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COMMUNICATION

Selection of Two Optional Covalent Bonds by Electric Stimuli: Dual Catalytic Switching of Redox-Active Copper

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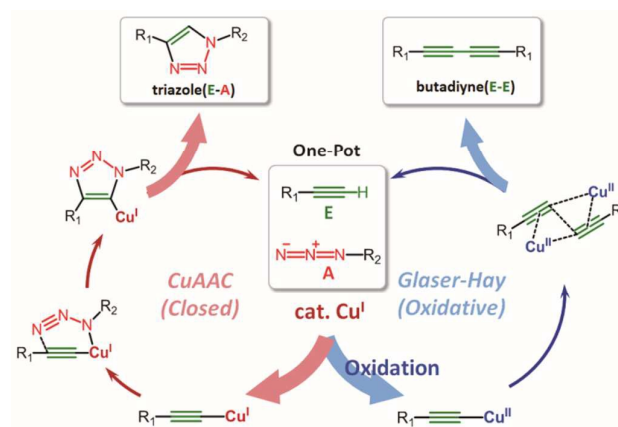
Two types of redox functionality were selected for covalent immobilization on a carbon electrode, using an electric potential as the sole stimulus. A redox-active copper catalyst transformed a terminal alkyne in two ways with and without an oxidation process, to form a triazole or butadiyne.

Artificial switchable catalysts targeting stimuli-responding molecular structures, as in natural enzymatic biosyntheses, have attracted considerable attention.^{1–3} Light, redox, metal ions, protons, and physical stresses have been used as human-generated signals to activate these catalysts. The major goal is to tailor various molecular structures at a specific location and time, by ordering based on these stimuli. However, most of these stimuli only control the activation/deactivation of a catalyst operating in a single reaction, and there have been few reports of multi-active switching catalysts.^{4–5} Compared with a single bond-forming reaction, it is much more difficult to find a pair of complementary reactions, with one exclusively activated over the other, depending on the stimulus, under identical reaction conditions.^{6–8}

Among various stimuli, redox processes are advantageous because they use a clean energy source. Redox-controlled catalytic activity^{4,5,9–16} also enables temporal and spatial control of a solid/liquid interfacial reaction on an electrode under a certain applied potential. These features are useful for constructing specific structures covalently immobilized on specific electrode chips for various applications.^{17–21}

Here, we report redox switching between two types of catalytic reaction with a terminal alkyne as a common substrate. Different types of substrate were selectively bound to the terminal alkyne, depending on the presence/absence of oxidation with a common Cu catalyst. These processes were applied to a terminal alkyne immobilized on an electrode surface, and temporal and spatial control of selective

Scheme 1 Redox-Selective Dual Coupling of Cu Catalyst.^{25, 29}



modification were achieved, solely by switching the electric potential applied through a basal electrode.

We selected two coupling reactions catalyzed by the same Cu complex in different oxidation states (Scheme 1). Cu-catalyzed Azide-Alkyne Cycloaddition (CuAAC)^{22–25} is a feasible click-type reaction, with Cu(I) as the active catalyst. Several groups applied this reaction to surface molecular immobilization, with the ON/OFF response of the Cu(I)/Cu(II) conversion depending on the applied electric potential.^{13–16} We chose the Glaser-Hay coupling,^{26–29} which oxidatively dimerizes alkyne C-H bonds to yield a butadiyne structure, as the other reaction. These two reactions proceed under similar conditions, and a parallel product formation has been discussed in several reports.^{30,31} The crucial difference between these reactions is the requirement of an external oxidation step for the Cu center. Oxygen gas is used as the standard oxidant in Glaser-Hay coupling, in contrast to the exclusion of aerobic Cu(I) oxidation in CuAAC for maintaining activity.^{32,33} While the transformation of surface-immobilized alkyne groups by both CuAAC and Glaser-Hay coupling was reported,³⁴ the reactions were carried out separately with different chemical compositions. We aimed *in situ* selection of these two reactions by an anodic control of the oxidation step in a same

