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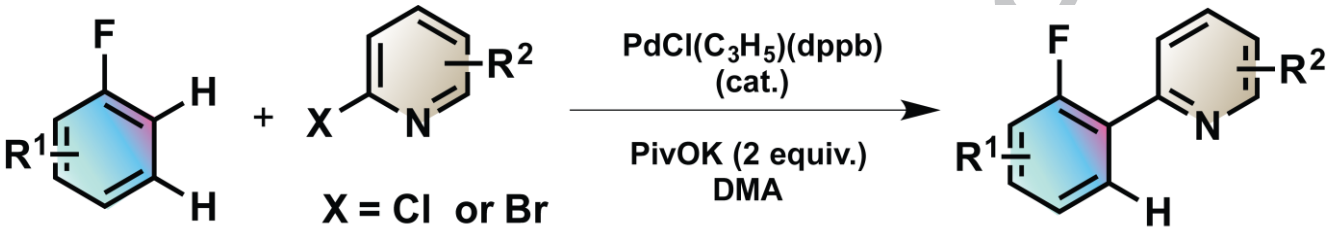
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Graphical Abstract

Synthesis of 2-(Fluorinated Aryl)pyridine Derivatives via Palladium-Catalyzed C–H Bond Arylation of Fluorobenzenes using 2-Halopyridines as Aryl Sources

R. Boyaala, R. Touzani, V. Guerchais, J.-F. Soulé[a,] * and H. Doucet [a,] *



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Synthesis of 2-(Fluorinated Aryl)pyridine Derivatives *via* Palladium-Catalyzed C–H Bond Arylation of Fluorobenzenes using 2-Halopyridines as Aryl Sources

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ABSTRACT

We report herein on palladium-catalyzed direct arylation of (poly)fluorobenzene derivatives in the presence of 2-halopyridines for the one-step synthesis of 2-[(poly)fluorinated aryl]pyridine derivatives. The reactivity of 2-bromopyridines strongly dependents on its substituents at C6 position. The reaction proceeds nicely using a diphosphine palladium catalyst, and potassium pivalate/dimethylacetamide (PivOK/DMA) as catalytic system. The reaction was regioselective and occurred at the *ortho*-position of fluorine atoms.

1. Introduction

2-[(Poly)fluorinated aryl]pyridines represent an important class of ligands, which have been employed for the preparation of luminescence cyclometalated iridium(III) complexes. For example, the archetype blue phosphorescent emitter **FIrpic** (bis(2-(4,6-difluoropyridine)(picolinato)iridium) that displays appealing luminescent properties has been used in organic light emitting diodes (Figure 1, left).[1] Cyclometalated iridium(III) complexes are also used as photocatalysts.[2] In addition, the motif 2-[(poly)fluorinated aryl]pyridine is present in many pharmaceuticals. As exemple, 2-(2-(2-fluorophenyl)pyridin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one **I** is an experimental drug currently under evaluation for the inibition of mitogen-activated protein kinase-2 in the treatement of rheumatoid arthritis (Figure 1, center).[3] Moreover, Vismodegib, which contains a similar structure, is an approved medicinal drug for the treatment of basal-cell carcinoma (Figure 1, right).

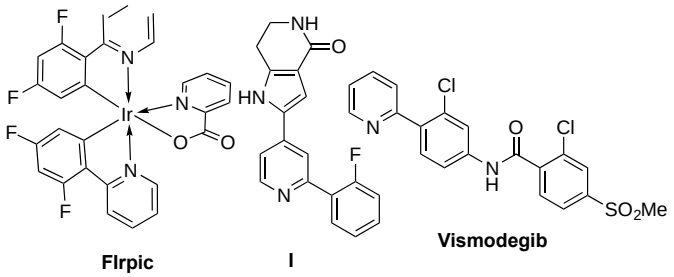


Figure 1. Relevant Structures Containing 2-[(Poly)fluorinated aryl]pyridines motifs

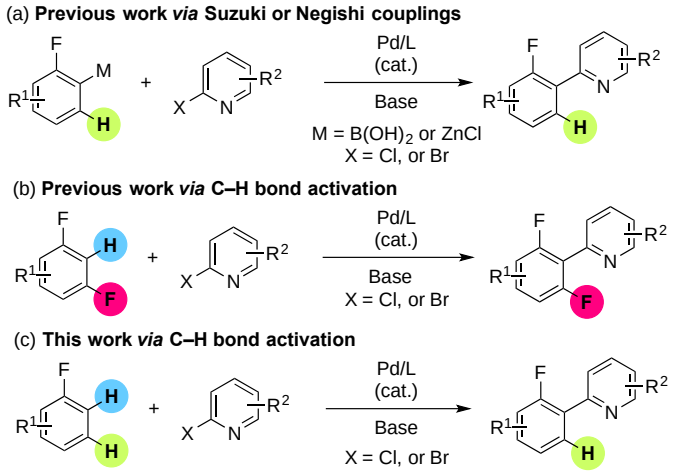
2-[(Poly)fluorinated aryl]pyridines are generally prepared using classical Suzuki reaction from fluorinated phenylboronic acids and 2-bromopyridine derivatives.[4] Alternativelely, they can be also synthetized using Negishi coupling reactions (Scheme 1a).[5] Since the pioneering work of Fagnou and co-workers on palladium-catalyzed direct arylation of electron-deficient poly(fluoro)benzenes,[6] this methodology proved as one of the most eco-friendly and straightforward access to (poly)(fluoro)biphenyls (Figure 2a).[7] However, palladium-catalyzed C–H bond functionalization of (hetero)arenes,[8] and especially poly(fluoro)benzene using 2-halopyridines as aryl source are very scarce. Only examples using the activated 1,3-

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difluorobenzene motif have been reported, to date (Scheme 1b).[9] However, this protocol did not allow the preparation of proligands suitable for the access of cyclometalated (C^N) complexes, albeit through a second step of selective defluorination.[10] We propose herein to synthetize a variety of 2-[(poly)fluorinated aryl]pyridine derivatives through palladium-catalyzed C-H bond activation of (poly)fluorobenzenes with 2-halopyridines as aryl sources (Scheme 1c).

