

Preface

The field of asymmetric synthesis evolved from the study of diastereoselectivity in reactions of chiral compounds, through auxiliary-based methods for the synthesis of enantiomerically pure compounds (diastereoselectivity followed by isomer separation and auxiliary cleavage), to asymmetric catalysis. In the former case, diastereomeric mixtures ensue, and an analytical technique such as chromatography is used for isomer purification. In the latter instance, enantiomers are the products, and chiral stationary phases can be used for chromatographic purification. Furthermore, many methods have now been developed that generate numerous stereocenters in a single step. Highly selective reactions that produce one or more stereocenters with a high degree of selectivity ($\geq 90\%$), along with modern purification techniques, allow the preparation - in a single step - of chiral substances in $\geq 98\%$ ee for many reaction types.

In this book, we introduce one new paradigm: the recognition of a distinction between interligand and intraligand asymmetric induction. Briefly (see Section 1.3), this distinction recognizes the intimate involvement of metals in nearly all highly stereoselective reactions, and reflects the evolutionary development of modern asymmetric synthesis from issues of simple stereoselectivity to asymmetric catalysis. We hope that readers - after they become cognizant of this distinction - will find it useful in their efforts to improve on the methods described in this book.

The field continues to grow at an exponential rate, so that comprehensive coverage in a monograph is no longer possible. To even address the topic in a significant way is a formidable task, and to render the subject manageable, decisions had to be made about what to include and what to leave out.

In the end, we have selected several reaction categories, which comprise many of the most useful synthetic tools. As the title implies, the focus is on the principles that govern relative and absolute configurations in transition state assemblies. There are only a few principles, but they recur constantly. For example, organization around a metal atom, $A^{1,3}$ strain, van der Waals interactions, dipolar interactions, etc., are factors affecting transition state energies, and which in turn dictate stereoselectivity *via* transition state theory. One might call these analyses *molecular recognition at a saddle point*.

In writing this book, we have adhered to fairly strict limitations regarding terminology (and ask others to do the same). Sloppy terminology (*e.g.* "optically active synthesis") serves no useful purpose and intended meanings are often obscured (especially to future generations). To help readers understand our wording and to guide proper usage, a detailed, annotated glossary of stereochemical terms is included (and highlighted at the page margin for easy reference). This glossary will be useful to readers who are unfamiliar with the precise definitions of stereochemical terms (or their source). Included also are a number of

stereochemical terms that are not in current usage, but which are included for reference purposes.

The book comprises 8 chapters. The first provides background, introduces the topic of asymmetric synthesis, outlines principles of transition state theory as applied to stereoselective reactions, and includes the glossary. The second chapter details methods for analysis of mixtures of stereoisomers, including an important section on sample preparation. Then follow four chapters on carbon-carbon bond forming reactions, organized by reaction type and presented in order of increasing mechanistic complexity: Chapter 3 is about enolate alkylations, Chapter 4 nucleophilic additions to carbonyls. Chapter 5 is on aldol and Michael additions (2 new stereocenters), while Chapter 6 covers rearrangements and cycloadditions. The last two chapters cover reductions and oxidations.

In addition to tables of examples that show high selectivity, a transition state analysis is presented to explain - to the current level of understanding - the stereoselectivity of many of the reactions covered. Examination of these rationales often exposes the weaknesses of current theories, in that they cannot always explain the experimental observations. These shortcomings provide a challenge for future mechanistic investigations.

The decision has been made to omit details about auxiliary and/or catalyst preparation, auxiliary attachment and removal, and details of experimental procedures. Although we usually do not comment on the ease of auxiliary or catalyst preparation or removal, we have tried to focus on methods where this issue is not a problem - at least not on a laboratory scale. Also, when comparing selectivity data among various reagents for a given reaction, the reader should recognize that the indicated selectivities are for individually optimized experimental conditions (*i.e.*, solvent, temperature, time, etc.) that may not be the same from entry to entry, making relative selectivity comparisons tenuous. Examples included in the tables and schemes do not necessarily reflect the scope and limitations of a reaction; in some cases only the more stereoselective examples are included. We also do not include much detail on synthetic applications of the methods described. Figures that illustrate synthetic targets prepared using asymmetric synthesis as a key step - with the relevant stereocenters highlighted - are included, but outlines of the synthetic plans are not. Names of specific target molecules may be found in the index.

This book is intended for advanced undergraduate or graduate students, and other chemists needing a guide to the principles of asymmetric synthesis and stereoselectivity, and for experts who seek leading references to the primary literature. The book could be used for a course in organic mechanisms, stereochemistry, reactions, or synthesis.

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Finally, it has not been possible to describe all of the contributions that are relevant to each of the topics in the book. To those authors who feel that their work has not been given its due, or whose work has been overlooked, we offer our apologies. Comments are welcome.

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