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Catalyst-Controlled Regiodivergent C–H Arylation Site of Fluorinated 2-Arylpyridine Derivatives: Application to Luminescent Iridium(III) Complexes

Rabab Boyaala,[1, 2] Rachid Touzani,[2] Thierry Roisnel,[1] Vincent Dorcet,[1] Elsa Caytan,[1] Denis Jacquemin,*[3] Julien Boixel,[1] Véronique Guerchais,*[1] Henri Doucet,*[1] and Jean-François Soulé*[1]

[1] Univ Rennes, CNRS UMR6226, F-3500 Rennes, France. [2] Laboratoire de Chimie Appliquée et Environnement (LCAE), Faculté des Sciences, Université Mohamed Premier, Oujda, Morocco. [3] UMR CNRS 6230, CEISAM, Université de Nantes, 2 rue de la Houssinière, 44322 Nantes Cedex 3, France.

KEYWORDS Catalysis • Palladium • Ruthenium • C–H Bond Functionalization • Luminescence • Iridium • TD-DFT

ABSTRACT: Regiodivergent C–H bond arylation of fluorinated 2-aryl-pyridines and -quinolines has been developed. The use of Pd catalyst allows to functionalize the C–H bond of the aryl flanked by two fluorine atoms (most acidic position); while using Ru catalyst, the arylation takes place at the *ortho* heterocycle position. Both reaction conditions exhibit a good functional group tolerance. The synthetically useful selectivity observed with Pd catalyst was applied to design novel C^N ligands for the preparation of luminescent cationic iridium(III) complexes. The influence of the incorporated aryl group onto the fluorinated phenyl unit and the fluorine position patterns on the photophysical properties is described.

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1. INTRODUCTION

Fluoroarene molecules represent one of the most prevalent entities within both pharmaceutical compounds,(1) and material sciences.(2) Among them, fluorinated 2-arylpyridines have been successfully used as building blocks in the preparation of medicine, e.g., **VX-702** is employed for the transient suppression of biomarkers of inflammation in ongoing rheumatoid arthritis.(3) In addition, fluorinated 2-arylpyridines are precursors of iridium complexes,(4) e.g., $[Ir(dFppy)_2(dmbpy)]PF_6$ (Figure 1, left).(4f) Such bis-cyclometalated complexes exhibit highly efficient optoelectronic properties, with widespread applications as photoredox catalysts,(5) biological staining agents,(6) or medicinal drugs.(7)

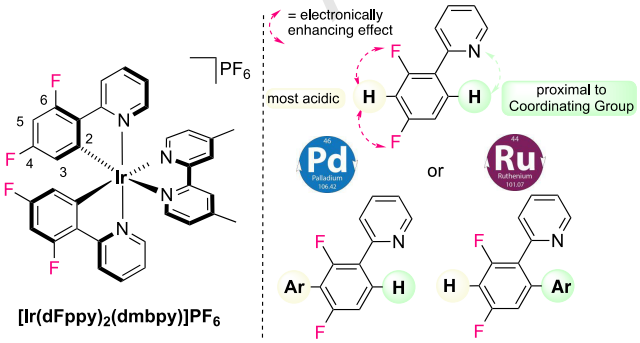


Figure 1. Relevant Structures containing Fluorinated 2-Arylpyridines and their Site Reactive C–H Bonds in Transition-Metal-Catalyzed Functionalizations.

The introduction of fluorine atoms often results in the modification of both HOMO and LUMO energy levels, enabling optimizing the carrier injection and tuning the electroluminescent color.(8) However, the access to well-decorated fluorinated 2-arylpyridines remains quite challenging and often involves multi-sept synthesis. Therefore, there is a high demand toward the discovery of user-friendly synthetic methods to modify such fluorinated ligands in order to adjust their photophysical properties and/or to develop more stable cyclometalated iridium(III) complexes.(9)

Over the past decades, transition metal catalyzed C−H bond functionalizations have emerged as a straightforward synthetic strategy to avoid additional steps related to the pre-activation of the substrates.(10) However, one of the major issues in this field remains the control and the switch of the regioselectivity to obtain diversely decorated structures in one-step.(11) In order to achieve C–H bond functionalization at the desired position, substrates bearing a directing/coordinating group for the *ortho* C–H bond cleavage were employed;(12) or specific templates to functionalize remote C–H bond were designed.(13) An alternative approach is to distinguish the C–H bonds by their electronic properties and to tailor the reaction conditions in function of the targeted position. This strategy has been widely applied for the regiodivergent C–H bond functionalization of 5-membered ring heteroarenes,(14) but scarcely studied in the case of benzene derivatives.(15) Fluoroarenes are ideal candidates for developing regioselective C–H bond functionalizations, as fluorine atoms often enhance the reactivity of the adjacent C–H bond owing its electronically properties.(16) To the best of our knowledge, the reactivity of fluorinated 2-arylpyridine derivatives in C–H bond arylation with enhancing site

