Book Review

# Combinatorial Chemistry on Solid Supports. Topics in Current Chemistry, 278 Edited by Stefan Bräse (Universität Karlsruhe, Germany). Springer: Berlin, Heidelberg, New York. 2007. xii + 360. $339.00. ISBN 978-3-540-72509-1.

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BOOK REVIEWS

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This book, written by an international group of renowned experts in their respective field, covers recent advances in important topics regarding combinatorial chemistry on solid supports. It consists of seven chapters of variable quality, as is often the case with multiauthor books.

The first chapter, "Multifunctional Linkers for Combinatorial Solid Phase Synthesis" by Jung et al., covers the latest developments in multifunctional linkers (MFLs), defined as attachments that allow for the generation of more than one functional group upon cleavage from a solid support. This concept evolved since the beginning of solid-phase organic chemistry (SPOC) in the early 1990s. The need for a wide spectrum of postcleavage functionalities other than the classical carboxylic acid or amide has been the impetus for developing MFLs, and it has helped propel the use of such strategies as diversity-oriented synthesis. MFLs are discussed in terms of assembly on solid supports, stability toward reaction conditions, and the introduction of multifunctionality.

The authors review one of the oldest and most important classes of MFLs, the ester-type linker. The possibilities for cleaving ester- and thioester-linkers and the presence of such linkers in several commercially available resins are highlighted. Experimental conditions and synthetic protocols for accessing several functionalities, such as ketones, aldehydes, alcohols, amines, and hydroxamates, are concisely discussed. Another important class of linkers, carbamates and carbonates, are also reviewed, and the importance of carbamate linkers for the synthesis of *N*-containing cycles and the generation of biologically relevant urea derivatives is addressed. The recent introduction of triazene linkers, excellent precursors of diazonium salts, and the resulting opportunities for constructing a variety of compounds—with particular emphasis on heterocyclic structures—are also covered. Sulfur linkers play an important role in SPOC with one of the most important features of sulfur-linked resins being the possibility to tune the release of target compounds based on the oxidation state of the sulfur atom. In this context, the cleavage possibilities for sulfonium ions, sulfones, sulfoxide, sulfonyloxy, and sulfamate linkers are exhaustively described. Finally the authors discuss stannane, boron, and olefinic linkers and the increasing importance of these linkers for several metal-catalyzed conversions. Due to the importance of C−C bond formation, further development and new applications of such linkers are certain to occur in forthcoming years.

The second chapter, "Solid Phase Organometallic Chemistry" by Ljungdahl et al., covers research in this area from 2000 to 2006. Although the main emphasis is on Pd-catalyzed reactions, other aspects of organometallic reactions are also discussed. The first section deals with metal carbonyl complexes. The authors highlight the advantages of using transition metal complexes as linkers instead of the more classical attachment of the substrate via an organic linker. These types of linkers are stable under many reaction conditions and may be cleaved using a wide range of protocols without affecting the integrity of the carbon scaffold. Examples include chromium, cobalt, and rhodium, among others. The discussion covers the less-explored group 6 metal−carbene complexes and the use of polymer-bound complexes to circumvent the need for stoichiometric amounts of metal. Metathesis is also addressed, with methods using polymer-bound substrates or catalysts immobilized on a solid support being described. Some recent examples of Grignard reactions on solid supports are also provided. The chapter is largely devoted to Pd-catalyzed cross-coupling reactions, whereby novel approaches to the synthesis of several structurally diverse heterocyclic systems via C−C-bond forming reactions, such as Stille, Suzuki, Sonogashira, and others, are possible.

Hahn and Schepers describe the solid-phase chemistry of biologically active polyamine analogues in the next chapter, "Solid-phase Chemistry for the Direct Synthesis of Biologically Active Polyamine Analogs, Derivatives, and Conjugates". These classes of compounds are of great biological importance and play fundamental roles in many physiological functions. Nearly half of this chapter is devoted to the therapeutic properties of this class of compounds, which is somewhat out of the scope of this book. The remainder concerns solid-phase synthesis of polyamine derivatives. The authors discuss the drawbacks of solution-phase polyamine chemistry, such as selective protection, directed reaction of the various secondary and primary amino functionalities, and asymmetric derivatization, as well as how these challenges could be overcome by the implementation of solid phase protocols, with modular generation of polyamine backbones as one of the most viable strategies. Recent examples of synthetic procedures based on alkylation by $S_N2$-displacement and Fukuyama alkylation, as well as examples of amide reduction and reductive amination, are included. In addition, a very useful and up-to-date table containing resins and amine protecting groups used in the SPOC of polyamines is provided.

