A Perspective **for Life**

The discovery that small organic molecules are excellent catalysts makes **Ben List**, Director at the **Max-Planck-Institut für Kohlenforschung**, one of the pioneers of a new research field in chemistry. His life, however, has been shaped just as much by a life-changing vacation experience.

TEXT **CATARINA PIETSCHMANN**

To be able to write about the work of a researcher, it is often sufficient to read a couple of their publications. These, however, don't disclose anything about the individuals themselves. A few hours is usually all it takes to get to know them and be able to sketch a portrait. It was different in this case, because Ben List and I had spent two years doing our doctorates together. That was a long while ago now, and we hadn't seen each other for nearly 20 years, so we had a lot to talk about when we met up again. Ben's life had followed an unusual course since our time together at our university. The Leibniz Prize, which the pioneer received in the field of organic catalysis in 2016, is an occasion to report about it.

The telephone call bearing the news that he is to be awarded the Leibniz Prize reaches Ben List in California on a sunny winter's morning. Perfect timing, as he has been invited to San Diego not only to give a talk – another employer wanted to entice him away. Live and do research here again? To be honest, that was really appealing. A laboratory with a view of the Pacific, where pelicans cruise through the air and whales swim past in January? "But the conditions I have at Max Planck, this autonomy – particularly now with the Leibniz Prize – that simply couldn't be beaten," says Ben List with a smile. The 49-year-old scientist has headed the Homogeneous Catalysis Department at the Max-Planck-Institut für Kohlenforschung since 2005.

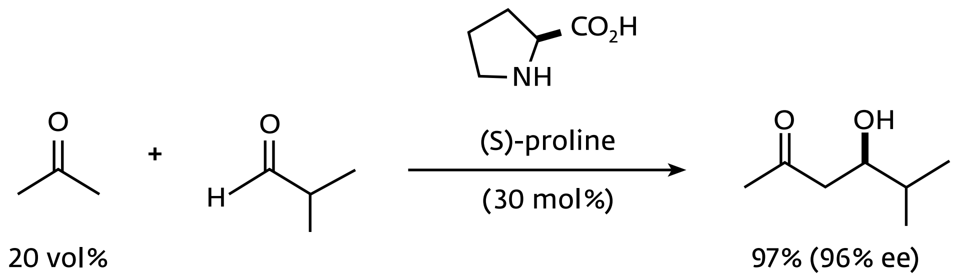
"I WOULD HAVE LIKED TO HAVE HAD A MUSICAL EDUCATION"

If there is such a thing as a researcher gene, it was firmly established in his family long before his time. Jacob Volhard (1834 –1910), a student of Justus von Liebig and, like him, a well-known chemist, was Ben List's great-great-grandfather. His great-grandfather Franz Volhard made his name as a nephrologist. And his aunt "Janni" (Christiane Nüsslein-Volhard), a developmental biologist and Max Planck colleague, received a Nobel Prize in 1995.

He grew up in an upper-middle-class family in Frankfurt, recounts List. When his mother's siblings got together at Christmas, one of Bach's Brandenburg Concertos was on the music stand. "It looks as if I was predestined to take this route. But reality was different." When Ben List is three, his parents divorce. His mother now works full time as an architect, and Ben List and his two brothers go to the *Kinderladen*, an anti-authoritarian nursery school. This type of education was all the rage at that time. "We had to fend for ourselves a lot. I would have liked to have had a musical education at an early age." He wasn't positively encouraged to learn an instrument, though. If the boys were interested in music, it

Photo: Frank Vinken

Yoga in the lab – Ben List is only doing this for the photographer. When he walks into his office in the morning, he has usually already done his exercises.



Above A plan for a new research field: Ben List was the first to catalyze this chemical reaction with the amino acid proline, shown above the arrow – and achieved a yield of 97 percent. One of the two mirror-image variants of the product was formed here with an excess (ee – enantiomeric excess) of 96 percent. Since then, many chemists have been looking for purely organic molecules in order to use them as reaction accelerators.

Below Chemical kitchenette: The apparatus in which chemists produce new substances are usually much more complex than the equipment in most kitchens. They do have hotplates, though.

would happen automatically, was his mother's view. You can do it! You can become anything you want – conductor, artist or a famous chemist. "She always had this confidence," says List looking back.

