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Reactivity of 3-Substituted Fluorobenzenes in Palladium-Catalysed Direct Arylations with Aryl Bromides

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Abstract: The influence of both electron-withdrawing and electron-donating substituents such as nitro, nitrile, chloro, bromo and methoxy at C-3 on fluorobenzenes for their palladium-catalysed direct C-2 arylation has been explored. With electron-withdrawing substituents, the reaction proceeds nicely using 2–4 mol% of an air-stable palladium complex and potassium pivalate/dimethylacetamide (PivOK/DMA) as catalytic system; and in general, a very regioselective arylation at C-2 was observed. Moreover, a variety of substituents on the aryl bromide coupling partner, such as benzoyl, formyl, nitro, nitrile, chloro and methyl, and also heteroaryl bromides were tolerated.

Keywords: aryl halides; atom economy; C–H bond functionalization; direct arylation; palladium

Introduction

The fluorobi(hetero)aryl motif is found in several bioactive compounds. For example, Flurbiprofen and Diflunisal are non-steroidal anti-inflammatory drugs, Brequinar is employed for the treatment of some cancers and Flucloxacillin and Radezolid are antibiotics (Figure 1). Therefore, the discovery of general simple routes for access to fluorobiphenyls has potential value for medicinal chemistry.

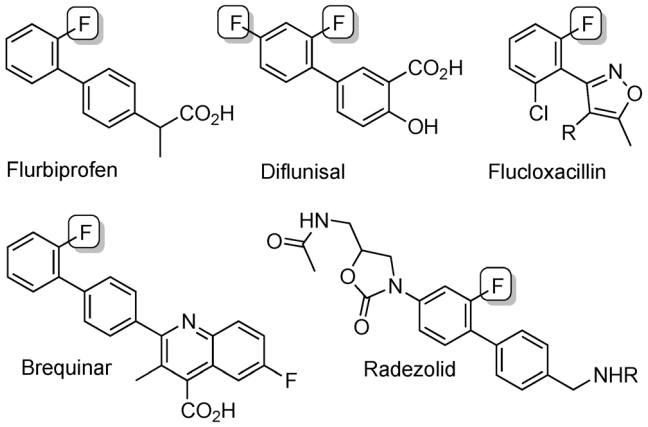
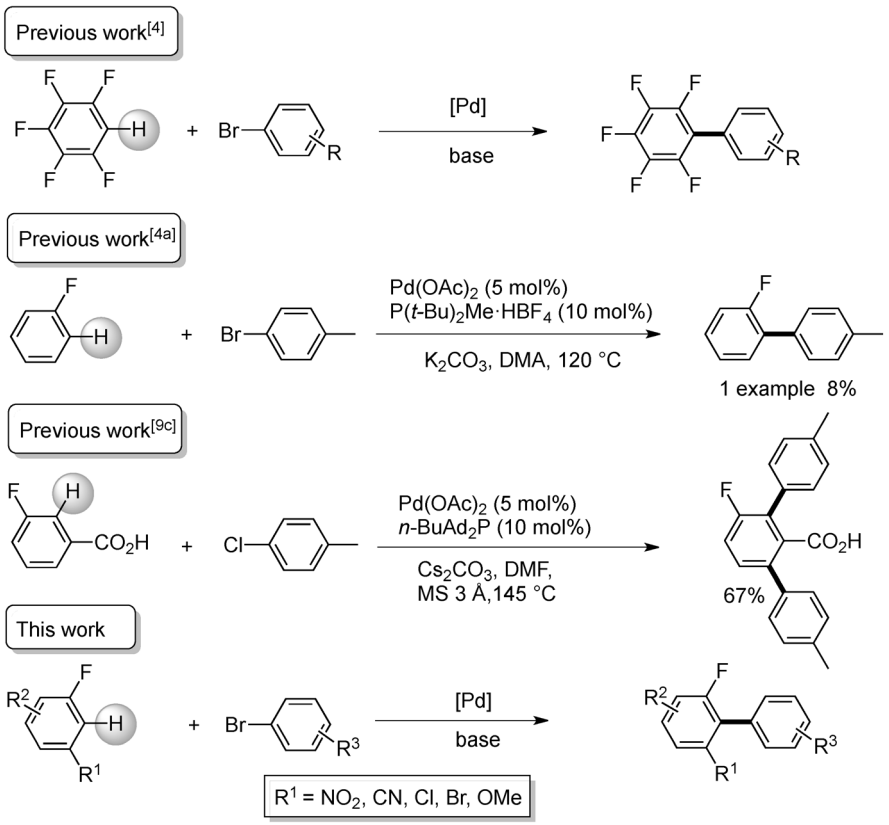


Figure 1. Examples of bioactive fluorobi(hetero)aryls.

Palladium-catalysed reactions such as Stille, Suzuki or Negishi couplings allow the efficient synthesis of a wide variety of biaryls.[1] However, these couplings require the preliminary synthesis of organometallic derivatives. Moreover, these reactions provide a stoichiometric amount of metallic side products. In 2006, Fagnou and co-workers reported the palladium-catalyzed direct arylations[2,3] of polyfluorobenzenes,[4,5] with aryl halides (Scheme 1, *top*). Since these results, the palladium- or copper-catalysed direct arylation of tri-, tetra- and especially pentafluorobenzenes[6] with aryl halides has proved to be a powerful method for the synthesis of a variety of poly-fluoro-containing biaryls.[4–8] On the other hand, little is known on the reactivity of monofluorobenzenes[9–11] for palladium-catalysed direct arylation. Fagnou and co-workers have reported a single example of direct arylation of fluorobenzene (Scheme 1, *middle*).[4a] Using 5 mol% $Pd(OAc)_2$ associated to 10 mol% $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ as catalyst, and 4-bromotoluene as the coupling partner, they obtained the C-2 arylated fluorobenzene in 8% yield. In a few cases, it has been demonstrated that a carboxylic acid group directs the arylation at *ortho*-position(s).[9] This method has been employed by Daugulis and co-workers for direct diarylation at C-2 and C-6 of 3-fluorobenzoic acid (Scheme 1, *middle*).[9a] The π-complexation of fluorobenzenes to



Scheme 1. Pd-catalysed direct arylation of (poly)fluorobenzenes.

$Cr(CO)_3$ also enhances their reactivity allowing Pd-catalysed C-2 arylation in high yields.[10a] A few *meta*-arylations of trifluoromethylbenzenes containing a fluoro-substituent,[10b] or using other metals as catalysts[11] have also been reported.

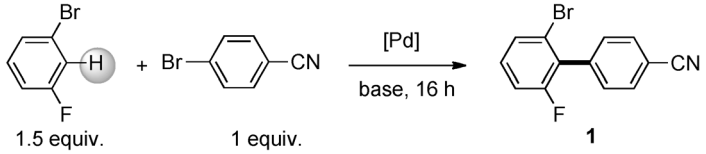
As very few examples of palladium-catalysed direct arylations of monofluorobenzene derivatives have been reported, the influence of the substituents on fluorobenzenes allowing a more general access to fluorobiphenyls, especially using fluorobenzenes bearing useful functional groups, needed to be investigated.

Herein, starting from a set of 3-substituted fluorobenzenes as reactants, we report (i) on the electronic influence of fluorobenzene substituents on their reactivity for palladium-catalysed direct arylation; (ii) on the access to a variety of fluorobiphenyls using a variety of fluorobenzenes and aryl bromides.

