



Electrosynthesis: A New Frontier in Aerobic Oxidation?

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The formation of alcohols and carbonyl derivatives via oxidation of the corresponding Csp³-H bonds is crucial to the chemical community. Historically chemists have relied for these transformations on the use of organic or inorganic oxidants, which are often toxic and produce stoichiometric amounts of harmful waste. As we strive for a more sustainable fine chemicals synthesis, for which typically larger amounts of waste per kilogram product are produced than for commodity chemicals, the use of greener oxidants has gained increasing attention. On paper, the high abundance, O content, low price, and the production of water as the only byproduct make O₂ an ideal reactant.¹ In a generalized and simplified view, air or pure O₂ are used in combination with a catalyst (metal complex, organocatalyst, or combinations thereof) to facilitate the formation of a carbon-centered radical, which will then react with O₂. These procedures have been widely applied to a number of molecules, but remain largely limited to the functionalization of *activated* C-H bonds, such as benzylic, allylic, or those *alpha* to a heteroatom.² *Unactivated* aliphatic C-H bonds, on the other hand, are more difficult to oxidize; moreover, selectivity is difficult to achieve due to their typical omnipresence in organic molecules. Oxidation of such substrates is therefore currently performed by using strong oxidants such as methyl(trifluoromethyl)dioxirane (TFDO) or transition metal catalysts featuring specifically designed ligands, in combination with hydrogenperoxide (Scheme 1A).³ Unfortunately, the problematic synthesis and storage of TFDO, and the cost of ligands in the catalysts considerably hamper the application of such strategies in larger scale processes.

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Baran and co-workers introduce a sustainable and scalable oxidation protocol for unactivated C-H bonds.

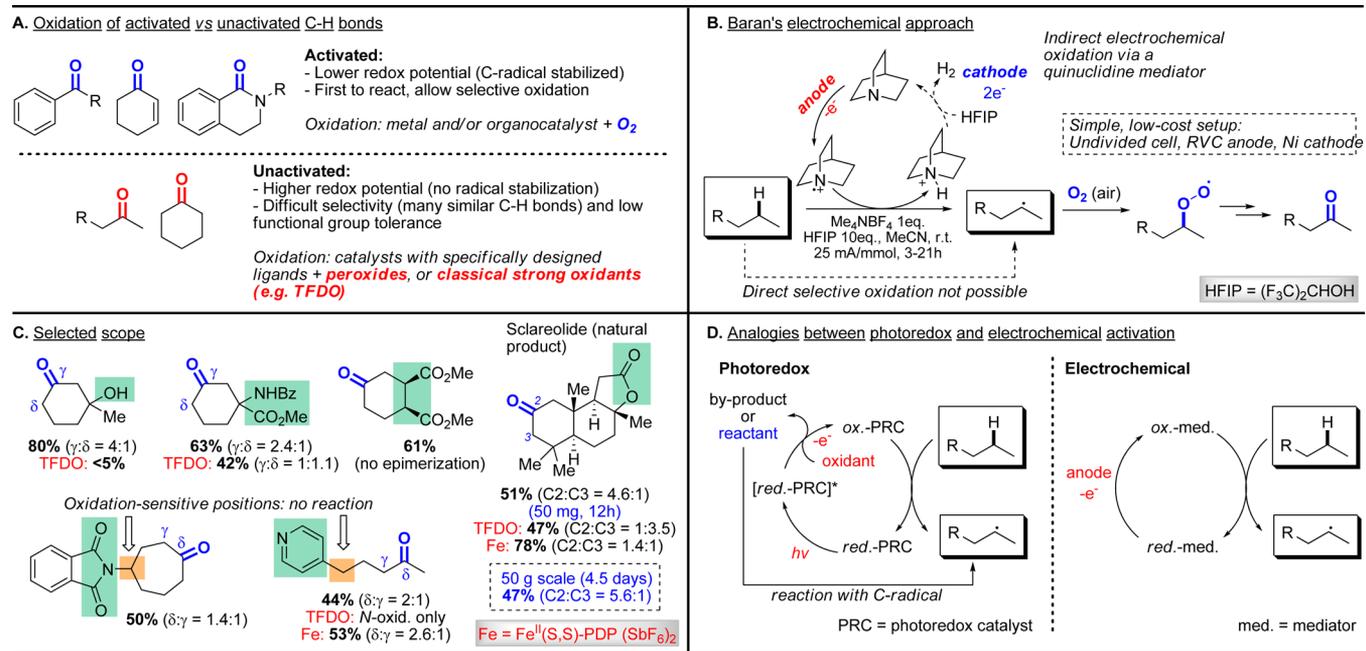
In a recent *Journal of the American Chemical Society* communication, the Baran group disclosed a selective aerobic oxidation of *unactivated* C-H bonds making use of electrochemistry.⁴ One important advantage of electrochemical over chemical oxidation is the possibility to apply at will a specific potential to the system. Nonetheless, the direct electrochemical generation of a radical from *unactivated* aliphatic C-H bonds is still not a practical option. *Unactivated* C-H bonds typically possess the highest oxidation potential in a molecule, and at the required potentials degradation of other functional groups and the solvent will occur. Baran and co-workers were able to solve this problem by using quinuclidine as an electrochemical mediator (Scheme 1B). Quinuclidine can be oxidized at much lower potentials than the C-H bond itself and easily abstract the hydrogen atom from the substrate, indirectly generating a C-centered radical which will in turn react with O₂, ultimately leading to the desired product. One downside to the setup is that although theoretically only a catalytic amount of mediator should be required in the process, in this case a stoichiometric amount had to be used to achieve good yields. A fluorinated alcohol, HFIP, as additive was also found to be crucial in the process, although it is not clear yet what its actual role is in the C-H activation.⁵ Interestingly, a recent benzylic aerobic oxidation process also uses this alcohol, in this case to achieve chemoselective oxidation to aldehydes.^{2a}

