AMPING UP THE PHARMA LAB

Companies explore the potential of electrochemistry

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Synthetic organic chemists are accustomed to pushing electrons around. They use reducing reagents to force electrons into molecules and oxidizing reagents to strip them out. But using electrons on their own as a tool to synthesize molecules—electrochemistry, in other words—has been a niche of just a few.

That's starting to change.

Over the past few years, interest in electrochemistry for organic synthesis has surged, thanks to a small but growing cadre of synthetic organic chemists. Unable to resist a pun, they all say the same thing: the technique has a lot of potential.

Pharmaceutical companies hope to tap into that potential, giving medicinal and process chemists tools for making both drug candidates and approved drugs.

For medicinal chemists, who design compounds for preclinical testing, the technique offers the ability to change one part of a complex molecule without affecting the rest of its structure. It can also let them construct molecules that are difficult or impossible to make any other way. For process chemists, who scale up syntheses of promising molecules for preclinical and clinical studies, the method can cut down on waste and offer improvements in cost, safety, and sustainability.

Yet not all drug industry chemists are charged up about electrochemistry. Some medicinal chemists are skeptical that it offers any new reactivity, while process chemists lament the lack of off-the-shelf equipment that would allow them to practice it at kilogram scale.

Synthetic organic electrochemistry typically happens at an electrode: a single electron gets pushed into a molecule or taken away, weakening certain bonds so that the compound becomes reactive. The technique is neither new nor an academic curiosity. Its discovery predates the light bulb by decades. Today, fine chemical companies use it to churn out compounds like the fragrance lysmeral at the metric-ton scale. Even so, chemists in pharma have only in the past 5 years started to bring it into their labs.

Learning to use electrochemistry for organic synthesis can be a burden, says Shannon Stahl, a chemistry professor at the University of Wisconsin–Madison who has worked in the field for more than a decade. "You have to learn everything the traditional synthetic chemist has to learn, and you have to learn all the mechanics, instrumentation, and analysis that goes into electrochemistry," he says. "It creates a barrier to this field."

Shelley Minteer, an electrochemistry expert at the University of Utah and director of the National Science Foundation–funded Center for Synthetic Organic Electrochemistry, also acknowledges the hurdles. "I think we've made electro-

In brief

Once considered a niche field, electrochemistry—using electricity to do chemical reactions like oxidation and reduction—has powered up over the past few years. Several high-profile reports touting electrochemistry and its potential as a tool for medicinal and pharmaceutical process chemistry are driving the shift. Researchers hope the technology will allow them to synthesize compounds that were difficult or impossible to make before and to do it in a more environmentally friendly way. Read on to learn how chemists in the drug industry are starting to experiment with electrochemistry to create new drug candidates and improve the synthesis of existing ones.

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chemistry challenging for organic chemists to understand," she says. But if chemists working at drug companies see that they can use electrons rather than harsh oxidizing and reducing agents, which generate lots of waste, "then we can make something that is safer, greener, and more energy efficient," Minteer says.

Phil Baran, a chemistry professor at Scripps Research in California, says the problem with getting synthetic organic chemists to plug into electrochemistry is the perception that you need to be an electronics whiz to create an electrochemical setup. "Even if you could conceptualize that it's just an oxidation and a reduction happening in the same pot—that it's not a big deal—how do you set it up?" Baran asks. "How do you convince a student to get a PhD in arts and crafts to build all the things you need?"

Kevin Rodriguez, a postdoc in Phil Baran's lab at Scripps Research, prepares to work with an ElectraSyn 2.0.

New equipment provides a jolt

Baran's lab started to explore electrochemistry in 2014 out of desperation. In the final step of his lab's synthesis of the antibacterial natural product dixiamycin B, his students needed to dimerize two halves of the molecule. After trying every imaginable chemical reaction, electrochemistry was the only thing that worked (*J. Am. Chem. Soc.* 2014, DOI: 10.1021/ja5013323). "If that reaction had worked with chemical means, we still, today, would not be doing electrochemistry," Baran says.

Around the same time, René Stiegelmann, president of the equipment maker Ika, visited Baran's lab hoping to collaborate. Baran recalls that he wasn't sure how his lab, which focuses on total synthesis of natural products, would collaborate with a company known for making rotary evaporators and stir plates. Nevertheless, he took Stiegelmann to see what his students had built to do electrochemistry.

The setup sprawled over half a fume hood and included a computer, a potentiostat, a soldering iron, a stir plate, special glassware, alligator clips, and wires "hanging out everywhere," Baran recalls. Stiegelmann was surprised at the crude setup. So Baran asked: Could Ika take the Rube Goldberg apparatus and make it as efficient and sleek as an iPhone?