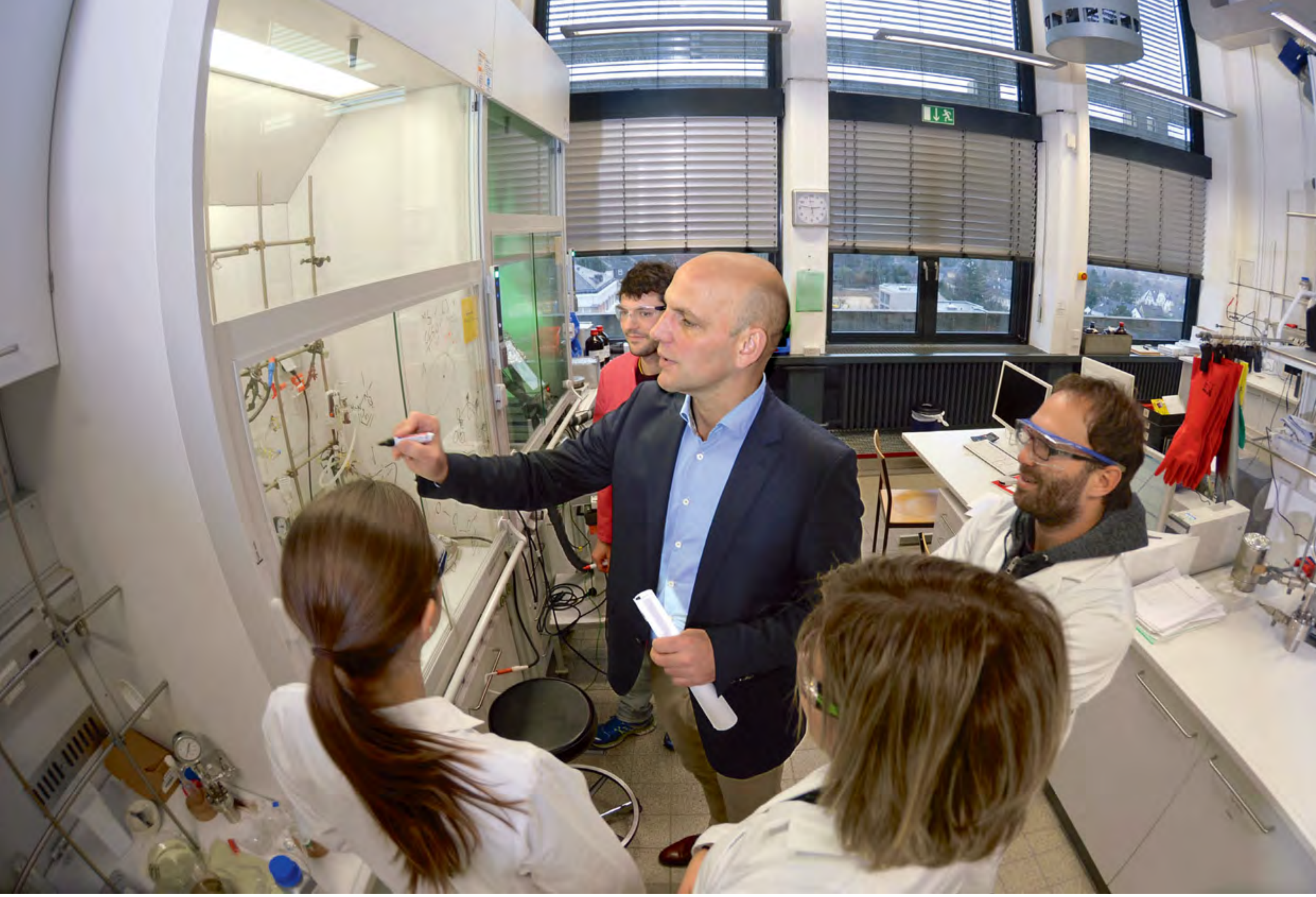
HIS AMBITIOUS GOAL: THE SYNTHESIS OF VITAMIN B_{12}

As a pupil, he was motivated by almost philosophical questions: What is the world made up of? What are human beings made up of? Chemistry promised to provide answers. Back then, List even thought chemists were all-knowing. "Pretty naive," he says today. "But when I found out that they don't have answers for everything, I was already fascinated by the discipline." After receiving his school-leaving certificate, the first thing he did was to spend three months traveling around India with two friends. The others had already made arrangements for their university courses. "I was the only one who hadn't given it any thought at all. When I returned, my mother became surprisingly vehement: Well, Ben, you really should do something now!" Study chemistry, of course, and in Berlin, of course. (A cousin lived there.) List called directory assistance and asked for the number of the University of Berlin. "Which one?" asked the irritated voice at the other end of the line. "Just choose one!" Ben List laughs. "Yes, that is how I landed at FU Berlin."

