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Trifluoroethylation of Alkynes: Synthesis of Allylic-CF_3 Compounds by Visible-Light Photocatalysis

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Two types of allylic trifluoromethylated compounds were synthesized by reacting alkynes with CF_3CH_2I using visible-light photocatalysis. Subtle differences in the catalytic system controlled the selectivity of iodotrifluoroethylation and hydrotrifluoroethylation. The iodotrifluoroethylated products were obtained in the presence of $[Ru(bpy)_3]Cl_2$ and TMEDA in CH_3CN under visible-light irradiation, whereas hydrotrifluoroethylated products were synthesized using *fac*-$[Ir(ppy)_3]$ and a mixture of DBU and K_2CO_3 in DMF. The iodotrifluoroethylation reaction worked particularly well, even at gram-scale, and the synthetic utility of iodotrifluoroethylated products was proved by their coupling reactions, providing complex CF_3-containing products.

Keywords trifluoroethylation, alkyne, visible-light, photocatalysis

Introduction

Trifluoromethylated organic molecules have gained considerable attention, especially in pharmaceuticals and agrochemicals, because the introduction of a CF_3 group to a molecule can change its physical, chemical, and biological properties, leading to higher biological stability, bioavailability, lipophilicity, and binding selectivity.[1] Because of the natural scarcity of CF_3 compounds and the enhancement of biological properties by introducing a CF_3 group, new and efficient synthetic methods for trifluoromethylation are in demand.[2] A plethora of metal-catalyzed, nucleophilic, electrophilic, and radical reactions have been developed for the incorporation of CF_3 groups.[3,4] However, these studies mainly focused on the construction of a $C(sp^2)-CF_3$ bond; $C(sp^3)-CF_3$ bond formation has been rarely studied. One of the methods for forming $C(sp^3)-CF_3$ bonds is by synthesizing allylic CF_3 compounds. In general, allylic CF_3 compounds have been obtained from alkenes, mainly by allylic C—H activation with trifluoromethyl sources such as Togni's and Umemoto's reagents in the presence of Cu catalysts [Figure 1(1a)].[5] However, the requirement of an allylic C—H bond has led to a limited substrate scope for allylic trifluoromethylations despite the efficiency of the reaction. Trifluoroethyl sources such as trifluoroethyl halides are alternative substrates for the synthesis of allylic CF_3 compounds from both alkenes and alkynes. However, trifluoroethylation has not been widely explored, and only one example with alkene[6] and one example with alkyne[7] have been reported (Figure 1b).

Herein, we have developed a mild, efficient, and selective method for the synthesis of allylic CF_3 compounds from alkynes using 1,1,1-trifluoro-2-iodoethane (CF_3CH_2I) as the trifluoroethyl source by visible-light photocatalysis [Figure 1(2)].[8,9] The choice of the base and photocatalyst is crucial to control the selectivity of two different types of products in the reactions of alkynes.[4m,10] The mechanistic pathway for the synthesis of allylic CF_3 products involves the initial visible-light-photocatalyzed formation of a $\bullet CH_2CF_3$ radical, which is added to the alkyne, forming the allylic CF_3 radical intermediate **1'**.[6] Depending on the presence of a base, the reaction may proceed either by radical propagation with CF_3CH_2I or by hydrogen-atom abstraction, producing iodo- (**2**) or hydrotrifluoroethylated (**3**) products, respectively [Figure 1(2)].

Experimental

Procedure for iodotrifluoroethylation

An oven-dried 50 mL round bottom flask equipped with a magnetic stir bar was charged with 2—3 mol% $[Ru(bpy)_3]Cl_2$ (0.02 mmol, 15 mg) in CH_3CN (5 mL). Alkyne **1** (1 mmol), 1,1,1-trifluoro-2-iodoethane (3 mmol, 296 μL for aliphatic alkyne and 4 mmol, 394 μL for aromatic alkyne), and TMEDA (2 mmol, 299 μL) were added. The round bottom flask was closed with a

