

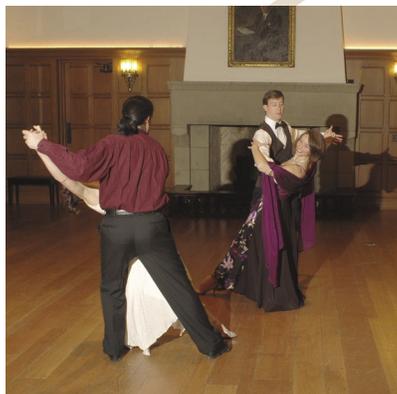
The Metathesis Waltz

by Douglas L. Smith



Robert Grubbs, the Atkins Professor of Chemistry, got a phone call from Stockholm in the late evening of October 5 in Christchurch, New Zealand, where he was on a fellowship at the University of Canterbury. The 2005 Nobel Prize in Chemistry had been split equally between him, Richard Schrock of MIT, and Yves Chauvin, retired from France's Centre National de la Recherche Scientifique, for what the Royal Swedish Academy of Sciences called "one of organic chemistry's most important reactions." The Academy's advanced supplementary material added, "Considering the short time during which Grubbs' and Schrock's catalysts have been available, the breadth of applications is truly remarkable. We have witnessed the synthesis of polymers with special properties, additives for polymers and fuels, and biologically active compounds such as insect pheromones, herbicides, and drugs." Small wonder, perhaps, that the normally impassive Swedes were moved to write, returning to the press release, "Imagination will soon be the only limit to what molecules can be built!" (Exclamation mark theirs.)

Grubbs is also an accomplished canyoneer and mountain climber. Here he descends a waterfall in the upper reaches of Eaton Canyon in the San Gabriel Mountains just north of Pasadena, heading for a refreshing dip in the pool below.



The metathesis waltz, as performed by the Caltech Ballroom Dance Team. A molecule containing a carbon-carbon double bond (grad student Kate Campbell, MS '03, and Robert Nissen) approaches a molecule with a metal-carbon double bond (grad students Megan Ferguson and Michael Cohen, whose back is to the camera). Silver-sashed (and shod!) Megan, dancing the catalyst, leads the joining of hands in a four-membered ring, and when the couples part, she is now dancing with Robert.

A second carbon-carbon double bond (grad student Candy Tong, MS '04, and Kenneth Kuo) approaches, and the figure repeats. At the end, Robert and Candy are paired up as the product molecule, and Megan is ready to begin the catalytic cycle again.

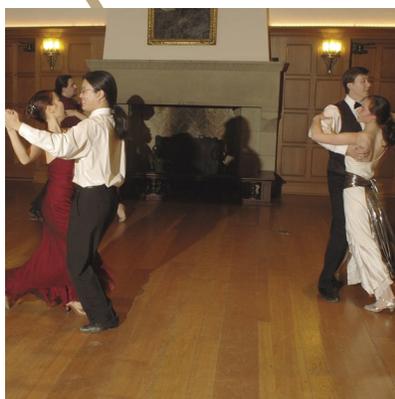
This marvelous reaction, called metathesis from the Greek word for transposition, may be visualized as a stately Viennese waltz. Picture a man and a woman dancing the roles of carbon atoms, holding both of each other's hands to form a carbon-carbon double bond. Another couple, similarly holding hands, approaches—but the second lady, in a shimmering silver sash, represents a metal atom. (A carbon atom double-bound to a metal atom is called a carbene—in general, the suffix “ene” in the name of an organic, i.e., carbon-based, compound signifies the presence of a double bond. Make a note of this, as it will save you a lot of flipping back to this page later.) The two couples join hands to form a square, then pair off again, changing partners as they do so. The silvery lady—our catalyst—dances her new partner over to another hand-holding couple—two more carbon atoms—to form a new square, and when this breaks up, all six dancers will have changed partners but all of them remain part of a double bond. To the outside observer, looking only at the final pairings, no bonds have been broken or new ones formed, yet somehow the atoms have traded places.

