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### Letter

# Bromotrifluoromethane: A Useful Reagent for Hydrotrifluoromethylation of Alkenes and Alkynes

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Yu-Yan Ren<sup>a</sup> Xing Zheng <sup>\*a</sup> Xingang Zhang <sup>\*b</sup> <sup>©</sup>

<sup>a</sup> Institute of Pharmacy and Pharmacology, Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, University of South China, 28 Western Changsheng Road, Hengyang, Hunan 421001, P. R. of China

<sup>b</sup> Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, P. R. of China

Zhengxing5018@yahoo.com xgzhang@mail.sioc.ac.cn

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**Abstract** Bromotrifluoromethane (CF<sub>3</sub>Br) is a simple, inexpensive and abundant industrial material employed as a trifluoromethylating reagent. However, only limited strategies using CF<sub>3</sub>Br as a fluorine source are reported. Herein, we describe a visible-light-induced hydrotrifluoromethylation of alkenes and alkynes with CF<sub>3</sub>Br. The reaction proceeds under mild conditions with good functional group tolerance, providing a new route for the application of BrCF<sub>3</sub> in organic synthesis.

**Key words** bromotrifluoromethane, hydrotrifluoromethylation, alkenes, alkynes, visible-light-induced

The increasing importance of trifluoromethylated compounds in pharmaceuticals, agrochemicals and advanced functional materials has triggered significant endeavors in developing general and efficient methods for incorporation of a trifluoromethyl group  $(CF_3)$  into organic molecules. Over the past decades, impressive achievements have been made in this area.<sup>1</sup> However, developing efficient and straightforward trifluoromethylation methods with an inexpensive and abundant trifluoromethylating reagent remains highly desirable. Bromotrifluoromethane (CF<sub>3</sub>Br) is a simple, abundant and inexpensive industrial material previously used in fire extinguishers,<sup>2</sup> and represents a straightforward fluorine source for trifluoromethylations.<sup>3</sup> However, only limited strategies for the transformation of CF<sub>3</sub>Br into trifluoromethylated compounds have been reported thus far. One common strategy for the transformation of CF<sub>3</sub>Br is via its conversion into a nucleophile with Zn,<sup>4</sup> Al<sup>5</sup> or P(NEt<sub>2</sub>)<sub>3</sub>,<sup>6</sup> followed by reaction with electrophiles, such as aldehydes, ketones, TMSCl, etc. The electrochemical trifluoromethylation of (hetero)aryl halides with CF<sub>3</sub>Br is another strategy to transform CF<sub>3</sub>Br,<sup>7</sup> providing an efficient approach to access trifluoromethylated (hetero)-



arenes. Alternatively, the direct introduction of CF<sub>3</sub> into (hetero)arenes with CF<sub>3</sub>Br based on a sulfinatodehalogenation reaction<sup>8</sup> or through transition-metal-induced singleelectron transfer (SET)<sup>9</sup> have emerged as more straightforward strategies. However, to the best of our knowledge, the reaction of CF<sub>3</sub>Br with alkenes and alkynes has not been reported.

Given the importance of trifluoromethylated alkanes and alkenes in life and materials science, we envisioned the feasibility of hydrotrifluoromethylation of alkenes and alkynes with CF<sub>3</sub>Br. Although such a transformation with a variety of trifluoromethylating reagents including TMSCF<sub>3</sub>, CF<sub>3</sub>SO<sub>2</sub>Na, Umemoto's reagent, Togni's reagent, etc., has been reported,<sup>10</sup> most of the reagents used are expensive and require additional step(s) to prepare from  $CF_3Br.^{3,6a,11}$ Therefore, from the point of view of step-economy and cost-efficiency, the use of CF<sub>3</sub>Br as a trifluoromethylating reagent to access trifluoromethylated alkanes and alkenes would be a promising alternative. To continue our interest in catalytic fluoroalkylations with inexpensive and readily available fluoroalkyl halides,<sup>12</sup> herein, we report the first example of visible-light-induced hydrotrifluoromethylation of alkenes and alkynes with CF<sub>3</sub>Br. The reaction proceeds under mild conditions with good functional group compatibility.

We began our initial studies with the reaction of but-3en-1-yl benzoate (**1a**) (0.3 mmol, 1.0 equiv) and CF<sub>3</sub>Br (**2**) (1.0 atm) under irradiation with a blue light-emitting diode (LED) (12 W,  $\lambda$  = 425 nm) in the presence of the photoredox catalyst *fac*-Ir(ppy)<sub>3</sub> (0.5 mol%) and a base in DMF at room temperature (Table 1). Initially, a 46% yield of hydrotrifluoromethylated product **3a** accompanied with bromotrifluoromethylated by-product **4a** (10%) and hydrodebrominated CF<sub>3</sub>H (**5**) (15%) were observed when 1 equivalent of K<sub>2</sub>CO<sub>3</sub> was used as the base (Table 1, entry 1). After a survey of different bases, we found that K<sub>2</sub>HPO<sub>4</sub> provided a comparable **Synlett** 

