

## Table of Contents

Preface XV

General introduction XVII

List of Authors XXI

### 1 Purification Principles in High-Speed Solution-Phase Synthesis 1

*Steffen Weinbrenner and C. Christoph Tzschucke*

1.1 Introduction 1

1.2 Liquid-Liquid Extraction 2

1.2.1 Aqueous Work-Up 2

1.2.2 Phase-Separation Techniques 6

1.2.3 Fluorous Biphasic Systems 6

1.2.4 Ionic Liquids 9

1.3 Solid-Phase Extraction 10

1.3.1 Silica Gel and Alumina 10

1.3.2 Fluorous Silica Gel 11

1.3.3 Ion Exchange 14

1.4 Covalent Scavengers 19

1.4.1 Solution Scavengers 19

1.5 Polymer-Assisted Solution-Phase Chemistry (PASP) 21

1.5.1 Scavenger Resins 21

1.5.2 Resin Capture 24

1.6 Complex Purification Strategies 26

1.7 Conclusion and Outlook 29

References 29

### 2 Linkers for Solid-Phase Organic Synthesis (SPOS) and Combinatorial

**Approaches on Solid Supports 33**

*Willi Bannwarth*

2.1 General 33

2.2 Linkers for Functional Groups 34

2.2.1 Linkers for Carboxyl Functions 34

2.2.2 Linkers for Amino Functions 36

2.2.2.1 Linkers Based on Benzyloxycarbonyl (Z) 36



2.2.2.2	Linker Based on <i>tert</i> -Butyloxycarbonyl (Boc)	40
2.2.2.3	A Urethane Linker Cleavable by Fluoride Ions	41
2.2.2.4	Benzyl-Linked Approaches for Secondary Amines	42
2.2.2.5	Linkers Based on Acetyldimedone	44
2.2.2.6	Trityl Linker	46
2.2.3	Linkers for the Attachment of Alcohols or Phenols	50
2.2.3.1	Linker Based on the Tetrahydropyranyl (THP) Group	50
2.2.3.2	Silyl Linker for the Attachment of Alcohols	53
2.2.3.3	Miscellaneous Linkers for Alcohols	56
2.2.3.4	Serine-Based Linker for Phenols	57
2.2.3.5	Carboxy-Functionalized Resins for the Attachment of Phenols	58
2.2.4	Acetal Linker for the Preparation of Aldehydes	58
2.3	Traceless Linker Systems	61
2.3.1	Application of Hofmann Elimination in Linker Design	61
2.3.2	Traceless Linkers Based on Silyl Functionalization	64
2.3.3	Traceless Linkers Based on C–C Coupling Strategies	68
2.3.4	Traceless Linkers Based on $\pi$ -Complexation	71
2.3.5	Traceless Linkers Based on Olefin Metathesis	71
2.3.6	Traceless Synthesis Using Polymer-Bound Triphenylphosphine	78
2.3.7	Decarboxylation-Based Traceless Linking	80
2.3.8	Traceless Linker Based on Aryl Hydrazides	81
2.3.9	Triazene-Based Traceless Linker	83
2.3.10	Traceless Linker Based on Sulfones	85
2.3.11	Traceless Concept Based on Cycloaddition-Cycloreversion	85
2.4	Photolabile Linker Units	89
2.4.1	Introduction	89
2.4.2	Linkers Based on <i>o</i> -Nitrobenzyl	89
2.4.3	Photocleavable Linker Based on Pivaloyl Glycol	91
2.5	Safety-Catch Linkers	93
2.6	Dual Linkers and Analytical Constructs	101
2.7	Summary and Outlook	105
	References	105

### 3 Cyclative Cleavage: A Versatile Concept in Solid-Phase Organic Chemistry 111

*Josef Pernerstorfer*

3.1	Principles	111
3.2	Carbon-Heteroatom Bond Formation	112
3.2.1	Hydantoins	112
3.2.2	Pyrazolones	115
3.2.3	2-Aminoimidazolones	116
3.2.4	Urazoles and Thiourazoles	118
3.2.5	Oxazolidinones	119
3.2.6	Diketopiperazine Derivatives	120
3.2.7	4,5-Dihydro-3(2 <i>H</i> )-pyridazinones	123



