PAPER

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Visible-light synthesis of 4-substituted-chroman-2-ones and 2-substituted-chroman-4-ones *via* doubly decarboxylative Giese reaction†

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Doubly decarboxylative, photoredox synthesis of 4-substituted-chroman-2-ones and 2-substituted-chroman-4-ones is described. The reaction involves two independent decarboxylation processes: the first one initiating the cycle and the second completing the process. Visible light, photoredox catalyst, base, anhydrous solvent and inert atmosphere constitute the key parameters for the success of the developed transformation. The protocol proved applicable for coumarin-3-carboxylic acids and chromone-3-carboxylic acids as well as *N*-(acyloxy)phthalimide which served as precursors of the corresponding alkyl radicals.

Chroman-2-ones and their derivatives constitute privileged structural motifs present in various natural products (Scheme 1).[1] Similarly, the chroman-4-one ring system can be found in various bioactive molecules relevant for the life-science industry.[2] Representative examples of both groups of compounds are shown in Scheme 1. Soulamarin, isolated from stem bark has found application in folk medicine to treat rheumatism, varicose veins, haemorrhoids and ulcers.[3] Recedensolide shows activity against human cervical epitheloid carcinoma.[4] Flavanoids, such as eriodictyol and pinocembrin, are associated with reducing risk of certain chronic diseases.[5] Natural flavanones isolated from flowers of *Chromolaena odorata* such as 4′-hydroxy-5,6,7-trimethoxyflavanone are reported to have antimycobacterial activity.[6]

The addition of free radicals to electron-deficient olefins is known in the literature as Giese reaction (Scheme 2).[7] Recently, owing to the development of photocatalysis, the synthetic potential of this and related reactions has been vastly expanded.[8] Advancements in this field arises from the development of photo-initiated methods allowing for free radical formation under mild and non-toxic conditions. An interesting way to generate free radicals involves the usage of *N*-(acyloxy) phthalimides.[9] The formation of free radical is initiated by one-electron reduction with subsequent decarboxylation. Recently,

the potential of this method has been confirmed in the Giese reaction with various electron-poor olefins.[10]

Decarboxylative Michael reaction that involves the addition to carboxylic-acid-activated olefins followed by decarboxylation reaction constitutes a powerful synthetic tool.[11] Coumarin-3-carboxylic acids **2** and chromone-3-carboxylic acids **4** are useful reactants participating in this reaction opening access to biologically relevant chroman-2-ones **3** and chroman-4-ones **5**.[12,13] Recently, doubly decarboxylative reactions involving these reagents have also been developed.[14] Surprisingly, decarboxylative Giese reaction with carboxylic-acid-activated olefins has not been a subject of studies so far. Herein, we report the first photocatalytic, doubly decarboxylative Giese reaction
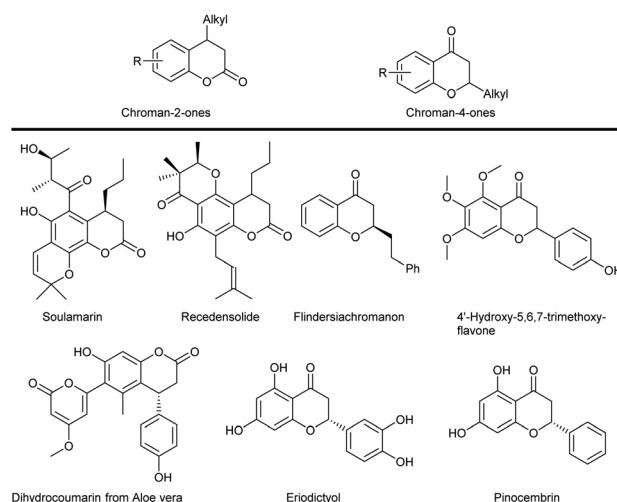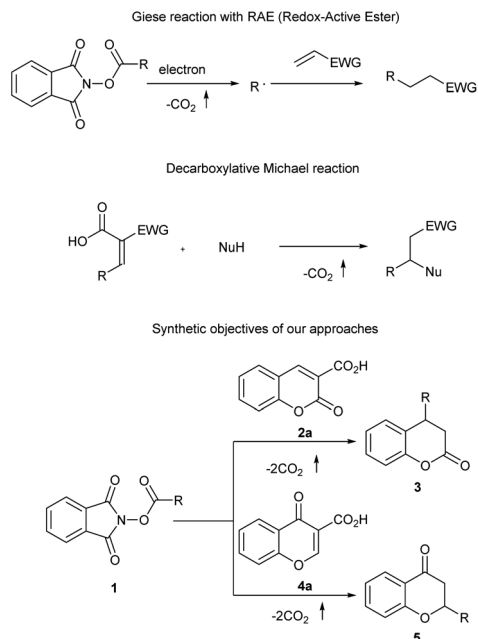

