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# Electroreductive cross-coupling of trifluoromethyl alkenes and redox active esters for the synthesis of *gem*-difluoroalkenes

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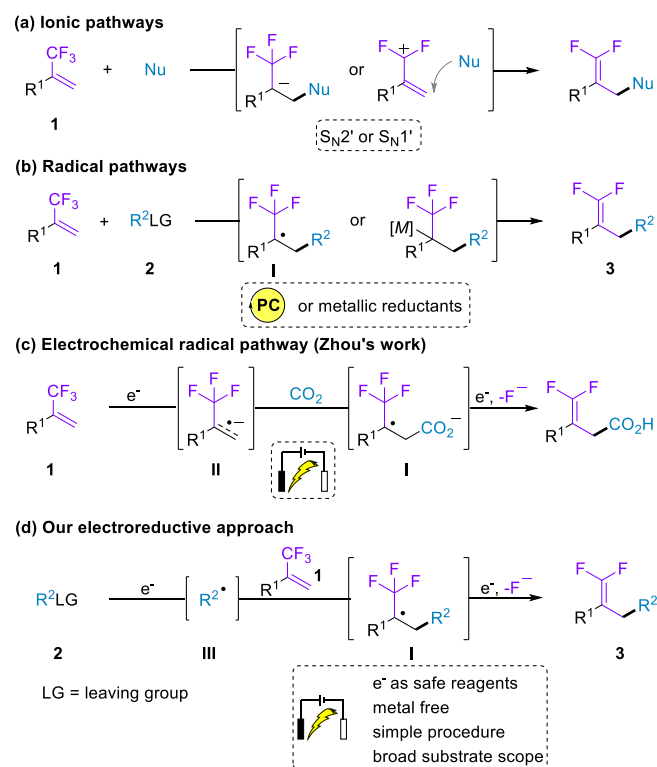
Supporting information for this article is given via a link at the end of the document.

**Abstract:** An electroreductive access to *gem*-difluoroalkenes has been developed through the decarboxylative/defluorinative coupling of *N*-hydroxyphthalimides esters and  $\alpha$ -trifluoromethyl alkenes. The electrolysis is performed under very simple reaction conditions in an undivided cell using cheap carbon graphite electrodes. This metal-free transformation features broad scope with good to excellent yields. Tertiary, secondary as well as primary alkyl radicals could be easily introduced.  $\alpha$ -aminoacids L-aspartic and L-glutamic acid-derived redox active esters were good reactive partners furnishing potentially relevant *gem*-difluoroalkenes. In addition, it has been demonstrated that our electrochemical approach toward the synthesis of *gem*-difluoroalkenes could use an easily prepared Krapcho salt as alkyl radical precursor via a deaminative/defluorinative carbonyl functionalization of trifluoromethylstyrene.

*gem*-Difluoroalkene, as carbonyl bioisoster, is a recurrent structural motif found in pharmaceuticals, agrochemicals, and material molecules.<sup>[1]</sup> Meanwhile, they are versatile building blocks precursors to value-added fluorinated compounds.<sup>[2]</sup> Accordingly, in the last decades, numerous methods to construct *gem*-difluoroalkenes have been reported.<sup>[3]</sup> Typical methods to prepare *gem*-difluoroalkenes, such as difluoroolefination of carbonyl<sup>[4]</sup> and diazo<sup>[5]</sup> compounds often suffer from moderate yields, harsh reaction conditions, and not easily available starting materials. Therefore, several new approaches have emerged.<sup>[6]</sup> Among these, the defluorinative functionalization of easily available 1,1-trifluoromethylalkenes **1** has recently attracted considerable attention.<sup>[7]</sup> In this context, two main strategies based on this methodology have been developed: (1) direct addition of various nucleophiles in the presence of bases, Lewis acids or organometallic species (Scheme 1a);<sup>[8]</sup> and (2) direct addition of radicals generated by metal<sup>[9]</sup> - or photo-catalyzed<sup>[10]</sup> processes (Scheme 1b). Despite these achievements, however, each method has its own restrictions (e.g., unstable reagents, toxic metal, requirement of highly oxidizing photocatalysts, etc.). Thus, the development of more environmentally friendly processes for the defluorinative functionalization of 1,1-trifluoromethylalkenes is still a remaining challenge.

