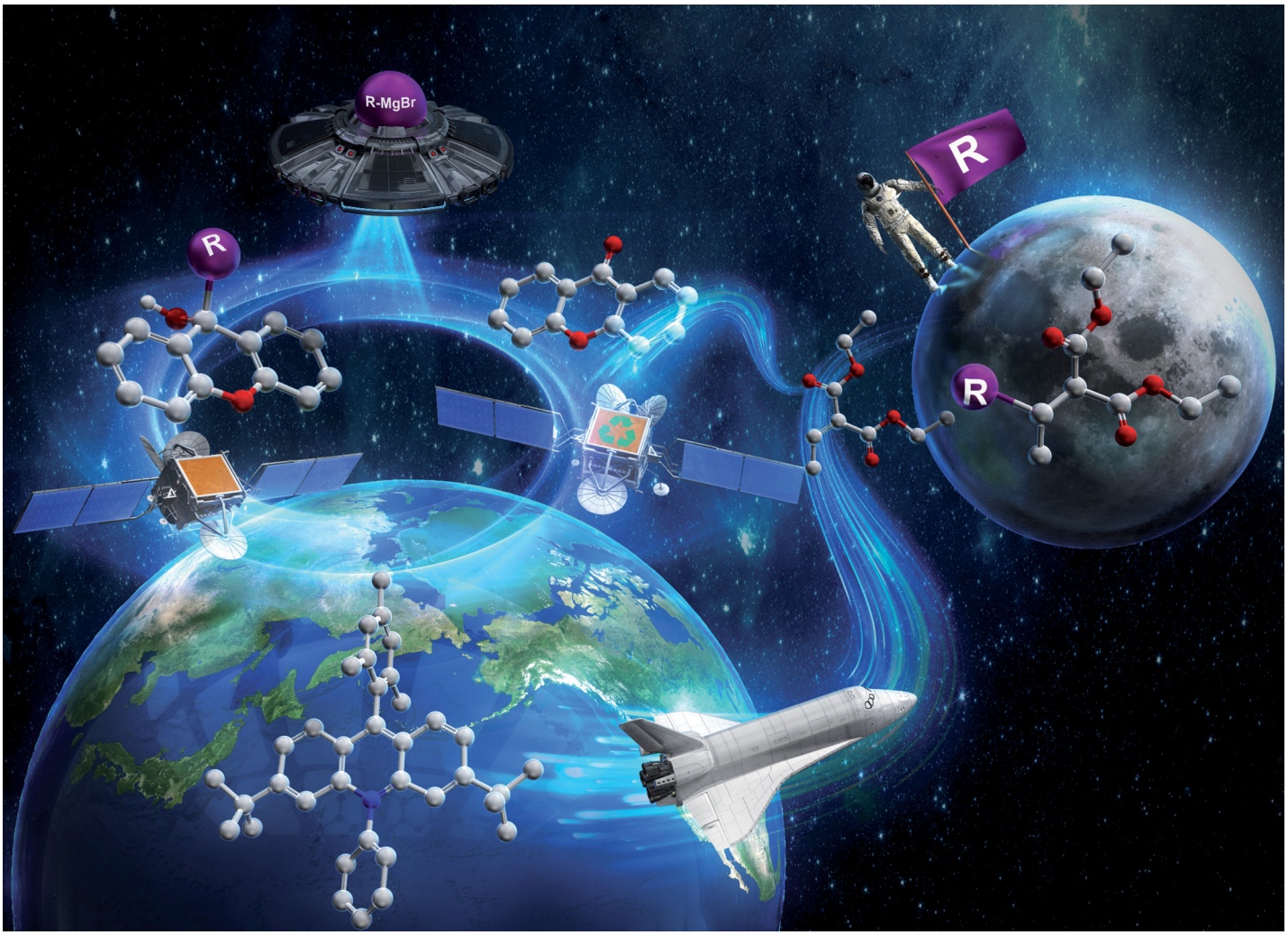

Showcasing research from Professor Kenta Tanaka's laboratory, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama, JAPAN.

