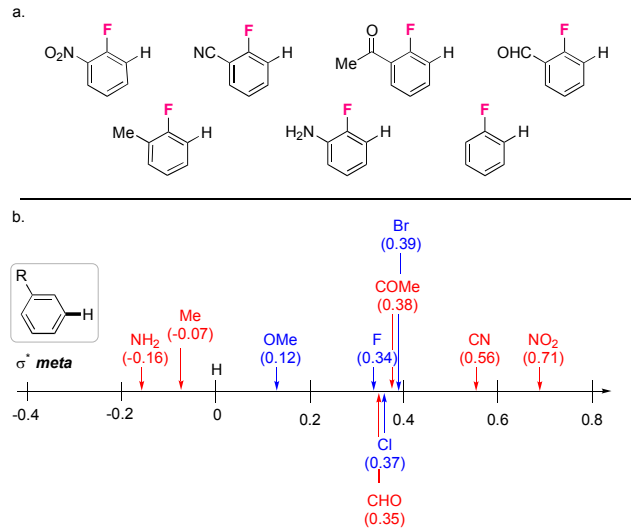
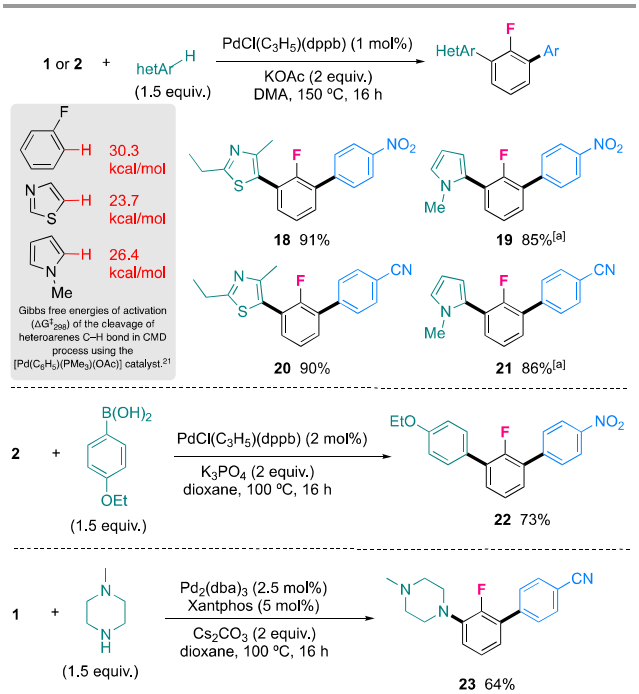
on benzene ring seems to be correlated only to some extent with the electronic factors and C–H bond acidity. Gorelsky rationalized the regioselectivity and reactivity for palladium-catalysed direct arylation of arenes by a combination of two factors: *(i)* arene distortion energy due to substituents and *(ii)* interaction energies with the metal catalyst.[21] This combination of factors might explain why the less acidic C–H bond on 2-fluoroanisole is more reactive than the C–H bond of 2-fluoronitrobenzene or 2-fluoroacetophenone.



Scheme 4. a) Unreactive *ortho*-substituted fluorobenzenes in Pd-catalyzed C–H bond arylation. b) Calculated Hammet constants for *meta*-substituents on benzenes.