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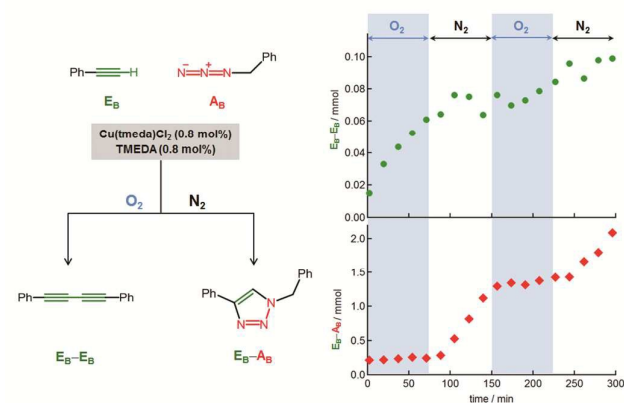


Figure 1. Time-course-dependent product formation upon alternate O_2/N_2 introduction into the reaction vessel. The starting solution was composed of E_B (4.3 mmol), A_B (3.2 mmol), $CuCl_2(tmEDA)$ (0.035 mmol) and $TMEDA$ (0.035 mmol) in 10 ml $MeOH-DME$ (1:1 v/v). Product formation was monitored by gas chromatography.

solution. The anode does not only convert the redox state between $Cu(I)$ and $Cu(II)$, but also acts as a source of the continuous external oxidation. In that sense, our system is somewhat different from the previous switching systems^{4,5,9-12} in which the stimuli acted only on the catalysts.

We first tried to switch these reactions in a one-pot solution by the presence/absence of oxygen as an oxidant. As a soluble catalyst, 0.8 mol% $CuCl_2(tmEDA)$ was added to a solution containing ethynylbenzene (E_B) and benzylazide (A_B). An excess of $TMEDA$ was added to trap protons released in oxidative coupling, and its amount was optimized to 1 equiv. to the Cu catalyst to prevent the formation of undesired byproducts.³⁵

In the one-pot solution under oxygen atmosphere (Figure 1, Figure S1), butadiyne (E_B-E_B) formation was observed without an increase in the formation of triazole. When the atmosphere was changed from oxygen to nitrogen, the product was completely inverted, leading to exclusive triazole (E_B-A_B) formation, and reaction switching could be performed several times. The formation of E_B-E_B was slower and delayed at the second oxygen purging, possibly because a copper triazolide formed during $CuAAC$ cycle trapped Cu species.^{28,29} It is also pointed out that some induction period is often required for $Cu(II)$ catalyst to reach a $Cu(I)/Cu(II)$ steady state in Glaser-Hay Coupling.²⁷

These results demonstrate that the Cu catalyst can act in a dual manner, merely controlled by the presence of O_2 oxidation of the $Cu(I)$ center. Since oxidative coupling also proceeds via outer-sphere $1e^-$ oxidation,²⁷ it is expected to proceed under anodic oxidation conditions. Electrochemical Glaser-Hay coupling was examined using phenylacetylene in 0.1 M tetrabutylammonium tetrafluoroborate as an electrolyte. Anodic electrolysis at +0.4 V (vs. Ag^+/Ag) yielded 1,4-diphenylbutadiyne with almost quantitative faradaic efficiency (Figure S2).

Next we replaced the soluble alkyne substrate with the surface-bound one, and examined its reactivity upon controlled changes in electrode potential (Figure 2). A glassy carbon electrode modified with terminal alkyne (E_S) was

