The 2021 Nobel Prize in Chemistry: asymmetric catalysis with small organic molecules

6 October 2021 brought exciting news to the synthetic organic chemistry community across the globe: The 2021 Nobel Prize in Chemistry was awarded jointly to Benjamin List, Max-Planck Institut für Kohlenforschung, Mülheim an der Ruhr, Germany, and David William Cross MacMillan, Princeton University, New Jersey, USA 'for the development of asymmetric organocatalysis'[1]. It was an even happier day for the practitioners of asymmetric catalysis as their field got recognition at the highest level once again after 20 years. In 2001, the Nobel Prize in Chemistry was awarded to K. Barry Sharpless, William S. Knowles and Ryoji Noyori for their ground-breaking works on the transition metal-catalysed asymmetric oxidation and hydrogenation reactions. The vast field of catalysis has never been an alien in the arena of the Royal Swedish Academy of Sciences. This is the fourth Nobel Prize in Chemistry of this century for catalysis. The other two were awarded in 2005 and 2010.

What is asymmetric catalysis and why is this year's Nobel Prize different from the 2001 Prize?

Certain organic (and also inorganic) compounds exhibit geometric properties similar to our hands, i.e. they exist as a pair of non-superimposable mirror images (Scheme 1). In chemical terminology, this class of compounds is called chiral, and such a pair of isomers is known as enantiomers. While synthesizing chiral compounds in the absence of any external influence, there is an equal probability for forming each of these two enantiomers, which therefore results in an equimolar mixture (known as a racemic mixture). However, for most practical applications, be it in the pharmaceutical, agrochemical or perfume industry, it is essential to synthesize these compounds in enantiomerically pure form. This is because only one enantiomer often possesses the desired property while the other does nothing or can even be harmful, especially for drugs[2]. Asymmetric catalysis is a method of synthesizing enantiomerically pure compounds in a catalytic fashion. With over a billion years of evolution, nature has perfected this art and produces chiral compounds in enantiomerically pure form routinely using its enzymatic machinery. This mastery of nature has, therefore, remained the primary source of inspiration for chemists.

For a long time, asymmetric catalysis in the synthetic chemistry laboratory was assumed to be the domain of enzymes and metal complexes. Despite nearly half the known enzyme active sites being metal-free, the prospect of catalysing chemical reactions with pure organic (naturally occurring or synthetic) molecules was underestimated until the end of the last century. This is notwithstanding the sporadic yet prominent examples of the use of organic molecules as catalysts in organic synthesis – already known for several decades.

This year's Nobel laureates in Chemistry, List and MacMillan brought this rather neglected sub-area of asymmetric catalysis (known as organocatalysis) into the limelight. Organocatalysis refers to catalysis with small organic molecules, where an inorganic element (even if present in the structure) is not a part of the active catalytic principle[3].

If the 2020 Nobel Prize in Chemistry is a tale of collaborative efforts between Jennifer Doudna and Emmanuelle Charpentier, the 2021 Prize will undoubtedly be remembered as a passionate competition between the two laureates born in the same year (1968) – at least during a good part of the first decade of their independent careers. While developing and popularizing the two interconnected and complementary modes of substrate activation by aminocatalysis (i.e. enamine and iminium catalysis, see below) separately, they often crossed paths and ended up reporting the same asymmetric transformations independently on more than one occasion. As the chemistry community has witnessed in the past, such academic competitions only resulted in the enrichment of the field. In this case, the competition between List and MacMillan actually led to the emergence of new concepts (such as organocascade catalysis, see below) and inspired hundreds of research groups across the world to take up asymmetric organocatalysis as their research field.

Before diving into their discoveries, let us take a brief look at the career paths of the two Nobel laureates. Born in Frankfurt, Germany, List completed his Ph.D. in 1997, working in the field of natural product synthesis under the guidance of Johann Mulzer at the Johann Wolfgang Goethe-Universität in Frankfurt. After a productive postdoctoral stint in the laboratories of Richard Lerner at The Scripps Research Institute, California, USA, studying catalytic antibodies, he became a Tenure Track Assistant Professor in the same Institute in January 1999. List moved to the Max-Planck-Institut für Kohlenforschung in 2003 as a group leader and became the Director of the Department of Homogeneous Catalysis in 2005. He is an honorary professor at the Universität zu Köln, Germany.

