Paired Electrochemical Reactions and the On-Site Generation of a Chemical Reagent.

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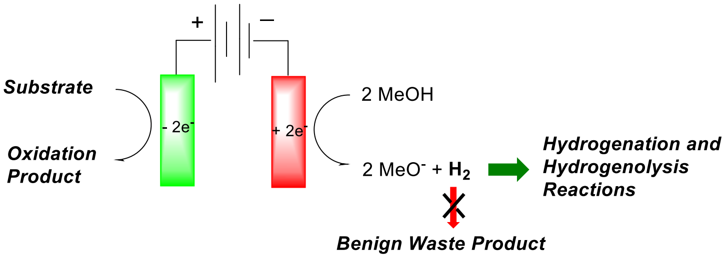
Supporting Information Placeholder



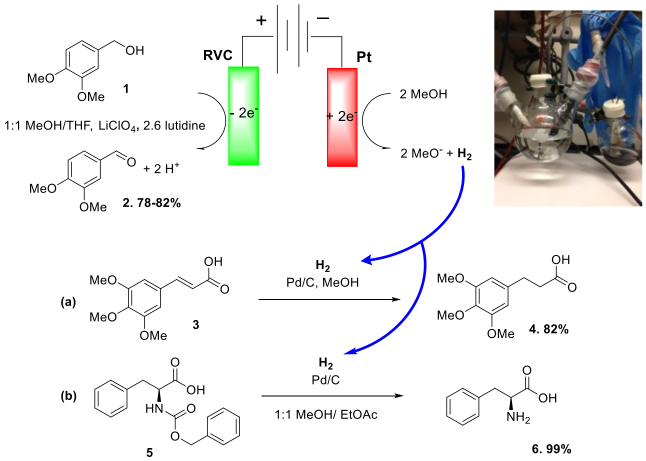
ABSTRACT: While the majority of reported paired electrochemical reactions involve carefully matched cathodic and anodic reactions, the precise matching of half reactions in an electrolysis cell is not generally necessary. During a constant current electrolysis almost any oxidation and reduction reactions can be paired, and in the presented work we capitalize on this observation by examining the coupling of anodic oxidation reactions with the production of hydrogen gas for use as a reagent in remote, Pd-catalyzed hydrogenation and hydrogenolysis reactions. To this end, an alcohol oxidation, an oxidative condensation, intramolecular anodic olefin coupling reactions, an amide oxidation, and a mediated oxidation were all shown to be compatible with the generation and use of hydrogen gas at the cathode. This pairing of an electrolysis reaction with the production of a chemical reagent or substrate has the potential to greatly expand the use of more energy efficient paired electrochemical reactions.

Paired electrochemical reactions that produce desirable products at both the anode and cathode are frequently put forth as a method for optimizing the energy efficiency of oxidation and reduction reactions,[2-4] and there are outstanding examples of their utility.[5-19] For example, the chloro-alkali process that generates sodium hydroxide (reduction of water at the cathode) and chlorine gas (oxidation of chloride at the anode) from sea water is currently conducted on a massive scale.[20] Many other efforts have been forwarded as well, particularly in the general area of energy conversion.[21-30]

However, in spite of the potential paired electrochemical reactions hold for running more sustainable processes and the impressive examples illustrating this potential, the technique remains primarily of interest to chemists specifically engaged in the development of new electrochemical methods. A number of factors contribute to this situation. These factors range from little need to consider the energy efficiency of synthetic methods conducted in an academic laboratory setting to the impression that paired electrochemical reactions require "carefully matched" oxidation and reduction reactions and hence have limited synthetic generality. With respect to the first point, academic chemists are becoming increasingly aware of the need for more sustainable synthetic methods and strategies. In that context, it makes sense to examine methods that meet the challenge from both a perspective of atom and energy economy. Paired electrolysis reactions offer just such an opportunity. The second point raised above represents a potentially more significant barrier. If paired electrochemical reactions really do require "carefully matched" oxidation and reduction reactions that limit the generality of the products that can be made, then interest in the reaction among the synthetic community will be equally limited. Fortunately, the perception that paired electrochemical reactions require "carefully matched" cathodic and anodic processes is not accurate. In a constant current electrolysis the working potential at both electrodes automatically adjusts to match that of the substrates in solution.[31] In such an electrolysis, any oxidation reaction can in principle be paired with any reduction reaction as long as sufficient energy is applied to the cell.

