Exploring the Performance of Nanostructured Reagents with Organic-Group-Defined Morphology in Cross-Coupling Reaction

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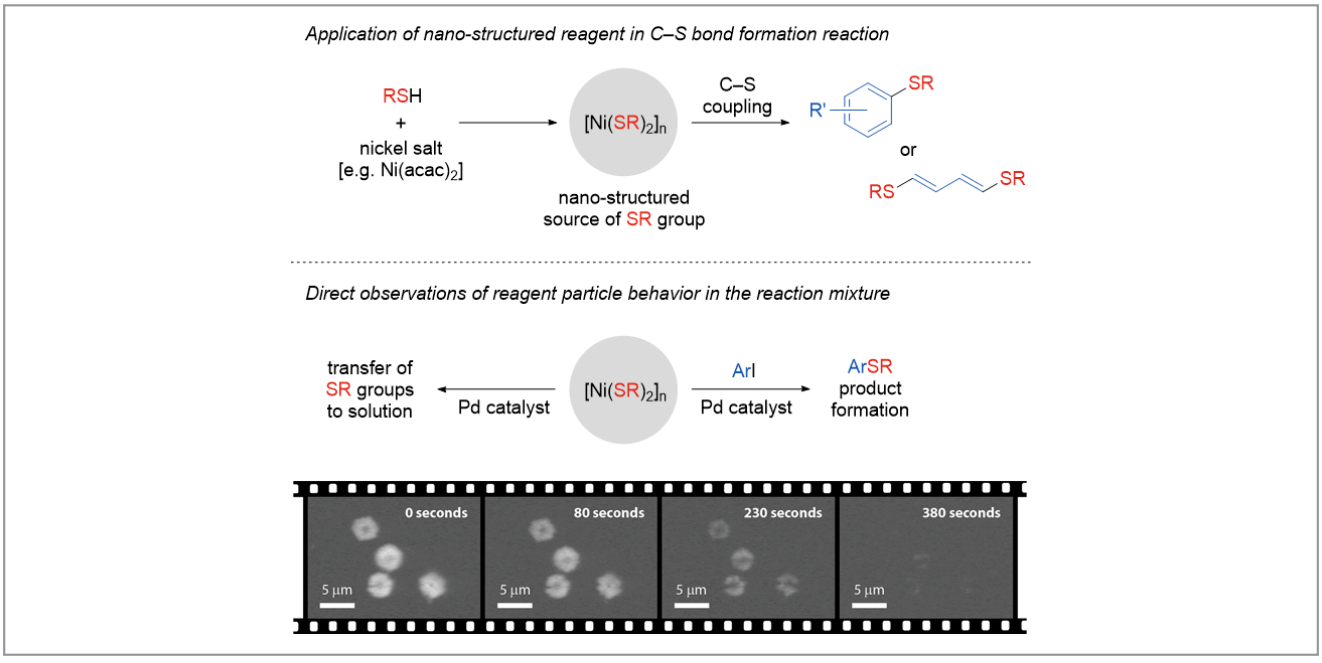
During recent decades tight bonds have arisen between various fields of chemistry, physics and other natural sciences and have pushed forward complex multidisciplinary approaches for solving many scientific problems. The group of Professor Valentine P. Ananikov at the Russian Academy of Science (Russian Federation) has striven to extend the tools, methods and, in general, the paradigm of nano-science to the classical synthetic organic chemistry. "The main idea was to use nano-structured reagents for the synthesis of typical small organic molecules in order to reveal the possibility of tuning the reactant properties at the micro- and nano-levels," explained Professor Ananikov.

The transition-metal-catalyzed C–S cross-coupling reaction was chosen as a proof of principle of their hypothesis. "From the practical point of view, this reaction is of particular importance because it allows the synthesis of organic sulfides to be carried out under mild conditions with a broad scope of substrates," said Professor Ananikov. Nickel thiolate coordination polymer $[Ni(SR)_2]_n$ was chosen as a candidate for unveiling the role of nano-structured reagents. "The wide range of thiolate morphologies can be generated in the simple reaction between nickel salt ($Ni(acac)_2$, for example) and various thiols (RSH)," added Professor Ananikov, who continued: "Nickel thiolates had already demonstrated excellent performance as nano-catalysts in the transfer of SR groups to unsaturated carbon–carbon bonds. Thus, we decided to use nickel thiolate as a source of SR groups for the cross-coupling with organohalides (Figure 1)."

