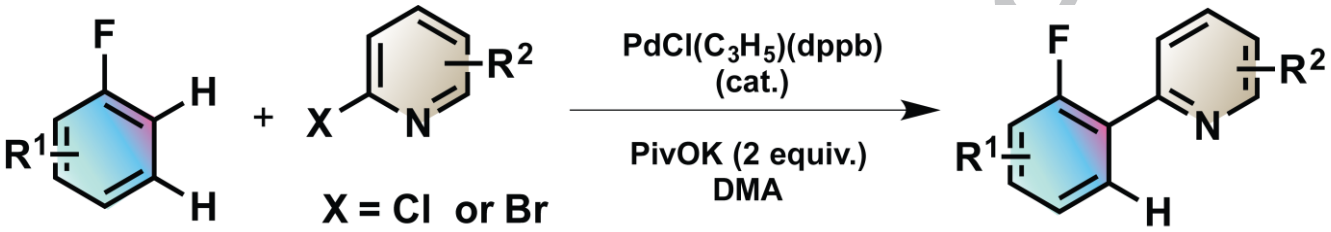
Synthesis of 2-(fluorinated aryl)pyridine derivatives via palladium-catalyzed C–H bond arylation of fluorobenzenes using 2-halopyridines as aryl sources

R. Boyaala, R. Touzani, V. Guerchais, Jean-François Soulé, H. Doucet

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,] *



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

Rabab Boyaala,[a,b] Rachid Touzani,[b, c] Véronique Guerchais,[a] Jean-François Soulé,[a, *] and Henri Doucet [a, *]

[a] *Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Universite de Rennes, "Organometalliques: Materiaux et Catalyse", Campus de Beaulieu, 35042 Rennes, France*

[b] *Laboratoire de Chimie Appliquée et Environnement (LCAE), Faculté des Sciences, Université Mohamed Premier, Oujda, Morocco*

[c] *Faculté Pluridisciplinaire de Nador, Université Mohammed Premier, BP: 300, Selouane 62700, Nador, Morocco*

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).

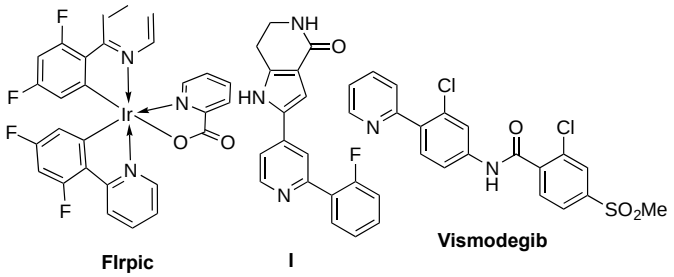


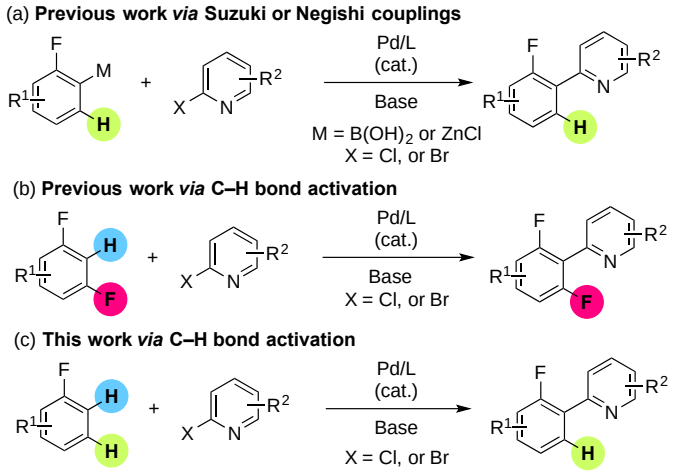
Figure 1. Relevant Structures Containing 2-[(Poly)fluorinated aryl]pyridines motifs

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-

* Corresponding author. Tel.: +33(0) 2 23 23 32 06; e-mail: jean-francois.soule@univ-rennes1.fr

* Corresponding author. Tel.: +33(0) 2 23 23 63 84; e-mail: henri.doucet@univ-rennes1.fr

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).

