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## Radical Reactions

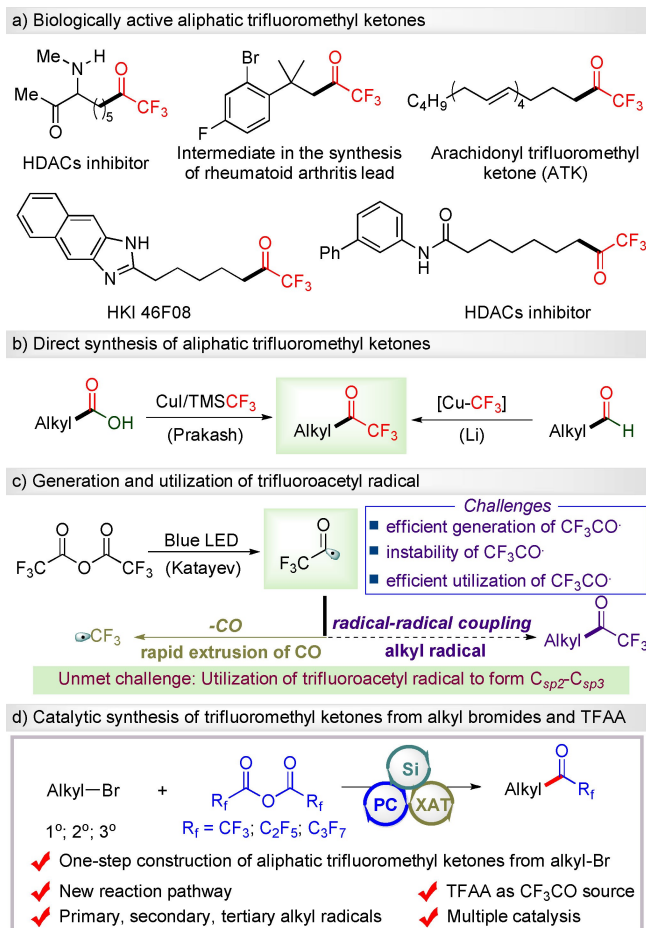
## Access to Trifluoromethylketones from Alkyl Bromides and Trifluoroacetic Anhydride by Photocatalysis

Hai-Wu Du, Yi-Dan Du, Xian-Wang Zeng, and Wei Shu\*

In memory of Professor Xiyan Lu.

**Abstract:** Aliphatic trifluoromethyl ketones are a type of unique fluorine-containing subunit which play a significant role in altering the physical and biological properties of molecules. Catalytic methods to provide direct access to aliphatic trifluoromethyl ketones are highly desirable yet remain underdeveloped, partially owing to the high reactivity and instability of trifluoroacetyl radical. Herein, we report a photocatalytic synthesis of trifluoromethyl ketones from alkyl bromides with trifluoroacetic anhydride. The reaction features dual visible-light and halogen-atom-transfer catalysis, followed by an enabling radical-radical cross-coupling of an alkyl radical with a stabilized trifluoroacetyl radical. The reaction provides straightforward access to aliphatic trifluoromethyl ketones from readily available and cost-effective alkyl halides and trifluoroacetic anhydride (TFAA).

Fluorine-containing compounds are widespread in pharmaceuticals, agrochemicals, and materials sciences due to their improved physicochemical properties, such as high thermal and chemical stability, high lipophilicity, and strong electronegativity, leading to enhanced biological activity.<sup>[1]</sup> In particular, trifluoromethyl ketones (TFMKs) represent one class of important fluorine-containing functional groups, which are widely found in bioactive targets (Figure 1a).<sup>[2]</sup> Moreover, TFMKs act as a powerful and selective coupling reagent, allowing for the introduction of the trifluoromethyl group into a wide range of substrates.<sup>[3]</sup> Additionally, TFMKs can also undergo various transformations, such as reduction<sup>[1c]</sup> and nucleophilic addition,<sup>[4]</sup> serving as highly valuable tools in the development of new synthetic methodologies. Traditional methods to access trifluoromethyl ketones heavily rely on stoichiometric trifluoromethylation of carbonyl compounds.<sup>[5]</sup> However, this method suffers



