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## From Styrenes to Fluorinated Benzyl Bromides: A Photoinduced Difunctionalization via Atom Transfer Radical Addition

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### Abstract

An operationally simple and practical method is disclosed to achieve the difunctionalization of styrenes, generating fluorinated benzyl bromides via a photoinduced atom transfer radical addition (ATRA) process. The developed method is mild, atom-economical, cost-effective, employs very low photocatalyst loading (1000 ppm), and is highly compatible with a broad range of functional groups on styrene. The versatility of the fluorinated benzyl bromides is demonstrated through their derivatization to a variety of valuable compounds.

### Graphical Abstract

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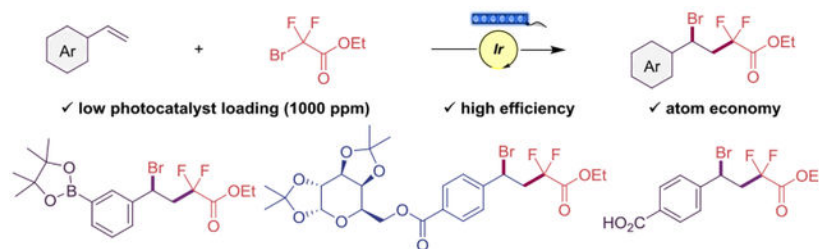
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#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Preparation of starting materials, general procedures, characterization data for products [nuclear magnetic resonance (NMR), infrared (IR), and mass spectrometry (MS)], mechanistic studies, and NMR spectra (PDF).

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The introduction of two different functional groups across a double bond, known as alkene difunctionalization, is an attractive method from a synthetic point of view, especially if such difunctionalization occurs atom economically in a single step. Thus, 1,2-difunctionalization of alkenes has been broadly explored employing transition metal-catalyzed,<sup>1</sup> photoredox-,<sup>2</sup> or hypervalent iodine reagents.<sup>3</sup> The introduction of fluorinated moieties into a bioactive molecule can influence lipophilicity and binding selectivity, and enhance metabolic stability as well.<sup>4</sup> The trifluoromethyl group is undoubtedly the most popular fluorinated functional group in medicinal chemistry,<sup>5</sup> and thus its introduction to organic molecules has been widely explored.<sup>6</sup> However, the difluoromethylene group is emerging as an equally interesting motif.<sup>7</sup> Difunctionalizations assembling C–CF<sub>2</sub>R and C–X bonds in a single step have been developed by traditional methods,<sup>8</sup> which typically require the use of hazardous chemicals and/or harsh conditions. Regarding the 1,2-difunctionalization of alkenes generating C–Br and C–CF<sub>2</sub>R bonds, several photoinduced methods<sup>9</sup> have been reported in the last decade (Scheme 1). Stephenson's group<sup>9a</sup> reported an atom transfer radical addition (ATRA) of haloalkanes and  $\alpha$ -halocarbonyls to olefins employing an Ir photocatalyst and stoichiometric LiBr. Later, the same group complemented the strategy using a Ru photocatalyst and substoichiometric LiBr.<sup>9b</sup> Further investigations involved the difunctionalization of alkenes using *gem*-dibromides<sup>9d</sup> or photoredox/copper dual catalysis approaches.<sup>9e,g</sup> Despite these precedents, the preparation of difluoromethylene-containing benzyl bromides still lacks a more versatile and milder method, thus suggesting the need for further exploration of reaction space.

Benzyl bromides have served as classic electrophiles in synthetic organic chemistry.<sup>10</sup> Regarding their application in synthesis, their use is not only limited to the classic nucleophilic substitution reaction - they have also been used for the preparation of aldehydes, ketones<sup>11</sup> or triazoles.<sup>12</sup> In addition, they have served as building blocks in biologically active molecules,<sup>13</sup> as precursors in cross-coupling reactions promoted by transition metals,<sup>14</sup> and they have found application in photoinduced reactions.<sup>15</sup> Classically, the most popular preparations of benzyl bromides rely on the use of *N*-bromosuccinimide and a radical activator.<sup>16</sup> The preparation from the corresponding benzylic alcohol using HBr or PBr<sub>3</sub> is also popular. Other benzylic monobromination methods include the use of diatomic bromine,<sup>17</sup> bromotrichloromethane,<sup>18</sup> or NaBrO<sub>3</sub>,<sup>19</sup> among others.<sup>20</sup> However, these methods generally have limited functional group tolerance, the formed byproducts are challenging to remove from the desired product, and, typically, only moderate to good yields are obtained.