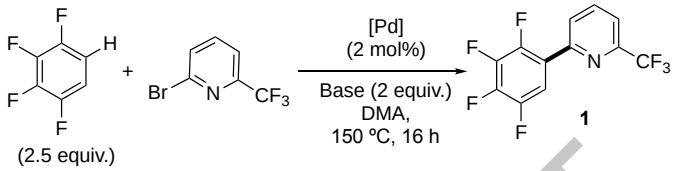


Scheme 1. Synthesis of 2-[(Poly)fluorinated aryl]pyridine Motifs

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).

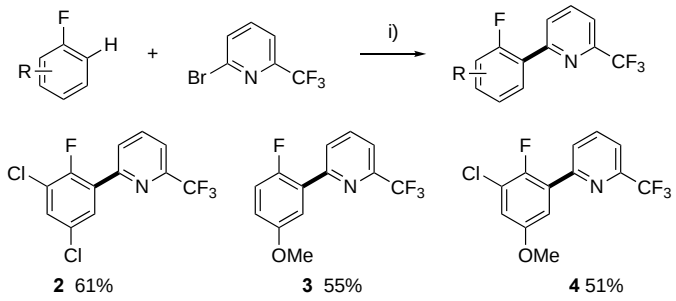
Table 1. Optimization of the Reaction Conditions.



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.

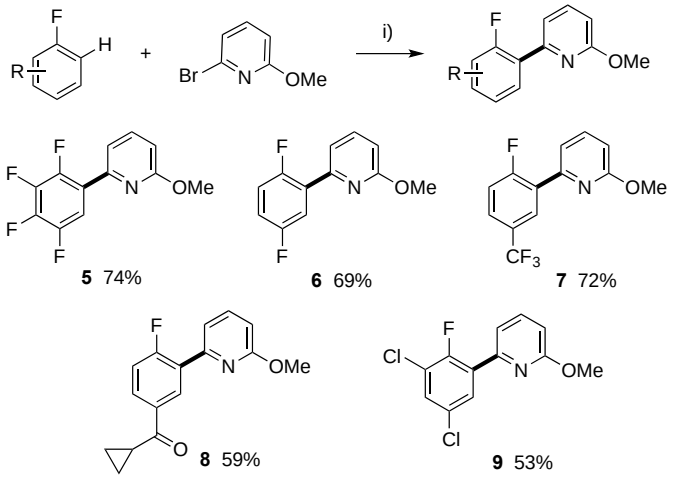


i) $PdCl(C_3H_5)$(dppb) (2 mol%), PivOK (2 equiv.), DMA, 150 ºC, 16 h.

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

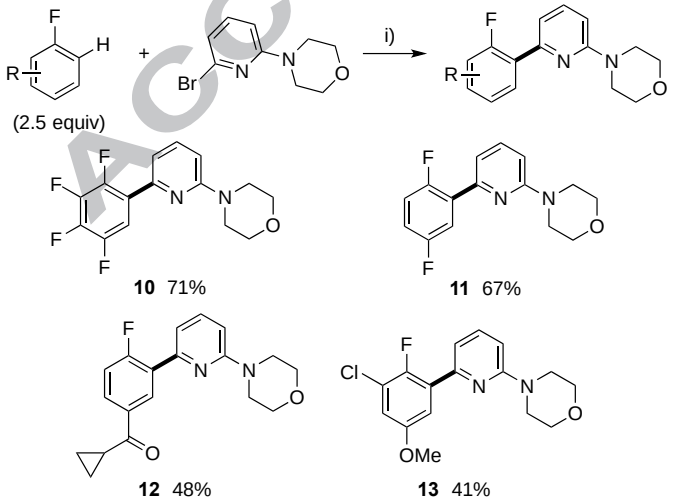
C(sp^2)–H and cyclopropyl C(sp^3)–H bonds– was exclusively arylated at the *ortho*-position to the fluorine atom to give **8** in 59% yield. It should be mentioned that no other regioisomers or arylated products resulting from cyclopropyl C(sp^3)–H bond activation, was observed. 2-Bromo-6-methoxypyridine 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.

