From Molecules to Molecular Surfaces. Exploiting the Interplay Between Organic Synthesis and Electrochemistry

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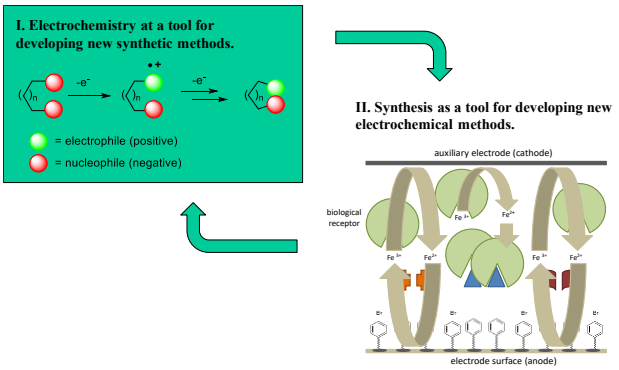


For many years, we looked at electrochemistry as a tool for exploring, developing, and implementing new synthetic methods for the construction of organic molecules. Those efforts examined electrochemical methods and mechanisms and then exploited them for synthetic gain. Chief among the tools utilized was the fact that in a constant current electrolysis the working potential at the electrodes automatically adjusted to the oxidation (anode) or reduction (cathode) potential of the substrates in solution. This allowed for a systematic examination of the radical cation intermediates that are involved in a host of oxidative cyclization reactions. The result has been a series of structure-activity studies that have led to far greater insight into the behavior of radical cation intermediates and in turn an expansion in our capabilities of using those intermediates to trigger interesting synthetic reactions. With that said, the relationship between synthetic organic chemistry and electrochemistry is not a "one-way" interaction. For example, we have been using modern synthetic methodology to construct complex addressable molecular surfaces on electroanalytical devices that in turn can be used to probe biological interactions between small molecules and biological receptors in "real-time" as the interactions happen. Synthetic chemistry can then be used to recover the molecules that give rise to positive signals so that they can be characterized. The result is an analytical method that both gives accurate data on the interactions and provides a unique level of quality control with respect to the molecules giving rise to that data. Synthetic organic chemistry is essential to this task because it is our ability to synthesize the surfaces that defines the nature of the biological problems that can be studied. But the relationship between the fields does not end there. Recently, we have begun to show that work to expand the scope of microelectrode arrays as bioanalytical devices is teaching us important lessons for preparative synthetic chemistry. These lessons come in two forms. First, the arrays have taught us about the on-site generation of chemical reagents, a lesson that is being used to expand the use of paired electrochemical strategies for synthesis. Second, the arrays have taught us that reagents can be generated and then confined to the surface of the electrode used for that generation. This has led to a new approach to taking advantage of molecular recognition events that occur on the surface of an electrode for controlling the selectivity of a preparative reaction. In short, the confinement strategy developed for the arrays is used to insure that the chemistry in a preparative electrolysis happens at the electrode surface and not in the bulk solution. This account details the interplay between synthetic chemistry and electrochemistry in our group through the years and highlights the opportunities that interplay has provided and will continue to provide in the future.

Introduction.

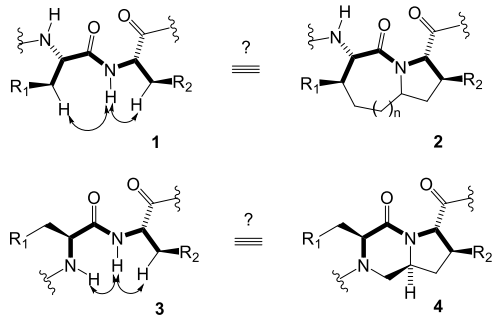
In 1986, Manuel M. Baizer (the inventor of the electrochemical adiponitrile process) stated that "….organic electrochemical synthesis has ceased to be a laboratory curiosity, a methodology to be tried when all else fails, a procedure that involves mysterious black boxes and dials and wires. The science and technology are now well developed although not mature….".[1] The truth of that statement was certainly debatable in 1986. For several decades following its publication, organic electrochemistry remained an obscure method that was primarily adopted by synthetic chemists as a matter of "last resort". However, in 2019 it appears that the synthetic chemistry community has now caught up with sentiment expressed by "Manny Baizer". Electrochemical methods are being adopted with increasing frequency, and numerous research groups are using those methods to forward an impressive array of synthetic advances.[2] Key to those efforts is the opportunity that electrochemistry offers for selectively conducting oxidation and reduction reactions at controlled potentials, under neutral conditions, and without the need for stoichiometric chemical reagents.[3] The reactions are frequently used to recycle chemical oxidants or reductants so that they can be used in a catalytic fashion, as well as for the generation of radical ion intermediates.

