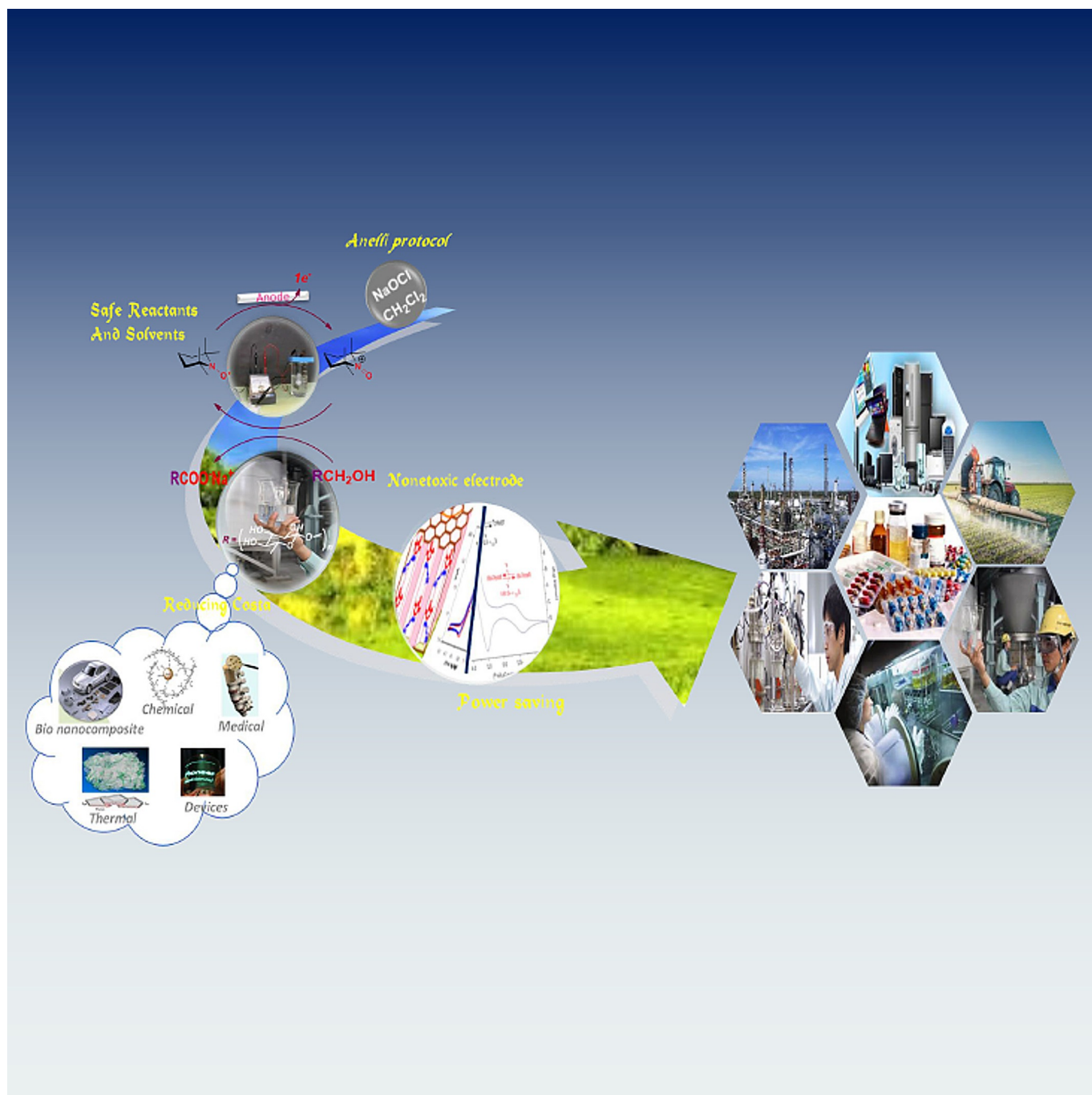


Electrochemical Alcohol Oxidation Mediated by TEMPO-like Nitroxyl Radicals

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The electrocatalytic oxidation of alcohols mediated by TEMPO-like nitroxyl radicals is an economically and industrially viable method that will shortly find commercial application in the

synthesis of valued substances including active pharmaceutical ingredients (APIs), valued natural product derivatives, fine chemicals, and valued nanomaterials.

