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HIGHLY C3-SELECTIVE DIRECT ALKYLATION AND ARYLATION OF 2-PYRIDONES UNDER VISIBLE-LIGHT-PROMOTED PHOTOREDOX CATALYSIS

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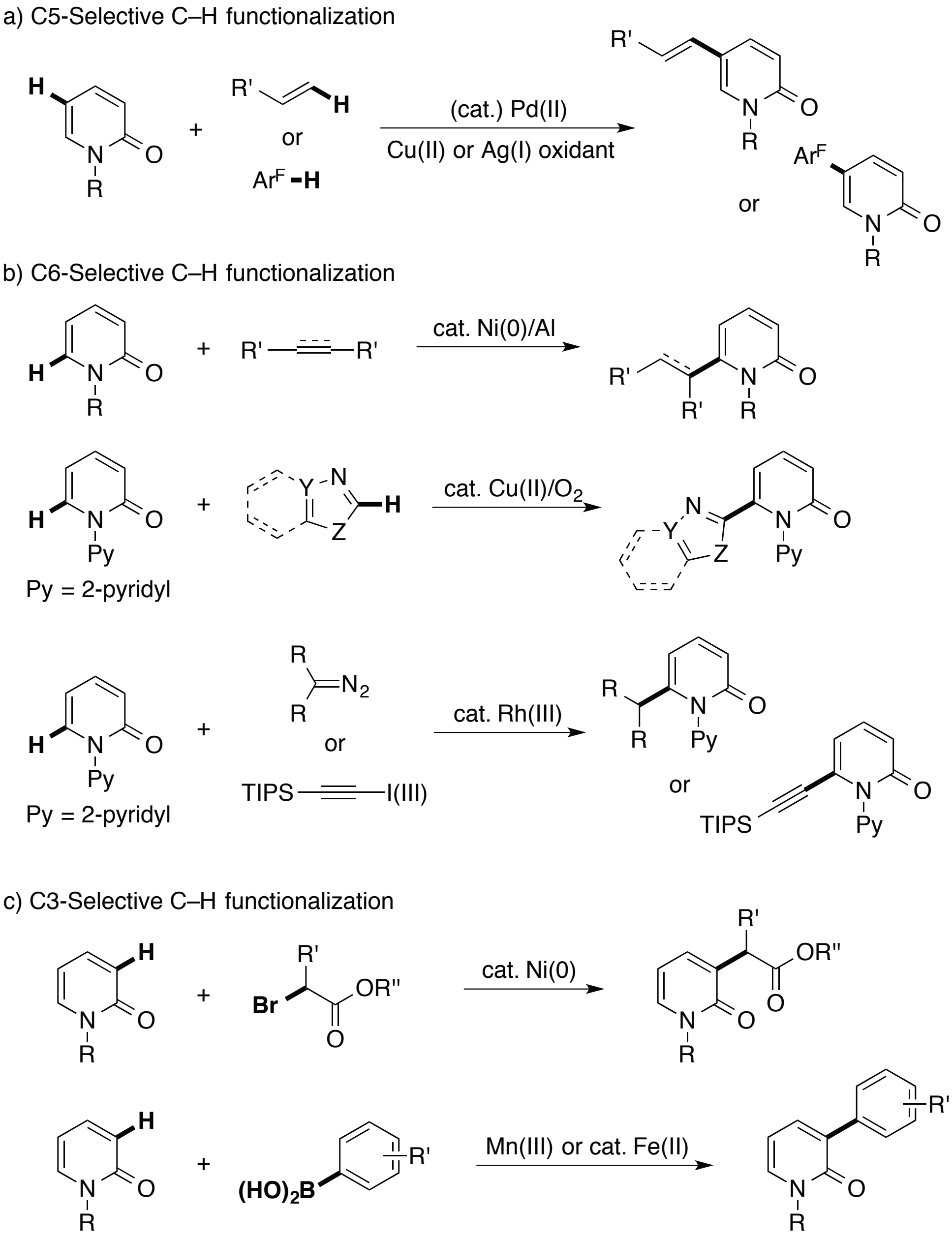
Abstract – An Ir photoredox catalyst-mediated highly site-selective direct alkylation and arylation of 2-pyridones has been developed. Under visible-light-promoted conditions, ethyl 2-bromo-2,2-difluoroacetate couples with various 2-pyridones exclusively at the C3 position. A similar photoredox catalysis is also effective for the direct C3-arylation with diaryliodonium triflates. Thus, these reactions occurs under very mild conditions (blue LEDs irradiation and ambient temperature) to form the corresponding C3-alkylated and arylated 2-pyridones of potential interest in medicinal and pharmaceutical chemistry.

INTRODUCTION

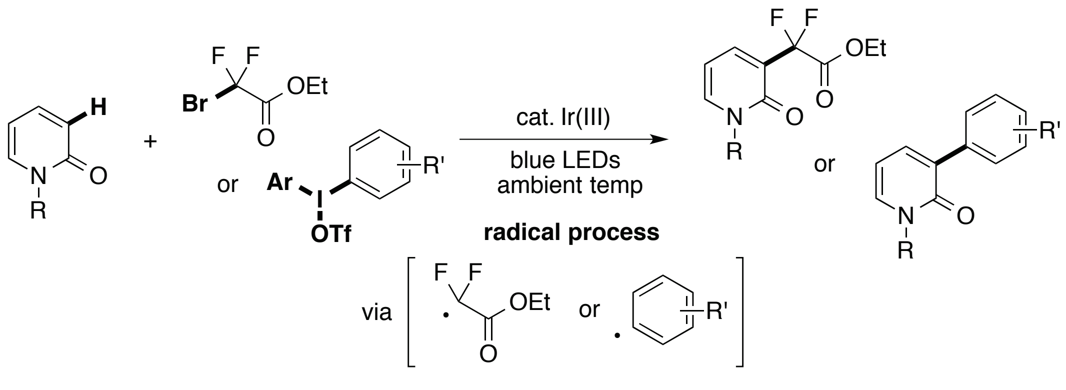
Since 2-pyridones are prevalent structural motifs in many pharmaceutical targets and biologically active natural and unnatural products, as exemplified by ciclopirox, milrinone, camptothecin, perampanel, fredericamycin, and PD180970,[1] the C–C forming process on the 2-pyridone ring ranks as one of long-standing important topics in synthetic organic chemistry. While most traditional strategies rely on preactivated halogenated 2-pyridones as starting materials, recent advances in the C–H functionalization[2] allow unfunctionalized 2-pyridones to be directly adopted in several types of C–C formations. The biggest challenge in the C–H functionalization of the 2-pyridone is the control of the site-selectivity. In 1984, Itahara and Ouseto reported the Pd-mediated direct alkenylation of the 2-pyridone with acrylates.[3] The reaction was stoichiometric in palladium, but the high C5-selectivity was observed. Li then developed the catalytic variant of this process by using a $Cu(OAc)_2$ terminal oxidant and also succeeded in the related C5-arylation with polyfluoroarenes under Pd/Ag catalysis (Scheme 1a).[4] Additionally, Nakao and Hiyama achieved the Ni/Al-catalyzed direct alkenylation and alkylation with alkynes and alkenes, respectively, at the otherwise difficult C6 position.[5] Our group also developed the Cu-mediated or Cu/O_2-catalyzed C6-selective heteroarylation with the aid of a pyridine directing group.[6] Since then, some groups successfully applied the pyridine-directed methodology to the Rh-catalyzed C6-selective alkylation and alkynylation (Scheme 1b).[7] On the other hand, the C3-selective C–H functionalization has been less studied, despite relatively high electron density at the C3 position.[8] In this context, we recently revisited the unique nature of classical carbon-centered radical species and developed the Ni-catalyzed[9] and Mn-mediated[10] radicalic direct C3 alkylation and arylation. Subsequently, Maiti reported a related arylation reaction in the presence of a Fe catalyst (Scheme 1c).[11] However, heating conditions (70–130 °C) and/or excess metallic salts are often necessary for a satisfactory conversion. Thus, despite certain advances mentioned above, there still remains a large demand for further development of the site-selective C–H functionalization of 2-pyridones, particularly at the relatively inaccessible C3 position. Herein, we report an Ir-catalyzed, radical-mediated direct C3-alkylation and arylation of 2-pyridones with ethyl 2-bromo-2,2-difluoroacetate and diaryliodonium triflates,[12] respectively. The reactions proceed smoothly at ambient temperature under visible-light-promoted conditions (Scheme 2).[13]