Scheme 1 The importance of chroman-2-ones and chroman-4-ones.

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Scheme 2 The importance of decarboxylative approaches in organic synthesis and the synthetic objectives of our study.

Table 1 Doubly decarboxylative Giese reaction – optimization studies involving coumarin-3-carboxylic acid **2aa**[a]

Entry	Cat	Solvent	Base	Cat. mol%	Yield [%]
1[b]	6a	CH₂Cl₂	DIPEA	10	—
2[c]	6b	CH₂Cl₂	DIPEA	10	—
3[d]	6c	CH₂Cl₂	DIPEA	10	56
4[d]	6d	CH₂Cl₂	DIPEA	10	63
5[b]	6e	CH₂Cl₂	DIPEA	10	26
6[b]	6f	CH₂Cl₂	DIPEA	10	82
7[b]	6g	CH₂Cl₂	DIPEA	10	42
8[b]	6h	CH₂Cl₂	DIPEA	10	—
9[b]	6f	CHCl₃	DIPEA	10	—
10[b]	6f	THF	DIPEA	10	—
11[b]	6f	PhMe	DIPEA	10	—
12[b]	6f	DMF	DIPEA	10	61
13[b]	6f	MeCN	DIPEA	10	58
14[b]	6f	CH₂Cl₂	TEA	10	47
15[b]	6f	CH₂Cl₂	Quinine	10	—
16[e]	—	CH₂Cl₂	DIPEA	—	—
17[b]	6f	CH₂Cl₂	—	10	—
18[f]	6f	CH₂Cl₂	DIPEA	10	—
19[b]	6f	CH₂Cl₂	DIPEA	5	53
20[g]	6f	CH₂Cl₂	DIPEA	10	35
21[h]	6f	CH₂Cl₂	DIPEA	10	—

[a] All reactions were performed in a 0.20 mmol scale using **1a** (1.2 equiv.) and **2a** (1.0 equiv.) in the presence of the corresponding photoredox catalyst **6** (10 mol%) and the corresponding base (2 equiv.) in the solvent (3 mL). [b] Reaction performed under irradiation with the blue light. [c] Reaction performed under irradiation with the violet light. [d] Reaction performed under irradiation with the green light. [e] Reaction performed without catalyst. [f] Reaction performed in the dark. [g] The reaction performed in the presence of DIPEA (1.2 equiv.). [h] Reaction performed in the presence of TEMPO (1 equiv.).

which is applicable to electron poor carboxylic acids. The developed strategy benefits from mild reaction conditions.

Optimization studies were performed using coumarin-3-carboxylic acid **2a** and 1,3-dioxoisoindolin-2-yl cyclohexane carboxylate **1a** (NHPI esters) as model substrates (Table 1). Initial experiments were performed in CH₂Cl₂ in the presence of DIPEA as a donor of electron and base the corresponding photoredox catalyst under LED irradiation (with the light source of suitable wavelength) under inert atmosphere. In the first part of the optimization studies, the catalytic activity of eight different photoredox catalysts was tested (Table 1, entries 1–8). When 9-mesityl-10-methylacridinium tetrafluoroborate **6a**, chloranil **6b** or **6h** were used, the formation of target product **3aa** was not observed (Table 1, entries 1 and 2). The best yield was obtained in the presence of Ru(bpy)₃(PF₆)₂ **6f** (Table 1, entry 6). In the course of further studies, the effect of the solvent on the reaction outcome was evaluated (Table 1, entries 9–13). The use of CHCl₃ did not ensure the product formation (Table 1, entry 9). Similar effect was observed in THF and toluene (Table 1, entries 10 and 11). The desired reaction took place also in acetonitrile and DMF, however, lower yield than in the case of CH₂Cl₂ was obtained (Table 1, entries 12 and 13). Subsequently, the effect of base on the reaction outcome was evaluated (Table 1, entries 14 and 15). When triethylamine was used, the yield of the reaction decreased (Table 1, entry 14) and the application of quinine did not result in the product **3aa** formation (Table 1, entry 15). In the course of further studies control experiments were performed (Table 1, entries 16–20). The reaction did not proceed in the absence of neither photoredox catalysts (Table 1, entry 16, presumably electron donor–acceptor complex of DIPEA with NHPI esters was not efficiently formed in this case), nor a base (Table 1, entry 17).[9a] Similar effect was observed