3.2.8	Dihydropyridines	124
3.2.9	5,6-Dihydropyrimidine-2,4-diones	125
3.2.10	2,4-(1 <i>H</i> ,3 <i>H</i> )-Quinazolinediones	126
3.2.11	Quinazolin-4(3 <i>H</i> )-ones	126
3.2.12	4-Hydroxyquinolin-2(1 <i>H</i> )-ones	128
3.2.13	3,4-Dihydroquinoxalin-2-ones	128
3.2.14	1,4-Benzodiazepine-2,5-diones	129
3.2.15	Oxacephams	129
3.2.16	Lactones	130
3.2.17	Tetrahydrofurans	133
3.3	Formation of C–C Bonds	133
3.3.1	Tetramic Acids	133
3.3.2	Wittig-Type Reactions	134
3.3.3	Stille Reactions	136
3.3.4	S-Ylides	137
3.3.5	Ring-Closing Metathesis	137
3.4	Miscellaneous	137
3.4.1	Furans	138
3.4.2	Phenols	138
3.5	Summary	140
	References	140
<b>4</b>	<b>C–C Bond-Forming Reactions</b>	<b>143</b>
	<i>Wolfgang K.-D. Brill and Gianluca Papeo</i>	
4.1	General	143
4.2	Transition Metal-Mediated Vinylations, Arylations, and Alkylations	143
4.2.1	The Suzuki Coupling	144
4.2.2	The Heck Reaction	159
4.2.3	The Sonogashira Coupling	164
4.2.4	The Stille Coupling	172
4.2.5	Remarks on Pd-mediated Couplings on a Polymeric Support	174
4.2.6	Experimental Approach	175
4.2.6.1	Materials and Methods	175
4.3	Miscellaneous Aryl-Aryl Couplings	189
4.3.1	Ullmann/Wurz Coupling on a Polymeric Support	189
4.3.2	Intermolecular Alkyl-Alkyl Coupling	190
4.3.3	Negishi Couplings	192
4.4	Alkene Metathesis Reactions	193
4.4.1	Ring-Closing Metathesis (RCM) Reactions	195
4.4.2	Cross-Metathesis (CM) Reactions	199
4.5	Cycloaddition Reactions on a Polymeric Support	200
4.5.1	C1 Fragments (Additions of Carbenes to Alkenes)	201
4.5.2	Electron-Deficient C2 Fragments (Cycloadditions Involving Azomethines, Nitrones, Nitrile Oxides, and Dienes)	207



4.5.3	Electron-Rich C2 Fragments ([2 + 1], [2 + 2], [2 + 3], [2 + 4]-Cycloadditions, Additions with Nitrile Imines, Nitrile Oxides, and Chalcones)	216
4.5.4	C-X Fragment on Solid Support	224
4.5.5	C-C-X Fragments on the Polymeric Support	229
4.5.6	C-X-C Fragment	233
4.5.7	C-X-Y-Fragment (Nitrile Oxide on Solid Phase)	235
4.5.8	C-C-C-C Fragments on Solid Phase	237
4.5.9	C-C-C-X Fragments on Solid Support	252
4.5.10	C-C-X-C Fragment on Solid Support (Grieco Three-Component Condensation)	254
4.5.11	C-X-X-C Fragment on Solid Support	255
4.5.12	C-C-X-X Fragment on Solid Support ([4 + 1]-Cycloaddition)	257
4.5.13	Cycloadditions Involving Larger Support-Bound Fragments: Intramolecular Hetero Diels-Alder	257
4.5.14	Pauson-Khand and Nicolas Reaction	260
4.5.15	C-Nitroalkene Additions	263
4.6	Multicomponent Reactions (MCRs)	263
4.6.1	Ugi Four-Component Reaction	264
4.6.1.1	Ugi Reaction with Solid-Supported Isonitriles	264
4.6.1.2	Ugi reaction with Solid-Supported Amines	267
4.6.1.3	Ugi Reaction with Solid-Supported Carboxylic Acid	269
4.6.1.4	Derivatization of Boronic Acids	270
4.6.2	Other MCRs Using Isonitriles	271
4.6.2.1	Petasis (Borono-Mannich) Condensation	271
4.6.2.2	Imidazo[1,2- $\alpha$ ]pyridines	272
4.6.2.3	Biginelli Dihydropyrimidines Synthesis	273
4.6.2.4	Thiophene Synthesis	275
4.6.2.5	Tetrahydropyridones	276
4.6.2.6	Cyclization	278
4.6.2.7	Cleavage	278
4.7	Electrophiles Bound to the Polymeric Support	278
4.7.1	Reactions with Organyls of Zn, Mg, Li	278
4.7.1.1	Reactions Involving Grignard Reagents, Organolithium, and Organozinc Reagents	279
4.7.1.2	Reactions with Water-Sensitive Reagents such as Grignard Reagents, Lithium Alkyls, or Zinc Organyls [375] on Solid Phases	279
4.7.2	Indium-Mediated Allylation of Support-Bound Aldehydes	282
4.7.3	Sn/Pd-Mediated C-Allylation of Solid-Phase-Bound Aldehydes	284
4.7.4	Metal-free Alkylations by Acyl Halides on Polymeric Supports	286
4.7.5	Nucleophilic Aromatic Substitution with C-Nucleophiles	286
4.7.6	Pyridine-N-Oxides	289
4.7.7	Trapping Phosphorus Ylides with a Ketone Bound to the Solid Phase	289



