DIVERSITY-ORIENTED SYNTHESIS
DIVERSITY-ORIENTED SYNTHESIS

Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology

Edited by

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WILEY
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FOREWORD

The gap between insights into human disease and therapeutics that arise from these insights is closing, but it cannot close fast enough. Society has patiently invested in science. But its expectation of scientists—that we mitigate suffering from disease—must be met if we expect to receive its support in the future.

Advances in human biology are revealing novel insights into the cause of disease and requirements for the maintenance of disease. But the therapeutic targets that are arising, such as transcription factors and RNA molecules, do not fit conveniently into what we believe is currently achievable in drug discovery. Overcoming this belief is the twenty-first century challenge for organic chemistry, organic synthesis, and chemical biology. If we can do so, drug discovery and human health will be transformed.

The insights provided in Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology leave me feeling optimistic. I can sense the fearlessness and audacity of the authors as they undertake the impossible. The three-dimensional world of biological macromolecules is now interfaced with the three-dimensional world of small molecules to a far greater degree. Therapeutic targets are now seeing the full force of modern organic chemistry. Using simple concepts exploited by nature’s synthesis of naturally occurring small molecules, small molecules with the physical properties required of drugs yet with the topographic properties needed for achieving the impossible are now accessible. Bravo!

STUART L. SCHREIBER

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October 2012
Since the early reports by Stuart L. Schreiber, diversity-oriented synthesis (DOS) has become a new paradigm for developing large collections of structurally diverse small molecules as probes to investigate biological pathways and to provide a larger array of the chemical space in drug discovery issues. The principles of DOS have evolved from the concept of generating structurally diverse compounds from a divergent approach consisting of a complexity-generating reaction followed by cyclization steps and appendage diversity, to the development of different cyclic structures through the build/couple/pair approach. The concept of expanding the molecular complexity to explore the chemical space more thoroughly produced new advances in generating chemical libraries. Moreover, technology advances followed the need of automation in this field, thus producing high-tech instrumentation for library development and compound management, as well as improving high-throughput screening facilities. The possibility of creating new highly diverse and complex molecular platforms and the achievement of hundreds to thousands to millions of compounds is producing significant advances in chemical biology and drug discovery. This is due primarily to improvement in the quality of chemical libraries, which are more stereochemically rich and structurally complex. Moreover, advances in bioinformatics and systems biology are enabling an interdisciplinary setting between chemistry and biology in advancing the knowledge about the functions of biological systems and the correlation between genes and function. Finally, drug discovery is also taking advantage of DOS concepts in several medicinal chemistry programs, which in the near future will produce advances in both target and ligand discovery.

The book has been conceived in four parts, encompassing synthetic methods to achieve small-molecule collections according to DOS principles, strategies to develop
DOS libraries, screening methods for ligand identification, and selected significant applications of small molecules in drug discovery and chemical biology.

The first chapter deals with the basics of diversity-oriented synthesis, including definitions of molecular diversity and chemical space, discussing how DOS relates to classic combinatorial chemistry and showing significant approaches that have been developed for expanding the chemical diversity, including the well-known build/couple/pair concept introduced by Schreiber.

Part I encompasses key chemical methods addressing the generation of small molecules according to DOS principles and also important classes of molecules generated through DOS approaches, including peptidomimetics and macrocycles. Accordingly, important topics for accessing complexity and diversity have been taken into account. Chapter 2 reports the application of multicomponent reactions as a powerful tool to introduce chemical diversity and multifunctional building blocks in a DOS approach. Chapter 3 covers the use of cycloaddition reactions in the fields of DOS as a key approach to provide cyclic and heterocyclic compounds with a high degree of structural complexity and skeletal diversity. Phosphine organocatalysis is described in Chapter 4 as a valid approach encompassing catalytic methods in the DOS area, and stimulating examples with a wide array of building blocks are reported, together with some applications in chemical biology. Chapter 5 introduces the role of domino reactions in DOS as a concept devoted to the generation of small molecules in few synthetic steps, taking advantage of pericyclic, anionic, radical, or transition metal–mediated domino processes. Finally, solid-phase methods are reported in Chapter 7 to present the use of this important technique in generating large collections of small molecules according to DOS principles. The application of DOS to achieve specific classes of compounds is exemplified in Chapters 6 and 8, where the generation of peptidomimetics and macrocyclic structures, respectively, are reported.

