Cobalt-Catalyzed Asymmetric Hydrogenation of Enamides Enabled by Single-Electron Reduction

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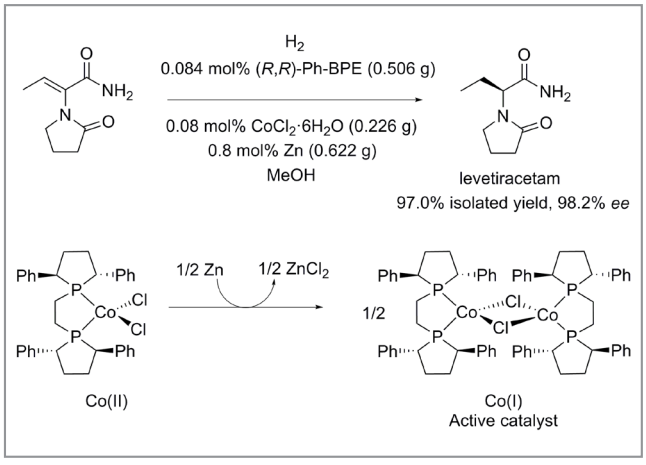
Many drug molecules, much like a pair of hands, have defined stereochemistry, meaning a specific orientation of the substituents in space. Chemists are challenged to discover methods to synthesize only one enantiomer of drug molecules rather than synthesize both and then separate. Metal catalysts, historically based on precious metals like rhodium, have been tasked with solving this challenge. Recently, a paper published in *Science* by the group of Professor Paul J. Chirik at Princeton University (USA) in collaboration with scientists from the MSD Research Laboratories (USA) demonstrated that a more Earth-abundant metal – cobalt – can be used to synthesize the epilepsy medication Keppra (levetiracetam) as just one enantiomeric form. Professor Chirik said: "The main findings of the paper are that cobalt is more active and selective than the patented rhodium route and operates in a greener solvent, methanol, than the current method. Our paper demonstrates a rare case where an Earth-abundant transition metal can surpass the performance of a precious metal in the synthesis of single-enantiomer drugs."

One of the members of Professor Chirik's team, Dr. Max Friedfeld, said: "In re-evaluating a catalyst system we developed in 2013, where it was demonstrated that cobalt could be used in hydrogenation to make single enantiomers of organic molecules, we identified certain criteria that limited the usefulness of the system. These detractions included relatively high catalyst loading (indicating a relatively inefficient catalyst), non-trivial catalyst synthesis steps (making wide-spread adoption less likely and lowering catalyst tunability), and the use of ultra-pure (anhydrous) non-coordinating solvents."

The authors wanted to develop a system that was more robust and easy to use. "We wanted to accomplish a large-scale hydrogenation with cobalt to show how efficient the catalyst was," explained Dr. Friedfeld. Professor Chirik remarked: "Our 2013 experiments were important demonstrations of principle but involved relatively simple and not medicinally active compounds. The solvents used in those studies were also hydrocarbons that required specialized handling. We were inspired to push our demonstration of principle into real-world examples and demonstrate that cobalt could outperform precious metals and work under more environmentally compatible conditions. Our new paper demonstrates just that and also reports that the method can be practiced on a pilot scale."

"In the new work reported in *Science* (Scheme 1), the team used high-throughput experimentation and analysis techniques coupled with traditional organometallic synthesis to develop a catalyst system that can be used in the synthesis of levetiracetam on 200 g scale using very low catalyst loading (0.08% catalyst relative to substrate)," said Dr. Friedfeld. He continued: "This catalyst system contains three commercially available components and can be prepared simply and in situ without any purification. The catalyst components are the cobalt chloride salt, the organic supporting framework for the cobalt ion, and zinc, which serves to reduce the cobalt. The reaction takes place in methanol, a commonly used industrial solvent that can be processed and safely disposed of easily. By studying the coordination chemistry of the cobalt catalyst, we were able to determine the role of zinc and the favorable oxidation state for catalysis."