Recalls Grubbs, “In 1968 I was a postdoc working with Jim Collman at Stanford, and he came

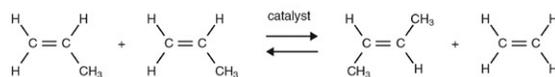




Special thanks to Caltech Ballroom Dance Club president Kate Campbell for the choreography, and to Grubbs graduate student Michelle Robbins for technical assistance.



back from a consulting trip talking about this crazy reaction he had just heard about. You passed propylene over a catalyst, and it turned it into ethylene and 2-butene.” (See above right.) “There was absolutely no clue about how it happened, and I was really interested in mechanisms, so it struck me as being a perfect place to start.” Of course, people knew how to make carbon-carbon double bonds, how to break them, and how to transform them into bonds with other atoms. But what was weird here was the *rearrangement*. The carbon atoms usually danced with the ones that brought them, but here they traded partners with abandon. Everyone was excited by this reaction because, if the process could be generalized and controlled, it would be

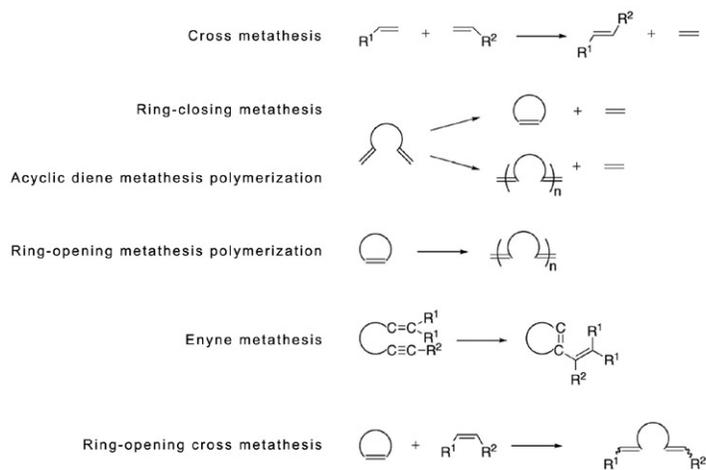


In a metathesis reaction discovered in the 1950s, two molecules of propylene (left), each with three carbon atoms, become a molecule of 2-butene, with four carbon atoms, and a molecule of ethylene with two carbon atoms. (Or vice versa—the reaction is reversible.)

the means to a whole lot of different ends. Metathesis had actually been employed industrially on a limited scale since the 1950s, and several patents had been issued on various processes that exploited it, but nobody knew how or why it worked.

Grubbs left Stanford for an assistant professorship at Michigan State in 1969. He continued thinking about metathesis, doing model studies to try to figure out how the carbon atoms could leap around like that, and even published a plausible mechanism that turned out to be completely wrong. Then, in 1971, Yves Chauvin, at that time with the Institut Français du Pétrole, and his student Jean-Louis Hérisson wrote a paper describing what turned out to be the correct mechanism. So Grubbs “designed some studies that helped convince people that the Chauvin mechanism was the best description of how the reaction proceeded. And that was probably the work that got me tenure.” (Grubbs became an associate professor at Michigan State in 1973.) These “labeling” studies involved replacing the two atoms of hydrogen attached to one of the carbon atoms in the dance with two atoms of deuterium, or “heavy hydrogen,” and noting where the deuterium wound up when the dance was over.