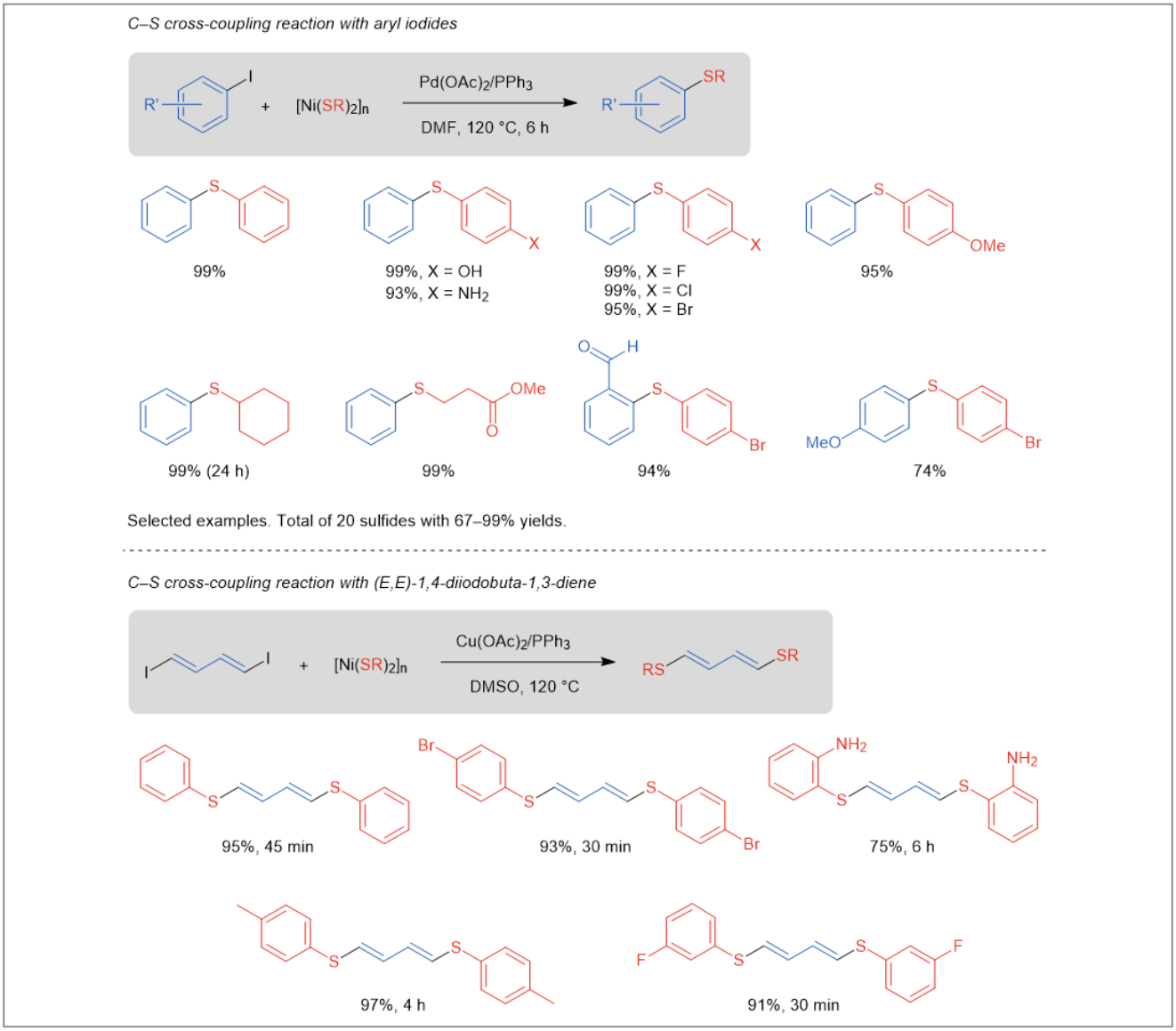
The nano-nature of the reagent gave the group one more outstanding opportunity – the direct observation of the reaction progress with electron microscopy. "In situ electron microscopy studies, including challenging observations in the liquid phase, are currently at the forefront of materials science and energy research; however, applications for organic reactions are still limited," explained Professor Ananikov. As further discussed by co-author of the paper, Dr. Kashin: "Elec-