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	0 + CF <sub>3</sub> Br 1a 2	blue LED $fac \cdot Ir(ppy)_3 (0.5 \text{ mol}\%)$ $K_2CO_3$ solvent, r.t., 30 h O X $CF_3$ 3a, X = H 4a, X = Br	+ CF <sub>3</sub> H 5	
Entry	Base (equiv)	Solvent (mL)	Yield (%) <sup>b</sup> <b>3a/4a/5</b>	
1	K <sub>2</sub> CO <sub>3</sub> (1)	DMF (2 mL)	46/10/15	
2	Na <sub>2</sub> CO <sub>3</sub> (1)	DMF (2 mL)	35/31/17	
3	Cs <sub>2</sub> CO <sub>3</sub> (1)	DMF (2 mL)	24/33/17	
4	K <sub>3</sub> PO <sub>4</sub> (1)	DMF (2 mL)	27/8/8	
5	K <sub>2</sub> HPO <sub>4</sub> (1)	DMF (2 mL)	46/20/18	
6	-	DMF (2 mL)	trace/29/4	
7	K <sub>2</sub> CO <sub>3</sub> (2)	DMF (2 mL)	46/trace/11	
8	K <sub>2</sub> CO <sub>3</sub> (3)	DMF (2 mL)	52/5/27	
9	K <sub>2</sub> CO <sub>3</sub> (3)	THF (2 mL)	65/6/51	
10	K <sub>2</sub> CO <sub>3</sub> (3)	THF (1.5 mL)	70 (63)/4/82	

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Table 1 Representative Results for the Optimization of the Visible-Light-Induced Hydrotrifluoromethylation of Alkene 1a with CE-Br<sup>a</sup>

<sup>a</sup> Reactions were carried out using **1a** (0.3 mmol, 1.0 equiv), CF<sub>3</sub>Br (1 atm), fac-Ir(ppy)<sub>3</sub> (0.5 mol%), blue LED (12 W), r.t., 30 h.

<sup>b</sup> Determined by <sup>19</sup>F NMR using fluorobenzene as an internal standard; the number in parentheses is the isolated yield. The yield of **5** was determined based on 1a.

yield of 3a, but led to 4a in a 20% yield (entry 5). The other bases tested, Na<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub>, were all less effective (entries 2-4). Furthermore, the absence of base led to only a trace amount of **3a**. However, the role of  $K_2CO_3$  in the current reaction remains elusive at this stage and will be addressed in the future. Further investigations of a series of reaction parameters, such as the amount of base, the type of photoredox catalyst and the solvent, to improve the yield



Scheme 1 Substrate scope of the visible-light-induced hydrotrifluoromethylation of alkenes with CF<sub>3</sub>Br. Reaction conditions: 1 (0.3 mmol, 1.0 equiv), CF<sub>3</sub>Br (1 atm), fac-Ir(ppy)<sub>3</sub> (0.5 mol%), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), THF (1.5 mL), blue LED (12 W), r.t., 30 h.

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of **3a** showed that increasing the loading amount of  $K_2CO_3$ to 3 equivalents increased the yield of **3a** to 52% (entry 8). Importantly, the formation of **4a** could be significantly suppressed under these conditions. Among all the tested iridium catalysts, *fac*-Ir(ppy)<sub>3</sub> was the optimum choice (for details, see the Supporting Information). The reaction was also sensitive to the solvent and the use of THF resulted in the formation of **3a** in 65% yield (entry 9) (for details, see the Supporting Information). We believe that THF probably serves as a good hydrogen atom source in the current reaction. Finally, the optimized reaction conditions were identified by increasing the reaction concentration, providing **3a** in an isolated yield of 63% (entry 11).

With optimized reaction conditions in hand, a range of alkenes was examined (Scheme 1). Generally, moderate to good yields of products **3** were obtained. The reaction exhibited good functional group tolerance, including ester, amide, cyano and bromide (**3a–h**), offering good opportunities for further transformations. Importantly, the amino acid based substrate **1i** was also a suitable substrate, thus providing a potential application in chemical biology. Alkenes bearing heteroaryl, such as pyridyl and thienyl, were also applicable to the reaction and produced the corresponding products **3j** and **3k** in moderate to good yields. Notably, higher reactivity was observed when the external cyclic alkene **1l** was utilized.

The reaction can also be extended to alkynes. However, only a 32% yield of **7a** in a mixture of E/Z isomers (E/Z = 4.3:1) was obtained under the standard reaction conditions. Switching the solvent from THF to DMF significantly improved the yield to 65% with an E/Z ratio of 3.1:1 (Scheme 2, a). Good functional group tolerance was also observed as demonstrated by the syntheses of **7b** and **7c** (Schemes 2, b and c). Furthermore, we found that the

alkyne bearing a sterically bulky group favored formation of the *E*-trifluoromethylated alkene (Scheme 2, c), probably due to steric effects.

To gain some mechanistic insights into the reaction, several experiments were conducted. As shown in Table 2, the results of radical inhibition experiments suggest that a trifluoromethyl radical may be involved in the reaction. When an electron transfer scavenger (1,4-dinitrobenzene) or a radical inhibitor (hydroquinone, 1 equiv) was added to the reaction of **1a** with CF<sub>3</sub>Br under standard reaction conditions,<sup>13</sup> the formation of **3a** was totally suppressed.

