SCIENCE CHINA
Chemistry

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January 2024 Vol.67 No.1: 368–373
https://doi.org/10.1007/s11426-023-1731-x

Divergent defluorocarboxylation of α-CF_3 alkenes with formate *via* photocatalyzed selective mono- or triple C–F bond cleavage

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Received June 14, 2023; accepted August 2, 2023; published online August 16, 2023

Unprecedented divergent synthesis of *gem*-difluorovinylacetic acid and glutaric acid derivatives from α-CF_3 alkenes with formate as the carbonyl source was disclosed. The reaction can undergo selective mono- or triple C–F bond cleavage by simply switching the photocatalyst and hydrogen atom transfer (HAT) catalyst under visible-light-induced conditions at room temperature. Foramte acts as both the C1 source and the reductant through the generation of $CO_2^{\bullet-}$ species, which underwent Giese radical addition to electron-deficient alkenes to trigger the consecutive C–F bond cleavage and carboxylation process.

C–F bond activation, defluorocarboxylation, carbon dioxide radical anion, visible light

Citation: Wang XY, Xu P, Liu WW, Jiang HQ, Zhu SL, Guo D, Zhu X. Divergent defluorocarboxylation of α-CF_3 alkenes with formate *via* photocatalyzed selective mono- or triple C–F bond cleavage. *Sci China Chem*, 2024, 67: 368–373, https://doi.org/10.1007/s11426-023-1731-x

1 Introduction

Due to the exceptional hydrogen bonding properties, pharmacokinetic properties, and enzymatic stability of the fluorine atom, great efforts have been made in the area of fluorinative transformations of organic molecules during the past decades [1]. Other than the installation of more fluorine atoms into the molecules with fluorination agents [2], the selective activation and functionalization of the C–F bond in a readily available trifluoromethyl (CF_3) group to access a diverse array of partially fluorinated compounds is one of the most significant yet challenging approaches in synthetic organic chemistry and degradation of fluorinated pollutants [3] (Scheme 1a).

Among them, the reductive defluorocarboxylation of α-trifluoromethyl styrenes to construct the fluorine degraded molecules is very attractive as the substrate is easy to get and the fluorinated moieties are intriguing boisosters widely utilized in drug development [4]. Furthermore, the carboxyl group could be used as a handle for further transformations to install more functional groups. However, the inertness of the C–F bond makes it the strongest carbon-heteroatom bond in nature and a poor leaving group in organic synthesis, especially under mild reaction conditions [5].

In 2019, Yu and co-workers [6] reported a novel protocol for defluorocarboxylation of α-CF_3 alkenes with CO_2 gas as the carbonyl source in the presence of a copper catalyst. One of the three fluorine atoms was replaced by the carbonyl functionality (Scheme 1b, right). Later, Zhou and co-workers [7] disclosed an electrochemical defluorocarboxylation of α-CF_3 alkenes *via* direct reduction of the electron-deficient substrate to form its radical anion that undergoes nucleophilic addition to CO_2 and triggers the ionic fluorine β-elimination to finish the defluorocarboxylation process (Scheme 1b, left). Very recently, Shu and co-workers [8] realized the first triple defluoro-functionalization of α-CF_3

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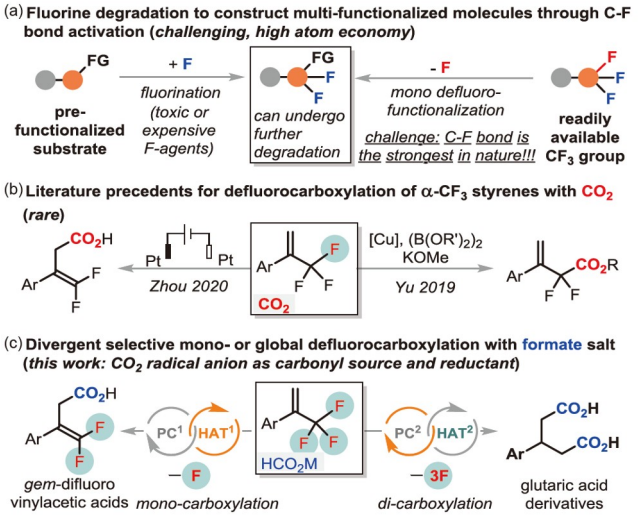