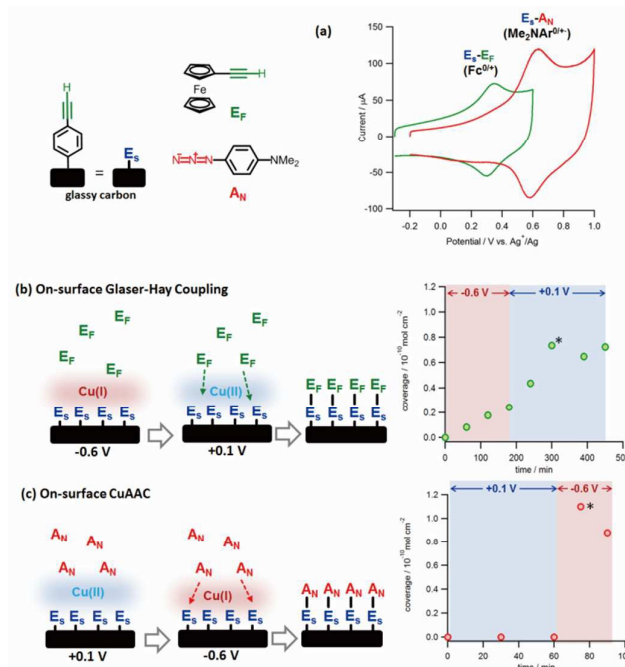


Figure 2. (a) Cyclic voltammograms of the immobilized species. Voltammograms were recorded at the point indicated by asterisks (*) in (b) and (c). (b)(c) The amount of the immobilized species on terminal alkyne-modified glassy carbon electrode with potential change at the electrode. The reaction solution was composed of E_F (37 mM in (b), 0 mM in (c)), A_N (0 mM in (b), 37 mM in (c)), $CuCl_2(tmEDA)$ (6.0 mM) and $TMEDA$ (5.5 mM) in 0.1 M $^nBu_4NPF_6-MeOH-DME$ (1:1 v/v). The immobilized species was detected in 0.1 M $^nBu_4NPF_6-MeCN$ after rinsing the reaction solution. Counter electrode: Pt wire, reference electrode: Ag^+/Ag .

prepared by electrografting of a diazonium salt according to the method described in the literature.³⁶ For its soluble counterparts, 4-(N,N -dimethylamino)azidobenzene (A_N) and ethynylferrocene (E_F) were used with redox functionalities for electrochemical detection of surface immobilization (Figure 2a).

First, the reactivity of these substrates was examined separately. In Glaser-Hay coupling, the modified electrode (E_S) was immersed in an electrolyte solution containing Cu complex as a catalyst and E_F as a single substrate. Then +0.1 V was applied to oxidize the catalyst into $Cu(II)$ state (redox potential of the catalyst $\Delta E_{1/2} = -0.19$ V, Figure S3). After certain duration of voltage application, the electrode was rinsed and the immobilized ferrocenyl moieties (E_S-E_F) were electrochemically detected in a blank electrolyte solution (Figure 2a). Gradual growth of the reversible redox wave at 0.31 V was observed with constant potential application, and eventually it saturated in 5 h.

The immobilization of ferrocenyl moiety onto the electrode was also corroborated by the linear dependence of peak current with the potential scan rate (Figure S5), and the symmetric wave shape with narrow peak-to-peak separation. When a potential of -0.6 V was applied for maintaining $Cu(I)$ state on the electrode, the increase in the redox wave was sluggish, and a sharp onset of increase was observed when the potential was changed from -0.6 V to +0.1 V (Figure 2b, Figure S4). Similar complementary experiments were operated with

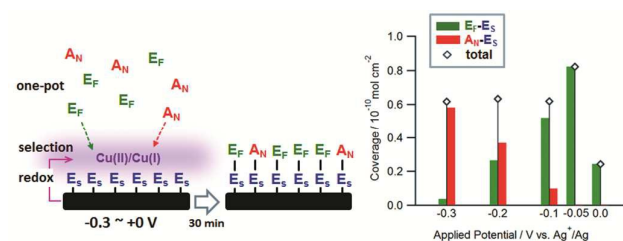


Figure 3. The amount of immobilized species on the terminal alkyne-modified glassy carbon electrode upon application of various electric potentials for 30 min. The reaction solution was composed of E_F (37 mM), A_N (37 mM), $CuCl_2(tmeda)$ (6.0 mM), and TMEDA (5.5 mM) in 0.1M nBu_4NPF_6 -MeOH-DME (1:1 v/v). The immobilized species were detected in 0.1 M nBu_4NPF_6 -MeCN after rinsing the reaction solution. Counter electrode: Pt wire, reference electrode: Ag^+/Ag .