RESULTS AND DISCUSSION

Prompted by recent rapid progress of the radical-mediated, visible-light-promoted photoredox catalysis,[14] we commenced optimization studies with *N*-methyl-2-pyridone (**1a**, 1.25 mmol) and ethyl 2-bromo-2,2-difluoroacetate (**2a**, 0.25 mmol)[15] as model substrates under blue LEDs irradiation (Table 1). Initial catalyst screening identified $Ir(ppy)_3$ to be a good candidate in MeCN, and the corresponding C3-alkylated 2-pyridone **3aa** was isolated in 74% yield: other representative photoredox catalysts, $Ir(ppy)_2(dtbpy)PF_6$, $Ru(bpy)_3Cl_2 \bullet 6H_2O$, and Eosin Y (Na), showed no catalytic activity (entries 1–4). Among solvents we tested, MeCN was found to be optimal (entries 5–8). The addition of external inorganic bases gave negligible or negative impact on the reaction efficiency (entries 9–12). A decrease of amount of the pyridone **1a** to 0.75 mmol provided a slightly lower but still synthetically useful yield of **3aa** (entry 13). The control experiments in the absence of light or catalyst resulted in no conversion (entry 14 and 15). Additionally, an investigation of on/off-switching of the light source revealed that the reaction progressed steady under blue LEDs irradiation and stopped in the dark (see the Experimental section). These outcomes suggest the operation of photoredox catalysis (vide infra).[16] Also note that the difluorinated α-bromo ester **2a** did not work at all under previously reported Ni-catalyzed conditions (data not shown).[9]

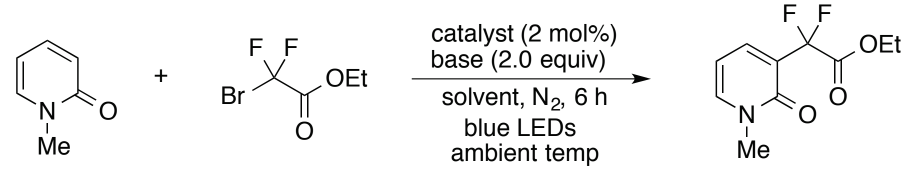


Scheme 1. Site-selective C–H functionalization approaches to substituted 2-pyridones



Scheme 2. Visible-light-promoted Ir photoredox catalysis for C3-selective direct alkylation and arylation of 2-pyridones at ambient temperature (this work)

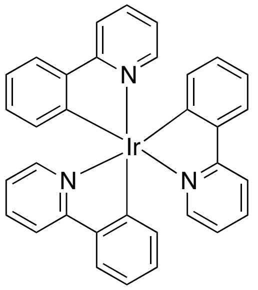
Table 1. Optimization studies for C3-selective alkylation of *N*-methyl-2-pyridone (**1a**) with ethyl 2-bromo-2,2-difluoroacetate (**2a**) under visible-light-promoted photoredox catalysis[a]



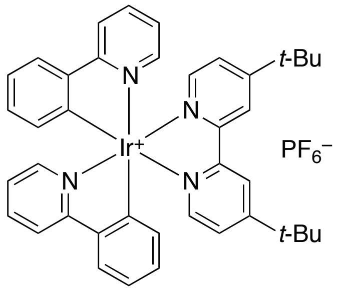
1a (5.0 equiv) **2a** **3aa**

entry	catalyst	base	solvent	yield of **3aa** (%)[b]
1	Ir(ppy)$_3$	none	MeCN	(74)
2	Ir(ppy)$_2$(dtbpy)PF$_6$	none	MeCN	0
3	Ru(bpy)$_3$Cl$_2$•6H$_2$O	none	MeCN	0
4	Eosin Y (Na)	none	MeCN	0
5	Ir(ppy)$_3$	none	DMSO	24
6	Ir(ppy)$_3$	none	1,4-dioxane	36
7	Ir(ppy)$_3$	none	DMF	20
8	Ir(ppy)$_3$	none	ClCH$_2$CH$_2$Cl	44
9	Ir(ppy)$_3$	K$_3$PO$_4$	MeCN	65
10	Ir(ppy)$_3$	Na$_2$CO$_3$	MeCN	73
11	Ir(ppy)$_3$	NaOAc	MeCN	73
12	Ir(ppy)$_3$	KOAc	MeCN	60
13[c]	Ir(ppy)$_3$	none	MeCN	(58)
14[d]	Ir(ppy)$_3$	none	MeCN	0
15	none	none	MeCN	0

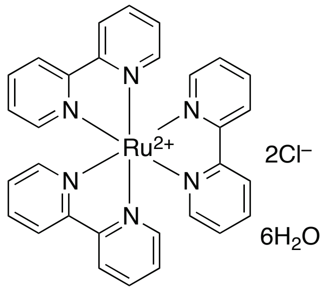
[a] Conditions: **1a** (1.3 mmol), **2a** (0.25 mmol), catalyst (0.0050 mmol), solvent (3.0 mL), ambient temp, blue LEDs irradiation, 6 h, N$_2$. [b] Yields are estimated by ^{1}H NMR or GC analysis. Isolated yields are in parentheses. [c] With 0.75 mmol (3.0 equiv) of **1a**. [d] In the dark.



