

Accepted Article

Title: In situ coupling of single molecules driven by Au-catalyzed electrooxidation

Authors: Yaping Zang, Ilana Stone, Michael Inkpen, Fay Ng, Tristan Lambert, Colin Nuckolls, Michael L. Steigerwald, Xavier Roy, and Latha Venkataraman

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201906215
Angew. Chem. 10.1002/ange.201906215

Link to VoR: <http://dx.doi.org/10.1002/anie.201906215>
<http://dx.doi.org/10.1002/ange.201906215>

COMMUNICATION

In situ coupling of single molecules driven by Au-catalyzed electrooxidationYaping Zang^{[a][d]}, Ilana Stone^{[b][d]}, Michael S. Inkpen^[a], Fay Ng^[b], Tristan H. Lambert^[c], Colin Nuckolls^[b], Michael L. Steigerwald^[b], Xavier Roy*^[b], Latha Venkataraman*^{[a],[b]}

Abstract: Understanding how chemical bonds are formed and broken is the foundation of molecular design. Observing these processes in individual molecules promises levels of detail and precision beyond those achieved through traditional ensemble techniques. Here we develop a single-molecule method based on the scanning tunneling microscope (STM) to selectively couple a series of aniline derivatives and create azobenzenes. The Au-catalyzed oxidative coupling is driven by the local electrochemical potential at the nanostructured Au STM tip. The products are detected in situ by measuring the conductance and molecular junction elongation and compared with analogous measurements of the expected azobenzene derivatives prepared *ex situ*. This single-molecule approach is robust, and it can quickly and reproducibly create reactions for a variety of anilines. We further demonstrate the selective synthesis of geometric isomers and the assembly of complex molecular architectures by sequential coupling of complementary anilines demonstrating unprecedented control over bond formation at the nanoscale.

Ubiquitous in biological processes, oxidative coupling reactions are important for chemical synthesis and bioconjugation^[1] as an alternative to traditional cross-coupling strategies.^[2] While several homogeneous and heterogeneous oxidants can effect oxidative coupling,^[3] the development of nanocatalysts and electrochemical techniques to drive such reactions has emerged as a new frontier in the search for versatile and environmentally friendly synthetic methods.^[4] However, the electrocatalytic coupling process is typically monitored through ensemble measurements.

In this work we use a scanning tunneling microscope-based (STM) technique^[5] to investigate nanocatalytic electrooxidative coupling in a series of anilines, and for the first time detect the *in situ* single-molecule formation of azobenzenes. Originally employed as dyes and pigments,^[6] aromatic azo compounds have generated interest for applications as smart materials,^[7] light-activated switches^[8] and therapeutic agents.^[9] Traditional methods of preparation employ diazonium salts or nitroso derivatives as reactants, or more practical building blocks such as nitrobenzenes and anilines.^[6, 10] Here we show that anilines can undergo a “one pot” selective oxidative coupling on a nanostructured Au STM tip under oxidative bias (Figure 1). The formation of single azobenzenes in the junction is validated by measuring their conductance and molecular junction length *in situ*

and comparing these values to control compounds prepared *ex situ*.^[1d] Capitalizing on the remarkable sensitivity of the STM technique, we demonstrate that either the *trans* or the less stable *cis* isomer forms selectively, the selectivity being determined by the group appended to the aniline. Expanding this strategy to more complex systems, we couple complementary aniline units to form molecules with multiple bridging diazenyl groups in the junction.

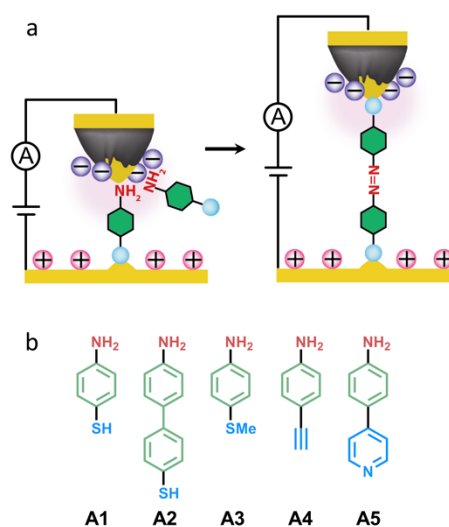


Figure 1. (a) Schematic illustrating the *in situ* coupling of two aniline-derivatives driven by Au-catalyzed electrooxidation in the molecular junctions. (b) Molecular structures of the anilines **A1-A5** used in this work to create azobenzene derivatives.