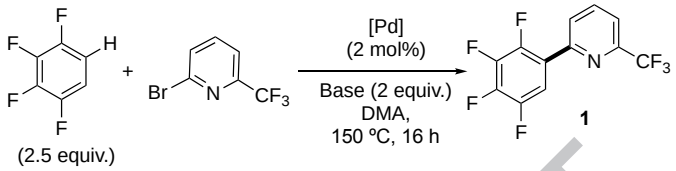


Scheme 1. Synthesis of 2-[(Poly)fluorinated aryl]pyridine Motifs

2. Results and Discussion

Based on our previous work on 2-halopyridines as aryl sources,[9c] and Pd-catalyzed C–H bond arylation of fluorobenzene derivatives,[11] we selected 1,2,3,4-tetrafluorobenzene and 2-bromo-6-(trifluoromethyl)pyridine as model substrates (Table 1). In the presence of $Pd(OAc)_2$ associated to KOAc in DMA at 150 ºC, the desired arylated product **1** was obtained in 21% yield (Table 1, entry 1). The use of 2 mol% of a diphosphine palladium catalyst [$PdCl(C_3H_5)$(dppb)] gave a better yield of 51% (Table 1, entry 2). When the reaction was performed using K_2CO_3 as base, no reaction occurred (Table 1, entry 3); whereas the use of potassium pivalate (PivOK) or potassium adamantane-1-carboxylate ($AdCO_2K$) gave **1** a in 68% and 48% yields, respectively (Table 1, entries 4 and 5). The dramatic influence of the bases for this coupling seems to confirm that a concerted metalation-deprotonation mechanism (CMD) takes place. [6, 12] It is important to note that under these optimized reaction condition, namely, 2 mol% of a diphosphine palladium catalyst [$PdCl(C_3H_5)$(dppb)] associated to 2 equivalents of potassium pivalate in DMA at 150 ºC, no reaction occurred using 2-bromopyridine as an aryl source (Table 1, entry 6). Based on our previous observations[9c] and this result we postulated that the C6 substituent can modulate the reactivity of 2-halopyridines: i) an electron-withdrawing group should favors the oxidative addition of the C–Br bond to palladium(0) (electronic effect); ii) a bulky group could prevent a strong pyridyl nitrogen atom coordination to palladium resulting in catalyst poisoning (steric effect).

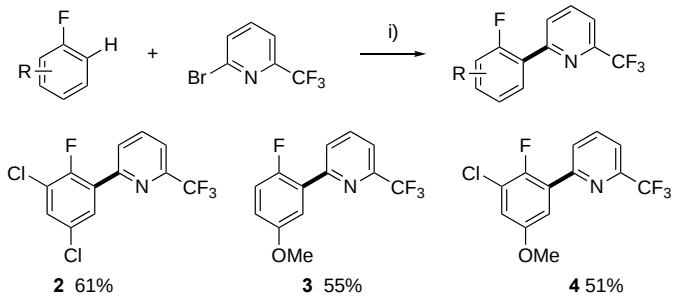
Table 1. Optimization of the Reaction Conditions.



Entry	[Pd]	Base	Yield **1** (%)
1	$Pd(OAc)_2$	KOAc	21
2	$PdCl(C_3H_5)$(dppb)	KOAc	51
3	$PdCl(C_3H_5)$(dppb)	K_2CO_3	0
4	$PdCl(C_3H_5)$(dppb)	PivOK	68
5	$PdCl(C_3H_5)$(dppb)	$AdCO_2K$	48
6[a]	$PdCl(C_3H_5)$(dppb)	PivOK	0

[a] Reaction performed using 2-bromopyridine instead of 2-bromo-6-(trifluoromethyl)pyridine

Under the same reaction conditions, we evaluated the reactivity a set of fluorobenzene derivatives with 2-bromo-6-(trifluoromethyl)pyridine as aryl source (Scheme 2). Conversely, under these conditions, no reaction occurred using 2-fluorobenzene as coupling partner. This result was expected as mono-fluorinated benzenes generally exhibit a poor reactivity in Pd-catalyzed C–H bond arylation.[7h] However, if appropriate additional functional groups are introduced at proper positions of 2-fluorobenzene, substituted derivatives can be used as reactive substrates.[11] As example, 1,3-dichloro-4-fluorobenzene, 4-fluoroanisole and 3-chloro-4-fluoroanisole were regioselectively arylated at the *ortho*-position of the fluorine atom in the presence of 2-bromo-6-(trifluoromethyl)pyridine to deliver the corresponding 2-(2-fluoroaryl)pyridines **2**–**4** in 51%–61% yields.



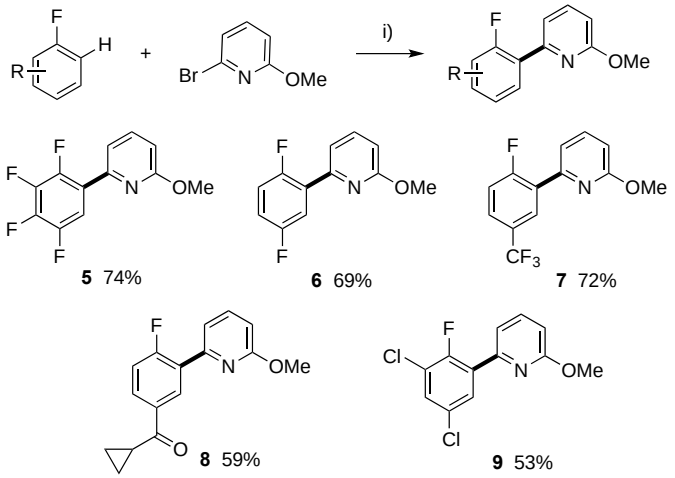
i) $PdCl(C_3H_5)$(dppb) (2 mol%), PivOK (2 equiv.), DMA, 150 ºC, 16 h.

