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Waste-free oxidation of alcohols at the surface of catalytic electrodes: What is required for industrial uptake?

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Abstract

The electrocatalytic oxidation of alcohols at the surface of stable catalytic electrodes functionalized with aminoxyl radicals results in a waste-free process affording highly valued carbonyl or carboxylic compounds using an electric current only. Hydrogen is the only by-product of the reaction, no hazardous chemical oxidants are used throughout the process, whereas the separation of the valued reaction product from cytotoxic and genotoxic TEMPO-like radicals is no longer required. We provide a critical insight on the economic, technological, and educational issues that, in our viewpoint, will drive the uptake of this eminently green and highly effective synthetic organic chemistry technology in the fine chemical and pharmaceutical industries.

1 | INTRODUCTION

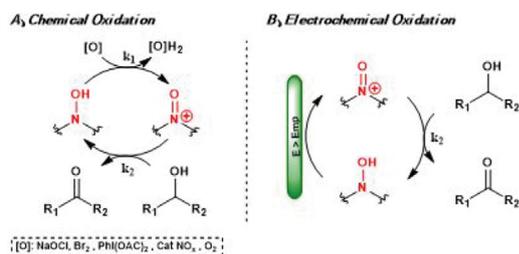
Found in late 2020 to be “underutilized and still in its infancy,”¹ the electrocatalytic oxidation of alcohols to carbonyl compounds (aldehydes and ketones) using chemically modified electrodes is highly desirable from environmental and economic viewpoints. Using electrons in place of chemical oxidants, indeed, the method generates no waste to produce aldehydes and ketones, which are amid the most valued fine chemicals, under safer and milder reaction conditions when compared to conventional catalysis. In the past decade, electroorganic synthesis has known a true renaissance,² even though precise control of the parameters used for electroorganic processes is crucial to ensure reproducibility of experiments.³ In this study, rather than reviewing recent advances in the electrocatalytic oxidation of alcohols, a topic recently reviewed in depth,¹ we provide critical insight on the (a) economic, (b) technological, and (c) educational issues that in our viewpoint will drive the uptake of this green chemistry technology in the fine chemical industry.

2 | ECONOMIC ASPECTS

Upon analyzing the energy consumption and energy efficiency of electro-organic syntheses, Waldvogel and co-workers have lately concluded that the most attractive electrosyntheses are those of fine chemicals, requiring smaller (and lower cost) electrolyzers whereas the product is sold for a high price.⁴ Manufactured in small amounts (<10 kt/a) and sold at a high price (> \$10/kg), fine chemicals (also called specialty or performance chemicals) are chemical products of high and well-defined purity generally produced by the fine chemical industry in batch processes carried out in a multi-purpose and multi-product plant (MPP).⁵ A few figures illustrate the scope and growth of the fine chemical industry recorded since the early 1990s. In 1993, the industry had \$42 billion revenues, with pharmaceutical companies absorbing 50% of production. Nearly 30 years later, in 2014, revenues had grown to \$128 billion, with the drug industry now absorbing 69% of production.⁶ The current global demand for fine chemical ingredients is large and forecasted to increase at a fast

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SCHEME 1 Chemical (A) and electrochemical (B) alcohol oxidation mediated by stable organic nitroxyl radicals. [Reproduced from Ref. 23, with kind permission]

pace (from \$155 billion in 2018 to \$219 billion by the end of 2024, growing at a compound annual growth rate of 7.1%)⁷ not only from the pharmaceutical industry but also from food and beverage, flavor and fragrance, cosmetic, personal care, electronic, and advanced materials industries.

Generally obtained through the oxidation of the corresponding primary and secondary alcohols,⁸ aldehydes and ketones are among the most important fine chemicals. Until the widespread industrial uptake of the Anelli-Montanari oxidation with NaOCl mediated by the nitroxyl radical TEMPO (2,2,6,6-tetramethyl-1-piperidine *N*-oxyl) in the course of the 2000s first decade,⁹ alcohol oxidation in the industry was carried out stoichiometrically with toxic and hazardous Cr⁶⁺ complexes such as pyridinium chlorochromate.¹⁰ Switching the TEMPO-mediated oxidation from using a primary oxidant such as NaOCl, hypervalent iodine reagents, and O₂ in combination with NO_x co-catalysts, to an electric current applied to the surface of an electrode modified with the TEMPO moiety makes the oxidation entirely clean and waste-free (Scheme 1).¹¹

