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Redox-neutral and metal-free synthesis of 3-(arylmethyl) chroman-4-ones *via* visible-light-driven alkene acylarylation

Yan Ding[1], Shengjiao Yu[2†], Man Ren[1], Ji Lu[1], Qiang Fu[1], Zhijie Zhang[1], Qin Wang[1*], Jun Bai[3], Na Hao[1], Lin Yang[1], Siping Wei[1], Dong Yi[1*] and Jun Wei[1*]

[1]Central Nervous System Drug Key Laboratory of Sichuan Province, Department of Medicinal Chemistry, School of Pharmacy, Southwest Medical University, Luzhou, China, [2]Department of Chemistry, School of Basic Medical Sciences, Southwest Medical University, Luzhou, China, [3]School of Public Health, Southwest Medical University, Luzhou, China

EDITED BY
Gu Zhan,
Chengdu University of Traditional Chinese Medicine, China

REVIEWED BY
Xiaoming Chen,
Lanzhou University, China
Xuan-Hui Ouyang,
Nanchang Hangkong University, China
Guang-Xun Li,
Chengdu Institute of Biology, Chinese Academy of Sciences (CAS), China

*CORRESPONDENCE
Dong Yi,
yidong@swmu.edu.cn
Jun Wei,
weijun@swmu.edu.cn
Qin Wang,
wq_ring@hotmail.com

†These authors have contributed equally to this work

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A metal- and aldehyde-free visible-light-driven photoredox-neutral alkene acylarylation with readily available cyanoarenes is described. A variety of 3-(arylmethyl)chroman-4-ones (i.e., homoisoflavonoids) and analogs are efficiently synthesized with good functional group tolerance. This mild protocol relies on a phosphoranyl radical-mediated acyl radical-initiated cyclization and selective radical-radical coupling sequence, and is also further highlighted by subsequent derivatization to chromone and 2*H*-chromene as well as its application in the three-component alkene acylarylation.

KEYWORDS

chroman-4-one, 3-(arylmethyl)chroman-4-ones, phosphoranyl radical, acyl radical, radical-radical coupling

Introduction

Chroman-4-one scaffolds, a class of important oxygen-containing structural motifs, are ubiquitous in a plethora of natural products, drug candidates, and biologically active molecules (Albrecht et al., 2005; Nibbs and Scheidt, 2011; Friden-Saxin et al., 2012; Lee et al., 2014; Seifert et al., 2014; Emami and Ghanbarimasir, 2015; Kumar et al., 2017; Mayuri et al., 2017). In the past years, the radical-initiated cascade cyclization strategy has attracted great attention for the construction of chroman-4-one scaffold and other (hetero)cyclic frameworks (Zhao et al., 2016; Yang et al., 2017; Hu et al., 2018a; Hu et al., 2018b; Liu et al., 2019; Sheng et al., 2019; Xiao et al., 2019; Zhou et al., 2019a; Das et al., 2020; Han et al., 2020; Huang et al., 2020; Liu et al., 2020; Mei et al., 2020; Xiong et al., 2020; Diana et al., 2021). Particularly, the photocatalytic radical-initiated cascade cyclization, including two mechanistically distinctive pathways, has emerged as an elegant, green, and powerful strategy for the synthesis of such scaffold and its