This generality offers a way to rethink how the increased sustainability associated with a paired electrochemical reaction can be implemented within a larger synthetic scheme. Imagine the electrochemical pairing of a required oxidation or reduction reaction with the generation of a chemical reagent or substrate needed for a second, potentially non-electrochemical reaction. The on-site production of that chemical reagent or substrate would allow the single electrochemical reaction used to improve the sustainability of more than one synthetic transformation. In this manuscript, we provide a proof-of-principle experiment that illustrates how anodic oxidation reactions that occur at different potentials, require the use of both undivided and divided cells, and involve both direct and indirect electrochemical methods can all be coupled to the on-site production of hydrogen gas for use in Pd-catalyzed hydrogenation and hydrogenolysis reactions. While the chemistry here is illustrated for the production of hydrogen gas, it is important to keep in mind that cathodic reductions can be used to generate a wide variety of reagents and catalysts.[32]

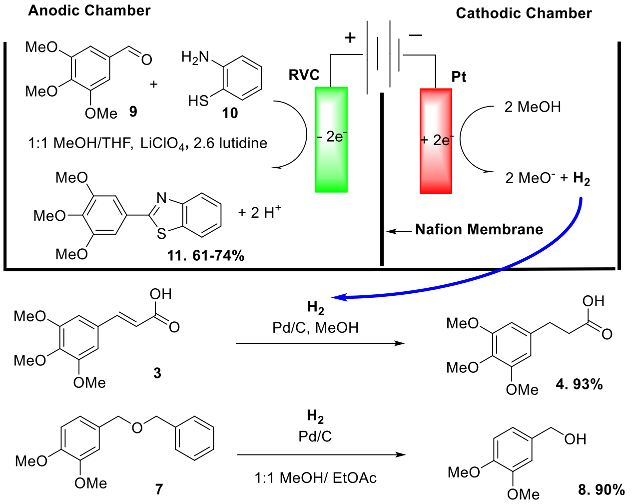
The desire to use cathodic processes to generate chemical reagents grew out of the chemistry shown in Scheme 1a.[33] The reaction highlighted was conducted as part of a program to valorize synthetic building blocks derived from lignin. This effort required a combination of both oxidation and hydrogenation reactions. The oxidation reactions were performed electrochemically, transformations that led to the generation of hydrogen gas at the cathode from the reduction of methanol. At the same time, the hydrogenation-based lignin valorization methods (Scheme 1a) were performed using hydrogen gas from a cylinder. The question became, why were we buying hydrogen gas and incurring unnecessary environmental and financial costs when we were already producing hydrogen gas during the oxidation reactions? With this in mind, a cannula was inserted into the headspace above an electrochemical alcohol oxidation and the hydrogen gas generated was transferred to a flask containing the unsaturated acid and a palladium catalyst. Both reactions led to their respective products in good yield.



Scheme 1. A paired electrolysis coupling an alcohol oxidation to two one of two reactions requiring hydrogen gas.

The alcohol oxidation reaction was also successfully paired with a Cbz deprotection reaction (Scheme 1b). While the initial reactions used a large excess of the alcohol,[33] the optimized conditions shown for the reaction of **3** to **4** and **5** to **6** were conducted with a ratio of 2.5/1 of the alcohol substrate (**1**) to the substrate required for the reduction. Improving techniques for sealing the flasks to minimize hydrogen loss during the transfer enabled this optimization.

Following the success of the chemistry highlighted in Scheme 1, we sought to demonstrate the premise stated above that the working potential at the electrodes in a paired electrolysis will autonomously adjust so that any two reactions can be coupled. To this end, a series of oxidation reactions were screened for their compatibility with the hydrogenation and hydrogenolysis reactions. For this effort, a simplified substrate (**7**) for the debenzylation was used for convenience. In the first of these reactions (Scheme 2), the oxidative condensation of an aldehyde (also derived from lignin)[33] with a phenyl diamine was paired with the hydrogenation of a different lignin derived building block. The reaction was used to illustrate the compatibility of the paired electrolysis with an oxidation reaction that is more mechanistically complex and requires the use of a divided cell to go to completion.[34] To this end, the anode and cathode for the reaction were separated with a Nafion 117 membrane. The cannula needed for the H_2 transfer was placed in the head space of the cathodic chamber. Once again, all of the reactions proceeded in high yields. The use of the more complex oxidation reaction did not influence either reduction reaction in any way.



