



Biphasic organic synthesis with continuous electro-flow

Pushpak Mizar^a, Sagar Arepally^b and Thomas Wirth^b

Abstract

Organic electrochemistry has recently witnessed a renaissance in research as a green and cost-efficient method for activating small molecules. Although some of the critical challenges of batch electrosynthesis remain, flow electrosynthesis can overcome several issues arising from batch electroorganic systems, such as mass transfer, ohmic drop, and selectivity. The combination of flow technology with electrochemistry affords practitioners a very precise control over reaction conditions, thereby enhancing the reproducibility of electrochemical processes. The use of gases in chemical reactions for the synthesis of value-added fine chemicals is of great significance. This review summarizes recent advances in flow electrochemistry for biphasic (gas–liquid) organic synthesis. We summarise recent examples of selective hydrocarbon oxidations using oxygen gas in an electrochemical flow reactor.

Addresses

^a Universitetet i Bergen, Kjemisk institutt, Postboks 7803, 5020 Bergen, Norway

^b School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, UK

Corresponding author: Corresponding author. (wirth@cf.ac.uk)

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Keywords

Continuous electro-flow, Biphasic synthesis, Organic synthesis, Oxidation, Flow-reactors.

Introduction

The Chemistry 4.0 & Industry 4.0 initiative seeks to enhance the energy efficiency of the chemical industry through the incorporation of advanced technologies such as artificial intelligence, digitization, and process intensification [1,2]. One idea of exploration involves diversifying energy sources, specifically by utilising electricity to optimise chemical processes. This approach, referred to as the “electrification of the

chemical industry,” holds promise for diminishing reliance on fossil fuels, reducing overall energy consumption, and elevating the efficiency and selectivity of reactions [3].

The recent resurgence of electrochemical synthesis as a secure and sustainable strategy for crafting organic molecules has generated considerable interest in scaling up this technology [4–7]. The combination of flow technology with electrochemistry affords practitioners precise control over reaction conditions, thereby enhancing the reproducibility of electrochemical processes [8]. In addition, electrochemical flow cells enable the safe generation and consumption of reactive intermediates and hazardous reagents, overcoming the limitations of traditional batch methods. Microreactors with typically very high surface-to-volume ratios provide precise control over reaction conditions, simplify scale-up and reduce safety concerns. Flow conditions in electrolysis reduce the risk of overoxidation compared to traditional batch cells [9].

Despite significant contributions in flow electroorganic synthesis during the past decade [10–15], the exploration of flow electrochemistry in biphasic (gas–liquid) organic synthesis is not much developed. Gas–liquid electrochemical organic reactions are a mainstay in a variety of important organic synthetic transformations, such as hydrogenations [16–19], oxidations [20–24] and carboxylations [25,26]. In batch, such reactions are typically performed in mechanically stirred vessels, either by sparging the gas into the liquid phase through bubbling to increase the interfacial area or through excessive mixing within the liquid phase to enhance the interaction between the two phases. While gas bubbling in batch reactors offers its own merits for conducting gas–liquid reactions (ease of access and assembly), it provides an inherent gas–liquid mass transfer limitation due to low specific interfacial areas [27]. In addition to increased safety concerns, such mass transfer limitations result in prolonged experimental times and mass transfer-limited reaction kinetics, thereby hindering further developments of important gas–liquid electrochemical reactions for organic synthesis.

Different gas–liquid flow microreactor designs have been reported which have been developed to facilitate gas–liquid reactions in organic synthetic chemistry [28–32]. Although the advantages of flow microreactor technology appear to be numerous, the renewed interest in organic electrochemistry has brought some old and

tedious technological problems to the surface. Electrochemistry can be considered a heterogeneous process due to the use of solid electrodes that can be quite challenging to those unfamiliar with mass transfer effects. This means that both mixing effects and inter-electrode distances are important parameters in the development process. Furthermore, the need for specialised equipment and the knowledge gap of most researchers in this often perceived as a specialized field are additional barriers to adopting electro-flow biphasic (gas–liquid) organic synthesis as viable alternative synthetic routes.