Ika opened a lab across from Scripps and sent engineers to work with Baran's students. In 2017, Ika and Baran unveiled the ElectraSyn 2.0, an electrochemistry module that combines a potentiostat, an analytical device, and a stir plate and costs about $2,000.

Baran notes that he gets no commission from sales of the instrument. He doesn't want people to think he's being disingenuous when he raves about what the ElectraSyn 2.0 can do for synthetic organic chemists. "I'm just happy to do this because I think it will open an area of chemistry that could be useful to medicinal and process chemists."

And industrial researchers do credit Baran for opening their eyes to electrochemistry. "What Phil and Ika have done is to democratize the technology for researchers," says Martin Eastgate, head of chemical research at Bristol-Myers Squibb. "They've enabled people with no prior expertise in electrochemistry to start exploring the space, which I think is a very powerful thing to have done."

Charles Yeung, a medicinal chemist at Merck & Co., agrees. "It has become so user friendly, and I think that's an important piece of the puzzle," he says. "It's as easy as putting something on a regular hot plate."

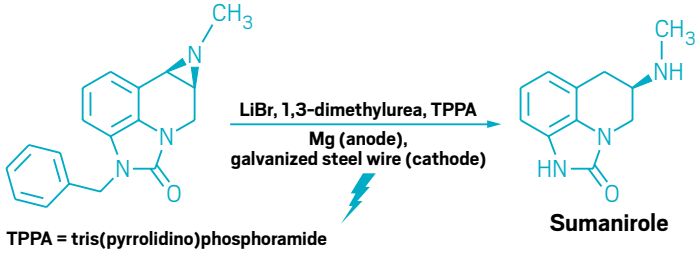
Shocking reactivity

Yeung says electrochemistry is another tool he and his medicinal chemistry colleagues can use to build the molecules they put forward in the clinic. The technique provides access to new building blocks and the ability to connect atoms in novel ways. "It allows us to think about constructing molecules through an unconventional approach," he says.

Baran's group has published several high-profile papers demonstrating the ElectraSyn 2.0's power to do novel chemistry. In February, Baran and colleagues reported they could use electrochemistry to do Birch reductions—reactions that involve using sodium or lithium metal in liquid ammonia.

Chemists from Pfizer approached Baran for help with the synthesis of the anti-Parkinson's drug candidate sumanirole. When the company used the classical Birch reduction to make the compound, it required cryogenic temperatures, custom equipment to deliver the lithium metal, and enough gaseous ammonia to fill three Boeing 747 airliners. When the chemists quenched the leftover lithium, it generated 2,300 L of hydrogen gas. They vowed never to do the reaction again.

Baran and colleagues developed an electrochemical approach to doing Birch reductions, eliminating the need for alkali metals, ammonia, and cryogenic temperatures. Baran says the reaction is safe enough to set up in a day-care center (*Science* 2019, DOI: 10.1126/science.aav5606).



TPPA = tris(pyrrolidino)phosphoramide

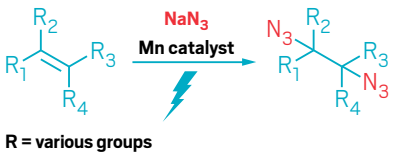
Sumanirole

An electrochemical Birch reduction forms the anti-Parkinson's drug candidate sumanirole.

CREDIT: JULIEN VANTOUROUT

In September, Baran's lab reported an improvement of the Hofer-Moest reaction, a troublesome synthesis of hindered ethers from carboxylic acids that dates back to 1902. His group's electrochemical version of the reaction provides easy access to molecules that were difficult to make previously (*Nature* 2019, DOI: 10.1038/s41586-019-1539-y).

"Electrochemistry has an infinite range of potential. It's essentially an imaginary reagent," says Cornell University chemistry professor Song Lin, whose group focuses on using electrochemistry for organic synthesis. He says the method gives chemists the ability to precisely dial in a potential, so they can differentiate functional groups that have very similar redox potentials. For example, if a complex molecule has two alcohol groups, it's possible to selectively oxidize just one of them because they have slightly different oxidation potentials.