With this electrochemical approach, Baran and co-workers were able to perform the selective oxidation of linear and cyclic hydrocarbon moieties without affecting functionalities like ketones, alcohols, esters, amides, heterocycles, and epimerizable centers (Scheme 1C). An important feature is

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Scheme 1



the regioselectivity observed for the C–H functionalization. In linear alkanes and in seven-membered rings, the oxidation occurs preferentially at the δ position from the closest electron-withdrawing group (or atom), but for six-membered rings, the preferred position is the γ carbon atom. No reaction at other oxidation-susceptible positions, such as tertiary carbons or benzylic carbons, was observed. Although, generally, similar selectivities and yields were achieved as with classical oxidation protocols, there are notable exceptions.

Besides product selectivity in complex molecules, a general challenge for aerobic oxidations is the scalability, due to the heterogeneity of the process (mass transfer limitation of gas into liquid), and the safety issues connected with the risk of combustion of flammable organic solvents. A remarkable aspect of Baran's protocol is the ease with which scale-up can be performed, as exemplified by the 50 g scale oxidation of sclareolide. No decrease in yield and selectivity was observed, although 4.5 days were required, and conversion was not complete. Both the use of air, rather than pure O₂, and room temperature are interesting features from a safety perspective. The simple and low-cost experimental setup (undivided electrochemical cell, glassy carbon anode and Ni cathode, cheap electrolyte and mediator) outperforms classical procedures in terms of price (even with stoichiometric mediator). Although the authors did not set out to provide a protocol immediately applicable to large-scale production of fine chemicals, there is certainly the potential for this if a solvent with a higher flash point than acetonitrile

(5.5 °C) can be used and higher reaction rates can be achieved with a suitable catalytic mediator.

While the fine chemicals industry mostly relies on (multipurpose) batch reactors using typically <10% O₂ in N₂ at a temperature at least 10–20 °C lower than the flash point of the solvent, most state-of-the-art aerobic processes developed in academia use air (~20% O₂) or pure O₂ with low flash point solvents. At first glance there seems to be a mismatch between available and required oxidation methodology. Fortunately, the recent transition from batch to flow reactors in the fine chemicals industry allows the safe use of higher concentrations of, and even pure, O₂ in liquid phase.⁶ Specifically related to the context of this commentary, the availability of electrochemical flow reactors is of great interest.^{6b}

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The use of electrochemistry for organic synthesis has been exploited for a long time, even at the industrial level, but has surprisingly not been explored much in the last few decades, although very recently the field seems to have revived considerably.⁷ The innate sustainability of the technology is a main driver for this. Noteworthy are the analogies between electrochemical and photoredox processes, another

flourishing research area in academia.⁸ In the latter case a photoredox catalyst (analogous to the electrochemical mediator) is activated by light and generates a reactive carbon radical by oxidation (Scheme 1D). The oxidants used here are typically sacrificial or generate a reactant *in situ*. Sustainability will be largely determined by the nature of this oxidant. Photoredox catalysts are often very expensive, which, unless recyclable, can prevent application in process chemistry. Examples of photoredox-catalyzed aerobic oxidation of *activated* methylenes have been reported. Oxidation of the catalyst by O₂ delivers superoxide or water, which can react with the carbon radical (cation), finally generating a ketone.⁹ Both photoredox and electro-synthesis hold great promise for future sustainable, scalable, and cost-effective C–H oxygenations reactions in fine chemicals synthesis.

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