Asymmetric organocatalysis

Nobel Lecture 8 December 2021 by
Benjamin List
Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr,
Germany.

Ladies and gentlemen,

I am deeply honored by this great recognition bestowed upon me, and I would like to thank the Royal Swedish Academy of Sciences as well as the Nobel committee and everybody else who was involved in making this amazing prize a possibility. I would also like to use this opportunity to thank my brilliant and truly awesome coworkers that I have had the pleasure to work with during the last 22 years for their hard work, their dedication and their excellent ideas they brought into this fantastic adventure. And – last but not least – I would like to thank all the other scientists who, during the last two decades, have helped to develop organocatalysis to what it is right now: a vibrant, dynamic, very productive field that has made an essential change to chemical synthesis. Thank you all so very much.

I am deeply fascinated with the science of catalysis. Just think about it: To design a catalyst – by providing a lower energy pathway to convert substrates into the desired product – is as close as chemists can ever come to magic. Providing this lower energy pathway without being used up enables us to use a very small amount of a catalyst to convert large amounts of starting materials into a useful product. This is something I find truly incredible. And there is so much more to it. Catalysis is not only a beautiful concept; it is a very important technology, too. Some would even state that it is the most important technology for humankind on this
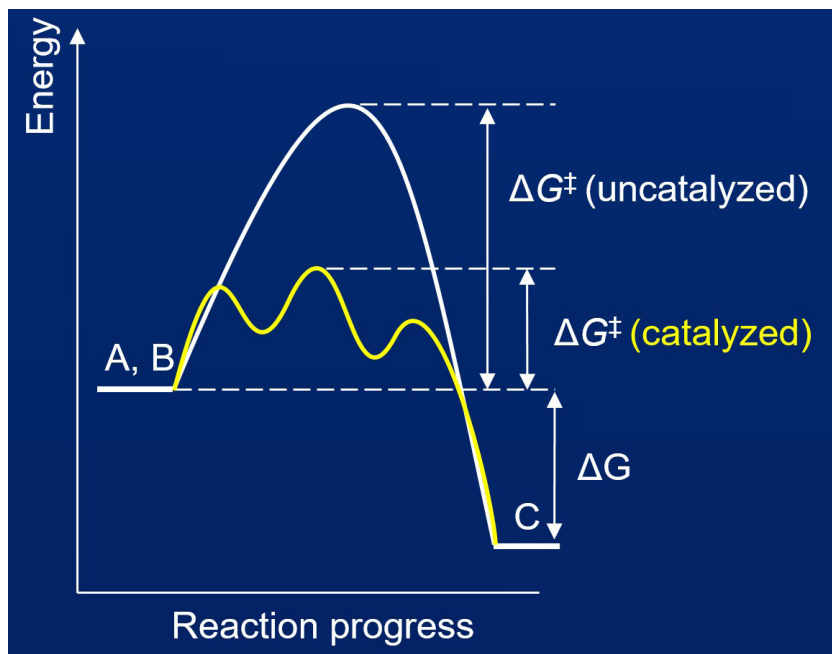
Figure 1. Catalysis.

planet. It is estimated that catalysis contributes to roughly one third of the GDP. These are figures in the trillions. I want to add that there is probably no other technology that can claim to feed, to heal, to warm and to transport humans and their goods. In addition to that, I want to underline that the challenges humanity faces right now – global warming, energy conversion – will be addressed with the help of catalysis. I have no doubt that catalysis will deliver – as it did in the past.

