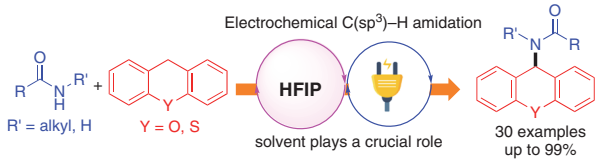
# Direct Electrochemical C(sp³)–H Amidation Enabled by Hexafluoroisopropanol (HFIP)

**Fengyi Li**[◊a]
**Ke Liu**[◊a]
**Qi Sun**[b]
**Sheng Zhang**[*a]
**Man-Bo Li**[*a]

[a] Institutes of Physical Science and Information Technology, Anhui University, Hefei, Anhui 230601, P. R. of China
shengzhang@ahu.edu.cn
mbli@ahu.edu.cn
[b] Hefei National Laboratory for Physical Sciences at Microscale, University of Science and Technology of China, Hefei, Anhui 230026, P. R. of China

[◊] These authors contributed equally

Published as part of the Virtual Collection
*Electrochemical Organic Synthesis*




Received: 01.08.2023
Accepted after revision: 14.09.2023
Published online: 14.09.2023 (Accepted Manuscript), 18.10.2023 (Version of Record)
DOI: 10.1055/a-2176-1840; Art ID: SO-2023-08-0054-L

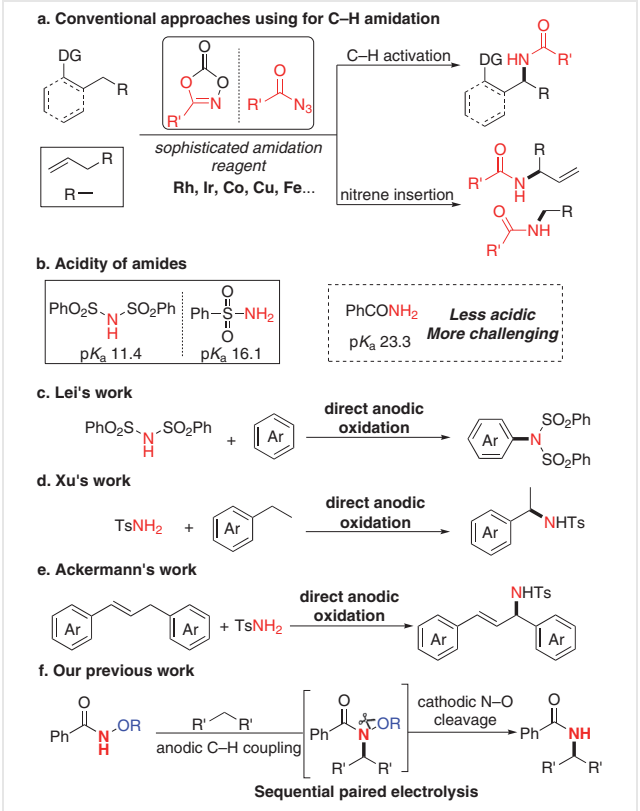


**Abstract** A direct electrochemical amidation of xanthene was readily achieved under direct anodic oxidation. The reactivity of benzamides was significantly enhanced by the virtue of the solvent effect of hexafluoroisopropanol (HFIP). An obvious hydrogen bonding between HFIP and benzamide was detected, and the proton-coupled electron-transfer (PCET) effect was proposed for the enhancement effect of HFIP. In this transformation, a broad range of primary and secondary amides were readily used as amidating reagents, including L-proline-, naproxen-, and probencid-derived amides. We proposed a plausible reaction mechanism for this direct amidation based on the experimental observations.

**Key words** electrochemical amidation, C(sp³)–H, hexafluoroisopropanol

Amides are prevalent in bioactive molecules. As mentioned by Ertl in the corresponding review:[1] 'The most frequent FG in bioactive molecules is the amide, in either its secondary or tertiary disposition, and this FG is present in 40.3% of all molecules.' Consequently, tremendous attention has been devoted to the synthesis of amides. Conventional approaches commonly require activated acylation reagents.[2] Growing concerns related to sustainable chemistry has shifted attention to the direct amidation of C(sp³)–H, which would provide an approach to upgrade primary or secondary amides to secondary or tertiary amides, respectively.