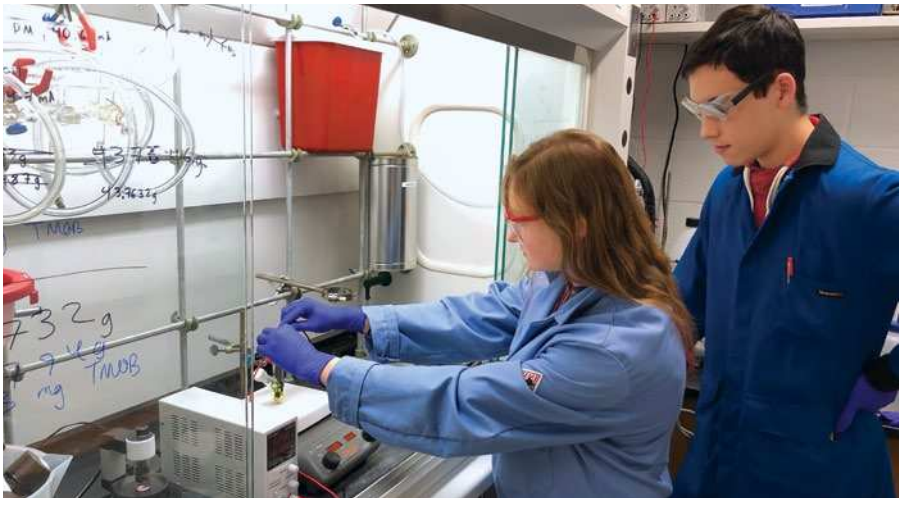


An electrochemical method transforms alkenes into vicinal diazides.

"I think what's really exciting to show people is that there are reactions that you really can't do with other methods," Lin says. In 2017, his group showed it was possible to use electrochemistry and a manganese catalyst to transform alkenes and sodium azide into vicinal diazides. Those compounds could then be reduced to make vicinal diamines—a motif that's common in pharmaceuticals and stereoselective catalysts (*Science* 2017, DOI: 10.1126/science.aan6206). Other methods for making vicinal diamines typically require harsh chemical oxidants, which can produce toxic by-products.

The same year, Lin's group reported using electrochemistry and a manganese catalyst to make vicinal dichlorides from alkenes and magnesium chloride (*J. Am. Chem. Soc.* 2017, DOI: 10.1021/jacs.7b09388). Other methods for making this type of compound usually call for oxidants that will destroy certain functional groups, limiting when the chemistry can be applied.

Last month, Lin's group reported an electrochemical method for making chiral nitriles via enantioselective alkene hydrocyanation. Electrochemistry allowed the group to seamlessly combine two classic radical reactions: cobalt-mediated hydrogen-atom transfer and copper-promoted radical cyanation. A chiral ligand guides the stereochemistry of the products (ChemRxiv 2019, DOI: 10.26434/chemrxiv.9784625.v1).



CREDIT: SONG LIN

Liat Kugelmass (left) and Jonas Rein, students in Song Lin's lab at Cornell University, prepare an electrochemical reaction.

Medicinal chemists plug in

These new reactions draw medicinal chemists to electrochemistry, says Max Ratnikov, who is part of a group at Novartis dedicated to learning about new technologies for chemistry. "In medicinal chemistry what we look for are selectivity and to do processes that we cannot do any other way," he says.

Ratnikov says he's seen medicinal chemists use electrochemistry to accomplish transformations on complex, functionalized molecules with high selectivity. That allows them to tweak pharmaceutical

candidates on the fly in case they need to adjust a structure to block metabolism or boost solubility. Ratnikov also says electrochemistry has helped medicinal chemists at Novartis couple molecules that were impossible to piece together any other way.

Ratnikov credits the ElectraSyn 2.0 for making electrochemistry more accessible. It cuts down on the number of parameters a chemist needs to optimize when doing a reaction—a critical factor, he says. "Time is short, and you want everything to work on the first try."

Chemists in pharma are eager to try new technologies in their quest to make increasingly complex structures, Ratnikov says. "Right now there is a quiet but steady revolution that is happening in medicinal chemistry and process chemistry where many different technologies are being deployed," he says. "It all started with flow chemistry, followed by photochemistry, and now it's electrochemistry."

Many chemists agree that pharma's adoption of photoredox chemistry—in which energy from light spurs chemical reactions via single-electron transfer—paved the way for synthetic organic electrochemistry. "When you start transferring one electron, it leads to radical chemistry," the University of Wisconsin's Stahl says. "And photoredox made radical chemistry cool again."