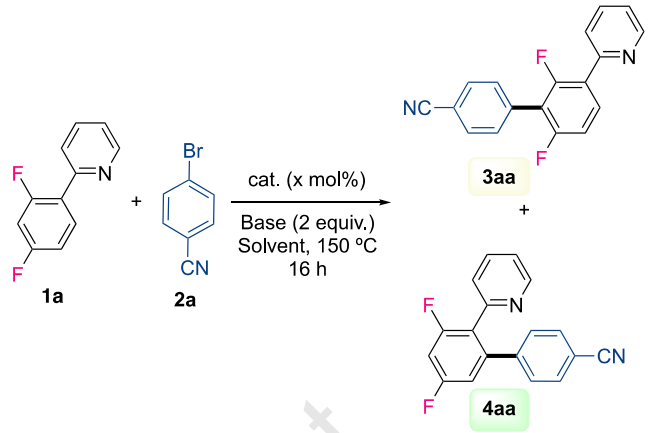
selectivity by fluorine atom was not developed yet, although the discovery of a catalyst-dependent method to control the site of the arylation of fluorinated 2-arylpyridine derivatives would allow a simple access to diversely decorated ligands, applicable in the preparation of new iridium(III) complexes. In the present work, we report (i) regiodivergent C–H bond arylation of fluorinated 2-aryl-pyridines and -quinolines *via* the choice of metal (Figure 1, right), (ii) the use of arylated ligands in the preparation of novel cyclometalated iridium(III) complexes, (iii) the characterization of the photoluminescent properties of these iridium(III) complexes with theoretical correlation by TD-DFT calculations.

2. RESULTS AND DISCUSSION

2.1 Optimization of the regiodivergent C–H bond arylation

To determine the regioselectivity of C–H bond functionalization with 2-arylpyridine derivatives bearing two fluorine atoms onto the aryl unit, we firstly examined the arylation of 2-(2,4-difluorophenyl)pyridine (**1a**) with 4-bromobenzonitrile (**2a**) in the presence of 2 equivalents of KOAc as base in DMA at 150 ºC using various Pd catalyst precursors (Table 1, entries 1-3). In all cases, we were pleased to find that the reaction mainly occurred at the most acidic C–H bond (the one flanked by the two *ortho*-fluorine atoms). Indeed, a 76:24 mixture of **3aa**/**4aa** was obtained in the presence of 2 mol% of phosphine-free Pd catalyst $Pd(OAc)_2$ (Table 1, entry 1). A similar ratio was observed using 2 mol% of $PdCl_2$ catalyst (Table1, entry 2). We reasoned that the use of diphosphine palladium catalyst $PdCl(C_3H_5)$(dppb), could inhibit the formation of the regioisomer **4aa** by preventing the coordination of the pyridine unit to Pd. Under these conditions, the regioselectivity (**3aa**/**4aa**) was greatly improved to 92:8 ratio (Table 1, entry 3). It is known that the base plays a critical role in concerted metalation-deprotonation mechanism, therefore using more soluble base, KOPiv, the **3aa**/**4aa** ratio was raised up to 95:5 (Table 1, entry 4). Full conversion of **2a** can be reached with a higher Pd loading of 5 mol%, and the regioisomer **3aa** was isolated in 76% yield (Table 1, entry 5). It is important to note that the previous protocols to prepare such arylated fluorinated 2-aryl-pyridines required the use of stochiometric amounts of organometallic reagents (magnesium and zinc) and multi-step synthesis.[17] It was also reported that *ortho*-C-H bond arylation of 2-phenylpyridine derivatives could be performed using Ru(II) catalyst through coordinating effect .[18] On the other hand, Ru(II) is also able to promote the C–H bond arylation of polyfluorobenzene derivatives at *ortho*-position, through electronic factors.[19] To the best of our knowledge, there is no study on the regioselectivity of the arylation of fluorinated 2-aryl-pyridines in the presence of Ru(II) catalysts. Interestingly, using 5 mol% of $[Ru(p\text{-cymeme})Cl_2]_2$ associated to KOAc in DMA, we were pleased to find that arylation of **1a** exclusively occurred at the C6 position leading the formation of the product **4aa**, i.e., the proximal position to the pyridine unit, in > 95:5 selectivity, albeit with a poor conversion (Table 1, entry 6). Changing the solvent to NMP, **4aa** was also obtained in 95% regioselectivity, but was isolated in 70% yield (Table 1 entry 8). Notably, for both sets of reaction conditions, we never observed the formation of side-products derived from the activation of C–F bonds.[20]

Table 1. Optimization of the Reaction Conditions



Entry	Cat. (x mol%)	Base	Solvent	Conv. (%)[a]	**3aa**/**4aa**[a]
1	$Pd(OAc)_2$ (2)	KOAc	DMA	54	76:24
2	$PdCl_2$ (2)	KOAc	DMA	58	77:23
3	$PdCl(C_3H_5)$(dppb) (2)	KOAc	DMA	65	92:8
4	$PdCl(C_3H_5)$(dppb) (2)	KOPiv	DMA	68	>95:5
5	$PdCl(C_3H_5)$(dppb) (5)	KOPiv	DMA	100	>95:5 (76%)[b]
6	$[Ru(p\text{-cymeme})Cl_2]_2$ (5)	KOAc	DMA	25	>5:95
7	$[Ru(p\text{-cymeme})Cl_2]_2$ (5)	KOAc	DMF	40	>5:95
8	$[Ru(p\text{-cymeme})Cl_2]_2$ (5)	KOAc	NMP	95	>5:95 (70%)[c]

[a] Determined by GC-analysis using *n*-dodecane as internal standard, conv = conversion based on the consumption of **2a**. [b] Isolated yield in **3aa**. [c] Isolated yield in **4aa**.

