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## Visible Light-Induced C-F Bond Activation for the Difluoroalkylation of Indoles

Scott T. Shreiber,

Albert Granados<sup>†</sup>,

Bianca Matsuo<sup>†</sup>,

Jadab Majhi<sup>†</sup>,

Mark W. Campbell,

Shivani Patel,

Gary A. Molander

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

### Abstract

An aryl disulfide-mediated C-F bond activation of the trifluoromethyl group to generate valuable *gem*-difluoroalkylindoles is described. This method relies on readily available commodity reagents under mild reaction conditions and represents the first transition metal-free redox-neutral C-F bond activation strategy. The reaction employs various substituted indoles and  $\alpha$ -fluoro-substituted esters. Further, this mode of C-F activation was also amenable to the activation of trifluoromethylated arenes for the preparation of *bis*-benzylic *gem*-difluoromethylenes between indole and arene substructures, providing access to a unique chemical space.

### Graphical Abstract

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**Corresponding Author:** Gary A. Molander – Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States; gmolandr@sas.upenn.edu.

<sup>†</sup>A.G., B.M., and J.M. contributed equally.

**Scott T. Shreiber** - Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States;

**Albert Granados** - Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States;

**Bianca Matsuo** – Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States;

**Jadab Majhi** – Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States;

**Mark W. Campbell** - Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

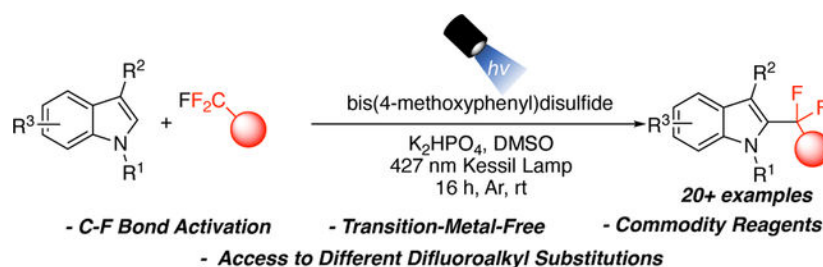
**Shivani Patel** - Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States;

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General procedures, characterization data for products (NMR, IR, MS), mechanistic studies details, gram scale reaction details and NMR spectra (PDF)

The authors declare no competing financial interest.



The incorporation of fluorine into organic molecules is well-known to alter chemical properties, including stability, reactivity, acidity, and conformational bias.<sup>1–3</sup> Therefore, substantial efforts have been invested in incorporating these motifs into organic frameworks.<sup>1, 2, 4, 5</sup> For example, over 50% of new agrochemicals introduced on the market from 1998–2020 contained at least one C-F bond,<sup>6</sup> and over 40% of new small molecule drugs in 2018 and 2019 were fluorinated compounds.<sup>7</sup>

Another important class of pharmaceutically relevant motifs are indoles,<sup>8, 9</sup> as they are among the most prevalent substructures in biologically active small-molecule drugs.<sup>10, 11</sup> Consequently, the ability to incorporate fluorine onto indoles is of high interest and has been pursued in both academic and industrial laboratories.<sup>12</sup> Specifically, the *gem*-difluoromethylene motif is an attractive bioisostere for common organic functional groups such as alcohols, amines, and ketones, and is known to improve biological properties while providing greater chemical stability.<sup>13, 14</sup>

