Capitalizing on Mediated Electrolyses for the Construction of Complex, Addressable Molecular Surfaces.

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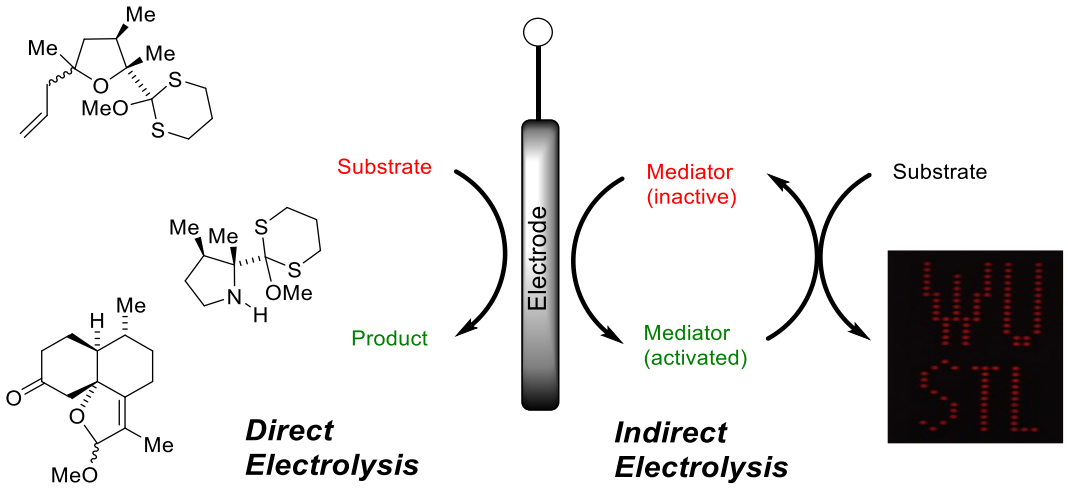
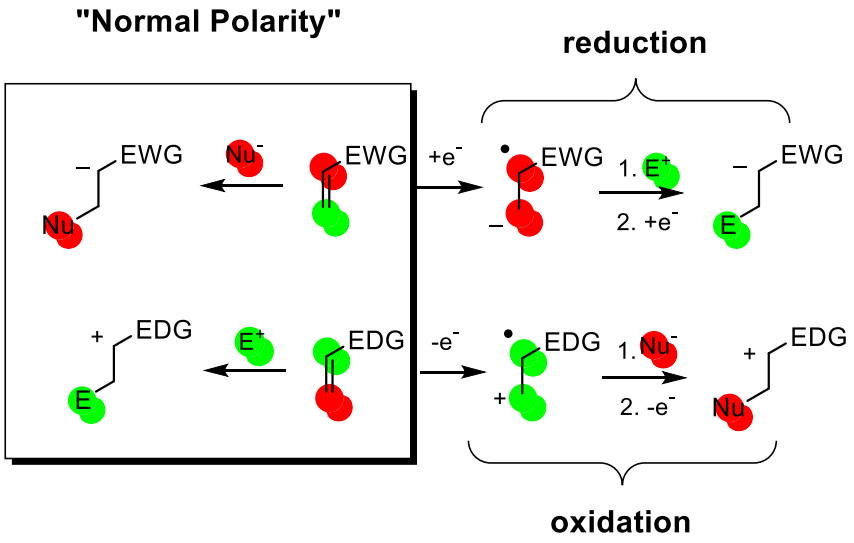


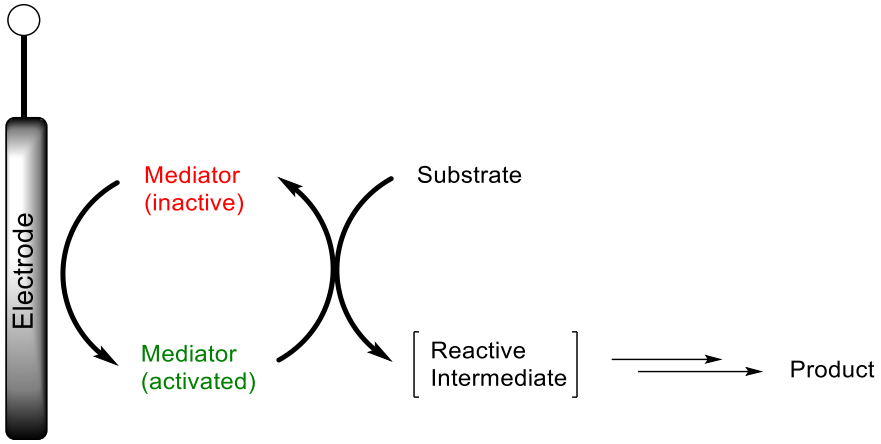
ABSTRACT: Synthetic organic chemists are beginning to exploit electrochemical methods in increasingly creative ways. This is leading to a surge in productivity that is only now starting to take advantage of the full-potential of electrochemistry for accessing new structures in novel, more efficient ways. In this perspective, we provide insight into the potential of electrochemistry as a synthetic tool gained through studies of both direct anodic oxidation reactions and more recent indirect methods, and highlight how the development of new electrochemical methods can expand the nature of synthetic problems our community can tackle.

Because electrochemistry can be used to oxidize and reduce a wide variety of substrates at controlled potentials while avoiding the generation of waste products, it has long intrigued members of the synthetic community.[1-16] Two main synthetic opportunities have fueled that intrigue. The first is that the direct oxidation or reduction of a substrate at the surface of an electrode can be used to reverse the polarity of a known functional group (Scheme 1).[17] This is one of the things that electrochemistry does



Scheme 1. Electrochemistry and Umpolung Reactions (EWG = electron-withdrawing group, EDG = electron-donating group, Nu = nucleophile, E = electrophile).

best. The reactions remove electrons from electron-rich groups, making them electron-poor, and add electrons to electron-poor groups, making them electron-rich. The result is an opportunity to utilize functional groups in new ways, and in turn capitalize on those opportunities to not only discover more efficient methods to accomplish transformations within a given synthetic sequence, but also to discover entirely new synthetic sequences. The second opportunity that makes electrochemistry an intriguing synthetic technique is the possibility of using an electrode to recycle a wide variety of chemical oxidants and reductants (Scheme 2).[4, 18] These indirect methods where a mediator is used between the electrode and a chemical substrate offer opportunities to both use known oxidants and reductants in more



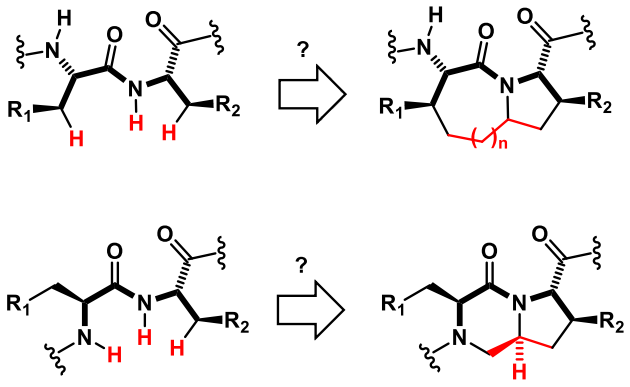
Scheme 2. A mediated or indirect electrolysis.

efficient ways and to synthesize new reagents or combinations of reagents that allow for novel synthetic transformations. Many examples are featured in the cited reviews. [1-17]

Because this paper is a "personal-perspective", it will primarily focus on efforts from our labs. However, it is important to note that those efforts would not be possible without the work of a dedicated collection of both past and present pioneers that continue to inspire us every day. Without the early efforts of Manuel Baizer, Henning Lund, Hans Schäfer, Dennis Peters, Al Fry, Christian Amatore, Anny Jutand, Sigeru Torii, Tatsuya Shono, James Utley, Jacques Simonet, Toshio Fuchigami, Kenji Uneyama, Petra Zuman, Jun-ichi Yoshida, Ikuzo Nishiguchi, Tsutomu Nonaka, Eberhard Steckhan, James Grimshaw, Jean Lessard, David Wayner, David Evans, John Swenton, Larry Miller, R. Daniel Little, Norman Weinberg, and so many others, our work would not have been possible. Over three decades ago, they welcomed a young scientist into the field of organic electrochemistry, showed him how much he needed to learn, and helped him to learn it. In return, we hoped to translate the beautiful work that was being accomplished by this energetic group of scientists into a message that could be better appreciated by the larger synthetic community.[19]

For this task, we looked for electrochemical reactions that could be used to address important synthetic challenges. Initially, we avoided the types of indirect electrochemical reactions that serve as the backdrop for this perspective because of the beautiful work being done by the Torii, Wayner, and Schäfer groups among others. They were demonstrating the use of indirect electrochemical oxidation reactions for the asymmetric dihydroxylation reaction,[20-22] Wacker oxidation,[23-25] and selective alcohol oxidations.[26-28] The development of those reactions was far from solved, but the effort did not seem to need our input as much as other areas. So, we focused instead on two known reactions: the Shono oxidation[29-30] – a vehicle for us to learn electrochemistry – and the oxidation of electron-rich olefins.[31-40] Both reactions were synthetically intriguing in ways we thought would be attractive to synthetic organic chemists interested in molecule building. Here, we will take a brief look at those two efforts and the foundation they laid for all of our subsequent efforts.

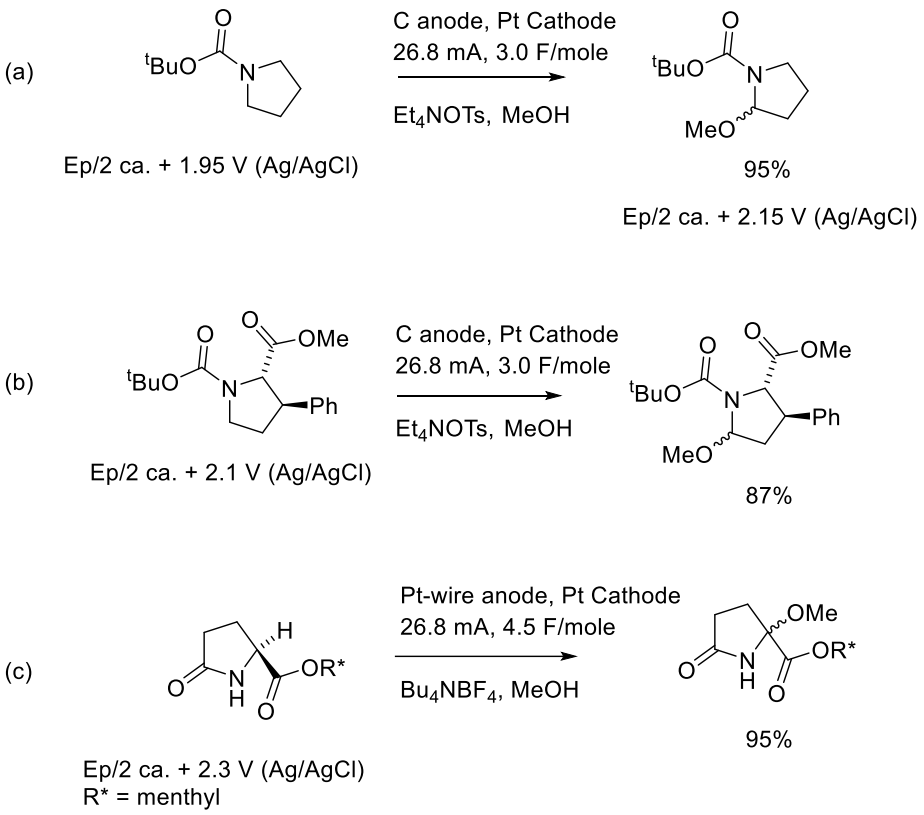
When we started, the Shono oxidation was already well-recognized for its synthetic potential, and the Shono group had published a paper in *Org. Syn.* that provided the community with a detailed procedure for how to conduct the reaction.[41-42] Many synthetic groups were capitalizing on the method.[43-45] At the time we were working to solve a synthetic challenge that had been brought to us by Professor Garland Marshall and his collaborators at the WUStL School of Medicine (Scheme 3).[46-47] They were working on approaches to "map" the conformational requirements of biological receptors and were hoping to take greater advantage of conformationally constrained peptidomimetics in that effort. The idea was to imbed peptide backbones into polycyclic ring structures so that the shape of the backbone could be manipulated. On paper, the approach was easy. One simply removed spatially close protons in the peptide conformation of choice and replaced them with a bridge. In the lab, the story was more complicated. Replacing hydrogen



Scheme 3. An initial problem – replacing spatially close protons with bridges.

atoms with bridges required oxidation chemistry, and as part of that effort we needed a method for functionalizing the carbon alpha to a nitrogen so that we could annulate rings onto proline, pipercolic acid, and pyroglutamic acid derivatives. For this effort, the Shono oxidation was ideal, especially since there was a detailed experimental procedure to help us get started.

