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Multicomponent Oxidative Trifluoromethylation of Alkynes with Photoredox Catalysis: Synthesis of α-Trifluoromethyl Ketones

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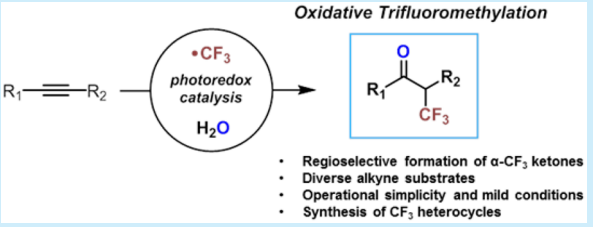
Supporting Information

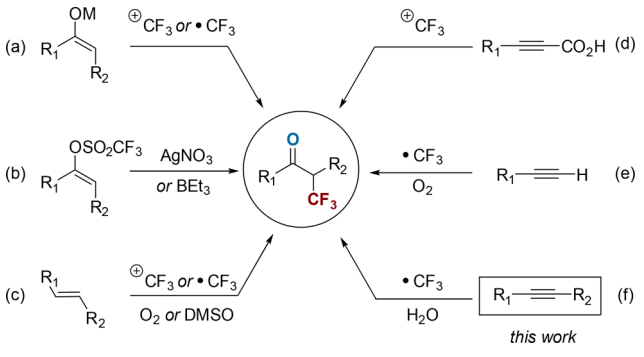
ABSTRACT: The direct oxidative addition of CF_3 and H_2O to alkynes was achieved with photoredox catalysis to obtain α-trifluoromethyl ketones via rapid enol-keto tautomerization. The reaction exhibits high functional group tolerance and regioselectivity. Heterocycles of various sizes containing CF_3 were synthesized from the α-CF_3-substituted diketones obtained through the protocol, thereby demonstrating the versatile applicability of the method. Mechanistic studies of the reaction with isotopes provided insight into the reaction pathway.



The incorporation of a fluoro-substituent in organic molecules has been studied extensively, because of its significant impact on biological properties, such as lipophilicity, binding affinity, and metabolic stability.[1] Among these reactions, the formation of α-CF_3 substituted ketones in particular is very attractive, because of their use as versatile building blocks for a variety of complex CF_3-containing molecules. The most common route to α-CF_3 ketones involves the use of enolates or enol ethers as substrates. For example, in-situ-generated Li, Ti, and Zn enolates were used to form α-CF_3 ketones in combination with a CF_3 radical.[2] In addition, silyl enol ethers were successfully employed by MacMillan and Kappe (see Scheme 1a).[3] Recently, Li and Kamimura reported the formation of α-CF_3 ketones using vinyl triflates via oxidative radical fragmentation (see Scheme 1b).[4] However, these types of reactions could not proceed without the prerequisite formation of appropriate enol-type substrates and needed existing carbonyl moieties.[5] Alternatively, the direct formation of α-CF_3 substituted ketones from alkenes was achieved (Scheme 1, c).[6] These bis-functionalization approaches are highly beneficial, because of the high availability of alkenes and no required preformation. Further attempts were made to extend this attractive approach to alkyne substrates. Hu used propionic acids in an electrophilic decarboxylative mechanism with $Cu(OAc)_2$ (Scheme 1d).[7] In addition, Maiti reported CF_3 radical and O_2 incorporation using $AgNO_3$ (Scheme 1e).[8] However, these methods still have major limitations, such as stoichiometric use of $Cu(OAc)_2$ (2 equiv) and high catalytic loading of $AgNO_3$ (20 mol %). In addition, only terminal alkynes and alkynyl acids can be employed to produce unsubstituted α-CF_3 ketones (Scheme 1, R_2 = H) as a result. Thus, an atom-economical and versatile method for use with a broad range of alkynes remained elusive and needed to be developed to obtain diversely substituted α-CF_3 ketones. Herein, in continuation of our efforts to develop novel CF_3-related bis-functionalization reactions,[9] we disclose the multicomponent oxidative trifluoromethylation of various internal and terminal alkynes with visible light catalysis for the formation of α-CF_3 substituted ketones. To the best of our knowledge, this reaction is the first direct synthesis of α-CF_3 substituted ketones from internal and terminal alkynes using photoredox catalysis (Scheme 1f).

