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Iron-Catalyzed Regioselective Decarboxylative Alkylation of Coumarins and Chromones with Alkyl Diacyl Peroxides

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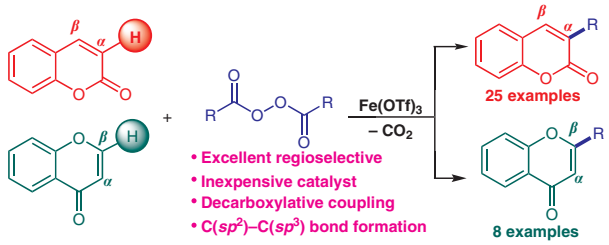

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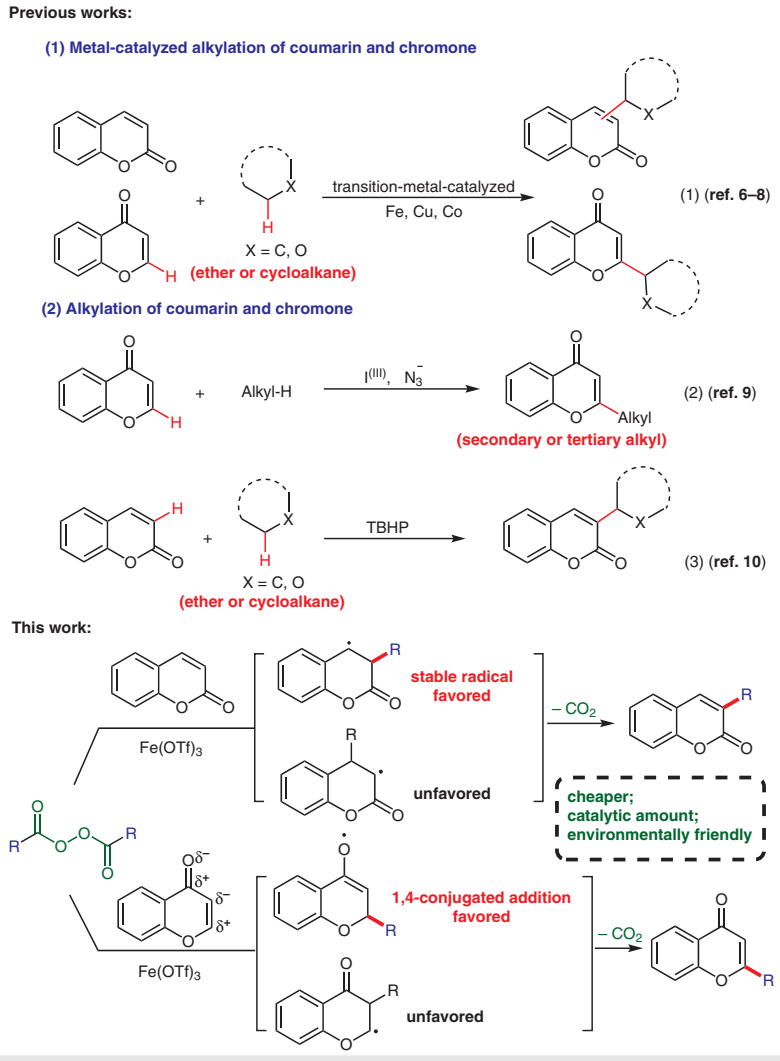
Abstract A facile iron-catalyzed decarboxylative radical coupling of alkyl diacyl peroxides with coumarins or chromones has been developed, affording a highly efficient approach to synthesize a variety of α-alkylated coumarins and β-alkylated chromones. The reaction proceeded smoothly without adding any ligand or additive and provided the corresponding products containing a wide scope of functional groups in moderate to excellent yields. This protocol was highlighted by its high regioselectivity, readily available starting materials, and operational simplicity.