Early efforts on the synthesis of *gem*-difluoromethylated indoles relied on the use of transition metal-mediated or -catalyzed reactions (Scheme 1A). These methods require the use of catalytic Pd,<sup>15</sup> Ni,<sup>16</sup> or Cu<sup>17, 18</sup> under elevated temperatures. Further, these methods make use of either the activated ethyl (iodo- or bromo)difluoroacetate precursor. Another report of a Rh-catalyzed method exists.<sup>19</sup> However, this approach requires the use of a difluorovinyl precursor at elevated temperatures. More recently, light-induced methods for the preparation of difluoromethylene-containing indoles have appeared in the literature as an alternative (Scheme 1B). These methods used either an iridium,<sup>20, 21</sup> ruthenium,<sup>22, 23</sup> or a triphenylphosphine photocatalyst.<sup>24</sup> However, these light-induced methods again relied on the use of activated, non-commodity reagents, and do not provide access to a large pool of available substrates. Thus, the ability to install the *gem*-difluoroalkyl group onto indoles with a more diverse precursor that did not require transition metals, harsh thermal conditions, or limited, active difluoro precursors under mild reaction conditions is an attractive goal.

Our group has a long-standing interest in *gem*-difluoro functionalization of organic molecules.<sup>25–30</sup> Recently, a photochemically mediated difluoroalkylation of olefins was developed utilizing a selective C-F bond activation method.<sup>31</sup> The difluoro precursor was derived from the commodity feedstock ethyl trifluoroacetate, which is estimated to be 50–120 times cheaper than iodo- or bromodifluoroacetates.<sup>31</sup> Therefore, we were interested in a C-F activation protocol that could be developed for installing the *gem*-difluoromethylene group onto indoles. This would overcome the reliance on more costly starting materials

used in previous methods, potentially provide a mild, light-induced method, and most importantly, allow greater diversification because a wider scope of fluorinated substrates would be accessible. To perform this transformation, we were interested in the recent work by Shang's group that utilized a light-induced strategy for C-F activation with aryl thiols (or disulfide).<sup>32</sup> Shang's work demonstrated that photoexcited aryl thiolates possess a low oxidation potential ( $-3.31$  V vs. SCE), which is capable of reducing trifluoromethyl precursors such as ethyl trifluoroacetate ( $-2.0$  V vs. SCE)<sup>31</sup> to difluoroalkyl radicals for Giese type additions.<sup>32</sup> Light-induced transformations utilizing various reactive sulfur species have become a topic of interest recently.<sup>33,34</sup> Inspired by this work, we became interested in developing a C-F activation protocol for fluoroalkylation utilizing aryl thiol species for reactions other than Giese type additions. Therefore, we were intrigued to explore whether active difluoroalkyl radicals generated from aryl thiols would add to indoles in a reaction that did not require stoichiometric reductants as used in Giese type additions.<sup>31,35-38</sup> This method would in turn provide the first transition metal-free redox-neutral C-F bond activation of ethyl trifluoroacetate and demonstrate the first transition metal-free C-F bond activation chemistry for fluoroalkylations beyond Giese type additions.

To explore the development of this proposed transformation, we used a microscale High-Throughput Experimentation (HTE) screening to assist in rapidly identifying conditions to enable the reaction described in Table 1 (bottom graph). Using readily available 1,3-dimethylindole (1a) as the model substrate for this optimization, we found the reaction with ethyl trifluoroacetate (2a), bis(4-methoxyphenyl) disulfide (3), and K<sub>2</sub>HPO<sub>4</sub> in DMSO under LED array 445 nm light irradiation provided the greatest relative yield in the HTE screen. Transitioning the reaction to the bench scale provided a 63% yield with 0.5 equiv of 3 (entry 1), and excess 2a under 427 nm Kessil light irradiation. Control reactions demonstrated that the absence of light (entries 2), base (entry 3), or disulfide (entry 4) results in no product formation. The reaction takes place under open-to-air conditions (entry 5). However, the yield was diminished. Consistent with the HTE screen, the use of other bases or solvent resulted in decreased yields (see SI for additional optimizations). Further, the use of the 4-methoxybenzenethiol monomer instead of the dimer resulted in similar yields with the same sulfur loading (Table 1, entry 6 vs. 1). We elected to continue with 3 because of its commercial availability as an odorless solid that is easy to work with on the bench. Utilizing the traditional photocatalyst, Ir(ppy)<sub>3</sub>, resulted in no product detection (entry 7). Increasing 3 to 1 equiv led to an increase in yield to 72% (entry 8), and an isolated yield of 4a in 63% yield was achieved (0.5 mmol scale).