By no means am I the only one fascinated by catalysis. Unsurprisingly, in the history of chemistry, catalysis has always been a very appealing concept to chemists. This is also reflected in the history of Nobel Prizes. The very first catalysis Nobel Prize was given in 1909 to Wilhelm Ostwald. He was recognized for his pioneering studies, the general physical aspects of
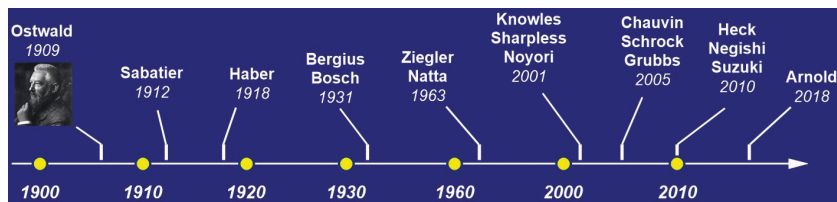

Figure 2. Nobel Prizes to catalysis research..

catalysis. But Ostwald also was more than aware of the fact that enzymes, which were known to be efficient asymmetric catalysts, are by no means different from the synthetic catalysts that chemists have made. There is one interesting vision that Ostwald mentioned in 1905 in a book review, in which he suggested that one day chemists would be able to create organic catalysts. He called them "organische Katalysatoren" and predicted that they would rival the efficiency and selectivity of enzymes while being more stable.

Remarkably, his graduate student Georg Bredig realized this vision as early as 1910 by describing a cinchona alkaloid catalyzed HCN addition to benzaldehyde. This is a reaction that is also catalyzed by enzymes. Bredig found – in a reproducible way – that enantioselectivity was obtained in this process. Curiously, though, chemists at that point had chosen to almost completely devote their attention to transition metal based catalysts. That is also reflected in the history of amazing Nobel Prize recipients. Paul Sabatier, for example, was rewarded the prize in 1912 for discovering that finely dispersed transition metal powders can catalyze hydrogenation reactions.

Along those lines, Fritz Haber and Carl Bosch – two other Nobel laureates – discovered one of the most important chemical reactions for our life on this planet: the Haber Bosch synthesis of ammonia. This reaction describes a heterogeneously catalyzed hydrogenation of nitrogen to produce ammonia. Friedrich Bergius, Nobel Prize laureate in 1931, developed coal hydrogenation processes with the help of heterogeneous catalysts that delivered fuels. At that time, those synthetic fuels were very important, as history has taught us.

A big change then occurred when in 1963 the first Nobel Prize was awarded to research on homogeneous transition metal catalyzed reactions. That starting point happens to have occurred in Mülheim an der Ruhr/Germany, at my institute, the Max-Planck-Institut für Kohlenforschung. Karl Ziegler discovered homogeneous transition metal complexes that catalyze polymerization reactions of ethylene and propylene. Ziegler and his Italian colleague Giulio Natta studied those complexes independently from one another and won the Nobel Prize in 1963. That marked the beginning of homogeneous transition metal catalysis; the next three Nobel Prizes in the series also went to that area.

The one probably most relevant for my presentation today is the Prize for William Knowles, Barry Sharpless and Ryōji Noyori, awarded in 2001 for their pioneering contributions to asymmetric catalysis of redox reactions. Four years later another Nobel Prize was given to a homogeneous transition metal catalyzed reaction – the olefin metathesis – to Yves Chauvin, Robert Grubbs and Richard Schrock. Five years later another Nobel Prize went to the same general area, namely to Richard Heck, Ei-ichi

Nigishi and Akira Suzuki for their pioneering studies on cross coupling methodologies using transition metal catalysts.

One could thus state that the last century was the century of transition metal catalysis. The only exception was actually the recent Nobel Prize for Frances Arnold in 2018 for her ground-breaking contributions to the directed evolution of enzymes, to furnish biological catalysts that can be more efficient or can catalyze reactions that are unknown in nature.

This is the surrounding I found myself in when I was a graduate student in the mid-nineties. Chemists were essentially convinced that when it comes to asymmetric catalysis, the selective production of mirror image molecules, there are only two options available. You can either use enzymes – and this was, as I said, already known to Ostwald in 1905 or even before that – or you can use synthetic soluble transition metal complexes as reflected in the Nobel Prize of 2001.