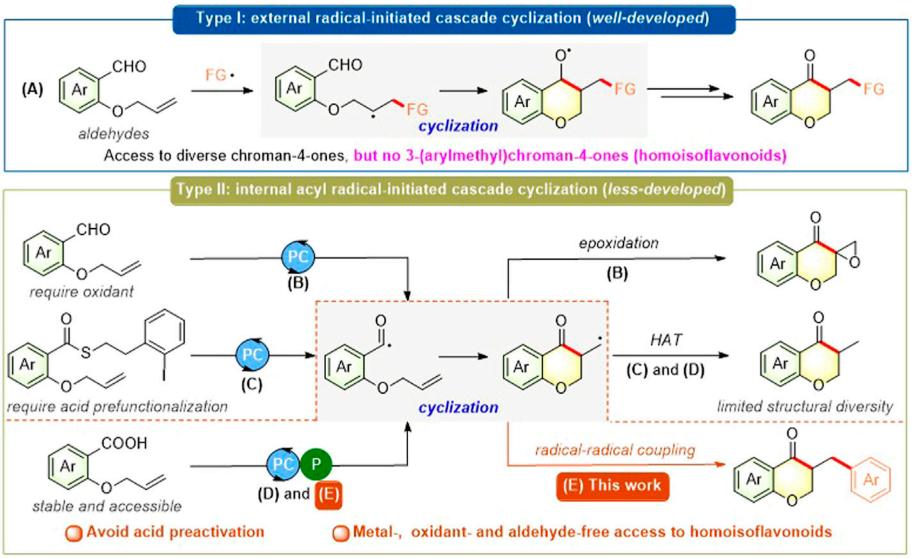
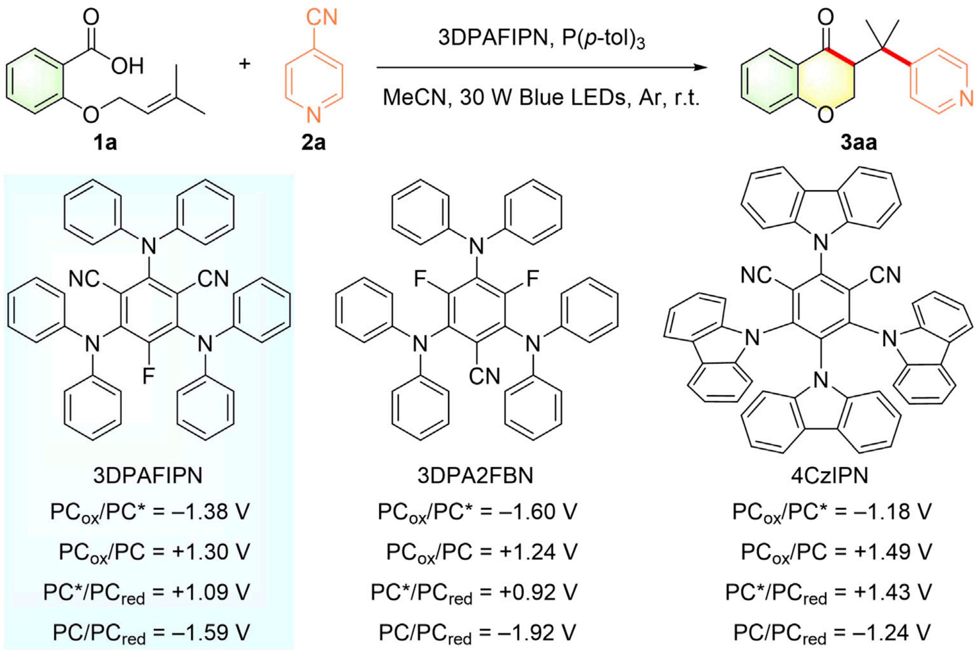


FIGURE 1
Photocatalytic radical-initiated cascade cyclization toward functionalized chroman-4-ones.

derivatives. The first photocatalytic approach to diversely functionalized chroman-4-ones *via* various external radical-initiated cascade cyclization of *o*-(allyloxy) arylaldehydes is well-developed by the groups of Zhu (Lu et al., 2017; Zhou et al., 2019b), Yu (Zhu et al., 2021), Xuan (He et al., 2019), and others (Zhou et al., 2019a; Huang et al., 2020; Mei et al., 2020; Liu et al., 2022) (Figure 1A). In contrast, there are only a few examples of photocatalytic internal acyl radical-initiated cascade cyclization (Jung et al., 2017; Norman et al., 2018; Stache et al., 2018; Zhou et al., 2021) (Figures 1B–D), which limits their application for the rapid assembly of structurally diverse chroman-4-ones. Recently, Hong group (Jung et al., 2017) and Wan group (Zhou et al., 2021) independently developed a visible-light-driven radical cyclization/epoxidation of *o*-(allyloxy)arylaldehydes toward spiroepoxy chroman4-one scaffolds using Ru $(bpy)_3Cl_2$ or organoselenium as photocatalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant (Figure 1B). In 2018, McErlean group (Norman et al., 2018) disclosed a photoredox-catalyzed indirect acyl radical generation from relatively stable Crich-type thioesters generated in a single step with carboxylic acid starting materials, followed by intramolecular alkene addition/cyclization to give various cyclic ketones including chroman-4-one scaffold (Figure 1C). However, these existing strategies are solely based on the elaboration of uneasily available *o*-(allyloxy)arylaldehydes (almost all) or carboxylic acid thioesters (only one) and also suffer from one or more drawbacks such as excess amounts of oxidants, limited structural diversity, and lack of functionality tolerance. Therefore, the development of alternative and efficient approaches to access diversely functionalized chroman-4-one and related cyclic ketone analogs *via* photocatalytic internal acyl radical-initiated cascade cyclization using accessible starting materials should be highly desirable.