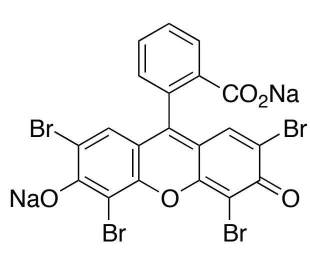
Ir(ppy)$_3$



Ir(ppy)$_2$(dtbpy)PF$_6$

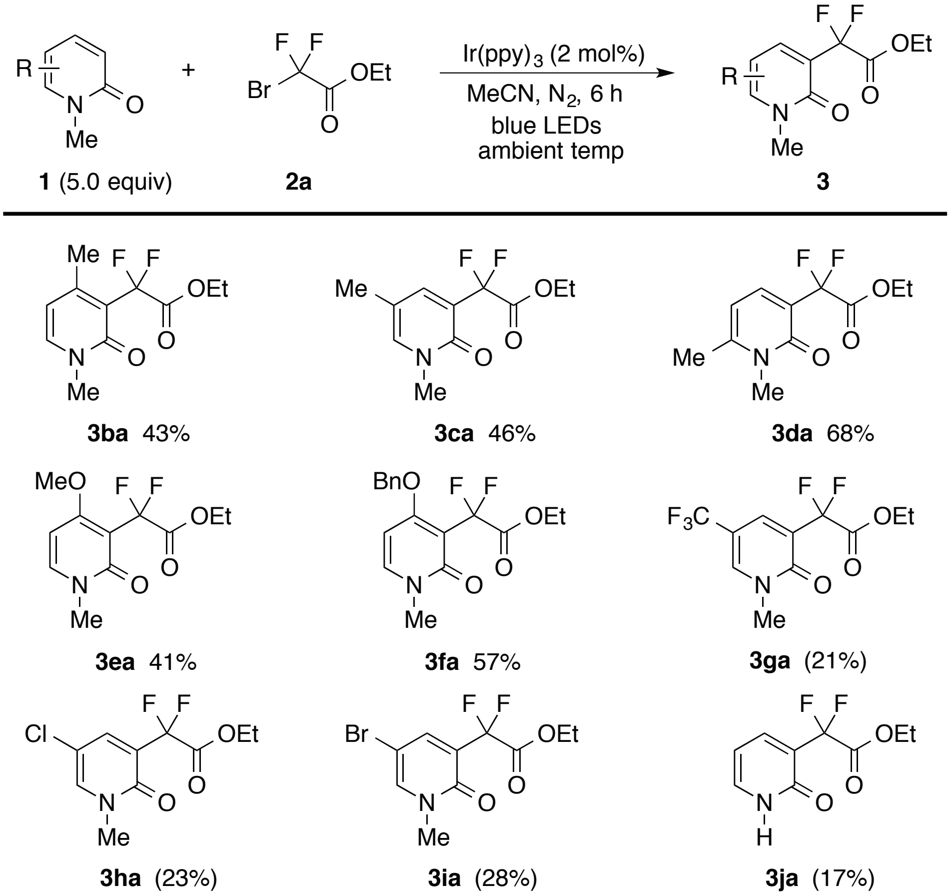


Ru(bpy)$_3$Cl$_2$•6H$_2$O

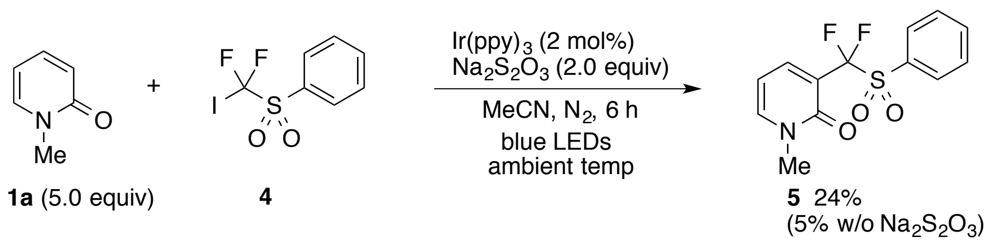


Eosin Y (Na)

Under the conditions of entry 1 in Table 1, we subsequently performed the direct alkylation of various substituted 2-pyridones **1** with **2a** (Scheme 3). Regardless of the substitution pattern of the methyl group, the reaction occurred exclusively at the C3 position, and the corresponding C3-difluoroalkylated products **3ba–3da** were formed in substantial yields. The Ir photoredox catalysis was tolerated with electron-donating methoxy and benzyloxy groups (**3ea** and **3fa**) while the electron-withdrawing trifluoromethyl and halogen substituents dropped the yield (**3ga–3ia**). The observed trend is consistent with the plausible radical mechanism including SOMO/HOMO interaction between the electrophilic difluoromethyl radicals and electron-rich pyridones.[9,10] We also tested the NH 2-pyridone but the yield was lower (**3ja**). In most cases, the starting alkyl bromide **2a** fully consumed despite the moderate yield of **3**. We could not identify any byproducts, but homocoupling and/or reduction of **2a** might competitively occur. Although we also tested other fluorinated alkyl halides,[17] only sulfone derivative **4** moderately reacted with **1a** under slightly modified conditions using $Na_2S_2O_3$ as an additive (Scheme 4).[18]

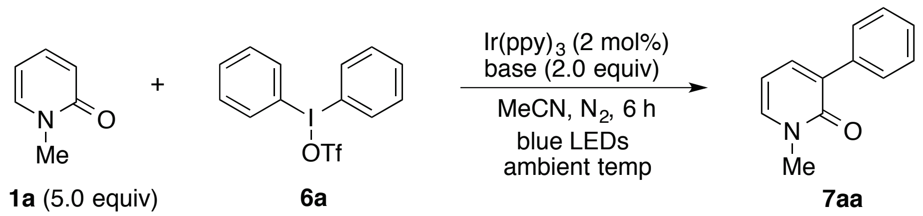


Scheme 3. C3-Selective direct alkylation of various 2-pyridones **1** with ethyl 2-bromo-2,2-difluoroacetate (**2a**) under visible-light-promoted $Ir(ppy)_3$ catalysis. Isolated yields are shown. ^1H NMR yields are in parentheses.



Scheme 4. C3-Selective direct alkylation of *N*-methyl 2-pyridone (**1a**) with [(difluoroiodomethyl)sulfonyl]benzene (**4**) under $Na_2S_2O_3$-modified conditions

Table 2. Optimization studies for C3-selective phenylation of *N*-methyl-2-pyridone (**1a**) with diphenyliodonium triflate (**6a**) under visible-light-promoted photoredox catalysis[a]



entry	base	yield of **7aa** (%)[b]
1	none	28
2	*i*-Pr_2NEt	7
3	LiOAc	29
4	NaOAc	30
5	KOAc	(40)
6	CsOAc	30
7	K_3PO_4	(39)
8	KO-*t*-Bu	2
9[c]	KOAc	(55)
10[d]	KOAc	0
11[e]	KOAc	0