This was the widespread mindset. At that time, I was considering what to do during my postdoc and I became fascinated with the idea of creating artificial biocatalysts. Chemists were discussing biocatalysts that would engage in the catalysis of non-natural reactions. One approach appeared to be particularly attractive to me: catalytic antibodies. I was very fortunate to be able to move to The Scripps Research Institute (now Scripps Research) in California and to work with Richard Lerner and Carlos Barbas on the utilization of aldolase catalytic antibodies. They had just discovered an antibody that would catalyze aldol reactions with both high efficiency and very high selectivity. I was excited to work in this field and I used this antibody to do large-scale experiments. I also used this antibody in the synthesis of natural products.

However, I was mainly interested in understanding how this antibody does its catalysis. Fortunately, a crystal structure of the molecule was available. This structure revealed that in the active site of the antibody you find an amino group derived of a lysine residue on the one side. In addition, on the other side you find a water molecule that bridges this amino group to a tyrosine hydroxyl group.

For me, this immediately suggested that the mechanism had to be bi-functional. The amino group, assisted by the acid, engages in the formation of an iminium ion from a ketone precursor. This iminium ion formation is quite important. It not only lowers the LUMO energy of the ϖ-system but also drastically increases the alpha C-H-bond acidity. This idea had already been suggested by William Jencks in the sixties, in the context of work on class I aldolases.

The conjugate base of the acid cocatalyst is able to abstract the proton to generate an enamine intermediate. This is a strategy evolved by nature to enable carbanion equivalent formation under physiological conditions in water without the availability of stoichiometric organometallic bases. The

enamine can then engage in a direct C-C-bond-formation with an aldehyde, again assisted by the Brønsted acid cocatalyst, which protonates the nascent oxyanion in the transition state to generate the iminium ion of the aldol product. Then hydrolysis occurs, once again assisted by the conjugate base of this acid cocatalyst, to generate the aldol product and to regenerate the bi-functional antibody.

Those were my thoughts that encouraged me to reflect again along the lines of Ostwald. This was much later, in January 1999, when I had become an assistant professor, thinking about my independent work. Why is it not possible, I asked myself, to design simple organic molecules that have all the machinery that is needed to catalyze such an aldol reaction? I realized that all that was necessary was an amino group and an acid.

I thus started to design potential small molecules catalysts when I remembered that there already is such a catalyst. In fact, there is an amino acid that catalyzes aldol reactions: Proline, as it was shown in the famous Hajos-Parrish-Eder-Sauer-Wiechert-reaction. I knew that reaction very well since my undergraduate studies in Berlin. In this reaction, proline catalyzes an intramolecular aldol reaction to give bicyclic ketones, which were considered as intermediates for the development of industrial routes to steroids. This, however, never became a reality, and until today, steroids are largely made from natural materials. This reaction was an important
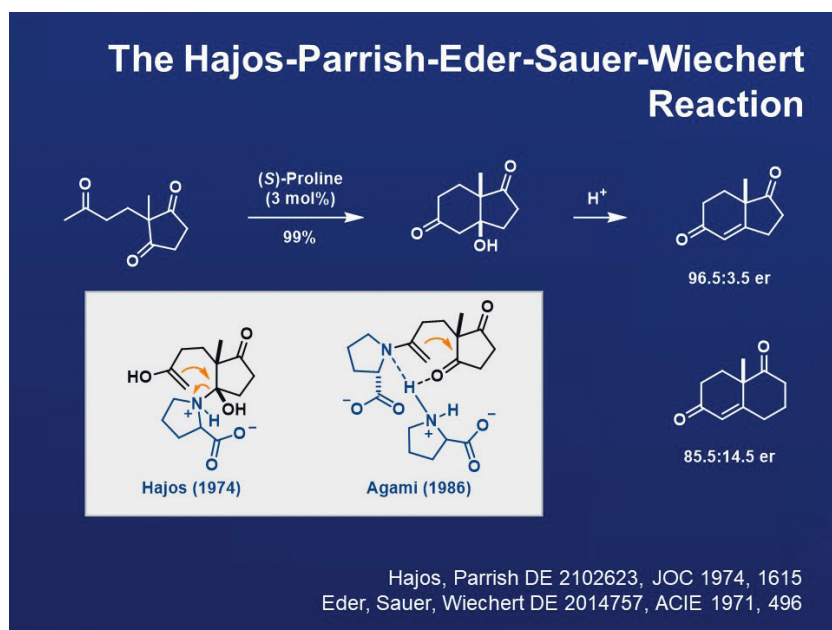

