

CHEMISTRY ON THE FAST TRACK

ADVANCES IN CATALYST RESEARCH COULD CREATE A SUPERHIGHWAY TO CLEAN ENERGY SOURCES AND A MORE-SUSTAINABLE CHEMICAL INDUSTRY.

BY XIAOZHI LIM

In her 1794 book, *An Essay on Combustion*, Scottish chemist Elizabeth Fulhame noted a peculiar fact: substances such as coal and charcoal burned better when they were damp. After many experiments to understand why, she concluded that the water briefly split into hydrogen and oxygen, which interacted with the other compounds in a way that made the combustion go faster. Yet at the end, Fulhame wrote, the process “forms a new quantity of water equal to that decomposed”.

Many historians consider this to be the first scientific account of a catalyst: a material that speeds reactions by making or breaking chemical bonds, without being consumed. It was hardly the last: modern chemistry would be almost inconceivable without catalysts. “They not only make transformations accessible, but also direct them in new ways,” says Susannah Scott, a chemist at the University of California, Santa Barbara. “That’s very powerful.”

Catalysts are used in some 90% of processes in the chemical industry, and are essential for the production of fuels, plastics, drugs and fertilizers. At least 15 Nobel prizes have been awarded for work on catalysis. And thousands of chemists around the world are continually improving the catalysts they have and striving to invent new ones.

That work is partly driven by an interest in sustainability. The aim of

catalysis is to direct reactions along precisely defined pathways so that chemists can skip reaction steps, reduce waste, minimize energy use and do more with less. And with growing concerns about climate change and the environment, sustainability has become increasingly important. Catalysis is a key principle of ‘green chemistry’: an industry-wide effort to prevent pollution before it happens.

Catalysts are also seen as the key to unlocking energy sources that are much more inert and difficult to use than coal, oil or gas, but much cleaner. Catalysis can make it more economically feasible to split water into oxygen and hydrogen fuel, or can open up new ways to use raw materials such as biomass or carbon dioxide. “These are feedstocks that are ripe for advances in catalysis,” says Melanie Sanford, a chemist at the University of Michigan in Ann Arbor.

These challenges have led to an explosion in catalyst innovation, with the annual number of publications on the subject tripling in the past decade. Many groups are coming up with new small-molecule complexes or are chemically tailoring biological enzymes in search of radically new catalytic activity. Others are pursuing advances in nanotechnology, which allow them to engineer the action of solid catalysts at the atomic scale. Still others are experimenting with catalysts that

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are activated by light, or that incorporate the DNA double helix. And everyone in the field is trying to streamline the search for better catalysts with modern computational modelling tools.

The pace of innovation is such that even the experts are struggling to keep up, says Scott, who leads the US Department of Energy's efforts to develop benchmarks for the new catalysts' performance'. "We need to make sure we are advancing the science that's most efficient," she says.

And the scope of catalysis is increasing rapidly. "Twenty years ago," says John Hartwig, a chemist at the University of California, Berkeley, "catalysis to make molecules that were complex did not exist." Anyone who wanted to modify a large complicated structure would have to tear it down and build it back up, says Sanford. But now, chemists can often edit parts of a molecule precisely. "It's incredibly enabling," she says.

CUT-PRICE CATALYSTS

Using a catalyst is like bulldozing a shortcut between reactants A and product B, bypassing convoluted chemical pathways that might otherwise take forever. Using a really good catalyst is like building a multilane superhighway. And some of the best are the 'homogeneous' catalysts: free-floating molecules that are mixed in with the reactants.

Industrial catalysts in this category most often consist of a metal ion that does the hard work of making or breaking chemical bonds, surrounded by 'ligands': connected groups, often carbon-based, that control the reactants' access to the ion. Much of the research in this field comes down to tailoring these ligands to produce a catalyst that performs only a desired reaction.

Unfortunately, many of the successes so far have come through the use of scarce and expensive metals such as palladium, platinum, ruthenium and iridium. Today, chemists are increasingly striving to build catalysts around cheaper, 'Earth-abundant' elements such as iron, nickel or copper — or to do without metals altogether.