Continuous flow electrochemistry can be performed using various techniques and technical variations, and currently, portable electrochemical reactors are available at a reasonable cost [33]. The exchange of electrons occurring on the electrode's surface serves as the driving force for electrochemical reactions. Therefore, reagents and electron mediators must meet the electrode surfaces. Consequently, creating suitable systems relies on understanding mass transport phenomena and improving electron transfer rates. These factors become even more critical when developing bi-phasic flow systems as illustrated in Figure 1 [8].

Principles and advantages of multiphase continuous flow electrochemistry

From our perspective, the significance of multiphase continuous electro-flow chemistry in organic synthesis has been overlooked until now. Multiphase reactions are prevalent in synthetic chemistry, involving both gas–liquid and liquid–liquid transformations [32]. In the realm of electrochemistry, gas–liquid reactions, such as hydrogen evolution at the counter electrode, are frequently encountered but pose engineering challenges due to the intricate nature of these reactions. The evolution of gas can result in a significant increase

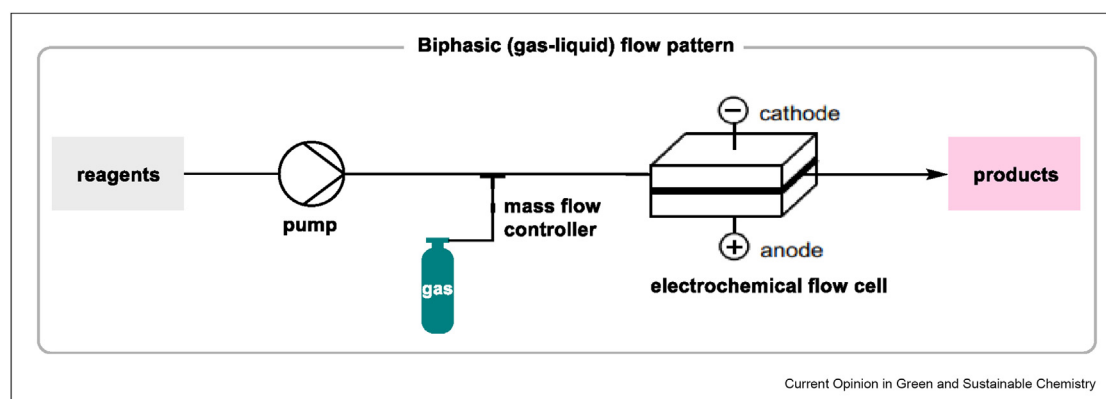
in ohmic resistance due to the formation of an insulating gas layer. However, the presence of gases can also enhance mass transport considerably.

Another critical aspect of multiphase electrochemistry arises when the reactant exists in a dispersed second phase. In this scenario, the reactant must either diffuse to the electrode or the continuous phase before undergoing the reaction. Rapid transport of the reactant to the second phase is essential for an efficient synthesis [32].

The utilization of microreactors (Figure 2) can address various challenges and technological hurdles encountered in biphasic electrochemical synthesis. Microreactors offer reduced distances between electrodes, increasing the ratio of electrode surface to reactor volume and concurrently minimizing ohmic resistance. This results in a significant enhancement of mass transfer on the electrode surfaces [34]. Additionally, improving the interfacial contact area proves advantageous for facilitating reactions that are typically impractical in conventional batch electrochemistry. Continuous flow setups offer better manageability, as their delivery can be controlled through dosing-controlled flow volumes, leveraging higher internal pressures to aid dissolution [35,36].