Given the interest in having fluorinated moieties in functionalized benzyl bromides, herein we report the development of a mild, rapid, and efficient visible light-mediated photocatalytic ATRA to styrenes using  $\alpha$ -bromo- $\alpha$ -fluorocarbonyls (Scheme 1). As is demonstrated, the prepared fluorinated benzyl bromides serve as valuable intermediates in further transformations through their functional groups.

To initiate the studies, we selected 4-acetoxystyrene (**1a**) as a model substrate for the transformation, along with ethyl bromodifluoroacetate **2a**. From the outset, full conversion of the styrene **1a** to the desired fluorinated benzyl bromide (**3a**) was observed using Ir(ppy)<sub>3</sub> as a photocatalyst in acetonitrile solvent after 15 h of blue ( $\lambda_{\text{max}} = 455 \text{ nm}$ ) LED strip irradiation (Table 1, entry 1). With these conditions in hand, our next aim was to explore the minimum catalyst loading necessary to achieve full conversion of the starting materials. Thus, the photocatalyst loading was further decreased to 0.1 mol % (1000 ppm) without decreasing yield efficacy. When the reaction was scaled to 0.5 mmol, 24 h was needed to consume all the starting material **1a** (Table 1, entry 5). Notably, and to the best of our knowledge, the use of only 1000 ppm of photocatalyst constitutes one of the lowest photocatalyst loadings used in a photoredox transformation.<sup>21</sup> We further reduced the photocatalyst loading to 500 ppm (Table 1, entry 6) using the same standard conditions, and observed a 64% yield. Nevertheless, this yield was improved to 95% when the reaction was maintained for 36 h (Table 1, entry 7).

The photochemical nature of this transformation was confirmed when control experiments in the absence of light irradiation or the photocatalyst showed no conversion to product **3a** (Table 1, entries 8 and 9). The atom-economy of this transformation and the use of volatile MeCN as the solvent makes straightforward isolation of **3a** remarkably easy by simple filtration through a short pad of silica.

With the reaction conditions established, we first explored the scope of this transformation using different styrenes (Scheme 2). In general, electron-rich, electron-neutral, and electron-poor styrenes were successfully difunctionalized. 4-Acetoxy- and 4-*tert*-butyl styrenes delivered the desired compounds (**3a** and **3b**) in 91% and 74% yield, respectively. The presence of strong electron-withdrawing groups in the *para* position served as excellent substrates, providing trifluoromethyl- (**3d**), nitrile- (**3e**), ester- (**3f**), and pinacol boronate- (**3j**) containing fluorinated benzyl bromides in excellent yields. Of note, unprotected *para*-vinylbenzoic acid was also used to provide the desired **3g** in 96% yield. A complete consumption of styrenes containing a carboxyl group and a boronic ester as substituents on the phenyl ring were achieved using 4 equiv of the radical precursor (**3g**, **3j-k**). Additionally, both *para* chloro- (**3h**), and *para*-bromo- (**3i**) substituted derivatives were prepared in high yields.

Furthermore, pinacol boronate (**3k**) and CF<sub>3</sub> (**3l**) groups in the *meta* position delivered the fluorinated benzyl bromide in 78% and 95% yields, respectively. Moreover, the reactivity of this transformation was not affected by steric effects, as *ortho* halosubstituted styrenes also worked well with the optimized conditions (**3m** and **3n**). Interestingly, the polyfluorinated benzyl bromide **3o** was obtained in quantitative yield.

