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Electrochemical carboxylation of α-fluoroalkyl cyclopropane with CO_2 to mono- or difluoropentenoic acid†

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An electrochemical carboxylation of α-fluoroalkyl cyclopropanes with CO_2 is reported in this work. This approach constitutes a rare example of defluorinative carboxylation of organofluorine compounds with the simultaneous cleavage of C–F and C–C bonds. Accordingly, both α-CF_2H and α-CF_3 cyclopropanes serve as effective substrates, facilitating the synthesis of pentenoic acids with an *E*-configured monofluoroalkene or *gem*-difluoroalkene moiety with high chemo- and stereoselectivity. The reaction can be also performed under a nonsacrificial anode system. The synthetic practicality is further highlighted by the diverse functionalizations of the resulting multifunctional fluorinated acids. Cyclic voltammetry studies were performed to provide mechanistic insights into the reaction's origins.

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Introduction

CO_2 serves as an ideal C1 feedstock in chemical transformations, which are crucial for the synthesis of high value-added chemicals in synthetic chemistry.[1] The carboxylation of CO_2 is considered one of the most efficient methods for constructing densely functionalized carboxylic acids.[2] From the standpoint of green synthesis, electrochemistry, which utilizes electrons as sustainable redox reagents, represents an alternative and eco-friendly strategy in organic synthesis.[3] Moreover, the readily tunable high reduction potential of electrochemistry offers a promising strategy for carboxylation of inert chemical bonds.[4] The established electrocarboxylation methods, which combine diverse inert chemical bonds, such as C–C,[5] C–F,[6] and others,[7] have primarily focused on the activation of a single inert chemical bond. In contrast, the electrochemical strategies for carboxylation that involve the activation of multiple inert chemical bonds are underdeveloped and remain a highly challenging area within the field.[4]

The C–F bond is the most robust carbon-heteroatom bond,[8] and the selective elecrocarboxylation of fluorinated compounds emerges as a pivotal approach to obtaining fluorinated carboxylic acids,[6] which are in high demand across organic synthesis, materials science, and medicinal chemistry.[9] Despite this demand, the electrochemical defluorinative carboxylation of organofluorine compounds that facilitate the concurrent cleavage of C–F bonds and other chemical bonds to synthesize multifunctional fluoro-carboxylic acids is largely uncharted (Scheme 1B).[10]

In 2020, we reported an electrochemical γ-carboxylation of α-CF_3 alkenes with CO_2.[10a] This process initiates with the single electron transfer (SET) reduction of the C=C double bond, followed by exclusive γ-position carboxylation and subsequent β-F elimination, giving butenoic acids with a *gem*-difluoroalkene moiety in high efficiency. Additionally, Xue and colleagues described a regiodivergent electroreductive defluorinative carboxylation of *gem*-difluorocyclopropanes with CO_2.[10b] Leveraging the cumulative effect of fluorine substitution, *gem*-difluorinated cyclopropanes exhibit greater reactivity than their nonfluorinated counterparts,[11] thus enabling the concurrent cleavage of the C–F and C–C bonds to produce branched and linear monofluoroalkene carboxylic acids with regioselectivity. Despite these advances, both types of reaction are limited to highly reactive substrates and can only yield di- or monofluorobutenoic acids, respectively. The carboxylation of more challenging materials for constructing valuable fluorinated carboxylic acids *via* the simultaneous activation of C–F and other chemical bonds remains a highly desirable goal.

