#### **Radical Reactions**

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

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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 trifluoromethyl radical. The reaction provides straightforward access to aliphatic trifluoromethyl ketones from readily available and costeffective alkyl halides and trifluoroacetic anhydride (TFAA).

**F**luorine-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

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*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 f 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 undergoing 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,  $K_2$ 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.[a]

Br N Boc 1a	Ir[dF(Me)ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub> (2 mol%) O TFAA ( <b>2a</b> , 4.0 equiv) Ph <sub>3</sub> SiH (4.0 equiv) additive (1.0 equiv) K <sub>2</sub> HPO <sub>4</sub> (0.3 equiv) MTBE, rt, hv, 12 h "standard conditions"	<sup>3</sup> <sup>n</sup> PrONO <sup>n</sup> F additive
Entry	Variation from "standard conditions"	Yield of <b>3 a</b> [%]
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	none $Ir(ppy)_3$ as PC $Ru(bpy)_3(PF_6)_2$ as PC 4CzIPN as PC Eosin Y as PC KOAc instead of $K_2HPO_4$ $Cs_2CO_3$ instead of $K_2HPO_4$ DABCO instead of $K_2HPO_4$ no base THF instead of MTBE DMF instead of MTBE CH_3CN instead of MTBE toluene instead of MTBE $Ph_2SiH_2$ instead of Ph_3SiH (TMS)_3SiH instead of Ph_3SiH (MeO)_3SiH instead of Ph_3SiH (MeO)_3SiH instead of Ph_3SiH pyridine as additive 2,6-dichloropyridine as additive	85 (80) 15 N.D. 24 N.D. 67 55 70 63 76 trace 43 10 52 N.D. N.D. trace 48 72
20 21	no additive no PC/No Ph₃SiH/no light	58 N.D.

[a] Reaction conditions: Unless otherwise noted, a mixture of **1a** (0.10 mmol), **2a** (0.40 mmol),  $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$  (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-

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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]  $Ir[dF(CF_3)ppy]_2(5,5'-dCF_3ppy)PF_6$  was used as the PC. [c] Acid anhydride (6.0 equiv),  $Ir[dF(CF_3)ppy]_2(5,5'-dCF_3ppy)PF_6$  (2 mol%),  $Ph_3SiH$  (8.0 equiv),  $K_2HPO_4$  (1.0 equiv), 20 h.

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ing trifluoromethyl ketone (3f) in 76% yield. Moreover, secondary alkyl bromides containing amides with free N-H (3g), imides (3h), sulfonates (3i-3k), esters (3l-3s), and nitriles (3m) could be tolerated in the reaction, giving desired products in moderate to good yields. In addition, halogens (3n, 3o, 3s) are compatible with the reaction conditions, leaving chemical space for further elaboration. Interestingly, this photocatalytic direct trifluoroacetylation strategy is applicable to late-stage functionalization of complex molecules. Glycosides and epiandrosterone based bromides were trifluoroacetylated to deliver the desired trifluoromethyl ketones (3t and 3u) in moderate yields. More steric hindered acyclic secondary alkyl bromides also successfully underwent trifluoroacetylation to give the corresponding target compounds in 55% and 48% yields (3v and 3w), respectively. Next, the scope of primary alkyl bromides was examined. Notably, a variety of primary alkyl bromides are good substrates for this photocatalytic direct trifluoroacetvlation reaction with TFAA. Phenylbutyl (4a) and *p*-chlorophenylethyl (4b) trifluoromethyl ketones can be obtained from corresponding alkyl bromides in 82 % and 64 % yields. 1-Bromodedecane was successfully converted to dedecanyl trifluoromethyl ketone (4c) in 68% yield. In addition, primary alkyl bromides with N-Boc (4d), aryl ethers (4e), phthalimides (4f), esters (4g-4o), and sulfonates (4p and 4q) could all be well-tolerated in this transformation. Partial debromination of aryl bromides was observed (41 and 40) under the reaction conditions. It is worth mentioning that the reaction also tolerated internal and terminal alkynes to give corresponding trifluoromethyl ketones (4r and 4s) in 42% and 55% yields, respectively. Additionally, tertiary alkyl bromides were tested and proved successful for this reaction, affording adamantanyl and 3,5dimethyladamantanyl trifluoromethyl ketones in 72% (5a) and 60% (5b) yields from corresponding tertiary alkyl bromides. Impressively, this protocol could be successfully extended to perfluoroalkyl carboxylic acid anhydrides, affording corresponding perfluoroalkyl ketones with alkyl bromides in synthetic useful yields (6a and 6b).

