The advent and development of organocatalysis

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The use of small organic molecules as catalysts has been known for more than a century. But only in the past decade has organocatalysis become a thriving area of general concepts and widely applicable asymmetric reactions. Here I present my opinion on why the field of organocatalysis has blossomed so dramatically over the past decade.

Organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was 'born', coalescing around a small number of articles that inspired an explosion of research[1]. Between 1998 and 2008, at least 1,500 manuscripts describing the use of organocatalysts in more than 130 discrete reaction types were published (Fig. 1), a remarkable number given that there were no reports of such catalysts in the year 1995. It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis; see page 314), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox (see page 323).

In this Commentary, I present my opinion on how chemists arrived at this point. It is useful to look back and consider this development, not least because it provides insight into how scientific communities can seemingly bypass an important area of research for many decades and then, at a given moment, embrace the same field with collective (and at times fervent) enthusiasm. I consider that three factors were crucial to the sudden birth and rapid growth of the field of organocatalysis: first, the conceptualization of the field; second, the advantages of organocatalytic research; and, third, the advent of generic modes of catalyst activation, induction and reactivity.

Conceptualization of the field of organocatalysis

New synthetic methods are most likely to be encountered in the fields of biological and organometallic chemistry.

Dieter Seebach (1990)[2]

Why was organocatalysis so long overlooked as an area of research by the chemical synthesis community? This question is difficult to answer in hindsight, given the now obvious nature of the concepts and catalysts involved. However, one perspective worth considering is that it is impossible to overlook a field that does not yet exist. This might seem cryptic, but it is similar to the idea that researchers cannot work on a problem that has not been identified. Between 1968 and 1997, there were only a few reports of the use of small organic molecules as catalysts for asymmetric reactions (the Hajos–Parrish reaction probably being the most famous), but these chemical studies were viewed more as unique chemical reactions than as integral parts of a larger, interconnected field[3–5]. In these early publications, there was no emphasis on the potential benefits of using organocatalysts or on the demonstration of

new organocatalytic concepts. Instead, these articles focused only on the individual transformations that had been accomplished. Because general lessons were not extrapolated from these reactions, the underlying catalytic concepts were not applied to multiple reaction types. As a result, chemists did not recognize that the use of small organocatalysts could be an overarching concept. One measure of this fact is that between 1960 and 1998, there were no review articles about the use of organocatalysts. In addition, Dieter Seebach, an organic chemist of great standing, omitted organocatalysis from his vision for synthetic methods in 1990, clearly illustrating that it is not easy to predict the success of a field that, at the time, does not exist.

In the late 1990s, however, things began to change when Yian Shi[6], Scott Denmark[7] and Dan Yang[8], and their co-workers, demonstrated that enantiomerically pure ketones could be used to catalyse the enantioselective epoxidation of simple alkenes. Shortly afterwards, Eric Jacobsen[9] and Elias J. Corey[10], and their co-workers, described the first examples of hydrogen-bonding catalysis, in an asymmetric Strecker reaction, and Scott Miller and his co-workers[11] introduced the concept of minimal peptides for the enantioselective kinetic resolution of alcohols. Although, collectively, this work did not conceptualize organocatalysis as a field of research, it demonstrated for the first time that small organocatalysts could be used to solve important problems in chemical synthesis. It was not until 2000, however, that the field of organocatalysis was effectively launched, by two publications that appeared almost simultaneously: one from Carlos Barbas, Richard Lerner and Benjamin List[12], on enamine catalysis; and the other from my research group[13], on iminium catalysis.

