Selective Electrosynthetic Hydrocarboxylation of α,β-Unsaturated Olefins with Carbon Dioxide

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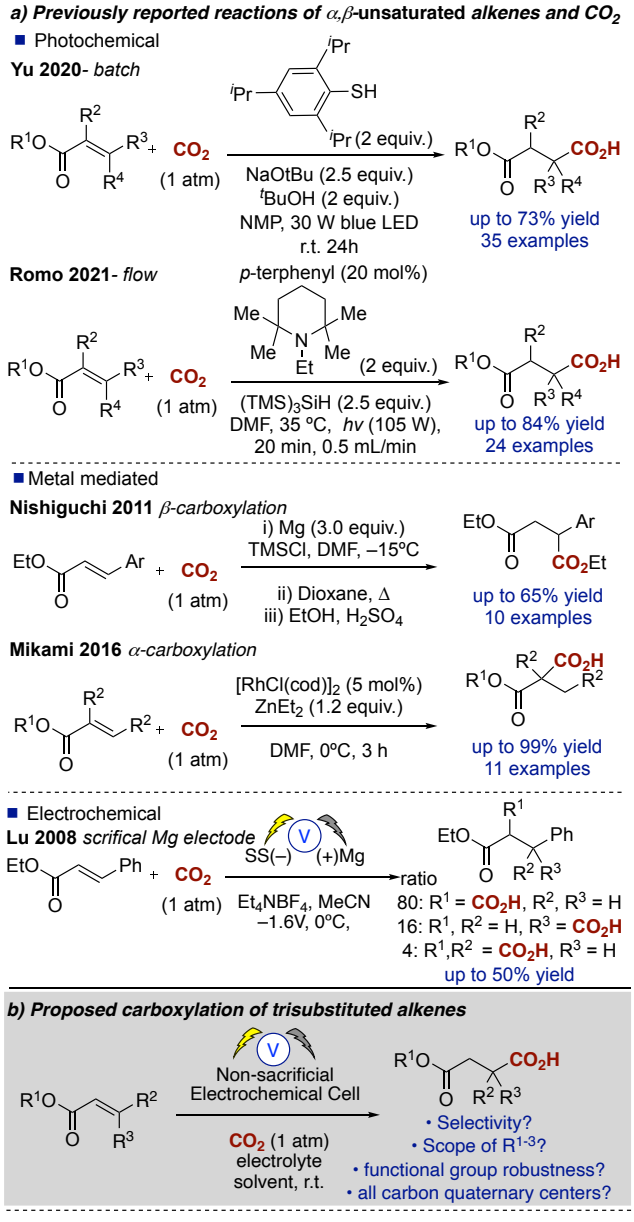
Abstract: The carboxylation of low value commodity chemicals to provide higher value carboxylic acids is of significant interest. Recently alternative routes to the traditional hydroformylation processes that used potentially toxic carbon monoxide and a transition metal catalyst have appeared. A significant challenge has been the selectivity observed for olefin carboxylation. Photochemical methods have shown a viable route towards the hydrocarboxylation of α,β-unsaturated alkenes but rely on the use of an excess sulfur or amine reagent. Herein we report our investigations of an electrochemical approach that is able to hydrocarboxylate α,β-unsaturated alkenes with excellent regioselectivity and the ability to carboxylate hindered substrates to afford α-quaternary centre carboxylic acids. The reported process requires no chromatography and the products are purified by simple crystallisation from the reaction mixture after work up.

