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Radical pathways for 2,4-chromandione synthesis *via* photoexcitation of 4-hydroxycoumarins†

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4-Hydroxycoumarins are well-known for their ground-state nucleophilic behavior, which has been widely exploited for their functionalization. Herein, we reveal a previously unexplored photochemical reactivity: upon deprotonation and excitation with purple light, 3-substituted 4-hydroxycoumarins reach an excited state and act as single-electron transfer (SET) reductants, generating radicals from stable substrates. This newfound reactivity enables the direct synthesis of 3,3-disubstituted 2,4-chromandiones *via* a radical dearomatization process. By enabling the incorporation of alkyl and perfluoroalkyl fragments, this protocol offers a straightforward and mild route to access synthetically valuable chromanone scaffolds featuring a quaternary stereocenter. Comprehensive photophysical studies confirmed that deprotonated 4-hydroxycoumarins are potent SET reductants in their excited state, making them suitable for initiating radical-based transformations.

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Introduction

4-Hydroxycoumarins and their derivatives play an important role in medicinal chemistry due to their diverse biological activities.[1] Traditionally, the functionalization of 4-hydroxycoumarins has relied on their well-established ground-state nucleophilic ionic reactivity.[2a] Several catalytic methods have been developed to trap electrophilic intermediates, leading to the formation of 3-substituted hydroxycoumarins (Fig. 1a).[2] More recently, a few studies demonstrated that radical pathways could also be useful,[3] as a single-electron transfer (SET) oxidation generates electrophilic radicals from 4-hydroxycoumarins, which are subsequently trapped by olefins (Fig. 1a, lower part). In contrast, the direct synthesis of biologically relevant 3,3-disubstituted chromandiones[4] through the functionalization of 3-substituted 4-hydroxycoumarins **1** at their carbon 3 has been less investigated (Fig. 1b). Existing methods are predominantly rooted in ionic chemistry, leveraging the nucleophilic nature of **1**, and are reliant on transition-metal catalysis.[5] These metal-based protocols come with significant drawbacks, including regioselectivity issues, as alkylation often occurs at both the carbon (C3) and oxygen (O) centers of hydroxycoumarins,[6] leading to a mixture of products.

Herein, we introduce a new playground for hydroxycoumarin chemistry by unveiling the previously untapped photochemical reactivity for 3-substituted 4-hydroxycoumarins **1** (Fig. 1c). We found that, upon deprotonation to afford **I** and excitation with purple light, 3-substituted 4-hydroxycoumarins **1** reach an excited state (**I***) and act as SET reductants, generating radicals from stable substrates **2**. The resulting electrophilic radicals are regioselectively intercepted at C3 by the nucleophilic ground-state substrate **1**. This novel light-driven reactivity enables the direct synthesis of 3,3-disubstituted chromandiones **3** *via* an overall radical dearomatization process. By incorporating alkyl and perfluoroalkyl groups at the 3-position of hydroxycoumarins, this radical-based approach offers a mild, efficient route to access valuable 2,4-chromandione scaffolds, which have applications in drug discovery.[7] The process also forges quaternary stereocenters, which are featured in many biologically relevant compounds.[8]

Results and discussion

We started out our investigations using 3-benzyl-4-hydroxycoumarin **1a** and perfluorohexyl iodide **2a** as the radical precursor (Table 1). This choice was informed by our previous studies on the direct excitation of electron-rich compounds,[9] including *in situ* generated enamines,[9a–c] enolates,[9d] phenolates,[9e] and sulfur[9f] anions, demonstrating that simple light excitation can turn such nucleophilic substrates into strong SET reductants. Given that 4-hydroxycoumarins are inherently nucleophilic, they fit within this photochemical reactivity platform. Moreover, 4-hydroxycoumarin derivatives are known for their absorption in the visible region and unique photophysical properties, including high non-radiative fluorescence.[10] However, their excited-state reactivity has not yet been explored in SET-based radical processes.[11] As for perfluoalkyl iodides of type **2a**, our previous studies[9c–e] indicated their utility as radical precursors due to their susceptibility to

