# <u>LETTERS</u>

## Stereoselective Photoredox-Catalyzed Chlorotrifluoromethylation of Alkynes: Synthesis of Tetrasubstituted Alkenes

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#### **(5)** Supporting Information

**ABSTRACT:** A new photoredox-catalyzed chlorotrifluoromethylation reaction of internal arylalkynes under mild conditions using visible light has been developed. The reactions proceed with high levels of regio- and stereoselectivity and utilize commercially available  $CF_3SO_2Cl$  as both the  $CF_3$  and Cl source. In the mechanistic pathway for this process, generation of the  $CF_3$  radical and chloride ion occurs by  $Ir(ppy)_3$ -photocatalyzed reductive decomposition of  $CF_3SO_2Cl$ . The synthetically important trifluor-



omethyl-substituted vinyl chlorides produced in this process can be readily transformed to 1,1-bis-arylalkenes by using Suzuki coupling.

T etrasubstituted alkenes are among the most useful structural motifs in organic synthesis.<sup>1</sup> Tetrasubstituted alkenes that contain a  $CF_3$  group are particularly useful intermediates<sup>2</sup> in the synthesis of pharmaceutical and agrochemical agents as well as substances used in material science because of their unique properties including modulated lipophilicity, binding selectivity, and metabolic stability.<sup>3</sup> Perhaps the most useful approaches that can be envisaged for preparation of  $CF_3$ -containing tetrasubstituted alkenes are those in which a halogen is simultaneously introduced because the presence of this group would facilitate further functionalization reactions (Scheme 1).

However, methods for introduction of halogen and CF<sub>3</sub> in one process are limited and usually involve multistep sequences. For example, Lu devised a multistep route to prepare alkenes that contain CF<sub>3</sub> and Br groups. In this sequence, reaction of ethyl trifluoromethylpyruvate with CBr<sub>4</sub> and DIBAL-H produces a 1,1-dibromoalkene, which then undergoes selective lithiation and alkylaion to form the desired alkene (Scheme 1, eq 1).<sup>4</sup> Similarly, Shimizu used a crosscoupling arylation reaction of dibromoalkenes, which are prepared from a CF<sub>3</sub>-substituted ketone (Scheme 1, eq 2).<sup>5</sup> In another approach, nucleophilic addition of an organolithium and NCS to trifluoromethyl phosphoranes is utilized to generate chloro- and CF<sub>3</sub>-substituted alkenes.<sup>6</sup>

In this sequence, the required phosphoranes are formed in advance from the corresponding anhydrides (Scheme 1, eq 3).<sup>7</sup> The protocols described above have several disadvantageous features including their multistep nature and required use of unstable organometallic species. Consequently, the development of a concise, versatile, and stereoselective method for the synthesis of tetrasubstituted alkenes that contain halogen and

Scheme 1. Synthesis of Trifluoromethyl, Halogen-Substituted Tetrasubstituted Alkenes

Previous works

$$O \stackrel{\mathsf{CF}_{3}}{\longrightarrow} \underbrace{\mathsf{CBr}_{4}}_{\mathsf{DIBAL-H, RX}} \xrightarrow{\mathsf{Br}} \underbrace{\mathsf{CF}_{3}}_{\mathsf{Br}} \xrightarrow{\mathsf{BuLi}} \underbrace{\mathsf{Me}}_{\mathsf{Mel}} \xrightarrow{\mathsf{CF}_{3}}_{\mathsf{Br}} (\mathsf{eq 1})$$

$$= {}_{3}C \bigcirc O \bigcirc CF_{3} \longrightarrow F_{3}COC \bigcirc CP_{3}^{/}Bu \xrightarrow{Ph_{3}P} \xrightarrow{RLi} {}^{/BuO_{2}C} \xrightarrow{CF_{3}} (eq 3)$$

This work

$$Ar \xrightarrow{\bigcirc} R \qquad CI \xrightarrow{\bigcirc} CF_3 \qquad \xrightarrow{photoredox} \qquad Ar \xrightarrow{\bigcirc} CF_3 \qquad (eq 4)$$

 $CF_3$  groups would be significant. In the studies described below, we developed a novel and facile visible-light-promoted photoredox-catalyzed process<sup>8</sup> that generates products in this family. The one-step method utilizes  $CF_3SO_2Cl$  as both the  $CF_3$  and Cl source (Scheme 1, eq 4).

