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# Electrochemical Synthesis of Itaconic Acid Derivatives via Chemodivergent Single and Double Carboxylation of Allenes with $CO_2$

Andrea Brunetti,[a, b] Mauro Garbini,[a, b] Giuseppe Autuori,[a] Chiara Zanardi,[c, d] Giulio Bertuzzi,*[a, b] and Marco Bandini*[a, b]

Leveraging electrochemistry, a new synthesis of non-natural derivatives of itaconic acid is proposed by utilizing carbon dioxide ($CO_2$) as a valuable C1 synthon. An electrochemical cross-electrophile coupling between allenoates and $CO_2$ was targeted, allowing for the synthesis of both mono- and di-carboxylation products in a catalyst- and additive-free environment (yields up to 87%, 30 examples). Elaboration of the model mono-carboxylation product, and detailed cyclovoltammetric, as well as mechanistic analyses complete the present investigation.

## Introduction

The integration of enabling technologies in organic synthesis has revolutionized the art and science of creating complex molecules.[1] In this dynamic landscape, the application of electrochemistry in the advancement of reductive and oxidative processes, offers an unparalleled opportunity to modulate the intrinsic chemical behavior of the reactive species through facile and precise adjustment of applied conditions (*i.e.*, current and potential).[2]

For instance, directing electrosynthesis towards the innovative design and synthesis of analogues of naturally occurring small molecules, represents a notable advantage of the "electrification" of organic synthesis. Whereas the "natural pool" gives access to a plentiful supply of a single specific molecule, analogues often prove to be inaccessible, resulting in limited tunability and impractical diversification.

Itaconic acid epitomizes this challenge remarkably. Produced industrially through either the thermal decomposition of citric acid or the bio-fermentation of carbohydrates, its trifunctional structure facilitates the synthesis of advanced polymers (Figure 1, pink background) or the generation of essential building blocks such as 3-methyl substituted tetrahydrofuran, γ-butyrolactone, pyrrolidine and pyrrolidone (orange background), or even more intricated heterocycles (yellow background).[3] Surprisingly, non-natural derivatives of itaconic acid, bearing substituents on the double bond or methylene unit remain underexplored in literature, primarily due to the limited availability of general and accessible synthetic methodologies for their preparation.[4]

Given the structural significance of the –COOH groups in itaconic acid, utilizing $CO_2$ for the development of a carboxylation protocol to synthesize its derivatives represents an exceptionally appealing strategy. Carbon dioxide ($CO_2$) is increasingly recognized as a valuable C1 synthon in organic chemistry, owing to its abundance, non-toxic nature, non-flammability, and cost-effectiveness.[5] Consequently, the incorporation of $CO_2$ into organic frameworks, particularly for the synthesis of low-molecular weight carboxylic acids, holds significant promise.[6] As $CO_2$ capture by nucleophilic agents represents one of the most exploited strategies in organic

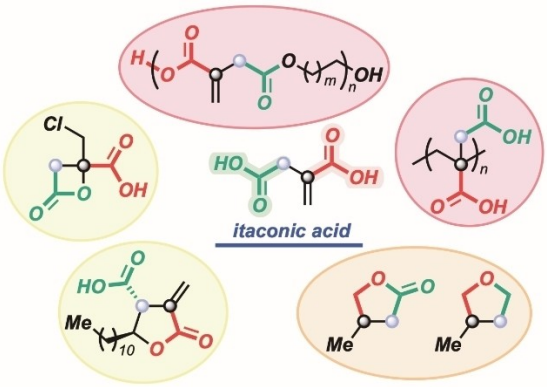


**Figure 1.** Itaconic acid as a platform in diverse chemical spaces.

[a] A. Brunetti, M. Garbini, G. Autuori, G. Bertuzzi, M. Bandini
Dipartimento di Chimica "Giacomo Ciamician", Alma Mater Studiorum, Università di Bologna, via P. Gobetti, 85, 40129 Bologna, Italy
E-mail: giulio.bertuzzi2@unibo.it
marco.bandini@unibo.it

[b] A. Brunetti, M. Garbini, G. Bertuzzi, M. Bandini
Center for Chemical Catalysis, C³, Alma Mater Studiorum, Università di Bologna, via P. Gobetti, 85, 40129 Bologna, Italy

