Letter

# Photoredox C–F Quaternary Annulation Catalyzed by a Strongly Reducing Iridium Species

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# Photoredox C–F Quaternary Annulation Catalyzed by a Strongly Reducing Iridium Species

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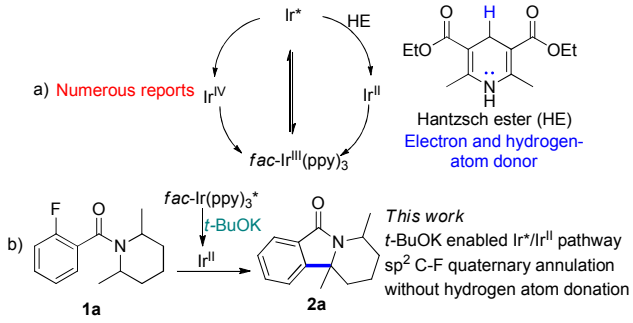
**ABSTRACT:** We report a *fac*-Ir(ppy)$_3$*-Ir$^{II}$-Ir$^{III}$ photocatalytic cycle involving *t*-BuOK as the terminal reductant in a visible-light-induced sp$^2$ C–F quaternary annulation reaction that proceeds in yields up to 98%. Because of the high activity of the Ir$^{II}$(ppy)$_3$ catalyst, even at a loading of 50 ppm, the annulation reaction was able to compete with an uncatalyzed nucleophilic aromatic substitution reaction. The annulation reaction was stereoconvergent, and an annulated product was synthesized with complete retention of enantiomeric excess.

**Keywords:** Annulation, C–F bond activation, quaternary alkylation, photocatalysis, stereoconvergence

In photoredox catalysis, the redox potentials of the photocatalyst at various stages of the catalytic cycle are important considerations in reaction design and mechanism elucidation.[1] The use of transition-metal complexes and organic molecules as photoredox catalysts is well documented.[2] Among the former, *fac*-Ir(ppy)$_3$ has been shown to have a strongly reducing excited state ($E_{1/2}^{IV/III*}$ = −1.73 V vs SCE) and to undergo oxidative quenching events in Ir*-Ir$^{IV}$-Ir$^{III}$ catalytic cycle.[3] If excited-state *fac*-Ir(ppy)$_3$ underwent a reductive quenching event, the resulting Ir$^{II}$ species, which is even more highly reductive ($E_{1/2}^{III/II}$ = −2.19 V vs SCE), could be used to achieve otherwise challenging reactions. However, the transfer of an electron to excited-state *fac*-Ir(ppy)$_3$ ($E_{1/2}^{III*/II}$ = +0.31 V vs SCE), requires a strong electron donor. Recently, a series of reports showed that Hantzsch esters can initiate single-electron transfer (SET) processes that lead to Ir*-Ir$^{II}$-Ir$^{III}$ redox cycles resulting in various novel transformations.[4] However, because HEs are prone to aromatization, transfer of a hydrogen atom from the HE to the product is frequently coupled to the SET process (Scheme 1a). This behavior limits the utility of HEs for reactions in which hydrogen atom transfer leads to undesirable side products. Therefore, to take advantage of the high reduction potential of an Ir$^{II}$ species without accompanying hydrogen atom transfer, a new reducing partner for *fac*-Ir(ppy)$_3$ is necessary.

It has been shown that *t*-BuOK can donate an electron to various substrates with a complexing reagent, and this ability has been used to accomplish a variety of novel transformations, including C–C coupling reactions,[5] photoreactions,[6] and C–X bond formation reactions.[7] In addition, Li and co-workers reported homolytic aromatic substitution (HAS) reactions that are mediated by *t*-BuOK/*fac*-Ir(ppy)$_3$ and that proceed via an Ir*-Ir$^{IV}$-Ir$^{III}$ pathway,[8] which suggests that the reduction potential of *t*-BuOK ($E_{1/2}^{red}$ = 0.10 V vs SCE)[9] may be sufficient to accomplish reverse electron transfer. To explore this possibility, we carried out a study of a *fac*-Ir(ppy)$_3$*-Ir$^{II}$-Ir$^{III}$ cycle involving *t*-BuOK.