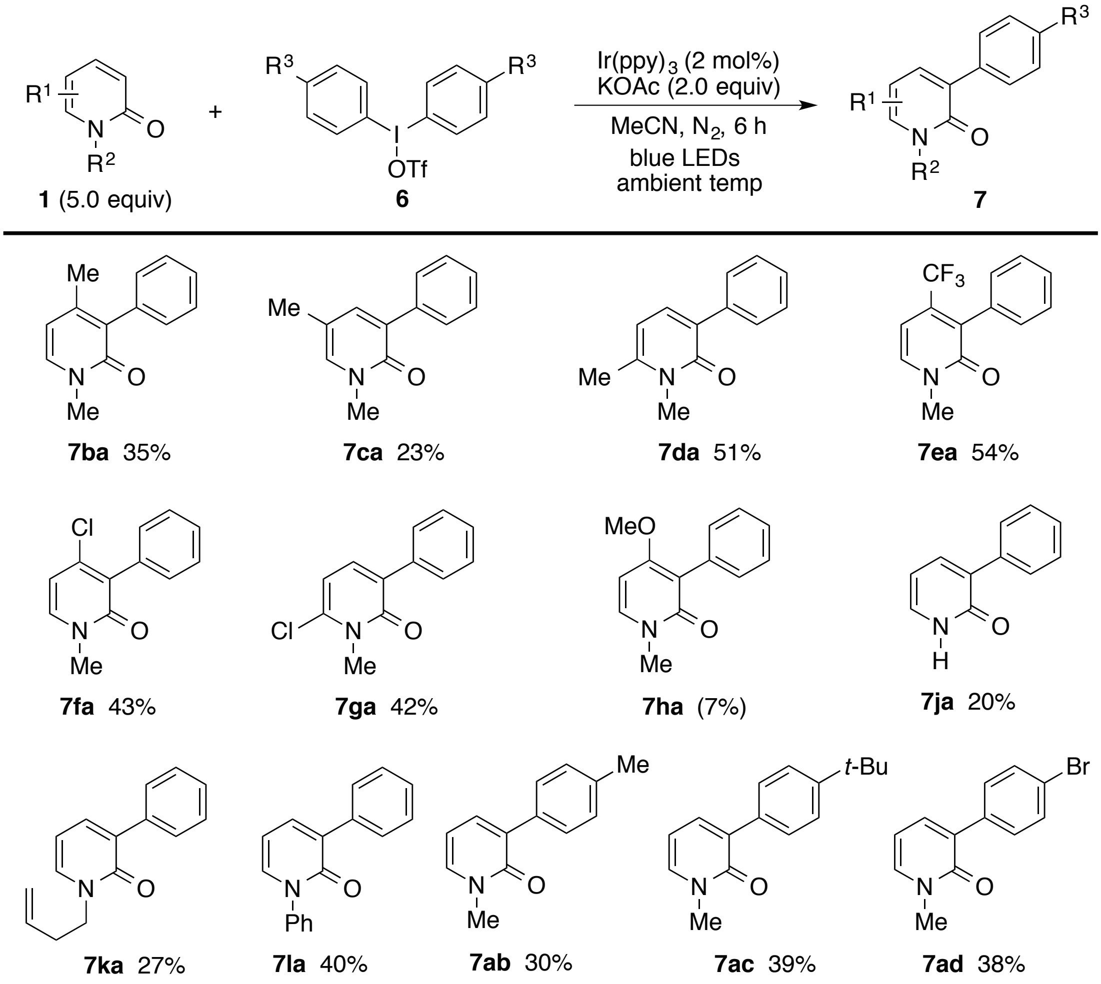
[a] Conditions: **1a** (1.3 mmol), **6a** (0.25 mmol), $Ir(ppy)_3$ (0.0050 mmol), MeCN (3.0 mL), ambient temp, blue LEDs irradiation, 6 h, N_2. [b] Yields are estimated by ^1H NMR or GC analysis. Isolated yields are in parentheses. [c] In MeCN (1.0 mL). [d] In the dark. [e] Without $Ir(ppy)_3$.

We then turned our attention to the related direct C3-phenylation of *N*-methyl-2-pyridone (**1a**) with diphenyliodonium triflate (**6a**) (Table 2).[19] The conditions same as those in Scheme 3 afforded the desired C3-phenylation product **7aa** albeit with 28% yield (entry 1). Given the liberation of strongly acidic TfOH, we investigated basic additives to quench with it (entries 2–8). Gratifyingly, some potassium inorganic bases improved the yield, with KOAc to be optimal (entry 5). Although additional solvent and catalyst screening gave no further improvement as far as we examined, we finally obtained 55% isolated yield of **7aa** by reducing the amount of MeCN solvent into 1.0 mL (entry 9). Also in the direct alkylation, both visible light and Ir(ppy)$_3$ were essential for the promotion of the reaction (entries 10 and 11).

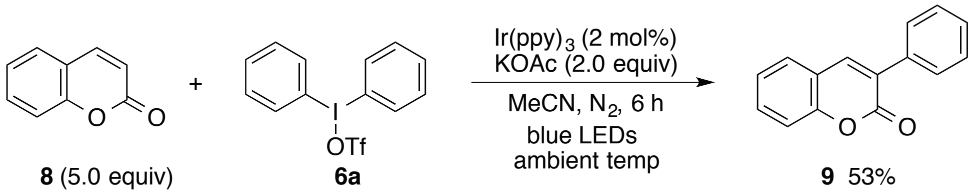
We next investigated the scope and limitation of the direct arylation reaction. Representative products are shown in Scheme 5. The C3 selectivity was uniformly high, and C4-, C5-, and C6-methylated substrates furnished the corresponding C3-phenylated pyridones **7ba–7da** as the single isomers. In contrast to the difluoroalkylation in Scheme 3, electron-withdrawing trifluoromethyl and chloro substituents were found to be better than electron-donating methoxy group (**7ea–7ga** vs **7ha**). This outcome could arise from an effective SOMO/LUMO interaction between nucleophilic phenyl radical and electron-deficient 2-pyridones.[9,10] The direct phenylation was compatible with 2-pyridones bearing *N*-butenyl, *N*-phenyl, and even free *N*-H substituents (**7ja–7la**). The introduction of 4-methylphenyl, 4-*tert*-butylphenyl, and 4-bromophenyl groups was also possible, and the corresponding C3-arylated products **7ab–7ad** were formed in moderate yields. In most cases, the yield was moderate probably because the Ir catalyst gradually decomposed during the course of the reaction. Actually, we recovered the starting diaryliodonium triflates **6** in some cases. Additionally, the *O*-analogue of 2-pyridone, coumarin (**8**), also coupled with **6a** under identical conditions (Scheme 6).

On the basis of the literature information[14] and our findings, the plausible catalytic cycle of the reaction of **1a** with **2a** or **6a** is illustrated in Scheme 7. Initial visible light irradiation excites the starting Ir(III) catalyst to the active Ir(III)* species. Subsequent reversible single electron transfer (SET) from Ir(III)* to **2a** or **6a** delivers the Ir(IV) of the higher oxidation state and anion radical species, which smoothly undergoes the fragmentation to the corresponding alkyl or aryl radical **10**. The 2-pyridone **2a** then reacts with **10** at the C3 position to afford the allylic radical intermediate **11**. The second SET process between **11** and Ir(IV) closes the Ir catalytic cycle and generates the cationic species **12**, which is finally deprotonated to furnish the observed C3-alkylated **3aa** or -arylated **7aa**. The regioselectivity can be determined in the radical addition step and controlled by the inherent nature of radical intermediates: the higher stability associated with the resonance effect of the allylic radical **11** and relatively large contributions of HOMO and LUMO at the C3 position of the 2-pyridone **2a**[9,10] may be major controlling factors. However, the exact mechanism still remains to be elucidated.[16]

