Organocatalytic Enantioselective Conjugate Addition Reactions

The ultimate challenge in organic synthesis is to identify new chemical strategies that make it possible to create complex molecules in an efficient and elegant manner, minimizing the number of manual operations and purifications. Asymmetric catalysis plays a central role in this endeavor, and the recent development of metal-free chiral catalysis (organocatalysis) has reinforced the field. Organocatalysts not only promote chemical transformations efficiently and selectively, but also satisfy the conditions usually required for industrial processes quite well. Although organocatalysis clearly had this inherent potential, and although examples of chemical reactions promoted by small organic molecules had been known since the beginning of the 20th century, it was not until about a dozen years ago that the explosive growth of this area of work began. Recently, important advances in the field have been achieved in two directions: in establishing the main mechanisms of organocatalytic activation, and in applications.

The book is focused on enantioselective organocatalysis in the context of conjugate addition reactions, a vast category of reactions that includes some of the most versatile carbon–carbon and carbon–heteroatom bond-forming reactions. The authors are themselves active contributors to the area, including the development of new methodologies. The content is organized in seven chapters, and covers the most recent advances in organocatalytic asymmetric conjugate addition reactions. The overall organization of this book is excellent, and is based on an appropriate selection of representative protocols that illustrate how different types of chiral organocatalysts can promote conjugate additions and control the stereochemical outcome.

Chapter 1 gives a concise description of the historical evolution of asymmetric organocatalysis, and presents a brief categorization of organocatalysts according to their acid/base reactivity or the covalent/non-covalent nature of the substrate activation mechanism. The subsequent chapters are presented according to these general activation modes. They deal in turn with catalytic conjugate addition reactions using chiral enamines, enantioselective conjugate additions to α,β-enals and -enones using iminium ion activation, reactions triggered by hydrogen bond activation, phase transfer catalysis (PTC), and miscellaneous other activation pathways. There is also one chapter devoted to cascade reactions initiated by a conjugate addition step.

Chapters 2 and 3 give a comprehensive overview of asymmetric conjugate addition reactions that are mediated by enamine and iminium ion species and involve primary or secondary chiral amine catalysts. The enamine and iminium ion strategies are closely related, and the same catalyst can often be used in either approach with similar efficiency. This concept is certainly relevant for understanding the cascade processes mediated by enamine or iminium ion formation that are described in Chapter 7.

Chapter 4 provides a concise review of enantioselective conjugate addition reactions activated by non-covalent hydrogen-bonding. As the authors correctly stress, non-covalent interactions play a crucial role in many biochemical reactions and are involved in many biological processes. Starting from seminal work in the late 1990s, the authors cover the most relevant H-donor catalysts and some representative applications of them in conjugate addition reactions. The well-chosen examples and didactic style of the descriptions in this chapter show clearly the potential of hydrogen-bonding catalysis for planning syntheses. Chapter 5 is a review of enantioselective conjugate addition reactions using phase transfer catalysis. As is evident from reading the other chapters of this book, the development of chiral ligands for phase transfer catalysis is a fast-evolving area where new milestone discoveries are constantly appearing. The introductory part of this chapter is followed by mechanistic considerations that are clearly explained. Chapter 6 is devoted to some other types of activation modes, including examples of conjugated addition reactions triggered by N-heterocyclic carbenes and chiral Brønsted bases. One must read the ending Chapter 7, where recent progress in the hot topic of enantioselective cascade reactions initiated by a conjugated addition step is discussed. In the light of the growing demand for complex organic molecules with multiple stereogenic centers, for example as building blocks for the preparation of pharmaceutical agents, the ability to synthesize such compounds in a few chemical steps, preferably in a one-pot process, is a highly appealing objective in organocatalysis.

In general, the book is written with clarity and is very well structured. Each chapter starts with an introduction to the mode of action of the catalysts concerned, which is reasonably comprehensive, provides key clues to understanding the structural aspects of catalyst design, and helps one to follow the underlying developments. Each topic is highlighted by seminal contributions from the pioneers on the subject area. A minor criticism is that it would have been useful to include brief comparisons between organocatalytic and metal-catalyzed methodologies for conjugate addition reactions. However, that omission does not significantly

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diminish the impact of the book, which is certainly a valuable reference source for readers engaged in all areas of organic, biomedical, or pharmaceutical chemistry research. It should also be useful for graduate-level students interested in the topic. Note, however, that notwithstanding the excellent literature coverage of the book, when it is used as a textbook the lecturer might need to provide more up-to-date references in this rapidly moving field.

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