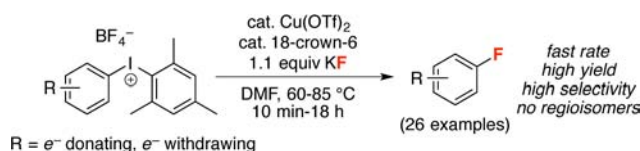


Cu-Catalyzed Fluorination of
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ABSTRACT



A mild Cu-catalyzed nucleophilic fluorination of unsymmetrical diaryliodonium salts with KF is described. This protocol preferentially fluorinates the smaller aromatic ligand on iodine(III). The reaction exhibits a broad substrate scope and proceeds with high chemoselectivity and functional group tolerance. DFT calculations implicate a Cu^I/Cu^{III} catalytic cycle.

Fluorinated organic molecules are well-known to possess unique stability, reactivity, and biological properties. Consequently, C–F bonds (particularly aryl fluorides) have become increasingly prevalent in agrochemicals, pharmaceuticals, and imaging agents.¹ Despite growing demand for organofluorine compounds, synthetic methods for the formation of Ar–F bonds remain underdeveloped. In particular, mild and efficient processes for introducing fluorine onto electron rich aromatic rings using inexpensive nucleophilic fluoride sources such as KF remain a major challenge.²

On the laboratory scale, two of the most common nucleophilic fluorination methods are halide exchange between aryl chlorides and alkali metal fluorides (MF)³ and reactions of diaryliodonium salts with MF.⁴ Both of these processes are generally limited by the requirement for

high temperatures (typically > 100 °C) and by poor reactivity of electron rich substrates. The scope of Ar₂I⁺ fluorinations can be increased by appropriate selection of directing ligands on I^{III} (e.g., 2-thienyl⁴ or cyclophane).⁶ However, the synthesis and purification of the I^{III} substrates in these systems can be particularly synthetically challenging. Furthermore, their reactions still generally involve high temperatures,^{4–6} aryl exchange between I^{III} centers can limit yields,^{4c} and regioisomeric products are often obtained.⁶

Tremendous recent effort has been directed at addressing these limitations via the development of transition-metal-mediated and -catalyzed aryl fluorination reactions,^{1a} and seminal reports have established the feasibility of Pd,⁷

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Cu,^{8,9} and Ni¹⁰ promoted nucleophilic fluorinations. Most relevant to the current work, Hartwig recently disclosed the Cu^{I/III}-mediated fluorination of ArI with AgF at 140 °C.^{8b} However, this method is limited by the requirement for a noble metal fluoride source, superstoichiometric quantities of Cu, and high temperatures.

We hypothesized that Cu salts could potentially catalyze the fluorination of diaryliodonium salts. Such a transformation would offer several key advantages over known nucleophilic fluorination methods.¹¹ First, the highly electrophilic Ar₂I⁺ salts are expected to undergo fast oxidative addition to Cu^I (the rate limiting step in Hartwig's ArI reactions).^{8b} This should enable the use of much milder reaction conditions compared to the related ArI fluorinations. Second, [Mes–I–Ar]⁺ (Mes = mesityl) derivatives are well-known to undergo *sterically controlled* oxidative addition at Cu^I, with selective transfer of the smaller aryl group.^{11,12} Such selectivity would be highly complementary to the analogous uncatalyzed fluorinations of [Mes–I–Ar]⁺¹³ and could potentially enable the fluorination of challenging electron rich substrates. Finally, the desired [Mes–I–Ar]⁺ reagents are readily synthetically accessible from commercially available MesI(OAc)₂ and aryl boronic acids.¹⁴

We initially examined (tBuCN)₂Cu(OTf) as a catalyst for the fluorination of [Mes–I–Ph]BF₄. This Cu complex was selected because it proved optimal in Hartwig's ArI fluorination.^{8b} Evaluation of a number of different conditions and fluoride sources (see Supporting Information for full details) revealed that this reaction proceeds smoothly over 18 h at just 60 °C using 20 mol % Cu and 1.1 equiv of KF. (tBuCN)₂Cu(OTf) afforded a 71% yield and good selectivity for PhF (**1**) over MesF (**2**) (96:4 ratio of **1**:**2**) (Table 1, entry 1). Both Cu^I(OTf)·benzene and Cu^{II}(OTf)₂ were also effective catalysts (entries 2 and 3), with the latter providing the highest yield (85%) and selectivity (98:2). The reaction time could be lowered from 18 to 3 h by the addition of 40 mol % of 18-crown-6 with only minimal erosion of yield and selectivity (entry 4). Under these conditions, fluorination proceeded in 81% yield with 97:3 selectivity for **1** over **2**. The background reaction (without Cu(OTf)₂) proceeded in low yield (30%) and