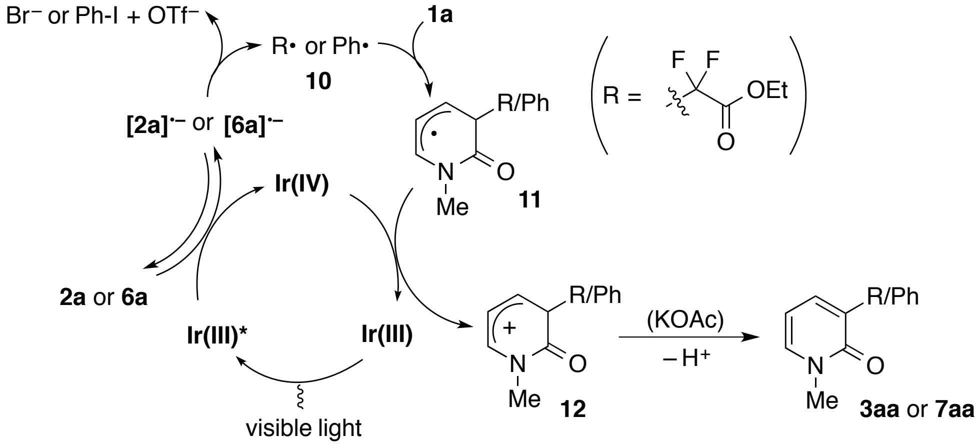
In the above arylation reaction, one aryl group of symmetrical diaryliodonium salts **6** was lost as the aryl iodide. This is problematic and less atom-economical particularly when more complex and highly functionalized aryl moiety is installed. Thus, we attempted the arylation with unsymmetrical Mes-I(III)-Ar reagent **13** (Mes = mesityl) instead of **6** (Scheme 8a). Although the yield was lower than that with the symmetrical **6**, the Mes group did not transfer at all, and the desired aryl group was selectively incorporated to the pyridone molecules. Trifluoromethyl- and ester-containing aromatic rings were also accessible (**7ae** and **7af**). Additionally notable is that the phenyldiazonium salt **14**, which is readily available from the corresponding aniline, is a potential alternative to the diaryliodonium salt (Scheme 8b).



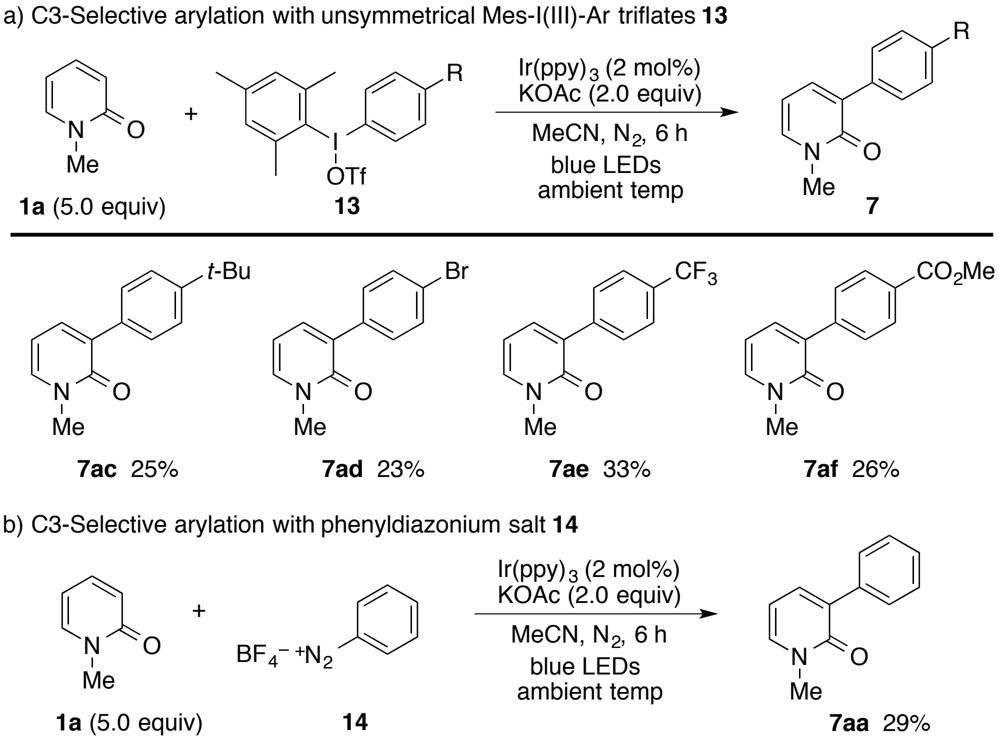
Scheme 5. C3-Selective direct arylation of 2-pyridones **1** with diaryliodonium triflates **6** under visible-light-promoted Ir(ppy)$_3$ catalysis. Isolated yields are shown. ^{1}H NMR yields are in parentheses.



Scheme 6. C3-Selective direct phenylation of coumarin (**8**) with diphenyliodonium triflate (**6a**) under visible-light-promoted Ir(ppy)$_3$ catalysis



Scheme 7. Plausible mechanism for C3-selective direct alkylation and arylation of 2-pyridone **1a** with **2a** or **6a** under visible-light-promoted Ir(ppy)$_3$ catalysis



Scheme 8. C3-Selective direct arylation of *N*-methyl-2-pyridone (**1a**) with unsymmetrical Mes-I(III)-Ar triflates **13** or phenyldiazonium salt **14** under visible-light-promoted Ir(ppy)$_3$ catalysis. Isolated yields are shown.

CONCLUSION

We have developed a highly C3-selective difluoroalkylation and arylation of 2-pyridones under visible-light-promoted Ir(ppy)$_3$ photoredox catalysis. The reactions proceed smoothly at ambient temperature and provide a direct access to the C3-functionalized 2-pyridones of great potential in medicinal and pharmaceutical chemistry, although the reaction efficiency is still moderate. The present catalysis can complement the known C–H functionalization protocols in view of the site-selectivity. Ongoing work seeks to develop new strategies for the site-selective and diverse C–H functionalization of 2-pyridones.

