Erick M. Carreira and Lisbet Kvaerno

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Classics in Stereoselective Synthesis

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Cover illustration
The cover illustration is taken from the *ex libris* of Prof. Vladimir Prelog (1906–1998). It is the artwork of the well-known Swiss artist Hans Erni. Prof. Prelog was awarded the Nobel Prize in Chemistry in 1975 with J. W. Cornforth for their work on stereochemistry.
We are grateful to Frau Kamilla Prelog for kindly allowing its use for this book and to Professor Duilio Arigoni (Eidgenössische Technische Hochschule Zürich) for his assistance in securing a high quality copy of the artwork.

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This book is warmly dedicated to Professor David A. Evans and all members of the Evans scientific family, past, present, and future.

I am a part of all that I have met
Ulysses, A. Tennyson

To thy happy children of the future, those of the past send greetings
University of Illinois at Urbana-Champaign, Alma Mater
(Proverbs 31–28)

Preface

Some four billion years ago countless combinatorial experiments in chemistry were occurring. Random condensations and oligomerizations in time produced large structures and macromolecular ensembles within differentiated complex networks of chemical processes. The emergence of linked processes, such as the ability to evolve, metabolize, and reproduce, defines what we know as life. Unlike the two-dimensional world described in Abbott's classic novella *Flatland* (1884) [1], the only life we know is three-dimensional in which chirality plays a leading role. Numerous mechanisms abound to account for the generation of optically active compounds in the prebiotic world, with chiral molecules as the norm instead of the exception. Thus, as with life itself, asymmetric synthesis may have been inevitable and merely contingent on the ground rules set some 10 billion years earlier. The stereoselective synthesis of molecules continues unabated by the hand of Nature in living organisms and the hands of chemists in laboratories engaged in the science of synthesis.

■ *We live in an old chaos of the sun. (W. Stevens)* ■

The scientific discipline of stereoselective synthesis has its origins in the late 1880's with Fischer's experiments aimed at the structural characterization of carbohydrates. In pondering the result that the addition of HCN to glucose produced a single diastereomer, Fischer stated: "*These observations are, to my knowledge, the first definitive experimental evidence that further synthesis with asymmetric systems proceeds in an asymmetric manner. Although this statement does not at all contradict theory, it by no means follows from it.*"[2] Fischer differentiated between absolute asymmetric (or enantioselective) synthesis and diastereoselective synthesis. It is clear that he was aware of the far-reaching significance of his observations. However, it would not be until the following century that stereoselective synthesis would gain its own footing theoretically and practically as a discipline on its own terms.

The early history of stereoselective synthesis is summarized in a book from 1933 by Patrick D. Ritchie entitled "*Asymmetric Synthesis and Asymmetric Induction.*" [3] It makes for curious and informative reading. For example, one learns that Fischer considered the possibility of asymmetric synthesis in living systems by resolution of enantiomers. In a lecture to the German Chemical Society in 1890 on "Synthesis in the Sugar Group" he is quoted as stating: "no fact hitherto speaks against the view that plant, like chemical synthesis, first prepares the inactive sugars: that it then resolves them into their active constituents ..." The book includes a discussion of the few reactions that were nominally stereoselective, even if only modestly so. The text is peppered with terms recognizable to the modern reader, such as "induction", albeit in unfamiliar settings. These are redolent of the prevailing uneasiness in the community with the underlying nature of the controlling forces. The primary objective of the narrative was to deal with the topic of vitalism and stereochemistry. For those interested in tracing developments in the field in a modern context, a number of sources are worth consulting: Morrison and Mosher's "*Asymmetric Organic Reactions*" [4]; the five-volume treatise "*Asymmetric Synthesis*" with Morrison as editor [5]; the

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multivolume series entitled "*Stereoselective Synthesis*" edited by Helmchen, Hoffmann, Mulzer, and Schaumann [6], and the three-volume compendium "*Comprehensive Asymmetric Catalysis*" edited by Jacobsen, Pfaltz, and Yamamoto [7]. However, there is no publication to date that selectively collects the highlights in stereoselective synthesis with the aim of providing a wide perspective on the field. Thus at the outset of our own venture, we felt confident of the need for such a book.

