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Communication

Aroyl Fluorides as Bifunctional Reagents for Dearomatizing Fluoroaroylation of Benzofurans

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ABSTRACT: The 2,3-dihydrobenzofuran scaffold is widely found in natural products and biologically active compounds. Herein, dearomatizing 2,3-fluoroaroylation of benzofurans with aroyl fluorides as bifunctional reagents to access 2,3-difunctionalized dihydrobenzofurans is reported. The reaction that occurs by cooperative NHC/photoredox catalysis provides 3-aroyl-2-fluoro-2,3-dihydrobenzofurans with moderate to good yield and high diastereoselectivity. Cascades proceed via radical/radical cross-coupling of a benzofuran radical cation generated in the photoredox catalysis cycle with a neutral ketyl radical formed through the NHC catalysis cycle. The redox-neutral transformation exhibits broad substrate scope and high functional group compatibility. With anhydrides as bifunctional reagents, dearomatizing aroyloxyacylation of benzofurans is achieved and the strategy can also be applied to *N*-acylated indoles to afford 3-aroyl-2-fluoro-dihydroindoles.

2,3-Dihydrobenzofurans are core motifs that appear in biologically active compounds (Scheme 1a).[1,2] For example, DNA-PK inhibitors, CB_2 receptor agonists, and furaquinocin A contain a functionalized 2,3-dihydrobenzofuran scaffold.[1−6] Therefore, it is important to develop methods to access such compounds.[7] Along these lines, benzofuran dearomatization is a straightforward route to 2,3-dihydrobenzofurans.[8] Known dearomatization strategies involve cycloaddition,[9−14] direct hydrogenation,[15,16] cyclopropanation,[17] radical cyclization,[18−20] and radical addition[21] among other reactions.[22−27] Halofunctionalizations have been used for benzofuran dearomatization.[28−30] However, a multistep operation for prior installation of substituents bearing nucleophilic moieties is generally required in these halofunctionalizations.

The incorporation of fluorine atoms into organic compounds generally improves their metabolic stability and bioavailability.[31,32] In this context, the development of methods for construction of the C−F bond is of significance. In the past, aroyl fluorides have attracted considerable attention in chemistry.[33−35] They are valuable alternatives for the other aroyl halides or anhydrides due to their higher stability.[36] Accordingly, aroyl fluorides have been used as acylation reagents in ionic transformations.[37−39] Moreover, transition-metal catalyzed cross-coupling of aroyl fluorides has also been developed (Scheme 1b).[33−35,40−44] In general, aroyl fluorides mainly serve as "RCO" or "R" sources but reports on their use as fluorination reagents remain rare.[45−48] Notably, reactions where the aroyl fluoride acts as a bifunctional reagent[49] with the aroyl moiety and also the fluoride being incorporated into the product are very rare.[48]

Photoredox catalysis[50−68] has been used for arene functionalization. Along with reductive processes, established reactivity is the single electron transfer (SET) oxidation of the arene to give an arene radical cation that can be deprotonated at the α-position of an alkyl substituent to give a benzylic radical (Scheme 1c).[69−76] Alternatively, the arene radical cation can be trapped by a nucleophile to give a cyclohexadienyl radical.[77−81] However, the trapping of an arene radical cation with a C-radical to generate a cyclohexadienyl-type cation has rarely been reported.[82−84] This is challenging since both the arene radical cation and the C-radical are reactive intermediates and should be present in low concentrations. Successful examples use photoinduced[82,83] or electrochemical[84] electron transfer to generate a C-radical and an arene radical cation in close proximity that allows for efficient coupling.

Herein, we present dearomatizing 2,3-fluoroaroylation of benzofurans with aroyl fluorides as bifunctional reagents for both C−C and C−F bond formation via cooperative NHC/photoredox catalysis (Scheme 1d).[85−97] Reaction of an aroyl fluoride with an NHC catalyst will lead to an aroyl azolium ion that can be SET reduced by a photocatalyst (PC) to generate a ketyl radical.[91−96] Oxidation of benzofuran by the PC will give its radical cation that should cross-couple with the ketyl radical to give an oxocarbenium ion. Trapping by the F-anion and NHC fragmentation should lead to the fluoroaroylation product. Since the F-anion is a poor nucleophile and is present in low concentration only, we assumed that the radical cation/radical cross-coupling to be faster than trapping by the F-anion. Moreover, potential deprotonation of the benzofuran radical cation (for R = primary or secondary alkyl) has to be suppressed.

