# 'Goldilocks system' boosts efficiency of nickel-catalyzed reactions

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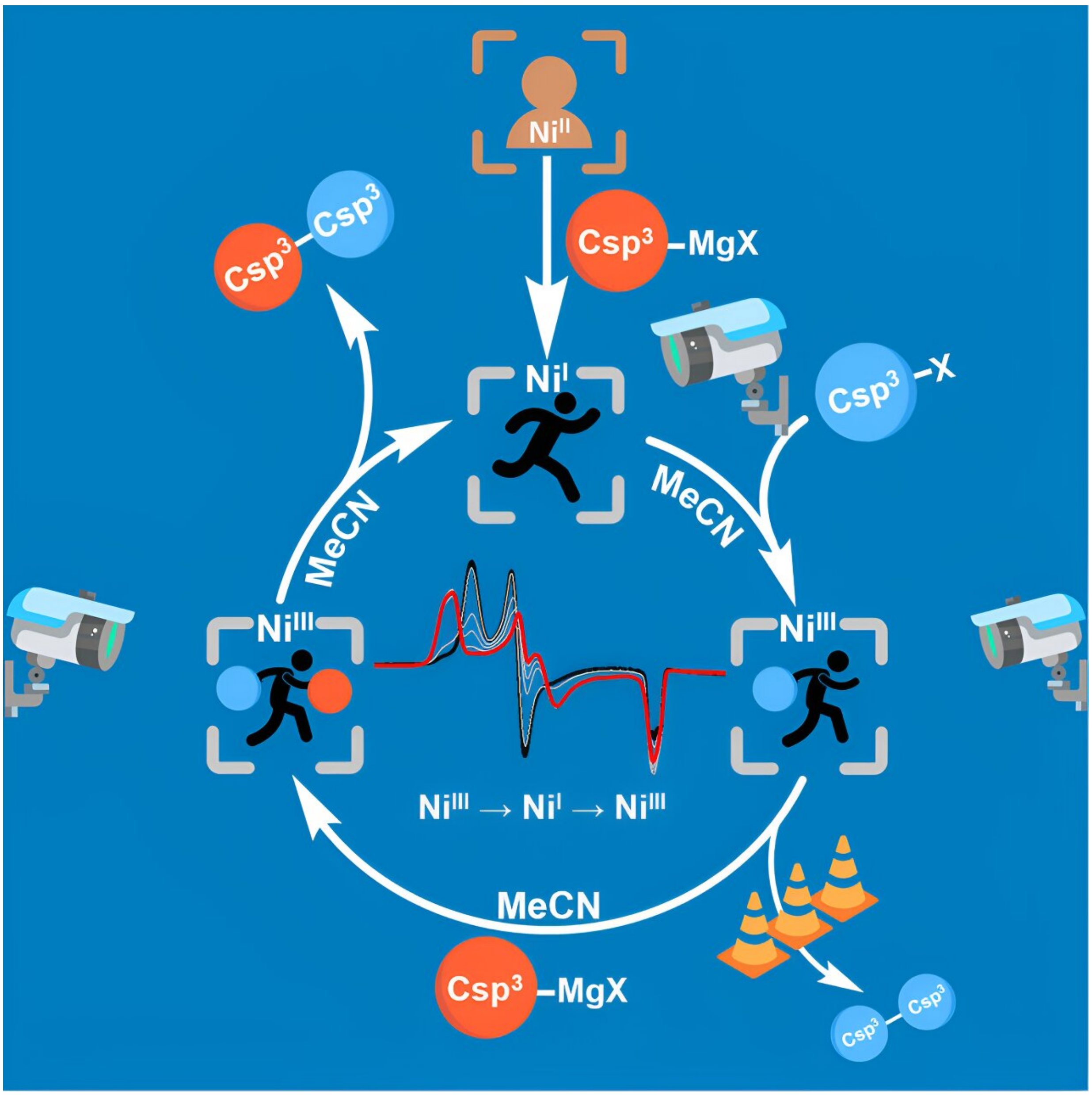


Credit: *Chem* (2023). DOI: 10.1016/j.chempr.2023.11.008

In the search for cheaper, greener alternatives to routinely used precious metal catalysts like palladium, nickel has become an increasingly popular choice in the last two decades for organic chemists assembling fragments of molecules for a variety of chemical applications, especially transformations called cross-coupling reactions.