2.2 Pd-catalyzed C–H bond arylation under Electronic Control

Having discovered two sets of conditions leading to highly regioselective C–H bond arylations: *i)* Pd catalysis for the arylation under electronic control; and *ii)* Ru catalysis for the arylation using coordination control, we turned our attention to the scope of these transformations (Schemes 1 and 2). Using Pd conditions, reactions with aryl bromides bearing electron-withdrawing substituents such as formyl, trifluoromethyl, and carboxyethyl gave the corresponding 2-(3-aryl-2,4-difluorophenyl)pyridines in excellent yields (**3ab**-**3ad**, 71-82% yields). *Ortho* and *meta* substituents on the aryl bromide are tolerated (**3ae**-**3ai**, 69-87% yield). The regioselectivity is not affected by the replacement of the pyridine by a quinoline unit, as the arylated 2-(2,4-difluorophenyl)quinolines **3ba**-**3bc** were isolated in 68-81% yields. The location of fluorine atoms for electronically enhancing site selective C–H bond functionalization is not limited to C2 and C4 positions on benzene or even to a 1,3-difluorobenzene motif. The introduction of fluorine atoms at 3 and 4 positions on the 2-arylquinoline [i.e., 2-(3,4-difluorophenyl)quinoline (**1c**)], allowed to control the arylation at C2 position affording **3ca** and **3cc** as single regioisomers in good yields. This high

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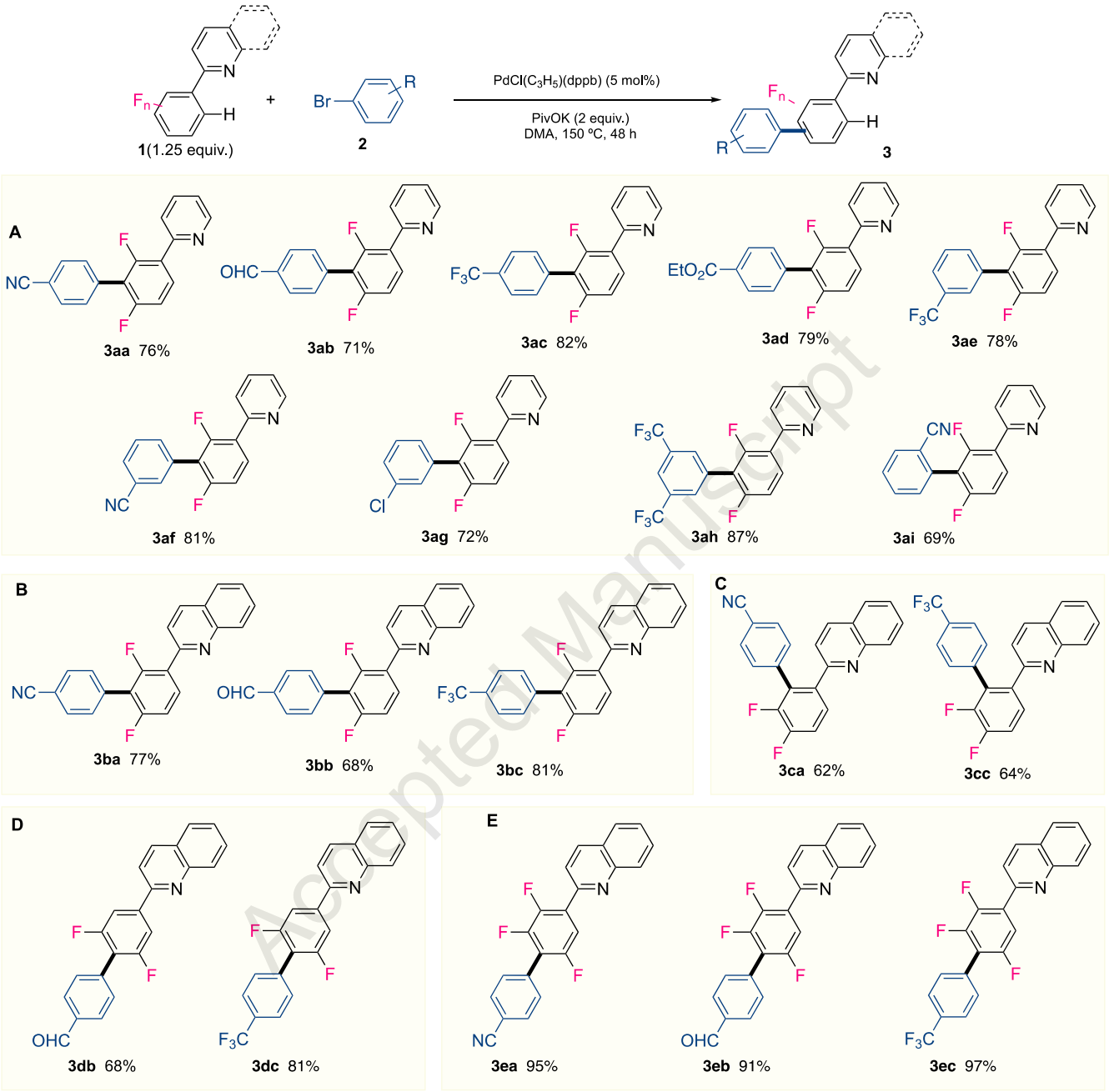
regioselectivity (no formation of C5-arylated product) might be explained by conjugated effects of the F atom and quinoline unit. Then, when the aryl bears fluorine atoms at C3 and C5 positions [i.e., 2-(3,5-difluorophenyl)quinoline (**1d**)], the arylation took place regioselectively at the C4-position giving direct access to the linear compounds **3db** and **3dc** in 68% and 81% yields. The presence of an additional fluorine atom at the C2 position allowed to improve the yield in favor the 2-(4-aryl-2,3,5-trifluorophenyl)pyridines **3ea-ec**.



