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Building addressable libraries: a site-selective allyl alkylation reaction

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ABSTRACT

A Pd(0) catalyst has been used to effect allyl alkylation reactions at pre-selected locations on an addressable microelectrode array. The reactions provide a new approach to site-selective carbon–carbon bond formation and a new method for placing substrates on the surface of a microelectrode array.

The use of chip-based molecular libraries[1,2] for probing biological systems would be greatly aided if each member in the library was individually addressable in a manner that allowed for monitoring its behavior in 'real-time'. For this reason, we have been working to develop the chemistry needed for building small molecule libraries on semi-conducting chips containing addressable arrays of microelectrodes.[3,4] The plan calls for building a molecular library such that each unique member of the library is located proximal to a unique, individually addressable microelectrode in the array. The microelectrodes can then be used to monitor the behavior of individual members of the library. To date, we have been working to make available transition metal-mediated synthetic methods as tools for accomplishing this goal. For example, both Pd(II)[5] and Pd(0)[6] reagents have been used to successfully conduct reactions at site-selective locations on an addressable microelectrode array. Because of the important role carbon–carbon bond formation plays in the synthesis of organic molecules, one of the first synthetic methods examined in this context was the Heck reaction.[6] In this effort, the microelectrode array was coated with an agarose polymer, and then an aryliodide substrate attached to the polymer proximal to each of the microelectrodes. The entire array was then submerged in a solution containing an unsaturated ester, $Pd(OAc)_2$, and allylmethylcarbonate. Selected microelectrodes in the array were used to reduce the Pd(II) species and to generate an active Pd(0)-catalyst that in turn triggered a Heck reaction involving the aryliodide substrate and an unsaturated ester in solution (Scheme 1). The allylmethylcarbonate added to the solution served as a confining agent by oxidizing the Pd(0) reagent before it could migrate to a neighboring electrode. The π-allyl palladium species generated in this reaction could be recycled at the electrode.[7]

The success of the Heck reaction led to questions about the generality of the procedure for performing alternative carbon-carbon bond forming reactions. For example, would the extremely useful Pd(0) catalyzed allylic alkylation reaction also provide an effective means for site-selectively coupling new molecules to the surface of a microelectrode array (Scheme 2)? Several key issues immediately arose concerning this question. First, the Heck reaction can be electrochemically accelerated, and it runs significantly faster when current is passed through it.[8] Would the same be true for the allylation reactions, and if not would the reactions still be site-selective for regions surrounding the activated electrodes in the array? Second, what substrate would be optimal for the reactions? Allylhalides, allylacetates, and allylcarbonates are all effective substrates for solution-phase reactions. Would microelectrode array-initiated reactions show a preference for one of these substrates? Finally, the allylmethylcarbonate strategy used to confine Pd(0) to selected electrodes in the Heck reaction is not compatible with an allylic alkylation reaction. As in the Heck reaction, oxidative addition of the Pd(0) to the allylmethylcarbonate would generate a π-allyl Pd(II). However, for the allylic alkylation reaction the solution phase π-allylpalladium species would compete with the surface-bound π-allyl Pd(II) species for the nucleophile in solution. This would not only consume the nucleophile, but also regenerate the Pd(0)-catalyst in the absence of an electrode, a situation that would lead to the catalyst not being confined to the regions of the chip surrounding the activated electrodes. In this manuscript, we report that Pd(0) catalyzed allylic alkylations can be site-selectively preformed at specific locations on an addressable microelectrode array using quinone as the confining agent.

The work started by looking at the effect of passing current through a trio of solution phase allylic alkylation reactions. The data are reported in Table 1. In each case, *t*-butyl acetoacetate was mixed with an allylic electrophile in the presence of $Pd(OAc)_2$, triphenylphosphine, and tetrabutylammonium bromide in a DMF/THF solvent solution. For reactions utilizing either the allylbromide substrate or the allylacetate substrate, DBU was added to deprotonate the acetoacetate substrate. No additional base was necessary for reactions originating from the allylcarbonate substrate. For the