Three examples of Shono oxidations used in this campaign are shown in Scheme 4. These specific examples were selected because in combination they highlight the versatility of electrochemistry and one advantage of the reactions relative to the use of alternative chemical oxidants, namely that no single chemical oxidant could accomplish all three transformations. For the first substrate (Scheme 4a), generation of the methoxylated product from the Shono oxidation raised the oxidation potential of the product by approximately 200 mV relative to the substrate.[42] The second[48] and third[47] substrates both oxidized at a potential equivalent to or higher than the product from the first oxidation. Hence, a chemical oxidant that would enable a selective oxidation of the first substrate would not be capable of oxidizing the other two substrates that both have higher oxidation potentials. At the same time, an oxidant that was capable of oxidizing the third substrate would clearly lead to over oxidation of the other two. A third oxidant would be needed for the substrate in the middle. The anodic oxidation approach offered a way to avoid this complexity. The method utilized was a constant current electrolysis where the potential at the anode was allowed to simply adjust to whatever substrate was present.[49-50] In each case, the potential at

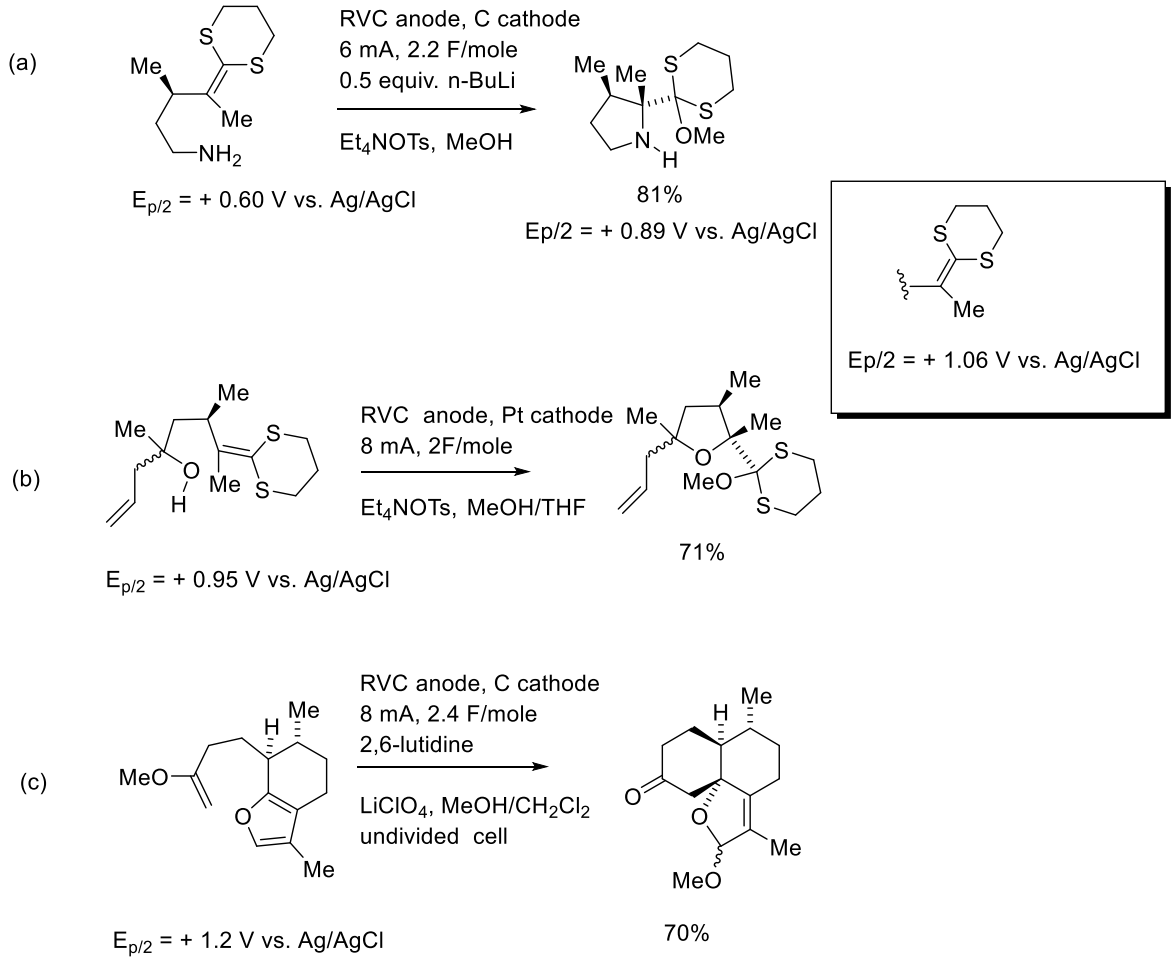


Scheme 4. Examples of the Shono oxidation.

the anode climbed until it reached that of the substrate to be oxidized and then held constant at that point until the majority of the substrate was consumed (at which case the potential would start to climb again). The result was a selective oxidation of all three substrates using the exact same method. The third oxidation (Scheme 4c) did require two changes to be made to the reaction conditions because the potential required for the oxidation was slightly higher than that required for the oxidation of the methanol solvent. For this reason, a "greasier" electrolyte was used in order to exclude methanol from the surface of the anode,[51] and a Pt-wire anode was used to increase the current density at the anode. This second change was made because in a constant current electrolysis when there is not enough substrate present to satisfy the current, the potential at the working electrode climbs. In this case, the higher current density and the electrolyte excluding the methanol caused the working potential to climb until it matched that of the amide

substrate. The result was a reaction that proceeded with a lower current efficiency but still provided a high yield of the desired product.

The second challenge we undertook made the point about the versatility of anodic electrochemistry even clearer. Our plan was to develop a new family of reactions that would take advantage of the umpolung chemistry illustrated in Scheme 1, and demonstrate how the use of an electrochemical oxidation reaction could open up new synthetic avenues for the construction of complex molecules.[52-53] The idea was to oxidize electron-rich olefins to generate highly reactive radical cation intermediates, and then use those intermediates to trigger new reactions that could overcome some of the challenges associated with



Scheme 5. Anodic Olefin Coupling Reactions.

tetrasubstituted carbon formation. Again, three examples have been selected for this perspective (Scheme 5). In the first, the anodic oxidation was used for the synthesis of a constrained amino acid derivative,[54] in the second it was used as a key step in the synthesis of nemorensic acid,[55] and in the third as a key step for the construction of the arteannuin ring skeleton.[56] In each case, the tetrasubstituted carbon was made in high yield showing the compatibility of the reactions for generating C-N, C-O, and C-C bonds. The reactions were again selected because no single chemical oxidant could accomplish all of them. An oxidant that could accomplish the first transformation without over-oxidizing the product would not be compatible with the second oxidation (or the third, with an oxidation potential near +1.2 V vs. Ag/AgCl). A chemical oxidant that could accomplish either the second or third oxidation would lead to over-oxidation of the first substrate. The first two reactions are particularly important for this illustration because both start with an oxidation of the same functional group. The difference in the potentials for the substrates are due to a Nernstian shift that reflects the rate of the cyclization reaction following the initial oxidation. A fast cyclization reaction removes the newly generated radical cation from the surface of the electrode. This changes the position of the equilibrium at the electrode surface and in turn lowers the potential measured for the reaction. The term "Nernstian shift" comes from the Nernst equation that relates the equilibrium at the electrode surface to the potential measured. Based on the potential of the starting dithioketene acetal (+ 1.06 V vs. Ag/AgCl) it would have been tempting to choose the same chemical oxidant for both substrates, a choice that would have made the reactions appear capricious when they did not behave the same. This is not a worry for an electrolysis reaction.

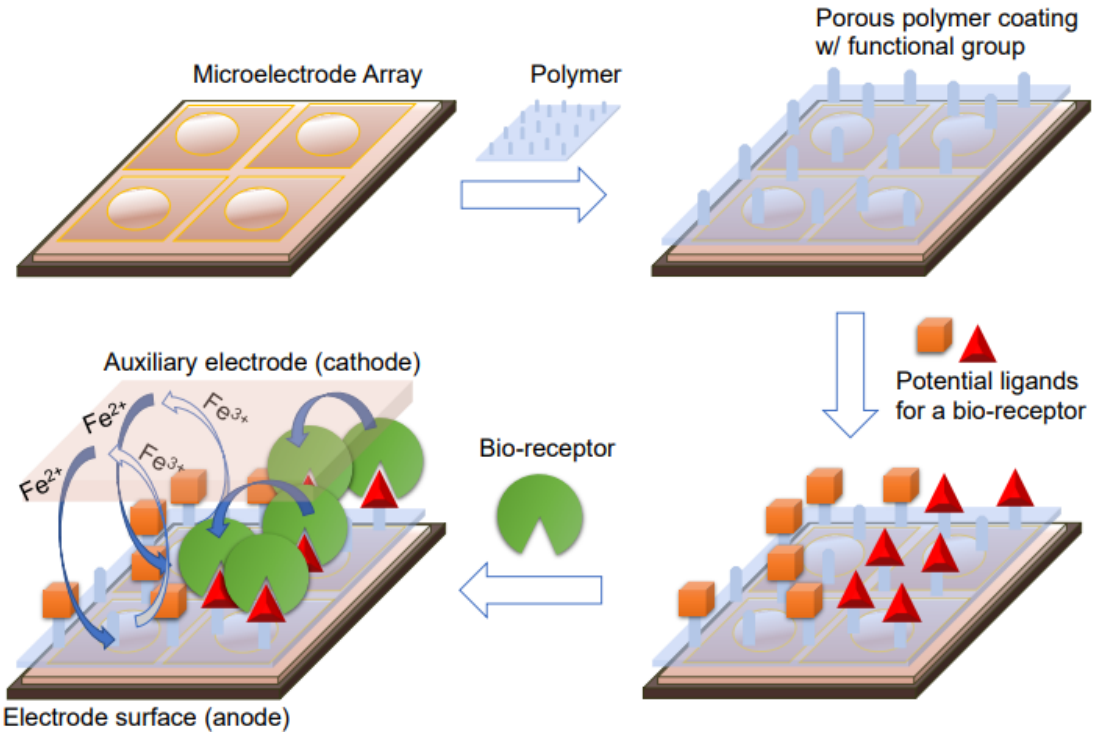
A comparison of all of the reactions shown in Schemes 4 and 5 illustrates how the constant current electrolysis reaction automatically adjusted to substrates ranging from +0.6 to + 2.3 V relative to Ag/AgCl while maintaining reaction selectivity of less than 200 mV, a truly impressive level of versatility. To oxidize these substrates with chemical oxidants would require multiple different reagents each of which has a potential matched to one of the substrates. In addition, the chemical reactions would all need to

operate under similar conditions so that the chemistry of the reactive intermediates generated could be compared and be neutral so that the dithioketene acetal substrates could be utilized. The use of electrochemistry avoided all of these issues and allowed for a systematic study of the reactive intermediates involved. [52] The result was a foundation for further synthetic efforts.