Scheme 1. Palladium-Catalyzed C–H Bond Arylation at *Ortho*-Positions of Fluorine Atoms: Electronic Control.

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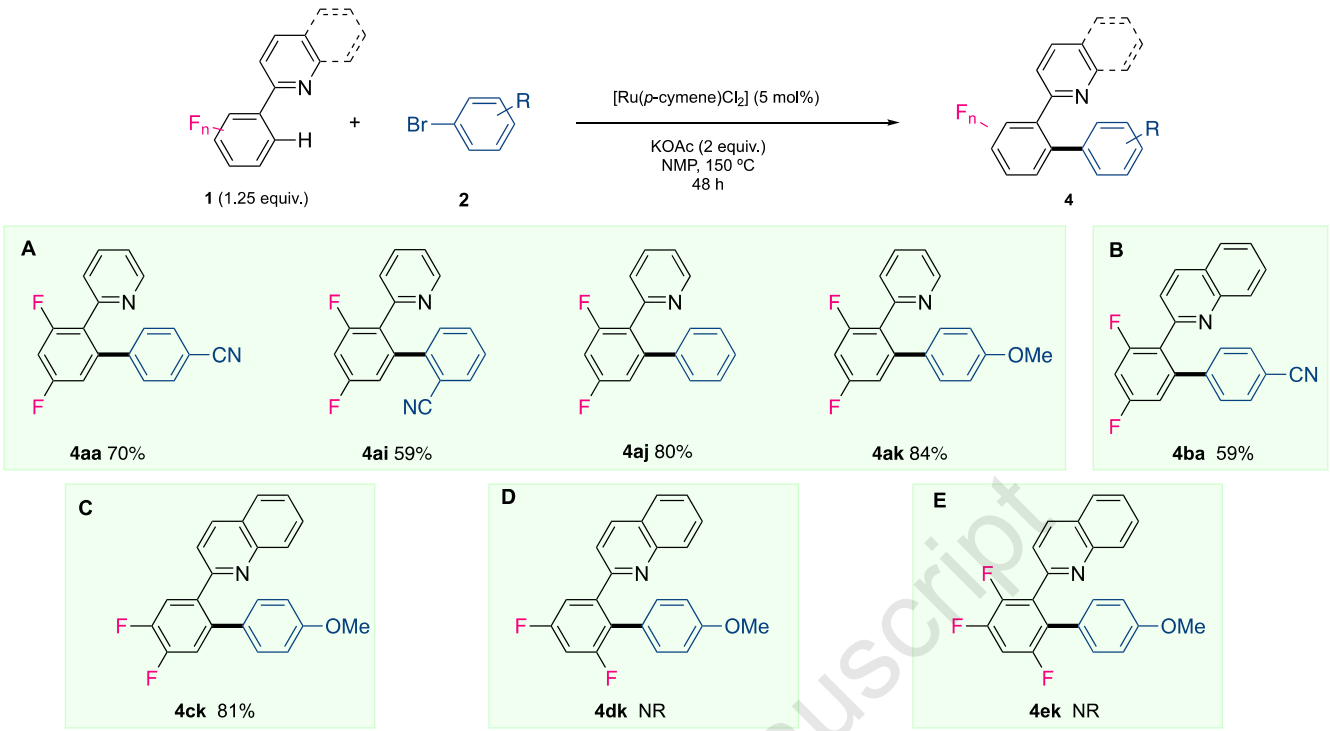
2.3 Ru-catalyzed C–H bond arylation under Coordination Control

Next, we investigated the scope of the reaction using Ru(II) catalyst in order to prepare C2-arylated products **4** *via* pyridine or quinoline direct *ortho*-arylations (Scheme 2). Electron-poor and electron-rich aryl bromides have been successfully coupled with **1a** to afford 2-(6-aryl-2,4-difluorophenyl)pyridines in good to excellent yields (**4aa** and **4ai-4ak**, 59-84% yields). From 2-(2,4-difluorophenyl)quinoline (**1b**) and 2-(3,4-difluorophenyl)quinoline (**1c**) arylations occurred at *ortho*-position of the quinoline group to afford **4ba** and **4ck** in 59% and 81% yield, respectively. In contrast, no reaction occurred when the C–H bond is at *ortho* position of both the quinoline unit and a fluorine atom, such as in **1d** and **1e**. This lack of

reactivity is in line with a base-assisted internal electrophilic-type substitution (BIES) process for the proximal C–H bond cyclometalation,[21] rather than concerted metalation-deprotonation mechanism.



Scheme 2. Ruthenium-Catalyzed C–H Bond Arylation at *Ortho*-position of Pyridine or Quinoline Units: Coordination Control