In the area of the intermolecular C(sp³)–H amidation, two main strategies involving C–H activation[3] and nitrene insertion[4] were developed (Scheme 1a). A range of sophisticated amidating reagents, such as dioxazolones, acyl azides, and hydroxamate were devised for these transformations. In the sharp contrast, primary amide as one of the most accessible amidating reagents has received far less attention due to its weak acidity and nucleophilicity. As depicted in the Scheme 1b, the p$K_a$[5] of benzenesulfonamide and benzamide ranges from 16.1 to 23.3.




**Scheme 1** Approaches for the C(sp³)–H amidation

The past decade has witnessed the explosive progress in synthetic electrochemistry[6] since it provides distinct and efficient solutions for conventionally challenging transformations. Electrochemical oxidative amination of C($sp^3$)–H has received tremendous attention. Sulfonamide as amidating reagent was explored by some groups. For instance, Lei[7] and coworkers used acidic sulfonimide as an amidating reagent in the reaction with arenes (Scheme 1c). A remarkable breakthrough in the site-selective C($sp^3$)–H amination was recently achieved by the Xu[8] group with benzenesulfonamide as nitrogen source (Scheme 1d). At almost the same time, Ackermann[9] independently developed an electrochemical approach for allylic C($sp^3$)–H sulfonamidation (Scheme 1e). Despite this impressive progress, using benzamide derivatives as a direct amidating reagent still suffer from formidable challenges. Very recently, we reported a paired-electrolysis strategy for the electrochemical amidation,[10] in which alkoxyamide was used as the precursor of primary amide (Scheme 1f). In our line of research[11] in synthetic chemistry, we questioned whether hexafluoroisopropanol (HFIP)[12] could enhance the reactivity of benzamide via proton-coupled electron-transfer (PCET)[13] effect to enable the direct electrochemical C($sp^3$)–H amidation. Indeed, a direct electrochemical amidation of C($sp^3$)–H was readily achieved by virtue of unique property[12] of HFIP.

At the outset, we probe the solvent effect of HFIP on the redox property of benzamide (**1a**). As shown in the cyclic voltammogram of benzamide (Figure 1a), a new oxidation peak at 1.12 V was detected upon introducing 1 equivalent of HFIP. This result suggests that the HFIP could significantly enhance the anodic oxidation of benzamide as compared to the former peak at 2.09 V. Additionally, a uniform enhancement effect of HFIP on the oxidation of other amides has also been recorded (see the Supporting Information for details). To rationalize the effect of HFIP, nuclear magnetic resonance ($^1$H NMR) study was conducted (Figure 1b). Mixing HFIP with benzamide lead to obvious variation of peaks of benzamide. Specifically, peaks of N–H shift to low field (δ = 5.92–6.08 ppm), indicating a hydrogen-bonding effect between HFIP and benzamide. Taken together, proton-coupled electron transfer (PCET) was proposed for the enhancement effect of HFIP on the oxidation of benzamide.

Having identified the solvent effect of HFIP, we selected xanthene as a reaction partner with benzamide (Figure 1c), which would allow a direct access to a broad range of bioactive scaffolds.[14] After a series of optimizations, the electrochemical C($sp^3$)–H amidation between xanthene and benzamide was readily achieved using mixed solvent ($CH_3CN$/HFIP), platinum anode, and graphite cathode; the desired product was accessed in 99% yield. Removal of HFIP or replacing it with methanol led to diminished yields.