1. Introduction

Widely employed by the fine chemical and pharmaceutical industries,^[1] the catalytic oxidation of alcohol to aldehydes or ketones based on the versatile organocatalyst TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy or 2,2,6,6-tetramethylpiperidine-1-oxyl), first synthesized by Lebedev and Kazarnowskii in 1960,^[2] is an highly selective metal-free route. Originally, industry has been using the method developed in 1990 by Anelli and Montanari, namely using aqueous NaOCl as primary oxidant kept under buffered alkaline conditions in contact with the alcohol solution in organic solvent at reaction temperature between 10 and 15 °C.^[3]

Today, pharmaceutical companies either carry out the Anelli–Montanari reaction under flow increasing the yield from 75 % (under batch conditions) to 90%,^[4] or even get rid of bleach by using air as the primary oxidant along with a catalytic amount of inexpensive CuI, *N*-methylimidazole (NMI), and less hindered ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl) at room temperature in high-flash-point *N*-methylpyrrolidone solvent;^[5] with primary laboratory chemical supplier commercializing the “Stahl oxidation solution” containing NMI, 2,2'-bipyridyl, and either TEMPO or ABNO. “All you have to do”, claims recent advertising, “is add the copper catalyst and your substrate”.^[6]

In principle, as first demonstrated by Semmelhack et al. in 1983,^[7] an even more convenient route is based on TEMPO-mediated electrochemical oxidation conducted in a simple electrochemical cell, in which the electric current replaces the oxidant (preventing the formation of undesired waste). The aldehyde and ketone reaction products thereby obtained are widely used as valued drug precursors, fragrances, and aromas, namely in commercial products, in which contamination with organic solvent and transition metals generally employed as reaction catalysts is subject to stringent limits.^[8]

Though being “innately sustainable”,^[9] synthetic organic electrochemistry^[10] in fine and medicinal chemistry is still applied to a few industrial productions, most notably for pharma-

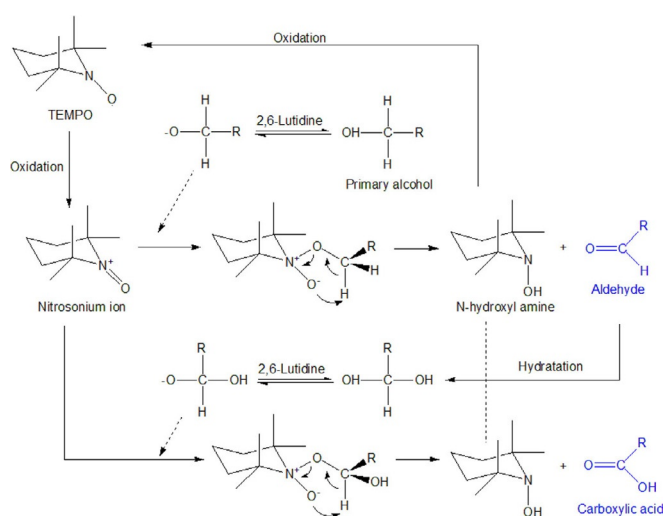
ceuticals such as cephalosporin antibiotic Cefditaben^[11] or the direct synthesis of the free base of cysteine.^[12]

Some of us have recently provided arguments for which sol-gel electrodes functionalized with TEMPO are likely to soon find practical application in the oxidation of alcohols.^[13] Studying the mechanism of alcohol electrocatalytic oxidation mediated by TEMPO, Karimi and co-workers, in 2014, identified the optimum conditions under which to obtain excellent yields in preparative conversions of widely different alcohols.^[14] More recently, Stahl and Badalyan reported that the electrochemical alcohol oxidation with an equimolar catalytic amount of (2,2'-bipyridine)Cu^I and TEMPO proceeds at an electrode potential a half-volt lower than that used for the TEMPO-only process (with even much faster rates).^[15]

Referring to selected recent works, we provide critical arguments aimed at showing that the electrocatalytic oxidation of alcohols mediated by TEMPO is an economically and industrially viable method that will shortly find commercial application in the synthesis of numerous valued substances including active pharmaceutical ingredients (APIs), natural product derivatives, fine chemicals, and nanomaterials.

