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Direct Electrochemical Defluorinative Carboxylation of *gem*-Difluoroalkenes with Carbon Dioxide

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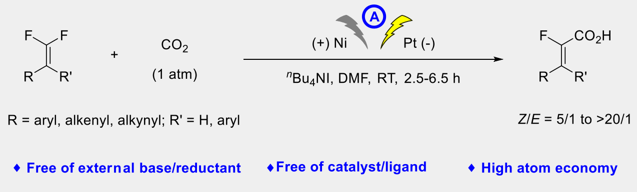
ABSTRACT: We report a facile and economical synthesis of α-fluoroacrylic acids via direct electrochemical defluorinative carboxylation of *gem*-difluoroalkenes with CO_2. By using a platinum plate as the working cathode and a cheap nickel plate as the anode in a user-friendly undivided cell under constant current conditions, the reactions proceed smoothly under room temperature, without the use of expensive transition metal catalysts, ligands, external base or reductant, affording the desired adducts in up to 83% yield and 20:1 Z/E ratio, with good functional group tolerance. A cyclic voltammetry study was conducted and suggested a novel ECEC process.



Using CO_2 as an abundant and renewable C1 resource to value-added chemicals has attracted wide attention from the viewpoint of resource utilization and environmental protection.[1] Over the past decade, more than 20 chemical transformations with CO_2 as a C1 resource have been realized, among which the carboxylation of C−hetero bonds has been a well-established method to synthesize carboxylic acids via a C−X bond-breaking and C−C bond-forming process.[2] However, C−F bond activation and transformation have been largely undeveloped, probably due to the following inherent difficulties.[3,4] First, the C−F bond is the strongest covalent single bond that carbon can form, possessing high thermodynamic stability; second, the fluoride in C−F bond is neither a good Lewis base nor a good leaving group, the activation of which is kinetically unfavorable. On the other hand, fluorinated carboxylic acids, in particular α-fluoracrylic acids, represent an important class of structural motifs widely existing in pharmaceuticals and bioactive compounds.[5] Although a number of synthetic routes to α-fluoracrylic acids have been reported,[6] the defluorinative carboxylation of *gem*-difluoroalkenes with CO_2 represents one of the most straightforward strategies, but only a limited number of processes have been developed with the current state-of-the-art represented by the photocatalysis and metal catalysis.[7−9]

In 2019, Feng and co-workers pioneered a dual catalytic system involving Ir-based photocatalyst and Pd-based co-catalyst, enabling the selective C−F bond carboxylation of *gem*-difluoroalkenes with CO_2 efficiently to afford a wide range of α-fluoroacrylic acids in good to excellent yields with the utilization of 3.0 equiv of $^iPr_2NEt$ and Cs_2CO_3. Of 24 examples examined, only six gave more than a 90:10 Z/E ratio (Scheme 1a).[7] Shortly thereafter, copper-catalyzed formal carboxylation of fluorinated alkenes with CO_2 was realized by Yu[8] and our group,[9] independently. It was demonstrated that the borocupration of alkene and subsequent β-F elimination gave the alkenylboronate intermediate with a perfect *Z*-configuration, the subsequent carboxylation of which with CO_2 delivered the desired α-fluoroacrylic acids with excellent *Z*-selectivity. However, the use of 1.5−1.8 equiv of expensive B_2Pin_2 and 3.0−3.5 equiv of LiO^tBu compromised the efficiency of this protocol because of the generation of substantial of waste (Scheme 1b). In light of this, the development of catalyst-, base-, and reductant-free defluorinative carboxylation of *gem*-difluoroalkenes with CO_2, with broad substrate scope under mild conditions, is still very much in demand.