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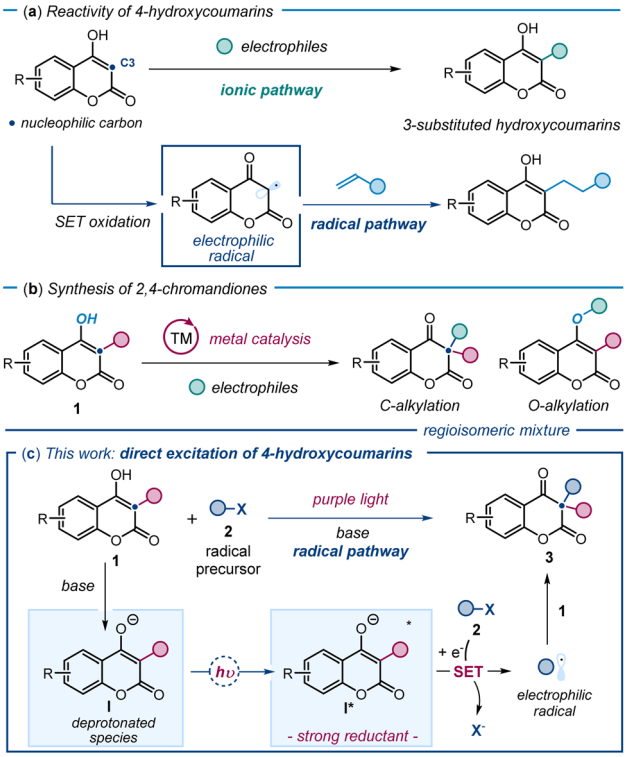
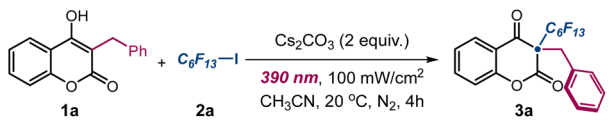


Fig. 1 (a) Functionalization of 4-hydroxycoumarins at C3 using traditional ground-state nucleophilic reactivity (upper panel) and an example[3a] of a radical path *via* SET oxidation (lower panel). (b) Metal-based methods for the synthesis of 2,4-chromandiones *via* alkylation of 3-substituted 4-hydroxycoumarins **1** suffer from regioselectivity issues. (c) Our new radical-based strategy, based on the excitation of 3-substituted 4-hydroxycoumarins **1**, enables the regioselective synthesis of 3,3-disubstituted 2,4-chromanediones **3**. Upon deprotonation and excitation with purple light, I* generates electrophilic radicals that are regioselectively trapped by **1**, forging quaternary stereocenters; SET: single-electron transfer.

Table 1 Optimization studies and control experiments[a]



Entry	Deviation	[%] Yield of **3a**[b]
1	None	82
2	No base, no light	0
3	Under air instead of N_2	0
4	427 nm or 456 nm light	0
5	Na_2CO_3 instead of Cs_2CO_3	56
6	TMG instead of Cs_2CO_3	78
7	1 equiv. Cs_2CO_3	37

[a] Reactions performed over 4 hours in 1 mL of CH_3CN using 0.15 mmol of **1a**, 0.45 mmol of **2a**, and base (2 equiv.) under irradiation by a Kessil lamp (λ_{max} = 390 nm, irradiance = 100 mW cm^{-2}). [b] Yield of **3a** determined by ^{1}H NMR analysis of the crude mixture using dibromomethane as the internal standard.

SET activation, leading to the formation of electrophilic perfluoroalkyl radicals upon iodide fragmentation. In addition, the direct incorporation of fluorinated fragments into biologically valuable scaffolds is synthetically relevant, as this modification can enhance pharmacological properties.[12]

Our optimization studies were conducted in acetonitrile under irradiation by a purple LED (λ_{max} = 390 nm) at 20 °C in an inert atmosphere (nitrogen). Using Cs_2CO_3 (2 equiv.) for deprotonation of 4-hydroxycoumarin **1a** and 2 equiv. of radical precursor **2a**, we obtained the desired perfluoroalkylated 2,4-chromandione product **3a** in 82% yield (Table 1, entry 1). Control experiments without light or base completely halted the reaction (entry 2), while an inert atmosphere was essential, as oxygen completely inhibited the reaction (entry 3).