Results and Discussion

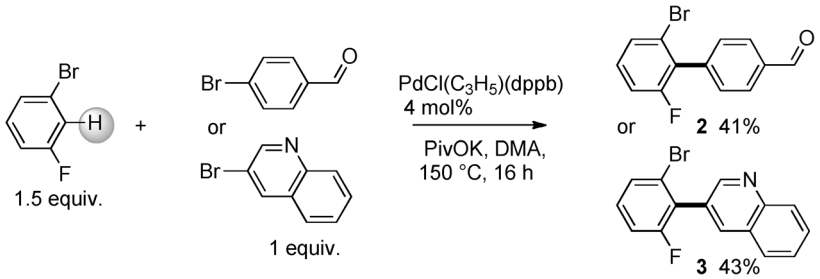
It is generally considered that, in the course of palladium-catalysed direct arylation with polyfluorobenzenes, the most electron-deficient fluorinated arene reacts preferentially.[4a] Therefore, based on previous results,[12] we first examined the reaction of 1-bromo-3-fluorobenzene with 4-bromobenzonitrile to form **1** (Table 1). In the presence of 2 mol% $PdCl(C_3H_5)$ (dppb) catalyst, using KOAc as base/ligand in DMA, **1** was formed regioselectively and without cleavage of the C–Br bond of 1-bromo-3-fluorobenzene moiety. However, **1** was obtained in only 31% yield due to a moderate conversion of both 4-bromobenzonitrile and 1-bromo-3-fluorobenzene and also to the formation of 4,4′-dicyanobiphenyl in low yield. The use of DMF and NMP as the solvents, with KOAc as the base, did not allow any improvement of the yield in **1** and the formation of unidentified side-products was observed (Table 1, entries 2 and 3). Xylene was completely ineffective for this reaction and 4-bromobenzonitrile was recovered (Table 1, entry 4). Then, we examined the influence of several bases for this reaction. CsOAc, NaOAc or K_2CO_3 led to **1** in very low yields (Table 1, entries 5–7). On the other hand, the use of PivOK in the presence of 2 mol% $PdCl(C_3H_5)$ (dppb) catalyst selectively gave **1** in 45% yield. A higher catalyst loading of 4 mol% allowed an increase in the yield of **1** to 69% (Table 1, entries 8 and 9). It should be noted that under these conditions, the use of fluorobenzene instead of 1-bromo-3-fluorobenzene led only to a trace amount of coupling product (detected by GC/MS analysis). This result confirms that the presence of a bromo-substituent at C-3 of fluorobenzene enhances the reactivity of the C-2 position.

Table 1. Influence of the reaction conditions for the palladium-catalysed direct 2-arylation of 1-bromo-3-fluorobenzene with 4-bromobenzonitrile.[a]



Entry	[Pd] catalyst [mol%]	Base	Solvent	Conversion [%]	Yield in **1** [%]
1	2	KOAc	DMA	56	31
2	2	KOAc	DMF	91	18
3	2	KOAc	NMP	42	–
4	2	KOAc	xylene	4	–
5	2	CsOAc	DMA	34	–
6	2	NaOAc	DMA	79	5
7	2	K_2CO_3	DMA	13	–
8	2	PivOK	DMA	51	45
9	4	PivOK	DMA	93	69

[a] $PdCl(C_3H_5)(dppb)$, 4-bromobenzonitrile (1 equiv.), 1-bromo-3-fluorobenzene (1.5 equiv.), base (2 equiv.), 150 °C, 16 h, conversion of 4-bromobenzonitrile.

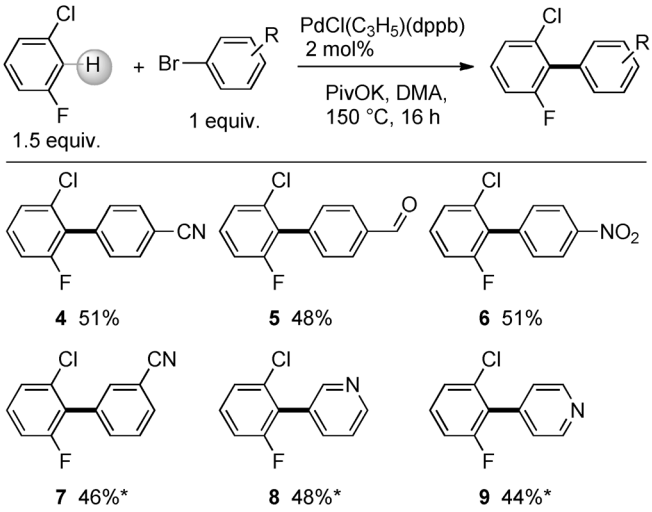


Scheme 2. Palladium-catalysed 2-arylation of 1-bromo-3-fluorobenzene with aryl bromides.

For all these reactions, no arylation of 1-bromo-3-bromobenzene with itself was observed due to the faster oxidative addition of 4-bromobenzonitrile to palladium.

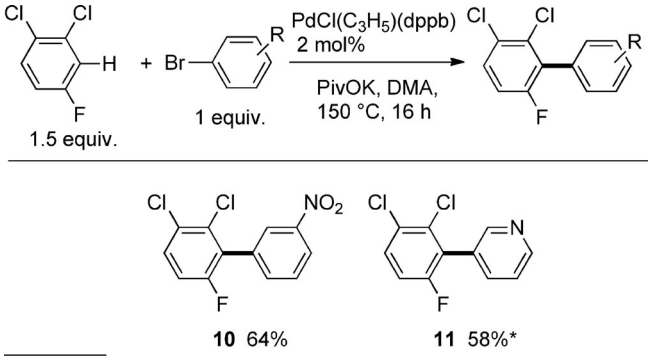
Then, we extended the scope of the coupling of 1-bromo-3-fluorobenzene to 4-bromobenzaldehyde and 3-bromoquinoline (Scheme 2). The desired products **2** and **3** were obtained in only 41% and 43% yields due to the formation of 4-bromobenzaldehyde and 3-bromoisoquinoline homo-coupling side-products.

The Hammet constants for *ortho*-chloro and *ortho*-fluoro substituents on benzenes are very similar (0.20 *vs.* 0.24).[13] Therefore, 1-chloro-3-fluorobenzene was expected to be a suitable coupling partner for palladium-catalysed direct arylations. Indeed, we observed that its couplings with 4-bromobenzonitrile, 4-bromobenzaldehyde and 4-bromonitrobenzene proceeded quite nicely to give **4**–**6** in 48–51% yields (Scheme 3). 3-Bromobenzonitrile and 3- or 4-bromopyridines were found to be slightly less reactive, and 5 mol% catalyst had to be employed to obtain high conversions of these aryl bromides.



* 5 mol% catalyst.

Scheme 3. Palladium-catalysed direct 2-arylation of 1-chloro-3-fluorobenzene with aryl bromides.



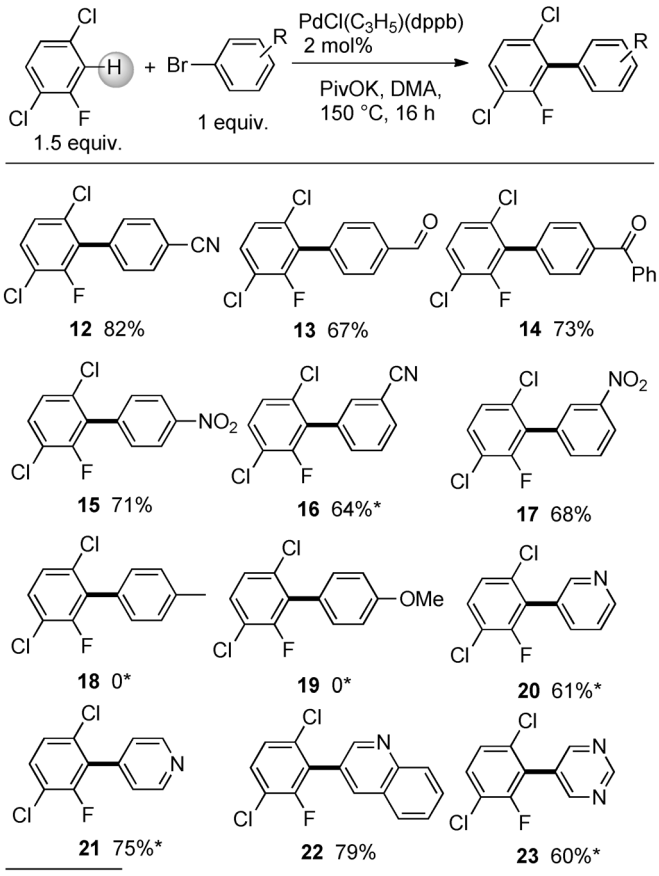
* 3 mol% catalyst.

Scheme 4. Palladium-catalysed direct 3-arylation of 1,2-dichloro-4-fluorobenzene with aryl bromides.

The introduction of a second chloro-substituent on fluorobenzene allowed us to obtain higher yields of coupling products (Scheme 4). The electron-deficient *meta*-substituted aryl bromide, 3-bromonitrobenzene, in the presence of 1,2-dichloro-4-fluorobenzene gave the desired product **10** in 64% yield (Scheme 4). A similar yield of 58% in **11** was obtained using 3-bromopyridine. Again, no cleavage of both C–Cl bonds was observed, allowing further transformations. However, with this reactant, another arylation product (likely arylation at C-5 of 1,2-dichloro-4-fluorobenzene) was detected by GC/MS of the crude mixture.