**Figure 1.** Significance and synthetic development of aliphatic trifluoromethyl ketones.

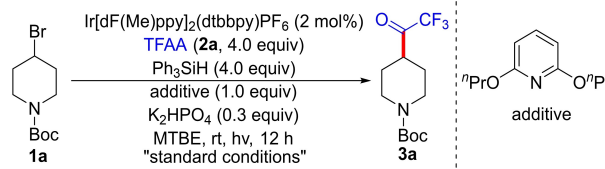
from low yields, multiple steps, use of expensive trifluoromethyl precursors and associated selectivity issues owing to the competing side reactions. In recent years, great efforts have been devoted to developing direct synthesis of TFMKs from readily available starting materials by the incorporation of a trifluoromethyl group. In 2018, the Li group reported an elegant example of oxidative trifluoromethylation of aldehydes mediated by (bpy)Cu(CF<sub>3</sub>)<sub>3</sub> in the presence of a silane (Figure 1b).<sup>[6]</sup> In 2021, Prakash and co-workers developed a copper-mediated trifluoromethylation of carboxylic acids by in situ generation of acyloxyphosphonium electrophiles in the presence of

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triphenyl phosphine.<sup>[7]</sup> However, catalytic methods for the synthesis of TFMKs remain unknown. Catalytic trifluoroacetylation of alkyl precursors is an attractive alternative for the synthesis of TFMKs yet extremely challenging for several reasons: 1) difficulties in accessing trifluoroacetyl radical; 2) fast decomposition of trifluoroacetyl radical, resulting in difficulties in cross-coupling between trifluoroacetyl radical and alkyl radicals. Recently, trifluoroacetic anhydride (TFAA) was found to be a cost-effective and ideal precursor. In 2021, Katayev and co-workers demonstrated a facile photocatalytic Giese-type trifluoroacetylation of olefins from TFAA (Figure 1c).<sup>[8]</sup> However, trifluoroacetyl radical is unstable and has a propensity to undergo rapid decarbonylation into carbon monoxide and trifluoromethyl radical.<sup>[9]</sup> Pan utilized this decarbonylation pathway of trifluoroacetyl radical to demonstrate that the resulting radical can be quenched by alkenes and arenes to yield trifluoromethylated products.<sup>[10]</sup> The instability of trifluoroacetyl radical introduces additional challenges in the radical coupling of trifluoroacetyl radical with alkyl radicals. To date, no strategies for utilizing trifluoroacetyl radicals that provide access to complementary alkylation products (TFMKs) have been successful (Figure 1c).<sup>[11]</sup> We envisioned the possibility of developing a new strategy to enhance the stability of trifluoroacetyl radical to enable subsequent alkylation reaction. Herein, we report an unprecedented protocol for the photoredox-catalyzed direct synthesis of TFMKs from readily available alkyl bromides and TFAA (Figure 1d). The reaction features the use of TFAA as a latent trifluoroacetyl radical and rapid utilization, allowing for the efficient trifluoroacetylation of primary, secondary, and tertiary alkyl bromides for the synthesis of aliphatic trifluoromethyl ketones.

We started the investigation using alkyl bromide **1a** and trifluoroacetic anhydride (TFAA, **2a**) as model substrates to evaluate the reaction conditions. After systematic evaluation of the reaction parameters, we defined the reaction of using Ir[dF(Me)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> (2 mol%) as catalyst, Ph<sub>3</sub>SiH as halogen atom transfer (XAT) reagent, K<sub>2</sub>HPO<sub>4</sub> (0.3 equiv) as base, 2,6-di-*n*-propoxypyridine (1.0 equiv) as additive in MTBE (0.33 M) under the irradiation of 30 W blue LEDs at room temperature as standard conditions, delivering trifluoroacetylation product **3a** in 80% isolated yield (Table 1, entry 1). Other tested photocatalysts gave inferior yields of **3a** (Table 1, entries 2–5). The reaction proceeded smoothly in the absence of base affording **3a** in 63% yield (Table 1, entry 9). Evaluation of base effect revealed that KOAc, Cs<sub>2</sub>CO<sub>3</sub> or organic base DABCO could mediate the reaction to afford the target product **3a** in lower yields (Table 1, entries 6–9). Evaluation of solvent effect revealed that the reaction proceeded smoothly in a wide range of solvents, delivering the optimal yields in ether solvents (Table 1, entries 10–13). Next, the selection of silane is essential for the success of the reaction (Table 1, entries 14–16). When Ph<sub>2</sub>SiH<sub>2</sub> was used instead of Ph<sub>3</sub>SiH, the yield of **3a** reduced to 52%. No desired trifluoroacetylation product **3a** was obtained using other types of silanes such as (TMS)<sub>3</sub>SiH and (MeO)<sub>3</sub>SiH. Moreover, the use of pyridine derivatives as additive significantly enhanced the yields of radical-radical