Scheme 1 Defluorinative carboxylations of α-CF_3 alkenes: previous reports and new developments (color online).

alkenes and synthesized various α-arylated carboxylic acid derivatives. In this reaction, no carbon atom was installed into the molecule, and water provided the oxygen atom on carbonyl functionalities.

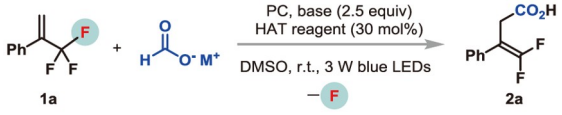
As an alternative C1 source for carboxylation, formate salt can be converted to $CO_2^{\bullet-}$ (*via* HAT, hydrogen atom transfer), which undergoes Giese radical addition to C–C double bonds to form carboxylic acids [9]. The original investigation on $CO_2^{\bullet-}$ derived from formate was started in 1969 [10], however, the synthetic applications of $CO_2^{\bullet-}$ have not been developed until recently by Li [11], Wickens [12], Li [13], and Jui's group [14]. Our group [15] has been focusing on the development of new applications of $CO_2^{\bullet-}$ under highly reductive conditions. Based on our recent findings on defluroalkylation and alkenes carboxylation with $CO_2^{\bullet-}$, we envisioned that the reaction of $CO_2^{\bullet-}$ with α-CF_3 styrenes would provide a range of structurally and medicinally interesting defluorocarboxylation products. Herein we report an interesting mono-defluorocarboxylation and an unprecedented triple defluorodicarboxylation of various α-CF_3 styrenes to access *gem*-difluorovinylacetic acids and glutaric acid derivatives, respectively, by simply switching the photocatalysts and HAT catalysts.

2 Results and discussion

Initially, we began the study by treating the α-CF_3 styrene **1a** with sodium formate to test the feasibility of our hypothesis. Based on our previous experience [15b], 1,4-diazabicyclo [2.2.2]octane (DABCO) was used as the HAT catalyst in the presence of Cs_2CO_3 with 4CzIPN as the photocatalyst. As we expected, the defluorocarboxylation product was formed but with a low yield (Table 1, entry 1). After careful evaluation of different bases and HAT catalysts, inorganic base K_2HPO_4 was found to be optimal to give the desired product in 44% isolated yield (Table 1, entries 2–4, see the Supporting Information online for more details). Replacement of DABCO with other tertiary amines, such as DIPEA (diisopropylethylamine), could not realize the transformation (Table 1, entry 5, see the Supporting Information online for more details). Screening of the formate salts and photocatalyst showed that the combination of lithium formate and 4CzIPN in the presence of H_2O additive is the best option and product **2a** was obtained in 71% yield (Table 1, entry 7). We envision that water can improve the solubility of inorganic bases in the reaction system and make the reaction homogeneous. Further control experiments in the absence of formate, DABCO, inorganic base, or photocatalyst were investigated and no product was observed in all cases (Table 1, entries 9–12).

With the optimized reaction conditions in hand, the substrate scope of styrenes **1** was investigated as shown in Table 2. Substituents on the aryl ring were first examined and the results showed that the alkyl and phenyl substituents on the *para*-position of the aryl ring were well tolerated to give the desired products in moderate to good yields (Table 2, **2a**–**2f**). Styrenes bearing strong electron-donating groups, such as methoxyl and phenoxyl groups, also worked well to form **2g** and **2h**, respectively, in moderate yields. Fluorine substituent was also tested and product **2i** was obtained in 80% yield.