MacMillan was born in Bellshill, Scotland, and earned his Ph.D. in 1996 from the University of California, Irvine, USA,

Benjamin List

David MacMillan

Courtesy: Niklas Elmehed © Nobel Prize Outreach.

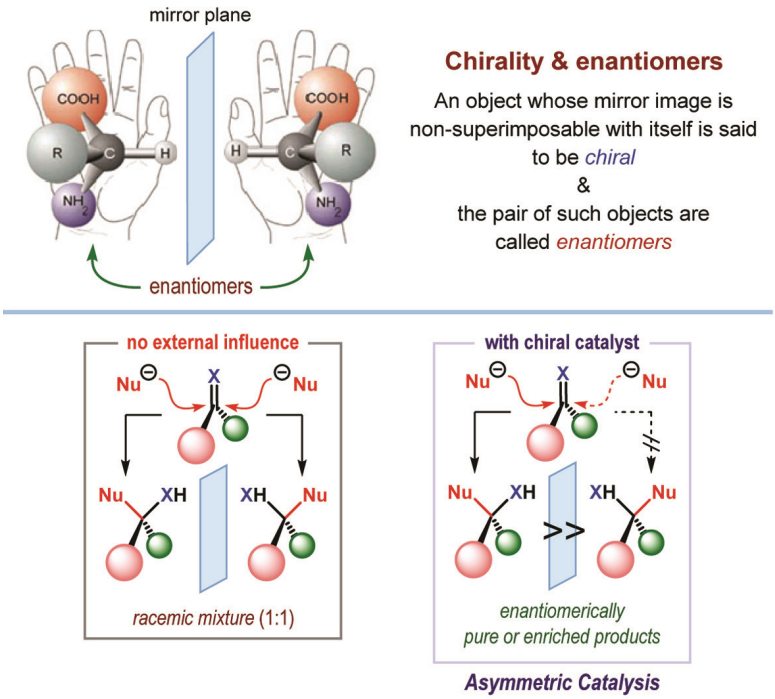
under the guidance of Larry Overman, also having worked in the field of natural product synthesis. Following postdoctoral studies with David Evans at Harvard University, Massachusetts, USA, he began his independent career at the University of California, Berkeley, USA in 1998. In 2000, he moved to the California Institute of Technology and, in 2006, to Princeton University, where he is currently the James S. McDonnell Distinguished University Professor.

In 2000, at the very beginning of his independent career, List developed the first proline-catalysed intermolecular asymmetric aldol reaction (Scheme 2 *a*)[4]. Within two months of List's report, MacMillan's discovery of the first amine-catalysed enantioselective Diels–Alder reaction appeared (Scheme 2 *b*)[5]. Both these reactions delivered products with high enantiomeric ratios (e.r.). At that time, these types of 'miscellaneous' processes were generally categorized under 'metal-free catalysis'. MacMillan did not like the idea of describing an area of catalysis in terms of what it was not. In his Diels–Alder paper[5], he first coined the term 'organocatalysis' and a field that already existed for more than three decades finally got a name.