Using visible light illumination at a higher wavelength proved ineffective, as the process was completely halted (entry 4). Replacing Cs_2CO_3 with Na_2CO_3 led to product **3a** with a moderate yield of 56% (entry 5), while tetramethyl guanidine (TMG) afforded **3a** in 78% yield, though not surpassing the efficiency of Cs_2CO_3 (entry 6). Using only 1 equiv. of Cs_2CO_3 significantly reduced the yield of **3a** to 37%, emphasizing the need for 2 equiv. of base for optimal results (entry 7).

We then carried out investigations to uncover mechanistic insights. UV-visible spectroscopic analysis of 4-hydroxycoumarin **1a** (Fig. 2a) showed no absorption in the visible region. However, upon addition of Cs_2CO_3, a bathochromic shift towards the visible region was observed, indicating that the deprotonated intermediate **Ia** was the chromophore in our process (red line). Further UV-vis analysis after adding perfluorohexyl iodide **2a** excluded the possibility of ground-state aggregation (*i.e.*, no electron donor–acceptor complexes were detected, blue line).[13] We then focused on the photophysical behavior of deprotonated hydroxycoumarin **Ia**, the sole absorbing species at 390 nm, the irradiation wavelength used in this study. Upon laser irradiation at 314 nm of a CH_3CN solution of **Ia** (in situ-generated by mixing **1a** with Cs_2CO_3), emission with a maximum at 407 nm was detected, confirming that **Ia** could access an electronically excited state (Fig. 2b). The 0–0 transition energy ($E_{0,0}$) was determined to be 3.43 eV from the cross-section, located at 361 nm of the normalized UV-visible absorption and emission spectra (Fig. 2b). Next, cyclic voltammetry analysis of **Ia** revealed an irreversible oxidation peak at +0.66 V *vs.* Ag/AgCl in CH_3CN (Fig. 2c). Applying the Rehm–Weller formalism,[14] the redox potential of excited **Ia** (E(**Ia**$^{\bullet}$/**Ia***)) was estimated to be −2.77 V *vs.* SCE, confirming its strong reducing power upon excitation. Stern–Volmer quenching studies (Fig. 2d) showed that the fluorescence of excited **Ia**, induced by a laser at 310 nm, was effectively quenched by perfluorohexyl iodide **2a**. This supported the ability of excited **Ia** to activate **2a** *via* an SET mechanism. Finally, the excited singlet-state lifetime of **Ia*** was measured as 5.1 ns by means of single photon counting technique, further confirming its potential for productive excited-state reactivity (Fig. 2e).

Under the optimal conditions outlined in entry 1 of Table 1, we explored the scope of the photochemical protocol for preparing various 3,3-disubstituted 2,4-chromandiones **3** (Fig. 3). Initially, we demonstrated the process's efficiency on