In Part II the concept of diversity-oriented synthesis is expanded to describe chemical libraries and how these two elements are related. Chapter 9 presents a synthesis of chemical libraries inspired by natural products as a key platform in addressing both chemical diversity and molecular complexity. Chapter 10 deals with chemoinformatic methods of analyzing the chemical space, and several methods for representing small-molecule libraries are outlined. Chapter 11 reports the approach of DNA-encoded chemical libraries as an innovative technology addressing the need of huge libraries for drug discovery issues and the requirement of a fast deconvolution method.

Part III is dedicated to modern approaches for screening DOS libraries, including the basics of high-throughput and high-content screening (Chapter 12), small-molecule microarrays (Chapter 13), and the use of yeast as a model in smart screening assays encompassing chemical genetics and chemical genomics (Chapter 14). In silico methods are described in Chapters 15 and 16, which are connected to the chemoinformatic concepts reported in Chapter 10, and they present, respectively, the virtual screening of chemical libraries and the concepts of activity landscapes and activity cliffs as powerful methods for the analysis of structure–activity relationship data.
Finally, Part IV presents significant applications of DOS libraries and small molecules in the fields of drug discovery (Chapter 17) and chemical biology (Chapter 18), reporting selected key studies in these research areas, and giving a picture of the prominent role of diversity-oriented synthesis in present and future biomedical research.

I express my thanks to the authors who contributed the careful and detailed reviews presented in this book. These presentations should interest not only those readers who currently work in the field of diversity-oriented synthesis, but also those who are considering this approach in the fields of drug discovery and chemical biology. I hope that these chapters will stimulate further advances in this rapidly developing field.

Also, I would like to thank my mentor, professor Antonio Guarna, for kind support during the development of this book, and throughout my career in research.

Andrea Trabocchi

Florence, Italy
October 2012
ABBREVIATIONS

\( \mu_w \) Microwave irradiation

1,3-DNB 1,3-Dinitrobenzene

3CR Three-component reaction

3D Three-dimensional

4CR Four-component reaction

AcOH Acetic acid

AcONH\(_4\) Ammonium acetate

AD Activating domain

AD-mix Asymmetric dihydroxylation-mix

ADME Absorption, distribution, metabolism, and elimination

AIBN 2,2'-Azobis(isobutyronitrile)