The work of Barbas, Lerner and List was significant because it showed that the underlying mechanism of the Hajos–Parrish reaction could be extended and applied to transformations that have a broader applicability (specifically, the intermolecular aldol reaction). Moreover, this work showed that small organic molecules (such as proline) could catalyse the same chemical reactions as much larger organic molecules (enzymes) by using similar mechanisms. Meanwhile, the report of iminium catalysis conceptualized 'organocatalysis' in three important ways: by delineating how organocatalysts could provide economic, environmental and scientific benefits; by describing a general activation strategy for organocatalysis that could be applied to a broad range of reaction classes (rather than simply allowing a single transformation); and by introducing the term organocatalysis to the chemical literature. You might ask, What's in a name? But consider the success of the terms nanotechnology and diversity-oriented synthesis at globally shifting the visibility and perception of areas of research. The term organocatalysis provided a strong identity and helped to unify a fledgling field, as well as attracting the attention of the broader chemical synthesis community. At the last count, the word organocatalysis, or one of its derivatives, has been used
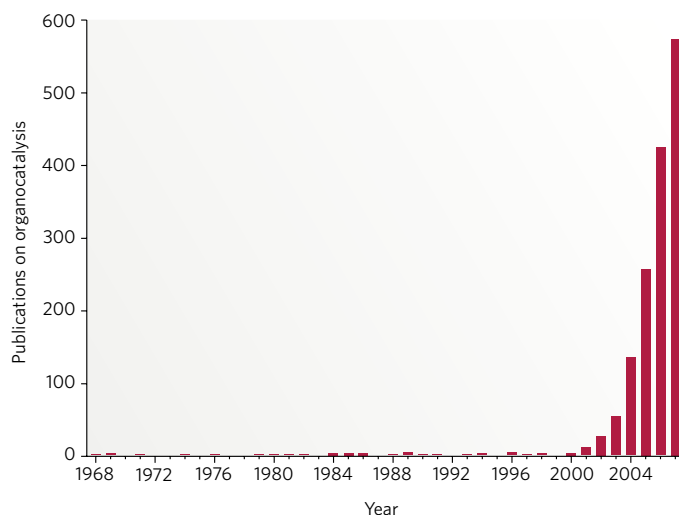
Figure 1 | **An explosion of interest.** The number of publications on the topic of organocatalysis has recently increased markedly. Data were obtained by a search of the ISI Web of Knowledge in May 2008 for the keyword organocatalysis and its derivatives, as well as the keywords phase transfer, enamine and Hajos (to locate articles on this topic before the term organocatalysis was coined). This search is unlikely to have found all publications on organocatalysis, and a conservative estimate is that more than 2,000 manuscripts have been published on this topic so far.

in more than 600 article titles and is the subject of more than 40,000 web pages (based on a survey of the ISI Web of Knowledge and of web pages indexed by Google in May 2008).

Advantages of organocatalytic research

Once the field of organocatalysis had been publicly defined, it grew quickly. Such rapid adoption is possible only when a field offers real advantages to the researchers who mine the area and to those who exploit the resultant technologies. In this case, the chemical synthesis community quickly recognized the fundamental advantages of organocatalysis, namely the ease and low cost of carrying out such reactions in the laboratory and the potential for new lines of academic thought and investigation. Before 1998, the state of the art in asymmetric catalysis involved metal-based chiral catalysts almost exclusively, and these catalysts allowed a wealth of oxidations, reductions, σ-bond insertions, π-bond activations and Lewis-acid-catalysed reactions. Although the impact of metal-based catalysts on chemical synthesis cannot be understated, some (but certainly not all) organometallic systems can be expensive, toxic and/or sensitive to air and moisture.

The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste (Fig. 2). These benefits arise from three factors. First, organic molecules are generally insensitive to oxygen and moisture in the atmosphere, so there is no need for special reaction vessels, storage containers and experimental techniques, or for ultra-dry reagents and solvents. Second, a wide variety of organic reagents — such as amino acids, carbohydrates and hydroxy acids — are naturally available from biological sources as single enantiomers. Simple organocatalysts are therefore usually cheap to prepare and readily accessible in a range of quantities, suitable for small-scale reactions to industrial-scale reactions. Third, small organic molecules are typically non-toxic and environmentally friendly, increasing the safety of catalysis in both biological research and chemical research across all research settings, including industry and academic institutions.

The combination of these factors substantially lowered the entry costs for researchers who were interested in developing enantioselective catalysts. With no need for gloveboxes, inert gases, ultra-dry solvents or even high levels of experimental expertise, it is not surprising that the field quickly became flooded with research groups from around the globe.

Indeed, the increase in competition helped to accelerate the pace of innovation and discovery, albeit perhaps at the expense of 'elbow room' for those in this popular field.