Understanding *how* the reaction worked was one thing; figuring out *what* made it work proved to be quite another. The catalysts were “heterogeneous,” which is to say that they were ill-defined mixtures of organic chemicals in dubious association with metal atoms in unknown oxidation states. “They were cobalt and molybdenum on alumina that you prepared in a sort of hocus-pocus way,” Grubbs remembers. “These were recipes, true recipes. Like tungsten hexachloride mixed with the right amount of alcohol and then some alkyl aluminum reagent and something magic happened. And sometimes the soluble part was the catalyst, and sometimes the insoluble part was the catalyst. You never knew.” And if you counted the active catalytic sites in this witches’ brew, it became apparent

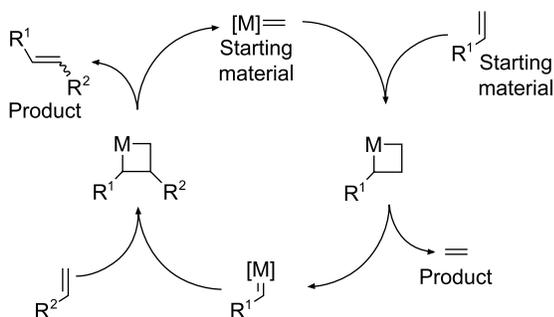


These examples of the types of rearrangements that metathesis can do give some hint of its versatility. In this drawing and those that follow, hydrogen atoms are not shown for clarity, and every vertex and every end of a line segment represents a carbon atom. R is shorthand for the rest of the molecule.

Chauvin's catalytic cycle. R²'s squiggly bond in its product molecule indicates that R² might also lie on the upper side of the double bond, the way R¹ does. In its simplest form, the reaction produces both products; part of the art of using metathesis is in engineering the reaction system to get the product you want.

that all the catalysis was being done by a small percentage of the metal atoms. Consequently, no one had any idea what the arrangement of atoms was that was actually doing the job, and like any other poorly understood piece of magic, it was hard to work with. (Just ask Harry Potter about his Potions classes.) For metathesis to live up to its potential, a molecule whose structure was well-known and whose behavior could be predicted—nay, designed—would be required. That wouldn't happen for some time, however.

Meanwhile, Caltech wooed Grubbs away from Michigan with a full professorship in 1978, and when he arrived he and graduate student Thomas Howard (MS '81) started doing model studies on a titanium-based catalyst that *was* well-defined, but painfully slow to react. This was actually a plus, as it allowed them to capture and identify the intermediate chemicals in the reaction for the first time. By then the Chauvin mechanism was pretty much accepted, says Grubbs. "We'd done most of the labeling stuff before I came to Caltech. Isolating the intermediates just nailed down the details. The labeling studies had basically ruled out all the other mechanisms—Schrock was doing stuff, we were doing stuff, and the consensus became that Chauvin's mechanism was the best explanation. So we knew to start looking for catalysts that



contained metal-carbon double bonds. And we knew that this titanium system contained such a bond, so we were able to isolate the first example of that kind of system that would do metathesis." The titanium catalyst proved to be really useful for making polymers, and Grubbs's lab spent the next decade doing just that. (See *ES&S*, Summer 1988.)

Metathesis's turning point came in 1980 at MIT, when Schrock made a well-defined catalyst with a tantalum-carbon double bond that worked at a reasonably zippy rate. A brace of more active tungsten-carbene catalysts followed, and then in 1987 a very active molybdenum carbene. (The most efficient molybdenum version, commercially available as "the Schrock catalyst," appeared in 1990.) But while these catalysts briskly and efficiently rearranged molecules containing just carbon and hydrogen, they tended to react irreversibly with oxygen atoms. This meant that they were sensitive to water—and air—which was a pain in the neck; worse, from an organic chemist's point of view (Schrock is an inorganic guy), it meant that you couldn't have any oxygenated "functional groups" in the molecules being catalyzed—no alcohols, no aldehydes, no amides, no esters, no carboxylic acids. "The functional groups killed the catalyst," says Grubbs. "And we were trying to make functionalized polymers, so none of the Schrock catalysts would work."

