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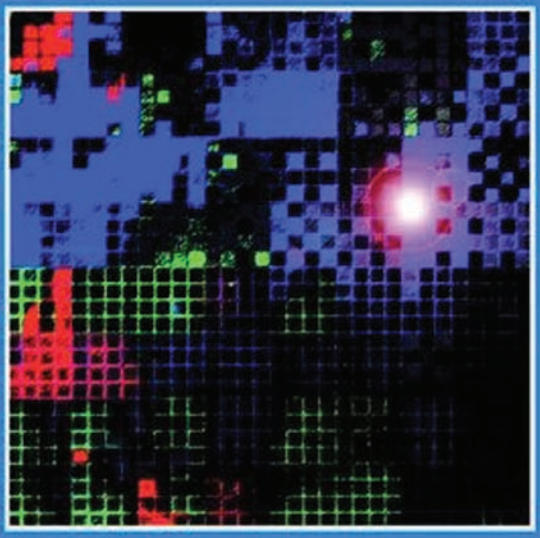
Combinatorial Chemistry

A Practical Approach

Edited by Willi Bannwarth and Eduard Felder



Methods and Principles in Medicinal Chemistry

Volume 9

Edited by
R. Mannhold,
H. Kubinyi,
H. Timmerman

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Preface

Different stages of the drug discovery process demand different qualities and quantities of the test compounds. The primary goal of lead discovery is to identify chemicals that bind to the selected target. This goal is nowadays achieved by developing high-throughput screening processes for the analysis of a large number of samples. Traditionally, pharmaceutical companies tested their in house collections containing large numbers of compounds. These collections are biased towards chemical classes developed or acquired by the company. As a main disadvantage, the expansion of chemical collections using conventional approaches is expensive.

Combinatorial chemistry offers a solution to bypass most of these problems; it allows the rapid and inexpensive synthesis of hundreds of thousands of compounds, and large combinatorial libraries can significantly supplement the chemical diversity of traditional collections. Analogs of the leads identified from chemical libraries can be easily synthesized.

After lead identification, the drug discovery process shifts to lead optimization: analogs of the original leads are synthesized to obtain compounds with the desired pharmacodynamic and kinetic properties. Synthesized compounds are tested in different assays, some of which require large quantities of material. Hundreds to thousands analogs are produced at the lead optimization stage. Traditionally, chemists had to rely on sequential exploration of structure-activity relationships of the synthesized analogs. Parallel synthesis makes this process more efficient by enabling the simultaneous preparation of hundreds and even thousands of analogs in quantities sufficient for the lead optimization stage.

The present book reviews the new tool combinatorial chemistry: after a general introduction into the principal methods main chapters cover in detail combinatorial chemistry in solution and solid phase chemistry. Further chapters deal with devices and equipment for combinatorial chemistry, the application of polymer-bound reagents and computer-assisted library design. The book is written by experts of the pharmaceutical industry who use combinatorial chemistry in their daily work and thus, the present volume differs in various aspects from other monographs on this topic. First of all, it covers the entire field of combinatorial chemistry and it primarily focuses on its practical aspects by giving concrete recipes. Last, but not least, a comprehensive literature collection on solid phase chemistry expresses its outstanding usefulness.

We thank the contributors to this volume, in particular Willi Bannwarth and Eduard Felder, for their cooperation. We are sure that scientists, interested in combinatorial chemistry, will find in this volume the adequate information to successfully apply the corresponding techniques.