With suitable conditions identified, the scope of the transformation was explored with various 3-substituted indoles (Scheme 2). Altering the substitution of the nitrogen with various alkyl groups (4a-4c) and the benzyl moiety (4d) was possible. The free, unprotected 3-methylindole (1e) was also successfully subjected to the reaction. However, utilizing indole or 2-methylindole resulted in low yields and a mixture of products by <sup>19</sup>F NMR. The reaction accommodated various indoles containing free NH's and N-methyl groups in good yields (4f-4h). Protected amine (4i) and alcohol (4j) substrates were also accommodated. Further, the natural product melatonin, bearing an amide and methoxy group, provided the corresponding difluorinated derivative in fair yields (4k). The reaction was successful when using amino acid derivative tryptophan (4l). Other heterocycles were explored in this

transformation but were largely unsuccessful (see Supporting Information and *vide infra*). Considering the importance of scaling up the protocol for further applications, we performed the reaction of 1a on a gram scale and found a slight decrease in yield to 41%. However, we were able to recover some unreacted starting material in this case.

Next, we evaluated the extension of the C-F activation protocol to other fluorinated starting materials (Scheme 3) Initial explorations utilized the isopropyl trifluoromethyl ester with 1a and 1b, in which cases fair yields were found for the generation of 5 and 6, indicating that varying the alkyl chain on the nitrogen is possible. To explore other fluorinated precursors, 1i was chosen as the model substrate to highlight the advantage of using this method for free, unprotected indoles and protected amines. Isopropyl trifluoromethyl acetate gave good yields with 1i, providing 7. Cyclohexane-containing ester provided 8, and the bulky adamantyl derivative 9 was synthesized in good yields. The ethyl pentafluoropropionate substrate selectively yielded 10, providing a product containing two unique fluorine containing functional units.

Using conditions established for the trifluoroacetate, trifluoromethyl arenes were not suitable substrates for this protocol. The use of formate salts, however, has been shown to assist in C-F functionalization reactions in conjunction with reactive thiol species to generate aryl difluoromethyl radicals in Giese type additions. Consequently, we explored the addition of sodium formate in the reactions with arenes.<sup>32,36–38</sup> Using this modified protocol allowed the synthesis of 11–13, generating a unique *bis*-benzylic *gem*-difluoromethylene motif between an arene and an indole. Prior methods to activate a C-F bond of trifluoromethyl arenes for coupling with other arenes required the use of Pd under thermal conditions, and was shown for trifluoromethyl arenes and aryl boronic acids.<sup>39</sup> Therefore, this transition metal-free C-F bond activation strategy, allowing the installation of the *bis*-benzylic *gem*-difluoromethylene between an indole and arene (11–13), provides a simple, unprecedented protocol to access a unique chemical space and structural motif.

Attention was then turned to exploring the reaction mechanism and the nature of the radical species that were generated *in situ*. The reaction of 1a, 2a, and 3 with base in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under standard reaction conditions inhibited the formation of product 4a, with detection of the thiol-TEMPO adduct 14 by GC-MS (Scheme 4A). Running the same reaction, replacing 3 with 4-methoxybenzenethiol, again inhibited product formation. However, in this case the difluorinated ester-TEMPO adduct 15 was detected by GC-MS (Scheme 4B). Therefore, based on these observations, we propose the reaction mechanism depicted in Scheme 3C. Upon irradiation with light, 3 undergoes homolytic cleavage of the disulfide (which was trapped by TEMPO in Scheme 3A), followed by hydrogen atom transfer (HAT) with solvent and deprotonation with a base to generate thiolate A.<sup>32</sup> The thiolate can be photoexcited with light to generate the photoexcited thiolate species (B).<sup>32</sup> Species B reduces 2a, generating C and D.<sup>32</sup> Radical C undergoes a spin-centered shift (SCS),<sup>31,40</sup> generating difluoroalkyl radical E (which was trapped by TEMPO as shown in Scheme 4B), which adds to the indole substrate, generating F. At this point, the thiyl radical D undergoes single electron transfer (SET) with F, regenerating thiolate A and cation G resulting from a radical/polar crossover. Deprotonation with the base then furnishes the product 4.