Aldehydes and ketones are among the most important fine chemical ingredients used by the pharmaceutical industry. In 2007, a team of researchers from different pharmaceutical manufacturers ranked fourth the search of new oxidation methods without the use of chlorinated solvents, including alcohol oxidation to carbonyl compounds, amid the reactions companies used but for which they “would strongly prefer better reagents.”¹² Reporting that the use of stoichiometric high valent Cr⁶⁺ had been replaced by the Anelli-Montanari oxidation in dichloromethane/water biphasic system, they identified “several deficiencies” of the new method: the use of chlorinated solvents in the great majority of oxidation reactions followed by generation of large volumes of aqueous waste due to the use of NaOCl in the form of a dilute aqueous solution.¹¹

Ten years later, alcohol oxidation reactions were still ranked among the top 10 key research areas in green chemistry identified by researchers from pharmaceutical companies among the “alternatives for oxidations, C–O

or C–N redox processes,”¹³ with the use of halogenated solvents still representing “a major concern to improve process greenness.” Replacing the homogeneously catalyzed TEMPO-mediated Anelli-Montanari oxidation with the heterogeneously catalyzed electrolytic process carried out in toluene would eliminate the use of both chlorinated solvent DCM and chlorine-based primary oxidant NaOCl, thereby eliminating the downstream processing cost which “is often neglected but is crucial for a later translation into technical use.”¹⁴ To anticipate whether or not the fine chemical industry will switch from alcohol oxidations carried out in batch using the Anelli-Montanari process to electrocatalytic oxidations mediated by catalytic electrodes it is useful to remind that the cost of any synthetic chemical process (C), includes the intrinsic process cost (C_i) plus the cost of disposing of unwanted by-products, namely waste: (C_w):¹⁴

$$C = C_i + C_w \quad (1)$$

To reduce production costs, a company will rightly undertake action to eliminate the C_w cost of producing and processing waste in Eq. 1, for instance adopting a new synthetic process affording little or no waste as green chemistry aims to achieve. The company, however, will adopt the new synthetic process only if the new overall cost C is significantly lower than the older production cost so as to allow a quick return on the investment. In the fine chemical industry driven by by-product, and not by process innovation, typically this time should be lower than 2 years. Otherwise, the new process will either not be adopted, or it will be abandoned. This happened, for instance, with the production at a fine chemical company in Great Britain that designed and commissioned a new multi-purpose plant to carry out synthetic processes in supercritical carbon dioxide in 2002. A few years later, the plant originally used for the heterogeneously catalyzed continuous hydrogenation of isophorone to 3,3,5-trimethylcyclohexanone was no longer operational, regardless of far superior product specification, because there was “no current commercial advantage in using this green technology for the manufacture of specialty chemicals at present.”¹⁵

Profitability drives all industries, including the fine chemical industry. In 2011, after the delocalization of fine chemical productions to China and India, there were 2,000-3,000 fine chemical companies across the world. Among the top 20, 17 were divisions of large chemical or pharmaceutical companies, with only three independent companies.¹⁶ These companies typically use MPPs comprised of stirred stainless-steel and glass-lined batch reactors with reflux condensers equipped with feed systems for gaseous, liquid, and solid reactants, for blanketing with inert gases and equipment for separation and purification

such as filters and centrifuges (most fine chemicals are solids), dryers (fluidized-bed, tray, and rotary dryers), and distillation equipment. A state-of-the-art MPP typically costs in excess of \$30 million.¹⁷ It is perhaps not surprising to learn that the adoption of green chemistry in the industry has been slow.