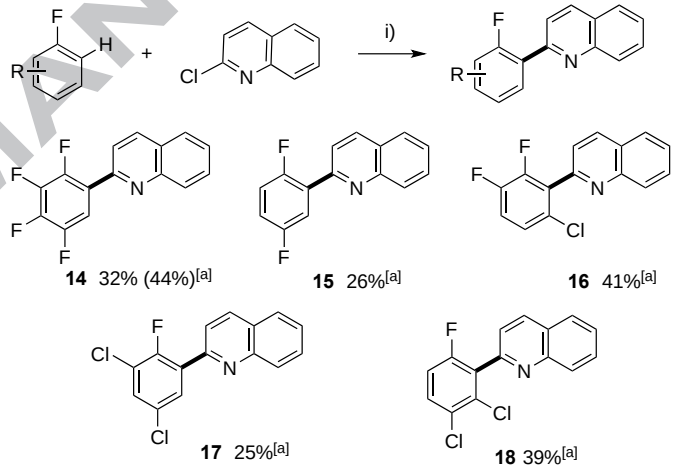
Next, we investigated the influence of an electron-donating bulky group at the pyridyl C6 position such as morpholine (Scheme 4). Noteworthy, 4-(pyridin-2-yl)morpholine is a very important motif embedded in some pharmaceuticals such as Befetupitant and Sonidegib. Again, 1,2,3,4-tetrafluorobenzene and 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.

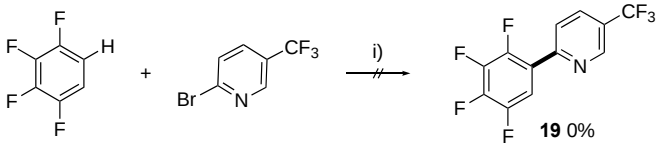
Finally, we investigated the reactivity of 2-chloroquinoline, which is less expensive than 2-bromoquinoline (Scheme 5). Using the previous reaction conditions, namely 2 mol% $PdCl(C_3H_5)$(dppb) catalysts associated to 2 equivalents of potassium pivalate in DMA at 150 °C, the 2-(2,3,4,5-tetrafluorophenyl)quinoline (**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,

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

R.B. is grateful to "Université Mohamed Premier, Oujda, Morocco" for providing financial support. We also thank CNRS and "Rennes Metropole" for providing financial support.

References and notes

[1] a) H.-W. Hong, T.-M. Chen, *Mater. Chem. Phys.* **2007**, *101*, 170-176; b) T.-R. Chen, H.-P. Lee, J.-D. Chen, K. H. C. Chen, *Dalton Trans.* **2010**, *39*, 9458-9461; c) T.-R. Chen, *J. Organomet. Chem.* **2008**, *693*, 3117-3130.

[2] K. Teegardin, J. I. Day, J. Chan, J. Weaver, *Org. Process Res. Dev.* **2016**, *20*, 1156-1163.

[3] a) S. Natesan, R. Subramaniam, C. Bergeron, S. Balaz, *J. Med. Chem.* **2012**, *55*, 2035-2047; b) R. K. Prasad, R. Sharma, *Am. J. Phytomed. Clin. Ther.* **2013**, *1*, 001-010, 010 pp.

[4] a) P. Coppo, E. A. Plummer, L. De Cola, *Chem. Commun.* **2004**, 1774-1775; b) M. Lysen, M. Madden, J. L. Kristensen, P. Vedsoe, C. Zoellner, M. Begtrup, *Synthesis* **2006**, 3478-3484; c) V. N. Kozhevnikov, K. Dahms, M. R. Bryce, *J. Org. Chem.* **2011**, *76*, 5143-5148; d) T. Sato, H. Awano, H. Katagiri, Y.-J. Pu, T. Takahashi, K. Yonetake, *Eur. J. Inorg. Chem.* **2013**, *2013*, 2212-2219; e) P.-H. Lanoe, C. M. Tong, R. W. Harrington, M. R. Probert, W. Clegg, J. A. G. Williams, V. N. Kozhevnikov, *Chem. Commun.* **2014**, *50*, 6831-6834; f) K. S. Bejoymohandas, A. Kumar, S. Sreenadh, E. Varathan, S. Varughese, V. Subramanian, M. L. P. Reddy, *Inorg. Chem.* **2016**, *55*, 3448-3461.

[5] a) W. Lumeras, F. Caturla, L. Vidal, C. Esteve, C. Balague, A. Orellana, M. Dominguez, R. Roca, J. M. Huerta, N. Godessart, B. Vidal, *J. Med. Chem.* **2009**, *52*, 5531-5545; b) D. Yu, C.-S. Wang, C. Yao, Q. Shen, L. Lu, *Org. Lett.* **2014**, *16*, 5544-5547; c) S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 10463-10467.

