Researchers revive a chemical synthesis method abandoned a century ago. Why?

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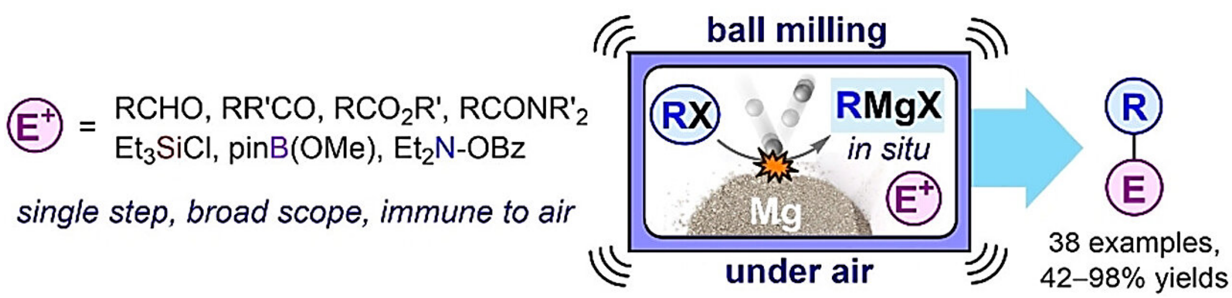

Graphical Abstract. Credit: *Angewandte Chemie International Edition* (2023). DOI: 10.1002/anie.202305775

Organic synthesis is the art of creating molecules, used for creating essential items like pharmaceuticals, agrochemicals, and materials for high-tech gadgets such as smartphones. Think of it as playing with LEGO bricks at a microscopic level—chemists connect simple building blocks to create complex molecules, just like snapping together LEGO bricks to make intricate structures. One crucial step in this puzzle is creating a bond between two carbon atoms.

Like LEGO bricks with their studs and anti-studs, carbon atoms must fit together to combine easily. However, there is a catch: the most reactive carbon atoms in organic compounds usually carry a positive charge, which makes them incompatible with each other. Imagine trying to connect two LEGO pieces with studs—they just will not stick together.

Barbier overlooked even though he showed the way

In the early days of organic chemistry, back in the nineteenth century, researchers discovered a clever workaround to this issue by using so-called organometallic compounds. By bonding carbon to metals like zinc or magnesium, they could switch the charge of the carbon atom from positive to negative.

This "polarity switch" enabled the creation of suitable combinations with other organic molecules, opening up a vast playground for chemical creativity. One of the most impactful discoveries was made by the French chemist Victor Grignard, who discovered a method for creating organic derivatives of readily available magnesium. This technique was so significant that it earned him a Nobel Prize in 1912. The Grignard method revolutionized the field, but it has its downsides.

The highly reactive metal-containing molecules are unstable and can easily break down when exposed to moisture or air, making industrial-scale applications difficult. A solution to this problem lies in the generation of organometallic compounds only as short-lived intermediates that keep reacting in the same environment and create stable compounds.

Grignard's scientific teacher, Philip Barbier, initially attempted to join carbon atoms this way, but only achieved unsatisfactory results—the yields of the desired products were low. Here is where the story takes an ironic twist: he tasked Grignard with perfecting his method, leading to the Nobel-winning discovery. Philip Barbier himself, however, despite being a pioneer of organometallic chemistry, never received the same acclaim.

Chemists turn the old into something new

More than a century later, a group of chemists of the supramolecular chemistry research group of TalTech, led by Prof. Riina Aav and senior researcher Dr. Dzmitry Kananovich, has breathed new life into the abandoned Barbier method. Instead of mixing chemicals with magnesium metal in organic solvents, as traditionally done by chemists for many years, they found that milling them together without a solvent in a device called a shaker mill results in extraordinary improvement, both in terms of efficiency and environmental friendliness.

This exciting development brings the Barbier method back into the spotlight, making it as effective as the famous Grignard method. The results have been recently published in *Angewandte Chemie International Edition*.

The technique used by the researchers is called mechanochemistry, which, despite being known since ancient times, had long been abandoned by the scientific community of organic synthesis in favor of the more traditional solution-based chemistry. Picture grinding coffee beans in a grinder. That is what many mechanochemical devices are like in both appearance and function. They allow chemical reactions to take place through quick blending, milling, and grinding of solid substances, rather than by mixing solutions.

An environmentally friendly solution from a century ago

Why is this old technique gaining traction again? The answer lies in its benefits for the environment and safety standards. Mechanochemistry avoids the use of dangerous organic solvents, which pose serious threats to both people and the planet. One particularly exciting area of focus in chemistry is the preparation of organometallic compounds, and many esteemed research groups are exploring this direction.

In their research, the team from TalTech revisited the original idea of Barbier, making the use of organometallic compounds even more straightforward and convenient. An exciting aspect of this new method is its resistance to air and even certain weak acids, which do not play well with traditional approaches like the Grignard technique.

As the organometallic compounds only exist briefly as intermediates and can keep reacting and create end products, this discovery holds great promise for revolutionizing the production of numerous valuable substances. Think about how this might change the way we manufacture things. It could lead to simpler, safer, and more environmentally friendly processes, especially in industries that produce substances with significant impact, such as the pharmaceutical industry.

The team of TalTech is now looking to take this innovation further, aiming to transform the pharmaceutical sector through mechanochemical production methods. Working with researchers from eleven other European countries, they are collaborating on the IMPACTIVE project, focused on making these benefits a reality.

This rediscovery and advancement of mechanochemistry could be the key to unlocking new opportunities in the chemical industry, making it safer and more sustainable for generations to come. It is a blend of the old and the new, with the promise of a brighter future.

More information: Jagadeesh Varma Nallaparaju et al, Mechanochemistry-Amended Barbier Reaction as an Expedient Alternative to Grignard Synthesis, *Angewandte Chemie International Edition* (2023). DOI: 10.1002/anie.202305775

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