Key words coumarins, chromones, C–C bond, iron-catalyzed, decarboxylation

Coumarin and chromone derivatives possessing carbonyl-conjugated olefin fragment in their structures exhibit a broad range of notable activities such as antimicrobial, anti-inflammatory, anticancer, and anti-HIV.[1] In the past decades, direct C–H functionalizations *via* a cross-coupling pathway has become one of the most straightforward and efficient methods for C–C or C–X bond formation because this protocol is more atom economical and environmentally friendly.[2] With the assistance of precious metals, such as Pd,[3] Rh,[4] Ru,[5] considerable progress has been made in the synthesis of aryl-substituted coumarin or chromone derivatives. For example, Shafiee and coworkers developed a regioselective arylation of chromenones *via* palladium-catalyzed oxidative boron Heck-type reaction.[3a] Subsequently, a more difficult task, that is alkylation of coumarins or chromones, was also realized under transition-metal catalysis[6–8] (Scheme 1, 1). In 2015, Ge's group developed two novel regioselective cross-dehydrogenation couplings of coumarins and chromones with different ethers *via* C(sp^3)–H functionalization process under catalysis of copper or iron salts.[7b] In addition, alkylation of coumarins and chromones was also achieved under metal-free conditions by the Antonchick and Jafarpour group.[9,10] Although great progress has been obtained in preparing alkylated coumarin or chromone compounds, some drawbacks such as the use of excess amounts of chemical oxidants, poor regioselectivity, and low conversions or yields are still the issues limiting the further application. Moreover, the method for preparation of primary alkyl-substituted coumarins or chromones is still an enormous challenge. Very recently, our group developed a visible-light-induced decarboxylative coupling reaction between coumarins and NHP esters mediated by visible light using expensive iridium as photocatalyst.[11] Applying this strategy, though primary alkylated coumarins were synthesized successfully, whereas the pursuit of cost-effective system to achieve C–H alkylation of coumarin or chromone is always an ongoing interest in our lab.

Alkyl diacyl peroxides which could be easily synthesized from the corresponding carboxylic acids were demonstrated to be effective alkyl sources because it can be easily decomposed to give alkyl radicals in the presence of inexpensive metal catalysts, such as Cu and Fe, while elimination of CO_2.[12] Therefore, we reasonably postulated that it should be possible to achieve the alkylation of coumarin or chromone *via* decarboxylative alkylation by employing primary alkyl diacyl peroxides as alkyl source, providing a practical and cheaper approach to offer the alkylated derivatives. In continuation of our interest in the development of C–H functionalization of coumarins or chromones, herein, we present our recent work on this iron-catalyzed decarboxylative coupling reaction between alkyl diacyl peroxides and coumarins or chromones for the synthesis of α-alkylated coumarins and β-alkylated chromones.

To begin our study, coumarin (**1a**) and lauroyl peroxide (LPO, **2a**) was chosen as the representative reactant to explore and optimize the decarboxylative coupling reaction (Table 1). Initially, the reaction was carried out in MeCN un-



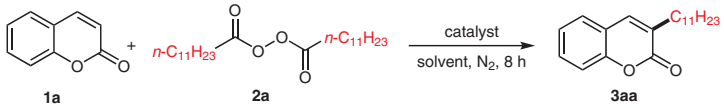
Scheme 1 Strategies for the synthesis of alkylated chromone or coumarin derivatives

der the catalysis of various copper salts (5 mol%) at 60 °C for 8 h. Disappointingly, the experimental results indicated that all of these screened copper catalysts, such as $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, or CuBr, were all ineffective for this transformation (Table 1, entries 1–4). Fortunately, when the reaction was performed in the presence of 5 mol% $FeCl_3$, it was pleased to find that the desired product **3aa** could be obtained in 25% yield (Table 1, entry 5). Encouraged by this result, another two iron salts were also studied, and $Fe(OTf)_3$ proved to be best with 58% yield for coupling product **3aa** (Table 1, entries 6 and 7). Subsequently, several other solvents including dioxane, DCM, and DCE were probed, and dioxane was proved to be the best choice (Table 1, entries 8–10). A significant improvement was observed when the temperature was elevated to 70 °C, however, we also found that a further increase of reaction temperature could not improve the efficiency of the reaction (Table 1, entries 11 and 12). Either increasing the amount of $Fe(OTf)_3$ to 10 mol% or decreasing to 2 mol% all did not display positive effects on this transformation (Table 1, entries 13 and 14). The optimization experiments also revealed that no desired product **3aa** was observed in absence of an iron catalyst, and the yield dropped obviously when the reaction was conducted under an air atmosphere (Table 1, entries 15 and 16).

