Microelectrode Arrays

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Building Addressable Libraries: Site-Selective Lewis Acid (Scandium(III)) Catalyzed Reactions**

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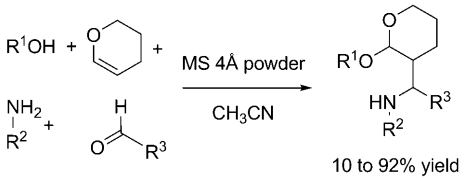
Microelectrode arrays[1,2] are potentially powerful tools for monitoring the binding of molecular libraries to biological receptors in "real time".[3] However, in order to capitalize on this potential, we must be able to synthesize the members of the molecular library in a manner that places each unique member of the library proximal to a unique, individually addressable microelectrode in the array. This is a daunting challenge because the arrays used for signaling contain 12544 microelectrodes cm^{-2}. With this in mind, we have been working to develop the synthetic methodology needed to site selectively conduct chemical reactions on micoelectrode arrays.[4–8] In connection with these studies, the ability to employ a Lewis acid catalyst in a site-selective fashion would be particularly intriguing. Lewis acid catalysts are used to accelerate reactions, trigger cycloadditions, introduce stereocontrol elements into reaction transition states, and assemble reagents for multicomponent synthetic strategies.

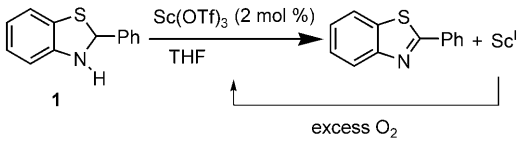
For example, Lavilla and co-workers recently demonstrated that a Sc^{III} species can be used as a Lewis acid to trigger multicomponent reactions that form tetrahydropyran-ring skeletons with three potential sites (R^1, R^2, R^3) for diversification (Scheme 1).[9] Multicomponent reactions of



Scheme 1. A Sc^{III}-catalyzed multicomponent reaction. MS: molecular sieves.

this type can be powerful tools for constructing the scaffolds that form the basis of small-molecule libraries. The ability to conduct such reactions site selectively on a microelectrode array would greatly expand the opportunities for building small-molecule libraries that can be monitored in real time. But how does one run a Lewis acid catalyzed reaction in a site-selective fashion?

The Sc^{III}-catalyzed reaction illustrated in Scheme 1 provided an excellent starting point for addressing this question. As with any microelectrode-array-based method, the key questions that needed to be addressed were 1) how to site selectively synthesize the desired reagent by using the microelectrodes and 2) how to confine the reagent to the area surrounding a selected electrode once it had been generated. For the reaction illustrated in Scheme 1, this meant that we needed a method of generating an active Sc^{III} catalyst at the desired microelectrodes and then a method for destroying the Sc^{III} species in the solution above the array. In principle, this scenario could be accomplished by using the microelectrodes to change the Sc oxidation state. If an inactive Sc^{I} reagent was introduced into the solution above a microelectrode array, then the desired Sc^{III} catalyst could be generated at selected microelectrodes in the array by using the electrodes as anodes to oxidize the Sc^{I} reagent to a Sc^{III} species, a transformation that takes place at approximately $E_{p/2} = +0.89$ V versus a Ag/AgCl reference electrode.[10] In solution, a reducing agent would be needed to convert the Sc^{III} catalyst back into the inactive Sc^{I}, thereby stopping the catalyst from migrating to neighboring electrodes. The chemistry outlined in Scheme 2



Scheme 2. The strategy for confinement. Tf: trifluoromethanesulfonyl; THF: tetrahydrofuran.

suggested that 2-phenylbenzothiazole might serve nicely as this solution-phase reducing agent. In the experiment illustrated,[11] the Sc^{III} reagent was used to mediate the oxidation of 2-aryl-2,3-dihydrobenzothiazole by oxygen. Without the presence of the oxygen, the oxidation proceeds until the Sc^{III} species is consumed and then stops. The reaction completely converts the original Sc^{III} reagent in to a Sc^{I} derivative. Hence, for a microelectrode-array-based reaction, one could, in principle, run the reaction outlined in Scheme 2 above an array and then use microelectrodes in the array in place of the oxygen in order to regenerate the Sc^{III} catalyst only where needed.