Scheme 2. Scope of Pd-Catalyzed Direct Arylation of Fluorobenzenes with 2-Bromo-6-(trifluoromethyl)pyridine.

Then, we investigated the influence of an electron-donating group such as a methoxy at the C6 position of the 2-bromopyridine for its coupling with fluorobenzene derivatives under palladium catalysis (Scheme 3). Using the same reaction conditions, 1,2,3,4-tetrafluorobenzene was arylated to give **5** in 74% yield. 1,4-Difluorobenzene was also a suitable coupling partner as it allowed the synthesis of 2-(2,5-difluorophenyl)-6-methoxypyridine (**6**) in 69% yield. Hou and co-workers had reported that 1-fluoro-4-(trifluoromethyl)benzene could be selectively mono-arylated at the *ortho*-position of the fluorine atom using palladium catalysis, but they did not employed 2-halopyridines as aryl sources.[13] Using our reaction conditions, the direct arylation of 1-fluoro-4-(trifluoromethyl)benzene with 2-bromo-6-methoxypyridine occurred again at the *ortho*-position of fluorine atom to provide the corresponding 2-arylpyridine **7** in an excellent 72% yield. Cyclopropyl 4-fluorophenyl ketone, which is a challenging substrate, –due to the presence of reactive

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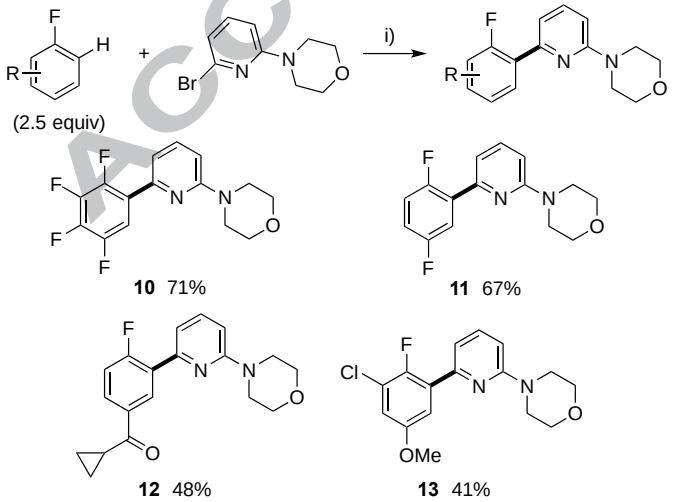
C(sp^2)–H and cyclopropyl C(sp^3)–H bonds– was exclusively arylated at the *ortho*-position to the fluorine atom to give **8** in 59% yield. It should be mentioned that no other regioisomers or arylated products resulting from cyclopropyl C(sp^3)–H bond activation, was observed. 2-Bromo-6-methoxypyridine and 2-bromo-6-(trifluoromethyl)pyridine displayed a similar reactivity in the direct arylation of 1,3-dichloro-4-fluorobenzene, as the resulting product **9** was isolated in 53% yield, comparable to the yield of **4**.



i) $PdCl(C_3H_5)$(dppb) (2 mol%), PivOK (2 equiv.), DMA, 150 °C, 16 h.

Scheme 3. Scope of Pd-Catalyzed Direct Arylation of Fluorobenzenes with 2-Bromo-6-methoxypyridine.

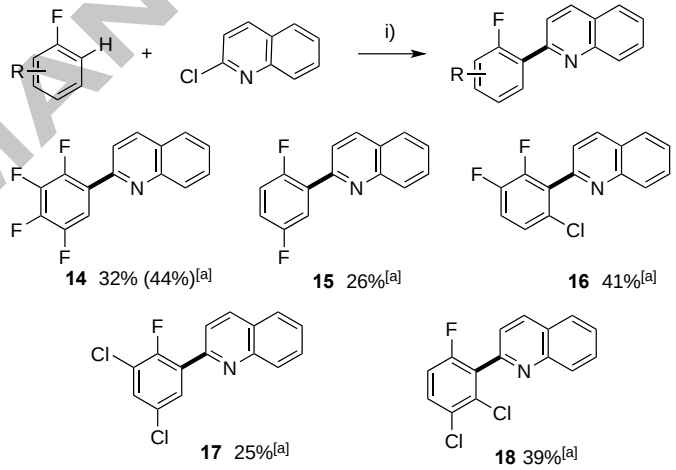
Next, we investigated the influence of an electron-donating bulky group at the pyridyl C6 position such as morpholine (Scheme 4). Noteworthy, 4-(pyridin-2-yl)morpholine is a very important motif embedded in some pharmaceuticals such as Befetupitant and Sonidegib. Again, 1,2,3,4-tetrafluorobenzene and 1,4-difluorobenzene were mono-arylated to give **10** and **11** in satisfactory yields of 71% and 67%, respectively. This morpholine-containing derivative displayed a lower reactivity with mono-fluorobenzenes, mainly due to the formation of homo-coupling products from the heteroaryl bromide. Indeed, from cyclopropyl 4-fluorophenyl ketone and 4-(6-bromopyridin-2-yl)morpholine, the 2-fluoroarylpyridine **12** was isolated in only 48% yield. A similar reactivity trend was observed with 3-chloro-4-fluoroanisole, which afforded **13** in 41% yield.



i) $PdCl(C_3H_5)$(dppb) (2 mol%), PivOK (2 equiv.) DMA, 150 °C, 16 h.