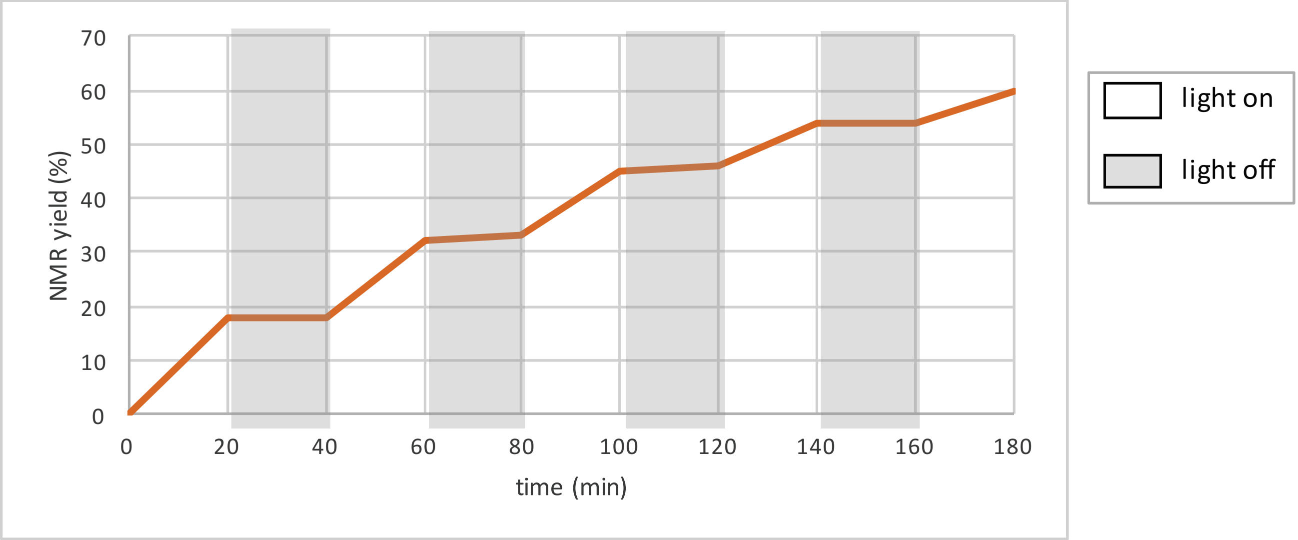
EXPERIMENTAL

General. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or a CBP-1 capillary column (i. d. 0.5 mm x 25 m). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Blue light irradiation was conducted by a blue LED tape light. Gel permeation chromatography (GPC) was performed with a $CHCl_3$ eluent (3.5 mL/min, UV detector). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. MeCN was dried on a Glass Contour Solvent dispending system (Nikko Hansen & Co., Ltd.) prior to use. Ir(ppy)$_3$ was synthesized from $IrCl_3$•$3H_2O$ and 2-phenylpyridine under the reported conditions.[20] Symmetrical and unsymmetrical diaryliodonium triflates were prepared according to the literature.[21]

Visible-light-promoted Ir(ppy)$_3$-catalyzed C3-alkylation of 2-pyridones. The reaction of **1a** with **2a** is representative (Table 1, entry 1). Ir(ppy)$_3$ (3.3 mg, 0.0050 mmol) was placed in a Schlenk tube. Nitrogen gas displacement was done by using the standard Schlenk technique, and *N*-methyl-2-pyridone (**1a**, 136.4 mg, 1.25 mmol) and ethyl bromodifluoroacetate (**2a**, 50.7 mg, 0.25 mmol) were added using syringe followed by addition of MeCN (3 mL). The mixture was stirred for 6 h under blue light LED irradiation (12 DC/3 W). Water (20 mL) was added, and extraction was done with EtOAc (15 mL x 3). The combined organic phase was dried over sodium sulfate and then concentrated in vacuo. Purification via column chromatography (Wakosil C-200, hexane/EtOAc = 20/1 to EtOAc/CH_2Cl_2/Et_3N = 1/1/0.05) provided pure ethyl 2,2-difluoro-2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate (**3aa**, 42.7 mg, 0.19 mmol, 74% yield).

Visible-light-promoted Ir(ppy)$_3$-catalyzed C3-arylation of 2-pyridones. The reaction of **1a** with **6a** is representative (Table 2, entry 9). In a glovebox filled with nitrogen, Ir(ppy)$_3$ (3.3 mg, 0.0050 mmol), Ph_2IOTf (**6a**, 136.4 mg, 0.25 mmol), and potassium acetate (49.1 mg, 0.50 mmol) were placed in a Schlenk tube. The tube was sealed with a septum and then taken out of the glovebox. A solution of *N*-methyl-2-pyridone (**1a**, 136.4 mg, 1.25 mmol) in MeCN (1 mL) was added using a syringe. The mixture was stirred for 6 h under blue light LED irradiation (12 DC/3 W). Water (20 mL) was added, and extraction was done with EtOAc (15 mL x 3). The combined organic phase was dried over sodium sulfate and then concentrated in vacuo. Purification via column chromatography (Wakosil C-200, hexane/EtOAc = 20/1 to EtOAc/CH_2Cl_2/Et_3N = 1/1/0.05) followed by GPC provided pure 1-methyl-3-phenylpyridin-2(1*H*)-one (**7aa**, 25.4 mg, 0.14 mmol, 55% yield).

Experiment of ON/OFF Switching of Light Source. In the glove box filled with nitrogen, $Ir(ppy)_3$ (1.3 mg, 0.0020 mmol), *N*-methyl-2-pyridone (**1a**, 54.6 mg, 0.50 mmol), ethyl bromodifluoroacetate (**2a**, 20.3 mg, 0.10 mmol), dibenzyl ether (internal standard, 12.3 mg), and MeCN-d_3 (0.75 mL) were placed in a NMR tube. The tube was sealed with a septum and taken out of the glovebox. After sonication for a few seconds, the on-off switching of light source was performed, and the reaction progress was monitored by ^1H NMR. The obtained result is shown in Scheme 9.



Scheme 9. Reaction progress in on/off switching of the light source

Characterization Data for Products

Ethyl 2,2-difluoro-2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate (3aa): 42.7 mg, 74%, yellow oil; IR (neat, cm^{-1}) 767, 1041, 1112, 1276, 1560, 1662, 1772; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 3.56 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.29 (t, *J* = 6.9 Hz, 1H), 7.44 (d, *J* = 6.9 Hz, 1H), 7.78 (dt, *J* = 6.9, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.89, 37.43, 62.98, 104.88, 111.54 (t, *J* = 247.7 Hz), 124.36 (t, *J* = 24.5 Hz), 137.60 (t, *J* = 7.0 Hz), 140.82, 159.96 (t, *J* = 5.0 Hz), 163.33 (t, *J* = 32.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.86; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{10}H_{12}F_2NO_3$: 232.0780, found: 232.0779.

Ethyl 2-(1,4-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-2,2-difluoroacetate (3ba): 26.3 mg, 43%, white solid, mp 83.8-85.9 °C; IR (neat, cm^{-1}) 785, 1114, 1354, 1604, 1654, 1772; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 2.44 (t, *J* = 4.0 Hz, 3H), 3.48 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.07 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.92, 20.19 (t, *J* = 5.4 Hz), 37.35, 62.64, 110.48, 113.86 (t, *J* = 247.3 Hz), 121.05 (t, *J* = 24.2 Hz), 138.77, 152.87, 160.57 (t, *J* = 6.43 Hz), 163.83 (t, *J* = 32.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.34; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{14}F_2NO_3$: 246.0936, found 246.0939.

Ethyl 2-(1,5-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-2,2-difluoroacetate (3ca): 28.2 mg, 46%, yellow oil; IR (neat, cm^{-1}) 744, 796, 1132, 1568, 1606, 1668, 1772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 2.15 (s, 3H), 3.52 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.22 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.89, 17.09, 37.23, 62.96, 111.61 (t, *J* = 247 Hz), 114.08, 123.72 (t, *J* = 24.0 Hz), 138.51, 139.90 (t, *J* = 6.6 Hz), 159.21 (t, *J* = 4.4 Hz), 163.41 (t, *J* = 32.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.75; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{14}F_2NO_3$: 246.0936, found 246.0931.