[c] C. Zanardi
Department of Molecular Sciences and Nanosystems, Ca' Foscari University of Venice, via Torino, 155, 30170 Venezia (Mestre), Italy

[d] C. Zanardi
Institute for Organic Synthesis and Photoreactivity (ISOF), National Research Council of Italy (CNR), via P. Gobetti 101, 40129 Bologna, Italy

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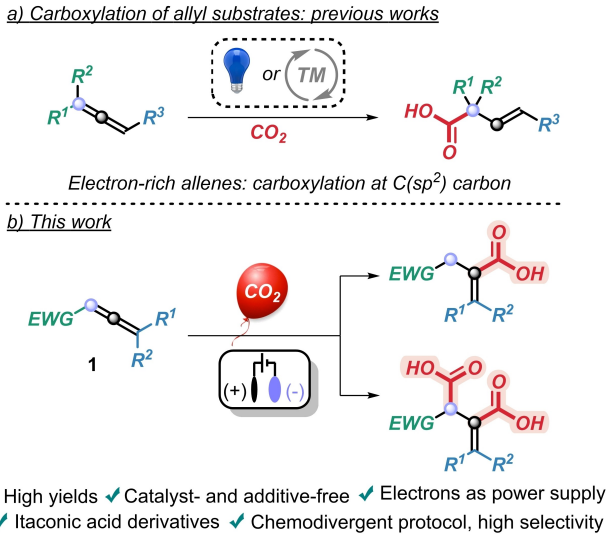
synthesis,[7] electrochemistry emerges as a particularly advantageous approach. This technique, relying solely on electricity for the efficient generation of transient nucleophilic species, can facilitate their conversion into functionalized carboxylic acids in a catalyst- and additive-free manner.[8]

In continuation of our ongoing exploration into selective radical-based transformations[9] for the electrochemical manipulation of electron-deficient olefins,[10] and the synthetic valorization of $CO_2$,[11] we have conceived the possibility of integrating these approaches to target the preparation of valuable itaconic acid derivatives. In our proposed synthetic approach, we envisioned allenoates **1**[12] as suitable and readily available starting materials. Notably, this strategy marks the first attempt to exploit the reactivity of electron-poor allenes in electrochemically mediated carboxylation protocols and can be carried out in a catalyst- and additive-free fashion (Scheme 1b). On the contrary, $CO_2$ fixation into allene substrates is typically achieved with electron-rich derivatives, predominantly through metal-catalyzed processes,[13] or, seldomly, through photo- or electrochemical methods,[14] leading to the formation of alkenyl-acetic acid derivatives (Scheme 1a).

Furthermore, the inherent flexibility of electrochemical protocols offers the potential to achieve not only single but also double $CO_2$ capture into olefinic platforms.[15] Considering the simple structure of allenes **1**, the realization of a di-carboxylation product would yield compounds where up to 50% of the final molecular weight originates from valorized $CO_2$, representing a highly sustainable approach. The challenges in executing this synthetic plan lie in developing a completely regiodivergent protocol capable of synthesizing the desired product from the same set of starting materials, on-demand. Ideally, the addition of any additive to manipulate reactivity should be avoided, maximizing the utilization of electricity alone to accomplish the desired task.



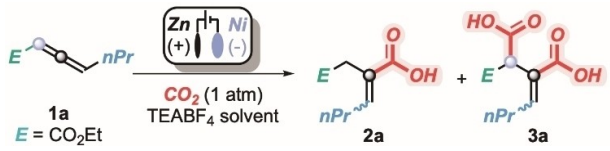

**Scheme 1.** $CO_2$-based carboxylations of allenes: known strategies and our proposal based on electrosynthesis.

## Results and Discussion

At the outset of our investigation, we subjected allenoate **1a** (easily prepared in one step from valeroyl chloride) to galvanostatic electrolysis (2.0 mA, 5.0 F/$mol_{1a}$) under a $CO_2$ atmosphere (1 atm), in the presence of $TEABF_4$ as supporting electrolyte (DMF, 0.05 M in **1a**) and using Ni and Zn rods as cathode and anode, respectively. We successfully isolated the desired product **2a** in moderate yield (46%), along with minor amounts of the di-carboxylation product **3a** detected in the crude mixture (Table 1, entry 1). To demonstrate that the desired chemodivergency can be achieved by tuning the electrolytic parameters, we conducted three different reactions increasing applied currents (6, 30, and 60 mA, entries 2–4 respectively) under otherwise identical conditions. These experiments revealed a notable trend correlating the increasing preferential formation of product **3a** with increasing current intensity, where a near complete switch in the **2a**/**3a** product distribution can be observed between 2.0 and 60 mA (entries 1 and 4).