AIDS Acquired immunodeficiency syndrome

AIV Avian influenza virus

All Allyl

ALPHA Amplified luminescent proximity homogeneous assay

ATP Adenosin triphosphate

B/C/P Build/couple/pair

BCL-2 \( \beta \)-Cell lymphoma 2

BD Binding domain

BEMP 2-t-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

BIOS Biology-oriented synthesis

BMMSG Bipartite matching molecular series graph

Bn Benzyl

Boc \( t \)-Butoxycarbonyl
<table>
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>Bredereck’s reagent</td>
<td>$t$-Butoxybis(dimethylamino)methane</td>
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<tr>
<td>BRET</td>
<td>Bioluminescence resonance energy transfer</td>
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<tr>
<td>BRo5</td>
<td>“Beyond the rule of 5”</td>
</tr>
<tr>
<td>Bs</td>
<td>Brosyl</td>
</tr>
<tr>
<td>BTPP</td>
<td>$t$-Butyliminotri(pyrrolidino)phosphorane</td>
</tr>
<tr>
<td>Bts</td>
<td>Benzothiazole-2-sulfonyle</td>
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<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<td>CAP</td>
<td>Complementary amphiphilic pairing</td>
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<td>Central nervous system</td>
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<tr>
<td>COX-1</td>
<td>Cyclooxygenase-1</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>CPCCG</td>
<td>Conrad Prebys Center for Chemical Genomics</td>
</tr>
<tr>
<td>CuAAC</td>
<td>Copper-catalyzed azide–alkyne cycloaddition</td>
</tr>
<tr>
<td>CXCR4</td>
<td>CXC chemokine receptor 4</td>
</tr>
<tr>
<td>Da</td>
<td>Dalton</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-Diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DAD</td>
<td>Dual activity difference</td>
</tr>
<tr>
<td>DAmP</td>
<td>Decreased abundance by mRNA perturbation</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>DCC</td>
<td>$N,N'$-Dicyclohexylcarbodiimide</td>
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<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>Ddz</td>
<td>$\alpha,\alpha$-Dimethyl-3,5-dimethoxybenzyloxy carbonyl</td>
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<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>Dess–Martin periodinane</td>
<td>1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one</td>
</tr>
<tr>
<td>DH-PH</td>
<td>Dbl homology/pleckstrin homology</td>
</tr>
<tr>
<td>DHFR</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td>(DHQD)PHAL</td>
<td>Hydroquinidine 1,4-phthalazinediyl diether</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
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<tr>
<td>DIC</td>
<td>$N,N'$-Diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>$N,N'$-Diisopropylethylamine</td>
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<tr>
<td>DKP</td>
<td>Diketopiperazine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>DMAD</td>
<td>Dimethylacetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>(N,N)-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td>DMEDA</td>
<td>(N,N)-dimethylethylenediamine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-Dimethylformamide</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DMT</td>
<td>(4,4')-Dimethoxytrityl</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DNMT</td>
<td>DNA methyltransferase</td>
</tr>
<tr>
<td>DOPA</td>
<td>3,4-Dihydroxyphenylalanine</td>
</tr>
<tr>
<td>DOS</td>
<td>Diversity-oriented synthesis</td>
</tr>
<tr>
<td>DPC</td>
<td>DNA-programmed chemistry platform</td>
</tr>
<tr>
<td>DPPA</td>
<td>Diphenylphosphoryl azide</td>
</tr>
<tr>
<td>DPPP</td>
<td>Diphenylphosphinopropane</td>
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<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
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<tr>
<td>DRCS</td>
<td>Delimited reference chemical spaces</td>
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<tr>
<td>DSC</td>
<td>Differential scanning calorimetry</td>
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<td>DTPA</td>
<td>Diethylenetriamine pentaacetic acid</td>
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<tr>
<td>DTS</td>
<td>DNA-templated synthesis</td>
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<tr>
<td>DTT</td>
<td>Dithiothreitol</td>
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<tr>
<td>EC</td>
<td>Endothelial cell</td>
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<tr>
<td>ECL3</td>
<td>Extracellular loop</td>
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<tr>
<td>EDCI</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>EGFP</td>
<td>Enhanced green fluorescent protein</td>
</tr>
<tr>
<td>ELSD</td>
<td>Evaporative light scattering detection</td>