Initial experiments were conducted with 3-methylbenzofuran (**1a**) and benzoyl fluoride (**2a**). Optimization revealed that

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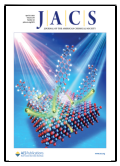

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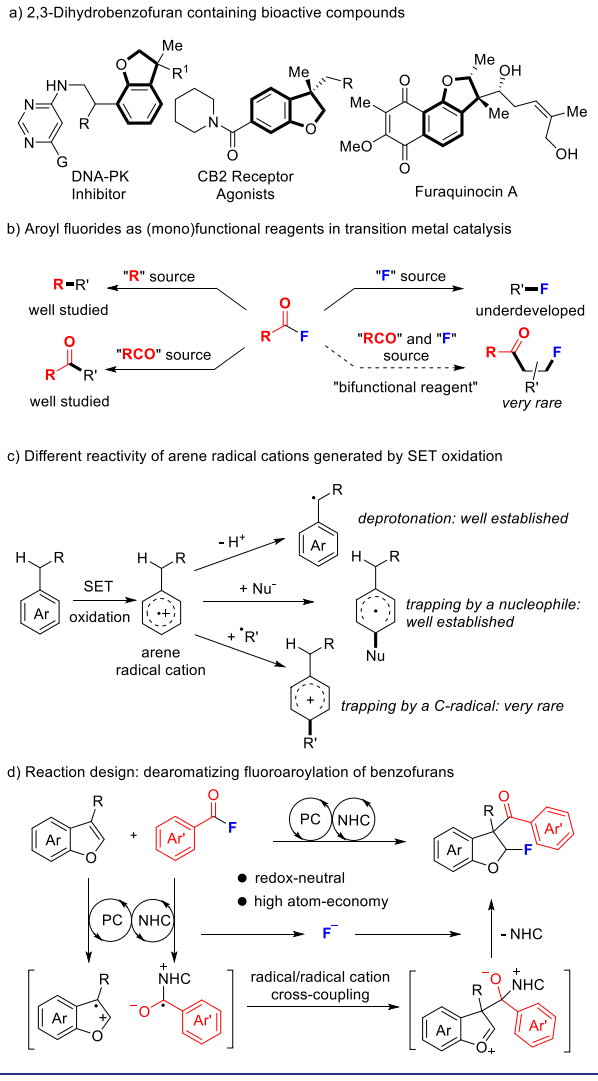
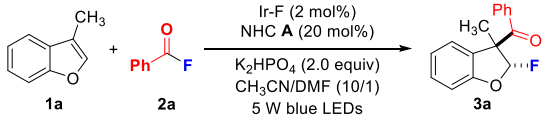
Scheme 1. Functionalized 2,3-Dihydrobenzofurans: Occurrence and Novel Synthetic Approach Using Aroyl Fluorides As Reagents via Redox Processes



this reaction is best conducted in a 10:1 mixture of CH_3CN/DMF, with K_2HPO_4 as base in the presence of Ir−F as the photocatalyst and the NHC catalyst **A** upon irradiation with a 5 W blue LED (λ_{max} = 450 nm) at room temperature for 24 h to provide the racemic dihydrobenzofuran **3a** in 70% isolated yield with high (15:1) *trans*-diastereoselectivity (Table 1, entry 1).[98] The relative configuration of the major isomer of **3a** was assigned in analogy to compound **6** where an X-ray structure was obtained (see below). With $Ru(bpy)_3(PF_6)_2$ or 9-mesityl-10-methylacridinium in place of Ir−F, **3a** was not formed (entries 2 and 3). In CH_3CN or in a mixture of CH_3CN/acetone, the yield of **3a** decreased (entries 4 and 5) and Cs_2CO_3 in place of K_2HPO_4 led to a reduced yield (entry 6). NHC catalyst screening showed the best result with the triazolium salt **A**, and no conversion or only a trace amount of **3a** was observed with precatalysts **B**−**D** (entries 7−9). Control experiments demonstrated the necessity of visible light irradiation, the photocatalyst, and also the NHC catalyst (entries 10−12).