We further demonstrated the potential of chemoselective C–H bond arylation of 2-bromo-1-fluorobenzene with the introduction of a second aryl group on the fluorobenzene unit. This method allows the two-step synthesis of tri(hetero)aryl derivatives containing a central fluorobenzene unit (Scheme 5, top). In order to perform the second arylation, only heteroarenes containing C–H bonds with lower Gibbs free energy of activation than fluorobenzene should be employed.[21] The direct arylation of 2-ethyl-4-methylthiazole at C5 position using 3-bromo-2-fluoro-4'-nitro-1,1'-biphenyl (**2**) as aryl source was performed using the same catalytic system than previously [i.e., $PdCl(C_3H_5)$dppb (1 mol%) in the presence of KOAc (2 equiv.) as base in DMA at 150 ºC], to afford the tri(hetero)aryl product **18** in 91% yield. The reaction can also be performed using *N*-methylpyrrole –albeit 4 equivalents were required to prevent the pyrrole C2,C5 diarylation– to afford the desired product **19** in 85% yield. Other triads **20** and **21** were obtained in 90% ad 86% yields, respectively from similar direct arylations of thiazole and pyrrole using 3'-bromo-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (**1**) as coupling partner. We also demonstrated the synthetic utility of 3'-Bromo-2'-fluoro-[1,1'-biphenyl] using a Suzuki cross-coupling reaction (Scheme 5, middle). From a mixture of 3-bromo-2-fluoro-4'-nitro-1,1'-biphenyl (**2**) and (4-ethoxyphenyl)boronic acid (1.5 equivalents) in the presence of 2 mol% of a diphosphine-palladium catalyst and 2 equivalents of K_3PO_4 in dioxane at 100 °C over 16 h, the *meta*-terphenyl **22** was obtained in 73% yield. We also performed a Buchwald-Hartwig cross coupling reaction (Scheme 5, bottom). Indeed, 3'-bromo-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (**1**) was coupled with 1-methylpiperazine to allow the formation of the amination product **23** in 64% yield using $Pd_2(dba)_3$/Xhantphos as catalyst and Cs_2CO_3 as base.



Scheme 5. Pd-catalyzed functionalizations of 3-bromo-2-fluoro-1,1'-biphenyl derivatives **1** and **2** with heteroarenes. [a] 4 Equivalents of 1-methylpyrrole were used.

Conclusions

In summary, we reported herein on the reactivity of *ortho*-substituted fluorobenzene derivatives in Pd-catalyzed C–H bond arylation using (hetero)aryl bromides as aryl sources. We showed that bromo, chloro or methoxy substituents at fluorobenzenyl *ortho*-position can be used to increase the reactivity of the C–H bond at the C3 position. On the contrary, other substituents such as nitro, nitrile, formyl, acetyl and amino on the fluorobenzene inhibited the reaction. This synthetic pathway is attractive and eco-friendly, as the major by-products are a base associated to HBr, and as it avoids the preliminary preparation of an organometallic reducing the number of steps for the preparation of such compounds. Interestingly, when 2-bromofluorobenzene was used with electron-deficient aryl bromides, the reaction was completely chemoselective allowing the synthesis 2,6-difunctinalized fluororobenzenes through Pd-catalyzed orthogonal functionalization, providing a new rapid and efficient method to discover drug candidates.

Experimental Section

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General: All reactions were carried out under argon atmosphere with standard Schlenk-tube techniques. HPLC grade DMA was stored under argon and used without further purification. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz or 300 MHz) spectrometer. Chemical shifts (d) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H ; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Preparation of the PdCl(C_3H_5)(dppb) catalyst:[22] An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The powder was used without purification. (^{31}P NMR 381 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for synthesis of fluorinated biphenyls: To a 25 mL oven dried Schlenk tube, *ortho*-substituted fluorobenzene (1 mmol), (hetero)arylbromide (1.5 mmol), KOAc (196 mg, 2 mmol), DMA (3-4 mL) and PdCl(C_3H_5)(dppb) (12.2 mg, 0.02 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 ºC (oil bath temperature) for 18-48 h (see tables and schemes). After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the desired arylated product.

3'-Bromo-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (1): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 4-bromobenzonitrile (270 mg, 1.5 mmol) affords **1** in 73 % (202 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77 (d, *J* = 8.3 Hz, 2H), 7.69 – 7.59 (m, 3H), 7.38 (ddd, *J* = 1.6, 5.8, 7.9 Hz, 1H), 7.16 (td, *J* = 1.0, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.9 (d, *J* = 249.9 Hz), 139.6, 133.9, 132.3, 129.7 (d, *J* = 3.1 Hz), 129.6 (d, *J* = 2.5 Hz), 128.7 (d, *J* = 14.4 Hz), 125.5 (d, *J* = 4.8 Hz), 118.6, 112.0, 110.4 (d, *J* = 21.9 Hz). Elemental analysis: calcd (%) for $C_{13}H_7BrFN$ (276.11): C 56.55, H 2.56; found: C 56.89, H 2.28.