when the transformation was attempted in the dark (Table 1, entry 18), thus confirming the crucial effect of photocatalyst and the source of light on the reaction outcome. The amount of the photocatalyst **6f** was possible to be lowered to 5 mol% resulting in decrease of yield to 53% after 24 hours (Table 1, entry 19). On the other hand, it was possible to perform the reaction with DIPEA (1.2 equiv.) but the yield of the reaction decreased (Table 1, entry 20). Noteworthily, the reactivity was quenched in the

presence of TEMPO confirming the radical mechanism of the process (Table 1, entry 21).

With the optimized reaction conditions in hand (Table 1, entry 6), the applicability of the developed methodology was studied (Schemes 3 and 4). Initially, various coumarin-3-carboxylic acids **2a–i** were tested (Scheme 3). Acids **2b–d** bearing electron-donating groups on the aromatic ring provided products **3ab–ad** with higher yields. Similarly, carboxylic acids **2e–i** with electron-withdrawing groups also provided products with good yields. The lowest yield was obtained for coumarin-3-carboxylic acid **2h** with chlorine substituent in the 8-position. In the second stage of the scope studies various *N*-(acyloxy)phthalimides **1a–e** were investigated (Scheme 3). *N*-(Acyloxy)phthalimides **1a–e** that served as precursors of secondary and tertiary alkyl radicals turned out to be suitable components in the developed reaction. Target products **3ba–ea** were efficiently formed. However, the use of primary radicals turned out to be problematic. In the case of benzylic radical precursor, a dimerization of the corresponding radical was faster than the addition to the electrophile **2a**.

In the second part of our studies, chromone-3-carboxylic acids **4** were tested as acceptors in the doubly decarboxylative Giese reaction employing the same conditions that were used in the case of coumarine-3-carboxylic acids **2** (Scheme 4). The use of **4b–d** bearing electron-donating groups provided **5ab**, **5ac**, **5ad** with good results. On the other hand, the reaction of chromone-3-carboxylic acids **4e–i** with electron-withdrawing groups provided products **5ae–5ai** with slightly lower efficiency. Chromone-3-carboxylic acid **4h** bearing two substituents with opposite electronic effects was also well-tolerated. Other alkyl radical precursors **1b–e** were also utilized in the reaction with chromone-3-carboxylic acid **4a**. The *tert*-butyl substituted
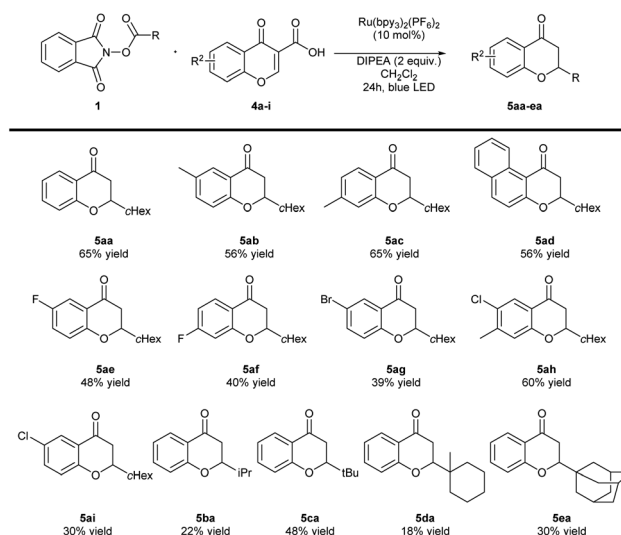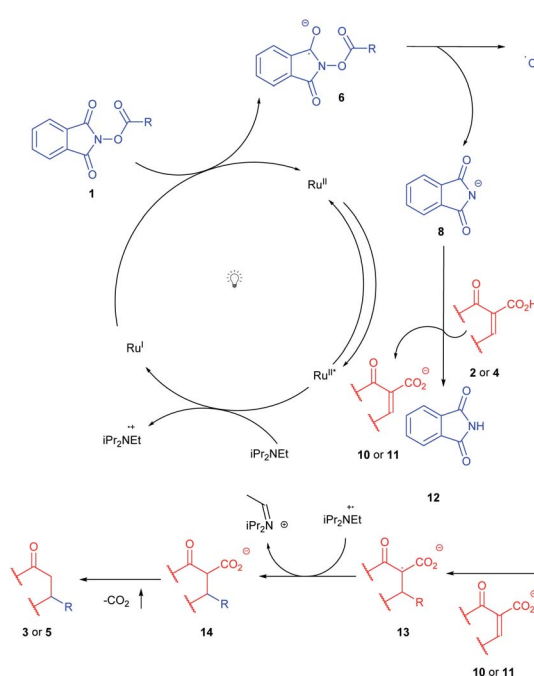