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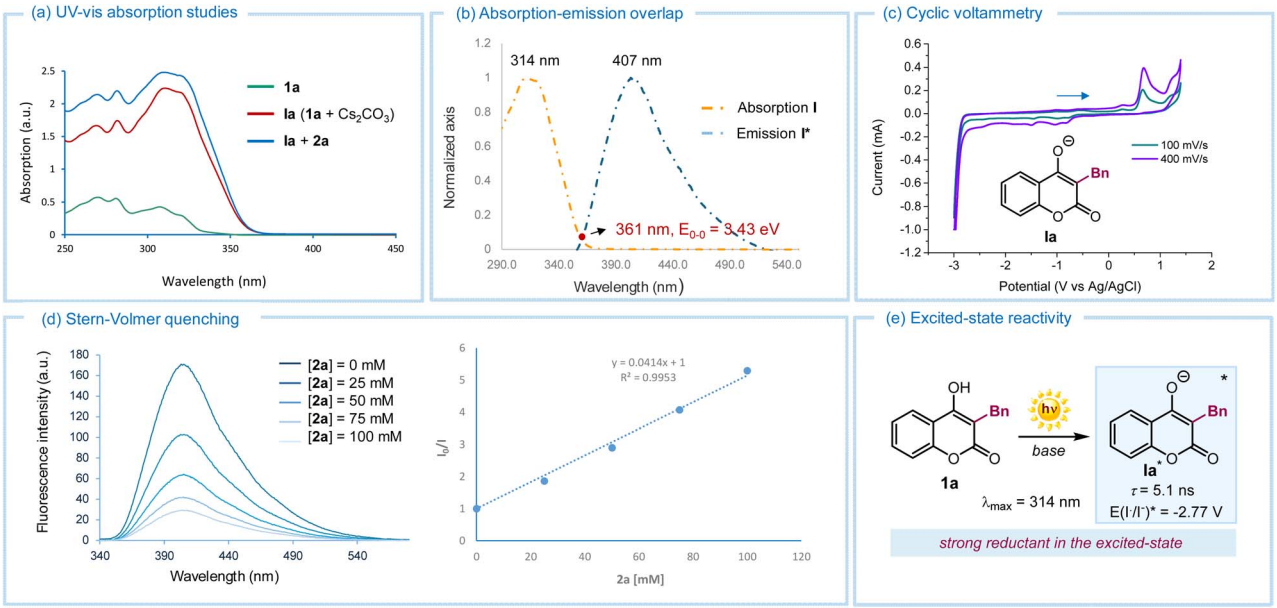

Fig. 2 (a) Absorption spectra recorded for 3-benzyl-4-hydroxycoumarin **1a**, its deprotonated form **Ia** (*in situ* generated from **1a** upon addition of Cs_2CO_3), and their mixture with perfluorohexyl iodide **2a** in CH_3CN (1×10^{-4} M). (b) Emission of the excited deprotonated intermediate **Ia*** in CH_3CN (*in situ* generated mixing **1a** with Cs_2CO_3) upon laser irradiation at 314 nm and its intercept at 361 nm with the absorption spectrum, with a 0–0 transition energy ($E_{0,0}$) determined to be 3.43 eV. (c) Cyclic voltammetry measurement of the deprotonated intermediate **Ia** carried out in CH_3CN *vs.* Ag/AgCl at a scan rate of 100 and 400 mV s^{-1}. (d) Stern–Volmer luminescence quenching studies of intermediate **Ia** (1×10^{-4} M in CH_3CN) with increasing amounts of perfluorohexyl iodide **2a** (excitation at 350 nm; emission was acquired from 360 nm to 440 nm).

a preparative scale (4 mmol scale), yielding 1.1 g of product **3a** (50% yield). We then examined the reactivity of substituted 3-benzyl-4-hydroxycoumarins **1**. The protocol tolerated a range of substituents on the aromatic ring of the benzyl moiety. Electron-donating groups at the *ortho*- and *meta*-positions were tolerated well (products **3b** and **3c**). Halogen functionalities, such as a 4-chloro substituent, afforded the desired product **3d** in 65% yield. Interestingly, a pyridyl group was also well tolerated, delivering product **3e** in high yield. Notably, aliphatic substituents at the 3-position of **1** maintained a productive photochemistry, yielding the corresponding products **3f** and **3g** in high yields. In contrast, the presence of an aromatic substituent led to a complex mixture, with only traces of the target 2,4-chromandione product. A complete list of unreactive or poorly reactive substrates is reported in Fig. S1 of the ESI.† Variation in the electronic properties of the coumarin ring within **1** was also tolerated: both electron-withdrawing (product **3h**) and electron-donating substituents (adduct **3i**) afforded the corresponding perfluoroalkylated 2,4-chromandiones in high yields. To evaluate the generality of the method, we reacted **1a** with iodides of different perfluoroalkyl chain lengths (Fig. 3b), successfully obtaining products **3j–l** in good to high yields. Sensitive iodo sulfonyl fluorides could also be used as radical precursors, enabling the synthesis of the heteroatom-dense products **3m** and **3n** in moderate to good yields. However, our attempts to use trifluoromethyl iodide as a radical precursor were unsuccessful (see Fig. S1†).