These applications have taught us a great deal about how electrochemistry can be used to open up new avenues for advancing synthesis.

The application of electrochemistry to explore and develop new synthetic methodology. A lesson in versatility.

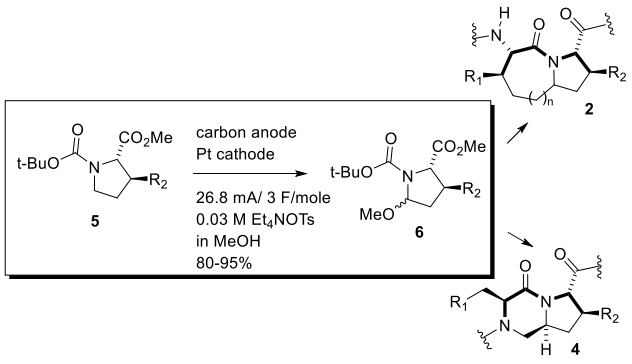
For our part, electrochemistry has provided the tools needed to systematically study a variety of intriguing oxidation reactions. Chief among these tools has been the use of constant current electrolysis. In a constant current electrolysis, the potential at the electrodes automatically adjusts to the substrate present in solution (*vide infra)*.[2g,3,4] It remains there until the substrate is consumed at which point the potential climbs until another substrate is found. If the current density of the reaction is kept low, then the reaction can be pushed to near completion without any loss of selectivity. Hence, the method can be used to oxidize substrates with a wide range of potentials under nearly identical conditions.

Perhaps the best way to understand this feature of the reactions is to look at a trio of reactions. The first is a reaction conducted during efforts to utilize the Shono oxidation for the annulation of rings on to amino acid derivatives.[5] In this chemistry, conformationally constrained peptidomimetics **2** and **4** were constructed by replacing spacially close hydrogens in a preferred conformation of the peptide like **1** and **3** with a bridge (Scheme 1). To accomplish this objective in the lab required a method to functionalize



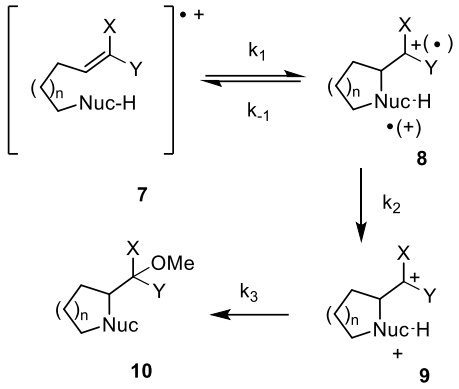
Scheme 1. The design of a peptidomimetic and a synthetic challenge.

proline derivatives like **5** as part of an annulation strategy, and to that end the Shono oxidation (Scheme 2) proved to be an ideal tool to build the bridge in **6** to get **2** or **4**.[6] The Shono oxidation converts amides or carbamates into their α-methoxyalkyl amide or carbamate derivative.



Scheme 2. Amide oxidations.

For this transformation, the electrochemical method is essential because it allows for oxidation potentials high enough to oxidize an amide or carbamate (on the order of + 2 V relative to a Ag/AgCl reference electrode) while still enabling the oxidation of a variety of substrates to occur selectively without over-oxidation of the methoxylated amide product which oxidizes at a potential only 150 to 200 mV higher than that of the starting material. The potential at the anode adjusts to match that of the substrate and stays there for the majority of the reaction. Hence, the product is not oxidized. Changes in substrate potential do not alter this picture, even when the substrate is a pyroglutamate derived secondary amide that requires a much higher oxidation potential.[7] In every case, the potential at the anode changes and then holds steady at that potential avoiding over-oxidation of the product.

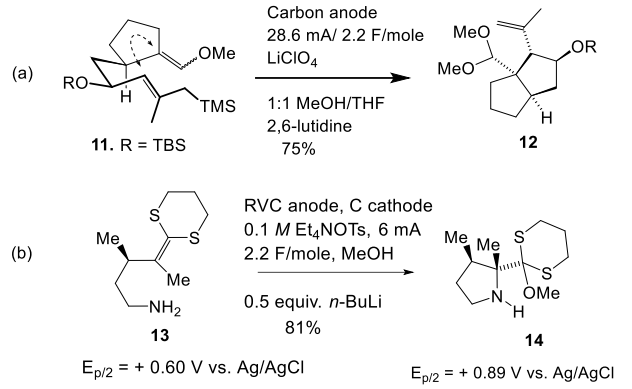


Scheme 3. Anodic Olefin Coupling Reactions.