Scheme 4. Scope of Pd-Catalyzed Direct Arylation of Fluorobenzenes with 4-(6-Bromopyridin-2-yl)morpholine.

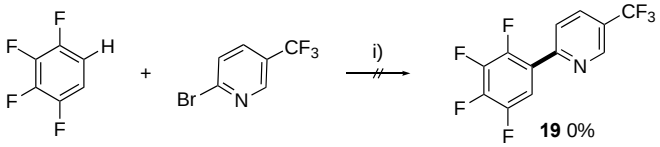
Finally, we investigated the reactivity of 2-chloroquinoline, which is less expensive than 2-bromoquinoline (Scheme 5). Using the previous reaction conditions, namely 2 mol% $PdCl(C_3H_5)$(dppb) catalysts associated to 2 equivalents of potassium pivalate in DMA at 150 °C, the 2-(2,3,4,5-tetrafluorophenyl)quinoline (**14**) was obtained in only 32% yield. Ammonium bromide salts are often used as additives for reaction with aryl chlorides to improve the yield by participating to the stabilization of the catalytic active species.[14] When the reaction was performed in the presence of 1.5 equivalents of tetrabutylammonium bromide, the yield in 2-arylpyridine **14** rose to 44%. 1,4-Difluorobenzene displayed a poor reactivity for this cross-coupling, as **15** was isolated in only 26% yield. 1-Chloro-3,5-difluorobenzene has been arylated with 2-chloroquinoline at the C–H bond flanked by fluorine and chlorine atoms allowing the formation of 2-(6-chloro-2,3-difluorophenyl)quinoline (**16**) in 41% yield. The formation of another regioisomer was observed by GC-MS and NMR analysis of the crude mixture, but in a very low yield. Mono-fluorinated benzenes have also been employed. 1,3-Dichloro-4-fluorobenzene was arylated at the *ortho* position of the fluorine atom to give **17** in poor 25% yield. 1,2-dichloro-4-fluorobenzene was mainly arylated at the C–H bond flanked by fluorine and chlorine atoms affording **18** in 39% yield, with the formation of another regioisomer in very low yield.



i) $PdCl(C_3H_5)$(dppb) (2 mol%), PivOK (2 equiv.), DMA, 150 °C, 16 h.
[a] Using 1.5 equiv of Bu_4NBr as additive

Scheme 5. Scope of Pd-Catalyzed Direct Arylation of Fluorobenzenes with 2-Chloroquinolines.

In addition, we observed that under the same reaction conditions 1,2,3,4-tetrafluorobenzene was not arylated using 2-bromo-5-(trifluoromethyl)pyridine as aryl source, demonstrating the critical role of the C6 pyridyl substituent (Scheme 6).



i) $PdCl(C_3H_5)$(dppb) (2 mol%), PivOK (2 equiv.), DMA, 150 °C, 16 h.

Scheme 6. Reactivity of 2-Bromo-5-(trifluoromethyl)pyridine.

3. Conclusion

In summary, we have demonstrated that 2-[(poly)fluorinated aryl]pyridines can be prepared in moderate to good yields from 6-substituted 2-halopyridines *via* palladium-catalyzed direct arylation of (poly)fluorobenzene derivatives. We demonstrate that the substituent at the pyridyl C6 position displays a critical role on the reactivity of 2-bromopyridine derivatives. Indeed,

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unsubstituted 2-bromopyridine exhibits no reactivity; while 2-bromopyridines bearing at the pyridyl C6 position a bulky group with electron-withdrawing character or an electron-donating group (e.g., CF_3, MeO or morpholine, resp.) are very reactive. The major by-products of these couplings are KBr / PivOH instead of metallic salts formed using more classical coupling procedures, making this process economically viable and environmentally attractive.

Acknowledgments

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Supplementary Material

DMA (*N*,*N*-dimethylacetamide) (99%) and PivOK were purchased from Acros. $[Pd(C_3H_5)Cl]_2$ (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 in vacuum. The powder was used without purification. (^{31}P 381 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for the synthesis of 1-18: As a typical experiment, the reaction of the 2-halopyridine (1 mmol), fluorobenzene derivative (2.5 mmol) and PivOK (0.154 g, 1.1 mmol) at 150 °C during 16 h in DMA (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12 mg, 0.02 mmol) (see tables or schemes) under argon affords the arylation product after evaporation of the solvent and filtration on silica gel.

2-(2,3,4,5-Tetrafluorophenyl)-6-(trifluoromethyl)pyridine (1): From 1,2,3,4-tetrafluorobenzene (268 µL, 2.5 mmol) and 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 85:15) to afford the desired compound **1** (201 mg, 68%) as a white solid mp = 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.04 – 7.93 (m, 2H), 7.77 – 7.70 (m, 1H), 7.70 – 7.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.8 (m), 148.2 (q, *J* = 35.7 Hz), 147.9 (td, *J* = 3.8 and 237.8 Hz), 146.5 (md, *J* = 246.5 Hz), 146.4 (md, *J* = 247.5 Hz), 141.9 (ddd, *J* = 5.6, 17.1 and 245.1 Hz), 138.4, 135.5 (ddd, *J* = 3.1, 12.6 and 18.4 Hz), 126.5 (d, *J* = 11.5 Hz), 121.3 (q, *J* = 274.6 Hz), 119.2 (q, *J* = 2.8 Hz), 110.8 (td, *J* = 2.9 and 22.3 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -138.2 (td, *J* = 8.5 and 12.9 Hz), -145.1 (ddd, *J* = 7.3, 13.4 and 20.9 Hz), -156.5 (ddd, *J* = 3.3, 9.1 and 20.5 Hz). Elemental analysis: calcd (%) for $C_{12}H_4F_7N$ (295.16): C 48.83, H 1.37; found: C 49.12, H 1.57.

