

the device is sensitive to multiple light characteristics, practical application of this capability is hampered by the complicated variations in the photovoltage. For example, two light waves with different wavelengths, powers or polarizations can yield the same photovoltage.

Ma *et al.* turned this problem on its head. They showed that the photovoltage characteristic of their device – the variation of the photovoltage with the two gate voltages – serves as a ‘fingerprint’ for the incident light. This fingerprint can be identified by a machine-learning algorithm. The algorithm bypasses the lack of a parsimonious and physically motivated model of the bulk photovoltaic effect by using a training process: it takes many examples (including a lot of redundant information) and fits a large number of tuning parameters to best approximate the relationship between the gate voltages and the photovoltage.

To learn the fingerprint of light, the authors used a convolutional neural network, which is a type of artificial neural network designed for image recognition⁸. The photovoltage pattern forms an abstract 2D image, which is fed into the neural network. The network then outputs the inferred characteristics of the incident light, in the form of ‘Stokes parameters’ that describe its power and polarization, as well as a label for the wavelength. After training the neural network to minimize the difference between its output and experimentally measured Stokes parameters and wavelength, Ma *et al.* tested it on a set of photovoltage patterns. The network succeeded in producing outputs that mostly fell in the range of experimentally measured values. This demonstrates that a compact photodetector is capable of inferring multiple characteristics of light.

Understanding the extent to which this scheme will be useful is a task for future investigations. It will be crucial to determine how translatable the trained neural networks are. Ma and colleagues’ photodetector was trained only at 5- and 7.7-micrometre wavelengths – it remains to be seen whether the device can be predictive at other wavelengths and powers without prior training.

The choice of machine-learning scheme, and details of how it is deployed, should also be further explored. For instance, how is the performance affected if it is scaled down to one tuning parameter or if more tuning parameters are added? How does this scheme compare with alternative methods that do not use neural networks? Finally, it would be worthwhile to explore similar schemes with other moiré materials in which large nonlinear responses to applied voltage have recently been uncovered⁹.

Ma and co-workers’ study combines machine learning with the fact that twisted double bilayer graphene can be gate-controlled to

produce a sensor that performs the functions of many devices in a single, compact package. Could this approach be applied more generally to other types of measurement? Instead of using specialized detectors, such a protocol would examine the way that a material behaves across a range of operating parameters to make statistical inferences about physical

“The key advantage of 2D materials is the fact that they can be customized.”

quantities of interest. For instance, such statistical methods could potentially be used in spectrometry for light that is characterized by a continuum of wavelengths, rather than a single wavelength, or to extract other observable properties such as the magnetic field. Opportunities abound.

Electrochemistry

Electrification promotes tricky synthetic reactions

Charlotte Willans

Chemical synthesis often relies on reactions catalysed by transition metals. Electrochemical methods have now been developed that negate this need, opening up pathways to previously challenging reactions. **See p.292**

The formation of bonds between carbon atoms is key to the synthesis of molecules used in diverse applications, including pharmaceuticals, agrochemicals and materials. However, it remains challenging to join together carbon atoms that are connected to four other atoms (known as sp^3 -hybridized carbon atoms). The coupling of carbon atoms that are connected to three other atoms (sp^2 -hybridized carbon atoms) is more straightforward and better established. But the coupling of sp^3 -hybridized carbon atoms produces molecules that have greater three-dimensionality than do molecules produced by the coupling of sp^2 -hybridized carbons, which are flatter. Having such three-dimensionality improves the success of drug molecules in clinical trials¹, and so efforts to overcome these challenges are clearly worthwhile. On page 292, Zhang *et al.*² report an electrochemical method for the formation of carbon–carbon bonds from reagents containing sp^3 -hybridized carbons.

Chemical reactivity stems from the

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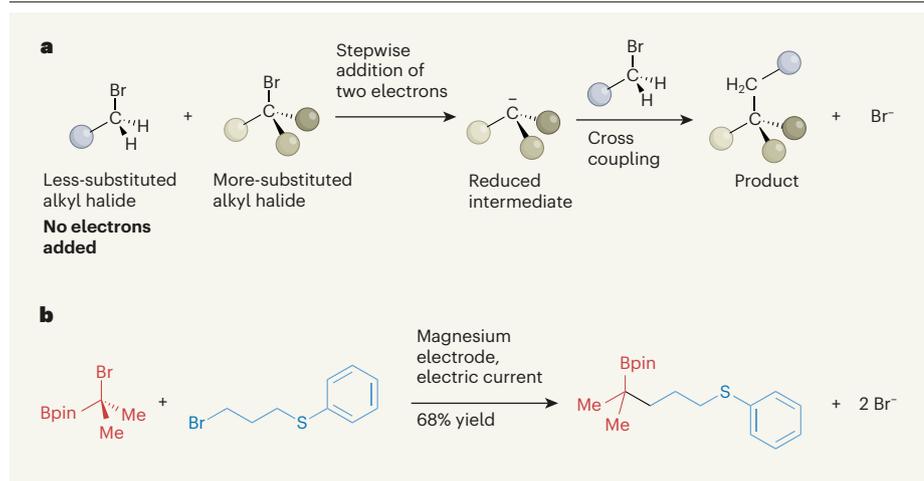