Further, the amenability of this difunctionalization reaction to late-stage complex molecule synthesis was examined using styrene-derived pharmaceuticals and biomolecules. Thus, bromine- and difluoroethyl acetate substituents were successfully installed in the styrene skeleton attached to the monosaccharide *D*-galactopyranose (**3p**), lipid-lowering agents gemfibrozil (**3q**) and clofibrate (**3r**), anti-inflammatories fenbufen (**3s**) and flurbiprofen (**3t**), and monoterpene alcohol *L*-menthol (**3u**). In these cases, the yields were good to excellent (66–92%).

Difunctionalization of indene provided **3v** in high yield and diastereomeric ratio. Of note, heterocyclic-based styrenes were also accommodated under standard conditions (**3w-z**), although in lower yield because of competing oligomerization. Finally, 4-phenyl-1-butene was successfully difunctionalized as a non-activated alkene substrate in 70% yield.

Subsequently, we tested the reaction conditions using **2b** and **2c** as bromofluorinated radical precursors. When using the standard conditions with these two substrates, the conversion of the styrene **3a** to the desired compounds (**4a** and **5a**) were 60% and 50%, respectively. We observed full conversion of the styrene when we increased the amount of iridium photocatalyst to 0.5 mol %. Bromo *N,N*-diethyl-difluoroacetamide (**2b**) was successfully installed on *p*-acetoxy styrene (**4a**) and styrene-containing *N*-Boc protected proline amino acid (**4b**) in high yields (86 and 85%). Finally, monofluoro derivative **2c** also served as a competent radical precursor for difunctionalization of styrenes. Thus, electron-rich (**5a**) and electron-poor styrenes (**5c** and **5d**) were amenable substrates, as well as more complex styrenes (**5b** and **5e**). Excellent yields were obtained in all tested cases. These brominated radical precursors (**2a-c**) have showcased they can serve as difunctional reagents<sup>22</sup> also on styrenes in a sustainable manner. Of note, even though the method is rooted in the use of a transition metal-based photocatalyst, all the scope described herein (**3a-3aa**, **4a-b**, **5a-e**) has been performed utilizing less than 20 mg of Ir in total (which implies around \$30 cost). This practical and selective fluorination protocol, based on the use of readily available starting materials and a cost-efficient photocatalyst, as well as the showcased functional group tolerance, makes it an attractive and general method for the assembly of fluoride-functionalized molecules.<sup>4d</sup>

To elucidate the reaction mechanism of this photoinduced reaction, photochemical quantum yield studies ( $\Phi$ ) were carried out (see Supporting Information). The experimental results reveal a  $\Phi$  value of 1.8, thus indicating a feasible radical chain mechanism.<sup>23</sup> Given previous reports<sup>9</sup> and the mechanistic findings described herein, a plausible mechanism for this transformation is shown in Scheme 3A. The photoexcited state of the photocatalyst reduces the  $\alpha$ -bromo- $\alpha$ -fluorocarbonyl (**2**) to the  $\alpha$ -fluorocarbonyl radical (**I**), which enters a radical chain cycle. At this stage, the styrene (**1**) intercepts the  $\alpha$ -fluorocarbonyl radical (**I**), generating the benzylic radical (**II**). This radical intermediate undergoes halogen-atom transfer (XAT)<sup>24</sup> with **1**, forming the final product (**3**) and regenerating the  $\alpha$ -fluorocarbonyl radical (**I**). Although a mechanistic scenario in which the carbocation (**III**) can be generated via oxidation by the Ir<sup>IV</sup> species and subsequently trapped by a bromide anion (radical/polar mechanism), it is an unlikely process with the described mechanistic findings depicted above.

Finally, to demonstrate the inherent synthetic value of the developed difunctionalization process, several derivatization experiments were undertaken (Scheme 3B). The crude benzyl bromide **3a** formed via the standard condition was simply filtered through a short pad of silica and then directly employed with derivatization conditions to generate products such as an azide **6**, useful for elaboration in click reactions. Further, treatment of **3a** under basic conditions furnished the elimination product **7**, and the reaction of **3a** in the presence of AgOAc provided the formation of a new C–O bond (**8**). Lastly, when using -substituted styrenes **1ac** or **1ad** under the standard conditions, we observed the direct formation of the kinetically stable alkenes **9** and **10** in moderate yields.