To push this idea further, the exact same electrochemical method can be used to study oxidative cyclization reactions of the type illustrated in Scheme 3. Oxidized substrate like **7** goes a cyclization and get **8**, which is followed by the second oxidation, and downstream eliminations that provide **9** and **10** in sequence. These reactions are triggered by the oxidation of electron-rich olefins that have oxidation potentials that range from+ 0.6 V vs. Ag/AgCl to +1.5 V vs. Ag/AgCl.[8-11] The selectivity required for the reactions to avoid over-oxidation of the product can be as low as 100-200 mV. For comparison to the amide oxidation chemistry shown in Scheme 2, consider the two reactions illustrated in Scheme 4. The first shows an oxidative coupling reaction between an enol ether and an allylsilane to form a bicyclic ring skeleton and a quaternary center.[12] The oxidation potential required for the transformation was approximately $E_{p/2}$ = + 1.4 V vs. Ag/AgCl. The second reaction highlights a similar reaction oxidative coupling reaction between two nucleophiles in a substrate that has an oxidation potential of $E_{p/2}$ = +0.6 V vs. Ag/AgCl.[13] In this case, the oxidation potential for the product was $E_{p/2}$ = +0.84 V vs. Ag/AgCl, only 240 mV greater than that of the substrate. This difference in oxidation potential was not an issue for the electrolysis, and the selective oxidation was achieved without any evidence of over-oxidation.

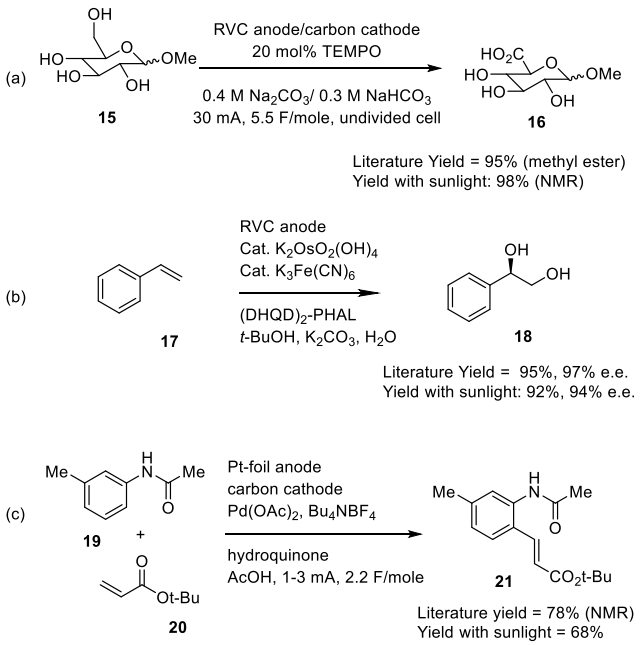
When the chemistry in Schemes 2 and 4 are considered together, the substrates used ranged in potential from +0.6 V to approximately +2.1 V vs. Ag/AgCl (the oxidation potential for the functionalized amino acid derivative). Two of the reactions utilized acid sensitive substrates, and two of the reactions required selectivity with respect to the potential over-oxidation of the products generated. No single chemical oxidant would be capable of studying these reactions as a group. An oxidant that was compatible with the oxidation of substrate **11** would clearly lead to oxidation of product **14**. An oxidant that was capable of selectively oxidizing substrate **13** and not product **14** would clearly not lead to any oxidation of substrate **11**. These issues were a problem for the constant current electrolysis method used to accomplish both transformations. In all three cases, the working potential at the anode simply adjusted to the oxidation potential of the substrate and then remained there for the bulk of the reaction leading to the

selectivity observed. It is clear that electrochemistry offers a highly versatile method for conduction oxidation reactions.



Scheme 4. Examples of Oxidative Cyclization reactions.

This versatility is not restricted to direct oxidation reactions.[14] In an indirect electrolysis, the reaction is mediated with a



Scheme 5. Mediated electrochemical oxidation reactions.

chemical reagent. This frequently leads to a level of synthetic selectivity in the reaction that cannot be obtained at an electrode surface alone. Consider the chemistry highlighted in Scheme 5. In the first reaction, a primary alcohol is oxidized over a number of more electron-rich secondary alcohols because of the use of a sterically hindered chemical mediator.[15] In the second, a product is generated with control over absolute stereochemistry because of the use of a chiral mediator.[16] In the third, a directed CH activation reaction is highlighted.[17] In each case, the chemical oxidant used to obtain the selectivity was recycled at an anode so that it could be used as a catalyst. The result was a series of reactions that capitalized on the selectivity of the chemical reagent while maintaining the advantages of sustainability offered by electrochemistry. Note that the chemical oxidants themselves were vastly different, and they have vastly different oxidation potentials. However, as in the case of the direct oxidation reaction highlighted above this was not an issue for the electrolysis. In each case, the potential at the working electrode automatically adjusted to the potential needed for recycling the chemical oxidant, and the same constant current electrolysis strategy used for the direct oxidations shown in Schemes 2 and 4 enabled all three of the reactions shown in Scheme 5.