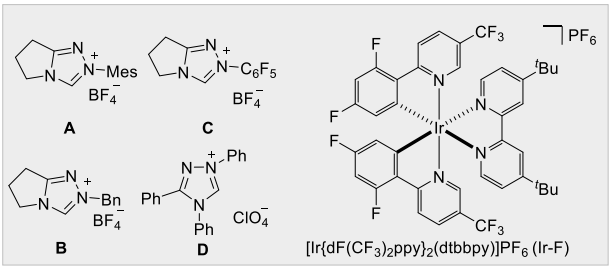
With the optimized conditions identified, the generality of the protocol by first varying the benzofuran was explored (Scheme 2). We found that various R^1-substituents on the

Table 1. Reaction Optimization[a]



entry	variation from the standard condition	yield of **3a** (%)[b]
1	none	73 (70)[c]
2	$Ru(bpy)_3(PF_6)_2$ instead of Ir−F	ND
3	9-Mesityl-10-methylacridinium instead of Ir−F	ND
4	CH_3CN instead of CH_3CN/DMF	50
5	CH_3CN/Acetone instead of CH_3CN/DMF	61
6	Cs_2CO_3 instead of K_2HPO_4	40
7	NHC **B** instead of NHC **A**	2
8	NHC **C** instead of NHC **A**	35
9	NHC **D** instead of NHC **A**	ND
10	no light irradiation	ND
11	no NHC catalyst	ND
12	no photocatalyst	ND

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.4 mmol), NHC **A** (20 mol %), Ir−F (2 mol %), K_2HPO_4 (2.0 equiv), and CH_3CN/DMF (1 mL/0.1 mL) under irradiation with 5 W blue LEDs for 24 h, 15:1 d.r. [b]Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield in brackets. ND = not detected.



aromatic ring were tolerated and the dihydrobenzofurans **3b**−**3j** were obtained with high *trans*-selectivity (8:1 to 30:1). Electronic effects at the C6-position are not pronounced and benzofurans bearing electron-donating (**1b**, **1c**) as well as halo substituents (**1d**) worked well, affording **3b**−**d** in 59−74% yields. However, lower yields were noted for C5-substituted systems. The methyl- and amide-substituted benzofurans **1e** and **1f** underwent dearomatizing fluoroaroylation in moderate yields with high diastereoselectivity (31−42%, 8:1−15:1 d.r.). For **1e**, a complex mixture resulted and **3e** was obtained in 31% yield. In contrast, benzofuran **1f** reacted cleanly, but conversion was low and starting material was recovered. A low efficiency was also found for the 5-bromo derivative **1g** (30%), where unreacted starting material was recovered. The disubstituted **1h** and **1i** engaged in the dearomatization to provide **3h** and **3i** in 60% and 32% yield. For **1i**, the reaction was clean and the low yield is a result of a low conversion with recovery of **1i**. Prolonging reaction time did not increase the conversion. The reason for the low conversion of **1f**, **1g**, and **1i** is not understood. Back-electron transfer after benzofuran oxidation might play a role.[99]

1-Methylnaphtho[2,1-*b*]furan **1j** was converted to **3j** with a high yield and high diastereoselectivity (74%, 20:1 d.r.). The influence of the R^2-substituent was investigated, and the ethyl **1k**, phenethyl **1l**, acetoxyethyl **1m**, isobutyl **1n**, pentyl **1o**, and cyclohexyl **1p** derivatives all worked rather well to deliver **3k**−**3p** with moderate to good yields and high diastereoselectivity (47−69%, 13:1−20:1 d.r.).