2.4 Preparation and characterization of cyclometalated Ir(III) complexes

Then, we anticipated that the new arylated-difluorophenylpyridine (dFppy) **3ac**, arylated-difluorophenylquinoline (dFqui) pro-ligands **3bc**, **3cc**, **3dc**, and arylated-trifluorophenylquinoline (tFqui) **3ec** –prepared in a single step thanks to the unique regioselectivity observed with Pd catalyst– can be used as cyclometalated C^N ligands to obtain heteroleptic bis-cyclometalated iridium(III) complexes. The corresponding cationic $[Ir(C^N)_2(N^N)]PF_6$ (N^N = dmbpy) complexes were prepared and isolated in 58-81% yields as yellow (**5b**) and orange (**6-9**) air-stable solids *via* a reported two-step procedure (Scheme 3).[22] The unsubstituted complex **5a** was also synthesized and used as the reference for comparative studies.[4f] This set of new complexes can be divided into two series. The first which includes complexes **5a** and **5b** allows assessing the impact of the incorporation of an aryl group (*p*-CF_3-phenyl) onto the dFppy ligand, on the electrochemical and photophysical properties. The second encompasses complexes **6-9** where the pyridine ring has been replaced by a quinoline (dFqui or tFqui), the *p*-CF_3-phenyl ring and two or three fluorine substituents diversely located onto the C^N ligand. The crystal structures of complexes **5b**, **6** and **8** are presented in Scheme 3. The pendant *p*-CF_3-phenyl is not coplanar with the C^N ligand; the torsion angles between the plane of the incorporated aryl group and that of cyclometalated phenyl ring of the two C^N ligands in **5b** vary among 48.2° and 84.7°.[23] These values, larger than those reported in the corresponding fluorine-free related complexes, breaks the conjugation within the ligand. Similarly, the pendant phenyl groups of **6** and **8** are twisted, the respective dihedral angles being 51.6° and 62.4°. This feature has been previously observed for the related 4-phenylsubstituted ppy complex.[23a]

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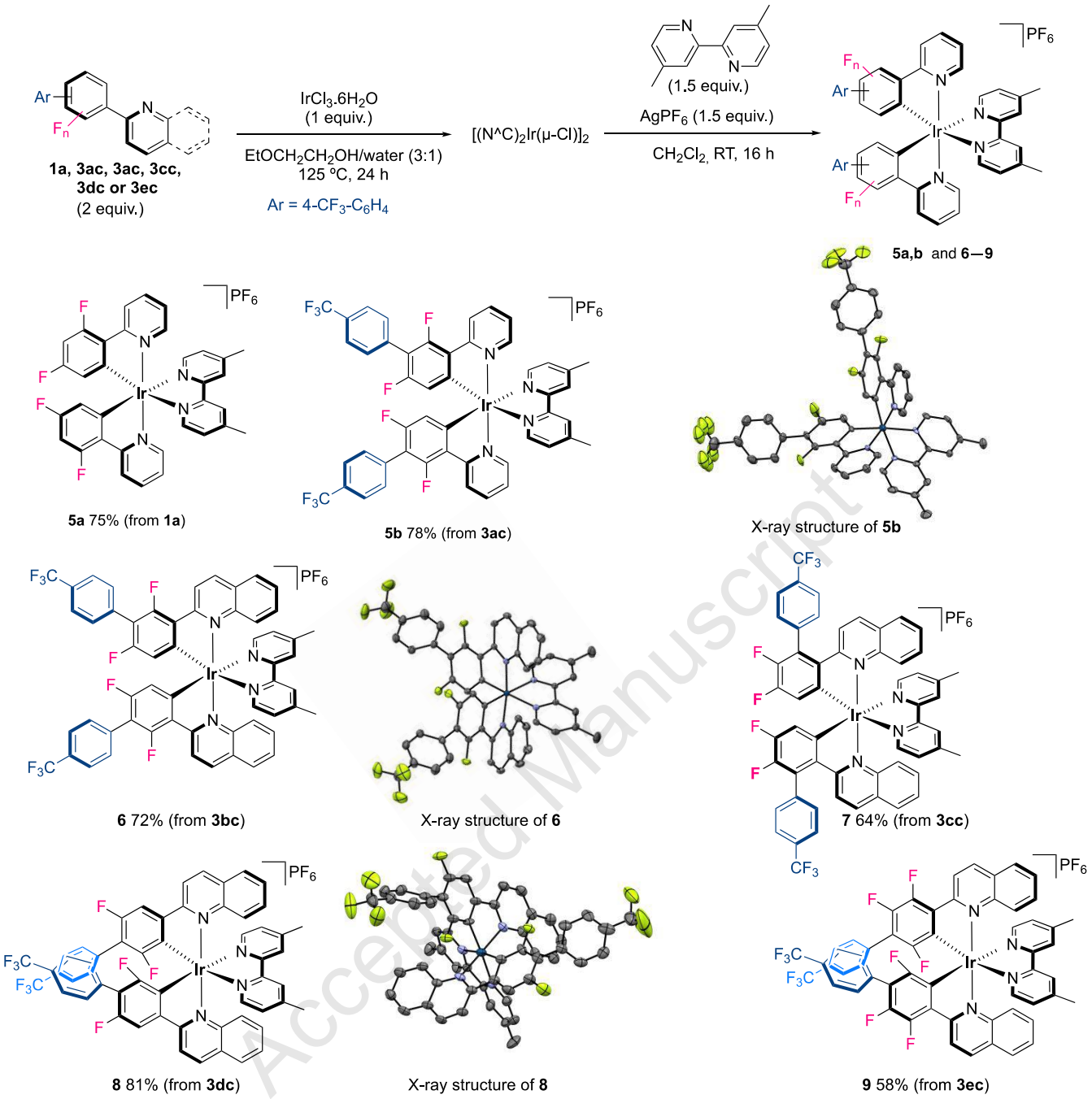

Scheme 3. Synthesis of cationic iridium(III) complexes and X-ray structures of **5b**, **6**, and **8** thermal ellipsoids are drawn at the 50 % probability level, hydrogen atoms, PF_6 counterion and solvent molecules are omitted for clarity