2-(3,5-Dichloro-2-fluorophenyl)-6-(trifluoromethyl)pyridine (2): From 2,4-dichloro-1-fluorobenzene (293 µL, 2.5 mmol) and 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 90:10) to afford the desired compound **2** (189 mg, 61%) as

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a white solid mp = 62–64 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.07 – 7.95 (m, 3H), 7.73 (dd, *J* = 2.5, 6.2 Hz, 1H), 7.51 (dd, *J* = 2.7, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (d, *J* = 252.7 Hz), 151.6 (d, *J* = 3.0 Hz), 148.5 (q, *J* = 35.0 Hz), 138.2, 131.2, 130.1 (d, *J* = 4.3 Hz), 129.4 (d, *J* = 2.2 Hz), 128.2 (d, *J* = 12.7 Hz), 126.9 (d, *J* = 11.1 Hz), 122.9 (d, *J* = 20.6 Hz), 121.3 (q, *J* = 273.5 Hz), 120.1 (m). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -68.3, -121.5. Elemental analysis: calcd (%) for $C_{12}H_5Cl_2F_4N$ (310.07): C 46.48, H 1.63; found: C 46.67, H 1.34.

2-(2-Fluoro-5-methoxyphenyl)-6-(trifluoromethyl)pyridine (3): From 4-fluoroanisole (283 µL, 2.5 mmol) and 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 95:5) to afford the desired compound **3** (149 mg, 55%) a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (d, *J* = 8.1 Hz, 1H), 7.95 (t, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 3.7, 6.8 Hz, 2H), 7.12 (dd, *J* = 9.0, 10.7 Hz, 1H), 7.00 – 6.93 (m, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.1, 155.2 (d, *J* = 244.2 Hz), 153.6, 148.2 (q, *J* = 35.0 Hz), 137.8, 127.0 (d, *J* = 11.6 Hz), 126.1 (d, *J* = 12.7 Hz), 121.5 (q, *J* = 273.5 Hz), 118.9 (q, *J* = 2.9 Hz), 117.2 (d, *J* = 1.9 Hz), 117.1 (d, *J* = 31.5 Hz), 114.8 (d, *J* = 2.7 Hz), 55.9. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -68.3, -127.7. Elemental analysis: calcd (%) for $C_{13}H_9F_4NO$ (271.21): C 57.57, H 3.34; found: C 57.41, H 3.28.

2-(3-Chloro-2-fluoro-5-methoxyphenyl)-6-(trifluoromethyl)pyridine (4): From 3-chloro-4-fluoroanisole (317 µL, 2.5 mmol) and 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 95:5) to afford the desired compound **4** (156 mg, 51%) as a white solid mp = 68–71 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.16 (d, *J* = 8.1 Hz, 1H), 7.93 – 7.90 (m, 1H), 7.87 (d, *J* = 10.0 Hz, 1H), 7.63 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.05 (d, *J* = 5.9 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.7, 152.9, 150.8 (d, *J* = 245.3 Hz), 138.1, 127.4 (d, *J* = 12.8 Hz), 127.0 (d, *J* = 11.1 Hz), 122.3, 122.1, 120.0, 119.4 (d, *J* = 2.9 Hz), 117.4, 114.0, 56.0. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -68.3, -121.5. Elemental analysis: calcd (%) for $C_{13}H_8ClF_4NO$ (305.66): C 51.08, H 2.64; found: C 51.19, H 2.78.

2-Methoxy-6-(2,3,4,5-tetrafluorophenyl)pyridine (5): From 1,2,3,4-tetrafluorobenzene (268 µL, 2.5 mmol) and 2-bromo-6-methoxypyridine (188 mg, 1 mmol), the residue was purified by flash chromatography on silica gel gel (petroleum ether-Et_2O, 95:5) to afford the desired compound **5** (190 mg, 74%) a yelow solid mp = 70–73 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.91 – 7.80 (m, 1H), 7.69 (t, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 1.5, 7.6 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.7, 147.1 (m), 147.0 (md, *J* = 250.1 Hz), 146.1 (md, *J* = 248.9 Hz), 141.1 (md, *J* = 250.7 Hz), 140.4 (md, *J* = 250.7 Hz), 139.3, 123.2 (ddd, *J* = 3.9, 6.8 and 10.2 Hz), 117.1 (d, *J* = 13.0 Hz), 111.1 (td, *J* = 3.0, 20.2 Hz), 111.1, 53.3. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -139.6 (dt, *J* = 13.9 and 24.3 Hz), -142.2 (td, *J* = 7.0 and 13.6 Hz), -155.3 – -156.8 (m). Elemental analysis: calcd (%) for $C_{12}H_7F_4NO$ (257.19): C 56.04, H 2.74; found: C 56.19, H 2.98.

2-(2,5-Difluorophenyl)-6-methoxypyridine (6): From 1,4-difluorobenzene (257 µL, 2.5 mmol) and 2-bromo-6-methoxypyridine (188 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 95:5) to afford the desired compound **6** (152 mg, 69%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90 (ddd, *J* = 3.3, 6.1, 9.5 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.05 (ddd, *J* = 3.5, 6.3, 9.0 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.6, 158.9 (dd, *J* = 2.3 and 240.6 Hz), 156.7 (dd, *J* = 2.3 and 247.6 Hz), 148.8 (dd, *J* = 1.8 and 3.6 Hz), 139.1, 117.3, 117.0 (dd, *J* = 4.6 and 32.3 Hz), 116.8 (d, *J* = 3.5 Hz), 116.6, 116.4 (dd, *J* = 12.5 and 27.7 Hz), 110.5, 53.3. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -119.1 (d, *J* = 18.3 Hz), -121.6 (d, *J* = 18.4 Hz). Elemental analysis: calcd (%) for $C_{12}H_9F_2NO$ (221.21): C 65.16, H 4.10; found: C 56.19, H 2.98.