Once we established that mono- or di-carboxylation events can be obtained selectively, we proceeded with dedicated optimizations for each protocol. Notably, a remarkable solvent effect was observed in optimizing the mono-carboxylation methodology: while a switch from DMF to ACN completely suppressed the reactivity (entry 5), the use of DMSO proved

**Table 1.**
Optimization of the reaction conditions.[a]




| Entry | *I* [mA] (F/$mol_{1a}$) | Solvent | **2a**/**3a**[b] | Isolated product (Yield [%]; *E*/*Z*)[c] |
|---|---|---|---|---|
| 1 | 2.0 (5.0) | DMF | 4.5:1 | **2a** (46; 1.6:1) |
| 2 | 6.0 (5.0) | DMF | 1:1.4 | **2a** (30, 1.6:1), **3a** (36, 1.9:1) |
| 3 | 30 (5.0) | DMF | 1:2.1 | **2a** (15, 1.7:1), **3a** (37; 2.1:1) |
| 4 | 60 (5.0) | DMF | 1:3.4 | **2a** (8, 1.6:1), **3a** (36; 2.0:1) |
| 5 | 2.0 (5.0) | ACN | - | - |
| 6 | 2.0 (5.0) | DMSO | 8.9:1 | **2a** (64, 1.8:1) |
| 7 | 4.0 (5.0) | DMSO | 8.8:1 | **2a** (87; 1.7:1) |
| 8 | 60 (15) | DMF | 1:3.5 | **3a** (51; 2.1:1) |
| 9[d] | 60 (15) | DMF | 1:20 | **3a** (64; 1.9:1) |
| 10 | 60 (15) | DMSO | - | - |
| 11[d] | 60 (15) | ACN | 1:20 | **3a** (75; 2.0:1) |

[a] All reactions were carried out with ElectraSyn 2.0 apparatus under constant current electrolysis (CCE) and at rt unless otherwise mentioned. See Supporting Information for extensive details. [b] Determined by $^1$H NMR analysis on the crude mixture. [c] Isolated yields after flash chromatography. *E*/*Z* ratio determined on the isolated product. [d] Reaction run at 0 °C.

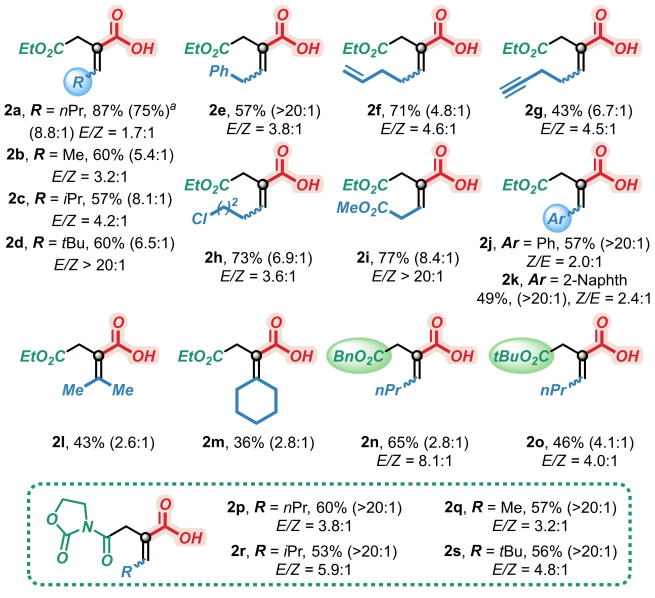
beneficial, increasing both the **2a**/**3a** ratio and isolated **2a** yield (entry 6, 64%). This was further improved by running the reaction at 4.0 mA (87% isolated yield) while maintaining an excellent **2a**/**3a** ratio (8.8:1).

