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# Photochemical direct perfluoroalkylation of phenols

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ABSTRACT

A metal-free photochemical strategy for the direct aromatic perfluoroalkylation of phenols is reported. This operationally simple approach occurs at ambient temperature and under illumination by a fluorescent light bulb. The chemistry is driven by the ability of phenolate anions, transiently generated upon deprotonation of phenols, to directly reach an electronically excited state upon light absorption while successively triggering the formation of reactive radical species from perfluoroalkyl iodides. Preliminary mechanistic studies are reported.

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## 1. Introduction

Fluorine-containing functional groups can profoundly alter the intrinsic properties of organic compounds. For this reason, incorporating perfluoroalkyl groups into aromatic scaffold is a chemical strategy often exploited in medicinal chemistry to modulate the biological activity of drug candidates.[1] Since 1957, over 150 fluorinated drugs have come to market (Fig. 1),[1a] justifying the profuse efforts made by the synthetic community to develop effective methodologies for directly incorporating perfluoroalkyl groups into aromatic compounds. To achieve this synthetic goal, cross-coupling methodologies that use stoichiometric amount of metals have been developed.[2] This approach requires that the fluorinated fragments are installed in place of halides or boronic acid derivatives. More recently, catalytic variants based on transition metals (especially copper and palladium) have been successfully realized.[3]

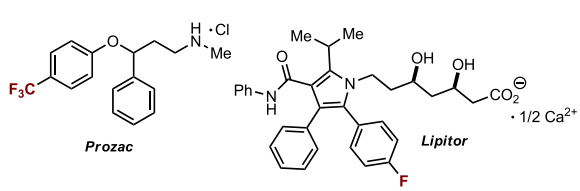


**Fig. 1.** Examples of major fluorinated drugs.

The direct functionalization of simple arenes, by avoiding the need for the pre-installation of a leaving group on the aromatics, provides a more straightforward approach. However, the direct introduction of perfluoroalkyl groups into a non-activated C–H bond of aromatic rings is a challenging transformation for which few strategies are available.[4] Typically, direct functionalization methodologies are based on radical reactivity. They capitalize upon the strongly electrophilic nature of the perfluoroalkyl radicals,[5] which are eager to react with arenes through the classical homolytic aromatic substitution (HAS) pathway.[6] Generating such radicals generally require harsh reaction conditions, including the use of high reaction temperature,[7a,b] stoichiometric amounts of radical initiators and/or metals,[7c–i] and potentially explosive oxidants.[7k–m] Recently, metal-based photoredox catalysis driven by visible light has been identified as a suitable approach to generate fluorinated radicals ($R_F^{\bullet}$) from perfluroalkyl iodidies ($R_FI$, **1**, $R_F$ indicates the perfluoroalkyl fragment) under mild reaction conditions (Scheme 1a).[8] In 2014, our research group developed an operationally simple strategy for the direct aromatic perfluoroalkylation of α-cyano arylacetates **I** that proceeded without the need for an external photosensitizer (Scheme 1b).[9] The metal-free process relied upon the formation of photon-absorbing electron donor-acceptor (EDA) complexes **II**,[10] generated in the ground-state upon association of $R_FI$ with the electron-rich enolate, formed by deprotonating α-cyano arylacetates **I**. Visible light irradiation of the colored EDA complex **II** induced a single electron transfer (SET), allowing access to perfluoralkyl radicals under mild conditions. This served as the

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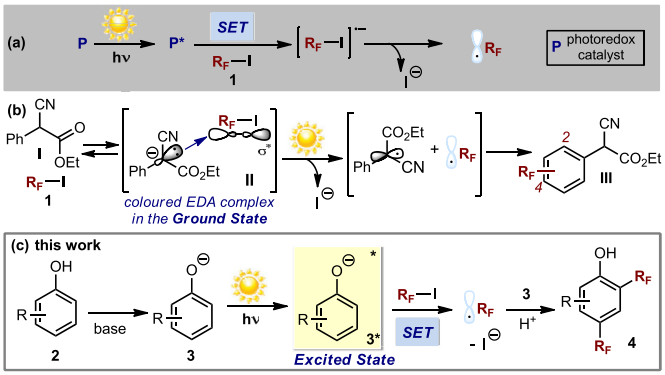
initiation step of a radical chain mechanism occurring trough a classical HAS pathway, and leading to product **III**.