The strategy used to design the new approach to prepare  $CF_{3}$ - and Cl-containing tetrasubstituted alkenes was based on the results of a previous study which led to the successful

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development of a photoredox-catalyzed alkene functionalization process.<sup>9</sup> We believed that  $CF_3SO_2Cl^{10}$  would serve as both a  $CF_3$  and halogen source in this process. Importantly,  $CF_3SO_2Cl$  is relatively inexpensive and convenient to use (liquid) in contrast with other substances such as  $CF_3I$  (gas), Umemoto's reagents, and Togni's reagents.<sup>11</sup> We anticipated that the new reaction would follow the photocatalyzed redox sequence displayed in Scheme 2. In the route, the excited state of the



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photoredox catalyst (\* $M^n$ ), generated by visible light absorption, would donate an electron to  $CF_3SO_2Cl$  to form a radical anion that fragments to yield the  $CF_3$  radical and chloride ion.

We anticipated that addition of the CF<sub>3</sub> radical to an alkyne would occur regioselectively to produce an aryl ring stabilized vinyl radical.<sup>12</sup> If  $M^{n+1}$  has an appropriate reduction potential, it would accept an electron from the vinyl radical to generate a vinyl cation and regenerate the photocatalyst  $M^n$ . Finally, addition of chloride to the vinyl cation would yield the target tetrasubstituted alkene. We also anticipated that because of electrostatic repulsion, chloride addition would take preferentially from a direction anti to the CF<sub>3</sub> group.<sup>13</sup>

To test this proposal, a mixture of the unsymmetrical alkyne 1a and  $CF_3SO_2Cl$ , containing  $K_2HPO_4$  as a base and  $Ru(bpy)_3$ as the catalyst in MeCN was subjected to visible light irradiation using blue LEDs. As predicted, this process leads to formation of the desired alkene 2a in 58% yield (Table 1, entry 1). A screen of various catalysts led to identification of fac-Ir(ppy)<sub>3</sub> as being optimal (67% yield, entries 2–4). The results of further optimization studies showed that  $Li_2CO_3$  (0.5 equiv) and acetone are ideal base and solvent combinations (78%, entry 9). In the absence of visible light irradiation, none of the desired product is formed (entry 10). Moreover, irradiation of a mixture not containing the photocatalyst leads to formation of a lesser amount of 2a (23%, entry 11), likely arising through an inefficient radical chain pathway promoted by direct light absorption by CF<sub>3</sub>SO<sub>2</sub>Cl. To clarify the mechanistic insight, a quantum yield of the reaction was determined. The quantum yield for the formation of 2a is 0.36, which supports the photocatalytic cycle. However, more detailed mechanistic study is necessary to confirm the reaction

Table 1. Optimization of the Chlorotrifluoromethylation Reaction of Alkynes $^{a}$ 

