Drugs, Catalysts, Materials (2-volume set)

Handbook of Combinatorial Chemistry

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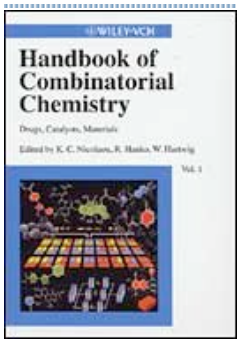

Combinatorial chemistry technology has matured from the initial promise of "make everything and something will work", to a more pragmatic and sophisticated field.

This is mainly do to the realization that no matter how many compounds are made, volume alone can never make up for poor library design. In fact, well-designed combinatorial libraries have been so successful in the pharmaceutical and drug discovery industries that this technology is now being adopted in other fields, including process development, catalysis and materials sciences.

This extensive, detailed and well referenced 2-volume set covers all aspects of combinatorial chemistry, including solid supports, linkers, chemical reactions, instrumentation, applications, philosophy, and so on, for both solution phase and solid phase methods. It covers the technical details of reaction mechanisms, as well as applications of those reactions. Many of the very recent, and hence elegant, methods are discussed, along with current applications and successful applications of this technology.

There are also several chapters that deal with the guiding principles behind library design — describing not just mechanical details, but how to apply these techniques effectively.

The two books are divided into a total of five main parts. The first five chapters serve as an introduction, giving background on history, general methodology and techniques. The next 15 chapters give detailed technical information on the various synthetic chemistry methods that can be applied in combinatorial chemisty, including basic reaction mechanisms and appropriate conditions. Several more specialized synthetic techniques, for special classes of compounds, are discussed in part III.

Part IV moves on to talk about guiding library design principles — what properties should be considered in the completed library, how to predict or measure those properties, and a successful case study. The final part, chapters 30 through 35, address special topics, such as novel applications in non-traditional fields.

The 35 chapters are written by a total of 73 authors, mainly from Germany and the United States. Each chapter is very thorough, with reaction schemes, photos of equipment, comprehensive tables, and

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extensive reference lists. Many chapters include website references for further reading. The vast number of chemical structures, reactions, and references make this thoroughly reseached volume a tremendous source of information on all types of organic chemistry (parts of it made me feel like I was back in an Advanced Organic class). I found particularly interesting the chapters on techniques and methods that are not yet well established, or in some cases even used, in combinatorial chemistry, but are moving in that direction.

The remainder of this review gives more specific details on the contents of this set.

The first part of the books is 'General Aspects', and covers the history and a general introduction to the methods used in combinatorial chemistry.

The first chapter, entitled 'Combinatorial Chemistry in Perspective', gives a very brief history of the development of combinatorial chemistry (both solution and solid phase methods), citing key references along the way. 'Introduction to Combinatorial Chemistry' is the second chapter, which provides an overview of the basic principles of combinatorial chemistry, and outlines the general operating principles that have been developed over years of use of this technology by a variety of groups. General descriptions of both solid- and solution-phase combinatorial methods are included, as well as the relative advantages of each method.

Chapter 3 is entitled 'Solid Phase and Soluble Polymers for Combinatorial Synthesis', and describes in detail the various types of solid supports and soluble polymeric supports that are currently available, as well as the various characteristics of each support (chemical stability, polarity, loading capacity). Understanding the properties of available polymers allows the chemist to decide which support is appropriate for the particular synthetic problem at hand.

The next chapter, 4, discusses 'Linkers for Solid Phase Synthesis'. This extensive chaper (110 pages and 589 references) discusses all aspects of linkers, the bifunctional chemical moieties that are used to attach the compound to the supporting resin. Detailed tables show cleavage conditions and structures that can be synthesized using each class of linker. Cleavage conditions for all classes of linkers are also discussed in detail, especially useful for developing orthogonal sets of reaction conditions.

With the large number of compounds involved in combinatorial synthesis, automated methods to track compound identity are required for efficiency. Technologies that are used to encode a member's reaction history (and hence it's chemical identity) onto the synthesis platform, called 'Encoding Technologies' are described in chapter 5. These include spatial (or positional) encoding, graphics, use of chemical tags, spectrometric encoding, or the newest and most advanced method — radiofrequency encoding.

'Instrumentation for Combinatorial Chemistry' is the focus of chapter 6. Its ability to be automated is one of the great strengths of combinatorial chemistry, and this chapter describes 15 currently available commercial systems for synthesis, as well as systems for purificaton and analysis and their characteristics — including their advantages and disadvantages.

With part II, the focus of the book shifts from an overview of general method to specific chemical reaction classes and their components. Each chapter discusses in detail a specific class, appropriate reaction conditions, and typical outcomes and byproducts.