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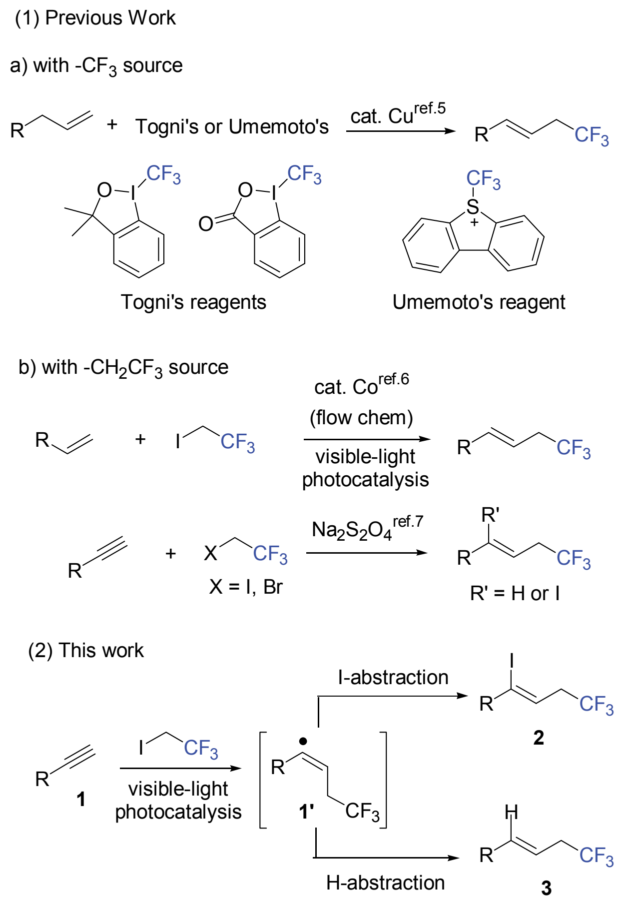


Figure 1 Synthesis of allylic-CF_3 compounds.

rubber cap, placed under blue LEDs (7 W), and stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC and gas chromatography. The flask was opened, and the reaction mixture was diluted with dichloromethane. After the aqueous work-up, the organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The desired iodotrifluoroethylated product **2** was purified by silica gel flash column chromatography using hexane as the eluent.

Procedure for hydrotrifluoroethylation

A 50 mL round bottom flask equipped with a magnetic stir bar was charged with 2 mol% *fac*-Ir(ppy)$_3$ (0.02 mmol, 13 mg) in DMF (10 mL). Alkyne **1** (1 mmol), 1,1,1-trifluoro-2-iodoethane (4 mmol, 394 μL), DBU (4 mmol, 600 μL), and K_2CO_3 (2 mmol, 276 mg) were added. The round bottom flask was closed with a rubber cap, placed under blue LEDs (7 W), and stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC and gas chromatography. The flask was opened, and the reaction mixture was diluted with dichloromethane. After the aqueous work-up, the organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The desired hydrotrifluoroethylated product **3** was purified by silica gel flash column chromatography using hexane as the eluent.

Results and Discussion

First, the reaction was carried out using phenylacetylene **1a** as the starting material and CF_3CH_2I as the CH_2CF_3 radical source. To our delight, a high yield of iodotrifluoroethylated product **2a** was obtained using various Ru and Ir photocatalysts in CH_3CN and TMEDA as the base under blue LED irradiation for 12 h. Among the catalysts including [Ru(bpy)$_3$]Cl$_2$, [Ru(phen)$_3$]Cl$_2$, *fac*-Ir(ppy)$_3$, *fac*-Ir(dFppy)$_3$, and [Ir(dtbbpy)(ppy)$_2$]PF$_6$, [Ru(bpy)$_3$]Cl$_2$ was selected for further studies on iodotrifluoroethylation because of the highest yield and low cost (Table 1, Entries 1—5). The use of 4 equiv. CF_3CH_2I increased the yield of the product, whereas a mixture of products was formed with a less amount (Table 1, Entries 6 and 7). Although the reactivity was similar, the use of 3 mol% [Ru(bpy)$_3$]Cl$_2$ increased the reproducibility of the results (Table 1, Entry 8). Acetonitrile was found to be the best solvent (Table 1, Entries 8—10).