To begin our inquiry, we needed an appropriate model reaction that would allow us to distinguish between reaction induced by *t*-BuOK alone, an Ir*-Ir$^{IV}$-Ir$^{III}$ pathway, and an Ir*-Ir$^{II}$-Ir$^{III}$ pathway. For this purpose, we chose *ortho*-fluoro benzamide **1a** as a substrate, for several reasons (Scheme 1b). First, if **1a** reacted with *t*-BuOK directly, no SET process would take place; a nucleophilic aromatic substitution reaction would occur instead (Table 1, entry 5). Second, even though photoredox activation of C–F bonds in multifluoroarenes,[10] *gem*-difluoroalkenes,[11] and a trifluoromethyl group[12] have been reported, cleavage of a sole sp$^2$ C–F bond ($E_{1/2}^{red}$ < −1.9 V vs SCE for **1a**; see SI, section 15) remains a challenge and requires novel chemistry such as Ir*-Ir$^{II}$-Ir$^{III}$ catalysis. Third, an annulation reaction of **1a** would afford a fused ring system in a single step.

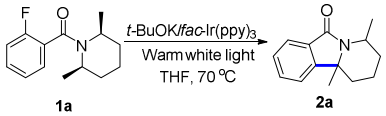



**Scheme 1. Role of *fac*-Ir(ppy)$_3$ and reducing Partners.**

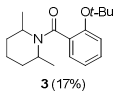
We began by carrying out reactions of **1a** in the presence of *t*-BuOK and *fac*-Ir(ppy)$_3$ under visible light irradiation (Table 1). Systematic screening of various reaction parameters revealed that the optimum irradiation source was warm white LEDs, which not only delivered light but also elevated the temperature (to 70 °C).[13] Under these conditions, reaction in THF afforded **2a** in 93% isolated yield in 3 h (entry 1). If *t*-BuOK was replaced with *t*-BuONa, no reaction occurred, a result that we attributed to the weaker ionization potential of *t*-BuONa relative to that of *t*-BuOK (entry 2). Weaker bases such as cesium carbonate did not work either (entry 3). When we used cold white light, which had no significant heating effect, the GC yield dropped considerably (to 63%, entry 4). In the absence of light or photocatalyst, **3**, produced from **1a** by means of a nucleophilic aromatic substitution reaction, was the

only product (entries 5 and 6).[14] Solvents other than THF were evaluated. MTBE gave comparable results, but no reaction occurred in DCE or DMSO, a solvent used by Li et al in their HAS reaction.[8] (entries 7–9). The reaction required 12 h when the catalyst loading was 50 ppm, and an 88% isolated yield of **2a** was obtained.

**Table 1. Optimization of C–F Quaternary Annulation Conditions**[a]



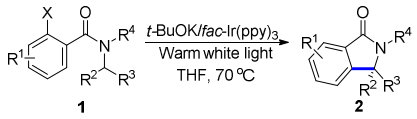

1a 2a

| Entry | Deviation from standard conditions | Yield (%)[b] |
|---|---|---|
| 1 | None | 100 (93) |
| 2 | *t*-BuONa | NR |
| 3 | $Cs_2CO_3$ | NR |
| 4 | Cold white light | 63 |
| 5 | No light, 12 h |  **3** (17%) |
| 6 | No $Ir(ppy)_3$ | **3** (11%) |
| 7 | MTBE | 98 |
| 8 | DCE | NR |
| 9 | DMSO | NR |
| 10 | 50 ppm $Ir(ppy)_3$ | 99 (88)[c] |

