# <u>LETTERS</u>

## Halogen-Bond-Promoted Photoactivation of Perfluoroalkyl lodides: A Photochemical Protocol for Perfluoroalkylation Reactions

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**Supporting Information** 

**ABSTRACT:** A new protocol for photochemical perfluoroalkylation reactions using perfluoroalkyl iodide, amine additive, and THF solvent is reported. This protocol does not require a photoredox catalyst and proceeds at ambient temperature with irradiation from a compact fluorescent lamp, low-intensity UV lamp, or sunlight. This protocol can be applied to the synthesis of perfluoroalkyl-substituted phenanthridines as well as effect the iodo-perfluoroalkylation of alkenes/alkynes and the C–H perfluoroalkylation of electron-



rich arenes and heteroarenes. This C-H perfluoroalkylation reaction offers a unique method for site-selective labeling of oligopeptides at the tryptophan residue.

espite recent advances, more efficient, practical, economical, and environmentally friendly perfluoroalkylation methods remain in demand for applications in pharmaceutical, agrochemical, and materials science.<sup>1,2</sup> Reactions of electrophilic perfluoroalkyl radicals generated from readily accessible perfluoroalkyl halide (Rf-X) precursors have offered a versatile means to incorporate various perfluoroalkyl groups into different unsaturated substrates.<sup>3-11</sup> For environmental and practical reasons, radical perfluoroalkylation methods employing photochemical radical initiation are preferable to those using reactive organic reagents such as azos, peroxides, and various metal catalysts. The addition reactions of perfluoroalkyl halides with alkenes and alkynes under high-intensity UV irradiation have been well studied.<sup>4</sup> Recently, more operationally convenient perfluoroalkylation methods have become available based on photoredox catalysis manifolds.<sup>5,7,9a</sup> Perfluoroalkylation reactions that do not require photocatalyst represent a further stage of development. Activation of perfluoroalkyl halides through photoactive electron donoracceptor (EDA) complexes have been employed for the visiblelight-mediated perfluoroalkylation of  $\beta$ -ketoesters and arenes.<sup>10</sup> Recently, Yu reported a halogen-bond-promoted activation of Rf-I's under visible-light irradiation (VL from LED lamp) for synthesis of quinoxalines from o-diisocyanoarenes using a Bn<sub>2</sub>NH promoter in CH<sub>3</sub>CN solvent.<sup>11</sup> Herein, we report a new photochemical protocol for perfluoroalkylation that requires perfluoroalkyl iodide, N,N,N',N'-tetraethylethylenediamine (TEEDA) additive, THF solvent, and a light source, which may be a compact fluorescent lamp, a low-intensity UV lamp, or sunlight.

Our interest in exploring perfluoroalkylation reactions using perfluoroalkyl halides was prompted by a report from Studer

and co-workers describing the synthesis of 6-perfluoroalkylated phenanthridines from 2-isocyanobiphenyls and perfluoroalkyl iodides via a radical cascade process (Scheme 1).<sup>12a</sup> Studer proposed that perfluoroalkyl radicals generated from the corresponding halides first add to the isocyanide, forming an imidoyl radical.<sup>12–14</sup> This imidoyl radical then undergoes an intramolecular addition reaction with the nearby phenyl ring at the ortho position, forming a cyclohexadienyl radical. This cyclohexadienyl radical is deprotonated, and reaction with perfluoroalkyl halide via single-electron transfer propagates the radical chain and provides phenanthridine product. Studer's optimized conditions for the reaction of 1 and 2 require 1.5 equiv of Cs<sub>2</sub>CO<sub>3</sub> in dioxane at 110 °C.<sup>12a</sup> Other alkali metal bases such as K<sub>2</sub>CO<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub> were ineffective, and the role of Cs<sub>2</sub>CO<sub>3</sub> was unclear. Intrigued, we began to investigate of the role of base in this reaction system. We found that the reaction proceeds to a small degree ( $\sim 10\%$  yield of 3) in the absence of Cs<sub>2</sub>CO<sub>3</sub> when conducted at 30 °C under irradiation from a household 25 W compact fluorescent lamp (CFL) in THF solvent (see the Supporting Information for details). No product 3 was formed when the reaction was performed in the dark. We were pleased to find that addition of 1.5 equiv of Et<sub>3</sub>N provided 3 in 64% yield in THF. Tetrahydropyran (THP) or 2-MeTHF solvent gave better results than dioxane, CHCl<sub>3</sub>, or CH<sub>3</sub>CN. Interestingly, reactions performed with irradiation from a Hg UV lamp of the same power intensity (25 W, 254 nm), and reactions performed with sunlight, gave comparable yields. Under UV irradiation but without Et<sub>3</sub>N, the reaction gave poor yield.