3-Bromo-2-fluoro-4'-nitro-1,1'-biphenyl (2): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 4-bromonitrobenzene (303 mg, 1.5 mmol) affords **2** in 69 % (204 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.66 (ddd, *J* = 1.7, 6.4, 8.0 Hz, 1H), 7.42 (ddd, *J* = 1.7, 6.9, 7.8 Hz, 1H), 7.18 (td, *J* = 1.0, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.0 (d, *J* = 250.1 Hz), 147.6, 141.5, 134.1, 129.9 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 2.4 Hz), 128.4 (d, *J* = 14.4 Hz), 125.6 (d, *J* = 4.8 Hz), 123.8, 110.5 (d, *J* = 21.9 Hz). Elemental analysis: calcd (%) for $C_{12}H_7BrFNO_2$ (296.10): C 48.68, H 2.38; found: C 48.52, H 2.10.

(3'-Bromo-2'-fluoro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (3): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 4-bromobenzophenone (392 mg, 1.5 mmol) affords **3** in 64 % (227 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92 (d, *J* = 8.3 Hz, 2H), 7.90 – 7.85 (m, 2H), 7.70 – 7.66 (m, 2H), 7.65 – 7.59 (m, 2H), 7.57 – 7.50 (m, 2H), 7.44 (ddd, *J* = 1.7, 6.9, 7.7 Hz, 1H), 7.16 (td, *J* = 1.0, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.2, 156.1 (d, *J* = 249.5 Hz), 139.1, 137.5, 137.1, 133.3, 132.6, 130.3, 130.0, 129.8 (d, *J* = 2.7 Hz), 129.4, 128.9 (d, *J* = 3.1 Hz), 128.4, 125.4 (d, *J* = 4.8 Hz), 110.3 (d, *J* = 22.1 Hz). Elemental analysis: calcd (%) for $C_{19}H_{12}BrFO$ (355.21): C 64.25, H 3.41; found: C 48.52, H 2.10.

3'-Bromo-2'-fluoro-[1,1'-biphenyl]-4-carbaldehyde (4): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 4-bromobenzaldehyde (278 mg, 1.5 mmol) affords **4** in 57 % (160 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.10 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.63 (ddd, *J* = 1.7, 6.3, 8.0 Hz, 1H), 7.42 (ddd, *J* = 1.7, 6.8, 7.7 Hz, 1H), 7.17 (td, *J* = 1.0, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.8, 155.9 (d, *J* = 249.5 Hz), 141.1, 135.8, 133.6, 129.9, 129.8 (d, *J* = 2.6 Hz), 129.7 (d, *J* = 3.2 Hz), 127.6 (d, *J* = 6.6 Hz), 125.4 (d, *J* = 4.7 Hz), 110.3 (d, *J* = 22.1 Hz). Elemental analysis: calcd (%) for $C_{13}H_8BrFO$ (279.11): C 55.94, H 2.89; found: C 56.18, H 3.19.

3'-Bromo-2'-fluoro-[1,1'-biphenyl]-3-carbonitrile (5): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 3-bromobenzonitrile (270 mg, 1.5 mmol) affords **5** in 67 % (185 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.84 (s, 1H), 7.81 – 7.76 (m, 1H), 7.71 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.60 – 7.56 (m, 1H), 7.37 (ddd, *J* = 1.6, 6.8, 7.8 Hz, 1H), 7.16 (td, *J* = 1.0, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.9 (d, *J* = 249.3 Hz), 136.3, 136.3, 133.7, 133.3 (d, *J* = 3.1 Hz), 132.5 (d, *J* = 3.0 Hz), 131.6, 129.4, 128.3 (d, *J* = 14.5 Hz), 125.5 (d, *J* = 4.7 Hz), 118.4, 113.0, 110.4 (d, *J* = 22.0 Hz). Elemental analysis: calcd (%) for $C_{13}H_7BrFN$ (276.11): C 56.55, H 2.56; found: C 56.21, H 2.34.