It turns out, nickel catalysts are very good at putting together the carbon-carbon bonds that form the basic building blocks of complex molecules in organic chemistry—especially C-C bonds between alkyl groups.

"It is a hot area in the context of organic methodology," said Liviu M. Mirica, a professor of chemistry at the University of Illinois Urbana-Champaign, whose research group over the last decade has been studying nickel-catalyzed reactions.

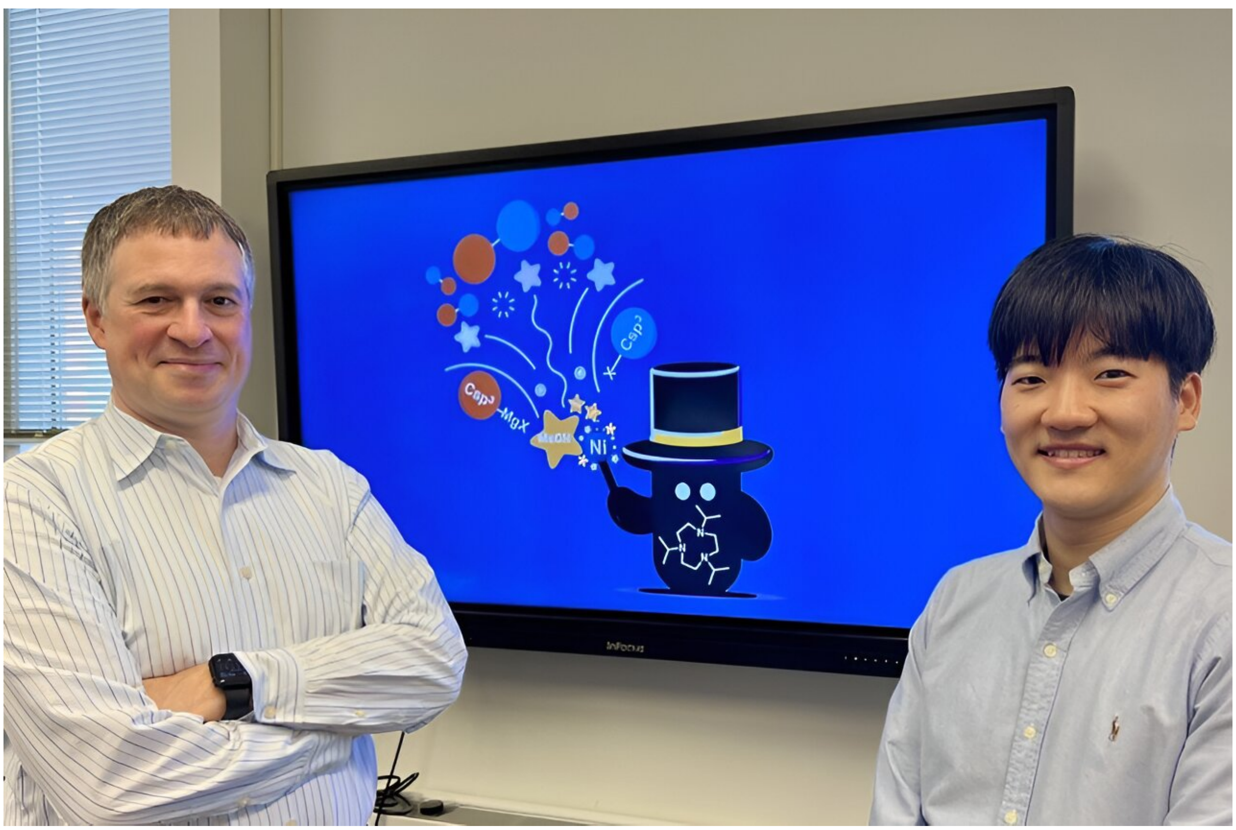
Despite the increasing popularity, scientists do not entirely understand the mechanisms of nickel-catalyzed reactions, especially cross-coupling reactions, and a more fundamental understanding of how they work could make them more useful and efficient.

Researchers in the Mirica lab have developed the ability to "see" each individual step of the nickel-catalyzed reaction and the roles of each participant in action, like a slow-motion replay.