Experimental details for the modified STM technique have been described previously.^[11] Briefly, break junction measurements are performed in an ionic environment using an insulated Au STM tip,^[12] with an exposed area of $\sim 1 \mu\text{m}^2$, and an Au substrate with an area larger than 0.5 cm^2 . When a potential bias is applied to the tip, a dense electric double layer builds up around the small tip area. The local electrochemical potential within the double layer can facilitate redox reactions. We measured the single-molecule conductance of a series of anilines (Figure 1) in propylene carbonate (10–100 μM concentration) with tetrabutylammonium perchlorate as supporting electrolyte (0.1 M concentration).

Figure 2a presents sample conductance-displacement traces for 4-mercaptoaniline (**A1**) at different junction bias voltages. When the tip bias is +100 mV, a short conductance plateau ($\sim 0.15 \text{ nm}$) appears at $\sim 10^{-2} G_0$ (where $G_0 = 2e^2/h$ is the conductance quantum), indicating the formation of single **A1** junctions. Increasing the tip bias to +600 mV (i.e. a more oxidative potential) results in a new, longer plateau ($\sim 0.6 \text{ nm}$) at a lower conductance of $\sim 9 \times 10^{-3} G_0$. To ensure these features are statistically reproducible, we repeat the measurement thousands

[a] Dr. Yaping Zang, Dr. Michael S. Inkpen, Prof. Latha Venkataraman
Department of Applied Physics and Applied Mathematics, Columbia University, New York
E-mail: lv2117@columbia.edu,
xr2114@columbia.edu

[b] Ilana Stone, Dr. Fay Ng, Prof. Colin Nuckolls, Dr. Michael L. Steigerwald, Prof. Xavier Roy, Prof. Latha Venkataraman
Department of Chemistry, Columbia University, New York

[c] Prof. Tristan H. Lambert
Department of Chemistry and Chemical Biology, Cornell University, Ithaca

[d] These authors contributed equally to this work

COMMUNICATION

of times at both tip biases and compile the traces into one-dimensional (1D) logarithmically-binned conductance histograms and two-dimensional (2D) conductance-displacement histograms without any data selection. This analysis provides two molecule-specific signatures: the most probable molecular conductance from the 1D histogram and the junction elongation (or molecular plateau length), which relates to the molecular backbone length, from the 2D histogram.^[13]

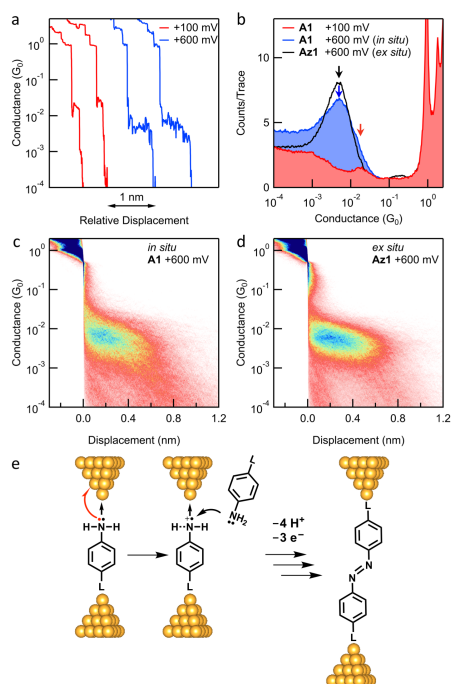


Figure 2. (a) Conductance traces of **A1** measured at a tip bias of +100 mV (red) and +600 mV (blue). (b) Logarithmically-binned 1D histograms of **A1** measured at +100 mV (red) and +600 mV (blue), and **Az1** prepared *ex situ* and measured at +600 mV (black). (c) 2D conductance-displacement histogram created by aligning and overlaying all **A1** traces measured at +600 mV. (d) 2D conductance-displacement histogram of **Az1** prepared *ex situ* and measured at +600 mV. (e) Proposed mechanism for the formation of azobenzene derivatives via electrooxidative coupling of anilines in single-molecule junctions. L = aurophilic linker group used here (thiol, thiomethyl, alkynyl or pyridyl).