AcHN	Me Me	CI-S-CF <sub>3</sub> blue LED	AcHN	CF <sub>3</sub> CI A
entry	v catalyst	solvent	additive (equiv)	yield (%) <sup>b</sup>
1	Ru(bpy) <sub>3</sub>	MeCN	K <sub>2</sub> HPO <sub>4</sub> (1.0)	58
2	[Ru(phen) <sub>3</sub> ]Cl <sub>2</sub>	MeCN	K <sub>2</sub> HPO <sub>4</sub> (1.0)	52
3	Ir[dF(CF3)ppy]2(dtbbpy)PF6	MeCN	K <sub>2</sub> HPO <sub>4</sub> (1.0)	51
4	fac-Ir(ppy) <sub>3</sub>	MeCN	K <sub>2</sub> HPO <sub>4</sub> (1.0)	67
5	fac-Ir(ppy) <sub>3</sub>	MeCN	K <sub>2</sub> HPO <sub>4</sub> (0.5)	53
6	fac-Ir(ppy) <sub>3</sub>	MeCN	Li <sub>2</sub> CO <sub>3</sub> (1.0)	65
7	fac-Ir(ppy) <sub>3</sub>	MeCN	Li <sub>2</sub> CO <sub>3</sub> (0.5)	73
8	fac-Ir(ppy) <sub>3</sub>	DCE	Li <sub>2</sub> CO <sub>3</sub> (0.5)	30
9	fac-Ir(ppy) <sub>3</sub>	acetone	Li <sub>2</sub> CO <sub>3</sub> (0.5)	78 (74) <sup>c</sup>
10 <sup>d</sup>	fac-Ir(ppy) <sub>3</sub>	acetone	Li <sub>2</sub> CO <sub>3</sub> (0.5)	-
11	-	acetone	Li <sub>2</sub> CO <sub>3</sub> (0.5)	23
	N, N	F <sub>3</sub> C F F CF <sub>3</sub> CF <sub>3</sub>	$ \begin{array}{c} & & F \\ N & & & F \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & $	fac-lr(ppy) <sub>3</sub>

<sup>*a*</sup>The reactions were carried out under N<sub>2</sub> atmosphere at 25 °C for 12 h using **1a** (0.1 mmol) and CF<sub>3</sub>SO<sub>2</sub>Cl (0.15 mmol). <sup>*b*</sup>Yields were determined by <sup>1</sup>H NMR. <sup>*c*</sup>Isolated yield. <sup>*d*</sup>In the dark.

cycle.<sup>14</sup> The regioselective nature of the process was confirmed by X-ray crystal analysis of a product.<sup>15</sup>

The alkyne scope of the process, carried out using the optimized conditions, was examined (Table 2, 1a-k). The results show that the reaction takes place efficiently using substrates that contain a variety of arene ring substituents. For example, reactions of alkynes containing acetyl-, *p*-tosyl-, and Boc-protected amine-substituted aryl groups undergo the reaction efficiently (74%, 85%, and 78% yields, respectively, Table 2, 2a-c). Furthermore, important functional groups such as an ether (70%, 2d), triflate (58%, 2e), cyano (62%, 2f), ester (71%, 2g), nitro (79%, 2h), and alkyl (62%, 2i) are unaltered by and do not affect the process. Notably, alkynes containing halogens 2j (Br, 53%) and 2k (Cl, 66%) are efficiently transformed to the desired products.

We also explored reactions of 4-acetaminophenylalkynes that contain various R groups at the nonaryl-substituted position (Table 3). The results demonstrate that while primary alkyl groups are well tolerated (Me (2a, 74%) and *n*-Bu (4a, 70%)), substrates possessing secondary and tertiary alkyl groups including cyclohexyl (4b, 60%), cyclopentyl (4c, 44%), and *t*-Bu (4d, 44%) react with lower efficiencies. This is attributed to a steric effect that influences the rates of CF<sub>3</sub> radical addition. In addition, amide (4e, 63%) and ester (4f, 44%) group containing alkynes react with good to moderate efficiencies. Moreover, the unprotected hydroxymethyl-substituted alkene is

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Table 2. Chlorotrifluoromethylation of Alkynes  $I^a$  Table 3. Chlorotrifluoromethylation of Alkynes  $II^a$ 