In the last decade, electrochemistry has received renewed interests as a green and powerful tool to generate one-electron open-shell species. By directly using electrons as safe reagents, redox reactions can be carried out under mild condition avoiding transition-metal catalysts or toxic reagents. Only recently, an electrochemical synthesis of *gem*-difluoroalkenes involving electroreductive polarity inversion of **1** via radical anion **II** followed by carboxylation has been reported. (Scheme 1c).<sup>[11]</sup> Based on our experience in electrochemical synthesis,<sup>[12]</sup> we envisioned a

different scenario for the preparation of *gem*-difluoroalkenes in which<sup>[13]</sup> the nucleophilic alkyl radical **III** generated by electroreduction could selectively react with 1,1-trifluoromethylalkenes **1** and the resulting  $\alpha$ -trifluoromethyl alkyl radical could undergo electrochemical single electron defluorinative reduction.



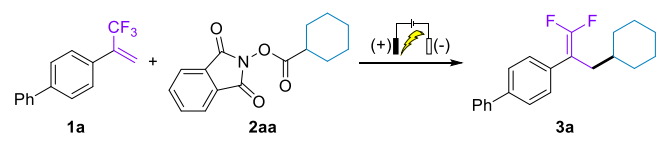
**Scheme 1.** Methods for the synthesis of *gem*-difluoroalkenes from 1,1-trifluoromethylalkenes **1**.

To realize the projected electroreductive–defluorinative carbonyl functionalization transformation, some criteria have to be fulfilled. The alkyl radical precursor **2** should be more easily reduced than (i) trifluoromethyl alkenes **1**<sup>[11]</sup> and (ii) *gem*-difluoroalkenes **3**.<sup>[14]</sup> Moreover, (iii) the nucleophilic radical **III** generated near the cathode should react with **1** prior to its homocoupling. Herein, we wish to report a novel electrochemical synthesis of *gem*-difluoroalkenes through electroreductive carbonyl functionalization of trifluoromethyl alkenes.

Inspired by previous studies, we tested two alkyl radical precursors featuring low reduction potential to favour the overall process: the easily available redox active alkyl N-hydroxyphthalimide (NHP) ester **2aa**<sup>[15-17]</sup> and the Katritzky salt **2ab** easily prepared from the corresponding primary amine.<sup>[18]</sup>

Our initial investigation was carried out with 1,1-trifluoromethylalkene **1a** and NHP ester **2aa** in an undivided cell equipped with a simple two electrodes arrangement under constant current electrolysis at 8 mA. The tested reaction conditions and results are summarized in Table 1. After extensive screening of reaction conditions, it was found that the decarboxylative/defluorinative carbofunctionalization proceeded smoothly to deliver *gem*-difluoroalkene **3a** in 91% yield with cheap carbon graphite cathode and anode in dimethylacetamide (DMA) employing *n*Bu<sub>4</sub>NBF<sub>4</sub> as electrolyte in the presence of triethylamine as sacrificial reductant (entry 1). Different solvents were screened for the carbofunctionalization reaction. Similar yield was obtained in DMF whereas a slight decrease was observed in CH<sub>3</sub>CN and DMSO (entries 2-4). Decreasing the amount of triethylamine had a negative impact on the yield (entry 5). The reaction also proceeded well with glassy carbon electrode or nickel plate as cathode (entries 6-7). Then, replacing the electrolyte *n*Bu<sub>4</sub>NBF<sub>4</sub> with other tetraalkylammonium salts does not have a significant influence on the efficiency but the yield dropped with lithium perchlorate (entries 8-11). No improvement was observed when the reaction was performed under a strict argon atmosphere, indicating that no specific precaution needs to be taken (entry 12). Finally, a last optimization revealed that the best yield was obtained at 4 mA (entry 13).<sup>[19]</sup>