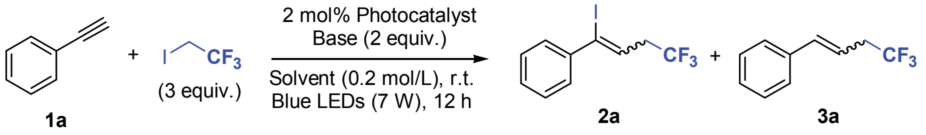
Interestingly, when the catalyst was changed from [Ru(bpy)$_3$]Cl$_2$ to *fac*-Ir(ppy)$_3$ in DMF, the yield of hydrotrifluoroethylated product **3a** increased (Table 1, Entry 11); the results prompted us to optimize the conditions for hydrotrifluoroethylation. The choice of base was crucial for the selectivity, because the base functions not only as an electron donor in the photocatalysis, but also as a hydrogen-atom source. Consistent with our previous reports on trifluoromethylation[4m] and difluoroalkylation,[10] the use of DBU resulted in the highest yield of **3a** among several bases (Table 1, Entries 11—15). Despite the selective hydrotrifluoroethylation with K_2CO_3, the reaction showed a lower conversion and yield (Table 1, Entry 14). Based on these observations, we tried the use of a combination of K_2CO_3 and DBU, which further increased the yield of **3a** (Table 1, Entry 16). The use of 2 equiv. K_2CO_3 and 4 equiv. DBU in DMF showed the highest reactivity for hydrotrifluoroethylation (Table 1, Entries 17—21). The control experiments confirmed the requirement of visible light and the photocatalyst (Table 1, Entries 22 and 23).

With the optimized conditions for both the reactions, we first evaluated the iodotrifluoroethylation of diverse aromatic/heteroaromatic and aliphatic alkynes (Table 2). Aliphatic alkynes were better substrates for the iodotrifluoroethylation as the reaction occurred smoothly with 3 equiv. of CF_3CH_2I and 2 mol% of [Ru(bpy)$_3$]Cl$_2$.

The use of benzenesulfonate **1k** provided **2k'** as the final product (Scheme 1). In the process, iodotrifluoroethylated product (**2k**) was initially obtained; then, **2k** was converted to **2k'** by an S_N2 reaction where the iodide anion, which was formed by the photocatalysis of CF_3CH_2I, attacked the benzenesulfonate moiety of **2k**.

The iodotrifluoroethylation of **1h** proceeded well even at a 5 mmol scale without a remarkable loss in the product yield, indicating that the reaction can be amenable to industrial use. Moreover, alkenyl iodide products **2** are valuable CF_3 building blocks because they can

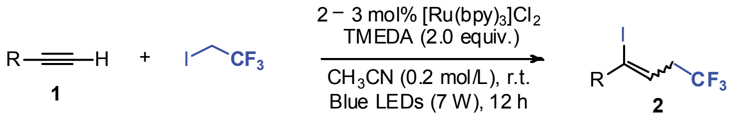
Table 1 Optimization for iodo- and hydrotrifluoroethylation of phenyl acetylene **1a**[a]