The versatility of the method was further highlighted by conducting the reactions with a sustainable but not altogether consistent source of electricity. Each of the reactions shown above can be run with the use of a photovoltaic as a power supply.[14] All that is necessary for the reactions to run and run in a selective manner is a source of current.

A reversal of fortunes. Using synthetic chemistry to advance an electroanalytic method.

The methods discussed above are part of a much larger effort to utilize electrochemistry as a tool for developing new synthetic methods. Recently, we have been finding that this relationship between electrochemistry and synthesis can also work in the other direction. Namely, synthetic chemistry can be a very effective tool for developing new electrochemical methods. This effort grew out of our interest in developing new analytical methods for rapidly gathering accurate information about the binding of small molecules to protein targets. In these efforts, it is important to gather data on molecules with both weak and strong binding affinities for the chosen target, a scenario that led us to search for methods that would allow for monitoring binding events in "real-time" without any need to label either the chemical probe or the biological target.

It was against this backdrop that we became aware of microelectrode arrays and their potential as bioanalytical tools.[18-22] In particular, we were interested in the experiment highlighted in Figure 1. In this experiment, a molecular library is synthesized

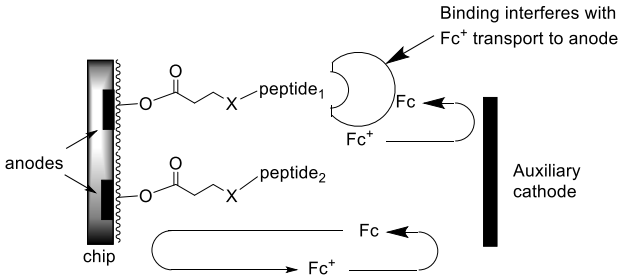


Figure 1. An approach to monitoring small molecule – receptor binding.

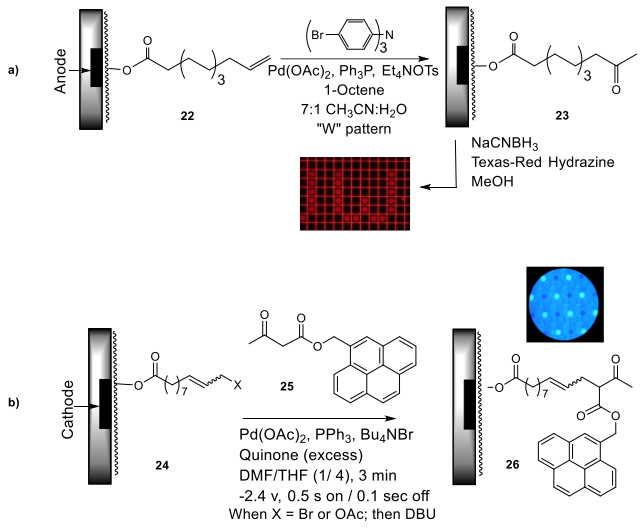
on a microelectrode array so that each member of the library is next to a unique, addressable electrode or set of electrodes in the array. The electrodes are then used to monitor the current associated with a redox mediator where the mediator is oxidized at the electrodes in the array and then reduced again at a remote cathode. When a receptor is added to the solution and binds to one of the molecules in the library, the receptor blocks the redox mediator from reaching the electrode below the molecule and the current at that electrode drops. This drop in current is used to monitor the binding event.

While the method is intriguing, its application to the analysis of small molecule libraries does require a new type of synthesis challenge. That challenge involves the construction of a complex, addressable molecular surface where each member of a molecular library is spatially isolated and located proximal to a specific electrode or set of electrodes in the array. The ability to solve this synthetic challenge in the end defines the types of problems the method can address. Fortunately, each site on the array is an addressable electrode that can support a current and be used for a constant current electrolysis, and as described above a constant current electrolysis is an extremely versatile tool for synthesis. With this in mind, we undertook an effort to explore and expand the scope of synthetic reactions that could be conducted site-

selectively on an array knowing that those methods would define the nature and range of biological problems that can be investigated using the devices.[22]

Key to this effort was the knowledge that we could not simply use the electrodes to trigger chemical reactions. The reactions had to be triggered at the electrodes and then confined to the region on the array immediately proximal to those electrodes. When this effort was begun, scientists at Combimatrix had illustrated an approach to accomplishing this for the generation of acid at selected sites on a microelectrode array.[20] In this effort, the array was treated with aqueous base and then acid generated at selected electrodes in the array by the oxidation of water. By controlling the concentration of base in solution and the rate of acid generated at the electrodes, acid catalyzed reactions could be confined to the surface of the array above the electrodes used for the oxidation. The methodology could easily be reversed for the site-selective generation of base on the arrays. The result was methodology compatible with the synthesis of DNA and peptide oligomers at electrodes in the array.