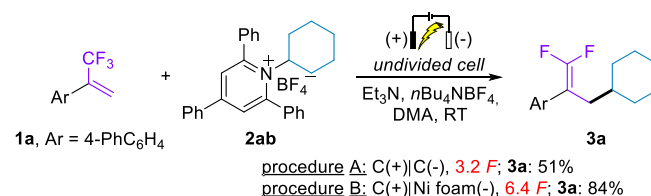
**Table 1.** Optimization studies for the decarboxylative/defluorinative carbofunctionalization of trifluoromethyl alkenes.<sup>[a]</sup>



Entry	Variations from the reaction conditions	Yield [%] <sup>[b]</sup>
1	None	91
2	DMF instead of DMA	90
3	CH <sub>3</sub> CN instead of DMA	80
4	DMSO instead of DMA	71
5	95 μL of Et <sub>3</sub> N instead of 0.2 mL	75
6	GC(+) GC(-) instead of C(+) C(-)	87
7	C(+) Ni plate (-) instead of C(+) C(-)	81
8	<i>n</i> Bu <sub>4</sub> NPF <sub>6</sub> instead of <i>n</i> Bu <sub>4</sub> NBF <sub>4</sub>	88
9	<i>n</i> Bu <sub>4</sub> NHSO <sub>4</sub> instead of <i>n</i> Bu <sub>4</sub> NBF <sub>4</sub>	89
10	Et <sub>4</sub> NBF <sub>4</sub> instead of <i>n</i> Bu <sub>4</sub> NBF <sub>4</sub>	86
11	LiClO <sub>4</sub> instead of <i>n</i> Bu <sub>4</sub> NBF <sub>4</sub>	34
12	Under strict Argon atmosphere	89
13	<b>4 mA</b>	<b>92 (90)</b>

[a] Reaction conditions: undivided cell, C(+)|C(-), **1a** (0.2 mmol), **2a** (0.4 mmol), DMA (2.5 mL), Et<sub>3</sub>N (0.2 mL), *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.1 M), CCE (8 mA), 3.2 F (2 h 03), RT. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard; isolated yield is written between parentheses.

The optimized reaction conditions were further evaluated on pyridinium salt **2ab** as alkyl radical precursor (Scheme 2). This preliminary attempt enabled the deaminative/defluorinative Csp<sup>3</sup>-Csp<sup>2</sup> cross-coupling with **1a** producing the target *gem*-difluoroalkene **3a** in moderate yield (51%). Delightfully, we found that a higher yield (84%) was achieved *via* slight modifications on the reaction conditions.<sup>[19]</sup> Nevertheless, this procedure required a higher amount of charge than the decarboxylative process (6.4 F vs 3.2 F respectively). Consequently, we decided to explore mainly the scope and limitations of the defluorinative-carbofunctionalization of trifluoromethyl styrene with NHP esters as alkyl radical precursors.

