The 2021 chemistry Nobel laureates and asymmetric organocatalysis

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Abstract

The 2021 Nobel Prize in Chemistry was awarded jointly to Benjamin List and David MacMillan “for the development of asymmetric organocatalysis.” This choice was remarkable for a number of reasons. It singled out a very “chemical” discovery, whereas in recent years, the chemistry prizes often went for discoveries in biochemistry, and it singled out two relatively young men. The concept of asymmetric organocatalysis has been around since the late 1920s, and in the early 1970s, even proline was recognized as capable of playing the role of an enzyme. Nonetheless, asymmetric organocatalysis has found major applications since about the year 2000 due to the discoveries and activities of the new laureates and their colleagues.

Keywords Benjamin List · David MacMillan · Asymmetric synthesis · Organocatalysis · Scripps Institute · Caltech · Zoltan Hajos

The 2021 Nobel Prize in Chemistry was awarded for a genuinely chemical discovery, “for the development of asymmetric organocatalysis.” The reason why this is remarkable that during the past decades, it has been estimated that a considerable fraction of the chemistry Nobel Prizes went for discoveries in biochemistry, as have a considerable fraction of the Nobel Prizes in Physiology or Medicine. So, it could be stated that discoveries in biochemistry have fared better than purely chemical or medicinal discoveries, whereas there is not even a biochemistry Nobel Prize. Of course, since Alfred Nobel’s time, the scope and structure of chemistry has undergone fundamental changes making the “lamentation” groundless. Nonetheless, it is uplifting that chemistry in its classical sense is still capable of discoveries that merit Nobel Prizes. The significance of the discovery that motivated this latest Nobel Prize is unquestionable and can be summarized in that producing only one of the two enantiomers for substances for which both are possible, has become of utmost importance for a number of reasons. For example, rigorous regulations stipulate such a choice for medicines where one version may be a cure and the other not, or even toxic. Another example is where one version finds use and the other is a waste, so it becomes economically prudent to produce only the usable one. I see something symbolic in

that one of the awardees works for a carbon research institute because it shows once again that carbon has many uses and many more important uses than just serving as fossil fuel and producing toxic effects for the environment. Burning fossil fuel is the least economical utilization of carbon as compared with a host of other uses that on top of it do not pollute the environment and have much smaller effect on climate change.

Benjamin List (b. 1968) is the second Nobel laureate in the history of the Coal Research Institute in Mülheim. The first was Karl Ziegler who received it jointly with the Italian Giulio Natta in 1963 for their discoveries in polymer chemistry and the structures of polymers of industrial significance. List was born in Frankfurt, did his undergraduate studies at the Free University of Berlin, and did his doctoral work with Johann Mulzer as his mentor at Goethe University in Frankfurt. Mulzer is a synthetic organic chemist whose principal interest was in asymmetric synthesis and who studied in Munich and did his postdoctoral work with the Nobel laureate organic chemist E.J. Corey at Harvard University. List earned his PhD in 1997. He was then a research associate at the Department of Molecular Biology, Scripps Research Institute, in La Jolla, California. First he was a postdoctoral researcher there in the groups of Carlos F. Barbas III and Richard Lerner, then, an assistant professor. In 2003, he joined the Coal Research Institute as a group leader and was elevated to the position of head of the Department of Homogeneous Catalysis in 2005. He is the second Nobel

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laureate in his extended family: His aunt is the developmental biologist Christiane Nüsslein-Volhard, herself a Max Planck Director who shared the Nobel Prize in Physiology or Medicine in 1995. Browsing List's career, it appears that he did his seminal discoveries for organocatalysts while he was at the Scripps Institute so that institution can have at least as much claim to the glory of the 2021 chemistry Nobel as the Mülheim institute (Fig. 1).