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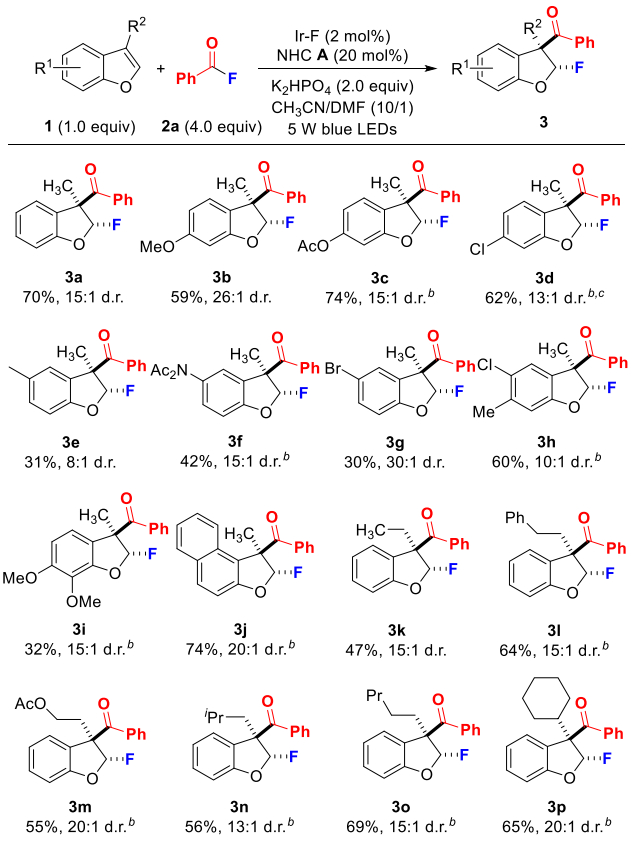
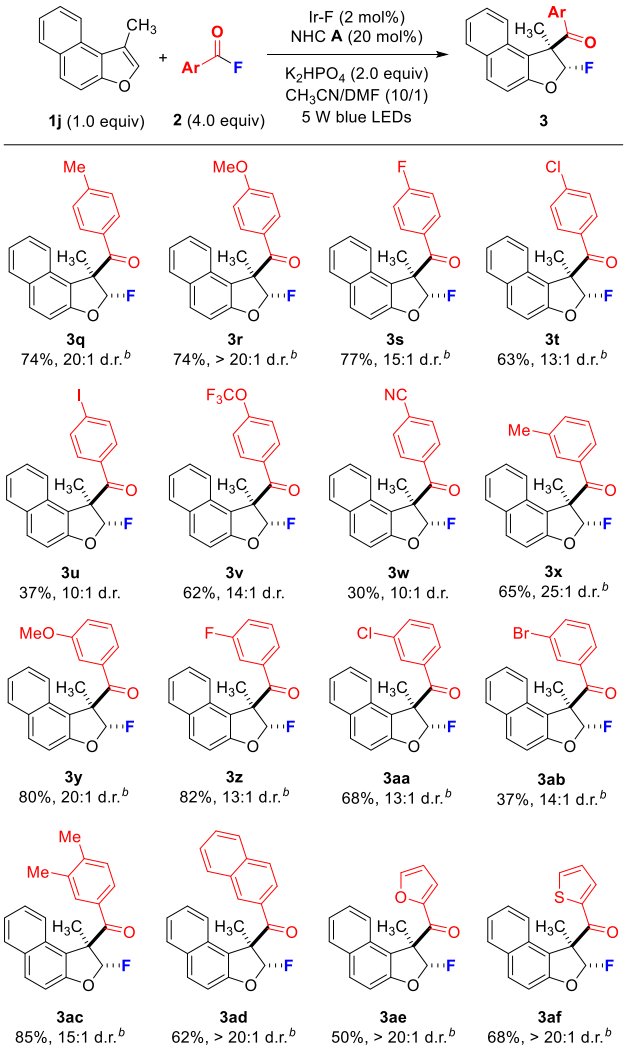
Scheme 2. Substrate Scope: Variation of the Benzofuran[a]



[a]Reactions conducted on a 0.1 mmol scale for 24 h. [b]Using 2 × 45 W blue LEDs. [c]Reactions conducted for 72 h.

Scheme 3. Substrate Scope: Varying the Aroyl Fluoride[a]



[a]Reactions conducted on a 0.1 mmol scale for 24 h. [b]Using 2 × 45 W blue LEDs

Next, we studied the scope with respect to the aroyl fluoride by using **1j** as the reaction partner (Scheme 3). Fluorides bearing electron-donating (e.g., Me, MeO) or electron-withdrawing (e.g., F, Cl, I, OCF_3, CN) substituents at the *para*-position of the phenyl ring are tolerated, and **3q**−**3w** were isolated in 30−77% yields with high diastereoselectivity. Moreover, aroyl fluorides with methyl, methoxy, fluoro, chloro, and bromo substituents at the *meta*-position of the phenyl ring engaged in the reaction to provide **3x**−**3ab** in 37−82% yields (13:1−25:1 d.r.). Hence, no clear trend regarding electronic effects could be deduced. The reaction of the 3,4-dimethylated benzoyl fluoride proceeded efficiently to give **3ac** (85%), and 2-naphthoyl fluoride was also compatible providing **3ad** in 62% yield and excellent diastereoselectivity (>20:1). Pleasingly, heteroaroyl fluorides such as the 2-furyl and 2-thienyl derivatives worked well to afford **3ae** and **3af** (50% and 68%, >20:1 d.r.).