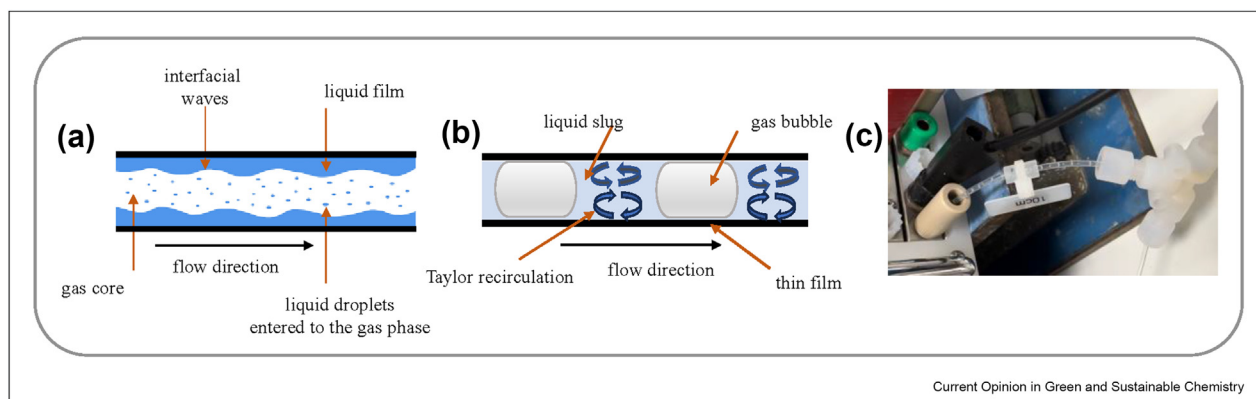
Microreactors exhibit various flow regimes based on the individual flow rates of the two phases. Two extremes are annular flow and segmented flow (also known as slug flow or Taylor flow). In annular flow, one of the two phases flows at a higher velocity in the centre of the capillary, while the other phase contacts the electrodes as a thin film. Although relatively uncommon in flow electrochemistry, intimate contact between the wetting phase and the electrode phase could provide advantages in specific situations [37].

Figure 1



Biphasic (gas–liquid) flow pattern for organic synthesis.

Figure 2



a. Annular flow in gas–liquid mixture, b. Taylor flow/segmented flow in gas–liquid mixture, c. Image of segmented flow.

In contrast, segmented flow is commonly observed in flow chemistry, characterized by alternating bubbles and liquid segments. Toroidal vortices form within these segments and bubbles, ensuring heightened mixing efficiency. Additionally, these fluid patterns play a crucial role in significantly improving mass transfer to the electrode surfaces [38]. Gas-liquid flow regimes, including segmented and annular flow patterns, offer significant advantages in organic synthesis. They significantly enhance the mass transfer efficiency to the electrode surfaces by providing a large interfacial area and turbulent mixing, facilitating reactions such as absorption, stripping, and chemical reactions. They promote improved heat transfer efficiency, making them suitable for condensation and evaporation processes. These flow regimes typically exhibit lower pressure drop, reducing energy consumption and operational costs. Their capacity for high flow rates suits industrial-scale production. They also enable the use of smaller and more compact equipment, leading to cost savings and space efficiency. Additionally, reaction times can substantially be shortened using this flow microreactor technology, due to the shorter diffusion distances to the electrodes and the large electrode surface-to-volume ratios. With greater operational stability and versatility, segmented and annular flow regimes are well-suited for biphasic organic electro-synthesis.

Examples of selective oxidations using oxygen gas in an electrochemical flow reactor