Concurrently, in the optimization aimed at the selective formation of di-acid **3a**, electrolysis at a current intensity of 60 mA resulted in a drop in the faradic efficiency, with incomplete conversion of starting material and diminished yield in isolated **3a** (entry 4). Thus, increasing the applied charge (15 F/mol$_{1a}$) proved advantageous (entry 8, 51% yield). Moreover, a completely chemoselective outcome was achieved by running the process at 0 °C (entry 9, **3a**/**2a** > 20:1), with a concomitant increase in isolated yield (64%), attributable to the suppression of parasitic pathways. Finally, while DMSO was found to be incompatible with the high current intensity required for this process (excessive reduction to DMS, entry 10), the use of ACN led to the optimized reaction conditions, resulting in an isolated yield of 75% and exclusive formation of di-acid **3a**. Further screening of electrodic materials and electrolytes proved detrimental to the reaction outcomes; additionally, the use of additives, although potentially beneficial for promoting selective mono- or di-carboxylation of activated olefins,[16] did not yield positive results (see Supporting Information for details).

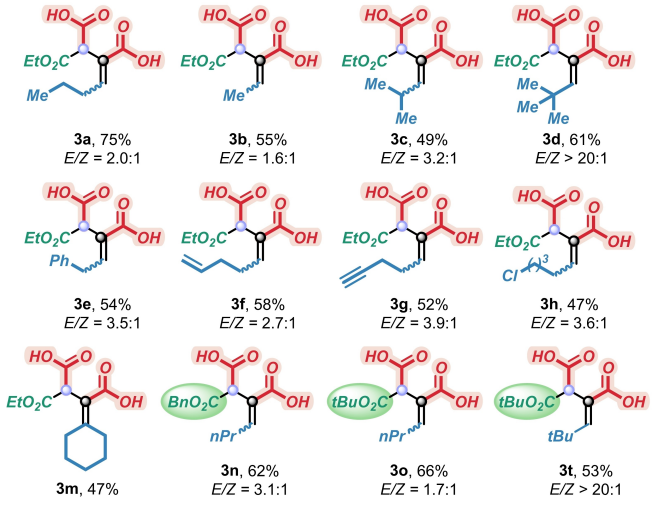
Once the optimized conditions for the chemodivergent carboxylation of allenes **1** were established, we proceeded to evaluate the generality of the reaction (Scheme 2). Importantly, efficient chromatographic separation facilitated the isolation of pure products **2** or **3** in all cases, even in the presence of mixtures in the reaction crudes.

First, employing the mono-carboxylation reaction protocol (Table 1, entry 7) on substrates **1** bearing increasingly bulky substituents (-Me **1b**, -*n*Pr **1a**, -*i*Pr **1c**, and -*t*Bu **1d**) we confirmed that steric encumbrance does not hinder the desired reactivity, showing good yields and chemoselectivities across all four cases (57–87% yield, **2**/**3** ratios as low as 5.4:1). Importantly, the protocol run on a 1.0 mmol scale of **1a** rendered the desired product **2a** in 75% yield, ascertaining the scalability of the process. Moreover, the presence of a bulky group such as *t*Bu (**2d**) enhanced the stereoselectivity, favoring the formation of the *E* isomer predominantly. Tolerance towards a benzyl substituent (**2e**) was observed without isomerization of the resulting double bond to a presumably more stable styrenic isomer, demonstrating exquisite chemoselectivity (**2e**/**3e** > 20:1). Compatibility with various functional groups, including double bonds, triple bonds, alkyl halides, and esters (**2f**, **2g**, **2h**, and **2i**, respectively), was ascertained (43–77% yield, **2**/**3** ratios as low as 3.6:1). Reactivity of conjugated aromatic allenes (**1j** and **1k**) was confirmed, yielding the respective products **2j** and **2k** in moderate yields (49–57%) Notably, a prevalence of the *Z* isomer formation was observed for these products, alongside exclusive presence of the mono-carboxylation products **2**. Additionally, allenes with double substitution on the terminal carbon (**1l** and **1m**) underwent the desired process, yielding the respective products **2l** and **2m** in moderate yields (36–43%), likely due to diminished chemoselectivity of the process (2.6:1 and 2.8:1 **2**/**3** ratios, respectively). Finally, variation of the electron-withdrawing group showed tolerance towards different ester substituents (benzyl **2n**, 65% yield, and *t*Bu **2o**, 46% yield), and the introduction of an oxazolidinone (**1p**–**1s**). In particular, for this moiety, exclusive formation of the mono-carboxylation products **2** was observed in all cases, alongside tolerance towards various sterically bulky groups on the terminal carbon of the allene moiety (53–60% yield), revealing results comparable to analogous esters (**1a**–**1d**).