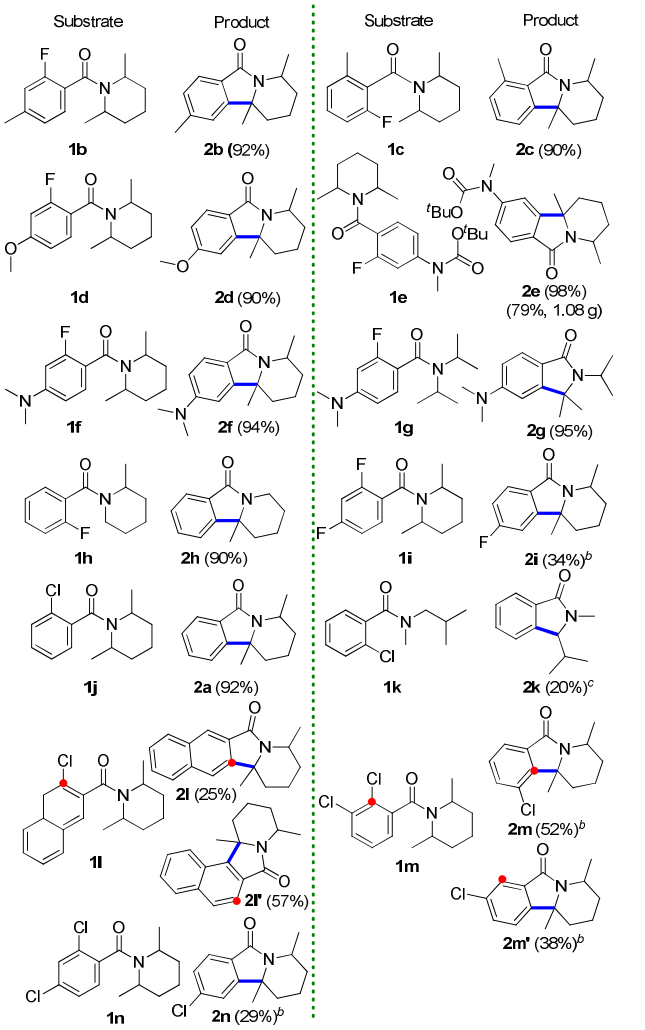
[a] Standard conditions: **1a** (0.2 mmol, 0.1 M), *t*-BuOK (1.2 equiv), *fac*-$Ir(ppy)_3$ (1 mol %), 70 °C heated with warm white LEDs , in sealed tube, 3 h. [b] GC-MS yields are provided, with isolated yields in brackets. NR, no reaction. [c] 12 h.

With the optimized conditions in hand, we explored the reactions of other substrates **1** with an *ortho* C–F bond (Table 2). Substrates with electron-donating groups on the phenyl ring (**1b–1d**)underwent the annulation reaction, furnishing the corresponding products in excellent yields. Boc-protected aniline derivative **1e** was transformed to **2e** almost quantitatively, and this reaction could be scaled up to 4 mmol to afford 1.08 g (79%) of **2e**. Annulation of 2,6-dimethyl piperidine **1f** gave **2f** in 94% yield, and substrate **1g**, in which the piperidine moiety was replaced with a diisopropyl amine moiety, also underwent the annulation reaction, giving **2g** in excellent yield. When a monomethyl-substituted piperidine group was introduced to the substrate (**1h**), the product of regioselective reaction at the tertiary carbon, **2h**, was obtained. When the substrate had two fluoro atoms (**1i**), annulation was accompanied by cleavage of the other C–F when the reaction was carried out in THF. However, by switching the solvent to MTBE, we were able to obtain **2i** in 34% yield. In addition to fluoro-substituted substrates, we also evaluated a series of *ortho*-chloro-substituted amides in this reductive photoredox annulation reaction. Substrate **1j** was as reactive as **1a** and afforded **2a** in 92% yield. *ortho*-Chloro-substituted amide **1k**, which has *N-sec*-butyl and methyl substituents, was prepared and then subjected to the annulation reaction conditions; this substrate was less reactive than 1j, and **2k** was obtained in 20% yield with about 50% dechlorination product in 12 hours. Reaction of naphthalene compound **1l** produced two regioisomers, **2l** and **2l′**. Dichloro-substituted compound **1m** gave regioisomers **2m** and **2m′** in 52% and 38% yields, respectively; and reaction of **1n** in MTBE gave **2n** in 29% yield. Substrates with *para*-halogen substituents (**1i** and **1n**) were highly labile during this transformation: dehalogenation lowered the yield of desired products **2i** and **2n**, and the major side product was **2a**. In contrast, *meta*-halogen substituents, like that in **1m,** survived the reaction conditions intact.

