JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b03306 • Publication Date (Web): 10 Feb 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of 2-Arylpyridines and 2-Arylbipyridines *via* Photoredox-Induced Meerwein Arylation with in-situ Diazotization of Anilines

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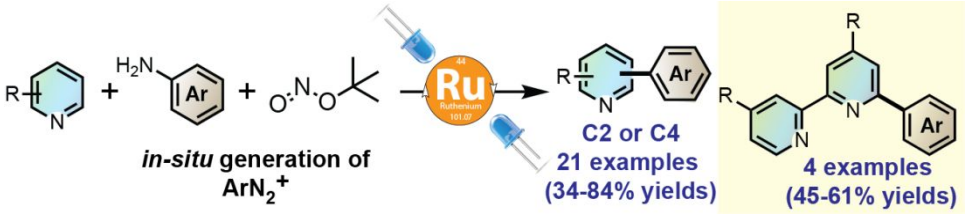
Abstract: We report herein a sustainable method for the preparation of 2-arylpyridines through C−H arylation of pyridines using *in-situ* formed diazonium salts (from commercially available aromatic amines) in the presence of a photoredox catalyst under blue LEDs irradiation. The reaction is tolerant to a wide range of functional groups (*e.g.*, halogen, nitrile, formyl, acetyl, ester). Applications to the C–H bond arylation of bipyridine ligands is also presented.



Introduction

The 2-arylpyridine derivatives are one of the essential scaffolds for the preparation of organometallic complexes with catalytic or material uses (Figure1). For example, *fac*-Ir(ppy)$_3$ with three 2-phenylpyridine is often employed as photoredox catalyst.[1] FIrPic with two 2-(2,4-difluorophenyl)pyridine is an highly phosphorescent *bis*-cyclometalated iridium complexes employed in OLEDs' manufacture.[2] Moreover, 2-arylpyridine is a common unit widely embedded in pharmaceutical drugs. For example, Enpiroline is an antimalarial agent.

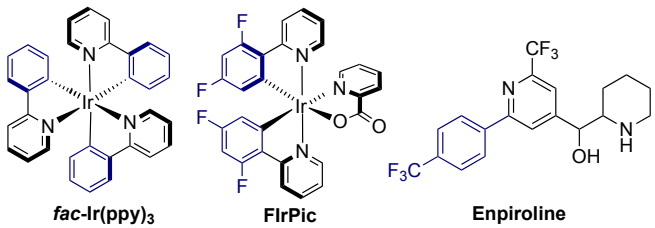


Figure 1. Representative 2-Arylpyridine in Organometallics and Pharmaceuticals.

Traditionally, 2-arylpyridines were synthesized from 2-halopyridines through cross-coupling reactions with aryl pseudo-halides as coupling partners in the presence of palladium catalysts[3]

or from metalated pyridines and aryl pseudo-halides.[4] Among these protocols, the use of 2-(tributylstannyl)pyridine remains the most employed starting materials, albeit it is a hazardous and harmful reagent (Figure 2a). More sustainable approaches based on transition-metal catalyzed C–H bond arylation of pyridines were often carried out under harsh reaction conditions and displayed a poor substrate scope,[5] or required the prior oxidation of pyridines to *N*-oxide pyridines.[6] Recently, photoredox catalysis has emerged as an eco-friendly alternative to build C–C bond from C(sp^2)–H bond under mild reaction conditions.[7] In 2014, Xue and co-workers reported the photoredox-catalyzed C–H bond arylation of pyridine derivatives at C2 or/and C4 positions with aryldiazonium salts using $Ru(bpy)_3^{2+}$ (Figure 2b).[8] This Merwein-type arylation of pyridines was also developed using different photosensitizers.[9] In 2017, Heinrich and co-workers demonstrated that the arylation of heteroarenes with aryldiazonium salts could also proceed in the absence of an external photosensitizer.[10] The reaction involves the formation of charge-transfer complexes[11] between the electron-poor aryl diazonium salts with electron-rich (hetero)aromatics. In the case of pyridine, only 3-hydroxypyridine has been arylated owing to its specific electronic nature, which allows the formation of charge-transfer complexes with aryl diazonium and is a good aryl radical acceptor. Besides the regioselectivity issue due to the low control of the radical additions, an additional challenge is the handling of the potentially unstable aryldiazonium precursors. In 2014, to avoid the use of such hazardous chemicals and employed commercially available chemicals, Martín, Carrillo, and co-workers have developed C–H bond arylation of (hetero) arenes using *in-situ* diazotization from anilines with *tert*-butyl that is promoted by catalytic amounts of L-ascorbic acid, with no heating or irradiation.[12] However, these protocols were limited to the direct arylation of 5-membered ring heteroarenes, electron-rich arenes and *N*-oxide pyridines (Figure 2c). The reaction can be also promoted by a mild base (Na_2CO_3),[13] or polyamine.[14] Later, Horan's group showed that the reaction can also proceed at 40 ºC in the absence of L-ascorbic acid.[15] In 2015, Frutos, Kappe, and co-workers also demonstrated that the C–H bond arylation of (hetero) arenes using *in-situ* diazotization from anilines with *tert*-butyl could proceeded at room temperate under visible-light irradiation.[16] Again, the scope of the reaction is limited to heteroarenes, electron-rich arenes and *N*-oxide pyridines.

To the best of our knowledge, there is no example of (photoredox-initiated) C–H bond arylation pyridines using anilines trough the *in-situ* generation of diazonium slats, albeit it might provide practical and sustainable access to 2-arylpyridine derivatives in one-step from commercially available starting materials (Figure 2b). In addition, there is no example of direct arylation of

bipyridines (even using aryldiazonium salts) although they are useful precursors for the preparation of CNN-cyclometalated complexes.