3'-Bromo-2'-fluoro-[1,1'-biphenyl]-3-carbaldehyde (6): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 3-bromobenzaldehyde (278 mg, 1.5 mmol) affords **6** in 52 % (144 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.10 (s, 1H), 8.05 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.45 – 7.38 (m, 1H), 7.20 – 7.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.9, 156.0 (d, *J* = 249.0 Hz), 136.7, 136.0, 134.9 (d, *J* = 3.1 Hz), 133.3, 130.2 (d, *J* = 2.7 Hz), 129.8 (d, *J* = 2.8 Hz), 129.3, 125.4 (d, *J* = 4.7 Hz), 110.2 (d, *J* = 22.0 Hz). Elemental analysis: calcd (%) for $C_{13}H_8BrFO$ (279.11): C 55.94, H 2.89; found: C 55.98, H 2.83.

3'-Bromo-2'-fluoro-[1,1'-biphenyl]-2-carbonitrile (7): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 2-bromobenzonitrile (270 mg, 1.5 mmol) affords **7** in 62 % (171 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (d, *J* = 8.6 Hz, 1H), 7.74 – 7.63 (m, 2H), 7.58 – 7.49 (m, 2H), 7.40 (ddd, *J* = 1.7, 6.8, 8.2 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.9 (d, *J* = 249.2 Hz), 138.6, 134.4, 133.4, 132.6, 130.9 (d, *J* = 2.2 Hz), 130.4 (d, *J* = 2.0 Hz), 128.7, 127.2 (d, *J* = 15.8 Hz), 125.2 (d, *J* = 4.6 Hz), 117.7, 112.8, 110.1 (d, *J* = 21.6 Hz). Elemental analysis: calcd (%) for $C_{13}H_7BrFN$ (276.11): C 56.55, H 2.56; found: C 56.46, H 2.69.

3-Bromo-2-fluoro-2'-nitro-1,1'-biphenyl (8): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 2-bromonitrobenzene (303 mg, 1.5 mmol) affords **8** in 58 % (171 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (d, *J* = 8.2 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.19 – 7.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.8 (d, *J* = 247.5 Hz), 133.7, 133.1, 132.5, 129.9, 129.4, 129.1 (d, *J* = 2.6 Hz), 127.3 (d, *J* = 17.2 Hz), 125.3 (d, *J* = 4.6 Hz), 124.7, 109.44 (d, *J* = 21.6 Hz). Elemental analysis: calcd (%) for $C_{12}H_7BrFNO_2$ (296.10): C 48.68, H 2.38; found: C 48.74, H 2.55.

3-(3-Bromo-2-fluorophenyl)quinoline (9): 1-Bromo-2-fluorobenzene (110 µL, 1 mmol) and 3-bromoquinoline (312 mg, 1.5 mmol) affords **9** in 65 % (196 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.10 (s, 1H), 8.35 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.79 (ddd, *J* = 1.4, 6.9, 8.4 Hz, 1H),

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7.68 – 7.58 (m, 2H), 7.52 (td, *J* = 1.5, 7.9 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.4 (d, *J* = 249.3 Hz), 150.4, 147.5, 135.8 (d, *J* = 3.5 Hz), 133.5, 130.1, 129.90 (d, *J* = 2.7 Hz), 129.3, 128.1, 127.6, 127.4, 127.3 (d, *J* = 2.5 Hz), 127.2, 125.59 (d, *J* = 4.7 Hz), 110.36 (d, *J* = 21.9 Hz). Elemental analysis: calcd (%) for $C_{15}H_9BrFN$ (302.15): C 59.63, H 3.00; found: C 60.02, H 2.98.