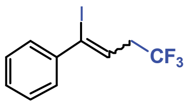


Entry	Photocatalyst	Base	Solvent	Variations	Yield[b]/%	
					2a	**3a**
1	$[Ru(bpy)_3]Cl_2$	TMEDA	CH_3CN		80	4
2	$[Ru(phen)_3]Cl_2$	TMEDA	CH_3CN		76	2
3	*fac*-$Ir(ppy)_3$	TMEDA	CH_3CN		80	7
4	*fac*-$Ir(dFppy)_3$	TMEDA	CH_3CN		67	0
5	$[Ir(dtbbpy)(ppy)_2]PF_6$	TMEDA	CH_3CN		77	9
6	$[Ru(bpy)_3]Cl_2$	TMEDA	CH_3CN	CF_3CH_2I (2 equiv.)	60	17
7	**$[Ru(bpy)_3]Cl_2$**	**TMEDA**	**CH_3CN**	**CF_3CH_2I (4 equiv.)**	**89**	**4**
8	**$[Ru(bpy)_3]Cl_2$**	**TMEDA**	**CH_3CN**	**CF_3CH_2I (4 equiv.), 3 mol% Ru**	**90**	**3**
9	$[Ru(bpy)_3]Cl_2$	TMEDA	CH_2Cl_2	CF_3CH_2I (4 equiv.), 3 mol% Ru	74	2
10	$[Ru(bpy)_3]Cl_2$	TMEDA	DMF	CF_3CH_2I (4 equiv.), 3 mol% Ru	24	1
11	*fac*-$Ir(ppy)_3$	TMEDA	DMF		35	36
12	*fac*-$Ir(ppy)_3$	TEA	DMF		20	2
13[c]	*fac*-$Ir(ppy)_3$	DBU	DMF		13	49
14[c]	*fac*-$Ir(ppy)_3$	K_2CO_3	DMF		0	44
15[c]	*fac*-$Ir(ppy)_3$	KO^tBu	DMF		0	0
16[c]	*fac*-$Ir(ppy)_3$	K_2CO_3/DBU	DMF	Base (2/2 equiv.)	0	66
17[c]	*fac*-$Ir(ppy)_3$	K_2CO_3/DBU	DMF	Base (2/2 equiv.), 0.1 mol/L	9	45
18[c]	*fac*-$Ir(ppy)_3$	K_2CO_3/DBU	DMF	Base (2/3 equiv.)	0	70
19[c]	*fac*-$Ir(ppy)_3$	K_2CO_3/DBU	DMF	Base (2/4 equiv.)	0	74
20[c]	*fac*-$Ir(ppy)_3$	K_2CO_3/DBU	DMF	Base (2/4 equiv.), CF_3CH_2I (4 equiv.)	0	79
21[c,d]	***fac*-$Ir(ppy)_3$**	**K_2CO_3/DBU**	**DMF**	**Base (2/4 equiv.), CF_3CH_2I (4 equiv.)**	**0**	**86**
22	—	K_2CO_3/DBU	DMF		0	0
23	*fac*-$Ir(ppy)_3$	K_2CO_3/DBU	DMF	no light	0	0

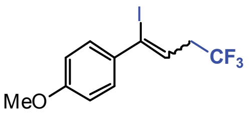
[a] Reaction scale: **1a** (0.1 mmol). [b] Yields were determined by GC using dodecane as the internal standard. [c] 24 h. [d] 0.1 mol/L.

Table 2 Substrate scope of the iodotrifluoroethylation of alkynes[a,b]

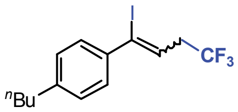




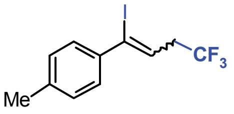
2a, 78% (*E*:*Z* = 1:1.9)



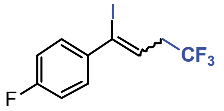
2b, 88% (*E*:*Z* = 1:1.7)



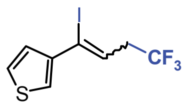
2c, 89% (*E*:*Z* = 1:1.3)



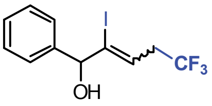
2d, 84% (*E*:*Z* = 1:1.1)



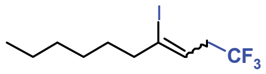
2e, 84% (*E*:*Z* = 1:1.4)



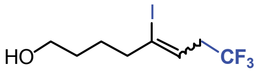
2f, 74% (*E*:*Z* = 1:1.3)



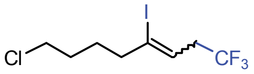
2g, 52% (*E*:*Z* = 1:3.8)



2h, 95% (*E*:*Z* = 1:1.9)



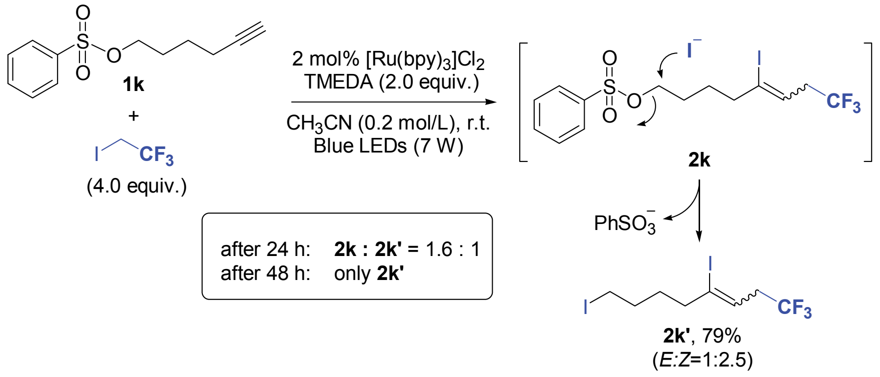
2i, 87% (*E*:*Z* = 1:1.1)