January 2000

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Contents

1 General Introduction
Willi Bannwarth 1

2 Combinatorial Chemistry in Solution
Willi Bannwarth 5

2.1 An Introduction to Solution Chemistry 5
2.2 Multicomponent Condensations (MMCs) 6
2.2.1 Introduction 6
2.2.2 MCC Reactions involving Isonitriles 6
2.2.3 Aminimides by Multicomponent Condensation 12
2.2.4 Biginelli more component reaction 13
2.2.5 Hantzsch Pyridine Synthesis 13
2.2.6 Three-Component Condensation Based on a 1,3-Dipolar Cycloaddition 16
2.2.7 More Component Reaction Based on the Tsuge Reaction 16
2.2.8 A $SmCl_3$-initiated Multicomponent Condensation 18
2.2.9 Mannich Reaction 18
2.2.10 Grieco Three-Component Reaction 20
References 21
2.3 Purification Principles in High-Speed Solution-Phase Synthesis
Steffen Weinbrenner 22
2.3.1 Introduction 22
2.3.2 Liquid – Liquid Extraction 22
2.3.2.1 Aqueous work-up 22
2.3.2.2 "Fluorous work-up" 26
2.3.2.3 Phase Separation Techniques 28
2.3.3 Solid-Phase Extraction 29
2.3.3.1 Silica Gel and Alumina 29
2.3.3.2 Fluorinated Silica Gel 30
2.3.3.3 Ion Exchange 30
2.3.4 Covalent Scavengers 35
2.3.4.1 Solution Scavengers 35
2.3.5 Polymer-Assisted Solution-Phase Chemistry (PASP) 37
2.3.5.1 Scavenger Resins 39
2.3.5.2 Resin Capture 40

2.3.6 Complex Purification Strategies 41
2.3.7 Conclusion and Outlook 44
References 45

3 Solid-Phase Chemistry
Willi Bannwarth 47

3.1 Linkers for Solid-Phase Organic Synthesis (SPOS) and Combinatorial Approaches on Solid Support 47
3.1.1 General 47
3.1.2 Linkers for Functional Groups 48
3.1.2.1 Linkers for Carboxyl Functios 48
3.1.2.2 Linkers for Amino Functions 48
3.1.2.2.1 Linkers Based on Benzyloxycarbonyl (Z) 49
3.1.2.2.2 Linker Based on Tert. Butoxycarbonyl (Boc) . . 53
3.1.2.2.3 A Urethane Linker to be Cleaved by Fluoride Ions 55
3.1.2.2.4 Benzyl-Linked Approaches for Secondary Amines 55
3.1.2.2.5 Linkers Based on Acetyldimedone 58
3.1.2.2.6 Trityl Linker 59
3.1.2.2.7 Hydroxylamine Linker for the Formation of Weinreb Amides 62
3.1.2.3 Linker for the Attachment of Alcohols or Phenols 62
3.1.2.3.1 Linker Based on the Tetrahydropyranyl (THP) Group 62
3.1.2.3.2 Silyl Linker for the Attachment of Alcohols . . 65
3.1.2.3.3 Miscellaneous Linkers for Alcohols 66
3.1.2.3.4 Serine-Based Linker for Phenols 67
3.1.2.3.5 Carboxy Functionalized Resins for the Attachment of Phenols 68
3.1.2.4 Acetal Linker for the Preparation of Aldehydes 68
3.1.3 Traceless Linker Systems 70
3.1.3.1 Application of Hofmann Elimination in the Linker Design 70
3.1.3.2 Traceless Linkers Based on Silylfunctionalization 72
3.1.3.3 Traceless Linkers Based on Olefin Metathesis 75
3.1.3.4 Traceless Synthesis by Using Polymer-Bound Triphenyl Phosphine 80
3.1.3.5 Decarboxylation-Based Traceless Linking 81
3.1.3.6 Traceless Linker Based on Arylhydrazide 81
3.1.3.7 Triazene-Based Traceless Linker 84
3.1.4 Photolabile Linker Units 84
3.1.4.1 Introduction 84
3.1.4.2 Linkers Based on o-Nitrobenzyl 85
3.1.4.3 Photocleavalble Linker Based on Pivaloylglycol 86
3.1.5 Safety Catch Linkers 88
3.1.6 Traceless Concept Based on Cycloaddition – Cycloreversion 93