**Table 1:** Reaction condition optimization.<sup>[a]</sup>

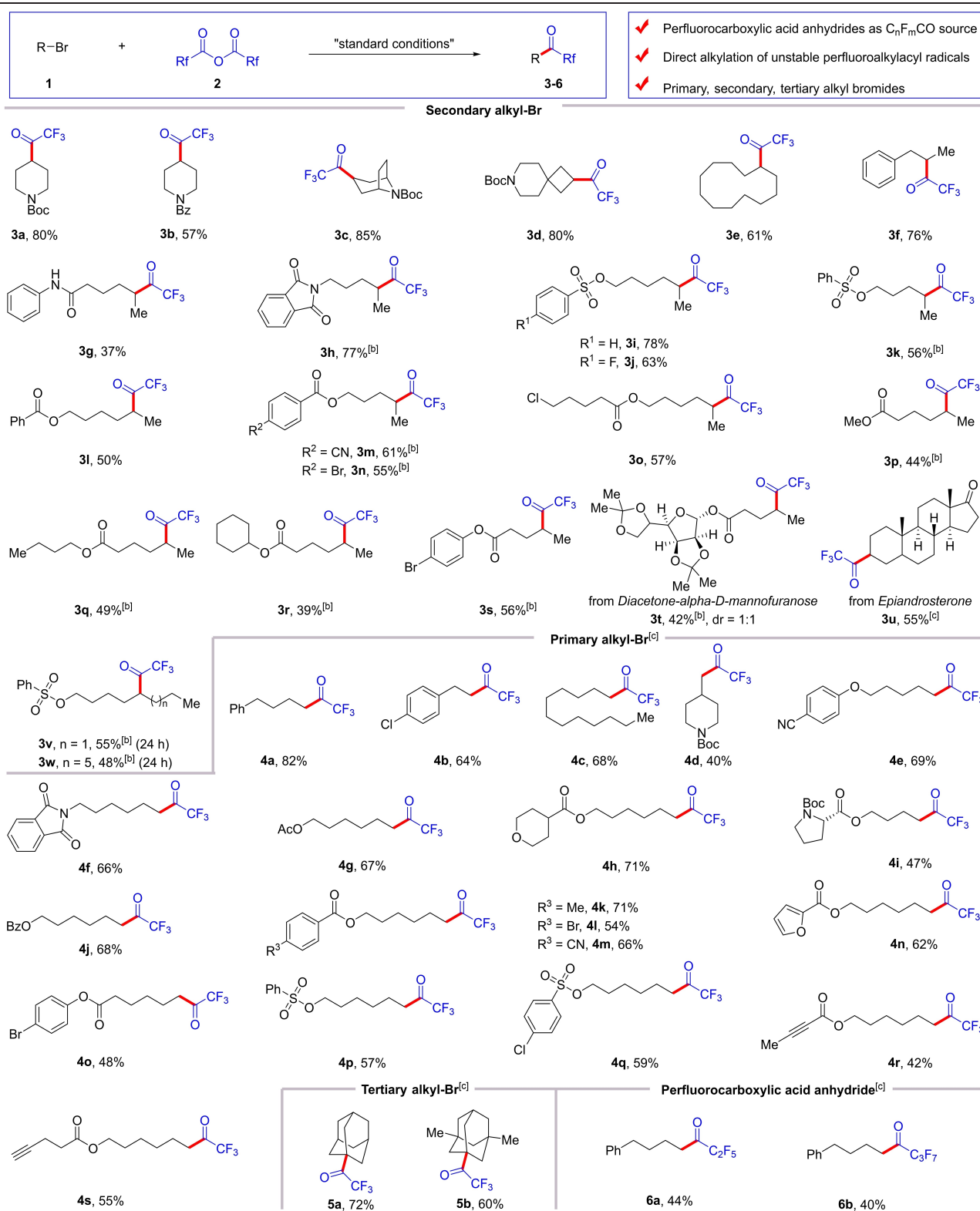


Entry	Variation from "standard conditions"	Yield of <b>3a</b> [%]
1	none	85 (80)
2	Ir(ppy) <sub>3</sub> as PC	15
3	Ru(bpy) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub> as PC	N.D.
4	4CzIPN as PC	24
5	Eosin Y as PC	N.D.
6	KOAc instead of K <sub>2</sub> HPO <sub>4</sub>	67
7	Cs <sub>2</sub> CO <sub>3</sub> instead of K <sub>2</sub> HPO <sub>4</sub>	55
8	DABCO instead of K <sub>2</sub> HPO <sub>4</sub>	70
9	no base	63
10	THF instead of MTBE	76
11	DMF instead of MTBE	trace
12	CH <sub>3</sub> CN instead of MTBE	43
13	toluene instead of MTBE	10
14	Ph <sub>2</sub> SiH <sub>2</sub> instead of Ph <sub>3</sub> SiH	52
15	(TMS) <sub>3</sub> SiH instead of Ph <sub>3</sub> SiH	N.D.
16	(MeO) <sub>3</sub> SiH instead of Ph <sub>3</sub> SiH	N.D.
17	pyridine as additive	trace
18	2,6-dichloropyridine as additive	48
19	2,6-dimethoxypyridine as additive	72
20	no additive	58
21	no PC/No Ph <sub>3</sub> SiH/no light	N.D.

[a] Reaction conditions: Unless otherwise noted, a mixture of **1a** (0.10 mmol), **2a** (0.40 mmol), Ir[dF(Me)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> (2 mol%), Ph<sub>3</sub>SiH (0.40 mmol), K<sub>2</sub>HPO<sub>4</sub> (0.03 mmol), additive (0.10 mmol) in MTBE (0.33 M) under N<sub>2</sub> was irradiated with 30 W blue LEDs at room temperature for 12 h. Yield was determined by <sup>1</sup>H NMR analysis of the crude mixture using PhTMS as the internal standard. Yield of the isolated product after flash chromatography is shown in parentheses. PC = photocatalyst, N.D. = not detected, DABCO = triethylenediamine, MTBE = *tert*-butyl methyl ether, DMF = *N,N*-dimethylformamide.