At a +100 mV tip bias, the conductance peak for **A1** is centered at $\sim 1.7 \times 10^{-2} G_0$ (red histogram in Figure 2b). The corresponding 2D histogram reveals a short junction elongation consistent with the short molecular length of **A1** (Figure S2b). At a +600 mV tip bias, a new well-defined peak emerges at a lower conductance of $\sim 4.6 \times 10^{-3} G_0$ (blue histogram in Figure 2b). The corresponding 2D histogram shows a markedly longer molecular plateau (Figure 2c). Together these distinct features signify the formation of a new junction with a molecule that is longer than **A1**. A negative (reductive) tip bias does *not* produce longer junctions with lower conductance (Figure S2). To account for these observations, we propose that under positive tip bias, **A1** undergoes an oxidative coupling reaction to form 4,4'-dimercaptoazobenzene (**Az1**).

To verify this hypothesis, we synthesized **Az1** *ex situ* (as the *trans* isomer), and compared its molecular conductance and junction elongation to those for the *in situ* coupling of **A1** at high

tip bias. The 1D histogram for **Az1** made *ex situ* shows a clear conductance peak (black histogram in Figure 2b) at the same value as that for the *in situ* coupling product of **A1**. The junction elongation displayed in the 2D histogram for **Az1** prepared *ex situ* (Figure 2d) is essentially the same as that for **Az1** formed *in situ* (Figure 2c). This confirms that the new molecule created in the junction is the azo compound **Az1** produced from the oxidative coupling of **A1**.

Figure 2e proposes a reaction mechanism for the electrooxidative dimerization of anilines. The transformation starts by breaking an Au point contact and forming a single-molecule junction containing the aniline bound to an undercoordinated Au atom through a donor-acceptor bond. Under oxidative bias, the aniline is oxidized at the tip, forming a radical cation. Consistent with this behavior, we have previously demonstrated that oligophenylenediamines trapped in molecular junctions can be electrochemically oxidized using the STM technique.^[14] The oxidized aniline then undergoes attack by a second aniline that is either bound to an electrode (and possibly oxidized), or in the surrounding solution. Proton loss leads to the formation of a hydrazine ($-\text{NH}-\text{NH}-$) which is known to oxidize readily to form the diazenyl ($-\text{N}=\text{N}-$) bridge.^[15] This mechanism is analogous to that previously proposed for the oxidative coupling of anilines into azobenzenes under aerobic conditions using Au nanoparticles supported on TiO_2 as catalyst.^[10] We note that the necessary voltage to trigger the electrooxidation at the tip (~ 0 mV versus the ferrocene/ferrocenium redox couple) is lower than the oxidation potential of aniline and its derivatives,^[16] suggesting that the redox transformation in the junction is facilitated by the attachment of the anilines to undercoordinated Au atoms (active sites). This contrasts with homogeneous bulk syntheses requiring strong oxidants, most often in stoichiometric quantities.^[6, 17]

We can also couple anilines with varying backbones and different aurophilic binding groups. For example, Figure S3 illustrates the coupling of the longer molecule **A2**, and Figure 1 shows the range of binding groups we have tested, including thiol, thiomethyl, alkynyl and pyridyl groups (**A3-A5**). In all cases the low tip bias measurements are typical of single-molecule junctions across the original aniline with high conductance and short elongation (Figure S4-S6 and Figure 3). At higher positive tip bias, junctions with lower conductance and longer plateaus are observed, indicating the formation of the azobenzene derivatives **Az3-Az5** via electrooxidative coupling. The diversity of aurophilic groups that can be used in the junction is a clear sign that the *in situ* reaction homocouples aniline moieties.

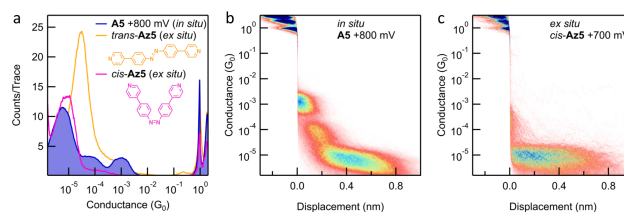


Figure 3. (a) Logarithmically-binned 1D histograms of **A5** measured at +800 mV (purple), and *cis-Az5* (pink) and *trans-Az5* (yellow) prepared *ex situ* (measured at +700 mV). Inset: structure of and *cis-Az5* and *trans-Az5*. (b) 2D conductance-displacement histogram of **A5** measured at +800 mV. The small conductance feature at $\sim 10^{-4} G_0$ comes from a different binding geometry of the pyridyl group in the **A5** junction in which the Au-N bond is perpendicular to the

COMMUNICATION

ring system, leading to lower electronic coupling.^[18] (c) 2D conductance-displacement histogram of *cis*-**Az5** prepared *ex situ* and measured at +700 mV.