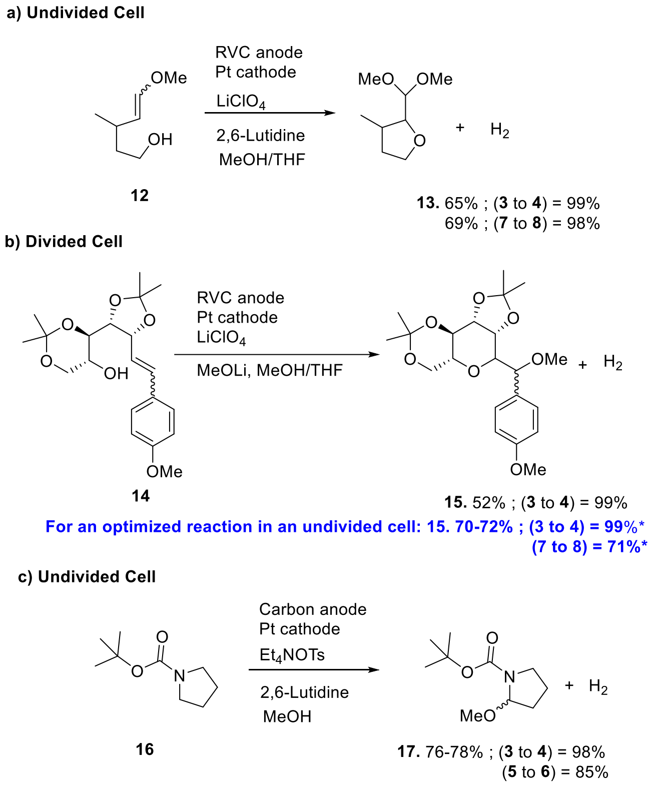
Scheme 2. A paired oxidative condensation with hydrogen generation in a divided cell.

The effort was continued with the reactions in shown in Scheme 3. The first oxidation reaction involved the intramolecular trapping of a radical cation with an alcohol (Scheme 3a).[35] The reaction was selected in order to show the generality of the undivided cell setup used for the reaction in Scheme 1. As in the earlier reactions, the oxidation was coupled to both the hydrogenation and the hydrogenolysis, and once again, neither reduction was altered by the change in the oxidation reaction. The oxidation reaction proceeded cleanly, but in this case the yield of the cyclization was not optimized because that effort relies more on rapid isolation of the sensitive product than it does the electrolysis itself.

In the second reaction (Scheme 3b), the anodic oxidation was used to generate a C-glycoside.[36] This reaction was chosen for the study because it is a challenging oxidative cyclization that requires the fast removal of a second electron for the efficient production of product. The reaction was initially conducted in a divided cell in spite of the fact the use of such a cell is not optimal for the generation of C-glycoside **15** and known to result in lower yields of product and the formation of polymerized side products.[36] This was done in order to probe the compatibility of the paired reduction reaction with an anodic reaction that was not optimal. What happens to the paired reduction reaction if something goes wrong with the oxidation reaction? The answer to this question is nothing. Even with a less efficient oxidation reaction, the reduction proceeded smoothly as long as current was passed through the cell.

Of course, the oxidation of substrate **14** could be optimized by conducting the electrolysis in an undivided cell (data in blue). This was accomplished without any change to the hydrogenation chemistry, a result that highlighted one of the advantages of employing the paired electrochemical reaction to make a chemical reagent that is used remotely. In such reactions, the oxidation and reduction reactions can be optimized independently, a situation that makes the paired electrochemical process very easy to implement.

The reaction highlighted in Scheme 3b did expose one weakness of the experimental setup being used for this study. Due to the lack of availability of substrate (**14**), the reactions were run on a smaller scale. This meant that a much smaller total volume of hydrogen gas was generated, and it was difficult to transfer that smaller volume of hydrogen gas quantitatively to the remote flask used for either

