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## COMMUNICATION

## Electric-Field-Induced Coupling of Aryl Iodides with a Nickel(0) Complex

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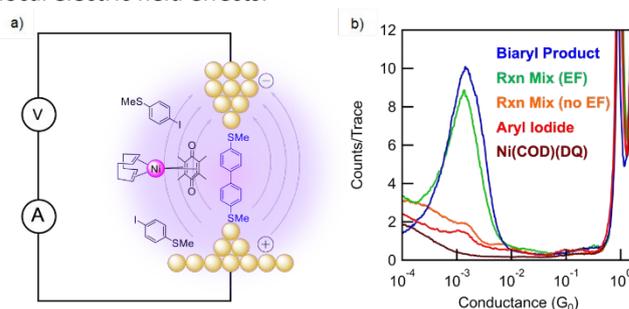
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**The formation of carbon-carbon bonds with transition metal reagents serves as a cornerstone of organic synthesis. Here, we show that the reactivity of an otherwise kinetically inert transition metal complex can be induced by an external electric field to affect a coupling reaction. These results highlight the importance of electric field effects in reaction chemistry and offers a new strategy to modulate organometallic reactivity.**

Biological systems achieve rapid, selective chemical transformations with earth-abundant metal centers through the stabilization of key transition states by powerful electric fields within enzyme cavities.<sup>1</sup> Similarly, permanent electric fields at electrode-solution interfaces have been demonstrated to influence chemical transformations.<sup>2</sup> We previously found that the powerful electric fields accessible with a STM-BJ can accelerate the intramolecular rearrangement of cumulenes in solution.<sup>3</sup> It has also been reported that intermolecular cycloaddition reactions can be enabled by the electric fields generated with an STM tip.<sup>4</sup> Computational studies have indicated that the oxidative addition of aryl halides to a palladium center can be influenced by an external electric field, though this has yet to be experimentally demonstrated.<sup>5</sup>

Here, we demonstrate for the first time that organometallic coupling reactions can be induced *via* applied electric fields in a scanning tunneling microscope in a break-junction (STM-BJ) environment. We chose the homocoupling of aryl iodides as a model reaction to expand the scope of electric-field-induced chemistry to transition-metal-mediated intermolecular couplings.<sup>7</sup> An air-stable nickel(0) olefin complex, Ni(COD)(DQ) (COD = 1,5-cyclooctadiene, DQ = duroquinone, **Figure 1a**), was selected as a model system due to its stability under ambient

conditions, its ability to generate reactive nickel (0) species in the presence of ancillary ligands and elevated temperatures, and its improved sustainability over noble metal catalysts.<sup>8,9</sup> Through a combination of *in-situ* STM-BJ measurements and *ex-situ* high-resolution mass spectrometry (HR-MS) studies, we demonstrate that the reactivity of this complex towards coupling of aryl iodides can be analogously induced by the application of an external electric field. Solvent- and bias-dependence studies further support the critical role of the electric field on the conversion of aryl iodide to biaryl product, and formation of the carbon-carbon bond was monitored *in-situ* via single molecular conductance measurements as well as *ex-situ* via HR-MS. This study represents the first experimental demonstration of an electric-field-induced aryl coupling reaction and offers a strategy to achieve the unrealized potential of Earth-abundant transition metals by harnessing local electric field effects.



**Figure 1.** (a) Schematic illustration of the STM-BJ environment. (b) Logarithmically binned 1D histograms created by compiling 5000 traces collected in TCB solution at 100 mV bias for: the expected biaryl product 4,4'-dithiomethylbiphenyl (blue), the reaction mixture under electric field influence for 20 hrs (green), the reaction mixture on Au substrate in the absence of applied field for 20 hrs (orange), the aryl iodide under electric field influence for 20 hrs (red), and Ni(COD)(DQ) under electric field influence for 20 hrs (dark red).

