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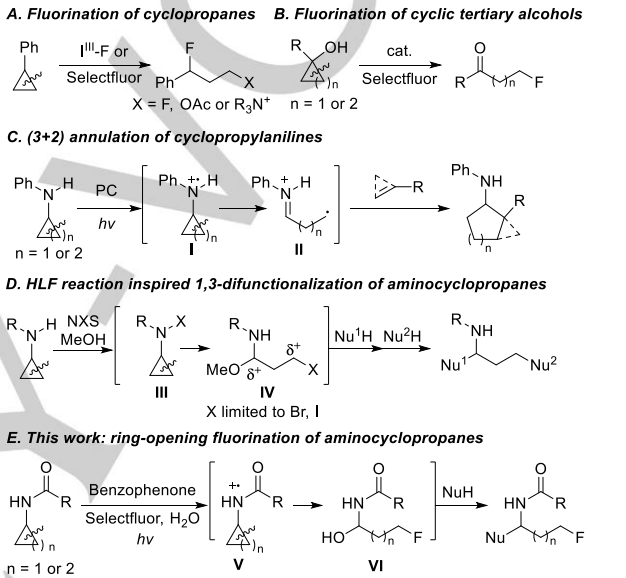
Oxidative Fluorination of Cyclopropylamides via Organic Photoredox Catalysis

Ming-Ming Wang and Jérôme Waser*[a]

Abstract: We report an oxidative ring-opening strategy to transform cyclopropylamides and cyclobutylamides into fluorinated imines. The imines can be isolated in their more stable hemiaminal form, with the fluorine atom installed selectively at the γ or δ position. Both cheap benzophenone with UV A light or organic and inorganic dyes with blue light could be used as photoredox catalysts to promote this process. Various fluorinated amines were then obtained by nucleophilic attack on the hemiaminals in one pot, giving access to a broad range of useful building blocks for medicinal chemistry.

Tremendous efforts have been devoted to the development of site-selective fluorination methods, given the significance of fluorinated compounds in medicine and agrochemistry.[1] Among these methods, the formation of C(sp^3)-F bonds via ring opening fluorination of carbocycles is an attractive route.[2] While success has been achieved in ring opening fluorination of arylcyclopropanes (Scheme 1A),[3] cyclopropanols[4] and cyclobutanols[4a,b] (Scheme 1B), their nitrogen-substituted counterparts were not studied yet, despite the importance of nitrogen-containing fluorinated drugs and agrochemicals.

Previous studies on ring-opening of aminocyclopropanes and aminocyclobutanes focused on Donor-Acceptor systems, which are more reactive.[5] Simple systems lacking electron-withdrawing groups have been less exploited, with most approaches using transition-metal catalyst for C-C activation.[6] Oxidative methods proceeding via radical pathways constitute an interesting alternative.[7] Zheng and co-workers demonstrated that cyclopropylanilines and cyclobutylanilines can be oxidized to a radical cation species **I** using photoredox catalysis (Scheme 1C).[8] After ring opening, the resulting iminium radical **II** underwent (3+2) annulation with alkenes or alkynes. Our group later extended this approach to cyclopropenes[9] and Stephenson and co-workers applied it to the synthesis of 1-aminonorbornanes.[10] They also developed an alternative strategy involving the activation of cyclopropylimines through their triplet excited state.[11] Our group exploited another approach based on a Hofmann–Löffler–Freytag (HLF)-inspired reaction to generate a nitrogen-centered radical from *N*-halogen aminocyclopropane **III** (Scheme 1D).[12] The N radical then underwent ring-opening and radical recombination to generate γ-halogenated imines isolable in their *N*,*O*-acetal form **IV**. However, this approach failed in the case of fluorination.



Scheme 1. Oxidative ring-opening fluorination of cyclopropanes (**A**). Fluorination of cyclopropanols and cyclobutanols (**B**). Photoredox catalysis enabled (3+2) annulation of cyclopropylanilines (**C**). 1,3-Difunctionalization of aminocyclopropanes (**D**). This work: oxidative fluorination of cyclopropylamides (**E**).