Carboxylic acids as starting materials are not only abundant, generally stable, and readily accessible in great structural diversity, and have also drawn much attention for their application as versatile radical precursors such as alkyl, aryl, carboxylic, and particularly acyl radicals (Mandal et al., 2018; Wang et al., 2019; Hu et al., 2020b; Chan et al., 2022; Kitcatt et al., 2022; Yan et al., 2022). Recently, an elegant strategy that combines photoredox catalysis and phosphoranyl radical-mediated deoxygenation makes it possible to form acyl radicals from carboxylic acids, providing streamlined access to structurally diverse ketones (Zhang et al., 2017; Stache et al., 2018). However, to the best of our knowledge, there are not only a few reports on the application of this powerful strategy to intermolecular and intramolecular alkene acylations including *ipso*-acylation (Li et al., 2022b), defluorinative acylation (Guo et al., 2020), and hydro-acylation (one example of hydro-acylation: one compound chroman-4-one using expensive iridium-based photocatalyst, Figure 1D) (Stache et al., 2018; Zhang et al., 2018; Martinez Alvarado et al., 2019; Merkens et al., 2021), but also no report on alkene difuntionalizations (especially carbon-acylation) with this strategy to date. Inspired by these work and seminal pioneering reports on the photoredox-catalyzed radical-type *ipso*-functionalizations of electron-deficient cyanoarene derivatives (Betori and Scheidt, 2019; Vorob'ev, 2019; Zhong et al., 2020; Zhou et al., 2020; Shen et al., 2021; Tong et al., 2021; Georgiou et al., 2022), we envisaged whether the radical relay strategy of the phosphoranyl radical-mediated acyl radical-initiated cascade cyclization from alkene-tethered carboxylic acids and subsequent

TABLE 1 Optimization of the reaction conditions[a,b].



Entry	Variation from the Standard Conditions	Yield
1	none	75%, 67%[c], 53%[d]
2	3DPA2FBN instead of 3DPAFIPN	66%
3	4CzIPN instead of 3DPAFIPN	n.d
4	PPh_3 instead of P(p-tol)$_3$	65%
5	$PMePh_2$ instead of P(p-tol)$_3$	53%
6	P(p-tol)Ph_2 instead of P(p-tol)$_3$	63%
7	P(p-MeO-C_6H_4)$_3$ instead of P(p-tol)$_3$	63%
8	P(o-MeO-C_6H_4)$_3$ instead of P(p-tol)$_3$	62%
9	$P(C_6F_5)_3$ instead of P(p-tol)$_3$	Trace
10	P(OEt)Ph_2 instead of P(p-tol)$_3$	17%
11	P(OEt)$_3$ instead of P(p-tol)$_3$	Trace
12	CH_2Cl_2 instead of MeCN	42%
13	DCE instead of MeCN	47%
14	DMF, DMSO, or THF instead of MeCN	n.d
15	no light or photocatalyst or P(p-tol)$_3$	n.d

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), 3DPAFIPN (2 mol%), phosphine (0.2 mmol), solvent (2 ml), 30 W blue LEDs, argon atmosphere, r.t., 24 h; n.d. = not detected.
[b] Yields were determined by ^1H NMR, using 1,3,5-trimethoxybenzene as an internal standard.
[c] 1 mol% 3DPAFIPN.
[d] 0.5 mol% 3DPAFIPN.

radical-radical coupling process could enable the rapid construction of 3-(arylmethyl)chroman-4-ones, which are one of the core frameworks in a variety of homoisoflavonoids with various biological activities (Eggler et al., 1991; Desideri et al., 1997; Eggler et al., 1997; Tait et al., 2006; Basavarajappa et al., 2015). Herein, we report an efficient and practical approach for the metal-, oxidant-, and aldehyde-free synthesis of 3-(arylmethyl)chroman-4-ones and other cyclic ketone analogs via visible light-driven photoredox-neutral alkene acylarylation (being a class of alkene carbon-acylation, Figure 1E).