In summary, a highly practical photoredox method for the formation of synthetically important fluorinated benzyl bromide products is reported. The process is not only mild and atom-economical, but also cost-effective as it requires only minimal loading of the photocatalyst. The method is vastly robust to accommodate a wide range of functional groups on styrene as well as medicinally relevant fluorinated groups. More importantly, the synthetic utility of the generated benzyl bromide was showcased by subjecting it to several derivatization conditions. Based on the mechanistic investigation and in accordance with experimentally determined quantum yield, we proposed a halogen-atom transfer (XAT) chain-mechanism for the developed process.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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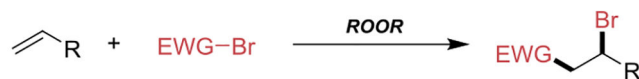
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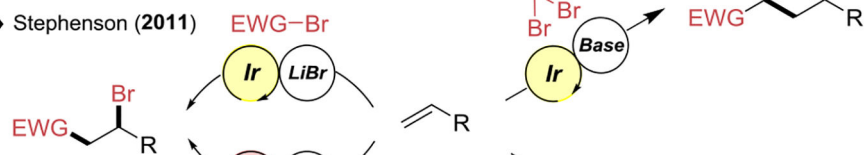
◆ Seminal work: Kharasch (1948)



◆ Photocatalysis

◆ Xie and Zhu (2017)

◆ Stephenson (2011)

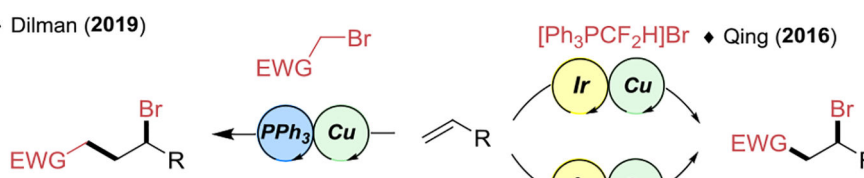


◆ Stephenson (2012)

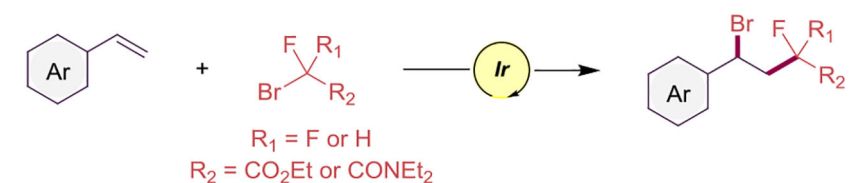


◆ Photoredox/Copper Dual Catalysis

◆ Dilman (2019)