We envisioned the possibility of a regioselective and chemoselective direct one-step conversion of aryl alkynes employing visible-light-mediated photoredox catalysis using a CF_3 radical and H_2O, as depicted in Scheme 2. Excitation of the

Scheme 1. Synthesis of α-Trifluoromethyl Ketones



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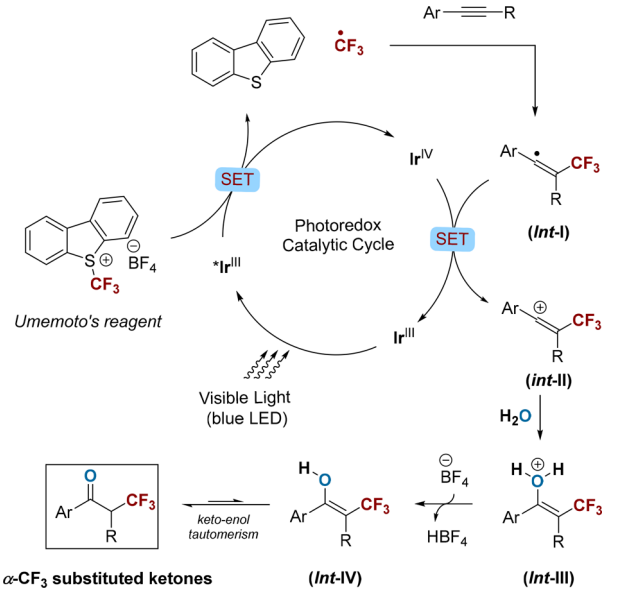
Scheme 2. Proposed Pathway for Direct α-Trifluoromethylation of Alkynes

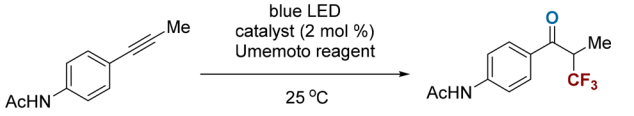


photoredox catalyst (from Ir^{III} to $*Ir^{III}$) with visible light can generate the CF_3 radical from Umemoto's reagent ($E_{1/2}$ = −0.37 V vs SCE), because of a high reducing power of *fac*-Ir(ppy)$_3$ ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE).[10] The CF_3 radical can be captured by alkynes to produce the vinyl radical **Int-I**. Regioselecive generation of the vinyl radical is anticipated, because of the stabilization effect of the adjacent aromatic ring.[9a,11] The resulting vinyl radical species can be oxidized by Ir^{IV} to a vinyl cation **Int-II** since the reduction potential of Ir^{IV} is sufficiently high ($E_{1/2}^{IV/III}$ = 0.77 V vs SCE).[10,12] This oxidation regenerates the catalyst Ir^{III} to close the catalytic cycle. In addition, the formed vinyl cations can easily be trapped with H_2O to generate **Int-III**. Deprotonation with the anion BF_4^- produces the enol **Int-IV**. The desired product could be readily obtained by enol-keto tautomerization.

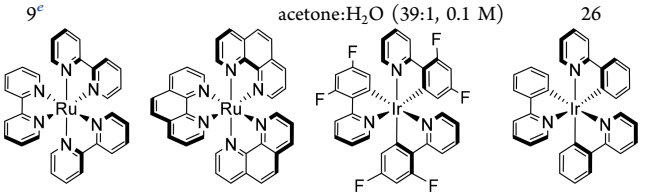
Based on the proposed pathway, we attempted the reaction with the internal alkyne **1a** under various photoredox catalytic conditions (see Table 1). To our delight, the desired product **2a** was obtained in 60% yield when H_2O and Umemoto's reagent were added with a catalytic amount of *fac*-Ir(ppy)$_3$ under blue LED irradiation (entry 1, Table 1). When the amount of H_2O was decreased, the yield was increased to as much as 77% (entries 1−3, Table 1). Catalyst screening enabled *fac*-Ir(ppy)$_3$ to be identified as the optimal catalyst (entries 3−6, Table 1).[13] The use of two equivalents of Umemoto's reagent resulted in improvement with an isolated yield of 77% (entry 7, Table 1). The absence of light irradiation completely quenched the reaction, proving that a light-mediated reaction was involved (entry 8, Table 1). Interestingly, without the catalyst, the reaction yielded 26% of the product, which is suspected to form via an inefficient radical pathway, resulting from the direct absorption of light by Umemoto's reagent (entry 9, Table 1).[9a]