We envisioned that a highly oxidizing excited photocatalyst should be able to activate cyclopropylamides via single electron transfer (SET) oxidation to give amidium radical **V** (Scheme 1E).[13] After ring-opening, the formed alkyl radical could be trapped by a fluorination reagent, and the imine stabilized as a hemiaminal **VI**. Herein, we report the successful implementation of this strategy, using either cheap benzophenone with black light (365 nm) or organic/inorganic dyes with blue LEDs, and Selectfluor acting as both oxidant and fluorination reagent. The reaction is complementary to the method of Lectka for the synthesis of fluorinated amines (Scheme 1A, R = NR_3^+),[3a] as a reversed regioselectivity is observed for fluorination compared with arylcyclopropanes. The obtained hemiaminals were easily converted into diverse products by reaction with nucleophiles.

With benzamide cyclopropane **1a** as substrate, the combination of benzophenone and Selectfluor under irradiation at 365 nm in MeCN/H_2O was optimal, yielding 3-fluorinated hemiaminal **2a** in 74% yield (Table 1, entry 1).[14] Control experiments showed no

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Supporting information for this article is given via a link at the end of the document. Raw data for NMR, IR and MS is available at zenodo.org, DOI: 10.5281/zenodo.3895605

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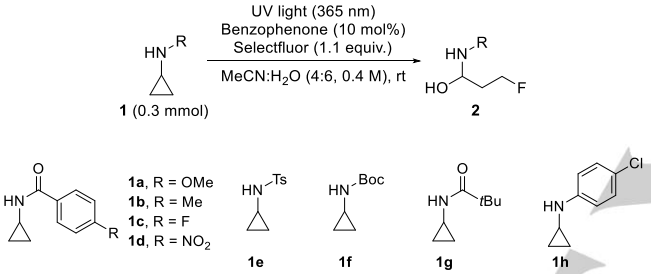
conversion in the absence of benzophenone or irradiation (Table 1, entries 2 and 3). Only 10% of product was observed when using NFSI as fluorinating reagent (Table 1, entry 4). 9-Fluorenone, which is efficient for the ring-opening fluorination of arylcyclopropanes, [3a] failed in this case (Table 1, entry 5). Other photocatalysts such as $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ and Mes-Acr$^+$ can also be utilized to achieve similar results using visible light (Table 1, entries 6 and 7). Lower yields were obtained with substrates containing less electron-donating substituents on the benzene ring of the amide (Table 1, entries 8 and 9). No conversion was observed with a strong electron-withdrawing substituent such as a nitrobenzoyl (Table 1, entry 10) or a tosyl (Ts) group (Table 1, entry 11). With a Boc group, no product was isolated due to fast decomposition of the hemiaminal (Table 1, entry 12). With a pivaloyl group, the yield dropped to 29% with incomplete conversion (Table 1, entry 13). When mixing cyclopropyl aniline **1h** with Selectfluor, fast degradation was observed even prior to UV irradiation (Table 1, entry 14).