Scheme 1 Top: New synthetic approach for C–S cross-coupling based on nano-structured reagent. Bottom: Electron microscopy observations of the reaction progress.

tron microscopy allowed us to observe evolution of the particles during the chemical reaction (Scheme 1). A combination of microscopy with molecular-level mass spectrometry observations and kinetic measurements allowed us to establish the mechanism of the reaction and reveal the impact of nano-level properties of the reactant on its performance. The leading role of the interface processes and the strong correlation between reaction rate and reagent particle morphology were demonstrated."

Synthesis of sulfides from nickel thiolates and various organohalides was performed under catalytic conditions with the use of metal acetate (palladium or copper) pre-catalyst in combination with PPh_3 ligand. "A palladium-based catalytic system allowed us to carry out the coupling of aryl iodides with nickel thiolates, resulting in the formation of aryl sulfides with yields up to 99% (Scheme 2)," remarked Dr. Kashin. He continued: "The reaction tolerated a wide range of functional groups. In addition, we showed the way to access sulfur-containing dienes. In this case, (*E*,*E*)-1,4-diiodobuta-1,3-diene was synthesized according to the procedure designed previously in our laboratory and was used as a substrate. Due to its high reactivity, it was possible to employ a cheaper copper



Scheme 2 Scope of the C–S cross-coupling reaction with the use of nano-structured reagents.

catalyst and obtain the corresponding dienes in high yields (Scheme 2)."

"Obviously, the current work is substantially a proof of concept," said Professor Ananikov. "We hope that our findings will give rise to studies at the border between nano-chemistry and classical organic synthesis and will encourage researchers to use electron microscopy in the studies of organic reaction mechanisms."

He concluded: "As demonstrated in the present study, video monitoring is especially powerful for observing nano-scale and micro-scale processes during catalytic synthesis. We anticipate that recording videos of chemical transformations will become a widespread tool for investigating organic reactions in the near future."

About the authors

The team that worked on the project. From left to right: Prof. Valentine P. Ananikov, Dr. Alexey S. Kashin, Dr. Evgeniya S. Degtyareva, Mr. Dmitry B. Eremin.

Alexey S. Kashin graduated from Higher Chemical College of the Russian Academy of Sciences (Russian Federation) with an MSc degree (chemistry) in 2011. Since 2009, he has been working at Zelinsky Institute of Organic Chemistry (Russian Federation), where he received his PhD degree (organic chemistry) in 2014 and took up a senior researcher position in 2017. His research interests are focused on transition-metal catalysis, in situ mechanistic studies, electron microscopy and X-ray spectroscopy.

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Dmitry B. Eremin received his summa cum laude in chemistry from Lomonosov Moscow State University (Russian Federation) in 2014 and moved to Zelinsky Institute of Organic Chemistry (Russian Federation) for his graduate studies under the supervision of Prof. Dr. Valentine P. Ananikov. Currently, he is a fourth-year graduate student, working on mechanistic insights into catalytic reactions. His research interests are focused on mass spectrometry, organometallic chemistry and in situ spectroscopic studies.

Valentine Ananikov received his Ph.D. in 1999, his Habilitation in 2003, and in 2005 he became Professor and Laboratory Head of the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences (Russian Federation). In 2008 he was elected a Member of the Russian Academy of Sciences. His research has been supported by grants of the President of Russia for young scientists (2004, 2007). He is recipient of the Russian State Prize for Outstanding Achievements in Science and Technology (2004), an Award of the Science Support Foundation (2005), a Medal of the Russian Academy of Sciences (2000), the Liebig Lectureship from the German Chemical Society (2010), and the Balandin Prize for Outstanding Achievements in Catalysis (2010). In addition, he has been named Actively Cited Researcher – Russia by Thomson Reuters (2015), recipient of the Organometallics Distinguished Author Award Lectureship by the American Chemical Society (2016), and of the Hitachi High-Technologies Award in Appreciation for Novel Approaches and Outstanding Contributions to Setting New Standards for Electron Microscopy Applications in Chemistry (2016). His scientific interests are focused on catalysis, organic synthesis, molecular complexity and transformations.

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