We then examined the reactivity of 1,4-dichloro-2-fluorobenzene (Scheme 5). A second chloro-substituent at this position appears to activate position C-3 and also to prevent arylation at less favourable sites. With this reactant, in all cases very regioselective arylations were observed. Moreover, in most cases high yields of the desired coupling products were obtained. For example, from 4-bromobenzonitrile, 4-bromobenzaldehyde, 4-bromopropiophenone or 4-bromonitrobenzene, **12**–**15** were obtained in 67–82% yields. The presence of *meta*-substituents on the aryl bromide was also tolerated as 3-bromobenzonitrile and 3-bromonitrobenzene, afforded **16** and **17** in 64% and 68% yields, respectively. On the other hand, no formation of products **18** and **19** was observed in the presence of the electron-rich aryl bromides, 4-bromotoluene or 4-bromoanisole. Pyridines, quinolines or pyrimidines are probably the most common heterocyclic motifs found in pharmaceutically active compounds. We observed that such heteroaryl bromides are also suitable coupling partners. The reaction of 3- or 4-bromopyridines, 3-bromoquinoline or 5-bromopyrimidine with 1,4-dichloro-2-fluorobenzene in the presence of 2–4 mol% $PdCl(C_3H_5)(dppb)$ proceeds nicely to afford **20**–**23** in 60–79% yields (Scheme 5, *bottom*).

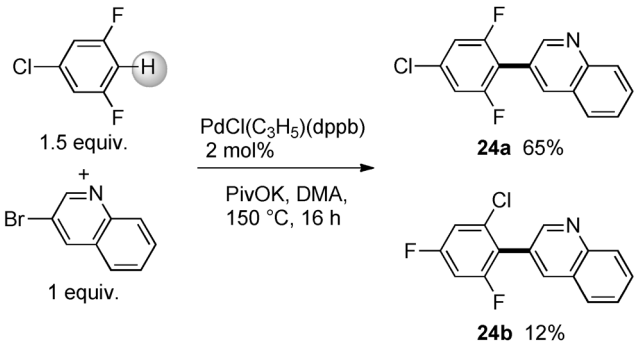
In order to further demonstrate the influence of fluoro substituents on the regioselectivity of the arylation, we studied the coupling of 3,5-difluorochlorobenzene with 3-bromoquinoline (Scheme 6). A mixture of 2- and 4-arylation products **24a** and **24b** was obtained in an 85:15 ratio. This result seems to confirm the directing effect of fluoro substituents for such arylations.



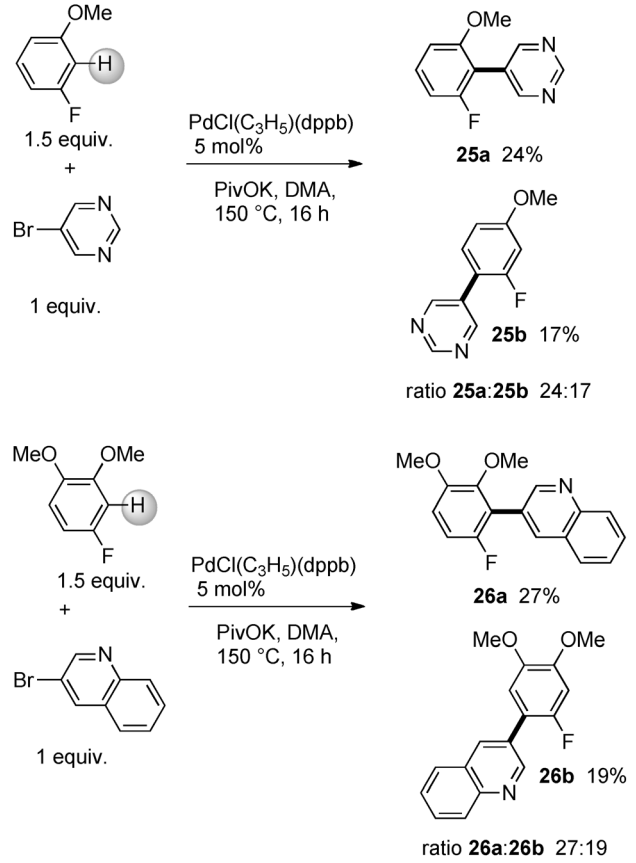
* 4 mol% catalyst.

Scheme 5. Palladium-catalysed direct 3-arylation of 1,4-dichloro-2-fluorobenzene with aryl bromides.

1-Fluoro-3-methoxybenzene was found to be much less reactive than 1-chloro-3-fluorobenzene, as its reaction with 5-bromopyrimidine led to a moderate conversion of this heteroaryl bromide (Scheme 7, *top*). Moreover, a poor regioselectivity was observed as the C-2 and C-4 arylation products **25a** and **25b** were produced in a 24:17 ratio. This lack of regioselectivity is certainly due to the electron-donating effect of the methoxy substituent (Hammet constants for an MeO *ortho*-substituent: −0.39). However, the higher reactivity of 1-fluoro-3-methoxybenzene *vs.* fluorobenzene reveals that the arylation of fluoroarenes does not only depend on the electron-withdrawing properties of fluoroarene substituents. A very similar result was obtained for the coupling of 4-fluoro-1,2-dimethoxybenzene with 3-bromoquinoline (Scheme 7, *bottom*). Again, a mixture of the arylation products **26a** and **26b** was obtained in a 27:19 ratio.



Scheme 6. Palladium-catalysed direct arylation of 3,5-difluorochlorobenzene with 3-bromoquinoline.



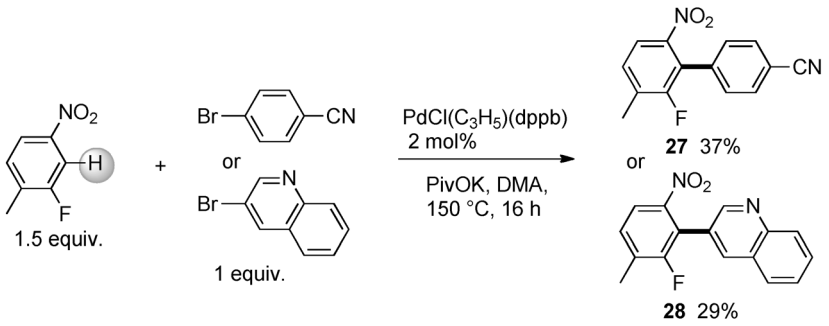
Scheme 7. Palladium-catalysed arylations of 1-fluoro-3-methoxybenzenes with aryl bromides.

As shown in the above sections, the introduction of an electron-withdrawing group such as Br or Cl in the *meta*-position of the fluorine atom of monofluorobenzenes enhances the reactivity of the C–H bond at the *ortho*-position. We next investigated others electron-withdrawing groups. Firstly, we tested the reactivity of 2-fluoro-1-methyl-4-nitrobenzene with 4-bromobenzonitrile or 3-bromoquinoline. Under the standard conditions, the coupling products **27** and **28** were obtained in 37% and 29% yields, respectively (Scheme 8). The methyl group at the C-1 position of the starting materials blocks this position and the arylation took place mainly in the C-3 position. However, trace amounts of another arylated product were detected in the crude mixtures.

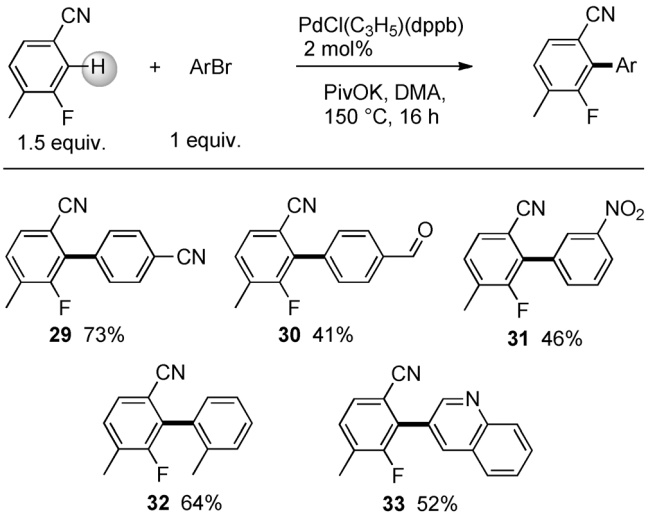
Next, we turned our attention to the CN group, which is less electron-withdrawing than the NO_2 group (Hammet constants for NO_2: 0.8, for CN: 0.71). Using 3-fluoro-4-methylbenzonitrile as the coupling partner, moderate to good yields of **29**–**31** and **33** were observed using diverse aryl bromides such as 4-bromobenzonitrile, 4-bromobenzaldehyde, 3-bromonitrobenzene, or 3-bromoquinoline. Moreover, from *ortho*-substituted 2-bromotoluene, **32** was also obtained in high yield (Scheme 9). In contrast to the NO_2 substituent, with the CN substituent the arylation took place only at the C-2 position and no other coupling products were detected by GC/MS analysis of the crude mixture.