4.7.8	Michael Acceptor on Solid Phase (Route to 3,4,6-Trisubstituted Pyrid-2-ones)	290
4.7.9	Solid phase N-Acyliminium Ions, Imines and Glyoxylate Chemistry	291
4.7.10	Solid-Supported Imines and Glyoxylate	294
4.7.11	Solid-Phase Pictet-Spengler Reactions	299
4.7.12	Solid-Phase Baylis-Hillman Reaction	307
4.7.13	Solid-Phase Fischer Indole Synthesis	310
4.7.14	Solid-Phase Madelung Indole Synthesis	311
4.7.15	Boron Enolates with Support-Bound Aldehydes	312
4.7.16	Summary of Solid-Supported Electrophiles	314
4.8	Generation of Carbanions on Solid Supports	314
4.8.1	Transition Metal-Mediated Carbanion Equivalent Formations	320
4.8.2	Lewis Acid-Mediated Electrophilic Substitutions	321
4.8.3	Generation of Stabilized Carbanions Under Basic Conditions	327
4.8.4	Experimental Approach	334
4.8.5	Stereoselective Alkylations on a Chiral Solid Phase	340
4.9	Solid-Phase Radical Reactions	340
4.10	Outlook	347
	References	347
<b>5</b>	<b>Combinatorial Synthesis of Heterocycles</b>	<b>361</b>
	<i>Eduard R. Felder and Andreas L. Marzinzik</i>	
5.1	Introduction	361
5.2	Benzodiazepines	363
5.3	Hydantoins and Thiohydantoins	369
5.4	$\beta$ -Lactams (Azetidin-2-ones)	375
5.5	$\beta$ -Sultams	376
5.6	Imidazoles	379
5.7	Pyrazoles and Isoxazoles	384
5.8	Thiazolidinones	387
5.9	Triazoles	390
5.10	Oxadiazoles	396
5.10.1	1,2,4-Oxadiazoles	397
5.10.2	1,3,4-Oxadiazoles	399
5.11	Piperazinones	401
5.12	Piperazinediones (Diketopiperazines)	406
5.12.1	Diketopiperazines via Backbone Amide Linker (BAL) [117]	406
5.12.2	Piperazinediones by Acid Cyclative Cleavage; Method A, including Reductive Alkylation	409
5.12.3	Piperazinediones by Acid Cyclative Cleavage; Method B, including $S_N2$ Displacement	410
5.13	Diketomorpholines	413
5.14	Triazines	413
5.15	Pyrimidines	417