**Scheme 1.** a & b: Previous photochemical strategies to generate perfluoroalkyl radicals ($R_F^{\bullet}$). c: the present metal-free strategy, which serves for the direct perfluoroalkylation of phenols **2** at ambient temperature.

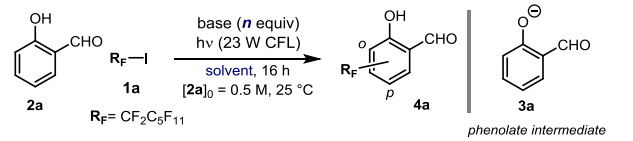
Herein, we describe a novel photochemical strategy for the direct perfluoroalkylation of phenols[11] with $R_FI$, which occurs under mild conditions, since it requires ambient temperature and illumination by a compact fluorescent light (CFL) bulb in order to proceed. The chemistry does not rely on the use of any external photoredox catalyst nor on the formation of ground-state EDA complexes to access radical reactivity patterns. Instead, the process is driven by the ability of phenolate anions **3**,[12] generated upon base-mediated deprotonation of phenols **2**, to directly reach an electronically excited state by light absorption while successively triggering the formation of the perfluoralkyl radicals from $R_FI$, **1** (Scheme 1c). Despite the propensity of excited phenolates to undergo a photo-induced electron ejection has been established in the 40's of the last century,[12,13] this mechanism has not found application in synthetic organic chemistry so far.

It is worth noting that, recently, Matsugi and co-workers developed a method for the direct perfluoroalkylation of phenols, which relied upon the use of stoichiometric amounts of a radical initiator while requiring a large excess of base (8 equiv of cesium carbonate) to deprotonate the phenols.[14] Our methodology, although is characterized by a similar reactivity, allows for a wider substrate scope. In addition, the systems are mechanistically distinguished by the way in which the perfluoroalkyl radical generation is achieved.

## 2. Results and discussion

Our initial explorations focused on the reaction between salicylaldehyde **2a** and perfluorohexyl iodide **1a** (Table 1). The experiments were conducted in $CH_3CN$ under irradiation by a 23 W CFL lamp. Performing the reaction in the presence of a base such as 1,1,3,3-tetramethyl guanidine (TMG, 1 equiv), so as to favor the formation of the corresponding phenolate **3a**, provided both the *ortho* and *para* functionalized products **4a** in a roughly 5:1 ratio, along with the *ortho-para* bifunctionalized adduct *o,p*-**4a** (entry 1, total yield of 31%). Increasing the amount of TMG (2.5 equiv, entry 2) resulted in a higher reactivity (77% total yield), while the adduct *o,p*-**4a** was formed as the major product. A control experiment revealed how the careful exclusion of light completely suppressed the process, thus establishing the photochemical nature of the reaction (entry 3). In addition, we confirmed that the photochemical activity of the phenolate **3a**, formed in situ upon deprotonation of **2a**, was essential for reactivity, since in the absence of a base the starting substrates were completely recovered (entry 4). It is worth