Results and discussion

To corroborate this hypothesis, we initially selected a model reaction of alkenoic acid **1a** and 4-cyanopyridine **2a** to explore

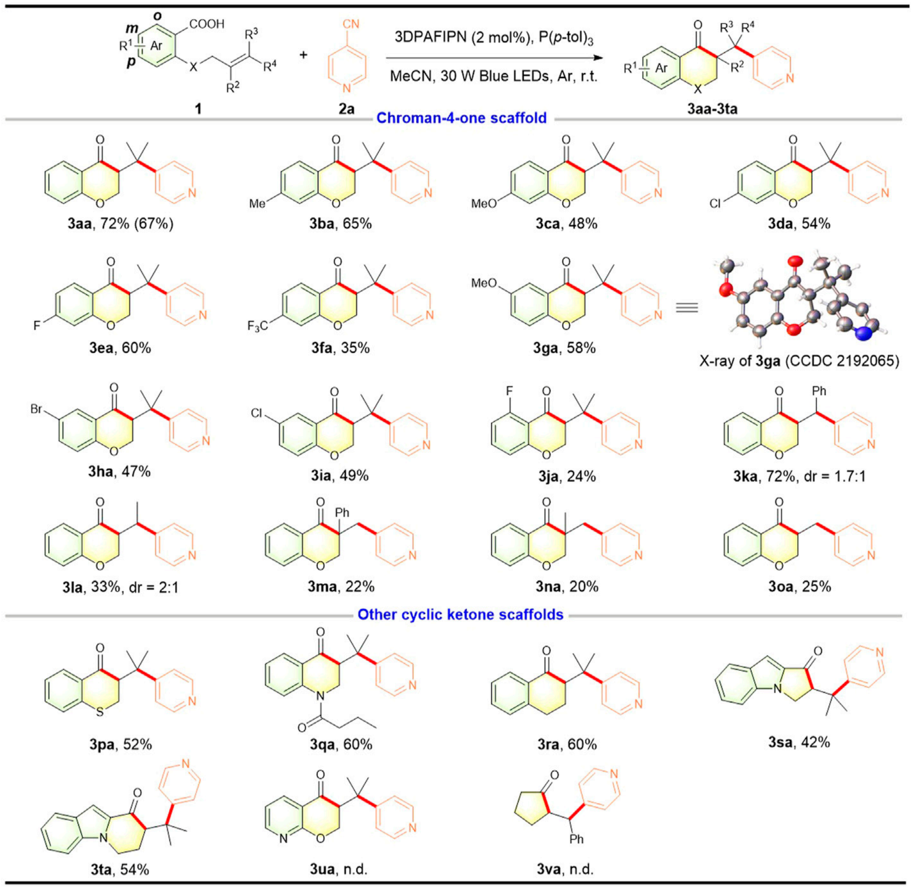


FIGURE 2
Scope of alkenoic acids. Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), 3DPAFIPN (2 mol%), P (p-tol)$_3$ (0.6 mmol), MeCN (6 ml), 30 W blue LEDs, argon atmosphere, r.t., 24 h. The isolated yield is based on **1**. Isolated yield in parentheses is obtained on a 1.0 mmol scale.

the reaction conditions under 30 W blue LED irradiation at room temperature (Table 1). To our delight, the desired 3-(pyridylmethyl)chroman-4-one **3aa** could be obtained in 75% yield by using 3DPAFIPN as a metal-free photocatalyst (entry 1). In light of the fact that the excited state *3DPAFIPN [$E_{1/2}$ (PC*/PC$^{\bullet -}$) = +1.09 V *vs.* SCE] is a strong oxidant (Speckmeier et al., 2018), single electron transfer (SET) could occur from P (p-tol)$_3$ ($E_{1/2}{}^{ox}$ = +1.03 V *vs.* SCE, Supplementary Figure S3) to *3DPAFIPN. Additionally, the presence of alkenoic acid **1a** shifted the reductive potential of **2a** from −1.81 V vs. SCE to −1.33 V vs. SCE (Supplementary Figure S4), thus enabling SET between the reduced 3DPAFIPN$^{\bullet -}$ [$E_{1/2}$ (PC/PC$_{red}$) = −1.59 V vs. SCE] and **2a** to complete the photocatalytic cycle without any aid of external reductant and oxidant. Next, decreasing the loading of the photosensitizer from 2 mol% to 1 mol% or 0.5 mol% obtained a slightly decreasing yield (entry 1). Other organic photosensitizers such as 3DPA2FBN with suitable oxidative-reductive potential (Speckmeier et al., 2018) could also afford the desired chroman-4-one in good yields, while using 4CzIPN (Speckmeier et al., 2018) led to no desired product (entries 2–3). Furthermore, other electron-rich trivalent phosphorus compounds could also be used as the phosphorus source in this deoxygenative transformation (entries 4–8), whereas using relatively electron-deficient ones instead of P (p-tol)$_3$ led to poor efficiency (entries 9–11). Then, the screening of solvents demonstrated that these photocatalytic reactions performed in CH_2Cl_2 or DCE also resulted in synthetically useful yields, while other solvents such as DMF, DMSO, and THF gave no desired product (entries 12–14). Further control experiments performed in the absence of light, photocatalyst, or phosphine failed to give the desired chroman-4-one, thus emphasizing their crucial role in this photocatalytic acylarylation (entry 15).