3.1.7 Summary and Outlook 95
References 95

3.2 Cyclative Cleavage: A Versatile Concept in Solid-Phase Organic Chemistry
Josef Pernerstorfer and Thomas Krämer 99
3.2.1 Principles 99
3.2.2 Carbon-Hetero Bond Formation 100
3.2.2.1 Hydantoins 100
3.2.2.2 Pyrazolones 102
3.2.2.3 Oxazolidinones 104
3.2.2.4 Diketopiperazines 105
3.2.2.5 Dihydropyridines 107
3.2.2.6 5,6-Dihydropyrimidine-2,4-diones 108
3.2.2.7 2,4(1*H*,3*H*)-Quinazolinediones 108
3.2.2.8 4-Hydroxyquinolin-2(1*H*)-ones 110
3.2.2.9 1,4-Benzodiazepine-2,5-diones 110
3.2.2.10 Tetrahydro-ß-Carboline Derivatives 111
3.2.2.11 Lactones 112
3.2.2.12 Tetrahydrofurans 113
3.2.3 Formation of C-C Bonds 114
3.2.3.1 Tetramic Acids 114
3.2.3.2 Wittig-Type Reactions 115
3.2.3.3 Stille Reactions 117
3.2.3.4 Ring Closing Metathesis 118
3.2.4 Miscellaneous 118
3.2.4.1 Furans 118
3.2.4.2 Phenols 119
3.2.5 Summary 120
References 121

3.3 C-C Bond Forming Reactions
Wolfgang Brill 123
3.3.1 General 123
3.3.2 Transition Metal-Mediated Vinylations and Arylations 123
3.3.2.1 Suzuki Coupling 123
3.3.2.2 Stille Coupling 126
3.3.2.3 The Heck Reaction 127
3.3.2.4 The Sonogashira Coupling 129
3.3.3 Remarks on Pd-Mediated Couplings on a Polymeric Support 130
3.3.4 Experimental Approach 131
3.3.4.1 Materials and Methods 131
3.3.4.2 Suzuki Couplings 132
3.3.4.3 Stille Coupling 134
3.3.4.4 Heck Reaction 135
3.3.4.5 Sonogashira Coupling 136
3.3.5 Reactions Involving Grignard Reagents or Organozinc Reagents . . . 138

3.3.5.1 Grignard Reagents, Lithium and Organozinc Reagents . . 138
3.3.5.2 Pd-Mediated Couplings with Organozinc Reagents 138
3.3.5.3 General remarks on preparations involving water-sensitive reagents. 139
3.3.5.4 Experimental: Grignard on Solid Phase 140
3.3.6 Olefin Metathesis 141
3.3.6.1 Mechanism 141
3.3.6.2 Experimental: Metathesis on Solid Phase 143
3.3.7 Generation of Carbanions and their Equivalents on the Solid Support 144
3.3.7.1 Experimental Approach 147
3.3.7.2 Comment on Reactions using Schwesinger Base 149
3.3.7.3 Wittig and Related Reactions 149
3.3.8 Radical Reactions to Achieve C-C Bonds 151
3.3.9 The Pauson – Khand Cyclization 152
3.3.9.1 Experimental Approach 152
3.3.10 Summary and Outlook 153
References 153

3.4 Combinatorial Synthesis of Heterocycles
Eduard R. Felder and Andreas L. Marzinzik 157
3.4.1 Introduction 157
3.4.2 Benzodiazepines 158
3.4.3 Hydantoins and Thiohydantoins 163
3.4.4 ß-Lactams (Azetidin-2-ones) 166
3.4.5 ß-Sultams 167
3.4.6 Imidazoles 169
3.4.7 Pyrazoles and Isoxazoles 171
3.4.8 Thiazolidinones 173
3.4.9 Thiotriazoles 175
3.4.10 Piperazinones 178
3.4.11 Piperazine-diones (Diketopiperazines) 181
3.4.11.1 Diketopiperazines Backbone via Amide Linker (BAL)[178] . 182
3.4.11.2 Piperazine-diones by acid cyclative cleavage.- Method A, including reductive alkylation 183
3.4.11.3 Piperazine-diones by acid cyclative cleavage.- Method B, including SN2 displacement 185
3.4.12 Diketomorpholines 186
3.4.13 Triazines 187
3.4.14 Pyrimidines 189
3.4.15 Indoles 191
3.4.16 Quinazolines 194
3.4.17 Benzopiperazinones 199
3.4.18 Tetrahydro-ß-carbolines 201
3.4.19 Outlook 205
References 205

