WHY CHEMISTS CAN'T QUIT PALLADIUM

A retracted paper highlights chemistry's history of trying to avoid the expensive, toxic — but necessary — catalyst.

By Ariana Remmel

ILLUSTRATION BY FABIO BUONOCORE

It's hard to find a place on Earth untouched by palladium. The silvery-white metal is a key part of catalytic converters in the world's 1.4 billion cars, which spew specks of palladium into the atmosphere. Mining and other sources add to this pollution. As a result, traces of palladium show up in some of the most remote spots on Earth, from Antarctica to the top of the Greenland ice sheet.

Palladium is also practically indispensable for making drugs. That's because catalysts with palladium atoms at their core have an unmatched ability to help stitch together carbon–carbon bonds. This kind of chemical reaction is key to building organic molecules, especially those used in medications. "Every pharmaceutical we produce at some point or another has a palladium-catalysed step in it," says Per-Ola Norrby, a pharmaceutical researcher at drug giant AstraZeneca in Gothenburg, Sweden. Palladium-catalysed reactions are so valuable that, in 2010, their discoverers shared a Nobel prize.

But despite its versatility, chemists are trying to move away from palladium. The metal is more expensive than gold, and molecules that contain palladium can also be extremely toxic to humans and wildlife. Chemical manufacturers have to separate out all traces of palladium from their products and carefully dispose of the hazardous waste, which adds extra expense.

Thomas Fuchß, a medicinal chemist at the life-sciences company Merck in Darmstadt, Germany, gives the example of a reaction to make 3 kilograms of a drug molecule for which the ingredients cost US$250,000. The palladium catalyst alone adds $100,000; purifying it out of the product another $30,000.

Finding less-toxic alternatives to the metal could help to reduce environmental harm from palladium waste and move the chemicals industry towards 'greener' reactions, says Tianning Diao, an organometallic chemist at New York University. Researchers hope to swap palladium for more common metals, such as iron and nickel, or invent metal-free catalysts that sidestep the issue altogether.

Several times in the past two decades, researchers have reported finding palladium-free catalysts. But in what has become a recurring pattern for the field, each heralded discovery turned out to be a mistake.

Then, last year, came an exciting result. A stunning report in January 2021 seemed to put the palladium-free dream within reach[1]. Researchers in China reported that a 'carbon coupling' reaction, one of the most common carbon-bond-forming reactions in the drug industry, could be catalysed without palladium or any other metal. If the findings were confirmed, the reaction would change everything we know about how carbon bonds are formed, says Norrby.

Chemists were instantly excited – and sceptical. Researchers around the world attempted to verify the extraordinary claims in their own laboratories. Within two months, three teams published preprints (working papers prior to peer review) arguing that palladium contamination was catalysing the coupling reaction.

Those critics would turn out to be right. The discovery-that-wasn't, and questions about how the mistake was made, has dominated discussion in some analytical and pharmaceutical chemistry circles. The saga serves as a cautionary tale about how incredibly difficult it is for chemists to keep their reactions and laboratories free from palladium contamination.

Cautionary tales

British chemist Nicholas Leadbeater says when he saw the new claims, the first thought that ran through his head was: "here we go again". In 2003, Leadbeater was pursuing a palladium-free route to carbon-coupling reactions at King's College London. His team was trying to catalyse common reactions with a combination of copper compounds and microwave heating. But when they ran a control experiment without any metals at all, the reactions still worked. Understanding what a remarkable feat this was, Leadbeater and his colleagues took great pains to ensure that no palladium had snuck into the reaction unnoticed.

The team's papers were met with huge acclaim; Leadbeater was sure that the discovery would be the linchpin of his career. Then he moved his research group to the University of Connecticut in Storrs, and things all came apart. "We couldn't make it work no matter what we tried," he says.

> **"WE'RE A LITTLE BIT SUPERSTITIOUS ABOUT ANYTHING RELATED TO PALLADIUM."**

After months of detective work, Leadbeater found the culprit. A common reagent bought from a UK chemical supplier had been contaminated with minute traces of palladium – around 50 parts per billion (p.p.b.) – that was absent from the same product bought in the United States. "That was enough to catalyse the reaction," he says. Leadbeater never retracted his original papers. The team instead published an analysis[2] showing that the metal-free reaction could yield a small amount of their desired molecule, but that palladium contamination was ultimately responsible for the previously reported results.

The same problem cropped up in 2008, when a paper by Robert Franzén at Tampere University of Technology in Finland and his colleagues reported an iron-catalysed version of another carbon-coupling reaction. A research team led by Robin Bedford at the University of Bristol, UK, found that palladium contaminants were responsible, and published a "cautionary tale" about the risks of false positives[3]. The Finnish team's paper was retracted. Norrby says that even his team's successful development of a nickel-catalysed reaction was initially plagued by palladium contamination that stymied progress[4].