With our continuous interest in CO_2 chemical fixation,[12] and encouraged by the advances of electrochemical transformation of C–F bonds,[13] we endeavour to develop an

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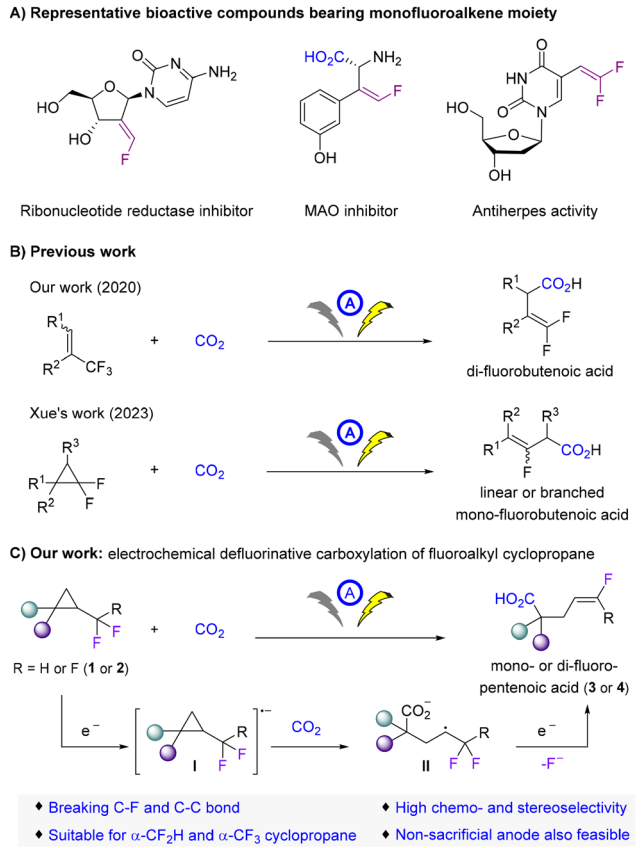


Scheme 1 C–F bond carboxylation with CO_2.

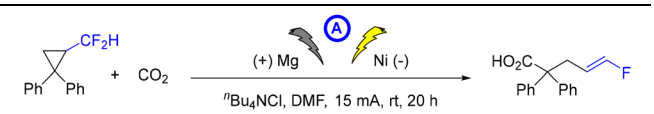
electrochemical carboxylation of α-fluoroalkyl cyclopropanes using CO_2 (Scheme 1C). Our hypothesis is that the SET reduction of substituted cyclopropanes might generate the corresponding radical anion **I**, whereas the following nucleophilic addition with CO_2 could give the carboxylated carbon radical **II**. The further SET reduction and the following β-fluoro elimination of the generated carbon anion would generate the desired fluorinated pentenoic acids.[14] However, several challenges must be overcome for such a transformation. For example, the dicarboxylation of the C–C bond,[5] as well as the carboxylation of the C–F bond,[6] might complicate the reaction dynamics. Moreover, the presence of C=C double bonds in the monofluoro-substituted pentenoic acids necessitates control over *E*/*Z* stereoselectivity, and the competitive further reductive carboxylation increases the complexity. Herein, we report a facile and efficient direct electrochemical defluorinative carboxylation of α-fluoroalkyl cyclopropanes with CO_2 for the synthesis of pentenoic acids that incorporate either monofluoro or difluoroalkene moieties with high chemo- and stereoselectivity under mild conditions, *via* a SET reduction-initiated C–C bond and C–F bond cleavage pathway. Notably, monofluoroalkenes could serve as peptide bond isosteres[15] and *gem*-difluoroalkenes could act as carbonyl bioisosteres with reduced susceptibility to *in vivo* metabolism.[16] Both motifs are crucial in drug development and are found in numerous biologically active compounds with various pharmacological activities. Therefore, the efficient and selective synthesis of pentenoic acids bearing such structural motifs is highly desirable (Scheme 1A).