**Table 2. Substrate Scope of Annulation Reaction**[a]




1 2

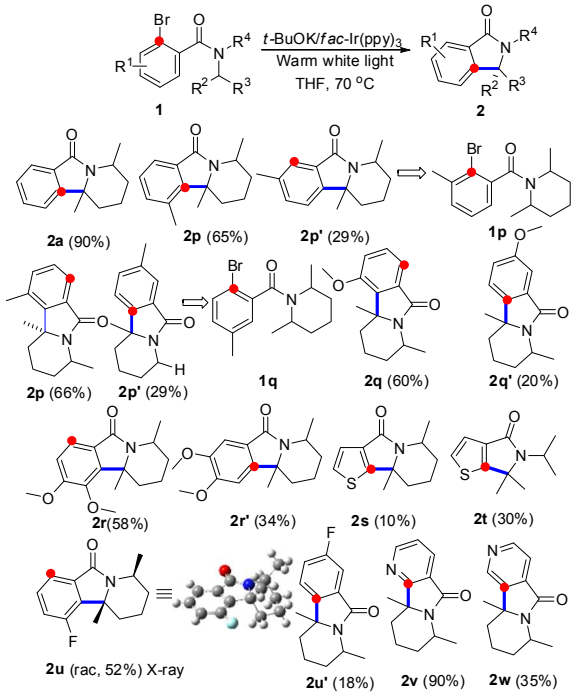



[a] Standard conditions: **1** (0.2 mmol, 0.1 M), *t*-BuOK (1.2 equiv), *fac*-$Ir(ppy)_3$ (1 mol %), THF, 70 °C (heated with warm white LEDs), in sealed tube, 3 h; isolated yields after chromatography are provided. [b] MTBE was used instead of THF. [c] 12 hours.

Because *ortho*-bromo benzoic acids are widely available, we evaluated the compatibility of our annulation protocol with various *ortho*-bromo-substituted compounds (Table 3).[15] Reaction of **1o** (in which the fluorine atom in **1a** is replaced by bromine) gave **2a** in excellent yield.[16] In addition, substrates **1p–1r** could be transformed to the corresponding tricyclic products with similar yields and site selectivities to fluoro compounds. Thiophene substrate **1s** gave only a 10% yield of

desired product **2s**; the low yield may have been due to high ring-strain during annulation. The ring strain was partially relieved in the case of substrate **1t**, which gave **2t** in slightly higher yield (30%). The structure of **2u** was determined by means of X-ray crystallographic analysis, which revealed that the two methyl groups were *cis* to each other. . Substrate **1v**, which bears a pyridine moiety was converted to **2v** as the only product in excellent yield. In contrast, the yield of pyridine **2w** was poor due to decomposition to unidentified side products.

