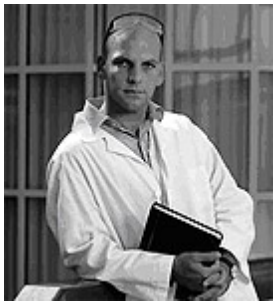
AUTHOR COMMENTARIES - 2009

May 2009

PDF



Benjamin List

Featured *Science Watch*® Newsletter Interview

Both humans and chemical compounds can be divided into the left- and right-handed versions, but for humans, the benefits of one over the other are mostly limited to a few positions in baseball. For chiral molecules, as they're known, which come in mirror-image versions like right and left hands—sugars, for instance, or amino acids or drugs—the functional difference between a compound and its mirror-image can be night and day. In pharmaceuticals, one might cure your headache while the other might be toxic, so the synthesis of compounds that come only in one form or the other—either all right-handed or all left—is fundamental to the industry.

Through the turn of this century, chemists relied on two methods of asymmetric catalysis to make their chiral compounds. One used transition-metal complexes, the other relied on naturally occurring enzymes known as biocatalysts to do the trick. In March 2000, the German chemist Benjamin List published a report in the Journal of the American Chemical Society *demonstrating the ease of creating chirally pure compounds using an organic molecule—the amino acid proline. In doing so, List effectively launched the field of organic asymmetric catalysis and propelled himself to the front ranks of hot chemistry. His 2000* JACS *paper has now been cited nearly 700 times (see table below, paper #1) and is just one of more than 20 of his reports published in the last decade that have accumulated more than 100 citations each. During 2008, his 10 Hot Papers published over the preceding two years earned him a spot in this publication's annual roundup of hot authors, as reported in the previous issue (March/April 2009).*

List, 41, did his undergraduate work in chemistry at the Free University of Berlin, graduating in 1993, and obtained his doctorate from the University of Frankfurt in 1997. He spent the next six years at the Scripps Research Institute in La Jolla, California, before returning to Germany in 2003 to become a group leader (associate professor) and, since 2005, a director (full professor) at the Max-Planck-Institut für Kohlenforschung (Coal Research) in Mülheim an der Ruhr, and an honorary professor at the University of Cologne.

List spoke to* Science Watch *from his Max Planck office.

SW: How would you describe the importance to the pharmaceutical industry of asymmetric reactions and the synthesis of chiral compounds?

The most important answer is that pharmaceuticals are often chiral. That means you have two mirror-image-like molecules, and most of the time, in fact, only one has a specific activity. The other enantiomer—the mirror image—is either inactive or, even worse, possibly toxic. This is a very common situation, and the number of chiral drugs nowadays is increasing. Indeed, the majority of pharmaceuticals may

now be chiral. Drug agencies demand the testing of these agents individually, each enantiomer, and you're required to make the pure enantiomer. This is what motivates the interest in making chiral enantiomerically pure compounds.

SW: What prompted your own interest in using asymmetric catalysis to make chiral compounds?

When I was a Ph.D. student I worked in natural-product synthesis. My Ph.D. supervisor Prof. Mulzer had a strong background in asymmetric synthesis. When I was doing my doctorate, the state of the art was something called chiral auxiliaries: you introduce chirality or asymmetry into the system by attaching an auxiliary to your substrate, then conducting the reaction and cleaving it off afterward. But this required several chemical operations and the use of a large amount of the auxiliary. In asymmetric catalysis, all you need is a tiny amount of your source of chirality, which is then amplified. Catalysis is basically a tool—it's like a hammer. You have one hammer, but you can hammer a million nails into the wall with it and the hammer remains unchanged. That's effectively what your catalyst does in a reaction; that's the beauty of it, and that's why I wanted to work in it.

"People are realizing that organic catalysis is effectively a new field," says Benjamin List of the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany.

SW: What made you think that organic asymmetric catalysis was even a viable possibility, and how did you first approach the problem?

When I became an assistant professor in 1999 at Scripps, I had to figure out what my line of work was going to be. My training had been in hardcore organic synthesis, but I had worked as a post-doc with biocatalysts—catalytic antibodies. Catalytic antibodies can be programmed for effectively any chemical reaction you want. I was fortunate at the time because I was working with these wonderful catalytic antibodies. Not all biocatalysts are superactive, but the one I was working with was really powerful. And these catalytic antibodies catalyze the intermolecular aldol reaction, which is important for the synthesis of chiral compounds. These enzymes have a special mechanism which involves so-called enamines, which are formed as covalent bonds between the catalyst and the substrate. Enamines are the key intermediate in this catalysis. Enamines have also been used by chemists in organic synthesis—most notably by Prof. Gilbert Stork and others—so this was a place where nature and chemical design came together. But chemists rarely used these enamines the way nature does, as catalytic intermediates—which is a much more beautiful way of doing things.