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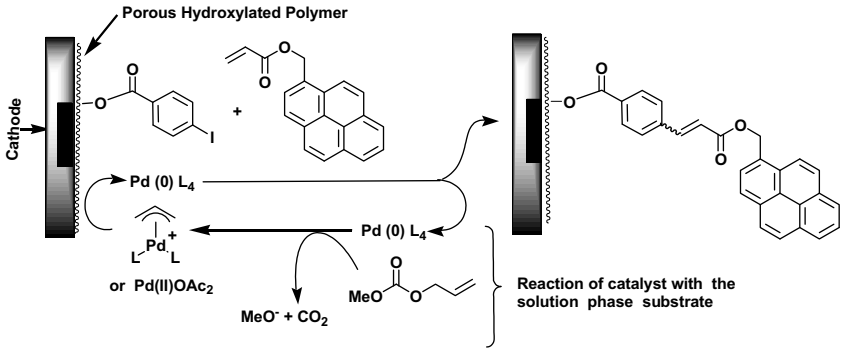
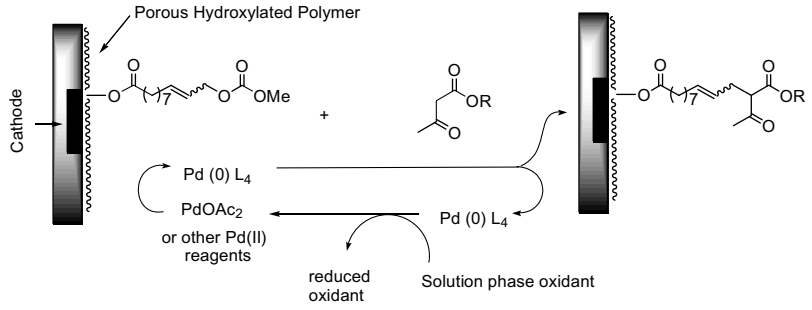
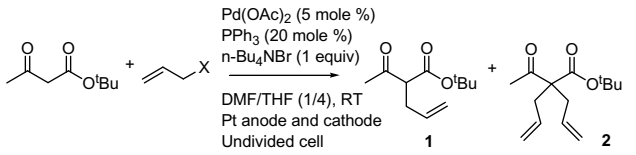


Scheme 1.



Scheme 2.

Table 1



Entry	X	DBU (equiv)	Time (h)	Electricity (F/mole)	% Yield (**1** + **2**/2:1)
1a	Br	1	24	None	72
1b	Br	1	3	3.0	75
2a	OAc	1	24	None	78
2b	OAC	1	4	2.9	79
3a	OCO_2Me	0	6	None	81
3b	OCO_2Me	0	2	1.6	82

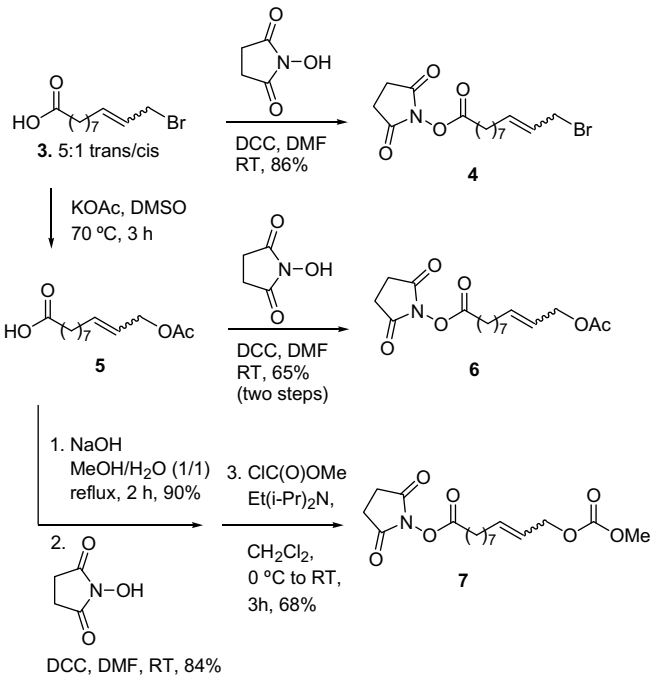
a: Chemical; **b**: electrochemical.

electrochemical reactions, two platinum electrodes were added, and a constant current of 20 mA passed through the solution. For each substrate, the passage of current through the reaction accelerated the transformation. Yields for both electrochemical and non-electrochemical reactions were comparable. The largest rate acceleration occurred with the use of the allylbromide substrate. In this case, passing current through the reaction led to an 8-fold rate acceleration that was similar to the rate accelerations observed for the electrochemically assisted Heck reaction (rate increases from 4.5- to 9-fold).[8] For reactions using the allylcarbonate substrate, a 3-fold increase in rate was observed. For the earlier Heck reaction, it was suggested that the current being passed through the cell accelerated the reactions by breaking up the Pd-clusters known to form inactive precipitates. This might be accomplished by the oxidation of Pd(0) to Pd(II) at the anode (all reactions are run in an undivided cell). Re-reduction of the Pd(II) at the cathode would then regenerate a catalytically active Pd(0) species, thereby ensuring a steady state of active catalyst in the reaction. At this point, this working model is also being used to explain the difference in the allylation reactions.