A New Challenge and the Need to Reassess an Early Decision:

Of course, when a synthetic chemist rules out exploring a method like indirect electrolysis, it is only a matter of time before a particular synthetic challenge leads one to break that "rule". In our case, that synthetic challenge again came from our collaborative efforts with the WUStL School of Medicine. In this case, the problem that arose had to do with how we could rapidly gather accurate biological data on molecules we were making so that the data could be used to guide further synthetic efforts. The need was especially acute as we moved toward an examination of molecules that could serve as probes for G-protein signaling pathways.[57-59] If one modifies a molecule that is selective for one pathway in the hopes of seeing activity in other pathways, then chances are good that the modified probe will have a weaker binding affinity with the G-protein associated with the new pathway. Weaker interactions of that nature can easily be missed using methods to monitor them that require washing steps, a situation that can lead to false negatives.

The desire to develop a method to help overcome these issues led us to consider expanding the use of microelectrode arrays as bioanalytical devices (Scheme 6).[60-63] The arrays are fascinating devices



Scheme 6. Microelectrode arrays and biological studies.

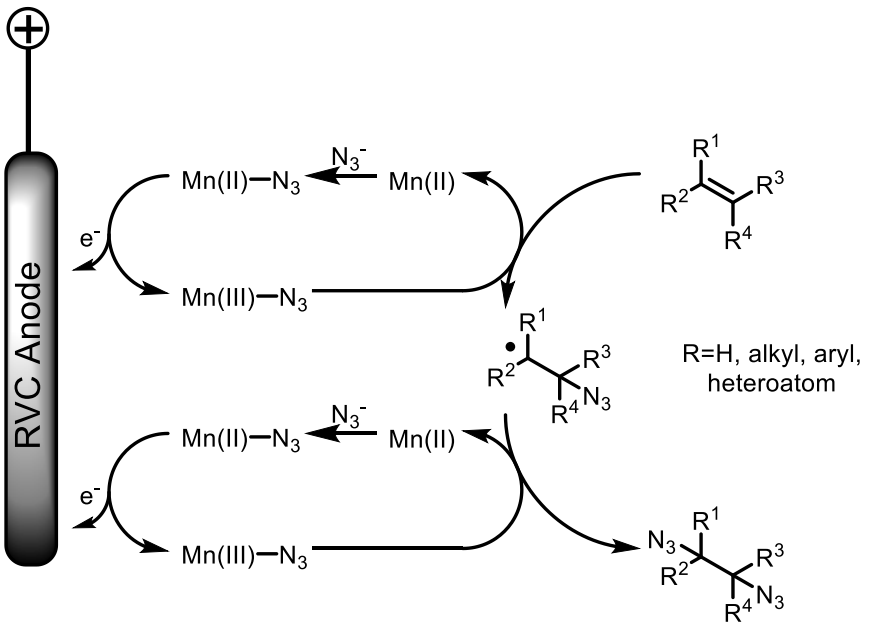
that contain thousands of electrodes in a small area (for the arrays we use that means 12,544 electrodes per square cm).[64-65] Each electrode is addressable and capable of measuring the CV of a molecule in the solution above the array. This capability means that the electrodes in the array have the potential to monitor biological binding events between the molecules in a molecular library and a target receptor in "real-time".[66-68] To do so, the array is first coated with a porous polymer that has functional group handles that can be used to add molecules to the surface of the electrodes in the array (Scheme 6, step 1). The members of the molecular library then need to be placed on the array above individually addressable electrodes (Scheme 6, step 2), and then the array placed in a solution containing a redox mediator and various concentrations of a biological target for the molecules in the library. The electrodes can then be used to measure a CV for the redox mediator (Scheme 6, step 3). When the biological target binds to a member of the library, it changes the surface of the array above the associated electrode and alters the current measured for the mediator. That change in current can be detected by the instrument and recorded.

Once again, on paper the approach is easy, but in the lab the story is more complicated because of a synthetic challenge. How does one build a two-dimensional addressable surface on the array so that each unique member of a molecular library is located proximal to a single electrode or group of individually addressable electrodes in an array (step 2)? Answering this question is the key to the whole approach, because in the end it is our ability to synthesize the surface that defines what can be studied using the array. It is a total synthesis challenge that requires not only solving the structural challenges associated with the molecules of interest, but also the logistical challenge of conducting that synthesis at a specific, predefined location. Fortunately, there is a synthetic handle at every site on the array, and that handle is the electrodes themselves. Those electrodes are coated with a porous polymer that renders direct electrolyses impossible, but as highlighted frequently in this special issue, electrodes are powerful tools when it comes to making and recycling chemical reagents and catalysts. With that conclusion, our group's reluctance to delve into indirect electrochemical reactions evaporated.[69-70]

Mediated Electrochemistry. A Primer:

In recent years, indirect or mediated electrochemical reactions have been dominating the development of new electroorganic synthetic methods. [1-17] They are popular because they retain all of the versatility and sustainability of electrochemical methods while capitalizing on the exquisite selectivity of chemical reagents and catalysts. Space in the context of a perspective will simply not allow us to highlight even a fraction of this work here. Instead, we will let this special issue fill in those details for us and focus on a few selected examples from the recent literature that serve to both illustrate the broad synthetic utility of employing electrochemistry to trigger new chemical transformations and highlight the use of mechanistically driven synthetic advances that provide the insights needed to apply the chemistry to new applications.

The push to advance mediated electrochemical processes has been motivated by two primary goals: the first is improving sustainability of chemical reactions by recycling reagents or replacing them with safer alternatives; the second is using mediators to introduce new modes of selectivity into chemical reactions. These two goals are not mutually exclusive. In their 2017 work, the Lin Group presented an elegant route towards accessing vicinal diazides from alkenes using a mediated electrochemical oxidation protocol that provides new opportunities for synthetic transformations in a sustainable way (Scheme 7).[71] The azide products generated can be readily converted to vicinal diamines, which are common motifs in natural products and are widely used as building blocks for stereoselective catalysts. Previous diazidation protocols for alkenes required harsh reagents that become dangerous upon scale-up. In addition, other routes to vicinal diamines utilized stoichiometric osmium or palladium complexes as nitrogen sources, neither of which present sustainable options for accessing this motif on an industrial scale. The Lin Group



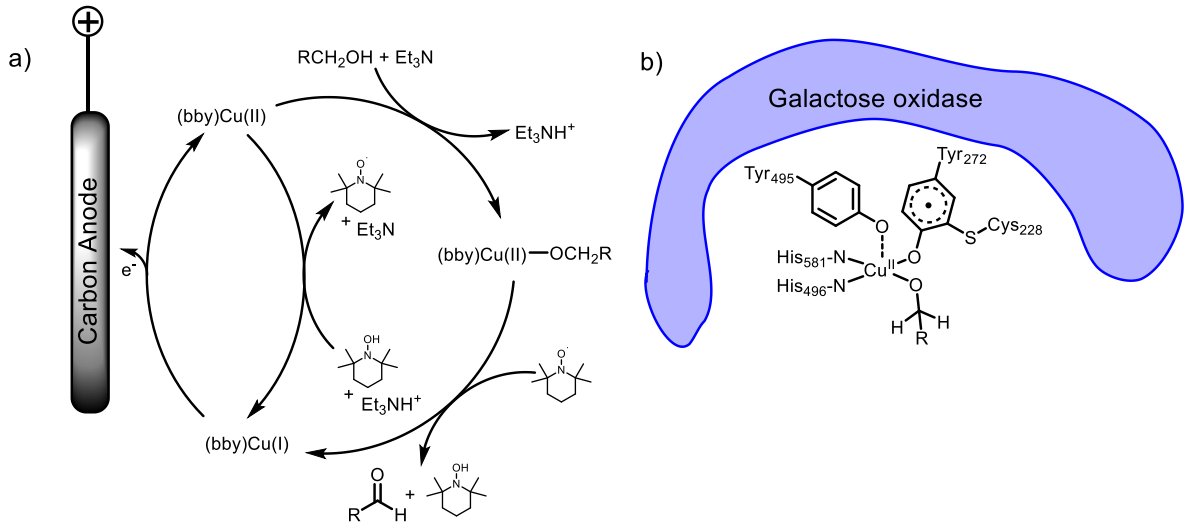
Scheme 7. The Lin Group and the oxidative functionalization of alkenes.

instead relied on sodium azide as a readily available and inexpensive nitrogen source and utilized an electrochemical method of turning over a manganese(II) catalyst that functioned both as the mediator for

the oxidation of the alkene and the catalyst to transfer the azide group to the amine carbon radical. The Mn(II) mediator was necessary to form the C-N bond; without it formation of byproducts rather than diazidation was predominant. The Mn(II) mediator also was able to successfully diazidate fully-substituted alkenes in a single step for the first time. The authors posit this is because the Mn(III)-N_3 complex activated the azide extremely well for group transfer to the carbon radical while maintaining a very small steric profile. Beyond using reagents that are sustainable, the only byproducts of the diazidation reaction are evolution of hydrogen gas and sodium acetate. In addition, spectroscopically pure material was obtained after simply passing the reaction mixture through a silica plug to remove electrolytes, obviating the need for excess solvent and water used in subsequent washing steps. In this work, the mediator gave the authors access to the group-transfer abilities of redox-active metal catalysts, which successfully led to a sustainable diazidation protocol with a very broad substrate scope owing to the electrochemical generation of the oxidized carbon radicals.

Many mediated electrolysis reactions benefit from consideration of both the electrochemical and chemical transformations involved and efforts to optimize both processes.[72] For example, the Stahl Group developed a Cu(II)/TEMPO co-mediator system for electrochemical oxidation of benzyl alcohol (Scheme 8).[73-75] TEMPO is the most widely studied electrocatalytic mediator for alcohol oxidation. Although organic nitroxyls have good turnover with a wide range of alcohol substrates, they are limited by the high electrode potentials necessary for generation of the reactive oxoammonium species. Other aerobic alcohol oxidation protocols rely on precious metals (such as palladium and ruthenium) and require pure O_2 rather than incorporating O_2 from the air. In this work, the authors set out to improve upon the electrocatalytic performance of TEMPO by pairing it with a Cu(II) catalyst. The optimized (2,2'-bipyridine)Cu(II)/TEMPO co-mediator system not only operates faster than the TEMPO system, but also is able to perform at an electrode potential half a volt lower than the TEMPO-only process. This strategy

mimics that used by nature in redox enzymes; specifically, the active side of galactose oxidase contains a Cu(II) that coordinates a tyrosine oxyl radical for cooperative oxidation.