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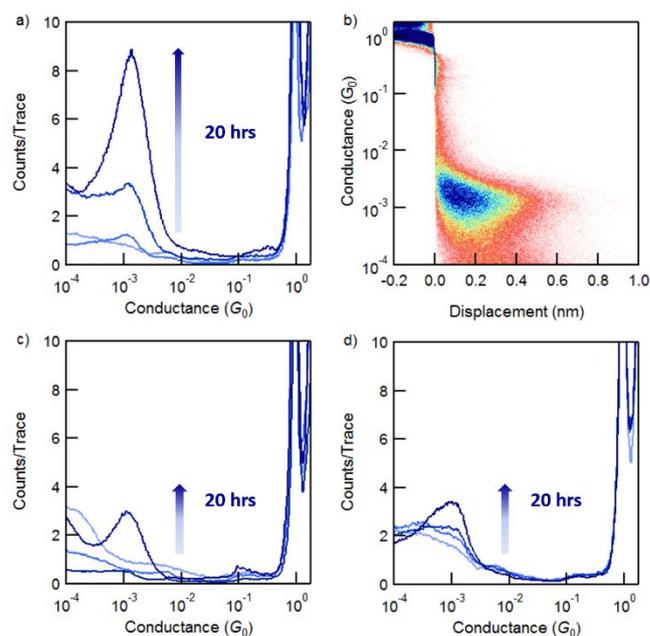
For the STM-BJ measurements, we utilize a custom apparatus that applies a large electric field to the molecular solution in the region between the STM tip and substrate (**Figure 1a**, experimental details provided in the methods section).<sup>10</sup> This setup enables the simultaneous *in-situ* measurement of the single-molecule junction conductance for any molecule that is trapped between the tip and substrate.<sup>11</sup> After collecting thousands of individual traces, we logarithmically bin them into one-dimensional (1D) and two-dimensional (2D) histograms with no data selection (1D histograms shown in **Figure 1b**). We place a 1:2 mixture of Ni(COD)(DQ) and aryl iodide in 1,2,4-trichlorobenzene (TCB) on the substrate and carry out STM-BJ measurements while applying a tip/substrate bias of 100 mV for a period of 20 hours. Over time, a new distinctive peak grows at a conductance value of  $10^{-3} G_0$ , demonstrating that a new molecular species is being generated in solution with two aurophilic linking groups (**Figure 1b**, green trace). In contrast, when we place this solution on the Au substrate with no applied field for 20 hours, this behavior is not observed (**Figure 1b**, orange trace), demonstrating the critical significance of the applied electric field. To unambiguously establish the identity of this new species, we measure the conductance of 4,4'-dithiomethylbiphenyl (**Figure 1b**, blue trace), confirming that the expected biaryl product is generated during the STM-BJ measurement.

To demonstrate that Ni(COD)(DQ) does not facilitate homocoupling of the aryl iodide (4-iodoanisole) under ambient conditions we monitored the reaction *ex-situ* using UV-Vis and <sup>1</sup>H-NMR spectroscopy. As shown in **Figure S1** and **S2**, we observe no change in the electronic transitions of Ni(COD)(DQ) in the presence of stoichiometric aryl iodide at 25 °C even after 24 hours of stirring in either TCB or N,N'-dimethylformamide (DMF). To rule out that the peak results from a Au-catalyzed coupling of the aryl iodide through an Ullmann-type mechanism, we measure a solution of the aryl iodide substrate under the same condition but without Ni(COD)(DQ). As shown in **Figure 1b**, we do not observe a molecular conductance peak consistent with the expected biaryl product (red trace). Furthermore, when we measure the Ni(COD)(DQ) without the aryl iodide we do not observe a conductance feature consistent with the expected biaryl product (dark red trace). To rule out a Faradaic reaction initiated by the applied bias, we explored electrochemical studies of the reaction mixture. Cyclic voltammetry in DMF solution of the reaction mixture with 0.1 M [NBu<sub>4</sub>][PF<sub>6</sub>] supporting electrolyte in a 500 mV window centered at the applied bias in the STM-BJ instrument indicates only passive capacitive charging of the electrode with no Faradaic current observed at these biases (**Figure S3**). Together, these results suggest that the electric field in the STM environment does not result in Faradaic electron transfer with the reaction components.