Generation of alkyl radicals *via* C(sp^3)–C(sp^3) bond cleavage of xanthene-based precursors for photocatalytic Giese-type reaction

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Generation of alkyl radicals *via* C(sp^3)–C(sp^3) bond cleavage of xanthene-based precursors for photocatalytic Giese-type reaction

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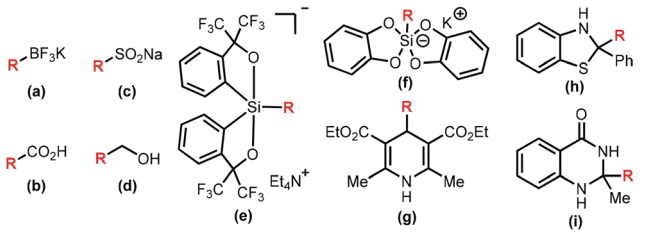
Novel xanthene-based alkyl radical precursors were developed and subjected to photocatalytic C(sp^3)–C(sp^3) bond cleavage for the efficient generation of alkyl radicals, which were subsequently reacted with various alkenes to afford the corresponding Giese-type products. After the reaction, the produced xanthones can be recovered in high yield.

Alkyl radicals are essential and versatile reactive species in organic chemistry. For their generation, the single-electron oxidation of electron-rich precursors is a crucial method. A variety of useful alkyl-radical precursors have been developed (Scheme 1), with a particular focus on the generation of alkyl radicals through carbon–heteroatom bond cleavage.[1–3] In contrast to the numerous studies on the generation of alkyl radicals *via* carbon–heteroatom bond cleavage, the cleavage of C(sp^3)–C(sp^3) bonds to form alkyl radicals remains largely unexplored, with the existing examples being restricted to the use of 1,4-dihydropyridines,[4] benzothiazolines,[5] dihydroquinazolinones.[6] More recently, photocatalytic cleavage of bulky and inert C(sp^3)–C(sp^3) bonds in alcohols[7] and the photoredox cleavage of C(sp^3)–C(sp^3) bonds in aromatic hydrocarbons have been developed.[8] Therefore, the development of novel alkyl-radical precursors for the generation of alkyl radicals *via* C(sp^3)–C(sp^3) bond cleavage is still highly desirable.

Recently, Knowles and coworkers have reported a new photocatalytic protocol for the redox-neutral isomerization of cyclic alcohols to linear ketones *via* C–C bond scission (Scheme 2(a)).[9] Specifically, the single-electron oxidation of tertiary cyclic alcohols that bear a *p*-methoxyphenyl (PMP) group using photoredox catalysts can produce alkoxy radicals under Brønsted-base-promoted proton-coupled-electron-transfer (PCET) conditions, enabling the ring-opening reaction *via* β-scission of the neighboring C–C bond to generate an aryl ketone and a new alkyl radical.

Motivated by these results, we designed novel xanthene-based alkyl-radical precursors that efficiently undergo C(sp^3)–C(sp^3) bond cleavage to generate alkyl radicals *via* photoredox catalysis (Scheme 2(b)). In our working hypothesis (Scheme 2(c)), xanthene-based alkyl-radical precursor **A** undergoes one-electron oxidation by the action of a photoredox catalyst to generate radical-cation intermediate **B**. Subsequent PCET between the hydroxyl group and the radical cation would result in the formation of alkoxyl radical **C**. Finally, β-scission of the C(sp^3)–C(sp^3) bond generates alkyl radical **D** and xanthone **E**. The xanthone could potentially be easily recovered and reconverted to alkyl-radical precursor **A** using organometallic reagents in a one-step process. This last step is particularly attractive because although various alkyl-radical precursors have been developed, the recovery of the core structure of the precursor remains less explored (*e.g.*, Scheme 1(e)).[3] More recently, a fluoroalkylation of alkenes *via* C(sp^3)–C(sp^3) bond cleavage of quaternary fluoroalkyl alcohols in the presence of a base and trifluoroethanol has been developed in 2025.[10] Despite being useful for the generation of fluoroalkyl radicals from xanthene-based precursors, this method requires a stoichiometric amount of base and trifluoroethanol, is limited to xanthene precursors substituted with fluoroalkyl groups, and



Scheme 1 Examples of electron-rich alkyl-radical precursors.