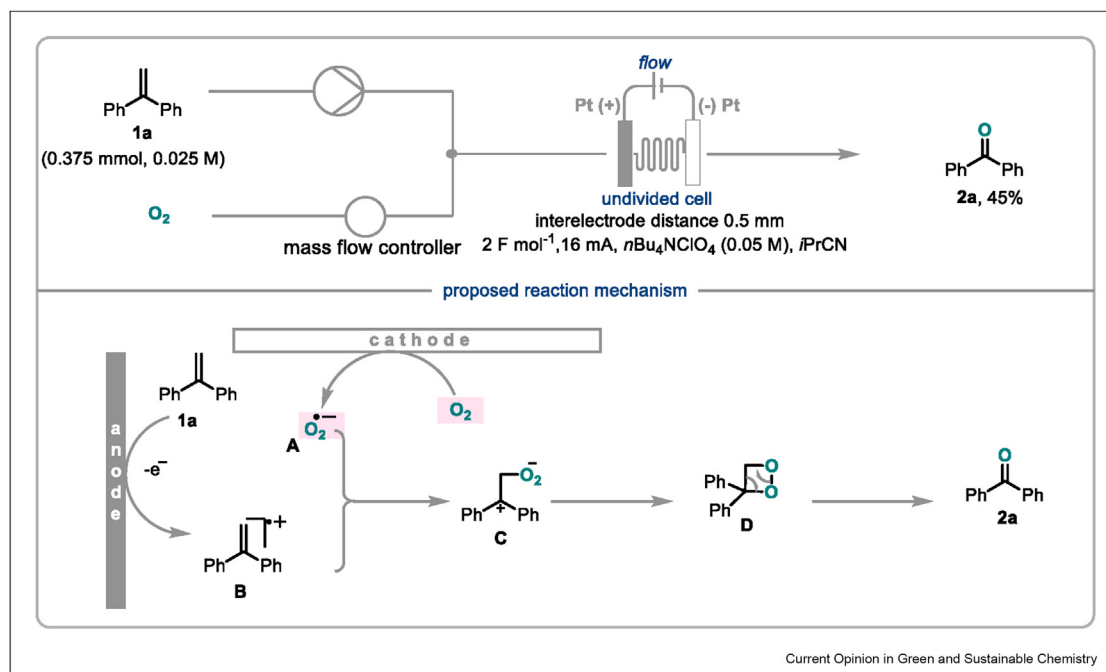
Over the past decade, there has been a concerted effort by flow chemists and electrochemists to advance continuous electrochemical flow systems tailored for organic synthesis applications [5,6,12,39]. Our research has been integral to the progress of electroorganic synthesis in continuous flow configurations [10,40,41]. Initially, we utilized our in-house electrochemical flow cells, encompassing both first and second-generation

models. Subsequently, we transitioned to employing the commercially available Vapourtec electrochemical Ion Reactor. This reactor presents numerous advantages, including the ability to adjust the reactor's temperature within the range of -10 to $+100$ °C, the capability to operate under pressures of up to 5 bar, significant flexibility in electrode spacing facilitated by various spacer options, the capacity to modify electrode area and reactor volumes, and the option to introduce a second flow stream into the reactor during electrolysis. Furthermore, it offers flexibility in the use of any electrode material, as electrodes can be easily changed or replaced.

As an example, we have shown a continuous gas–liquid biphasic electrochemical flow method to efficiently generate superoxide radical anions and oxidatively cleave di- and trisubstituted alkenes into their corresponding carbonyl compounds [42]. This is a mild and straightforward approach that uses molecular oxygen in combination with flow electrochemistry. The proposed reaction mechanism is shown in Scheme 1. Initially, oxygen undergoes a one-electron reduction to form the corresponding superoxide radical anion **A** ($\text{O}_2^{\bullet-}$) which is stable enough to capture the radical cation of the alkene **B** generated by the one-electron oxidation of the alkene. This could form the intermediate **C** followed by the generation of dioxetane intermediate **D**, which decomposes to the corresponding carbonyl compound **2a**.

Recently, Einaga, Yamamoto, and their collaborators have developed a selective oxidation of cumene utilizing an electrochemical flow reactor [43]. As the oxidation of the benzylic carbon–hydrogen bond in cumene into cumene hydroperoxide is an important step of the cumene process for industrial phenol production, achieving cumene oxidation under mild conditions holds paramount importance. In their prior investigation involving batch electrolysis of cumene, cumene hydroperoxide suffered

Scheme 1



Electrochemical synthesis of carbonyl compounds from alkene and oxygen.