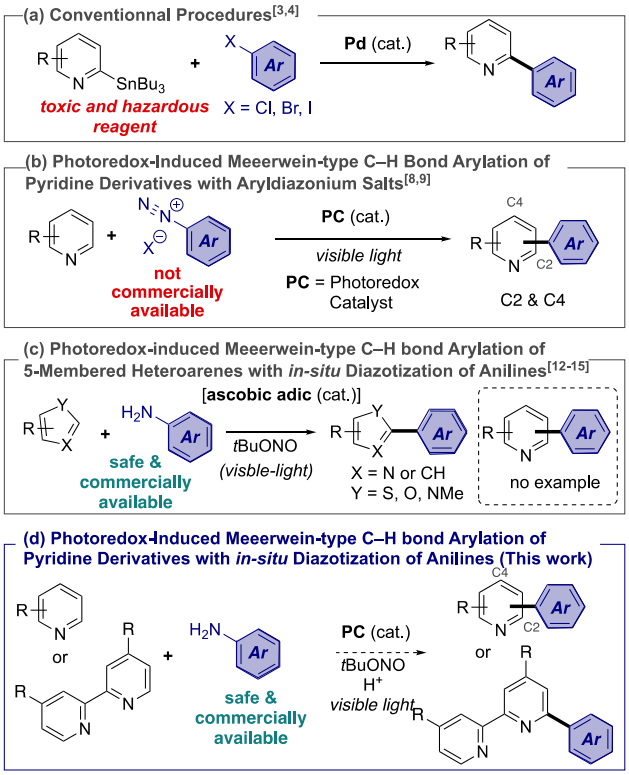


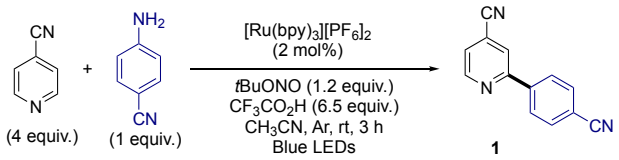
Figure 2. Synthesis of 2-Arylpyridines

Results & Discussion

Firstly, we selected 4-cyanopyridine and 4-aminobenzonitrile as model substrates. During the reaction development, we determined that Meerwein-type arylation reaction of pyridine ring was efficient in CH_3CN containing 2 mol% $[Ru(bpy)_3[PF6]_2$ and 1.2 equivalent of *tert*-butyl nitrite (*t*BuONO) and 6.5 equivalents of CF_3CO_2H (1.6 equivalents by pyridine) under blue LEDs irradiation, affording the C2-arylated pyridine **1** in 72% isolated yield after 3 h (Table 1, entry 1). Other metal-based photoredox catalyst, such as *fac*-$Ir(ppy)_3$ or $(Ir[ppy]_2(dtbbpy))PF_6$, gave lower yield in **1**, while a similar yield was observed with $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$. The use of eosin Y as organic dye afforded **1** in only 21% yield (Table 1, entries 2-5). Moreover, the arylated pyridine **1** is obtained in a low yield without photoredox catalyst (Table 1, entry 6). The presence of acid is required to obtain a good yield (Table 1, entries 7 and 8). As explained by Opatz and co-workers, DFT-calculation shows that the use of acid allows the protonation of the pyridine lowering the energy of its LUMO and facilitating the radical addition.[17] A slightly larger amount of acid compared to pyridine is required owing that acid is also essential for the generation of the aryldiazonium salts from aniline and *t*BuONO. The

reaction can be performed in DMSO or water solvents, albeit in slightly lower yields (Table 1, entries 9 and 10). Control experiments showed that blue LEDs are mandatory, as **1** was not obtained when the reaction is carried out using white light or in the dark (Table 1, entries 11 and 12). As expected, no reaction occurred when the reaction is set up without tBuONO (Table 1, entry 13). Usually, a fan is used to keep the temperature at 30- 35 ºC. Without a fan, the temperature reached 65 ºC due to the heat released from the LEDs; but this higher temperate has no effect on the production of **1** (Table1, entry 14). A shorter reaction time (1h) gave a partial conversation, while longer reaction time (12 h) did not affect the chemical yield (Table 1, entries 15 and 16). The conditions reported by Carrillo's group for the C–H bond arylation of heteroarenes and *N*-oxide pyridines with L-ascorbic acid as catalyst in absence of light was inefficient with 4-cyanopyridine (Table 1, entry 17).[15]

Table 1. Reaction Development and Control Experiments

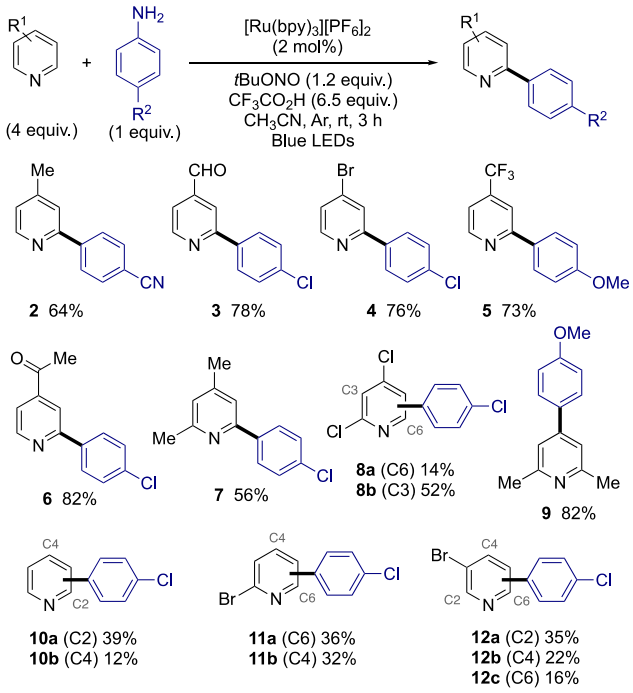


Entry	Variation from above conditions	Yield in **1** (%)[a]
1	–	81 (72%)
2	*fac*-Ir(ppy)$_3$ as catalyst	65
3	(Ir[ppy]$_2$(dtbbpy))PF$_6$ as catalyst	58
4	(Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ as catalyst	80
5	Eosin Y as catalyst	21
6	without photoredox catalyst	15
7	CF_3CO_2H (4 equiv.)	45
8	Without CF_3CO_2H	15
9	Using DMSO instead of CH_3CN	76
10	Using water instead of CH_3CN	67
11	Using white light	0
12	In the dark	0
13	Without *t*BuONO	0