Using this optimization protocol, various alkynes were subjected to the reaction conditions. First, substrates with substituents on the aromatic rings were tested with 1-phenyl-1-propyne and its various derivatives (Table 2, **1a**−**1n**). Acetyl and tosyl protected amines containing alkynes were smoothly converted to their product in 77% (**2a**), 81% (**2b**), and 81%

Table 1. Optimization of the Oxidative Trifluoromethylation of Alkynes[a]



entry	catalyst	solvent	yield (%)[b]
1	*fac*-Ir(ppy)$_3$	acetone:H_2O (9:1, 0.1 M)	60
2	*fac*-Ir(ppy)$_3$	acetone:H_2O (19:1, 0.1 M)	69
3	*fac*-Ir(ppy)$_3$	acetone:H_2O (39:1, 0.1 M)	77
4	Ru(bpy)$_3$	acetone:H_2O (39:1, 0.1 M)	23
5	[Ru(phen)$_3$]Cl$_2$	acetone:H_2O (39:1, 0.1 M)	55
6	Ir(dFppy)$_3$	acetone:H_2O (39:1, 0.1 M)	60
7[c]	*fac*-Ir(ppy)$_3$	acetone:H_2O (39:1, 0.1 M)	81 (77)
8[d]	*fac*-Ir(ppy)$_3$	acetone:H_2O (39:1, 0.1 M)	0
9[e]		acetone:H_2O (39:1, 0.1 M)	26



[a]Reactions were carried out under N_2 atmosphere at 25 °C for 12 h using **1a** (0.1 mmol), catalyst (2 mol %), and Umemoto's reagent (0.15 mmol). [b]Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard (isolated yield after flash silica gel column given in parentheses). [c]Umemoto's reagent (0.20 mmol). [d]In darkness. [e]Without a catalyst.

(**2c**) yields, respectively. In addition, a Boc-protected amine gave the desired product in moderate yield (**2d**, 50%). A tertiary amine substituent such as in dimethyl aniline also produced the desired product with moderate reactivity (**2e**, 51% yield). Methoxy- and mesyl-protected alcohols were efficiently transformed to the α-CF_3 substituted ketones in 75% and 63% yields, respectively (**2f** and **2g**). In particular, unprotected alcohol substituents in the form of phenolic and benzyl alcohols were also not detrimental to forming the desired products **2h** (81%) and **2i** (65%). In addition, substrates with halide substituents on the aromatic rings were stably converted to the products (**2j**−**2l**) in good to moderate yields (68%−50%). Unsubstituted (**2m**) and alkyl-substituted (**2n**) aromatic rings proved to be good substrates for the reaction (70% and 77% yields).

In another set of experiments, we varied the R_2 group as in substrates **3a**−**3l** to investigate the steric effect and functional tolerance on the alkynic position (see Table 3). Longer alkyl chains from Me to *n*-Bu did not hinder the progress of the reaction to give **4a** (71%). Even the bulky cyclopentyl and cyclohexyl rings were found to be tolerant under the reaction conditions to give the desired products (**4b** (80%) and **4c** (63%)). Interestingly, the benzyl product (**4d**) was obtained in moderate yield (50%). Noticeably, the bis α-trifluoromethylated ketone (**4e**, 66%) can be formed when the CF_3-containing alkyne **3e** is used as a starting material. It is important to note here that terminal alkynes were also proven to be efficient substrates for the transformation, as shown in the examples of the formation of **4f**−**4h** in good to high yields (55%−70%). Most interestingly, we could also achieve the formation of the CF_3-containing ketoester **4i** in satisfactory yield (62%), thereby