2. A Versatile Oxidation Method

In TEMPO-mediated oxidations, the cyclic oxoammonium ion, which is the actual oxidant species, is generated in situ electrochemically by applying a small electric potential (0.7 V vs. Ag/AgCl) to a solution of nitroxyl radicals.^[7] The oxidation mechanism^[16] involves the oxoammonium ion, which oxidizes the alcohol function (Scheme 1) and is then regenerated either elec-



Scheme 1. Electrochemical oxidation of a primary alcohol mediated by TEMPO. At alkaline pH, primary hydroxyl groups are selectively oxidized to carboxylates via aldehydes.

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trochemically from the hydroxylamine or, in solution, by a disproportionation reaction of the latter species with unreacted TEMPO. A Brønsted base (2,6-lutidine mostly used) acts as crucial proton acceptor.

Karimi and co-workers have shown that, in the presence of alcohols, the oxoammonium ion is regenerated through the direct oxidation of the hydroxylamine reduced form of TEMPO, via a two-electron-transfer process at the electrode surface.^[14] By comparing the oxidation peak currents in the presence of alcohols to their values in the absence of alcohols (a measure of the catalytic activity of electrogenerated oxoammonium ion) at the same alcohol and TEMPO concentrations at pH 9.6, identified as the optimum and most informative kinetically controlled condition, the team also confirmed the remarkable difference in reactivity of the nitrosonium ion toward the oxidation of primary alcohols, in comparison to secondary alcohols (Figure 1).

The benzylic > allylic > aliphatic reactivity for primary alcohols is analogous to the order observed for secondary alcohols. As expected, the reactivity of TEMPO⁺ towards aliphatic alcohols with two or more hydroxyl groups is proportional to the number of hydroxyl groups, and generally higher than that of monofunctional alcohols. Finally, the activity towards alcohols

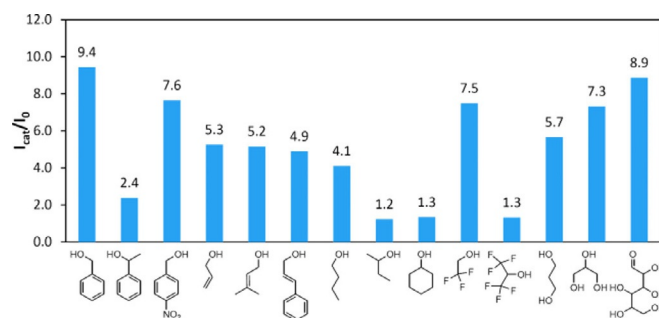


Figure 1. Ratio between the anodic-peak current of TEMPO in the presence and in the absence of alcohols in aqueous solution buffered at pH 9.6. Reproduced with permission from Ref. [14]. Copyright (2014) Wiley-VCH..

with strong electron-withdrawing groups such as *p*-nitrobenzylalcohol and trifluoroethanol is comparable and even higher than that shown towards their simpler homologues. Showing evidence of the method applicability on preparative scale, carrying out the reaction in an undivided three-electrode cell 10 mmol of benzyl alcohol and 1 mmol of *n*-heptanol dissolved in 150 mL of water buffered at pH 9.6 afforded 92 and 94% of benzaldehyde and heptanal, respectively. Indeed, benzylic, allylic, and aliphatic alcohols typically dissolved in water or in a water/organic solvent mixture, are converted in good yield and selectivity to carbonyls.^[17] Furthermore, carbohydrates dissolved in water are smoothly converted into valued glucuronates.^[18] Whatever the substrate and the solvent mixture, the electrochemical oxidation does not generate waste, although there is another reaction taking place at the counter electrode that should not be ignored along with degradation of the catalyst, whereas the reaction does not always take place with 100% yield without side reactions.