To visualize the time-evolution of this system under STM-BJ measurement conditions, we generate 1D histograms for the reaction mixture in TCB over 20 hours of data collection. As shown in **Figure 2a**, no molecular plateau was observed during the first two hours. Following 6 hours of measurement, a molecular conductance peak begins to form at a conductance

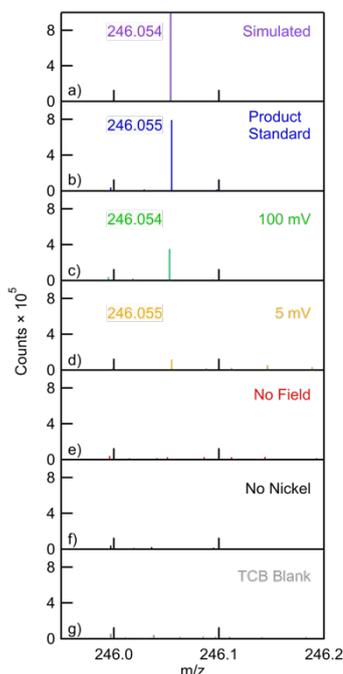
value of  $10^{-3} G_0$ . As the measurement proceeds, the intensity of this plateau increases until an intense peak is observed at the expected conductance of  $10^{-3} G_0$  with the expected junction length of  $\sim 0.5$  nm for 4,4'-dithiomethylbiphenyl (after considering a  $\sim 0.5$  nm Au-Au contact snapback correction) as determined by the displacement profile in the 2D histograms (**Figure 2b**).

As a further demonstration of the critical role of the applied electric field in this homocoupling reaction, we next modulate the electric field strength to observe its impact on the homocoupling reaction. The penetration depth of the applied electric field into the solution surrounding the break junction cavity can be decreased either by decreasing the applied bias or by selecting a solvent with a greater dielectric constant which engages in more effective solvent screening.<sup>12</sup> At a low bias of 5 mV in TCB, the molecular conductance peak was not observed until 12 hours of measurement (**Figure 2c**) and the peak intensity observed after 20 hours of measurement was significantly lower than observed at high bias. At a high bias of 100 mV in a solvent with a higher dielectric constant, DMF, we discern only a minor peak in the 1D histogram after 12 hours of measurement (**Figure 2d**) and the peak intensity observed after 20 hours of measurement was lower than that observed in TCB at 100 mV. These results both suggest that the extent of homocoupling product formation is modulated by the magnitude of the applied electric field.



**Figure 2.** (a) Logarithmically binned 1D histograms created by compiling 5000 traces collected in TCB solution at 100 mV bias for the reaction mixture, (b) logarithmically binned 2D histogram created by compiling 5000 traces collected in TCB solution at 100 mV bias for the reaction mixture after 20 hours, (c) logarithmically binned 1D histograms created by compiling 5000 traces collected in TCB solution at 5 mV bias for the reaction mixture, (d) logarithmically binned 1D histograms created by compiling 5000 traces collected in DMF solution at 100 mV bias for the reaction mixture.

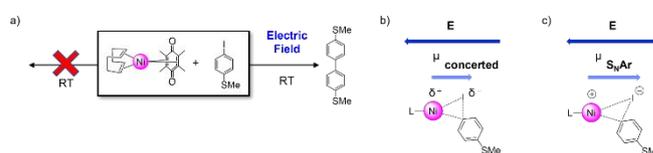
Following STM-BJ measurements, solutions were analyzed by HRMS to confirm formation of the biaryl homocoupling product based on the expected HRMS signature (**Figure 3a,b**). When a mixture of aryl iodide and Ni(COD)(DQ) in TCB was subjected to STM-BJ measurements at 100 mV for 20 hrs the biaryl product was detected (**Figure 3c**). When the reaction mixture was treated with a low bias of 5 mV, the homocoupling product was detected at lower intensity (**Figure 3d**). A solution of the reaction mixture that was placed on a Au substrate for 20 hours but not subjected to an applied bias confirms that no biaryl is generated in the absence of the electric field (**Figure 3e**). Similarly, no biaryl was detected for a solution of aryl iodide that was subjected to STM-BJ for 24 hours in the absence of Ni(COD)(DQ), confirming that the gold substrate is not sufficient for product formation (**Figure 3f**). We also extended these studies to the electric-field driven heterocoupling of p-iodothioanisole and 4-iodo-4'-thiomethylbiphenyl under STM-BJ conditions, demonstrating that all three expected products (4,4'-dithiomethylbiphenyl, 4,4'-dithiomethylterphenyl, and 4,4'-dithiomethyltetraphenyl) are generated in a comparable ratio to that observed for the analogous reaction with Ni(COD)<sub>2</sub> (**Figure S4**). Notably, no product could be detected by <sup>1</sup>H NMR studies highlighting the sensitivity of STM-BJ as a single-molecule detection tool and providing further support to the hypothesis that the reaction only proceeds in close proximity to the STM tip. As such, attempts to quantify product formation were prevented by the detection limit of ex-situ characterization techniques, though a qualitative analysis supports the formation of the expected product.