The third semester courses included organic chemistry, which meant lectures with Johann Mulzer. "They were absolutely perfect!" With no haste and a lot of colored chalk, the specialist for enantioselective natural product synthesis drew gigantic diagrams on the board that he used to show the step-by-step path by which complicated antibiotics or hormones are created. There was no question about it, Ben List simply had to join Mulzer's team.

And he had set himself an ambitious goal: vitamin B_{12} was to become his molecule! One can guess how complex the structure is from its cumulative formula $C_{72}H_{100}CoN_{18}O_{17}P$ – and Mulzer didn't warn him. "In my ignorance, I thought: one half for my bachelor's degree, the other as my doctoral thesis. That was the plan." Vitamin B_{12} was first synthesized in 1972 by Albert Eschenmoser (ETH Zurich) and Robert B. Woodward (Harvard) together. "More than 100 doctoral students and postdocs had spent ten years working on it. And I thought I could do it alone," says List, with a shake of his head. His goal was to produce the molecule more elegantly and in fewer steps – and all by himself. At some stage, Mulzer put the brakes on. It would be sufficient if he managed the two top rings, the "northern side," so to speak. The maiden ascent of a north face was more like it. But List arrived at the peak of the mountain and looked down with pride. There was a "summa cum laude" at the bottom.

Photo: Catarina Pietschmann



That could be it! Ben List and his colleagues team up to develop ideas for new reactions. Not unusual: their blackboard is the front pane of a fume hood, which permits any gases that may be released to be directly pumped out.

"Assembling a molecule piece by piece is highly elegant and aesthetic, almost a work of art." Chemists call this procedure total synthesis. Reproducing natural products in this way was absolutely en vogue in the 1990s – but total synthesis was never really practical. There were always by-products, which meant complex separation processes and a lot of waste, says List today.

Wouldn't it be better to selectively control reactions with the aid of catalysts – that is, in such a way that only the desired product is produced? Just like enzymes often do in nature? That would be truly elegant! At the end of the 1980s, research into abzymes – antibodies that express catalytic activity, like those formed by the immune system – was a hot-button topic. At the Scripps Research Institute in La Jolla (southern California), Richard Lerner tried to use abzymes to selectively catalyze just about any catalyzable reaction. List had read about it: sounded crazy – but exciting. That was what he wanted to do! "Without asking anybody, of course, let alone my dissertation supervisor." Ben List was used to making his decisions alone – this is where his anti-authoritarian education made itself felt. "I've also used it with my kids from time to time," he adds, grinning. "You may only be 12, but if you think it will do you good to eat ten chocolate bars, then go ahead and do it. I have faith in you. But my advice is: I wouldn't do it."

FROM 1999: THE EXPEDITION INTO HIS OWN RESEARCH FIELD

No advice, however well meant, would likely have put him off going to the Scripps Research Institute. He managed it with a fellowship from the Alexander von Humboldt Foundation. How cool! This is where researchers such as K.C. Nicolaou and Barry Sharpless were working – names well known from chemical reactions or molecules. "They all wore shorts and T-shirts, were addressed simply as 'Bill' or 'Nic' – it was California, after all! The activation threshold to get into conversation was extremely low." There was hardly any need for mediators – in contrast to the situation with many molecules that are set up to react with each other. They need catalysts to lower the energy threshold that inhibits them from coming into contact.

Biocatalysts in particular – that is, enzymes – rapidly accelerate specific reactions, some by a factor of 10^{18}! A catalytic antibody for the aldolase enzyme, which "turbocharged" the process in the Erlenmeyer flask by no less than a factor of 10^{8}, had just been discovered at the Scripps Institute. Ben List was now able to go for it. "It was a euphoric time. I published 17 papers in renowned journals in less than two years."

