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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.

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 (Fig. 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 example, 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 inhibition of mitogen-activated protein kinase-2 in the treatment of rheumatoid arthritis (Fig. 1, center).[3] Moreover, Vismodegib, which contains a similar structure, is an approved medicinal drug for the treatment of basal-cell carcinoma (Fig. 1, right).

2-[(Poly)fluorinated aryl]pyridines are generally prepared using classical Suzuki reaction from fluorinated phenylboronic acids and 2-bromopyridine derivatives.[4] Alternatively, 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 (Scheme 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-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).

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 °C, the desired arylated product **1** was obtained in 21% yield (Table 1,

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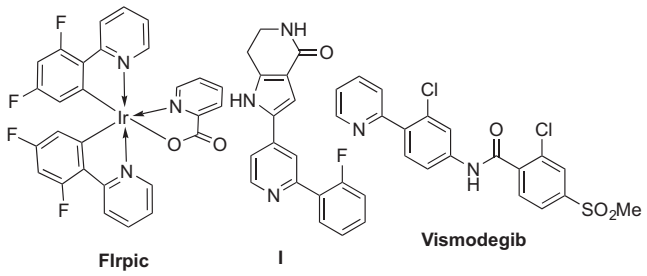
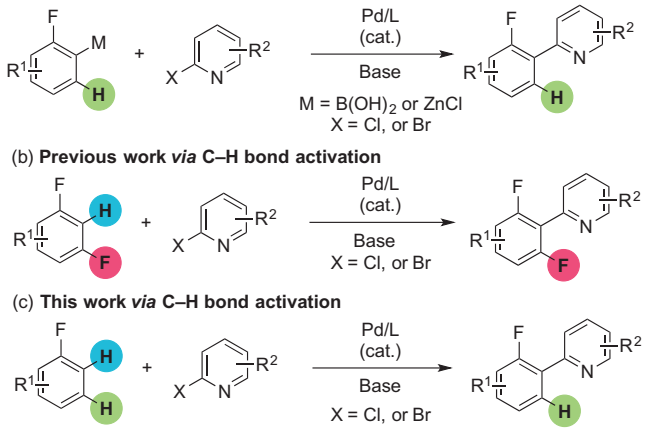
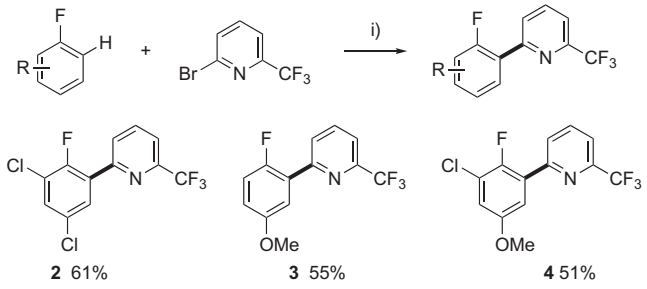


Fig. 1. Relevant Structures Containing 2-[(Poly)fluorinated aryl]pyridines motifs.



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



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

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 °C, 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

Table 1
Optimization of the Reaction Conditions.

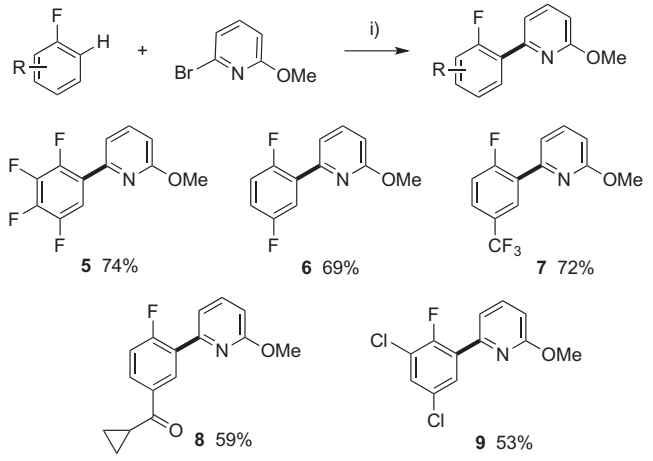
Entry	[Pd]	Base	Yield in **1** (%)
1	$Pd(OAc)_2$	KOAc	21
2	PdCl(C_3H_5)(dppb)	KOAc	51
3	PdCl(C_3H_5)(dppb)	K2CO3	0
4	PdCl(C_3H_5)(dppb)	PivOK	68
5	PdCl(C_3H_5)(dppb)	$AdCO_2K$	48
6[a]	PdCl(C_3H_5)(dppb)	PivOK	0

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

pyridyl nitrogen atom coordination to palladium resulting in catalyst poisoning (steric effect).

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.