coupling product **3a** (Table 1, entries 17–20). Control experiments showed that photocatalyst, silane and light were all required for this desired transformation (Table 1, entry 21).

With the optimized reaction conditions in hand, we set out to explore the scope of this transformation (Table 2). This protocol tolerated a broad spectrum of functional groups with diverse substitution patterns with respect to alkyl bromides. First, the functional group compatibility of secondary alkyl bromides was investigated. Both cyclic and acyclic alkyl bromides could be successfully transformed into corresponding alkyl trifluoromethyl ketones (**3a–3w**). The secondary cyclic alkyl bromides containing *N*-Boc (**3a**), *N*-Bz (**3b**) functional groups, as well as secondary cyclic alkyl bromides with bridged cyclic (**3c**) and spirocyclic (**3d**) structures could be converted into the corresponding target compounds in good yields. In addition, 1-bromocyclododecane was successfully trifluoroacetylated in 61% yield (**3e**). Acyclic secondary alkyl bromides are also good substrates for the photocatalytic trifluoroacetylation reaction (**3f–3w**). 2-Bromophenylpropane was converted into the correspond-

**Table 2:** Scope for the photocatalyzed trifluoroacetylation of alkyl bromides.<sup>[a]</sup>

[a] Standard conditions were used unless otherwise stated. For details of standard conditions, see Table 1, entry 1. [b] Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(5,5'-dCF<sub>3</sub>bpy)PF<sub>6</sub> was used as the PC. [c] Acid anhydride (6.0 equiv), Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(5,5'-dCF<sub>3</sub>bpy)PF<sub>6</sub> (2 mol%), Ph<sub>3</sub>SiH (8.0 equiv), K<sub>2</sub>HPO<sub>4</sub> (1.0 equiv), 20 h.