Nickel is a particularly attractive candidate for mimicking the chemistry of palladium and platinum because it sits directly above them in the periodic table, and therefore has similar properties. At the Swiss Federal Institute of Technology in Lausanne, for example, synthetic chemist Xile Hu and his group are working with a remarkably versatile nickel complex² that they first reported in 2008. The complex consists of a nickel ion surrounded by a single, large ligand that binds to it in three places, leaving a fourth binding spot available for catalysing reactions. A similar ligand is already used in certain palladium catalysts. But the radius of a nickel ion is almost 20% smaller than that of a palladium ion, so Hu had to shrink the ligand to fit it more closely around the nickel. To do so, he replaced phosphorus atoms in the ligand with smaller nitrogen ones.

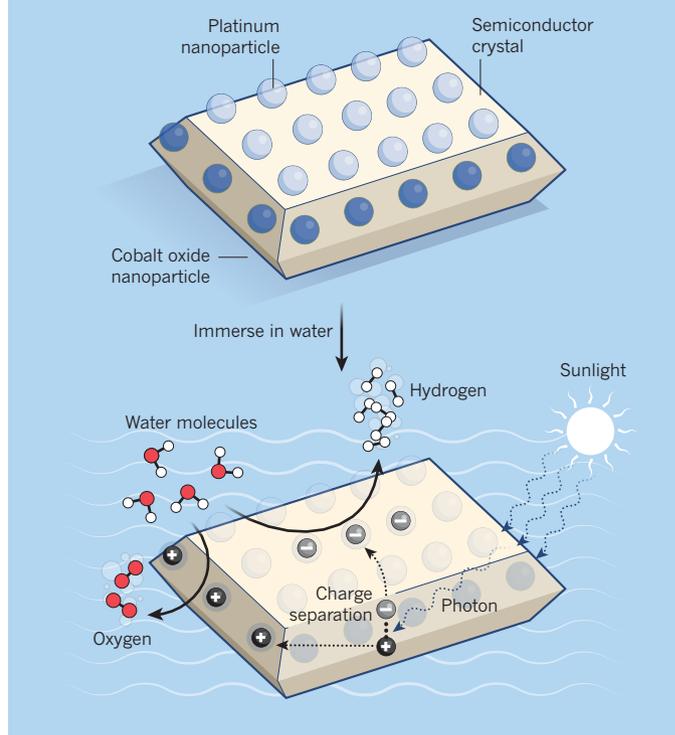
The result is a rigid ligand that stabilizes the nickel ion as it performs a wide array of reactions³⁻⁵. The original nickel catalyst is already available commercially, and Hu is systematically modifying the ligand to make a whole family of catalysts.

In 2008, chemists discovered that certain standard catalysts could be made more powerful by combining them with a technique known as photoredox catalysis. When photoredox catalysts absorb light, an electron leaps from the metal ion to the ligand and becomes stuck there, leaving the molecule in an unstable state. "The catalyst becomes desperate to fill the hole in the metal and get rid of the electron in the ligand," explains David MacMillan, a chemist at Princeton University in New Jersey who first reported⁶ the idea in collaboration with chemist David Nicewicz from the University of North Carolina at Chapel Hill. But the only way the photoredox system can accomplish this is to trade electrons with the standard catalyst, supercharging it and triggering chemical transformations that were previously impossible. As a bonus, the photoredox catalysis drives the process with energy that it absorbed from light, reducing the heat required to keep the reaction going.