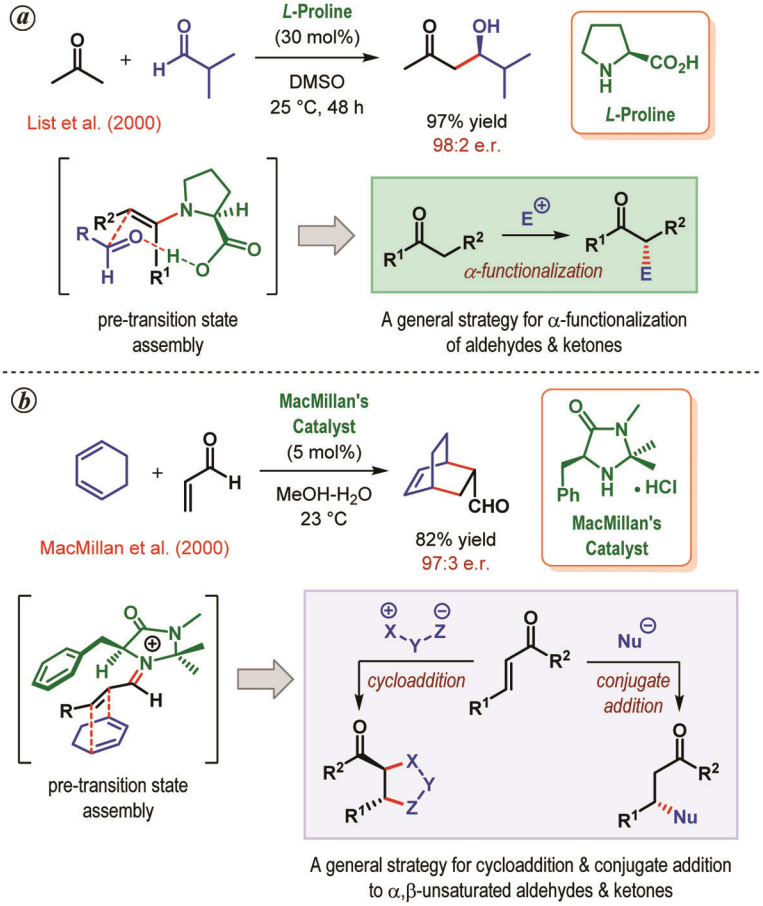
At this point, it must be mentioned that the proline-catalysed enantioselective aldol reaction, was first reported in 1971 by two industrial research groups – Hajos and Parrish (Hoffmann-La Roche, New Jersey, USA)[6,7] and Eder, Sauer and Wiechert (Schering AG, Berlin, Germany)[8,9]. This intramolecular aldol reaction, now known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction was, in fact, the first example of a highly enantioselective organocatalytic process. Although the mechanism of this reaction, was not well understood until 2001 (ref. 10) despite efforts from various research groups[7,11,12], this groundbreaking discovery found immediate application in the synthesis of steroids.

In the backdrop of his postdoctoral experience with catalytic antibodies, the initial studies by List were evidently influenced by the enamine-based mechanism of class I aldolases as well as aldolase antibodies, and therefore may be considered as biomimetic. At the same time, the success of the Hajos–Parrish–Eder–Sauer–Wiechert reaction must undoubtedly have inspired List to use proline as the catalyst for the closely related intermolecular aldol reaction[13].

In contrast, in the absence of any natural analogue, the motivation behind



Scheme 1. Chirality and asymmetric catalysis.



Scheme 2. The early breakthroughs in asymmetric (***a***) enamine and (***b***) iminium catalysis and their generalization.

MacMillan's design features of iminium catalysis was purely chemical and inspired by the well-established Lewis acid catalysis. However, the origin of iminium (and to some extent enamine) catalysis can be traced back to 1894 with Knoevenagel's discovery of the secondary amine-catalysed condensation reaction between aldehydes and active methylene compounds such as malonic acid[14]. Although delving into the history of aminocatalysis is beyond the scope of this note[13], a few important milestones should be mentioned. The first iminium-catalysed conjugate addition, an oxa-Michael reaction, was reported by Langenbeck in 1937 (ref. 15). Amine-catalysed Michael and related reactions, proceeding via iminium intermediates, were also applied for the synthesis of natural products in the second half of the 20th century. For example, Woodward utilized proline-catalysed retro-sulpha-Michael/sulpha-Michael/aldol cascade reactions to effect the deracemization of a key intermediate in the total synthesis of erythromycin – published in 1981 (ref. 16). Although Baum described a significant rate acceleration in the Diels–Alder reaction using iminium salts in 1976 (ref. 17), MacMillan's report of 2000 is the first example of an asymmetric cycloaddition reaction using iminium catalysis[5].

The impact of the seminal reports of List and MacMillan goes beyond the reactions described therein. In addition to providing clear mechanistic pictures, these two reports presented enamine[18] and iminium catalysis[19] as generic modes of substrate activation for asymmetric catalysis (Scheme 2). MacMillan, in fact, went ahead and described iminium catalysis using the modern term of 'LUMO-lowering activation' to show its analogy with Lewis acid catalysis[20]. In the same terminology, enamine catalysis is referred to as 'HOMO activation', as enamines are more nucleophilic than the corresponding enols and their formation leads to the enhancement of HOMO energy.