Results and discussion

The electrochemical defluorinative carboxylation was evaluated using the reaction of α-CF_2H-substituted cyclopropane **1a** with CO_2 as a model reaction. Following a series of conditional optimizations (for details, see section 2.1 of ESI†), the targeted monofluoropentenoic acid **3a** was isolated in 81% yield, under the condition of 15 mA constant current at room temperature, in DMF containing $^{n}Bu_4NCl$ as an electrolyte, with a Ni plate as the cathode and Mg plate as an anode (Table 1, entry 1). Subsequent investigations indicated that the choice of electrode materials obviously influenced the reaction outcome.[17] In particular, the yield was reduced to 73% using Pt plates as cathode (entry 2). Replacing the anode with Zn plate resulted in a decreased 79% yield (entry 3). The impact of the supporting electrolyte was also examined;[18] substitutions with $^{n}Bu_4NClO_4$ or $^{n}Bu_4NI$ yielded inferior results (entries 4 and 5). Then, the solvent effect was investigated by conducting the reaction in DMSO or NMP,[19] resulting in lower 75% and 72% yields, respectively (entries 6 and 7). The variation of electrolyte concentration or current did not yield improved results (entries 8–10). Notably, during the investigation, only the *E*-configured **3a** was detected, with its structure unambiguously determined by single-crystal X-ray diffraction. Furthermore, the absence of competitive C–C bond dicarboxylation, C–F bond carboxylation, or overreduction of the C=C bond underscore the high chemo- and stereoselectivity of this electrochemical defluorinative carboxylation process.

Having optimized the reaction conditions, we proceeded to evaluate the substrate scope (Table 2). Encouragingly, both

Table 1 Condition optimization



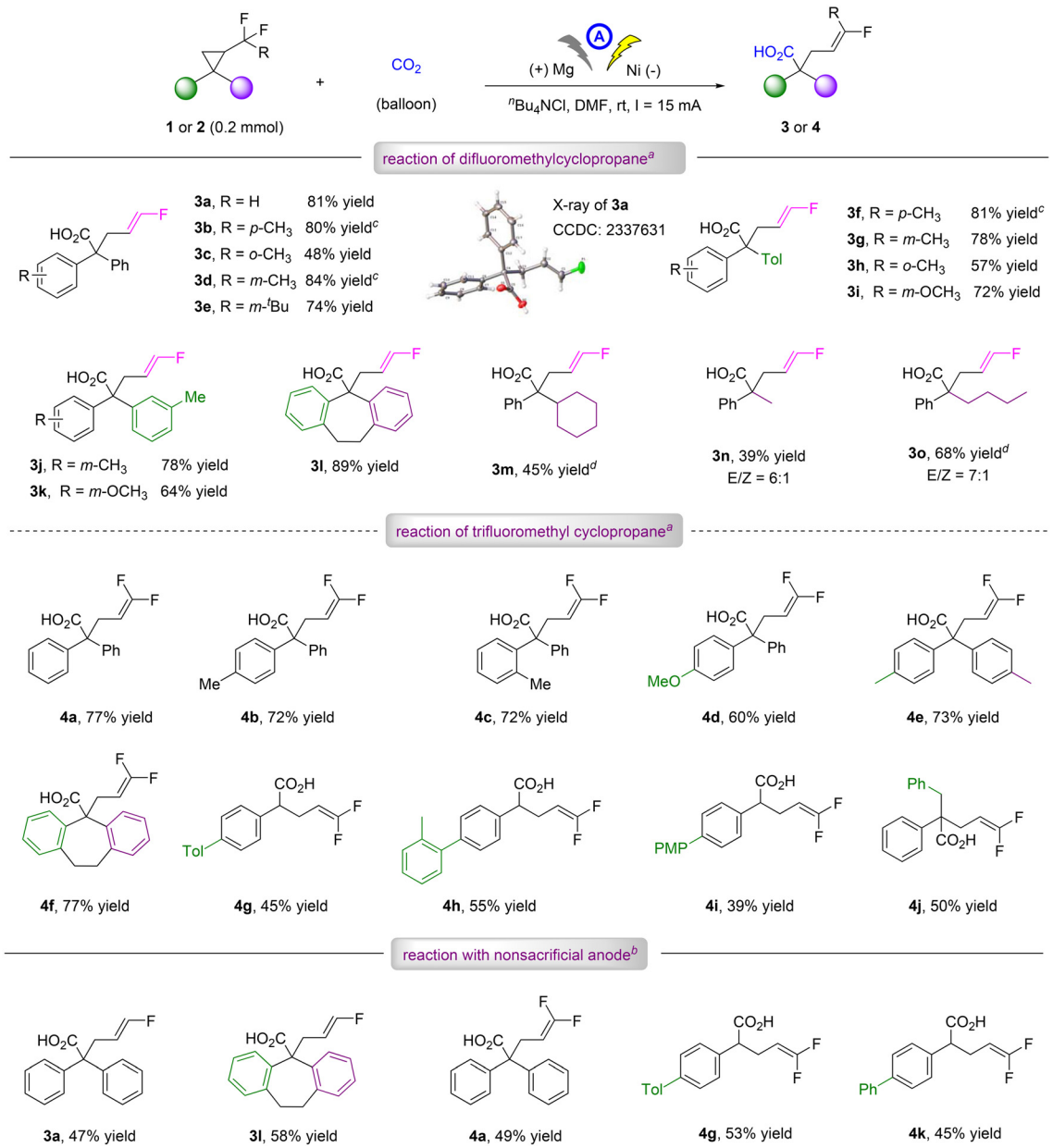
Entry	Variations	Yield of **3a** [a] [%]
1	None	81[b]
2	Pt instead of Ni	73
3	Zn instead of Mg	79
4	$^{n}Bu_4NClO_4$ instead of $^{n}Bu_4NCl$	65
5	$^{n}Bu_4NI$ instead of $^{n}Bu_4NCl$	76
6	DMSO as solvent	75
7	NMP as solvent	72
8	With $^{n}Bu_4NCl$ (0.15 M)	73
9	10 mA instead of 15 mA	54
10	20 mA instead of 15 mA	74