We then considered whether the strong reducing power acquired by the 4-hydroxycoumarins **1** upon excitation could be harnessed to activate radical precursors beyond perfluoroalkyl iodides, thereby expanding the scope of the protocol (Fig. 4).

We successfully activated (phenylsulfonyl)alkyl iodide **4a**, 2-bromo-*N*,*N*-dimethylacetamide **4b**, and bromomalonate **4c** *via* SET reduction, generating the corresponding electrophilic carbon-centered radicals. These radicals efficiently reacted with 4-hydroxycoumarins, yielding the desired products **5a–5c** in high yields (Fig. 4).

Importantly, in all the experiments reported in this study, we observed complete regioselectivity for C3 functionalization, with no O-alkylated products detected. This suggests that the radical reactivity can bypass regioselectivity issues typically encountered in alternative pathways.

We then assessed the potential to enhance productivity in our photochemical protocol using flow photochemistry (Fig. 5).[15] This method offers benefits like improved light exposure and controlled residence time, resulting in more efficient and consistent reactions. We used a 3D-printed flow reactor with a 0.5 mm inner diameter and a total volume of 2 mL, connected to a syringe pump for precise flow rate control (see Section F in the ESI† for details). Irradiation was performed with a Kessil LED light source (λ_{max} = 390 nm), consistent with our batch experiments. Using 1 equivalent of TMG as a soluble organic base, we achieved complete alkylation of 4-hydroxycoumarins in just 10 minutes, significantly reducing reaction time compared to batch reactions. High yields of alkylated products **3a**, **3k**, and **5a** were obtained with improved productivity. For comparison, a batch reaction afforded product **3a** in 80% yield after 240 minutes, while the flow system yielded **3a** in 10 minutes, using half the amount of base. The flow system achieved a productivity of 0.924 mmol h^{-1}, a 23-fold enhancement over the batch process's

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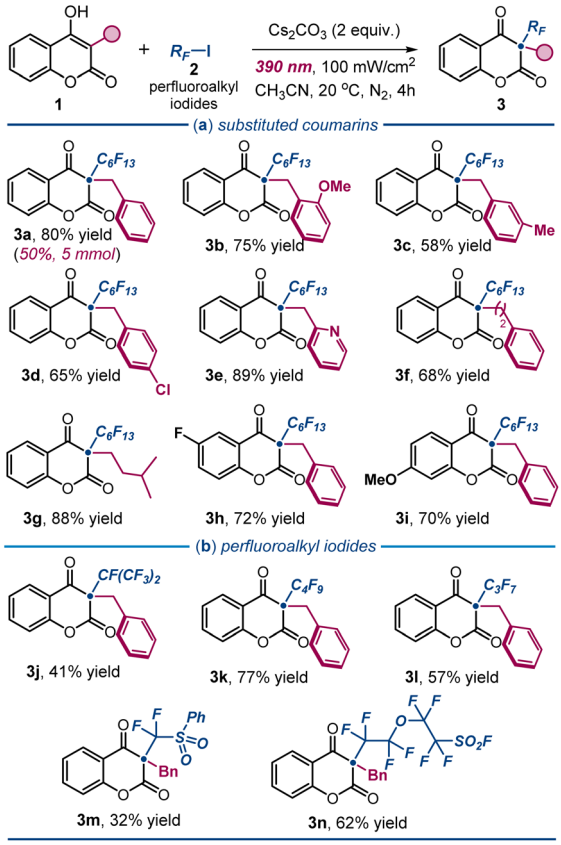

Fig. 3 Photochemical radical synthesis of 2,4-chromandiones **3**: survey of the (a) 4-hydroxycoumarin derivatives **1** and (b) perfluoroalkyl iodides **2** that can participate in the process. Reactions performed using **1** (0.2 mmol), **2** (0.6 mmol), Cs_2CO_3 (2 equiv.) in 1 mL of CH_3CN under irradiation by a Kessil lamp (λ_{max} = 390 nm, irradiance = 100 mW cm^{-2}). Yields of the isolated products **3** are reported below each entry; results are averaged from two runs. R_F: perfluoroalkyl chain.