From the previous experiments, we have shown that the introduction of a bromo-substituent at C-3 of fluorobenzene has an activating effect (Table 1, Scheme 2). We next selected 4-bromo-2-fluoro-1-methoxybenzene as substrate. The effect of both *m*-OMe and *o*-Br substituents led to similar yields as the reactions with 1-halo-3-fluorobenzene. Reactions with 3-bromobenzonitrile, 3-bromoquinoline or 5-bromopyrimidine afforded **34**, **35**, and **36** in 38–48% yields (Scheme 10).

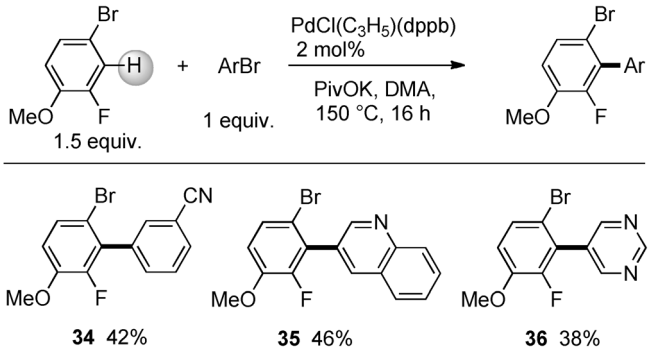
The Hammet constants of *ortho*- and *meta*-substituents on benzenes (Figure 2) seems to be quite effective to rationalise the reactivity of C-2–H of 3-substituted fluorobenzenes. For Cl or F substituents, the σ constant is 0.20 or 0.24, respectively and they are



Scheme 8. Palladium-catalysed 3-arylation of 2-fluoro-1-methyl-4-nitrobenzene with aryl bromides.



Scheme 9. Palladium-catalysed 2-arylation of 3-fluoro-4-methylbenzonitrile with aryl bromides.



Scheme 10. Palladium-catalysed 3-arylation of 4-bromo-2-fluoro-1-methoxybenzene with aryl bromides.

more reactive than 3-fluoroanisole (σ*o* OMe −0.39). A *meta*-substituent with a donating effect such as a chloro (σ*m* Cl 0.37) also favours the reaction.

In order to gain more insight into the influence of substituents on fluorobenzene, we also performed six competition reactions to probe the substituent preference of this catalyst system for such couplings (Scheme 11). From an equimolar mixture of 1,3-difluorobenzene and 1-chloro-3-fluorobenzene using 4-bromobenzonitrile as the coupling partner, in the presence of 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst, the formation of a mixture of **4** and **37** in a 41:59 ratio was obtained. This result indicates that a chloro-substituent at an *ortho*-position of a C–H is a slightly less activating group than a fluoro substituent. A very similar result was obtained from a mixture of 1,3-difluorobenzene and 1-bromo-3-fluorobenzene, with a ratio of products **1**:**37** of 38:62. On the other hand, 1,4-dichloro-2-fluorobenzene was found to be more reactive than 1,3-difluorobenzene, as from an equimolar mixture of these reactants, **12** and **37** were obtained in a 71:29 ratio. As expected, an equimolar mixture of 4-fluoro-1,2-dimethoxybenzene and 1,3-difluorobenzene using 3-bromoquinoline as the coupling partner led to a mixture of **26a**+**26b** and **38** in a 24:76 ratio, confirming a deleterious influence of methoxy substituents on benzene for such couplings. From, an equimolar mixture of 2-fluoro-1-methyl-4-nitrobenzene and 1,3-difluorobenzene, again **37** was the major product with a **27**:**37** ratio of 33:67. It should be noted that with this mixture of reactants, only a partial conversion of 4-bromobenzonitrile was observed indicating a partial poisoning of the catalyst by the nitro function. Finally, an equimolar mixture of 3-fluoro-4-methylbenzonitrile and 1,3-difluorobenzene gave **32** and **37** in a 42:58 ratio. In summary, electron-withdrawing substituents at C-3 of fluorobenzenes such as chloro or cyano favour the reaction; whereas electron-donating substituents such as methoxy are less favourable. The reactivity order determined by these competition experiments does not correlate

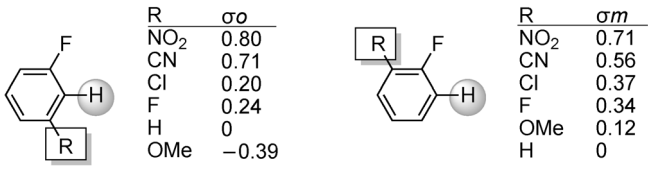
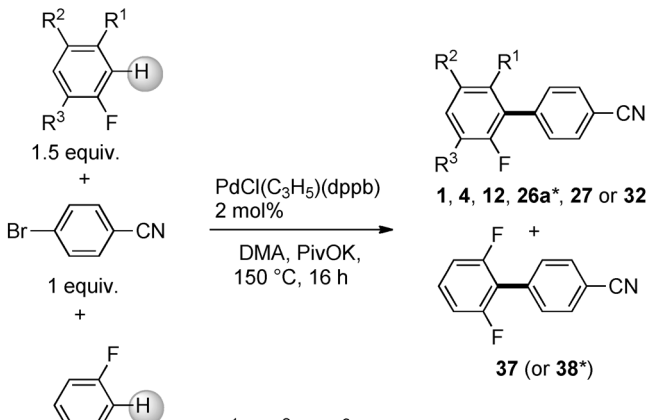


Figure 2. Calculated Hammet constants for *meta*- or *ortho*-substituents on benzenes.[13]



R^1	R^2	R^3	conv.	ratio
Cl	H	H	100	**4**:**37** = 41:59
Br	H	H	97	**1**:**37** = 38:62
Cl	H	Cl	100	**12**:**37** = 71:29
OMe	OMe	H	99	**26a**+**26b**:**38** = 24:76*
NO_2	H	Me	56	**27**:**37** = 33:67
CN	H	Me	100	**32**:**37** = 42:58

reactivity order: F > Cl, CN > Br > NO_2 > OMe > H

* Reaction with 1 equiv. of 3-bromoquinoline instead of 4-bromobenzonitrile.

Scheme 11. Competitive experiments using equimolar mixtures of fluorobenzenes for palladium-catalysed direct arylations.

with the Hammet constants. Gorelsky recently rationalised 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.[14] This combination of factors might explain why the less acidic C–H bond on 1-fluoro-3-methoxybenzene is more reactive than the C–H bonds of fluorobenzene. The arene distortion energy in 1-fluoro-3-methoxybenzene appears to be more favourable for C–H activation than that in fluorobenzene.

Conclusions

The influence of both electron-withdrawing and electron-donating substituents such as nitro, nitrile, chloro, bromo and methoxy at C-3 on fluorobenzenes for their palladium-catalysed direct C-2 arylation has been explored. With electron-withdrawing substituents, the reaction proceeds nicely using 2–4 mol% of an air-stable palladium catalyst and PivOK in DMA; and in general, a very regioselective arylation at C-2 was observed. Moderate to high yields in C-2 arylated 3-substituted fluorobenzenes were obtained using chloro, bromo or cyano substituents at C-3 on the fluorobenzenes. On the other hand, electron-donating substituents at C-3 of fluorobenzenes such as a methoxy substituent are less favourable and led to mixtures of regioisomers and low yields; although such substrates are more reactive than fluorobenzene. These arylations were performed using an air-stable catalyst and an inexpensive base. Moreover, a variety of substituents such as benzoyl, formyl, nitro, or nitrile on the bromobenzene coupling partner was tolerated. The major by-products of these reactions are a base associated to HBr, and the method avoids the preliminary preparation of an organometallic reducing the number of steps to prepare these compounds. For these reasons, this process gives an economically viable and environmentally attractive access to fluorobiphenyl derivatives.

Experimental Section

DMA (*N*,*N*-dimethylacetamide) (99%) was purchased from Acros. KOAc (99%), $[Pd(C_3H_5)Cl]_2$ (56.5%) and dppb [1,4-bis(diphenylphosphino)butane] (98%) were purchased from Alfa Aesar. These compounds were not purified before use.

Preparation of the $PdCl(C_3H_5)(dppb)$ Catalyst[15]

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 under vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 19.3$ (s).