In order to explore the potential of the methodology, dearomatizing indole 2,3-difunctionalization was tested (Scheme 4a). Pleasingly, *N*-acetyl and *N*-benzoyl substituted indoles **4a** and **4b** reacted under slightly modified conditions using 4CzIPN as the PC (5 mol %) with **2a** to give the fluorodihydroindoles **5a** and **5b** in moderate yield and excellent diastereoselectivity. 5-Methyl and 5-methoxy *N*-acetyl-indole also reacted well, but the corresponding fluorinated indoles were unstable and could not be isolated. The 5-bromo and 6-fluoro *N*-acetyl-indole reacted with very low efficiency to the corresponding unstable products that were not isolable. Moreover, a larger scale reaction of **1j** with **2a** was conducted without compromising the yield (Scheme 4b). Next, various follow-up transformations were carried out to document the value of the products. Treatment of **3j** with hydroxylamine hydrochloride afforded the oxime **6** in 57% yield along with 10% of the cyclized 2-isoxazoline **7** (Scheme 4c). The relative configuration in **6** was assigned by X-ray structure analysis. We found that **6** fully cyclizes to **7** in the presence of *p*-TsOH (4 equiv) (Scheme 4c). Reduction of **3j** with $NaBH_4$ provided quantitatively the alcohol **8** as a 1:1 diastereoisomeric mixture (Scheme 4d).

To elucidate the mechanism, control experiments were performed (Scheme 5). When adding a stoichiometric amount of TEMPO, complete suppression of the dearomatization was noted and benzofuran was recovered (Scheme 5a). Reaction of the acylazolium ion **9** and benzofuran **1j** in the presence of $NEt_3{\cdot}3HF$ (1 equiv) without the NHC and K_2HPO_4 afforded **3j** (Scheme 5b). This result demonstrated that acyl azoliums of type **2a-I** are competent intermediates. In addition, Stern−Volmer quenching experiments revealed that benzofuran **1j** could efficiently quench the excited photocatalyst while acylazolium ion **9** did not quench the excited state of the PC (see Supporting Information). Importantly, running the