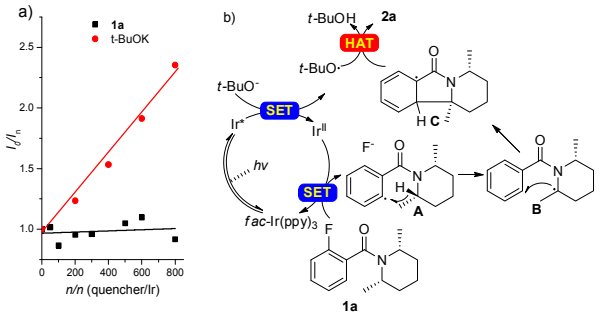
**Table 3. Reactions of *ortho*-Bromo Benzamides**[a]




[a] Standard conditions: **1** (0.2 mmol, 0.1 M), *t*-BuOK (1.2 equiv), *fac*-Ir(ppy)$_3$ (1 mol %), THF , 70 °C (heated with warm white LEDs), in sealed tube, 3 h; isolated yields after chromatography are provided.

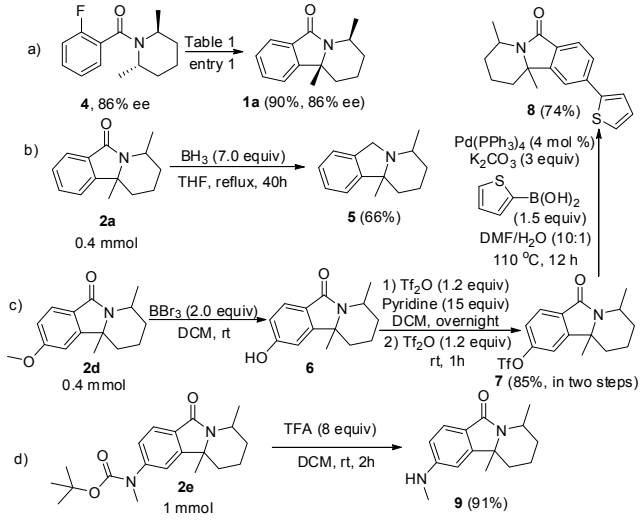
To determine whether the reaction proceeded via an Ir*/Ir$^{II}$ cycle, we performed a emission-quenching experiment at 70 °C (Scheme 2a). Substantial quenching of excited-state Ir(ppy)$_3$ by *t*-BuOK was observed, and no significant interaction between **1a** and the photocatalyst was detected. On the basis of this result, we suggest that the reaction proceeds via the pathway shown in Scheme 2b. First, electron transfer from *t*-BuOK to excited-state Ir(ppy)$_3$* gives an Ir$^{II}$ species, which then transfers an electron to substrate **1a**. Subsequent mesolysis of **1a** generates sp$^2$ carbon radical **A** and fluoride anion.[17] Then an intramolecular 1,5-H shift results in the formation of sp$^3$ carbon radical intermediate **B**, and subsequent addition of the carbon radical to the phenyl ring affords annulated species **C**. Finally, hydrogen atom transfer furnishes product **2a**.

We also explored some synthetic applications of this annulation protocol (Scheme 3). Because the X-ray structure of **2t** indicated that the reaction gave products with *cis* methyl groups, we hypothesized that stereoselectivity could be achieved with an appropriate substrate. When we subjected




**Scheme 2. Emission Quenching and Plausible Reaction Pathway.**[a] **Emission quenching of *fac*-Ir(ppy)$_3$ by 1a and *t*-BuOK.** [b] **Plausible reaction pathway.**

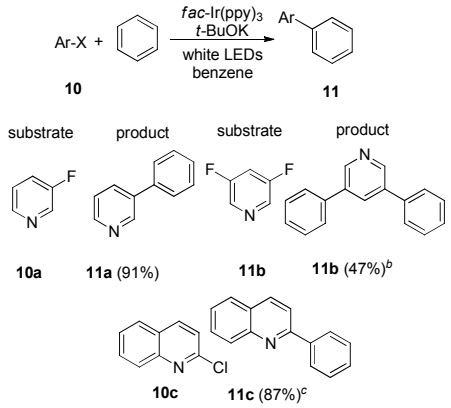
chiral substrate **4** (86% ee) to the photoredox catalysis conditions, we obtained **2a** in 90% yield with 86% ee, suggesting that reversible deprotonation of the carbon alpha to the nitrogen atom did not occur. In addition, we carried out several derivatization reactions of products **2**. Specifically, the amide group in **2a** was reduced with borane to give amine **5** in 66% yield, and **2d** was transformed to corresponding coupling product **8** in 63% yield over three steps. Removal of the Boc group of **2e** with TFA furnished aniline **9**.