Nowadays, increasing attention has been paid to organic synthetic electrochemistry, and electrochemical carboxylation has become one of the most sustainable and efficient methods for fixation of CO_2 into organic compounds.[10] By using electricity as a driving force, it can overcome the inherent high thermodynamic stability of CO_2, thus avoiding the utilization of expensive reducing chemicals and enable the reaction to be performed under mild ambient conditions.[11] Along with our continual interest in chemical fixation of CO_2,[12] just recently we realized an direct electrochemical γ-carboxylation of α-CF_3 alkenes with CO_2 under constant current conditions, in which an opposite regiocontrol was observed for the corresponding copper-catalyzed transformation.[13] Encouraged by this research, we envisioned whether the electrochemical defluor-

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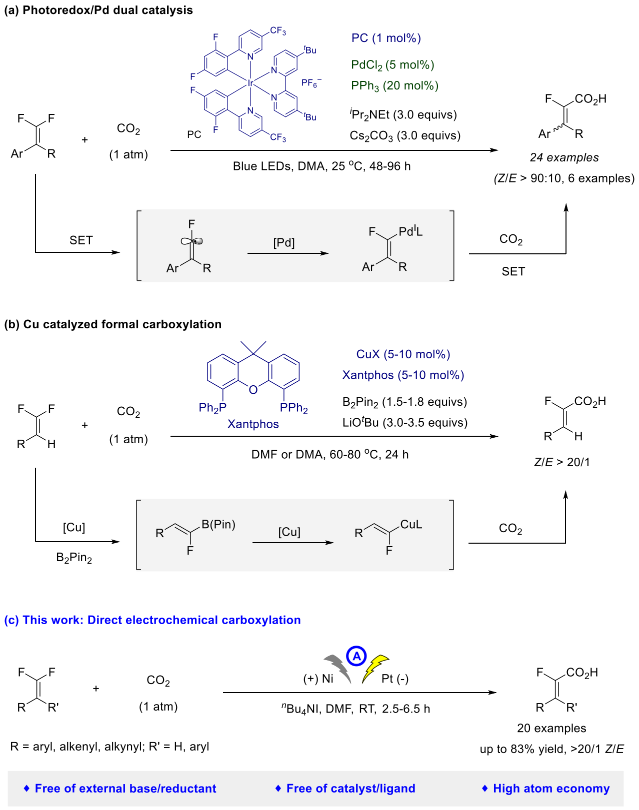
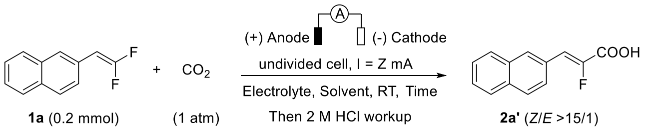
Scheme 1. C−F Bond Carboxylation of *gem*-Difluoroalkenes



inative carboxylation of *gem*-difluoroalkenes with CO_2 could constitute a direct and facile entry to α-fluoroacrylic acids. Accordingly, it could be performed free of external expensive transition-metal catalysts, ligands, excessive reductants, or bases, thus possessing higher atomic economy. In addition, the milder reaction condition should enable a better functional group compatibility. Herein, we report our preliminary results on this research work (Scheme 1c).

We started our research by evaluating the electrochemical carboxylation of 2-(2,2-difluorovinyl)naphthalene (**1a**) with CO_2 as shown in Table 1. Initially, constant current electrolysis (8 mA) of **1a** with bubbling CO_2 in an undivided cell equipped with a Pt plate as cathode and anode at room temperature could give α-fluoroacrylic acid (**2a′**) in 24% yield with excellent *Z* selectivity (entry 1). Considering that the utilization of the nonsacrificial Pt-plate anode might result the undesired oxidation of starting material or carbonate product, we focused our efforts on using cheap metal as the sacrificial anode. To our delight, when the Pt-plate was changed to Mg-, Al-, or Ni-sheet as the anode material, the reaction yield increased gradually to 48%, 32%, and 60%, respectively (entries 2−4). Then the influence of cathode materials on the transformation was studied with an Ni-sheet as anode. Graphite rod and RVC were noneffective for this carboxylation, and glassy carbon gave an inferior result compared to that of the Pt-plate (entries 5−7 vs 4). Considering that the oxidized nickel might plate out into the cathode, the utilization of a Ni-plate as cathode was also attempted, with only 35% yield received (entry 8). Fortunately, when the reaction time was reduced to 4.5 h, with a total charge of 6.7 Faraday/mol, 75% NMR yield could be achieved, with the methyl esterification product **2a** obtained in 71%