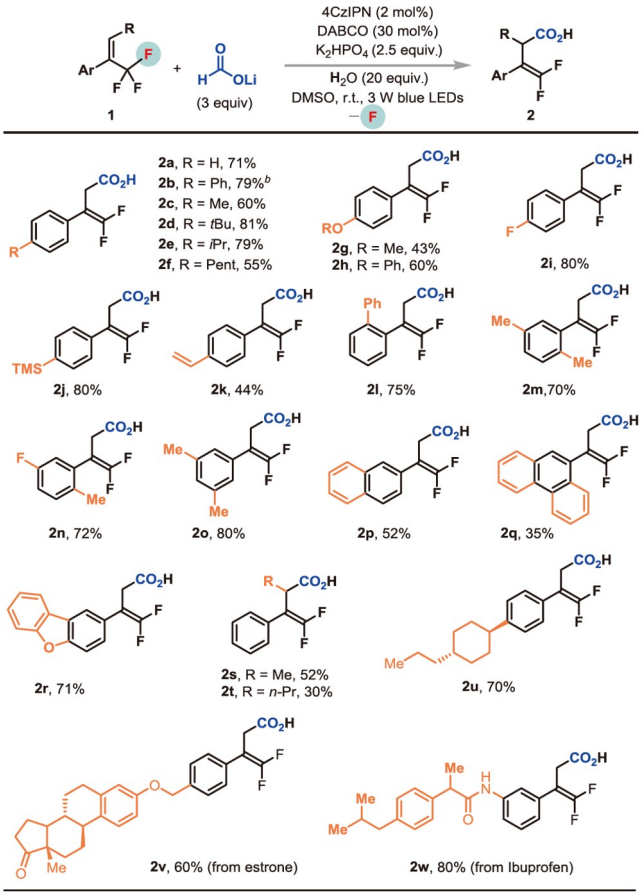
Table 1 Optimization of reaction conditions[a)]



Entry	PC (2 mol%)	Base	HAT	Formate	Yield (%)
1	4CzIPN	Cs_2CO_3	DABCO	HCO_2Na (2)	19
2	4CzIPN	K_2CO_3	DABCO	HCO_2Na (2)	24
3	4CzIPN	K_3PO_4	DABCO	HCO_2Na (2)	15
4	4CzIPN	K_2HPO_4	DABCO	HCO_2Na (2)	44[b)]
5	4CzIPN	K_2HPO_4	DIPEA	HCO_2Na (2)	trace
6	*fac*-Ir(ppy)$_3$	K_2HPO_4	DABCO	HCO_2Na (2)	7
7	4CzIPN	K_2HPO_4	DABCO	HCO_2Li (3)	71[c,d)]
8	4CzIPN	K_2HPO_4	DABCO	HCO_2Li (3)	0[e)]
9	4CzIPN	K_2HPO_4	DABCO	–	0
10	4CzIPN	K_2HPO_4	–	HCO_2Li (3)	0
11	4CzIPN	–	DABCO	HCO_2Li (3)	0
12	–	K_2HPO_4	DABCO	HCO_2Li (3)	0

a) Reaction conditions: **1a** (0.2 mmol), HCOOM (0.4–0.6 mmol), PC (2 mol%), DABCO (30 mol%) and base (0.5 mmol) in DMSO (2 mL) at certain temperature for 48 h. b) Yields were determined by ^{1}H NMR analysis with 1,2-dicloroethane as an internal standard. c) Isolated yields. d) 20 equiv. of H_2O was added. e) No light.

Table 2 Substrate scope of various trifluoromethylated strenes **1**[a)]