2-(2-Fluoro-5-(trifluoromethyl)phenyl)-6-methoxypyridine (7): From 1-fluoro-4-(trifluoromethyl)benzene (293 µL, 2.5 mmol) and 2-bromo-6-methoxypyridine (188 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 90:10) to afford the desired compound **7** (195 mg, 72%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.47 (dd, *J* = 2.4, 7.2 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.50 (dd, *J* = 2.0 and 7.5 Hz, 1H), 7.34 – 7.20 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.05 (d, *J* = 2.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.8, 162.3 (d, *J* = 255.6 Hz), 148.5 (d, *J* = 3.2 Hz), 139.2, 128.7 (m), 127.7 (d, *J* = 12.2 Hz), 127.1 (d, *J* = 3.7 Hz), 127.0 (d, *J* = 3.7 Hz), 123.8 (q, *J* = 270.1 Hz), 117.3 (d, *J* = 11.9 Hz), 117.0 (d, *J* = 25.0 Hz), 110.7, 53.4. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -62.1, -110.6. Elemental analysis: calcd (%) for $C_{13}H_9F_4NO$ (271.21): C 57.57, H 3.34; found: C 57.45, H 3.69.

Cyclopropyl(4-fluoro-3-(6-methoxypyridin-2-yl)phenyl)methanone (8): From cyclopropyl(4-fluorophenyl)methanone (360 µL, 2.5 mmol) and 2-bromo-6-methoxypyridine (188 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 70:30) to afford the desired compound **8** (160 mg, 59%) as a white solid mp = 68–72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.84 (dd, *J* = 2.4, and 7.6 Hz, 1H), 8.05 (ddd, *J* = 2.4, 4.7 and 8.5 Hz, 1H), 7.68 (dd, *J* = 7.4 and 8.2 Hz, 1H), 7.48 (ddd, *J* = 0.8, 2.1 and 7.4 Hz, 1H), 7.27 (dd, *J* = 2.0 and 10.6 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.06 (s, 3H), 2.74 (tt, *J* = 4.5 and 7.8 Hz, 1H), 1.29 (dt, *J* = 3.2 and 4.3 Hz, 2H), 1.15 – 1.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.1, 163.8, 163.3 (d, *J* = 257.0 Hz), 149.3 (d, *J* = 3.1 Hz), 139.1, 134.5 (d, *J* = 3.3 Hz), 131.5 (d, *J* = 4.5 Hz), 130.0 (d, *J* = 9.9 Hz), 127.2 (d, *J* = 11.8 Hz), 117.3 (d, *J* = 11.1 Hz), 116.6 (d, *J* = 24.3 Hz), 110.3, 53.3, 17.1, 11.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -109.3. Elemental analysis: calcd (%) for $C_{16}H_{14}FNO_2$ (271.29): C 70.84, H 5.20; found: C 71.01, H 5.12.

2-(3,5-Dichloro-2-fluorophenyl)-6-methoxypyridine (9): From 2,4-dichloro-1-fluorobenzene (293 µL, 2.5 mmol) and 2-bromo-6-methoxypyridine (188 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 90:10) to afford the desired compound **9** (144 mg, 53%) as a white solid mp = 77–79 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, *J* = 2.7, 6.0 Hz, 1H), 7.68 (dd, *J* = 7.4 and 8.3 Hz, 1H), 7.49 – 7.39 (m, 2H), 6.79 (dd, *J* = 0.7 and 8.2 Hz, 1H), 4.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.8, 154.8 (d, *J* = 251.2 Hz), 148.0, 139.2, 129.9 (d, *J* = 4.2 Hz), 129.5 (m), 129.0, 122.8 (d, *J* = 21.7 Hz), 117.4 (d, *J* = 12.0 Hz), 111.1, 53.4. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -120.5. Elemental analysis: calcd (%) for $C_{12}H_8Cl_2FNO$ (272.10): C 52.97, H 2.96; found: C 52.75, H 3.08.

4-(6-(2,3,4,5-Tetrafluorophenyl)pyridin-2-yl)morpholine (10): From 1,2,3,4-tetrafluorobenzene (268 µL, 2.5 mmol) and 4-(6-bromopyridin-2-yl)morpholine (242 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 80:20) to afford the desired compound **10** (222 mg, 71%) as a white solid mp = 144–145 ºC.. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 – 7.70 (m, 1H), 7.61 (ddd, *J* = 1.9, 7.5 and

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8.5 Hz, 1H), 7.22 (dt, *J* = 2.2 and 7.5 Hz, 1H), 6.68 (dd, *J* = 1.4 and 8.5 Hz, 1H), 3.91 – 3.85 (m, 4H), 3.63 – 3.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.1, 147.9, 147.0 (md, *J* = 247.5 Hz), 146.1 (md, *J* = 248.7 Hz), 141.0 (dtd, *J* = 3.4, 14.8 and 253.1 Hz), 140.2 (dtd, *J* = 3.4, 14.6 and 256.1 Hz), 138.4, 124.0 (ddd, *J* = 3.7, 6.7 and 9.9 Hz), 114.2 (d, *J* = 11.9 Hz), 111.14 (td, *J* = 3.0 and 20.8 Hz), 106.8, 66.7, 45.4. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -139.7 – -139.9 (m), -141.7 – -142.8 (m), -155.7 – -157.2 (m). Elemental analysis: calcd (%) for $C_{15}H_{12}F_4N_2O$ (312.27): C 57.70, H 3.87; found: C 57.97, H 4.05.