Azobenzenes have received a lot of attention due to their ability to undergo *cis/trans* isomerization when irradiated with visible or UV light.^[9] By synthesizing the products *ex situ*, we explored the selective formation of *cis* and *trans* isomers in the junction. For example, the 1D and 2D histograms for the *in situ* coupling of **A1** and **A4** agree very well with those of *trans*-**Az1** (Figure 2) and *trans*-**Az4** (Figure S5), suggesting that these anilines form the more stable *trans* isomer at the STM tip. Remarkably, the pyridyl aniline **A5** does not produce *trans*-**Az5** in the junction (Figure 3). To demonstrate that **A5** instead forms the less stable *cis* isomer, we synthesized both *cis*-**Az5** and *trans*-**Az5** geometric isomers *ex situ* and measured their single-molecule conductance. Because the conductance features of the isomers are distinct, we can differentiate between. In the 1D histogram, the conductance peak for the *in situ* conversion of **A5** (blue) overlays that of *cis*-**Az5** synthesized *ex situ* (pink) and is distinct from *trans*-**Az5** (yellow). In the 2D histogram, the molecular plateau for the *in situ* formation of **Az5** is the same length as that of *cis*-**Az5** and much shorter than that of *trans*-**Az5** (Figure S6). This difference in selectivity for **A5** could arise from either the geometric or electronic constraints imposed by the binding modes of the pyridine linkers to the nanostructured Au electrodes.^[18]

We next investigated more complex single-molecule reactions. Figure 4a shows the double oxidative coupling of complementary aniline units **A1** and benzidine **A6** into the longer bis-azo compound **Az1-6-1**. The reactants **A1** and **A6** were first combined in propylene carbonate in a 1:5 stoichiometric ratio (10–100 μ M). Measurements at a tip bias of +700 mV show two types of traces (Figure 4b), each having a lower conductance and longer molecular plateau than **A1**. We collected 5000 traces in this mixed solution and compiled them into a 1D histogram (Figure 4c). This histogram shows two clear peaks. The peak at $\sim 5 \times 10^{-3} G_0$ is analogous to that shown in Figure 2a, and corresponds to the **Az1** junction. The lower conductance peak at $\sim 8 \times 10^{-5} G_0$ has a significantly longer plateau, which we attribute to **Az1-6-1** based on the conductance and plateau length. The vast majority of traces show only one of the two plateaus, but a small fraction contains both. We therefore analyze the data and select 28% ($\sim 1400/5000$) and 26% ($\sim 1300/5000$) of the traces that have a feature in the range of the lower and higher conductance peaks. These selected traces are then compiled into separate 2D histograms (Figure 4d,e) to clearly show the differences between traces corresponding to **Az1** (Figure 2c) and those featuring plateaus consistent with the molecular length of **Az1-6-1** (~ 2.3 nm).

To further verify that this new molecular junction is not from the single coupling reaction of **A1** and **A6**, we coupled **A1** and **A2** *in situ* to create an asymmetric azobenzene (**Az1-2**) whose conductance features should resemble that of the putative **Az1-6-1** product. The 1D and 2D histograms for **Az1-2** (Figure S7) show a higher conductance ($\sim 10^{-3} G_0$) and a shorter plateau than **Az1-6-1**, a clear indication that the peak at $\sim 8 \times 10^{-5} G_0$ in Figure 4c is from the coupling of two **A1** units to **A6**. Note that the diamine **A6** alone does not yield well-defined conductance signatures of a

single azo compound at high bias as the coupling reaction does not terminate.^[14] We can therefore create asymmetric azo compounds or even polymers with complex architectures.