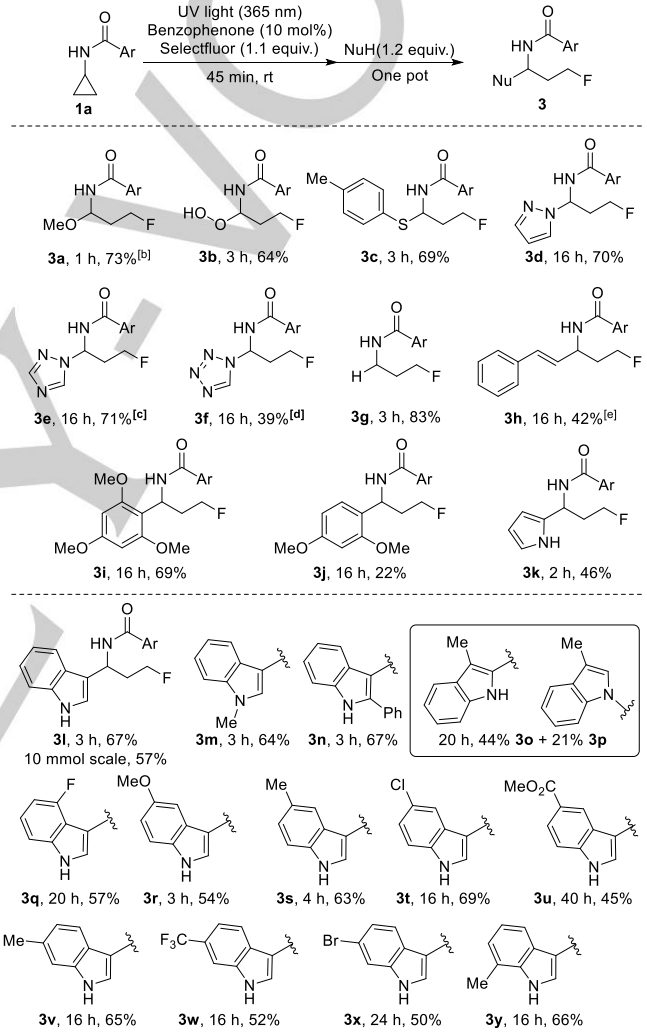
Table 1. Optimization of the reaction conditions[a]



Entry	Deviation from standard condition	Yield[b]
1	none	74%
2	no benzophenone	0
3	no irradiation	0
4	NFSI instead of Selectfluor	10%[c]
5	9-fluorenone instead of benzophenone	6%[c]
6	$[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ with blue LED[d]	76%[c]
7	Mes-Acr$^+$ with blue LED[e]	75%[c]
8	**1b** as substrate[f]	48%
9	**1c** as substrate[f]	43%
10	**1d** as substrate	0
11	**1e** as substrate	0
12	**1f** as substrate	decomposed
13	**1g** as substrate	29%[g]
14	**1h** as substrate	decomposed

[a]Reaction conditions: 0.30 mmol scale for 45 min. [b]Yield of isolated product. [c]Yield determined by ^1H NMR using CH_2Br_2 as internal standard. [d]With 1 mol% $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ and 1.5 equiv. Selectfluor for 1 h. [e]With 2 mol% 9-mesityl-10-methylacridiniumperchlorate (Mes-Acr$^+$) and 1.5 equiv. Selectfluor for 3 h. [f]Reaction run for 4 h. [g]Reaction run for 10 h and product **2g** converted to an indole adduct to simplify purification.

We then developed one pot protocols to replace the hydroxy group by adding nucleophiles to the reaction mixture (Scheme 2). We focused on benzophenone as catalyst, because of its broad availability and low prize. *N*,*O*-, *N*,*S*- or *N*,*N*- acetals can be accessed in 39-73% yield (products **3a-f**). The hemiaminal can also be reduced by $NaBH_3CN$, affording **3g** in 83% yield. A Petasis reaction[15] gave allylic amine **3h** in 42% yield. 1,3,5-Trimethoxybenzene afforded **3i** in 69% yield while only 22% yield of **3j** was observed when using 1,3-dimethoxybenzene. With pyrrole, C2 addition product **3k** was isolated in 46% yield.



Scheme 2. Scope of nucleophiles in the one-pot ring-opening fluorination reaction. [a]Reactions were run at a 0.30 mmol scale for 45 min, then a solution of nucleophile (1.2 equiv.) in 0.5 mL MeCN was added and the mixture was kept stirring at room temperature for the indicated time, Ar = *p*-MeO-Ph. [b]MeOH (1.0 mL, 82 equiv.) was used. [c]1,2,4-1*H*-Triazole (2.0 equiv.) was used. [d]1,2,3,4-*1H*-Tetrazole (2.0 equiv.) was used. [e]Potassium *trans*-styryltrifluoroborate (2.0 equiv) was used.