[a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as a standard. [b] Isolated yield.

α-CF_2H- and α-CF_3-substituted cyclopropanes yielded the desired pentenoic acids with either monofluoro or difluoroalkene moieties in good to high yields. We initially examined the reaction of β,β-disubstituted α-CF_2H cyclopropanes with CO_2 to synthesize monofluorinated pentenoic acids featuring all-carbon quaternary stereocenter.[20] A variety of α-CF_2H cyclopropanes with β,β-diaryl substituents underwent smooth reactions, irrespective of the position or steric effects of the aryl groups, affording the *E*-isomer monofluorinated pentenoic acids **3a–k** in up to 84% yield. Cyclopropanes containing a dibenzosuberan moiety also served as suitable substrates, yielding the desired pentenoic acid **3l** in 89% yield. β-Alkyl-substituted α-CF_2H cyclopropanes reacted efficiently to produce pentenoic acids **3m–o**, with yields ranging from 39% to 68% and a decreased *E*/*Z* ratio for those substituted with methyl or butyl groups.

Building on the success of defluorinative carboxylation of α-CF_2H cyclopropanes, we expanded our investigation to

Table 2 Substrate scope of the electrochemical defluorinative carboxylation



[a] Condition A: **1** or **2** (0.2 mmol), $^nBu_4NCl$ (0.6 mmol) in 6 mL DMF with CO_2 balloon in undivided cell using Mg anode and Ni cathode, under constant current of 15 mA at room temperature for 15–20 h. [b]Condition B: **1** or **2** (0.2 mmol), Na_2S (0.4 mmol), $^nBu_4NI$ (0.6 mmol) in 6 mL of NMP with CO_2 bubbling in undivided cell, using C rod anode and GF cathode, under constant current of 15 mA at room temperature for 12 h. [c]With $^nBu_4NBr$. [d]With NMP and Nb cathode.