Electrochemical measurements were carried out in MeCN solution (see the SI for details), each complex exhibits a reversible or quasi-reversible metal-centered oxidation. The oxidation potentials of **5a**, **5b** and **6** are very similar, despite the incorporation of the aryl group and/or substitution of the pyridine by a quinoline ring. Upon addition of an extra fluorine atom in **9** at the 6'-phenyl position with respect to **8**, expectedly the oxidation wave is anodically shifted (0.18 V). The UV-visible absorption data and emission spectral data (MeCN and in EPA at 77 K) of **5a**, **5b** and **6-9** are summarized in Figure 2b and Figures S1-S3. These spectra have been interpreted with the help of TD-DFT calculations (see Table S2 and SI for details and Figure 3 for the key MOs). Complexes **5a** and **5b** show intense absorption bands in the UV with maxima at about 300 nm, which are ascribed to spin-allowed $\pi \rightarrow \pi^*$ transitions of the (C^N and N^N) ligands. Lower energy bands between 350 and 400 nm correspond to spin-allowed metal-to-ligand (^{1}MLCT), ligand-to-ligand charge transfer (^{1}LL'CT, $\pi_{N^\wedge C} \rightarrow \pi^*_{N^\wedge N}$) and intra-ligand charge transfer (^{1}LLCT, $\pi_{N^\wedge C} \rightarrow \pi^*_{N^\wedge C}$) transitions whereas the low intensity tails up to 450 nm arise from triplet transitions of mixed ^{3}MLCT/^{3}LL'CT character and very weakly allowed singlet transitions of the same character.

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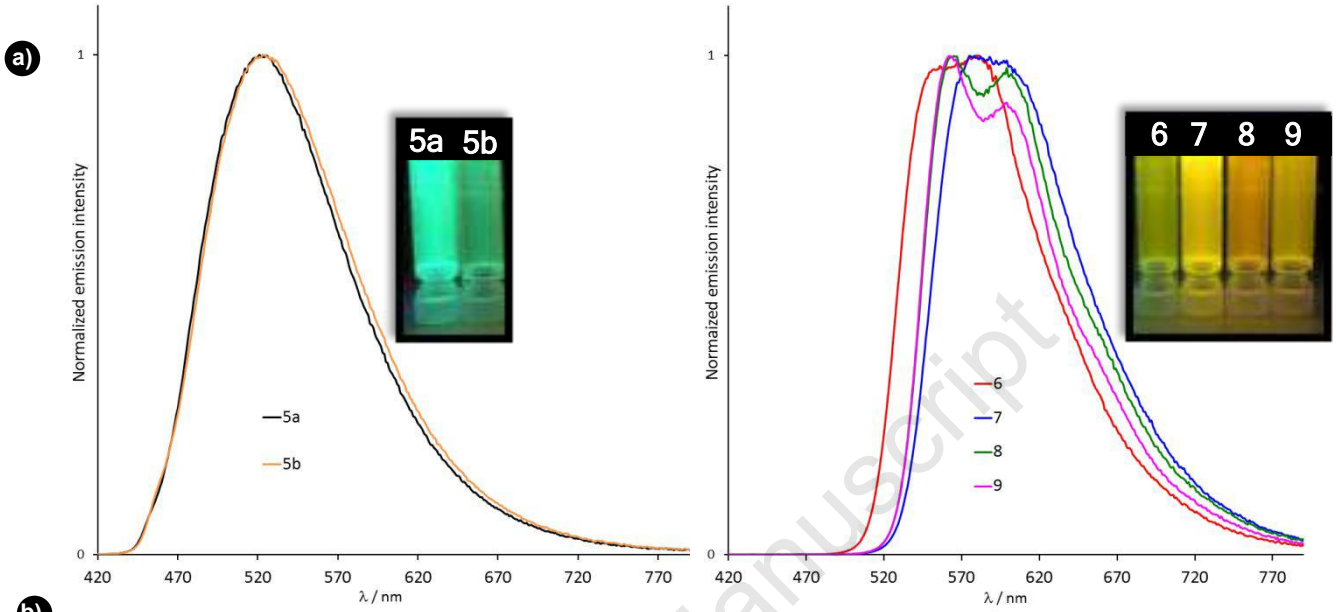
Indeed, the S_1 state computed at 426 nm in both **5a** and **5b** present an oscillator strength of ca. 5 x 10^{-4}. Comparing the spectra of these two compounds, one notes very small differences (Figure S1) in accordance with the topology of the frontier orbitals that show no contribution from the *p*-CF_3-Ph moieties in **5b** (Figure 3 and S3). Note that in **5a** and **5b** the LUMO is exclusively located on the ancillary N^N ligand (Figure 3). The absorption profile of complexes **6-9** are similar, the replacement of dFppy ligand by dFpq or tFpq in the C^N ligands lead to a more intense and broad absorption $\pi \rightarrow \pi^*$ intraligand bands at 350-360 nm, more interestingly a now more marked absorption in the 400-450 nm domain (Figure S1). This trend is well restored by theory with a significant absorption in that region, absent in **5a** and **5b** (Table S2). This new band presents a mixed ^{1}MLCT and ^{1}LLCT ($\pi_{N^\wedge C} \rightarrow \pi^*_{N^\wedge C}$) character and its emergence can be explained by the fact that the LUMO of **6-9** are now centered on the C^N rather than N^N ligand (Figure 3).



b)

