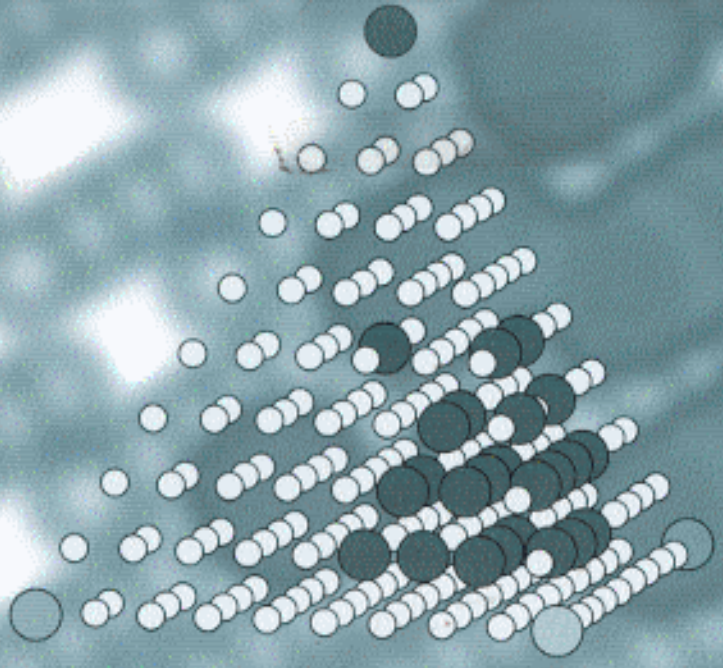

Combinatorial Chemistry

Edited by

Hicham Fenniri

PRACTICAL APPROACH

Contents

Preface *page* v
List of protocols *xxiii*
Abbreviations *xxvii*

1 Synthesis of combinatorial libraries using the portioning-mixing procedure *1*
Árpad Furka, Linda K. Hamaker, and Mark L. Peterson

1 Introduction 1
2 The portioning-mixing (split-mix) synthesis *1*
Basic principles *1*
Important features of the synthesis 3
3 Manual and automated synthesis *5*
Manual synthesis *5*
Automated synthesis *8*
4 Preliminary considerations for library design *12*
The weight of the libraries *12*
The weight of the solid support 12
The significance of the number of resin beads *13*
5 Synthetic strategies for library construction *13*
Soluble libraries 14
Tethered libraries *15*
6 Summary *29*
Acknowledgements *29*
References *29*

2 One-bead one-compound combinatorial library method *33*
Gang Liu and Kit S. Lam

1 Introduction *33*
2 Synthesis of the peptide library *34*
Preparation of the amino acid solutions 34
Synthesis of a linear peptide library on solid phase using TentaGel resin with 19 eukaryotic amino acids (cysteine excluded) *35*

Synthesis of disulfide cyclic peptide library 38
Synthesis of Dpr-Dpr cyclic peptide (oxime bond) library 39
On-resin synthesis of a cyclic peptide library using Lys and Glu side-chains 40

3 Library screening 42

References 48

3 Synthesis and screening of positional scanning synthetic combinatorial libraries 51

Clemencia Pinilla, Jon R. Appel, Sylvie E. Blondelle, Colette T. Dooley, Jutta Eichler, Adel Nefzi, John M. Ostresh, Roland Martin, Darcy B. Wilson, and Richard A. Houghten

1 Introduction 51

2 Mixture-based synthetic combinatorial libraries 51
Positional scanning concept 52
Synthesis of a tripeptide PS-SCL 54
Alkylation of peptide PS-SCL 56
PS-SCL reduction 59
From peptides to small organic and heterocyclic compounds 60

3 Screening mixture-based libraries 61
PS-SCL deconvolution 62
Assay optimization 63

4 Library screening using ELISA 64

5 Identification of T cell-specific ligands 67

6 Identification of antimicrobial and antifungal compounds 69

7 Library screening using a radioreceptor assay 70

8 Identification of enzyme inhibitors using PS-SCLs 71

References 72

4 High-throughput combinatorial synthesis of discrete compounds in multimilligram quantities: non-chemical encoding and directed sorting 75

Xiao-Yi Xiao and K. C. Nicolaou

1 Introduction 75

2 Non-chemical encoding and directed sorting 76
Radiofrequency tags 77
Radiofrequency tagged MicroKans 78
Radiofrequency tagged MicroTubes 78
2D bar codes and bar coded microreactors 78

3 Applications in combinatorial synthesis 79
R_f tagged MicroKans: synthesis of taxoid, epothilone, and muscone libraries 79
R_f tagged MicroTubes: synthesis of a tyrphostin library 88
Bar coded microreactors: application to oligonucleotide synthesis 91

4 Conclusion 92

References 92

5 Positionally addressable parallel synthesis on continuous membranes 95
Holger Wenschuh, Heinrich Gausepohl, Lothar Germeroth, Mathias Ulbricht, Heike Matuschewski, Achim Kramer, Rudolf Volkmer-Engert, Niklas Heine, Thomas Ast, Dirk Scharn, and Jens Schneider-Mergener