3-Chloro-2-fluoro-4'-nitro-1,1'-biphenyl (10): 1-Chloro-2-fluorobenzene (105 µL, 1 mmol) and 4-bromonitrobenzene (303 mg, 1.5 mmol) affords **10** in 67 % (169 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.50 (ddd, *J* = 1.8, 6.8, 8.2 Hz, 1H), 7.37 (ddd, *J* = 1.8, 6.9, 8.4 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.2 (d, *J* = 251.7 Hz) , 147.6, 141.4, 131.1, 129.9 (d, *J* = 3.2 Hz), 128.8 (d, *J* = 2.4 Hz), 128.45 (d, *J* = 13.3 Hz), 125.1 (d, *J* = 4.9 Hz), 123.8, 122.4 (d, *J* = 18.5 Hz). Elemental analysis: calcd (%) for $C_{12}H_7ClFNO_2$ (251.64): C 57.28, H 2.80; found: C 57.43, H 3.07.

3'-Chloro-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (11): 1-Chloro-2-fluorobenzene (105 µL, 1 mmol) and 4-bromobenzonitrile (270 mg, 1.5 mmol) affords **11** in 70 % (162 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.69 – 7.64 (m, 2H), 7.49 (ddd, *J* = 1.7, 6.8, 8.0 Hz, 1H), 7.34 (ddd, *J* = 1.7, 6.8, 8.0 Hz, 1H), 7.22 (td, *J* = 1.1, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.1 (d, *J* = 251.6 Hz), 139.5, 132.3, 130.9, 129.7 (d, *J* = 3.2 Hz), 128.8 (d, *J* = 2.5 Hz), 125.0 (d, *J* = 5.0 Hz), 122.31 (d, *J* = 18.6 Hz), 118.5, 112.0. Elemental analysis: calcd (%) for $C_{13}H_7ClFN$ (231.65): C 67.40, H 3.05; found: C 67.14, H 2.91.

3'-Chloro-2'-fluoro-[1,1'-biphenyl]-3-carbonitrile (12): 1-Chloro-2-fluorobenzene (105 µL, 1 mmol) and 3-bromobenzonitrile (270 mg, 1.5 mmol) affords **12** in 51 % (118 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.81 – 7.77 (m, 1H), 7.74 – 7.68 (m, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.48 (ddd, *J* = 1.8, 6.8, 8.0 Hz, 1H), 7.33 (ddd, *J* = 1.8, 6.8, 7.8 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.1 (d, *J* = 251.1 Hz), 136.2, 133.8, 133.3 (d, *J* = 3.3 Hz), 132.9, 132.5 (d, *J* = 3.0 Hz), 131.6, 130.8, 129.5, 128.4 (d, *J* = 13.3 Hz), 125.0 (d, *J* = 5.0 Hz), 122.2 (d, *J* = 18.6 Hz), 113.0. Elemental analysis: calcd (%) for $C_{13}H_7ClFN$ (231.65): C 67.40, H 3.05; found: C 67.56, H 3.28.

3-Chloro-2-fluoro-2'-nitro-1,1'-biphenyl (13): 1-Chloro-2-fluorobenzene (105 µL, 1 mmol) and 2-bromonitrobenzene (303 mg, 1.5 mmol) affords **13** in 47 % (118 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (dd, *J* = 1.3, 8.2 Hz, 1H), 7.72 (td, *J* = 1.3, 7.6 Hz, 1H), 7.61 (td, *J* = 1.5, 7.7 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.26 – 7.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (d, *J* = 248.9 Hz), 148.7, 133.1, 132.5, 130.8, 129.8, 129.5, 128.3 (d, *J* = 2.4 Hz), 127.4 (d, *J* = 16.0 Hz), 124.7, 124.9 (d, *J* = 4.8 Hz), 121.5 (d, *J* = 18.1 Hz). Elemental analysis: calcd (%) for $C_{12}H_7ClFNO_2$ (251.64): C 57.28, H 2.80; found: C 57.10, H 2.71.