Complexes	298 K λ_{abs} [nm][i] (ε x 10^3 [$M^{-1}cm^{-1}$])	λ_{em} [ii] [nm]	λ_{em} [ii,iii]	τ[ii, iv] [µs]	k_r×10^{-5} [s^{-1}]	k_{nr}×10^{-5} [s^{-1}]	77 K λ_{em}[v] [nm]	τ[iv] [µs]
5a	365 (12.2), 392 (6.0)	522	0.63	1.5	4.2	2.5	450, 482, 516, 558sh	4.1
5b	372 (7.8), 363 (8.2), 400 (4.1)	525	0.88	1.1	8.0	1.1	452, 484, 520, 562sh	4.9
6	346 (24.9), 424 (5.8)	552, 579	0.82	8.2	1.0	0.2	534, 576, 622	7.7
7	338 (26.2), 365sh (14.0), 439 (6.5)	562, 600	0.85	5.4	1.6	0.3	543, 588, 640	6.6
8	331sh (33.1), 345 (37.0), 357sh (33.0), 434 (6.9)	589	0.76	3.8	2.0	0.6	555, 599, 650	5.7
9	351 (47.2), 430 (7.0)	566, 600	0.69	7.1	0.9	0.4	548, 591, 646	8.3

[*i*] in MeCN conc. ≈ 1.5 x 10^{-5} M. [*ii*] in deaerated MeCN with : conc. ≈ 1.5 x 10^{-5} M, λ_{exc} = 380 nm. [*iii*] ref = $Ru(bpy)_3Cl_2$ (Φ = 0.04). [*iv*] λ_{exc} = 375 nm. [*v*] in EPA, λ_{ex} = 380 nm.

Figure 2 a) Emission spectra of the Ir(III) complexes **5a**, **5b**, and **6-9** in degassed acetonitrile at 298 K b) Table with absorption and emission data of the Ir(III) complexes **5a**, **5b**, and **6-9**

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Upon excitation at 380 nm, complex **5b** shows similar spectral feature than the reference complex **5a**, with a broad emission band at λ_{em} = 525 nm presenting a lifetime in the µs regime, indicative of an emission with charge-transfer character (Figure 2a left). The fact that **5b** bearing a *p*-trifluoromethylphenyl group shows similar emission energy than **5a** is consistent with previous studies.[23] As mentioned above, the twist between the aryl group and the 4,6-difluorophenyl ring disrupts the conjugation between these two aryl groups, minimizing the impact of the substituent on the emission wavelength. Interestingly, this site selective arylation on the difluoroaryl unit of **5a** leads to an enhancement of the photoluminescence quantum yield, a feature not observed when the arylation occurred on the pyridine ring.[23d] This analysis is corroborated by the computed spin densities of the lowest triplet states that are mainly located on the metal and ancillary ligand in both **5a** and **5b** (Figure S4). The computed emission wavelength of 528 and 532 nm for **5a** and **5b**, respectively, also agree well with the measurements at both RT and 77K.

The second family of complexes **6-9** containing a quinoline exhibit intense luminescence in the yellow-orange domain (Figure 2a right). For instance, the emission maxima of **6** was found at 552 nm and 579 nm with a long lifetime of 8 µs. In all cases, the presence of quinoline gives rise to a red-shifted and structured emission band, characteristic of a significant contribution of ^{3}LC excited state localized on the C^N ligand. Interestingly, position isomers allow a fine-tuning of the emission energy without significantly affecting the photoluminescence quantum yields. This analysis is again supported by theoretical calculation that show that the lowest

triplet state of **6** and **9** locates principally on one of the two C^N ligands (Figure S4). For those two compounds, the computed phosphorescence energies are 634 and 654 nm, respectively, strongly redshifted compared to **5a** and **5b**, and again nicely fitting the low temperature measurements.

