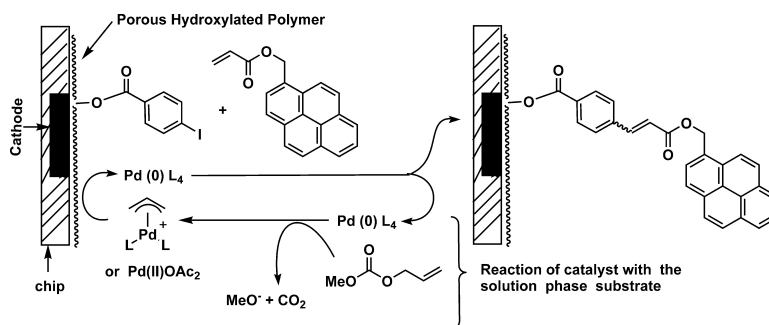


Building Addressable Libraries: The Use of Electrochemistry for Spatially Isolating a Heck Reaction on a Chip

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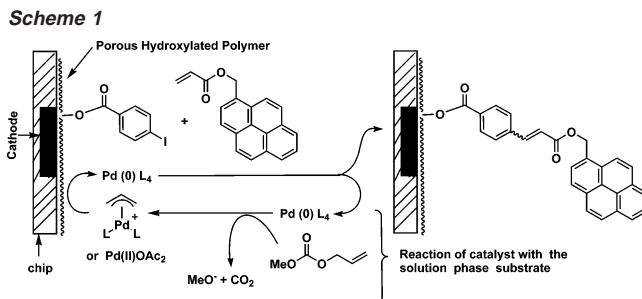
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As part of a broader effort to build addressable chip-based molecular libraries,^{1,2} scientists at CombiMatrix have been utilizing active semiconductor chips that incorporate arrays of individually addressable microelectrodes to synthesize molecules.^{3,4} In this way, each unique set of molecules in a library can be located proximal to a unique electrode or set of electrodes that can in turn be used to monitor their behavior.⁵ This is accomplished by coating the microelectrode-containing chips with a porous polymer and then utilizing the electrodes to both attach monomers to the chips and then generate reagents capable of performing reactions on the monomers. The reagents generated at any given electrode are confined to the area surrounding the electrode by placing a substrate in the solution above the electrode that consumes the reagent. Recently, we showed that this strategy, originally developed in connection with the generation of acids and bases on the chips, could be utilized to site-selectively generate a Pd(II) reagent on the chip.⁶ The Pd(II) reagent was generated by utilizing the electrodes on the chip as anodes to oxidize a Pd(0) reagent added to the solution above the chip. The Pd(II) reagent generated was confined to the sites of its generation with the use of ethyl vinyl ether. With this system, conditions were developed for effecting Wacker oxidations site-specifically at preselected electrodes on the chip.

The success of this effort led us to wonder if the process could be reversed. Specifically, could the electrodes be used as cathodes to reduce a Pd(II) reagent to a Pd(0) reagent at preselected sites on the chip, and if so, could an efficient confinement strategy be developed for the Pd(0) reagent generated? This idea was intriguing because of the wide range of synthetic methods that currently utilize Pd(0) catalysts. For an initial effort, the Heck reaction was selected for study. Two rationales influenced this decision. First, the Heck reaction is a powerful synthetic tool⁷ that allows the efficient generation of new carbon-carbon bonds. The availability of a Heck reaction on the chip would dramatically expand the types of molecules that could be constructed proximal to an electrode. Second, the Heck reaction represents a unique challenge for a site-selective reaction on a chip because it is catalytic with respect to Pd(0). This is an important issue. The earlier chip-based Wacker oxidation involved moving a well-known electrochemically mediated reaction to a new environment. In a typical mediated electrolysis reaction, the electrochemical step is used to regenerate a reagent that is consumed during the reaction. In the case of the Wacker oxidation, Pd(II) is used as a stoichiometric oxidant. The electrode is used to regenerate the Pd(II) oxidant so that it can be used in a catalytic fashion. On a chip this fits perfectly. The reagent generated at the selected electrode is consumed by the reaction. The ethyl vinyl ether added to the solution above the chip to confine the Pd(II) generated merely needed to scavenge any excess reagent. Such is not the case for the proposed Heck reaction. In this case, the reaction does not consume the catalyst, and a confining agent is needed to keep all of the reagent