The work used the synthesis of a generic drug as a case study to learn about how to make very efficient base metal catalysts. "In the process of optimizing this chemistry, we made important discoveries in terms of reaction conditions and catalyst activation," remarked Mr. Michael Shevlin, one of the researchers from the MSD Research Laboratories. He continued: "We were able to show that in this case we could teach an earth-abundant metal how to do chemistry that was



Scheme 1 Cobalt-catalyzed asymmetric hydrogenation of an enamide

previously conducted with precious metals, and that we could actually get more reactivity from cobalt than was previously possible with rhodium. In the process, we showed that these new reaction conditions produced orders of magnitude more cobalt catalysts that could perform asymmetric hydrogenation, and that these conditions were generally useful across many catalysts with several different substrates."

The collaboration between MSD and Princeton was crucial, with the authors commenting that they would not have made the same types of advances without it. The Catalysis Lab in Process Research & Development uses high-throughput experimentation tools adapted from biology and biochemistry for chemical research. "Instead of trying just a few experiments to test a hypothesis, we can quickly set up large arrays of experiments that cover orders of magnitude more chemical space," explained Mr. Shevlin. He continued: "We've used these tools for years in our lab for pharmaceutical R&D, and they're just as powerful for doing fundamental chemistry research." Being different types of chemists that approach problems with fundamentally different perspectives also helped. "The biggest strength of the Catalysis Lab is that we have the tools to quickly discover and optimize new chemical reactions and the experience to be able to implement them as robust processes on manufacturing scale," explained Mr. Shevlin. He continued: "The Chirik group is really good at being able to understand the fundamental behavior of catalysts, particularly base metal catalysts that are very difficult to study. The synergy is tremendous; scientists like Max Friedfeld and Aaron Zhong can conduct hundreds of experiments in our lab, and then take the most interesting results back to Princeton to study in detail. What they learn there then informs the next round of experimentation here."

As with much research, there were a few unexpected findings along the way. "We were surprised to learn that one of the catalyst components, zinc, was so effective at generating active catalysts," said Dr. Friedfeld. He explained further: "One challenge we had with the original system was that when we used high-throughput experimentation techniques with a harsh catalyst activator, we only generated a couple of active catalyst species. While these species were highly active and selective, it felt like we were searching for a needle in a haystack – out of hundreds and hundreds of combinations searched, only a few were good catalysts. With zinc, however, catalyst activation goes through a different mechanism and is much more effective at generating active catalysts. This is depicted in Figure 2 of the *Science* paper. Then, it was like searching for a needle in a sewing shop!"

It was also a surprise that these reactions performed best in protic solvents such as methanol. Mr. Shevlin noted: "Many base metal catalysts in low oxidation states react with protic solvents and decompose. But our reduced cobalt catalysts not only tolerate methanol, they're an order of magnitude more reactive in it than they were in aprotic solvents like THF or toluene."

Professor Chirik recalled the first unexpected event during the work: "We were surprised to see that the phosphine ligand – the key source of stereochemical information – fell off the starting cobalt complex! In catalysis, this usually translates on to poor performance and most likely catalyst death. Cobalt is special; we learned that the phosphine falling off was reversible – meaning that under the activation of conditions provided by the zinc, the catalyst can heal itself. This is a special consequence of the light transition metal where changes in electronic states by one enable molecules to come and go from the cobalt, keeping it active ("alive") in the catalytic reaction."

The group was also surprised to learn that cobalt worked most optimally in green solvents like alcohols. For a decade, catalysts based on earth-abundant metals like iron and cobalt required very dry and pure conditions, meaning the catalysts themselves were very fragile. By operating in methanol, not only is the environmental profile of the reaction improved but the catalysts are much easier to use and handle. This means that cobalt should be able to compete or even outperform precious metals in many applications that extend beyond hydrogenation.