As the researchers explain in a recently published paper in the journal *Chem*, their work has revealed unambiguous evidence of how nickel-catalyzed reactions work, but their research has also revealed an unexpected player in the action. The solvent, acetonitrile, increased the amount of product generated by the reactions in their study.

"We dissect at a very fine level every single step in this catalytic cycle, which allowed us to see this beneficial role of acetonitrile, which has not been observed before," said Mirica, whose research team—former graduate student Dr. Leonel Griego and current graduate student Ju Byeong Chae, co-first authors of this work—dissected the catalytic cycle through mechanistic studies involving EPR spectroscopy, electrochemical methods, and radical trap studies.

"That also allows us to find beneficial additives or uncover roles that were not observed before and that's exactly what happened with this solvent, acetonitrile, which is not a solvent that's commonly used by organic chemists in this type of cross-coupling reaction."



University of Illinois Urbana-Champaign chemistry Professor Liviu M. Mirica, left, and graduate student Ju Byeong Chae pose with a graphic illustrating the magical effect of their “Goldilocks system” in nickel-catalyzed cross-coupling reactions. Credit: UIUC Department of Chemistry

According to the research team, acetonitrile and the ligand system they created in their lab form a perfectly balanced combination and exhibit "a magical effect" that can be employed by organic chemists to benefit a wide range of nickel-mediated organometallic transformations.

Their mechanistic study shows that the acetonitrile not only stabilizes the nickel in various stages of the reaction, but it stabilizes it in just the right amount, while also actually promoting the key step of the catalytic reaction called reductive elimination.

"So, acetonitrile is the Goldilocks solvent in that system that stabilizes just the right amount but also promotes the right type of reaction," Mirica said.

At each step of a nickel-mediated catalytic reaction, there are reactive intermediates in which nickel adopts different oxidation states. The Mirica group has developed the ability to make special types of ligands, which are molecules that bind to a central metal atom and allow for the fine-tuning of the stability of the nickel intermediates, which is vital for studying useful catalytic reactions. Typically, in synthetic chemistry, more stable means less reactive, so there is a balance between the two that is important for a reaction.

Where Mirica and his research team have been focusing most recently—and this paper is a great example—is developing ligand systems that make the intermediates slightly more stable, which allows researchers to study the mechanics in detail, but they have also made the intermediates catalytically active, which makes them useful for chemistry.

"So, this is the real sweet spot," Mirica said, referring to their "bulky" ligand and acetonitrile creating a Goldilocks system that is "just right."

The ligand, he said, is just bulky enough to protect the nickel center from other side reactions, but not too bulky to prohibit the binding of the two molecular fragments you want to stitch together. And the acetonitrile solvent further assists to support the reactive intermediates that are neither too stable nor too reactive.

"It's a very fine balance of stabilizing intermediates but also promoting the reactivity but only promoting the desired reactivity," Mirica said. "So, it's not only the ligand, but the solvent mixture and the right reaction conditions that allow us to actually improve the yield."

Chae said they also discovered there is a chemical equilibrium at work. The product yield depends on the amount of acetonitrile. Chae explained that previous acetonitrile-nickel studies theorized that the solvent was a player in only part of the cycle.

"What we found here is that acetonitrile is involved in all catalytic intermediates. That's what is different from the previous studies. Once we figured out the mechanism and the role of acetonitrile, we have been able to improve the catalytic product formation in a logical way," he said. "So, I think that's the beauty of our study."

Mirica said Chae is now exploring a wider range of substrates and a wider range of ligands to improve their "Goldilocks" system and to see what other transformations could be possible.

"The long-term goal that organic methodology is focusing on is developing more straightforward ways, more streamlined methods, of building more complex molecules and putting together fragments to build that complexity. So, you can make more useful pharmaceuticals, or more complex molecules for materials science applications. [Nickel-mediated catalysis] is a very fundamental way of putting molecules together," Mirica said.

**More information:** Leonel Griego et al, A bulky 1,4,7-triazacyclononane and acetonitrile, a Goldilocks system for probing the role of $Ni^{III}$ and $Ni^{I}$ centers in cross-coupling catalysis, *Chem* (2023). DOI: 10.1016/j.chempr.2023.11.008

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