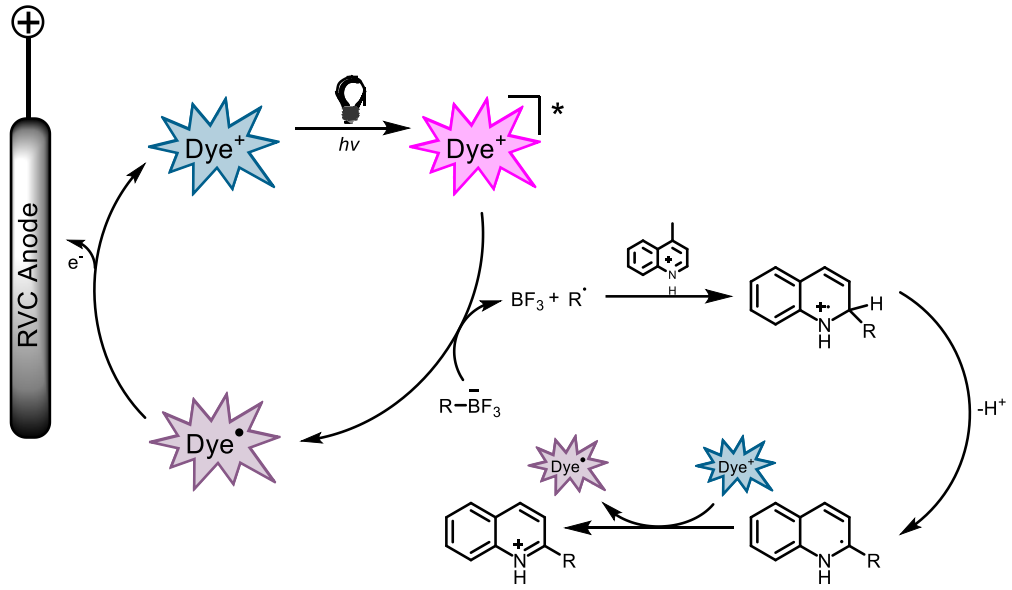


Scheme 8. The Stahl Group and the use of co-mediators.

What makes the (bpy)Cu(II)/TEMPO system able to function so well in alcohol oxidation is that it utilizes the low-potential TEMPO/TEMPOH 1-electron redox couple, rather than the high-potential TEMPO/TEMPO$^+$ 2-electron couple. Thus, this system relies on two1-electron transfers at lower potential, rather than one higher potential 2-electron transfer. In fact, the oxidation occurs at the (bpy)Cu(II)/(bpy)Cu(I) redox potential, rather than the nitroxyl potential. The nitroxyl is required for the alcohol oxidation to proceed, but functions as an electron-proton acceptor that is regenerated by subsequent reduction of (bpy)Cu(II) and deprotonation, rather than the standard TEMPO-mediated oxidation mechanism. The authors note that the nitroxyl component of the co-mediator system is modular. When they exchanged TEMPO for the less-sterically hindered ABNO, improved rates of reaction for all alcohols tested were observed, with the exception of methanol due to its small steric footprint. This work is an important foray into the development of electrocatalysts that do not rely on precious metals. The authors have shown that electron-proton transfer mediators such as nitroxyls can work in cooperation with

a first-row transition metal to provide proton-coupled two-electron reactivity at faster rates and lower overpotentials than traditional nitroxyl-only systems.

Another example of gaining enhanced reactivity from an existing system by utilizing a new mediator was provided by the Xu Group (Scheme 9).[76] In their 2019 publication, they developed a



Scheme 9. The Xu Group and the use of photoelectrocatalytic mediators.

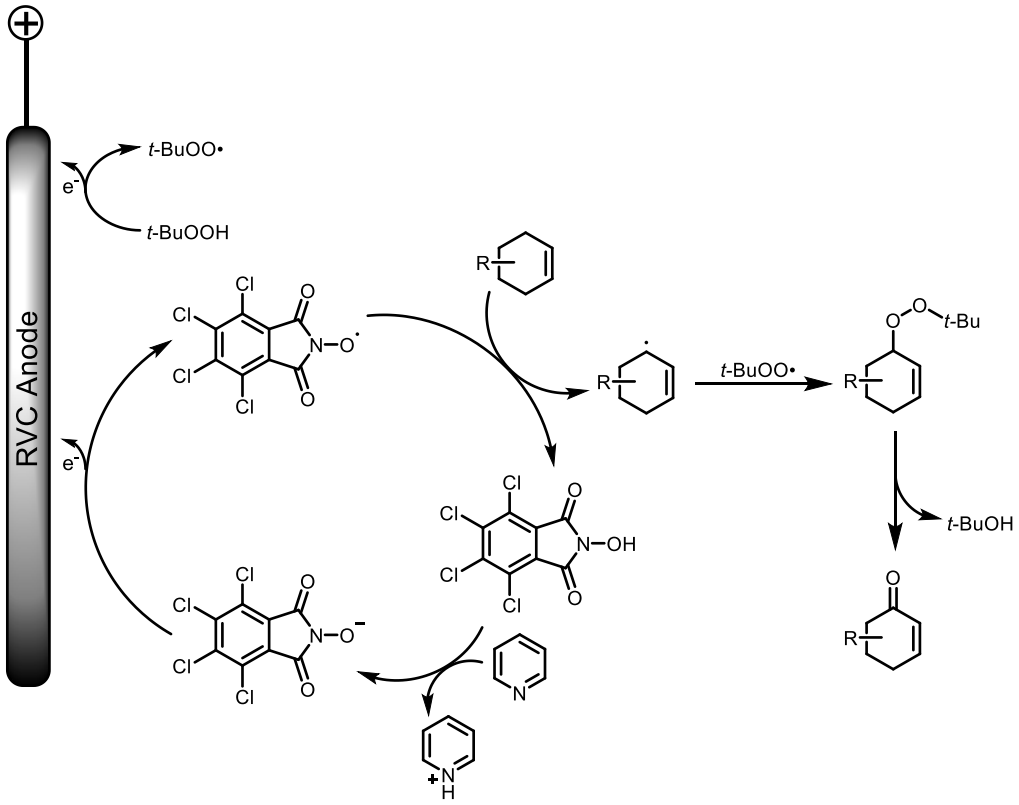
photoelectrocatalytic mediator that was able to facilitate C-H alkylation of heteroarenes by organotrifluoroborate radical precursors. Heteroarenes are prevalent in many biologically active compounds, from drugs and drug precursors to molecular building blocks like nucleic acids and amino acid side chains. In this work, the authors functionalized a library of heteroarenes using primary, secondary, and tertiary alkyltrifluoroborates with excellent control over regioselectivity and chemoselectivity.

This method utilized a sustainable photoelectrochemical oxidation for the formation of alkyl radicals. Classical methods of generating alkyl radicals often are hampered by over-oxidation to the carbocation. This stems from traditional radical precursors having higher oxidation potentials than the

radical being formed, especially in the case of stabilized radical species bearing π-systems or other α-stabilizing groups. Use of photoredox catalysts as mediators gets around issues of over-oxidations due to the transient nature of the redox-active excited state. In these reactions, an excited state of the redox-active catalyst is employed to oxidize the trifluoroborate and generate the alkyl radical. The excited state of the oxidant has a significantly higher oxidation potential than its ground state, a situation that facilitates radical formation. The anode is then used to regenerate the catalyst. The use of electrochemistry avoids the need to add a sacrificial oxidant for this effort. With this approach in place, Xu and coworkers chose organotrifluoroborates as the alkyl radical source because they are stable and readily obtainable. After screening several photocatalysts, the authors selected the organic dye $[Mes\text{-}Acr^{+}]ClO_4^{-}$ as photocatalytic mediator. While the reaction proceeds without removal of O_2, the yield in their screening conditions dropped from an isolated 87% to 63% in the presence of air. Interestingly, when the authors increased the current they saw a decrease in conversion, which implies that the photoexcitation step must occur on a similar timescale as the electron transfer step.

Using these optimized conditions, the authors were able to monoalkylate a large array of heteroarenes, while retaining functional groups sensitive to oxidation such as amines. They also explored the scope of the organotrifluoroborates that could be used to supply alkyl radicals. A host of cyclic and acyclic secondary organotrifluoroborates successfully alkylated the lepidine test substrate, including those containing functional groups such as carbonyls and Boc-protected amines. The authors also show that the approach can be used to generate alkyl radicals from a 1,4-dihydropyridine instead of the organotrifluoroborate thus further expanding the scopes of substrates that can be used. Finally, Xu and coworkers demonstrate that the reaction conditions could be used to successfully instigate an oxidative addition-cyclization cascade. The work discussed in this publication has provided a successful starting point towards using photoelectrochemical mediators to promote other oxidative radical transformations that do not rely on toxic oxidizing agents or radical initiators.

Another example a mediated electrolysis being used to expand the scope of a chemical transformation while improving sustainability was forwarded by Baran and coworkers in connection with their development of protocols for the oxidation of allylic systems (Scheme 10).[77] Allylic oxidations are



Scheme 10. The Baran Group and allylic oxidations.

among the most prevalent C-H functionalization reactions due to the diverse transformations that can be performed on enones and allylic alcohol intermediates generated. The electrolysis reactions circumvent the need to employ the more traditional methods that either use toxic reagents such as chromium and selenium or rely on precious heavy metal catalysts. This is important because the classical approaches were not compatible with performing allylic oxidations on an industrial scale. Indeed, prior to this work there was no sustainable method for performing allylic oxidations on a large scale. Thus the authors set out not only to devise an electrochemical oxidation protocol, but to ensure that the conditions developed

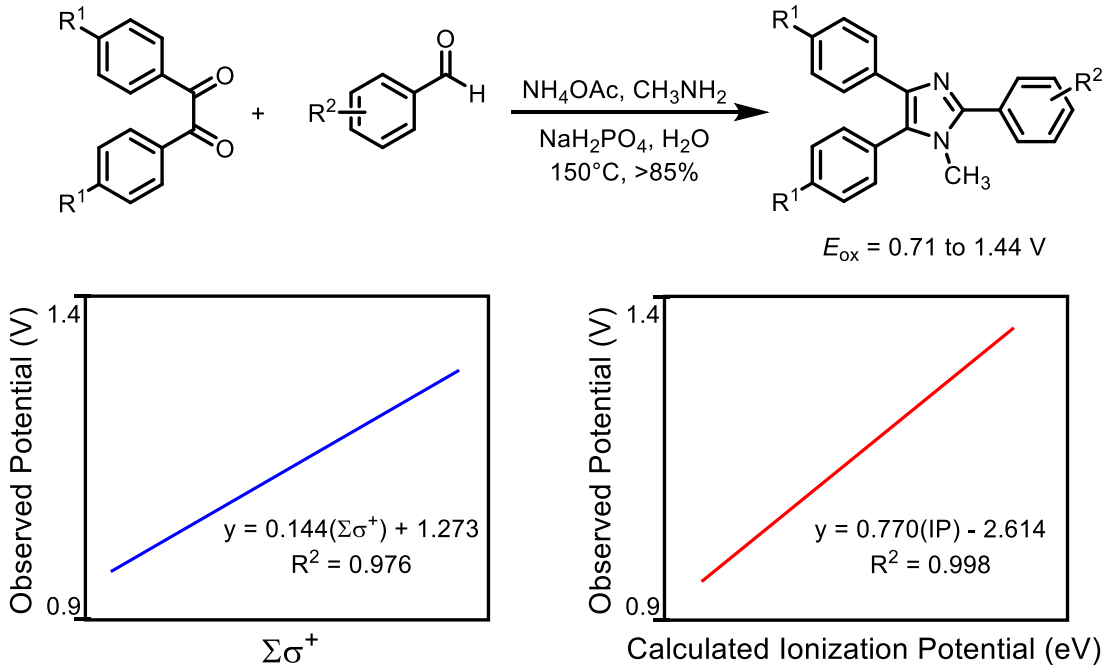
were inexpensive (both on the reagent side and the electrochemical setup) and readily adapted to an industrial scale.