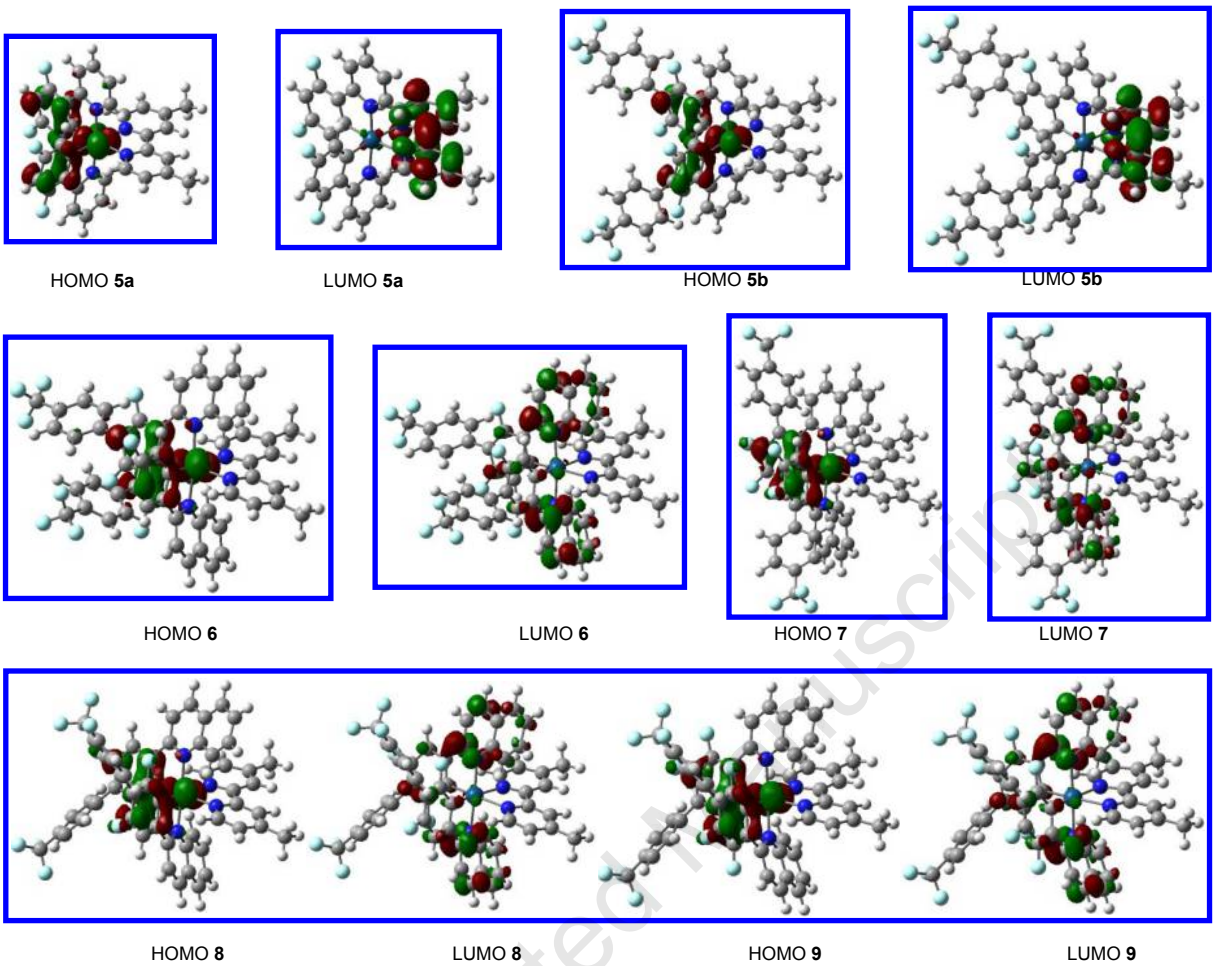

Figure 3. Frontier MOs of the different compounds (contour threshold: 0.04 au)

3. CONCLUSION

In summary, we have showed that depending on the choice of the transition metal catalyst, one can achieve regiodivergent C–H bond arylations of fluorinated 2-arylpyridines and 2-arylquinolines. Highly *ortho*-to-fluorine-selectivity is obtained using palladium catalyst. Interestingly, the electronically enhanced site selectivity is not altered by the presence of heterocycle coordinating group and by the position pattern of the fluorine atoms. In contrast, the use of ruthenium enables pyridine or quinoline *ortho*-directed C–H bond arylations of the fluoroarenes. The regioselectivity of the Pd-catalyzed C−H arylation was applied to efficient synthesis of proligands for the preparation of Ir(III)-complexes displaying tunable photophysical properties. Incorporation of the CF3-aryl group at the C3-position of the dFppy C^N ligand (complex 5b) does not modify the emission energy but induces an enhanced photoluminescence quantum yield. Moreover, a subtle modulation of the emission color can be readily achieved by changing the location of the incorporated aryl group at the cyclometalated phenyl ligand. These studies represent a unique example of late-stage modification of fluorinated 2-arylpyridines opening a facile access to regioselectively substituted bis-cyclometalated complexes with tailoring photophysical properties. In the near future, this approach should contribute to the efficient tuning of photoredox catalysts and of luminescence properties of complexes useful for the fabrication of optoelectronic devices such as OLEDs and LEECs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

Denis Jacquemin: Denis.Jacquemin@univ-nantes.fr
Veronique Guerchais: veronique.guerchais@univ-rennes1.fr
Henri Doucet: henri.doucet@univ-rennes1.fr
Jean-François Soulé: jean-francois.soule@univ-rennes1.fr

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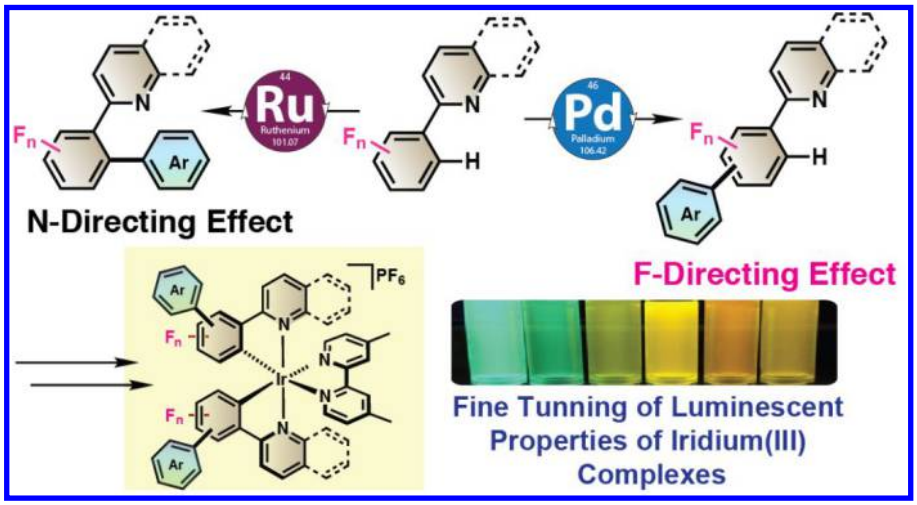

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