After a year, his girlfriend moved over from Germany. They had a very romantic wedding on the beach. At almost

Photo: David Ausserhofer

Would also look good in an art gallery: The chemists in Mülheim use the test tubes to investigate the products of chemical reactions.

Photo: Frank Vinken

the same time, Richard Lerner offered him a position as assistant professor at the Scripps Institute. At the beginning of 1999, Ben List set off on the expedition into his own research field with two members of staff.

"I wanted to design small organic molecules that act as catalysts." That was unknown territory. Nobody before him had pursued this concept. The conventional catalysts tried and tested in industry were usually, and still are, mostly based on transition metals, such as palladium, nickel and titanium. They are expensive, often toxic, and have to be separated off again in a complex process. Enzymes do it so much more gently, with simple organic groups such as carboxylic acids, amines and alcohols. "But the organic chemists put hardly any faith in their own molecules."

What was known of the enzyme whose antibody analog Ben List now knows by heart was that an amino group and an acid radical were located at the active center. Amino ... acid!, was going though List's mind. Hadn't he heard something about that at university? In a reaction that was later given the unwieldy name Hajos-Parrish-Eder-Sauer-Wiechert reaction, the amino acid proline had been successfully used as a catalyst – a bizarre thing to do at the time. But what if proline now worked with a mechanism similar to that of an enzyme? And what if it catalyzed other reactions as well?

"YOU THINK: MAYBE THIS WAS A CRAZY IDEA"

List took a glass flask, added a little proline and two reactants, and left it to be stirred overnight at room temperature. It was his first independent experiment. "I was very uncertain. You don't think: Ha! I designed this! And now I'll become world famous! No, it's more a case of: Hmm ... maybe this was an extremely crazy idea. Other people have probably tried this already and also know why it doesn't work."

The next day, the reactants had reacted completely, and 72 percent of the mixture had become one of two possible desired products. "Shortly afterward, we achieved an enantiomeric excess of nearly 100 percent with a similar reaction!" Enantiomers are the two versions of substances whose molecules have the same structure, apart from the fact that one enantiomer is the mirror image of the other. The two versions are chemically so similar that it's difficult to synthesize only one of them. Biologically, the enantiomers usually behave differently: one of them can have a pharmaceutical effect, the other possibly no effect at all or even a harmful one.

It is therefore hardly surprising that the paper that was published in the Journal of the American Chemical Society in 2000 both puzzled and fascinated the scientific community and has since been cited 2,200 times. An organic catalyst! A cheap, edible molecule that exists in the human body and isn't only catalytically active, but is even

» An organic catalyst! An inexpensive, edible molecule that exists in the human body – and is even more selective than any other catalyst before? Amazing!

more selective than any other catalyst before it? How could that be? Amazing! Three months later, a paper by David MacMillan was published: he had discovered a similar reaction almost simultaneously in Berkeley. The doubters now believed it, too.

Then the avalanche started. "At first it was only a few, then later hundreds of groups in the US, Japan, China and Europe were now catalyzing their reactions with proline or similar organic catalysts and publishing their findings. Everyone wanted to be part of the trend. It was completely crazy," List remembers. He himself was in an uncertain situation: he now had a family, only a tiny team and still no tenure. But then finally he obtained a large grant from the National Institutes of Health (NIH).

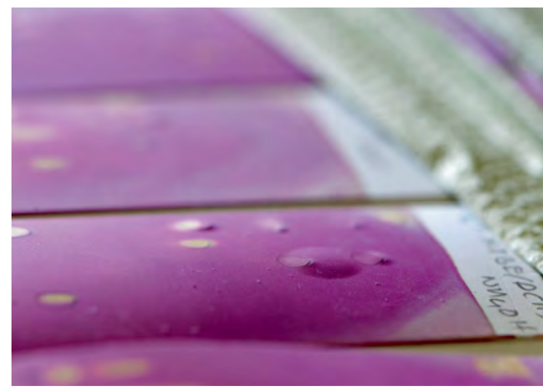
In 2002, Alois Fürstner, Director of the Organometallic Chemistry Department at the Max Planck Institute in Mülheim, visited List in his office. Fürstner had given a talk at Scripps and was surprised. "What? You are German? You have to come back to Germany! To us!" One week later, List flew to Mülheim. He was offered a permanent position, with the prospect of a post as director – and he accepted. By summer 2004, the director's post was already within his reach. Before he assumes the post, List takes his wife and two sons for a vacation in the sun over Christmas – to the beaches of Khao Lak, Thailand. The trip would become a life-changing experience.