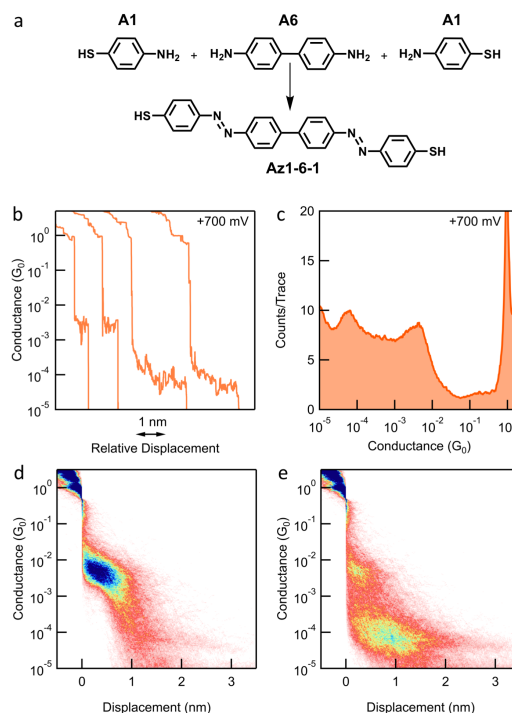


Figure 4. (a) Reaction that couples two **A1** and one **A6** into **Az1-6-1**. (b) Sample conductance traces for mixture of **A1** and **A6** measured at +700 mV. The two traces on the left show a plateau corresponding to **Az1** while the two traces on the right show a much longer plateau corresponding to **Az1-6-1**. (c) Logarithmically-binned 1D histogram for the *in situ* coupling of **A1** and **A6** at a tip bias of +700 mV. The two peaks correspond to **Az1** and **Az1-6-1**. (d) 2D conductance displacement histogram of ~ 1300 traces selected out of 5000 with conductance plateaus around $5 \times 10^{-3} G_0$. (e) 2D conductance displacement histogram of ~ 1400 selected traces with conductance $\sim 8 \times 10^{-5} G_0$.

In summary, by trapping and oxidizing aniline derivatives in molecular junctions comprised of nanostructured Au electrodes, we have developed a new method to form $-N=N-$ bonds. The electrooxidative coupling reaction is facilitated by the Au and proceeds with a variety of molecules. The azobenzenes formed *in situ* and their geometric configurations were characterized by their distinct conductance and verified by measuring the products synthesized *ex situ*. By combining complementary building units that can form multiple diazenyl groups, we can create longer and more complex molecules. This precise control over single-molecule bond formation introduces an archetype for unraveling the mechanistic reaction pathways of synthetic redox reactions and illuminates new avenues for molecular design.

Acknowledgements

We thank Zhen-Fei Liu for discussions. We thank Brandon Fowler for high-resolution mass-spectrometry. This research was supported by the National Science Foundation grant DMR-

COMMUNICATION

1807580 and National Science Foundation MRSEC program through the Center for Precision Assembly of Superstratic and Superatomic Solids (DMR-1420634), the U.S. Air Force Office of Scientific Research (AFOSR) grant FA9550-18-1-0020, and the NSF (CHE-1464992). M.S.I acknowledges support through the Marie Skłodowska-Curie Global Fellowship (MOLCLICK: 657247) within the Horizon 2020 Programme.

Keywords: Electrooxidation, electrocatalysis, aniline, azobenzene, single-molecule measurements.