**Scheme 3. Synthetic Applications.**

In addition to the C-F quaternary annulation reaction, we explored the application of this *fac*-Ir(ppy)$_3$/*t*-BuOK in other reactions (Table 4). 3-Fluoropyridine **10a** could couple with benezen at 100 °C with 100 W white LEDs, giving biaryl product **11a** in 91% isolated yield. 3,5-Difluoropyridine **10b** was transformed to **11b** in 47%. Another substrate **10c** bearing a chloro atom was subjected to this photoredox reaction and coupling product **11c** was achieved in 87% yield with the LEDs used in Table 2 at 70 °C.

**Table 4 Intermolecular Coupling Reaction with *fac*-Ir(ppy)$_3$/*t*-BuOK**[a]




[a] Standard conditions: **10** (0.2 mmol), *t*-BuOK (1.2 equiv), *fac*-Ir(ppy)$_3$ (1 mol %), benzene, 100-104 °C (heated with 100 W white LEDs), in sealed tube, 6 h; isolated yields after chromatography are provided. [b] with *fac*-Ir(ppy)$_3$ (5 mol %) and *t*-BuOK (2.5 equiv). [c] 70 °C with warm white LEDs.

In summary, we have described a *fac*-Ir(ppy)$_3$*-Ir$^{II}$-Ir$^{III}$ photocatalytic cycle involving *t*-BuOK, an electron donor that does not also donate a hydrogen atom, as the terminal reductant. This chemistry was used to carry out intramolecular C–F quaternary annulation reactions, which proceeded in yields up to 98%. This reaction was stereoconvergent, and substrate control could be used to achieve enantioenriched annulation products by means of the efficient protocol. Intermolecular C-F coupling was also achieved with this catalysis.

## ASSOCIATED CONTENT

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### Notes

The authors declare no competing financial interests.

### Supporting Information

Experimental procedures, characterization of new compounds, NMR spectra, GC and HPLC traces, UV–vis spectra, fluorescence spectra, and crystal data. The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

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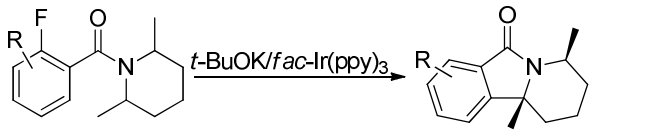
(13) For details, see SI, general procedure E.

(14) If *t*-BuONa was used instead of *t*-BuOK, no $S_NAr$ reaction took place. It was possible due to the weaker ionization of *t*-BuONa than that of *t*-BuOK in THF.

(15) (a) For examples of C–Br alkylation reactions, see: Wertjes, W. C.; Wolfe, L. C.; Waller, P. J.; Kalyani, D. *Org. Lett.* **2013,** *15*, 5986. (b) Bhakuni, B. S.; Yadav, A.; Kumar, S.; Patel, S.; Sharma, S.; Kumar, S. *J. Org. Chem.* **2014,** *79*, 2944. (c) Chen, J.Q.; Wei, Y.L.; Xu, G.Q.; Liang, Y.M.; Xu, P.F. *Chem. Commun.* **2016,** *52*, 6455.

(16) The order of reactivity of **1a** < **1j** < **1o** (F < Cl < Br) was observed. For details, see SI, section 10.

(17) We found the 2,6-disubstitution on the piperidine ring is important to ensure the reacitivity. The possible reason was the steric effect could enhance the distortion of C-X bond from the plane of arene to effect the fragmentation.




50 ppm catalyst loading
stereoconvergent
*fac*-Ir(ppy)$_3$*-Ir$^{II}$-Ir$^{III}$ cycle