Baran and coworkers built upon previous reports of electrochemical allylic oxidations and found that choice of mediator was critical to improving reaction yield and making the reaction scalable. Previous work relied on *N*-hydroxyphthalimide (NHPI) as the mediator and dissolved O_2 as the oxygen source.[78] Switching to *t*-butylhydroperoxide as the oxygen source raised the yield from 18% to 51%. In their initial mediator screen, the original NHPI mediator gave the highest yields. However, the authors propose that a deprotonation is necessary to generate the nitroxyl radical from the hydroxylamine precursor, leading the authors to hypothesize that addition of electron withdrawing groups would increase reactivity of the mediator. The conversion of NHPI to the N-oxide could also occur via a concerted proton-coupled electron transfer, as put forth by Stahl and coworkers.[79] This pathway would also be accelerated by electron-withdrawing groups. Thus mediator optimization to tetrachloro-*N*-hydroxyphthalimide (readily prepared from the industrial non-toxic flame retardant tetrachlorophthalic anhydride) further raised the yield to 77%. Notably, this yield was achieved without isolating reactions from O_2 or water and by only using reagents and solvents purchased in technical grade state.

In addition to the low cost and sustainability of these new electrochemical allylic oxidation conditions, a couple key aspects of the substrate scope are worth noting: first, substrates containing unprotected tertiary alcohols were compatible without elimination of the alcohol and aromatization, and second, no allylic rearrangement occurred. Both side reactions are common in chromium-based allylic oxidation reactions. For the bulk of the substrates investigated (cycloalkenes, monoterpenes, diterpenes, sesquiterpenes, and steroid-derived scaffolds), yields were compatible to previous non-sustainable methods. The work generated a host of pharmaceutically-relevant small molecule enone products. The authors did note a limitation in that reactions utilizing acyclic substrates led to lower conversions of

starting material. Still, the utility of the electrochemical method for maximizing sustainability while minimizing costs and enabling the oxidation of a wide variety of substrates was truly impressive.

One of the advantages of mediated electrochemical processes is the tunability of the mediator itself, as seen by increase in reaction yield in the previous example highlighted from the Baran-group. Taking this aspect of mediator design a step further, many research groups have developed modular mediator platforms, primarily for oxidative processes.[4, 9] A recent publication out of the Little group highlights this approach to mediator design and functionality (Scheme 11).[80] In their work, the



Scheme 11. The Little-group and the development of oxidative mediators.

authors built upon their previous efforts at developing a modular synthesis of triarylimidazoles as redox mediators.[81] These mediators facilitate the oxidation of electron-rich benzylic alcohols and ethers, converting them to the corresponding carbonyl. The authors made a large series of triarylimidazoles mediators with tunable redox potentials spanning more than a 700 mV range in redox potential. The

mediators in this work have oxidation potentials from 0.71 to 1.44 V, enabling them to oxidize a host a functional groups. The authors point out that this window of redox mediator potentials can actually be used with substrates that have an extended upper limit in oxidation potentials, since mediators can oxidize substrates over 500 mV higher in potential, depending upon the equilibrium constant and rate of subsequent oxidations involving the reactive intermediate generated from the substrate.[39] The triarylimidazoles form a mediator class that is complementary to the triarylamines developed in the Fry-group.[82]

In an effort to understand how the electronic properties of the component aryl rings affect the oxidation potential of the triarylimiazole, the authors performed a host of experimental measurements and complimentary computational studies. They were able to make a linear correlation between observed oxidation potential and both the calculated ionization potential and the sum of the Hammett σ^+ values for the substituents on the aryl rings. Although substituent effects did not drastically alter the observed oxidation potential, they did so in a predictable manner that was very similar to effects found in triarylamine frameworks. The authors hypothesize that the small influence of substituent effects on observed potential arises from bond rotation and distortion from planarity in the adjacent aryl rings. In a follow-up publication, Little and Francke locked these adjacent rings into planarity by bridging them into a phenanthrol[9,10-*d*]imidazole system.[83] Computational and voltametric studies supported the hypothesis. Interestingly, DFT calculations showed that in the phenanthroimidazole mediators the charge in the oxidized radical cation resides more in the imidazole core, suggesting that further modification by more strongly electron-withdrawing groups could increase the potential range of these mediators. In addition, CV studies indicate that the phenanthroimidazoles display far more reversible electron transfer behavior than the triarylimidazoles. Thus the authors developed a mediator platform that is straightforward to synthesize and characterize and spans a large range in potentials, further adding to the toolset of well-characterized redox mediators available for oxidative transformations.

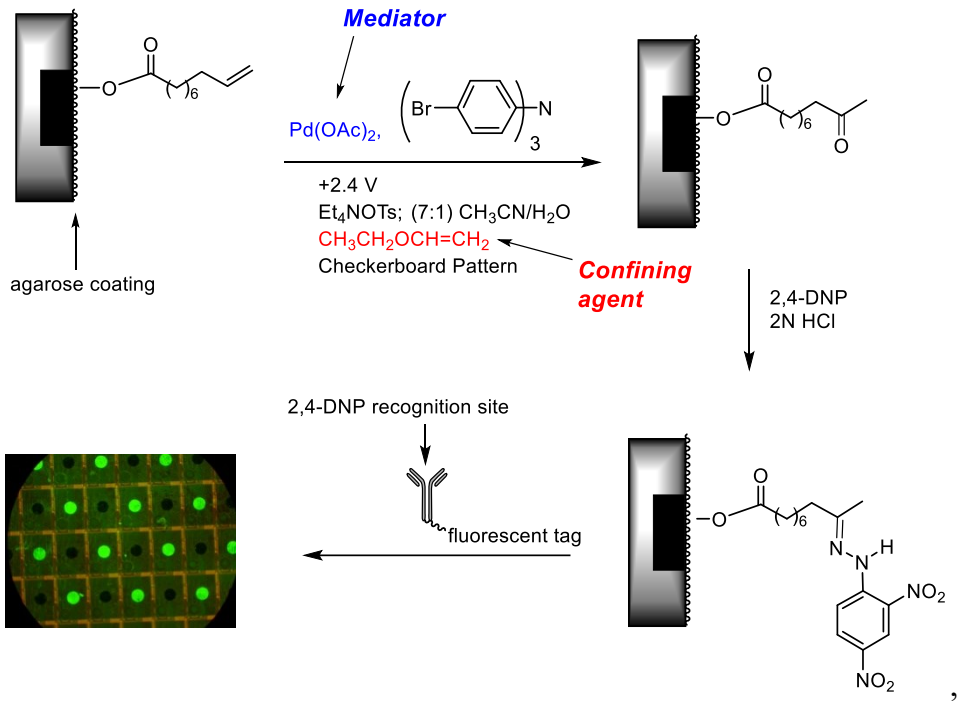
Mediated Reactions: Selectivity on an Array

Hopefully, it is becoming clear from that backdrop that indirect electrochemical reactions are powerful synthetic tools, and that the mechanistic understanding of the processes is such that we can design new transformations and applications. Our goal was to harness that synthetic potential and use it to conduct synthetic transformations at selected electrode(s) in a microelectrode array. It is our hope here that readers will see how the same approach to synthesis, methodology development, and the use of physical organic chemistry concepts that they are familiar with can be employed to shape the construction of an entirely new type of platform – microelectrode arrays.

From the start, part of the problem was easy to solve. Electrodes can be used to generate acids, bases, oxidants, reductants, nucleophiles, electrophiles, Lewis acid catalysts, transition metal catalysts, etc. Thus a large portion of synthetic chemistry can be initiated with an electrode; this includes the electrodes in a microelectrode array. The key was a plan for keeping those reagents and catalysts at the sites on the array where they were generated and required to react. When we started, scientists at CombiMatrix (now CustomArray) had just found a potential solution to those issues.[65, 84-85] They demonstrated that an acid generated at an electrode in an array could be confined to the surface of that electrode by conducting the reaction in a basic medium. The base neutralized the acid before it could migrate to remote sites on the array. By generating acid at a fast enough rate at an electrode, the amount of acid generated would overwhelm the base at that site and allow for an acid catalyzed reaction at that electrode. The exact opposite approach could be used to conduct basic reactions at selected electrodes in an array. We figured that if such an approach worked for acid and base, then a similar strategy might work for the confinement of a wide variety of catalysts and reagents.[69-70] One just needed something in the solution above the array to destroy whatever reagent or catalyst was generated.

What was needed was a suitable chemical starting point for testing the idea. For this, Pd-based chemistry seemed ideal because of the ease with which palladium can be cycled between stable reduced and oxidized species, an observation that led us to the choice of the electrochemical Wacker oxidation pioneered by Torii and Wayner.[23-25] An array based version of this reaction is shown in Scheme 12.[86] The effort began by coating an array with agarose. The agarose provides a porous polymer coating on the array that can be used to attach molecules (substrates for synthesis, ligands for a particular receptor, etc.) to the surface of the array above the electrodes. The surface must be porous enough for electrochemical mediators to pass through to the electrode below and yet stable to both the synthetic chemistry being used on the array and any subsequent signaling experiment. To date, several surfaces have been developed for these efforts.[87-88] It should be noted that we have avoided using self-assembled monolayers for attaching molecules to the surface of the electrodes because the requirement for long-term stability. Our goal is to build molecular libraries on the arrays and then use them to probe molecular interactions with biological targets without having to resynthesize the library for each new study. Self-assembled monolayers do not have lifetimes consistent with that objective.[89] For the initial study shown in Scheme 12, agarose was selected for the surface because it could be removed easily after the reaction and the array then recoated and reused. This is a common strategy for the development of new array reactions.

Following coating of the array, a base-catalyzed addition to the surface was employed to place an olefin-containing substrate by every electrode in the array. This reaction was accomplished by using all of the electrodes to reduce vitamin-B12 to generate a base, which could then catalyze an esterification reaction between the alcohols in the agarose and a N-hydroxysuccinimide ester. The constant current electrolysis was conducted by setting the electrodes in the array at a negative potential relative to a remote Pt-electrode. With the substrate placed on the array, every other electrode in the array was then used as an anode by setting the potential of the electrodes to a positive potential relative to the remote Pt-electrode.

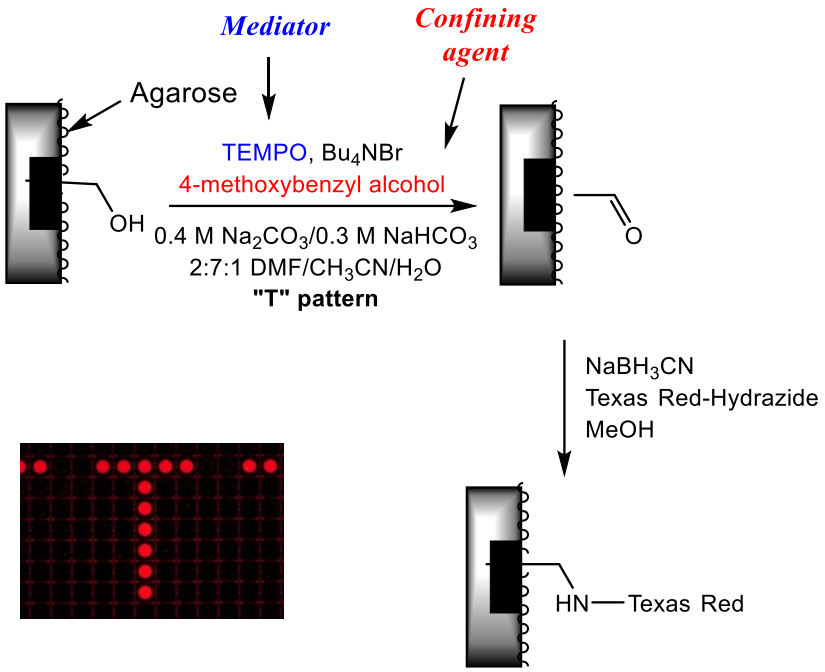


Scheme 12. The Wacker oxidation and a starting point.