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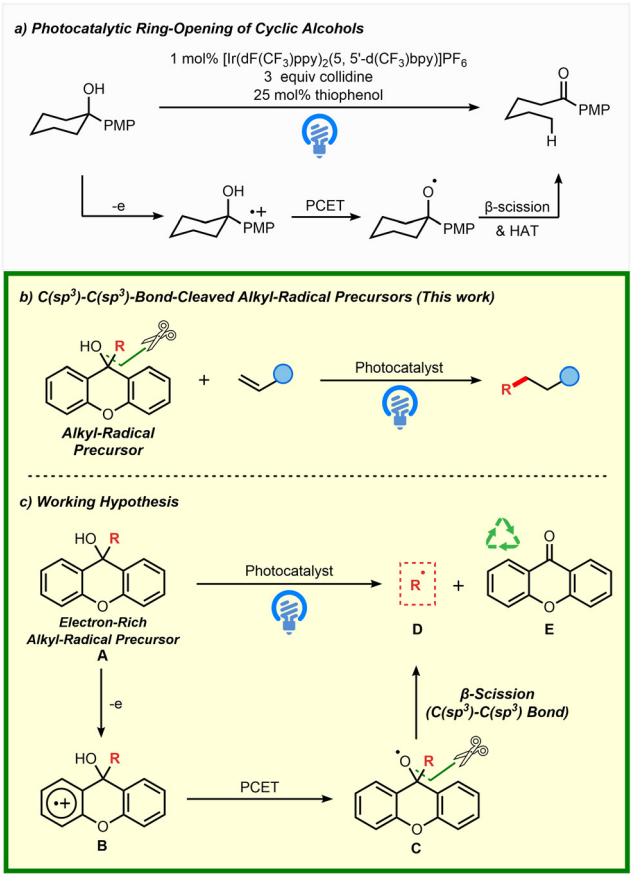
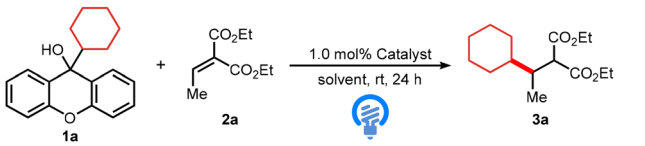


Scheme 2 C(sp^3)–C(sp^3) bond cleavage in alkyl-radical precursors.

does not address the recovery of the produced xanthones. Herein, we report the C(sp^3)–C(sp^3) bond cleavage of xanthene-based alkyl-radical precursors for the photocatalytic Giese-type reaction and the recovery of the resulting xanthones.

We initially investigated the reaction of alkyl-radical precursor **1a** with alkene **2a** in the presence of an organophotoredox catalyst at room temperature under blue-light irradiation for 24 h (Table 1). Eosin Y and 4CzIPN did not promote the reaction owing to their low excited-state reduction potentials (Eosin Y: $E_{1/2}$ ($C^*/C^{\bullet-}$) = +1.23 V *vs.* SCE; 4CzIPN: $E_{1/2}$ ($C^*/C^{\bullet-}$) = +1.35 V *vs.* SCE) compared with the oxidation potential of **1a** ($E_{p/2}$ = +1.75 V *vs.* SCE; Table 1, entries 1 and 2).[11] The reaction furnished the desired product when using the moderately oxidizing catalyst TXT ($E_{1/2}$ ($C^*/C^{\bullet-}$) = +1.76 V *vs.* SCE; Table 1, entry 3).[12] Strongly oxidizing photocatalysts such as Me-Acr-Mes and Ph-Acr-Mes yielded the product in moderate-to-high yield. These results suggest that these catalysts can smoothly oxidize alkyl-radical precursor **1a** owing to their high excited-state reduction potentials (Me-Acr-Mes: $E_{1/2}$ ($C^*/C^{\bullet-}$) = +2.08 V *vs.* SCE; Ph-Acr-Mes: $E_{1/2}$ ($C^*/C^{\bullet-}$) = +2.15 V *vs.* SCE; Table 1, entries 4 and 5). Toluene decreased the yield of the product, whereas medium-to-high polar solvents were tolerated (Table 1, entries 6–9). Conducting the reaction for 6 h also gave a high yield of the corresponding product (Table 1, entry 10). The xanthene alkyl-radical precursor bearing methoxy group led to a significantly lower product yield in 18%.[13] This result

