Even trailblazing scientists can have a hard time resisting the allure of the familiar. “There is a trend, particularly in pharmaceuticals, for chemists to rely on a relatively low number of transformations that are very efficient and work very well,” says Paolo Braiuca, marketing manager at Thermo Fisher Scientific.

Medicinal chemists are creatures of habit who lean heavily on a small number of transformation types when planning synthetic routes. This toolbox includes amide bond formations and carbon-carbon bond formations (more often than not using a Suzuki-Miyaura coupling). Numerous reviews of reaction preferences published over the past few decades, both in the pharmaceutical and patent literature, have confirmed this behavior.1 In these analyses, researchers typically find that a handful of reaction types account for more than half of all the reactions in the published synthetic routes.
There are good reasons for sticking to well-trodden paths, including readily available reagents and a reduced likelihood of coming up against technical challenges during scale-up for manufacture. But it means that the structures of many small-molecule drugs have wound up looking pretty similar. “If you look at the chemical landscape that is being produced at the moment, it’s relatively narrow,” Braiuca says. For example, he adds, a lot of drugs contain biaryl scaffolds because cross-coupling reactions work well with these.

The estimated number of stable molecules with drug-like properties is vast—somewhere in the region of $10^{60}$. By contrast, PubChem (a comprehensive database of synthesized small molecules maintained by the US National Institutes of Health) contains just over 110 million ($1.1 \times 10^8$) structures. Due to this favoring of just a few reaction types, these synthesized molecules are not at all evenly distributed across chemical space but bunched together in just a few regions.

This prompts some questions: Are the drug molecules in these highly populated pockets of chemical space really the best ones for the job? Have we already identified the most fertile regions of chemical space or does using just a handful of reaction types mean medicinal chemists miss out on exploring potentially more fruitful locations in chemical space?

---

**What’s your favorite catalyst?**

**Frank Leibfarth: (2-PhInd)$_2$ZrCl$_2$**  
A zirconium complex with aromatic ligands. Geoffrey Coates and Robert Waymouth used this catalyst to switch selectivity between atactic and isotactic geometries during a polymerization reaction. This was an early example of a using a catalyst designed for small-molecule synthesis for polymerization.

**Josep Cornella: Ni(COD)$_2$**  
A nickel complex with two 1,5-cyclooctadiene ligands. When Günther Wilke discovered this in the 1960s, it opened up a whole new field of nickel research and allowed so much new chemistry.

**Osvaldo Gutierrez: Fe(acac)$_3$**  
An iron complex with three acetylacetonate ligands. Gutierrez says this is his favorite catalyst because it is so robust.

**Paolo Braiuca: RuCl$_2$(BINAP)(diamine)**  
A ruthenium complex with chiral diphosphine ligands. Discovered by Ryōji Noyori in the 1980s, this asymmetric hydrogenation catalyst started a revolution in the synthetic approach to chiral molecules.

*Responses are edited for length and clarity*
The only way to definitively answer those questions is to explore the vast chemical unknown more deeply. Braiuca believes that innovations in metal catalysts will be the key to enabling such investigations. Metal catalysts already play a vital role in pharmaceutical manufacture, speeding up reactions and enabling otherwise hard-to-achieve chiral control. New catalysts will open the door to more structural diversity among the molecules that end up in high-throughput screening libraries and therefore potentially in the drugs that reach the pharmacy shelf, Braiuca says.

**IMPERSONATOR BISMUTH**

“Catalysts empower us to do stuff that is different,” says Josep Cornella, a research group leader from the Max Planck Institute for Coal Research. “Organic chemistry has these rules, these things that you can and cannot do. New catalytic methods can sometimes break those canonical rules and take you into uncharted territory,” Cornella says.

His group is developing novel bismuth redox complexes that mimic the catalytic mechanisms used by the more popular transition-metal catalysts. Bismuth is pretty benign but, because it’s sandwiched between two highly toxic elements—lead and polonium—it has been largely ignored by catalyst developers, Cornella explains. Palladium, platinum, and other transition metals owe their catalytic properties to their ability to switch between different oxidation states. In doing so, they loan electrons to and borrow electrons from reactants to facilitate reactions. Cornella has shown that bismuth complexes can do the same.

The end goal isn’t to replace transition-metal catalysts with bismuth, Cornella says. Instead, he wants to use bismuth complexes to carry out reactions that transition-metal catalysts cannot—thereby opening the door to new regions of chemical space. This potential for novel reactivity comes from bismuth’s unusually large number of stable oxidation states and ability to coordinate up to nine ligands.

Cornella’s group has so far achieved several novel reactions using its bismuth catalysts. These include a bismuth-catalyzed cross-coupling to form single carbon-oxygen bonds in molecules where forming such a bond would normally be challenging. This reaction, between arylboronic acids with perfluoroalkyl sulfonate salts, uses a bismuth(III)/bismuth(V) redox cycle. “This is a reaction that in theory a transition metal should not be able to do,” Cornella says. His team is now designing catalysts that use a bismuth(I)/bismuth(III) redox cycle.

**AIR-STABLE NICKEL**

The catalytic potential of nickel has long been scrutinized as an abundant and affordable replacement for palladium and platinum, two rare elements in heavy use as catalysts that sit directly below nickel in the periodic table. Like bismuth, nickel can inhabit a larger-than-normal number of stable oxidation states, meaning that it can catalyze a wider range of chemical reactions.
Issues with the air stability of these complexes have limited their commercial use, however. “There is a lot of nickel chemistry that is yet to be picked by the medicinal and process chemists because of its air sensitivity,” Cornella says.