The result was a mediated oxidation of Pd(0) to Pd(II) at those electrodes in the presence of the olefin attached to the electrode surface and water. The Pd(II) reagent served as the oxidant for the mediated electrochemical reaction. The reaction falls into the category of a "doubly mediated" process in which the trisbromophenyl amine is the species that undergoes the direct oxidation at the anode. The resulting radical cation then oxidizes the Pd(0)-species present. The reaction was conducted in this manner in order to optimize the electrode process and avoid Pd-deposition on the electrodes in direct analogy to the preparative Wacker-oxidation. The result of conducting this process at selected electrode in the array was a Wacker oxidation of the substrate attached to the surface of those electrodes selected for the transformation. The Pd(II)-oxidant being generated was confined to the surface of those electrodes with the addition of ethyl vinyl ether to the reaction solution above the array. Ethyl vinyl ether undergoes a rapid Wacker oxidation with Pd(II) in the presence of water to generate ethyl acetate and reduce the Pd(II)-species. The ethyl acetate generated was easily removed following the reaction. At the time, we thought that a more reactive olefin toward the Wacker oxidation might be needed to optimize the confinement

reaction, but this turned out not to be necessary and even simple alkyl olefins in the solution above the array were effective confining agents. After the reaction was complete, we did need a method to prove that both the reaction had worked at the selected electrodes and that the confinement-strategy had been successful. To this end, the array was treated with 2,4-dinitrophenylhydrazine to convert any ketones or aldehydes generated on the array from the Wacker oxidation into a 2,4-DNP derivative. The array was then incubated with a fluorescently tagged antibody that recognizes 2,4-DNP derivatives in order to label any hydrazine present on the surface of the array. As can be seen in the image provided, the Wacker oxidation proceeded nicely at only the electrodes selected for the reaction and we had our first example of an indirect electrolysis reaction that could be scaled down and used site-selectively on an array.

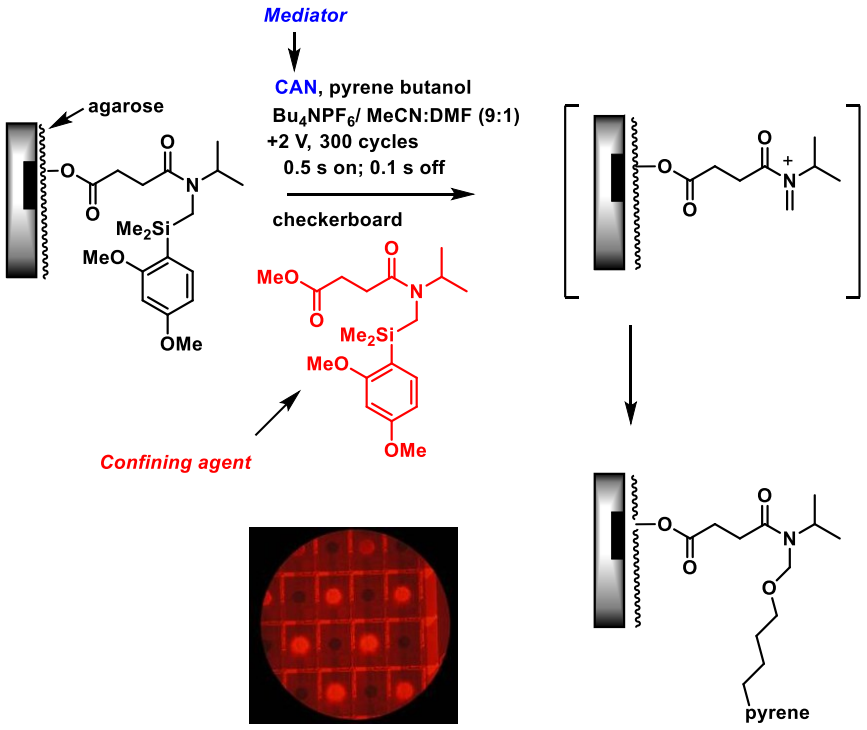
Following that initial success, we turned our attention to a series of reactions that would serve to define the generality of the approach taken. Next up was the TEMPO oxidation strategy developed beautifully for preparative reactions by Schäfer, Nonaka, and others (Scheme 13).[7, 26-28] In this case, the agarose surface itself was used as the substrate, a glucose derivative used as a confining agent, and a reductive amination reaction used to label the carbonyls generated on the surface of the array.[90] By using the surface coating on the array as the substrate, we hoped to gain insight into how well a reaction could be confined on the array, because the substrate was not only located by every electrode in the array, but also in between the electrodes. Glucose was selected as a confining agent because it was the substrate used by Schäfer and coworkers for their preparative reactions. So, we knew it would efficiently destroy any oxidant that escaped from the surface of an electrode used to generate it. As can be seen in the image provided, the reaction again worked beautifully. The array shown has 12,544 electrodes/cm^2, and even with substrate located in between the electrodes the reaction was confined to only the surface of the electrodes used for the oxidation.



Scheme 13. A site-selective TEMPO oxidation.

While a number of additional oxidation reactions have been conducted on the arrays, one more deserves mention here because of what it taught us about the ease of designing "site-selective" oxidation reactions (Scheme 14).[91] In this reaction, an N-acyliminium ion was generated at selected electrodes in an array. The confining agent used in solution was the same molecule used on the surface of the array. The chemistry was accomplished by setting up a solution phase oxidation of the substrate with only a catalytic amount of CAN, which was rapidly consumed. An array functionalized at every electrode with the same substrate was then inserted into the pre-oxidized reaction mixture, and selected electrodes turned on as anodes. The CAN oxidant was regenerated at those anodes and an oxidation of the surface bound substrate occurred. Any CAN that escaped from the surface of the selected electrodes was consumed by the excess of substrate in solution. In this case, the electrodes were cycled on for 0.5 sec and off for 0.1 sec. This was done to slow formation of the oxidant so that its concentration would not overwhelm the confining agent present. This is a common trick that is used to optimize the confinement of an array reaction when it is not ideal. It frequently provides a finer level of control than adjusting the concentration

of the confining agent. To determine the success of the reaction and confinement strategy, the reaction was conducted in the presence of pyrene butanol, which trapped the N-acyliminium ion generated. The surface of the array was then incubated with acid and a fluorescently labeled alcohol, which would react with any exposed N-acyliminium groups. The array could then be viewed under a fluorescence microscope to determine success of the reaction and degree of confinement obtained.

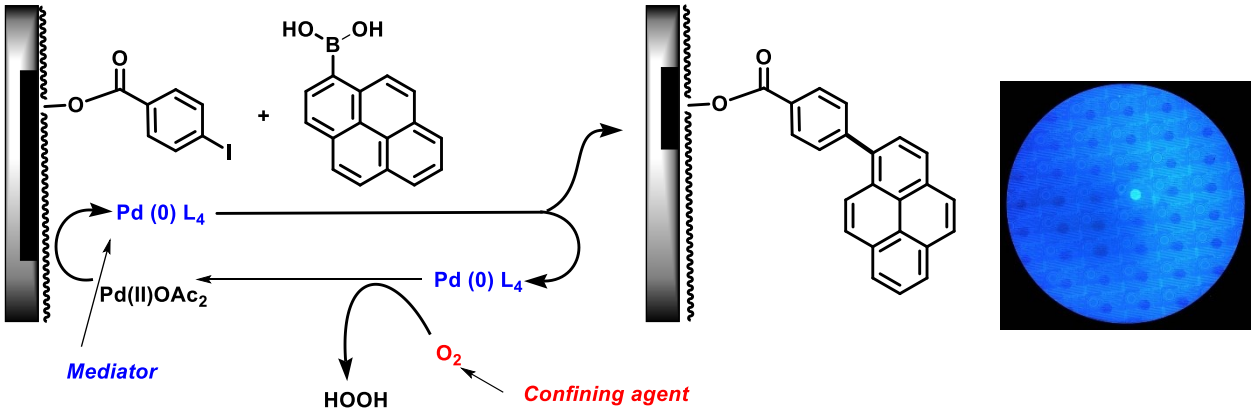


Scheme 14. An array based CAN oxidation.

In principle, any array-based oxidation reaction can be designed and conducted in the same manner. The reactions are constant current electrolyses. The potential shown in the Schemes represents the difference in potential between the electrode in the array and the counter electrode. In other words, the cell potential. Just like in the earlier described direct oxidation reactions, the working potential at the electrodes in the array is simply allowed to adjust to whatever substrate is in solution. The only difference is that in these cases the substrate is an oxidant that is recycled. So, unlike the previous cases wherein the working potential will climb after consumption of the substrate, in array-based electrolyses the substrate

is not consumed so the working potential at the electrode holds constant for the entire process. This is true for any indirect electrolysis reaction; processes on the array can be boiled down to just that – routine indirect electrolyses. The array-based Wacker oxidation reaction was a scaled down preparative reaction that took full advantage of the fact that the array reactions and preparative reactions are the same. The reactions can be scaled in the opposite direction, and reactions developed on the arrays can be scaled up to provide new preparative transformations.[92]

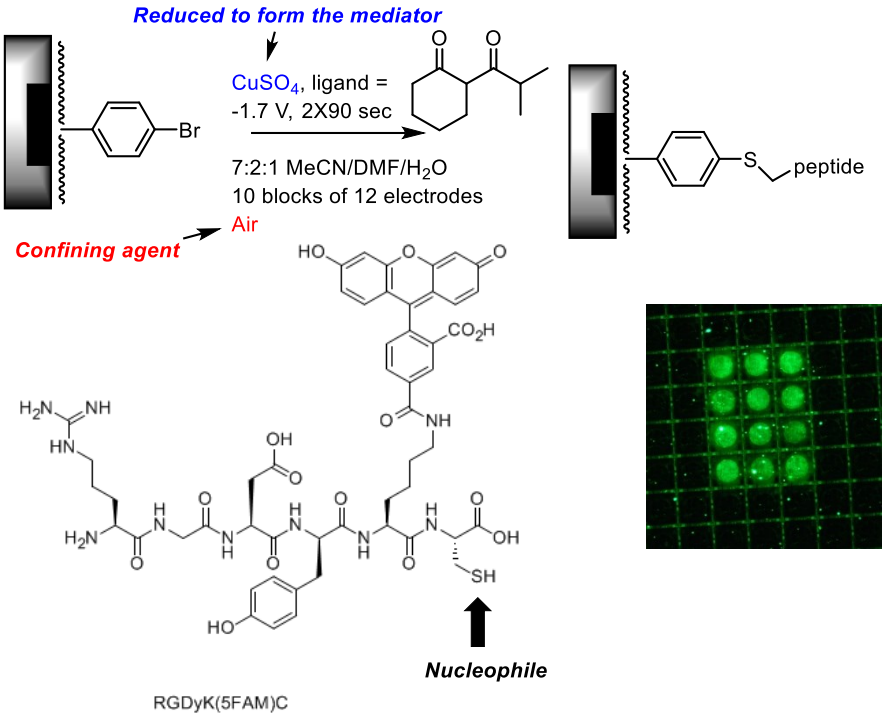
In parallel with the development of oxidation strategies on the arrays, we focused on reduction strategies; an effort that also began with the development of Pd-based chemistry. Chief among the reactions of interest were the Suzuki reaction and the Heck reaction because of their intrinsic ability to couple molecules to the surface of an array in new ways.[93] Of course, in this case the proposed array-chemistry had no precedent since there was no need for an electrochemical version of the preparative reactions. Both transformations are redox neutral and both already employ the Pd species in a catalytic manner. For an array reaction, we needed to stop the catalytic process so that we could isolate it to specific locations where it was needed. The strategy is highlighted in Scheme 15 for the Suzuki reaction.[94] The



Scheme 15. A Pd(0)-catalyzed reaction conducted on an array.

reaction works by adding an oxidant to the solution above the array (either oxygen, allylacetate, quinone, etc.) so that any Pd(0) in solution will be quickly converted to Pd(II), and then employing selected

electrodes in the array as cathodes to reduce the Pd(II) back to the Pd(0) catalyst needed for the reaction. The confinement of the reaction to any electrode selected for the reaction is tuned by adjusting the rate of the reduction reaction (current flow) relative to the concentration of the confining agent in solution. As can be seen from the image provided for an array utilizing only one electrode, the reaction can be confined nicely, an observation that proved equally true for array-based Heck reactions.[95] The generality of the confinement strategy is something that we have found to be common. Once a confining strategy has been developed for the use of a given catalyst on an array, it can be used to confine a family of related reactions.