CF<sub>3</sub>SO<sub>2</sub>CI Ir(ppy)<sub>3</sub> (2 mol %) Li<sub>2</sub>CO<sub>3</sub> (0.5 equiv) R 25 °C, acetone 3a-k 4a-k entry substrate productb AcHN AcHN 1 *`n-*Bu ċι `*n-*Bu 3a **4a** (70%) AcHN AcHN 2 ςι 3b 4b (60%) AcHN AcHN 3 3c 4c (44%) AcHN AcHN CF<sub>3</sub> 4 -Bu ćι t-Bu **4d** (44%)<sup>c,d</sup> 3d AcHN AcHN 5 ςι 3e ö 4e (63%) AcHN AcHN OEt 6 OEt ċι 3f ő **4f** (44%) AcHN AcHN 7 OH. ĊI 3g **4g** (73%) AcHN AcHN 8 `CF₃ ċι 3h **4h** (55%) AcHN AcHN 9 ċι 3i **4i** (34%)<sup>c,e</sup>

blue I FD

AcHN

AcHN

<sup>*a*</sup>Reactions were carried out under N<sub>2</sub> atmosphere at room temperature for 12 h using alkyne (0.1 mmol) and CF<sub>3</sub>SO<sub>2</sub>Cl (0.15 mmol). <sup>*b*</sup>Isolated yield after purification by chromatography on SiO<sub>2</sub>. <sup>*c*</sup>Yields were determined by using <sup>1</sup>H NMR <sup>*d*</sup>Reaction provided E/Z mixture of stereoisomers. <sup>*e*</sup>O.2 mmol scale of alkyne.

generated in high yield (4g, 73%). Interestingly, when a  $CF_3$ substituted alkyne 3h was submitted to the reaction conditions, the 1,1-bis- $CF_3$ -substituted alkene is produced (4h, 55%). The terminal alkyne 3i yields the target 4i in only 34% yield along with a complicated mixture of unidentified byproducts.

To demonstrate how the new methodology can be incorporated into sequences to prepare complex targets, alkene 2a was utilized in Suzuki coupling reactions<sup>16</sup> with various boronic acids (Scheme 3). As expected, the chloro group in 2a



 $^a$ The reactions were carried out under N<sub>2</sub> atmosphere at 90  $^\circ$ C for 18 h using 2a (0.1 mmol), Pd<sub>2</sub>dba<sub>3</sub> (5 mol %), XPhos (10 mol %), K<sub>3</sub>PO<sub>4</sub> (3.0 equiv), relevant R-B(OR')<sub>2</sub> (2.0 equiv), and toluene (0.5 mL). <sup>b</sup>The reaction was carried out under N<sub>2</sub> atmosphere at 90 °C for 18 h using 2a (0.1 mmol), Pd<sub>2</sub>dba<sub>3</sub> (10 mol %), XPhos (20 mol %), K<sub>3</sub>PO<sub>4</sub> (3.0 equiv), relevant R-B(OR')<sub>2</sub> (2.0 equiv), and toluene (0.5 mL).

serves as the reactive center in these processes that yield 1,1diarylalkenes arising from introduction of ethoxyphenyl (5a, 90%), methylpyrazole (5b, 75%), furanyl (5c, 74%), and benzothiophene (5d, 71%) groups. This sequence provides versatile method to synthesize complex tetrasubstituted alkenes.

In summary, the studies described above have led to the development of a new, facile, and stereo- and regioselective method for the preparation of CF<sub>3</sub>- and Cl-containing tetrasubstituted alkenes. The efficiency and concise nature of the process, along with the mild conditions employed, serve as major advantages of the new approach. The ability to use commercially available liquid CF<sub>3</sub>SO<sub>2</sub>Cl as CF<sub>3</sub> and Cl sources makes the method highly attractive and significant.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00470.

X-ray data for compound 2b (CIF)

Detailed experimental procedures and characterization for all new compounds as well as spectral and X-ray crystallographic data (PDF)

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#### Notes

The authors declare no competing financial interest.

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(14) In the case of electron-withdrawing substituents on an aromatic ring, a radical-chain pathway is possibly a main reaction pathway due to the difficult oxidation of the corresponding vinyl radical. See the Supporting Information for the detail of a quantum yield determination.

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