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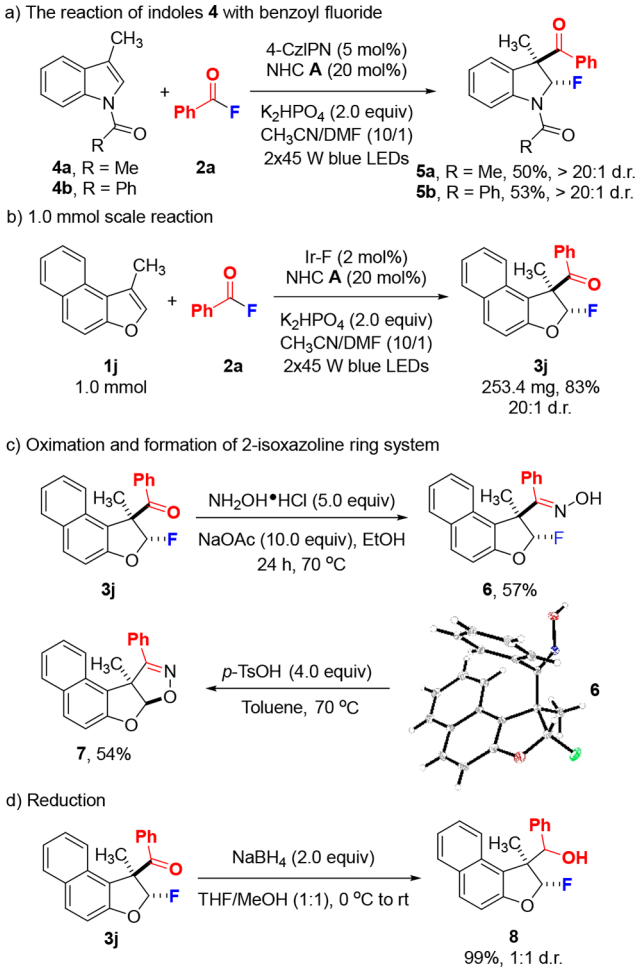
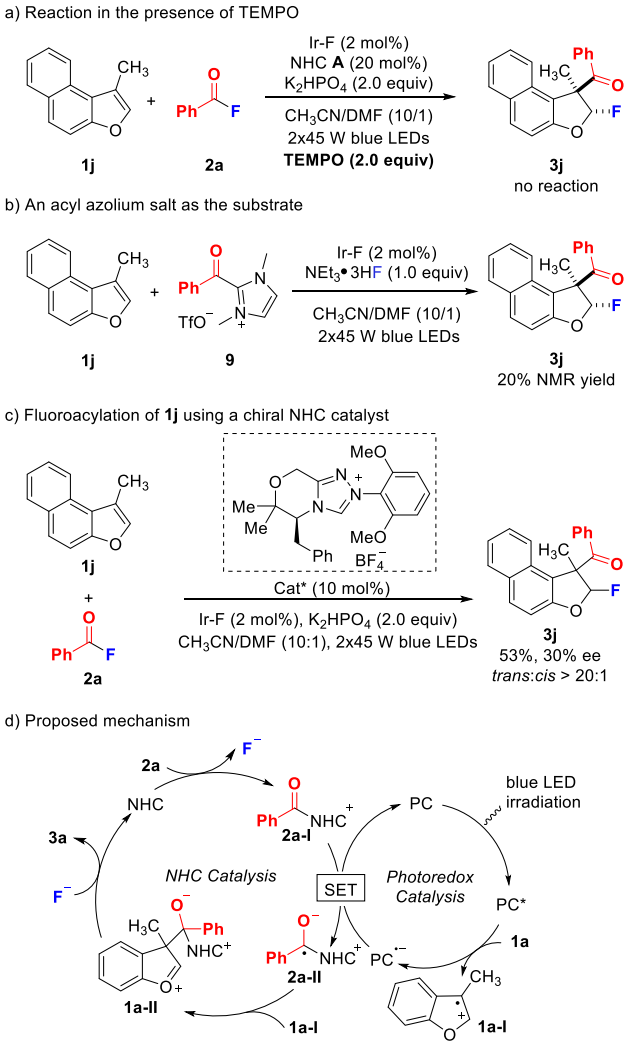
Scheme 4. Indole Dearomatization and Synthetic Applications



[a]**5** (0.1 mmol), **2a** (0.4 mmol), NHC **A** (20 mol %), 4-CzIPN (5 mol %), K_2HPO_4 (2.0 equiv), and CH_3CN/DMF (1 mL/0.1 mL) under irradiation with 2 × 45 W blue LEDs for 24 h. [b]**1j** (1.0 mmol), **2a** (4.0 mmol), NHC **A** (20 mol %), Ir−F (2 mol %), K_2HPO_4 (2.0 equiv), and CH_3CN/DMF (10.0 mL/1.0 mL) under irradiation with 2 × 45 W blue LEDs for 24 h. [c]Hydroxylamine hydrochloride (5.0 equiv), NaOAc (10.0 equiv), EtOH, 70 °C; *p*-TsOH (4.0 equiv), Toluene, 70 °C. [d]$NaBH_4$ (2.0 equiv), MeOH/THF (1:1), 0 °C.

reaction of **1j** with **2a** with a chiral NHC provided **3j** in 53% yield with 30% ee and complete diastereoselectivity (Scheme 5c). This experiment indicated that the radical C−C coupling as the enantiodetermining step may occur prior to C−F bond formation. Although another reaction pathway involving C−F bond formation prior to C−C coupling might be possible and cannot be totally ruled out, the fact that moderate enantioselectivity was observed when chiral NHC catalyst was used in the reaction argues in favor of a preferential occurrence of radical cross-coupling. On basis of these experiments and previous reports,[91−96,100] a mechanism is proposed in Scheme 5d. Upon visible light irradiation, benzofuran **1a** ($E_{1/2}$= 1.28 V vs SCE) is oxidized to its radical cation **1a-I** by photoexcited Ir(III)*. On the other hand, the reaction of **2a** with the NHC gives the acyl azolium ion **2a-I** ($E_{1/2}$= −1.29 V vs SCE),[91] which is reduced by Ir(II) ($E_{1/2}$(P/P$^{\bullet-}$) = −1.37 V vs SCE) to regenerate Ir(III) with the formation of the persistent ketyl radical **2a-II**.[91−96,100]

Scheme 5. Mechanistic Studies



Subsequent cross-coupling of **2a-II** with the radical cation **1a-I** leads to the oxocarbenium ion **1a-II**. Diastereoselective trapping of this carbenium ion by the F-anion *trans* to the bulky alcoholate moiety and NHC fragmentation provide **3a** closing the NHC catalysis cycle. Alternatively, NHC fragmentation can occur prior the trapping of the oxocarbenium ion by the F-anion.