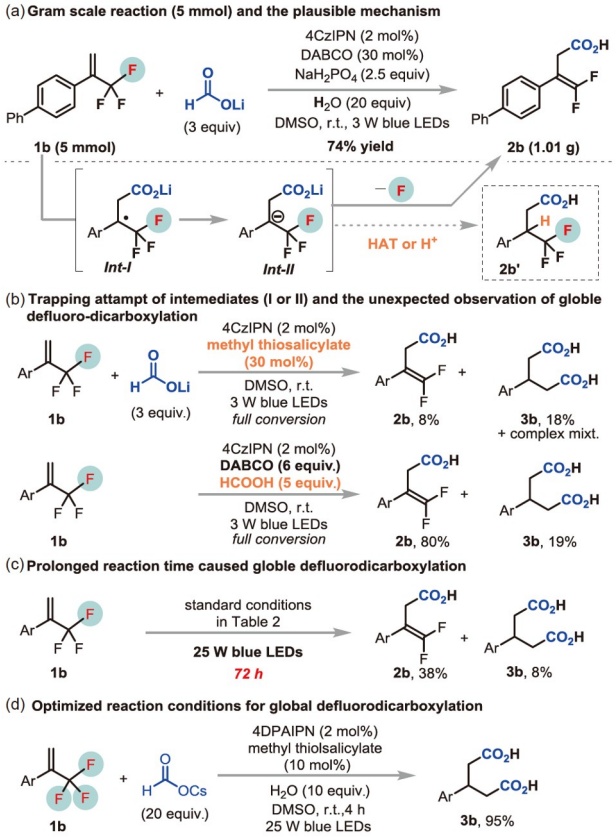


a) Reaction conditions: **1** (0.2 mmol), HCOOLi (0.6 mmol), PC (2 mol%), DABCO (30 mol%) and K_2HPO_4 (0.5 mmol) in DMSO (2 mL) at r.t. for 12–48 h. b) NaH_2PO_4 instead of K_2HPO_4.

Other vulnerable functional groups such as trimethylsilyl (TMS) and activated alkenes were well tolerated during the reaction (Table 2, **2j**, **2k**). Afterward, several steric hindered substrates with *ortho*-substituents were examined, and no decrease in the reaction yields was observed (Table 2, **2l**–**2o**). Polyaryl substrates, including heteroaromatic rings, were also tested to give the desired products in 35%–71% yields (Table 2, **2p**–**2r**). Afterward, the trisubstituted alkenes **1s** and **1t** were investigated to give the corresponding products in synthetic useful yields (Table 2, **2s**, **2t**). Complex substrates derived from liquid crystal and natural products were then examined to give the later stage modified products in good yields (Table 2, **2u**–**2w**).

To further elaborate the synthetic application, a large scale reaction was examined in 5 mmol scale with substrate **1b**. The desired product **2b** was obtained in 74% yield, which is comparable with small scale reaction without significant decrease. Based on our initial hypothesis, the $CO_2^{\bullet-}$ generated from formate should be able to undergo Giese addition to the alkene **1b** to give the intermediate **I** (***Int-I***) that was further reduced to form ***Int-II*** and triggered the F elimination. Interestingly, there is no side product **2b'** was observed, which means the reduction of ***Int-I*** and F elimination step is very fast. In order to trap the ***Int-I*** or ***Int-II***, reactions in Scheme 2b were conducted in the presence of aryl thiol or formic acid. Still, no HAT or protonation was observed and no detection of **2b'**. Interestingly, around 20% of glutaric acid **3b** was isolated and characterized in each case. To the best of our knowledge, the exhaustive defluorodicarboxylation of α-CF_3 alkenes to synthesize the valuable glutaric acid derivatives has never been reported. This encouraged us to put more effort into further exploration. By simply prolonging the standard reaction time of Table 2 under 25 W blue LEDs, the yield of product **2b** dropped to 38% and 8% of **3b** was isolated. With the same light source, reaction conditions were screened carefully and the combination of 4DPAIPN and Methyl thiosalicylate was found to be the best with excess amounts of formate (see Supporting Information online for details). In this case, the H_2O additive might play a role in anion intermediates protonation steps to improve the reaction efficiency. However, the mono-fluorinated carboxylic acid product was never observed, maybe due to the requirement of transition metals to stabilize the corresponding intermediates [6,16].