Molybdenum, tungsten, tantalum, and titanium are all early transition metals. That is, they lie near the left edge of the periodic table, a little to the right of the alkaline earths such as magnesium and calcium. If you think of a metal atom as tract housing for electrons, the early transition metals are fresh-built subdivisions with lots of vacancies—unoccupied *d* orbitals—in their outer precincts. Thus they eagerly recruit the two rich, nonbonding electron pairs on an oxygen atom, passing over the less upwardly mobile single electron pair available at a carbon-carbon double bond. But as you travel to the right across the periodic table, the *d* orbitals gradually fill up. This makes the metals choosier about the electron pairs they pick to fill their remaining orbitals, and so they are able to reject an oxygen atom in favor of a carbon-carbon double bond. In fact, some even prefer the latter, as an unoccupied antibonding orbital on the double bond can soak up some of their greater electron density—as the neighborhood gets crowded, the metal's electrons like a little elbow room. So grad student Bruce Novak (PhD '89) began looking at the late transition metals.

Other chemists had used solutions of ruthenium trichloride to do metathesis with some success, but, says Grubbs, "if you did site counting, the number of metal centers that became active was incredibly low. Less than a percent. They seemed to be extremely active but very short-lived." Novak discovered that the ruthenium atom had to be in the right oxidation state—Ru⁺² instead of Ru⁺³—and came up with a catalyst that, while it didn't set any

speed records, was unaffected by all the functional groups that Schrock's catalysts fell prey to. It still wasn't well-defined, but, says Grubbs, "we realized that there had to be a ruthenium-carbon double bond there. Some people had made ruthenium carbenes before, but none of them worked for metathesis because, as we now know, they were in the wrong oxidation state. And this catalyst was clearly a very special one, because it survived water and air."

You can let Novak's concoction sit in a beaker by the sink overnight, whereas Schrock's catalysts need to be kept under an inert atmosphere in a drybox—an airtight chamber with an air lock for getting things in and out, and rubber gloves sealed to the walls to allow manipulation of the materials within—and reactions using Schrock's catalysts have to be run in elaborate vacuum systems using all kinds of special techniques.

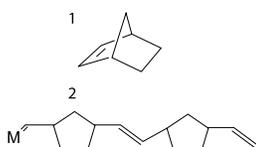
The ruthenium catalyst had one serious drawback—it needed a little extra oomph to get it going. It only worked when the carbon-carbon double bond was under strain, bowed like a stick ready to snap. Practically speaking, this meant that the carbon-carbon double bond had to be part of a ring containing five or fewer atoms. The ability to open rings is a useful thing, but Schrock's catalysts worked happily on unstrained, linear molecules.

Now that the Grubbs group had found the magic metal and its all-important oxidation state, it fell to Sonbinh Nguyen (PhD '95) to build a working ruthenium carbene from scratch. "Sonbinh was just an amazing kid," beams Grubbs, "and he's the graduate student I invited to go to Stockholm. He did the breakthrough reaction." The lab had been experimenting with different ways to make Schrock catalysts, including using cyclopropene—a highly reactive molecule containing three carbon atoms in a triangle, one of whose sides is a double bond—to make tungsten carbenes. "It was some intelligent

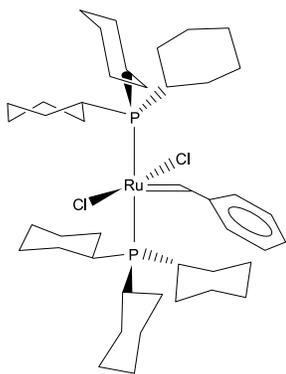
design and some evolution," says Grubbs. "He applied the cyclopropene route to ruthenium, and it sort of all worked. I'd proposed this approach to a few other people, and it hadn't quite worked. It all happened pretty fast, and I still remember the group meeting where Sonbinh got up and talked about this, and afterward one of the guys who had been working on this area for a long time went up to him and said, 'You lucky son of a bitch!' And Sonbinh just smiled. It wasn't luck. He'd got it all put together right." Nguyen's first catalyst, developed in late 1991, also only opened strained rings. But he kept at it, and by 1993 he had an improved version that worked on straight-chain molecules, just like Schrock's did. "And it was tolerant of water, fairly tolerant of air, and tolerant of almost all functional groups," says Grubbs. "So that really was the break that started all the applications."