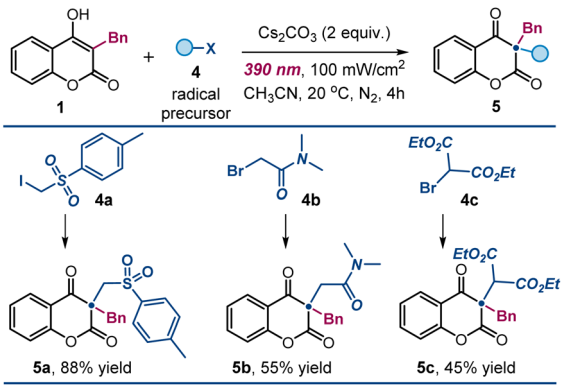

Fig. 4 Expanding the pool of radical precursors. Reactions performed using **1** (0.2 mmol), **4** (0.6 mmol), Cs_2CO_3 (2 equiv.) in 1 mL of CH_3CN under irradiation by a Kessil lamp (λ_{max} = 390 nm, irradiance = 100 mW cm^{-2}). Yields of the isolated products **5** are reported below each entry; results are averaged from two runs.

productivity of 0.04 mmol h^{-1}. These results underscore the advantages of flow photochemistry in terms of speed, efficiency, and scalability.

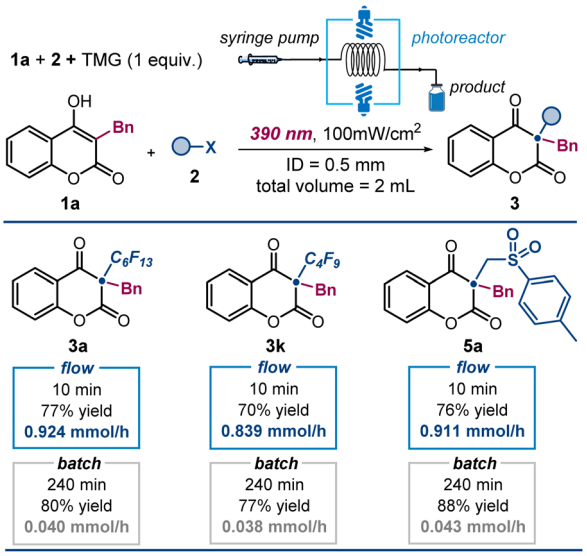

Fig. 5 Flow photocatalysis for improved productivity. Reactions performed using **1** (0.2 mmol), **2** (0.6 mmol), TMG (1 equiv.) in 2 mL of CH_3CN under illumination by two single wavelength Kessil LED (λ_{max} = 390 nm, irradiance = 100 mW cm^{-2}) inside a photoreactor. Yields of the isolated products **3** are reported below each entry. ID: inner diameter. Conditions for batch reactions are detailed in Fig. 3 (4 hours reaction time, using 2 equiv. of Cs_2CO_3).

Finally, we surmised that our protocol could be extended to achieve alkylation at the C3 position of unsubstituted 4-hydroxycoumarins **6** by trapping electrophilic radicals generated through photoexcitation. This approach could complement existing ionic methods[2] for synthesizing 3-substituted 4-hydroxycoumarins **7** by expanding the reaction scope to include radical pathways.[3] As illustrated in Fig. 6, we successfully applied the optimized conditions to the radical perfluoroalkylation of unsubstituted 4-hydroxycoumarins **6**, demonstrating that also these substrates exhibit productive photochemistry when irradiated with purple light. This enabled the generation of electrophilic radicals from a variety of stable halide precursors, including trifluoromethyl iodide, which was unreactive in our previous studies with 3-substituted 4-hydroxycoumarins (adduct **7c**). The corresponding perfluoroalkylated