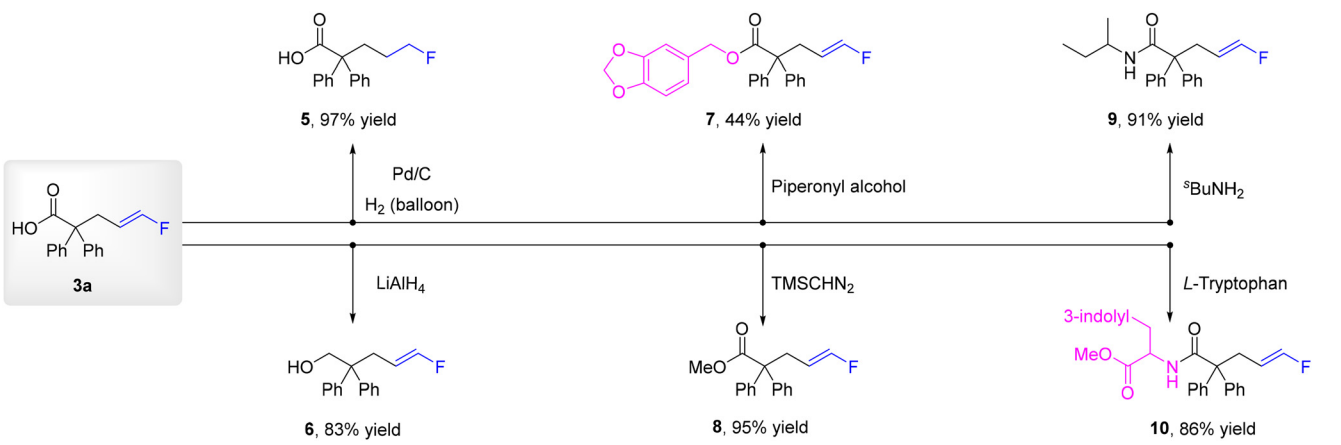
cyclopropanes with α-CF_3 substituents, targeting the synthesis of pentenoic acids with difluoroalkene moieties. Cyclopropanes featuring various β,β-diaryl groups all reacted efficiently, affording δ,δ-difluorinated pentenoic acids **4a–e** with all-carbon quaternary stereocenters in 60% to 77% yields. The α-CF_3 cyclopropane containing a dibenzosuberan moiety was also compatible, yielding product **4f** in 77% yield. β-Monoaryl-substituted cyclopropanes reacted well, producing the corresponding pentenoic acids **4g–i** in up to 55% yield. Additionally, the cyclopropane with a β-benzyl group was also viable substrate, delivering the desired product **4j** in 50% yield.

Subsequently, we explored electrochemical defluorinative carboxylation under a nonsacrificial anode system, which is more sustainable but challenging because the metal ions from sacrificial anodes could not only inhibit overoxidation of substrates and active intermediates but also act as anionic stabilizers in the reaction.[21] After performing systematic optimization (for details, see section 2.2 of ESI†), we discovered that the addition of cheap and easily available Na_2S as reductant and C-rod as the nonsacrificial anode allowed the carboxylation of α-CF_2H or α-CF_3 cyclopropanes with CO_2 to proceed smoothly, giving the corresponding mono- or difluoropentenoic acids smoothly, albeit with slightly lower yield than that obtained with sacrificial anode system.