4 Polymer-Supported Reagents: Preparation and Use in Parallel Organic Synthesis
Berthold Hinzen 209

4.1 Polymer-Supported Reagents 209
4.2 Preparation and Use of Polymer-Supported Reagents 210
4.2.1 Covalent Linkage Between the Active species and Support 211
4.2.1.1 PSR Prepared by Solid-Phase Chemistry 211
Activators for Amide Couplings 211
Wittig Reagents 214
Polymer-Supported Triphenylphosphine and Pd-Complexes 215
Polymer (PEG)-Supported Burgess Reagent 216
Organotin Reagents 217
4.2.1.2 PSR Prepared by Polymerization 218
Supported Borane Amino Alcohol Complexes and Other Supported Lewis Acids 219
Polymer-Supported Quinine Based Catalysts 221
Supported (Salen) Complexes 223
Polymer-Supported Schiff Base Zinc Complexes 223
4.2.2 Immobilization using Ionic Interactions 224
4.2.2.1 Oxidants 224
4.2.2.2 Reducing Agents 227
4.2.2.3 Alkoxides Bound to a Polymer Support 227
4.2.2.4 Horner – Emmons Reagents on Support 228
4.2.2.5 Halogenating Agents 228
4.3 Support-Bound Sequestering and Scavenging Agents 230
4.4 Combination of PSRs 231
4.5 Summary and Conclusion 235
References 236

5 Encoding Strategies for Combinatorial Libraries
Berthold Hinzen 239

5.1 Introduction 239
5.2 Positional Encoding 239
5.3 Graphical/Barcode Encoding 240
5.4 Chemical Encoding 240
5.5 Mass Spectroscopic Encoding 241
5.6 Radiofrequency Encoding 241
5.7 Conclusion 242
References 242

6 Automation and Devices for Combinatorial Chemistry and Parallel Organic Synthesis
Christian Zechel 243

6.1 Introduction 243
6.2 Synthesis 244
6.2.1 General Remarks 244
6.2.2 Manual Systems 246
6.2.3 Semiautomated Systems 256
6.2.4 Automated Systems 259
6.2.5 Special Applications 268
6.2.5.1 Process Development 268
6.2.5.2 Equipment for Parallel Reactive Gas Chemistry 269
6.3 Liquid – Liquid Extraction 269
6.4 Equipment for High-Throughput Evaporation 271
6.5 Automated Resin Dispensing 273
6.6 Suppliers 274

7 Computer-Assisted Library Design
Andreas Dominik 277

7.1 Introduction 277
7.1.1 Optimizing Combinatorial Libraries 277
7.1.2 A Computer-Assisted Design Strategy 278
7.1.3 What is diversity? 279
7.1.3.1 First Examples 279
7.1.3.2 Diversity of Drug Molecules 280
7.1.3.3 Diversity and Similarity 281
7.2 How Do We compute Diversity? 283
7.2.1 An Overview 283
7.2.2 Descriptors 284
7.2.3 Classification and Mapping 284
7.2.4 Interpretation of Results: Summary 285
7.3 Descriptors 285
7.3.1 Simple filters 287
7.3.2 Physico-chemical Constants 288
7.3.2.1 Estimation of logP Values 288
7.3.2.2 Estimation of pK_A Values 288
7.3.3 Drug-Likeness 289
7.3.3.1 Rule of 5 289
7.3.3.2 Artificial Neural Networks 290
7.3.3.3 Further Improvements of Drug-Likeness Prediction 291
7.3.4 Molecular Fingerprints 291
7.3.5 Substructure Descriptors 291