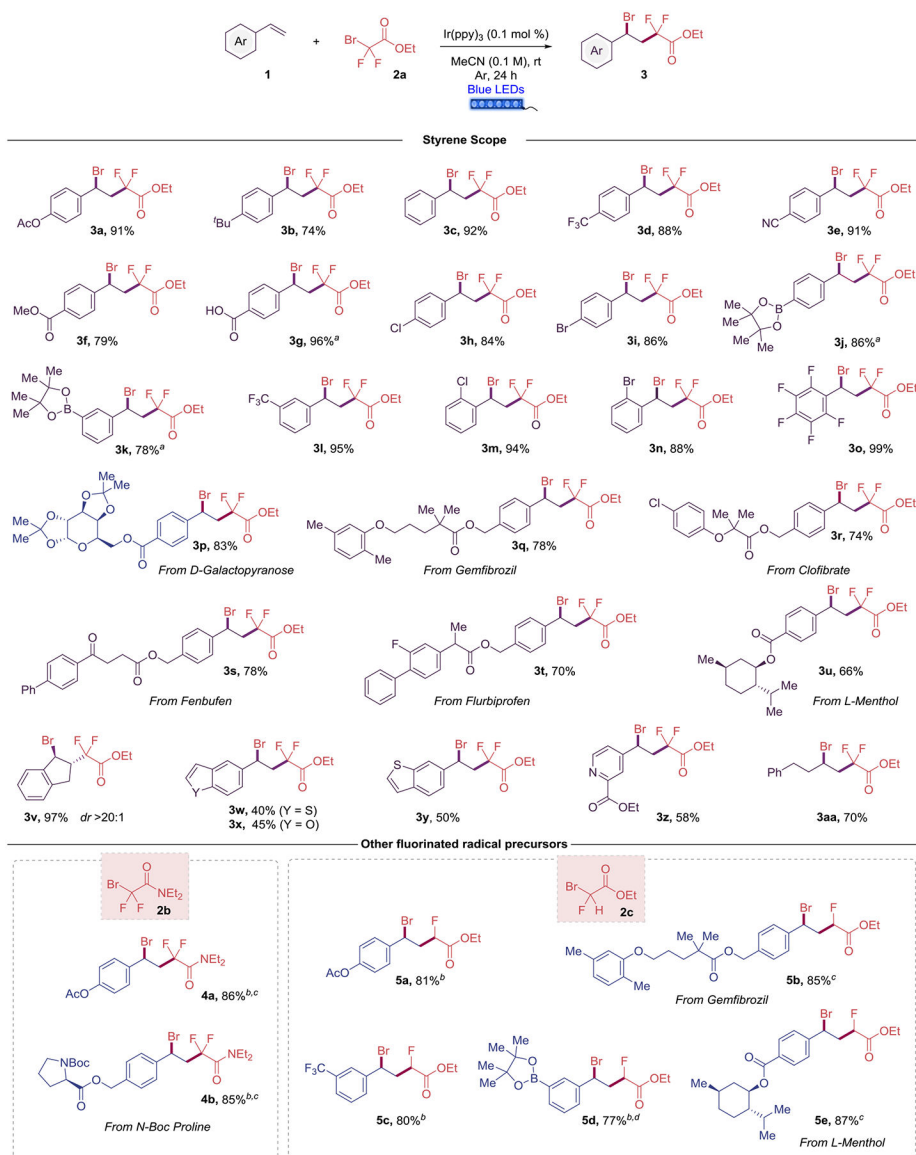


◆ This work

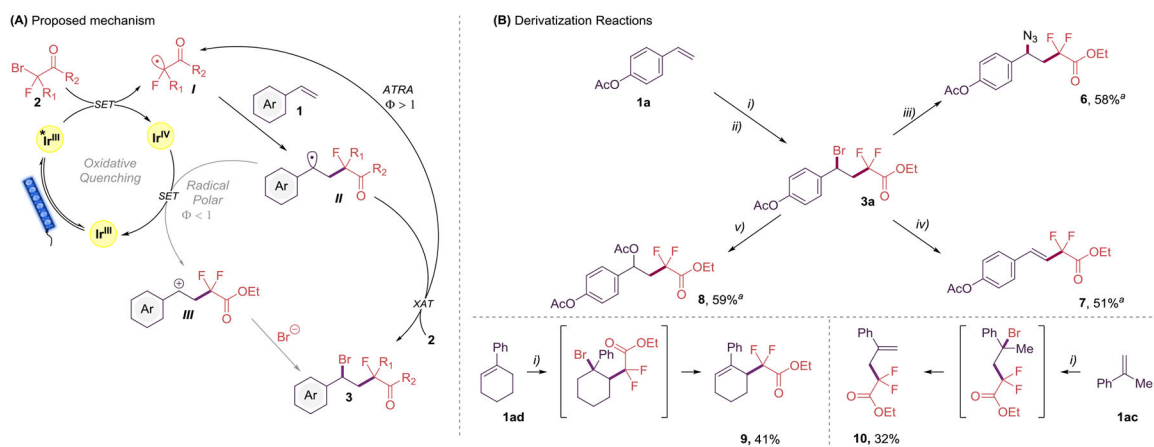


- low photocatalyst loading (1000 ppm)
- commodity reagents
- mild conditions
- diverse scope
- high efficiency