generated from migrating to areas of the chip where it is not wanted. In other words, rather than using an electrolysis reaction to make a normally stoichiometric reaction catalytic, for the Heck reaction the chip-based environment must be used to make a normally catalytic reaction stoichiometric, thereby confining the catalyst to preselected sites on the chip.

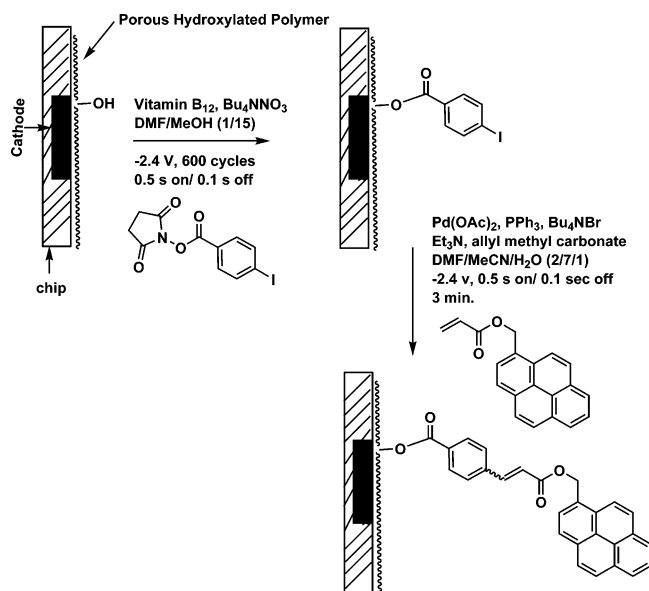
To test the feasibility of this idea, the experiment outlined in Scheme 1 was designed. First, an aryl iodide would be placed on the surface of the chip, and then the chip would be submerged in an electrolyte solution containing 1-pyrenemethyl acrylate, palladium acetate, triphenylphosphine ligand, and allyl methyl carbonate. If successful, selected cathodes would then be used to reduce the palladium acetate to the desired Pd(0) catalyst that would in turn trigger a Heck reaction between the surface-bound aryl iodide and the 1-pyrenemethyl acrylate. This would place the fluorescent pyrene group onto the surface of the chip in the region surrounding the electrode, thereby affording a method for monitoring the success of the reaction. Following the reaction, the active Pd(0) catalyst would be scavenged by the allyl methyl carbonate to generate a Pd(II) π -allyl complex and stop the catalytic process. Reformation of the Pd(0) catalyst at either this electrode or another selected electrode would then require either reduction of more of the Pd-(OAc)₂ reagent or reduction of the π -allyl Pd(II) complex.⁸ By balancing the rate at which the Pd(II) is reduced at the selected electrodes with the concentration of the allyl methyl carbonate in solution, the Heck reaction would be confined to just the regions surrounding the selected electrodes.

Efforts to realize this experiment began by examining a series of solution-phase Heck reactions to determine reaction conditions that would allow for an electrochemically generated Heck reaction. Two key discoveries were made along these lines. First, a Heck reaction between methyl 4-iodobenzoate and 1-pyrenemethyl acrylate proceeded slowly (18 h/82% yield) with Pd(OAc)₂ in a 9:1 DMF:H₂O solution containing triethylamine and tetrabutylammonium bromide, while the same reaction proceeded to completion in just 3 h when a cathode was inserted and the Pd(OAc)₂ was reduced electrochemically. Second, the Heck reaction did not proceed at all (0% after 18 h) in the absence of the cathode when the DMF solvent was exchanged for acetonitrile. The corresponding electrochemical reaction proceeded to completion (76% yield) in 12 h. Hence, using acetonitrile as the solvent for the reactions would

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Scheme 2



ensure that the Heck reaction would not spontaneously occur at sites on the chip without a working cathode. Even if the more efficient DMF reaction conditions were eventually needed on the chip, it appeared that the nonelectrochemical background reaction would be slow enough to be negligible, especially since on the chip a high concentration of the catalyst would be generated at the electrodes directly next to the selected substrates.