[6] M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754-8756.

[7] a) Y. Wei, J. Kan, M. Wang, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 3346-3349; b) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564-1567; c) S. Fan, J. Yang, X. Zhang, *Org. Lett.* **2011**, *13*, 4374-4377; d) L. Ackermann, S. Fenner, *Chem. Commun.* **2011**, *47*, 430-432; e) J. W. W. Chang, E. Y. Chia, C. L. L. Chai, J. Seayad, *Org. Biomol. Chem.* **2012**, *10*, 2289-2299; f) F. Guo, J. Han, S. Mao, J. Li, X. Geng, J. Yu, L. Wang, *RSC Adv.* **2013**, *3*, 6267-6270; g) X. Fang, Y. Huang, X. Chen, X. Lin, Z. Bai, K.-W. Huang, Y. Yuan, Z. Weng, *J. Fluorine Chem.* **2013**, *151*, 50-57; h) M. He, J.-F. Soulé, H. Doucet, *ChemCatChem* **2014**, *6*, 1824-1859; i) T. Miao, L. Wang, *Adv. Synth. Catal.* **2014**, *356*, 429-436.

[8] a) J. Fournier Dit Chabert, L. Joucla, E. David, M. Lemaire, *Tetrahedron* **2004**, *60*, 3221-3230; b) F. A. Zhuravlev, *Tetrahedron Lett.* **2006**, *47*, 2929-2932; c) I. Čerňa, R. Pohl, B. Klepetářová, M. Hocek, *Org. Lett.* **2006**, *8*, 5389-5392; d) A. K. Mohanakrishnan, P. Amaladass, J. Arul Clement, *Tetrahedron Lett.* **2007**, *48*, 539-544; e) G. L. Turner, J. A. Morris, M. F. Greaney, *Angew. Chem. Int. Ed.* **2007**, *46*, 7996-8000; f) F. Derridj, A. L. Gottumukkala, S. Djebbar, H. Doucet, *Eur. J. Inorg. Chem.* **2008**, 2550-2559; g) M. Baghbanzadeh, C. Pilger, C. O. Kappe, *J. Org. Chem.* **2011**, *76*, 8138-8142; h) S. K. Kim, J.-H. Kim, Y. C. Park, J. W. Kim, E. K. Yum, *Tetrahedron* **2013**, *69*, 10990-10995; i) S.-C. Yin, Q. Zhou, X.-Y. Zhao, L.-X. Shao, *J. Org. Chem.* **2015**, *80*, 8916-8921; j) J. Wippich, I. Schnapperelle, T. Bach, *Chem. Commun.* **2015**, *51*, 3166-3168.

[9] a) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian, K. Fagnou, *J. Org. Chem.* **2011**, *76*, 749-759; b) D. Yu, L. Lu, Q. Shen, *Org. Lett.* **2013**, *15*, 940-943; c) W. Hagui, N. Besbes, E. Srasra, J.-F. Soulé, H. Doucet, *RSC Advances* **2016**, *6*, 17110-17117.

[10] Z. Chen, C.-Y. He, Z. Yin, L. Chen, Y. He, X. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 5813-5817.

[11] a) T. Yan, L. Zhao, M. He, J.-F. Soulé, C. Bruneau, H. Doucet, *Adv. Synth. Catal.* **2014**, *356*, 1586-1596; b) M. He, J.-F. Soulé, H. Doucet, *ChemCatChem* **2015**, *7*, 2130-2140; c) N. Laidaoui, M. He, D. El Abed, J.-F. Soulé, H. Doucet, *RSC Advances* **2016**, *6*, 62866-62875.

[12] a) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067; b) D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880-6886; c) S. I. Gorelsky, *Organometallics* **2012**, *31*, 4631-4634; d) S. I. Gorelsky, *Coord. Chem. Rev.* **2013**, *257*, 153-164.

[13] Y.-N. Wang, X.-Q. Guo, X.-H. Zhu, R. Zhong, L.-H. Cai, X.-F. Hou, *Chem. Commun.* **2012**, *48*, 10437-10439.

[14] D. Roy, S. Mom, S. Royer, D. Lucas, J.-C. Hierso, H. Doucet, *ACS Catal.* **2012**, *2*, 1033-1041.

[15] T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365-376.

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

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

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

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