- 5.16 Indoles 421
- 5.17 Quinazolines 428
- 5.18 Benzopiperazinones and Tetrahydroquinoxalines 439
- 5.19 Tetrahydro- $\beta$ -carboline 443
- 5.20 Outlook 449
- References 449
- 6 Polymer-Supported Reagents: Preparation and Use in Parallel Organic Synthesis 457**  
*Berthold Hinzen and Michael G. Hahn*
- 6.1 Introduction 457
- 6.2 Preparation and Use of PSRs 459
  - 6.2.1 Covalent Linkage Between the Active Species and Support 459
    - 6.2.1.1 PSRs Prepared by Solid-Phase Chemistry 459
    - 6.2.1.2 PSRs Prepared by Polymerization 483
  - 6.2.2 Immobilization Using Ionic Interactions 490
    - 6.2.2.1 Oxidants 490
    - 6.2.2.2 Reducing Agents 492
    - 6.2.2.3 Alkoxides Bound to a Polymer Support 494
    - 6.2.2.4 Horner-Emmons Reagents on Supports 494
    - 6.2.2.5 Halogenating Agents 495
- 6.3 Support-Bound Sequestering and Scavenging Agents 497
- 6.4 Combination of PSRs 497
- 6.5 Summary and Conclusion 509
- References 509
- 7 Encoding Strategies for Combinatorial Libraries 513**  
*Berthold Hinzen*
- 7.1 Introduction 513
- 7.2 Positional Encoding 514
- 7.3 Graphical/Barcode Encoding 514
- 7.4 Chemical Encoding 514
- 7.5 Mass Spectrometric Encoding 515
- 7.6 Radiofrequency Encoding 516
- 7.7 Conclusion 516
- References 516
- 8 Automation and Devices for Combinatorial Chemistry and Parallel Organic Synthesis 519**  
*Christian Zechel*
- 8.1 Introduction 519
- 8.2 Synthesis 520
  - 8.2.1 General Remarks 520
  - 8.2.2 Manual Systems 522



8.2.3	Semi-Automated Systems	540
8.2.4	Automated Systems	540
8.2.5	Special Applications	546
8.2.5.1	Process Development	546
8.2.5.2	Equipment for Parallel Reactive Gas Chemistry	549
8.3	Liquid-Liquid Extraction	550
8.4	Equipment for High-Throughput Evaporation	551
8.5	Automated Solid and Resin Dispensing	555
8.6	Suppliers	556
<b>9</b>	<b>Computer-Assisted Library Design</b>	<b>559</b>
	<i>Andreas Dominik</i>	
9.1	Introduction	559
9.1.1	Optimizing Combinatorial Libraries	559
9.1.2	A Computer-Assisted Design Strategy	560
9.1.3	What is Diversity?	562
9.1.3.1	First Examples	562
9.1.3.2	Diversity of Drug Molecules	562
9.1.3.3	Diversity and Similarity	564
9.2	How Do We Compute Diversity?	566
9.2.1	An Overview	566
9.2.2	Descriptors	567
9.2.3	Classification and Mapping	567
9.2.4	Interpretation of Results: Summary	568
9.3	Descriptors	568
9.3.1	Simple Filters	571
9.3.2	Physico-chemical Constants	571
9.3.2.1	Estimation of logP Values	571
9.3.2.2	Estimation of pK <sub>A</sub> Values	572
9.3.3	Drug-Likeness	572
9.3.3.1	The Rule of 5	572
9.3.3.2	Artificial Neural Networks	573
9.3.3.3	Further Improvements of Drug-Likeness Prediction	573
9.3.3.4	ADME and Toxicity Profiling	574
9.3.4	Molecular Fingerprints	575
9.3.5	Substructure Descriptors	575
9.3.6	Single Atom Properties	576
9.3.6.1	Atom Charges	577
9.3.6.2	Atomic Lipophilicity Parameters	577
9.3.7	Topological Indices	577
9.3.7.1	Atom Indices	577
9.3.7.2	Molecule Indices	578
9.3.8	Topological Autocorrelation and Cross-correlation Coefficients	578
9.3.9	Scaffold-based Similarity	580
9.3.10	Descriptors from a Pharmacophore Model	580