Afterward, the α-CF_3 alkenes substrate was examined again with the optimized new reaction conditions. As shown

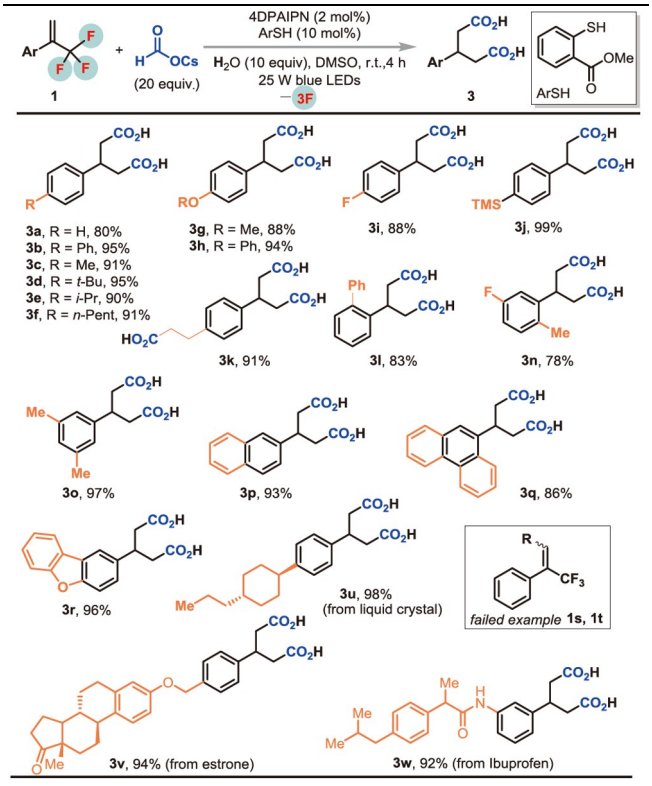


Scheme 2 Large scale reaction and observation of triple defluorodicarboxylation (color online).

in Table 3, substrates **1a**–**1j** were converted to the corresponding diacid **3** in excellent yields within 4 h. The florine and TMS functional groups were still intact after the reaction. The sterically hindered alkenes slightly decreased the yields (Table 3, **3l** and **3n**). Polyaromatic including heteroaromatic substrates also reacted well to give the diacids in up to 96% yield (Table 3, **3p**–**3r**). Moreover, later stage modification of substrates derived from liquid crystal, natural products, and pharmaceutical drugs was also viable (Table 3, **3u**–**3w**). Unfortunately, the trisubstituted substate **1s** and **1t** only provided inseparable mixtures of different unknown compounds.

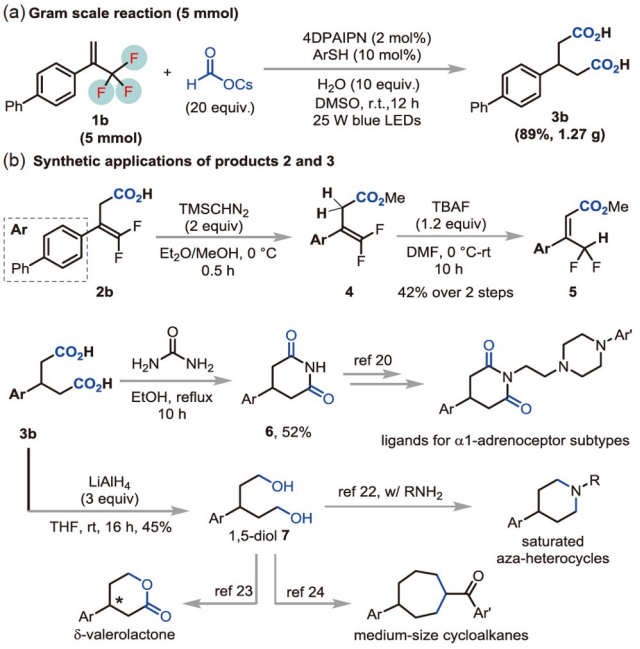
Next, synthetic elaboration of the selective mono- or triple defluorocarboxylation reaction was conducted as shown in Scheme 3. The gram-scale reaction showed the reaction yield was not decreased and the isolated product **3b** could be further transformed to ester **4**, which can be isomerized into difluoromethyl substituted acrylate **5** [17]. The glutaric acid **3b** was then treated with urea in reflux ethanol to construct the piperidine-2,6-dione **7**, which is the backbone of ligands for α1-adrenoceptor subtypes [18]. Diacid **3b** can also be reduced by $LiAlH_4$ to form the 1,5-diol **9**, which is the versatile synthetic precursor for saturated aza-heterocycles [19], *δ*-valerolactones [20], and the medium-sized cycloalkanes [21] as depicted in Scheme 3b.