Nguyen's molecule had several parts. There was the ruthenium-carbon double bond, of course, plus a couple of chlorine atoms bound to the ruthenium to maintain the correct oxidation state—a leftover from the original ruthenium chloride system that Novak had started with. And there was some inconsequential stuff attached to the carbene that was basically debris from the molecule's synthesis. The carbene and the chlorines lay in a plane around the ruthenium's equator, as it were, and Nguyen's critical innovation—the introduction of two phosphorus atoms attached to some other organic groups—were affixed to the north and south poles. The phosphorus atoms supported, in the second version, a parasol made of three cyclohexyl groups—big, bulky, six-carbon rings. The northern cyclohexyl phosphine, as it's called, guards the approaches to the catalytic center, directing potential dance partners to the carbene below, and it also lends some of its electron density to help stabilize that critical step in the waltz where the ruthenium and three carbon atoms all hold hands. But the southern cyclohexyl phosphine is the key to the whole shebang—it activates the catalyst by detaching itself from the molecule, taking two electrons with it. Ruthenium⁺² with five atoms bound to it has 16 electrons to play with, and metathesis only occurs when it has 14 electrons. "We obviously didn't know that at the time," Grubbs admits. "We found that out in the studies that came later. The way things work in this area is you make a guess and then you make something. And part of the time it works. Or it works better, but for a different reason than you thought it was going to. Or it does something you didn't intend really, really well. As I reassured one of my students recently, 'If you plan something and it works, then you're a scholar. If you plan something and it does something else even better, then you're creative!'"

Nguyen's preparation methods were very labor-intensive, and it proved impossible to make his molecules in bulk. So Marcia France (PhD '95) and postdoc Peter Schwab came up with an easier

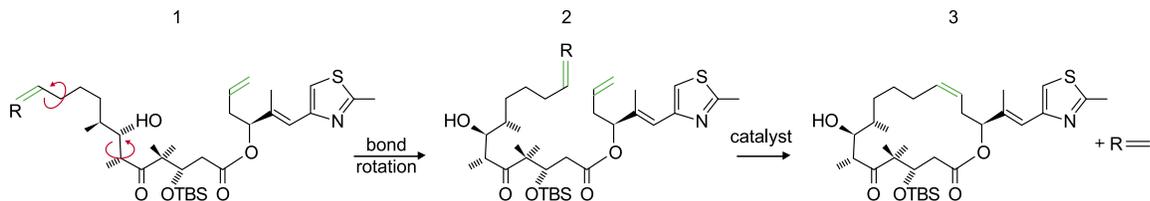


A molecule of norbornene (1) looks like the business end of an eggbeater, and its double bond is highly strained. When it polymerizes (2), it becomes a flatter, much happier molecule. (The M represents the catalyst metal atom.)



The first-generation Grubbs catalyst. Solid triangles indicate bonds that stick out of the plane of the page toward the viewer. Shaded triangles show bonds that recede behind the page.

A critical step in the synthesis of epothilone A, a potential anticancer drug, involves creating a 16-membered ring. This is complicated by the fact that the unclosed ring is a long, floppy chain (1). Solvent molecules banging into the chain cause it to writhe around, and eventually its various links will rotate in just the right way to bring the two green double bonds close together (2). The waiting catalyst then does its magic (3).



synthetic route, which postdoc Michael Giardello was able to scale up. This catalyst, published in 1995, is commercially available as the “first-generation Grubbs catalyst.”