The chemistry literature is littered with palladium-related controversies such as these, researchers say: some have been definitively debunked, while suspicion lingers over others. "This has become a minefield," Leadbeater says.

Phantom catalysis

Medicinal compounds are often large, complex molecules, so chemists have to synthesize them piece by piece. Carbon-coupling reactions join those fragments together. But the energy needed to make and break bonds in the coupling partners can render these reactions slow, if not impossible, without a catalyst, says Diao. Palladium catalysts are especially good at overcoming these energetic barriers because the metal's unique electronic structure makes it a versatile matchmaker for a huge diversity of molecular fragments, she says.

But palladium compounds are now so widely used that the metal gets everywhere. Even scratches in the whirling magnetic stir bars, used routinely to mix liquids in chemistry labs, can trap trace amounts of palladium sufficient to jump-start some reactions, according to a 2019 study led by Valentine Ananikov at the Russian Academy of Sciences in Moscow[5]. This 'phantom catalysis' can make it seem as if a reaction is proceeding without a catalyst, Ananikov says. "One must be extremely careful, because palladium can penetrate through contaminated labware, as well as through impurities in chemicals and solvents," he says.

Chemists with experience of staving off unwanted palladium follow strict protocols to limit its spread. Gergely Tolnai and Zoltán Novák, synthetic organic chemists at Eötvös Loránd University in Budapest, restrict palladium use to a designated quadrant of the research lab. Tolnai's team also labels its spatulas for exclusive use with particular metals to avoid any possible cross-contamination. In Bedford's lab, researchers are prohibited from sharing glassware and they use new stir bars when palladium contamination is a concern. They even treat commercial reagents, marketed as ultra-pure, to remove any lingering palladium. Researchers analyse the final reaction mixture for contamination, too, in case an unknown agent introduced impurities along the way.

"We're a little bit superstitious about anything related to palladium," says Tolnai.

Three years of precautions

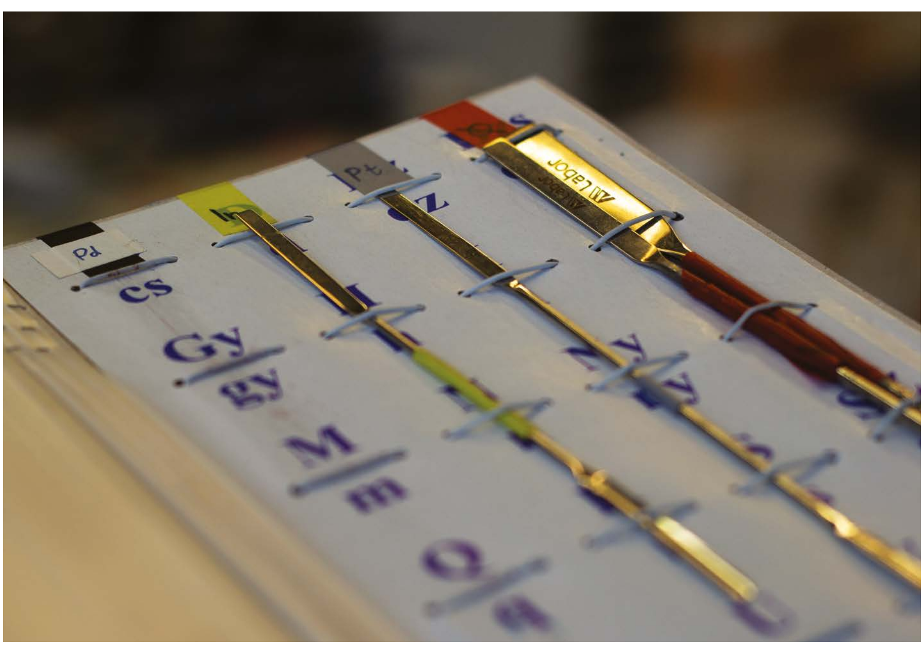
The chemists in China who reported a palladium-free reaction in 2021 claimed that their carbon-coupling catalyst contained no metals: only an organic molecule with nitrogen-containing structures called amines. The snag was that they used palladium to make their amine catalyst.

The team, led by Hua-Jian Xu at the Hefei University of Technology and Hai-Zhu Yu at Anhui University in Hefei, knew that palladium hanging over from this synthesis could foul their later experiments. So they went to great lengths to ensure that this didn't happen.