Table 1. Optimization of Reaction Conditions.[a]



entry	anode	cathode	electrolyte	solvent	*Z* (mA)	time (h)	yield[b] (%)
1	Pt	Pt	$^{n}Bu_4NI$	DMF	8	5.5	24
2	Mg	Pt	$^{n}Bu_4NI$	DMF	8	5.5	48
3	Al	Pt	$^{n}Bu_4NI$	DMF	8	5.5	32
4	Ni	Pt	$^{n}Bu_4NI$	DMF	8	5.5	60
5	Ni	C	$^{n}Bu_4NI$	DMF	8	5.5	trace
6	Ni	RVC	$^{n}Bu_4NI$	DMF	8	5.5	trace
7	Ni	GC	$^{n}Bu_4NI$	DMF	8	5.5	53
8	Ni	Ni	$^{n}Bu_4NI$	DMF	8	5.5	35
9	Ni	Pt	$^{n}Bu_4NI$	DMF	8	4.5	75 (71)[c]
10	Ni	Pt	$^{n}Bu_4NI$	DMF	8	3.5	58
11	Ni	Pt	$^{n}Bu_4NBr$	DMF	8	4.5	34
12	Ni	Pt	$^{n}Bu_4NBF_4$	DMF	8	4.5	34
13	Ni	Pt	$^{n}Bu_4NClO_4$	DMF	8	4.5	13
14	Ni	Pt	Et_4NI	DMF	8	4.5	27
15	Ni	Pt	$^{n}Bu_4NI$	DMF	6	4.5	60
16	Ni	Pt	$^{n}Bu_4NI$	DMF	10	4.5	39
17	Ni	Pt	$^{n}Bu_4NI$	DMA	8	4.5	59
18	Ni	Pt	$^{n}Bu_4NI$	NMP	8	4.5	39
19	Ni	Pt	$^{n}Bu_4NI$	CH_3CN	8	4.5	43

[a] Reaction conditions: electrolyte (0.07 M), solvent (7 mL), undivided cell, rt. [b] Determined by ^{19}F NMR with *p*-$MeOC_6H_4CF_3$ as internal standard. [c] Isolated yield of methyl esterification product **2a**. GC (glassy carbon).

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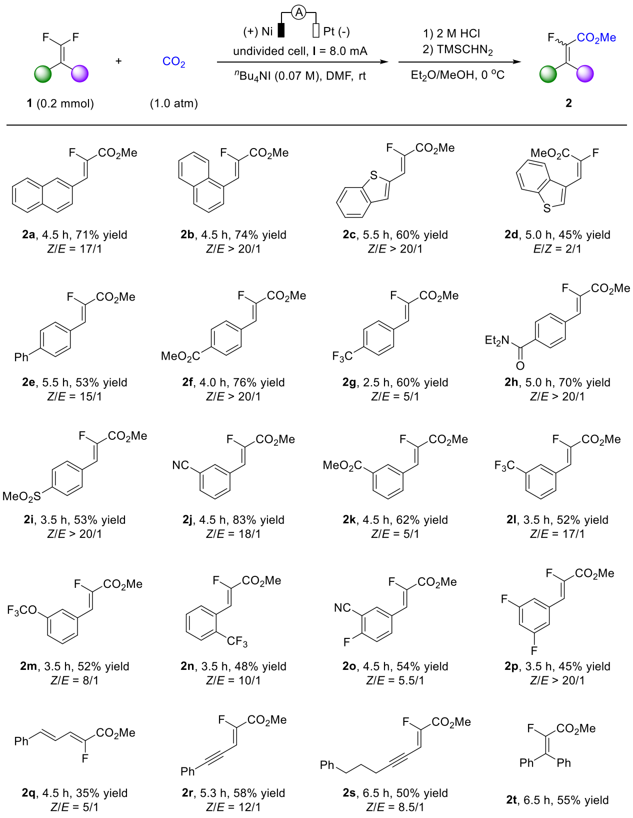
isolated yield (entry 9). The choice of supporting electrolyte also has a crucial influence on the reaction. When the electrolyte was changed from ^{n}Bu$_4$NI to ^{n}Bu$_4$NBr, ^{n}Bu$_4$NBF$_4$, ^{n}Bu$_4$NClO$_4$, or Et$_4$NI, the reaction yield decreased in different degrees (entries 11−14). Reducing the current to 6 mA gave a lower 60% yield due to incomplete reaction, but increasing the current to 10 mA led to a dramatic decrease of the reaction yield (entries 15 and 16). The solvent effect was also evaluated, but no better results than that of DMF were obtained (entries 17−19).