We then proceeded to assess the generality of the di-carboxylation protocol (Table 1, entry 11) on a selection of allenes **1**, previously utilized in the mono-carboxylation process (Scheme 3). Under these conditions, exclusive formation of products **3** was consistently observed in all reactions. The same level of tolerance exhibited by the previous protocol towards



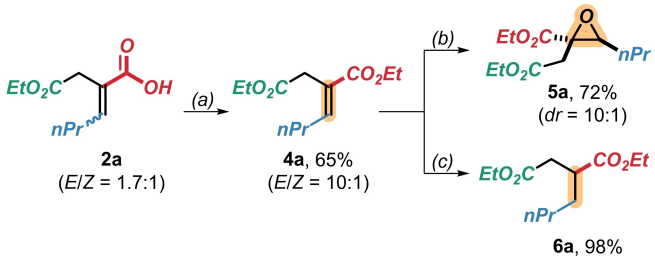

**Scheme 2.** Scope of the reaction: mono-carboxylation procedure. In brackets the **2**/**3** ratio. a) Reaction run on 1.0 mmol scale (see Supporting Information for details).




**Scheme 3.** Scope of the reaction: di-carboxylation procedure.

steric hindrance (**3a**–**3d**, yielding 49–75%) and various functional groups such as benzyls (**3e**, 54% yield), alkenes (**3f**, 58% yield), alkynes (**3g**, 52% yield), and halogens (**3h**, 47% yield) was confirmed. Notably, all these products were isolated with low to moderate *E*/*Z* ratios (up to 3.9:1), except for bulky allenes **1d** and **1t**, having a *t*Bu-substituted olefin, that delivered the respective products as the *E* isomer exclusively. Additionally, triple substitution of the formed double bond (**3 m**) and different ester groups (**3n**, **3o** and **3t**) were also tolerated, rendering the respective products in good yields (47–72%).

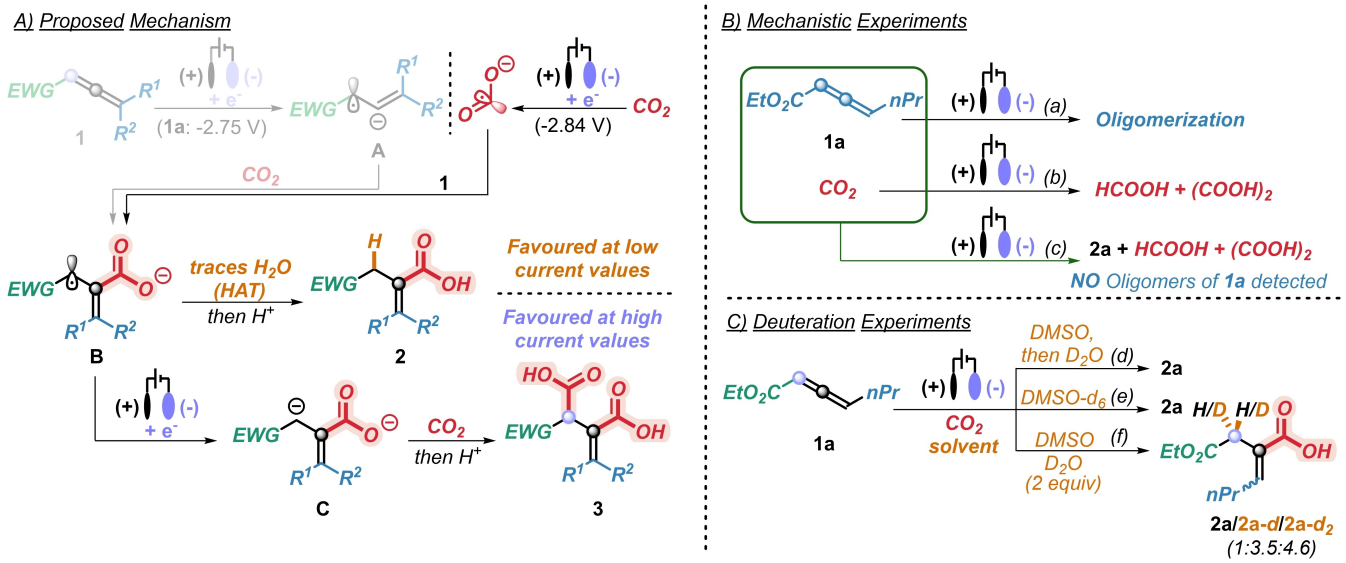
To demonstrate the synthetic utility of the newly described class of itaconic acid derivatives **2** we subjected the model product **2a** to selected relevant transformations (Scheme 4). Esterification of the carboxylic acid allowed diastereomeric enrichment of the obtained product **4a** by chromatographic purification (65% yield, *E*/*Z* = 10:1). The reactivity of the olefinic system of **4a** was then tested by successfully realizing an epoxidation reaction with *m*-CPBA (**5a**, 72% yield, *dr* = 10:1) and a Pd/C catalyzed hydrogenation towards substituted succinate **6a** (98% yield).