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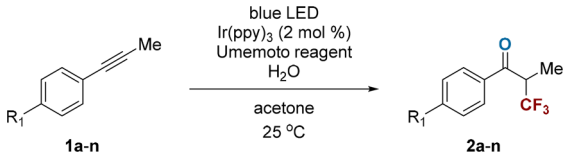
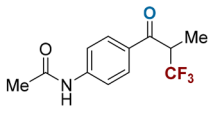
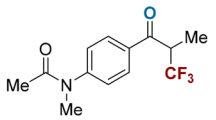
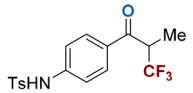
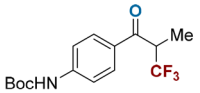
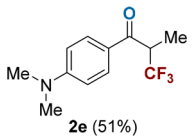
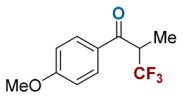
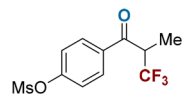
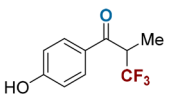
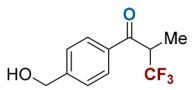
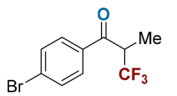
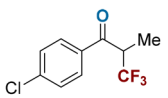
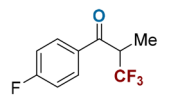
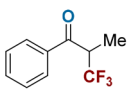
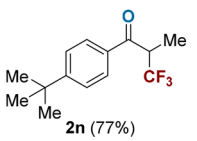
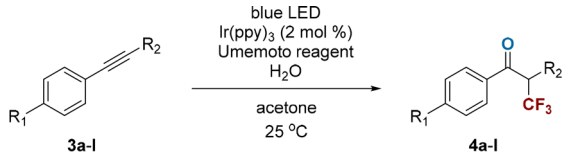
Table 2. Direct Oxidative Trifluoromethylation of Alkynes 1[a,b]

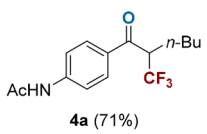
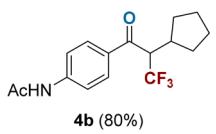
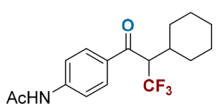
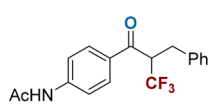
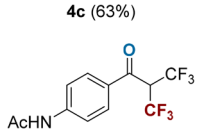
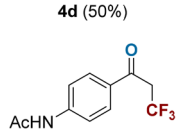
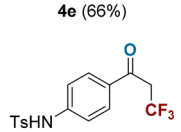
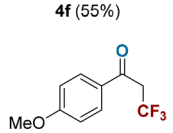
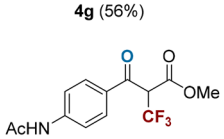
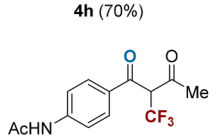
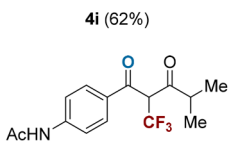
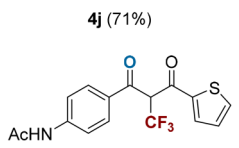


product	product
 **2a** (77%)	 **2b** (81%)
 **2c** (81%)	 **2d** (50%)
 **2e** (51%)	 **2f** (75%)
 **2g** (63%)	 **2h** (81%)
 **2i** (65%)	 **2j** (68%)
 **2k** (57%)	 **2l** (50%)
 **2m** (70%)	 **2n** (77%)

[a]Reactions were carried out under N_2 atmosphere at 25 °C for 12 h using alkyne (0.2 mmol), *fac*-Ir(ppy)$_3$ (2 mol %) and Umemoto's reagent (0.4 mmol). [b]Isolated yields after column chromatography are given in parentheses.

Table 3. Direct Oxidative Trifluoromethylation of Alkynes 3[a,b]



product	product
 **4a** (71%)	 **4b** (80%)
 **4c** (63%)	 **4d** (50%)
 **4e** (66%)	 **4f** (55%)
 **4g** (56%)	 **4h** (70%)
 **4i** (62%)	 **4j** (71%)
 **4k** (72%)	 **4l** (55%)

[a]Reactions were carried out under N_2 atmosphere at 25 °C for 12 h using alkyne (0.2 mmol), *fac*-Ir(ppy)$_3$ (2 mol %) and Umemoto's reagent (0.4 mmol). [b]Isolated yields after column chromatography are given in parentheses.

demonstrating the strong tolerability of the reaction and its extensibility to the synthesis of complex molecules.[14] Similarly, other 1,3-diketo compounds were produced with methyl (**4j** (71%)), isopropyl (**4k** (72%)), and heteroaromatic (**4l** (55%)) substitutions.