Introduction

Direct selective carboxylation of α,β-unsaturated esters with carbon dioxide remains a challenging task despite a number of successful attempts via either metal mediated, electrochemical or photochemical means (Scheme 1a).[1-3] Recently Yu introduced a photochemical approach to a range of α,β-unsaturated esters providing good yields of the corresponding β-hydrocarboxylated products.[3a] Romo, utilizing the conditions originally reported by Jamison for the hydrocarboxylation of styrenes,[4] has shown that the photochemical hydrocarboxylation of α,β-unsaturated esters can also be carried out under flow conditions and some of the products containing all-carbon quaternary centres can be accessed in good to excellent yield. Additionally, they showed that these products are versatile building blocks for lactonization.[3b] A magnesium mediated (3 equivalents) approach has provided β-carboxylated products from aryl cinnamate esters through a sequence of decarboxylation and mono-decarboxylation and Makami has disclosed a rhodium catalysed approach to α-carboxylation requiring the use of diethyl zinc (1.2 equivalents) to successfully provide the desired products.[1a,b]

At present there are no satisfactory reports of utilizing electrosynthesis in the carboxylation of non-aryl α,β-unsaturated esters and those reported with aryl substituents such as that by



Scheme 1. Current/proposed approach to α,β-unsaturated ester carboxylation

Lu with *trans*-cinnamate esters provide a mixture of mono- and dicarboxylated products and rely on a sacrificial magnesium anode.[2a]

The formation of all-carbon quaternary centres bearing a potentially labile carboxylic acid group represents a significant challenge in organic synthesis.[5] Interest in this area stems from the unique structural features of quaternary centers for applications in synthesis, which is further enabled by the resultant synthetic flexibility of the carboxylate group. Although many excellent methods have been reported that allow for the carboxylation of olefins these are limited to styrenes with little or no substitution about the double bond.[6] Recently, research efforts in this laboratory have explored the utility of electrosynthesis for carbon dioxide incorporation including aryl alkenes and dienes,[7a,b] with a limited range of trisubstituted alkenes affording all-carbon quaternary centers.[7a] Pivotal to the success of this work was the development of a cell that comprised a non-sacrificial electrode.

In order to directly form all-carbon quaternary centers bearing a carboxylic acid group one would typically rely on hydroformulation followed by oxidation to access these types of compounds, thus requiring precious metal catalysts (typically Rh) at high pressures of CO (>20 atm) and at high temperatures.[8] Often these conditions result in migration of the double bond thus giving rise to carbonylation at a different site to the original location of the double bond.[9] To address this challenge, we envisioned applying our recently reported hydrocarboxylation approach to provide direct access to the desired functionalized quaternary center,[7a] avoiding migration of the double bond and thus expanding the methods by which to access these highly desirable building blocks.

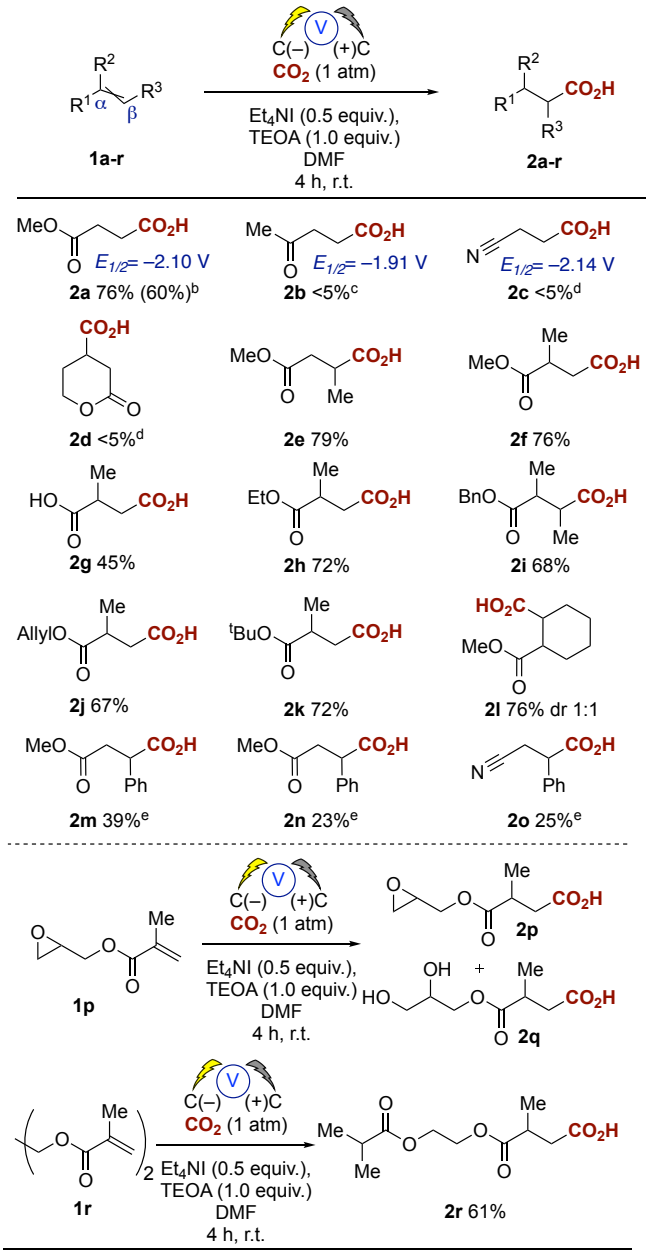
With our operationally simpler methodology that was previously applied to aryl alkenes we wished to understand the scope and limitations of this electrochemical approach and crucially determine the robustness of our methodology so that it could be future benchmarked. To this end we herein report the first highly selective electrochemical hydrocarboxylation of α,β-unsaturated esters, that requires no column chromatography, and is concentrated on the development of all-carbon quaternary centres.