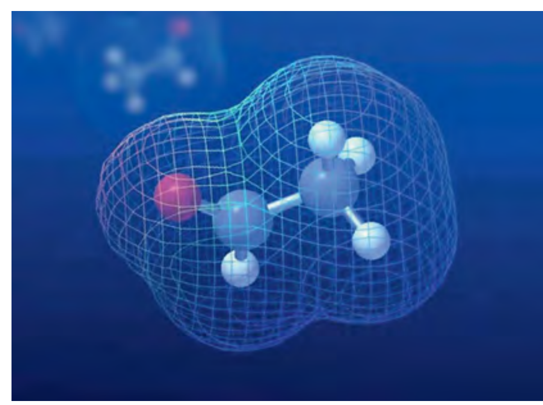
On the last day of their vacation – their suitcases were already packed – they were woken by a tremor. "Probably one of the small earth tremors, we thought, and quickly forgot it again." It was December 26, 2004. After breakfast, they went to the pool one last time. Theo and Paul, his three- and five-year-old boys, are splashing about in the water; Ben List is reading on a chaise longue when he hears a noise that gets louder and louder. He looks toward the beach, and now he hears the shouts. Run! Run! RUN!! "I looked at my wife, we each grabbed one child and started to run."

THE GRAY SLUDGE SWEEPS BEN LIST ALONG WITH IT

The pool hut behind which he seeks cover is made of wood – a piece of cake for the huge tsunami wave. The dirty, gray sludge rises rapidly, sloshes over the roof and takes the hut and Ben List with it. Debris rains down on him. "Paul, who had been in my arms only a second ago, was suddenly gone." Ben List is pushed underwater, briefly surfaces again and is then pulled downward for a long, long time. That's it then ... what a pity ... a little early, is what is going through his mind. "There was no panic, more astonishment." But he comes to the surface again, starts to fight and saves himself by climbing onto a tree. List has a number of cuts and a large wound on his foot. It had been an extremely narrow escape even for him – Paul couldn't possibly have survived it. He asks around: someone had seen his wife, with a child. Thank God, she had obviously saved Theo. When Ben List finally finds them, it is Paul who is with her.

"He was very pale, with injuries to his rib cage. I'm OK, dad, he whispered." >





Top Chemists use thin-layer chromatography to separate the different products formed in reactions. To this end, they add a solvent to the substance mixture on one side of the chromatography plate. When the solution creeps across the plate, the different products deposit at different locations. The violet color makes it easier for the researchers to recognize the individual substances.

Bottom Unlike other reaction accelerators, the amino acid proline also catalyzes chemical reactions of the small acetaldehyde molecule, which is shown here.

Photo: David Ausserhofer; graphic: MPI für Kohlenforschung

» When you survive something like that, your values change. You are alive, healthy, and you have your family. That's all that matters.

A particularly nice prize: Ben List's uncle alluded to the Leibniz Prize the chemist was awarded in 2016 with a framed Leibniz cookie.

But no trace of Theo. A truck brings them and other injured people 150 kilometers inland to a medical center. While Paul is being treated, Ben List traipses nervously through the rooms. At the very back, a small young boy is sitting on a bed – it is Theo. An Englishman had found him and brought him here. He has only a few small bruises.

ORGANIC CATALYSTS ARE STATE OF THE ART

Unbelievable, they had all survived. "The time afterward was pure euphoria. When you survive something like that, your values change," says List. "You are alive, healthy, and you have your family. That's all that matters." As time passed, normality returned. The trauma was gone, but so was the euphoria. "What has remained until this day is my gratitude for everything I have." Six months after the tsunami, Ben List becomes a Max Planck Director.

Lying on his desk today are molecules of catalysts, models from the 3-D printer. Compared with the newest catalysts from List's lab, proline looks like David next to Goliath. "Since relatively large amounts of proline are needed, we searched for more effective molecules." With the most recent candidate, a tree-like branched phosphoric acid ester, one forty-thousandth of the amount of proline needed is already sufficient. And this catalyst accelerates reactions that couldn't be catalyzed at all before!