14	At 65 ºC	78
15	1 h	55
16	12 h	82
17	L-ascorbic acid (10 mol%), without light	0

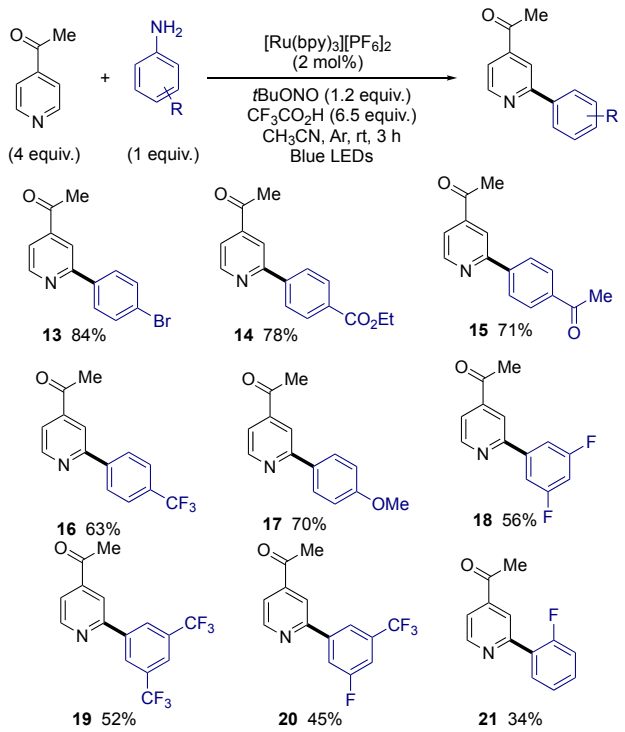
[a] The yield was determined by GC-analysis using *n*-dodecane as internal standard, the isolated yield is shown in parentheses.

With the optimized conditions in hands, we turned our attention to the scope of the reaction with the respect of pyridine (Scheme 1). Firstly, we investigated a set of 4-substituted pyridines to avoid the formation of other regioisomers.[8] 4-Methylpyridine, an electron-rich pyridine, exhibited a slightly lower reactivity with 4-aminobenzonitrile, affording the 2-arylated pyridine **2** in 64% yield. Nicotinaldehyde was arylated at C2 position with 4-chloroanaline to give **3** in 78% without deformylation. Interestingly, the reaction was tolerant to C–Br bond on the pyridine unit, as the coupling reaction between 4-bromopyridine and 4-chloroaniline afforded the C2-arylated pyridine **4** in 76% yield without the cleavage of both C–Br and C–Cl bonds providing the possibility for further diversification *via* Pd-catalyzed selective cross-coupling reactions. 4-(Trifluoromethyl)pyridine and 4-acetylpyridine were also arylated at C2-position using *in-situ* diazotization of *p*-anisidine or 4-chloroaniline in 73% and 82% yield, respectively. Disubstituted pyridines can also be employed. From 2,4-lutidine, the C6-arylated pyridine **7** was isolated in 56% yield as a single regioisomer. In contrast, when the reaction is carried out with 2,4-dichloropyridine, a mixture of C6 and C3 arylated pyridines **8a** and **8b**, which can be isolated separately, are obtained in 14% and 52% yield, respectively. The formation of **8b** as the major product might be attributed to the high electrophilic character of the carbon atom flanked by the two chlorine atoms. The arylation of 2,6-lutidine took place at C4 position affording **9** in 82% yield. Reaction with unsubstituted pyridine provided a mixture of C2 and C4 arylated products **10a** and **10b** with are isolated in 39% and 12% yield, respectively; but both isomers can be isolated separately by column chromatography. From 2-bromopyridine, C6 and C4 regioisomers **11a** and **11b** were isolated separately in 36% and 32% yield, respectively. We then carried out the reaction with 3-bromopyridine and we isolated the C2, C4 and C6 regioisomers **12a**, **12b**, **12c** in 35%, 22% and 15% yield, respectively. The regioselectivities observed are similar to those observed with aryldiazonium salts,[8-9] and more generally with those observed for radical addition to pyridines.[18] The LUMO coefficients at C-2 and C-4 of pyridine derivatives are often very similar, which explained the formation of the mixtures of regioisomers if at least one position is not blocked.[17]



Scheme 1. Scope of Pyridine in C–H Bond Arylation with *in-situ* Diazotization of Anilines under Photoredox Catalysis

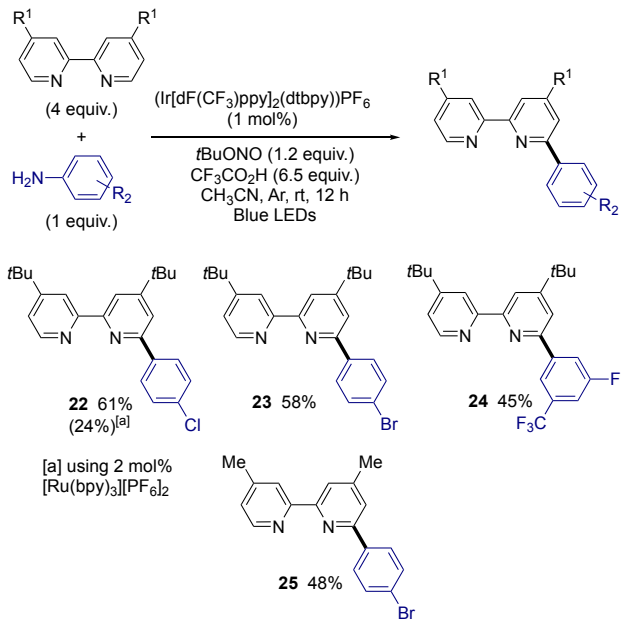
Next, we moved to the scope of anilines for the C2-arylation of 4-acetylpyridine under photoredox conditions (Scheme 2). From, 4-bromoaniline, the reaction was chemoselective and occurred only *via* diazonium coupling affording the C2-arylated pyridine **13** in 84% yield, while the C–Br bond remains untouched. *para*-substituted anilines by an electron-withdrawing group (e.g., ester, acetyl, trifluoromethyl) smoothly underwent *in-situ* diazotization–photoredox-triggered radical arylation to afford the C2-arylated pyridines **14-16** in 63-78% yields. Electron-rich *p*-anisidine was efficiently coupled to give **17** in 70% yield. Meta-substituted anilines such as 3,5-difluoroanilne, 3,5-bis(trifluoromethyl)aniline, and 3-fluoro-5-(trifluoromethyl)aniline were successfully employed to prepare the corresponding C2-arylated pyridines **18-20** in 45-56% yield. The reaction is more sensitive to the presence of an *ortho*-substituent, as the coupling between 4-acetylpyridine and 2-fluoroaniline led to the formation of **21** in only 34% yield.