Results and Discussion

Our initial aim was to gain an understanding of the scope of the substituents attached at the alkene. We therefore utilized our previously reported conditions for aryl alkene hydrocarboxylation and screened a range of α,β-unsaturated alkenes (**1a-r**, Table 1).[7a] Replacement of triethanolamine (TEOA) with water as a proton source did not affect regioselectivity, however resulted in slightly lower yields of **1a** (60% vs 76%). Although the use of H_2O is attractive, in this instance we chose to utilize the higher yielding TEOA conditions, one possible reason for the higher yield in the case of TEOA is its ability to solubilize CO_2.[10] Under our standardized conditions we noticed that a number of alkenes rapidly underwent reduction to the corresponding alkane (**1b**,**m-o**) or did not react (**1c,d**). We wondered whether this could be due to the reduction potential of the alkene, however, at this point there does not seem to be a logical correlation between reduction potential and reduction/carboxylation e.g. **2a** $E_{1/2}$= –2.10 V & **2c** $E_{1/2}$= –2.14 V vs SCE in MeCN.[11] A reduction in the voltage applied to the system did not change the outcome of the reaction when dropped to 5V, below this level we saw little to no reaction of the alkenes. It is noteworthy that α,β-unsaturated esters such as **1a** worked particularly well with excellent regioselectivity for carboxylation at the β-position and required no column chromatography for purification, they could simply be crystallized after isolation from the reaction mixture.

We then screened a range of substitution patterns and substituents on the ester (**1f-k**) to evaluate the scope of the approach (Table 1). Acids were isolated by crystallisation and a range of common esters were tolerated under the reaction conditions (**1f-k**). In addition, the reaction also preceded when