Figure 3. The Hajos-Parrish-Eder-Sauer-Wiechert Reaction.

though somewhat underappreciated discovery. Also, researchers were at that time somewhat confused about its mechanism. In 1999, I realized what was probably happening: Proline is just the essence of an aldolase enzyme. It has all that is needed: an amino group, actually a privileged pyrrolidine-based amino group for iminium ion and enamine formation, and it has a carboxylic acid that can act as the Brønsted-acid cocatalyst.

That was the hypothesis that I developed as a fresh assistant professor at The Scripps Research Institute. I proposed that proline would function like a micro-aldolase, as I called it, by converting first the ketone, assisted by the Brønsted acid, into the corresponding iminium ion. In the next step, the carboxylate would deprotonate this iminium ion to form the corresponding enamine. The enamine, in turn, would then be able to react with an aldehyde to form the carbon-carbon bond, while the proton of the freshly generated carboxylic acid would be transferred onto the nascent oxyanion of the aldehyde. In a last step, the iminium ion would be hydrolyzed to form the aldol product, regenerating the Proline catalyst.

Funnily enough, this was one of only a few designed catalytic cycles that actually worked when I did the experiment. I was obviously very excited when I discovered that proline catalyzes intermolecular aldol reactions of ketones with aldehydes to produce very valuable aldol products in excellent
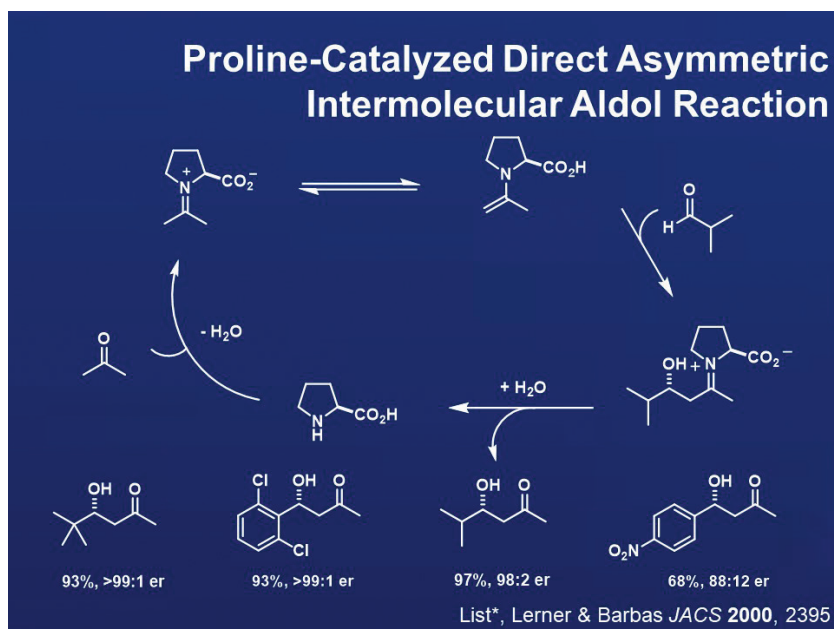

Figure 4. Proline-Catalyzed Direct Asymmetric Intermolecular Aldol Reaction.

yields and state of the art enantioselectivity. I would like to mention in this context that the so-called "direct asymmetric aldol reaction" was at that time considered one of the biggest challenges of asymmetric catalysis. There had been only one solution to this problem and that was a transition metal-based catalyst developed in the group of Masakatsu Shibasaki in Tokyo.

All of a sudden, it turned out that there existed an edible, non-toxic, readily available catalyst that provides the same kind of reactivity with state-of-the-art selectivity. This was a big breakthrough for me, and we were really happy to see that the reaction was not limited to one aldehyde. In fact, we could convert several other aldehydes as well to yield the desired aldol products, in some cases with enormous enantioselectivity. Actually, we have just submitted a manuscript to Organic Synthesis that will hopefully enable all undergraduate students in the world to do these experiments on a multi-gram scale.