Scheme 4 Doubly decarboxylative Giese reaction – reaction involving chromone-3-carboxylic acids **4**.

product **5ca** was obtained with the highest yield in this part of the study. Unfortunately, the rest of examples showed lower responsiveness to participate in the reaction.

The postulated mechanism of both developed reactions is similar and begins with photocatalyst excitation (Scheme 5). Then the electron transfer from the amine to the photocatalyst takes place. Fluorescence quenching and cyclic voltammetry experiments confirmed the lack of quenching in the case of acids **2a** or **4a** as well as *N*-(acyloxy)phthalimide **1a** (for details see ESI†). Subsequently, Ru(ɪ) species acts as reductant of the *N*-(acyloxy)phthalimide **6**. In turn, **7** undergoes decarboxylative
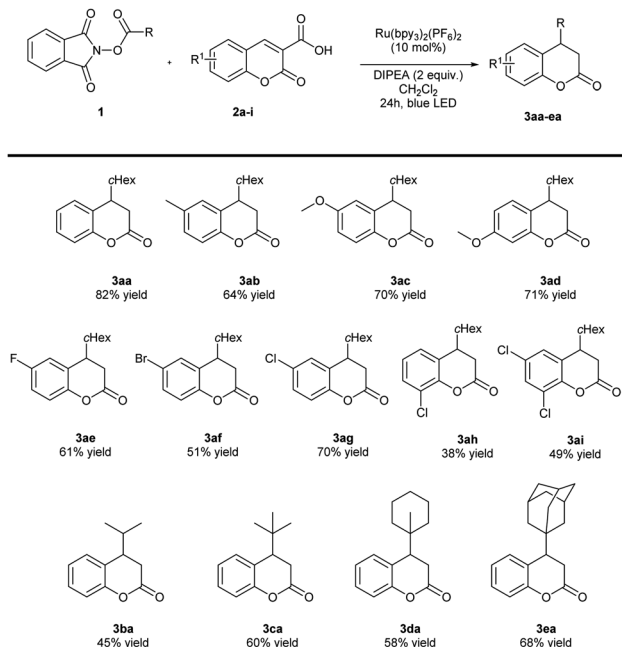
Scheme 3 Doubly decarboxylative Giese reaction – reaction involving coumarin-3-carboxylic acids **2**.