My plan in 1999 was to design small organic molecules called amines that could catalyze the intermolecular aldol reaction, effectively mimicking enzymes with their active site amino group. These wouldn't be proteins, which are big molecules, but small, easy-to-use molecules that would also catalyze this reaction and would do it using the same mechanism. That was how I got started, but I also remembered that back in the 1970s two industrial groups had independently realized that certain intramolecular aldol reactions could be catalyzed with exactly the kind of thing that I had in mind—a small chiral organic molecule with an amino group. What they used as a catalyst was the amino acid proline. At the time I assumed that this wouldn't really work—that somebody must have tried it in the almost 30 years since these two industrial groups had reported it. So before I even got to trying out all the molecules I had designed, I tried proline and it did the job pretty well—representing, in fact, the state of the art in the field.

SW: Why was this such a big deal?

All of a sudden, one of the most interesting transformations in asymmetric catalysis—the direct asymmetric intermolecular aldol reaction—could be carried out with a simple, nontoxic, readily available organic catalyst: proline. This discovery started to make people realize that the poorly understood intramolecular aldol reaction was not an exotic isolated example, but that there might be a general principle behind it. This principle is now called enamine catalysis and has inspired literally hundreds of publications.

SW: How did your research and the field itself evolve after the 2000 paper?

We became part of this movement of pushing enamine catalysis, assuring that this really is a general strategy for asymmetric catalysis, that you can catalyze various different reactions using this principle. There are now several dozen groups around the world working with this catalysis principle, and they've

also begun to explore, as we have, other areas of organic catalysis that, like enamine catalysis, might not have been appreciated before as being really general.

SW: Can you give us a simple example of one of these other areas?

One thing we tried to do later was develop reactions that utilize organic catalysis to hydrogenate organic compounds. This was something people had thought was impossible for a long time. Hydrogenation—the addition of the element of hydrogen, two H atoms, to an organic substrate—is ubiquitous in chemistry and in the pharmaceutical industry; all living organisms also use hydrogenations.

For some reason everybody thought that if you did hydrogenation, if you transferred these hydrogen atoms and did it asymmetrically, you'd have to use a metal—either as a reagent or as a catalyst, using a transition metal like palladium or platinum. I gave a talk back in 2001 where I was challenged: someone in the audience said, okay, this intermolecular aldol reaction is nice, but can you do something really, really challenging, like a metal-free hydrogenation reaction? Again I took my inspiration from nature. How does nature hydrogenate its substrate? And nature very rarely uses hydrogen. We use it because it's cheap and nice to deal with, but it has a little drawback: it's a gas and can be explosive. That's a bit of risk when you work with hydrogen. What nature does is to use organic co-factors, dihydropyridines, which can donate hydrogen, but not in the form of elemental hydrogen, H_2. It's done indirectly.

So back in 2004, we came up with a solution to this: the first completely metal-free catalytic hydrogenation of an olefin (this is the carbon-carbon double-bond-containing molecule), which is another word for alkene. Nature uses these dihydropyridines, and we also used a very simple dihydropyridine, an organic compound that can donate hydrogen to organic substrates. Again, it was known for a long time what these molecules did, but no one had tried to use them for asymmetric catalysis. They're very rarely used in catalysis at all. Over the years, we and other groups have taken to using this same compound in other reactions—reducing imines, for instance, which is another very important class of organic compounds. The produced chiral amines are ubiquitous in chiral drugs, so this was a very important development.