> **"THIS WORK HAS COST US A LOT OF TIME AND MONEY."**

First, the researchers purified their amine catalyst from palladium by using a kind of chromatography, based on the principle that molecules with different polarities (a property related to the distribution of electric charge) move through a silica gel at different speeds. This aimed to separate the catalyst from any leftover metal complexes.

Then they mixed the purified amine catalyst with a scavenger complex that was supposed to bind to and remove any remaining traces of palladium.



Spatulas labelled for use exclusively with certain metals, to prevent contamination.

GERGELY L. TOLNAI

Finally, they dunked a sample of the amine catalyst in a nitric acid solution to chew the compound up into fragments. That would liberate any residual palladium atoms tied up in organic complexes. These acid-digested parts could then be analysed using mass spectrometry to search for any signals indicating the presence of palladium on the basis of mass and charge. The technique is the gold standard for detecting metal contamination, other researchers say.

These experiments showed less than 1 p.p.b. of palladium, and any other potentially reactive metal, in the catalyst or the reaction mixture. Even when the researchers deliberately added palladium to their reactions, the product would not form without the amine catalyst, Xu wrote in February 2021 in a blog post addressing questions about the work. (The post was later taken down.) He also wrote that the team spent more than three years reproducing and validating the results before publishing its paper in *Nature Catalysis*.

These were all sensible precautions, says Bedford. When he and his colleagues tried to replicate the work by following the paper's methods, the results were consistently reproducible – until the purportedly crucial amine catalyst was made without palladium. Then, the reaction stopped working.

Setting the record straight

Attempts to independently verify the *Nature Catalysis* report began within weeks of its publication. As the paper circulated among researchers on Twitter, chemists quickly homed in on the potential complications posed by the amine catalyst synthesis. Scientific collaborations started to coalesce out of the Twitter threads, and soon preprint manuscripts appeared critiquing the work.

By February 2021, Tolnai and Novák had reported[6] that trace palladium impurities left over after making the amine catalyst were the true catalyst for the reaction. In March 2021, Bedford and his colleagues reported[7] the exact palladium species involved – a compound that chemists already knew to be a highly active catalyst (see 'Carbon coupling').

Unknown to Xu and Yu's team, the palladium left behind in the amine catalyst's synthesis formed a metal complex that was uncannily capable of evading their purification efforts. This complex has a similar polarity to the catalyst itself, so the two don't separate in the chromatography protocol the researchers used. Xu, Yu and their colleagues also chose a scavenger that's not good at binding to this particular compound. The gold-standard spectrometry technique also missed the lingering palladium because the nitric acid digest preparation wasn't harsh enough to break down the complexes, so the instrument reported no clear signal of palladium. Novák says that only by using concentrated acids at high temperatures was it possible to break apart the palladium interloper.

Then in April 2021, Kazunori Koide, an organic chemist at the University of Pittsburgh, Pennsylvania, and his colleagues published a third set of findings on the reaction[8]. Koide's team used a new detection system, developed in his lab, involving a molecular sensor that fluoresces when it reacts with dissolved palladium. The team's analysis corroborated the presence of palladium contamination. Koide is working with collaborators at Merck Research Laboratories in Rahway, New Jersey, to develop this platform as an alternative to mass spectrometry for spotting palladium adulterants.

Nature Catalysis posted an editorial expression of concern on the paper of Xu and Yu's team in March 2021, but the case was not officially closed for another nine months, when Xu and his colleagues formally retracted the paper on 8 December 2021. At the same time, *Nature Catalysis* published peer-reviewed versions of the reports by the teams of Tolnai and Novák, Bedford and Koide. In an editorial[9] published alongside the retraction, *Nature Catalysis* editors said the editors and authors involved – including critics – did not want to rush the process of examining the initial claim, and the retraction came only after everyone involved agreed that the original conclusions were flawed.