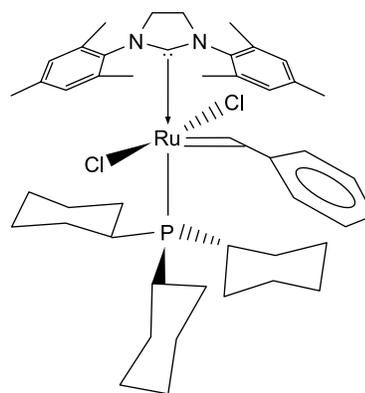
Meanwhile, postdoc Gregory Fu used Nguyen’s catalyst to demonstrate ring-closing metathesis—a critical step in many pharmaceutical syntheses. These drug rings, like their criminal counterparts, are large, multifunctional, and flexible. They often contain a dozen or more members—epothilone A has 16—and before the ring is closed the free ends can lie quite some distance apart along a loose, floppy backbone. There are innumerable ways that things can go wrong when you attempt to round up your suspects, but planting double bonds at the right spots and using metathesis to handcuff the end atoms together greatly raises the odds of making a successful collar. Just this past June, Boehringer-Ingelheim, a German pharmaceutical company, reported the manufacture of some 400 kilograms of a hepatitis C protease inhibitor for use in possible Phase II clinical trials. The process uses ring-closing metathesis in the 20th step of a 25-step synthesis. No metathesis-based pharmaceutical has yet reached Phase III, the final hurdle before a drug goes to the FDA for approval, but several are in Phases I and II.

A “second-generation” catalyst came out in 1999. Developed by grad students Matthias Scholl (PhD ’00), Tina Trnka and John Morgan (both PhD ’03), and undergrad Sheng Ding (BS ’99), it is even more reactive, is stable at higher temperatures, and is now the catalyst of choice for splicing dissimilar molecules together in what’s called cross metathesis.

There wouldn’t be all this fanfare if none of these wonderful products ever made it out of the lab. The chemical industry is embracing metathesis because, besides being easy to use, it’s more efficient. Products can be made in fewer steps, using fewer reagents, and generating less waste. And, if you’re using Grubbs’s catalysts, you can do a lot of reactions in water that you would otherwise have to do in a toxic solvent such as benzene. The Nobel press release calls metathesis “a great step forward for ‘green chemistry’” because it allows us to make stuff we can’t (or don’t want to) live without, in the most

environmentally friendly way possible.

Not surprisingly, a company has been formed around these catalysts. Materia Incorporated, headquartered in Pasadena, has Grubbs and Schrock on its scientific advisory board. Materia manufactures and sells all of their catalysts as well as those developed by Boston College’s Amir Hoveyda, a frequent collaborator of Schrock’s, and licenses their use. Materia also uses these catalysts to make products, including polydicyclopentadiene resin, which, in the words of Grubbs’s former postdoc Giardello, now Materia’s CEO, is “tough, durable, corrosion-resistant, and amenable to large-part fabrication.” A 1½-inch-thick layer will stop a 9-millimeter copper-jacketed bullet within its own length, and it can be molded into things as diverse as hulls for personal watercraft or body panels for farm equipment. It is also used for valves and pipes to handle chlorine, concentrated alkalis, and strong acids—some of the nastiest substances in the chemical industry. Easton Sports even injected it into low-grade, porous wood, turning out baseball bats—approved for use in every league but the majors—until the Chinese construction boom soaked up all the cheap timber.



The second-generation Grubbs catalyst has an even better donor of those dance-promoting electrons at its north pole.

PICTURE CREDITS:
21 — Luca Chiarabini; 22–23 — Herb Shoebridge; 25, 26 — Doug Cummings; 27 — Materia, Inc.

Some of the catalysts available from Materia. The dark purple one at bottom right is the first-generation Grubbs catalyst, and the reddish-brown one at center left is the second-generation Grubbs catalyst.



Materia also makes pheromones, chemical signals secreted by an animal to communicate with other members of its own species. One favorite message, roughly translated, is “Hello, sailor—come here often?” Since insect mating is induced by chemical cues rather than sexy lingerie or whispered nothings, organic farmers use pheromones instead of pesticides, wafting scents that lure amorous males into death traps and leave the females high and dry. It takes a fair amount of patience to go completely green, but a reasonable middle ground can be achieved by setting a few pheromone-baited traps and then applying pesticides judiciously when the fleet comes in.