Ethyl 2-(1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-2,2-difluoroacetate (3da): 41.7 mg, 68%, white solid, mp 107.2-108.2 °C; IR (neat, cm^{-1}) 1112, 1296, 1575, 1653, 1774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 3.53 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.17 (d, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.91, 21.16, 31.09, 62.86, 105.58, 111.89 (t, *J* = 246.9 Hz), 120.84 (t, *J* = 24.5 Hz), 136.59 (t, *J* = 6.6 Hz), 149.75, 160.68 (t, *J* = 5.3 Hz), 163.60 (t, *J* = 33.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.70; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{14}F_2NO_3$: 246.0936, found: 246.0936.

Ethyl 2,2-difluoro-2-(4-methoxy-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate (3ea): 26.8 mg, 41%, yellow solid, mp 104.7-106.5 °C; IR (neat, cm^{-1}) 788, 1028, 1263, 1363, 1544, 1654, 1772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 3.47 (s, 3H), 3.92 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.09 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.95, 37.18, 56.56, 62.60, 70.57, 94.46, 105.64 (t, *J* = 24.2 Hz), 113.17 (t, *J* = 246.2 Hz), 141.48, 161.09, 164.15 (t, *J* = 32.1 Hz), 168.00; ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.17; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{14}F_2NO_4$: 262.0885, found: 262.0881.

Ethyl 2-(4-(benzyloxy)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2,2-difluoroacetate (3fa): 48.0 mg, 57%, white solid, mp 84.5-86.1 °C; IR (neat, cm^{-1}) 1080, 1109, 1152, 1363, 1541, 1653, 1772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 3.45 (s, 3H), 4.34 (q, *J* = 7.2 Hz, 2H), 5.22 (s, 2H), 6.09 (d, *J* = 7.8 Hz, 1H), 7.32-7.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.93, 37.11, 62.57, 70.88, 95.55, 106.07 (t, *J* = 23.6 Hz), 113.20 (t, *J* = 246.8 Hz), 126.78, 128.33, 128.74, 135.16, 141.52, 161.10 (t, *J* = 4.7 Hz), 164.17 (t, *J* = 31.7 Hz), 167.12; ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.90; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{17}H_{18}F_2NO_4$: 338.1198, found: 338.1198.

3-(Difluoro(phenylsulfonyl)methyl)-1-methylpyridin-2(1*H*)-one (5): 18.3 mg, 24%, white solid, mp 174.2-176.2 °C; IR (neat, cm^{-1}) 590, 1074, 1165, 1550, 1653; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 3H), 6.28 (t, *J* = 6.8 Hz, 1H), 7.56 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.62 (t, *J* = 8.1 Hz, 2H), 7.76 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.80 (dd, *J* = 7.5, 4.1 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.12, 104.35, 116.80 (t, J = 20.5 Hz), 121.52 (t, J = 287.6 Hz), 129.18, 130.92, 133.42, 135.15, 143.00 (t, J = 7.3 Hz), 143.24, 158.71; ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.64; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{13}H_{12}F_2NO_3S$: 300.0500, found: 300.0500.

1-Methyl-3-phenylpyridin-2(1*H*)-one (7aa): 20.8 mg, 55%, white solid, mp 106.4-108.4 ºC; IR (neat, cm^{-1}) 702, 773, 1583, 1647; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.25 (t, J = 7.0 Hz, 1H), 7.32 (tt, J = 7.2, 2.1 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.49 (dd, J = 7.0, 2.1 Hz, 1H), 7.69 (dd, J = 7.0, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.24, 105.82, 127.66, 128.10, 128.62, 131.64, 136.83, 137.41, 137.59, 161.95; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{12}H_{12}NO$: 186.0913, found: 186.0914.

1-Methyl-3-(*p*-tolyl)pyridin-2(1*H*)-one (7ab): 15.0 mg, 30%, white solid, mp 135.2-137.1 ºC; IR (neat, cm^{-1}) 825, 1282, 1560, 1585, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.61 (s, 3H), 6.23 (t, J = 6.7 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 2.0, 6.7 Hz, 1H), 7.46 (dd, J = 2.0, 7.0 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.23, 38.20, 105.79, 128.45, 128.80, 131.63, 133.93,137.06, 137.10, 137.45, 162.02; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{13}H_{14}NO$: 200.1070, found: 200.1070.

3-(4-(*tert*-Butyl)phenyl)-1-methylpyridin-2(1*H*)-one (7ac): 23.5 mg, 39%, yellowish-brown solid, mp 94.5-96.2 ºC; IR (neat, cm^{-1}) 570, 1595, 1647, 2960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.61 (s, 3H), 6.24 (t, J = 6.8 Hz, 1H), 7.29 (dd, J = 6.8, 2.0 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.48 (dd, J = 6.8, 2.0 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.33, 34.58, 38.21, 105.83, 125.08, 128.26, 131.56, 133.88, 137.08, 137.16, 150.60, 162.06; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{16}H_{20}NO$: 242.1539, found: 242.1541.

3-(4-Bromophenyl)-1-methylpyridin-2(1*H*)-one (7ad): 25.1 mg, 38%, white solid, mp 157.0-158.5 ºC; IR (neat, cm^{-1}) 1008, 1550, 1583, 1647; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.25 (t, J = 6.9 Hz, 1H), 7.33 (dd, J = 6.9, 2.0 Hz, 1H), 7.48 (dd, J = 6.9, 2.0 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 38.27, 105.83, 121.77, 130.21, 130.36, 131.22, 135.70, 137.55, 137.80, 161.67; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{12}H_{11}BrNO$: 264.0019, found: 264.0027.

1-Methyl-3-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (7ae): 20.7 mg, 33%, brown solid, mp 98.9-101.0 ºC; IR (neat, cm^{-1}) 773, 840, 1112, 1161, 1327, 1554, 1595, 1647; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 6.29 (t, J = 6.9 Hz, 1H), 7.37 (dd, J = 6.9, 2.0 Hz, 1H), 7.53 (dd, J = 6.9, 2.0 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.29, 105.81, 124.26 (q, J = 270.4 Hz), 125.03 (q, J = 3.9 Hz), 128.86, 129.55 (q, J = 32.2 Hz), 130.14, 138.26, 138.35, 140.40, 161.63; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{13}H_{11}F_3NO$: 254.0787, found: 254.0789.

Methyl 4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)benzoate (7af): 15.8 mg, 26%, white solid, mp 132.5-134.6 ºC; IR (neat, cm^{-1}) 759, 1109, 1290, 1558, 1595, 1653, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ

3.63 (s, 3H), 3.93 (s, 3H), 6.28 (t, J = 6.9 Hz, 1H), 7.36 (dd, J = 6.9, 2.1 Hz, 1H), 7.48 (dd, J = 6.9, 2.1 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 5.59 (d, J = 8.3 Hz, 2H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 38.31, 52.08, 105.84, 128.49, 129.09, 129.40, 130.40, 138.25, 138.30, 141.45, 161.63, 167.02; HRMS (APCI) *m/z* (M+H)$^+$ calcd for $C_{14}H_{14}NO_3$: 244.0968, found: 244.0968.