Organic catalysts have since become state of the art. There is hardly a pharmaceutical or chemical company that doesn't work with them. The technical production of several drugs, including the HIV drug Darunavir®, involves organic catalysts such as proline.

This is almost history as far as Ben List is concerned. Working together with the textile research institute in Krefeld, he has since chemically bonded more advanced catalysts to nylon fabric with the aid of UV light. A heterogeneous catalyst is thus formed from a homogeneous one that, like the reaction partners, for example, is dissolved in a liquid. This has enormous advantages for use in chemical production, because unlike homogeneous catalysts, heterogeneous ones don't have to be separated from the reaction medium. "We put a piece of cloth into the glass beaker, add the liquid reagent and stir. We then decant it, quickly rinse the cloth and can then reuse it." And we can do this at least 400 times, as a very patient doctoral student incidentally discovered.

Materials coated with catalysts aren't only of interest for the production of chemicals. "Conceivable ideas include covers for furniture, curtains or carpets that clean themselves when you put water on them." After all, detergents also contain catalysts to break down dirt – just that these disappear in large amounts in the waste water and pose problems for water treatment plants. "The only question is what the detergent manufacturers will think of our idea," says Ben List, laughing.

LIST IS A CHEERFUL, OPEN PERSON

Now he is thinking about catalytic drugs: monoclonal antibodies armed with a catalyst that bond to cancer cells and convert a non-toxic active substance into a toxic drug only when it actually arrives at the tumor. "Selective organocatalysis is interesting for other areas as well, for instance in the production of fragrances or in pest control."

Unlike his doctoral supervisor, who really belittled those in his seminars who struggled with chemical brainteasers, sometimes in front of everyone (as the author remembers), Ben List is considered to be more of a soft boss. He has found his own form of "postmortem." "I call it the shit sandwich," he says with a smile. "Excellent talk! Well done. The less pleasant (middle) part follows in private: This and that could be better. And that was rubbish! Finally, the encouraging base: But I believe you have talent, and we can do this together!"

List is a cheerful, open person – completely at ease and always attentive. His calm, positive air is conducive

Photo: David Ausserhofer

Relaxed thanks to a borderline experience: After Ben List and his family survived the 2004 tsunami in Thailand, the researcher knows that his career and his award are nice, but he could also live without them.

to a creative working atmosphere. "In my experience, creativity never emanates from concentration and stress. Your thoughts can only flow when you are relaxed." And he has physically created this space for himself as well – by moving the department up to the tenth floor of the Institute. Through a long wall of windows, there is a commanding view of the countryside. On the left, the industrial plants of Duisburg, some of which are already museum pieces; in the middle, a lot of forest around Mülheim and Oberhausen; and on the very right, the outskirts of Essen and in the distance Düsseldorf. When List walks into his office in the morning, he has already done his yoga exercises. He grins. "Standing on your head gives you a different perspective on a lot of things."

A small Buddha figurine stands next to the group of chairs, a present from his wife. It is a symbol of their shared love of Asia – but also a reminder of how fragile life is. Looking back, List sees the borderline experience as something positive, because it made him realize what really counts. His career, all the awards on the wall behind his desk – one of the nicest is a framed Leibniz cookie with best wishes from his uncle – that's fantastic. But life would be possible without all this. Maybe it is this insight that gives Ben List the inner freedom to steadfastly go his own way. After all, what's the worst thing that could happen? ◂

GLOSSARY

Abzyme: The neologism coined from "antibody" and "enzyme" designates an antibody that has a catalytic effect.

Enantiomers always occur in pairs. Chemically, both variants have an almost identical structure but they differ in the spatial arrangement of their molecular parts, like an original and its mirror image, or the right and left hand that can't be made fully congruent. They behave in largely the same way physically and chemically; it is only with other enantiomers that they react differently. Most biomolecules, such as amino acids and sugars, exist only in the form of one enantiomer, which is why enantiomers have different physiological effects.

Organocatalysis describes the selective catalysis with relatively small, purely organic molecules in which a metal isn't part of the active principle. Until their catalytic effect was discovered, conventional wisdom held that only enzymes and metal catalysts were suitable for selective catalysis.