**Scheme 4.** Synthetic elaborations of mono-acid **2a**. a) DIC (1.5 equiv), EtOH (5.0 equiv), DMAP (30 mol%), DCM, 0 °C to rt, 18 h. b) *m*-CPBA (2 equiv), $CHCl_3$, 65 °C, 18 h. c) $H_2$ (balloon), Pd/C (5 mol%), MeOH, rt, 2 h. DIC = *N*,*N*′-diisopropylcarbodiimide; DMAP = 4-dimethylaminopyridine; *m*-CPBA = *meta*-chloroperbenzoic acid.

We then moved to propose a mechanistic rationale for the observed reaction outcomes and the current-dependent chemodivergency. First, a cyclovoltammetric analysis revealed that cathodic reduction of allenoate **1a** to intermediate **A** (−2.75 V *vs* Fc/Fc$^+$) and the one of $CO_2$ to the respective radical anion ($CO_2^{\bullet-}$, −2.84 V *vs* Fc/Fc$^+$) occur concomitantly (see Supplementary Information for details).[17] Thus, both carboxylation at the C(sp$^2$) site of intermediate **A** and nucleophilic addition of $CO_2^{\bullet-}$ at the electrophilic central C(sp) carbon of **1a** are deemed likely (Scheme 5A). We thus investigated the reactivity profile of $CO_2$ and **1a** under electrolytic conditions, in order to discern between the two competing pathways. Subjection of **1a** to the standard conditions (Table 1, entry 6) in the absence of $CO_2$, led to the formation of a complex mixture of oligomers (dimers and trimers detected by GC-MS analysis, Scheme 5B, reaction a). Parallelly, by subjecting $CO_2$ alone to the same conditions, the formation of oxalic and formic acid was detected by $^{13}C$ NMR (reaction b). These data are in accordance with the CV analyses, suggesting that electroreduction of $CO_2$ and **1a** can occur under similar conditions. However, as in the crude reaction mixture comprising both $CO_2$ and **1a**, formic and oxalic acid were detected ($^{13}C$ NMR) along with no traces of the oligomers of **1a** (reaction c), we suggest that, under the working conditions, reduction of $CO_2$ occurs preferentially and its capture by electrophilic **1a** leads to the formation of radical carboxylate intermediate **B**.