With the optimized reaction conditions in hand, we investigated the scope and limitations of this reaction using a variety of alkenoic acids (Figure 2). It was worth mentioning that

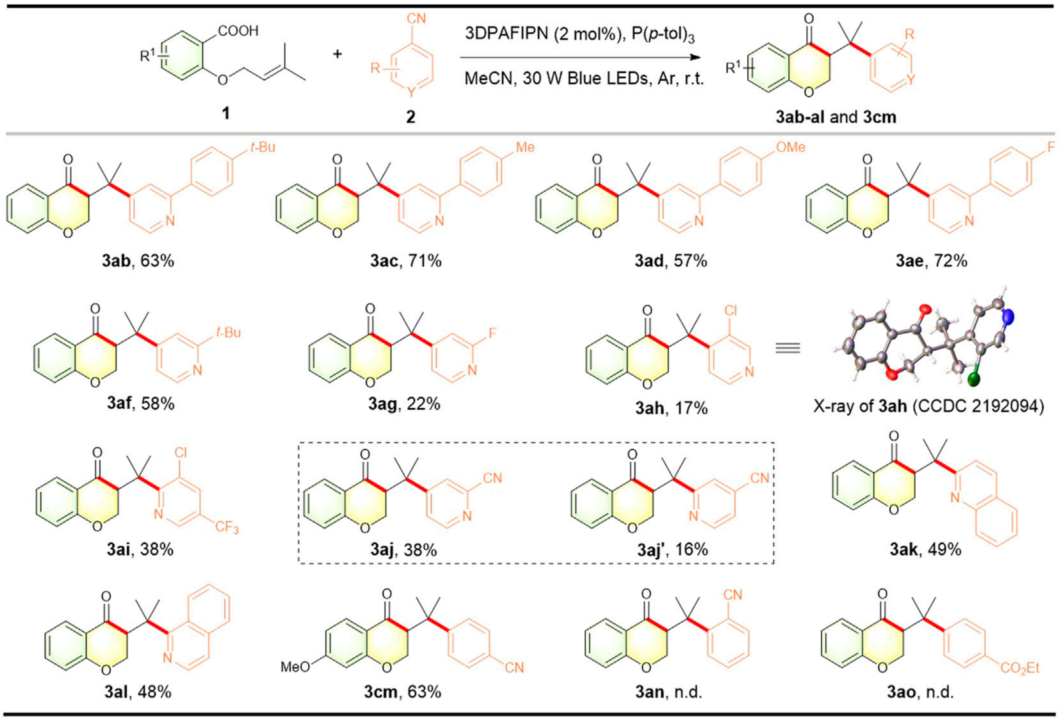


FIGURE 3
Scope of cyano (hetero)arenes. Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), 3DPAFIPN (2 mol%), P (p-tol)$_3$ (0.6 mmol), MeCN (6 ml), 30 W blue LEDs, argon atmosphere, r.t., 24 h. The isolated yield is based on **1**.