2j, 89% (*E*:*Z* = 1:1.1)

[a] Reaction scale: **1** (1.0 mmol), CF_3CH_2I (3.0 mmol for aliphatic alkynes and 4.0 mmol for aromatic alkynes). [b] Yields of products are the sum of the yields of both *E*/*Z* isomers; the *E*/*Z* ratios were determined by gas chromatography and NOE experiments.

Scheme 1 Exceptional substrate for iodotrifluoroethylation



be transformed into CF$_3$-containing trisubstituted alkenes, commonly found as the structural motifs in pharmaceuticals and agrochemicals, by various cross-coupling reactions. To prove this, the isolated product **2h** was further subjected to Pd-catalyzed Suzuki and Sonogashira coupling reactions, forming trisubstituted alkenes **4** and **5**, respectively. This shows the utility of alkenyl iodide products **2** as the CF$_3$ building blocks (Scheme 2).

The substrate scope of the hydrotrifluoroethylation of alkynes was also investigated under the optimized conditions where 2 mol% *fac*-Ir(ppy)$_3$ and 2∶1 ratio of DBU/K$_2$CO$_3$ were used in DMF (Table 3). The reaction showed a limited substrate scope; only aromatic and heteroaromatic alkynes participated in the reaction, producing styrene derivatives **3**. Moreover, the reaction at a larger scale ($>$1.0 mmol) resulted in a decreased yield of the products.

Compared to terminal alkynes, internal alkynes such as 4-octyne and diphenylacetylene, were not good substrates both for iodo- and hydrotrifluoroethylations with significantly reduced reactivity. Reactions did not go to completion and most starting material remained even with longer reaction time.

Based on the results, a plausible mechanism for the iodo and hydrotrifluoroethylation of alkynes is proposed in Figure 2. The visible-light irradiation of [M^{n}L$_x$] provides the photo excited complex [M^{n+1}L$_x^{\bullet-}$] by metal-to-ligand charge transfer. Then, the activated complex is reductively quenched by a single electron transfer form an amine, resulting in the formation of [M^{n}L$_x^{\bullet-}$]$^-$. This complex donates one electron to CF$_3$CH$_2$I, regenerating [M^{n}L$_x$] and forming a carbon-centered •CH$_2$CF$_3$ radical. The addition of this radical species to alkyne **1** generates trifluoroethylated vinyl radical **1'**. Then, the reaction of

Scheme 2 Pd-catalyzed cross-coupling processes using **2h**

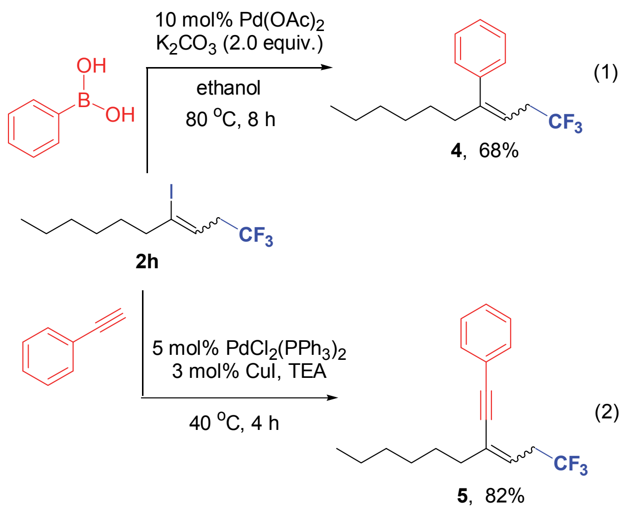
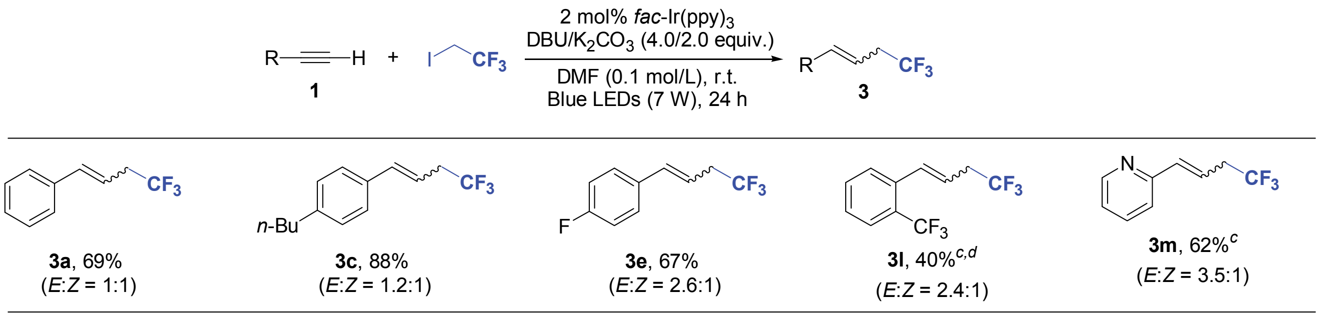