1 Introduction 95
2 SPOT synthesis of peptides on continuous cellulose surfaces 96
Preparation of the cellulose matrix 96
Positionally addressable array synthesis on SPOT membrane 98
The peptide synthesis cycle 99
Cleavage of the peptides and subsequent handling 101
3 Synthesis of PNA arrays using the SPOT technique 102
Reagents and equipment 102
Reagents preparation 102
Linker chemistry 103
Membrane preparation 104
Synthesis verification 104
Final work-up 105
Quality control 105
Comments 105
4 Preparation of stable polymeric membranes for SPOT synthesis of organic compound libraries 106
Hydroxy-functionalized PEG acrylate polypropylene membranes (PP-g-P(PEGMA)) 106
Amino-functionalized ester-free PEG methacrylamide polypropylene membranes (PP-g-P(AmPEGMAm)) 110
Comments on the functionalization procedures and applications of the novel polymeric membranes 113
References 116

6 Resins and anchors for solid phase organic synthesis 117
Martin Winter and Ralf Warrass

1 Introduction 117
Why do organic synthesis on a solid support? 117
The orthogonality principle 117
The practice of solid phase synthesis 118
2 Solid supports 118
Physical properties of solid supports 118
Families of solid supports and their specific properties 121
3 Linkers and anchors in SPOS 127
Choosing the right linker 128
Introduction of the first building block 133
Determination of the loading of the resin 135
Cleavage 136
Acknowledgements 136
References 136

7 Organic reactions on solid support—an overview *139*
William M. Bennett
1 Introduction 139
2 Solid phase organic reactions—1998 140
Anchoring reactions 140
Amide bond forming reactions 145
Aromatic substitution 148
Condensation reactions 151
Cycloaddition reactions 154
Organometallic reactions 155
Michael addition 157
Heterocycle forming reactions 158
Multi-component reactions 161
Olefin forming reactions 162
Oxidation reactions 163
Reduction reactions 165
Substitution reactions 167
Protection/deprotection reactions 172
Other solid phase reactions 174
Cleavage from supports 178
Polymer-supported reagents 185
Scavenger resins 191
References 192
3 Solid phase organic reactions—1999 198
Anchoring reactions 199
Amide bond forming reactions 204
Aromatic substitution 208
Condensation reactions 213
Cycloaddition reactions 216
Organometallic reactions 217
Michael addition 218
Heterocycle forming reactions 220
Multi-component reactions 224
Olefin forming reactions 225
Oxidation reactions 226
Reduction reactions 227
Substitution reactions 231
Protection/deprotection reactions 236
Other solid phase reactions 239
Cleavage reactions 245
Resin-supported reagents 252
Scavenger resins 256
References 257

8 Analytical methods in combinatorial chemistry *263*
Bing Yan, Yen-Ho Chu, Michael Shapiro, Ramsay Richmond, Jefferson Chin, Lina Liu, and Zhiguang Yu
1 Introduction 263
2 Analytical methods in reaction optimization 263
FTIR methods 264

Gel phase NMR *267*
Magic angle spinning (MAS) NMR *268*
Spectrophotometric methods *270*

3 Quality control of libraries from parallel synthesis *272*
MS analysis *272*
MS-guided purification *274*
High-throughput NMR *274*

4 Analysis of compounds from pooled libraries *275*
MS analysis *276*
Other methods *276*

5 The screening of pooled combinatorial libraries *278*
On-bead screening *278*
Solution affinity selection methods *281*

6 Concluding remarks *284*

References *285*

9 Multi-component reactions (MCRs) of isocyanides and their chemical libraries *287*
Ivar Ugi and Alexander Dömling

1 Introduction *287*

2 Isocyanide chemistry *288*

3 MCR chemistry *290*

4 Stereoselective U-4CRs and their applications in the synthesis of α-amino acids, peptides, and related compounds *293*

5 Multi-component reactions of five and more reactants *296*

References *299*

10 Multi-step solution phase combinatorial synthesis 303
Dale L. Boger and Joel Goldberg

1 Introduction *303*

2 Aspects of solution phase combinatorial chemistry *303*
Solution phase versus solid phase combinatorial chemistry *303*
Synthesis of mixtures versus individual compounds *305*
Development of solution phase combinatorial chemistry *305*

3 Cyclic anhydride chemistry with extractive purification *306*

4 Higher order libraries *312*
Dimerization, trimerization, or tetramerization of iminodiacetic acid diamide libraries *312*
Dimerization coupling with dicarboxylic acids *313*
Dimerization via olefin metathesis coupling *316*
Tetramerization of iminodiacetic acid diamides *318*

5 Deconvolution *323*
Introduction to deconvolution 323
Iterative/recursive deconvolution *323*
Deletion synthesis deconvolution and scanning deconvolution *324*