■ *Memory is the treasury and guardian of all things. (Cicero)* ■

To write a book that purports to identify the classics in stereoselective synthesis seemed a daunting challenge. It is inherently an interdisciplinary field, which has interested inorganic, organic, physical, theoretical chemists, and, with particular intensity, those who enjoy the thrill of building molecules. R. B. Woodward has written a rather insightful epigraph: "There are no generalities in chemistry, that's the beauty of it." [8] The practitioner of chemical synthesis can surely relate to this, as structure and reactivity space is uncompromisingly large. This is a concept that is often missed by those who are not engaged in the day-to-day activities in chemical synthesis. In analogy to biological systems, basic problems in synthesis are not solved once, rather the synthetic chemist must address the challenges specific to each different setting. Thus, the asymmetric synthesis of complex, and even of not so complex, structures is a multivariable and multidimensional problem.

■ *Only those who will risk going too far can possibly find out how far one can go. (T. S. Eliot)* ■

Despite the bevy of activity that has occurred in numerous research laboratories, certain advances can be identified that are quantum leaps in the field, which demark a clear break with the past and have served to propel the field forward. Because of the nature of the field, these are associated with certain reactions that serve as beacons; they are the standard bearers or points of reference. These may be largely driven by and attributed to key personalities with vision, determination, and imagination. Consequently, a book on the classics in asymmetric synthesis will inevitably at times focus on individuals whose names form a repeating motif. Nonetheless, no group works in a vacuum, and the efforts of countless investigators are indispensable to the health of the discipline and the progress it continues to make. This is a feature we have attempted to highlight in writing this book.

■ *Creativity: a type of learning process where the teacher and pupil are located in the same individual. (A Koestler, 1964)* ■

■ *The past is not dead. In fact, it is not even past. (W. Faulkner)* ■

The daunting question that we first had to address was the definition of a classic; this haunted us until the very last sentence. By looking to fellow chemists for their perspective, it became clear that a cacophony of opinions on the matter abound. Various possible definitions of a classic in stereoselective synthesis include the first example for a given reaction, as well as the method displaying highest selectivity, scope, or utility. Each of these criteria alone pose difficulties in any approach to defining a canon of stereoselective reactions. Some of these categorizations may ignore the significance of early work critical to delineating the intellectual context of problems and defining the solutions that followed. These also may not account for contributions made in understanding underlying theoretical aspects. The formulation of models and mechanistic constructs has been critical in setting the stage for further discovery and innovation. Moreover, these narrow definitions are inherently biased against new developments in a discipline that remains far from mature. There is yet another important issue that merits emphasizing, namely, a term such as "reaction" as commonly employed in synthesis can refer to both a broad

class of reactions as well as a very specific transformation; this can lead to absolute statements of unclear significance such as "the asymmetric Diels-Alder reaction is a solved problem." The common transformations are actually a collection of a multitude of reactions. Consequently, it is possible to identify a multitude of classic aldol additions or Diels-Alder cycloadditions, each of which addresses various stereochemical challenges in asymmetric synthesis: *anti* versus *syn* diastereoselective aldol additions, *endo* versus *exo* selective cycloadditions, auxiliary versus catalyst control. Thus, any compilation of classic reactions must necessarily deal with these nuances, each of which addresses unique problems in the interplay of structure and reactivity.

■ *All is experiment and adventure. We are forever mixing ourselves with unknown quantities. What is to come? I know not. (V. Woolf)* ■

In this book we have attempted to amalgamate the various definitions described above. Thus, in many circumstances we have made efforts to include the first example of a certain stereoselective transformation, even if the selectivity was modest. We have incorporated early examples of auxiliaries or catalysts that helped to guide and define the development of the field, although they may have subsequently been surpassed. In trying to include exemplars of many of the reactions employed by the practioners of the field, we have inevitably faced the difficulty that any number of prototypes could have been selected, all of equal merit. Under these circumstances, there is no way of getting around the fact that the selection becomes subject to the authors' own background and personal biases.