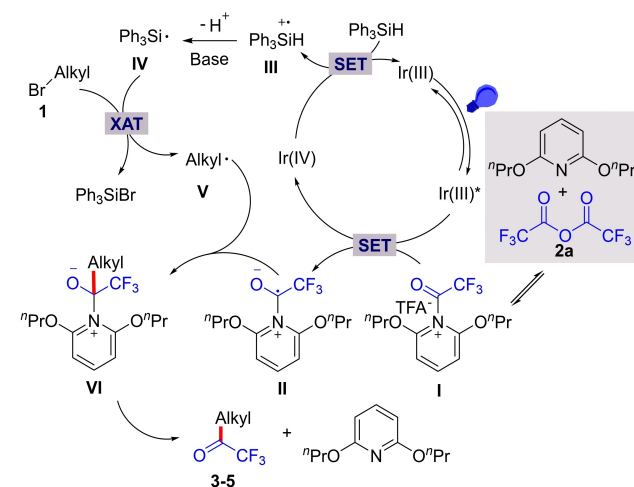
quench effect to excited photocatalyst (Ir(III)\*) than the mixture of TFAA with pyridine additive.

Based on the experimental results and literature precedent,<sup>[9,14]</sup> a possible mechanism for this reaction is proposed and depicted in Scheme 2. First, TFAA and pyridine derivative form a highly redox-reactive adduct intermediate **I**,<sup>[15]</sup> which undergoes a single-electron-transfer (SET) process with the excited photocatalyst Ir(III)\* to generate the radical zwitterionic intermediate **II** and Ir (IV). The oxidative Ir (IV) ( $E_{1/2}^{Ox} [Ir^{III}/Ir^{IV}] = 1.94$  V vs. SCE for  $Ir[dF(CF_3)ppy]_2(5,5'-dCF_3bpy)PF_6$ )<sup>[16]</sup> oxidized triphenyl silane ( $E_{1/2}^{Ox} = 0.81$  V vs SCE)<sup>[17]</sup> to regenerate Ir(III) and form cationic radical **III**, which could form a silicon-centered radical (**IV**). Halogen atom transfer (XAT) between alkyl bromides (**1**) with **IV** generated triphenyl silane bromide and alkyl radical **V**,<sup>[18]</sup> which could rebound with **II** to form zwitterionic intermediate **VI**. Release of pyridine from **VI** gave the desired alkyl trifluoromethyl ketones **3-5**. At this stage, the direct quench of excited photocatalyst by TFAA could not be completely ruled out.

In summary, a photocatalyzed trifluoroacetylation of alkyl bromides was developed to provide direct access to perfluoroalkyl ketones. The reaction features the use of TFAA as the latent trifluoroacetyl radical precursor, which is prone to extrusion of carbon monoxide to form trifluoromethyl radical. Notably, primary, secondary, and tertiary alkyl bromides are all well-tolerated and deliver diverse TFMKs. Moreover, the reaction could be extended perfluoroalkyl acylation of alkyl bromides with the corresponding anhydrides. The mild protocol enables the direct radical coupling of trifluoroacetyl radical with alkyl radicals, providing a straightforward and efficient method to access active trifluoromethyl ketones.

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**Scheme 2.** Proposed mechanism for the reaction.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Anhydrides · Halogen Atom Transfer · Photocatalysis · Radical-Radical Coupling · Trifluoroacetylation

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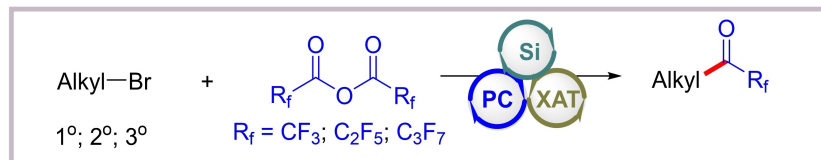
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## Communications

## Radical Reactions

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Access to Trifluoromethylketones from Alkyl Bromides and Trifluoroacetic Anhydride by Photocatalysis



Catalytic methods for direct access to aliphatic trifluoromethyl ketones from feedstocks remain underdeveloped, partially owing to the high reactivity and instability of the trifluoroacetyl radical. Reported herein is the photocatalytic synthesis of trifluoromethyl ketones

from alkyl bromides and trifluoroacetic anhydride. The reaction features visible-light catalysis and halogen-atom transfer (XAT), followed by an enabling radical-radical cross-coupling of the alkyl radical with a stabilized trifluoroacetyl radical.