Table 3 Substrate scope of hydrotrifluoroethylation of alkynes[a,b]



[a] Reaction scale: **1** (0.5 mmol), CF$_3$CH$_2$I (2.0 mmol). [b] Yields of products are the sum of the yields of both *E*/*Z* isomers. The *E*/*Z* ratios were determined by gas chromatography and NOE experiments. [c] The reaction did not go to completion even at a 0.2 mmol scale. [d] The yield of **3l** was determined by ^{19}F NMR spectroscopy due to its volatility.

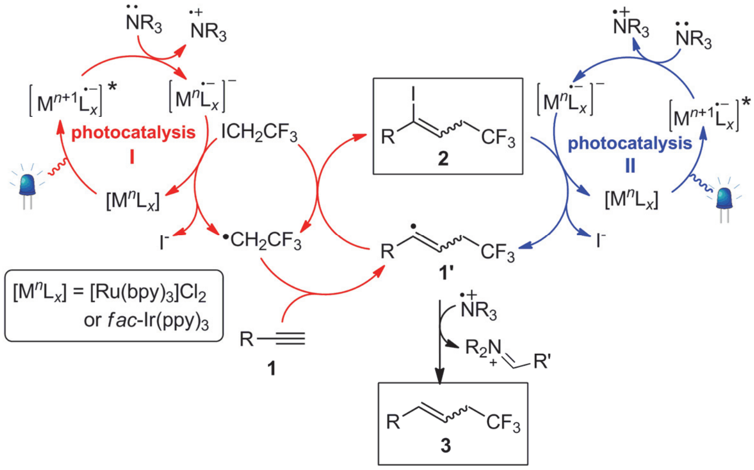


Figure 2 Proposed mechanism.

1' can proceed by several pathways depending upon the conditions. The iodide abstraction of **1'** from CF_3CH_2I provides alkenyl iodide **2**. On the other hand, hydrotrifluoroethylated product **3** can be synthesized either through the direct hydrogen abstraction by **1'** from an amine radical cation $[NR_3]^{\bullet+}$or through the deiodination from **2** using the same photocatalytic system.

Conclusions

An efficient method was developed for the synthesis of allylic CF_3 compounds. Iodo- and hydrotrifluoroethylated compounds were obtained selectively from alkynes and CF_3CH_2I by visible-light photocatalysis. Subtle differences in the combination of the catalyst, base, and solvent controlled the reactivity and selectivity of the reaction. The iodotrifluoroethylated products were obtained in the presence of $[Ru(bpy)_3]Cl_2$ and TMEDA in CH_3CN, whereas the hydrotrifluoroethylated products were produced using *fac*-$Ir(ppy)_3$ and a mixture of DBU and K_2CO_3 in DMF. The iodotrifluoroethylation reaction worked particularly well, even at gram-scale, and the synthetic utility of the iodotrifluoroethylated products was proved by their coupling reactions, providing complex CF_3-containing products.

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