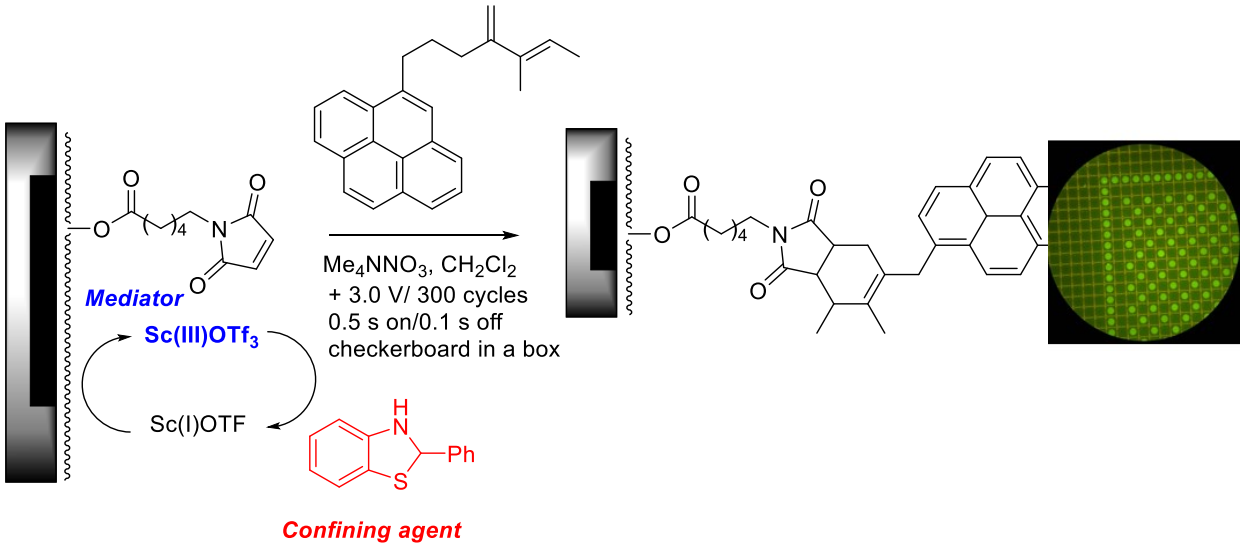


Scheme 16. The use of a Cu-(I)-catalyst.

Very similar methods were employed using Cu(I)-catalysts in place of Pd(0), which allowed for the addition of alcohols, amines, and thiols to the surface of the arrays.[64] The chemistry followed the beautiful work forwarded by the Buchwald group and others,[96] with oxygen being used as the confining agent on the arrays (the use of quinone as an oxidant is also very effective). The example shown in Scheme

16 was used to add an RGD-peptide to the surface of the array for subsequent signaling studies that provided a proof of principle experiment for the overall approach.[66] Due to the synthetic emphasis of this perspective, the analytical studies will not be discussed here.

The use of non-redox based catalysts on an array is not restricted to transition metal-mediated reactions. Consider the Lewis acid catalyzed Diels-Alder reaction shown in Scheme 17.[97] In this case, a Sc(III)-catalyst was generated at the array by using the electrodes as

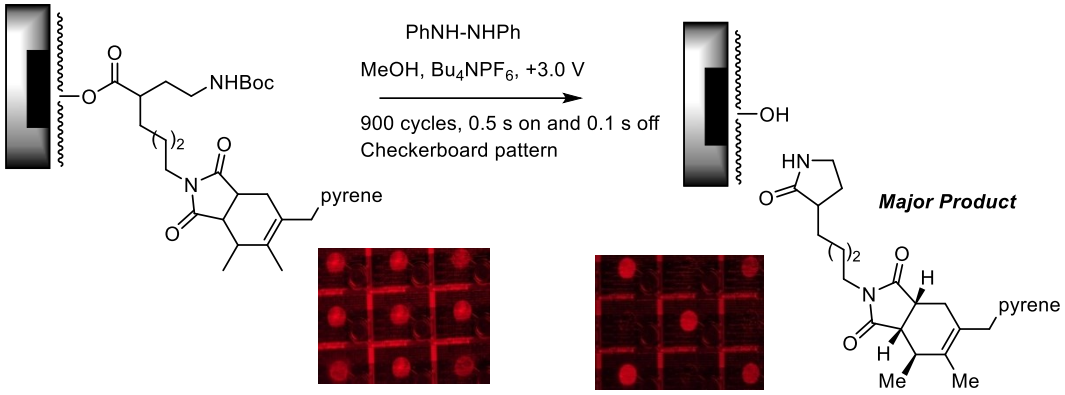


Scheme 17. A site-selective Diels-Alder reaction.

anodes. The Sc(III)-catalyst was scavenged in the solution above the array by using a known chemical oxidation pathway that employs Sc(III) as the oxidant. In this case, the working potential of the electrodes in the array simply adjusted to the potential needed for the oxidation of Sc(III). The overall strategy employed was the same as the one used for the array-based CAN reaction discussed above.

While fluorescence imaging of the array provided a nice visual assessment that the reaction had occurred and the confinement strategy used was successful, this method of characterization of the product is not truly satisfying for a synthetic chemist. A Diels-Alder reaction makes a product with stereochemistry. How does conducting the reaction on a surface influence that stereochemistry? Questions of this nature require characterization of the molecule that was made, which means it must be removed

from the surface after its synthesized. Recovery of the products on the array surface was accomplished by taking advantage of a Kenner-type safety catch linker strategy (Scheme 18).[87-88] In this strategy, the substrate for the molecule to be synthesized is connected to the array with

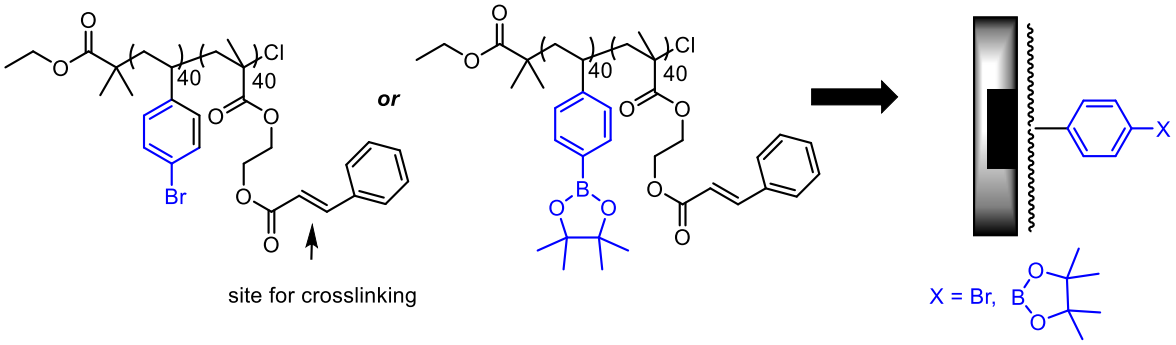


Scheme 18. Characterization using a Kenner-type safety-catch linker.

a linker that contains a protected amine or alcohol. After a synthesis or subsequent analytical experiment is complete, deprotection of the amine or alcohol leads to a cyclization reaction that cleaves the molecule from the surface (Scheme 18). The molecule can be isolated, characterized by LCMS, and compared to authentic, independently synthesized product. In the example shown, the Diels-Alder product was synthesized by every electrode in the array. The linker was then site-selectively cleaved by the oxidation of diphenylhydrazine to form two equivalents of acid and the corresponding azo-compound. Excess diphenyl hydrazine was used as a base in solution above the array in order to confine the acid generated to the selected electrodes. Two items about this reaction deserve further comment here. First, the Diels-Alder reaction did provide the desired product and the endo/exo ratio was only slightly influenced by the surface, with the ratio being a bit smaller than that observed for the solution-phase reaction. Second, the use of the electrodes in the array for cleavage of the safety-catch linker and the ability to confine that reaction to the selected electrodes is important. Biological interactions on an array are monitored using the electrodes. So, if a biological interaction between a member of a molecular library and a target receptor

is detected on the array, then the same electrode used to record that interaction can also be used to selectively remove the molecule giving rise to that signal from the array for characterization. The use of the same electrode for both signaling and recovery insures that the fidelity between the observed signal and the molecule characterized is perfect, a level of quality control not available for other surface based methods.

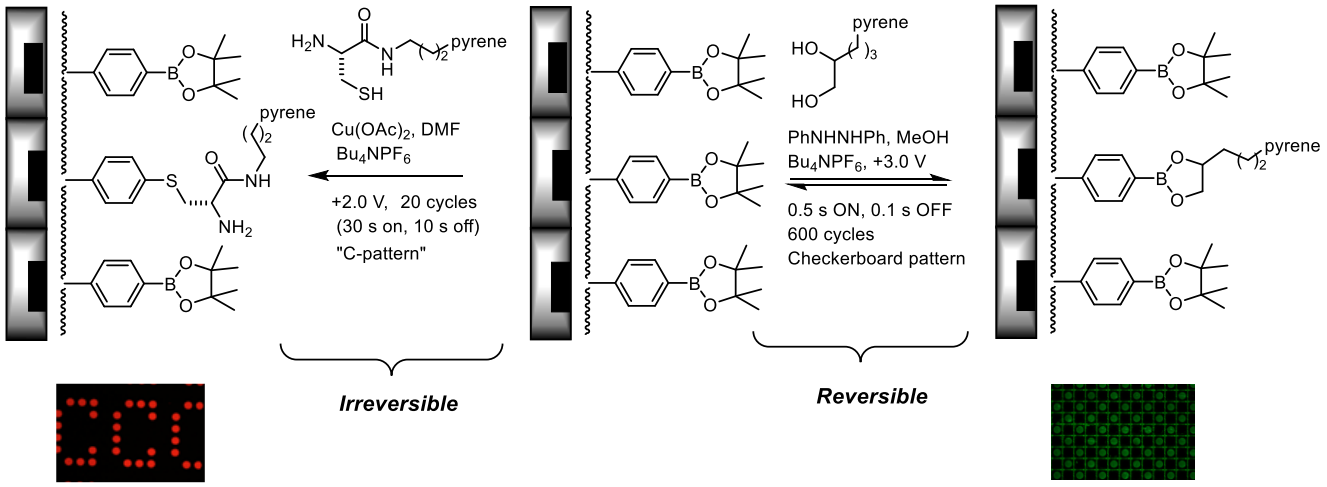
With the ability to conduct synthetic reactions at any electrode in an array and a strategy in place for characterizing the molecules made, attention was turned to the surface itself. While the



Scheme 19. Diblock copolymer surfaces for the arrays.

agarose and sucrose based surfaces initially employed were fine for placing molecules on an array and verifying the utility of the arrays for signaling experiments with small biomolecules,[65, 68, 84-86, 98-99] these sugar-based surfaces were not stable enough for long-term use or inert enough for total synthesis efforts. Even the Pd(0)-catalyzed reactions described above were problematic on the sugar surfaces – not because the reactions were not stable to Pd(0), but rather due to the fact that the arrays are undivided cells. The 12-K arrays are thin film flow cells that place the electrodes close to each other. While a sugar surface is stable to the reduction chemistry at the cathode, it is not stable to either the acid generated at the anode counter electrode or the Pd(II) precursor needed for the generation of the Pd(0) catalyst. These issues could be mitigated by controlling the pH of the reactions, but in the end a more stable, inert surface was needed. This need led to the development of the diblock copolymers shown in Scheme 19.[87-88] The

surfaces are not perfect, and work to optimize the polymer coating on the array is still a matter of importance. However, they are stable and their use has enabled efforts to further develop the synthetic and analytical capabilities of the arrays. The diblock copolymers are comprised of one block that is hydrophobic and can be used to functionalize the array surface and one block that is hydrophilic and modified with a cinnamate group that can be used for crosslinking and adding stability to the polymer surface. The first block contains either an aryl bromide for use in the Suzuki, Heck, or Cu(I)-based coupling reactions described above or an arylborate that was used in connection with building a tunable surface (Scheme 20).[100]



Scheme 20. Tunable surfaces and the use of both reversible and irreversible transformations.