Chapter 4, "Combinatorial Solid-phase Natural Product Chemistry" by Mentel and Breinbauer, is a well-written, timely, and comprehensive review on the subject. Natural products chemistry is an important part of the drug discovery process since natural products contain important functionalities and/or scaffolds that interact with biological targets. Until now the structural complexity of natural products imposed serious challenges to implementing SPOC protocols, and the latest strategies on this topic are presented. Several representative examples of natural product libraries generated by modifying core structures, including those involving a frequently occurring natural product scaffold, as well as total synthesis of very complex polycyclic compounds are provided. Finally, the

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authors describe the use of polymer support reagents as strategies for improving the synthetic approach to structurally diverse natural products.

In the next chapter, "Multiple Peptide Synthesis to Identify Bioactive Hormone Structures", Haack and Beck-Sickinger address some of the concepts and methods in multiple peptide synthesis to determine the structural requirements of the ligand for binding to, and activation of, the corresponding receptor. Their focus is on the development of peptide ligands able to interact with the G protein-coupled receptor family. The role of these biological targets for signal transduction makes this topic of utmost importance for medicinal chemists. Several strategies for the design of peptide ligands, including backbone cyclization, peptide chimeras, and amide bond replacements, are covered in detail, and a very useful study of ligand−receptor interaction is provided.

Chapter 6, "Automated Solid Phase Oligosaccharide Synthesis" by Castagner and Seeberger, is both well written and descriptive. The authors discuss the role of glycosyl phosphates and glycosyl trichloroacetimidates in the automated assembly of oligosaccharides onto octenediol-functionalized polystyrene resin and also highlight the speed of the automated process versus classical carbohydrate synthesis. Automated oligosaccharide synthesis will undoubtedly play a key role in understanding the function of glycoconjugates in living cells.

Winssinger et al. emphasize the impact of automation in combinatorial chemistry from the point of view of small molecule microarrays (SMMs) in the final chapter, "Probing Biology with Small Molecule Microarrays". The success of DNA microarray technologies has facilitated the exploration of SMMs as an effective tool to probe biological events. The coverage encompasses all the stages involved in SMM preparation, including the most common strategies for immobilization, and various methods for SMM screening. In general, this review is excellent material for newcomers to this exciting field.

Considering the general title of the book, *Combinatorial Chemistry on Solid Support*s is far from being comprehensive, although very important aspects are covered. It will be a useful addition to the review literature and should be of interest to a significant segment of colleagues working in SPOC.

**Rolando Perez-Pineiro and Hicham Fenniri,**
*University of Alberta*

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**Computational and Structural Approaches to Drug Discovery: Ligand-Protein Interactions**. Edited by Robert M. Stroud and Janet Finer-Moore (University of California, San Francisco). Royal Society of Chemistry: Cambridge. 2008. $189.00. ISBN 978-0-85404-365-1.

In this book, computational and structural approaches to drug discovery are explored in five sections. The first consists of two chapters that provide "overviews of the drug-discovery field, written from the points of view of structural chemists and a medicinal chemist, respectively", to quote from the Preface. The remaining sections expand upon the themes introduced in the first and include discussions and examples of structure-based methods of drug design, the use of docking in drug discovery, high-throughput screening, and fragment-based methods in drug design. A subject index completes the book.

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**Catalysts for Fine Chemical Synthesis: Regio- and Stereo-Controlled Oxidations and Reductions, Volume 5**. John Wiley & Sons, Ltd.: Chichester. 2007. xvi + 312 pp. $200. ISBN 978-0-470-09022-0.

This book is part of the five-part series *Catalysts for Fine Chemical Synthesis*, the first of which was published in 2002. Although each volume has been published separately and has its own ISBN, all five may currently be purchased as a set. In this volume, "new or improved redox catalysts" are discussed, including organometallic systems, biocatalysts, and biomimetics. The opening chapter is an overview of industrially important catalysts for oxidation and reduction reactions, and the remaining eight are entitled: Asymmetric Hydrogenation of Alkenes, Enones, Ene-Esters and Ene-Acids; Asymmetric Reduction of Ketones; Imine Reduction and Reductive Amination; Oxidation of Primary and Secondary Alcohols; Hydroxylation, Epoxidation and Related Reactions; Oxidation of Ketones to Lactone or Enones; Oxidation C−C Coupling; and Oxidation of Sulfides and Sulfoxides. Each of these chapters includes a list of materials and equipment used, step-by-step details of the procedure for the transformation of each compound, a conclusion, and references. Many also include helpful tips and notes. A subject index completes the book.