A_N for CuAAC (Figure 2c, S6, S7). No increase was observed upon application of +0.1 V, and the potential jump from +0.1 V to -0.6 V boosted the reaction and resulted in immediate redox-wave saturation of the immobilized dimethylaminophenyl moiety (E_S-A_N , $\Delta E_{1/2} = 0.70$ V). The splitting of the oxidation wave may be caused by strong intermolecular interactions between bound E_S-A_N species, because of its highly planar and polar structure.

These results show that the two reactions have complementary activation modes corresponding to different applied potentials (+0.1 V vs. -0.6 V). The coverages of these two moieties calculated from redox peak area are also very similar (ca. 8×10^{-11} mol cm^{-2}), corresponding to 23% of dense molecular coverage of the ferrocenyl moiety.³⁷

Subsequently, the reactivity of the E_S -bound electrode in the solution containing both E_F and A_N substrates and the Cu catalyst was monitored at various applied potentials (Figure 3, S8). The reaction was apparently favorable for E_S-A_N formation in the negative potential region, and a clear inversion to E_S-E_F formation was observed at ca. -0.2 V, while the sum of these two modifications is very similar over these potentials. The minimum potential difference required for obtaining opposite selectivity was $\Delta E = 0.2$ V, which is a reasonable value considering the redox equilibrium of $Cu(II)/Cu(I)$ as a reversible system. Application of potentials above +0.1 V led to a decrease in E_S-E_F formation. The A_N substrate seems to be involved in the inhibition of E_S-E_F butadiyne formation, as the reaction without it proceeded even upon +0.1 V application (Figure 2b). During these one-pot experiments, a coincident reaction between A_N and E_F was observed in the bulk solution, but the extent of this reaction was not sufficient to cause a depletion of these substrates, for about half of the monomers were estimated to remain in the reaction solution as monitored by 1H NMR. The current yield for the surface butadiyne formation was calculated as 2.3×10^{-5} (for -0.05 V, 30 min application). The low yield is likely due to the excess amount of the soluble Cu catalyst to the surface immobilized alkyne groups. The sluggish Glaser-Hay coupling process seems to make a thick diffusion layer of $Cu(II)$, which is eventually consumed in the dimerization of E_F in the bulk solution.

The above potential-selectivity in immobilization is sufficient to apply spatial and temporal control of these reactions. First, two terminal alkyne modified carbon electrodes were