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Scheme 1. Evaluation of Amine Promoters for Synthesis of Phenanthridine 3 from 1 and  $C_4F_9$ -I under CFL Irradiation\*



<sup>\*</sup>CFL: 25 W. UV (254 nm): low-pressure Hg vapor lamp, 25 W. Sunlight: direct irradiation for 4 h. Yields are based on <sup>1</sup>H NMR analysis of the crude reaction mixture on a 0.2 mmol scale performed in a 4 mL borosilicate glass vial under Ar. <sup>*a*</sup>Isolated yield on 0.2 mmol scale. <sup>*b*</sup>Isolated yield on 1 mmol scale.

Next, we examined the performance of other organic bases as additives in the photochemical reaction of 1 and 2 under CFL irradiation (25 W) in THF solvent. A variety of amines promote the reaction. In general, tertiary amines are slightly more effective than secondary and primary amines (see EtNH<sub>2</sub>, Et<sub>2</sub>NH, and Et<sub>3</sub>N). Electron-rich amines give better results than electron-deficient amines (see *N*-ethylpiperidine vs *N*-ethylmorpholine). Pyridines are ineffective. *N*,*N*,*N'*,*N'*-Tetraethylethylenediamine (TEEDA) was the most effective additive, providing 3 in 91% isolated yield after 36 h of CFL irradition.<sup>15</sup> With TEEDA additive, the reaction also gave excellent yields under irradiation from a low-intensity Hg UV lamp (254 nm, 25 W) or sunlight.

The scope of the phenanthridine synthesis was explored under the optimized conditions with TEEDA additive and CFL irradiation (Scheme 2). As seen in 4–6, 2-isocyanobiphenyls bearing various substitution patterns can react with  $C_4F_9-I$  2 in good to excellent yield and regioselectivity. An isocyanide substrate containing a pyridine ring was tolerated (see 7). As shown in 10–15, linear and branched perfluoroalkyl iodides of various lengths provided excellent results.  $\alpha$ -Bromoacetates bearing one or two  $\alpha$ -substituents also provide phenanthridine product in good yield under slightly modified conditions (16– 18). Scheme 2. Substrate Scope of Phenanthridine Synthesis\*

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<sup>\*</sup>Isolated yield on 0.2 mmol scale under the standard CFL irradiation conditions. <sup>*a*</sup>Excess of CF<sub>3</sub>I was used (sparging THF solution with CF<sub>3</sub>I gas; see the Supporting Information). <sup>*b*</sup>5 equiv of bromide and 3 equiv of TEEDA were used.

As shown in Scheme 3A, perfluoroalkyl halides can undergo 1,2-addition reactions with terminal alkenes to give iodoperfluoroalkylated products with excellent regioselectivity under our standard conditions with CFL irradiation.<sup>4,5</sup> Functional groups such as PhthN, benzoate ester, phenyl ether, and ketone are tolerated. Notably, subjecting quinine, which contains hydroxyl and pyridine moieties, to the reaction provided 24 in good yield and selectivity. As seen in 19, the reaction performed well with irradiation from either a lowintensity UV lamp or sunlight. As shown in Scheme 3B, perfluoroalkyl halides react with terminal alkynes to give iodoperfluoroalkylation products in good yield and excellent regioselectivity. Perfluoroalkyl radicals generated via the photochemical activation of perfluoroalkyl halides likely add to the alkene or alkyne substrate to form a secondary alkyl or vinyl radical intermediate. The resulting radical could then abstract an I atom from a perfluoroalkyl iodide molecule to give difunctionalized product and propagate the radical chain.<sup>1</sup>

The C–H perfluoroalkylation of electron-rich arenes and heteroarenes with perfluoroalkyl iodides has been achieved using several different radical initiation systems.<sup>6,7</sup> As shown in Scheme 4, reactions of electron-rich arenes such as aniline and heteroarenes such as pyrrole using our standard method provided perfluoroalkylated products in moderate yield (27–29). 3-Methylindole was subjected to reaction with perfluoroalkyl iodides of varied chain lengths, providing C<sub>2</sub>-perfluoroalkylated products 30–32 in good to excellent yield. The same reaction using a 25 W Hg UV lamp or sunlight gave similar results (see 32). As seen in 33 and Trp 34, unprotected

Scheme 3. Addition of Perfluoroalkyl Iodide to Alkenes and Alkynes\*

A) Addition to alkenes<sup>a</sup>



<sup>\*</sup>Isolated yield on 0.2 mmol scale under the standard CFL irradiation conditions. <sup>*a*</sup>The other regioisomers were not observed in <sup>19</sup>F NMR analysis of the crude reaction mixture. <sup>*b*</sup>UV(254 nm): low-pressure Hg vapor lamp, 25 W.