General Procedure for the Synthesis of 1–33

As a typical experiment, the reaction of the aryl bromide (1 mmol), fluorobenzene derivative (1.5 mmol) and PivOK (0.280 g, 2 mmol) at 150 °C during 16 h in DMA (3 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) (see Tables or Schemes) under argon affords the arylation product after evaporation of the solvent and filtration on silica gel.

6′-Bromo-2′-fluorobiphenyl-4-carbonitrile (1): From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-bromo-3-fluorobenzene (0.262 g, 1.5 mmol), **1** was obtained; yield: 0.190 g (69%). ^1H NMR (400 MHz, CD_3CN, 25 °C): $\delta = 7.84$ (d, $J = 8.1$ Hz, 2H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.36 (q, $J = 7.3$ Hz, 1H), 7.25 (t, $J = 9.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 159.5$ (d, $J = 250.3$ Hz), 139.1, 131.9, 131.0, 130.6 (d, $J = 9.0$ Hz), 129.1 (d, $J = 18.2$ Hz), 128.8 (d, $J = 3.5$ Hz), 123.5 (d, $J = 2.8$ Hz), 118.5, 115.1 (d, $J = 22.9$ Hz), 112.2; elemental analysis: calcd. (%) for $C_{13}H_7BrFN$ (276.10): C 56.55, H 2.56; found: C 56.37, H 2.39.

6′-Bromo-2′-fluorobiphenyl-4-carbaldehyde (2): From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1-bromo-3-fluorobenzene (0.262 g, 1.5 mmol), **2** was obtained; yield: 0.114 g (41%). ^1H NMR (400 MHz, CD_3CN, 25 °C): $\delta =$ 10.07 (s, 1H), 8.00 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 8.1$ Hz, 1H), 7.55 (d, $J = 8.1$ Hz, 2H), 7.36 (q, $J = 7.3$ Hz, 1H), 7.25 (t, $J = 9.0$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN, 25 °C): $\delta =$ 193.2, 160.3 (d, $J = 250.3$ Hz), 141.4, 137.2, 132.0 (d, $J =$ 9.4 Hz), 131.8, 130.5 (d, $J = 18.6$ Hz), 130.2, 129.8 (d, $J =$ 3.3 Hz), 124.2 (d, $J = 3.1$ Hz), 116.0 (d, $J = 23.1$ Hz); elemental analysis: calcd. (%) for $C_{13}H_8BrFO$ (279.10): C 55.94, H 2.89; found: C 56.14, H 3.11.

3-(2-Bromo-6-fluorophenyl)-quinoline (3): From 3-bromoquinoline (0.208 g, 1 mmol) and 1-bromo-3-fluorobenzene (0.262 g, 1.5 mmol), **3** was obtained; yield: 0.130 g (43%). ^1H NMR (400 MHz, CD_3CN, 25 °C): $\delta = 8.84$ (s, 1H), 8.28 (s, 1H), 8.12 (d, $J = 8.5$ Hz, 1H), 7.96 (d, $J = 8.5$ Hz, 1H), 7.82 (t, $J = 8.0$ Hz, 1H), 7.69–7.60 (m, 2H), 7.42 (q, $J = 7.3$ Hz, 1H), 7.31 (t, $J = 9.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 160.3$ (d, $J = 250.3$ Hz), 151.2, 147.4, 137.3, 130.6 (d, $J = 9.0$ Hz), 130.1, 129.3, 128.8 (d, $J = 3.4$ Hz), 128.1, 127.6, 127.5 (d, $J = 18.4$ Hz), 127.4, 127.0, 124.6 (d, $J =$ 2.9 Hz), 115.1 (d, $J = 23.0$ Hz); elemental analysis: calcd. (%) for $C_{15}H_9BrFN$ (302.14): C 59.63, H 3.00; found: C 59.91, H 2.87.

2′-Chloro-6′-fluorobiphenyl-4-carbonitrile (4): From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-chloro-3-fluorobenzene (0.195 g, 1.5 mmol), **4** was obtained; yield: 0.118 g (51%). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.75$ (d, $J =$ 8.1 Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 7.35–7.30 (m, 2H), 7.15–7.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta =$ 159.2 (d, $J = 249.8$ Hz), 137.3, 133.8 (d, $J = 4.0$ Hz), 131.9, 131.1, 130.1 (d, $J = 9.4$ Hz), 127.2 (d, $J = 18.3$ Hz), 125.7 (d, $J = 3.6$ Hz), 118.6, 114.5 (d, $J = 22.8$ Hz), 112.2; elemental analysis: calcd. (%) for $C_{13}H_7ClFN$ (231.65): C 67.40, H 3.05; found: C 67.57, H 3.18.

2′-Chloro-6′-fluorobiphenyl-4-carbaldehyde (5): From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1-chloro-3-fluorobenzene (0.195 g, 1.5 mmol), **5** was obtained; 0.112 g (48%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.09 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.35–7.30 (m, 2H), 7.15–7.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 191.8, 159.2 (d, J = 249.8 Hz), 138.8, 135.9, 133.9 (d, J = 4.0 Hz), 131.0, 129.8 (d, J = 9.4 Hz), 129.4, 127.7 (d, J = 18.5 Hz), 125.6 (d, J = 3.5 Hz), 114.4 (d, J = 23.0 Hz); elemental analysis: calcd. (%) for $C_{13}H_8ClFO$ (234.65): C 66.54, H 3.44; found: C 66.40, H 3.21.

2-Chloro-6-fluoro-4′-nitrobiphenyl (6): From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1-chloro-3-fluorobenzene (0.195 g, 1.5 mmol), **6** was obtained; yield: 0.128 g (51%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.32 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.35–7.30 (m, 2H), 7.17–7.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.4 (d, J = 249.8 Hz), 147.7, 139.2, 133.9 (d, J = 3.8 Hz), 131.4, 130.3 (d, J = 9.5 Hz), 126.9 (d, J = 18.3 Hz), 125.7 (d, J = 3.3 Hz), 123.4, 114.5 (d, J = 22.9 Hz); elemental analysis: calcd. (%) for $C_{12}H_7ClFNO_2$ (251.64): C 57.28, H 2.80; found: C 57.04, H 2.61.

2′-Chloro-6′-fluorobiphenyl-3-carbonitrile (7): From 3-bromobenzonitrile (0.182 g, 1 mmol) and 1-chloro-3-fluorobenzene (0.195 g, 1.5 mmol), **7** was obtained; yield: 0.106 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.72 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.35–7.30 (m, 2H), 7.15–7.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.4 (d, J = 249.8 Hz), 134.7, 134.0 (d, J = 3.7 Hz), 133.9, 133.8, 131.8, 130.1 (d, J = 9.5 Hz), 129.0, 126.7 (d, J = 18.6 Hz), 125.7 (d, J = 3.6 Hz), 118.4, 114.5 (d, J = 22.8 Hz), 112.6; elemental analysis: calcd. (%) for $C_{13}H_7ClFN$ (231.65): C 67.40, H 3.05; found: C 67.27, H 3.17.

3-(2-Chloro-6-fluorophenyl)-pyridine (8): From 3-bromopyridine (0.158 g, 1 mmol) and 1-chloro-3-fluorobenzene (0.195 g, 1.5 mmol), **8** was obtained; yield: 0.099 g (48%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.65 (d, J = 4.1 Hz, 1H), 8.62 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.40 (dd, J = 7.8, 4.1 Hz, 1H), 7.35–7.30 (m, 2H), 7.15–7.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.3 (d, J = 249.8 Hz), 150.7, 149.3, 137.7, 134.5 (d, J = 3.9 Hz), 130.0 (d, J = 9.5 Hz), 128.7, 125.6 (d, J = 3.7 Hz), 125.4, 123.0, 114.4 (d, J = 23.0 Hz); elemental analysis: calcd. (%) for $C_{11}H_7ClFN$ (207.63): C 63.63, H 3.40; found: C 63.47, H 3.41.

4-(2-Chloro-6-fluorophenyl)-pyridine (9): From 4-bromopyridine hydrochloride (0.194 g, 1 mmol) and 1-chloro-3-fluorobenzene (0.195 g, 1.5 mmol), **9** was obtained; yield: 0.091 g (44%). ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 8.69 (d, J = 3.8 Hz, 2H), 7.38–7.30 (m, 4H), 7.15–7.06 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 159.9 (d, J = 249.8 Hz), 150.2, 141.0, 134.0 (d, J = 4.2 Hz), 130.8 (d, J = 9.5 Hz), 126.7, 126.1 (d, J = 3.7 Hz), 125.4, 114.9 (d, J = 22.9 Hz); elemental analysis: calcd. (%) for $C_{11}H_7ClFN$ (207.63): C 63.63, H 3.40; found: C 63.71, H 3.57.