4-(6-(2,5-Difluorophenyl)pyridin-2-yl)morpholine (11): From 1,4-difluorobenzene (257 µL, 2.5 mmol) and 4-(6-bromopyridin-2-yl)morpholine (242 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 85:15) to afford the desired compound **11** (185 mg, 67%) as an orange solid mp = 58–59 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (ddd, *J* = 3.3, 6.1 and 9.5 Hz, 1H), 7.60 (t, *J* = 8.6 Hz, 1H), 7.29 (dd, *J* = 2.3 and 7.5 Hz, 1H), 7.10 (ddd, *J* = 4.5, 9.0 and 10.5 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.00 – 3.80 (m, 4H), 3.80 – 3.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.1, 158.9 (dd, *J* = 2.9 and 241.8 Hz), 156.8 (dd, *J* = 2.9 and 241.8 Hz), 149.7 (dd, *J* = 1.8 and 3.3 Hz), 138.2, 129.1 (dd, *J* = 7.7 and 13.5 Hz), 117.3 (dd, *J* = 8.6 and 26.7 Hz), 116.8 (dd, *J* = 3.7 and 25.3 Hz), 116.2 (dd, *J* = 9.1 and 24.5 Hz), 114.4 (d, *J* = 12.0 Hz), 106.3, 66.8, 45.5. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -119.1 (d, *J* = 18.3 Hz), -121.7 (d, *J* = 18.3 Hz). Elemental analysis: calcd (%) for $C_{15}H_{14}F_2N_2O$ (276.29): C 65.21, H 5.11; found: C 64.98, H 4.86.

Cyclopropyl(4-fluoro-3-(6-morpholinopyridin-2-yl)phenyl)methanone (12): From cyclopropyl(4-fluorophenyl)methanone (360 µL, 2.5 mmol) and 4-(6-bromopyridin-2-yl)morpholine (242 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 70:30) to afford the desired compound **12** (157 mg, 48%) as a white solid mp = 76–79 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.73 (dd, *J* = 2.4 and 7.6 Hz, 1H), 8.04 (ddd, *J* = 2.4, 4.7 and 8.6 Hz, 1H), 7.62 (dd, *J* = 7.5 and 8.4 Hz, 1H), 7.27 – 7.21 (m, 2H), 6.72 – 6.62 (m, 1H), 3.93 – 3.84 (m, 4H), 3.66 – 3.57 (m, 4H), 2.72 (tt, *J* = 4.6 and 7.8 Hz, 1H), 1.30 – 1.26 (m, 2H), 1.12 – 1.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.2, 163.4 (d, *J* = 257.8 Hz), 159.3, 150.2 (d, *J* = 2.7 Hz), 138.1, 134.5 (d, *J* = 3.2 Hz), 131.6 (d, *J* = 4.6 Hz), 129.9 (d, *J* = 9.9 Hz), 128.0 (d, *J* = 12.1 Hz), 116.5 (d, *J* = 24.3 Hz), 114.5 (d, *J* = 10.1 Hz), 106.2, 66.8, 45.6, 17.1, 11.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -109.5. Elemental analysis: calcd (%) for $C_{19}H_{19}FN_2O_2$ (326.37): C 69.92, H 5.87; found: C 70.13, H 6.09.

4-(6-(3-Chloro-2-fluoro-5-methoxyphenyl)pyridin-2-yl)morpholine (13): From 3-chloro-4-fluoroanisole (317 µL, 2.5 mmol) and 4-(6-bromopyridin-2-yl)morpholine (242 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 85:15) to afford the desired compound **13** (132 mg, 41%) as while solid mp = 123–125 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (dd, *J* = 7.5 and 8.5 Hz, 1H), 7.46 (dd, *J* = 3.2 and 5.6 Hz, 1H), 7.22 (dd, *J* = 2.6 and 7.5 Hz, 1H), 6.97 (dd, *J* = 3.2 and 5.5 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 3.91 – 3.85 (m, 4H), 3.85 (s, 3H), 3.62 – 3.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.1, 155.3 (d, *J* = 2.7 Hz), 150.8 (d, *J* = 245.8 Hz), 138.1, 129.5 (d, *J* = 13.1 Hz), 121.9 (d, *J* = 20.8 Hz), 114.5 (d, *J* = 10.5 Hz), 114.3 (d , *J* = 2.2 Hz), 106.4, 66.8, 56.0, 45.5. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -129.1. Elemental analysis: calcd (%) for $C_{16}H_{16}ClFN_2O_2$ (322.76): C 59.54, H 5.00; found: C 59.69, H 4.96.

2-(2,3,4,5-Tetrafluorophenyl)quinoline (14): From 1,2,3,4-tetrafluorobenzene (268 µL, 2.5 mmol), 2-chloroquinoline (163 mg, 1 mmol), and *n*- tetrabutylammonium bromide (484 mg, 1.5 mmol) the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 90:10) to afford the desired compound **14** (122 mg, 44%) as while solid mp = 127–130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.02 – 7.83 (m, 3H), 7.80 (ddd, *J* = 1.5, 6.9 and 8.4 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.6, 147.1, 146.2 (dm, *J* = 246.2 Hz), 145.1 (md, *J* = 250.8 Hz), 140.1 (md, *J* = 248.2 Hz), 139.8 (md, *J* = 256.5 Hz), 135.9, 129.1, 128.6, 126.5, 126.4, 126.2 (d, *J* = 3.9 Hz), 122.8 (m), 120.6 (d, *J* = 9.5 Hz), 111.1 (dd, *J* = 20.3 Hz, 2.7 Hz). This product is known and NMR are identical to those reported in the literature.[10]