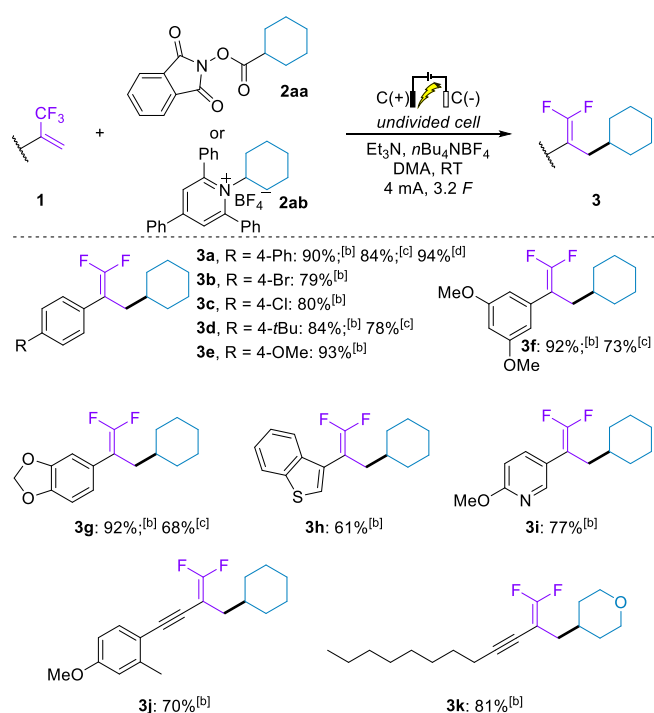


**Scheme 2.** Deaminative/defluorinative carbofunctionalization of trifluoromethyl alkene.<sup>[a,b]</sup> [a] Reaction conditions: undivided cell, **1** (0.2 mmol), **2a** (0.4 mmol), DMA (2.5 mL), *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.1 M), CCE (4 mA), RT. Procedure A: C(+)|C(-), Et<sub>3</sub>N (0.2 mL), 3.2 F (2 h 03). Procedure B: C(+)|Ni foam(-), Et<sub>3</sub>N (95 μL), 6.4 F (8 h 34). [b] Isolated yield.

We started to modify the structure of trifluoromethyl alkenes for the decarboxylative process (Scheme 3). The reaction proceeded smoothly with different trifluoromethyl styrenes bearing various substituents on the aromatic ring to afford the corresponding products **3a-f** with good to excellent yields (79 to 92%). Slightly higher yields were accomplished with electron-donating substituents (**3e-f**) compared to electron-withdrawing substituents (**3b-c**). Heteroaromatic rings such as benzo[d][1,3]dioxole, benzothiophene and pyridine were also suitable producing the target compounds (**3g-i**) in moderate to excellent yields (61-92%). Unfortunately, no reaction occurred with  $\alpha$ -alkyl-substituted trifluoromethyl alkene. Remarkably, successful coupling reactions were realized with conjugated 2-trifluoromethyl-1,3-enynes producing the corresponding alkynyl-difluoroalkenes **3j-k** in good yields (76-81%). Finally, the deaminative difluoroallylation of pyridinium salt **2ab** was assessed with styrenes **1d**, **1f-g** to deliver the corresponding *gem*-difluoroalkenes in good yields.

Our survey of the scope of the defluorinative carbofunctionalization reaction with regard to NHP esters is shown in Scheme 4. Cyclic as long as acyclic secondary and tertiary NHP esters were all suitable coupling partners to furnish products **3l-r** in high to excellent yields (70-94%). Notably, *gem*-difluoroalkene **3n** featuring a tetrahydro-2H-pyran ring could be produced in good yield (85%). Radical precursors with  $\alpha$ -stabilizing heteroatoms exhibited a slightly higher reactivity, and