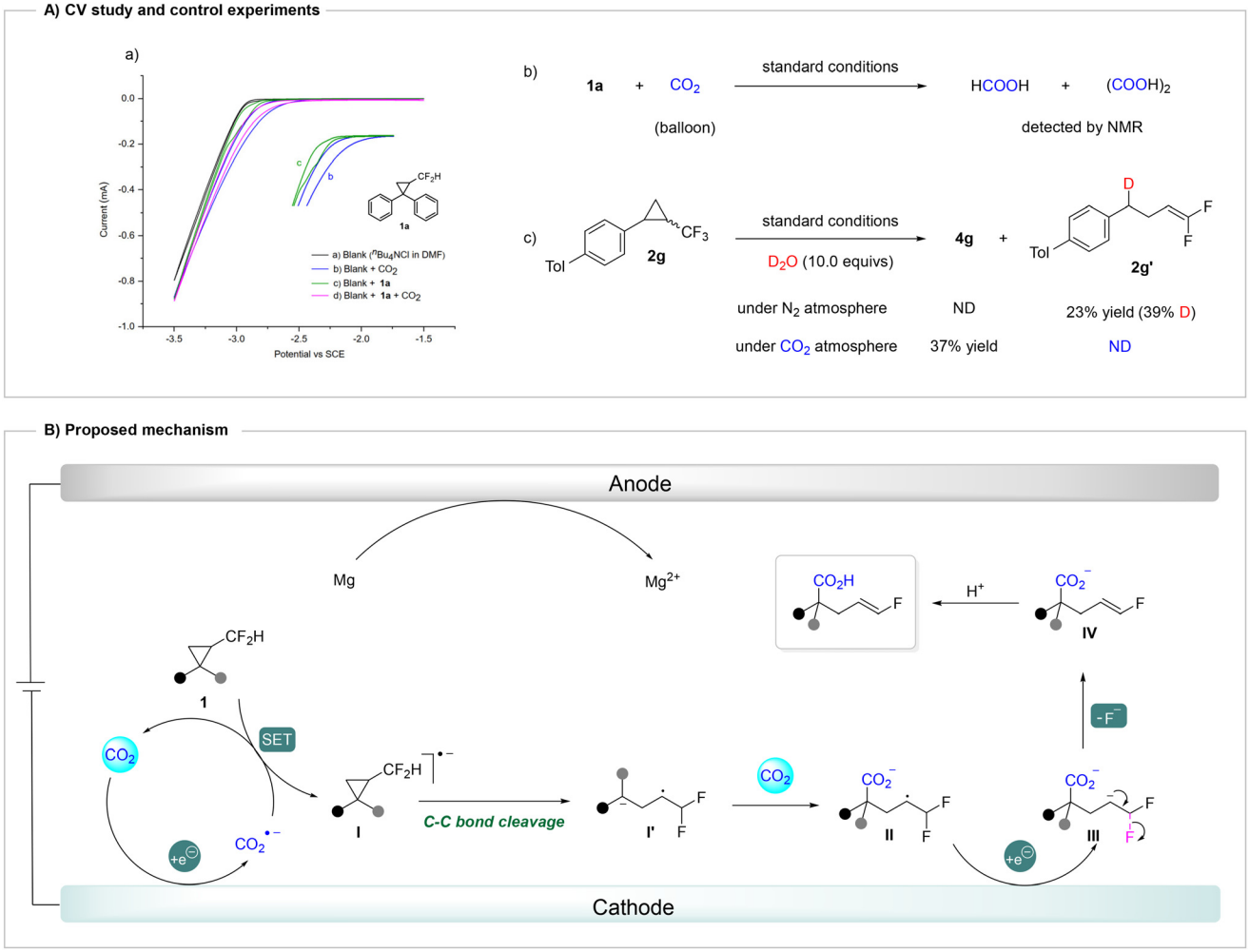
Having established the electrochemical defluorinative carboxylation of α-fluoroalkyl cyclopropanes, we next demonstrated their synthetic utility by converting the obtained carboxylic acids into valuable fluorine-containing molecules (Scheme 2). Under Pd/C catalysis, the alkene moiety of **3a** was readily hydrogenated to afford γ-monofluoromethyl carboxylic acid **5** in 97% yield. Selective reduction of the carboxylic acid moiety with $LiAlH_4$ afforded 5-fluoropentenol **6** in 83% yield. Condensation of **3a** with piperonyl alcohol or esterification with $TMSCHN_2$ effectively afforded esters **7** and **8** in 44% and 95% yields, respectively. Amidation of **3a** with $^{s}BuNH_2$ or methyl L-tryptophan provided direct access to amides **9** and **10** in 91% and 86% yield, respectively.