3-(3-Chloro-2-fluorophenyl)quinoline (14): 1-Chloro-2-fluorobenzene (105 µL, 1 mmol) and 3-bromoquinoline (312 mg, 1.5 mmol) affords **14** in 52 % (134 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.10 (s, 1H), 8.36 (s, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.80 (dd, *J* = 6.9, 8.4 Hz, 1H), 7.63 (t, *J* = 6.8, 8.2 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.29 – 7.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.6 (d, *J* = 250.8 Hz), 150.4 (d, *J* = 3.2 Hz), 147.5, 136.1, 135.8 (d, *J* = 3.5 Hz), 130.5, 130.1, 129.3, 129.1 (d, *J* = 2.7 Hz), 128.1, 127.6, 127.2, 125.1 (d, *J* = 4.9 Hz), 122.3 (d, *J* = 18.4 Hz). Elemental analysis: calcd (%) for $C_{15}H_9ClFN$ (257.69): C 69.91, H 3.52; found: C 70.26, H 3.85.

2-Fluoro-3-methoxy-4'-nitro-1,1'-biphenyl (15): 1-Fluoro-2-methoxybenzene (112 µL, 1 mmol) and 4-bromonitrobenzene (303 mg, 1.5 mmol) affords **15** in 41% (101 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.21 (td, *J* = 1.5, 8.0 Hz, 1H), 7.11 – 6.99 (m, 2H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.5 (d, *J* = 250.8 Hz), 148.4 (d, *J* = 11.1 Hz), 147.3, 142.3, 129.9 (d, *J* = 3.4 Hz), 124.4 (d, *J* = 5.0 Hz), 124.2, 123.7, 121.6 (d, *J* = 1.9 Hz), 113.68 (d, *J* = 2.0 Hz), 56.5. Elemental analysis: calcd (%) for $C_{13}H_{10}FNO_3$ (247.23): C 63.16, H 4.08; found: C 63.29, H 4.19.

2'-Fluoro-3'-methoxy-[1,1'-biphenyl]-4-carbonitrile (16): 1-Fluoro-2-methoxybenzene (112 µL, 1 mmol) and 4-bromobenzonitrile (270 mg, 1.5 mmol) affords **16** in 44% (100 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.19 (td, *J* = 1.5, 8.0 Hz, 1H), 7.06 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.04 – 6.98 (m, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.5 (d, *J* = 249.5 Hz), 148.4 (d, *J* = 11.1 Hz), 140.3, 132.2, 129.8 (d, *J* = 3.4 Hz), 128.0 (d, *J* = 10.5 Hz), 124.4 (d, *J* = 4.9 Hz), 121.5 (d, *J* = 2.0 Hz), 118.8, 113.5 (d, *J* = 2.1 Hz), 111.5, 56.4. Elemental analysis: calcd (%) for $C_{14}H_{10}FNO$ (227.24): C 74.00, H 4.44; found: C 73.91, H 4.56.

2'-Fluoro-3'-methoxy-[1,1'-biphenyl]-3-carbonitrile (17): 1-Fluoro-2-methoxybenzene (112 µL, 1 mmol) and 3-bromobenzonitrile (270 mg, 1.5 mmol) affords **17** in 40% (91 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (s, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.68 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.19 (td, *J* = 1.6, 8.0 Hz, 1H), 7.05 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.99 (ddd, *J* = 1.6, 6.5, 8.0 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.7 (d, *J* = 249.5 Hz), 148.5 (d, *J* = 11.1 Hz), 137.1, 131.3, 133.6 (d, *J* = 3.3 Hz), 132.7 (d, *J* = 3.0 Hz), 129.4, 127.7 (d, *J* = 10.6 Hz), 124.5 (d, *J* = 4.9 Hz), 121.7 (d, *J* = 2.0 Hz), 118.8, 113.5 (d, *J* = 2.0 Hz), 112.9, 56.7. Elemental analysis: calcd (%) for $C_{14}H_{10}FNO$ (227.24): C 74.00, H 4.44; found: C 74.10, H 4.29.