7.3.6 Single Atom Properties . . . 293
7.3.6.1 Atom Charges . . . 293
7.3.6.2 Atomic Lipophilicity Parameters . . . 293
7.3.7 Topological Indices . . . 293
7.3.7.1 Atom Indices . . . 294
7.3.7.2 Molecule Indices . . . 294
7.3.8 Topological Autocorrelation and Crosscorrelation Coefficients . . . 295
7.3.9 Descriptors from a Pharmacophore Model . . . 295
7.3.10 Stereochemistry . . . 297
7.3.11 Descriptors from the Three-Dimensional Structure . . . 298
7.3.12 Distance Matrix . . . 300
7.3.13 Autocorrelation Coefficients . . . 300
7.3.13.1 Based on Atom Coordinates . . . 300
7.3.13.2 Based on Surface Properties . . . 301
7.3.13.3 Based on Potential Fields . . . 301
7.3.14 Virtual Screening . . . 301
7.4 Clustering and Mapping Algorithms . . . 302
7.4.1 Distance Metric . . . 302
7.4.1.1 Tanimoto Coefficient . . . 302
7.4.1.2 Euclidean Distance . . . 303
7.4.1.3 Nonlinear Distance Scaling . . . 303
7.4.1.4 Mahalanobis Distance . . . 303
7.4.2 Dissimilarity-Based Selection . . . 304
7.4.3 Mapping-Based Selection . . . 305
7.4.3.1 Nonlinear Mapping . . . 306
7.4.3.2 Self-Organizing Maps . . . 306
7.4.3.3 Minimal Spanning Tree . . . 307
7.4.4 Cluster-Based Selection . . . 307
7.4.4.1 Hierarchical Clustering Analysis . . . 308
7.4.5 Partition-Based Selection . . . 308
7.5 Strategies for Compound Selection . . . 308
7.5.1 Optimization Based on Diversity of Building Blocks . . . 309
7.5.1.1 Advantages of Educt-Based Optimization . . . 309
7.5.2 Optimization Based on Diversity of Product Libraries . . . 309
7.5.2.1 Advantages of Product-Based Optimization . . . 310
7.5.3 Library Selection . . . 312
7.5.4 Evolutionary Design Circle . . . 312
7.6 Comparison of Descriptors and Selection Methods . . . 313
7.6.1 Topological Descriptors . . . 315
7.6.2 Descriptors Based on Three-Dimensional Structure . . . 316
7.6.3 Clustering Methods . . . 317
7.6.4 Summary . . . 318
7.7 Example Library of Thrombin Inhibitors . . . 318
7.7.1 Virtual Library Design . . . 320
7.7.2 Final Library Design . . . 321

7.7.2.1 Maximum Diversity Library 321
7.7.2.2 Targeted Library 322
7.7.2.3 Descriptor Sets 322
7.7.3 Comparison of the Libraries 322
7.7.4 Summary 324
References 325

8 Organic reactions on solid phase – A survey of the literature from 1970 to 1998
Anne Scannell-Lansky and Christian Zechel 329

8.1 Introduction
Abbreviations 330

8.2 Nucleophilic aliphatic substitution reactions
8.2.1 N-alkylation 333
8.2.1.1 Alkylation of amines (amines + alkyl halide or sulfonate) . 333
8.2.1.2 Alkylation of amides 334
8.2.1.3 Alkylation of carbamates 335
8.2.1.4 Alkylation of sulfonamides 335
8.2.1.5 Alkylation of azides 335
8.2.1.6 Other N-alkylations and substitutions 335
8.2.2 N-acylation 335
8.2.2.1 Acylation of amines 335
8.2.2.2 Acylation of amides 336
8.2.2.3 Acylation of sulfonamides 336
8.2.2.4 Other N-acylations 336
8.2.3 N-sulfonation and sulfination 336
8.2.4 N-phosphination 337
8.2.5 O-alkylation 337
8.2.5.1 Alkylation of alcohols (alcohol + alkyl halide) 337
8.2.5.2 Mitsunobu reactions 338
8.2.5.3 Other O-alkylations 338
8.2.6 O-acylation 339
8.2.6.1 Ester formation 339
8.2.6.2 Mitsunobu reactions 339
8.2.6.3 Transesterification 339
8.2.7 O-phosphonation 339
8.2.8 O-phosphorlation 339
8.2.9 O-sulfonation 339
8.2.10 P-alkylation 340
8.2.11 S-alkylation 340
8.2.12 S-acylation 340
8.2.13 C-alkylation 341
8.2.14 C-acylation 342