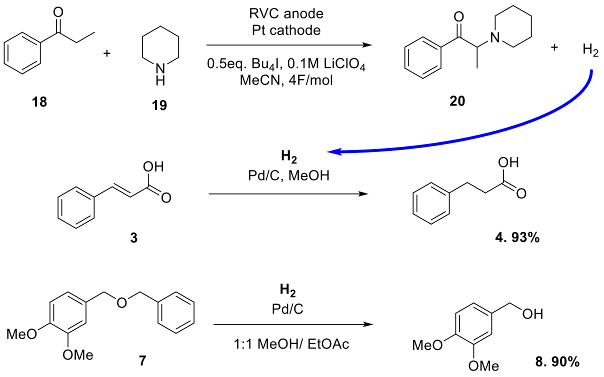


Scheme 3. Paired anodic cyclization reactions. * For these examples a 10:1 ratio of the C-glycoside substrate to the reduction substrates was used.

the hydrogenation or hydrogenolysis. For this reason, the reduction reactions had to be conducted on a smaller scale relative to the oxidaton (a 10:1 ratio of the C-glycoside to the reduction substrate was employed). This issue can potentially be resolved by either scaling the oxidation reaction in order to generate more hydrogen gas or reengineering the current reaction setup to be more efficient with respect to the hydrogen transfer. Neither was done as part of the current study since the reactions had already illustrated the main point for which they were conducted.

In the third reaction (Scheme 3c), an amide was oxidized and paired with two reduction reactions. These paired electrolyses were conducted to show the versatility of the reactions with respect to the oxidation potential of the substrate. While the previous reactions involved a number of different substrates, the oxidation potnetials required for the reactions all fell within a relatively narrow range (*ca.* +1.1 to +1.4 V vs. Ag/AgCl). In contrast, the carbamate substrate in Scheme 3c undergoes oxidation at a potential over half a volt higher (+1.95 V vs. Ag/AgCl).[37] This difference did not matter. The anodic oxidation reaction was conducted using the optimized conditions developed previously,[38] and the paired hydrogenation and hydrogenolysis (the deprotection of phenylalanine derivative **5**) reactions both led to high yields of product. The working potential at the anode automatically adjusted to the higher potential needed for oxidation of the carbamate without any influence on the paired reduction reactions.

Finally, each of the reactions above involved the direct oxidation of a substrate at the anode. This is not a requirement. In the reaction highlighted in Scheme 4, electrochemically generated "I$^+$" was used as a mediator to functionalize the carbon alpha to a carbonyl.[39] The oxidation involves the iodination of an enol in the presence of a nucleophilic amine. This results in a net amination of the targeted carbon; a transformation that cannot be accomplished with the use of a direct oxidation because such a process would lead to oxidation of the amine. The added complexity of the indirect electrolysis did not interfere with either the hydrogenation or hydrogenolysis reaction using the hydrogen generated at the cathode. In this case the oxidation reaction occurred at a potential of only +0.31 V vs Ag/AgCl. When compared to the amide oxidation, the paired electrolyses reactions have been shown compatible with oxidation substrates that differ by over 1.6 V in energy. Clearly, any oxidation reaction can be used to drive the reduction chemistry.



Scheme 4. The use of an indirect oxidation reaction in paired processes.

To be clear, we are not suggesting that electrochemistry is the best way to access the hydrogen gas needed for an isolated synthetic transformation. Instead, we are suggesting that many of the common oxidation reactions we utilize on a routine basis can be viewed in the larger context of an overall synthetic effort. If one needs to conduct a hydrogenation or hydrogenolysis reaction in a synthetic sequence and they are already conducting a larger scale oxidation reaction elsewhere in the lab, then why not use that oxidation reaction as an on-site source of hydrogen gas and avoid the cost and energy required for the purchase and shipping of hydrogen gas made at a remote location?

Finally, it is important to note that the paired electrolysis reactions illustrated above represent ideal examples. The reduction of protons to generate hydrogen gas is an extremely efficient cathodic reaction. For that reason, it is the half reaction selected as the counter reaction for the vast majority of anodic oxidation reactions reported in the literature. However, cathodic reactions are not restricted to the production of hydrogen gas. Cathodes can be used to make bases, nucleophiles, radical anions, radicals, transition metal reagents, etc.[2,4,32] So, an anodic reaction can in principle be paired with the generation of a variety of chemical reagents and synthetic transformations. For example, the oxidative condensation reaction shown in Scheme 2 has been paired with the production of carbon monoxide.[30] Efforts to further expand the reactions along these lines are underway as part a larger program to illustrate how the inclusion of an electrochemical reaction in a synthetic sequence can be used to improve the sustainability of not only that particular reaction, but also a variety of other non-electrochemical reactions in the sequence.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and characterization (^{1}H & ^{13}C NMR, IR, and HRMS data) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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