Table 1. Reaction Optimization^a

entry	[Cu]	time (h)	additive	yield (%) ^b	1 : 2
1	(tBuCN) ₂ CuOTf	18	none	71	96:4
2	CuOTf·benzene	18	none	57	96:4
3	Cu(OTf) ₂	18	none	85	98:2
4	Cu(OTf) ₂	3	18-crown-6	81	97:3
5	none	3	18-crown-6	30	20:80

^a Conditions: [Mes–I–Ph]BF₄ (1 equiv), [Cu] (0.2 equiv), KF (1.1 equiv), additive (0 or 0.4 equiv), DMF (0.1 M), 60 °C. ^b Combined yield of **1** and **2** determined by ¹⁹F NMR.

opposite selectivity under these conditions (ratio of **1**:**2** = 20:80, entry 5).¹³

We next investigated the scope of this transformation with substrates of general structure [Mes–I–Ar]BF₄ (Ar = electron rich (hetero)aromatic ring), as these are typically the most challenging substrates for nucleophilic fluorination reactions.^{1,2} As summarized in Figure 1, fluorinated products **3**–**16** were obtained in good yield and high selectivity. All products with boiling points over 180 °C were isolated, and the purity of isolated products was >98% unless otherwise noted. Remarkably, even 2-fluorothiophene (**16**) could be formed, albeit under more forcing conditions (130 °C for 2 h).⁵ With these electron rich substrates, the analogous Cu-free reactions proceeded in modest yields and provided Mes–F (**2**) as the major product.

Substrates bearing electron-withdrawing substituents on the Ar ring were also investigated. When the substituents were moderately electron-withdrawing, Cu catalysis resulted in significant enhancements in yield and selectivity (e.g., Figure 1, **18**–**22**) relative to the uncatalyzed fluorination reaction. In contrast, substrates with strongly electron withdrawing groups (e.g., **24**–**26**) reacted in good yield and selectivity in both the presence and absence of Cu. This trend is consistent with prior reports of uncatalyzed fluorination of diaryliodonium reagents.¹³

One particularly noteworthy substrate in this series is chloropyridine **23**. Cu-catalyzed fluorination generated **23** in a modest 33% yield but with high selectivity for fluorination at the 5-position. This substitution pattern is often challenging to access in nucleophilic fluorination reactions due to the high propensity of 2-chloropyridines to participate in S_NAr.³

As expected, a steep erosion in selectivity was observed with electron rich substrates bearing *ortho*-substituents (eq 1). For instance, **27** underwent unselective fluorination to provide a 62% yield of a 50:50 mixture of **28** and **2**. In contrast, the electronically similar, but less hindered,

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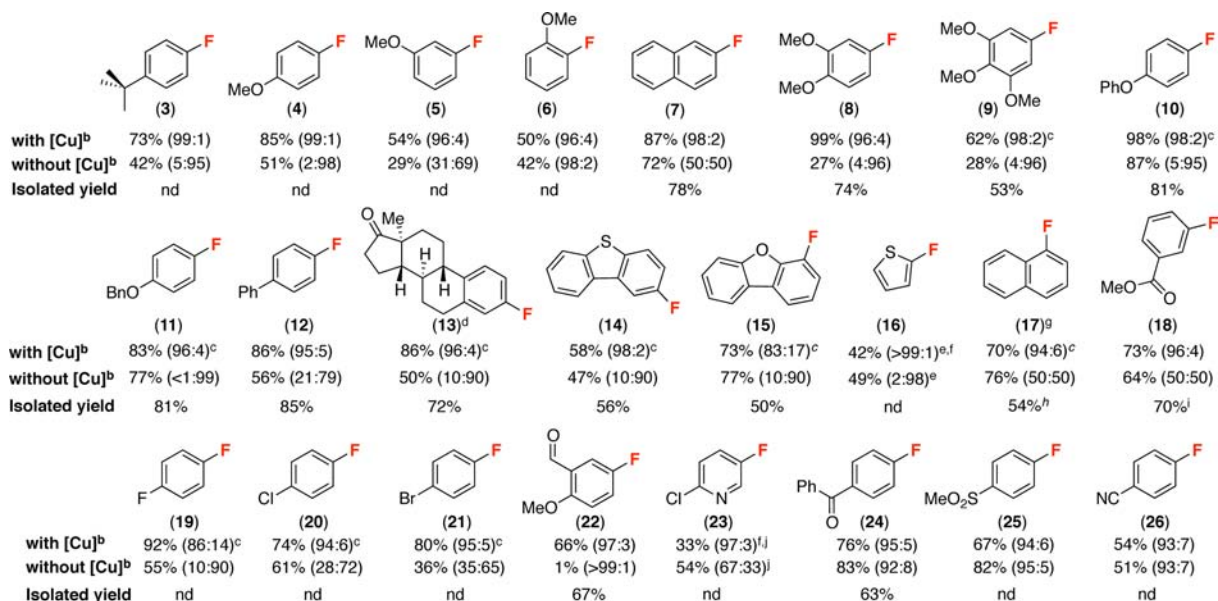
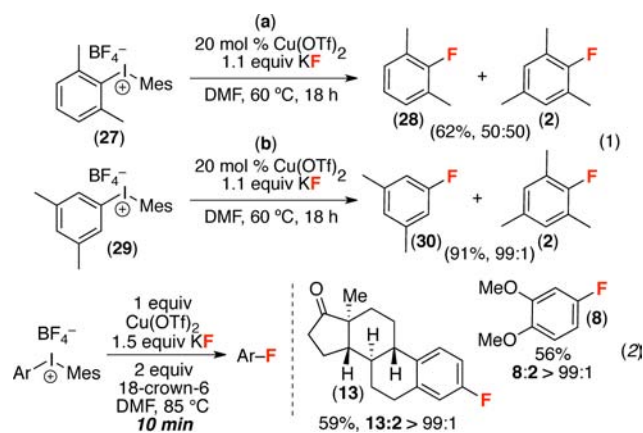