Most recently, Stahl and co-workers have shown that the best catalytic rates are obtained with TEMPO derivatives bearing an electron-withdrawing substituent in the 4-position, such as inexpensive 4-acetamido-TEMPO. In detail, the reaction rate is positively correlated with the mid-point potential (E_{mp} , Figure 2) of the one-electron nitroxyl/oxoammonium couple, providing evidence that the oxoammonium reduction poten-

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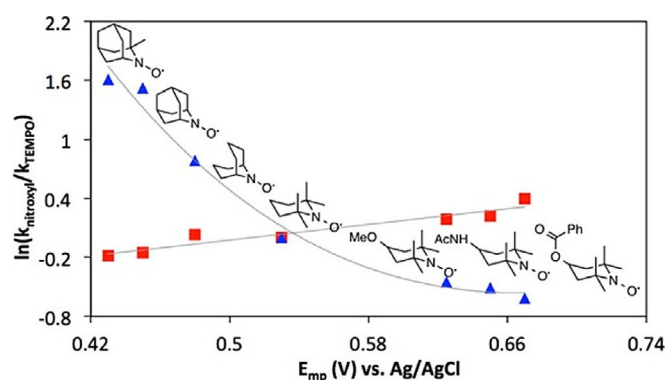


Figure 2. Linear-free-energy correlations for nitroxyl-catalyzed oxidation of 1-butanol with bleach (blue triangles) and under electrochemical conditions (red squares). Reproduced with permission from Ref. [19]. Copyright (2015) American Chemical Society.

tial is more significant than steric effects in controlling the reaction rate.^[19]

The reaction can be successfully carried out under flow by flowing the reaction solution (a buffered aqueous *tert*-butanol reaction medium) as a thin film between two closely spaced electrodes in a microflow electrolysis cell fitting into commercial microflow reactor.^[20] The small separation between the electrodes reduces the resistance of the cell and allows the oxidation of some 15 alcohols to aldehydes and ketones to be carried out continuously at ambient temperature and without added electrolyte.

In 2006, Krasutsky et al. disclosed the high-yield (90 %) electrochemical oxidation of betulin (a antitumor, antiviral, antidiabetic, antiinflammatory and anti-fungal bioactive pentacyclic triterpenoid contained in the bark of white birch)^[21] to betulin aldehyde using a catalytic amount of TEMPO (Figure 3), with-

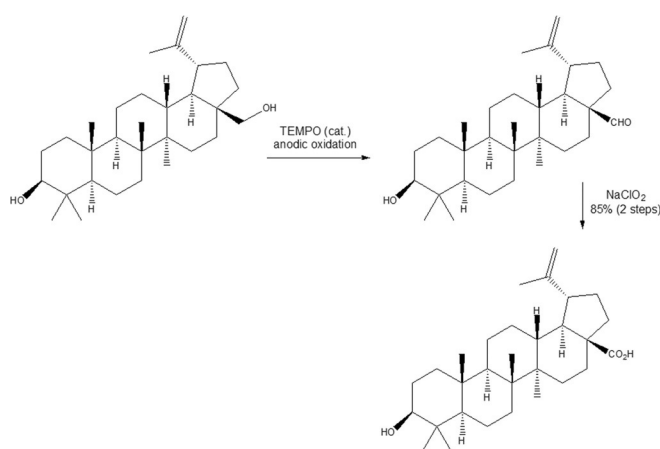


Figure 3. Electrochemical oxidation of betulin into betulin aldehyde mediated by TEMPO.

out affecting the secondary hydroxyl group (95 % selectivity).^[22] Subsequent oxidation with NaClO_2 affords betulinic acid, a valued substance ($\$570 \text{ g}^{-1}$) known for being a selective inhibitor of human melanoma,^[23] with anti-HIV (Human Immunodeficiency Virus)^[24] activity by inhibiting the maturation of the virus, also contained in the bark of white birch, though in limited amount (ca. 0.025 %). The industrial feasibility of this process was proved at a 40 L pilot-scale undivided electrochemical cell (platinum anode, copper cathode) still operational at Minnesota-based company Betula Extractives.