2,3-Dichloro-6-fluoro-3′-nitrobiphenyl (10): From 3-bromonitrobenzene (0.202 g, 1 mmol) and 1,2-dichloro-4-fluorobenzene (0.247 g, 1.5 mmol), **10** was obtained; yield: 0.183 g (64%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.35–8.28 (m, 1H), 8.23 (s, 1H), 7.70–7.65 (m, 2H), 7.53 (dd, J = 8.8, 5.4 Hz, 1H), 7.12 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.2 (d, J = 249.8 Hz), 148.2, 136.2, 134.0, 132.7 (d, J = 4.0 Hz), 130.9 (d, J = 9.8 Hz), 129.4, 129.2 (d, J = 4.0 Hz), 128.3 (d, J = 19.2 Hz), 125.2, 123.5, 115.3 (d, J = 24.1 Hz); elemental analysis: calcd. (%) for $C_{12}H_6Cl_2FNO_2$ (286.09): C 50.38, H 2.11; found: C 50.51, H 2.01.

3-(2,3-Dichloro-6-fluorophenyl)-pyridine (11): From 3-bromopyridine (0.158 g, 1 mmol) and 1,2-dichloro-4-fluorobenzene (0.247 g, 1.5 mmol), **11** was obtained; yield: 0.140 g (58%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.66 (d, J = 3.8 Hz, 1H), 8.59 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.49 (dd, J = 8.8, 5.4 Hz, 1H), 7.41 (dd, J = 7.8, 3.8 Hz, 1H), 7.09 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.5 (d, J = 249.8 Hz), 150.4, 149.6, 137.5, 133.0 (d, J = 4.1 Hz), 130.6 (d, J = 8.9 Hz), 129.1 (d, J = 3.8 Hz), 128.7, 127.2 (d, J = 19.5 Hz), 123.1, 115.2 (d, J = 24.3 Hz); elemental analysis: calcd. (%) for $C_{11}H_6Cl_2FN$ (242.08): C 54.58, H 2.50; found: C 54.31, H 2.37.

3′,6′-Dichloro-2′-fluorobiphenyl-4-carbonitrile (12): From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **12** was obtained; yield: 0.218 g (82%). ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 7.69 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.33 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 155.2 (d, J = 251.5 Hz), 136.6, 132.1 (d, J = 2.8 Hz), 132.0, 130.9, 130.6, 128.4 (d, J = 18.4 Hz), 125.9 (d, J = 4.3 Hz), 120.5 (d, J = 19.2 Hz), 118.3, 112.7; elemental analysis: calcd. (%) for $C_{13}H_6Cl_2FN$ (266.10): C 58.68, H 2.27; found: C 58.41, H 2.04.

3′,6′-Dichloro-2′-fluorobiphenyl-4-carbaldehyde (13): From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **13** was obtained; yield: 0.180 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.08 (s, 1H), 7.99 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 191.7, 155.5 (d, J = 251.3 Hz), 138.0, 136.2, 132.2 (d, J = 2.6 Hz), 130.8, 130.3, 129.6, 129.0 (d, J = 18.5 Hz), 125.8 (d, J = 4.3 Hz), 120.4 (d, J = 19.2 Hz); elemental analysis: calcd. (%) for $C_{13}H_7Cl_2FO$ (269.10): C 58.02, H 2.62; found: C 58.27, H 2.47.

(3′,6′-Dichloro-2′-fluorobiphenyl-4-yl)-phenylmethanone (14): From 4-bromobenzophenone (0.261 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **14** was obtained; yield: 0.252 g (73%). ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 7.89 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.60–7.50 (m, 5H), 7.40 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 196.7, 156.5 (d, J = 248.0 Hz), 138.7, 138.2, 137.0, 133.6, 133.2 (d, J = 2.6 Hz), 131.5, 131.0, 130.7, 130.6, 130.1 (d, J = 18.5 Hz), 129.4, 127.1 (d, J = 4.3 Hz), 120.9 (d, J = 19.2 Hz); elemental analysis: calcd. (%) for $C_{19}H_{11}Cl_2FO$ (345.19): C 66.11, H 3.21; found: C 66.02, H 3.17.

3,6-Dichloro-2-fluoro-4′-nitrobiphenyl (15): From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **15** was obtained; yield: 0.203 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.34 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 155.5 (d, J = 251.3 Hz), 147.9, 138.4, 132.1 (d, J = 2.6 Hz), 131.2, 130.8, 128.1 (d, J = 18.5 Hz), 126.0 (d, J = 4.3 Hz), 123.6, 120.6 (d, J = 19.2 Hz); elemental analysis: calcd. (%) for $C_{12}H_6Cl_2FNO_2$ (286.09): C 50.38, H 2.11; found: C 50.48, H 2.19.

3′,6′-Dichloro-2′-fluorobiphenyl-3-carbonitrile (16): From 3-bromobenzonitrile (0.182 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **16** was obtained; yield: 0.170 g (64%). ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 7.80–7.70 (m, 1H), 7.67 (s, 1H), 7.65–7.60 (m, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 156.0 (d, J = 251.5 Hz), 134.9, 134.0, 133.6, 132.8 (d, J = 2.8 Hz), 132.7, 131.0, 129.7, 128.4 (d, J = 18.4 Hz), 126.4 (d, J = 4.2 Hz), 120.8 (d, J = 19.0 Hz), 118.6, 113.2; elemental analysis: calcd. (%) for $C_{13}H_6Cl_2FN$ (266.10): C 58.68, H 2.27; found: C 58.78, H 2.32.

3,6-Dichloro-2-fluoro-3′-nitrobiphenyl (17): From 3-bromonitrobenzene (0.202 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **17** was obtained; yield: 0.194 g (68%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.24 (d, J = 8.2 Hz, 1H), 8.19 (s, 1H), 7.64–7.58 (m, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 155.6 (d, J = 251.5 Hz), 148.2, 136.2, 133.4, 132.4 (d, J = 2.4 Hz), 130.7, 129.4, 127.8 (d, J = 18.4 Hz), 125.9 (d, J = 4.2 Hz), 125.3, 123.6, 120.6 (d, J = 19.0 Hz); elemental analysis: calcd. (%) for $C_{12}H_6Cl_2FNO_2$ (286.09): C 50.38, H 2.11; found: C 50.18, H 2.25.

3-(3,6-Dichloro-2-fluorophenyl)-pyridine (20): From 3-bromopyridine (0.158 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **20** was obtained; yield: 0.148 g (61%). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 8.61 (d, J = 3.6 Hz, 1H), 8.53 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.60–7.50 (m, 2H), 7.41 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 157.1 (d, J = 251.5 Hz), 150.9, 150.3, 139.9 (d, J = 0.9 Hz), 134.0 (d, J = 2.5 Hz), 132.2, 130.3, 127.8 (d, J = 18.6 Hz), 127.4 (d, J = 4.2 Hz), 125.2, 121.5 (d, J = 19.1 Hz); elemental analysis: calcd. (%) for $C_{11}H_6Cl_2FN$ (242.08): C 54.58, H 2.50; found: C 54.41, H 2.49.

4-(3,6-Dichloro-2-fluorophenyl)-pyridine (21): From 4-bromopyridine hydrochloride (0.194 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **21** was obtained; yield: 0.181 g (75%). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 8.67 (d, J = 4.9 Hz, 2H), 7.33 (t, J = 7.8 Hz, 1H), 7.25–7.18 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 156.5 (d, J = 251.5 Hz), 150.5, 142.6, 133.2 (d, J = 2.9 Hz), 132.4, 128.7 (d, J = 18.5 Hz), 127.5 (d, J = 4.4 Hz), 126.7, 121.6 (d, J = 18.9 Hz); elemental analysis: calcd. (%) for $C_{11}H_6Cl_2FN$ (242.08): C 54.58, H 2.50; found: C 54.41, H 2.49.

3-(3,6-Dichloro-2-fluorophenyl)-quinoline (22): From 3-bromoquinoline (0.208 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **22** was obtained; yield: 0.231 g (79%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.89 (s, 1H), 8.19 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 156.0 (d, J = 251.5 Hz), 150.8, 147.6, 137.4, 132.9 (d, J = 2.9 Hz), 130.5, 130.3, 129.3, 128.1, 127.3, 127.1, 126.8 (d, J = 18.5 Hz), 125.9 (d, J = 4.1 Hz), 125.2, 120.5 (d, J = 19.1 Hz); elemental analysis: calcd. (%) for $C_{15}H_8Cl_2FN$ (292.13): C 61.67, H 2.76; found: C 61.57, H 2.89.