Already during those studies, I realized there is probably more to this kind of chemistry. Proline is not just a micro-aldolase. Proline is a catalyst that can convert carbonyl compounds catalytically, without requiring a stoichiometric reagent or an auxiliary, into the corresponding enamine. This led to what since then has been called a "generic activation mode" of organocatalysis. Proline features this generic activation mode that we call "enamine catalysis". It converts carbonyl compounds into the corresponding enamine, which should not only be able to react with aldehydes in aldol reactions, but in principle be capable of reacting with any type of electrophile, including imines, Michael-acceptors, alkyl halides, oxygen electrophiles such as nitrosobenzene and nitrogen-electrophiles, for example dialkyl azodicarboxylates.

This hypothesis became our research program for the following years, and our slowly growing group could indeed show that enamine catalysis is a solid and broad concept. We discovered a number of different reactions. In those early days, we initiated a fruitful collaboration with Professor Ken Houk at UCLA. He provided theoretical computations on the mechanism of our reaction while we did kinetic work.

This collaboration led to what is now called the Houk-List transition state. This model has a powerful predictive character, and the stereochemical outcome of most of the reactions I will be discussing with you in this lecture could have or has been predicted based on this transition state. For example: the stereochemistry of our proline-catalyzed aldol reaction is well explained by the Houk-List transition state, and so is that of other intramolecular aldol reactions we discovered: the enolexo aldolization of dialdehydes to produce cyclic aldols and also the first catalytic asymmetric transannular aldolizations to yield natural product precursors.

In addition to carbonyl compounds, you can use other electrophiles. We were, for example, excited to find the first catalytic asymmetric alpha alkylation of a aldehydes. This involved a new type of reactivity – not an addition but a substitution reaction, and also yielded cyclic products. As early as 2000, we showed that the first catalytic three-component Mannich reactions of a ketone, an aldehyde, and an amine can be catalyzed with proline. We made β-amino ketones and later a number of other products on the basis of this very general reaction, including acetalydehyde-based Mannich products in good yields and enantioselectivities. Last but not least, I would like to highlight one proline-catalyzed reaction in which not a C-C but a C-N bond is generated in the formation of these alpha-hydrazido aldehydes, which are amino acid precursors.

At this point, I want to emphasize that little by little, this research became a field. Many groups have started to engage in enamine catalysis, developing many novel reactions. This is just a small fraction of all the beautiful transformations that were discovered during those days. Some people called them "the Gold Rush in Organocatalysis".

I would like to highlight one additional reaction that is timely; a proline catalyzed intermolecular aldol reaction of two different aldehydes. The development of this process goes back to work done in my laboratory. The group of my co-laureate David MacMillan later advanced it, and a group at DSM in the Netherlands found that this cross aldolization of two different aldehydes gives an aldol product that can be readily converted into Darunavir, an anti-viral used for the treatment of HIV infections. HIV has probably created one of the worst pandemics of all time. It is rewarding to see that organocatalysis has contributed to making this a treatable disease, and consequently, you do not hear that much about this pandemic anymore.

However, enamine catalysis is not the whole story: It is just one example of an organocatalytic generic activation mode. Many other such activation modes have been developed in the meantime, for example iminium ion catalysis, Professor MacMillan's main area of research in the early days of organocatalysis, which he used in conjugate additions and cycloadditions.

But there are other, powerful activation modes, such as "anion binding catalysis", where H-bonding catalysts bind to anions, generating supramolecular chial anions that can engage in nucleophile additions with high enantioselectivity, a very fruitful concept that has led to numerous important publications. Similarly, "acyl ammonium ion catalysis" is yet another generic activation mode, mostly used in acyl transfer reactions. Or "carbene catalysis", an unusual mode or reactivity that has massively been advanced during the last twenty years, where aldehydes are "umpoled", from normally being an electrophile to a nucleophile.