The formation of trifluoromethylated dicarbonyl products (**4i**–**4l**) highlights the importance of the protocol over previously reported procedures. The strong versatility in the application of dicarbonyl compounds as synthons is well-established and was demonstrated here by the synthesis of various trifluoromethylated heterocyclic compounds,[15] using the diketo product **4m** (Scheme 3).[16] For example, five-membered rings, such as isoxazole (**5a**, 62%) and pyrazole (**5b**, 57%) were efficiently synthesized by condensation with hydroxylamine hydrochloride and phenyl hydrazine, respectively.[17] Furthermore, simple urea treatment gave the 2-hydroxy pyrimidine product (**5c** (52%)). Particularly, the CF_3-incorporated pyrazole (**5b**) shares the core structure with the nonsteroidal anti-inflammatory drug (NSAID) Celecoxib and its structural analogues,[18] which highlights the high applicability of this methodology to the field of medicinal chemistry.

The reaction pathway was examined more closely by conducting isotope labeled experiments, as shown in Scheme 4. Even though the optimized solvent system is acetone/H_2O, in these experiments MeCN was used instead of acetone, because the high exchange rates of deuterium with the methyl protons of acetone[19] and ^{18}O with the carbonyl oxygen of acetone[20] would complicate the interpretation. When $H_2{}^{18}O$ was used under the optimized conditions, ^{18}O was incorporated into 87% of the product **6a** (see Scheme 4, eq 1). In addition, when D_2O was used, we observed that 72% of the deuterium was incorporated in the product **6b** (Scheme 4, eq 2). These isotope studies clearly show that the product is formed as a

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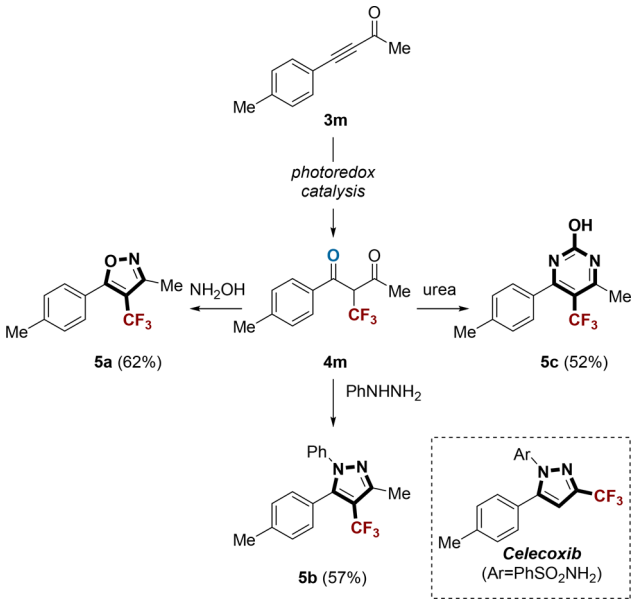
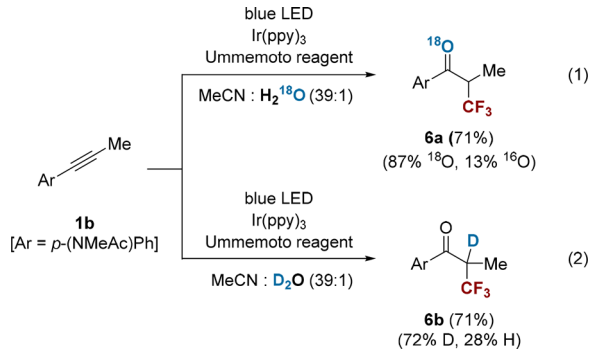
Scheme 3. Synthesis of CF_3-Containing Heterocyclic Compounds



Scheme 4. Isotope-Labeled Experiments



result of an attack by water and tautomerization of the enol, as depicted in Scheme 2.

In conclusion, we developed a direct oxidative trifluoromethylation using photoredox catalysis to obtain various α-CF_3 incorporated ketones from various alkynes. The mechanistic study revealed that H_2O can be used as a nucleophile, and that enol-keto tautomerization is occurring. The broad scope of functional group tolerance, operational simplicity, and the synthesis of various CF_3-incorporated heterocyclic compounds demonstrate the strong versatility of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00410.

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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