Figure 1. Substrate scope of Cu-catalyzed fluorination. ^a Conditions: [Mes–I–Ar]BF₄ (1 equiv), Cu(OTf)₂ (0 or 0.2 equiv), KF (1.1 equiv), 18-crown-6 (0.4 equiv), DMF (0.1 M), 60 °C, 18 h. ^b Yields (combined of Ar–F + **2**) determined by ¹⁹F NMR. ^c With 0.5 equiv of Cu(OTf)₂. ^d This represents a 53% overall yield from the corresponding boronic acid. ^e 5 equiv of CsF, 130 °C, 2 h. ^f With 1 equiv of Cu(OTf)₂. ^g Substrate was **S17a**, which contains diisopropylphenyl instead of Mes. ^h 97% purity. ⁱ 95% purity. ^j With 1.1 equiv of CsF at 25 °C.

substrate **29** afforded a 91% yield of **30** with high selectivity (**30:2** = 99:1).



One potential application of this method would involve the introduction of ¹⁸F for PET imaging. Because of the short lifetime of ¹⁸F (*t*_{1/2} = 109.7 min), radiofluorination reactions must be extremely rapid.¹ The results described above demonstrate that both Cu(OTf)₂ and 18-crown-6 accelerate fluorination; we hypothesized that the rate could be further increased by using larger quantities of these catalysts. Indeed, fluorinated products **8** and **13** were formed with > 99:1 selectivity in 56% and 59% isolated yield, respectively, in just 10 min at 85 °C using 1 equiv of Cu(OTf)₂ and 2 equiv of 18-crown-6 (eq 2).

A possible Cu^{I/III} catalytic cycle for this reaction is depicted in Scheme 11. In the proposed mechanism, the Cu^{II}(OTf)₂ precatalyst is first transformed to the active Cu^I catalyst **A** via either reduction by solvent or

disproportionation.¹⁵ Ligand exchange provides Cu^I–F **B**, which is then oxidized by the diaryliodonium reagent to afford Cu^{III}–aryl intermediate **C**. Subsequent reductive elimination provides a putative π -complex **D**, which then releases the aryl–F product and regenerates the Cu^I catalyst **A**.

To gain further mechanistic insights, we conducted DFT calculations on the Cu(OTf)₂-catalyzed fluorination of [Ph₂I]BF₄ with F[–]. Assuming initial reduction of Cu(OTf)₂ to [Cu(OTf)₂][–], we began by examining the reaction of [Cu(OTf)₂][–] with free fluoride to form [CuF(OTf)][–].¹⁶ This transformation is highly thermodynamically downhill (ΔG = –20.8 kcal/mol), suggesting [CuF(OTf)][–] as a reasonable starting point for catalysis. The reaction of [Ph₂I]⁺ with free fluoride to form Ph₂IF is also thermodynamically favorable (ΔG = –16.1 kcal/mol). However, there is not enough fluoride in solution to completely form both [CuF(OTf)][–] and Ph₂IF. On the basis of the thermodynamic preference for [CuF(OTf)][–] over Ph₂IF we assigned [Ph₂I]⁺ + [CuF(OTf)][–] as reference points.