Another field in which stable nitroxyl radicals will shortly be employed for clean electrochemical oxidation is the production of cellulose nanofibers. The oxidation of the primary hydroxyl groups occurs only on the surfaces of the insoluble fibrils. Anionic carboxylate groups at the outer surface of microfibrils promote electrostatic repulsion, eventually resulting in individualization of cellulose microfibrils dispersed in water.

In the mid-1990s, Pagliaro worked in the Netherlands with de Nooy,^[25] when he first applied TEMPO-mediated oxidation with NaOCl to water-soluble polysaccharides such as starch, amylo-dextrin, and pullulan for regioselective conversion of C6 primary hydroxyls to carboxylate groups.^[26] Ten years later, Nishiyama,

working with Vignon in France and Isogai in Japan, applied the same process to the oxidation of native (never dried) cellulose fibers, obtaining, after a simple mechanical treatment of the oxidized product with a Waring Blendor, homogeneous suspensions of single cellulose nanofibers of 3–4 nm in width and a few microns in length,^[27] later dubbed cellulose nanofibers (CNFs).^[28] Another ten years later, and a Japanese paper company started the production of such cellulose defibrated to the nanoscale level obtained from wood fiber (pulp) through TEMPO catalytic oxidation (30 t/y), aimed toward customer commercialization of the first deodorant and antibacterial sheets,^[29] comprising CNFs surface-functionalized with metal nanoparticles and further coated onto paper.^[30]

In general, CNFs are a new transparent material with potential applications in a wide range of industrial fields, with large potential to replace traditional materials such as glasses and plastics, for example, in optoelectronic and energy-storage devices.^[31] Along with being transparent, lightweight, renewable, and nontoxic in nature, CNFs exhibit further outstanding characteristics including large specific surface area, high-strength (elastic modulus as high as that of aramid fibers), very little thermal expansion and contraction coefficient (on par with glass), and high barrier properties against oxygen and other gases.

Here, the electrochemical oxidation of cellulose mediated by TEMPO would clearly provide numerous benefits, getting rid of bleach and its NaCl/NaBr by-products, while reducing depolymerization. In 2010, Isogai and co-workers reported that the electrochemical oxidation of regenerated cellulose fiber, curdlan, and amylo-dextrin with 4-acetamido-TEMPO at pH 6.8 afforded selectively oxidized products whose molecular mass is much higher than that of samples prepared by the TEMPO/ NaBr/NaClO system at pH 10.^[32]

Similar results were extended shortly afterwards to wood cellulose, affording excellent cellulose nanofibrils.^[33] Remarkably, in the case of wood cellulose, along with 1 mmol g^{-1} C6-carboxylate groups, significant amounts of C6-aldehyde groups ($0.17\text{--}0.38 \text{ mmol g}^{-1}$) are also formed after oxidation for 48 h with TEMPO at pH 10 and with 4-acetamido-TEMPO at pH 6.8. However, whereas in the former case the degree of polymerization decreased from 2200 to 520 at pH 6.8, the degree of polymerization went from 2200 to 1400 only. In both cases, the original cellulose crystal structure was retained, showing that C6-oxidized groups selectively form cellulose microfibril surfaces. Upon dispersion in water (Figure 4), the oxidized celluloses with carboxylate contents $> 0.9 \text{ mmol g}^{-1}$ were converted into individual cellulose nanofibrils in $> 80\%$ yield. In general, the optimal reaction required 48 h, affording a highly viscous and optically transparent CNF gel-like dispersion.