To further illustrate the synthetic utility of this photocatalytic direct trifluoroacetylation reaction of alkyl bromides, the reaction was successfully carried out on 1.0 mmol scale, affording the desired trifluoroacetylated product 3a in 72% isolated yield (Scheme 1a). Moreover, this method could be applied to direct synthesis of the pharmaceutical active molecule 7 in 39% yield from corresponding alkyl bromide in one step. The compound 7 is a class of histone deacetylase inhibitors that widely used in biomedicine and other fields (Scheme 1b).<sup>[12]</sup> Then, a series of experiments were carried out to probe the reaction mechanism. First, the reaction was conducted in the presence of a radical scavenger under otherwise standard conditions (Scheme 1c). Radical scavengers, such as butylated hydroxytoluene (BHT), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,1-diphenylethylene all inhibited the reaction, delivering trace amount of adducts of trifluoroacetyl radical, indicating the reaction might be a radical course and that trifluoroacetyl radical may be generated and serve as intermediate for the reaction. Next, light on-off experiments were carried a) Scale-up reaction (1.0 mmol scale)



Scheme 1. Synthetic applications and mechanistic investigations.

out. It is found that this transformation could not proceed in the absence of light (Scheme 1d). The results suggested the reaction may undergo a catalytic radical reaction instead of a radical chain pathway.<sup>[13]</sup> Moreover, luminescence quenching experiments with different components were examined in the reaction of 1a with TFAA under the standard conditions. As shown in Scheme 1e, the mixture of TFAA with pyridine additive showed significantly enhanced quench effect on excited photocatalyst (Ir(III)\*) versus that of TFAA, whereas alkyl bromide 1a, silane or additive did not show significant quench effect of excited photocatalyst. The results indicated the photocatalyst is likely to be quenched by the adduct of TFAA and pyridine derivatives. To further prove the hypothesis, N-trifluoroacetyl pyridinium salt was isolated and tested in the luminescence quenching experiments (Figs. S10 and S11), which showed much stronger

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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)  $(E_{1/2}^{Ox} [Ir^{III}/Ir^{IV}] = 1.94 \text{ V vs. SCE for}$  $Ir[dF(CF_3)ppy]_2(5,5'-dCF_3bpy)PF_6)^{[16]}$  oxidized triphenyl silane  $(E_{1/2}^{Ox}=0.81 \text{ V vs SCE})^{[17]}$  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  $\mathbf{V}_{,}^{[18]}$  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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dong Basic and Applied Basic Research Foundation (2022A1515011806), Department of Education of Guangdong Province (2022JGXM054 and 2021KTSCX106), The Pearl River Talent Recruitment Program (2019QN01Y261), Shenzhen Science and Technology Innovation Committee (JCYJ20220519201425001), and Guangdong Provincial Key Laboratory of Catalysis (no. 2020B121201002) is sincerely acknowledged. We acknowledge the assistance of the SUSTech Core Research Facilities. We thank Dr. Lin Min (SUSTech) for reproducing the results of **3e**, **3r**, **4a**, and **4m**.