With the optimal conditions in hand, a broad range of amides was examined to illustrate the reaction generality (Scheme 2).[15] First, electronic property effect was explored by using *para*-substituted benzamides as substrates (**3b–h**). It showed that the redox-labile iodine group (**3f**) and the strongly electron-withdrawing cyano group (**3h**) resulted in lower yields. Second, it was found that changing the *para* substitution to *meta* (**3i**) or *ortho* (**3j**) substitution marginally affected the reaction efficiency. Third, other aromatic amides (**3k–m**), alkenyl amides (**3n–o**), and aliphatic amides (**3p–q**) were also amenable to afford the desired amidation products, although aliphatic amides led to diminished yields due to its inactive redox property. It is noteworthy that the bioactive molecule **XAA** (**3o**)[14a] can be directly accessed with this electrochemical protocol. Subsequently, secondary amides (**3r–t**), carboxamide (**3u**), phosphinamide (**3v**), and sulfinamide (**3w**) were also employed as the amidating reagents, and the corresponding products (**3r–w**) were delivered in moderate to good yields. To demonstrate the synthetic utility of this approach, amides derived from natural product (L-proline) and pharmaceuticals (naproxen, probenecid) were subjected to the op-

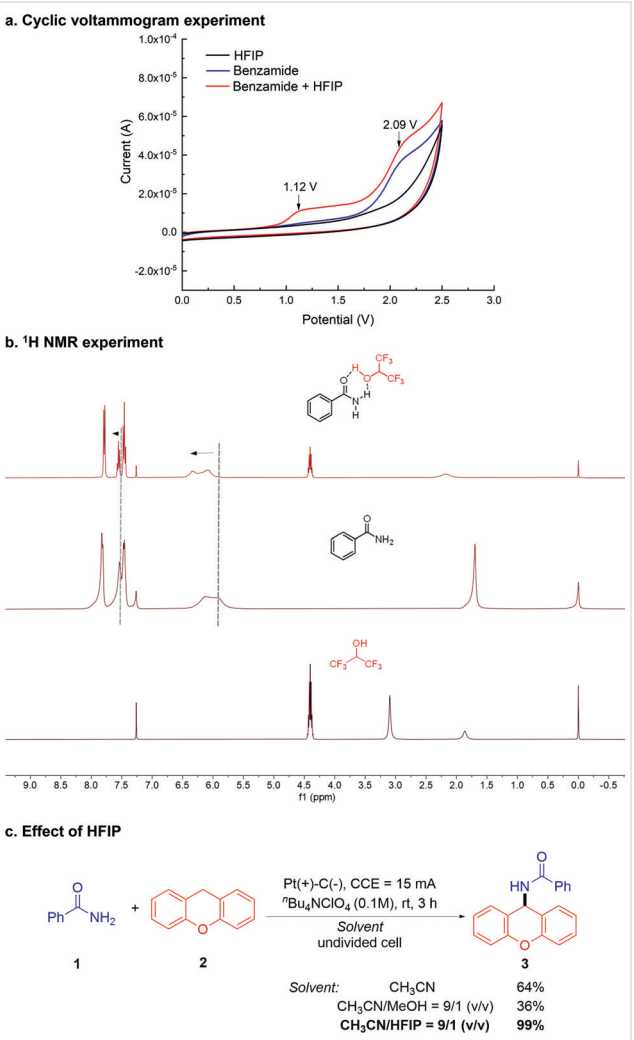
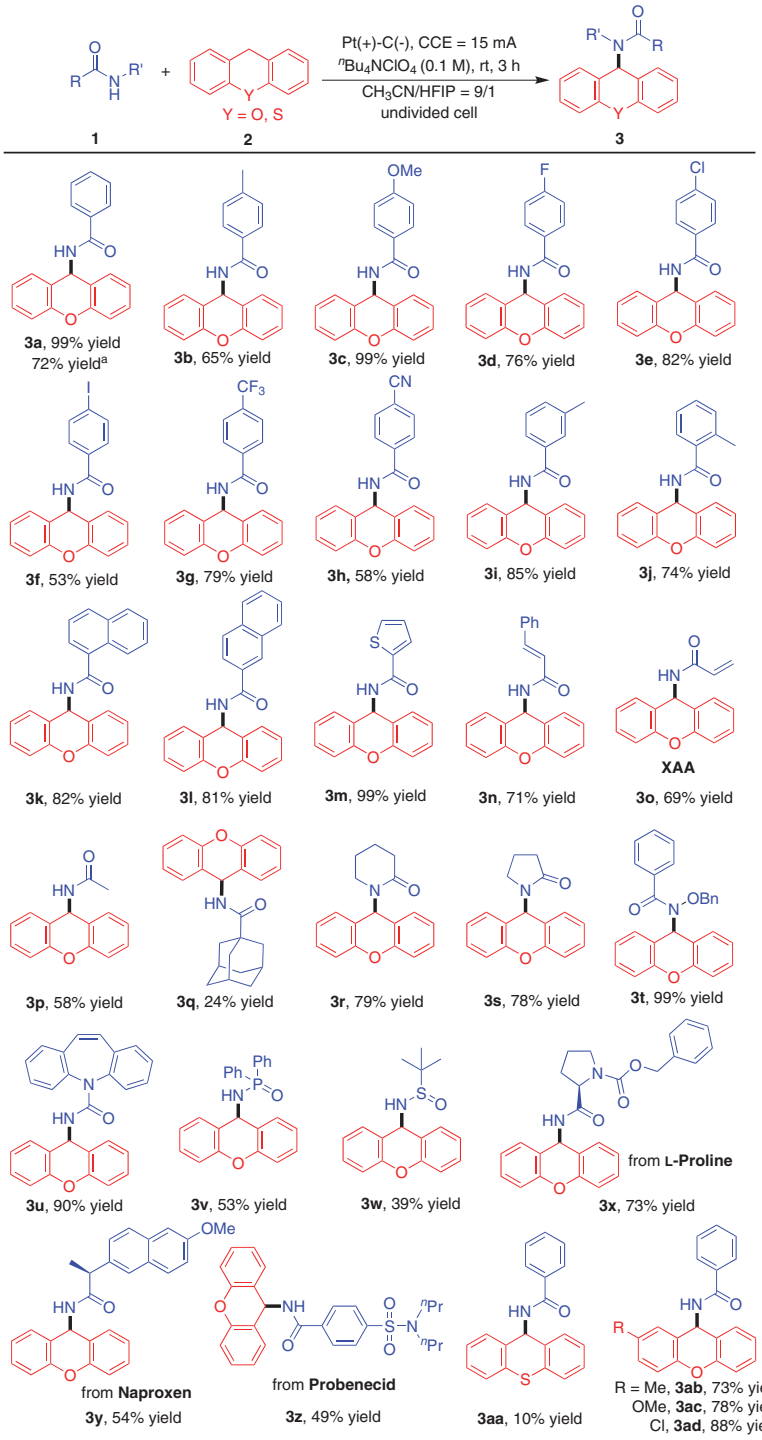