**Table 1**
Reaction optimization[a]




| Entry | Base (n) | Solvent | % Yield[b] | *o*-**4** | *p*-**4** | *o,p*-**4**%[c] |
|---|---|---|---|---|---|---|
| 1 | TMG (1) | $CH_3CN$ | 31 | 52% | 9% | 39% |
| 2 | TMG (2.5) | CH3CN | 77 | 32% | 8% | 60% |
| 3[d] | TMG (2.5) | $CH_3CN$ | 0 | — | — | — |
| 4 | None | $CH_3CN$ | 0 | — | — | — |
| 5[e] | TMG (2.5) | $CH_3CN$ | 68 | 35% | 6% | 59% |
| 6 | KOH (2.5) | $CH_3CN$ | 0 | — | — | — |
| 7 | $NaHCO_3$ (2.5) | $CH_3CN$ | 0 | — | — | — |
| 8 | $K_2CO_3$(2.5) | $CH_3CN$ | 32 | 28% | 0% | 72% |
| 9 | $Cs_2CO_3$ (2.5) | $CH_3CN$ | 21 | 5% | 0% | 95% |
| 10 | TMG (2.5) | DCM | 62 | 39% | 13% | 48% |
| 11 | TMG (2.5) | Toluene | 36 | 32% | 8% | 60% |
| 12 | TMG (2.5) | DMF | 65 | 28% | 6% | 68% |
| 13 | TMG (2.5) | MeOH | 26 | 54% | 30% | 16% |
| 14 | TMG (2.5) | EtOAc | 70 | 38% | 11% | 51% |

[a] TMG: 1,1,3,3-tetramethylguanidine. Reactions performed on a 0.1 mmol scale using 3 equiv of **1a**, $[\mathbf{2a}]_0$=0.5 M, and a 23 W CFL bulb to illuminate the reaction vessel.
[b] Total yield determined by $^1H$ and $^{19}F$ NMR analysis using 1-fluoro-2-nitrobenzene as the internal standard.
[c] Percent distribution of the *para* (*p*-**4**), *ortho* (*o*-**4**) and *ortho*, *para* (*o,p*-**4**) functionalized products.
[d] Reactions performed *i*) in the dark, or *ii*) in air, or *iii*) in the presence of 2 equiv of TEMPO, were all completely inhibited.
[e] Reaction performed using a 300 W Xenon lamp, equipped with a cut-off filter at 385 nm.

noting that, upon addition of TMG, the solution of salicylaldehyde **2a**, which was almost colorless, immediately turned to a bright yellow color, indicating the ability of the phenolate **3a** of absorbing in the visible spectral region (blue line in Fig. 2). Addition of the iodide **1a** did not bring about any appreciable change of the

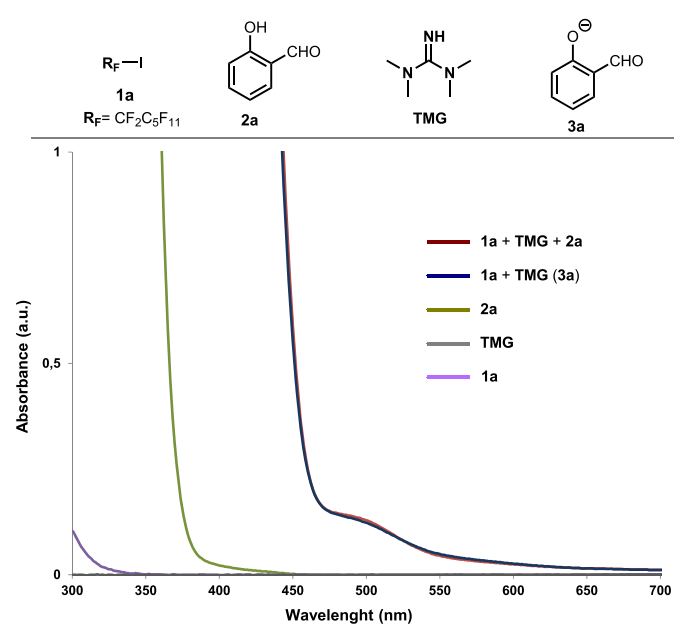



**Fig. 2.** Optical absorption spectra recorded in $CH_3CN$ in quartz cuvettes (1 cm path) using a Shimadzu 2401 PC UV-visible spectrophotometer. [**2a**]=0.0025 M, [**1a**]=0.0075 M; [TMG]=0.00625 M. While the substrates **1a**, **2a**, and TMG are almost colorless, the formation of the phenolate anion **3a**, generated upon TMG addition, determines a strong bathochromic shift (blue line). Its combination with perfluorohexyl iodide **1a** does not lead to any appreciable change of the absorption spectrum (red line perfectly overlays the blue line).

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