Scheme 2. Scope of Anilines in C–H Bond Arylation of Pyridine with *in-situ* Diazotization of Anilines under Photoredox Catalysis

2-Arylbipyrines (precursor of CNN ligands) are generally prepared using a two-steps procedure with aryl lithium reagents under cryogenic conditions,[19] *via* transition metal-catalyzed C–H bond functionalization using organometallic reagents (e.g., diaryl zinc or aryl boronic acids),[20] or by C–H bond borylation of bipyridine followed by Suzuki reaction.[21] To the best of our knowledge, no example of Meerwein-type arylation reaction of bipyridines is reported, yet. Although it will be a sustainable synthetic pathway to a wide variety of CNN pro-ligands, including some bearing a sensitive functional group toward organometallic reagents. Therefore, we also investigated the reactivity of 4,4'-di-*tert*-butyl-2,2'-bipyridine (Scheme 3). The coupling reaction between 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 equiv.) and of 4-chloroaniline (1 equiv.) –in a mixture of CH_3CN/TFA (8:1) solvent containing 2 mol% $[Ru(bpy)_3[PF_6]_2$ and 1.2 equivalents of *t*BuONO under blue LEDs irradiation– afforded **22** in 24% yield. The use of 1 mol% $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, which displayed a lower redox potential [Ir(III)/Ir(II) = -1.37 V vs Ru(II)/Ru(I) = -1.33 V] allowed the formation of **22** in 61% yield. From 4-bromopyridine and 4,4'-di-tert-butyl-2,2'-bipyridine the functionalized CNN pro-ligand **23** is obtained in 58%. Notably, this bipyridine could not be obtained using previous protocols due to the lithiation reaction. 3-Fluoro-5-(trifluoromethyl)aniline was efficiently coupled to give the 2-arylbipyridine **24** in 45% yield. 4,4'-Dimethyl-2,2'-bipyridine was also arylated at C2

position using *in-situ* diazotization of 4-bromoaniline leading to the formation of **25** in 48% yield.



Scheme 3. Application de the Late-Stage Modification of Bipyridine Ligands

To have a better understanding of the mechanism, a radical control experiment was carried out in the presence of a radical scavenger (Figure 3a). When two equivalents of 2,2,6,6-tetramethylpiperidine1-oxyl (TEMPO) was added to the reaction mixture under the standard conditions, no desired product **1** was detected. However, we have observed the formation of the 4-benzonitrile–TEMPO adduct **26** (determined by GC−MS), which arises from radical deamination of the aniline through the *in-situ* formation of diazonium salts.[22] Also, we conducted two competitive reactions to probe the substituent preference for such couplings (Figure 3b). From an equimolar ratio of 4-cyanopyridine (4 equiv.) and 4-methylpyridine (4 equiv.) in the presence of 4-aminobenzonitrile (1 equiv.), we observed the formation of a mixture of **1** and **2** in a 77:23 ratio suggesting that an electron-withdrawing substituent on the pyridine ring favor the reaction. This result is in line with the aryl radical addition onto the pyridine ring. From an equimolar ratio of *p*-anisidine (1 equiv.) and ethyl 4-aminobenzoate (1 equiv.) in the presence of 1 equivalent of tBuONO and 4-acetylpyridine (4 equiv.), we observed the formation of a mixture of **14** and **17** in a 9:91 ratio suggesting that electron-rich anilines react faster with *t*BuONO. Moreover, KIE value of 1.1 was determined from parallel completion reactions, suggesting that the C–H bond cleavage event is not involved in a rate-determining step (RDS) (Figure 3c).[23]