The addition of indole provided **3l** in 67% yield. Upon scaling up this reaction to 10 mmol, 1.86 grams (57% yield) of **3l** were

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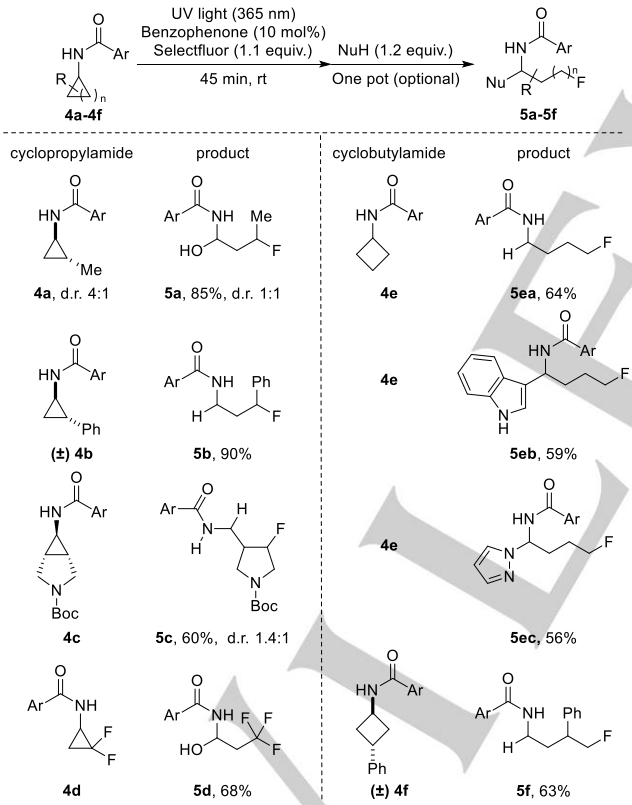
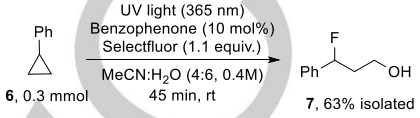
obtained. Indoles bearing a *N*-methyl or a 2-phenyl group provided the corresponding products **3m** and **3n** in 64 and 67% yield. With 3-methyl indole, **3o** and **3p** resulting from *C* and *N* alkylation were isolated in 65% yield in 2:1 ratio. 4-Fluoro indole was well tolerated, giving **3q** in 57% yield. Indoles bearing electron-donating substituents like methoxy (**3r**) and methyl (**3s**), as well as electron-withdrawing substituents like a chloro (**3t**) and an ester groups (**3u**) at the C5 position gave yields ranging from 45% to 69%. A methyl (**3v**), a CF_3 (**3w**) and a bromo (**3x**) group at C6 or a methyl at C7 position (**3y**) led to product formation in 50-66% yield.

We then examined the scope of aminocyclopropanes and aminocyclobutanes (Scheme 3). When using 2-methyl substituted aminocyclopropane **4a** (d.r.= 4:1), **5a** was isolated as a mixture of two diastereoisomers in a 1:1 ratio. With 2-phenyl substituted aminocyclopropane **4b**, **5b** was obtained in 90% yield after reduction by $NaBH_3CN$. When using bicyclic compound **4c**, a mixture of two diastereoisomers in a ratio of 1.4:1 was isolated in 60% yield. 2,2-Difluoro aminocyclopropane **4d** afforded trifluoromethyl hemiaminal **5d** in 68% yield.