Nicewicz and MacMillan have independently used photoredox catalysis to make major improvements to the Buchwald-Hartwig reaction, which is frequently used to bond carbon with nitrogen when making drugs. Typically, the reaction requires the use of palladium salts,

LIGHT SPLITTER

Attaching catalyst nanoparticles to different faces of a semiconductor crystal allows light to split water, but keeps the explosive products — hydrogen and oxygen — separate.



expensive, phosphorus-based ligands and difficult-to-make reactants. But in 2015, Nicewicz's group announced⁷ that it had not only made a carbon–nitrogen bond using a completely metal-free catalyst, but had done so starting from cheaper and more accessible reactants; it is already being used by pharmaceutical companies, says Nicewicz. In June, MacMillan's group and its collaborators at Merck Research Laboratories in Rahway, New Jersey, reported⁸ making the Buchwald-Hartwig reaction work with minute amounts of an iridium light absorber and a nickel salt, eliminating the need for ligands.

A specific challenge for many researchers is to find better ways of creating the carbon–fluorine bonds at the heart of fluorinated compounds that are widely used in pharmaceuticals, agrochemicals and medical imaging. Currently, the bonds are made using expensive specialized reagents or the highly corrosive gas hydrogen fluoride. In 2013, a team of researchers led by Sanford showed⁹ how to make such bonds with a safer potassium fluoride salt using a copper catalyst. First, the catalyst is exposed to a compound that strips away three of its electrons. This leaves the catalyst so hungry for electrons that it can pull some from a nearby fluoride ion, which holds them in a notoriously tight grip. The fluoride is then so desperate for a replacement electron that it will readily bind with a carbon atom to get it.

PEBBLES IN A STREAM

Despite their versatility, many homogeneous catalysts are fragile. Their internal bonds weaken after prolonged exposure to heat and collisions with reactant molecules, and their ligands start disintegrating. "They die after a while," says Sanford.

That is a big reason why large-scale industry tends to use 'heterogeneous' catalysts: solid materials that are fixed in place while the reactants stream past. A classic example is the mix of powdered platinum and other metals found in the catalytic converters that clean vehicle exhaust gases. In the past, chemists had a tough time designing heterogeneous catalysts with atomic precision because it was difficult

to make and study the active sites, where catalysis occurs, in a solid material. Mostly they had to optimize the catalysts through trial and error. But what's changing, says Scott, "is the synthetic control that we can exert over the materials". In particular, rapid advances in nanotechnology are allowing chemists to work towards systems with the robustness of solid catalysts and the high performance of homogeneous ones.

At the Chinese Academy of Sciences' State Key Laboratory of Catalysis in Dalian, director Can Li has used platinum and cobalt oxide nanoparticles to create a catalyst for splitting water with sunlight¹⁰ (see 'Light splitter'). He starts by sticking the nanoparticles to crystals of a semiconductor called bismuth vanadium oxide, with each type of particle carefully isolated on a specific face of each crystal. Then, when he immerses the crystals in water and exposes them to light, photons strike the semiconductor and loosen electrons. The result is a flow of current that the nanoparticles use to break water molecules into hydrogen and oxygen. Oxygen gas comes bubbling off the cobalt oxide sites, while positively charged hydrogen ions migrate to the platinum particles. "We separated the active sites to block the reverse reaction," says Li — that is, a dangerously explosive conversion of hydrogen and oxygen back into water. (To simplify the experimental set-up, the hydrogen ions are currently captured by a separate compound rather than turned into gas.) The process is not yet efficient enough to be economically viable, says Li. But his team is testing combinations of semiconductors and metal catalysts to refine the design.

Audrey Moores, a chemist at McGill University in Montreal, Canada, is tackling a bothersome issue in the pharmaceutical, cosmetics and food industries, which often use heavy-metal-ion catalysts. Ions of palladium, ruthenium and platinum are toxic, so products made with them cannot be sold until they have been through a series of meticulous and expensive cleansing steps. Moores is working on alternative catalysts based on iron, which is much safer.

In 2014, her research group prepared a series of hollow, magnetic iron oxide nanoparticles for making benzaldehyde¹¹: a molecule that smells like almonds and is widely used in flavourings. It is typically manufactured by reacting certain electron-hungry compounds with styrene: a sweet-smelling but hazardous liquid that is better known as a raw material for plastics. The process tends to generate a relatively small amount of benzaldehyde mixed with other molecules. But Moores' iron nanoparticles catalyse a more controllable reaction between styrene and oxygen, yielding almost pure benzaldehyde. And as an added advantage, iron is magnetic, so at the end of the reaction the iron nanoparticles can be extracted for reuse with a magnet.