Table 1 Photocatalytic Giese-type reaction of xanthene-based precursor **1a**[a]



Entry	Catalyst	Solvent	Yield (%)
1	Eosin Y	EtOH	0
2	4CzIPN	EtOH	0
3	TXT	EtOH	5
4	Me-Acr-Mes	EtOH	69
5	Ph-Acr-Mes	EtOH	82
6	Ph-Acr-Mes	Toluene	27
7	Ph-Acr-Mes	DMF	59
8	Ph-Acr-Mes	THF	66
9	Ph-Acr-Mes	CH_2Cl_2	71
10[b]	Ph-Acr-Mes	EtOH	83
11[b]	—	EtOH	0
12[bc]	Ph-Acr-Mes	EtOH	0

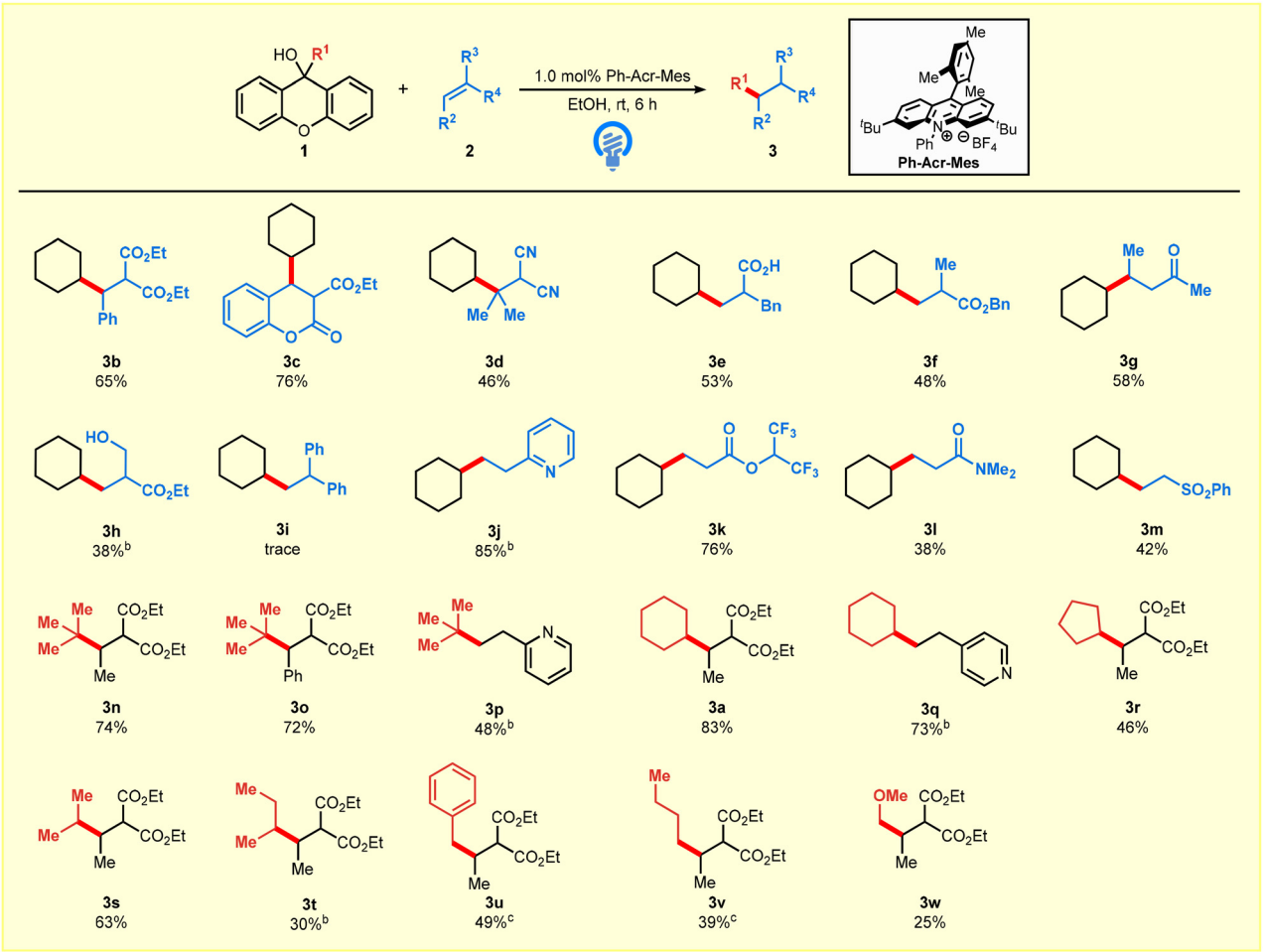
[a] All reactions were carried out using **1a** (0.2 mmol), **2a** (0.8 mmol), and the photocatalyst (1.0 mol%) in the specified solvent at room temperature under irradiation with blue light (18 W; λ_{ex} = 425 nm) for 24 h. [b] 6 h. [c] Without light.