The radical clock experiment further confirmed the existence of a trifluoromethyl radical in the reaction (Scheme 3, a). When the diene compound **8** was subjected to CF<sub>3</sub>Br under the standard reaction conditions, cyclized compound **9** (45% yield) was obtained, demonstrating that a radical pathway was involved in the reaction. To probe whether the hydrogen was derived from the solvent, deuterated tetrahydrofuran- $d_8$  (THF- $d_8$ ) was used as the reaction medium (Scheme 3, b). We found that the deuterated product **10** was formed when the reaction of **1a** with CF<sub>3</sub>Br was performed in THF- $d_8$  under standard reaction conditions, thus demonstrating that the solvent can serve as a hydrogen atom source.

On the basis of above results and previous reports,<sup>14</sup> a plausible reaction mechanism can be proposed (Scheme 4). Firstly, the photocatalyst *fac*-Ir<sup>III</sup>(ppy)<sub>3</sub> **A** was excited to *fac*-Ir<sup>III</sup>(ppy)<sub>3</sub>\* **B** under irradiation by the blue LED, and subsequent single-electron transfer from **B** to CF<sub>3</sub>Br generated a trifluoromethyl radical and *fac*-Ir<sup>IV</sup>(ppy)<sub>3</sub> **C**. The resulting trifluoromethyl radical reacted with the alkene or alkyne to deliver a new alkyl or vinyl radical, which then abstracted a hydrogen atom from the solvent, providing the hydrotriflu-



# SynlettY.-Y. Ren et al.LetterTable 2 Radical Inhibition Experiments $\int_{1a} \int_{2} \int_{2} \int_{2} \int_{3a} \int_{2} \int_{3a} \int_{2} \int_{additive} \int_{3a} \int_{additive} \int_{3a} \int_{additive} \int_{3a} \int_{additive} \int_{additive} \int_{3a} \int_{additive} \int_{additive} \int_{3a} \int_{additive} \int_{$

Entry	Additive (equiv)	Yield (%) <sup>b</sup> of <b>3a</b>
1	none	70 (63)
2	1,4-dinitrobenzene (0.2)	0
3	hydroquinone (0.2)	11
4	hydroquinone (1)	0

<sup>a</sup> Reactions were carried out using **1a** (0.3 mmol, 1.0 equiv), CF<sub>3</sub>Br (1 atm).

<sup>b</sup> Determined by <sup>19</sup>F NMR using fluorobenzene as an internal standard; the number in parentheses is the isolated yield.



Scheme 3 Mechanistic studies

oromethylated product and the solvent-derived radical. Finally, the solvent-derived radical was oxidized by **C** to regenerate **A** and other solvent-derived by-products.



In conclusion, we have developed the first example of the visible-light-induced hydrotrifluoromethylation of alkenes and alkynes with CF<sub>3</sub>Br.<sup>15,16</sup> The reaction proceeds under mild conditions with good functional group compatibility, providing a new route for the application of BrCF<sub>3</sub> in organic synthesis. Preliminary mechanistic studies revealed that a trifluoromethyl radical is involved and that the solvent can serve as a hydrogen source for the reaction.

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#### **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591944.

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#### (15) Hydrotrifluoromethylation with CF<sub>3</sub>Br;Typical Procedure

To a 25 mL Schlenk tube were added fac-Ir(ppy)<sub>3</sub> (0.5 mol%) and K<sub>2</sub>CO<sub>3</sub> (126 mg, 0.9 mmol, 3.0 equiv). The mixture was then evacuated and backfilled with argon (3 times). The mixture was evacuated again and backfilled with CF<sub>3</sub>Br (1 atm), followed by the addition of alkene **1b** (0.3 mmol, 1.0 equiv) and anhydrous THF (1.5 mL). The tube was screw-capped and irradiated with a blue LED (12 W) at room temperature. After stirring for 30 h, the reaction mixture was diluted with EtOAc (2 mL) and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel chromatography (hexane/EtOAc, 20:1) to give product **3b** (50 mg, 60% yield) as a colorless oil.

#### (16) 5,5,5-Trifluoropentyl 4-Methoxybenzoate (3b)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.98 (d, *J* = 8.3 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 4.29 (t, *J* = 5.9 Hz, 2 H), 3.83 (s, 3 H), 2.23–2.06 (m, 2 H), 1.86–1.76 (m, 2 H), 1.76–1.65 (m, 2 H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 166.2, 163.4, 131.5, 127.0 (q, *J* = 276.4 Hz), 122.5, 113.6, 63.8, 55.4, 33.4 (q, *J* = 28.7 Hz), 27.9, 18.8 (q, *J* = 3.0 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ = -66.5 (t, *J* = 10.8 Hz, 3 F); MS (EI): *m/z* (%) = 276 [M]<sup>+</sup>, 135 (100); HRMS (EI): *m/z* [M]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>O<sub>3</sub>F<sub>3</sub>: 276.0973; found: 276.0978.