In the subsequent decade, however, the outcomes of radical innovation in catalysis and process chemistry thanks to the development of flow continuous processes applied to the synthesis of organic molecules in small flow reactors, enable to dramatically lower both production costs (Eq. 1) as well as the capital expenditure required to buy (and maintain) the new MPP: a set of flow reactors.¹⁸ Likewise to similarly photocatalytic processes underutilized by the chemical industry for over a century,¹⁹ previously neglected electroorganic syntheses, are ideally carried out in flow electrolytic cells.²⁰ The lack of electrocatalytic processes in the fine chemical industry, indeed, rather than to lack of equipment and standardized protocols, has been due to the poor chemical stability of most electrodes at the relatively high voltage required by most electroorganic processes carried out in poorly conductive organic solvent. Thanks to radical advantages in flow electrochemistry^{18,21} and electrocatalysis, especially applied to alcohol selective oxidations,^{22–24} these limitations have been overcome opening the route to practical applications.

3 | TECHNOLOGICAL CHALLENGES

Discussing electrochemical TEMPO-mediated oxidations in which the cyclic oxoammonium ion is easily generated *in situ* by applying a small electric potential (0.7 V vs. Ag/AgCl) to a solution of nitroxyl radicals, in 2017 we forecasted that the electrocatalytic oxidation of alcohols mediated by TEMPO would have shortly found commercial application in the synthesis of numerous valued substances including active pharmaceutical ingredients (APIs), natural product derivatives, fine chemicals, and nanomaterials.²⁵ Today, selected companies selectively oxidize alcohols to carbonyl or carboxylic compounds using this approach. One recent example might be (companies in general do not disclose proprietary production processes) the synthesis of the chiral carboxylic acid precursor to a generic epilepsy drug-mediated by 4-acetamido-TEMPO (ACT) retaining $\geq 97\%$ enantiomeric purity in a divided flow electrolysis cell.²⁶

Getting to the heterogeneously catalyzed electro-oxidation, the first account on catalytically active sol-gel electrodes functionalized with stable nitroxyl radicals emphasized how “in addition to good selective activity and broad applicability to different substrates, the electrode’s stability is perhaps the most important factor that

will drive the adoption of this eminently clean technology by the fine chemical and pharmaceutical industry”.¹¹ Two years later, Stahl and co-workers reported that a new pyrene-TEMPO conjugate adsorbed at the surface of a carbon cloth electrode modified with commercially available multiwalled carbon nanotubes had excellent electrocatalytic performance, far exceeding that of dissolved ACT.²⁷ A few months later, our teams reported the discovery of new highly stable and active sol-gel electrodes functionalized with the TEMPO moiety.²³ Easily and reproducibly obtained by modifying the method to deposit an ordered mesoporous silica thin film onto solid electrode surface via the electro-assisted self-assembly (EASA),²⁸ the new electrode (dubbed “ZEmOEI”) is comprised of a thin layer of periodic mesoporous organically modified silica (ORMOSIL) whose inner surface is functionalized with covalently attached TEMPO moieties after direct grafting with a TEMPO-containing Si alkoxide. Organosilica thin films with 30% degree of methylation or 10% degree of phenyl modification are particularly active and stable. Immersed in aqueous bicarbonate solution at room temperature the 30% methyl-modified and 10% phenyl-modified ZEmOEI anodes quickly and selectively mediate the oxidation of several benzylic alcohols, including deactivated species chloro-substituted benzyl alcohols (Table 1), without the need of any co-catalyst under ultra-mild conditions (1 mmol alcohol in 0.15 M sodium hydrogencarbonate solution at room temperature electrolyzed at $E = 1$ V/ vs. SCE). The new hybrid electrodes do not suffer from mass transfer and diffusion limitations of amorphous organically modified silica electrodes,²⁹ as well as of the poor stability of the exceptionally active TEMPO-functionalized mesoporous hybrid silica electrode film with perpendicular mesochannels.³⁰ Showing evidence of the high stability of the new electrodes, after each run, the anodes washed with EtOAc and dried for 1 h at 70°C prior to reuse of another chloro benzyl alcohol derivative under the same electrolysis conditions (entries 3–6 in Table 1), fully retained their activity even after four consecutive runs.

