## SINGLE-MOLECULE JUNCTIONS

# Chemical mechanisms, one molecule at a time

Transport measurements through a single molecule unveil the mechanism of the catalytic Suzuki-Miyaura cross-coupling reaction.

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nsights into the mechanisms of chemical reactions, the sequence of steps by which an overall chemical change occurs, are vital for better control of the reactions — but can we prove chemical mechanisms? Most chemistry textbooks argue that this is impossible. Yet experiments can determine the likelihood of certain mechanisms over others. Key measurements in this direction include the study of temperature dependence, the determination of the stereochemistry of products, isotope labelling of reactants and the direct observation of reaction intermediates (species that are produced in

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Fig. 1| Suzuki-Miyaura cross-coupling in a single-molecule junction with an integrated Pd catalyst. a, Schematic of the single-molecule electronic device in which a single N-heterocyclic carbene-Pd-based catalyst is covalently bonded between two graphene nano-electrodes. b, The chemical intermediates of the Suzuki-Miyaura catalytic cycle. c, A schematic representation of the four conductance states corresponding to the four different intermediates in b. From low to high conductance: (1) the Pd(0) catalyst, (2) the species after ligand exchange, (3) the pre-transmetallation intermediate and (4) the intermediate before the reductive elimination step.

one step but consumed in the subsequent steps of the same reaction). The latter is perhaps the most effective for unravelling reaction mechanisms, but capturing the intermediates of reactions is often challenging. Some reaction intermediates are short-lived and therefore can only be probed by fast spectroscopic methods. Hence, developing practical yet sensitive methods that can decipher chemical mechanisms remains of utmost importance.

Writing in *Nature Nanotechnology*<sup>1</sup>, Chen Yang, Lei Zhang and co-workers now report a single-molecule electrical measurement that detects the intermediates of the Suzuki-Miyaura reaction. The cross-coupling reaction is one of the most widely used methods in synthetic chemistry for forming C-C bonds. The researchers used a single molecule of a catalyst consisting of palladium (Pd) with an N-heterocyclic carbene ligand. This molecule is covalently bonded to two nano-gapped graphene point electrodes (Fig. 1a). The authors used an on-chip approach in which an array of nanoscale gaps is introduced in a parallel fashion using a lithographic dash-line cutting of a graphene sheet<sup>2</sup>. Each gap is then tested for the presence of one molecule by measuring the current-voltage properties of that specific junction, as well as by single-molecule resolution fluorescence imaging. Gaps with a confirmed single-molecule connection are then selected to perform the catalysis reaction. The reaction reagents are introduced in solution, and the electrical conductance signals from the single-molecule circuit are recorded (Fig. 1b,c). Furthermore, Yang et al. carried out a series of control experiments to assign each electrical signal to a specific intermediate of the catalytic cycle. These include adding the reagents sequentially or adding specific reagents that stop the catalytic cycle at a certain intermediate.

Based on the switching amplitude and sequence of the electrical signals, which identify the different conductance states of the molecule, the researchers were able to detect the intermediates and distinguish between several possible pathways of the Suzuki-Miyaura reaction. Their results show a rapid anion exchange with *tert*-butoxide (O'Bu) before the appearance of the pre-transmetallation signals. This observation indicates that in Pd-catalysed Suzuki-Miyaura cross-coupling, the transmetallation step (the transfer of ligands from boron to palladium) occurs via an anion-exchange-first mechanism, a step that is debated in the literature (Fig. 1b)<sup>3,4</sup>. The method also allowed the determination of kinetic and thermodynamic constants

of each individual step and of the overall catalytic cycle.

Using molecular circuits to study chemical reactions has previously been challenging because of the mechanical instability of single-molecule wires formed between conventional metal electrodes. Additional complications arise from the nature of traditional single-molecule junction measurements, which often require moving at least one of the junction electrodes, meaning that a single molecule is only momentarily present in the junction. Yang et al., however, have developed fixed graphene-molecule-graphene circuits<sup>2</sup> in which the catalyst is covalently attached to the graphene electrodes — an exceedingly robust platform that enables simple interpretation of the electrical signals arising from the Suzuki-Miyaura reaction. A similar approach could be potentially used to study a wide range of reactions. Within the context of organometallic catalysis, similar circuits may provide insights into metal-catalysed C-H bond activation mechanisms, which will help to develop new methods for the functionalization of hydrocarbons. These chemicals, which currently mainly serve as cleaning reagents or as fuel, may then become key precursors for pharmaceuticals. The technique could also be valuable in bioanalysis, for example for the investigation of the thermodynamic binding affinity of biological systems and an improved understanding of enzymatic activities. Because the presented method involves very low concentrations of reactants, it could also be useful for studying chemical reactions that produce toxic intermediates or side-products.

The study by Yang et al. is released during a renaissance in the field of molecular electronics, which has been traditionally driven by interests in developing miniaturized electronics<sup>5,6</sup>. During the past few years, however, the field has been shifting from using chemistry for making nanoelectronics to using nanoelectronics for making and understanding chemistry7. Molecular circuits are now routinely used to understand chemical reactivity and as ultrasensitive analytical measurement tools<sup>8,9</sup>. What makes the single-molecule approach particularly attractive for chemical analysis is its high sensitivity in differentiating between reaction intermediates. Tiny changes in the structure or the composition of a molecule can lead to a large change in the conductance fingerprint. The method represents an alternative to ensemble analytical techniques such as NMR and infrared spectroscopy, in which subtle changes in

the chemical structure or composition of different intermediates are difficult to resolve at ambient conditions. In addition, single-molecule electrical measurements have high temporal resolution (microseconds, in this work), and the field is continuously developing, so detection below the microsecond timescale may soon be possible.

Challenges remain in mass production of single-molecule devices, but the authors have made good progress, with 17% of their devices showing the desired properties, which brings us to the long-awaited era of practical single-molecule devices. In comparing the single-molecule method with ensemble analytical techniques, it is particularly interesting to study the effect of the confined environment supplied by the connecting electrodes on the dynamics of chemical reactions. The confinement effect may increase or decrease reaction barriers and could stabilize intermediates that are short-lived in the free solution environment<sup>10</sup>. The study will stimulate experimentalists to study other type of reactions but will also motivate theoreticians to push for a better understanding of reaction mechanisms in confined environments. Although there are well-established theories for reaction rate and energy calculations in gas and solution phases, the development of similar theories for molecules in an electronic junction environment, which is confined in space and can experience large electric fields and tunnelling currents, has only just started<sup>11</sup>. 

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## Published online: 02 September 2021

https://doi.org/10.1038/s41565-021-00948-7

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#### Competing interests

The author declares no competing interests.