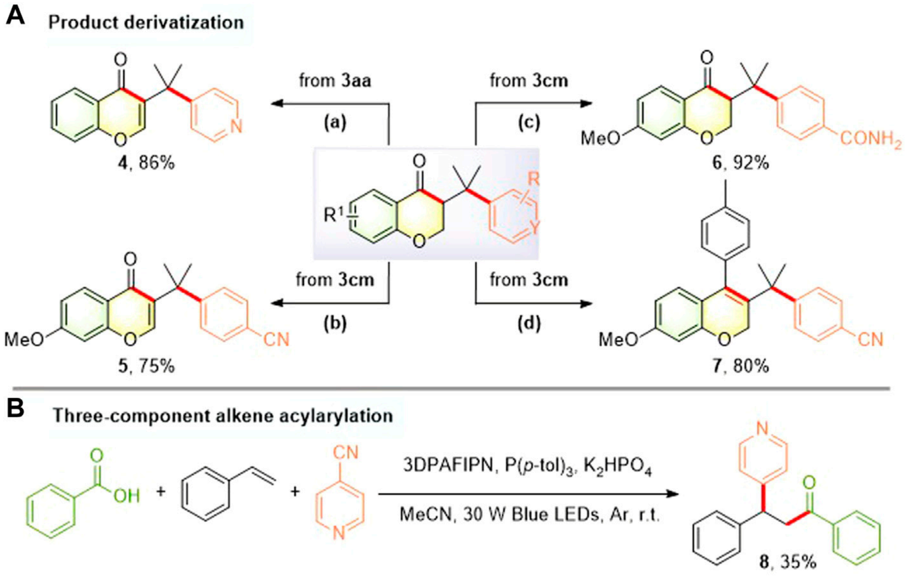


FIGURE 4
Product derivatization **(A)** and three-component alkene acylarylation **(B)**. Reaction conditions: (a) I_2, DMSO, reflux 2 h (b) I_2, DMSO, reflux 2 h (c) 30% H_2O_2, K_2CO_3, DMSO, 0°C to r.t., 24 h (d) 2,6-di-*tert*-butylpyridine, Tf_2O, CH_2Cl_2, 0°C to r.t., 5 h; $Pd(PPh_3)_4$, p-tolylboronic acid, DIPEA, NMP, 170°C, 10 min.

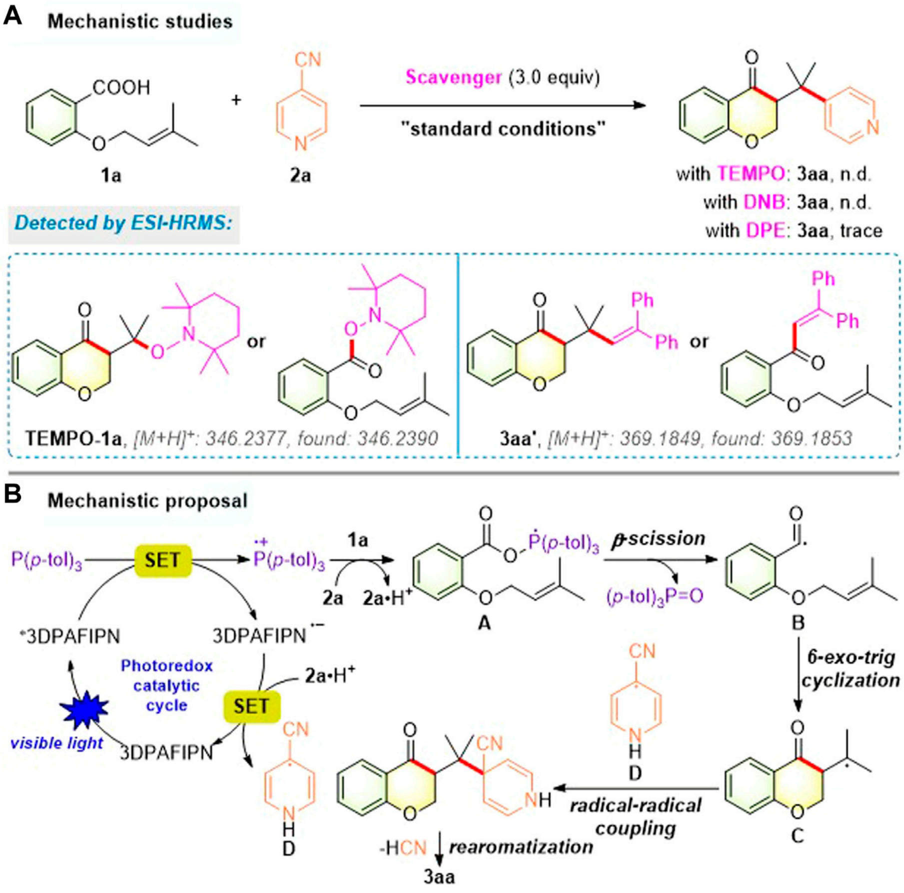


FIGURE 5
Mechanistic studies **(A)** and mechanistic proposal **(B)**.