8. 'Radical Reactions in Combinatorial Chemistry'. (While radical reactions have not yet been used in in the synthesis of combinatorial libraries, this chapter provides many example

reactions that demonstrate the potential in this area, as well as recently developed polymer supported reagents. As initial problems with complicated work-ups and purification are now being solved, this type of chemistry will become more widely used.)

9. 'Nucleophilic Substitution in Combinatorial and Solid-phase Synthesis'
10. 'Electrophilic Substitution in Combinatorial and Solid-phase Synthesis'
11. 'Elimination Chemistry in the Solution- and Solid-phase Synthesis of Combinatorial Libraries'
12. 'Addition to C–C Multiple Bonds (Except C–C Bond Formation)'
13. 'Addition to Carbon-Hetero Multiple Bonds'
14. 'Chemistry of the Carbonyl Group'
15. 'Oxidation Except C–C Double Bonds'
16. 'Reductions in Combinatorial Synthesis'
17. 'Cycloadditions in Combinatorial and Solid-Phase Synthesis'
18. 'Main Group Organometallics'
19. 'Enolates and Related Species in Combinatorial and Solid-phase Synthesis'
20. 'Solid-phase Palladium Catalysis for High-throughput Organic Synthesis'
21. 'Olefin Metathesis and Related Processes for C–C Multiple Bond Formation'

The second volume of this two-volume set begins with Part III, 'Special Synthetic Topics'. The four chapters in this section delve into more complicated synthetic areas and reactions.

While natural products have always played an important role in drug discovery and biological chemistry, it was only recently that their synthesis was even attempted by solid-phase methods. Chapter 21, 'Solid-phase Synthesis of Natural Products and Natural Product-like Libraries', goes through five examples of solid-phase synthesis of natural product analogs, though immobilization of the natural product skeleton on a solid support. It then goes on to discuss several studies of solid-phase syntheses of natural products, several novel linking and cleavage strategies.

Chaper 22, 'Solid-phase Synthesis of Heterocyclic Systems (Heterocycles Containing One Heteroatom)', systematically examines solid-phase synthesis of heterocycles containing one nitrogen, oxygen or sulfur atom. It is also organized by ring size and degree of unsaturation, and includes a table that lists all libraries of this type that were published between 1992 and 2000.

The next chapter talks about 'Multicomponent Reactions', or condensation reactions that involve three or more educts. These reactions have become more important over the last few decades, and examples of their use in solid- and solution-phase are discussed.

Carbohydrates are one of the most important classes of biological strucures, and chapter 24 discusses 'Strategies for Creating the Diversity of Oligosaccharides', with particular attention to potential application to automated combinatorial synthesis, an area that still face technical problems.

Part IV moves on to talk about 'Molecular Design and Combinatorial Compound Libraries'.

Chapter 25, 'Design Criteria', talks about general principles for designing libraries of compounds whose physiochemical properties match those of successful drugs, how to design diverse libraries, and certain structural motifs that deserve special attention. The next chapter, 'Estimation of Physicochemical and ADME Parameters', describes several methods for predicting pharmacokinetic properties, a major source of failure of drug candidates.

Chapter 27 gives a brief overview of computational methods used to assess diversity and drug-likeness of libraries before synthesis (virtual compound libraries), as well as methods used to quantitate molecular similarity.

Chapter 28 is 'Erythropoietin Sensitizer — A Case Study', describing both failures along the way and ultimate success. Chapter 29, discusses both empirical and model based approaches to 'Estimation of Stability and Shelf Life for Compounds, Libraries, and Repositories in Combination with Systematic Discovery of New Rearrangement Pathways', an area that is often neglected.

The final Part of this book discusses 'Novel Applications of Combinatorial Chemistry'. Now that chemists have over a decade of experience in combinatorial chemistry and high-throughput screening, mainly in the pharmaceutical drug discovery arena, these techniques are beginning to be applied in a variety of new areas. The chapters in this section discuss applications, outcomes, and future directions in a variety of areas.

30. 'Concepts of Combinatorial Chemistry in Process Development'
31. 'High-throughput Screening Applied to Process Development'
32. 'Combinatorial Methods in Catalysis'
33. 'Diversity-Based Identification of Efficient Homochiral Organometallic Catalysts for Enantioselective Synthesis'
34. 'Combinatorial Aspects of Materials Science'
35. 'Reprogramming Combinatorial Biology for Combinatorial Chemistry'

Volume II concludes with a brief index that covers both volumes.

Lisa M. Balbes
10 December 2002