As a natural consequence of these mechanistic revelations, a series of conceptually related enantioselective transformations were developed in the next few years – initially by List and MacMillan, followed by other research groups across the world[18,19]. Within a few years, enamine catalysis became the most preferred strategy for the enantioselective α-functionalization of aldehydes and ketones. On the other hand, iminium catalysis became the most popular choice for the enantioselective conjugate addition and cycloaddition reactions involving α,β-unsaturated aldehydes and ketones. More importantly, the complementary nature of these two modes of catalysis led to the emergence of aminocatalytic α,β-difunctionalization of aldehydes and ketones starting from their α,β-unsaturated counterparts[21–24]. This strategy, known as the organocascade catalysis (another term introduced by MacMillan)[22], literally opened the floodgate of reaction development. Hundreds of enantioselective transformations, many seemingly impossible otherwise, were developed using simple and easily accessible starting materials, and applied to synthesize complex targets. With these aminocatalytic concepts at hand, valuable pharmaceuticals can now be synthesized in just a few steps and even within a few hours, starting from easily accessible building blocks[25].

Notwithstanding its impact in igniting the initiation of this field, organocatalysis is by no means confined to enamine and iminium catalysis. Alongside, and even before these aminocatalytic modes became a 'household' tool, other organocatalytic concepts flourished independently[26]. While some of these strategies rely on the activation and asymmetric induction through covalent substrate modification, others do so with non-covalent interactions (e.g. hydrogen bonding, electrostatic interaction, etc.) with the substrates or the reactive intermediates. Phase-transfer catalysis using quaternary ammonium salts, aldehyde and ketone catalysis, *N*-heterocyclic carbene catalysis, bifunctional catalysis using tertiary amino(thio)ureas or squaramides, general Brønsted acid catalysis (also known as hydrogen-bonding catalysis) using diols, (thio)ureas or squaramides and specific Brønsted acid catalysis with chiral phosphoric acids, sulphonic acids and their derivatives are just a few names in this long list. In this context, the pioneering contributions of many other research groups, along with List and MacMillan, in popularizing this research area must be appreciated and acknowledged. With the existing and ever-emerging new concepts, the activation of nearly all functional groups is now possible using one or more modes of organocatalysis.

Apart from substrate activation, unprecedented modes of asymmetric induction were developed using organocatalysts. In analogy with the traditional cationic phase-transfer catalysis, at least three different modes of asymmetric induction using chiral anions are now available – not just for organocatalytic but also for transition metal-catalysed transformations[27,28].

What does the future hold for asymmetric organocatalysis?

An exciting aspect of organocatalysis is the compatibility of various catalysts, which makes it possible to combine more than one catalytic mode, not just among themselves but also with traditional transition metal catalysis and even with the emerging photoredox catalysis. Such combinations open up countless new avenues for reaction development. We have been witnessing some of these exciting combinations since the beginning of the last decade, and more are certain to follow.

Just like this year's Nobel laureates, who are relatively young and exciting scientific contributions are expected from their laboratories in the years to come, the field of asymmetric organocatalysis is still delivering new concepts not just for forging bonds, but doing so enantioselectively.

Despite all the advantages of organocatalysis mentioned above, a key limitation, especially when compared to transition metal catalysis, is the generally low turnover number and the requirement of high catalyst loading (typically 10 mol%). However, with the development of more powerful organocatalysts, enantioselective reactions that use only 1–2 mol% catalyst are not uncommon anymore. In fact, reactions using sub-mol% and even ppm levels of organocatalyst are also a reality now[29]. In any case, even with relatively high catalyst loading, organocatalysts still hold an edge over transition metal catalysis on various fronts.

The major problems of using heavy-metal catalysts are that some of them are not just toxic to humans and the environment, but their resources are also limited. Organocatalysts, on the other hand, can be synthesized and modified at will, are generally non-toxic, and can be recovered and reused on most occasions. More importantly, organocatalysts are much easier to work with as no special precautions are generally required to protect the catalysts and reactions from air and moisture. With these advantages coupled with easy scalability, organocatalytic asymmetric methods have already made their way into the pharmaceutical industry[30]. This year's Nobel Prize in Chemistry would hopefully trigger further applications of organocatalysis in the industry.