The large porosity of the periodic mesoporous silica comprised of ordered vertical pores of about 2 nm in diameter perpendicular to the underlying support in a tightly packed geometric array ensures quick substrate diffusion and electrooxidation; whereas the organic modification of the silica structure stabilizes the inorganic silica structure towards dissolution in the alkaline solution, similarly to what happens when entrapping the TEMPO moieties in ORMOSIL matrices using the resulting catalysts in the Anelli-Montanari oxidation.³¹

These findings opened the route to a new use of sol-gel coatings as modifying films on working electrodes, so far chiefly used for analytical applications,³² as

TABLE 1 Scope of the electro-oxidation of the benzyl alcohol derivatives using ZEMOEL electrodes. [Reproduced from Ref. 23, with kind permission]



No.	R	30-Me@TES		10-Ph@TES	
		Time (h)	Aldehyde (%)	Time (h)	Aldehyde (%)
1	H	4	96	4	96
2	4-Methoxy	6	84	6	66
3	4-Chloro	3	99	3	97
4	2-Chloro ^a	4	97	4	96
5	3-Chloro ^b	8	96	8	96
6	2,4-Dichloro ^c	8	97	8	97

^aElectrode washed with EtOAc and dried at 70°C for 1 hour, reused to oxidise 2-chloro BzOH (Run 2).

^bElectrode washed with EtOAc and dried at 70°C for 1 hour, reused to oxidise 3-chloro BzOH (Run 3).

^cElectrode washed with EtOAc and dried at 70°C for 1 hour, reused to oxidise 4-chloro BzOH (Run 4).

electrocatalysts for important synthetic applications starting from the waste-free conversion of alcohols into carbonyls. In light of industrial applications, it is also of similar relevance of the fact that these chemically stable and mechanically robust glassy coatings are particularly well suited for modifying the anodes of state-of-the-art electrochemical microreactors with electrodes arranged in parallel. In these microreactors, the small electrode gap and the laminar flow conditions ensure both a homogeneous flow and fast heat transfer (an important issue when scaling up exothermic alcohol oxidation reactions).²¹

4 | EDUCATIONAL ISSUES

Reviewing the main electrochemical industrial syntheses, Sequeira and Santos in 2009 emphasized how electrochemical processes would rather be “better able to compete in the higher added value low volume area, for example, pharmaceuticals and specialty chemicals.”³³ Indeed, today fine chemical companies regularly use organic electrochemistry to synthesize fine chemical ingredients and intermediates. When asked to comment for the present study, a leading organic electrochemistry researcher based in Europe noticed that:

“Nowadays there are numerous companies that synthesize fine chemicals electro-oxidatively using electro-catalysts. Many of the synthesized substances are intermediate for subsequent chemicals and pharmaceuticals, and therefore parts of certain production processes that remain internal company secrets”.³⁴

Upon patenting, however, industrial researchers working at chemical and pharmaceutical companies today frequently publish their findings, which often include the outcomes of scale-up experiments, in the scientific literature. One example concerning the electrocatalytic hydrogenation of nitroarenes at the surface of carbon electrodes functionalized with Ag or Cu nanoparticles under continuous flow was reported in 2019.³⁵ The researchers emphasized how the easily scalable reactor geometry enables to produce anilines without having to employ an expensive and hazardous reagent such as pressurized hydrogen. Amid the new electrochemical synthetic processes used by the fine chemical industry lately reviewed,³⁶ another noticeable example is the electrochemical reduction process affording racemic homoceystein thiolactone (in hydrochloride form) on a 200 kg scale from homocysteine at the surface of a carbon electrode covered by a lead-bismuth alloy. Once again, beyond selectivity, the key progress that made possible commercialization was the chemical modification of the C electrode with the Pb/Bi alloy to improve its stability and thus prolong its service life.³⁷ An important aspect that remains to be addressed in numerous countries to increase the industrial uptake of electrochemical conversions in the fine chemical and pharmaceutical industries is the need for improved electrochemistry education. For example, noting that rigorous training of electrochemists is generally lacking at academic institutions in their country, recently Kempler and other scholars based in the USA identified the need to reinvigorate electrochemistry education.³⁸ Offering a clear example of chemistry educators using recent research outcomes and digital tools to inform new teaching of chemistry,³⁹ the aforementioned scholars suggested how to use today’s digital technology (offering new tools for teaching, such

as inexpensive electronics and open-source software) for a balanced teaching split between classroom teaching, laboratory experiments, and simulations to visualize mass-transport processes occurring at the nanoscale.³⁸ Making education practice-oriented, students for example are taught that industrial electrochemical reactors generally are flow electrochemical cells stacked in parallel with a low interelectrode gap, and large electrode area because this lowers the cell voltage and thus the energy costs.⁴⁰ Indeed, from the ohmic potential drop $\Delta U = IR_{\text{drop}}$ where $R_{\text{drop}} = d/\kappa A_e$ it can be seen that the ohmic potential drop and thus the generated heat or energy loss as Joule heat ($P = \Delta UI = I^2 R_{\text{drop}}$) at constant current I are lower the larger the active electrode area A_e and the electrolyte conductivity κ are, and the shorter the distance between electrodes d is.