This last species is then responsible for the observed chemodivergency, depending on the reaction conditions. We indeed propose that, upon successive reduction of **B** to anion **C** and subsequent carboxylation, di-acid **3** would be formed. This process is thus supposed to be facilitated at higher current values (and thus, higher voltages, selectivity towards **3** at 60 mA). Alternatively, the formation of mono-acid **2** is observed when the radical in **B** is quenched before being reduced, for example, by Hydrogen-Atom-Transfer (HAT).[18] This process is




**Scheme 5.** A) Mechanistic proposal. B) Experimental evidence for the preferential reduction of $CO_2$ in the working conditions. C) Deuteration experiments. Reactions (a) to (f) were run under the conditions reported in Table 1, entry 6. See Supporting Information for detailed procedures.

then supposed to be favored under milder electrochemical conditions (selectivity towards **2** at 2 or 4 mA). In order to verify this last hypothesis, we performed dedicated deuteration experiments (Scheme 5C). First of all, observing no deuterium incorporation by $D_2O$ quenching of the reaction mixture after electrolysis (reaction d), we excluded the possibility of the formation and survival of dianion **C** in the reaction mixture until the final acidic work-up. Then, we suggest that traces of water in the reaction medium are indeed responsible for the HAT step generating **2** (carboxylate) from **B**, as the reaction run in DMSO-$d_6$ showed no deuteration of **2** (reaction e) while the addition of 2 equivalents of $D_2O$ in the reaction mixture led to 90% deuterium incorporation in **2a** (reaction f).[19]

## Conclusions

In conclusion, an unprecedented synthetic strategy to valorize $CO_2$ as C1 synthon for the preparation of itaconic acid derivatives in a chemodivergent manner, by means of readily available allenoates as convenient chemical platform has been developed. The process led to the production of mono- (18 examples) and di-carboxylation products (12 examples) with high yields (up to 87%). This synthetic protocol offers new opportunities for targeting densely functionalized carboxylic acids under catalyst- and additive-free conditions. Overall, the synthesis of non-natural itaconic acid derivatives through electrochemical carboxylation represents a significant advancement in sustainable organic synthesis, offering access to valuable chemical space for applications in chemistry and materials science.

## Experimental Section

Representative procedure for the electrochemical mono- and di-carboxylation of allenes **1**. The ElectraSyn vial (5 mL), equipped with a stir bar, was charged with allene **1** (0.15 mmol), and $TEABF_4$ (0.30 mmol, 65.1 mg). The ElectraSyn vial cap, equipped with anode (Zn) and cathode (Ni), was inserted into the mixture, and closed with a rubber septum. The vessel was evacuated and backfilled with $CO_2$ (balloon) three times, then dry DMSO (3.0 mL) for the mono-carboxylation protocol or dry ACN (3.0 mL) for the di-carboxylation protocol, was added, and the mixture was stirred until complete dissolution of the solids occurred. Then, the solution was bubbled with $CO_2$ (balloon) under stirring for 1 min. The reaction mixture was electrolyzed (under $CO_2$, balloon) at room temperature, at a constant current of 4.0 mA, until a total charge of 0.75 mF (5.0 F/mol$_1$) was reached in the case of the mono-carboxylation protocol, or at 0 °C, at a constant current of 60 mA, until a total charge of 2.25 mF (15 F/mol$_1$) was reached in the case of the di-carboxylation protocol. The ElectraSyn vial cap was removed, and the electrodes and vial were rinsed with EtOAc (10 mL) and $HCl_{(aq)}$ (2M, 10 mL), which were combined with the crude mixture in a separatory funnel. Then, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with $HCl_{(aq)}$ (0.1 M, 3×10 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was finally purified by FC to afford pure products **2** or **3**.