Utilizing catalytic amounts of **3** (see Supporting Information) led to a decrease in yields. In control experiments of **3** with **2a** in the presence of a base, difluoroalkylated arylthiol products were formed under light irradiation (see Supporting Information). Thus, the electron rich disulfide/thiol undergoes side reactions with the radical species **E**, in turn requiring higher loadings of **3** for suitable formation of the desired *gem*-difluoroalkylation products. We believe this side reaction is why less electron-rich heterocycles were not amenable in this protocol, and this finding will be critical in future methods developments utilizing arylthiols or disulfides.

In summary, a new method for the *gem*-difluoroalkylation of indoles was described. The reaction represents the first transition metal-free, redox-neutral C-F bond activation of the inexpensive commodity feedstock chemical ethyl trifluoroacetate utilizing arylthiol or disulfide. This method is highlighted by utilizing a spin-centered shift C-F bond activation mechanism. The reaction is tolerant of a variety of functional groups, and further allows the installation of different fluorinated motifs and esters. Finally, the protocol was expanded to provide a unique *bis*-benzylic *gem*-difluoromethylene unit between two aromatic systems. This new synthetic method is simple, mild, and provides access to pharmaceutically relevant motifs, and was successfully scaled to the gram-scale level.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

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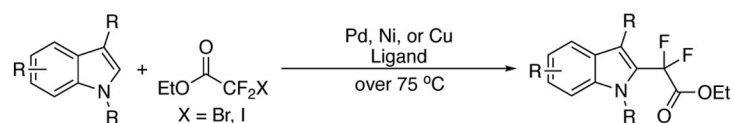
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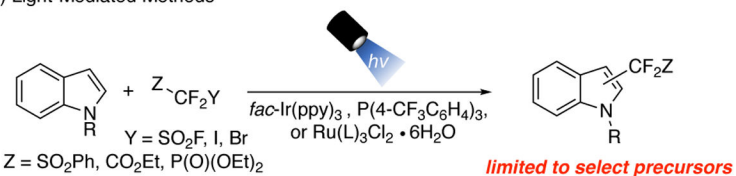
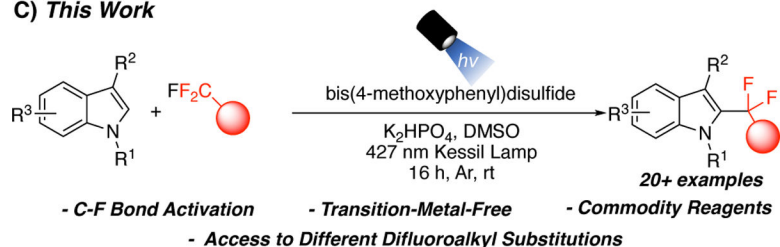
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**Previous Work**