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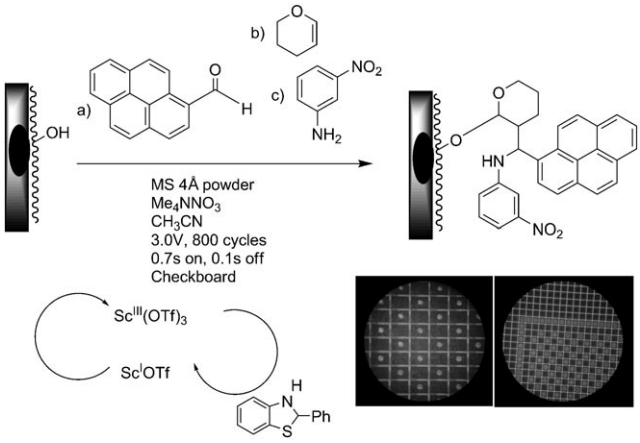
In order to test whether such an approach can be used to site selectively initiate reactions on a microelectrode array, a multicomponent reaction analogous to the chemistry illustrated in Scheme 1 was designed (Scheme 3). In this reaction,

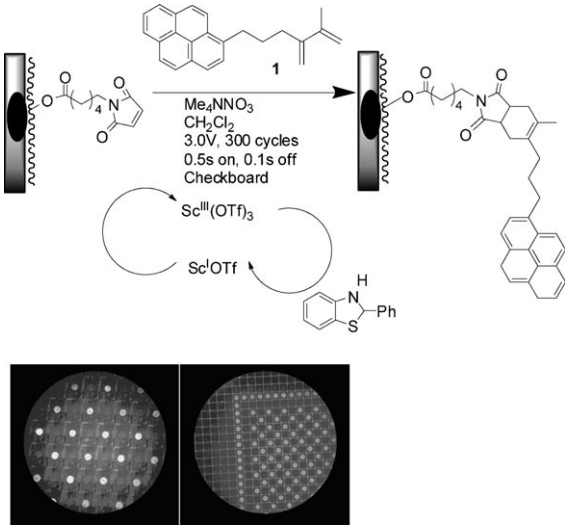


Scheme 3. The Sc^{III}-catalyzed tetrahydropyran synthesis. Below: Fluorescence microscopy images of the arrays with 1024 (left) and 12544 (right) microelectrodes cm^{-2}.

the agarose coating on a microelectrode array was to be used as the alcohol component in the reaction. The aryl aldehyde to be used was a pyrene derivative. Hence, a successful multicomponent reaction would place a fluorescent group onto the surface of the array.

The reaction was begun by premixing a catalytic amount of $Sc(OTf)_3$ with an excess of 2-aryl-2,3-dihydrobenzothiazole in acetonitrile for 30 min. This was done to insure that all of the Sc^{III} catalyst was reduced to a Sc^{I} species prior to the start of the reaction. The pyrene aldehyde, dihydrofuran, and *m*-nitroaniline were then added to this solution, along with tetramethylammonium nitrate as an electrolyte. A microelectrode array spin coated with agarose was then submerged in the solution, along with a remote Pt wire that served as an auxiliary cathode. The Sc^{III} catalyst needed for triggering the multicomponent reaction was then produced at selected electrodes by cycling the electrodes on at a potential of $+3.0$ V, relative to the remote Pt-wire auxiliary electrode set to ground (0 V), for a period of 0.7 s and then off again for a period of 0.1 s. To generate the image shown on the left in Scheme 3, 800 such cycles were used in a checkerboard pattern on an array containing 1024 electrodes in a 1 cm^2 area (a 1K array). The image was obtained by washing any excess pyrene aldehyde off of the chip after the reaction and then examining the array with a fluorescence microscope. In the image shown, the microelectrodes have a diameter of 95 microns. As a control, the reaction was repeated without the presence of scandium. In this case, no pattern was observed. When scandium was present, both the potential used and the time associated with the cycles could be varied and the pattern was retained. However, the conditions reported above were the most consistent for generating a bright pattern of spots on the array. Clearly, the strategy for generating and confining a Sc^{III} Lewis acid catalyst on the array worked very well. In a similar manner, the reaction was conducted on an array of 12544 electrodes in a 1 cm^2 area (a 12K array). Once again, a high level of confinement was observed for the reaction (right-hand image in Scheme 3).