Based on the outcome of the condition screening, we decided to evaluate the substrate scope by performing the reaction in DMF containing ^{n}Bu$_4$NI using constant current of 8 mA in an undivided cell with CO$_2$ bubbling and a Ni-sheet as anode and a Pt-plate as cathode at room temperature. To facilitate product isolation and analysis, the original carboxylic acid was converted to the corresponding methyl ester.

At first, the performance of alkenes containing fused aromatics was evaluated (Scheme 2). The reaction of 1-naphthyl or 2-benzothiophene substituted *gem*-difluoroalkene could deliver the desired products **2b** and **2c** in 74% and 60% yield, respectively, with a *Z*-configuration. However, for the carboxylation of **1d** possessing a 3-benzothiophene moiety, **2d** was obtained in only 45% yield with a reversed *E*/*Z* selectivity. The reason why for this phenomenon is still unclear.

Scheme 2. Electrocarboxylation of *gem*-Difluoroalkenes[a]



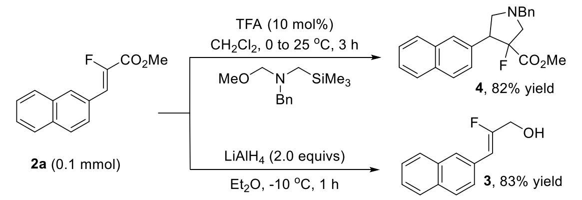
[a]Isolated yield, with *Z*/*E* ratio determined by ^{19}F NMR study of reaction mixture.

Then the influence of the substituents on the phenyl ring of 2-aryl-1,1-difluoroalkenes was investigated. Substrates bearing a variety of functional groups, such as phenyl, ester, amide, sulfuryl, cyano, fluoro, CF$_3$, or OCF$_3$, all showed good reactivity to give the carboxylate products **2e**−**p** in moderate to high yields. The location of the substituents on the phenyl ring also has a negligible influence on the reaction. For instance, the reaction of isomeric substrates with an ester or CF$_3$ group at the *para*-, *meta*-, or *ortho*-position worked well to give the corresponding products **2f**,**g** and **2k**−**n** in similarly moderate to good yields. Notably, for substrates bearing different sp^2 or sp^3 C−F bonds, the defluorinative carboxylation occurred exclusively at the *gem*-difluoroalkene position, with the Ar−F, CF$_3$, or OCF$_3$ moiety remaining untouched.

Apart from *β*-aryl-substituted *gem*-difluoroalkenes, substrates possessing a *β*-alkenyl or alkynyl moiety were also competent in this reaction, producing **2q**−**s** in 35%, 58%, and 50% yield, respectively. The reaction of tetrasubstituted alkene **1t** was further conducted, affording the corresponding product **2t** in 55% yield. These results clearly demonstrated the good tolerance of our method. Notably, the reaction could be scaled up to gram scale, as demonstrated by the electrocarboxylation of 6 mmol of **1a**, with 62% yield obtained (for details, see the SI).

The thus obtained *α*-fluoroacrylic acids could be easily elaborated to other valuable fluorinated compounds, further demonstrating the synthetic utility of this electrochemical defluorinative carboxylation. For instance, the reduction of carboxyl moiety with LiAlH$_4$ gave alcohol **3** in 83% yield. In addition, the TFA catalyzed [3 + 2] cycloaddition could deliver the 3-fluoropyrrolidine derivate **4** in 82% yield (Scheme 3).