Scheme 5 Doubly decarboxylative Giese reaction – mechanism.

degradation with the formation of an alkyl radical **9**. The newly formed radical **9** undergoes Giese reaction with the acceptor **10** or **11**. Transfer of the hydrogen atom from the radical cation originating from amine and subsequent decarboxylative protonation terminates the reaction affording **3** or **5** as target products.[10a]

Conclusions

In conclusion, we have developed a doubly decarboxylative photocatalytic Giese reaction. It exemplifies the unique application of a free carboxylic-acid-activated olefins in a radical transformation. The reaction was applicable to a carboxylic acids as various coumarin-3-carboxylic acids **2a–i** and chromone-3-carboxylic acids **4a–i** served as effective Giese acceptors. The reaction can be described as doubly decarboxylation process with the first decarboxylation initiating the cycle and the second completing the process. Target, biologically relevant 4-substituted-chroman-2-ones **3aa–ea** and 2-substituted-chroman-4-ones **5aa–ea** were obtained in good to high yields under mild reaction conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

References

1 (a) D. P. Kamat, S. G. Tilve, V. P. Kamat and J. K. Kirtany, Syntheses and Biological Activities of Chroman-2-ones, *Org. Prep. Proc. Int.*, 2015, **47**, 1; (b) T. Okamoto, T. Kobayashi and S. Yoshida, Chemical aspects of coumarin compounds for the prevention of hepatocellular carcinomas, *Curr. Med. Chem.*, 2005, **5**, 47; (c) F. Asai, M. Iinuma, T. Tanaka and M. Mizuno, Complex flavonoids in farinose exudate from Pityrogramma calomelanos, *Phytochemistry*, 1991, **30**, 3091.

2 (a) Ø. M. Andersen and K. R. Markham, *Flavonoids: Chemistry, Biochemistry and Applications*. CRC, Taylor & Francis, Boca Raton, FL, 2006; (b) S. Emami and Z. Ghanbarimasir, Recent advances of chroman-4-one derivatives: synthetic approaches and bioactivities, *Eur. J. Med. Chem.*, 2015, **93**, 539; (c) K.-S. Masters and S. Bräse, Xanthones from fungi, lichens, and bacteria: the natural products and their synthesis, *Chem. Rev.*, 2012, **112**, 3717; (d) A. D. Patil, A. J. Freyer, D. S. Eggleston,

R. C. Haltiwanger, M. F. Bean, P. B. Taylor, M. J. Caranfa, A. L. Breen, H. R. Bartus and R. K. Johnson, The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, Calophyllum inophyllum Linn, *J. Med. Chem.*, 1993, **36**, 4131; (e) D. L. Galinis, R. W. Fuller, T. C. McKee, J. H. II Cardellina, R. J. Gulakowski, J. B. McMahon and M. R. Boyd, Structure-Activity Modifications of the HIV-1 Inhibitors (+)-Calanolide A and (−)-Calanolide B1, *J. Med. Chem.*, 1996, **39**, 4507.

3 G. C. L. S. Ee, H. Mah, S. S. Teh, M. Rahmani, R. Go and Y. H. Taufiq-Yap, Soulamarin, a new coumarin from Stem Bark of Calophyllum soulattri, *Molecules*, 2011, **16**, 9721.

4 Y. Shen, L. Wang, A. Khalil and Y. Kuo, Chromanones and dihydrocoumarins from Calophyllum blancoi, *Chem. Pharm. Bull.*, 2004, **52**, 402.

5 D. Genovese, C. Conti, P. Tomae, N. Desideri, M. Setin, S. Catone and L. Flore, Effect of chloro-, cyano-, and amidino-substituted flavanoids on enterovirus infection in vitro, *Antiviral Res.*, 1995, **27**, 123.

6 A. Suksamrarn, A. Chotipong, T. Suavansri, S. Boongird, P. Tirnsuksai, S. Vimuttipong and A. Chuaynugu, Antimycobacterial Activity and Cytotoxicity of Flavonoids from the Flowers of Chromolaena odorata., *Arch. Pharmacal Res.*, 2004, **27**, 507.