**Figure 3.** High-resolution mass spectrometry results for (a) simulated spectrum of 4,4'-dithiomethylbiphenyl, (b) 1  $\mu$ M 4,4'-dithiomethylbiphenyl in TCB, (c) p-iodothioanisole and Ni(COD)(DQ) in TCB after 20 hours of STM-BJ measurement at 100 mV, (d) p-iodothioanisole and Ni(COD)(DQ) in TCB after 20 hours of STM-BJ

measurement at 5 mV, (e) and Ni(COD)(DQ) in TCB after 20 hours on a Au substrate with no applied bias, (f) p-iodothioanisole in TCB after 20 hours of STM-BJ measurement at 100 mV, and (g) TCB blank.

A summary of the results from *ex-situ*, *in-situ*, and control studies is illustrated in **Figure 4a**. Under ambient conditions in either TCB or DMF, we observe no coupling product for a mixture of Ni(COD)(DQ) and the p-iodothioanisole electrophile after 24 hours based on <sup>1</sup>H NMR, UV-Vis, STM-BJ, and HRMS analysis. Remarkably, we can induce reactivity under ambient conditions by the application of an external electric field in the STM-BJ environment as confirmed by both STM-BJ and HRMS studies. Prior computational studies have predicted that an applied electric field will stabilize the transition state for the oxidative addition of a transition metal catalyst across a carbon-halide bond.<sup>5</sup> Here, we experimentally confirm this prediction for the first time. As either a concerted mechanism (**Figure 4b**) or an S<sub>N</sub>Ar mechanism (**Figure 4c**) for oxidative addition are predicted to proceed through polarized transition states with dipoles ( $\mu$ ) resulting from positive charge accumulation on nickel and negative charge accumulation on the iodide, an external electric field should amplify this charge separation and lower the activation barrier.<sup>13</sup> This stabilizing influence is reminiscent of the electrostatic basis for enzymatic catalysis—which has been proposed as the dominant source of rate enhancement in enzymes—whereby powerful localized electric fields in the active site cavities stabilize key transition states in mechanistic pathways. Just as enzymes can apply local electric fields to modulate the reactivity of Earth-abundant transition metal active sites, this study demonstrates that synthetic transition metal complexes can be analogously influenced with local electric fields to affect organic transformations.



**Figure 4.** Summary of homocoupling results for *ex-situ* and *in-situ* reactivity studies (a) and schematic illustration of polarized transition state models for a concerted (b) or S<sub>N</sub>Ar-type (c) mechanism for oxidative addition of a nickel center across the carbon-iodide bond.

In this report we demonstrate, for the first time, that organometallic coupling reactions can be modulated with local electric fields in a nanojunction environment. We utilized a bifunctional STM-BJ apparatus both to generate a large local electric field and to detect the formation of biaryl product *in-situ* by single-molecule conductance measurements. We demonstrate that only in the presence of this electric field does the nickel complex engage in aryl iodide coupling chemistry at room temperature, and the formation of the expected biaryl complex is confirmed both by *in-situ* conductance measurements and *ex-situ* high resolution mass spectrometry studies. We further demonstrate that both bias modulation and solvent choice offer strategies to control the strength of this local electric field and, subsequently, the extent of the organic transformation. Just as localized electric fields have been

proposed to facilitate rapid catalysis with Earth-abundant transition metals in enzyme cavities, we demonstrate that the localized electric field in an STM-BJ nanojunction can reveal the unrealized potential of synthetic transition metal complexes for organic transformations.

### Author Contributions

N.M.O., M.L.S., C.N., and L.V. conceived the project and designed the experiments. N.M.O. performed the STM-BJ measurements. N.M.O. and S.G. performed the synthesis and characterization experiments. N.M.O. prepared the manuscript, and the other authors helped revise the paper.

### Conflicts of interest

There are no conflicts to declare.

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