After the reaction conditions were screened, it could be concluded that the optimized reaction conditions should be performed under the catalysis of 5 mol% $Fe(OTf)_3$ at 70 °C in dioxane under N_2 atmosphere.

With the optimized conditions in hand, different sets of experiments were carried out to investigate the scope and limitation of this reaction. Initially, a series of coumarins were investigated *via* the decarboxylative coupling reaction with LPO (**2a**) under the optimized conditions. As given in Scheme 2, this method was found to be applicable to a wide

Table 1 Optimization of the Reaction Conditions[a]



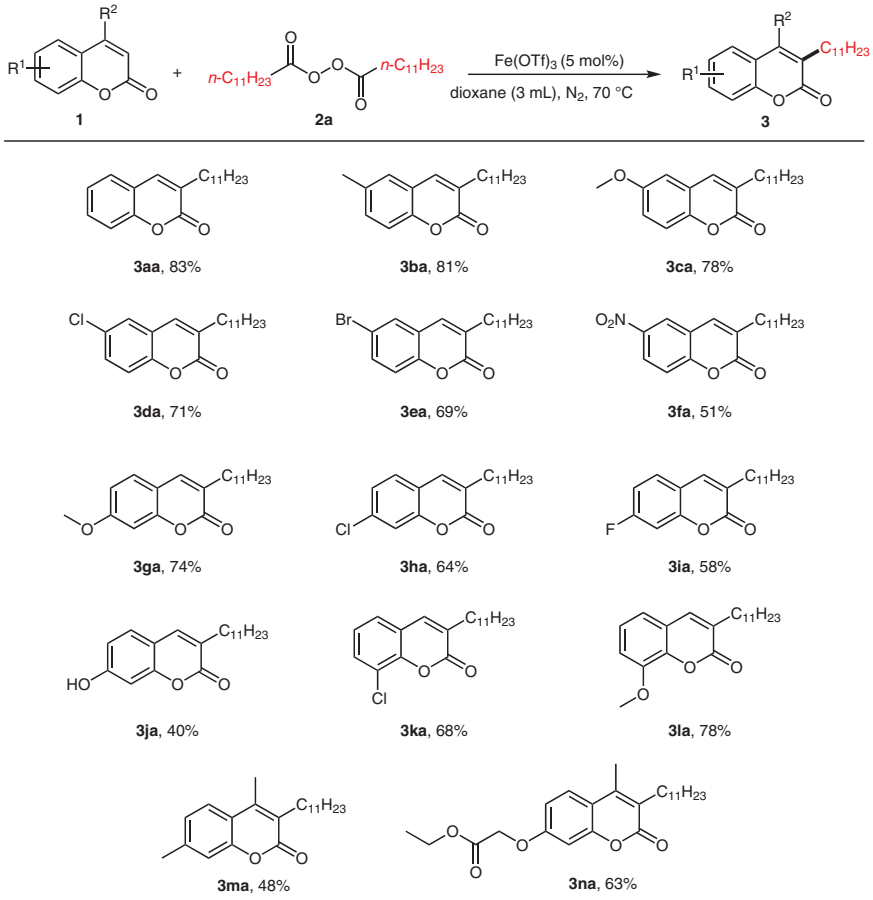
1a 2a 3aa

Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]
1	$CuCl_2$	MeCN	60	N.D.
2	$CuBr_2$	MeCN	60	N.D.
3	$Cu(OAc)_2$	MeCN	60	N.D.
4	CuBr	MeCN	60	N.D.
5	$FeCl_3$	MeCN	60	25
6	$Fe(OTf)_2$	MeCN	60	53
7	$Fe(OTf)_3$	MeCN	60	58
8	$Fe(OTf)_3$	dioxane	60	65
9	$Fe(OTf)_3$	DCM	60	50
10	$Fe(OTf)_3$	DCE	60	60
11	$Fe(OTf)_3$	dioxane	70	83
12	$Fe(OTf)_3$	dioxane	80	67
13[c]	$Fe(OTf)_3$	dioxane	60	82
14[d]	$Fe(OTf)_3$	dioxane	60	75
15	–	dioxane	60	N.D.
16[e]	$Fe(OTf)_3$	dioxane	60	65