7 (a) B. Giese, J. A. Gonzalez-Gomez and T. Witzel, The Scope of Radical CC-Coupling by the "Tin Method", *Angew. Chem., Int. Ed.*, 1984, **23**, 69; (b) L. Chu, C. Ohta, Z. Zuo and D. W. C. MacMillan, Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (±)-Pregabalin, *J. Am. Chem. Soc.*, 2014, **136**, 10886; (c) J. Schwarz and B. König, Metal-Free, Visible-Light-Mediated, Decarboxylative Alkylation of Biomass-Derived Compounds, *Green Chem.*, 2016, **18**, 4743; (d) N. P. Ramirez and J. C. Gonzalez-Gomez, Decarboxylative Giese-Type Reaction of Carboxylic Acids Promoted by Visible Light: A Sustainable and Photoredox-Neutral Protocol, *Eur. J. Org. Chem.*, 2017, 2154; (e) J. Rostoll-Berenguer, G. Blay, J. R. Pedro and C. Vila, Photocatalytic Giese Addition of 1,4-Dihydroquinoxalin-2-ones to Electron-Poor Alkenes Using Visible Light, *Org. Lett.*, 2020, **22**, 8012; (f) F. El-Hage, C. Schöll and J. Pospech, Photo-Mediated Decarboxylative Giese-Type Reaction Using Organic Pyrimidopteridine Photoredox Catalysts, *J. Org. Chem.*, 2020, **85**, 13853.

8 (a) R. Brimioulle, D. Lenhart, M. M. Maturi and T. Bach, Enantioselective Catalysis of Photochemical Reactions, *Angew. Chem., Int. Ed.*, 2015, **54**, 3872; (b) L. Buzzetti, G. E. M. Crisenza and P. Melchiorre, Mechanistic Studies in Photocatalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 3730; (c) A. Vega-Peñaloza, J. Mateos, X. Companyó, M. Escudero-Caso and L. Dell'Amico, A Rational Aproach to Organo-Photocatalysis Novel Designs and Structure-Property Relationships, *Angew. Chem., Int. Ed.*, 2021, **60**, 1082; (d) N. A. Romero and D. A. Nicewicz, Organic Photoredox Catalysis, *Chem. Rev.*, 2016, **17**, 10075; (e) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, Photocatalytic

decarboxylative alkylations mediated by triphenylphosphine and sodium iodide, *Science*, 2019, **363**, 1429.

9 (*a*) S. K. Parida, T. Mandal, S. Das, S. K. Hota, S. De Sarkar and S. Murarka, Single Electron Transfer-Induced Redox Processes Involving *N*-(Acyloxy)phthalimides, *ACS Catal.*, 2021, **11**, 1640; (*b*) S. Shibutani, K. Nagao and H. Ohmiya, Organophotoredox-Catalyzed Three-Component Coupling of Heteroatom Nucleophiles, Alkenes, and Aliphatic Redox Active Esters, *Org. Lett.*, 2021, **23**, 1798; (*c*) Y. Dong, P. Ji, Y. Zhang, Ch. Wang, X. Meng and W. Wang, Organophotoredox-Catalyzed Formation of Alkyl-Aryl And -Alkyl C-S/Se Bonds from Coupling of Redox-Active Esters with Thio/Selenosulfonates, *Org. Lett.*, 2020, **22**, 9562; (*d*) T. Saget and B. König, Photocatalytic Synthesis of Polycyclic Indolones, *Chem. Eur. J.*, 2020, **26**, 7004; (*e*) C. Zheng, G.-Z. Wang and R. Shang, Catalyst-free Decarboxylation and Decarboxylative Giese Additions of Alkyl Carboxylates through Photoactivation of Electron Donor-Acceptor Complex, *Adv. Synth. Catal.*, 2019, **361**, 4500; (*f*) K. Okada, K. Okamoto, N. Morita, K. Okubo and M. Oda, Photosensitized decarboxylative Michael addition through *N*-(acyloxy)phthalimides *via* an electron-transfer mechanism, *J. Am. Chem. Soc.*, 1991, **113**, 9401; (*g*) G.-Z. Wang, M.-C. Fu, B. Zhao and R. Shang, Photocatalytic decarboxylative alkylations of C(sp³)–H and C(sp²)–H bonds enabled by ammonium iodide in amide solvent, *Sci. China Chem.*, 2021, **64**, 439; (*h*) M. Tian, Y. Wang, X. Bu, Y. Wang and X. Yang, An ultrastable olefin-linked covalent organic framework for photocatalytic decarboxylative alkylations under highly acidic conditions, *Catal. Sci. Technol.*, 2021, **11**, 4272.