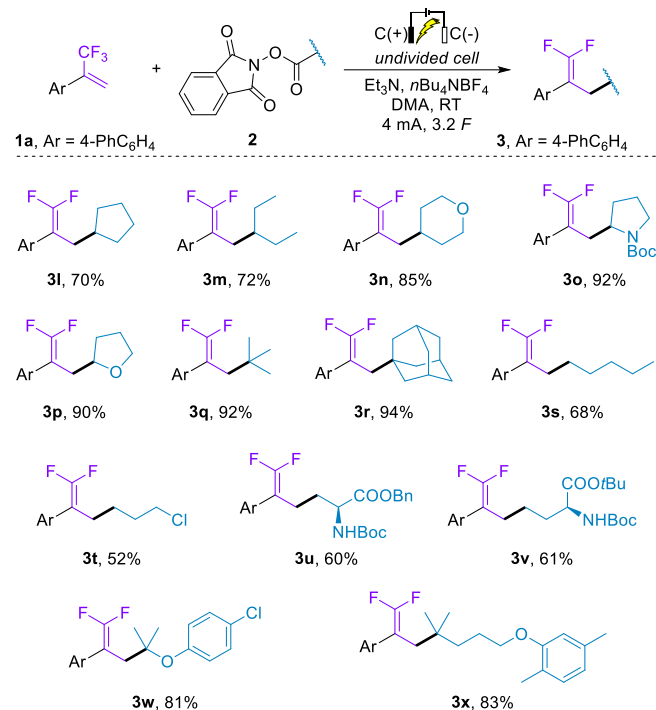
reacted smoothly to provide the corresponding *gem*-difluoroalkenes **3o** and **3p** in 92 and 90% yield, respectively. Primary alkyl chains could be also introduced albeit with slightly lower yields (**3s-v**, 52-68%). Interestingly, chlorine atom was a compatible substituent (product **3t**). Moreover, Boc-L-aspartic acid  $\alpha$ -benzyl ester and Boc-L-glutamic acid  $\alpha$ -tert-butyl ester derivatives<sup>[20]</sup> were successfully engaged in this process yielding to chiral unnatural  $\alpha$ -amino acids **3u-3v** in good yields (60-61%). To our pleasure, the carboxylic groups of the natural product Clofibric acid and the synthetic drug Gemfibrozil could be readily modified with good efficiency to incorporate the desired *gem*-difluoroalkene moiety (products **3w-x**). Finally, the practicability of this electrosynthesis was demonstrated by conducting the coupling between **1a** and **2a** on 1 mmol scale leading to product **3a** in high similar yields (94%, Scheme 3).



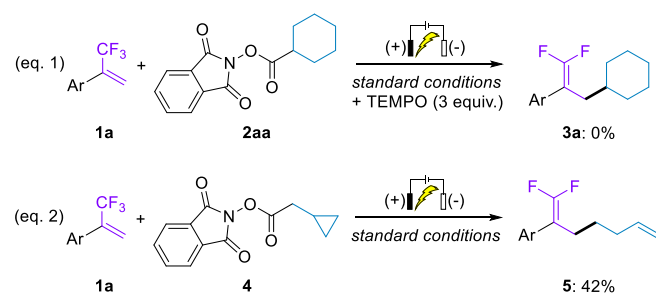
**Scheme 3.** Substrate scope with respect to trifluoromethyl alkenes **1**.<sup>[a]</sup> [a] Isolated yield. [b] Reaction conditions: undivided cell, C(+)|C(-), **1** (0.2 mmol), **2a** (0.4 mmol), DMA (2.5 mL), Et<sub>3</sub>N (0.2 mL), *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.1 M), CCE (4 mA), 3.2 F (4 h 17), RT. [c] Reaction conditions: undivided cell, C(+)|Ni foam(-), **1** (0.2 mmol), **2a** (0.4 mmol), DMA (2.5 mL), Et<sub>3</sub>N (95  $\mu$ L), *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.1 M), CCE (4 mA), 6.4 F (8 h 34), RT. [d] Decarboxylative process conducted on 1 mmol scale.

To gain mechanistic insight into this electrochemical transformation, several control experiments were performed (Scheme 5). The reaction did not occur in the absence of current (Table 1, entry 14). The addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as radical scavenger under standard conditions totally inhibited the transformation (Scheme 5, eq. 1). Radical clock experiment between **1a** and 2-cyclopropylacetic acid-derived redox active ester **4** yielded exclusively ring-opening product **5**. These experiments strongly supported a radical process in this transformation. Then, the redox behaviors of the components were examined by cyclic voltammetry analysis.<sup>[18]</sup> Trifluoromethyl styrene **1a** and redox active ester **2a** displayed irreversible reduction peaks at  $E^\circ = -1.77$  V and  $-1.42$  V vs Ag<sup>+</sup>/Ag

in DMA respectively. In contrast, no reduction peak on product **3a** was observed between 0 and  $-2$  V. This study indicated that the transformation was initiated by SET reduction of **2a** under constant current electrolysis.