2-(2,5-Difluorophenyl)quinoline (15): From 1,4-difluorobenzene (257 µL, 2.5 mmol), 2-chloroquinoline (163 mg, 1 mmol), and *n*- tetrabutylammonium bromide (484 mg, 1.5 mmol) the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 95:5) to afford the desired compound **15** (63 mg, 26%) as while solid mp = 59–62 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* = 8.6 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.97 – 7.86 (m, 3H), 7.78 (ddd, *J* = 1.5, 6.8 and 8.4 Hz, 1H), 7.60 (ddd, *J* = 1.2, 6.8 and 8.1 Hz, 1H), 7.24 – 7.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.1 (dd, *J* = 3.1 and 242.7 Hz), 158.0, 156.8 (dd, *J* = 3.1 and 242.7 Hz), 152.7, 148.3, 136.4, 129.8 (d, *J* = 5.0 Hz), 127.5, 127.4, 127.0, 122.1 (d, *J* = 9.3 Hz), 117.6 (dd, *J* = 3.5 and 25.7 Hz), 117.6 (d, *J* = 8.5 Hz), 117.3 (dd, *J* = 2.2 and 8.9 Hz), 117.1 (d, *J* = 8.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -118.7 (d, *J* = 18.2 Hz), -123.1 (d, *J* = 18.4 Hz). Elemental analysis: calcd (%) for $C_{15}H_9F_2N$ (241.24): C 74.68, H 3.76; found: C 74.97, H 3.55.

2-(6-Chloro-2,3-difluorophenyl)quinoline (16): From 4-chloro-1,2-difluorobenzene (279 µL, 2.5 mmol), 2-chloroquinoline (163 mg, 1 mmol), and *n*- tetrabutylammonium bromide (484 mg, 1.5 mmol) the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 95:5) to afford the desired compound **16** (113 mg, 41%) as while solid mp = 98–100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (d, *J* = 8.6 Hz, 1H), 8.25 – 8.18 (m, 1H), 7.96 (dt, *J* = 2.4 and 5.7 Hz, 1H), 7.89 (dtd, *J* = 2.3, 2.5 and 8.5 Hz, 2H), 7.79 (ddd, *J* = 1.5, 6.9 and 8.4 Hz, 1H), 7.62 (ddd, *J* = 1.2, 6.8 and 8.1 Hz, 1H), 7.30 (ddd, *J* = 2.8, 6.5 and 9.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.4 (m), 150.9 (dd, *J* = 15.1 and 252.1 Hz), 148.2, 148.0 (dd, *J* = 15.1 and 252.1 Hz), 136.7, 130.7 (d, *J* = 10.2 Hz), 130.0, 129.8, 129.3 (dd, *J* = 4.3 and 9.0 Hz), 127.5, 127.5, 127.3, 126.0 (dd, *J* = 1.8 and 3.5 Hz), 121.9 (d, *J* = 8.6 Hz), 118.2 (d, *J* = 20.5 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm) -134.7 (d, *J* = 20.5 Hz), -144.4 (d, *J* = 22.4 Hz). Elemental analysis: calcd (%) for $C_{15}H_8ClF_2N$ (275.68): C 65.35, H 2.93; found: C 65.49, H 3.08.

2-(3,5-Dichloro-2-fluorophenyl)quinoline (17): From 2,4-dichloro-1-fluorobenzene (293 µL, 2.5 mmol), 2-chloroquinoline (163 mg, 1 mmol), and *n*-tetrabutylammonium bromide (484 mg, 1.5 mmol) the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 90:10) to afford the desired compound **17** (73 mg, 25%) %) as a white solid mp = 144–146 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (dd, *J* = 1.9 and 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.05 (dd, *J* = 2.7 and 5.7 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.79 (td, *J* = 1.8 and 7.8 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.56 – 7.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (d, *J* = 252.1 Hz), 151.7 (d, *J* = 2.4

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Hz), 148.2, 136.7, 130.7, 130.3 (d, *J* = 13.7 Hz), 130.1, 129.9 (d, *J* = 4.2 Hz), 129.8, 129.7 (d, *J* = 2.6 Hz), 127.5, 127.5, 127.3, 122.8 (d, *J* = 20.4 Hz), 121.9 (d, *J* = 8.6 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ (ppm) -121.6. Elemental analysis: calcd (%) for $C_{15}H_8Cl_2FN$ (292.13): C 61.67, H 2.76; found: C 61.97, H 2.54.

2-(2,3-Dichloro-6-fluorophenyl)quinoline (18): From 1,2-dichloro-4-fluorobenzene (293 µL, 2.5 mmol), 2-chloroquinoline (163 mg, 1 mmol), and *n*-tetrabutylammonium bromide (484 mg, 1.5 mmol) the residue was purified by flash chromatography on silica gel (petroleum ether-Et_2O, 85:15) to afford the desired compound **18** as a (114 mg, 39%) as a white solid mp = 145–147 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 7.4 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.79 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1H), 7.61 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H), 7.37 (d, *J* = 10.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.7 (d, *J* = 253.2 Hz), 151.5, 148.2, 136.6, 133.9 (d, *J* = 10.8 Hz), 132.5 (d, *J* = 3.9 Hz), 129.9 (d, *J* = 25.2 Hz), 128.8 (d, *J* = 3.6 Hz), 127.8, 127.7, 127.5, 127.4, 127.1, 121.8 (d, *J* = 9.5 Hz), 118.6 (d, *J* = 28.0 Hz). $^{9}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ (ppm) -117.0 Elemental analysis: calcd (%) for $C_{15}H_8Cl_2FN$ (292.13): C 61.67, H 2.76; found: C 61.48, H 3.04.

Highlights.

- *(Poly)fluorobenzenes* can be efficiently coupled with halide halides
- C6 substituent of 2-bromopyridines were essential to be reactive.
- C–H bond activation was developed instead of classical Suzuki-reaction.
- The major by-products of these couplings are KBr / PivOH instead of metallic salts formed

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