[a] Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.6 mmol), **2a** (1.2 mmol), and catalyst (0.03 mmol) in dioxane (3 mL) under N_2 atmosphere for 8 h.
[b] Isolated yield.
[c] $Fe(OTf)_3$(10 mol%).
[d] $Fe(OTf)_3$ (2 mol%)
[e] Under air atmosphere.

range of coumarins (**1a–n**), giving the corresponding products **3aa–na** in 40–83% yields. Coumarins bearing electron-donating groups at 6-position of aromatic ring, such as methyl (**1b**) or methoxy (**1c**) could provide the desired products **3ba** and **3ca** in 81% and 78% yields, respectively. Meanwhile, the coumarins containing electron-withdrawing groups at 6-position of the aromatic ring, even though the strong-withdrawing group (nitro), were also well tolerated for this decarboxylative coupling reaction, affording the corresponding α-substituted products **3da–fa** in 51–71% yields. Subsequently, coumarins with substituents at different positions of the benzene ring were also tested. The experiment results indicated that this decarboxylative coupling reaction was not very sensitive to the substituted positions of functional groups. Coumarins bearing either electron-donating groups or electron-withdrawing groups at the 7 or 8-position of the aromatic ring were all suitable for this transformation and gave the desired product **3ga**,**ha**,**ia**,**ka**,**la** in 58–78% yields. To our delight, unprotected 7-hydroxycoumarin **1j** was also well compatible with these reaction conditions, giving the corresponding product **3ja** in moderate yield. In addition, it was worth noting that 4-methyl-substituted coumarins **1m** or **1n** also could undergo this decarboxylative coupling process well, achieving the target products **3ma** and **3na** in high efficiency, whereas C(sp^3)–H bonds were unaffected. Compared with the previous photocatalytic method,[12] this strategy possessed a wider scope of coumarins, including the nitro-substituted **1f**, unprotected substrate **1j**, and 4-methyl-substituted **1m** or **1n**, that were all tolerated for this transformation.

After the scope of coumarins was examined, we then turned our attention to explore the scope of alkyl diacyl peroxides *via* decarboxylative coupling reaction with coumarin (**1a**). The results are summarized in Scheme 3. This method was found to be applicable to a variety of alkyl diacyl peroxides, which were able to undergo the decarboxylative coupling process to provide the desired α-position-substituted alkylated coumarin derivatives **3ab–ak** in moderate to good yields. Initially, a series of simple primary alkyl-substituted diacyl peroxides **2b–e** bearing *n*-octyl, *n*-propyl, 3-methylbutyl, and 2,2-dimethylpropyl were probed, and these substrates all showed good tolerance for this reaction, affording the corresponding products **3ab–ae** in 58–79% yields. Moreover, alkyl diacyl peroxides with ad-



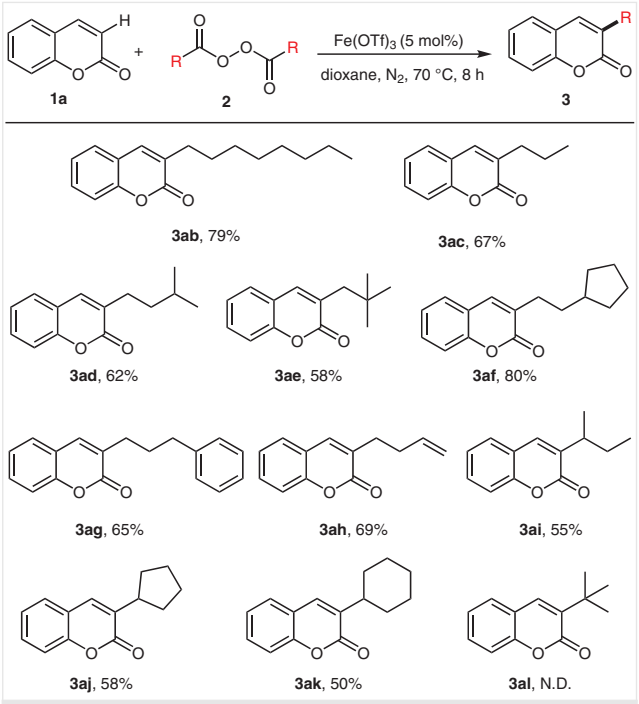
Scheme 2 Substrate scope of coumarins. All reactions were performed with **1** (0.6 mmol), **2a** (1.2 mmol), and $Fe(OTf)_3$ (0.03 mmol) in dioxane (3 mL) at 70 °C under N_2 atmosphere for 8 h.