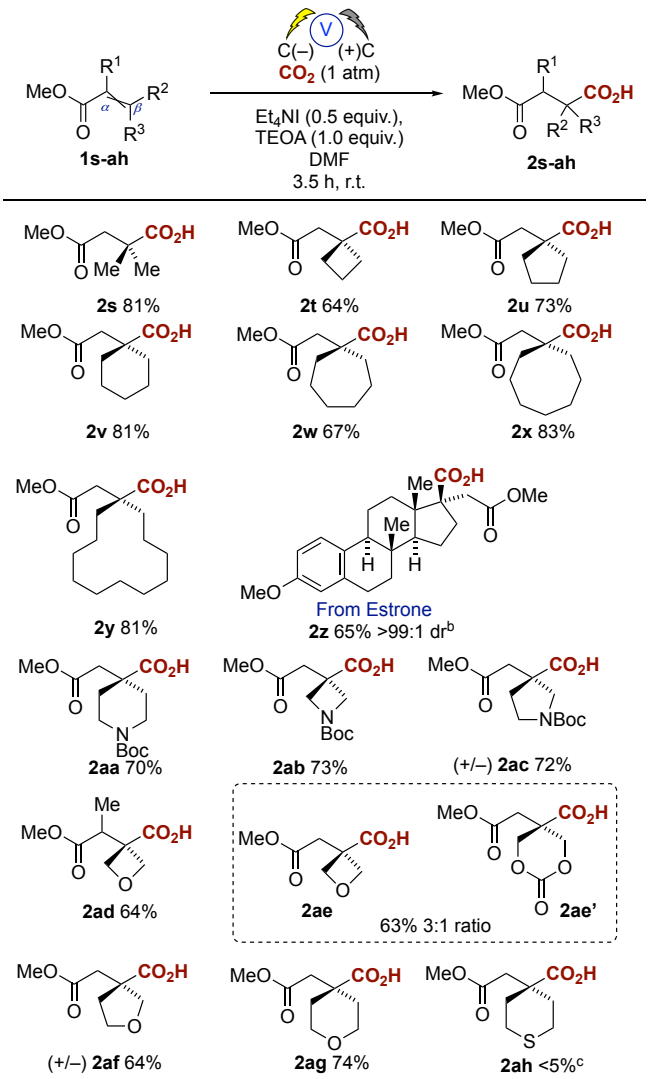
Table 1: Screening of α,β-unsaturated alkenes



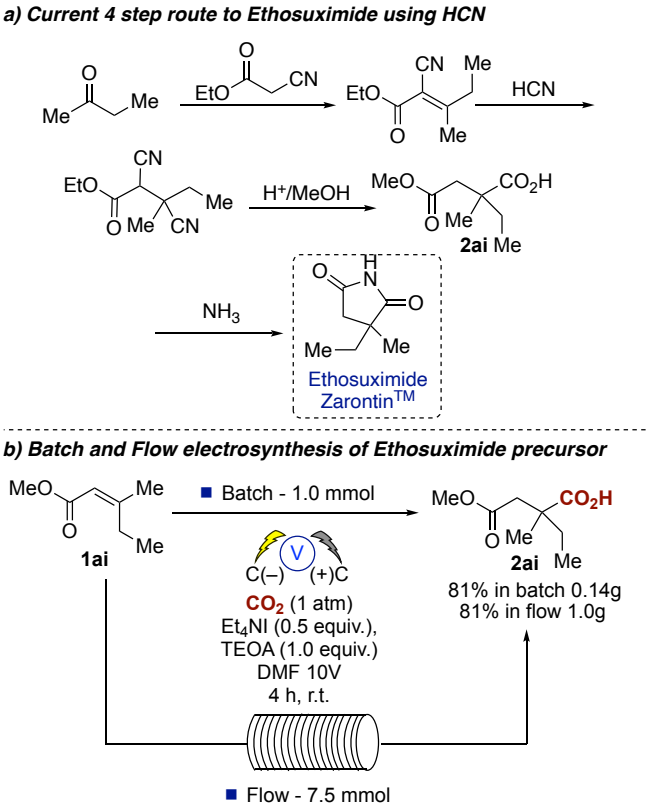
[a]General conditions: CO_2 (1 atm), carbon anode and cathod, Et_4NI (0.5 equiv.), TEOA (1.0 equiv.), DMF, single compartment cell, 10V (60-100 mA), 4 h rt. [b]Yield in parenthesis refers to the corresponding reaction using H_2O instead of TEOA as proton source. [c]Major product identified by GC-MS was butan-2-one. [d]Major product identified by GC-MS was unreacted starting material. [e]competing product of these reactions was the reduced compound by GC-MS analysis.