EVEN-HANDEDNESS

When making large, complex molecules such as steroids, antibiotics or hormones, a major challenge involves chirality, or the 'handedness' of a carbon atom. Such an atom carrying four different groups can have two configurations that are mirror images of each other, like human hands. A complex molecule may contain many such carbon atoms — and if even one of them has the wrong configuration, the compound can end up interacting badly with the human body. One notorious example is thalidomide, a drug developed in the 1950s for treating morning sickness in pregnant women. One chiral configuration seems to have been effective and safe for that purpose. But many chemists believe its mirror image, which was present in the over-the-counter drug, is what caused babies to be born with severe limb deformations.

Molecules from biomass feedstocks contain a wide variety of chiral carbon atoms in a chain, and it is almost impossible to distinguish one from another. "A small-molecule catalyst wouldn't recognize it," says Hartwig. Instead, chemists are turning to biological enzymes, which can be large enough to recognize the overall shape of the target molecule and home in on the bond where the reaction should occur. Enzymes also have the advantage of using water as a solvent and working at body

temperatures, which makes them more environmentally friendly than processes that require toxic solvents and large amounts of heat.

Naturally occurring enzymes don't always catalyse the reactions that chemists want, however — which is why one frontier of catalysis research is to rework these proteins so that they do. Hartwig has been looking at the haem enzyme, which is similar to the compounds that carry oxygen in red blood cells, and has developed¹² an artificial enzyme that substitutes an iridium complex for the haem's iron centre. Although this runs contrary to the goal of replacing precious metals with Earth-abundant ones, says Hartwig, iridium can work with strong bonds such as those between carbon and hydrogen, which iron cannot. His team is using crystallographic data to study the enzyme's structures near the iridium site and is systematically modifying them so that they can precisely transform a carbon-hydrogen bond into a carbon-carbon bond with the desired chiral configuration — a formidable challenge. The chemists can prepare hundreds or even thousands of new enzymes in this way, limited only by the time it takes to test them and analyse their activity.

Still, enzymes are very specific to their target, and although they yield a product with a single chiral configuration, it is often the configuration that isn't wanted. "If you're interested in the other, you're in trouble," says Stellos Arseniyadis, a synthetic chemist at Queen Mary University of London. To address that problem, Arseniyadis is collaborating with Michael Smietana of the University of Montpellier in France to make catalysts from DNA. Although most natural DNA spirals in only one direction, it is possible to make an artificial version

that twists in the opposite direction. The two researchers and their teams make their catalysts by choosing a natural or non-natural helix of DNA and then attaching a metal ion inside it. The spiral grooves align the reactants so that they fuse with the desired chiral configuration. In 2015, Arseniyadis and Smietana reported a recyclable DNA-copper catalyst¹³ that created the correct chiral products as reactants flowed past. With endless combinations of base pairs and metal ions, "there's a plethora of parameters that you can fine-tune", says Arseniyadis.

Chemists are continuing to push the boundaries of catalysis research. Li, for example, is experimenting with housing enzymes inside nanoparticles¹⁴ to help them last longer. Others are synthesizing completely artificial enzymes¹⁵ using techniques from synthetic biology. And earlier this year, an international team of researchers reported¹⁶ using an electric field to catalyse the formation of ring-shaped carbon compounds. These ideas are starting to constitute entire new research fields in which conventionally distinct disciplines overlap — for example, combining chemical synthesis and DNA. That, says Arseniyadis, leaves "a lot of room for serendipity". ■

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CORRECTION

The News Feature 'Chemistry on the fast track' (*Nature* **537**, 156–158; 2016) implied that birth defects were definitely caused by one chiral configuration of thalidomide, but the actual mechanism remains unclear.