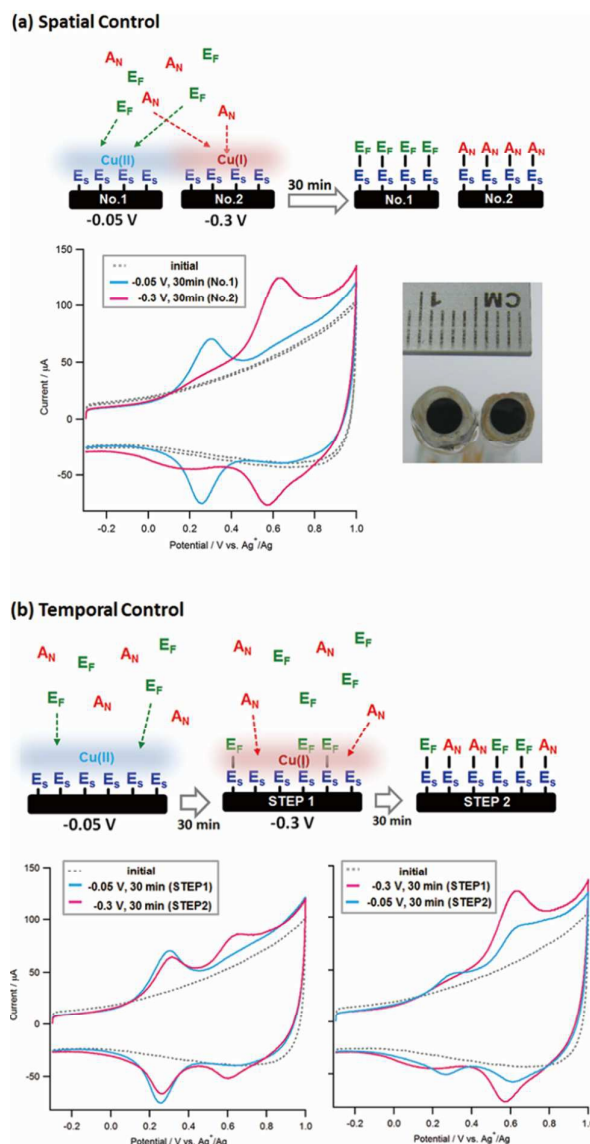


Figure 4. The spatially and temporally controlled selective reaction of terminal alkyne immobilized on the glassy carbon electrode. (a) Potentials of -0.05 V and -0.3 V were simultaneously applied to two adjacent electrodes (3mm ϕ , shown in the photograph). (b) Successive application of -0.05 V (30 min) and -0.3 V (30 min) on an electrode, with monitoring of immobilized species at each step. The reaction solution was composed of E_F (37 mM), A_N (37 mM), $CuCl_2(tmeda)$ (6.0 mM) and TMEDA (5.6 mM) in 0.1M nBu_4NPF_6 -MeOH-DME (1:1 v/v). The immobilized species were detected in 0.1 M nBu_4NPF_6 -MeCN. Counter electrode: Pt wire, reference electrode: Ag^+/Ag .

simultaneously immersed into the one-pot mixture, and an electric potential of -0.05 V or -0.3 V was applied to each electrode for 30 min. One of the redox functionalities were immobilized exclusively, with an opposite selectivity for each electrode (Figure 4a). This result manifests that different redox species can be distributed by covalent immobilization on chemically uniform electrodes according to the applied electric potential.

Next, temporal control on a single electrode immersed in a one-pot mixture was performed (Figure 4b, left). Initially, a

potential of -0.05 V was applied for 30 min, to achieve partial occupation of the terminal alkyne by E_S-E_F (0.33 V). On subsequent application of -0.3 V for 30 min, another redox wave, corresponding to the dimethylaminophenyl unit, emerged at 0.69 V. No further increase in the immobilized ferrocenyl moiety wave was observed on application of -0.3 V for a second time; this explicitly shows orthogonal electric switching of the two catalytic reactions on the same electrode. When the potential was applied in inverse order, the E_S-A_N group was first detected on the electrode after the -0.3 V application, and then the E_S-E_F group appeared after the second -0.05 V application (Figure 4b, right). The decrease of the E_S-A_N group in second monitoring was due to the decomposition caused by oxidation of dimethylaminophenyl groups upon monitoring.

Similar experiments with other redox-functionalized azide substrates (ferrocenylmethylazide and 4-nitrophenylazide), with different redox potentials, were performed, to show stepwise increases in each redox wave on application of different potentials (Figures S9, S10). These results suggest that the present potential-responsive selection can introduce various molecular functionalities covalently on a surface. Mixed modified surfaces can be produced in a controlled manner by electric potential application, and their functionalities are significantly affected by how they are distributed.³⁸⁻⁴¹

In conclusion, we have shown selective immobilization of redox-functionalized molecular moieties on an electrode surface, with a single control mode, i.e., an applied electric potential. This method can be used for geometric control of surface molecular modification on electrodes with various patterns of applied potentials, and stepwise molecular assembly with a temporally varied potential. These results add much progress on recent works applying various catalytic reactions on electrode surfaces³⁴, but have only made uniformly modified surfaces so far. Investigation of applications of this method to more elaborate molecular structures and various molecular functionalities is now in progress.

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