**Figure 1** Experiment study on the solvent effect of HFIP

timal conditions. To our delight, the desired amidated xanthenes (**3x–z**) were successfully accessed in satisfactory yields. Replacing xanthene with thioxanthene (**3aa**) caused a significant drop in the reaction yield, while substituted oxanthenes (**3ab–ad**) were well tolerated with good yields. This result might attribute to the overoxidation of the prod-




**Scheme 2** Substrate scope. *Reagents and conditions*: **1** (0.5 mmol), **2** (0.75 mmol), platinum plate anode (1.5 × 1.5 $cm^2$), graphite rod cathode (0.6 × 10 cm), constant current electrolysis (15 mA, 3 h, 3.3 F/mol), mixed solvent ($CH_3CN$/HFIP = 9/1, v/v), undivided cell. [a] 5 mmol scale, 75 mA, 6 h.

uct **3aa**. Remarkably, this electrochemical protocol can be readily scaled up, and gram-scale product **3a** was readily accessed in 72% yield.

To get insight into the reaction mechanism, control experiments and a cyclic voltammogram experiment were conducted. As shown in the Figure 2a, some radical scavengers were introduced to the reaction conditions. Obvious suppression effect was observed, although the desired product **3a** still can be accessed in 13–78% yield. This result suggests that the radical species is involved in this reaction. The kinetic isotope effect was also studied (Figure 2b), and it indicates that the cleavage of C($sp^3$)–H is the rate-determining step in the reaction. Finally, a cyclic voltammogram experiment (Figure 2c) showed that closed onset-waves were detected for the substrates benzamide (**1a**) and xanthene **2a** in the mixed solution of acetonitrile and HFIP. This result supports that two substrates are oxidized simultaneously over the surface of the anode.