**Scheme 1.**  
Bromine Transfer Radical Addition Strategies

**Scheme 2.****Evaluation of Substrate Scope**

General reaction conditions: styrene **1** (0.5 mmol), **2a** (1.0 mmol), Ir(ppy)<sub>3</sub> (0.1 mol %) in MeCN (5.0 mL, 0.1 M), 24 h irradiation with blue LED strips ( $\lambda_{\max}$  = 456 nm). <sup>a</sup>4 equiv (2.0 mmol) of **2a** were used. <sup>b</sup>0.5 mol % Ir(ppy)<sub>3</sub> was used. <sup>c</sup>1.1 equiv (0.55 mmol) of **2b** was used. <sup>d</sup>4 equiv (2.0 mmol) of **2c** were used. See Supporting Information for further details.

**Scheme 3.**

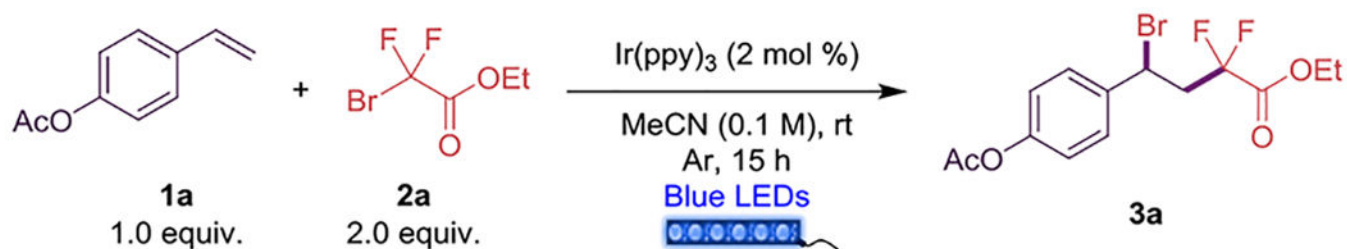
Proposed mechanism (A) and Derivatization Reactions (B)

(A) Proposed mechanism for the preparation of fluorinated benzyl bromides **3**. (B)

Derivatization reactions. Reaction conditions: *i)* **1** (0.5 mmol), **2a** (1.0 mmol), Ir(ppy)<sub>3</sub> (0.1 mol %) in MeCN (5.0 mL, 0.1 M), 24 h irradiation with blue LED strips ( $\lambda_{\text{max}} = 456 \text{ nm}$ ).

*ii)* Filtration through a short pad of silica. *iii)* NaN<sub>3</sub> (0.75 mmol) in DMSO (5 mL, 0.1 M), overnight at rt. *iv)* EtONa (2.5 mmol) in EtOH (5 mL, 0.1 M), overnight at rt. *v)* AgOAc (0.5 mmol) in MeCN, 4 h at 50 °C. <sup>a</sup>Isolated yield from **1a**.

Table 1.

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

Entry	Deviation from std conditions	Yield of <b>3a</b> (%) <sup>b</sup>
1	None	99
2	1 mol % Ir	99
3	0.5 mol % Ir	99
4	0.2 mol % Ir	99
5	<b>0.1 mol % Ir (1000 ppm)</b>	<b>99 (91)<sup>c</sup></b>
6	0.05 mol % Ir (500 ppm)	64
7	<b>0.05 mol % Ir (500 ppm)</b>	<b>95<sup>d</sup></b>
8	no light	0
9	no Ir	0
10	open-to-air	traces

<sup>a</sup>Reaction conditions: styrene **1a** (0.1 mmol), **2a** (0.2 mmol), Ir(ppy)<sub>3</sub> (2 mol %) in MeCN (1.0 mL, 0.1 M), 15 h irradiation with blue LED strips ( $\lambda_{\text{max}} = 456 \text{ nm}$ ).

<sup>b</sup>Yields were determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

<sup>c</sup>Isolated yield at 0.5 mmol scale and 24 h.

<sup>d</sup>Reaction for 36 h. std: standard.