5-(3,6-Dichloro-2-fluorophenyl)-pyrimidine (23): From 5-bromopyrimidine (0.159 g, 1 mmol) and 1,4-dichloro-2-fluorobenzene (0.247 g, 1.5 mmol), **23** was obtained; yield: 0.146 g (60%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.28 (s, 1H), 8.78 (s, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.5, 127.6, 155.8 (d, J = 251.5 Hz), 132.6 (d, J = 2.9 Hz), 131.4, 126.6, 126.1 (d, J = 4.4 Hz), 123.4 (d, J = 18.2 Hz), 120.8 (d, J = 19.0 Hz); elemental analysis: calcd. (%) for $C_{10}H_5Cl_2FN_2$ (243.06): C 49.41, H 2.07; found: C 49.32, H 2.05.

3-(2,4-Dichloro-6-fluorophenyl)quinoline (24a) and 3-(2,6-dichloro-4-fluorophenyl)quinoline (24b): From 3-bromoquinoline (0.208 g, 1 mmol) and 1,3-dichloro-5-fluorobenzene (0.178 μL, 1.5 mmol), **24a** and **24b** were obtained as a mixture; yield: 0.224 g (77%) in an 85:15 ratio. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.89 (bs, 0.85H, **24a**), 8.81 (d, J = 2.1 Hz, 0.15H, **24b**), 8.20 (bs, 1.7H, **24a**), 8.18 (bs, 0.15H, **24b**), 8.13 (d, J = 1.9 Hz, 0.15H **24b**), 7.89 (dd, J = 1.5 and 7.7 Hz, 1H, **24a** and **24b**), 7.8 (ddd, J = 1.6, 7.0, and 8.8 Hz, 1H, **24a** and **24b**) 7.62 (ddd, J = 1.0, 6.6 and 7.9 Hz, 1H, **24a** and **24b**), 7.42 (t, J = 1.9 Hz, 0.85H, **24a**), 7.25 (s, 0.15H, **24b**), 7.22 (dd, J = 2.0 and 8.8 Hz, 0.85H, **24a**), 6.86 (s, 0.15H, **24b**); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 160.3 (d, J = 254.0 Hz), 150.9, 147.5, 137.7, 135.4 (d, J = 4.7 Hz), 135.1 (d, J = 12.0 Hz), 130.4, 129.2, 128.0, 127.4, 127.2, 126.0 (d, J = 2.7 Hz), 125.0, 124.3 (d, J = 18.7 Hz), 115.6 (d, J = 26.6 Hz); elemental analysis: calcd. (%) for $C_{15}H_8ClF_2N$ (275.68): C 65.35, H 2.92; found: C 65.17, H 3.11.

5-(2-Fluoro-6-methoxyphenyl)-pyrimidine (25a) and 5-(2-fluoro-4-methoxyphenyl)-pyrimidine (25b): From 5-bromopyrimidine (0.159 g, 1 mmol) and 1-fluoro-3-methoxybenzene (0.189 g, 1.5 mmol), **25a** and **25b**; yields: 0.049 g (24%) and 0.034 g (17%), respectively.

25a: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.16 (s, 1H), 8.81 (s, 2H), 7.36 (q, J = 7.9 Hz, 1H), 6.89–6.78 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.3 (d, J = 247.1 Hz), 158.0 (d, J = 2.2 Hz), 157.8 (d, J = 6.5 Hz), 157.2, 130.8 (d, J = 10.9 Hz), 126.2, 111.6 (d, J = 17.3 Hz), 108.5 (d, J = 22.8 Hz), 106.8 (d, J = 3.0 Hz), 56.1; elemental analysis: calcd (%) for $C_{11}H_9FN_2O$ (204.20): C 64.70, H 4.44; found: C 64.87, H 4.28.

25b: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.17 (s, 1H), 8.89 (s, 2H), 7.36 (t, J = 8.2 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 12.5 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 161.8 (d, J = 1.4 Hz), 158.0 (d, J = 250.8 Hz), 157.1, 156.0 (d, J = 4.0 Hz), 130.3 (d, J = 5.1 Hz), 129.7, 114.2 (d, J = 14.3 Hz), 111.1 (d, J = 3.0 Hz), 102.4 (d, J = 25.9 Hz), 55.7.

3-(6-Fluoro-2,3-dimethoxyphenyl)-quinoline (26a) and 3-(2-fluoro-4,5-dimethoxyphenyl)-quinoline (26b): From 3-bromoquinoline (0.208 g, 1 mmol) and 4-fluoro-1,2-dimethoxybenzene (0.234 g), **26a** and **26b** were obtained; yields: 0.076 g (27%) and 0.054 g (19%), respectively.

26a: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.00 (s, 1H), 8.27 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 6.95–6.92 (m, 2H), 3.91 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 153.2 (d, J = 241.3 Hz), 150.9 (d, J = 1.6 Hz), 148.5 (d, J = 3.0 Hz), 146.5 (d, J = 5.4 Hz), 146.0, 136.4 (d, J = 2.0 Hz), 128.7, 128.1, 127.1, 126.7, 125.7, 124.0, 119.9 (d, J = 16.9 Hz), 111.6 (d, J = 10.0 Hz), 109.5 (d, J = 23.9 Hz), 59.9, 55.4; elemental analysis: calcd. (%) for $C_{17}H_{14}CFNO_2$ (283.30): C 72.07, H 4.98; found: C 72.27, H 5.14.

26b: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.08 (s, 1H), 8.27 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 6.99

(d, J=7.3 Hz, 1H), 6.79 (d, J=11.6 Hz, 1H), 3.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=154.3 (d, J=242.1 Hz), 150.8 (d, J=3.8 Hz), 150.1 (d, J=9.7 Hz), 147.0, 145.9 (d, J=2.5 Hz), 135.0 (d, J=3.4 Hz), 129.5, 129.2, 128.9 (d, J=2.1 Hz), 127.9, 127.8, 126.9, 116.3 (d, J=15.0 Hz), 112.4 (d, J=4.7 Hz), 100.8 (d, J=28.6 Hz), 56.6, 56.3.

2′-Fluoro-3′-methyl-6′-nitrobiphenyl-4-carbonitrile (27): From 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-fluoro-1-methyl-4-nitrobenzene (0.232 g, 1.5 mmol), **27** was obtained; yield: 0.095 g (37%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.70 (d, J=9.0 Hz, 1H), 7.67 (d, J=8.3 Hz, 2H), 7.35–7.30 (m, 3H), 2.34 (d, J=2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=157.8 (d, J=252.0 Hz), 147.3, 136.2, 132.4, 132.1 (d, J=19.2 Hz), 131.6 (d, J=6.1 Hz), 129.9 (d, J=1.5 Hz), 129.1, 123.2 (d, J=21.4 Hz), 120.1 (d, J=4.4 Hz), 118.6, 112.7, 15.4 (d, J=3.7 Hz); elemental analysis: calcd. (%) for $C_{14}H_9FN_2O_2$ (256.23): C 65.62, H 3.54; found: C 65.48, H 3.44.

3-(2-Fluoro-3-methyl-6-nitrophenyl)-quinoline (28): From 3-bromoquinoline (0.208 g, 1 mmol) and 2-fluoro-1-methyl-4-nitrobenzene (0.232 g, 1.5 mmol), **28** was obtained; yield: 0.082 g (29%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=8.76 (s, 1H), 8.11 (s, 1H), 8.75 (d, J=8.0 Hz, 1H), 7.79–7.68 (m, 3H), 7.53 (t, J=8.1 Hz, 1H), 7.33 (t, J=8.1 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=158.3 (d, J=249.5 Hz), 149.9, 147.7, 147.4, 136.0, 131.8 (d, J=19.1 Hz), 131.2 (d, J=5.5 Hz), 130.2, 129.3, 128.0, 127.4, 127.2, 124.4, 121.4 (d, J=20.6 Hz), 119.9 (d, J=4.0 Hz), 14.2; elemental analysis: calcd. (%) for $C_{16}H_{11}FN_2O_2$ (282.27): C 68.08, H 3.93; found: C 68.17, H 3.90.