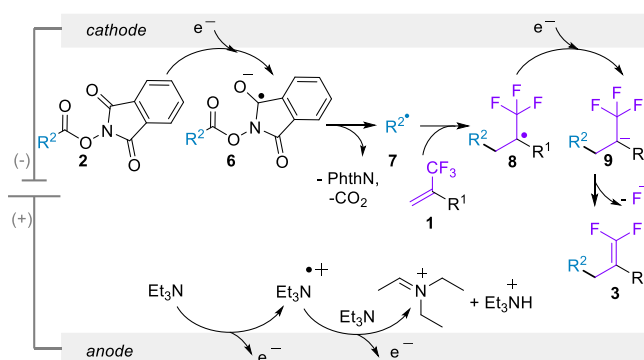
**Scheme 4.** Substrate scope with respect to NHP esters **2**.<sup>[a,b]</sup> [a] Reaction conditions: undivided cell, C(+)|C(-), **1** (0.2 mmol), **2a** (0.4 mmol), DMA (2.5 mL), Et<sub>3</sub>N (0.2 mL), *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.1 M), CCE (4 mA), 3.2 F (4 h 17), RT. [b] Isolated yield. [c] Reaction conducted on 1 mmol scale.



**Scheme 5.** Control experiments.

Based on the above results and previous reports,<sup>[10,17]</sup> a possible reaction mechanism is depicted in Scheme 6. Thus, it is reasonable to propose the initial cathodic reduction of active ester **2** to the radical anion **6**. The latter would undergo fragmentation/decarboxylation sequence to form nucleophilic alkyl radical **7**. Subsequent regioselective addition to electron poor styrene **1** would produce  $\alpha$ -trifluoromethyl alkyl radical **8**. Final SET cathodic reduction and defluorination of anion **9** through an E1cB type mechanism delivered *gem*-difluoroalkenes **3**. At the anode, two SET oxidation of triethylamine took place to balance the overall transformation.

In conclusion, we have developed an electrochemical approach toward *gem*-difluoroalkenes through decarboxylative/defluorinative carbofunctionalization of  $\alpha$ -trifluoromethyl alkenes using easily prepared redox-active esters as alkyl radical precursors. Our novel electroreductive protocol provides mild access to a broad range of *gem*-difluoroalkenes in good to excellent yields with simple reaction conditions. Moreover, it has been demonstrated that this defluorinative carbofunctionalization could be extended to a deaminative process from readily available Katritzky salt as C-centered radical precursor. Further electroreductive processes toward the synthesis of *gem*-difluoroalkenes are undergoing in our laboratory.



**Scheme 6.** Proposed mechanism for the decarboxylative/defluorinative carbofunctionalization of  $\alpha$ -trifluoromethyl alkenes.

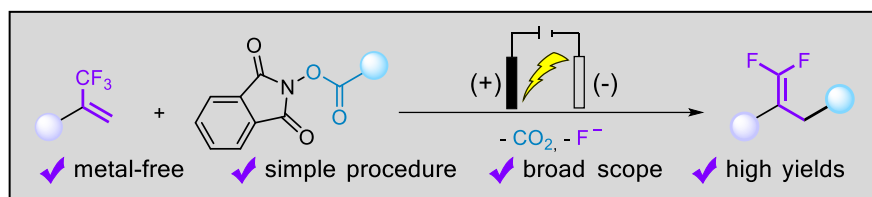
**Keywords:** electrochemistry • *gem*-difluoroalkene • alkyl radical • decarboxylation • deamination

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## Entry for the Table of Contents



An electroreductive decarboxylative/defluorinative cross-coupling between redox-active esters and  $\alpha$ -trifluoromethyl styrenes enabled the access to a wide range of *gem*-difluoroalkenes. The transformation can be conducted efficiently under simple metal-free reaction conditions and features broad scope with high yields.