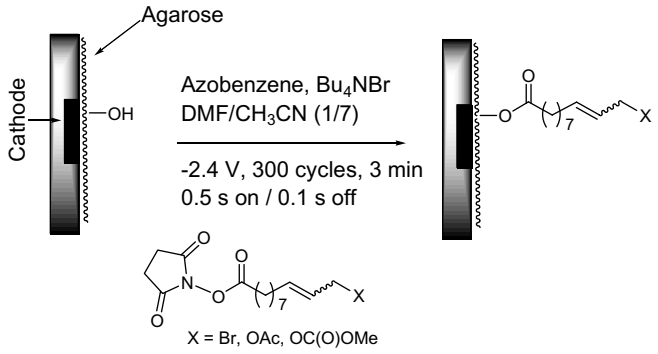
All of the allylation reactions formed both mono- and dialkylated products in a 2:1 ratio. The passage of current through the reaction cell did not alter this ratio. While the solution-phase reactions could be optimized for the formation of monoalkylated product, this effort was deemed unnecessary because in the microelectrode array reactions, a large excess of the nucleophile is used. This should favor formation of the monosubstituted product. In addition, dialkylation would still fix the substrate to the surface of the chip proximal to a selected electrode and hence still accomplish the overall goal of the work.

With an electrochemically assisted allylation reaction in place, attention was turned to the microelectrode array reactions. The plan was to place the allylation substrate on the surface of the microelectrode, and then to utilize a solution-phase acetoacetate nucleophile for the addition reaction. Accordingly, a trio of allylation substrates was constructed (Scheme 3). Each of the substrates contained an *N*-hydroxysuccinimide ester for use in attaching the substrates to the agarose polymer coating the microelectrode array.[9]

Placement of the substrates onto the array was initially attempted by employing the previously developed method for electrochemically catalyzing an esterification reaction between the agarose polymer and the *N*-hydroxysuccinimide ester. This was done by using the microelectrodes in the array as cathodes in order to reduce vitamin-B_{12} and to generate a base catalyst. While this reaction may have worked fine, the subsequent allylation reaction showed no product formation on the microelectrode array. Something was wrong with one of the reactions. In order to gain a feel for which reaction was problematic, a series of solution-phase studies were done. During these studies, it was found that the radical anion of vitamin-B_{12} reacts with the allylic leaving group of the desired substrates. Such a reaction is consistent with the formation of a π-allyl cobalt type species.[10]



Scheme 3.

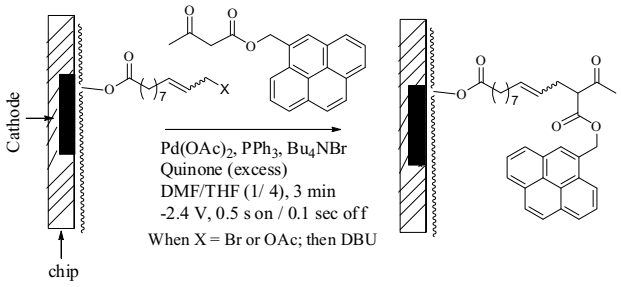


Scheme 4.

Fortunately, these problems could be avoided with the use of a different electrogenerated base (Scheme 4).[11,12] To this end, the microelectrode array was coated with agarose and then treated with a solution of the *N*-hydroxysuccinimide ester, azobenzene, and tetrabutylammonium bromide in a 1:7 mixture of DMF and acetonitrile. The microelectrodes were then used as cathodes (0.5 s on/0.1 s off for 300 cycles) in order to reduce the azobenzene and to trigger the base catalyzed esterification reaction between the agarose polymer and the *N*-hydroxysuccinimide ester. The result was attachment of the substrate to the agarose polymer proximal to the microelectrodes in the array.