this photocatalytic reaction could be run on a 1.0 mmol scale to provide the target product **3aa** in 67% yield. Firstly, we examined the effect of the aromatic moiety of the substrate alkenoic acid. It was found that the electron-donating group (Me, OMe) and electron-withdrawing groups (F, Cl, Br, CF_3) at the *para*- and *mata*-position with respect to the carboxylic acid were well compatible with this transformation and the corresponding chroman-4-ones were obtained with satisfactory yields (**3ba**–**3ia**). The structure of **3ga** was confirmed by X-ray diffraction analysis (CCDC 2192065). Moreover, the *ortho*-F substituted alkenoic acid was also employed in this transformation, providing the desired chroman-4-one **3ja** albeit in a relatively low yield. Then, we investigated the scope of the alkene moiety of the substrate alkenoic acid. 1,2-Disubstituted nonterminal alkenoic acid with a phenyl group at the terminal carbon participated well in such acylarylation to give the expected product **3ka**, while one with an alkyl group was transformed into the compound **3la** with a low yield. And 1,1-disubstituted or mono-substituted terminal alkenoic acid could also be subjected to this transformation, affording the corresponding chroman-4-ones (**3ma**–**3oa**) albeit with diminished yields. Interestingly, replacing the oxygen atom at the *ortho*-position with respect to the carboxylic acid by an atom of sulphur, nitrogen, or carbon favored the photocatalytic acylarylation, leading to the corresponding chroman-4-one analogs such as thiochroman-4-one **3pa**, dihydroquinolin-4(1*H*)-one **3qa**, and dihydronaphthalen-1(2*H*)-one **3ra**. Additionally, *N*-(homo)allylindole-2-carboxylic acids were proved to be suitable heteroaromatic substrates for this photocatalytic process and gave the architecturally intriguing and valuable tricyclic ketone framework including 1*H*-pyrrolo [1,2-*a*]indol-1-one (**3sa**) and pyrido [1,2-*a*]indol-9(6*H*)-one (**3ta**) in comparable yields. These experimental outcomes fully highlighted the synthetic potential to construct structurally complex ketone-containing (hetero)cycles. However, pyridyl-substituted alkenoic acid **1u** and acyclic aliphatic alkenoic acid **1v** could be not suitable for this alkene acylarylation.

To further explore the synthetic potential of our methodology, we then investigated differently substituted cyanoarene partners in this photocatalytic acylarylation

(Figure 3). Firstly, the substituted phenyl and alkyl group at the 2-position of cyanopyridine were well tolerated, providing the corresponding 3-(pyridylmethyl)chroman-4-ones (**3ab**–**3af**) in moderate to good yields. Cyanopyridines bearing halogen substituents at 2- or 3-position afforded the desired products albeit in decreased yields (**3ag**–**3ai**), offering opportunities for further derivatization. The structure of **3ah** was confirmed by X-ray diffraction analysis (CCDC 2192094). Notably, using 2, 4-dicyanopyridine as a coupling partner underwent selective coupling at the most electron-poor 4-position to produce the corresponding chroman-4-one **3aj** in a synthetically useful yield along with C2-coupled chroman-4-one **3aj′**. Additionally, non-pyridine cyanoarenes including quinoline and isoquinoline scaffolds were also successful with the standard conditions, leading to the formation of the corresponding chroman-4-ones **3ak** and **3al** with 49% and 48% yields, respectively. To our delight, other electron-withdrawing cyanoarene 1, 4-dicyanobenzene was also compatible with our protocol to give a satisfactory yield of 3-benzylchroman-4-one **3cm** (belonging to classical homoisoflavonoid skeleton), while 1,2-dicyanobenzene **2n** and ethyl 4-cyanobenzoate **2o** were not suitable.