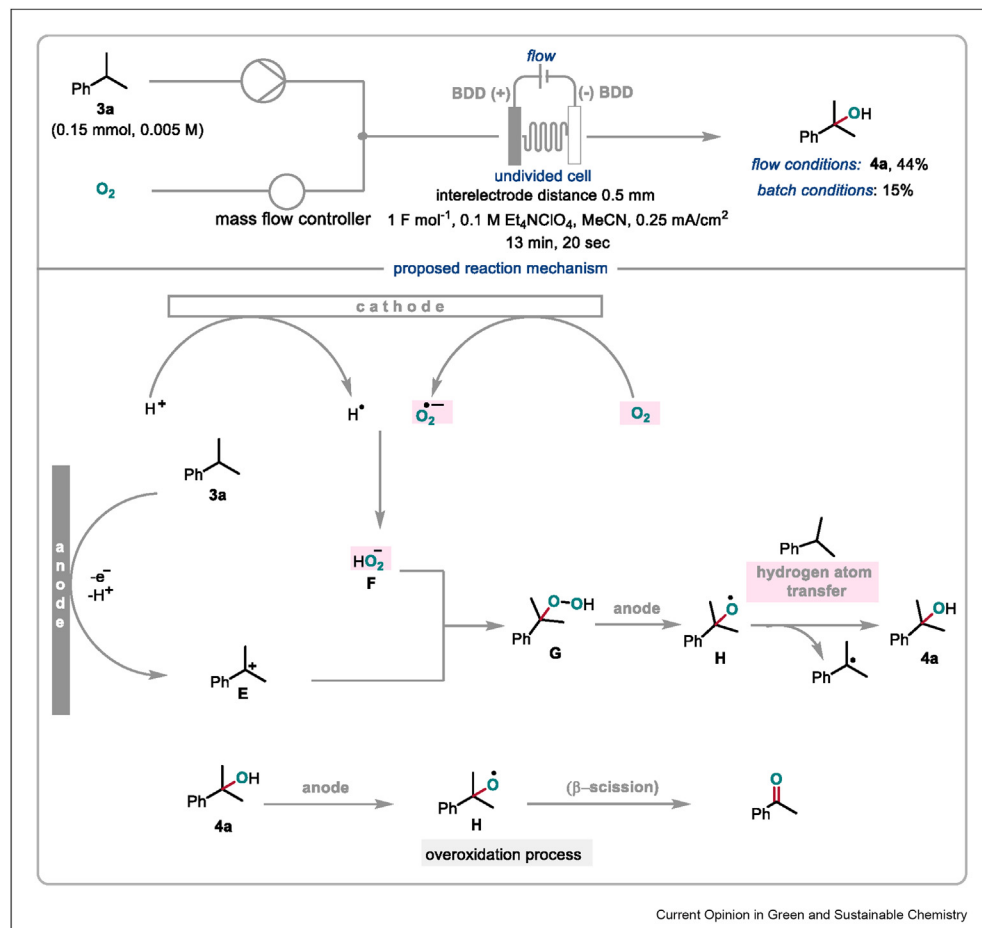
from over-oxidation to acetophenone [44]. The current study employed a biphasic electrochemical flow method to mitigate overoxidation, aiming for the selective conversion of cumene into cumene hydroperoxide. Consequently, cumyl alcohol was selectively obtained, indicating successful suppression of the over-oxidation of cumyl alcohol into acetophenone in flow electrolysis. The authors also observed the superiority of flow electrolysis over batch electrolysis for cumyl alcohol synthesis within a specific reaction time, as illustrated in Scheme 2. While batch and biphasic electrochemical flow methods of cumene resulted in acetophenone and cumyl alcohol as the primary products, respectively, this study convincingly illustrates the ability to switch the product selectivity of cumene oxidation by a simple change in electrolysis mode [43].