suggests that since the electron donating group effectively increases the stability of radical cation,[14] methoxy group would stabilize the xanthene radical cation intermediate, thereby preventing β-scission. Blank experiments in the absence of a photocatalyst or light confirmed that these two factors are essential for the reaction to proceed (Table 1, entries 11 and 12). It should also be noted here that previously reported reactions required stoichiometric amounts of base and trifluoroethanol,[10] whereas the present reaction proceeds smoothly without any additives.

Next, we investigated the scope of xanthene-based alkyl-radical precursors and alkenes (Table 2). When tri- and tetra-substituted alkenes were used, the reaction smoothly afforded the corresponding products (**3b–3d**) in moderate-to-good yield. Notably, the reaction could also be applied to cyclic heteroalkenes such as coumarin **2c**. A variety of di-substituted α,β-unsaturated esters furnished products **3e–3h**. On the other hand, electron-rich alkene was not suitable for the reaction (**3i**). Alkenes containing pyridyl, trifluoromethyl, amide, or benzenesulfonyl groups furnished the desired products (**3j–3m**) in moderate-to-high yield. These results demonstrate that the reaction tolerates a diverse range of functional groups. An alkyl-radical precursor bearing the sterically congested ^{t}Bu group afforded the desired products (**3n–3p**) in moderate-to-good yield. Furthermore, alkyl-radical precursors with secondary and primary alkyl groups could be used in this reaction (**3a, 3q–3w**).

Subsequently, we examined the recovery of xanthone **4** after the reaction (Scheme 3). When the reaction was carried out with alkyl-radical precursor **1a** and alkene **2x**, the desired xanthone (**4**) was obtained in high yield together with product **3x**. Given that xanthone **4** can be easily converted into alkyl-radical precursor **1a** in one step, the present reaction constitutes a sustainable alkylating system.

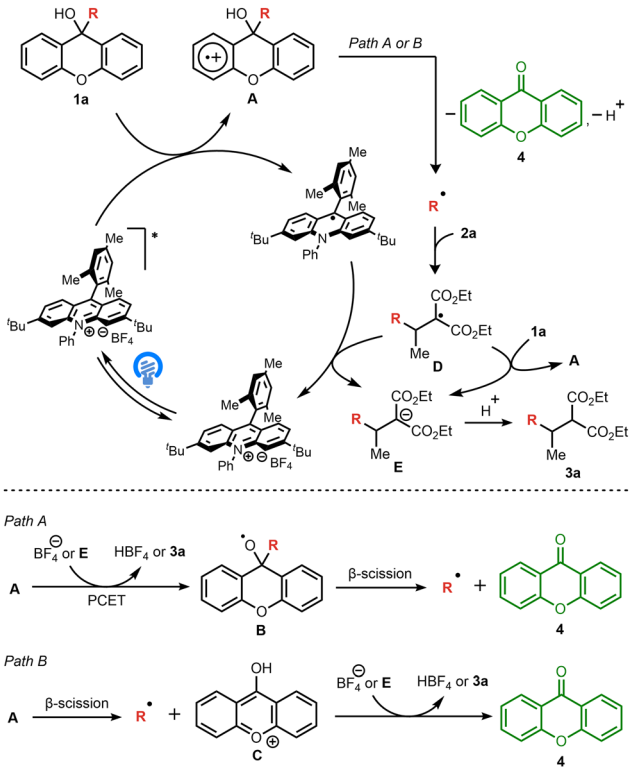
Table 2 Scope of alkyl-radical precursors and alkenes[a]