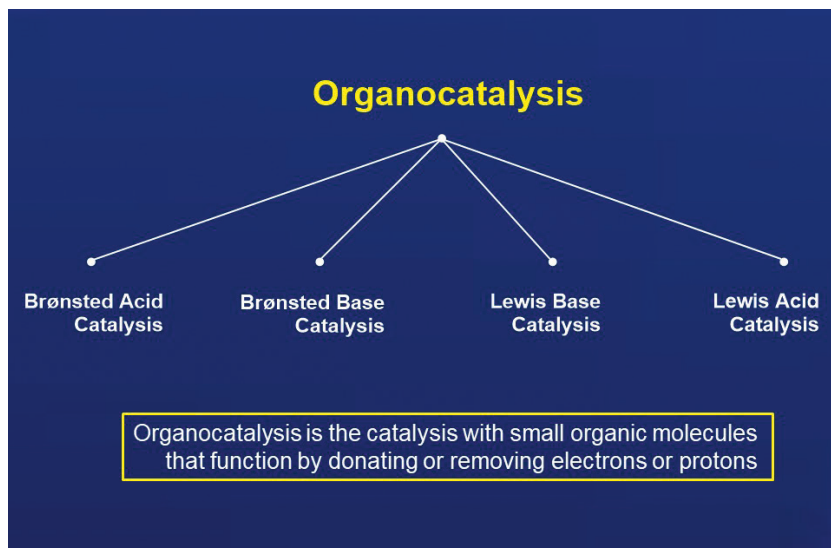The last generic activation mode I would like to mention is, because of

Figure 5. Organocatalysis.

the high importance it has gained recently, Brønsted acid catalysis. This is just a small collection of new generic activation modes that came out of the organocatalysis concept, there are many, many more. And these activation modes in turn have led to numerous different transformations, some of which have been applied on a technical scale in the synthesis of pharmaceuticals and scent molecules, for example.

As the field has grown that much it is helpful to organize organocatalysis. I found a useful way in doing so that goes along with the following definition: Organocatalysis is the catalysis with small molecules, where a metal is not part of the activation principle, and that functions by donating or removing protons or electrons. This definition automatically creates four sub-areas of organocatalysis: Brønsted acid catalysis, Brønsted base catalysis, Lewis base catalysis, and Lewis acid catalysis. These catalysts either donate or remove protons or donate or remove electrons.

Thus, some organization is being brought to the field of organocatalysis, but gaps in the field are also being revealed. My laboratory, for example, became particularly interested in one of those gaps, the utilization of Lewis acid organocatalysts. We are fascinated by the power and potential of acid catalysis because of its universality. After all: All that acids need for catalysis is electron density, which is essentially what chemistry is all about. We realized that possibly the vast majority of all catalyzable reactions can be catalyzed by acids.
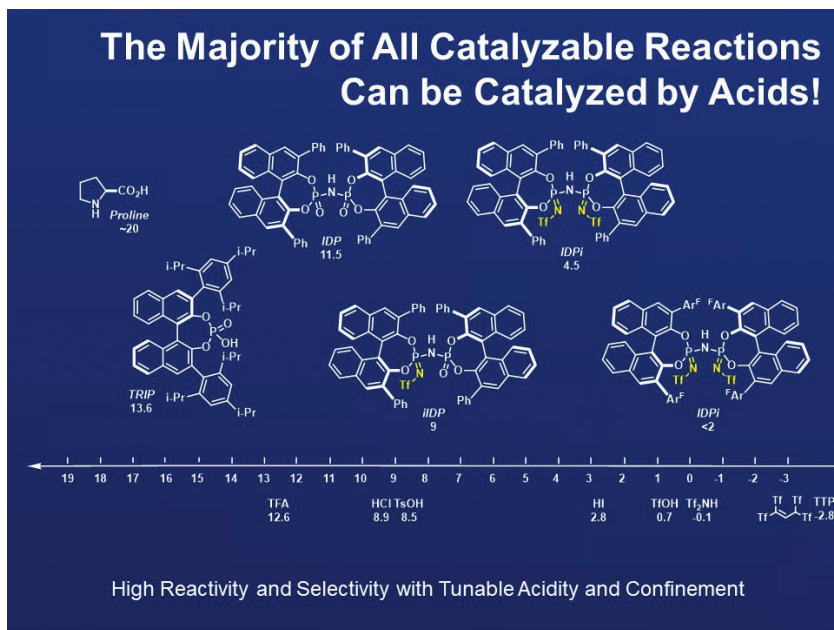
Figure 6. The majority of all catalyzable reactions can be catalyzed by acids.