So he was thrilled when a graduate student in his group accidently created a nickel precatalyst that is air stable. The structure has since been tweaked to further improve its air stability, creating a complex with a central nickel protected from oxygen in the air by three bulky stilbene ligands with trifluoromethyl groups. The group has shown that this can replace the highly air-sensitive bis(1,5-cyclooctadiene)nickel or Ni(COD)₂, the current go-to nickel precatalyst, in numerous types of reactions. These include C–C bond formations (using Suzuki-Miyaura couplings and Heck reactions) and carbon-nitrogen bond formations (using Buchwald-Hartwig reactions).

The group has commercialized two air-stable nickel precatalysts, and Cornella is hopeful that the achievement will enable nickel to reach its full catalytic potential. His group is also probing the structure of its air-stable nickel complexes with the aim of developing a still-better catalyst.

**IRON CASCADES**

Osvaldo Gutierrez, an assistant professor at the University of Maryland, is also pushing the frontiers of nontraditional metal redox catalysts. The metal he is most interested in is iron. “Iron is very cheap” and very abundant compared with the noble metals typically used to catalyze the formation of C–C bonds, Gutierrez explains.

Iron catalysts have the potential to slash the cost of manufacturing pharmaceuticals whose production relies on more expensive catalysts, he says. “This means only certain countries can afford [certain drugs]. The current pandemic has really resurfaced those issues. We want to make catalysts that anybody around the world can use.”

The Gutierrez group catalysts are also facilitating easy access to underexplored parts of chemical space. In a 2020 paper, for example, the researchers describe using an iron catalyst to simultaneous form C–C single bonds at both ends of nonactivated alkenes. Nonactivated alkenes are notoriously difficult to get to...
react, as they have no directing or electron-withdrawing groups attached to boost their reactivity.

This new reaction was the first step toward a larger goal: to use cascade (or domino) reactions to rapidly build up complex molecular structures, such as those seen in many natural products. In that same paper, an iron catalyst was shown to control cascade reactions on a series of nonactivated 1,6-dienes (molecules containing two double bonds six carbons apart) to produce three C–C carbon–carbon bonds in one go.

The plan is to keep adding more reactions to this cascade. The path a cascade reaction takes is normally governed by the inherent reactivity of the substrate, Gutierrez explains. “We want the catalyst to control and divert pathways so we can make five, six, seven, eight carbon–carbon bonds at the same time under really fast conditions. To mimic what enzymes do.”

Gutierrez aims to accelerate not only the synthesis of complex molecules but catalyst development using computational chemistry. Traditionally, he says, designing a catalyst involves “a lot of trial and error.” When searching for a catalyst for a particular reaction of interest, chemists will purchase and systematically try out many different precatalysts and ligands. By contrast, Gutierrez’s team will not bring catalysts into the lab until they have been probed extensively in silico. “When we truly understand a system, that

Source: Osvaldo Gutierezz
leads us to much faster reaction development compared to trial and error," he says.

**MATERIALS RESEARCH**

It’s not just the pharmaceutical industry that is stuck in a rut in terms of the catalysts it uses. “A large portion of global polymer production is reliant on a single transition-metal-mediated catalysis technique that converts small building blocks, derived from petroleum resources, into commodity plastics,” says Frank Leibfarth, an assistant professor at the University of North Carolina at Chapel Hill.¹⁰

Leibfarth is referring to the Ziegler-Natta catalysts used to polymerize polyethylene, polypropylene, and other mass-produced plastics. These plastics are all made from alkene monomers acquired from fossil fuels. His group is working to develop catalysts that turn alkene monomers derived from more sustainable sources, such as plants, into novel polymers.

The Ziegler-Natta catalysts are incompatible with alkenes containing oxygens and nitrogens, such as those produced by nature. “If you add any polar moiety into that polymerization, it will bind to the transition-metal center [of the catalyst] and inhibit polymerization,” Leibfarth says. His group has instead been using a catalytic method that was originally designed for making small organic molecules but that it revamped for polymers.

An important goal here was to introduce stereocontrol into the finished polymer. The stereochemistry affects the physical properties of plastics, Leibfarth says. The classic example is glucose: when it is polymerized, just changing one stereocenter dictates whether the end product is cellulose or starch. “These two very different materials are chemically identical, they’re just different stereoisomers,” he says.

The vinyl ethers were the first polymer building blocks the Leibfarth group worked with.¹¹ These monomers have long been used for making polymers, but the traditional polymerization method produces a structure with side chains that stick out in a random arrangement. These polymers are viscous.
liquids. By using a catalytic system that controls the stereochemistry during the polymerization, Leibfarth produced a polymer with every side chain protruding out the same side of the polymer chain. This new plastic is solid and has potential uses in packaging and composite materials.

Leibfarth’s catalytic system is a titanium tetrachloride anion together with a phosphoric acid cation based on 1,1′-Bi-2-naphthol. The cation is chiral, and its presence directs the stereoselectivity during the addition of each vinyl ether monomer onto the growing polymer chain. The group is working to find a commercial application for these polymers and is developing catalysts that can control the polymerization of a wider range of monomers.

**SUMMARY**
Catalytic innovations will enable access to new pockets of chemical space. The thrill of exploring the unknown is a worthy pursuit on its own, but the possibility of discovering drugs and other important molecules makes this work even more important. After all, these catalysts may lead to areas of chemical space populated with molecules that can be used as universal cures for cancer, ones that can stop a pandemic in its tracks, or a high-performance polymer that somehow knows to decompose immediately after use.

**REFERENCES**
9. Lei Liu et al., “Fe-Catalyzed Three-Component Dicarbofunctionalization of
Unactivated Alkenes with Alkyl Halides and Grignard Reagents,” *Chem. Sci.* 11, no. 31 (July 2020): 8301–305, [https://doi.org/10.1039/d0sc02127j](https://doi.org/10.1039/d0sc02127j)