ditional functional groups, such as cyclopentyl (**2f**), phenyl (**2g**), and alkenyl (**2h**), were also well tolerated for this transformation, and the desired products **3af–ah** could be obtained in satisfied yields. Subsequently, we explored whether the secondary alkyl diacyl peroxides could adapt to this reaction. To our delight, 1-methylpropyl diacyl peroxide (**2i**), cyclopentyl diacyl peroxide (**2j**), and cyclohexyl diacyl peroxide (**2k**) all could be well tolerated, and the alkylated products **3ai**,**aj**,**ak** were isolated in 55%, 58%, and 50% yields, respectively. Apart from primary or secondary alkyl diacyl peroxides, tertiary alkyl diacyl peroxide (**2l**) was also employed to react with the coumarin (**1a**) under the optimized conditions. However, it failed to give the desired product **3al** mainly due to the poor stability of tertiary alkyl diacyl peroxides compared with the primary or secondary alkyl diacyl peroxides.

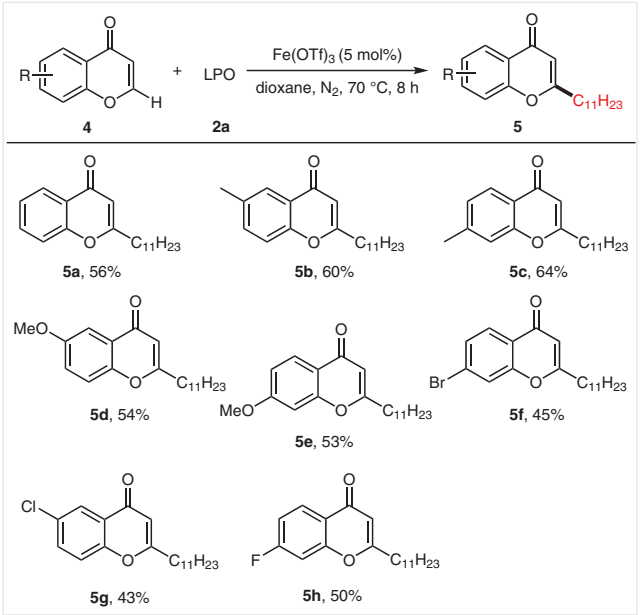
Applying the optimized reaction conditions found above, various chromones containing a wide scope of functional groups on the benzene ring were also reacted with LPO (**2a**) as depicted in Scheme 4. Expectedly, chromones bearing either electron-withdrawing (fluoro, chloro, bromo) or electron-donating groups (methyl, methoxy) on the 6- or 7-positions of the benzene ring were all able to undergo this decarboxylative coupling process well, giving the alkyl-substituted chromone derivatives **5a–h** in moderate yields.

Noticeably, the electron-rich alkyl radical was more prone to add to the electron-deficient β-position of the chromone, rather than the relatively electron-rich α-position, regioselectively providing the β-substituted alkylated chromone derivatives.