To investigate the practical utility of this photocatalytic acylarylation process, several illustrative examples of simple derivatization of 3-(arylmethyl)chroman-4-ones were provided (Figure 4). For example, I_2-mediated dehydrogenation of the resulting 3-(arylmethyl)chroman-4-ones (**3aa** and **3cm**) proceeded well to provide the extensively studied and medicinally important chromones [**4** (Zheng et al., 2015; Gobbi et al., 2016) and **5** (Kirkiacharian et al., 1989; Cavalli et al., 2005; Kirkiacharian and Gomis, 2005; Rao et al., 2008; Kupcewicz et al., 2013; Noshita et al., 2021)] with 86% and 75% yields, respectively. 3-Benzylchroman-4-one **3cm** was treated with H_2O_2 in the presence of K_2CO_3 to obtain the corresponding amide **6** in 92% yield. Moreover, elaborated alkenyl triflate derived from **3cm** could undergo Pd-mediated Suzuki coupling to afford biologically intriguing 3-benzyl 2*H*-chromene (Srikanth et al., 1997; Conti and Desideri, 2009) **7** in 80% yield. To our delight, the first example for the more challenging three-component alkene acylarylation using simple and easily accessible feedstocks could be realized to afford *β*-pyridylated ketone **8** albeit in a relatively low yield (Figure 4B), which is complementary to the previously reported two-component synthesis of pyridyl-containing ketones (Zhu et al., 2020; Yang et al., 2021; Li et al., 2022a).

To elucidate the mechanism of this photocatalytic acylarylation, several control experiments using substrates **1a** and **2a** were carried out as shown in Figure 5A. When three equivalents of the radical scavenger TEMPO or the electron-transfer scavenger *p*-dinitrobenzene (DNB) were added under standard conditions, no product **3aa** was observed and the corresponding TEMPO-adduct (**TEMPO-1a**) was detected by ESI-HRMS analysis. Additionally, when the model reaction was performed with an external radical-trapping reagent 1,1-diphenylethylene (DPE), the formation of the desired chroman-4-one **3aa** was significantly inhibited and the corresponding radical-trapping product **3aa′** was also detected by ESI-HRMS analysis. Taken together, these results indicate that a radical/SET-based pathway might be involved in our photocatalytic acylarylation.

Based on the above experimental results and previous reports (Jiang et al., 2019; Hu et al., 2020a; Clarke et al., 2020; Nicastri et al., 2020; Pan et al., 2020; Rossi-Ashton et al., 2020; Shao et al., 2020; Zhou et al., 2020; Tong et al., 2021), a plausible mechanistic pathway for this photocatalytic acylarylation is proposed as described in Figure 5B. Under the blue LED irradiation, the photocatalyst 3DPAFIPN was initially raised to the excited state *3DPAFIPN, which was reductively quenched by P (*p*-tol)$_3$ to form the strongly reducing 3DPAFIPN$^{\bullet-}$ and phosphine radical cation. Subsequently, the phosphine radical cation recombined with the carboxylate anion of **1a** to produce the phosphoranyl radical intermediate **A**, which underwent a facile *β*-scission to form acyl radical **B** and tri-*p*-tolylphosphine oxide. Then, the resulting radical **B** proceeded *via* intramolecular 6-exo-trig cyclization with the alkene moiety to provide alkyl radical **C**. Meanwhile, SET between the reduced 3DPAFIPN$^{\bullet-}$ and **2a·H**$^+$ gave a persistent arene radical **D** and regenerated 3DPAFIPN. Finally, the alkyl radical **C** underwent intermolecular radical-radical coupling with radical **D** and sequential rearomatization *via* the elimination of both cyano anion and proton to achieve the corresponding chroman-4-one **3aa**.

Conclusion

In summary, we have developed a novel visible-light-driven photoredox-neutral alkene acylarylation with cyanoarenes, enabling metal-, oxidant-, and aldehyde-free access to structurally diverse 3-(arylmethyl)chroman-4-ones (i.e., homoisoflavonoids) as well as other cyclic ketone analogs such as thiochroman-4-one, dihydroquinolin-4(1*H*)-one, dihydronaphthalen-1(2*H*)-one, pyrrolo [1,2-*a*]indol-1-one, and pyrido [1,2-*a*]indol-9(6*H*)-one. Furthermore, the resulting chroman-4-ones can be scale-up synthesized and also readily parlayed into skeletally diverse and valuable compounds such as chromone and 2*H*-chromene. In addition, the developed powerful protocol involves phosphoranyl radical-mediated acyl radical-initiated cascade cyclization followed by radical-radical coupling with the persistent aryl radical, enabling the concomitant introduction of ketone and aromatic fragments to organic molecules.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.ccdc.cam.ac.uk/structures/- CCDC 2192065.

Author contributions

QW, DY, and JW conceived and designed the study, and wrote the paper. YD, SY, MR, JL, QF, ZZ, and JB performed experiments and mechanistic studies. NH, LY, and SW analyzed the experiments. All authors contributed to the analysis and interpretation of the data.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2022.1059792/full#supplementary-material

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