The use of pheromones for pest control is still in its infancy, generating perhaps only several millions of dollars in annual sales worldwide versus the more than one billion dollars spent on pesticides by U.S. farmers alone. But the market share grows each year. Says Giardello, “We target only the pests our chemistry is best suited for. This is mainly the *Lepidoptera*—moths and butterflies—whose larvae do tremendous damage to stone fruits such as peaches.” Materia’s peach twig borer pheromone did several hundred thousand dollars in sales last year, its first year on the market. And a spruce budworm pheromone, now in development with the Canadian government, could be a multimillion-dollar seller in a few years.

But the faux pheromone of the future may be the one for the omnivorous leafroller, which is very fond of grape leaves but also likes those of apple, pear, peach, and nectarine trees. The compound is produced from jojoba oil and 3-hexene in a six-step process with a 50 percent overall yield. (The jojoba, from whose edible seeds the oil is extracted, is a shrub native to the American southwest and Mexico.) By contrast, the traditional synthetic method takes 14 steps, starts entirely with petroleum-based compounds, and gives a 15 percent overall yield at three times the production cost.

What’s neat is that Materia’s process requires no solvent of any kind whatsoever—you just process the jojoba oil to extract its main component, and add the 3-hexene and the catalyst to the extract.

“It’s its own solvent,” says Grubbs. “And essentially all the products you make are useful. So it provides a way of making bonds without wasting solvents, and without generating by-products and streams of pollutants.” Caltech, Materia, agribusiness giant Cargill, and the Department of Energy are working on a joint project to expand this whole notion of solventless processes to seed oils in general—corn oil, soybean oil, and what have you. As any viewer of margarine commercials knows, these oils consist mostly of unsaturated fatty acids, which is just a fancy way of saying molecules with double bonds in them. Cargill’s goal, says Grubbs, is “a process where, as they describe it, they take a barrel of vegetable oil and sprinkle a little magic dust to make it a new product. And the less magic dust you have to add, the happier they are.”

And that’s the greenest thing of all—seed oils are renewable resources. If we could cheaply and efficiently convert seed oils into products that are normally made from petroleum, we’d be one step closer toward kicking our oil habit. Giardello says that Cargill has already come up with a process that “converts a renewable feedstock into a proprietary industrial product with household applications that’s going to be really big,” but he’s cagey about saying more before the patents go public next summer.

Grubbs’s research group is now working to extend catalyst lifetimes. Obviously, the more stuff you can crank out per molecule before something goes wrong, the cheaper the process becomes, and the more opportunities arise to use it. “We’ve got some reactions where the catalyst does a few hundred-thousand turnovers, that’s the high end, and then for some really hard reactions, it’s as low as four or five turnovers.” This means that, “in terms of stuff you’re selling, very few things are worth it. But in terms of academic applications, I’ve had people say, ‘Look, I don’t care if it only turns over once. I just want to make this compound.’” So the lab is exploring all the side reactions that can kill the catalyst or tear it apart. “If we can find all the mechanisms for decomposition and termination, maybe we can design strategies for preventing them from taking place. And we’ve already come a pretty long way in that.

“Right now we’re still in the nitty-gritty of getting the first round of products out, and developing the next round of catalysts. What’s been amazing to me about this research is that when I first started, I didn’t think we would ever be able to make catalysts that tolerated functionality. And then we did that, and we didn’t think that we’d be able to make catalysts that would tolerate air and water. And we did that. I didn’t think that we’d be able to do metathesis on double bonds that contained functional groups directly on the double bonds. And we can do that, now. So I keep getting surprised. And every surprise leads to a new direction to go in.” □



A rear view of a sheet of polydicyclopentadiene resin into which several bullets of various calibers have been fired, including a 9-millimeter copper-jacketed one (left center) and a .44 Magnum hollow-point (lower right).