Turning to the significance of the work, Mr. Shevlin said: "Base metals are orders of magnitude less expensive than precious metals, but the chiral ligands we use on the metal are even more expensive than precious metals, and that cost is unlikely to change because chiral ligands are complex molecules that take many synthetic steps to make. The real motivation for base metal catalysis in my opinion is that there's also risk involved with using precious metals in industrial processes because their availability is limited by scarcity and their prices are tied to a volatile market. In contrast, cobalt is so abundant that it's essentially free when used in catalytic quantities. In this work, we've shown that cobalt has the potential for similar, maybe even better performance than rhodium." Further, Dr. Friedfeld remarked that the work is significant because they were able to harness one-electron oxidation state changes at the metal catalyst (normally considered deleterious to reactivity) to activate the catalyst components, achieving high reactivity and enantioselectivity in a way that is operationally simple to achieve. He commented: "We hope this will inspire other chemists to use this catalyst system for alkene hydrogenation reactions they're working on, and to consider applying toward other catalytic reactions." Professor

Chirik agreed and highlighted an important principle in green chemistry, namely that the more environmentally friendly solution can also be the preferred one chemically. He said: "Here the catalyst is based on an earth-abundant metal but is also faster and operates in a greener solvent than rhodium. It tells the community – precious metals beware – after 50 years, cobalt and other first row metals can not only compete, but because of the way electrons flow in a unique manner, they offer new opportunities!"

Mr. Shevlin pointed out: "Many topics in chemistry are considered "solved problems", but chemistry that works on simple molecules on small scale in an academic lab isn't necessarily practical to implement on an industrial scale for making complicated molecules. So much of modern catalysis was developed with precious metals because they have useful reactivity and it's relatively easy to study their behavior. But using some of the rarest and most expensive elements on earth isn't a great way to make complicated molecules in a cost-effective manner. Earth-abundant metals are much less studied, so there's a wealth of new chemistry waiting to be discovered. The best way to do that is with modern techniques like high-throughput experimentation and collaborations between labs with complementary expertise."

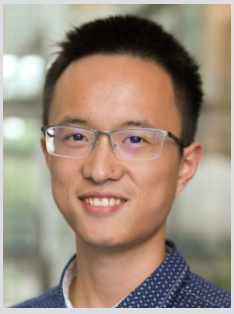
Professor Chirik would like readers to take away the message that chemists are continually working to improve the synthesis of important drug molecules. "We are concerned about the environment, reducing waste and learning how to discover more effective medicines in a faster more sustainable way," he remarked, continuing: "We are also still uncovering the secrets of the periodic table and learning how to take advantage of them for the benefit of society."

Professor Chirik concluded: "This is a great example of an academic–industrial collaboration and highlights how combination of the very fundamental – how do electrons flow differently in cobalt versus rhodium? – can inform the applied – how to make an important medicine in a more sustainable way. I think it is safe to say that we would not have discovered this breakthrough had the two groups at MSD and Princeton acted on their own."

About the authors

Dr. M. Friedfeld

Max Friedfeld obtained his B.Sc in chemistry from the University of Virginia (USA) in 2011, doing undergraduate research with Professor Brent Gunnoe and his Ph.D. in chemistry from Princeton University (USA) in 2016, under the mentorship of Paul Chirik. There he studied asymmetric catalysis with cobalt complexes. He is currently a Washington Research Foundation postdoctoral fellow at the University of Washington (USA), studying nanomaterial nucleation and growth mechanisms under the mentorship of Professor Brandi Cossairt.



H. Zhong

Hongyu "Aaron" Zhong obtained his B.S. degree in chemistry in 2016 from the University of North Carolina (USA) at Chapel Hill with highest honor. During his undergraduate studies, he worked in Professor Michael Gagne's group on Lewis acid catalyzed diastereoselective carbohydrate de(functionalization). Fascinated by the beauty of organometallic chemistry, he joined Professor Paul Chirik's lab at Princeton (USA) for his graduate studies. He is now working on developing cobalt-catalyzed enantioselective alkene hydrogenation in collaboration with scientists at Merck & Co., Inc. (MSD) in Kenilworth, NJ (USA).