using the acrylic acid **1g** as the starting material, the yield was somewhat lower than the corresponding esters (e.g. **2f**) but we believe this due to the increased water solubility of the diacid product. Substitution at either or both the α- or β-positions also provided good yields of the corresponding products (**2e,f** or **2i**) and at no point did we observe carboxylation at the α-position or dicarboxylation at both the α,β-positions (monitored by GC-MS and ^{1}H NMR spectroscopy). Carboxylation of the conjugated aromatic alkenes **1m,n** and the nitrile containing **1o** resulted in exclusive carboxylation at the β-carbon albeit in somewhat lower yield due to competing reduction of the double bond to the alkane (observed by GC-MS analysis). The glycidylmethacrylate substrate **1p** did afford the desired carboxylic acid **2p**, however, we were unable to prevent some degree of ring opening of the epoxide to the diol **2q**. Interestingly the symmetrical diene **1r** resulted in mono-carboxylation with concomitant reduction of the second double bond as the major product, the expected symmetrical carboxylated product was not observed.

Table 2: Screening of α,β-unsaturated esters[a]



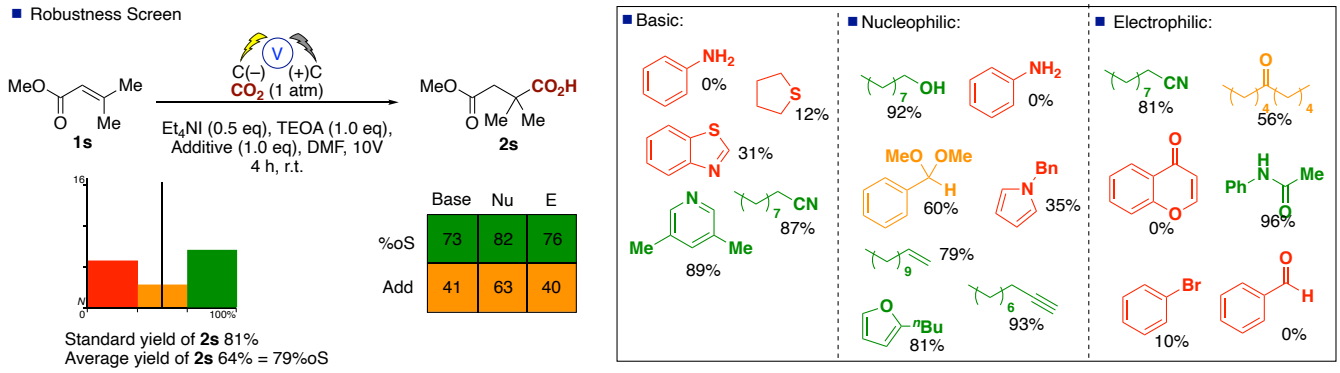
[a]General conditions: CO_2 (1 atm), carbon anode and cathode, Et_4NI (0.5 equiv.), TEOA (1.0 equiv.), DMF, single compartment cell, 10V (60-100 mA), 4 h rt. [b] Isolated analytically pure by column chromatography. [c] Carboxylation was observed by GC-MS however we were not successful in isolating the product.



Scheme 2. Application of the hydrocarboxylation process to the flow synthesis of anti-epilepsy and absence seizure drug Ethosuximide precursor **2ai**