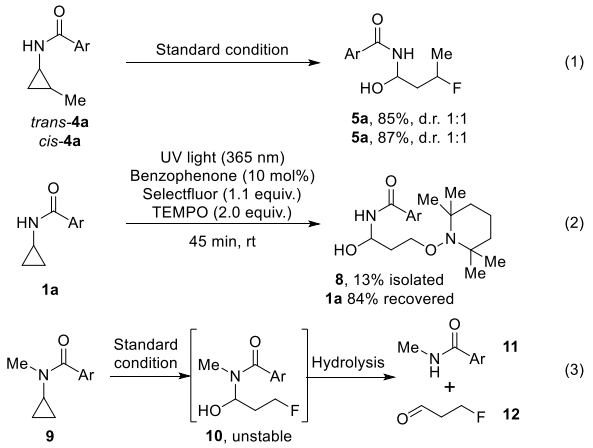
Scheme 3. Scope of multi-substituted aminocyclopropanes and aminocyclobutanes in the ring-opening fluorination reaction. Ar = p-MeO-Ph. See supporting Information for detailed reaction conditions.

With aminocyclobutane **4e**, a series of products **5ea-5ec** was obtained in 56-64% yield, by simply adding different nucleophiles (hydride, indole or pyrazole) for the second step. When using 3-phenyl aminocyclobutane **4f**, **5f** resulting from selective C1-C2 bond cleavage next to nitrogen was obtained in 63% yield, while C3-C4 bond cleavage was observed only in traces by ^{19}F NMR in the reaction mixture. With cyclopropylbenzene (**6**) oxyfluorinated product **7** was isolated in 63% yield, with the same regioselectivity as previously observed for aminofluorination (Scheme 4).[3] This shows that selectivity for ring-opening is substrate controlled and not originating from our different reaction conditions.



Scheme 4. Oxy-fluorination of cyclopropylbenzene (**6**).

In order to better understand the mechanism, we performed several control experiments (Scheme 5). When the *trans* and the *cis* isomers of **4a** were submitted separately to the reaction conditions, the same diastereomeric ratio was observed for product **5a**, supporting the formation of a ring-opened intermediate (Scheme 5, equation 1). When adding TEMPO, we obtained product **8** in 13% yield and recovered 84% **1a**, suggesting that a primary alkyl radical was formed (Scheme 5, equation 2). In order to exclude initiation by hydrogen atom transfer (HAT) to form a neutral amidyl radical, we tested the reaction of *N*-cyclopropyl-4-methoxy-*N*-methylbenzamide (**9**). Products **11** and **12** were obtained, resulting probably from the hydrolysis of unstable hemiaminal intermediate **10** (Scheme 5, equation 3). Attempts to synthesize a *N*-fluorinated aminocyclopropane corresponding to **1a** were unsuccessful,[16] and an independently synthesized *N*-fluoro amide did not react under our reaction conditions (See Supporting Information for details).[17] This makes N-H fluorination as a first step highly improbable.



Scheme 5. Mechanistic investigations.