2-Ethyl-5-(2-fluoro-4'-nitro-[1,1'-biphenyl]-3-yl)-4-methylthiazole (18): 3-Bromo-2-fluoro-4'-nitro-1,1'-biphenyl (**2**) (148 mg, 0.5 mmol) and 2-ethyl-4-methylthiazole (95 mg, 0.75 mmol) affords **18** in 91% (156 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.53 – 7.41 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 1H), 3.06 (q, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.44 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 156.5 (d, *J* = 251.9 Hz), 149.9, 147.4, 142.1, 132.8 (d, *J* = 2.9 Hz), 130.5 (d, *J* = 3.0 Hz), 130.0 (d, *J* = 3.3 Hz), 127.7, 124.6 (d, *J* = 4.6 Hz), 123.7, 122.8, 121.3 (d, *J* = 16.6 Hz), 27.0, 16.1 (d, *J* = 2.7 Hz), 14.2. Elemental analysis: calcd (%) for $C_{18}H_{15}FN_2O_2S$ (342.39): C 63.14, H 4.42; found: C 63.29, H 4.61.

2-(2-Fluoro-4'-nitro-[1,1'-biphenyl]-3-yl)-1-methylpyrrole (19): 3-Bromo-2-fluoro-4'-nitro-1,1'-biphenyl (**2**) (148 mg, 0.5 mmol) and 1-methylpyrrole (162 mg, 2 mmol) affords **19** in 85% (126 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.49 – 7.41 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.82 (dd, *J* = 1.8, 2.7 Hz, 1H), 6.31 (dd, *J* = 1.8, 3.7 Hz, 1H), 6.28 (dd, *J* = 2.6, 3.6 Hz, 1H), 3.63 (d, *J* = 1.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.7 (d, *J* = 250.1 Hz), 147.3, 142.4, 132.8 (d, *J* = 3.3 Hz), 130.0 (d, *J* = 3.3 Hz), 129.9 (d, *J* = 3.0 Hz), 127.5, 127.3 (d, *J* = 14.5 Hz), 124.5 (d, *J* = 4.5 Hz), 123.9, 123.7, 122.4 (d, *J* = 16.6 Hz), 110.5 (d, *J* = 1.5 Hz), 108.1, 34.8 (d, *J* = 4.7 Hz). Elemental analysis: calcd (%) for $C_{17}H_{13}FN_2O_2S$ (296.30): C 68.91, H 4.42; found: C 69.04, H 4.21.

3'-(2-Ethyl-4-methylthiazol-5-yl)-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (20): 3'-Bromo-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (**1**) (138 mg, 0.5 mmol) and 2-ethyl-4-methylthiazole (95 mg, 0.75 mmol) affords **20** in 90% (145 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77 (d, *J* = 8.4 Hz, 2H), 7.69 (d,

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J = 8.4 Hz, 2H), 7.48 – 7.40 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 3.05 (q, *J* = 7.6 Hz, 2H), 2.41 (d, *J* = 1.3 Hz, 3H), 1.44 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 156.4 (d, *J* = 251.6 Hz), 149.8, 140.2, 132.6 (d, *J* = 2.7 Hz), 132.3, 130.5 (d, *J* = 3.1 Hz), 129.8 (d, *J* = 3.2 Hz), 128.0 (d, *J* = 14.2 Hz), 124.6 (d, *J* = 4.6 Hz), 122.9, 121.2 (d, *J* = 16.6 Hz), 118.7, 111.7, 27.0, 16.1 (d, *J* = 2.7 Hz), 14.2. Elemental analysis: calcd (%) for $C_{19}H_{15}FN_2$ (322.40): C 70.78, H 4.69; found: C 71.02, H 5.00.