 $NH_2$  and  $CO_2H$  groups were tolerated. Furthermore, we were delighted to find that tryptophan (Trp) containing short peptides can be perfluoroalkylated at the  $C_2$  position of the Trp residue in good yield and excellent selectivity under the standard reaction conditions. This reaction offers a valuable orthogonal strategy for peptide labeling based on underexplored Trp chemistry.

Perfluoroalkyl iodides can form halogen bond (XB) complexes/adducts with Lewis bases (LB) such as amines.<sup>16-19</sup> In these adducts, the amine, designated as the acceptor in the XB complex, uses its lone-pair electrons to interact with the  $\sigma^*$ antibonding orbital of the C-I bond of perfluoroalkyl iodides (designated as XB donor). Using an <sup>19</sup>F NMR titration method and a Job's plot analysis, we observed formation of the 1:1 complex between NEt<sub>3</sub> and  $C_{10}F_{21}$ -I with a binding constant  $K_{\rm a}$  of 0.72 M<sup>-1</sup> in CHCl<sub>3</sub> (see the Supporting Information for details).<sup>11,20</sup> TEEDA and C<sub>10</sub>F<sub>21</sub>–I form a 1:1 complex with a slightly higher  $K_a$  (1.1 M<sup>-1</sup>). Interestingly, THF and  $C_{10}F_{21}$ -I also form a 1:1 complex with a  $K_a$  of 0.28 M<sup>-1</sup> in CHCl<sub>3</sub>. A smaller  $K_a$  of 0.17 M<sup>-1</sup> was observed for dioxane and  $C_{10}F_{21}-I_{1}$ likely due to its additional electron-withdrawing O atom. Choice of light source clearly has an impact on the yield of reaction of 1 and 2 (see the Supporting Information for details). Irradiation by red, yellow, or green LEDs (25W) gave little product 3. However, a blue LED (25W) gave 21% yield, while a purple LED (25W) gave 57% yield. Irradiation with a UV lamp (254 or 365 nm), a CFL of the same power intensity,

Scheme 4. C-H Perfluoroalkylation of Electron-Rich Arene and Heteroarenes\*



<sup>\*</sup>Isolated yield on 0.2 mmol scale under the standard CFL irradiation conditions. <sup>*a*</sup>RSM: recovered starting material. <sup>*b*</sup>UV(254 nm): lowpressure Hg vapor UV lamp, 25 W. <sup>*c*</sup>Isolated as a Bn ester after treatment with BnBr. <sup>*d*</sup>Isolated as a N $\alpha$ -Boc-protected product after treatment with Boc<sub>2</sub>O. <sup>*e*</sup>O.1 mmol scale, 10 equiv of Rf–I, and 6 equiv of TEEDA were used.

or sunlight gave excellent yields. It is known that CFLs emit a small amount of UV light. Taken together, these results suggest that low-intensity irradiation in the UV region is responsible for the observed halogen bonding promoted photochemical reactivity of perfluoroalkyl iodides.

In summary, we have developed a simple, mild, and efficient protocol for photochemical perfluoroalkylation reactions using inexpensive perfluoroalkyl iodides, amine additive, and THF solvent. This protocol does not require photoredox catalyst and takes place under the irradiation of a compact fluorescent lamp, low-intensity UV lamp, or sunlight at ambient temperature. This protocol can be applied to the synthesis of perfluoroalkylsubstituted phenanthridines, to addition reactions of alkenes/ alkynes, and the C–H perfluoroalkylation of electron-rich arenes and heteroarenes. This protocol can be used for C–H perfluoroalkylation of Trp, offering a unique method for siteselective labeling of oligopeptides. Mechanistic studies suggest that halogen-bond interactions between perfluoroalkyl iodides and amine and THF solvent promote the photochemical reactivity of perfluoroalkyl iodides under low-intensity UV irradiation.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b00375.

Additional experimental procedures and spectroscopic data for all new compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

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