5 | CONCLUSIONS

In conclusion, the commercialization of the waste-free selective oxidation of alcohols to carbonyl or carboxylic compounds at the surface of catalytic electrodes requires the development of economically affordable and stable catalytic anodes suitable for prolonged use. Pointing to ongoing industrial interest when asked to comment for the present study Stahl noted how:

“I am not aware of any commercial applications. One of our collaborators has worked on commercial development for another application”.⁴¹

Remarkably, in 2018 Stahl's team in a joint work with industrial researchers reported the first scalable electrocatalytic oxidation of numerous primary alcohols and aldehydes to the corresponding carboxylic acids mediated by low-cost ACT in an aqueous solution at room temperature.⁴² A 1 L jacketed cylindrical reactor was used in a batch electrochemical cell comprised a tubular reticulated vitreous carbon block as a working electrode, and a spiral platinum wire counter electrode. Safe carbonate/bicarbonate acted both as base and electrolyte, leading the scholars to conclude that the method should be “highly appealing” to the pharmaceutical industry. This relevance to the industry is even reinforced when switching to the heterogeneously catalyzed process, in which no prolonged workup is required for the separation of the reaction products from cytotoxic and genotoxic TEMPO-like aminoxyl radicals.⁴³ Will thus the fine chemical industry composed of about 3000 companies mostly located in

South East Asia and western Europe⁶ adopt heterogeneously catalyzed electrochemical alcohol oxidation? The answer to this question is similar for this and any other new “green” process technology. The industry will switch to this new synthetic technology when both the operating (“opex”) and the capital (“capex”) expenses of the technology will be low enough to ensure quick (<18-24 months) return on the investment (due to dramatically reduced product isolation and waste processing costs).¹⁴ Two such catalytic electrodes are Stahl's carbon cloth electrode modified with commercially available multiwalled carbon nanotubes further functionalized with a pyrene-TEMPO conjugate;⁴⁴ and the first sol-gel catalytic electrode comprised of periodic mesoporous ORMOSIL functionalized with aminoxyl radicals.²³ Obtained in a highly controllable and atom-economic fashion through an electrochemical deposition route discovered in 1999 for organosilica films,⁴⁵ and expanded in 2007 to synthesize periodic mesoporous silica made of hexagonally packed one-dimensional channels perpendicularly to the electrode surface,²⁸ sol-gel electrodes are ideally suited for today's flow electrochemical cells wherein the laminar flow conditions promote fast heat transfer and high selectivity.²¹ The use of thin glassy ORMOSIL coatings coupled to the aforementioned highly efficient electrodeposition process ensures minimal consumption of the expensive silicon alkoxides, whose high cost has been responsible for the limited use of silica-based sol-gel functional products across many industries.⁴⁶ Along with affordable cost, highly stable multiwalled carbon nanotube and sol-gel glassy electrodes are ideally suited for being integrated in commercial flow electrochemistry reactors in which alcohol substrates are quickly and safely converted into carbonyl or carboxylic compounds with no hazardous chemical oxidant, quick heat dissipation, and minimal power consumption.²⁴

Looking to the near future, a crucially important and often overlooked factor that will drive the industrial uptake of this and related electrocatalytic technologies in the fine chemical industry is improved electrochemistry³⁸ (and catalysis)⁴⁷ education. Only through expanded education in electrochemistry and catalysis applied to synthetic process chemistry, will a sufficient number of young talented professionals be available to industry to operate and innovate electrocatalytic systems. In this respect, and in agreement with the global relevance of recent pleas for “reinvigorating electrochemistry education,”³⁸ we will shortly report our approach to educate undergraduate chemistry students in electrochemistry applied to synthetic organic chemistry.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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