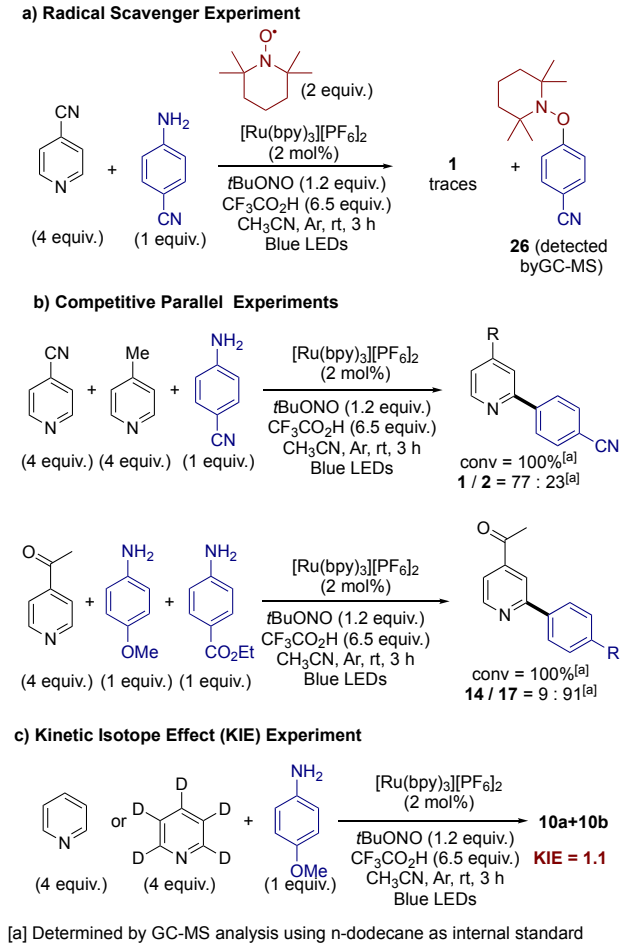


Figure 3. Mechanistic Investigation

Based on the above experimental results and literature on photoredox-catalyzed C–H bond arylations,[8, 24] a plausible mechanism is illustrated in Figure 4. Firstly, under acidic conditions aniline derivatives reacted with *t*BuONO to generate aryl diazonium salts. Upon the generation of excited state catalyst *PC from ground state of $[Ru(bpy)_3[]PF_6]_2$ or $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ by blue LEDs irradiation, a single electron transfer (SET) occurs from *[PC] to the aryl diazonium salts leading to the formation of a free aryl radical ($Ar^{\bullet}$) – after the extrusion of dinitrogen– among with the oxidized catalyst [PC^{+}]. Then, the aryl radical adds to the protonated pyridine at C2 or/and C4 position(s) –depending on its substitution patterns– yielding the pyridine radical-cation intermediate (**A**). Then, **A** is subsequently transformed into a carbocation intermediate **B** *via* a SET from [Ir^{2+}] with the loss of a proton. Finally, the rearomatization gives the desired arylated pyridine.

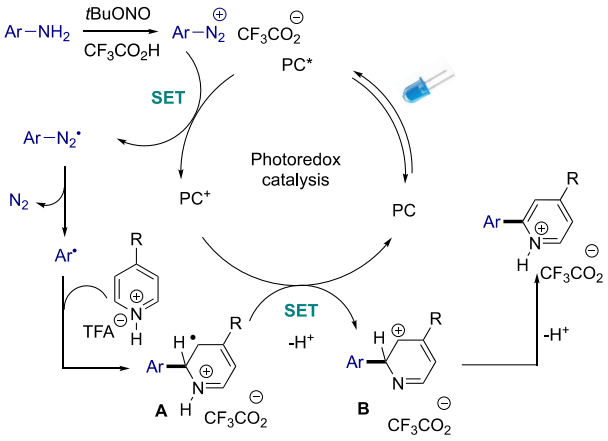


Figure 4. Proposed Mechanism

Conclusion

In summary, a highly effective visible light-promoted C–H bond arylation of pyridines has been developed. The reaction proceeds at room temperature with $[Ru(bpy)_3[]PF_6]_2$ as a photosensitizer with commercially available anilines as safe aryl radical precursors *via* in-situ diazotization using *tert*-butyl nitrite. A wide variety of substituted pyridines and anilines have been efficiently coupled under these reaction conditions affording only the monoarylated products with different regioselectivities. Moreover, bipyridines have been arylated at the C2 position using or $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ as a photosensitizer. This procedure is a practical and sustainable method for the synthesis of nitrogen ligands useful for the preparation of novel organometallics.

Experimental Section

General Remarks: All reactions were run in Schlenk tubes under argon atmosphere. Commercial pyridines and anilines were used after purification according the literature (distillation or recrystallisation). The reactions were followed by GC and NMR. 1H and 13C spectra were recorded with a Bruker 400 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (7.26 for 1H NMR and 77.0 for 13C NMR). Flash chromatography was performed on silica gel (230–400 mesh). GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM- 5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 ºC for 5 minutes, then rate 20 ºC/min until 280 ºC and 280 ºC for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at

the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1.

General Procedure for C–H bond arylation of pyrdines: To a 15 mL oven dried Schlenk tube, $[Ru(bpy)_3][PF_6]_2$ (10.3 mg, 0.012 mmol, 2 mol%) or $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (6.6 mg, 0.006 mmol, 1 mol%), pyridine (2.4 mmol, 4 equiv.), aniline (0.6 mmol, 1 equiv), CH_3CN (1.2 mL), TFA (0.3 mL) were successfully added under an argon atmosphere. Then, *t*BuONO (88 µL, 0.62 mmol, 1.2 equiv.) was slowly added. The Schlenk was positioned on a stir plate approximately 2 – 3 cm from two ABI PAR38 (24W) LED lamp supplying blue light (λ = 440-460 nm). Fans were used for cooling. After irradiation for 3 hours, the reaction mixture was poured in a saturated aqueous solution of K_2CO_3 (10 mL), and extracted several times with AcOEt (4x 15 mL). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate) to afford the desired product.

2-(4-Cyanophenyl)isonicotinonitrile (1): Following the general procedure using isonicotinonitrile (250 mg, 2.4 mmol) and 4-aminobenzonitrile (70 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 90-10) to afford the desired compound **1** (89 mg, 72%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, J = 5.0 Hz, 1H), 8.61 (s, 1H), 8.34 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 5.0, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 155.6, 151.4, 141.5, 133.3, 128.0, 125.7, 123.6, 121.3, 119.0, 117.2, 112.9. HRMS (ESI) Calcd for: $C_{13}H_8N_3$: 206.0713; Found: 206.0712 $[M+H]^+$.

4-(4-Methylpyridin-2-yl)benzonitrile (2): Following the general procedure using 4-methylpyridine (233 µL, 2.4 mmol) and 4-aminobenzonitrile (70 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **2** (75 mg, 64%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 5.0 Hz, 1H), 8.12 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.60 (s, 1H), 7.15 (d, J = 4.8 Hz, 1H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.8, 149.7, 148.0, 143.7, 132.6, 127.3, 124.2, 121.7, 118.8, 111.9, 21.2. The NMR data are identical to those reported in the literature.[25]

2-(4-Chlorophenyl)isonicotinaldehyde (3): Following the general procedure using isonicotinaldehyde (210 µL, 2.4 mmol) and 4-chloroaniline (76 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **3** (101 mg, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.96

(d, J = 4.9 Hz, 1H), 8.12 (s, 1H), 8.04 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 4.9, 1H), 7.50 (d, J = 7.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 191.4, 157.8, 151.1, 142.5, 136.6, 135.9, 129.1, 128.2, 120.9, 118.4. HRMS (ESI) Calcd for: $C_{12}H_9NO^{35}Cl$: 218.0367; Found: 218.0367 $[M+H]^+$.