With a successful confinement strategy for the Sc^{III} reagent in place, attention was turned toward exploring the generality of the reaction. Diels–Alder reactions have also been successfully catalyzed with Sc^{III} species.[12] To determine the feasibility of a site-selective Diels–Alder reaction, a pyrene-labeled diene **1** (Scheme 4) was prepared in four steps from 1-pyrenebutanol. As a control, the diene was treated with *N*-methylmaleimide and 10 mol% $Sc(OTf)_3$ in dichloromethane. The reaction afforded the Diels–Alder adduct in 90% yield after 12 h at room temperature.

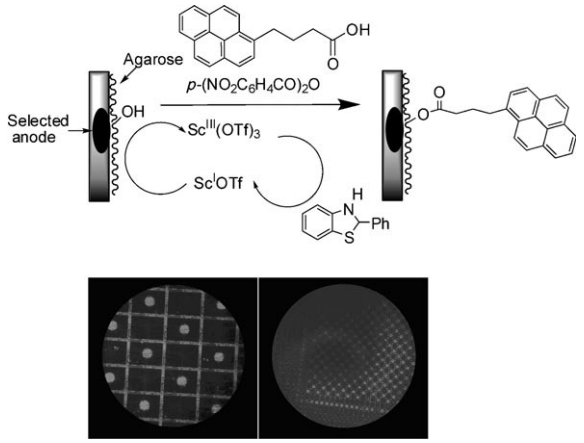


Scheme 4. The Sc^{III}-catalyzed Diels–Alder reaction. Below: Fluorescence microscopy images of the arrays with 1024 (left) and 12544 (right) microelectrodes cm^{-2}.

The microelectrode-array-based reaction was started with the placement of the dienophile onto the array proximal to each of the microelectrodes. This was accomplished by placing a maleimide dienophile on the array proximal to each of the electrodes by using the vitamin-B_{12}-mediated esterification chemistry developed previously.[5–8] The array was then treated with a premixed solution of $Sc(OTf)_3$ and 2-aryl-2,3-dihydrobenzothiazole in the same manner as described above. The pyrene-labeled diene **1** and tetramethylammonium nitrate, as an electrolyte, were added into this mixture. The reaction was conducted at selected electrodes by turning the electrodes on at a potential of $+3.0$ V versus a remote Pt wire for 0.5 s and then off again for 0.1 s. 300 such cycles were used. Both 1K and 12K arrays were used. On the 1K array, a checkerboard pattern of microelectrodes was selected for the generation of the Sc^{III} catalyst. On the 12K array, a checkerboard in a box pattern was selected. (In a 12K array, the microelectrodes have a diameter of approximately 45 microns.) Both arrays were imaged by using a fluorescence microscope after the reaction. The images are shown in Scheme 4. In both cases, the Diels–Alder reaction was clearly confined to the selected microelectrodes, which demonstrates

that the conditions developed for the multicomponent reaction are also applicable to the Diels–Alder reaction.

In principle, many other types of Lewis acid catalyzed reactions can be performed in this manner. For example, consider the esterification reaction illustrated in Scheme 5.[13] This acid-catalyzed esterification reaction would provide a complimentary approach to the base-catalyzed methods used previously for making ester linkages between a molecule and the surface of the array. Once again, the reaction could be conducted with both 1K and 12K arrays by using the same conditions developed for the multicomponent reaction above.



Scheme 5. The Sc^{III}-catalyzed esterification reaction. Below: Fluorescence microscopy images of the arrays with 1024 (left) and 12544 (right) microelectrodes cm^{-2}.

In conclusion, we have found that Sc^{III}-catalyzed reactions can be conveniently performed site selectively on microelectrode arrays with the use of 2-arylbenzothiazole as a confining agent. The reactions represent a new class of site-selective reactions involving Lewis acid catalysis. The reactions allow for the construction of cyclic scaffolds on the arrays. Efforts to explore the stereochemistry of the array-based reactions and expand the use of Lewis acids on the array platform are underway.

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