Considering the synthetic usefulness of this carboxylation approach we were interested as to whether this chemistry could be applied to *tri-* or *tetra-* substituted alkenes and thus upon carboxylation would yield an all-carbon quaternary centre at the β-position. Initial reaction with the β,β-dimethyl substrate **1s** gave an excellent yield of the mono-carboxylated product **2s** (81%) as a single regioisomer. Pleasingly we were able to apply these conditions to a range of unfunctionalized β,β-disubstituted cyclic esters (**1t-y**) and to the amino and oxygen containing heterocyclic systems with varying ring sizes (**1aa-ag**). In each case good yields of the corresponding hydrocarboxylated all-carbon quaternary centre products were observed, again requiring no chromatography during isolation. The sulfur containing substrate **1ah** was however, problematic we could observe carboxylation by GC-MS analysis but were unable to isolate the final product. This was also true when we attempted carboxylation of the corresponding sulfone substrate. A highlight of the approach is exemplified in the highly diastereoselective hydrocarboxylation of the alkene **1z** derived from estrone. The sterically crowded alkene afforded the all-carbon quaternary centre on the 5-membered ring of **2z** in good yield and >99:1 d.r.

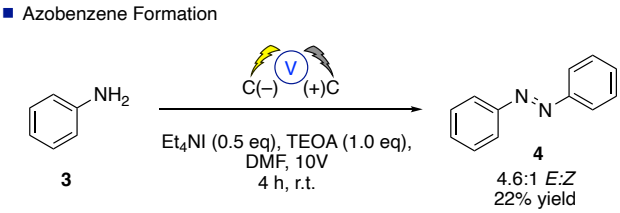
We subsequently utilized our approach to successfully install a β-all-carbon quaternary centre to prepare compound **2ai** in 81% yield (Scheme 2). **2ai** Is in fact a precursor to the anti-epilepsy and absence seizure drug ethosuximide (Zarontin™) which is manufactured in 4 steps (Scheme 2a).[12] Our approach removes the requirement for the use of toxic hydrogen cyanide through the direct carboxylation of the α,β-unstaurated ester **1ai** (Scheme 2b).



Scheme 3. Application of Glorius' robustness screen (percentage yields shown next to the additives refer to remaining additive quantified by GC-MS analysis at the end of the reaction)

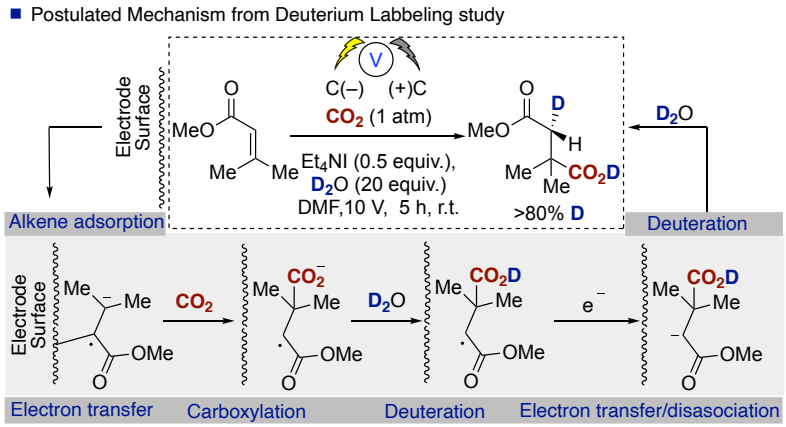
We then explored the possibility of converting our process from a commercial batch reactor to a commercial flow reactor and our unoptimized conditions utilizing carbon-carbon sheet electrodes, Et_4NI (0.5 equiv.), TEOA (1.0 equiv.), DMF resulted in 81% yield of the desired product after 4 hours at 7.5 mmol scale of **1ai**, delivering the ethosuximide precursor **2ai** on gram scale. Thus, illustrating the simplicity of our approach and the requirement for no bespoke equipment.