3. Green Industrial Electrooxidation?

To answer the question whether or not green organic electro-oxidation of alcohols based on nitroxyl radicals will be adopted by fine chemical and pharmaceutical companies, it is helpful to look at the rapidly evolving industrial context. The fine and specialty chemicals industry selling high value-added products

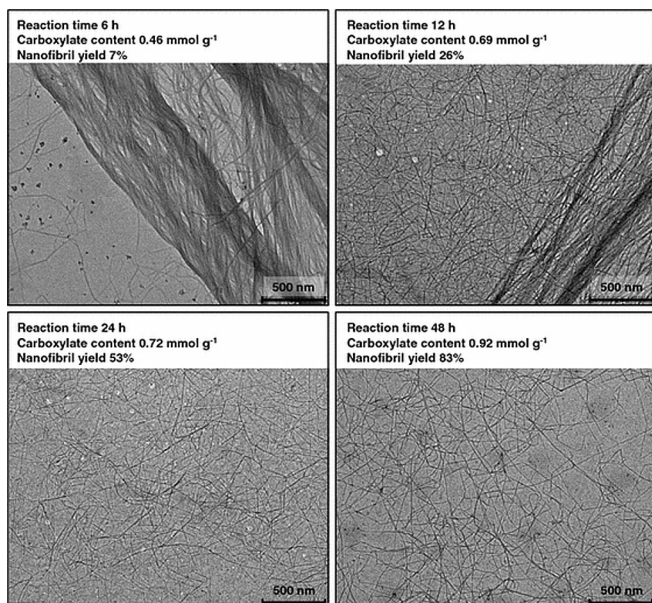


Figure 4. Cellulose TEM images of oxidized and then water-dispersed cellulose fibrils electrochemically oxidized with 4-acetamido-TEMPO at pH 6.8 for 6, 12, 24 and 48 h. Reproduced with permission from Ref. [33]. Copyright (2011) Springer.

ranging in price from a few dollars per kilogram (basic intermediates) to thousands of dollars per kilogram for active pharmaceutical intermediates (APIs), is driven by cost.^[34]

Customers in pharmaceutical and agrochemical industries (pharmaceuticals, pesticides and herbicides are the main outlets for fine chemicals) demand a supply of raw material products with high purity at ever lower prices.^[35] To reduce cost and retain profitability, starting in the early 1990s, fine chemical manufacturers traditionally based in western Europe and in the US shifted a large part of the production capacity to world's regions of low labor cost, namely China and India.

This very same delocalization, for example, has brought the cost of TEMPO nitroxyl radical, originally manufactured by a single company based in Germany in >80% of market share, from >\$200 kg⁻¹ in the early 1990s to the current price of \$2 kg⁻¹, making industrial oxidations with TEMPO dissolved in solution (the Anelli-Montanari process) economically viable.

Along with Teles and Della Pina,^[36] we have recently provided arguments for why industry will adopt new catalytic processes provided either that 1) the new synthetic process is inherently much cheaper than the existing process or that 2) the new catalytic process can be adapted as a drop-in solution, in which the new synthetic step is smoothly introduced in the existing synthetic process. The electro-synthesis of betulinic acid described above, for instance, is a nice example of the latter option.

Today's electrochemistry companies have developed user-friendly electrolytic reactor cells that use nontoxic, stable electrodes (in place of costly Pt or toxic Hg obsolete electrodes) such as those comprised of graphite or glassy carbon or copper of suitable shape. Today's electrochemical cells, as an undivided electrochemical cell, overcome the inherently poor design and mass-transport regime (suited only for 100 mg scale reactions) of beaker cells lamented by Brown^[37] and

Pletcher^[38] on trying to explain the limited adoption of electro-synthesis both in industry and in academic laboratories. The undivided electrochemical cell provides significant advantages including lower construction cost, longer cell life time, and lower internal resistance over the divided cell, resulting in substantially lower power costs. Furthermore, the electrolytic process is suited to either batch, semi-batch, or continuous operation, when a part of the electrolyte solution is continuously discharged from the electrochemical cell and the carbonyl reaction product recovered through conventional separation methods. In brief, the situation is similar to that of flow chemistry techniques, in which flow chemistry companies, following two decades of poor industry feedback, have developed numerous drop-in solutions in which one or more existing synthetic step can be switched from batch to continuous mode with little effort and limited changes to the existing infrastructure.

