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.

1. INTRODUCTION

Fluoroarene molecules represent one of the most prevalent entities within both pharmaceutical compounds,1,2 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)]PF6 (Figure 1, left).5,6 Such bismo-catalyzed complexes exhibit highly efficient optoelectronic properties, with widespread applications as photoredox catalysts,3 biological staining agents,6 or medicinal drugs.5,7

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 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

Figure 1. Relevant Structures containing Fluorinated 2-Arylpyridines and their Site Reactive C–H Bonds in Transition-Metal-Catalyzed Functionalizations.
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-aryl-pyridines 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-
fluorobenzonitrile (2a) in the presence of 2 equivalents of
KOAc as base in DMA at 150 °C 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 (Table 1, entry 2). We reasoned that the use of
diphosphine palladium catalyst PdCl(C_5H_5)(dpbb), 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 [Rup-cymene]Cl_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>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (x mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>Conv. (%)</th>
<th>3aa/4aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)_2 (2)</td>
<td>KOAc</td>
<td>DMA</td>
<td>54</td>
<td>76:24</td>
</tr>
<tr>
<td>2</td>
<td>PdCl_2 (2)</td>
<td>KOAc</td>
<td>DMA</td>
<td>58</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>PdCl(C_5H_5)(dpbb) (2)</td>
<td>KOAc</td>
<td>DMA</td>
<td>65</td>
<td>92:8</td>
</tr>
<tr>
<td>4</td>
<td>PdCl(C_5H_5)(dpbb) (2)</td>
<td>KOPIv</td>
<td>DMA</td>
<td>68</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>5</td>
<td>PdCl(C_5H_5)(dpbb) (5)</td>
<td>KOPIv</td>
<td>DMA</td>
<td>100</td>
<td>&gt;95:5 (76%)(^{(20)})</td>
</tr>
<tr>
<td>6</td>
<td>[Ru(p-cymene]Cl_2 (5)</td>
<td>KOAc</td>
<td>NMP</td>
<td>25</td>
<td>&gt;5:95</td>
</tr>
<tr>
<td>7</td>
<td>[Ru(p-cymene]Cl_2 (5)</td>
<td>KOAc</td>
<td>NMP</td>
<td>25</td>
<td>&gt;5:95</td>
</tr>
<tr>
<td>8</td>
<td>[Ru(p-cymene]Cl_2 (5)</td>
<td>KOAc</td>
<td>NMP</td>
<td>95</td>
<td>&gt;5:95 (70%)(^{(20)})</td>
</tr>
</tbody>
</table>

[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-3be
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
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.


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](image)

### 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 \([\text{Ir}(\text{C=N})_2(\text{N}^\text{N})]\) 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.\(^{4b}\) 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.\(^{23a}\)
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, PF₆⁻ 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 \((\text{C}^\text{N} \text{ and } \text{N}^\text{N})\) ligands. Lower energy bands between 350 and 400 nm correspond to spin-allowed metal-to-ligand \((1\text{MLCT})\), ligand-to-ligand charge transfer \((1\text{LL'CT}, \pi^\text{N,C} \rightarrow \pi^*\text{N,N})\) and intra-ligand charge transfer \((1\text{LLCT}, \pi^\text{N,C} \rightarrow \pi^*\text{N,C})\) transitions whereas the low intensity tails up to 450 nm arise from triplet transitions of mixed \(3\text{MLCT}/1\text{LL'CT}\) character and very weakly allowed singlet transitions of the same character.
Indeed, the S₁ 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-CF₃-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 π → π* 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 (πN⁢C → π*⁢N⁢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).

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. 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. 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 contribution of 1⁢MLCT and 1⁢LLCT (πN⁢C → π*⁢N⁢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).

**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.
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.

![HOMO 5a](image) ![LUMO 5a](image) ![HOMO 5b](image) ![LUMO 5b](image)

![HOMO 6](image) ![LUMO 6](image) ![HOMO 7](image) ![LUMO 7](image)

![HOMO 8](image) ![LUMO 8](image) ![HOMO 9](image) ![LUMO 9](image)

**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 LEEDs.

**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


(18.) (a) Arokiam, P. B.; Bruneau, C.; Dixneuf, P. H., Ruthenium(II)-Catalyzed C–H Bond Activation and Functionalization. Chem. Rev. 2012, 112, 5870-5918; (b) Nareddy, P.; Jordan, F.; Szostak, M.,


Insert Table of Contents artwork here

N-Directing Effect

F-Directing Effect

Fine Tunning of Luminescent Properties of Iridium(III) Complexes