Some critics suggest that low turnover numbers might limit the potential uses of organocatalysis for industrial applications, but this view is simplistic and dogmatic. For any large-scale catalytic process, the most salient considerations are cost and safety. Because organocatalysts are often cheaper than metal-based catalysts, organocatalysts can be used in larger quantities than metal-based ones for the same price. Moreover, it is widely recognized in manufacturing that the removal of toxic catalyst-related impurities from the waste stream can often have a larger financial impact than the turnover number of the catalyst. Organocatalysts are typically less toxic than metal-based catalysts, can be tolerated to a large extent in waste streams and are more easily removed from waste streams, again mitigating the cost of high catalyst loadings.

With respect to industrial applications, organocatalytic reactions are of great use to medicinal chemists. These researchers are the largest body of industrial synthetic chemists in the world, and their technological needs often differ from those of chemists in manufacturing or process development. Medicinal chemists need to find rapid, broadly applicable ways of constructing new candidate drugs for testing, so the most important considerations for a catalyst are its generality, convenience and robustness. Organocatalysts meet all of these operational requirements. Indeed, organocatalysts have already been taken up by some medicinal chemists in pursuit of therapeutic agents enriched for a particular enantiomer[14].

Advent of generic modes of activation and induction

Perhaps most crucial to the success of organocatalysis in the past decade has been the invention or identification of generic modes of catalyst activation, induction and reactivity. A generic activation mode describes a reactive species that can participate in many reaction types with consistently high enantioselectivity (as opposed to one or two unique transformations). Such reactive species arise from the interaction of a single chiral catalyst with a basic functional group (such as a ketone, aldehyde, alkene or imine) in a highly organized and predictable manner.

The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for designing new enantioselective reactions. Indeed, most of the 130 organocatalytic reactions that have been reported since 1998 are founded directly on only five or six activation modes. The small number of activation modes in organocatalysis (and in catalysis in general) is not surprising — when devising a new enantioselective reaction, it is far easier to make use of a known activation mode than to invent a new one (together with a new catalyst). Hence, the number of enantioselective catalytic reactions will always be much larger than the number of activation modes that underpin them.
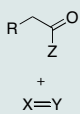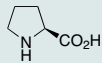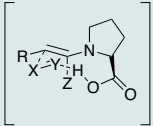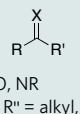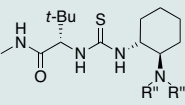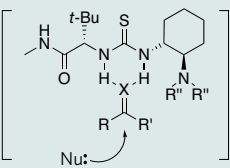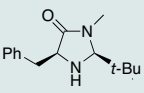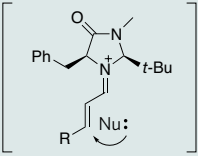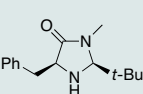
In many ways, this is beneficial to chemists, because it leads to the development of catalysts or catalyst families that are useful for a wide range of asymmetric reactions. At the same time, it is clear that discovering new activation modes is important for all types of catalysis. In the field of organocatalysis, iminium catalysis, reported in 2000, was the first
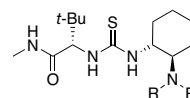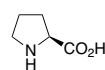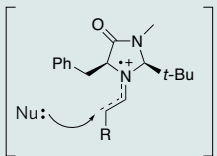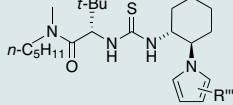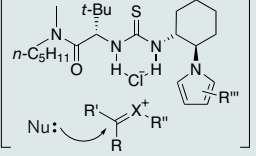

- Stable in air and water
- Available from biological materials
- Inexpensive and easy to prepare
- Simple to use
- Both enantioseries available
- Non-toxic

Figure 2 | **Typical organocatalysts and the advantages of using organocatalysts.** L-Proline (top) is often used as an organocatalyst for many reactions, notably for functionalizing carbonyl-containing molecules at the α-carbon. The mechanism involves the formation of a reactive enamine intermediate. Thioureas (bottom) catalyse several reactions by forming hydrogen bonds with the substrate. The typical advantages of using organocatalysts are listed. R, alkyl; t-Bu, tert-butyl.