[a] All reactions were carried out using **1** (0.2 mmol), **2** (0.8 mmol), and Ph-Acr-Mes (1.0 mol%) in EtOH at room temperature under irradiation with blue light (18 W; λ_{ex} = 425 nm) for 6 h. [b] 24 h. [c] 72 h.

Scheme 3 Recovery of xanthone **4**.

A plausible reaction mechanism is shown in Scheme 4. The Ph-Acr-Mes photocatalyst is photoexcited under irradiation with blue LED light, and the resulting photoexcited photocatalyst (Ph-Acr-Mes*) oxidizes alkyl-radical precursor **1a** ($E_{p/2}$ = +1.75 V *vs.* SCE) to generate radical-cation **A**.[9a,15] The results of Stern–Volmer experiments suggested that the transfer of an electron from **1a** to the photocatalyst should occur smoothly.[13] The alkyl radical and xanthone **4** can be generated *via* path A or Path B. In path A, subsequent PCET between the hydroxyl group and the radical cation may generate alkoxyl radical **B**.[7,9,15] Considering that the reaction occurs in the absence of a base, the tetrafluoroborate anion from the photocatalyst or anion intermediate **E** can be considered as possible proton acceptors.[7a] Alkoxyl radical **B** readily undergoes selective β-scission of the C(sp^3)–C(sp^3) bond, producing an alkyl radical and xanthone **4**. In path B, the direct cleavage of the C(sp^3)–C(sp^3) bond proceeds *via* a radical cation **A**, generating an alkyl radical and an oxonium ion **C**. Subsequently, either the tetrafluoroborate anion from the photocatalyst or the anionic intermediate **E** may serve as a proton acceptor, affording xanthone **4**. According to previous reports,[16] primary alkyl radicals are not generated *via* direct C(sp^3)–C(sp^3) bond cleavage due to their inherent instability, their formation is feasible through a PCET mechanism.[7a] In contrast, secondary and tertiary radicals can be generated through either the PCET pathway or direct C(sp^3)–C(sp^3) bond cleavage. When the reaction was conducted in the presence of TEMPO as a radical scavenger, no product was obtained.[13] Instead, a cyclohexyl radical trapped by TEMPO was detected using mass spectrometry. The alkyl radical then reacts with alkene **2a** to form intermediate **D**, which is reduced by the photocatalyst or **1a**, leading to the formation of anion intermediate **E**. The quantum yield of the reaction (Φ = 4.17)



Scheme 4 Proposed reaction mechanism.

indicates that the reaction mainly proceeds *via* radical chain pathways. Finally, intermediate **E** undergoes protonation to give the desired product (**3a**).

In summary, we have developed novel xanthene-based alkyl-radical precursors for the generation of alkyl radicals *via* C(sp^3)–C(sp^3) bond cleavage. Primary, secondary, and tertiary alkyl radicals were effectively generated from the xanthene-based precursors and reacted with various alkenes. Alkenes that bear various functional groups, such as ester, carboxylic acid, alcohol, pyridyl, amide, ketone, trifluoromethyl, and sulfonyl groups, are suitable for this reaction. After the reaction, the produced xanthone can be recovered in high yield. The present reaction offers a promising approach for the sustainable generation of alkyl radicals *via* C(sp^3)–C(sp^3) bond cleavage with broad applications in organic chemistry.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI. See DOI: https://doi.org/10.1039/d5cc02699g.

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