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

Nicholas M. Orchanian,[a] Sophia Guizzo,[b] Michael L. Steigerwald,[a]* Colin Nuckolls,[a]* and Latha Venkataraman[a,b,*]

The influence of electric fields has been postulated as a major factor for rapid catalysis in enzymatic systems. Here, we show that external electric fields can modulate the reactivity of an otherwise kinetically inert transition metal complex to affect a coupling reaction. An air-stable nickel(0) complex is demonstrated to exhibit no reactivity towards the oxidative addition of aryl iodides at room temperature. However, when an external electric field was applied to this reaction solution with a scanning tunneling microscope, the biaryl coupling product was detected in-situ through single-molecule conductance measurements and ex-situ through high-resolution mass spectrometry. These results highlight the importance of electric field effects in reaction chemistry, and demonstrate the application of STM studies towards electric field induced organometallic transformations.

Introduction

It has been hypothesized that 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.[1] Similarly, permanent electric fields at electrode-solution interfaces and permanent dipoles in small molecule catalysts have been demonstrated to influence chemical transformations.[2] Previously, we found that the powerful electric fields accessible with a STM-BJ can accelerate the intramolecular rearrangement of cumulenes in solution.[3] It has also been reported that intermolecular cycloaddition reactions can be enabled by the electric fields generated with an STM tip.[4] 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.[5] Of particular interest to the development of sustainable chemical transformations is the application of this electric field effect to accelerate or induce reactivity of Earth-abundant transition metal complexes. These reactions traditionally employ costly precious metal reagents with ancillary ligands to optimize activity and selectivity.[6] To enable continued progress in the diversification of small molecules, it is of growing interest to explore alternative strategies to accelerate these reactions, including the application of external electric fields to facilitate catalysis in analogy to enzymatic systems.

Here, we demonstrate for the first time that aryl iodide 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.[7] 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 and its ability to generate reactive nickel (0) species in the presence of ancillary ligands and elevated temperatures. 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.

Results and discussion

We employed a kinetically-inert metal complex in stoichiometric quantities to determine if it would engage in coupling reactions upon exposure to a local electric field. We selected a nickel(0) complex as model systems owing to their ubiquitous use in stoichiometric and catalytic coupling

reactions, their unique reactivity relative to palladium systems, and their Earth-abundance relative to palladium.[8] Specifically, we selected Ni(COD)(DQ) as its structure, reactivity, and ability to serve as a precatalysts for organic transformations had already been explored.[9]
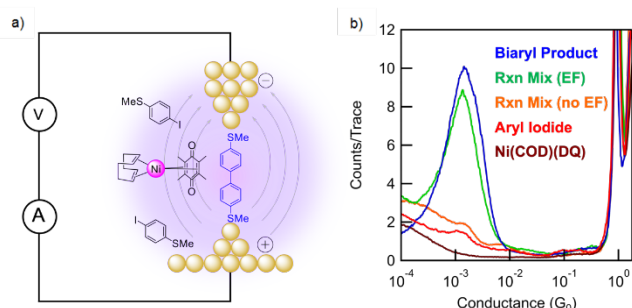

Figure 1. (a) Schematic of the STM-BJ setup where an external electric field is applied across a Au tip and substrate in a solution of the reaction mixture, p-iodothioanisole and Ni(COD)(DQ), illustrating how the expected biaryl product can be detected *via in-situ* conductance measurements. (b) Logarithmically 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 homocoupling reaction mixture under electric field influence for 20 hrs (green), the homocoupling 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).

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).[10] 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.[11] 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-iodothioanisole) under ambient conditions we monitored the reaction *ex-situ* using UV-Vis and ^{1}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$_4$][PF$_6$] 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 S5**). 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 ~ 0.5 nm for 4,4'-dithiomethylbiphenyl (after considering a ~ 0.5 nm Au-Au contact snapback correction) as determined by the displacement profile in the 2D histograms (**Figure 2b**).
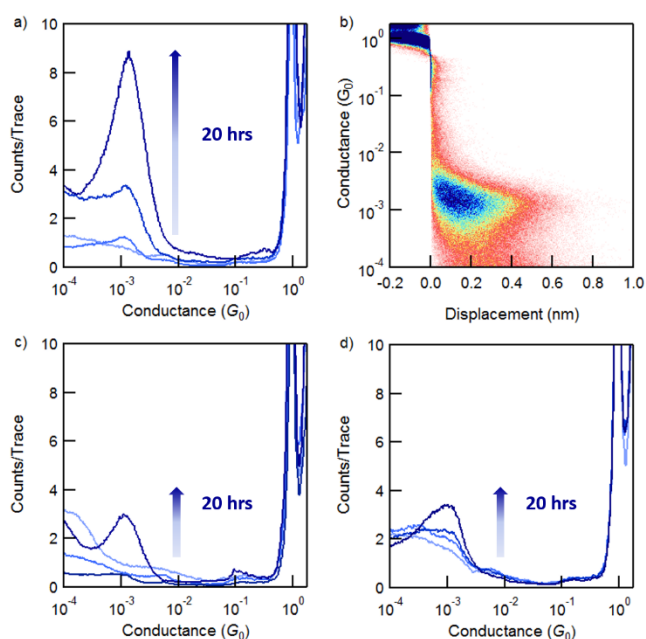
Figure 2. (a) Logarithmically binned 1D histograms created by compiling 5000 traces collected in TCB solution at 100 mV bias for the reaction mixture, (b) logarithmically binned 2D histogram created by compiling 5000 traces collected in TCB solution at 100 mV bias for the reaction mixture after 20 hours, (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.