To gain the insight into the mechanism of the reaction, several control experiments were carried out as shown in Scheme 5. Firstly, in order to determine if radicals were involved in these two decarboxylative coupling reactions, 1,1-diphenylethylene was used as radical scavenger adding into the reaction system, and the transformation was completely suppressed (Scheme 5, 1). As expected, the corresponding product **3aa** or **5a** was not found by ESI-MS. Subsequently, the further step confirmed the formation of alkyl radical, and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was then added into the decarboxylative coupling reaction between coumarin (**1a**) and LPO (**2a**) under the standard



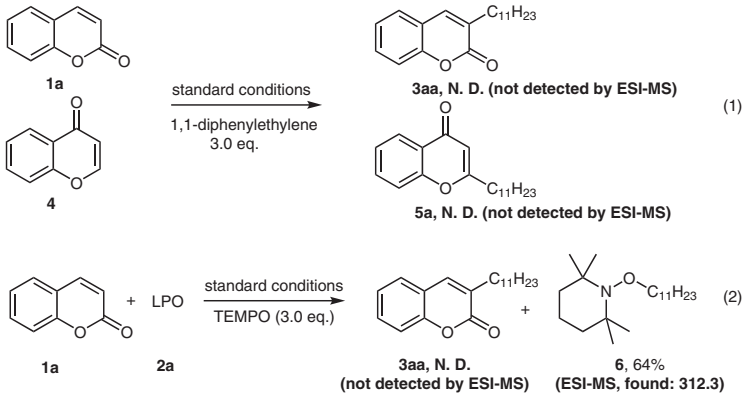
Scheme 3 Substrate scope with alkyl diacyl peroxides. All reactions were performed with **1a** (0.6 mmol), **2** (1.2 mmol), and $Fe(OTf)_3$(0.03 mmol) in dioxane (3 mL) at 70 °C under N_2 atmosphere for 8 h.



Scheme 4 Substrate scope of chromones. All reactions were performed with **4** (0.6 mmol), **2a** (1.2 mmol), and $Fe(OTf)_3$ (0.03 mmol) in dioxane (3 mL) at 70 °C under N_2 atmosphere for 8 h.

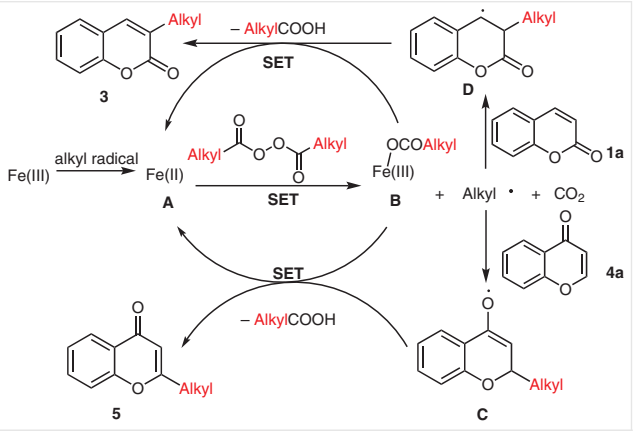
conditions. The experiment result indicated that no desired product **3aa** was found, meanwhile, the radical trapping product **6** was detected by ESI-MS and isolated in 64% yield (Scheme 5, 2). The similar result was obtained when TEMPO was added into another coupling reaction between chromone **5a** and LPO **2a**. These experiment results indicated that radicals were involved in both two decarboxylative coupling reactions.

Based on the control-experiment results and previous reports,[12] a plausible mechanism has been proposed in Scheme 6. Bao's group has demonstrated that the Fe(III) was initially reduced by alkyl radical to afford the Fe(II). Then Fe(II) could be oxidized by the alkyl diacyl peroxide to provide the alkyl radical by releasing a molecule of carbon dioxide, accompanied with oxidation of Fe(II) to Fe(III) *via* a SET process. Subsequently, the alkyl radical could attack the α-position of coumarin, generating a thermodynamically stable radical **D**, which could be transformed into the desired product **3** *via* a SET process, followed by elimination of AlkylCOOH. Because the α-position of chromone possessed a higher electron density than the β-position, the electron-



Scheme 5 Control experiments

rich alkyl radical exhibited some nucleophilicity and was prone to react at the electron-deficient β-position of chromone instead of the α-position, generating the radical intermediate **C**. After a SET process and elimination of AlkylCOOH, radical C was finally transformed into the desired product **5**.