The Pd(0)-catalyzed allylation reaction was then conducted in a fashion nearly identical to the solution phase electrolysis reactions described above. Namely the microelectrode array was treated with a 1:4 DMF to THF solution containing $Pd(OAc)_2$, an acetoacetate nucleophile, triphenylphosphine, tetrabutylammonium bromide, and DBU when the allylbromide or allylacetate substrates were used. No additional base was added when the allylmethyl carbonate substrate was used (Scheme 5).

The acetoacetate nucleophile employed was functionalized with a pyrene group for use in subsequent fluorescence studies



Scheme 5.

to determine the success of the reaction. Selected microelectrodes (a checkerboard pattern) in the array were then used as cathodes for the reduction of $Pd(OAc)_2$ and generation of the active Pd(0) catalyst. A remote Pt wire was used as the auxiliary anode for the electrolysis. The only difference between this experiment and the earlier solution-phase electrolysis was the addition of excess quinone as a confining agent for preventing migration of the Pd(0) catalyst generated at the selected electrodes to remote sites on the array. The plan was for the quinone to oxidize any Pd(0) in the solution to a Pd(II) reagent that would not catalyze the allylation reaction. It was hoped that the oxidation would be fast enough so that the allylation reaction would only happen close to the electrodes selected as cathodes. In the area surrounding these electrodes, Pd(0) generation would occur at a rate too fast for the oxidation reaction to keep up.

For the microelectrode array reactions, the selected electrodes were cycled in a manner identical to the base-catalyzed esterification reaction. Each selected cathode was turned on for a period of 0.5 s and then turned off for 0.1 s. Microelectrodes that were not selected were left off for the entire time. After 300 cycles, the microelectrode array was removed from the solution, washed, and then examined with the use of a fluorescence microscope.

The selective allylation reaction with all three substrates worked nicely. However, the reactions originating from the allylbromide substrate did not give as consistent results as reactions originating from either the allylacetate or allylcarbonate substrate. With the allylbromide substrate, confinement across the microelectrode array was always maintained, but the degree of reaction (measured by the intensity of the fluorescent spots) at the selected electrodes varied. While it is not clear why this is the case, use of the allylbromide substrate does lead to the formation of a significantly stronger acid than does the use of the other substrates. It is possible that acid-catalyzed cleavage of the ester linkage connecting the product to the agarose polymer is a problem. In any event, the use of either the allylacetate or allylcarbonate substrate circumvented this problem (Fig. 1). Both reactions led to clear confinement of the reaction to the selected electrodes. In fact, little difference was observed for the two reactions. In the figure, the image in blue is for a reaction originating from the allylacetate substrate. The image in red is for a reaction originating from the allylcarbonate substrate (an experimental 'trick' used to keep the experiments separate).

The difference in the images results from the emission of the pyrene (λ_{max} ca. 400 nm) matching closely with the blue light used (360 nm for excitation). The fluorescence observed with the red light is due to a long lived component of the pyrene excimer emission (λ_{max} ca. 480 nm)[13] that does not match as closely with the light source used (560 nm for excitation). Hence, with the blue light the intensity of the light used does not have to be as high. This reduces the background fluorescence from the chip and preserves more of the fine details associated with the chip itself.

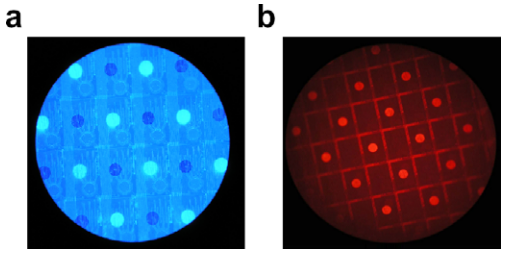


Figure 1. (a) Fluorescence microscope image of an array following an allylic alkylation starting with X = OAc (Scheme 5). (b) Fluorescence microscope image of an array following allylic alkylation starting with X = $OC(O)OCH_3$.

In conclusion, the strategy used for running site-selective Heck reactions on a microelectrode array can be readily adapted to accomplish site-selective allylic alkylation reactions. The reactions take advantage of an azobenzene reduction to place the substrates onto the microelectrode arrays and quinone as an oxidant for confining the Pd(0) catalyst generated to the selected electrodes. This development of the site-selective allylic alkylation reaction provides a second method for generating carbon–carbon bonds on a microelectrode array, as well as opens the door for the site-selective cleavage of alloc-protecting groups. Work to capitalize on these reactions is continuing.

Acknowledgments

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