Furthermore, advances in nanochemistry make it possible to produce highly active and recyclable electrodes functionalized with the TEMPO moiety, such as gold electrodes, which are easily functionalized with TEMPO nanoparticles and used at length because of the extremely high stability of the Au electrode while replenishing degraded TEMPO moieties through simple surface derivatization with thiol-functionalized nanoparticles.^[39]

As mentioned in the Introduction, Stahl has recently extended his Cu/ligand/nitroxyl system for alcohol oxidation from aerobic to electrochemical oxidation (Figure 5).^[15] The significant novelty is that the new process is mediated by the Cu^I/Cu^{II} oxidation cycle, exploiting the low potential of the TEMPO/TEMPOH (rather than TEMPO/TEMPO⁺) redox process. Once again, owing to the steric effects on the reaction, the (bpy)Cu/ABNO catalyst exhibits higher activity than (bpy)Cu/TEMPO for most alcohol substrates.

From the applicative viewpoint, the half-Volt reduction in potential needed to achieve reaction (from 0.36 to -0.14 V) translates into significant power savings that may not be relevant for fine chemicals produced at <1000 t/yr; but, it will be extremely important for the production of cellulose nanofibers, whose high manufacturing cost was identified as of early 2016 as the main bottleneck to the rapid commercialization of CNFs. Cost of

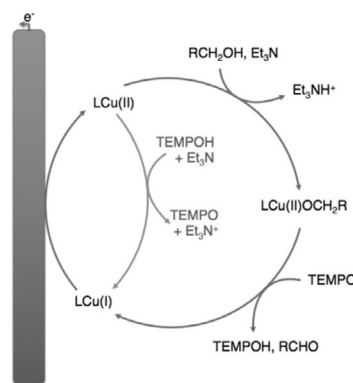


Figure 5. Mechanism of (bpy)Cu/TEMPO-mediated alcohol electrooxidation. Reproduced with permission from Ref. [15]. Copyright (2016) Springer Nature.

5000 to 10000 Yen per kilogram (namely €43 to €86 kg⁻¹, 1 Yen = 0.0087 €) for CNFs compares to 200 Yen for steel, which has five times the weight of CNFs and one-fifth its strength.^[40]

4. Outlook and Conclusions

The electrochemical synthesis of aldehydes, ketones, and carboxylic acids (including polymers) through electrochemical oxidation of the primary alcohol function mediated by TEMPO-like nitroxyl radicals provides numerous key advantages.^[4,9,19,11,15] As briefly shown by the selected studies reviewed in this Minireview, the reaction can be run at affordable cost under mild reaction conditions, affording highly pure oxidized reaction products along with little or no waste, getting rid of environmentally unfriendly hypochlorite used in the Anelli–Montanari process; or of the potential hazards associated with working in oxygen-containing atmospheres employed in aerobic oxidation protocols. The method is, indeed, increasingly used in industry, with examples including the synthesis of betulinic acid. Chemical companies normally do not disclose their manufacturing practices. Hence, it is likely that the method is employed by chemical manufacturers for the synthesis of other valued substances.

Almost 35 years after the first electrochemical route reported by Semmelhack et al. in 1983,^[7] numerous research groups are working to improve the method by reducing cost and by developing specific routes to specific products. We expect that the outcome of these studies will eventually establish organic nitroxyl radicals as the catalysts of choice for the selective oxidation of alcohols of relevance to the fine and specialty chemical industry. For example, stable nitroxyl radicals such as 4-acetamido TEMPO or ABNO are significantly more reactive than TEMPO, whereas the use of Stahl's Cu^I/bpy/nitroxyl co-catalyst system allows the electrode potential used to run the reaction to be lowered, thereby reducing the cost. Finally, advances in microflow chemistry and electrode technology, such as extended electrolysis cells with carbon/polymer composite anode enabling the synthesis of tens of grams of product in a single pass,^[38] further support our hypothesis that electrochemical alcohol oxidation mediated by nitroxyl radicals will eventually emerge as an ubiquitous technology in the fine chemical and pharmaceutical industries.

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Keywords: alcohols · electrooxidation · green chemistry · nitroxyl radical · TEMPO

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