In addition to environmental and economic advantages, drawbacks of overoxidation have been overcome in a flow setting, and even easily oxidizable substrates are good yielding. This could be explained by a variety of factors such as the short residence time of the solution in the electrochemical cell or the nature of the flow regime that is laminar and hence reduces the contact of the either product with the anode due to selective oxidation into the cumyl alcohol followed by its diffusion closer to the cathode where it is less likely to undergo subsequent oxidation.

Similar to their previous work [44], the authors proposed the following mechanism for the flow electrolysis of cumene (Scheme 2). A hydroperoxide anion **A** generated at the cathode added to a cumyl cation **E** generated at the anode to form **G**. The O–O bond in **G** was cleaved anodically to form alkoxy radical **H**, which underwent a hydrogen atom transfer (HAT) with cumene **3a** to yield **4a**. Furthermore, **4a** was oxidized into **H**, followed by β -scission to yield acetophenone. Therefore, it was suggested that the selective conversion of **3a** into **4a** in flow electrolysis was due to suppressing overoxidation of **4a** into **H**.

Another interesting example involves the oxidation of C(sp²)–H bonds, in which cyclic olefins are converted into aliphatic (di)carboxylic acids in an electrochemical flow setup [45]. This eco-friendly approach relies on nitrate salts serving a dual function as an anodic mediator and supporting electrolyte, with the added benefit of being recoverable and recyclable. The reduction of molecular oxygen as a cathodic counter reaction ensures efficient and synergistic utilization of both electrode reactions. By circumventing the use of transition metals and chemical oxidizers, this methodology establishes a sustainable oxo-functionalization process, making a significant contribution to the sustainable transformation of petrochemical feedstocks into synthetically valuable fine chemicals and commodities.

Scheme 2



Electrochemical selective oxidation of cumene to cumyl alcohol.

In a small-scale trial, it was observed that cyclododecene **5a** at a concentration of 0.05 mol L^{-1} in isobutyronitrile resulted in the formation of dodecanedioic acid **6a** with a yield of 76%. In the context of larger technical applications, a shift in solvent was implemented, and a scaling-up initiative was undertaken. Following several variation trials within the same set-up, optimization of the reaction was achieved by employing a non-toxic dimethyl carbonate/isopropanol (DMC/*i*-PrOH) mixture and adjusting the substrate concentration to 0.5 mol L^{-1} , yielding **6a** with a 52%.