#### 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

- a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 2008, 37, 320–330; b) J. Wang, M. Sanchez-Rosello, J. Asena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, Chem. Rev. 2014, 114, 2432–2506; c) T. Fujiwara, D. O'Hagan, J. Fluorine Chem. 2014, 167, 16–29; d) N. A. Meanwell, J. Med. Chem. 2018, 61, 5822–5880; e) H. Yan, C. Zhu, Sci. China Chem. 2017, 60, 214–222; f) M. Drouin, J. Gamel, J. Paquin, Synthesis 2018, 50, 881–996; g) T. Furuya, A. S. Kamlet, T. Ritter, Nature 2011, 473, 470–477; h) K. Müller, C. Faeh, F. Diederich, Science 2007, 317, 1881–1886; i) H. Tang, X. Zhang, Y. Zhang, C. Feng, Angew. Chem. Int. Ed. 2020, 59, 5242–5247; j) W. K. Hagmann, J. Med. Chem. 2008, 51, 4359–4369.
- [2] a) H.-X. Huang, S.-J. Jin, J. Gong, D. Zhang, H. Song, Y. Qin, *Chem. Eur. J.* 2015, 21, 13284–13290; b) Y. Wang, Z. Yu, H. Yuan, H. Chen, N. Xie, Z Wang, Q. Sun, W. Zhan, *Bioorg. Chem.* 2021, 106, 104461; c) C.-J. Gong, A.-H. Gao, Y.-M. Zhang, M.-B. Su, F. Chen, L. Sheng, Y.-B. Zhou, J.-Y. Li, J. Li, F.-J. Nan, *Eur. J. Med. Chem.* 2016, 112, 81–90; d) J. Cai, H. Wei, K. H. Hong, X. Wu, X. Zong, M. Cao, P. Wang, L. Li, C. Sun, B. Chen, G. Zhou, J. Chen, M. Ji, *Bioorg. Med. Chem.* 2015, 23, 3457–3471; e) A. Dominguez, M. Puigmarti, M. P. Bosch, G. Rosell, R. Crehuet, A. Ortiz, C. Quero, A. Guerrero, *J. Agric. Food Chem.* 2016, 64, 3523–3532; f) C. Meyners, M. Mertens, P. Wessig, F. Meyer-Almes, *Chem. Eur. J.* 2017, 23, 3107–3116.
- [3] a) C. Zhu, R. Zhu, H. Zeng, F. Chen, C. Liu, W. Wu, H. Jiang, Angew. Chem. Int. Ed. 2017, 56, 13324–13328; b) A. Cheng, L. Zhang, Q. Zhou, T. Liu, J. Cao, G. Zhao, K. Zhang, G. Song, B. Zhao, Angew. Chem. Int. Ed. 2021, 60, 20166–20172; c) T. He, C. Liang, S. Huang, Chem. Sci. 2023, 14, 143–148; d) M. Moens, N. D. Kimpe, M. D'hooghe, J. Org. Chem. 2014, 79, 5558–5568; e) Z. Yuan, S. Chen, Z. Weng, Org. Chem. Front. 2020, 7, 482–486; f) Q.-L. Wang, H. Huang, M. Zhu, T. Xu, G. Mao, G.-J. Deng, Org. Lett. 2023, 25, 3800–3805.

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- [4] a) J. H. Park, J. H. Sim, C. E. Song, Org. Lett. 2019, 21, 4567–4570; b) L. Dai, S. Ye, ACS Catal. 2020, 10, 994–998; c) N. W. Mszar, M. S. Mikus, S. Torker, F. Haeffner, A. H. Hoveyda, Angew. Chem. Int. Ed. 2017, 56, 8736–8741; d) J. Wang, W.-G. Kong, F. Li, J. Liu, Q. Shen, L. Liu, W.-X. Zhao, Org. Biomol. Chem. 2015, 13, 5399–5406; e) Y. Zheng, Y. Tan, K. Harms, M. Marsch, R. Riedel, L. Zhang, E. Meggers, J. Am. Chem. Soc. 2017, 139, 4322–4325; f) C. Pareja, E. Martín-Zamora, R. Fernández, J. M. Lassaletta, J. Org. Chem. 1999, 64, 8846–8854; g) K. Yearick, C. Wolf, Org. Lett. 2008, 10, 3915–3918; h) X.-H. He, Y.-L. Ji, C. Peng, B. Han, Adv. Synth. Catal. 2019, 361, 1923–1957.
- [5] a) C. B. Kelly, M. A. Mercadantea, N. E. Leadbeater, *Chem. Commun.* **2013**, *49*, 11133–11148; b) M. Kirihara, K. Suzuki, K. Nakakura, K. Saito, R. Nakamura, K. Tujimoto, Y. Sakamoto, Y. Kikkawa, H. Shimazu, Y. Kimura, *J. Fluorine Chem.* **2021**, *243*, 109719; c) X. Liu, L. Liu, T. Huang, J. Zhang, Z. Tang, C. Li, T. Chen, *Org. Lett.* **2021**, *23*, 4930–4934; d) A. Sanz-Marco, G. Blay, M. C. Muñoz, J. R. Pedro, *Chem. Eur. J.* **2016**, *22*, 10057–10064; e) L. Anthore, S. Z. Zard, *Org. Lett.* **2015**, *17*, 3058–3061; f) T. C. Judd, D. B. Brown, *Tetrahedron Lett.* **2017**, *58*, 4455–4458; g) Y. Zhou, D. Yang, G. Luo, Y. Zhao, Y. Luo, N. Xue, J. Qu, *Tetrahedron* **2014**, *70*, 4668–4674; h) Y. Kadoh, M. Tashiro, K. Oisaki, M. Kanai, *Adv. Synth. Catal.* **2015**, *357*, 2193–2198.
- [6] P. Zhang, H. Shen, L. Zhu, W. Cao, C. Li, Org. Lett. 2018, 20, 7062–7065.
- [7] X. Ispizua-Rodriguez, S. B. Munoz, V. Krishnamurti, T. Mathew, G. K. S. Prakash, *Chem. Eur. J.* **2021**, *27*, 15908– 15913.
- [8] K. Zhang, D. Rombach, N. Y. Nötel, G. Jeschke, D. Katayev, Angew. Chem. Int. Ed. 2021, 60, 22487–22495.
- [9] a) W. Wu, Y. You, Z. Weng, *Chin. Chem. Lett.* 2022, *33*, 4517–4530;
  b) J. W. Beatty, J. J. Douglas, K. P. Cole, C. R. J. Stephenson, *Nat. Commun.* 2015, *6*, 7919.