1,4-Dimethyl-3-phenylpyridin-2(1*H*)-one (7ba): 17.4 mg, 35%, white solid, mp 65.0-67.0 ºC; IR (neat, cm^{-1}) 771, 1263, 1598, 1647; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.04 (s, 3H), 3.54 (s, 3H), 6.11 (d, J = 7.0 Hz, 1H), 7.18 (d, J = 7.0 Hz, 1H), 7.25 (d, J = 7.1 Hz, 2H), 7.31 (tt, J = 1.4, 7.1 Hz, 1H), 7.40 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.44, 37.76, 108.92, 127.20, 128.16, 129.95,131.02, 135.69, 136.15, 147.03, 162.32; HRMS (APCI) *m/z* (M+H)$^+$ calcd for $C_{13}H_{14}NO$: 200.1070, found: 200.1073.

1,5-Dimethyl-3-phenylpyridin-2(1*H*)-one (7ca): 12.5 mg, 23%, white solid, mp 114.0-115.2 ºC; IR (neat, cm^{-1}) 694, 1282, 1419, 1577, 1595, 1653; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.13 (s, 3H), 3.58 (s, 3H), 7.09 (d, J = 2.3 Hz, 1H), 7.29-7.41 (m, 4H), 7.69 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 17.21, 38.04, 114.61, 127.60, 128.06, 128.64, 131.01, 135.04, 136.89, 140.28, 161.15; HRMS (APCI) *m/z* (M+H)$^+$ calcd for $C_{13}H_{14}NO$: 200.1070, found: 200.1070.

1,6-Dimethyl-3-phenylpyridin-2(1*H*)-one (7da): 23.9 mg, 51%**,** white solid, mp 104.4-106.2 ºC; IR (neat, cm^{-1}) 785, 1120, 1259, 1431, 1566, 1587, 1639; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.40 (s, 3H), 3.60 (s, 3H), 6.38 (d, J = 7.2 Hz, 1H), 7.28 (tt, J = 5.3, 1.3 Hz, 1H), 7.36-7.40 (m, 3H), 7.66-7.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.15, 31.70, 106.43, 127.28, 128.05, 128.08, 128.55, 136.89, 137.40, 145.49, 162.58; HRMS (APCI) *m/z* (M+H)$^+$ calcd for $C_{13}H_{14}NO$: 200.1070, found: 200.1070.

1-Methyl-3-phenyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (7ea): 33.9 mg, 54%, brown oil; IR (neat, cm^{-1}) 702, 769, 945, 1136, 1184, 1325, 1606, 1659; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.61 (s, 3H), 6.45 (d, J = 7.2 Hz, 1H), 7.23-7.26 (m, J = 7.1 Hz, 2H), 7.26-7.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 38.46, 101.49 (q, J = 4.9 Hz), 122.34 (q, J = 274.3 Hz), 127.93, 128.25, 129.35, 132.80, 133.36, 137.55 (q, J = 30.9 Hz), 137.85, 162.25; ^{19}F NMR (376 MHz, CDCl$_3$) δ -59.5749; HRMS (APCI) *m/z* (M+H)$^+$ calcd for $C_{13}H_{11}F_3NO$: 254.0787, found: 254.0785.

4-Chloro-1-methyl-3-phenylpyridin-2(1*H*)-one (7fa): 23.6 mg, 43%, brown oil; IR (neat, cm^{-1}) 696, 758, 1047, 1076, 1259, 1546, 1643; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.56 (s, 3H), 6.34 (d, J = 7.3 Hz, 1H), 7.23 (d, J = 7.3 Hz,1H), 7.35-7.38 (m, 3H), 7.41-7.45 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.94, 108.21, 128.06, 129.12, 130.00, 130.51, 134.07, 136.44, 143.66, 161.62; HRMS (APCI) *m/z* (M+H)$^+$ calcd for $C_{12}H_{11}ClNO$: 220.0524, found: 220.0522.

6-Chloro-1-methyl-3-phenylpyridin-2(1*H*)-one (7ga): 23.1 mg, 42%**,** white solid, mp 99.1-100.8 ºC; IR (neat, cm^{-1}) 700, 781, 1047, 1446, 1533, 1596, 1641; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.76 (s, 3H), 6.41 (d, J = 7.6 Hz, 1H), 7.33 (tt, J = 7.3, 1.3 Hz, 1H), 7.37-7.42 (m, 3H), 7.64 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 33.80, 106.58, 127.86, 128.21, 128.51, 129.31, 136.39, 136.67, 136.76, 162.10; HRMS

(APCI) *m/z* $(M+H)^+$ calcd for $C_{12}H_{11}ClNO$: 220.0524, found: 220.0524.

3-Phenylpyridin-2(1*H*)-one (7ja): 8.6 mg, 20%, white solid, mp 199-201 ºC; IR (neat, cm^{-1}) 1458, 1508, 1541, 1558, 1535, 1653, 1683; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (t, *J* = 6.7 Hz, 1H), 7.26-7.32 (m, 2H), 7.36 (td, *J* = 7.2, 1.3 Hz, 2H), 7.52 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.64 (d, *J* = 7.0 Hz, 2H), 12.66 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.00, 127.81, 127.28, 127.49, 130.74, 132.68, 135.48, 138.63, 162.74; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{11}H_{10}NO$: 172.0757, found: 172.0761.

1-(But-3-en-1-yl)-3-phenylpyridin-2(1*H*)-one (7ka): 15.2 mg, 27%, brown oil; IR (neat, cm^{-1}) 698, 754, 918, 1217, 1379, 1460, 1550, 1597, 1645; ^1H NMR (400 MHz, $CDCl_3$) δ 2.57 (q, *J* = 7.2 Hz, 2H), 4.06 (t, *J* = 7.2 Hz, 2H), 5.06-6.14 (m, 2H), 5.83 (ddt, *J* = 15.5, 10.2, 7.0 Hz, 1H), 6.24 (t, *J* = 7.0 Hz, 1H), 7.2-47.27 (m, 1H), 7.32 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.48 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.69 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.26, 50.25, 105.67, 117.89, 127.64, 128.08, 128.66, 131.83, 134.19, 136.90, 136.92, 137.49, 161.36; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{15}H_{16}NO$: 226.1226, found: 226.1230.

1,3-Diphenylpyridin-2(1*H*)-one (7la): 24.4 mg, 40%, brown oil; IR (neat, cm^{-1}) 698, 752, 1265, 1544, 1604, 1654; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (t, *J* = 6.9 Hz, 1H), 7.32 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.38-7.45 (m, 6H), 7.46-7.53 (m, 2H), 7.58 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.74 (dd, *J* = 7.0, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.00, 126.72, 127.83, 128.08, 128.43, 128.72, 129.25, 132.56, 136.62, 137.10, 137.86, 141.32, 161.43; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{17}H_{14}NO$: 248.1070, found: 248.1073.

3-Phenyl-2*H*-chromen-2-one (9): 29.4 mg, 53%, white solid, mp 133.0-134.8 ºC; IR (neat, cm^{-1}) 694, 758, 1118, 1454, 1716; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.37-7.49 (m, 4H), 7.54 (t, *J* = 8.2 Hz, 2H), 7.72 (t, *J* = 6.7 Hz, 2H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.50, 119.70, 124.50, 127.91, 128.42, 128.49, 128.55, 128.88, 131.41, 134.73, 139.87, 153.56, 160.60; HRMS (APCI) *m/z* $(M+H)^+$ calcd for $C_{15}H_{11}O_2$: 223.0754, found: 223.0754.

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