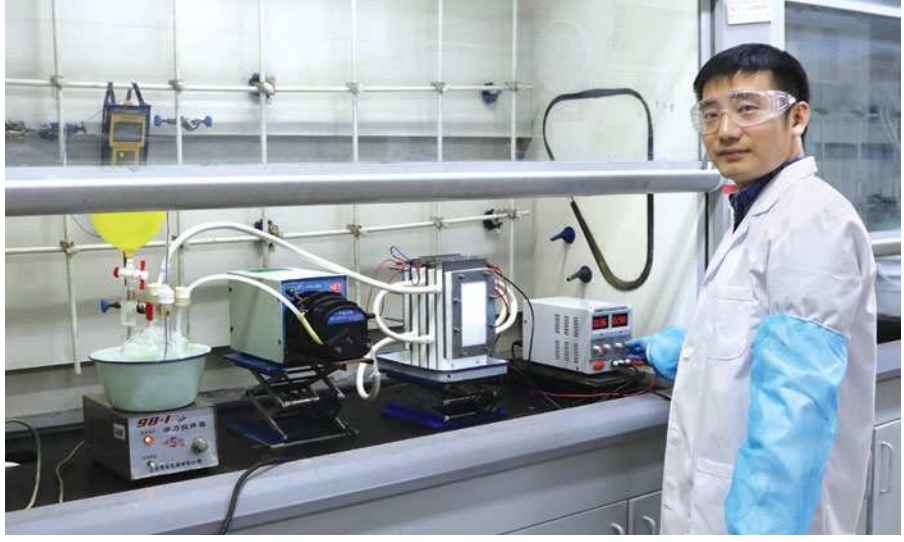
But despite all the hype, the field still has challenges, Stahl acknowledges. For medicinal chemists, he says, the inevitable questions are: What is electrochemistry doing that's new? Is electrochemistry doing things better or just differently? "I think the burden on us in the field is really to show how electrochemistry enables new reactivity in chemical synthesis," he says.

Amping up process chemistry

Process chemists are also looking to explore new reactivity, but for different reasons. These chemists want to take known processes and use electrochemistry to make them greener, safer, and cheaper, says Matthew Graaf, a process chemist at AbbVie.

Neil Strotman, a process chemist at Merck & Co., explains that medicinal and process chemists have different goals. Medicinal chemists, he says, are looking for synthetic approaches in which they can take a common intermediate and use the same type of transformation to go in different directions. "In process chemistry, we know the one molecule that we want to make," he says, "so all our efforts are on making that in as few steps as possible."

Novartis's Ratnikov thinks process chemists will drive the adoption of electrochemistry by pharmaceutical companies. "They're always under pressure to streamline processes and make them safer and generate less waste," he says. "More importantly, they have more time to optimize a given reaction."



Zhen Yao, a chemist at Asymchem, is using flow chemistry to scale up electrochemical reactions.

But Ratnikov notes that process chemists who want to do electrochemistry face an equipment gap. The ElectraSyn 2.0 works well for small-scale syntheses, and chemists have dedicated equipment for doing electrochemistry on a large scale. Working in the space in between can be a challenge.

Eric Hansen, a process chemist at Pfizer, agrees. "Going from lab demonstration to intermediate scale and having the confidence that you can go to as large a scale as you might need without reengineering the system each time is really important," he says. "We don't necessarily have that technology."

"In process chemistry, electrochemistry is in the early stages," says Seble Wagaw, head of organic chemistry process R&D at AbbVie. While there's plenty of interest, it's not obvious how to use it for projects in the pipeline. "I think that's where industry is at now," she says, "understanding exactly where it's applicable and also understanding how to scale up chemistry that we identify."

> "Electrochemistry is moving beyond just being a curiosity to something people involved in designing large-scale processes should consider."
>
> **—James Gage,** chief science officer, Asymchem

"The biggest challenge right now—once we identify a transformation that we want to use—is being able to scale it up on multikilo scale within a reasonable time frame," Graaf says. "Large-scale and even commercial organic electrochemistry is nothing new, but those typically use very large facilities that we don't have the capability to commit to for a single transformation." Instead, he says, process chemists are working to find a reactor design that can handle high-throughput multikilo synthesis with a minimal reactor footprint.

The contract manufacturer Asymchem has been using flow chemistry to bridge the equipment gap, says James Gage, its chief science officer. Flow makes it possible to transform a lot of material in a continuous way with a small electrochemical cell. For example, Gage explains, it's possible to have a reservoir loaded with substrate and pump it through an electrochemical cell once or even multiple times. Chemists at Asymchem used this strategy to convert hundreds of kilograms of a sulfide into a sulfone.

Novartis's Ratnikov cautions that not all electrochemical reactions are suitable for flow. Some are just too slow.

Still, Gage says Asymchem's customers have started to ask about using synthetic organic electrochemistry. "Electrochemistry is moving beyond just being a curiosity to something people involved in designing large-scale processes should consider," he says. "Up until now, at least in the pharma industry, I think it's been overlooked. I would like to see people in pharma consider what else they can do by adding electrochemistry to their toolbox." ■

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