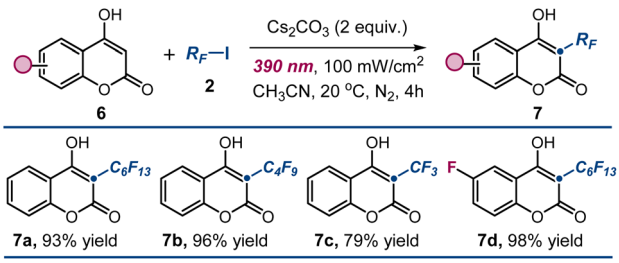

Fig. 6 Extending the photochemistry to unsubstituted 4-hydroxycoumarins. Reactions performed using **6** (0.2 mmol), **7** (0.6 mmol), Cs_2CO_3 (2 equiv.) in 1 mL of CH_3CN under illumination by a single Kessil lamp (λ_{max} = 390 nm, irradiance = 100 mW cm^{-2}). Yields of the isolated products **7** are reported below each entry. R_F: perfluoroalkyl chain.

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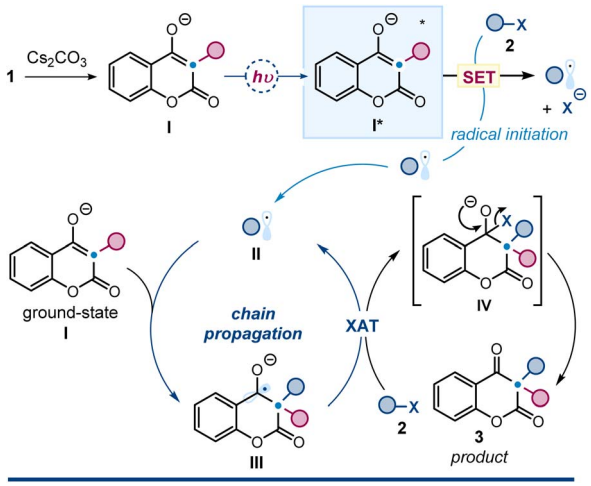

Fig. 7 Proposed mechanism.

products **7a–d** were obtained with high efficiency, highlighting the versatility of our methodology.

Lastly, we conducted further investigations to elucidate the mechanism. Specifically, we determined the quantum yield (Φ) of the photochemical reaction between **1a** and **2a**, which was 8.4, strongly supporting a radical chain mechanism.[16] Based on this finding, alongside the photophysical studies and control experiments reported in Fig. 2 and Table 1, we propose the mechanism depicted in Fig. 7, where radical propagation is responsible for product formation.

The process begins with the deprotonation of 3-subtituted 4-hydroxycoumarin **1**, facilitated by Cs_2CO_3, followed by excitation of intermediate **I** under purple light (390 nm). The resulting excited intermediate **I*** acts as a strong SET reductant ($E(\mathbf{I}^{\bullet}/[\mathbf{I}^*]) = -2.77$ V), capable of activating alkyl iodides. Mesolytic cleavage of the carbon–iodine bond then generates an electrophilic radical **II**. This step represents the light-driven initiation of the chain process. This electrophilic radical is intercepted by the ground-state nucleophilic 3-substituted 4-hydroxycoumarin **1**, forming a nucleophilic ketyl radical intermediate **III**. This intermediate abstract a halogen atom from the radical precursor **2** *via* a halogen atom transfer (XAT)[17] mechanism, generating intermediate **IV** (ref. 18) while affording radical **II**, thus propagating the chain. Finally, intermediate **IV** collapses to yield product **3**. The overall mechanism fits within the framework of an atom-transfer radical addition (ATRA) process.[19]

Conclusions

In summary, we have developed a photochemical radical-based method for the dearomatization of 4-hydroxycoumarin derivatives, enabling efficient introduction of fluoroalkyl and alkyl substituents at C3. This strategy leverages the unique excited-state reactivity of hydroxycoumarins, which act as strong SET reductants under purple light irradiation, driving radical formation. This new reactivity expands the functionalization possibilities of biologically relevant hydroxycoumarins and provides direct access to 2,4-chromandiones with quaternary stereogenic centers.

Data availability

All experimental data are provided in the ESI.†

Author contributions

S. M., E. S., and H. W. performed the experiments. S. M. conceptualized the project. P. M. directed the project. P. M. wrote the manuscript with assistance from all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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