4-bromo-2-(4-chlorophenyl)pyridine (4): Following the general procedure using 4-bromopyridine (466 mg, 2.4 mmol) and 4-chloroaniline (76 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 99-1) to afford the desired compound **4** (122 mg, 76%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.89 (s, 1H), 7.47 (d, J = 8.4, 2H), 7.43 (d, J = 6.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.6, 150.4, 136.4, 135.8, 133.6, 129.0, 128.2, 125.5, 123.6. HRMS (ESI) Calcd for: $C_{11}H_8N^{35}Cl^{79}Br$: 267.9523; Found: 267.9526 $[M+H]^+$.

2-(4-methoxyphenyl)-4-(trifluoromethyl)pyridine (5): Following the general procedure using 4-(trifluoromethyl)pyridine (257 µL, 2.4 mmol) and 4-methoxyaniline (74 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 96-4) to afford the desired compound **5** (113 mg, 73%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 5.0 Hz, 1H), 8.02 (d, J = 8.9 Hz, 2H), 7.88 (s, 1H), 7.40 (d, J = 5.7 Hz, 1H), 7.04 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H**).** $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.1, 158.3, 150.4, 139.0 (q, J = 33.7 Hz), 130.6, 128.3, 123.0 (q, J = 273.2 Hz), 116.7 (q, J = 3.4 Hz), 115.1 (q, J = 3.6 Hz), 114.3, 55.3. The NMR data are identical to those reported in the literature.[8]

1-(2-(4-chlorophenyl)pyridin-4-yl)ethan-1-one (6): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 4-chloroaniline (76 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **6** (114 mg, 86%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 5.0 Hz, 1H), 8.13 (s, 1H), 8.00 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 6.4 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 2.68 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.2, 157.5, 150.8, 143.8, 136.9, 135.7, 129.0, 128.2, 120.0, 117.6, 26.7. The NMR data are identical to those reported in the literature.[26]

2-(4-Methoxyphenyl)-4,6-dimethylpyridine (7): Following the general procedure using 2,4-lutidine (277 µL, 2.4 mmol) and 4-methoxyaniline (74 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **7** (73 mg, 56%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.6 Hz, 1H), 7.30

(s, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.90 (s, 1H), 3.87 (s, 3H), 2.58 (s, 3H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 160.1, 157.9, 156.5, 147.6, 132.5, 128.2, 121.9, 117.9, 113.9, 55.3, 24.5, 21.0. The NMR data are identical to those reported in the literature[8]

2,4-dichloro-6-(4-methoxyphenyl)pyridine (8a) and 2,4-dichloro-3-(4-methoxyphenyl)pyridine (8b): Following the general procedure using 2,4-dichloropyridine (354 mg, 2.4 mmol) and 4-methoxyaniline (74 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 98-2) to afford the desired compounds **8a** (22 mg, 14%) as a white solid and **8b** (81 mg, 52%) as a white solid. **8a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.49 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 150.6, 150.1, 144.1, 135.1, 130.7, 126.5, 124.7, 114.0, 55.4. **8b** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.3 Hz, 1H), 7.40 (d, *J* = 5.3 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 159.8, 152.3, 148.1, 145.7, 135.7, 130.6, 126.9, 123.8, 113.9, 55.2. HRMS (ESI) Calcd for: $C_{12}H_9NO^{35}Cl_2Na$: 275.9953; Found: 275.9953 $[M+Na]^+$.

4-(4-Methoxyphenyl)-2,6-dimethylpyridine (9): Following the general procedure using 2,6-lutidine (277 µL, 2.4 mmol) and 4-methoxyaniline (74 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 80-20) to afford the desired compound **9** (105 mg, 82%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.17 (s, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.59 (s, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 160.3, 158.0, 148.5, 130.9, 128.1, 117.8, 114.3, 55.3, 24.5. HRMS (ESI) Calcd for: $C_{14}H_{16}NO$: 214.1226; Found: 214.1226 $[M+H]^+$.

2-(4-methoxyphenyl)pyridine (10a) and 4-(4-methoxyphenyl)pyridine (10b): Following the general procedure using pyridine (193 µL, 2.4 mmol) and 4-methoxyaniline (74 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compounds **10a** (43 mg, 39%) as a white solid and **8b** (13 mg, 12%) as a white solid. **10a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.7 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.76–7.66 (m, 2H), 7.20 (m, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H). **10b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.0 Hz, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 1H). The NMR data are identical to those reported in the literature.[8]

2-Bromo-6-(4-chlorophenyl)pyridine (11a) and 2-bromo-4-(4-chlorophenyl)pyridine (11b): Following the general procedure using 2-bromopyridine (229 μL, 2.4 mmol) and 4-chloroaniline (76 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compounds**11a** (58 mg, 36%) as a white solid and **11b** (51 mg, 32%) as a white solid. **11a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.48 – 7.42 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.3, 142.2, 139.1, 136.0, 135.9, 129.0, 128.2, 126.6, 118.8. The NMR data are identical to those reported in the literature.[27] **11b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.1 Hz, 1H), 7.70 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.5, 150.0, 143.1, 136.1, 135.1, 129.5, 128.3, 125.7, 120.6. The NMR data are identical to those reported in the literature.[28]