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**Targets in Heterocyclic Systems: Chemistry and Properties, Volume 10 (2006)**. Edited by Orazio A. Attanasi (University of Urbino, Italy) and Domenico Spinelli (University of Bologna, Italy). Italian Society of Chemistry: Rome. 2007. viii + 360 pp. $129.00. ISBN 978-88-86208-51-2.

This latest edition of *Targets in Heterocyclic Systems* comprises 15 chapters covering the "synthesis, reactivity, activity (including medicinal), and mass spectrometry of different heterorings", to quote from the Preface. A sampling of the chapters includes "Macrocyclic Peptoids: *N*-Alkylated Cyclopeptides and Depsipeptides" by Wessjohann et al.; "From Acylsilanes to Fluorinated Heterocycles" by Plantier-Royon and Portella; and "Organophosphorus Reagents as a Versatile Tool in the Synthesis of α-Alkylidene-γ-butyrolactams" by Janecki. There is no subject index.

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**Creative Chemical Sensor Systems. Topics in Current Chemistry, 277**. Edited by Thomas Schrader (University of Duisburg-Essen, Germany). Springer: Berlin, Heidelberg, New York. 2007. xiv + 304 pp. $269.00. ISBN 978-3-540-71546-7.

Cram, Lehn, and Pedersen won the 1987 Nobel Prize "for their development and use of molecules with structure-specific interactions of high selectivity." Building on this legacy, organic chemists have pursued numerous creative approaches to solving the problem of molecular recognition, both inorganic and organic, which range in complexity from monovalent anions and cations to the plastic surface of a biomacromolecule. Inroads have even been made regarding the more formidable problem of building useful catalysts that hinge on molecular recognition. These intertwined problems are incredibly challenging, and we are still far from being able to dial affinity, selectivity, and activity into scaffold architectures. The momentum in the field of chemical sensing continues to grow, and Schrader has compiled an excellent set of articles that present a current snapshot of chemical sensing utilizing state-of-the-art approaches ranging from combinatorial receptor libraries to artificial membrane pores.

The focus of this compendium is on the "higher-hanging fruit", or rather synthetic approaches that offer the promise of bottom-up solutions and ultimately a clearer understanding of the forces of molecular recognition at play rather than the alternative "low-hanging fruit" that relies upon powerful biochemical solutions utilizing antibodies, proteins, and aptamers. Schrader has organized the contributions into two parts, the first focusing on new approaches for recognition of natural targets, and the second on clever chemical approaches for detecting analytes. The natural targets in the first section range from peptides and proteins to carbohydrates, which are targeted by combinatorial synthetic libraries, calixarenes, peptides, and boronic acids. The detection techniques in Part II cover colorimetric analyte responsive vesicles, small-molecule sensor array technology, approaches using synthetic pores, screening techniques for combinatorial catalyst libraries, and finally dynamic combinatorial library-derived sensor architectures.

Schmuck and Wich start the volume with a thoughtful review of how one might combine designed receptors and combinatorial peptide libraries, which has seen many advances since Still's pioneering work to target small peptides. In the second article, Coleman et al. provide a brief yet thorough overview of the calix[*n*]arene-based scaffolds for protein-sensing, a rapidly emerging area. Next, Baltzer presents current efforts in combining designed polypeptide−small molecule conjugates that provide a clever means for controlling affinity as well as specificity. To end the first section, the powerful approach involving boronic acid receptors for targeting carbohydrates and their practical application to PET-based sensors is presented by James.

In the beginning of Part II, Jelinek and Kolusheva describe recent efforts in biomimetic vesicle architectures for sensing a wide range of analytes from whole bacteria to ions utilizing light-responsive polydiacetylene impregnated vesicles. Anslyn and co-workers then present the state-of-the-art in mimicking olfactory and gustatory systems by creating sensor ensembles or the "electronic tongue," where a judicious choice of small-molecule receptor arrays allows for accurately identifying analytes ranging from small molecules and aminoglycosides to proteins. In the next chapter, Matile and co-workers discuss recent advances in utilizing designed synthetic pore-based platforms that, much like natural ion channels and membrane receptors, can transduce a wide variety of signals ranging from optical to electrical to detect analytes even in the single-molecule regime. Revell and Wennemers follow with an overview of screening approaches to better harness the power of catalyst design utilizing combinatorial chemistry. Finally, Otto and Severin review emerging approaches in designing and utilizing dynamic combinatorial libraries in combination with chemometric approaches for creating useful sensors.