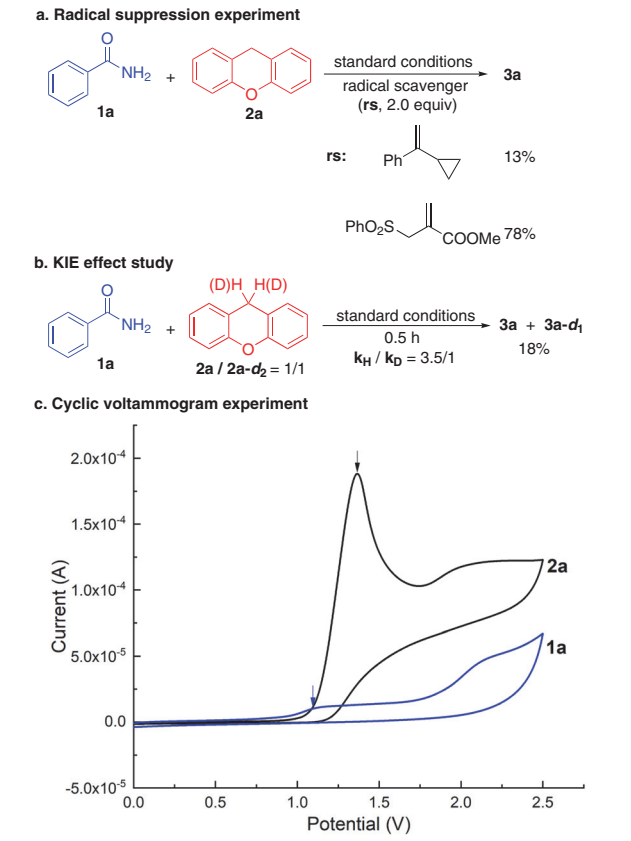
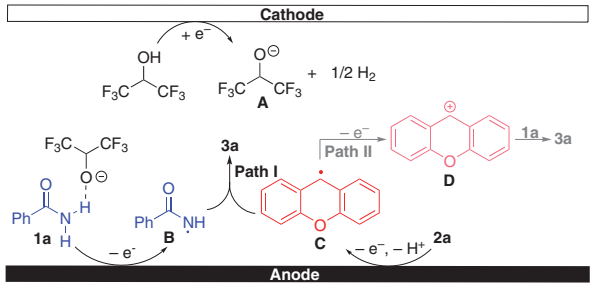



**Figure 2** Mechanism study

Based on the experimental observations and previous report,[16] a plausible reaction mechanism was proposed (Scheme 3). Under cathodic reaction, acidic solvent HFIP is reduced to hydrogen and the conjugated base **A**. With the PCET assistance of base **A**, benzamide **1a** is oxidized to amidyl radical **B**. Simultaneously, xanthene **2a** proceeds with a sequential single-electron transfer and deprotonation to afford a persistent radical **C**, which is immediately intercepted by **B** to give the final product **3a**. Alternatively, radical **C** can be further oxidized to carbocation **D** (path II). Under nucleophilic attack of **1a**, the desired product **3a** is delivered.




**Scheme 3** Proposed reaction mechanism

In conclusion, a direct electrochemical amidation between xanthene and benzamides was reported. In this transformation, a significant enhancement effect of HFIP on the reaction performance was observed. Proton-coupled electron-transfer effect was proposed for the role of HFIP in the reaction according to the $^1$H NMR study. Further investigation on the solvent effect of HFIP is ongoing in our laboratory.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding Information

We are grateful to the National Natural Science Foundation of China (21702113, 92061110, and 22001241), the Anhui University (S020318006/069 and S020118002/113), the Anhui Provincial Natural Science Foundation (2108085Y05 and 2308085Y14), and the Hefei National Laboratory for Physical Sciences at the Microscale (KF2020102) for their financial support.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2176-1840.