Table 3 Substrate scope to access glutaric acid derivatives **3**[a)]

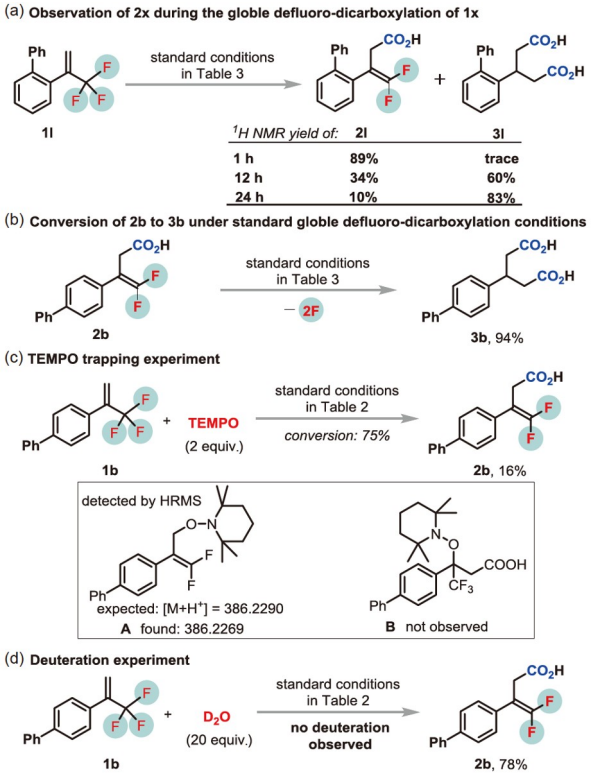


a) Reaction conditions: **1** (0.2 mmol), HCOOCs (4 mmol), PC (2 mol%), methyl thiolsalicylate (10 mol%) and H_2O (2 mmol) in DMSO (2 mL) at r.t. for 4–24 h.

To further probe the reaction mechanism, control experiments in Scheme 4 were investigated. When the sterically hindered substrate **1l** was examined under the standard conditions in Table 3, crude proton nuclear magnetic re-



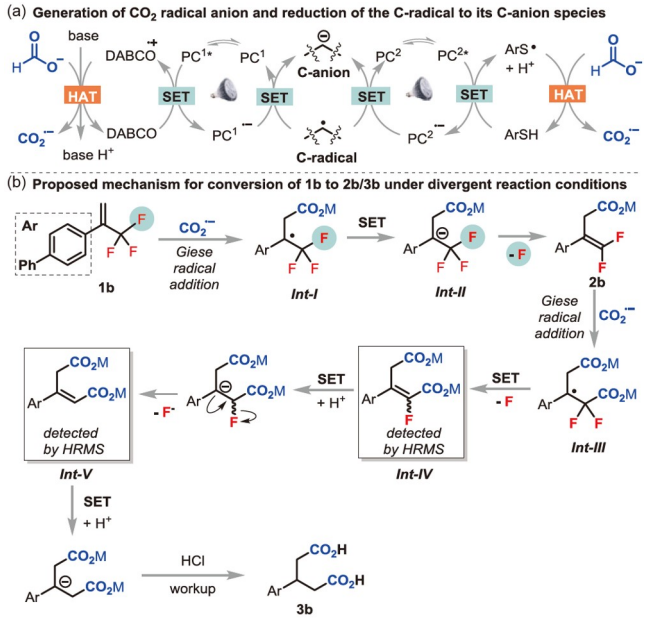
Scheme 3 (a) Large scale reaction and (b) synthetic applications of products **2** and **3** (color online).