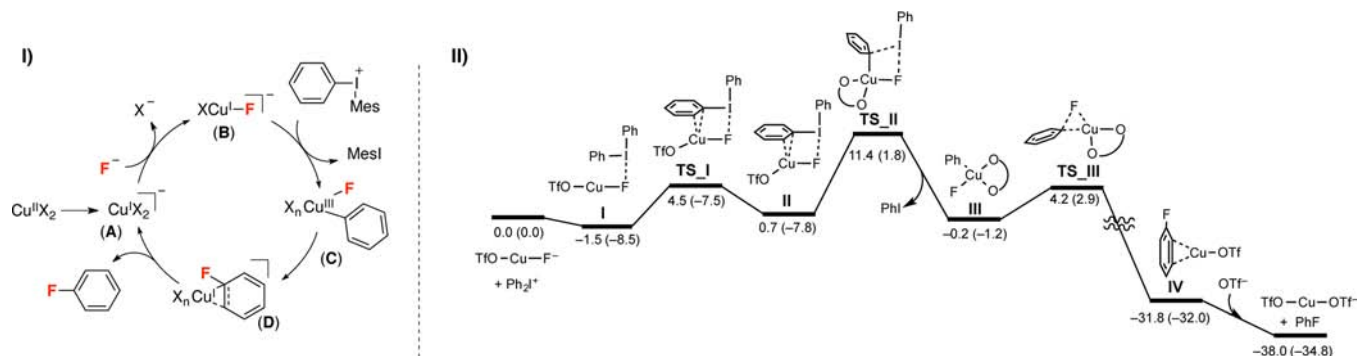
The computational analysis was guided by our recent study of the reaction of Pd^{II} complexes with [Ph₂I]⁺.¹⁷ In the Pd system, [Ph₂I]⁺ initially interacts with an oxygen

(15) For reduction/disproportionation of Cu^{II} to Cu^I, see: Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668 and references therein.

(16) Gaussian 09 was used at the BP86 level for calculations with *N,N*-dimethylformamide as solvent and utilizing the quadruple- ξ valence polarized def2-QZVP basis set on Cu and iodine along with the corresponding ECP and the 6-311+G(2d,p) basis set on other atoms. See Supporting Information for full details.

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Scheme 1. (I) Possible Cu^I/Cu^{III} Catalytic Cycle; (II)^{a,b} Free Energy Profile for the Reaction of [Ph₂I]⁺ with [CuF(OTf)][−]



^a Energies ΔG (ΔH) in kcal/mol. ^b Cu–O distances for bidentate triflate, with O trans to F listed first: **TS_II** (2.068, 2.282), **III** (1.936, 2.213), **TS_III** (2.000, 2.285).

atom of an acetate ligand to afford a T-shaped I^{III} intermediate. This then leads to a transition structure with a four-centered Pd $\cdots(\mu\text{-Ph})\cdots\text{I}\cdots\text{O}$ motif. In the Cu system, a similar low energy precursor complex **I** and subsequent transition structure **TS_II** (through intermediate **II**) were identified (Scheme 1II). In going from **TS_I** to **TS_II**, the Cu \cdots Ph distance decreases while the corresponding Ph \cdots I distance increases. The I \cdots F interaction is retained from **I** through **TS_II**, and the F–Cu–O angle in **TS_I** through **TS_II** is well-removed from linear.¹⁸

Computation shows that the barrier for C–F reductive elimination from Cu^{III} complex **III** to form Cu^I adduct **IV** is very low ($\Delta G^\ddagger = 4.4$ kcal/mol). Complex **IV** could then react with either OTf[−] (as illustrated) or Ph₂IF to release Ph–F and complete the catalytic cycle. Alternative pathways for reductive elimination have been explored, including the addition of TfO[−] to **III** to form [PhCuF(OTf)₂][−], or reaction with Ph₂IF to form *cis*- and *trans*-[PhCuF(OTf)₂][−], followed by C–F bond formation. However, these are considered less likely in view of the low barrier for direct elimination from **III** and energy barriers anticipated for the addition reactions (see Supporting Information for full details).

(18) An alternative and energetically competitive oxidation pathway was also identified, involving initial I \cdots OTf interactions. See Supporting Information for full details.

In summary, this paper describes a Cu-catalyzed method for the fluorination of diaryliodonium salts with KF. The iodonium substrates are readily available in a single step from commercial MesI(OAc)₂ and diverse boronic acid derivatives, and the less-sterically hindered aryl ligand on iodine is fluorinated with high selectivity. Highly electron rich aryl fluoride products can be produced under mild conditions (including just 10 min at 85 °C). Preliminary DFT calculations support the involvement of a Cu^I/Cu^{III} catalytic cycle in this reaction. These DFT calculations also provide valuable mechanistic information about the oxidation of Cu^I by diaryliodonium salts, a topic of great current interest in the literature.¹¹ More detailed studies of the mechanism and applications of this method are currently underway.

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Supporting Information Available. Complete details of the experimental and computational work. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.