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

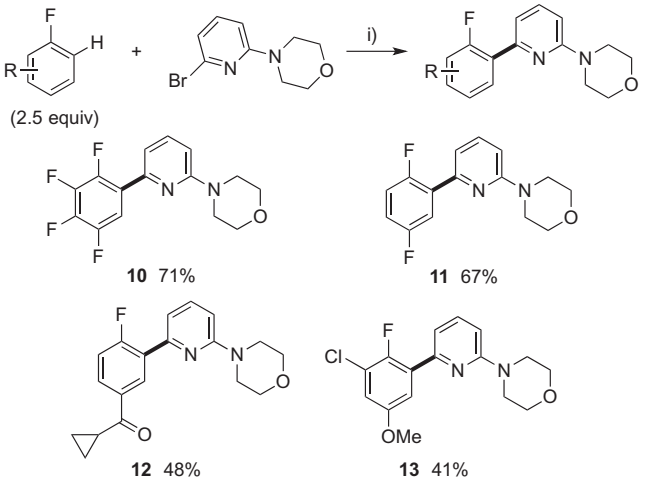


Scheme 3. Scope of Pd-Catalyzed Direct Arylation of Fluorobenzenes with 2-Bromo-6-methoxypyridine.

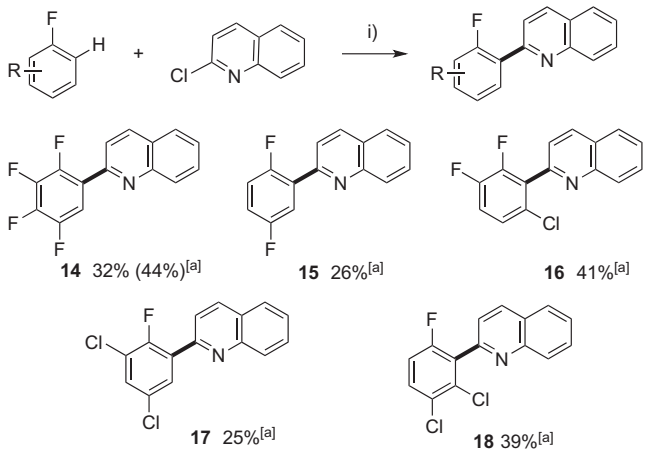
synthesis of 2-(2,5-difluorophenyl)-6-methoxypyridine (**6**) in 69% yield. Hou and co-workers had reported that 1-fluoro-4-(trifluoromethyl)benzene could be selectively mono-arylated at the *ortho*-position of the fluorine atom using palladium catalysis, but they did not employed 2-halopyridines as 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**.

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.

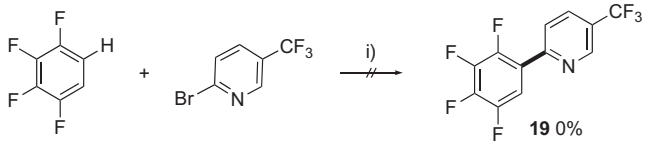
Finally, we investigated the reactivity of 2-chloroquinoline, which is less expensive than 2-bromoquinoline (Scheme 5). Using the previous reaction conditions, namely 2 mol% $PdCl(C_3H_5)(dppb)$ catalysts associated to 2 equivalents of potassium pivalate in DMA at 150 °C, the 2-(2,3,4,5-tetrafluorophenyl)quinoline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



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



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



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

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.

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).

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.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.06.075.