■ *Lend me the stone strength*
of the past
And I will lend you.
The Wings of the Future
(R. Jeffers, 1924) ■

We have made extensive use of inserts/asides at the margins of each page to augment the text. These are not in general discussed, and it is expected that their positioning in a given chapter hopefully makes their relevance obvious. There are a handful of instances when the asides include an example, which was simply otherwise difficult to incorporate in the structure chosen for the book and/or the chapter. In some cases the asides constitute recent examples in the literature that surfaced in the final phases of the writing, which were judged as noteworthy of inclusion. These situations were simply too good to pass up. Asides may also involve quotes; some are insightful, thought-provoking, and some even comical. In the words of Montaigne, "I quote others only the better to express myself."

The reader of this book is expected to have a thorough understanding of the fundamentals of synthetic organic chemistry. Significantly, the book is not a text book, and this liberates the authors from strict pedagogical restrictions in the presentation of the materials. We chose an overarching construct in which these various aspects of the discipline are interwoven and the presentation proceeds according to major reaction types. The field of stereoselective synthesis abounds with deep-seated concepts involving the interplay of structure and reactivity within innovative mechanistic constructs. We have chosen to include mechanistic models when they are particularly valuable for understanding or predicting the observed stereoselectivity. When we have provided a detailed mechanistic description, we have opted not to alter the proposal by the original investigator when no new data requiring its modification is available.

■ *Everything should be made as simple as possible but not simpler. (Albert Einstein)* ■

The book is partitioned into 18 chapters that reflect the typical common grouping of synthetic transformations, even if this results in some thematic overlap. The chapters on macrocyclic stereocontrol and chiral acetals (Chapters 1 and 6, respectively) may seem old-fashioned; yet, these have formed

■ *Everything is complicated; if that were not so, life and poetry and everything else would be a bore. (W. Stevens)* ■

the basis of important considerations in the asymmetric synthesis of molecules and continue to play a role in modern synthetic strategy. One chapter would seem to be overtly specific, namely Chapter 10: Amino Acids. We felt that this is a class of compounds that holds a special place at the interface of synthesis and biology, and for the synthetic chemist conjures up specific ideas and a collection of reaction processes. Many chapters are inherently interconnected, as exemplified by Chapters 3, 11 and 12 dealing with reactions of enolates, imines and 1,4-acceptors, respectively. In this regard, enolates are by definition the reaction partners in the Mannich and Michael addition reactions. For the imine or conjugate addition processes the focus is the electrophilic partner, with the nature of the nucleophile being secondary. By contrast, Chapter 3 on α-functionalizations of enolates is limited to a discussion of reactivity focused on the enolate itself, such as alkylations and halogenations. Two chapters deal with transformations involving formal allylation processes, namely Chapters 5 and 14. The first of these, "Allylations of C=O Bonds", is a collection of carbonyl addition reactions by σ-bonded allylmetal reagents, such as allylboron or allylsilicon species. The second, "Metal-Catalyzed Allylations", includes primarily reactions that are traditionally classified as organometallic. This family of reactions is mechanistically rich and has evolved independently, leading to a diverse set of transformations that largely involve η^3-bound intermediates along with S_N2' displacement reactions. Chapter 13 entitled "Chiral Carbanions" could have included some of the reactions involving organometallic allylation reagents, as some of these can likewise be considered carbanionic. However, the term chiral carbanions typically conjures up a specific class of transformations that involve primarily organolithium reagents, and thus, this serves as the organizing point. Additionally, a collection of metal-catalyzed, enantioselective carbometallation reactions of olefins have been incorporated in this chapter. Chapter 15 groups cyclopropanation and C–H activation processes, as these two reaction classes seem to have evolved hand-in-hand. Admittedly, a shortcoming of the organization we adopted is that there were transformations that were difficult to classify within any of the designated chapters and did not warrant an entire chapter. We were faced with either excluding material or accepting a poor fit. This is a situation where the use of asides proved helpful.