## A) Traditional Metal-Mediated Methods

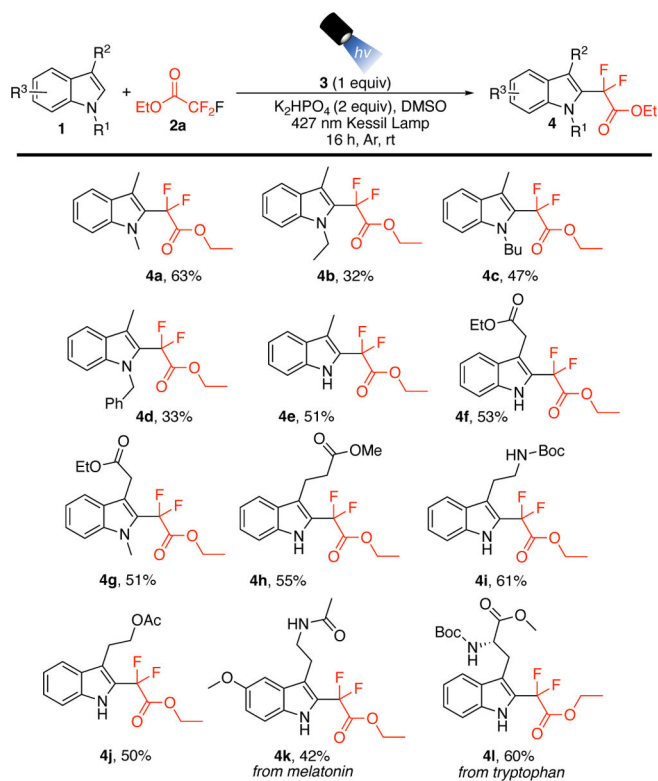


## B) Light-Mediated Methods

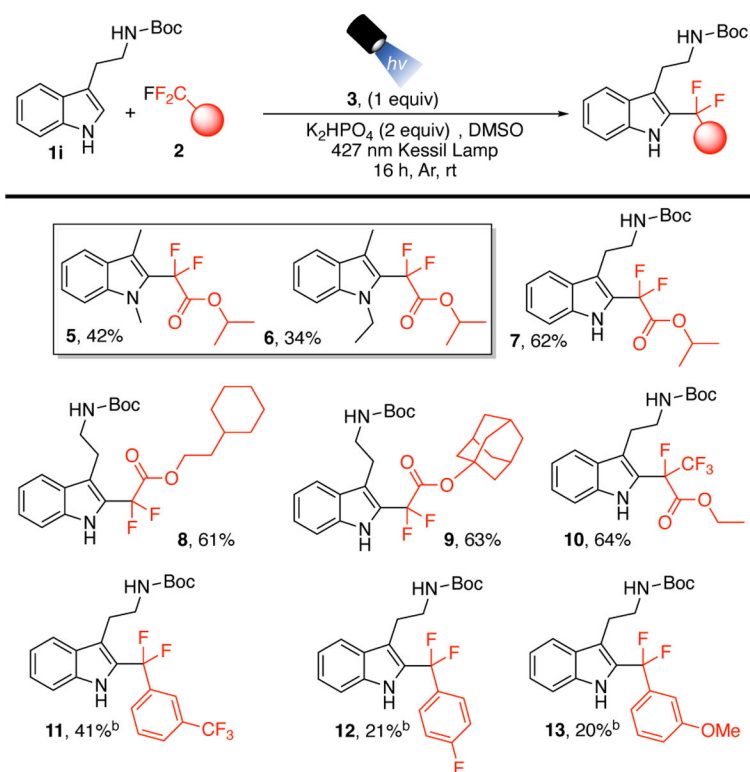
**C) This Work**

**Scheme 1.**  
Difluoroalkylation of Indoles



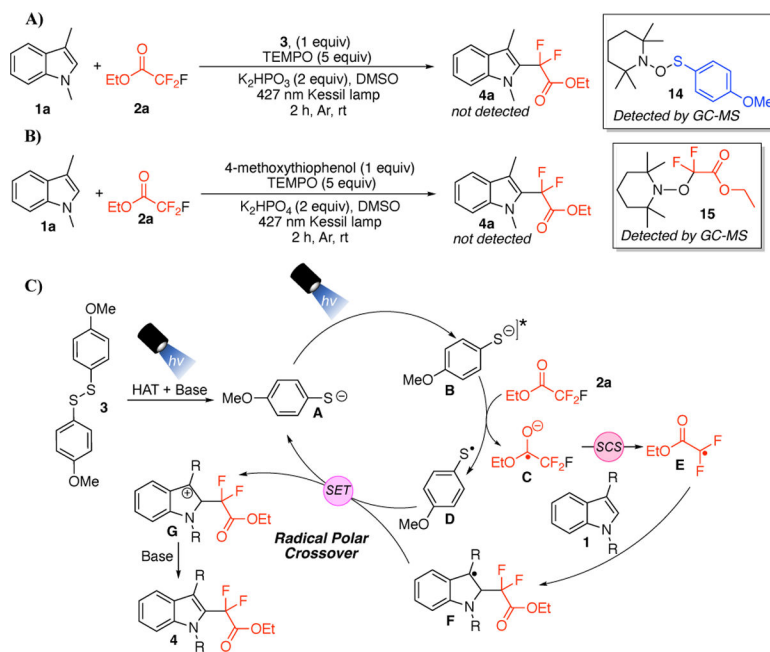
**Scheme 2. Substrate Scope of Indoles<sup>a</sup>**

<sup>a</sup>Reaction conditions: 1 (0.5 mmol), 2a (5 mmol), 3 (0.5 mmol),  $K_2HPO_4$  (1.0 mmol) under Ar in DMSO (5 mL) and 427 nm Kessil lamp irradiation. Isolated yields.



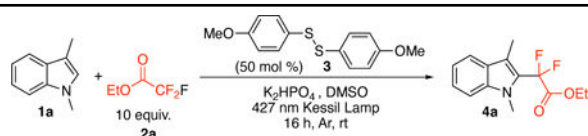
**Scheme 3. Substrate Scope of Fluorinated Precursors<sup>a</sup>**

<sup>a</sup>Reaction conditions: 1 (0.5 mmol), 2a (5 mmol), 3 (0.5 mmol), K<sub>2</sub>HPO<sub>4</sub> (1.0 mmol) under Ar in DMSO (5 mL) and 427 nm Kessil lamp irradiation. Isolated yields. <sup>b</sup>Sodium formate (0.75 mmol) was added.