References

1. (a) Hong H-W, Chen T-M. *Mater Chem Phys*. 2007;101:170–176;
   (b) Chen T-R, Lee H-P, Chen J-D, Chen KHC. *Dalton Trans*. 2010;39:9458–9461;
   (c) Chen T-R. *J Organomet Chem*. 2008;693:3117–3130.
2. Teegardin K, Day JI, Chan J, Weaver J. *Org Process Res Dev*. 2016;20:1156–1163.
3. (a) Natesan S, Subramaniam R, Bergeron C, Balaz S. *J Med Chem*. 2012;55:2035–2047;
   (b) Prasad RK, Sharma R. *Am J Phytomed Clin Ther*. 2013;1(001–010):010.
4. (a) Coppo P, Plummer EA, De Cola L. *Chem Commun*. 2004;1774–1775;
   (b) Lysen M, Madden M, Kristensen JL, Vedsoe P, Zoellner C, Begtrup M. *Synthesis*. 2006;3478–3484;
   (c) Kozhevnikov VN, Dahms K, Bryce MR. *J Org Chem*. 2011;76:5143–5148;
   (d) Sato T, Awano H, Katagiri H, Pu Y-J, Takahashi T, Yonetake K. *Eur J Inorg Chem*. 2013;2013:2212–2219;
   (e) Lanoe P-H, Tong CM, Harrington RW, et al. *Chem Commun*. 2014;50:6831–6834;
   (f) Bejoymohandas KS, Kumar A, Sreenadh S, et al. *Inorg Chem*. 2016;55:3448–3461.
5. (a) Lumeras W, Caturla F, Vidal L, et al. *J Med Chem*. 2009;52:5531–5545;
   (b) Yu D, Wang C-S, Yao C, Shen Q, Lu L. *Org Lett*. 2014;16:5544–5547;
   (c) Roesner S, Buchwald SL. *Angew Chem Int Ed*. 2016;55:10463–10467.
6. Lafrance M, Rowley CN, Woo TK, Fagnou K. *J Am Chem Soc*. 2006;128:8754–8756.
7. (a) Wei Y, Kan J, Wang M, Su W, Hong M. *Org Lett*. 2009;11:3346–3349;
   (b) Xie K, Yang Z, Zhou X, et al. *Org Lett*. 2010;12:1564–1567;
   (c) Fan S, Yang J, Zhang X. *Org Lett*. 2011;13:4374–4377;
   (d) Ackermann L, Fenner S. *Chem Commun*. 2011;47:430–432;
   (e) Chang JWW, Chia EY, Chai CLL, Seayad J. *Org Biomol Chem*. 2012;10:2289–2299;
   (f) Guo F, Han J, Mao S, et al. *RSC Adv*. 2013;3:6267–6270;
   (g) Fang X, Huang Y, Chen X, et al. *J Fluorine Chem*. 2013;151:50–57;
   (h) He M, Soulé J-F, Doucet H. *ChemCatChem*. 2014;6:1824–1859;
   (i) Miao T, Wang L. *Adv Synth Catal*. 2014;356:429–436.
8. Fournier Dit Chabert J, Joucla L, David E, Lemaire M. *Tetrahedron*. 2004;60:3221–3230;
   (b) Zhuravlev FA. *Tetrahedron Lett*. 2006;47:2929–2932;
   (c) Čerňa I, Pohl R, Klepetářová B, Hocek M. *Org Lett*. 2006;8:5389–5392;
   (d) Mohanakrishnan AK, Amaladass P, Arul Clement J. *Tetrahedron Lett*. 2007;48:539–544;
   (e) Turner GL, Morris JA, Greaney MF. *Angew Chem Int Ed*. 2007;46:7996–8000;
   (f) Derridj F, Gottumukkala AL, Djebbar S, Doucet H. *Eur J Inorg Chem*. 2008;2550–2559;
   (g) Baghbanzadeh M, Pilger C, Kappe CO. *J Org Chem*. 2011;76:8138–8142;
   (h) Kim SK, Kim J-H, Park YC, Kim JW, Yum EK. *Tetrahedron*. 2013;69:10990–10995;
   (i) Yin S-C, Zhou Q, Zhao X-Y, Shao L-X. *J Org Chem*. 2015;80:8916–8921;
   (j) Wippich J, Schnapperelle I, Bach T. *Chem Commun*. 2015;51:3166–3168.
9. (a) Lapointe D, Markiewicz T, Whipp CJ, Toderian A, Fagnou K. *J Org Chem*. 2011;76:749–759;
   (b) Yu D, Lu L, Shen Q. *Org Lett*. 2013;15:940–943;
   (c) Hagui W, Besbes N, Srasra E, Soulé J-F, Doucet H. *RSC Adv*. 2016;6:17110–17117.
10. Chen Z, He C-Y, Yin Z, Chen L, He Y, Zhang X. *Angew Chem Int Ed*. 2013;52:5813–5817.
11. (a) Yan T, Zhao L, He M, Soulé J-F, Bruneau C, Doucet H. *Adv Synth Catal*. 2014;356:1586–1596;
   (b) He M, Soulé J-F, Doucet H. *ChemCatChem*. 2015;7:2130–2140;
   (c) Laidaoui N, He M, El Abed D, Soulé J-F, Doucet H. *RSC Adv*. 2016;6:62866–62875.
12. (a) Garcia-Cuadrado D, Braga AAC, Maseras F, Echavarren AM. *J Am Chem Soc*. 2006;128:1066–1067;
   (b) Garcia-Cuadrado D, de Mendoza P, Braga AAC, Maseras F, Echavarren AM. *J Am Chem Soc*. 2007;129:6880–6886;
   (c) Gorelsky SI. *Organometallics*. 2012;31:4631–4634;
   (d) Gorelsky SI. *Coord Chem Rev*. 2013;257:153–164.
13. Wang Y-N, Guo X-Q, Zhu X-H, Zhong R, Cai L-H, Hou X-F. *Chem Commun*. 2012;48:10437–10439.
14. Roy D, Mom S, Royer S, Lucas D, Hierso J-C, Doucet H. *ACS Catal*. 2012;2:1033–1041.