While this work was extremely successful, we needed a much broader set of chemical reactions in order to meet the challenge of building small molecule libraries on the arrays. With this in mind, we turned our attention toward the use of transition metal reagents and catalysts on the arrays. The idea was to treat the arrays with a precursor for the transition metal reagent or catalyst and then to use the electrodes to made the catalyst or reagent where it was needed. A chemical reagent would be added to the solution above the array to destroy the reagent or catalyst before it could migrate to neighboring electrodes in the array. As examples of these efforts, two complementary reactions are shown in Scheme 6. The first is a

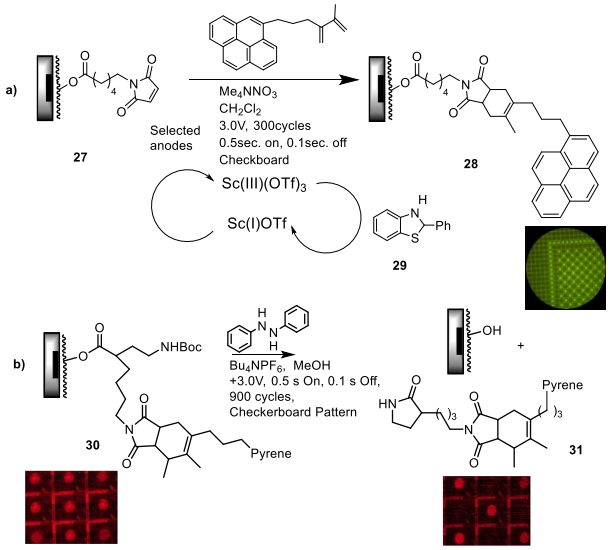


Scheme 6. Examples of complementary array reactions.

Pd(II)-mediated Wacker oxidation reaction,[23] and the second is a Pd(0)-catalyzed allylation reaction.[24] For both reactions, the array was coated with a porous reaction layer (agarose for the cases shown but frequently a diblock copolymer[25]), the substrate attached to that coating proximal to the electrodes in the array, and then a constant current passed between the array and a Pt-counter electrode. The first used the electrodes in the array as anodes and the second as cathodes. So the direction of current for the two reactions was opposite. Once the current in the cell was established, the working potential of the electrodes in the array automatically adjusted to match that of the substrate in solution. For the Wacker oxidation, the potential adjusted to that needed to oxidize a triarylamine in solution that then oxidized the Pd(0) pre-catalyst. For the allylation reaction, the potential adjusted to that needed to reduce the Pd(II) species in solution.

Of course, two reactions required the use of very different confining agents. For the Wacker oxidation, selected electrodes in the array are used to oxidize Pd(0) and generate the Pd(II)-oxidant then interacts with the double bond and facilitates formation of the carbonyl. The reagent is consumed by the reaction, so the use of a confining agent is needed only to keep any unreacted Pd(II)-oxidant from migrating to the neighboring electrodes. The best way of accomplishing this is to employ a substrate for the Wacker oxidation in solution. While we were able to demonstrate that the same substrate used on the surface of the array can also be used in solution to consume any excess Pd(II),[23] the better method is to use the electron-rich ethyl vinyl ether that is both fast and leads to ethyl acetate as the product from the reaction. The ethyl acetate evaporates from the surface of the chip following the reaction providing a "traceless" method for confining Pd(II) to the region surrounding the electrodes where it is generated.

Initially, reactions like that allylation reaction were trickier to design. In these cases, the reactions themselves are reduction reactions and the Pd(0) substrate is not consumed in the transformation. It is a catalyst. Hence, a solution phase variant of the surface reaction cannot be used as a confinement strategy to destroy the Pd(0) reagent. Instead, an oxidant is needed to destroy the catalyst. the confining agent in this case is used to destroy the catalyst. In the example shown, quinone was used as this oxidant. Oxygen is another frequent oxidant for these reaction. so that there is a need to continually regenerate it. Of course, the trick is that regeneration of the catalyst can be located at specific sites in the array. The result is again a confined reaction.