Scheme 6 Proposed mechanism

In summary, we have succeeded in developing a novel iron-catalyzed regioselective alkylation of coumarins and chromones by employing cheap and available alkyl diacyl peroxides as the alkyl source, preparing a variety of alkyl-substituted derivatives with alkyl group on the α-position of coumarins and the β-position of chromones.[13] The use of inexpensive and nontoxic iron salts as the catalyst made this transformation environmentally friendly and practical. Remarkably, this transformation has been proven to be compatible with a wide range of alkyl diacyl peroxides, especially the primary alkyl-substituted peroxides, and a variety of coumarins or chromones bearing various functional groups also exhibited good tolerance for this transformation. Mechanistic studies have revealed that these two decarboxylative coupling reactions all proceed through a radical process.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611864.

References and Notes

(1) (a) Musa, M. A.; Cooperwood, J. S.; Khan, M.; Omar, F. *Curr. Med. Chem.* **2008**, *15*, 2664. (b) Spino, C.; Dodier, M.; Sotheeswaran, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3475. (c) Wang, X. H.; Bastow, K. F.; Sun, C. M.; Lin, Y. L.; Yu, H. J.; Don, M. J.; Wu, T. S.; Nakamura, S.; Lee, K. H. *J. Med. Chem.* **2004**, *47*, 5816.

(2) (a) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Yeung, C. S.; Dong, M. V. *Chem. Rev.* **2011**, *111*, 1215. (c) Cho, S. H.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Sun, B.; Wang, Y.; Li, D. Y.; Jin, C.; Su, W. K. *Org. Biomol. Chem.* **2018**, *16*, 2902. (e) Sun, B.; Yin, S.; Zhuang, X. H.; Jin, C.; Su, W. K. *Org. Biomol. Chem.* **2018**, *16*, 6017. (f) Sun, B.; Deng, J. C.; Li, D. Y.; Jin, C.; Su, W. K. *Tetrehedron Lett.* **2018**, *59*, 4364. (g) Sun, B.; Yan, Z. Y.; Jin, C.; Su, W. K. *Synlett.* **2018**, *29*, 2432. (h) Lv, Y. H.; Li, Y.; Xiong, T.; Lu, Y.; Liu, Q.; Zhang, Q. *Chem. Commun.* **2014**, *50*, 2367. (i) Vogl, O.; Rondestvedt, C. S. *J. Am. Chem. Soc.* **1954**, *77*, 3067. (j) Zhao, W. N.; Xu, L.; Ding, Y. C.; Niu, B.; Xie, P.; Bian, Z. G.; Zhang, D. H.; Zhou, A. H. *Eur. J. Org. Chem.* **2016**, 325.

(3) (a) Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.* **2012**, *48*, 2985. (b) Min, M.; Hong, S. *Chem. Commun.* **2012**, *48*, 9613. (c) Jafarpour, F.; Barzegar, M.; Olia, A.; Hazrati, H. *Adv. Synth. Catal.* **2013**, *355*, 3407.

(4) (a) Nibbs, A. E.; Scheidt, K. *Eur. J. Org. Chem.* **2012**, 449. (b) Samanta, R.; Narayan, R.; Antonchick, A. P. *Org. Lett.* **2012**, *14*, 6108. (c) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285.

(5) Kim, K.; Choe, H.; Jeong, Y.; Lee, J. H.; Hong, S. *Org. Lett.* **2015**, *17*, 2550.

(6) Dian, L. Y.; Zhao, H.; Zhang-Negrerie, D.; Du, Y. F. *Adv. Synth. Catal.* **2016**, *358*, 2422.

(7) (a) Banerjee, A.; Santra, S. K.; Khatun, N.; Ali, W.; Patel, B. K. *Chem. Commun.* **2015**, *51*, 15422. (b) Niu, B.; Zhao, W. N.; Ding, Y. C.; Bian, Z. G.; Pittman, C. U. Jr.; Zhou, A. H.; Ge, H. B. *J. Org. Chem.* **2015**, *80*, 7251. (c) Doan, S. H.; Nguyen, V. H. H.; Nguyen, T. H.; Pham, P. H.; Nguyen, N. N.; Phan, A. N. Q.; Tu, T. N.; Phan, N. T. S. *RSC Adv.* **2018**, *8*, 10736.