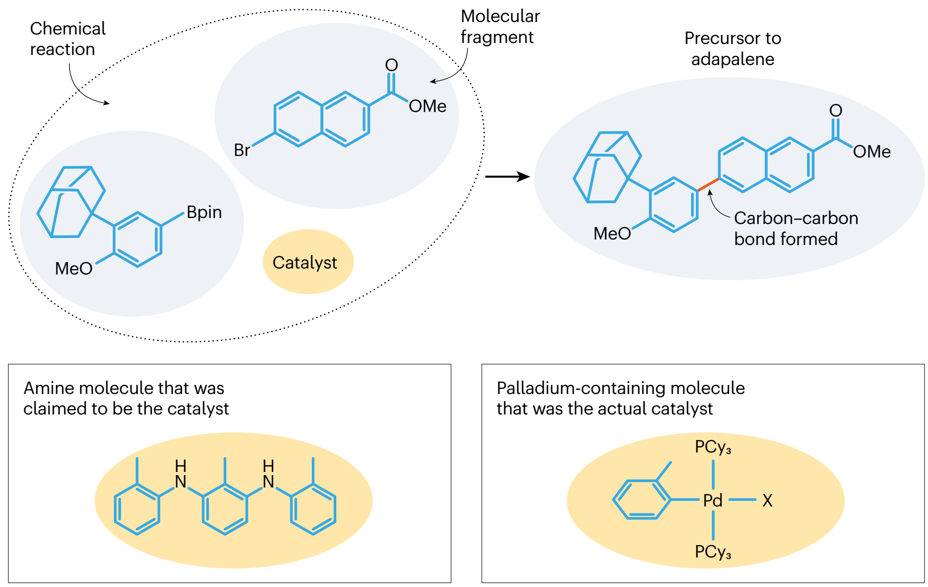
Xu and Yu declined to answer questions, save for an e-mailed statement in which Xu acknowledged that the palladium used to make the amine was the primary cause of the "misjudgement". Xu added: "This event and many previous reports also reflect that the challenge of non-palladium-catalysed classical coupling reaction is indeed very difficult".

In the accompanying editorial, *Nature Catalysis* editors said the episode was a testament to the effectiveness of self-correcting science. They also noted that concerns about trace palladium had been raised during the paper's initial peer review, but that the scientists' tests seemed to rule out metal contamination. A spokesperson said the editorial was the journal's full statement on the matter.

To some extent, given the layers of precautions described in the paper's methods, the researchers were just unlucky, Bedford says. And in a study that used methods from several disciplines, such as organic synthesis, reaction kinetics and analytical chemistry, critics needed deep knowledge of many subject areas to get the bottom of the issue, Tolnai and Novák say. Novák was tipped off to problems with the spectrometry analysis only because he was reading the paper over breakfast with his wife Zsuzsanna Czégény, an analytical chemist at the Institute of Materials and Environmental Chemistry in Budapest. Although Czégény is not a specialist in metal-detecting spectroscopy, she recognized issues with the sample-preparation methods, which Novák

CARBON COUPLING

A common reaction in making drugs is 'carbon coupling': linking two molecular fragments together by a carbon–carbon bond. This process requires a catalyst that usually contains palladium (Pd). In 2021, chemists claimed to do it using an amine catalyst, but others showed that a Pd-containing molecule was responsible. This example shows part of the synthesis of an acne treatment called adapalene.



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and his colleagues later proved in their paper.

The instant discussion on Twitter, fast publication of preprints, and rapid expression of concern issued by *Nature Catalysis* did demonstrate how quickly chemists could vet palladium-free claims. Just one paper, published in *Chemical Science* in October 2021 (ref. 10), cited Xu and Yu's results before their retraction. One of the paper's authors, Bien Tan at Huazhong University of Science and Technology in Wuhan, China, said in an e-mailed statement that his team was eager to apply Xu and Yu's "ground-breaking progress" to their own research. He says that the methods were highly reproducible, and he didn't see the criticism on social media because he does not use Twitter. Tan says he did not learn of concerns until after his paper was published, when editors at *Chemical Science* brought them to his attention. Tan and his team retracted their paper after a month. "This work has cost us a lot of time and money," he says.

Forging ahead

Many researchers say they're undeterred in their pursuit of alternative ways to build carbon-based molecules without palladium. Scientists continue to chip away at the palladium problem piece by piece – here and there finding reactions catalysed by specialized iron- or nickel-containing compounds.

But these isolated examples have so far struggled to make the transition from small batch reactions in academic labs to the massive production needs of manufacturers. Process chemists in the pharmaceutical industry are still left with only a handful of alternative catalysts to perform a small fraction of their routine reactions, says Fuchß.

Even if chemists can't quit palladium entirely, the search for alternative catalysts could still reveal fresh ways of building molecules, says Diao. She hopes that understanding more about how successful catalysts shuffle electrons to make challenging bonds could "lead to new, revolutionary chemistries" that don't use palladium.

Her lab has focused on designing nickel catalysts that can fill in for some palladium-catalysed reactions. And Diao has her sights set on the next frontiers of organic synthesis, such as catalysts that harness light energy to drive reactions. "I think the greatest potential for nickel is to catalyse the reactions that palladium can't do," she says.

Will the lessons of this failed attempt at palladium-independent coupling stick? It's probably too soon to tell, researchers say. "I wouldn't be surprised if this happens again ten years from now," Koide says.

Ariana Remmel is an assistant editor at *Chemical & Engineering News* in Little Rock, Arkansas, and was a news intern at *Nature* in 2021.

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