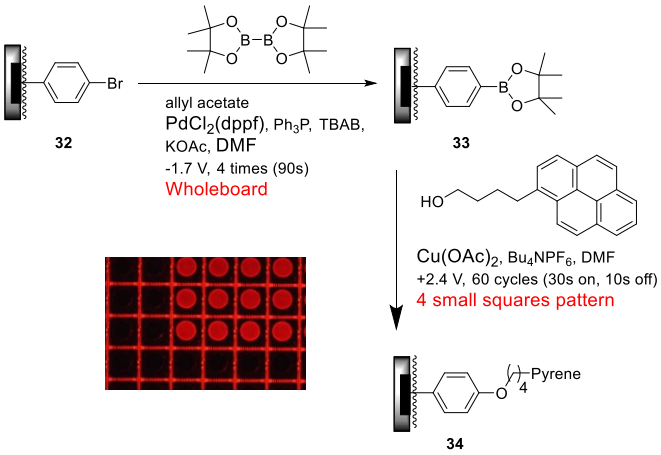


Scheme 7. Additional examples of site-selective reactions.

Both the oxidation and reduction strategies developed in connection with the use of Pd(II) and Pd(0) on the arrays are general, and a wide variety of chemical reagents have now been used site-selectively on an array.[22,26] As illustrated in Schemes 7 and 8 these new synthetic methods offer new opportunities for expanding the capabilities of array-based analytical methods. The chemistry shown in Scheme 7 highlights new opportunities for quality control of an addressable molecular library. In the first reaction shown in Scheme 7, selected electrodes in the array to generate a Sc(III) Lewis acid that then catalyzed a Diels-Alder reaction involving a dienophile on the surface of the array.[27] The Lewis acid was confined to the electrodes selected for the reaction by placing an electron-rich aryl ring in the solution above the array. This aryl ring reduced the Sc(III)-catalyst before it could reach a neighboring electrode. The second reaction shown illustrates how the product from this Diels-Alder reaction can be characterized. In

this case, the dienophile for the reaction was attached to the array with a Kenner-type safety catch linker that can be cleaved with acid.[28] The Diels-Alder reaction was then run at every electrode in the array. The product was then recovered from selected sites on the array by using the neighboring electrode to generate acid by the oxidation of diphenyl hydrazine. The acid cleaved the Boc protecting group on the amine leading to lactam formation and removal of the linker and product from the array. The lactam was characterized by LCMS and independent synthesis. The overall approach allows for the characterization of any molecule generated and analyzed on an array. Since the same electrodes are used for placing or synthesizing a molecule on the array, monitoring binding events involving those molecules, and recovering the molecule from the surface using the cleavable linker, the fidelity between a positive signal in a biological study and characterization of the molecule or molecules on the surface of the electrode leading to that signal is perfect.

In Scheme 8, a reaction strategy for solving a key challenge faced when assembling and studying array based libraries is presented.[29] One of the key elements required for employing the



Scheme 8. Sequential reduction-oxidation sequences and a synthetic solution to a difficult challenge.

arrays as outlined is the porous polymer surface used to coat the arrays and provide attachment points for fixing molecules proximal to the electrodes in the array. To date, the most effective surface in terms of reactivity, stability, and compatibility with signaling studies has been a diblock copolymer surface that contains a polystyrene block for adding groups to the polymer and a cinnamate functionalized methacrylate block that allows one to add stability to the surface through photochemical crosslinking.[25] Two such surfaces are particularly useful. One is derived from a bromostyrene group leading to arrays like **32** and the other from a borate ester substituted styrene leading to arrays like **34**. The bromostyrene surface is an outstanding surface for synthetic efforts but is not suitable for signaling studies. It is not very polar so it does not swell sufficiently in water to be permeable with respect to the redox mediator used. Therefore, only small currents can be measured for the redox mediator.

On the other hand, the borate ester derived surface is more hydrophilic, swells better in water, allows for larger currents and hence better data when used to support signaling studies. However, it is not stable enough for synthetic efforts. The result is that one surface is ideal for synthesis but bad for signaling and the other is ideal for signaling but bad for synthesis. Fortunately, as illustrated in Scheme 8 this is a problem that can be resolved by taking advantage of the synthetic methodology developed for the arrays. Arylborate esters can be made from arylbromides using either a Pd(0) or Cu(I) catalyst,[30] and both catalysts have been used site selectively on an array. With this in mind, an array coated with the arylbromide based polymer was treated with a Pd(II) precursor and the dipinacol borane. The electrodes in the array were all used as cathodes to reduce the Pd(II) precursor into a Pd(0) catalyst that in turn facilitated a transformation of the arylbromide surface into the arylborate by every electrode in the array. Following that reaction, the array was treated with a Cu(I) precursor and a fluorescently labeled alcohol. Blocks of 12 electrodes each were then used as anodes to site-selectively oxidize the Cu(I) reagent to form the Cu(II) reagent needed for a Chan-Lam coupling reaction. The success of the Chan-Lam reaction, which does not work with the arylbromide surface, can be seen in the image provided in Scheme 8. This image also highlights the success of the first reaction because the Cu(I) precursor would catalyze an addition of the alcohol nucleophile to the arylbromide surface.[21] Hence, the absence of fluorescence at the sites not selected for the Chan-Lam coupling reaction shows that conversion to the borate ester was complete at those electrodes.