David MacMillan (b. 1968) is the James S. McDonnell Distinguished University Professor of Chemistry at Princeton University and former chair of the Department of Chemistry. His main research goal has been establishing new concepts in organic chemical synthesis and gaining access to structural and stereochemical units that heretofore had not been available from work employing conventional methods. He always had an eye on the application of the newly produced substances in medicine, agriculture, and in building bioactive scaffolds. Although the Princeton chemistry department could boast such greats as the stereochemist Kurt Mislow, MacMillan is its first Nobel laureate. In contrast, the Princeton Department

of Physics has had several Nobel laureates over the years. Syukuro Manabe, one of the 2021 physics Nobel laureates, is also a Princeton associate—Princeton's chief meteorologist. MacMillan was born in Bellshill, Scotland; he did his undergraduate studies at the University of Glasgow, and earned his PhD at the University of California, Irvine, in 1996. He started his research career in 1998 at the University of California, Berkeley. He was at the California Institute of Technology between 2000 and 2006, when he joined Princeton University. So, in MacMillan's case, perhaps three institutions can claim at least shares of his Nobel glory, viz., the University of California Berkeley, Caltech, and Princeton University (Fig. 2).

In the introduction of this note, I remarked the not too frequent Nobel awards occurring for “genuinely” chemical discoveries. Still there is some relationship of the 2021 chemistry prize to the 2001 Nobel Prize in Chemistry. Half of it went to K. Barry Sharpless “for his work on chirally catalyzed oxidation reactions,” and William S. Knowles and Ryoji Noyori shared the other half “for their work on chirally catalyzed hydrogenation reactions.”

Fig. 1 Benjamin List (Illustrator: Niklas Elmehed © Nobel Prize Outreach)

Fig. 2 David MacMillan (Illustrator: Niklas Elmehed © Nobel Prize Outreach)

The Nobel Foundation does a great deal to disseminate science through the popularization of the Nobel Prize and distinguishes between the levels for the broader public and researchers of the fields concerned in the respective awards. The 2021 account of the Nobel Committee for Chemistry is a true scientific treatise, which presents a detailed description of the prize-winning work and discoveries. Furthermore, it goes back in science history and shows that the prize-winning achievements did not happen in vacuum; rather, they can be considered to be a continuation of earlier work, right from the late 1920s, culminating in the early 1970s when, for a variety of reasons, the circumstances were not yet ripe for the concepts and related innovations to develop further [1, 2].

Being at the Budapest University of Technology and Economics (formerly, Budapest Technical University), I feel obliged to single out a part of the story narrated in [1], pp 4 and 5, and the relevant References and Scheme are also given in [1]:

“Some important findings preceded this work. In the early 1970s, the groups of Hajos and Parrish (1971, 1974) and Eder, Sauer and Wiechert (1971) independently reported pioneering contributions to the field of asymmetric catalysis. They showed that *L-proline catalyses* the cyclisation of the achiral triketone to furnish the Wieland-Miescher ketone (the Hajos-Parrish-Eder-Sauer-Weichert, or HPESW, reaction), which is an important intermediate in the synthesis of several natural products. (emphasis by me) For example, the HPESW reaction has been used for the synthesis of steroids. The reaction proceeds in high yields ... The paper by Wiechert and colleagues is rather laconic and provides no information about the scope and mechanism of the reaction. In contrast, Hajos and Parrish put forward a mechanism involving a carbinolamine that is now obsolete, since it is appreciated that the reaction proceeds through enamine catalysis, but, perhaps more importantly, the authors recognized that *the proline catalyst plays the same role as an enzyme*. However, these studies were not followed up by the authors, nor did they result in a general concept of using chiral amines in asymmetric enamine catalysis.” (emphasis by me)

On the basis of these two paragraphs, as well as his other contributions, Zoltan G. Hajos (b. 1926) is among the

pioneers in what is called today “organocatalysis.” Hajos graduated from Budapest Technical University in 1947 as a chemical engineer, and earned his doctorate in 1949 under the mentorship of Zoltán Csűrös. Hajos left Hungary upon the suppression of the 1956 anti-Soviet Revolution and spent his career in the USA and in part in Canada, in a small fraction in academia, but mostly with big-name pharmaceutical companies. The last sentence of the second paragraph quoted above explains why Hajos, David R. Parrish, and the others involved are not higher on the Nobel ranking today. Hajos, who lives in the USA, received the “Iron Diploma” in 2012 from his Budapest alma mater, due to graduates still alive 65 years since graduation. He has received no recognition for his pioneering work. Let this paragraph be a token tribute to him.

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