(8) (a) Banerjee, A.; Santra, S. K.; Mishra, A.; Khatun, N.; Patel, B. K. *Org. Biomol. Chem.* **2015**, *13*, 1307. (b) Zhou, S. L.; Guo, L. N.; Duan, X. H. *Eur. J. Org. Chem.* **2014**, 8094. (c) Zhu, Y. F.; Wei, Y. Y. *Chem. Sci.* **2014**, *5*, 2379. (d) Wang, C. Y.; Mi, X.; Li, Q. R.; Li, Y. B.; Huang, M. M.; Zhang, J. Y.; Wu, Y. S.; Wu, Y. J. *Tetrahedron* **2015**, *71*, 6689.

(9) Narayan, R.; Antonchick, A. P. *Chem. Eur. J.* **2014**, *20*, 4568.

(10) Jafarpour, F.; Darvishmolla, M. *Org. Biomol. Chem.* **2018**, *16*, 3396.

(11) Jin, C.; Yan, Z. Y.; Sun, B.; Yang, J. *Org. Lett.* **2019**, *21*, 2064.

(12) (a) Pan, C. D.; Fu, Y.; Ni, Q. T.; Yu, J. T. *J. Org. Chem.* **2017**, *82*, 5005. (b) Cui, Z. H.; Du, D. M. *J. Org. Chem.* **2018**, *83*, 5149. (c) Qian, B.; Chen, S.; Wang, W. T.; Zhang, X. H.; Bao, H. L. *J. Am. Chem. Soc.* **2017**, *139*, 13076. (d) Zhu, X. T.; Deng, W. L.; Chiou, M. F.; Ye, C. Q.; Jian, W. J.; Zeng, Y. H.; Jiao, Y. H.; Ge, L.; Li, Y. J.; Zhang, X. H.; Bao, H. L. *J. Am. Chem. Soc.* **2019**, *141*, 548. (e) Deng, W. L.; Feng, W. W.; Li, Y. J.; Bao, H. L. *Org. Lett.* **2018**, *20*, 4245. (f) Jian, W. J.; Ge, L.; Jiao, Y. H.; Qian, B.; Bao, H. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 3650. (g) Babu, K. R.; Zhu, N. B.; Bao, H. L. *Org. Lett.* **2017**, *19*, 46. (h) Yu, F.; Wang, T.; Zhou, H.; Li, Y. J.; Zhang, X. H.; Bao, H. L. *Org. Lett.* **2017**, *19*, 6538. (i) Kawamura, S.; Henderson, C. J.; Aoki, Y.; Sekine, D.; Kobayashi, S.; Sodeoka, M. *Chem. Commun.* **2018**, *54*, 11276.

(13) **General Procedure for the Synthesis of 3 or 5 (3aa as an Example)**
A 10 mL Schlenk tube was charged with coumarin (**1a**, 88 mg, 0.6mmol), LPO (**2a**, 477 mg, 1.2 mmol), $Fe(OTf)_3$ (15 mg, 0.03

mmol), and dioxane (3.0 mL). The tube was evacuated and backfilled with N_2 for three times. The mixture was then heated at 70 ℃ and stirred for 8 h. After the reaction finished, the reaction mixture was extracted with DCM (30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (ethyl acetate/hexane, 1:80) to afford **3aa** (149 mg, 83%) as a white solid.

Compound **3aa**: white solid; mp 59.6–60.3 ℃, 83% (149 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 7.45–7.42 (m, 2 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 2.56 (t, *J* = 7.8 Hz, 2 H), 1.68–1.60 (m, 2 H), 1.39–1.25 (m, 16 H), 0.88 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 153.1, 138.3, 130.4, 130.1, 127.1, 124.2, 119.6, 116.4, 31.9, 30.8, 29.63, 29.60, 29.56, 29.4, 29.3, 28.0, 22.7, 14.1. HRMS: *m/z* calcd for $C_{20}H_{29}O_2$ [M + H]$^+$: 301.2162; found: 301.2170.