## References and Notes

(1) Ertl, P.; Altmann, E.; McKenna, J. M. *J. Med. Chem.* **2020**, *63*, 8408.
(2) For the synthesis of amides, see: (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (b) Ojeda-Porras, A.; Gamba-Sánchez, D. *J. Org. Chem.* **2016**, *81*, 11548. (c) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(3) For the approaches involving C($sp^3$)–H activation, see: (a) Wang, H.; Tang, G.; Li, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 13049. (b) Tan, P. W.; Mak, A. M.; Sullivan, M. B.; Dixon, D. J.; Seayad, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 16550. (c) Antien, K.; Geraci, A.; Parmentier, M.; Baudoin, O. *Angew. Chem. Int. Ed.* **2021**, *60*, 22948.

(4) For the approaches involving nitrene insertion, see: (a) Knecht, T.; Mondal, S.; Ye, J.-H.; Das, M.; Glorius, F. *Angew. Chem. Int. Ed.* **2019**, *58*, 7117. (b) Burman, J. S.; Harris, R. J.; Farr, C. M. B.; Bacsa, J.; Blakey, S. B. *ACS Catal.* **2019**, *9*, 5474. (c) Lei, H.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 2268. (d) Tang, J.-J.; Yu, X.; Wang, Y.; Yamamoto, Y.; Bao, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 16426. (e) Bakhoda, A.; Jiang, Q.; Badiei, Y. M.; Bertke, J. A.; Cundari, T. R.; Warren, T. H. *Angew. Chem. Int. Ed.* **2019**, *58*, 3421.

(5) (a) Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* **2010**, *75*, 5250. (b) Kütt, A.; Tshepelevitsh, S.; Saame, J.; Lõkov, M.; Kaljurand, I.; Selberg, S.; Leito, I. *Eur. J. Org. Chem.* **2021**, 1407.

(6) For reviews of synthetic electrochemistry, see: (a) Francke, R.; Little, R. D. *Chem. Soc. Rev.* **2014**, *43*, 2492. (b) Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117*, 13230. (c) Jiang, Y.; Xu, K.; Zeng, C.-C. *Chem. Rev.* **2018**, *118*, 4485. (d) Yoshida, J.-i.; Shimizu, A.; Hayashi, R. *Chem. Rev.* **2018**, *118*, 4702. (e) Moeller, K. D. *Chem. Rev.* **2018**, *118*, 4817. (f) Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. *Chem. Rev.* **2018**, *118*, 6706. (g) Yuan, Y.; Lei, A. *Acc. Chem. Res.* **2019**, *52*, 3309. (h) Xiong, P.; Xu, H.-C. *Acc. Chem. Res.* **2019**, *52*, 3339. (i) Jiao, K.-J.; Xing, Y.-K.; Yang, Q.-L.; Qiu, H.; Mei, T.-S. *Acc. Chem. Res.* **2020**, *53*, 300. (j) Gandeepan, P.; Finger, L. H.; Meyer, T. H.; Ackermann, L. *Chem. Soc. Rev.* **2020**, *49*, 4254. (k) Novaes, L. F. T.; Liu, J.; Shen, Y.; Lu, L.; Meinhardt, J. M.; Lin, S. *Chem. Soc. Rev.* **2021**, *50*, 7941. (l) Cheng, X.; Lei, A.; Mei, T.-S.; Xu, H.-C.; Xu, K.; Zeng, C. *CCS Chem.* **2022**, *4*, 1120.

(7) Hu, X.; Zhang, G.; Nie, L.; Kong, T.; Lei, A. *Nat. Commun.* **2019**, *10*, 5467.

(8) Hou, Z.-W.; Liu, D.-J.; Xiong, P.; Lai, X.-L.; Song, J.; Xu, H.-C. *Angew. Chem. Int. Ed.* **2021**, *60*, 2943.

(9) Wang, Y.; Lin, Z.; Oliverira, J. C. A.; Ackermann, L. *J. Org. Chem.* **2021**, *86*, 15935.

(10) Li, F.; Liang, Y.; Zhan, X.; Zhang, S.; Li, M.-B. *Org. Chem. Front.* **2022**, *9*, 5571.