Table 1 | Generic modes of activation commonly used in organocatalysis

Substrate	Catalyst	Activation mode	Number of new reactions	Examples of new reaction variants	References
Enamine catalysis					
R = any organic chain or ring system; X = C, N, O, S; Y = generic organic atom; Z = alkyl, H		HOMO activation	25	• Aldehyde–aldehyde cross aldol coupling • Intramolecular α-alkylation • Mannich reaction • Michael reaction • α-Amination • α-Oxygenation • α-Halogenation • α-Sulphenylation	First application: 1971, ref. 3. First use as a generic mode of activation: 2000, ref. 13
Hydrogen-bonding catalysis					
X = O, NR; R, R', R" = alkyl, aryl		LUMO activation	30	• Strecker reaction • Mannich reaction • Ketone cyanosilylation • Biginelli reaction • Pictet–Spengler reaction • Reductive amination	First application: 1996–1999, refs 9–11. First use as a generic mode of activation: 2002, ref. 17
Iminium catalysis					
R = alkyl, aryl		LUMO activation	50	• Conjugate Friedel–Crafts reaction • Ketone Diels–Alder reaction • exo-Selective Diels–Alder reaction • Mukaiyama–Michael reaction • Conjugate hydride reduction • Conjugate amination • Conjugate oxygenation • Conjugate sulphenylation • Cyclopropanation • Epoxidation, aziridination	First application and first use as a generic mode of activation: 2000, ref. 14
SOMO catalysis					
R = alkyl, aryl		SOMO activation	4	• α-Allylation • α-Enolation • α-Vinylation • α-Heteroarylation	First application and first use as a generic mode of activation: 2007, ref. 25
Counterion catalysis					
X= O, NR; R, R', R", R''' = alkyl, aryl		LUMO activation	2	• Acyl-Pictet–Spengler reaction • Oxocarbenium addition reaction	First application and first use as a generic mode of activation: 2007, ref. 28

In HOMO activation, the energy of the highest-occupied molecular orbital (HOMO) is increased. In LUMO activation, the energy of the lowest-unoccupied molecular orbital (LUMO) is decreased. In SOMO activation, an electron is located in a singly occupied molecular orbital (SOMO) to generate a highly reactive species that can participate in many reaction types. Nu, nucleophile; Ph, phenyl.

activation mode identified as being suitable for more than one reaction type, a feature that was central to its design[13]. Enamine catalysis was also demonstrated to be a generic activation mode by its application to the Mannich reaction in 2000 (ref. 15), and Jacobsen and Anna Wenzel were the first to demonstrate that hydrogen-bonding catalysis had multiple-reaction utility, in 2002 (ref. 16). The activation modes discussed in this section and described in Table 1 are representative of modes that have been invented or identified in the past decade.

Enamine catalysis

In 1971, there were two independent reports — one by Zoltan Hajos and David Parrish[3], and another by Rudolf Weichert, Gerhard Sauer and Ulrich Eder[4] — of an enantioselective intramolecular aldol reaction that was catalysed by proline in the synthesis of the Wieland–Miescher ketone. This extraordinary result was well received by the community, but the underlying activation mode was not exploited for other reactions until more than 30 years later. It was in 2000, with the ingenious work of

Barbas, Lerner and List — who used enamine catalysis to functionalize carbonyl-containing compounds at the α-carbon — that the broad applicability of this mode of activation became evident[12]. Since then, a tremendous amount of research has been directed towards identifying new types of chiral enamine catalysts.

Mechanistically, enamine catalysis might be better described as bifunctional catalysis because the amine-containing catalyst (proline in Table 1) typically interacts with a ketone substrate to form an enamine intermediate but simultaneously engages with an electrophilic reaction partner through either hydrogen bonding or electrostatic attraction. This mode of activation has now been used in a wide range of enantioselective carbonyl α-functionalization processes[17].