Finally, symmetrical anhydrides were tested as bifunctional reagents for the dearomatizing aroyloxyacylation of benzofurans (Scheme 6). Under slightly modified conditions (CH_3CN in place of CH_3CN/DMF), the symmetric anhydrides **10a**−**10c** were converted with moderate to good yield and excellent diastereoselectivity to **11a**−**11c** (46−64%, > 20:1 d.r.). The relative configuration of **11c** was assigned by X-ray structure analysis. Repeating the reaction of **1j** with **10a** using a chiral NHC afforded **11a** in 39% ee indicating that a similar mechanism as with the aroyl fluorides is operative.

In summary, fluoroaroylation of benzofurans via cooperative NHC and photoredox catalysis has been achieved. Aroyl fluorides were shown to react as bifunctional reagents to incorporate both the aroyl moiety and also the fluoride into the product. The mild photocatalytic protocol shows a broad scope and high functional group tolerance. Of note, *N*-acyl indoles were found to be eligible substrates for the 2,3-difunctionalizing dearomatization. The synthetic value was

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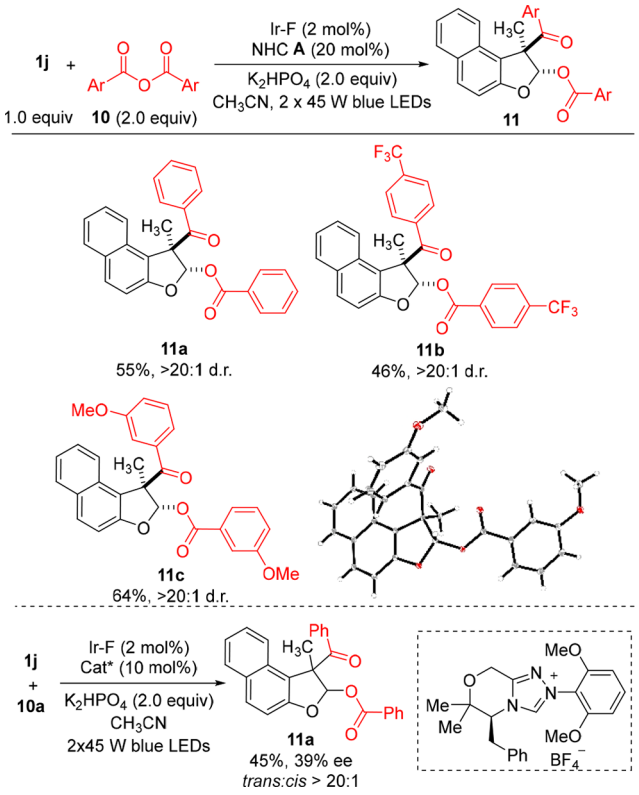
Scheme 6. Dearomatizing Benzofuran Functionalization with Anhydrides[a]



[a]**1j** (0.1 mmol), **10** (0.2 mmol), NHC **A** (20 mol %), Ir−F (2 mol %), K_2HPO_4 (2.0 equiv), and CH_3CN/DMF (1.0 mL/0.1 mL) under irradiation with 2 × 45 W blue LEDs for 24 h.

further demonstrated by follow up transformations. Along with aroyl fluorides, anhydrides also serve as bifunctional reagents for benzofuran dearomatization. Mechanistic studies reveal that these transformations proceed via a rare radical/radical cation cross-coupling reaction as a key step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c01735.

Experimental details and characterization data; NMR spectrum of new compounds; X-ray data (PDF)

Accession Codes

CCDC 2150837 and 2150839 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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This paper published ASAP on March 22, 2022 with an error in Scheme 1. The scheme was replaced and the revised manuscript reposted on March 29, 2022.

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