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.[12] At a low bias of 5 mV in TCB (ε_0 = 2.24), 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 (ε_0 = 37.51), 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.[12]
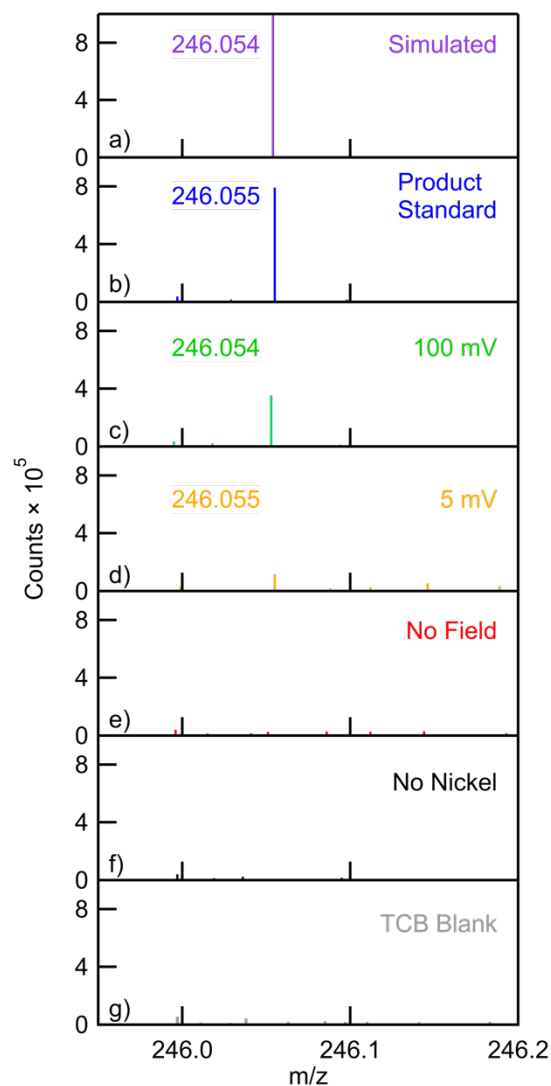

Figure 3. High-resolution mass spectrometry results for (a) simulated spectrum of 4,4'-dithiomethylbiphenyl, (b) 1 μM 4,4'-dithiomethylbiphenyl in TCB, (c) a mixture of p-iodothioanisole and Ni(COD)(DQ) in TCB after 20 hours of STM-BJ measurement at 100 mV, (d) a mixture of p-iodothioanisole and Ni(COD)(DQ) in TCB after 20 hours of STM-BJ measurement at 5 mV, (e) a mixture of p-iodothioanisole 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.

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)$_2$ (**Figure S4**).

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 ^{1}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. [5] Here, we experimentally confirm this prediction for the first time. The possible mechanisms for this oxidative addition include the concerted mechanism (**Figure 4b**) in which Ni-I and Ni-C bonds are formed concurrently, or an S$_N$Ar mechanism (**Figure 4c**) in which Ni-C bond formation accompanies elimination of I$^-$. Both these processes for oxidative addition are predicted to proceed through polarized transition states with dipoles (μ) resulting from positive charge accumulation on nickel and negative charge accumulation on the iodide. As such, an external electric field should amplify this charge separation and lower the activation barrier.[13] And while electric fields have been postulated to specifically influence oxidative addition, our results suggest that the electric field may also influence the ligand exchange process which generates the association products depicted in **Figure 4b,c** ([NiL(4-iodothioanisole)], L= COD, DQ), as dissociation of either the COD or DQ ligand can be expected to precede oxidative addition. This electric field 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.
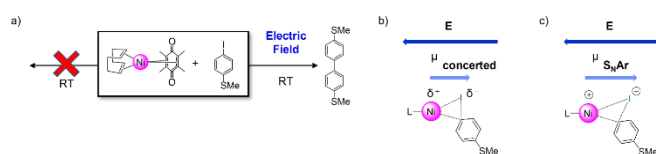
Figure 4. Summary of homocoupling results for *ex-situ* and *in-situ* reactivity studies (a) and schematic illustration of polarized transition state models for a concerted (b) or S$_N$Ar-type (c) mechanism for oxidative addition of a nickel center across the carbon-iodide bond.

Conclusions

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 kinetically sluggish nickel(0) 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.

Acknowledgements

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