Dr. R. T. Ruck

Rebecca T. Ruck earned her A.B. summa cum laude from Princeton University (USA) in 1998 before moving on to Harvard as an NSF fellow in the lab of Prof. Eric Jacobsen and continued her career as an NIH post-doctoral fellow at UC-Berkeley (USA) in the lab of Prof. Robert Bergman. She started in Process Research & Development at Merck & Co., Inc. (MSD) in Kenilworth, NJ (USA) in 2005, steadily assuming roles of increasing amounts of responsibility in the intervening years. She has managed a Discovery Process Chemistry team at the interface of medicinal and process chemistry,

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served as Director of Catalysis and Automation, which also involved managing efforts around reaction mechanism and flow chemistry, and is currently Executive Director of Process Chemistry. She has made contributions to programs related to hepatitis C, diabetes and antibacterials, among others. For her role in the chemistry of the beta-lactamase inhibitor, MK-7655, she was recognized as an ACS Division of Organic Chemistry Young Investigator in 2014 and, for her commitment to both scientific excellence and advancing women in chemistry, was recognized as one of the ACS Women Chemists Committee (WCC) 2016 Rising Stars. During her time at MSD, Rebecca has played a significant role in MSD's commitment to safety and is highly active in a variety of external reputation activities, including serving as the departmental recruiting lead, running a series of MSD-sponsored academic lectureships and coordinating an MSD-sponsored research award and accompanying symposium for undergraduate women in collaboration with the WCC. Rebecca was recently named the 2018 winner of the ACS Award for Encouraging Women into Careers in the Chemical Sciences.

M. Shevlin

Michael Shevlin is an Associate Principal Scientist in the Catalysis Laboratory in the Department of Process Research & Development at Merck & Co., Inc. (MSD) in Kenilworth, NJ (USA). Since joining the company in 2006, Michael has become the departmental expert in asymmetric hydrogenation through work on over 40 projects. Michael is a passionate advocate of high-throughput experimentation for reaction discovery, development, and mechanistic elucidation. He is the liaison for a collaboration with Professor Paul Chirik at Princeton University (USA) to develop base metal asymmetric hydrogenation catalysts. Michael received his M.S. degree from the University of Illinois-Chicago (USA) in 2004 and spent two years teaching at Ivy Tech State College in Lafayette, Indiana (USA).

Prof. P. Chirik

Paul Chirik was born in 1973 outside of Philadelphia, PA (USA). In 1995 he earned his Bachelor of Science in chemistry from Virginia Tech (USA). During that time, he conducted undergraduate research with Professor Joseph S. Merola studying aqueous iridium chemistry. Chirik earned his Ph.D. with Professor John Bercaw at Caltech (USA) in 2000 and was awarded the Hebert Newby McCoy award for his dissertation on metallocene-catalyzed olefin polymerization. After a brief postdoctoral appointment with Professor Christopher Cummins at MIT (USA), Chirik began his independent career at Cornell University (USA) in 2001. In 2006, he was promoted to Associate Professor and in 2009 was named the Peter J. W. Debye Professor of Chemistry. In 2011, Chirik and his research group moved to Princeton University (USA) where he was named the Edwards S. Sanford Professor of Chemistry. His teaching and research have been recognized with an Arthur C. Cope Scholar Award, the Blavatnik Award for Young Scientists, a Packard Fellowship in science and engineering, a Camille Dreyfus Teacher Scholar Award and an NSF CAREER Award. He is currently the Editor-in-Chief of *Organometallics* and the recipient of the 2016 Presidential Green Chemistry Challenge Award and 2017 ACS Catalysis Lectureship in Catalysis Science. He is the corresponding author on over 175 peer-reviewed manuscripts in publications including *Science, Nature, Journal of the American Chemical Society, Angewandte Chemie International Edition* and *ACS Catalysis*.