Importantly we wanted to understand the scope and limitations of this electrochemical approach to alkene functionalization and enable future users to be able to benchmark against our process. Glorius has developed a useful approach to examine functional group tolerance through utilisation of a protocol to rapidly determine reaction condition compatibility.[13] A range of photochemical processes have been examined, identifying photobleaching as an issue, but to the best of our knowledge this approach has not been applied to examine the functional group robustness of electosynthetic reactions. Utilising Glorius' truncated robustness screen[15c] chemistry we screened substrate **1s** under our standard batch reactor conditions and observed an overall good level of tolerance against a range of basic, nucleophilic and electrophilic additives (Scheme 3). The standard yield of the reaction as highlighted in Table 2 was 81%, the average yield (by GC-MS) from the 16 additive reactions studied was 64% which equates to a functional group robustness of 79%os (percent of the standard yield), which was fairly consistent across the basic (73%), nucleophilic (82%) and electrophilic (76%) additives. The percentage of additives unreacted was somewhat lower, showing that whilst the desired reaction **1s** to **2s** was only marginally affected by the additives, the additives themselves could undergo other reactions under the electrochemical conditions. For example, aniline **3** was completely consumed under the reaction conditions although **2s** was produced in 62%. Further examination with a blank reaction in the absence of **1s** but with aniline present resulted in isolation of azobenzene **4** in 22% unoptimised yield (Scheme 4), possibly opening up a new route to these important molecules and a complimentary process to the photochemical route recently reported by Vannucci.



Scheme 4. Blank reaction containing only the aniline **3** additive from the robustness screen

We recently investigated the mechanism of hydrocarboxylation of both styrenes and dienes.[9a,b] The reduction potential of CO_2 and styrenes have been reported to be very similar, $^{\bullet}CO_2^-$ $E_{1/2}$= –2.21 V, styrene $E_{1/2}$= –2.58 V vs SCE in DMF,[16] and that of the acrylates studied in this work are also in a similar range e.g. methylacrylate **1a** $E_{1/2}$= –2.10 V and methylcrotonate **1e** $E_{1/2}$= –2.41 V vs SCE in MeCN).[14] In our previous studies we noted that in the cathodic regime and in the absence of CO_2, the onset of radical anion formation lead to a steep and irreversible reduction due to cathodic polymerisation, but when the solution was saturated with CO_2,[9a] the onset of the reduction process did not change and we did not observe CO_2 reduction. The ability to be able to carry out successful reduction of the acrylates in this study in the absence of carbon dioxide points to activation by addition



Scheme 5. Proposed mechanism at the cathode of the electrochemical cell after deuterium labelling study

of an initial electron to the surface bound alkene and subsequent carbon dioxide capture by the anion (Scheme 5§§). In addition, the inability to isolate oxalic acid (the CO_2 dimerisation product is known to rapidly form when $^{\bullet}CO_2$ is present)[15] also indicates this is the likely pathway. We attempted to isolate adducts of TEMPO and AMBO radical traps but were unsuccessful perhaps due to the rapid reduction of these species under the reaction conditions (TEMPO-OH and AMBO-OH being readily visible by GC-MS analysis). Deuteration studies provide [D]**2s** with high levels of deuterium incorporation when running the reaction with D_2O instead of TEOA leading us to propose the mechanism highlighted in Scheme 4. The acrylate **1s** is adsorbed to the surface of the cathode and electron transfer proceeds to form the adsorbed radical anion of **1s**, subsequent carboxylation and further electron transfer results in disassociation from the electrode and deuteration from D_2O to afford the final mono-carboxylated product.

Conclusion

A highly regioselective hydrocarboxylation process that enables the direct formation of carboxylic acids from α,β-unsaturated esters, requiring no chromatography has been developed. The electrosynthetic system is capable of β-carboxylation to afford all carbon α-quaternary centred carboxylic acids in good yield. The process has been simply converted into flow to deliver gram scale synthesis of a precursor to the anti-epilepsy and absence seizure drug ethosuximide and crucially we have scrutinized our system utilizing Glorius' reaction robustness scene to enable future benchmarking and improvement of modified electorchemical, photochemical or transition metal systems for alkene hydrocarboxylation. In summary the current process goes beyond the electrochemical state-of-the-art enabling selective mono-carboxylation of α,β-unsaturated esters to afford all carbon quaternary centers.

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Keywords: Electrosynthesis • Acrylate • Carbon Dioxide • Reduction • Electron Transfer

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