Overall, the two sections play very well off each other, like two sides of the same coin, where the design of new molecular tool kits influences detection methodologies and, similarly, new detection architectures impact the synthesis of new classes of molecules. This volume is an excellent read for the budding and seasoned bioorganic chemist, chemical biologist, or supramolecular chemist as well as for those in allied fields who wish to apply emerging chemical techniques to solve current problems in chemical sensing. I highly recommend addition of this text to the collections of science libraries.

**Indraneel Ghosh,** *University of Arizona, Tucson*

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**Fluorescence of Supermolecules, Polymers, and Nanosystems. Springer Series on Fluorescence, 04**. Edited by M. N. Berberan-Santos (Instituto Superior Técnico, Lisboa, Portugal). Series edited by O. S. Wolfbeis. Springer: Berlin, Heidelberg, New York. 2008. xviii + 468 pp. $269.00. ISBN 978-3-540-73927-2.

This book was developed from presentations at the "9th International Conference on Methods and Applications of Fluorescence: Spectroscopy, Imaging and Probes" held in Lisbon in September 2005. There are 18 chapters grouped under the following headings: History and Fundamental Aspects; Molecular and Supramolecular Systems; Polymers, Semiconductors, Model Membranes and Cells; and Nanotubes, Microparticles and Nanoparticles. A subject index completes the book.

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**Superelectrophiles and Their Chemistry**. By George A. Olah (University of Southern California, Los Angeles) and Douglas A. Klumpp (Northern Illinois University, DeKalb). John Wiley & Sons, Inc.: Hoboken, NJ. 2007. viii +302 pp. $125.00. ISBN 978-0-470-04961-7.

Superacids are very much associated with the award of the Nobel Prize in 1994 to Olah, the first author of this work, for his discovery of methods for the study of long-lived carbocations. His earlier books *Carbocations and Electrophilic Reactions* in 1973 and *Superacids* in 1985 (with a second Edition now in preparation) summarize much of this work. He and Klumpp, a former postdoctoral associate, have now written this monograph, which presents a nice up-to-date picture of the generation, structure, and properties of superelectrophiles, a new field that is a further outgrowth of work done in superacid media. The discovery of superelectrophiles stems from the work of Brouwer and Kiffen in 1973, in which acetyl cation and other oxycations in superacids were able to abstract hydride ions from

alkanes, and Olah's attribution in 1975 of this high reactivity to a superelectrophilic species, protonated acetyl cation, a dication or protosolvated cation. Similar behavior was noted for the nitronium ion. By now, a large number of related supernucleophiles have been discovered. Both the high reactivity and also the dicationic (or tricationic, etc.) nature of these putative intermediates define them as "superelectrophiles".

This volume builds on reviews by Olah and co-workers from 1983, 1989, 1993, and 2004 and reviews by Pagni in 1984 and by Nenajdenko et al. in 2003. It is comprehensive, with some 500 references, many from the laboratories of the authors themselves. Chapter 2 is a good summary of reactivity and kinetics that provides experimental evidence for the involvement of superelectrophilic intermediates. Spectroscopic studies are often limited by the low concentration of dicationic species in solution, but some examples have been directly observed by NMR and IR spectroscopy. Such studies are more definitive when they are reinforced with predicted NMR chemical shifts and IR frequencies and intensities from *ab initio* calculations. Gas-phase experiments by mass spectrometry on dications and a summary of theoretical studies are also presented in this chapter. Chapter 3 covers methods for the generation of superelectrophiles in solution. The authors nicely organize the studies on known superelectrophiles according to structure and the distance between the charged centers: geminal, vicinal gitonic and 1,3 gitonic, and distonic (Chapters 4−7).

A final chapter is a discussion of the significance and outlook for the field. Superelectrophiles are of fundamental interest in their own right, but they are also relevant to problems in media that are less acidic than superacids, such as zeolites, Nafion-H and H-ZSM-5, and certain active sites of enzymes. The ability of such species to functionalize simple hydrocarbons and other practical applications will make this a subject of interest to industrial chemists in both the petrochemical and pharmaceutical industries. The book is quite readable. It will be indispensable for those working in the field and a valuable source for students and others with a general interest in learning about superelectrophiles.

**Donald D. Aue,** *University of California, Santa Barbara*

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