Characterization data of model mono-carboxylation product **2a**. White solid. FC eluent: *n*-hexane/EtOAc: 7:3 + 1% HCOOH. Yield = 87%, (0.131 mmol, 26.2 mg); *E*/*Z* = 1.7:1; **2a**/**3a** = 8.8:1 in the crude mixture, > 20:1 after chromatography. **$^1$H NMR** (600 MHz, $CDCl_3$) δ = 7.04 (t, *J* = 7.6 Hz, 1H *E*-**2a**), 6.13 (t, *J* = 7.4 Hz, 1H *Z*-**2a**), 4.08 (q, *J* = 7.2 Hz, 2H *Z*-**2a**) partially overlapped with 4.07 (q, *J* = 7.1 Hz, 2H *E*-**2a**), 3.27 (s, 2H *E*-**2a**), 3.19 (s, 2H *Z*-**2a**), 2.52 (q, *J* = 7.4 Hz, 2H *Z*-**2a**), 2.13 (q, *J* = 7.5 Hz, 2H *E*-**2a**), 1.50–1.37 (m, 2H *E*-**2a** + 2H *Z*-**2a**), 1.18 (t, *J* = 7.1 Hz, 3H *E*-**2a** + 3H *Z*-**2a**), 0.88 (t, *J* = 7.1 Hz, 3H *E*-**2a**) partially overlapped with 0.87 (t, *J* = 7.2 Hz, 3H *Z*-**2a**); **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ = 172.5 (*E*-**2a**), 172.3 (*Z*-**2a**), 171.5 (*Z*-**2a**), 170.7 (*E*-**2a**), 150.6 (*Z*-**2a**), 148.4 (*E*-**2a**), 125.2 (*E*-**2a**), 124.5 (*Z*-**2a**), 60.9 (*E*-**2a**), 60.9 (*Z*-**2a**), 40.0 (*Z*-**2a**), 32.1 (*E*-**2a**), 31.8 (*Z*-**2a**), 31.1 (*E*-**2a**), 22.4 (*Z*-**2a**), 21.6 (*E*-**2a**), 14.1 (*E*-**2a**), 14.1 (*Z*-**2a**), 13.8 (*E*-**2a**), 13.8 (*Z*-**2a**); **HRMS (ESI)** m/z: $[M\text{-}H]^-$ calcd. for $C_{10}H_{15}O_4$ 199.0976; found 199.0985.

Characterization data of model di-carboxylation product **3a**. Colourless sticky oil. FC eluent: *n*-hexane/EtOAc: 7:3 + 1% HCOOH. Yield = 75%, (0.093 mmol, 22.7 mg); *E*/*Z* = 2.0:1; **3a**/**2a** > 20:1 in the crude mixture, > 20:1 after chromatography. **$^1$H NMR** (600 MHz, $CDCl_3$) δ = 10.57 (bs, 2H *E*-**3a** + 2H *Z*-**3a**), 7.16 (t, *J* = 7.7 Hz, 1H *E*-**3a**), 6.32 (t, *J* = 7.4 Hz, 1H *Z*-**3a**), 4.41 (s, 1H *E*-**3a**), 4.26 (s, 1H *Z*-**3a**), 4.23–4.14 (m, 2H *E*-**3a** + 2H *Z*-**3a**), 2.58 (qd, *J* = 7.4, 1.8 Hz, 2H *Z*-**3a**), 2.19 (ddt, *J* = 16.7, 15.1, 7.5 Hz, 2H *E*-**3a**), 1.54–1.41 (m, 2H *E*-**3a** + 2H *Z*-**3a**), 1.20 (t, *J* = 7.1 Hz, 3H *E*-**3a**) partially overlapped with 1.19 (t, *J* = 7.0 Hz, 3H *Z*-**3a**), 0.89 (t, *J* = 7.4 Hz, 3H *E*-**3a**) partially overlapped with 0.88 (t, *J* = 7.7 Hz, 3H *Z*-**3a**); **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ = 172.1 (*Z*-**3a**), 171.3 (*E*-**3a**), 171.3 (*Z*-**3a**), 170.3 (*E*-**3a**), 169.9 (*E*-**3a**), 169.1 (*Z*-**3a**), 153.2 (*Z*-**3a**), 150.8 (*E*-**3a**), 125.3 (*E*-**3a**), 124.2 (*Z*-**3a**), 62.8 (*E*-**3a**), 62.5 (*Z*-**3a**), 55.5 (*Z*-**3a**), 48.4 (*E*-**3a**), 31.9 (*Z*-**3a**), 31.4 (*E*-**3a**), 22.2 (*Z*-**3a**), 21.5 (*E*-**3a**), 13.9 (*Z*-**3a**), 13.8 (*E*-**3a**), 13.8 (*E*-**3a**), 13.7 (*Z*-**3a**); **HRMS (ESI)** m/z: $[M\text{-}H]^-$ calcd. for $C_{11}H_{15}O_6$ 243.0874; found 243.0881.

## Supporting Information Summary

Additional screening data, synthetic procedures and analytical data are provided in the Supporting Information. Additional references cited within the Supporting Information.[20]

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## *Conflict of Interest*

The authors declare no conflict of interest.

**Keywords:** Electrosynthesis · Carboxylation · $CO_2$ · Allenoates · Itaconic acid

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