Over the years we have advanced our little proline molecule (also a Brønsted acid!) to much more acidic and sophisticated acids, which have reached extreme pKa's (in acetonitrile) of <2! That means these acids approach the acidities of super acids such as triflimide. But in addition to their acidity, they have a unique feature that we call confinement. Around the acid functionality a confined pocket evolves, with this catalyst design, simulating somehow how enzymes catalyze their reactions. With this combination of high acidity and confinement, a number of highly challenging transformations have been realized. I would like to highlight six of them to you. The first is a Mukaiyama aldol reaction of the acetaldehyde derived enolsilane with another aldehyde to yield the aldol product in excellent yield and selectivity. While this transformation looks rather simple, it is an amazing reaction that normally would just lead to a polymerization, since both starting material and product have an identical functional group, an α-unbranched aliphatic aldehyde. The magic of the confined acids enables single aldolizations, because the product is simply not a substrate anymore.

Secondly, we can catalyze Mukaiyama aldol reaction of silyl ketene acetals with ketones, with parts-per-million catalyst loadings and we even describe one example with < 1ppm catalyst loading, which I think is the lowest catalyst loading in any C-C-bond forming reaction. There might be enzymes that are as good as this, but I am not aware of them. Third, we can catalyzed Diels-Alder reactions with challenging rather unreactive dienes

with poorly reactive dienophiles with excellent selectivity. Fourth, hetero-Diels-Alder reactions of all-types of dienes with all-types of doienophiles have been realized to yield useful products. Such a transformation had previously been unprecedented even with achiral catalysts. With this high reactivity, we have also been able to activate olefins, which previously has largely been the domain of transition metal catalysis. But now organocatalysts can also activate simple olefins, to first form a carbocation, which can then engage in nucleophilic addition reactions.

Last but not least, I would like to share one recent discovery of my group: we found that string and confined IDPi catalysts can mediate the addition of TMSCN to 2-butanone. It might look simple, but it turns out that this technically useful product in the synthesis of at least two pharmaceuticals can be accessed by all different types of catalyst classes, including transition metal catalysts, organocatalysts, and even engineered enzymes. And yet none of these previously developed catalysts provided the product with >95:5 e.r. A milestone in the history of organocatalysis. We are very excited about our latest findings.

Ostwald's idea finally came true. We are now able to design organic molecules that enable enzyme-like selectivity and reactivity. I think we have just opened a door. I expect an exciting and great future for asymmetric organocatalysis, and I am very happy to be part of this.

Figure 7. Colleagues and coworkers in Mülheim, October 6th 2021.

I would finally like to thank the funding agencies that have supported us, The most important among many is, of course, the Max Planck Society, which has given me the freedom and privilege to pursue an idea to the depth that I wanted to. This has been a great honor, and I am more than happy to be part of this awesome scientific society. I also want to thank my colleagues and coworkers in Mülheim. When we celebrated on October 6th it was a delight to see the joy in the eyes of everybody at our Max Planck Institut für Kohlenforschung. Glass blowers, wood workers, steel workers, scientific colleagues, cleaning personnel and administration: It was an institution in an excited state. This shared joy made me even more grateful.

And last but not least I would like to acknowledge the most important people in my life: *Meine geliebte Familie, vielen Dank ihr Lieben. Meine süßen Jungs und meine Frau, ich danke euch, dass ihr in all den Jahren an meiner Seite gestanden habt und dass ihr Katalyse-Fans geworden seid. Tausend Dank!*