</tr>
<tr>
<td>ER</td>
<td>Endoplasmic reticulum</td>
</tr>
<tr>
<td>ERK</td>
<td>Extracellular signal-regulated kinase</td>
</tr>
<tr>
<td>ESAC</td>
<td>Encoded self-assembling chemical libraries</td>
</tr>
<tr>
<td>ESR</td>
<td>Electron spin resonance</td>
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<tr>
<td>F-SPE</td>
<td>Fluorous solid-phase extraction</td>
</tr>
<tr>
<td>FACS</td>
<td>Fluorescence-activated sorting instrument</td>
</tr>
<tr>
<td>FBDD</td>
<td>Fragment-based drug discovery</td>
</tr>
<tr>
<td>FGI</td>
<td>Functional group interconversion</td>
</tr>
<tr>
<td>FI</td>
<td>Fluorescence intensity</td>
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<tr>
<td>FKBP</td>
<td>FK506-binding protein</td>
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<tr>
<td>Fmoc</td>
<td>Fluorenylmethyloxycarbonyl</td>
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<td>FOS</td>
<td>Function-oriented synthesis</td>
</tr>
<tr>
<td>FP</td>
<td>Fluorescence polarization</td>
</tr>
<tr>
<td>FRET</td>
<td>Fluorescence resonance energy transfer</td>
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<tr>
<td>FTase</td>
<td>Farnesyltransferase</td>
</tr>
<tr>
<td>GBP</td>
<td>Glycan-binding protein</td>
</tr>
<tr>
<td>GEF</td>
<td>Guanine nucleotide exchange factor</td>
</tr>
<tr>
<td>GFP</td>
<td>Green fluorescent protein</td>
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<tr>
<td>GGTase</td>
<td>Geranylgeranyltransferase</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Gli</td>
<td>Glial transcription factor</td>
</tr>
<tr>
<td>Glu</td>
<td>Glutamic acid</td>
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<tr>
<td>GLUT</td>
<td>Glucose transporters</td>
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<tr>
<td>GNF</td>
<td>Genomics Institute of the Novartis Research Foundation</td>
</tr>
<tr>
<td>GPCRs</td>
<td>G-protein-coupled receptors</td>
</tr>
<tr>
<td>Grb2</td>
<td>Growth factor receptor-bound protein 2</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>Benzylidene–bis(tricyclohexylphosphate) dichlororuthenium; bis(tricyclohexylphosphate) benzylidine ruthenium(IV) dichloride</td>
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<tr>
<td>Grubbs II</td>
<td>[1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(phenylmethylene)(tricyclohexylphosphate) ruthenium</td>
</tr>
<tr>
<td>GSIS</td>
<td>Glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>GST</td>
<td>Glutathione S-transferase</td>
</tr>
<tr>
<td>GST-PBD</td>
<td>GST fusion protein of the p21-binding domain of PAK1</td>
</tr>
<tr>
<td>GTPase</td>
<td>Guanine triphosphatase</td>
</tr>
<tr>
<td>HA</td>
<td>Hemagglutinin</td>
</tr>
<tr>
<td>HaM</td>
<td>Heck-aza-Michael</td>
</tr>
<tr>
<td>HATU</td>
<td>N,N,N′,N′-Tetramethyl-2-(azabenzotriazol-1-yl)uronium hexafluorophosphate</td>
</tr>
<tr>
<td>HBA</td>
<td>Hydrogen-bond acceptors</td>
</tr>
<tr>
<td>HBD</td>
<td>Hydrogen-bond donors</td>
</tr>
<tr>
<td>HCS</td>
<td>High-content screening</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HDAC</td>
<td>Histone deacetylase</td>
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<tr>
<td>Hh</td>
<td>Hedgehog</td>
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<tr>
<td>HIP</td>
<td>Haploinsufficiency profiling</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HMDS</td>
<td>Hexamethyldisilazide</td>
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<tr>
<td>HMG-CoA</td>
<td>3-Hydroxy-3-methylglutaryl coenzyme A</td>
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<tr>
<td>HMPT</td>
<td>Hexamethylphosphorous triamide</td>
</tr>
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<td>hMSC</td>
<td>Human mesenchymal stem cell</td>
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<td>HOP</td>
<td>Homozygous profiling</td>
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<td>Hoveyda–Grubbs II</td>
<td>[1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(2-isopropoxyphenylmethylene)ruthenium</td>
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<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
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<tr>
<td>HPNCC</td>
<td>Hereditary nonpolyposis colorectal cancer</td>
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<tr>
<td>Hsc</td>
<td>Heat shock cognate protein</td>
</tr>
<tr>
<td>Hsp</td>
<td>Heat shock protein</td>
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<tr>
<td>HTS</td>
<td>High-throughput screening</td>
</tr>
<tr>
<td>ICCB</td>
<td>Harvard Medical School's Institute for Chemistry and Cell Biology</td>
</tr>
<tr>
<td>IDPCR</td>
<td>Interaction-dependent PCR</td>
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</tbody>
</table>