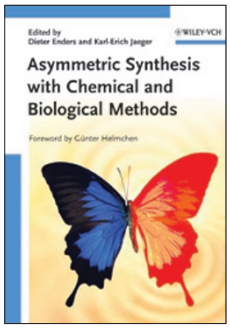
Creating chirality



Asymmetric Synthesis with Chemical and Biological Methods

Edited by Dieter Enders & Karl-Erich Jaeger

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Reviewed by Yun-Ming Lin

The handedness of small organic molecules has fascinated many generations of scientists, particularly owing to the pioneering contributions of Louis Pasteur and Emil Fischer. Modern science has established that the molecular recognition of left- or right-handed small organic molecules by a macromolecular target can result in drastically different biological consequences. Thus, the biological implications of chirality demand that we improve our ability to access chiral small molecules as pure entities. Though the field of asymmetric synthesis has its roots in organic chemistry, modern applications of biosynthetic methods and molecular biology have built on the transformations made possible using traditional chemical methods. However, the challenges inherent to applying these techniques and answering new synthetic questions continue, underscoring the ongoing need for asymmetric synthesis.

To fulfill the potential of having a diverse set of chemical and biological tools for making chiral small molecules, scientists in Germany set up a collaborative research center among several institutions in 1994 to focus on challenging problems in asymmetric synthesis. Fittingly, *Asymmetric Synthesis with Chemical and Biological Methods*, edited by Dieter Enders (Rheinisch-Westfaelische Technische Hochschule Aachen University, Germany) and Karl-Erich Jaegar (Heinrich-Heine University of Dusseldorf, Germany), summarizes the exciting collective research progress from these German laboratories.

Part 1 of the book focuses on one of the stalwarts of asymmetric synthesis: chiral auxiliaries, or readily accessible chiral small molecules. These compounds have historically been exploited as chiral templates to impart chirality transfer to the products. Overall, this section focuses on the extension of known chiral auxiliaries to new reactions. For example, Dieter Enders and Wolfgang Bettray nicely detail the applications of Enders' chiral auxiliary (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) to the chemical syntheses of several chiral building blocks that are important in constructing biologically interesting small molecules. The overall strategy is perhaps best exemplified in Enders' elegant synthesis of callystatin A, a polyketide natural product that inhibits the growth of cancer cells, but that can only be isolated in small quantities from nature.

Notwithstanding the remarkable synthetic utility of chiral auxiliaries in asymmetric synthesis, removing the "helper" auxiliaries upon completion of the reaction constitutes extra chemical steps. In contrast to auxiliary-based processes, catalytic asymmetric synthesis requires a much smaller quantity of chiral catalysts to impart chirality transfer. Part 2 of the book thus summarizes not only the tremendous advantages chiral catalysts offer over their stoichiometric counterparts (particularly for recyclable catalysts) but also the inherent challenges associated with developing a catalytic process (for example, improving catalyst turnover, or crafting new chiral space). The application of planar chirality (chirality resulting from metal π-complexation) in asymmetric catalysis is particularly noteworthy.

The diverse chiral space covered by enzymes can also be exploited for creating chiral small molecules. Biocatalysis often provides a complementary approach to its synthetic counterparts, as organic reactions that would typically require inert atmospheric conditions and/or protecting groups can be carried out in aqueous buffers, without using protecting groups. On the other hand, the substrate specificity conferred by enzymes also renders them only active for a limited set of substrates. Thus, not only harnessing but also manipulating the exquisite selectivity displayed by enzymes for asymmetric catalysis is an exciting research area. As a result, seven chapters highlight the challenges, opportunities and strategies in applying biosynthetic machinery to modern asymmetric synthesis. In addition to the structural and mechanistic aspects of enzymatic catalysis, the book contains detailed experimental procedures for site-directed mutagenesis and directed evolution for making enzyme variants with enhanced stability or different substrate preferences. For example, Wolf-Dieter Fessner's application of recombinant enzyme technology to access complex oligosaccharides avoids the tedious protecting group manipulations used in traditional approaches. Because modified oligosaccharides present on cell surfaces have a significant role in biological functions (for example, inflammation, metastasis), new enzymatic approaches to gain rapid access to these complex small molecules should facilitate both an increased understanding of their biological function and the development of new therapeutic agents.

Finally, part 3 offers a brief overview of technological developments in the field. This book serves as an appropriate venue for this discussion because the pharmaceutical significance of chiral small molecules as potential drugs means that advances in asymmetric synthesis can stimulate the commercialization of new technology.

Taken as a whole, this book is a delight to read. The detailed biology procedures will be especially useful for organic chemists who are interested in biocatalysis but are less experienced in manipulating recombinant DNA and proteins. A more comprehensive picture of the landscape of modern asymmetric synthesis might have been provided if scientists from other countries had been involved. Similarly, including other topics such as organocatalysis or cooperative multifunctional/bifunctional catalysis would have enriched its content, but these topics might be beyond the intended scope. Nevertheless, this book will be a useful reference for scientists in academia or industry, and especially for chemical biologists working at the interface of chemistry and biology.

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