■ *Accuracy of observation is the equivalent of accuracy of thinking. (W. Stevens)* ■

The early development of organic chemistry, during which many of the concepts and terms arose, predates the current advances in instant communications. The field of stereochemistry is replete with nomenclatural nuances. The reader is encouraged to consult both Gawley and Aube's book "*Principles of Asymmetric Synthesis*" [9] as well as Helmchen's introduction in Volume 1 of "*Stereoselective Synthesis*" [10] for accurate and proper treatment of definitions and usage of terms relating to stereochemistry. There are terms that have firmly anchored themselves in the field despite the fact that it is commonly held that they are to be frowned upon. Although they are formally incorrect, they do seem to have the characteristic of readily conveying a meaning or capturing a concept in a unique way, which has contributed to their common usage. In some respects, the extent to which these transgressions are tolerated or discouraged have acquired a geographical component. Anyone who has experienced the North American and European cultures will recognize that there are differences in the usage of no-

menclature. This is most obvious in the use of terms such as stereochemistry vs. configuration, but there are many others: (*E*)- and (*Z*)- versus *trans*- and *cis*-enolates, and conformation versus conformer. There are even differences in the way in which some of the concepts are taught (i.e. Fürst-Plattner rules versus diaxial attack in cyclohexene). Even name reactions are not sacrosanct: the anglophile's Eschweiler–Clarke is often referred to as the Leuckart–Wallach in the German-speaking world, even if the two are subtly different. There are ongoing polemics; for example, consider the Hajos–Parrish versus Eder–Hajos–Parrish–Sauer–Weichert reaction. Ultimately, we have made every effort to lucidly and effectively communicate reactions and concepts employing proper terminology and usage, without overtly restricting ourselves. As an example, the difficulties with the nomenclature of enolates in discussing the mechanism of the aldol reaction is well known. A given geometric isomer of an ester enolate will bear different designators ((*Z*)- versus (*E*)-) simply as a function of whether it incorporates a lithium or sodium counterion. This is an unfortunate consequence of rules because the stereospecific (another commonly misused term) correlations between enolate geometry and relative configuration of the products that ensues from the Zimmerman-Traxler transition state is blurred by this nomenclatural inconvenience. We have retained the (*E*)-/(*Z*)- nomenclature, however, we have defaulted to the use of *cis*- and *trans*- designators when warranted by the discussion at the risk of being inconsistent.

In the field of literary criticism [11], it has been claimed that the true classics can only be identified when a language has matured and reached its pinnacle, when any further refinement is impossible. In this construct, a vibrant discipline has many high points, but cannot be said to possess a true closed set of classics, because to designate the classics implies subsequent decline. We are convinced that the science of stereoselective synthesis is in fact far from mature. The number of asymmetric transformations reported continues to grow exponentially, transformations that would have been undreamed of a mere decade ago. Many cannot be adequately explained with existing theory, underscoring the fact that much remains outside of our current grasp of the field. Indeed, one of the most difficult things we had to deal with in completing the book was when to stop incorporating new reports appearing in the literature, truly an affirmation of the health of the discipline.

Despite our attempts at trying to be inclusive, there is no doubt we have overlooked examples that certainly merit consideration as classics. We close with a quote by Faraday written in 1853, which was brought to our attention by Professor Jack Dunitz. It is a quote that is truer than ever today, and we use it [12] to apologize to anyone whose work we have overlooked:

"I very fully join in the regret that scientific men do not know more perfectly what has been done, or what their companions are doing; but I am afraid the misfortune is inevitable. It is certainly impossible for any person who wishes to spend a portion of his time to chemical experiment, to read all the books and papers that are published in connection with his pursuit; their number is immense, and (...) most persons (...) are quickly induced to make a selection in their reading, and thus, inadvertently, at times, pass by what is really good." [13]

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Contents

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