A tunable surface is desirable because of the non-specific binding events that frequently complicate surface-based analytical methods. No one surface is suitable for minimizing such interactions with every protein one might want to target with a synthesized library. However, a tunable surface that had the molecular library permanently attached above the electrodes but could otherwise be varied has the potential to provide a versatile solution to the issue. To build such a surface, two types of electrochemically triggered, site-selective reactions were needed; one irreversible reaction for placing or

building the library members on the surface and one reversible reaction for changing the surface so that non-specific binding events can be minimized. The borate ester surface seemed ideal for both.

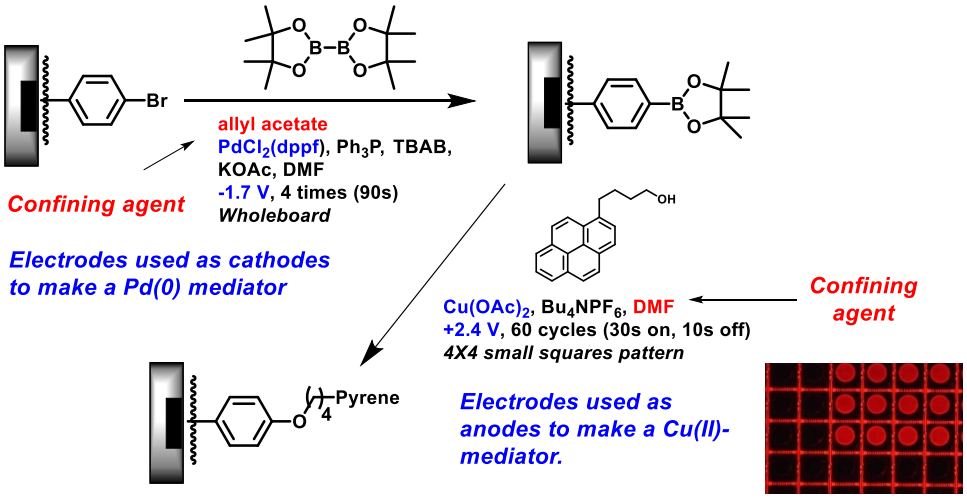
For the irreversible reaction, the Cu(II)-mediated Chan-Lam coupling was ideal (Scheme 20, left). It uses Cu(II) as a stoichiometric reagent to replace the borate ester with alcohol, thiol, amine, or acetylene groups.[67, 100] Cu(II) can be generated from Cu(I) by using the electrodes in the array as anodes, and it can be confined to those electrodes with the use of excess substrate that either undergoes oxidation or oxidative dimerization with Cu(II). In the example shown, a "C-pattern" of electrodes was used to but a pyrene labeled cysteine onto the surface of the selected electrodes. The Chan-Lam coupling reaction has proven to be a versatile method for setting up biological studies on the arrays.[67]

For the reversible reaction, an acid-catalyzed diol exchange reaction was found to work well (Scheme 20 to the right). The acid catalyzed reaction allowed the pinacol on the original borate ester to be exchanged for a new diol. In the Scheme, the diol was labeled with a pyrene ring so that the confinement strategy could be evaluated using fluorescence microscopy. In this case, the same hydrazine-based approach highlighted in Scheme 18 was used. As mentioned earlier, once a confinement strategy is established for a particular reagent or catalyst, it is general. In this case, the success of the reaction can again be seen in the image provided.

While the two surfaces were effective and each had their own strengths, there was an underlying problem in that those strengths were both important and each only found in one of the polymers. The arylbromide surface was great for synthesis; it is stable, it does not undergo a significant number of undesirable background reactions, and it compatible with multistep synthetic sequences. However, it does not swell well in water. Since the subsequent signaling studies examine proteins in water, this creates a problem, because the lack of swelling reduces the amount of redox mediator that can reach the electrodes below and leads to signals that are small and difficult to monitor. On the other hand, the borate ester

surface swells beautifully in water and is ideal for the signaling studies, butit is very reactive with a variety of reagents. One can add groups to the borate with acid, base, a Lewis acid, etc. This makes the surface compatible with only a small handful of chemical reactions (the two best ones are shown in Scheme 20), making it incompatible with a multistep synthesis effort. So, one surface is ideal for synthesis and the other for signaling, and neither does both well enough.

Initially, the problem appears to be a daunting one with no acceptable choice other than to start looking at new surfaces that hopefully have all of the correct properties. However, that assessment ignores the presence of the electrodes and the opportunity they provide for synthetic chemistry. Arylborates can be synthesized from arylbromides using either Pd(0)- or Cu(I)-catalysis, and those catalysts can be used and confined on the surface of a microelectrode array (Scheme 21).[101] In the example shown, the first reaction employed a Pd(0) catalyst for the conversion of the arylbromide surface to an arylborate by every



Scheme 21. The synthesis of arylborates on a microelectrode array.

electrode in the array. A site-selective Chan-Lam coupling reaction was then used to replace the newly synthesized borate ester with a fluorescently labeled alcohol nucleophile at a selected set of electrodes in the array. The image provided in the Scheme highlights three key observations. First, the reaction definitely converted the arylbromide to the arylborate, because the subsequent Cu(II)-promoted Chan-

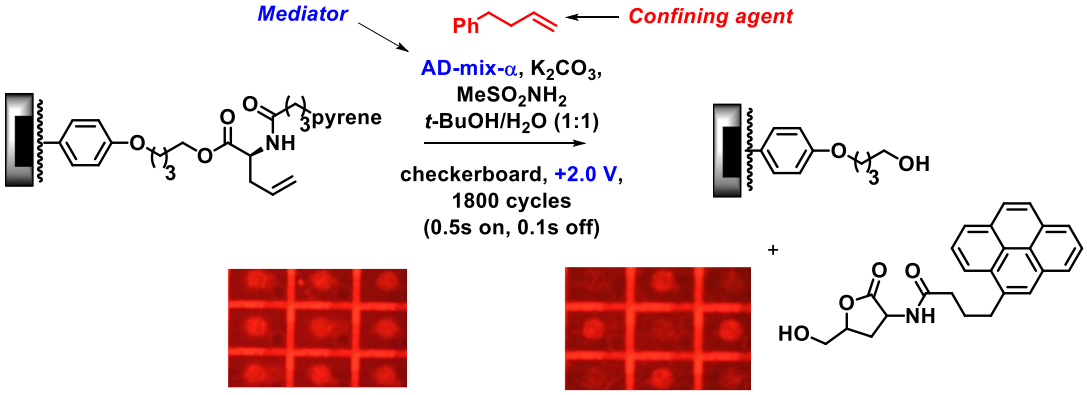
Lam coupling reaction only works on the borate. Second, the amount of arylbromide converted to the arylborate was very high. In order to conduct the subsequent Cu(II)-Chan Lam coupling reaction, the entire array surface is incubated in a solution containing a Cu(I)-precursor (a reduction product of Cu(II) and DMF). As seen in Scheme 16 above, Cu(I) catalyzes the addition of an alcohol to the arylbromide surface. Since this side reaction did not occur anywhere on the array in Scheme 21 (observed as a loss of confinement), the first step conducted at all of the electrodes in the array must have gone to completion. Finally, again note how the electrodes in the array were again used as both cathodes and anodes in order to accomplish the desired synthetic sequence.

The chemistry shown in Scheme 21 illustrates just how powerful synthetic chemistry can be as a tool for building new analytical devices. In the end, no decision needs to be made about which surface is to be used on an array and no compromise in function needs to be weighed. Instead, both surfaces can be used for the construction and analysis of a molecular library on a single array with each surface being used to optimize the part of the process it is ideally suited for.

Future Directions:

With the ability to conduct a wide variety of reactions at any given electrode or set of electrode in an array in place, a strategy available for characterizing the products of those arrays, and a polymer support in place to serve as a platform for those efforts, attention is now focused on developing the synthetic strategies needed to conduct the total synthesis of new molecular libraries directly on the arrays; an effort that is needed if larger molecular libraries are to be used. Those synthetic strategies will need to take advantage of the same chemical transformations that the synthetic community uses to build any molecular library. They need to target the synthesis of molecules with control of stereochemistry and geometry and the construction of privileged scaffolds, etc. The methods developed will also need to provide orthogonal methods for characterizing the molecules synthesized. We know now that moving

those reactions to an array format is both possible and straight forward. We also know that we can use electrochemical methods to take advantage of many of the synthetic methods we already use in creative new ways to address synthesis in the array environment. For example, the chemistry in Scheme 22 illustrates how the Torii electrochemical adaptation of the Sharpless cis-hydroxylation reaction can be incorporated into a safety-catch linker in order to provide an orthogonal strategy for characterizing peptide derivatives synthesized on an array.[102]



Scheme 22. A new, orthoganol safety-catch linker strategy.

We hope by now it has become clear that strategies like the one illustrated in Scheme 22 capitalize on the interplay between two larger themes. One is that electrochemistry is an extremely versatile tool for making and recycling chemical reagents. Constant current electrolyses automatically adjust to the potential needed to make a wide variety of chemical oxidants, reductants, acids, bases, nucleophiles, electrophiles, and catalysts that can be used to effect a large number of synthetic transformations. In that way, the array-based chemistry shown above is not an example of an isolated, novel area, but rather one application of a broad, general synthetic effort. In fact, the first array-based reactions were scaled down versions of preparative reactions developed in chemical engineering settings, and reactions that were initially developed for the arrays have now been used as preparative processes.[92] So the same set of

synthetic tools can be applied to both the synthesis of complex molecules and the construction of complex, addressable molecular surfaces.

Second, it is important to recognize that the lessons we are learning from using synthesis to empower new opportunities for the development of microelectrode-array based bioanalytical tools are also more broadly applicable. There are times as synthetic chemists that we think of complex molecules and certain types of synthetic targets as being "proper" applications of our craft. But as a community, we should not limit ourselves to those types of challenges. There are many biological and materials science efforts that take advantage of synthesis, but in reality they currently capitalize on only a small subset of the modern reactions and capabilities we are developing. We can change that by expanding our own view of what the tools we create can do.

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