Figure 1 | An electrochemical cross-coupling reaction. **a**, Alkyl halides are organic compounds in which a halogen atom is attached to a carbon; here, the halogens are bromine atoms. More-highly substituted alkyl halides have fewer hydrogen atoms attached to that carbon than do less-substituted ones. Spheres represent any non-hydrogen atom or chemical group. Zhang *et al.*² report an electrochemical reaction, known as cross-coupling, in which two alkyl halides react to form a carbon–carbon bond. Electrons add selectively to the more-substituted alkyl halide, forming a negatively charged, chemically reduced intermediate that attacks the less-substituted alkyl halide. **b**, An example of electrochemical cross coupling. Me, methyl group; Bpin, boron-containing group.

reactions and their associated products.

Electrochemical synthesis involves the formation of new bonds by direct use of the electrons in an electric current, removing the need to use electron-shuttling reagents. Different molecules have distinct redox potentials (a measure of the ease with which a molecule can accept an electron), and this allows electrochemical reactions to be tuned for optimal product selectivity.

Researchers from one of the groups that contributed to Zhang and colleagues' work have previously developed electrochemical methods to overcome challenges in organic synthesis. These included an approach for incorporating a methyl (CH₃) group at specific molecular sites at a late stage in the synthesis of complex biologically active molecules⁵. This is useful because the addition of a methyl group can enhance the binding affinity of a compound for its biological target by more than 1,000-fold, a phenomenon known as the magic methyl effect⁶. Zhang *et al.* now describe electrochemical methods for making *sp*³-hybridized C–C bonds through electrochemical cross coupling of compounds called alkyl halides, by exploiting the different redox properties of two types of these reagents.

For the reaction to succeed, one alkyl halide must accept an electron more easily than the other. The authors initially used computational studies and cyclic voltammetry, a technique for measuring redox potentials, to establish how the number of chemical groups attached to alkyl halides affects the ease with which these compounds are chemically reduced. The researchers concluded that highly substituted alkyl halides, which have many chemical

groups attached, are more easily reduced than are less-substituted alkyl halides. Highly substituted alkyl halides would therefore be expected to pick up electrons in the electrochemical step of the proposed cross-coupling reaction, forming a reduced intermediate that would attack the less-substituted reagent to form a new C–C bond.

Zhang *et al.* tested this hypothesis experimentally, and observed that cross coupling does indeed occur as expected (Fig. 1). The authors then used this chemistry to pre-

“The authors used their chemistry to prepare a diverse array of products.”

pare a diverse array of cross-coupled products, including examples in which carbon–silicon and carbon–germanium bonds were formed. Several of the molecules synthesized are relevant to medicinal chemistry. For instance, the authors incorporated their electrochemical method into a reaction sequence that adds a methyl group to ibuprofen methyl ester (a derivative of the painkiller ibuprofen), and to a compound that activates the receptor for retinoic acid, a metabolite of vitamin A.

One of the challenges in the field of electrochemical synthesis is that a broad range of variables (for example, current, voltage and electrode material) must be considered in addition to the variables that affect conventional organic reactions, such as concentration and temperature. Optimizing all of these variables for each reaction would be extremely

time-consuming, and the optimal set of conditions for one reaction might not be optimal for related reactions. An understanding of the intricacies of electrochemical reactions to predict outcomes is key to using electrochemical methodology and technology to address unmet needs.

In Zhang and colleagues' electrochemical cross-coupling reactions, the optimal electrode material is magnesium. However, this metal is itself electrochemically active – it releases magnesium salts during the reactions, and these form a layer on the electrode that eventually prevents further reactions. Extension of the work to address this limitation, ideally by modifying the electrode material to prevent the formation of metal salts, could bring the new reactions closer to use in industrial applications.

Electrochemical synthesis has undergone a renaissance in the past decade, with the advent of user-friendly technologies enabling a broad range of researchers to become involved in the field⁷. Compared with conventional organic synthesis, electrochemistry is viewed as being more safe, selective, sustainable and environmentally friendly. Many synthetic chemists are now using electrochemical reactions, but often overlook many of the variables that should be considered for reaction optimization. Nevertheless, a wealth of information is available to help them with this, as a result of substantial work by physical chemists and electrochemists. Further fundamental studies and collaboration between synthetic chemists and electroanalytical scientists are now needed to enable all aspects of electrochemical synthetic reactions to be fully understood and better used.

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