Hydrogen-bonding catalysis

In the early 1980s, researchers uncovered several catalytic asymmetric processes that suggested that the activation of a substrate and the organization of the transition state could occur through well-defined hydrogen-bonding interactions[18–20]. These reports were widely appreciated; however, they were considered to be exceptions to the generally held idea that hydrogen bonding was insufficiently activating or directional for use in asymmetric catalysis. This reasoning was disproved by reports published in 1998 and 1999, when Jacobsen[9] and Corey[10] independently reported an asymmetric variant of the Strecker reaction that used well-defined hydrogen-bonding organocatalysts that activate imine electrophiles. Moreover, four years later, Jacobsen showed that these thiourea catalysts could be used for other synthetic reactions[16], launching the generic use of enantioselective hydrogen-bonding catalysis. This powerful activation mode has become the foundation of a large and dynamic area of research. More than 30 new asymmetric reactions have been developed on the basis of this principle[21].

Iminium catalysis

Iminium catalysis was the first organocatalytic activation mode to be designed (rather than discovered) and introduced as a general strategy for asymmetric organic synthesis. It is based on the capacity of chiral amines to function as enantioselective catalysts for several transformations that traditionally use Lewis acid catalysts. The concept was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α,β-unsaturated aldehydes and chiral amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis (that is, lowest-unoccupied molecular orbital (LUMO)-lowering activation). With its tailor-made family of imidazolidinone catalysts, iminium catalysis is now used in more than 50 highly enantioselective protocols[22], many of which have been developed by my research group and that of Karl Anker Jørgensen.

SOMO catalysis

Introduced by my research group in 2006, SOMO catalysis is based on the idea that one-electron oxidation of an electron-rich enamine selectively generates a reactive radical cation with three π-electrons. The electrophilicity of the singly occupied molecular orbital (SOMO) of this intermediate allows it to react readily with a variety of weakly nucleophilic carbon-based 'SOMOphiles' at the α-carbon of the parent enamine, resulting in formal alkylation products[23]. Applying this principle in a catalytic system that uses chiral secondary amines and a suitable one-electron oxidant has been highly successful, opening up new avenues for catalysing the asymmetric α-functionalization of carbonyl-containing compounds. Although SOMO catalysis is one of the most recently discovered activation modes, it has already yielded a series of enantioselective transformations that complement those produced by enamine catalysis[24–26].

Counterion catalysis

Jacobsen recently developed a conceptually novel form of organocatalytic activation that directs highly enantioselective additions into transiently generated N-acyl-iminium ions and oxocarbenium ions[27,28]. In this system, chiral thiourea catalysts, which are known to form strong complexes with halide ions, electrostatically bind to, and ionize, the weak

carbon–chlorine bonds of chloroamides and chloroacetals to generate a transient ion pair. The resultant anionic catalyst–chloride complex functions as a chiral counterion, biasing the approach of nucleophiles to a single face of one enantiomer of the transient α-heteroatom-stabilized cationic species. The initial results are remarkable in that forces acting through space, rather than through bonds, are sufficient to transfer stereochemical information from the catalyst to the substrate with high fidelity. Although this mode of activation is still in its infancy, it has the potential to solve many persistent and outstanding problems in asymmetric catalysis.

The future

It is always a risk to predict what the future holds for any field, but several aspects of organocatalysis will undoubtedly attract researchers' attention. Tremendous efforts will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. In addition, although SOMO catalysis and counterion catalysis have been developed only recently, it is clear that at least ten new asymmetric transformations will arise from these modes of activation. Moreover, given the substantial impact of new generic modes of activation, it is probable that many young and ambitious chemists will focus their research efforts on attaining this ideal. More specific challenges that are likely to be addressed include the organocatalytic activation of carbon–hydrogen bonds and the catalysis of photoredox reactions. There will also probably be further advances in the area of organocatalytic cascade reactions, in which activation modes are combined to provide powerful transformations that generate complex molecules[29,30]. Although cascade catalysis is rarely used at present, it is likely to become more prevalent for the synthesis of natural products and medicinal agents. Furthermore, it is probable that computational models will increasingly be used to aid in not only the understanding of organocatalytic processes but also the design of new organocatalysts (see page 309).

But perhaps the most crucial area of research in the future will be the identification of important transformations and new reactivities that are not available using other branches of catalysis. Given the huge growth and impact of organocatalysis in the past decade, it will certainly be exciting to observe the development of the field over the next decade. ■

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