From a somewhat humble beginning and later on, complementing the well-established enzyme and transition metal catalysis,

organocatalysis has definitely come of age to the point that asymmetric transformations, not possible even with transition metal catalysis, can now be planned using organocatalysts.

Indeed, a much deserved recognition for a research field that was once criticized for its conceptual and operational simplicity!

1. https://www.nobelprize.org/prizes/chemistry/2021/summary/
2. Mellin, G. W. and Katzenstein, M., *New Engl. J. Med.*, 1962, **267**, 1184–1192.
3. List, B., *Chem. Rev.*, 2007, **107**, 5413–5415.
4. List, B., Lerner, R. A. and Barbas III, C. F., *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.
5. Ahrendt, K. A., Borths, C. J. and MacMillan, D. W. C., *J. Am. Chem.*, *Soc.*, 2000, **122**, 4243–4244.
6. Hajos, Z. G. and Parrish, D. R., 1971, DE 2102623.
7. Hajos, Z. G. and Parrish, D. R., *J. Org. Chem.*, 1974, **39**, 1615–1621.
8. Eder, U., Sauer, G. R. and Wiechart, R., 1971, DE 2014757.
9. Eder, U., Sauer, G. R. and Wiechart, R., *Angew. Chem.*, *Int. Ed.*, 1971, **10**, 496–497.
10. Bahmanyar, S. and Houk, K. N., *J. Am. Chem. Soc.*, 2001, **123**, 12911–12912.
11. Agami, C., Puchot, C. and Sevestre, H., *Tetrahedron Lett.*, 1986, **27**, 1501–1504.
12. Rajagopal, D., Moni, M. S., Subramanian, S. and Swaminathan, S., *Tetrahedron: Asymmetry*, 1999, **10**, 1631–1634.
13. List, B., *Angew. Chem*., *Int. Ed.*, 2010, **49**, 1730–1734.
14. Knoevenagel, E., *Chem. Ber.*, 1894, **27**, 2345–2346.
15. Langenbeck, W. and Sauerbier, R., *Chem. Ber.*, 1937, **70**, 1540–1541.
16. Woodward, R. B. *et al.*, *J. Am. Chem. Soc.*, 1981, **103**, 3210–3213.
17. Baum, J. S. and Viehe, H. G., *J. Org. Chem.*, 1976, **41**, 183–187.
18. Mukherjee, S., Yang, J. W., Hoffmann, S. and List, B., *Chem. Rev.*, 2007, **107**, 5471–5569.
19. Erkkilä, A., Majander, I. and Pihko, P. M., *Chem. Rev.*, 2007, **107**, 5416–5470.
20. Lelais, G. and MacMillan, D. W. C., *Aldrichim. Acta*, 2006, **39**, 79–87.
21. List, B., *Chem. Commun.*, 2006, 819–824.
22. Huang, Y., Walji, A. M., Larsen, C. H. and MacMillan, D. W. C., *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053.
23. Yang, J. W., Fonseca, M. T. H. and List, B., *J. Am. Chem. Soc.*, 2005, **127**, 15036–15037.
24. Marigo, M., Schulte, T., Franzén, J. and Jørgensen, K. A., *J. Am. Chem. Soc.*, 2005, **127**, 15710–15711.
25. Hayashi, Y., *Acc. Chem. Res.*, 2021, **54**, 1385–1398.
26. List, B. (ed.), *Chem. Rev.*, 2007, **107**(12), 5413–5884; a special issue on organocatalysis.
27. Mahlau, M. and List, B., *Angew. Chem*., *Int. Ed.*, 2013, **52**, 518–533.
28. Brak, K. and Jacobsen, E. N., *Angew. Chem*., *Int. Ed.*, 2013, **52**, 534–561.
29. Bae, H. Y. *et al.*, *Nature Chem.*, 2018, **10**, 888–894.
30. Humphrey, G. R. *et al.*, *Org. Process Res. Dev.*, 2016, **20**, 1097–1103.

Santanu Mukherjee, Department of Organic Chemistry, Indian Institute of Science, Bengaluru 560 012, India.
e-mail: sm@iisc.ac.in