- [1] a) J. Cai, P. Ruffieux, R. Jaafar, M. Bieri, T. Braun, S. Blankenburg, M. Muoth, A. P. Seitsonen, M. Saleh, X. Feng, K. Mullen, R. Fasel, *Nature* **2010**, *466*, 470-473; b) D. G. de Oteyza, P. Gorman, Y.-C. Chen, S. Wickenburg, A. Riss, D. J. Mowbray, G. Etkin, Z. Pedramrazi, H.-Z. Tsai, A. Rubio, M. F. Crommie, F. R. Fischer, *Science* **2013**, *340*, 1434-1437; c) A. C. Aragones, N. L. Haworth, N. Darwish, S. Ciampi, N. J. Bloomfield, G. G. Wallace, I. Diez-Perez, M. L. Coote, *Nature* **2016**, *531*, 88-91; d) M. S. Inkpen, Y. R. Leroux, P. Hapiot, L. M. Campos, L. Venkataraman, *Chem. Sci.* **2017**, *8*, 4340-4346.
- [2] a) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780-1824; b) A. Lei, W. Shi, C. Liu, W. Liu, H. Zhang, C. He, *Oxidative Cross-Coupling Reactions*, Wiley, **2016**.
- [3] I. Funes-Ardoiz, F. Maseras, *ACS Catalysis* **2018**, *8*, 1161-1172.
- [4] a) V. R. Stamenkovic, D. Strmcnik, P. P. Lopes, N. M. Markovic, *Nat. Mater.* **2016**, *16*, 57-69; b) Z. W. Seh, J. Kibsgaard, C. F. Dickens, I. Chorkendorff, J. K. Nørskov, T. F. Jaramillo, *Science* **2017**, *355*; c) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230-13319.
- [5] a) B. Q. Xu, N. J. Tao, *Science* **2003**, *301*, 1221-1223; b) L. Venkataraman, J. E. Klare, C. Nuckolls, M. S. Hybertsen, M. L. Steigerwald, *Nature* **2006**, *442*, 904-907.
- [6] E. Merino, *Chem. Soc. Rev.* **2011**, *40*, 3835-3853.
- [7] Y. Zhao, T. Ikeda, *Smart light-responsive materials: azobenzene-containing polymers and liquid crystals*, John Wiley & Sons, **2009**.
- [8] a) B. L. Feringa, R. A. van Delden, N. Koumura, E. M. Geertsema, *Chem. Rev.* **2000**, *100*, 1789-1816; b) C. Zhang, M. H. Du, H. P. Cheng, X. G. Zhang, A. E. Roitberg, J. L. Krause, *Phys. Rev. Lett.* **2004**, *92*, 158301; c) B. Y. Choi, S. J. Kahng, S. Kim, H. Kim, H. W. Kim, Y. J. Song, J. Ihm, Y. Kuk, *Phys. Rev. Lett.* **2006**, *96*, 156106; d) V. Ferri, M. Elbing, G. Pace, M. D. Dickey, M. Zharnikov, P. Samori, M. Mayor, M. A. Rampi, *Angew. Chem. Int. Ed.* **2008**, *47*, 3407-3409.
- [9] J. Broichhagen, J. A. Frank, D. Trauner, *Acc. Chem. Res.* **2015**, *48*, 1947-1960.
- [10] A. Grirrane, A. Corma, H. Garcia, *Science* **2008**, *322*, 1661-1664.
- [11] a) L. Venkataraman, J. E. Klare, I. W. Tam, C. Nuckolls, M. S. Hybertsen, M. L. Steigerwald, *Nano Lett.* **2006**, *6*, 458 - 462; b) B. Capozzi, J. Xia, O. Adak, E. J. Dell, Z.-F. Liu, J. C. Taylor, J. B. Neaton, L. M. Campos, L. Venkataraman, *Nat. Nanotechnol.* **2015**, *10*, 522-527.
- [12] L. A. Nagahara, T. Thundat, S. M. Lindsay, *Rev. Sci. Instrum.* **1989**, *60*, 3128-3130.
- [13] M. Kamenetska, M. Koentopp, A. Whalley, Y. S. Park, M. Steigerwald, C. Nuckolls, M. Hybertsen, L. Venkataraman, *Phys. Rev. Lett.* **2009**, *102*, 126803.
- [14] Y. Zang, A. Pinkard, Z.-F. Liu, J. B. Neaton, M. L. Steigerwald, X. Roy, L. Venkataraman, *J. Am. Chem. Soc.* **2017**, *139*, 14845-14848.
- [15] a) J. Lukkari, K. Kleemola, M. Meretoja, T. Ollonqvist, J. Kankare, *Langmuir* **1998**, *14*, 1705-1715; b) I. B. Stone, J. Jermaks, S. N. MacMillan, T. H. Lambert, *Angew. Chem. Int. Ed.* **2018**, *57*, 12494-12498.
- [16] a) M. Jonsson, J. Lind, T. E. Eriksen, G. Merenyi, *J. Am. Chem. Soc.* **1994**, *116*, 1423-1427; b) A. S. Pavitt, E. J. Bylaska, P. G. Tratnyek, *Environmental Science: Processes & Impacts* **2017**, *19*, 339-349.
- [17] Y. Takeda, S. Okumura, S. Minakata, *Angew. Chem. Int. Ed.* **2012**, *51*, 7804-7808.
- [18] S. Y. Quek, M. Kamenetska, M. L. Steigerwald, H. J. Choi, S. G. Louie, M. S. Hybertsen, J. B. Neaton, L. Venkataraman, *Nat. Nanotechnol.* **2009**, *4*, 230-234.

COMMUNICATION

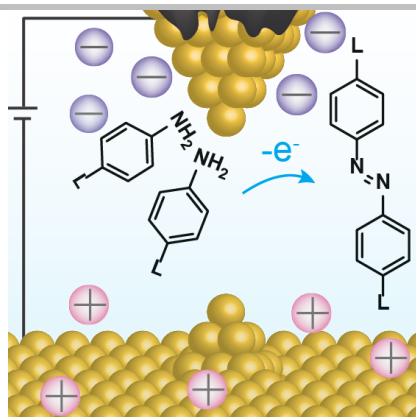


Table of Contents Summary: We selectively create azobenzene derivatives from anilines through an Au-catalyzed oxidative coupling that is driven by the local electrochemical potential at an Au STM tip. The products are determined through single-molecule conductance measurements and compared with azobenzene derivatives prepared ex situ.