3-Bromo-2-(4-chlorophenyl)pyridine (12a), 3-bromo-4-(4-chlorophenyl)pyridine and 5-bromo-2-(4-chlorophenyl)pyridine (12c): Following the general procedure using 3-bromopyridine (231 μL, 2.4 mmol) and 4-chloroaniline (76 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compounds **12a** (56 mg, 35%) as a white solid, **12b** (35 mg, 22%) as a white solid and **12c** (26 mg, 16%) as a white solid. **12a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.4 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 2H), 7.89 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.6, 150.8, 139.4, 136.6, 135.5, 129.1, 128.0, 121.4, 119.6. The NMR data are identical to those reported in the literature.[29] **12b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 – 8.80 (m, 1H), 8.62 – 8.53 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.24 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.6, 148.5, 148.4, 136.5, 135.1, 130.8, 130.2, 128.7, 128.2, 125.4. HRMS (ESI) Calcd for: $C_{11}H_8N^{35}Cl^{79}Br$: 267.9524; Found: 267.9526 $[M+H]^+$. **12c** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.01 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.17 (dd, *J* = 4.6, 8.1 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.0, 148.2, 141.4, 137.9, 134.9, 130.8, 128.2, 127.0, 123.5, 119.7. HRMS (ESI) Calcd for: $C_{11}H_8N^{35}Cl^{79}Br$: 267.9526; Found: 267.9526 $[M+H]^+$.

1-(2-(4-Bromophenyl)pyridin-4-yl)ethan-1-one (13): Following the general procedure using 4-acetylpyridine (264 μL, 2.4 mmol) and 4-bromoaniline (103 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **13** (139 mg, 84%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 5.0 Hz, 1H), 8.14 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 8.6 Hz,

2H), 2.68 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 197.2, 157.5, 150.9, 143.8, 137.4, 132.0, 128.5, 124.1, 120.0, 117.5, 26.7. The NMR data are identical to those reported in the literature.[26]

Ethyl 4-(4-acetylpyridin-2-yl)benzoate (14): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and ethyl 4-aminobenzoate (99 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 80-20) to afford the desired compound **14** (126 mg, 18%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 8.16 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 5.0 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.68 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 197.1, 166.2, 157.5, 150.9, 143.8, 142.4, 131.2, 130.0, 126.8, 120.4, 118.2, 61.1, 26.7, 14.3. HRMS (ESI) Calcd for: $C_{16}H_{15}NO_3Na$: 292.0944; Found: 292.0944 $[M+Na]^+$.

1-(2-(4-Acetylphenyl)pyridin-4-yl)ethan-1-one (15): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 4'-aminoacetophenone (81 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 90-10) to afford the desired compound **15** (102 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 4.9 Hz, 1H), 8.25 (s, 1H), 8.19 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 5.0 Hz, 1H), 2.72 (s, 3H), 2.69 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 197.7, 197.1, 157.4, 151.0, 143.8, 142.7, 137.6, 128.9, 127.1, 120.5, 118.3, 77.3, 26.7. HRMS (ESI) Calcd for: $C_{15}H_{13}NO_2Na$: 262.0839; Found: 262.0840 $[M+Na]^+$.

1-(2-(4-(Trifluoromethyl)phenyl)pyridin-4-yl)ethan-1-one (16): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 4-(trifluoromethyl)aniline (96 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 96-4) to afford the desired compound **16** (100 mg, 63%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.20 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 5.0 Hz, 1H), 2.72 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 197.1, 157.2, 151.1, 143.9, 141.8, 131.3 (q, J = 32.5 Hz), 127.3, 125.8 (q, J = 3.8 Hz), 120.7, 124.1 (q, J = 272.2 Hz), 118.2, 26.8. HRMS (ESI) Calcd for: $C_{14}H_{10}NOF_3Na$: 288.0607; Found: 288.0607 $[M+Na]^+$.

1-(2-(4-Methoxyphenyl)pyridin-4-yl)ethan-1-one (17): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 4-methoxyaniline (74 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 85-15) to afford the desired compound **17** (95 mg, 70%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83

(d, J = 5.0 Hz, 1H), 8.12 (s, 1H), 8.03 (d, J = 8.9 Hz, 2H), 7.60 (d, J = 5.0 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 2.68 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.6, 160.9, 158.4, 150.6, 143.6, 131.1, 128.3, 118.9, 117.1, 114.2, 55.3, 26.7. The NMR data are identical to those reported in the literature.[26]

1-(2-(3,5-difluorophenyl)pyridin-4-yl)ethan-1-one (18): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 3,5-difluoroaniline (77 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 96-4) to afford the desired compound **18** (78 mg, 56%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 5.0 Hz, 1H), 8.14 (s, 1H), 7.73 (d, J = 5.0, 1H), 7.64 – 7.60 (m, 2H), 6.91 (tt, J = 8.6, 2.3 Hz, 1H), 2.71 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.9, 163.5 (dd, J = 248.4, 12.7 Hz), 156.1, 150.9, 143.9, 141.8 (t, J = 9.3 Hz), 120.8, 117.8, 109.9 (d, J = 26.6 Hz), 104.7 (t, J = 25.4 Hz), 26.7. HRMS (ESI) Calcd for: $C_{13}H_9NOF_2Na$: 256.0544; Found: 256.0545 $[M+Na]^+$.

1-(2-(3,5-bBs(trifluoromethyl)phenyl)pyridin-4-yl)ethan-1-one (19): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 3,5-bis(trifluoromethyl)aniline (93 µL, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 96-4) to afford the desired compound **19** (104 mg, 52%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J = 5.0 Hz, 1H), 8.56 (s, 2H), 8.27 (s, 1H), 7.98 (s, 1H), 7.80 (d, J = 6.4 Hz, 1H), 2.74 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.8, 155.4, 151.3, 144.2, 140.1, 132.3 (q, J = 33.7 Hz), 123.0, 127.1, 123.3 (q, J = 273.3 Hz), 121.4, 117.6, 26.8. HRMS (ESI) Calcd for: $C_{15}H_{10}NOF_6$: 334.0661; Found: 334.0659 $[M+H]^+$.