Scheme 3. Synthetic Elaboration of 2a



To gain more insight into the reaction mechanism, cyclic voltammetry (CV) analysis were conducted (Figure 1).[14] For the CV of *gem*-difluoroalkene **1f**, a one-electron reduction peak at the potential of −2.7 V and the second one at −3.0 V was observed (blue line, c). Notably, at a potential of −2.7 V, the reduction current of CO$_2$ is significantly lower than that of **1f** (0.15 vs 0.6 mA), which indicated that the latter was much easier to be reduced. When CO$_2$ was introduced into the

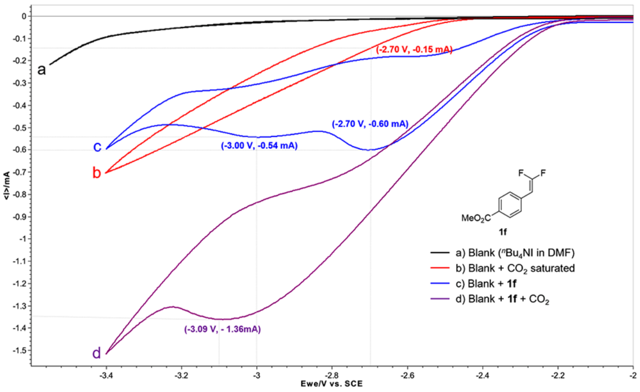


Figure 1. CV analysis of **1f**.

solution of **1f**, only one reduction peak at −3.09 V was observed with the peak current increased greatly to 1.36 mA, indicating a fast interaction of the one-electron reduction species with CO_2. Meanwhile, the doubled peak current suggested that the electrochemical reduction of the *gem*-difluoroalkenes with CO_2 at a cathode might be a two-times one-electron reduction process.

Based on CV experiments, along with previous literature reports,[15] a putative ECEC[16] reaction mechanism was proposed as shown in Figure 2. First, a one-electron reduction of *gem*-difluoroalkene on the cathode generated a radical anion **A**, followed by a quick selective fixation of CO_2 at difluorocarbon to give intermediate **B**. Then a secondary one-electron reduction of **B** and the subsequent defluorination delivered the carboxylate anion **C**, which was developed to be their salt forms by capturing Ni ion formed at the anode. Finally, the acidification gave the target α-fluoroacrylic acid.

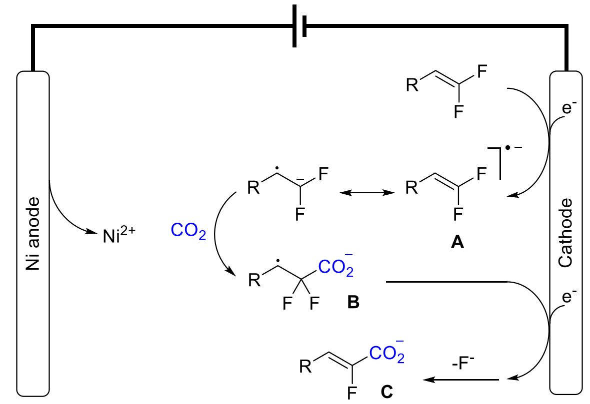


Figure 2. Proposed reaction mechanism.

On the basis of electrochemistry, a facile and economical direct defluorinative carboxylation of *gem*-difluoroalkenes with CO_2 is developed. The reaction is performed with Pt-plate as working cathode and cheap Ni-sheet as anode, under continuous current electrolysis. The aryl-, alkenyl-, and alkynyl-substituted *gem*-difluoroalkenes are all viable substrates to give the structurally diverse α-fluoroacrylic acids in up to 83% yield and 20/1 *Z*/*E* ratio under mild room temperature. The synthetic utility is further demonstrated by the elaboration to fluorinated alcohol and heterocyclic compound. CV analysis reveals that a ECEC (single-electron reduction, reaction with CO_2, single-electron reduction, loss of fluoride) process should be involved, which is novel and totally different from the photoredox/Pd- and Cu-catalyzed pathway. Considering that both CO_2 and hydrofluorocarbons are recognized to be greenhouse gases,[17] this study on electrochemical defluorinative carboxylation should also be meaningful to green and sustainable chemistry. Further developments of CO_2-incorporating transformations with the help of electrochemistry to value-added chemicals are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03051.

Experimental procedures, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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