References 326

11 Experimental techniques in fluorous synthesis: a user's guide *327*
Dennis P. Curran, Sabine Hadida, Armido Studer, Mu He, Sun-Young Kim, Zhiyong Luo, Mats Larhed, Anders Hallberg, and Bruno Linclau

1 Introduction *327*
2 General aspects of fluorous chemistry 328
Features of fluorous techniques 328
Reaction and extraction solvents *330*
Fluorous starting materials *331*
Fluorous reverse phase silica gel *331*
3 Fluorous tin chemistry *333*
Synthesis of representative perfluorohexylethyltin reagents *333*
Parallel synthesis with a fluorous tin hydride *336*
Synthesis and reaction of a fluorous tin azide *336*
Rapid fluorous Stille coupling reactions with microwave heating *338*
Synthesis of 'propylene-spaced' fluorous allyltin reagents *340*
Parallel allylation of aldehydes with fluorous allyltins *341*
4 Fluorous synthesis *343*
Fluorous isoxazoline synthesis without intermediate purification *344*
Fluorous Ugi sequence *346*
5 Fluorous quenching (scavenging) *347*
Tin hydride quench of alkenes by hydrostannation *347*
Fluorous amine quenching in robotic parallel synthesis of ureas *349*
6 Conclusions *351*
Acknowledgements *351*
References *351*

12 Combinatorial synthesis on multivalent oligomeric supports *353*
Ronald M. Kim and Jiang Chang

1 Introduction *353*
2 Use of supports in organic synthesis *353*
Solid phase synthesis *353*
Liquid phase synthesis *354*
3 Overview of combinatorial synthesis on multivalent oligomeric supports (COSMOS) 355
4 Supports for COSMOS *356*
General considerations *356*
PAMAM dendrimers *357*
Polyethylene glycol-armed supports *358*
5 Organic synthesis in COSMOS *361*
6 Size-based purification of homogeneous reaction products in COSMOS *363*
General considerations *363*
Ultrafiltration *364*
Size exclusion chromatography *364*
Size exclusion chromatography resins for COSMOS purification *365*
Methods for COSMOS purification via SEC *367*
Automation and parallelization of COSMOS purification by SEC *370*
References *371*

13 Automated solution phase synthesis and its application in combinatorial chemistry *373*
Tohru Sugawara and David G. Cork

1 Introduction *373*
2 Automated synthesis systems and workstations *373*
The automated synthesis hardware *375*
The automated synthesis control software *377*
3 Applications of automated synthesis systems *379*
Unusual amino acid derivatives *379*
Condensed azole derivatives *380*
Fragment peptide derivatives *384*
β-Lactam derivatives *388*
4 Applications of automated synthesis workstations *391*
Preparative multigram scale synthesis *391*
Automated synthesis with supported reagents *396*
Catalytic hydrogen transfer *398*
References *400*

14 Combinatorial discovery and optimization of electrocatalysts *401*
Erik Reddington, Jong-Sung Yu, Benny C. Chan, Anthony Sapienza, Guoying Chen, Thomas E. Mallouk, Bogdan Gurau, Rameshkrishnan Viswanathan, Renxuan Liu, Eugene S. Smotkin, and S. Sarangapani

1 Introduction *401*
Combinatorial materials discovery *401*
Electrocatalysts for the direct methanol fuel cell (DMFC) *402*
2 Optimization of the catalyst processing conditions *403*
Reduction of metal salts *404*
Optimization of reduction parameters *404*
3 Preparation of electrode arrays *406*
Selecting a substrate *406*
Mapping the arrays *407*
Automating the synthesis of arrays *407*
General rules *410*
4 Optimizing the screening and testing conditions *412*
Optimization of screening conditions of anode electrocatalysts *412*
DMFC testing experiments *414*
Testing and screening of methanol-tolerant cathode materials *414*
5 Results and conclusions *416*
Results *416*
Conclusions *418*
Acknowledgements *419*
References *419*

15 Combinatorial library synthesis using polymer-supported catalysts *421*
Shu Kobayashi

1 Introduction *421*
2 Tetrahydroquinoline library *423*

3 β-Amino ketone and ester library *426*
4 α-Amino nitrile library *429*
5 Conclusion *430*
Acknowledgements *431*
References *431*

16 Combinatorial approaches to chiral catalyst discovery *433*
Marc L. Snapper and Amir H. Hoveyda
1 Introduction *433*
Background *434*
Lewis acid catalysis *434*
2 Catalyst discovery (optimization of reactivity) *435*
Indexed grid *436*
High-throughput screening *441*
3 Catalyst optimization (optimization of selectivity) *442*
Positional scanning of ligand structure *443*
Positional scanning for optimal ligand structure in Strecker reaction *446*
4 Discussion *451*
Overview of current status *451*
Future opportunities *452*
Acknowledgements *453*
References *453*

A1 *List of suppliers* *457*

Index *463*