The chemistry highlighted in Scheme 8 illustrates how the electrodes in an array can be used as both cathodes and anodes in a synthetic sequence. In each case, the potential at the electrode surface adjusts to the reagent present by simply setting the array to be either negative (the reduction) or positive (the oxidation) relative to a remote Pt-electrode. The result is that the ideal surface for synthesis and the ideal surface for signaling can both be used on the same array; a situation that assures that a molecular library can be synthesized with the optimal surface and then analyzed with the optimal surface.

A second reversal. Lessons from the arrays and their application to the development of new synthetic advances.

While the use of the synthetic chemistry on the array has been mainly focused on developing the arrays as bioanalytical tools, the development of that chemistry has led to significant opportunities to advance synthesis as well. One particularly intriguing opportunity involves the confinement of reactions run on the arrays. In an array based experiment, the reagent, catalyst, or substrate generated at the electrode is confined to within 25 microns of its site of origin. This means that the ensuing chemical transformation occurs at a specific site in the reaction. A similar confinement of a preparative scale reaction might afford interesting new possibilities for selectivity conducting reactions. Consider the experiment suggested in Figure 2. In this experiment, two alcohols would be subjected to an oxidation reaction mediated with a

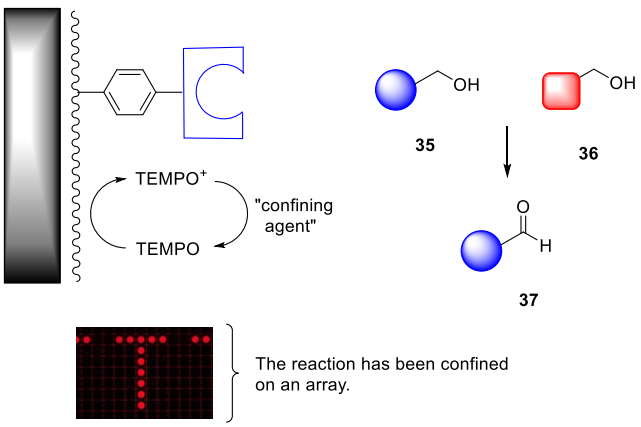
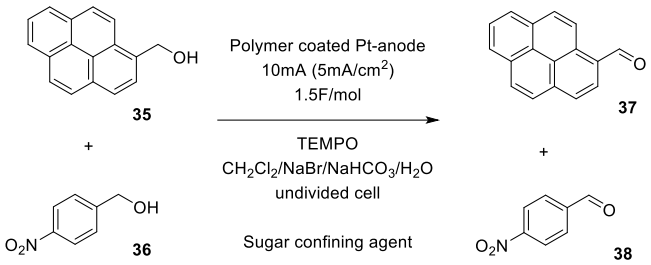


Figure 2. A new plan for selectivity.

TEMPO-based oxidant generated at an anode. One of the alcohols would have an affinity for the surface of the anode. The other would not. The TEMPO-based oxidant would be generated at the electrode and then a confining agent added to solution in order to destroy any TEMPO-based oxidant that migrated away from the

electrode. Hence, the oxidation reaction would only occur in the region of the reaction proximal to the electrode, a situation that should favor selective oxidation of the alcohol that bound to the surface of the array. In essence, the binding event would increase the local concentration of one of the alcohols in the exact location where the TEMPO was being generated and confined. An image is shown in the Figure 2 for a related array-based TEMPO mediated oxidation that illustrates just how effective the confinement strategy can be. In the array reaction, the TEMPO-based oxidant was generated in a T-pattern in the presence of a solution phase electron-rich aryl ring substrate for the TEMPO oxidant.[26] The resulting alcohol oxidation was clearly confined to only the T-pattern of electrodes. The same strategy utilized in a preparative reaction would insure that the only TEMPO available in the reaction for the oxidation reaction would be at the electrode surface.

As a proof of principle experiment for this approach, the competition study shown in Scheme 9 was selected. In this



Scheme 9. The planned competition study.