9.3.11	Stereochemistry	581
9.3.12	Descriptors from the Three-Dimensional Structure	582
9.3.13	Polar Surface Area (PSA)	583
9.3.14	Distance Matrix	583
9.3.15	Autocorrelation Coefficients	583
9.3.15.1	Based on Atom Coordinates	585
9.3.15.2	Based on Surface Properties	585
9.3.15.3	Based on Potential Fields	586
9.3.16	Radial Basis Function (RBF)	586
9.3.17	Virtual Screening	586
9.4	Clustering and Mapping Algorithms	587
9.4.1	Distance Metric	587
9.4.1.1	Tanimoto Coefficient	587
9.4.1.2	Euclidean Distance	589
9.4.1.3	Nonlinear Distance Scaling	589
9.4.1.4	Mahalanobis Distance	589
9.4.2	Dissimilarity-Based Selection	589
9.4.3	Mapping-Based Selection	590
9.4.3.1	Nonlinear Mapping	590
9.4.3.2	Self-Organizing Maps	591
9.4.3.3	Minimal Spanning Tree	592
9.4.4	Cluster-Based Selection	592
9.4.4.1	Hierarchical Clustering Analysis	592
9.4.5	Partition-Based Selection	593
9.5	Strategies for Compound Selection	593
9.5.1	Optimization Based on Diversity of Building Blocks	594
9.5.1.1	Advantages of Educt-Based Optimization	594
9.5.2	Optimization Based on Diversity of Product Libraries	595
9.5.2.1	Advantages of Product-Based Optimization	595
9.5.3	Library Selection	597
9.5.4	Evolutionary Design Circle	598
9.6	Comparison of Descriptors and Selection Methods	599
9.6.1	Topological Descriptors	599
9.6.2	Descriptors Based on Three-Dimensional Structure	602
9.6.3	Clustering Methods	602
9.6.4	Summary	603
9.7	Example Library of Thrombin Inhibitors	603
9.7.1	Virtual Library Design	605
9.7.2	Final Library Design	606
9.7.2.1	Maximum Diversity Library	607
9.7.2.2	Targeted Library	607
9.7.2.3	Descriptor Sets	607
9.7.3	Comparison of the Libraries	607
9.7.4	Summary	609
	References	610



<b>10</b>	<b>Assays for High-Throughput Screening in Drug Discovery</b>	<b>615</b>
	<i>Christian M. Apfel and Thilo Enderle</i>	
10.1	Screening in Drug Discovery	615
10.1.1	The Role of HTS	615
10.1.2	Overview of Screening Assays	617
10.1.3	Requirements for Successful HTS	617
10.1.4	Target Classes	619
10.1.4.1	Overview	619
10.1.4.2	G-Protein-Coupled Receptors (GPCR)	619
10.2	Assay Methods Based on Different Readouts	621
10.2.1	Radioactivity	621
10.2.1.1	General	621
10.2.1.2	Scintillation Proximity Assay (SPA)	622
10.2.1.3	FlashPlate™/Scintistrip™/Cytostar-T™	624
10.2.1.4	Instrumentation for Radioisotope Assays	625
10.2.2	Colorimetry	626
10.2.3	Fluorescence	628
10.2.3.1	General	628
10.2.3.2	Fluorescence Intensity (FI)	631
10.2.3.3	Fluorescence Polarization (FP)	632
10.2.3.4	Fluorescence Resonance Energy Transfer (FRET)	635
10.2.3.5	Time-Resolved Fluorescence (TRF)	637
10.2.3.6	Fluorescence Lifetime (FLT)	641
10.2.3.7	Fluorescence Correlation Spectroscopy (FCS)	641
10.2.3.8	Fluorescent Intensity Distribution Analysis (FIDA)	641
10.2.4	Chemiluminescence and Bioluminescence	642
10.2.4.1	General	642
10.2.4.2	Aequorin Ca <sup>2+</sup> Assay	643
10.2.4.3	AlphaScreen™	644
10.2.4.4	BRET™	645
10.3	Special Assay Applications with Optical Readout	646
10.3.1	Fluorimetric Imaging Plate Reader (FLIPR)	646
10.3.2	Reporter Assays	646
10.3.3	Assays Based on Enzyme Fragment Complementation (EFC)	648
10.3.3.1	General	648
10.3.3.2	Low Affinity Complementation System	648
10.3.3.3	High Affinity Complementation System	648
	Abbreviations	649
	Trademarks and Suppliers	650
	References	651
	<b>Appendix: Cheminformatics and Web Resources for Combinatorial Chemistry</b>	<b>659</b>
	<i>Berthold Hinzen and Johannes Köbberling</i>	
A.1	Websites	659



## XIV | *Table of Contents*

A.2	(Online) Journals	660
A.3	Companies and Academic Groups Involved in Combinatorial Chemistry	660
A.4	Reaction Databases	661
A.5	Summary	661
<b>Index</b>		<b>663</b>