1-(2-(3-Fluoro-5-(trifluoromethyl)phenyl)pyridin-4-yl)ethan-1-one (20): Following the general procedure using 4-acetylpyridine (264 µL, 2.4 mmol) and 3-fluoro-5-(trifluoromethyl)aniline (76 µL, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **20** (76 mg, 45%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 5.0 Hz, 1H), 8.40 (dd, J = 7.1, 2.3 Hz, 1H), 8.29 (s, 1H), 7.77 (d, J = 6.6 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.39 – 7.31 (m, 1H), 2.71 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.0, 162.2 (d, J = 256.2 Hz), 153.2 (d, J = 2.5 Hz), 151.1, 143.6, 128.8 (q, J = 3.9 Hz), 128.1 (dq, J = 3.6, 9.9 Hz), 127.3 (d, J = 12.6 Hz), 123.7 (q, J = 272.1 Hz), 122.1 (d, J = 10.3 Hz), 120.7, 117.2 (d, J = 24.6 Hz), 26.8. HRMS (ESI) Calcd for: $C_{14}H_9NOF_4Na$: 306.0513; Found: 306.0515 $[M+Na]^+$.

1-(2-(2-Fluorophenyl)pyridin-4-yl)ethan-1-one (21): Following the general procedure using 4-acetylpyridine (264 μL, 2.4 mmol) and 2-fluoroaniline (57 μL, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 95-5) to afford the desired compound **21** (44 mg, 34%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 5.0 Hz, 1H), 8.24 (s, 1H), 8.01 (td, *J* = 7.9, 1.7 Hz, 1H), 7.71 (d, *J* = 5.0 Hz, 1H), 7.44 – 7.41 (m, 1H), 7.34 – 7.27 (m, 1H), 7.25 – 7.17 (m, 1H), 2.68 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.4, 160.5 (d, *J* = 250.1 Hz), 154.9, 150.8, 143.4, 131.0 (d, *J* = 4.6 Hz), 131.0 (d, *J* = 1.1 Hz), 126.8 (d, *J* = 11.3 Hz), 124.6 (d, *J* = 3.6 Hz), 122.2 (d, *J* = 9.4 Hz), 119.8, 116.3 (d, *J* = 22.9 Hz), 26.8. HRMS (ESI) Calcd for: $C_{13}H_{10}NOFNa$: 238.0639; Found: 238.0637 $[M+Na]^+$.

4,4'-Di-*tert*-butyl-6-(4-chlorophenyl)-2,2'-bipyridine (22): Following the general procedure using 4,4'-di-*tert*-butyl-2,2'-bipyridine (634 mg, 2.4 mmol) and 4-chloroaniline (76 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 99-1) to afford the desired compound **22** (139 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.3 Hz, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.76 (s, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 4.5 Hz, 1H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.9, 160.8, 156.4, 156.3, 155.2, 148.9, 138.4, 134.8, 128.8, 128.3, 120.8, 118.4, 117.1, 117.0, 35.2, 34.9, 30.7, 30.6. HRMS (ESI) Calcd for: $C_{24}H_{28}N_2{}^{35}Cl$: 379.1936; Found: 379.1936 $[M+H]^+$.

6-(4-Bromophenyl)-4,4'-di-*tert*-butyl-2,2'-bipyridine (23): Following the general procedure using 4,4'-di-*tert*-butyl-2,2'-bipyridine (634 mg, 2.4 mmol) and 4-bromoaniline (103 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 99-1) to afford the desired compound **23** (147 mg, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.2 Hz, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.75 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 5.2 Hz, 1H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.9, 160.9, 156.4, 156.2, 155.3, 148.9, 138.9, 131.8, 128.6, 123.1, 120.8, 118.4, 117.1, 117.1, 35.2, 34.9, 30.7, 30.6. HRMS (ESI) Calcd for: $C_{24}H_{27}N_2{}^{79}BrNa$: 445.1250; Found: 445.1250 $[M+Na]^+$.

4,4'-di-*tert*-butyl-6-(3-fluoro-5-(trifluoromethyl)phenyl)-2,2'-bipyridine (24): Following the general procedure using 4,4'-di-*tert*-butyl-2,2'-bipyridine (634 mg, 2.4 mmol) and 3-fluoro-5-(trifluoromethyl)aniline (76 μL, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 99-1) to afford the desired compound **24** (116 mg, 45%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.2 Hz, 1H), 8.62 – 8.60 (m, 2H), 8.48

(s, 1H), 7.91 (s, 1H), 7.71 – 7.67 (m, 1H), 7.38 – 7.31 (m, 2H), 1.47 (s, 9H), 1.43 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.4 (d, J = 254.6 Hz), 161.9, 161.0, 156.4, 156.2, 150.7 (d, J = 3.0 Hz), 149.0, 129.1 (q, J = 4.1 Hz), 128.5 (d, J = 12.5 Hz), 127.3 – 126.9 (m), 123.9 (q, J = 272.0 Hz), 121.5 (d, J = 10.4 Hz), 121.0, 118.4, 117.5, 117.0 (d, J = 24.9 Hz), 25.2, 35.0, 30.7, 30.5. HRMS (ESI) Calcd for: $C_{25}H_{27}N_2F_4$: 431.2105; Found: 431.2105 $[M+H]^+$.

6-(4-Bromophenyl)-4,4'-dimethyl-2,2'-bipyridine (25): Following the general procedure using 4,4'-dimethyl-2,2'-bipyridine (442 mg, 2.4 mmol) and 4-bromoaniline (103 mg, 0.6 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 98-2) to afford the desired compound **25** (98 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.9 Hz, 1H), 8.42 (s, 1H), 8.24 (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.57 (s, 1H), 7.17 (d, J = 4.3 Hz, 1H), 2.52 (s, 3H), 2.50 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 155.8, 155.3, 148.9, 148.8, 148.1, 138.4, 131.8, 128.6, 124.7, 123.2, 122.1, 121.0, 120.7, 21.4, 21.3. HRMS (ESI) Calcd for: $C_{18}H_{15}N_2{}^{79}BrNa$: 361.0311; Found: 361.0312 $[M+Na]^+$.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. ^{1}H and ^{13}C NMR spectra for all new compounds. Details for tempo-trapping and KIE experiments.

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ACKNOWLEDGMENT

Financial support from CNRS, Univ. Rennes 1, Rennes Métropole, and Région Bretagne (Boost'Europe 18003332) is acknowledged.

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