experiment, a 1:1 mixture of a pyrene methyl alcohol and a p-nitrobenzyl alcohol was added to a dichloromethane solution containing TEMPO, sodium bromide, sodium bicarbonate, and water. This solution was placed in an undivided cell with the Pt-anode and Pt-cathode. The Pt-anode could be coated with a polystyrene based polymer known to have an affinity with the pyrene group in one of the substrates, and an excess amount (10 equivalent to substrate) of confining agent (a methoxy sugar derivative - methyl-α-D-glucopyranoside) could be added to the solution in order to restrict the reactions in solution to the functionalized surface. And since this is a two-phase system at the beginning, a vigorous stirring is needed during the reaction. The reaction was run to 50% conversion so for an unselective reaction a 1:1:1:1 mixture would be obtained for the two starting materials and the two products. The reaction was monitored by proton NMR for the production of the two aldehydes. The data for three experiments is shown in Figure 3. In the first of these experiment (Figure 3. A), the reaction was conducted on a bare Pt-anode with no polymer coating. This control experiment led to the formation of the aldehyde products in a roughly 1:1 ratio. Clearly, there was no selectivity observed. When the electrode was coated with the polystyrene polymer with known affinity for the pyrene group, a small amount of selectivity was seen for the pyrene based substrate (Figure 3. B). However, the selectivity was on the order of 2:1 to 1.6:1. Most of the reaction occurred away from the electrode surface.

This conclusion changed dramatically when the confining agent was added to the reaction with the polymer coated electrode (Figure 3. C). In this event, the TEMPO-based oxidant was confined to the region of the reaction proximal to the electrode. Hence, the substrate with the greatest affinity for the polymer was selectively oxidized. In this case, that meant that the pyrene labelled alcohol was favored in the reaction; a situation that could be clearly seen in the proton NMR. Oxidation of the pyrene substrate was preferred in a 17:1 to 14:1 ratio. Even when the current density of the reaction was increased from 5 mA/cm^2 to 20 mA/cm^2 (a change meant to overwhelm the confining agent and increase the reaction in the bulk solution), an 11:1 ratio favoring oxidation of the pyrene-based substrate (Figure 3. D). Clearly, *confinement of the reaction to the surface of the electrode allowed for a new type of selectivity in the preparative reaction*.

This is a potentially powerful observation. The selectivity in the reaction was not dependent on the oxidant itself, but rather where the oxidant was located. Hence, it is easy to imagine that a similar type of selectivity could be gained for any mediated electrochemical reaction. Furthermore, since the selectivity is based on a molecular recognition event between the surface of the array and the substrate that does not involve the reacting center, the recognition element in the substrate does not need to be located anywhere near the reacting center, a situation that would allow for the control of a reaction using a remote asymmetric center, aromatic ring, etc. Work to explore the generality of this new method for chemical selectivity is underway.

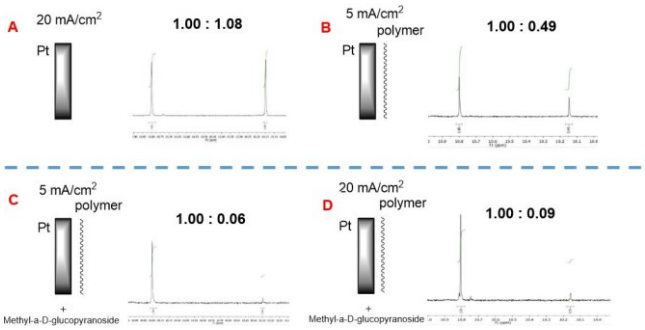


Figure 3. Data from the selectivity experiment. The downfield aldehyde signal is due to the pyrene aldehyde **37**.

Conclusions

For many years, the fields of organic synthesis and electrochemistry have thrived, frequently as independent enterprises. Fortunately, recent developments have begun to remove this divide as synthetic chemists further embrace the opportunities that electrochemistry provides for directly making reactive intermediates and enabling the use of chemical oxidants and reductants as catalysts. We are also beginning to realize that organic synthesis can empower electrochemical methods in ways previously not possible. Certainly synthetic methods have been used to modify electrode surfaces in the past, but now with increasing emphasis on the development of new electrochemically driven synthetic methods a significantly larger synthetic toolbox is available to electrochemists wishing to capitalize on that approach. In turn, those efforts are now providing new lessons about how electrochemical reactions work and can be controlled; lessons that can inform the development of even newer approaches to synthesis and chemical selectivity. This synergistic relationship between synthesis and electrochemistry results in both fields offering opportunities to expand and improve the utility of the other. These opportunities include the development of new catalysts for optimizing the chemical selectivity of electrochemical transformations, the exploration of new transformations that capitalize on both oxidation and reduction reactions in the same flask, the use of multiple electrocatalysts to control different steps in a multistep reaction sequence, the utilization of highly reactive radical cation and radical anion intermediates to trigger cascade reactions and overcome the barriers associated with strained rings and sterically hindered centers, and the use of new synthetic methods to build more complex, targeted, and electrochemically addressable molecular libraries. Yet while it is easy for an individual pair of authors to list such a collection of ideas, the true

opportunity for science on the electrochemistry – synthesis interface lies not in that specific view but rather in the fact that the barriers separating the two fields have come down in a manner that enables the imagination of both communities to capitalize on the tools developed by the other.

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