Highly Cited Papers by Benjamin List and Colleagues, Published Since 2000
(Ranked by total citations)

Rank	Papers	Cites
1	B. List, *et al.*, "Proline-catalyzed direct asymmetric aldol reactions," *J. Am. Chem. Soc.*, 122(10): 2395-6, 2000.	665
2	B. List, "Proline-catalyzed asymmetric reactions," *Tetrahedron*, 58(28): 5573-90, 2002.	523
3	J. Seayad, B. List, "Asymmetric organocatalysis," *Org. Biomolec. Chem.*, 3 (5): 719-24, 2005.	389
4	B. List, "The direct catalytic asymmetric three-component Mannich reaction," *J. Am. Chem. Soc.*, 122(38): 9336-7, 2000.	309
5	B. List, *et al.*, "The proline-catalyzed direct asymmetric three-component Mannich reaction: Scope, optimization, and application to the highly enantioselective synthesis of 1,2-amino alcohols," *J. Am. Chem. Soc.*, 124(5): 827-33, 2002.	302

SOURCE: Thomson Reuters *Web of Science*®

SW: Has the pharmaceutical industry picked up on all these developments?

Yes, heavily, especially in the synthesis of drug candidates. The industry, however, has been notoriously slow in picking up these new methods for manufacturing. In fact, they often prefer to synthesize enantiomer-pure compounds using a method that's even more old-fashioned than the chiral auxiliary method. What they do is make a mixture of two enantiomers, by any means, and then separate off the wrong one and burn it or, ideally, at least recycle it and convert it to something useful. This, unfortunately, is still the most common method used in the pharmaceutical industry for making chiral, enantiomer-pure molecules. And this is why we've been working so hard to push asymmetric catalysis and make it more industry friendly. For both environmental and economic reasons, it's not exactly ideal to throw away half your product.

SW: Why do you think the industry is so averse to more modern methods?

One reason that comes immediately to mind is that there's always a delay in integrating academic research into industrial contexts. Sometimes just scaling up is difficult. Sometimes the catalysts are not commercially available, or are considered too expensive or are too hard to make. Sometimes the technique is not yet sufficiently reliable. The situation, however, is changing now. Transition-metal catalysis has recently entered the pharmaceutical industry; biocatalysis, with enzymes, is now being

used. And organic catalysis, the third pillar of asymmetric catalysis, will probably enter the industry soon enough because it's often easier to use and can be less expensive than the other two methods.

If you have a sophisticated organic molecule that requires 15 steps to make, it may indeed be more expensive. But there are many organic catalysts that are very easy to make and commercially available. Proline is a perfect example. You can isolate it from natural sources in large quantities. It's nontoxic and inexpensive. If for some reason you want to recycle it, that can be done easily. This, of course, is an ideal case. Organic catalysts can typically be made in one or two steps. There are some very famous organic catalysts made from amino acids. Others you can make from sugars in a couple of steps. Those have the potential for being used industrially, because they're so easy and inexpensive and often recyclable. On other hand, there are transition-metal catalysts that are expensive, but they're so active that the price is not so important. In industry, the only thing that ultimately matters is the cost of the process.

SW: So how would you describe the state of the science of organic asymmetric catalysis circa 2009, and its prospects for the future?

It's a good time to look back. The field is now almost ten years old. In the beginning, there was already this perception in the community of chemists that somehow there would always be big drawbacks with organic catalysis. The scope might not be so large, and you might always have to use relatively large amounts of catalyst, and there'd be other drawbacks on top of that. Meanwhile, transition-metal catalysis is very efficient, and it works for hundreds of reactions. So, nowadays, the old perception is starting to change. People are realizing that organic catalysis is effectively a new field. While it has a long history, the activity was almost negligible over the entire last century. People are now starting to appreciate that there's a tremendous amount of development going on—that you can find really, really active organic catalysts that are highly enantioselective. I think this is something that very few would ever have thought possible. My vision is that in another ten years chemists will be using biocatalysts; they'll be using transition-metal catalysts, and they'll certainly be using organic catalysts more and more.

The beauty of all this is that in nature, in living organisms, almost half of all enzymes come with a metal ion in the active site of the enzyme, and remaining enzymes are metal free. So nature already is using an equal measure of both metal-containing catalysts and organic catalysts. I predict the same thing will happen in synthetic chemistry. We'll also be using organic molecules more and more for catalysis, and I have very little doubt that there will be industrial processes utilizing organic asymmetric catalysis as well.

KEYWORDS: BENJAMIN LIST, ASYMMETRIC ORGANIC SYNTHESIS, PROLINE, ALDOL REACTION, ALKENE, ENAMINES, HYDROGENATION, ASYMMETRIC CATALYSIS.

PDF

back to top

2009 : May 2009 - Author Commentaries : Benjamin List - Science Watch® Newsletter Interview

Scientific Home | About Scientific | Site Search | Site Map