6-Fluoro-5-methylbiphenyl-2,4′-dicarbonitrile (29): From 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-fluoro-4-methylbenzonitrile (0.203 g, 1.5 mmol), **29** was obtained; yield: 0.172 g (73%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.72 (d, J=8.3 Hz, 2H), 7.53 (d, J=7.8 Hz, 2H), 7.43 (d, J=7.9 Hz, 1H), 7.28 (t, J=7.8 Hz, 1H), 2.34 (d, J=1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ =157.7 (d, J=249.0 Hz), 136.5, 132.3, 132.1 (d, J=5.6 Hz), 132.0, 130.7 (d, J=1.6 Hz), 130.5 (d, J=19.2 Hz), 129.1 (d, J=4.8 Hz), 118.3, 117.0 (d, J=4.1 Hz), 113.0, 111.0 (d, J=4.5 Hz), 15.2 (d, J=4.0 Hz); elemental analysis: calcd. (%) for $C_{15}H_9FN_2$ (236.24): C 76.26, H 3.84; found: C 76.40, H 3.99.

6-Fluoro-4′-formyl-5-methylbiphenyl-2-carbonitrile (30): From 4-bromobenzaldehyde (0.203 g, 1 mmol) and 3-fluoro-4-methylbenzonitrile (0.203 g, 1.5 mmol), **30** was obtained; yield: 0.098 g (41%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=10.0 (s, 1H), 7.95 (d, J=8.3 Hz, 2H), 7.59 (d, J=8.3 Hz, 2H), 7.43 (d, J=7.9 Hz, 1H), 7.27 (t, J=7.5 Hz, 1H), 2.34 (d, J=2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=191.7, 157.7 (d, J=245.6 Hz), 137.8, 136.5, 132.0, 131.8 (d, J=5.9 Hz), 131.3 (d, J=19.0 Hz), 130.7 (m), 129.8, 129.1 (d, J=4.5 Hz), 117.3 (d, J=4.4 Hz), 111.9 (d, J=4.9 Hz), 15.3 (d, J=3.9 Hz); elemental analysis: calcd. (%) for $C_{15}H_{10}FNO$ (239.24): C 75.30, H 4.21; found: C 75.09, H 4.07.

6-Fluoro-5-methyl-3′-nitrobiphenyl-2-carbonitrile (31): From 1-bromo-3-nitrobenzene (0.202 g, 1 mmol) and 3-fluoro-4-methylbenzonitrile (0.203 g, 1.5 mmol), **31** was obtained; yield: 0.118 g (46%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=7.48 (d, J=8 Hz, 1H), 7.42–7.35 (m, 2H), 7.34–7.28 (m, 2H), 7.23 (dd, J=7.2 and 0.8 Hz, 1H), 2.41 (d, J=2.1 Hz, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=156.9 (d, J=249.6 Hz), 147.2, 134.8 (d, J=1.6 Hz), 132.4, 131.2 (d, J=5.6 Hz), 131.0, 129.9 (d, J=18.5 Hz), 128.7, 128.0 (d, J=4.8 Hz), 124.0 (d, J=2.5 Hz), 123.0, 116.0 (d, J=4.3 Hz), 110.2 (d, J=4.2 Hz), 14.3 (d, J=4.2 Hz); elemental analysis: calcd. (%) for $C_{14}H_9FN_2O_2$ (256.23): C 65.62, H 3.54; found: C 65.78, H 3.40.

6-Fluoro-5,2′-dimethylbiphenyl-2-carbonitrile (32): From 2-bromotoluene (0.171 g, 1 mmol) and 3-fluoro-4-methylbenzonitrile (0.203 g, 1.5 mmol), **32** was obtained; yield: 0.144 g (64%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=7.48 (d, J=8.0 Hz, 1H), 7.42–7.35 (m, 2H), 7.34–7.28 (m, 2H), 7.23 (dd, J=7.2, 0.8 Hz, 1H), 2.41 (d, J=2.1 Hz, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=156.9 (d, J=248.7 Hz), 135.5, 131.6 (d, J=22.3 Hz), 130.7, 130.3, 130.0 (d, J=5.6 Hz), 129.3, 128.7, 128.3, 127.3 (d, J=4.2 Hz), 124.9, 116.2 (d, J=3.8 Hz), 111.2 (d, J=4.9 Hz), 18.6 (d, J=1.9 Hz), 14.2 (d, J=4.1 Hz); elemental analysis: calcd. (%) for $C_{15}H_{12}FN$ (225.26): C 79.98, H 5.37; found: C 79.78, H 5.17.

3-Fluoro-4-methyl-2-quinolin-3-ylbenzonitrile (33): From 3-bromoquinoline (0.208 g, 1 mmol) and 3-fluoro-4-methylbenzonitrile (0.102 g, 1.5 mmol), **33** was obtained; yield: 0.136 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=8.91 (s, 1H), 8.25 (s, 1H), 8.09 (d, J=8.5 Hz, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.71 (t, J=7.5 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.27 (t, J=7.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=158.1 (d, J=248.7 Hz), 150.4 (d, J=2.3 Hz), 147.7, 137.2, 131.9 (m), 130.5, 129.3, 129.2 (d, J=4.4 Hz), 128.9, 128.2, 127.3, 127.2, 125.1, 117.2 (d, J=3.7 Hz), 111.6 (d, J=4.4 Hz), 15.2; elemental analysis: calcd, (%) for $C_{17}H_{11}FN_2$ (262.28): C 77.85, H 4.23; found: C 77.89, H 4.09.

6′-Bromo-2′-fluoro-3′-methoxybiphenyl-3-carbonitrile (34): From 3-bromobenzonitrile (0.182 g, 1 mmol) and 4-bromo-2-fluoro-1-methoxybenzene (0.102 g, 1.5 mmol), **34** was obtained; yield: 0.128 g (42%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.66–7.61 (m, 1H), 7.58 (s, 1H), 7.52–7.48 (m, 2H), 7.34 (dd, J=8.9, 2.0, 1H), 6.84 (t, J=8.7 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=149.9 (d, J=251.5 Hz), 147.6 (d, J=11.0 Hz), 135.6, 134.7, 133.8, 131.9, 129.1, 129.0 (d, J=15.1 Hz), 128.0 (d, J=4.8 Hz), 118.5, 114.2 (d, J=2.9 Hz), 113.3 (d, J=2.0 Hz), 112.6, 56.5; elemental analysis: calcd. (%) for $C_{14}H_9BrFNO$ (306.13): C 54.93, H 2.96; found: C 55.11, H 3.08.

3-(6-Bromo-2-fluoro-3-methoxyphenyl)-quinoline (35): From 3-bromoquinoline (0.208 g, 1 mmol) and 4-bromo-2-fluoro-1-methoxybenzene (0.102 g, 1.5 mmol), **35** was obtained; yield: 0.153 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=8.80 (s, 1H), 8.07 (d, J=8.0 Hz, 1H), 8.06 (s, 1H), 7.76 (d, J=8.0 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H), 7.48 (t, J=7.8 Hz, 1H), 7.34 (d, J=8.5 Hz, 1H), 6.81 (t, J=6.7 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=151.1 (d, J=1.6 Hz), 150.2 (d, J=250.3 Hz), 147.5 (d, J=11.9 Hz), 147.4, 137.2, 130.0, 129.2, 128.0, 127.9 (d, J=4.7 Hz), 127.7 (d, J=15.1 Hz), 127.4 (d, J=18.3 Hz), 126.9, 114.0 (d, J=3.2 Hz), 113.9, 56.4, elemental analysis: calcd. (%) for $C_{16}H_{11}BrFNO$ (332.17): C 57.85, H 3.34; found: C 57.99, H 3.10.

5-(6-Bromo-2-fluoro-3-methoxyphenyl)-pyrimidine (36): From 5-bromopyrimidine (0.159 g, 1 mmol) and 4-bromo-2-fluoro-1-methoxybenzene (0.102 g, 1.5 mmol), **36** was obtained; yield: 0.108 g (38%). ^{1}H NMR (400 MHz, $CDCl_3$,

25 °C): $\delta = 9.19$ (s, 1H), 8.70 (s, 2H), 7.38 (dd, $J = 8.9$, 2.0 Hz, 1H), 6.89 (t, $J = 8.7$ Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 158.2$, 157.6 (d, $J = 1.6$ Hz), 150.1 (d, $J = 252.2$ Hz), 147.7 (d, $J = 11.7$ Hz), 128.8, 128.3 (d, $J = 4.8$ Hz), 124.4 (d, $J = 15.6$ Hz), 114.8 (d, $J = 2.4$ Hz), 113.4 (d, $J = 1.6$ Hz), 56.6; elemental analysis: calcd (%) for $C_{11}H_8BrFN_2O$ (283.10): C 46.67, H 2.85; found: C 46.47, H 3.12.

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of the new compounds are available in the Supporting Information.

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