- [10] Y. Song, B. Zheng, S. Yang, Y. Li, Q. Liu, L. Pan, Org. Lett. 2023, 25, 2372–2376.
- [11] S. Han, K. L. Samony, R. N. Nabi, C. A. Bache, D. K. Kim, J. Am. Chem. Soc. 2023, 145, 11530–11536.
- [12] A. S. Madsen, C. A. Olsen, Med. Chem. Comm. 2016, 7, 464– 470.
- [13] X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, M. B. André, W.-J. Xiao, Angew. Chem. Int. Ed. 2014, 53, 12163– 12167.
- [14] a) J.-J. Chen, H.-M. Huang, *Tetrahedron Lett.* **2022**, *102*, 153945; b) S. Crespi, M. Fagnoni, *Chem. Rev.* **2020**, *120*, 9790–9833; c) F. Juliá, T. Constantin, D. Leonori, *Chem. Rev.* **2022**, *122*, 2292–2352.
- [15] a) J. A. King, J. Am. Chem. Soc. 1988, 110, 5764–5767; b) U. Anthoni, D. Christensen, C. Christophersen, H. Nielsen, Acta Chem. Scand. 1995, 49, 203–206.
- [16] a) S. Ladouceur, D. Fortin, E. Zysman-Colman, *Inorg. Chem.* 2011, 50, 11514–11526; b) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu, R. R. Knowles, *Nature* 2016, 539, 268–271.
- [17] J. Zhu, W.-C. Cui, S. Wang, Z.-J. Yao, Org. Lett. 2018, 20, 3174–3178.
- [18] a) C. Chatgilialoglu, Acc. Chem. Res. 1992, 25, 188–194; b) M. Ballestri, C. Chatgilialoglu, K. B. Clark, D. Griller, B. Giese, B. Kopping, J. Org. Chem. 1991, 56, 678–683; c) P. Zhang, C. C. Le, D. W. C. MacMillan, J. Am. Chem. Soc. 2016, 138, 8084–8087; d) R. T. Smith, X. Zhang, J. A. Rincon, J. Agejas, C. Mateos, M. Barberis, S. García-Cerrada, O. Frutos, D. W. C. MacMillan, J. Am. Chem. Soc. 2018, 140, 17433–17438; e) G. H. Lovett, S. Chen, X.-S. Xue, K. N. Houk, D. W. C. MacMillan, J. Am. Chem. Soc. 2019, 141, 20031–20036.

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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 visiblelight catalysis and halogen-atom transfer (XAT), followed by an enabling radicalradical cross-coupling of the alkyl radical with a stabilized trifluoroacetyl radical.