10 (*a*) K. N. Tripathi, Md. Belal and R. P. Singh, Organo Photoinduced Decarboxylative Alkylation of Coumarins with N-(Acyloxy)phthalimide, *J. Org. Chem.*, 2020, **85**, 1193; (*b*) S. Das, S. Kumar Parida, T. Mandal, S. K. Hota, L. Roy, S. D. Sarkar and S. Murarka, An organophotoredox-catalyzed redox-neutral cascade involving *N*-(acyloxy)phthalimides and maleimides, *Org. Chem. Front.*, 2021, **8**, 2256.

11 (*a*) J.-J. Zhang, J.-C. Yang, L.-N. Guo and X.-H. Duan, Visible-Light-Mediated Dual Decarboxylative Coupling of Redox-Active Esters with α,β-Unsaturated Carboxylic Acids, *Chem.–Eur. J.*, 2017, **23**, 10259; (*b*) K. Xu, Z. Tan, H. Zhang, J. Liu, S. Zhang and Z. Wang, Photoredox catalysis enabled alkylation of alkenyl carboxylic acids with *N*-(acyloxy) phthalimide *via* dual decarboxylation, *Chem. Commun.*, 2017, **53**, 10719; for reviews on decarboxylative strategies, see: ; (*c*) Y. Pan and C.-H. Tan, Catalytic Decarboxylative Reactions: Biomimetic Approaches Inspired by Polyketide Biosynthesis, *Synthesis*, 2011, 2044; (*d*) Z.-L. Wang, Recent Advances in Catalytic Asymmetric Decarboxylative Addition Reactions, *Adv. Synth. Catal.*, 2013, **355**, 2745; (*e*) S. Nakamura, Catalytic enantioselective decarboxylative reactions using organocatalysts, *Org. Biomol. Chem.*, 2014, **12**, 394; (*f*) J. Bojanowski and A. Albrecht, Carboxylic-Acid-Activated Olefins in Decarboxylative Reactions, *Asian J. Org. Chem.*, 2019, **8**, 746.

12 (*a*) L. Xu, Z. Shao, L. Wang and J. Xiao, Tandem sp3 C-H Functionalization/Decarboxylation of 2-Alkylazaarenes with Coumarin-3-carboxylic Acids, *Org. Lett.*, 2014, **16**, 796; (*b*) F. Han, S. Xun, L. Jia, Y. Zhang, L. Zou and L. Hu, Traceless-Activation Strategy for Rh-Catalyzed Csp2 −H Arylation of Coumarins, *Org. Lett.*, 2019, **21**, 5907.

13 (*a*) Z. Shao, L. Wang, L. Xu, H. Zhao and J. Xiao, Facile synthesis of azaarenes-2-substituted chromanone derivatives *via* tandem sp3 C–H functionalization/ decarboxylation of azaarenes with 4-oxo-4H- chromene-3-carboxylic acid, *RSC Adv.*, 2014, **4**, 53188; (*b*) A. G. Neo, J. Diaz, S. Marcaccinib and C. F. Marcos, Conjugate addition of isocyanides to chromone 3-carboxylic acid: an efficient one-pot synthesis of chroman-4-one 2-carboxamides, *Org. Biomol. Chem.*, 2012, **10**, 3406.

14 (*a*) S. Nakamura, A. Toda, M. Sano, T. Hatanaka and Y. Funahashi, Organocatalytic Enantioselective Conjugate Addition of Malonic Acid Half Thioesters to Coumarin-3-carboxylic Acids Using *N*-Heteroarenesulfonyl Cinchona Alkaloid Amide, *Adv. Synth. Catal.*, 2016, **358**, 1029; (*b*) S. Peng, L. Wang, H. Guo, S. Sunb and J. Wang, Facile synthesis of 4-substituted 3,4-dihydrocoumarins *via* an organocatalytic double decarboxylation process, *Org. Biomol. Chem.*, 2012, **10**, 2537; (*c*) A. Albrecht, Utilization of Chromone-3-Carboxylic Acids as Acceptors in the Michael-Type Decarboxylative Addition, *Eur. J. Org. Chem.*, 2018, 648.