Anodic Electrochemistry: New Methods for Building Chip-Based Molecular Libraries

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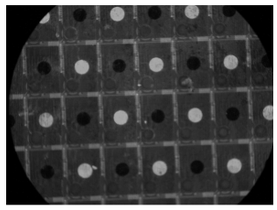
Because chip-based molecular libraries contain a large number of molecules within a tiny area, they allow for the simultaneous evaluation of complex mixtures of gene products on a scale consistent with the minute amounts of material produced by biological systems. Such libraries are particularly useful if they are constructed so that each molecule is spatially isolated and individually addressable. In this way, the selective binding of a gene product to a molecule in the library separates it from the other products in the mixture and allows it to be characterized.

But how does one rapidly assemble large arrays of spatially isolated, individually addressable molecules on the surface of a chip? In answer to this question, scientists at CombiMatrix have begun to utilize chips that are microfabricated with arrays of electrodes. The electrodes are used to first selectively deposit substrate molecules onto the chip and then to generate chemical reagents that transform the newly localized substrates into the molecules desired for the library. The result is a molecular library having each individual member located proximal to a unique, addressable electrode. To date, libraries containing both DNA and peptide oligomers have been constructed by utilizing the electrodes to generate acids and bases.

Yet while this work has been very successful, it has only begun to tap the potential of using electrochemistry to build molecular libraries on chips. Electrochemical reactions are not restricted to the generation of acids and bases, but in fact have been used to trigger a wide variety of transition metal based oxidation and reduction reactions. In addition, the unique chemical environment associated with chip-based electrolysis reactions should allow for the spatial isolation of transition metal catalysts on the chip, a development that would make available for chip-based synthesis many of the powerful transition metal catalyzed reactions used in modern organic synthesis. The availability of these methods would make it possible to construct diverse arrays of molecular libraries on the chips targeting a wide variety of biological problems.

With this in mind, we have begun to explore the synthetic viability and overall utility of transition metal based reactions on the chips. For example, in the experiment illustrated in Figure 1, an olefin was converted into a ketone

Figure 1



at every other electrode on a chip containing a micro array of 1,000 electrodes in a one cm^2 area. This was done by using the selected electrodes to generate a Pd (II) reagent and trigger a Wacker oxidation. The bright spots in the checkerboard pattern indicate locations where the olefin was converted to a ketone (and imaged via its 2,4-DNP derivative using an fluoroscene tagged antibody).[1]

More recent efforts are exploring the use of Pd (0) reagents on the chips as well as the development of a variety of both intramolecular and intermolecular reactions on the chips. The results of these efforts will be presented.

1. For a preliminary report on this work please see: Tesfu, E.; Maurer, K.; Ragsdale, S. R.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, ASAP.