To elucidate the reaction mechanism and identify possible pathways, we conducted experimental studies (Scheme 3A). Initially, cyclic voltammetry (CV) analyses were performed to probe the electrochemical behavior at the cathode. The reduction potential of α-CF_2H cyclopropane **1a** under a nitrogen atmosphere was determined as $E_{p/2}$ = −2.9 V in DMF *versus* SCE, which is more negative than that of CO_2 (E^{o} = −2.2 V in DMF *versus* SCE)[22] and is completely suppressed under a CO_2 atmosphere. A similar observation was made for the CV analysis of α-CF_3 cyclopropane **2a** (for details, see section 8 of the ESI†). These findings suggest that the electrochemical reduction of CO_2 should be favored over that of α-fluoroalkyl cyclopropanes during the reaction course. Additionally, during the electrochemical carboxylation of **1a** under standard conditions, the formation of formic acid and oxalic acid was detected by NMR analysis. These results imply the potential SET reduction of CO_2 to the corresponding radical anion at the cathode. Furthermore, a deuteration experiment with **2g** under optimal conditions, utilizing 10.0 equivalents of D_2O instead of CO_2 as the electrophilic reagent, led to the formation of deuterated difluoroalkene **2g′** in 23% yield with 39% deuterium incorporation, suggesting the possible involvement of carbanion intermediates in the transformation. Notably, the deuteration of **2g** under a CO_2 atmosphere gave no deuterated product, indicating that the carboxylation might occur more easily than the protonation process.

Based on the above investigation, together with our previous work[10a] and studies from electrochemical carboxylation of C–F bond[6] and C–C bonds,[5] a putative reaction pathway was proposed (Scheme 3B). Initially, a SET reduction of CO_2 generates the CO_2 radical anion, which donates an electron to α-fluoroalkyl cyclopropanes to form intermediate **I**.[23] Subsequently, ring-opening-induced C–C bond cleavage and the following nucleophilic addition with CO_2 give the carboxylated carbon radical **II**. Further SET reduction of intermediate **II** yields the carbanion intermediate **III**. The C–F bond cleavage induced by the β-F elimination leads to the formation of intermediate **IV**, which ultimately yields the desired fluorinated



Scheme 2 Synthetic elaboration of **3a**.



Scheme 3 Mechanistic study and proposed mechanism.

pentenoic acids upon workup with aqueous HCl. Notably, for certain fluoroalkyl cyclopropanes that possess sufficient reduction potential, the direct reduction of the substrates may also represent a viable pathway for initiating the reaction.

Conclusions

We have developed a highly efficient electrochemical defluorinative carboxylation of α-fluoroalkyl cyclopropanes with CO_2, utilizing a user-friendly undivided cell under constant current conditions. This method achieves the simultaneous cleavage of C–F and C–C bonds. Both α-CF_2H and α-CF_3 cyclopropanes are effective in this process, yielding structurally diverse pentenoic acids bearing monofluoroalkene or *gem*-difluoroalkene moieties in acceptable yields under mild conditions. Additionally, the reaction can be performed under a nonsacrificial anode system with the inexpensive and readily available Na_2S as an additive. The resulting pentenoic acids can be readily transformed into various fluorine-containing molecules through the modification of the fluoroalkene or carboxylic acid moieties. Mechanistic investigations indicate that CO_2 serves not only as a carboxylative reagent but also as a promoter, enabling the effective reduction of α-fluoroalkyl cyclopropanes. We are currently exploring the application of this electrocarboxylation strategy for the synthesis of a variety of fluorinated carboxylic acids *via* reductive C–F bond cleavage.

Data availability

The data supporting this article have been included as part of the ESI.†

Crystallographic data for **3a** has been deposited at the CCDC under 2337631† and can be obtained from Cambridge Crystallographic Data Centre.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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