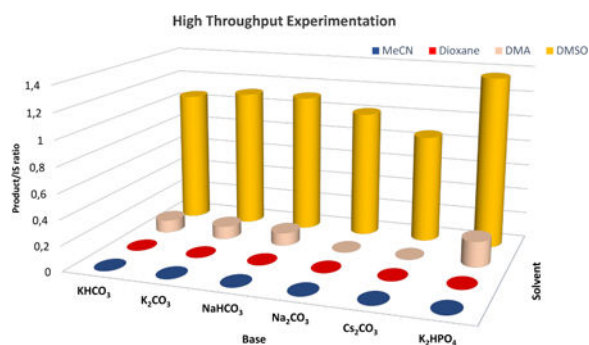
**Scheme 4.**

A and B) Radical Trapping Experiments with TEMPO, and C) Proposed Mechanism for *gem*-difluoroalkylation of indoles.

Table 1.

Optimization of the Reaction Conditions<sup>a</sup>

entry	deviation	<sup>19</sup> F NMR yield <sup>b</sup> (%)
1	none	63
2	no Kessil	n.d.
3	no base	n.d.
4	no <b>3</b>	n.d.
5	open to air	40
6	4-methoxybenzenethiol (100 mol %)	61
7	Ir(ppy) <sub>3</sub> (5 mol %)	n.d.
8	<b>3</b> (100 mol %)	72 (63) <sup>c</sup>



<sup>a</sup>Reaction conditions: indole **1a** (0.1 mmol), **2a** (1.0 mmol), K<sub>2</sub>HPO<sub>4</sub> (0.2 mmol), **3** (0.05 mmol) in DMSO (1 mL), stirred 16 h under 427 nm Kessil light irradiation at rt using a fan.

<sup>b</sup>Yields were determined by <sup>19</sup>F NMR analysis using 2-bromo-5-(trifluoromethyl)pyridine as an internal standard.

<sup>c</sup>Isolated yield.