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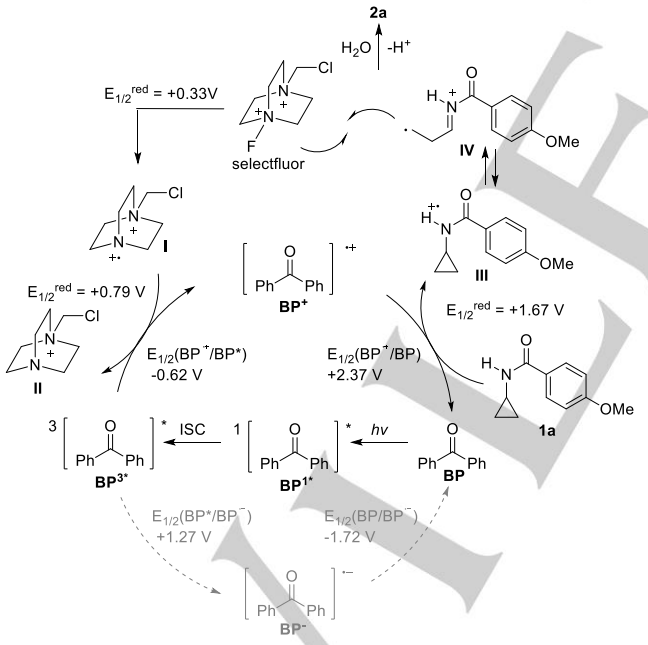
Based on these results and literature precedence, a first speculative reaction mechanism can be proposed (Scheme 6). Photo-excited ketones such as benzophenone (**BP**) in their triplet state can initiate processes such as hydrogen atom transfer (HAT),[18] triplet energy transfer (EnT)[19] and single electron transfer (SET).[20] By comparing the reduction potentials of cyclopropylamide **1a**, Selectfluor and triplet state benzophenone (**BP^{3*}**), neither Selectfluor ($E_{1/2}^{red}$ = +0.33 V)[21,22] nor triplet state benzophenone ($E_{1/2}^{BP*/BP^-}$ = +1.27 V)[23] are able to oxidize cyclopropylamide **1a** (measured $E_{1/2}^{red}$ = +1.67 V). However, Selectfluor or the Selectfluor-derived radical cation (**I**, $E_{1/2}^{red}$ = +0.79 V)[24] could oxidize triplet state benzophenone (**BP^{3*}**, $E_{1/2}^{BP+/BP3*}$ = -0.62 V) to the benzophenone radical cation **BP^{+}**, which is oxidizing enough to convert **1a** to radical cation intermediate **III** ($E_{1/2}^{BP+/BP}$ = +2.37 V). For [Ir(dF-CF$_3$ppy)$_2$(dtbbpy)]PF$_6$, a similar catalytic cycle could be proposed when considering its redox properties ($E_{1/2}^{Ir(III)*/Ir(II)}$ = +1.21 V, $E_{1/2}^{Ir(III)*/Ir(IV)}$ = -0.89 V and $E_{1/2}^{Ir(IV)/Ir(III)}$ = +1.69 V).[21] For the stronger oxidizing Mes-Acr^{+} dye ($E_{1/2}^{red}$ = +2.06 V),[25] another mechanism may be operative. After SET oxidation, **III** would undergo ring opening to form **IV**, followed by radical fluorination with Selectfluor and nucleophilic addition of water to the iminium to yield **2a**. The reversal of regiochemistry observed compared to the work of Lectka can be tentatively attributed to the low stability of **III** leading to ring-opening, whereas the radical cation obtained from arylcyclopropanes is more stable and undergoes first nucleophilic addition.



Scheme 6. Speculative reaction mechanism.

In summary, we have developed a strategy for the ring-opening fluorination of cyclopropylamides and cyclobutylamides using cheap benzophenone as organophotoredox catalyst. The hemiaminal products can be converted to other building blocks by substituting the hydroxy group with diverse nucleophiles. Based on the simple reaction procedure and the structural diversity of nitrogen- and fluorine-containing building blocks obtained, we believe that this methodology will be useful in synthetic and medicinal chemistry.

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Keywords: aminocyclopropanes • ring-opening • photoreaction • fluorination • benzophenone

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[14] See Supporting Information for details of tested reaction conditions. It is interesting to note that standard borosilicate glass tubes can be used, as less than 10% light is absorbed at 365 nm, see: https://www.pgo-online.com/intl/borofloat.html.

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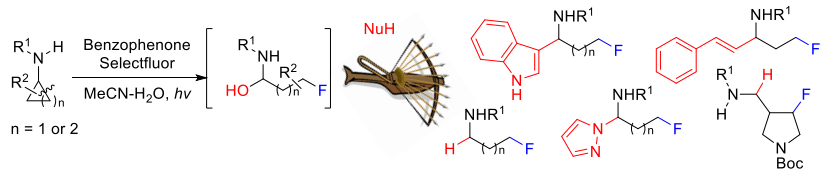

Make it shine: We report a photocatalyzed ring-opening fluorination of cyclopropylamides and cyclobutylamides. Both cheap benzophenone with UV A light or organic and inorganic dyes with blue light could be used to promote this process. Various fluorinated amines were then obtained by nucleophilic attack on the formed hemiaminals in one pot, giving access to a broad range of useful building blocks for medicinal chemistry.

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