(11) (a) Zhang, S.; Li, L.; Zhang, J.; Zhang, J.; Xue, M.; Xu, K. *Chem. Sci.* **2019**, *10*, 3181. (b) Zhang, S.; Li, L.; Li, J.; Shi, J.; Xu, K.; Gao, W.; Zong, L.; Li, G.; Findlater, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 7275. (c) Zhang, S.; Shi, J.; Li, J.; Li, M.-B.; Li, G.; Findlater, M. *CCS Chem.* **2022**, *4*, 1938. (d) Liang, Y.; Zhan, X.; Li, F.; Bi, H.; Fan, W.; Zhang, S.; Li, M.-B. *Chem. Catal.* **2023**, *3*, 100582. (e) Zhang, S.; Liang, Y.; Liu, K.; Zhan, X.; Fan, W.; Li, M.-B.; Findlater, M. *J. Am. Chem. Soc.* **2023**, *145*, 14143. (f) Zhang, S.; Findlater, M. *ACS Catal.* **2023**, *13*, 8731.

(12) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1*, 0088.

(13) Murray, P. R. D.; Cox, J. H.; Chiappini, N. D.; Roos, C. B.; McLoughlin, E. A.; Hejna, B. G.; Nguyen, S. T.; Ripberger, H. H.; Ganley, J. M.; Tsui, E.; Shin, N. Y.; Koronkiewicz, B.; Qiu, G.; Knowles, R. R. *Chem. Rev.* **2022**, *122*, 2017.

(14) For bioactive xanthene, see: (a) Luo, L.; Jia, B.-Z.; Wei, X.-Q.; Xiao, Z.-L.; Wang, H.; Sun, Y.-M.; Shen, Y.-D.; Lei, H.-T.; Xu, Z.-L. *Sens. Actuators, B* **2021**, *332*, 129561. (b) Park, I.-S.; Seo, H. R.; Kim, K.; Lee, H.; Shum, D.; Choi, I.; Kim, J. *Biochem. Biophys. Res. Commun.* **2020**, *527*, 709. (c) Watterson, K. R.; Hansen, S. V. F.; Hudson, B. D.; Alvarez-Curto, E.; Raihan, S. Z.; Azevedo, C. M. G.; Martin, G.; Dunlop, J.; Yarwood, S. J.; Ulven, T.; Milligan, G. *Mol. Pharmacol.* **2017**, *91*, 630.

(15) **General Procedure for the Electrochemical Amidation (3a as an Example)**

An undivided cell was equipped with a magnet stirrer, platinum plate (1.5 × 1.5 $cm^2$), and graphite rod (0.6 × 10 cm), as anode and cathode, respectively (the electrolysis setup is shown in Figure S1). Substrate benzamide (**1a**, 61 mg, 0.5 mmol), 9*H*-xanthene (**2a**, 137 mg, 0.75 mmol), and *n*-$Bu_4NClO_4$ (342 mg, 1 mmol) were added to the solvent MeCN/HFIP (9/1 mL). The resulting mixture was allowed to stir and electrolyze under constant current conditions (15 mA) at room temperature for 3 h. The reaction mixture was condensed with a rotary evaporator. The residue was purified by column chromatography (PE/EtOAc = 20/1 to10/1, V/V) on silica gel to afford the desired product **3a** (149 mg) in 99% yield.

***N*-(9*H*-Xanthen-9-yl)benzamide (3a)**

149 mg, 99% yield; white solid, mp 227–228 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.16–7.10 (m, 4 H), 6.78 (d, *J* = 12.0 Hz, 1 H), 6.61 (d, *J* = 8.0 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 166.5, 151.1, 134.0, 131.8, 129.7, 129.4, 128.6, 127.0, 123.7, 121.0, 116.7, 44.3.

(16) (a) Lin, M.-Y.; Xu, K.; Jiang, Y.-Y.; Liu, Y.-G.; Sun, B.-G.; Zeng, C.-C. *Adv. Synth. Catal.* **2018**, *360*, 1665. (b) Yang, Y.-Z.; Song, R.-J.; Li, J.-H. *Org. Lett.* **2019**, *21*, 3228. (c) Wei, B.; Qin, J.-H.; Yang, Y.-Z.; Xie, Y.-X.; Ouyang, X.-H.; Song, R.-J. *Org. Chem. Front.* **2022**, *9*, 816. (d) Chen, X.; Liu, H.; Gao, H.; Li, P.; Miao, T.; Li, H. *J. Org. Chem.* **2022**, *87*, 1056.