Scheme 4 Control experiment to probe the reaction mechanism (color online).

sonance (^{1}H NMR) yields of **2l** and **3l** collected from different reaction times showed the *gem*-difluorovinyl acetic acid **2l** is the potential intermediate for glutaric acid product **3l** (Scheme 4a). Therefore, the isolated product **2b** was treated with conditions in Table 3 and the desired diacid product **3b** was obtained in 94% yield (Scheme 4b). When 2,2,6,6-tetramethylpiperidoxyl (TEMPO) was added to the reaction, the yield of **2b** dropped to 16% and most of the starting material was recovered. Only the TEMPO addition adduct **A** was detected by high resolution mass spectrometer (HRMS) and no adduct **B** was observed might be due to the steric hindrance. Stern-Volmer quenching experiment showed the photocatalyst can be easily quenched by TEMPO to cause the low conversion of the reaction. The deuteration reaction as shown in Scheme 4d gave the product **2b** in 78% yield without any deuteration was observed. Therefore, the Giese radical addition is the first step to constructing the C–C bond (see Supporting Information online for details).

Based on the above control experiments and our previous understanding of the reactivity of $CO_2^{\bullet-}$, the plausible mechanism of the defluorocarboxylation was depicted in Scheme 5. Under blue light irradiation, $CO_2^{\bullet-}$ could be generated *via* HAT by the DABCO radical cation or the thiol radical formed by reductive quenching of the exited photocatalyst (for Stern-Volmer experiments, see Supporting Information online). The reductive state of the photocatalyst is able to reduce carbon-centered radicals that formed in the reaction system (Scheme 5a). After the $CO_2^{\bullet-}$ was generated, it could undergo Giese radical addition to the electron-deficient alkene **1b** and form the radical intermediate ***Int-I***, which was quickly reduced *via* single electron transfer (SET) by either $CO_2^{\bullet-}$ or $PC^{\bullet-}$ to form the anionic intermediate ***Int-II***. In this step, both 4CzIPN$^{\bullet-}$ ($E_{1/2}$ = −1.21 V) and 4DPAIPN$^{\bullet-}$ ($E_{1/2}$ = −1.52 V) are able to reduce the benzyl radical to the anion form. Followed by consequent β-elimination of fluorine anion, product **2b** could be generated. In the presence of excess amounts of $CO_2^{\bullet-}$, product **2b** could be further attacked by the nucleophilic $CO_2^{\bullet-}$ species and triggered the exhaustive defluorination. Electron-deficient alkene intermediate ***In-V***, which was detected by HRMS could be reduced by the highly reductive photocatalyst 4DPAIPN$^{\bullet-}$ or $CO_2^{\bullet-}$ to provide the final diacid product **3b** [14].



Scheme 5 Proposed reaction mechanism (color online).

3 Conclusions

In summary, we have reported unprecedented divergent defluorocarboxylations of α-CF_3 alkenes with formate *via* photocatalyzed selective mono- or triple C–F bond cleavage. These results would provide a more insightful understanding of the new reactivity of $CO_2^{\bullet-}$. Various *gem*-difluorovinylacetic acids and glutaric acid derivatives were synthesized under mild reaction conditions and their synthetic transformations were also elaborated.

Acknowledgements This work was supported by the National Natural Science Foundation of China (22001224), the Natural Science Foundation of Jiangsu Province (BK20201014, BK20200106), and the Start-up Funding provided by Xuzhou Medical University. This work was also supported by the Jiangsu Specially-Appointed Professor Program (Xu Zhu) and Jiangsu Province Shuangchuang PhD Program (Pei Xu, JSSCBS20211267). The Public Experimental Research Centre of Xuzhou Medical University was also acknowledged.

Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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