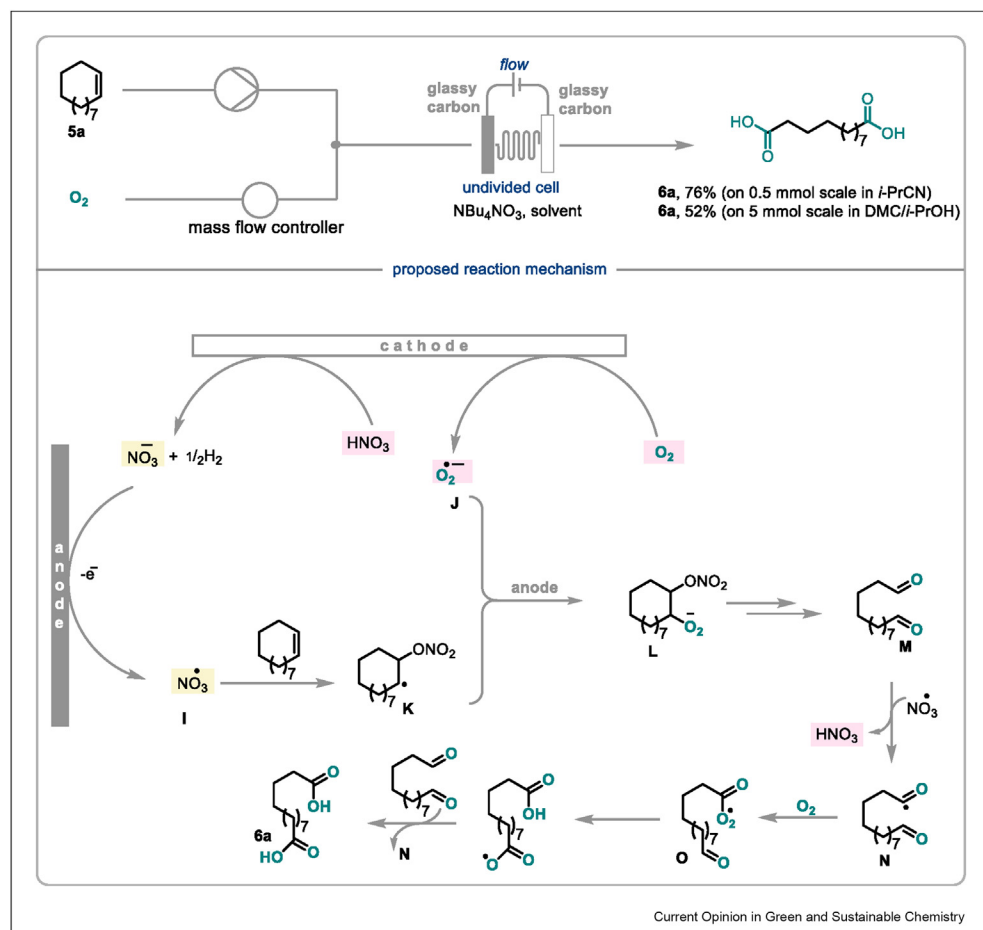
Based on the control experimental results, the proposed mechanism (Scheme 3) involves the electrochemical oxidation of nitrite **I** (serve as anodic mediator), which would react with alkene **5a** and generate hydrocarbon radical **K**. For the C=C double bond cleavage, an addition of the nitrate radical **I** onto the double bond **5a** is proposed, according to the findings of the control experiments and literature descriptions [46]. The cathode counter reaction is provided by the reduction of

dissolved oxygen and the resulting superoxide radical anion **J** is assumed to react with **K** to peroxide intermediates **L**. Further reaction with a superoxide radical lead via an unknown pathway to the formation of aldehydes **M** that are obtained as possible intermediates (HRMS analysis of the crude reaction mixture). Afterwards, literature described an autooxidation like mechanism from aldehydes **M** to carboxylic acids **6a** [47].

Conclusion

Basic principles and advantages of continuous flow microreactors for carrying out multiphase synthetic organic electrochemistry are illustrated. This includes a discussion on the importance of mass and heat transfer, on multistep reaction sequences and enabling controlled biphasic reaction conditions. Recent examples show how to improve reaction selectivity, and scale-up of reactions. Despite significant contributions in the field of electroorganic synthesis under flow conditions over the past decade, multiphase electrochemistry remains underdeveloped, probably due to the lack of

Scheme 3



Electrochemical oxo-functionalization of cyclic alkenes using nitrate and oxygen.

standardized protocols and detailed understanding. The deployment of continuous flow microreactors for multiphase synthetic organic electrochemistry holds the promise of exploring new and uncharted chemical spaces. The development of competitive and sustainable biphasic flow electrochemical processes for the manufacture of building blocks, APIs (i.e. Active Pharmaceutical Ingredients), and commodities is imperative for the advancement and continued growth of academia and manufacturing industries.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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The authors of the article reports an electrochemical approach for the direct functionalization of both C(sp³)-H and C(sp²)-H bonds, allowing rapid access to valuable products from simple petrochemicals. The method converts cyclic alkanes and (cyclic) olefins into cycloaliphatic ketones as well as aliphatic (di)carboxylic acids employing nitrate salts, serving as both anodic mediator and supporting electrolyte, which can be fully recovered and recycled. Furthermore, the reduction of molecular oxygen as the cathodic counter reaction ensured an efficient convergence of both electrode reactions.

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