Chip-based experiments were initiated by depositing the aryl iodide onto the chip using the same methodology employed in the earlier Wacker oxidation experiment (Scheme 2).⁶ To this end, all of the electrodes on the chip were utilized as cathodes to reduce vitamin B₁₂, thereby generating a base. The base served to catalyze an esterification reaction between the hydroxyl groups of the polymer coating on the chip and the *N*-hydroxysuccinimide ester of 4-iodobenzoic acid. The effect of this process was to concentrate the aryl iodide substrate near the electrodes on the chip. The Heck reaction was then performed by submerging the chip in a 2:7:1 DMF/MeCN/H₂O solution containing Pd(OAc)₂, triphenylphosphine, triethylamine, allyl methyl carbonate, and tetrabutylammonium bromide electrolyte. Selected cathodes were turned on at a voltage of -2.4 V (relative to a Pt auxiliary electrode) to generate a box with a dot in the center. The electrodes (Pt) were cycled for 0.5 s on and then 0.1 s off for 3 min. Following the reaction, the chip was repeatedly washed with ethanol to remove any unreacted pyrene containing substrate, and then the chip was imaged using a fluorescent microscope.⁹ The result is shown in Figure 1. The figure shows an expanded view of 81 of the 1024 electrodes on the chip. The bright spots in the figure are formed by pyrene on the chip's surface and coincide perfectly with the activated electrodes. The dark spots are electrodes that were not activated and block the background fluorescence of the chip. Clearly, the confining agent worked well, and the Heck reaction was restricted to only the selected electrodes.

Several aspects of this reaction deserve further comment. First, the use of triphenylphosphine as a ligand for the palladium was necessary for keeping the Pd(0) generated at the cathode from plating out on the chip. Second, without the presence of some DMF in the reaction mixture the reaction failed to produce any product. However, the reaction could not be done using DMF/H₂O as solvent because the DMF dissolved the polymer coating off the chip. Therefore, a mixture of solvents was used. Third, it was found that voltages higher than -2.4 V or reaction times longer than three minutes led to a decrease in the intensity of the product spots on the chip.

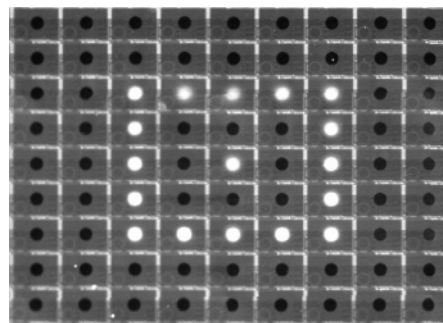


Figure 1. 1-Pyrenemethylacrylate was deposited at selected microelectrodes on an active semiconductor chip by using the electrodes as cathodes to reduce Pd(II) to Pd(0). The Pd(0) triggered a Heck reaction between the substrate and an aryl iodide on the chip's surface. Bright spots indicate electrodes that were activated.⁹

Apparently, the harsher conditions or longer reaction times led to cleavage of the newly formed pyrene product from the chip. At the present, we speculate that the cleavage occurs because of base generated from either the reaction of Pd(0) with the allyl methyl carbonate¹⁰ or the reduction of water at the cathode. Finally, the presence of the confining agent was necessary. A reaction without the allyl methyl carbonate led to significant spreading of the fluorescence away from the selected electrodes.

In conclusion, a Heck reaction has been performed at preselected sites on an electrochemically addressable chip. The experiment highlights the utility of a Pd(0) reagent on the chips and for the first time demonstrates the potential for employing a transition metal catalyst to selectively construct molecules proximal to specific addressable electrodes.

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Supporting Information Available: Sample procedures and images for the control experiments conducted. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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