2'-Fluoro-3'-(1-methyl-1H-pyrrol-2-yl)-[1,1'-biphenyl]-4-carbonitrile (21): 3'-Bromo-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (**1**) (138 mg, 0.5 mmol) and 1-methylpyrrole (162 mg, 2 mmol) affords **21** in 86% (119 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.30 (dd, *J* = 1.8, 3.7 Hz, 1H), 6.28 (dd, *J* = 2.7, 3.6 Hz, 1H), 3.62 (d, *J* = 1.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.6 (d, *J* = 249.8 Hz), 140.5, 132.6 (d, *J* = 3.3 Hz) 132.2, 129.8 (d, *J* = 3.3 Hz), 127.8, 127.6 (m) 124.5 (d, *J* = 4.6 Hz), 123.9, 122.3 (d, *J* = 16.6 Hz), 118.7, 111.5, 110.5, 108.1, 65.8. Elemental analysis: calcd (%) for $C_{18}H_{13}FN_2$ (276.31): C 78.24, H 4.74; found: C 78.48, H 5.03.

4-Ethoxy-2'-fluoro-4''-nitro-1,1':3',1''-terphenyl (22): The reaction of 3-bromo-2-fluoro-4'-nitro-1,1'-biphenyl (**2**) (148 mg, 0.5 mmol), (4-ethoxyphenyl)boronic acid (124 mg, 0.75 mmol) and K_3PO_4 (212 mg, 1 mmol) at 100 °C over 16 h in 1,4-dioxane (2-3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (6 mg, 0.01 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **22** in 73% (123 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 (d, *J* = 8.9 Hz, 2H), 7.77 (dd, *J* = 1.7, 8.8 Hz, 2H), 7.56 – 7.47 (m, 3H), 7.40 (td, *J* = 1.9, 7.2 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.9, 156.5 (d, *J* = 250.4 Hz), 147.2, 142.8, 131.3 (d, *J* = 3.9 Hz), 130.3 (d, *J* = 3.1 Hz), 130.1 (d, *J* = 3.4 Hz), 129.1 (d, *J* = 2.9 Hz), 127.7 (d, *J* = 9.9 Hz), 127.5, 124.7 (d, *J* = 4.6 Hz), 124.2, 123.6, 114.6, 63.6, 14.8. Elemental analysis: calcd (%) for $C_{20}H_{16}FNO_3$ (33.7.35): C 71.21, H 4.78; found: C 71.52, H 5.03.

2'-Fluoro-3'-(4-methylpiperazin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (23): The reaction of 3'-bromo-2'-fluoro-[1,1'-biphenyl]-4-carbonitrile (1) (138 mg, 0.5 mmol), 1-methylpiperazine (75 mg, 0.75 mmol) and Cs_2CO_3 (325 mg, 1 mmol) at 100 °C over 16 h in 1,4-dioxane (2-3 mL) in the presence of $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol) and XantPhos (14 mg, 0.025 mmol) under argon affords, after evaporation of the solvent and purification on silica gel, product **23** in 64% (95 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.07 – 6.98 (m, 2H), 3.18 (t, *J* = 4.9 Hz, 4H), 2.65 (t, *J* = 4.7 Hz, 4H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.5 (d, *J* = 249.3 Hz), 140.8 (t, *J* = 4.6 Hz), 132.6 (d, *J* = 6.3 Hz), 132.1, 129.8 (d, *J* = 3.2 Hz), 127.99 (d, *J* = 12.8 Hz), 124.7 (d, *J* = 4.5 Hz), 123.3 (d, *J* = 2.7 Hz), 119.5 (d, *J* = 3.2 Hz), 118.8, 111.3, 55.1, 50.6 (d, *J* = 3.4 Hz), 46.1. Elemental analysis: calcd (%) for $C_{18}H_{18}FN_3$ (295.36): C 73.20, H 6.14; found: C 72.89, H 6.40.

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Table of Contents

We reported herein palladium-catalyzed C–H bond arylation of fluorobenzene derivatives at the *ortho*-position to the fluorine atom. We have demonstrated that bromo, chloro or methoxy substituents at fluorobenzenyl *ortho*-position can be used to increase the reactivity of the C–H bond at the C3 position. Thanks to this method, we reported an efficient synthesis of 2,6-difunctionalized fluorobenzenes from 1-bromo-2-fluorobenzene *via* palladium-catalyzed orthogonal cross-coupling reactions.