8.2.15 Epoxide opening 342
8.2.16 Halogenation 342
8.2.16.1 Chlorination 342
8.2.16.2 Bromination 342
8.2.16.3 Iodination 343
8.2.16.4 Halogen exchange 343

8.3 Nucleophilic aromatic substitution reactions
8.3.1 N-nucleophiles 343
8.3.2 O-nucleophiles 343
8.3.3 S-nucleophiles 343
8.3.4 Other nucleophilic aromatic substitutions 344

8.4 Electrophilic aromatic substitution reactions
8.4.1 Halogenation 344
8.4.1.1 Chlorination 344
8.4.1.2 Bromination 344
8.4.1.3 Iodination 344
8.4.2 Formation and reactions of metalated aromatic compounds 344
8.4.2.1 Epoxide opening 344
8.4.2.2 Addition to carbonyl compounds 344
8.4.2.3 Acylation reactions 344
8.4.2.4 Alkylation reactions 344
8.4.2.5 Silylation 345
8.4.2.6 Sulfide/selenide formation 345
8.4.2.7 Sulfinate formation 345
8.4.2.8 Boronate formation 345
8.4.2.9 Other reactions of metalated aromatic compounds 345
8.4.3 Friedel-Crafts acylation 345
8.4.4 Friedel-Crafts alkylation 345

8.5 Addition reactions
8.5.1 Grignard and related reactions 345
8.5.1.1 with aldehydes 345
8.5.1.2 with ketones 345
8.5.1.3 with imines 346
8.5.1.4 with Weinreb amides 346
8.5.1.5 with esters 346
8.5.1.6 with acid chlorides 346
8.5.1.7 Reactions with support bound Grignard reagents 346
8.5.1.8 Other Grignard reactions 346
8.5.2 Michael and related reactions 346
8.5.2.1 C-nucleophiles 346
8.5.2.2 N-nucleophiles 346
8.5.2.3 S-nucleophiles 347
8.5.2.4 O-nucleophiles 347

8.5.3 Other 1,2-additions . . . 347
8.5.3.1 Additions to alkenes and alkynes . . . 347
8.5.3.2 Additions to imines . . . 347
8.5.3.3 Additions to carbonyl groups . . . 347
8.5.4 Radical additions . . . 348

8.6 Elimination reactions
8.6.1 Hofmann eliminations . . . 348
8.6.2 Other eliminations . . . 348

8.7 Condensation reactions
8.7.1 Aldol condensation . . . 348
8.7.2 Knoevenagel condensation . . . 348
8.7.3 Dieckmann condensation . . . 349
8.7.4 Claisen condensation . . . 349
8.7.5 Benzoin condensation . . . 349

8.8 Multicomponent reactions
8.8.1 Ugi reaction . . . 349
8.8.2 Mannich reaction . . . 350
8.8.3 Baylis-Hillman reaction . . . 350
8.8.4 1,3-dipolar cycloadditions . . . 350
8.8.5 Other multicomponent reactions . . . 350

8.9 Olefination reaction
8.9.1 Wittig and related reactions . . . 350
8.9.2 Metathesis reactions . . . 351
8.9.2.1 Cross metathesis . . . 351
8.9.2.2 Ring closing metathesis . . . 351
8.9.3 Other olefination reactions . . . 352

8.10 Cycloadditions reactions
8.10.1 [2+2]-cycloadditions . . . 352
8.10.2 [3+2]-cycloadditions . . . 352
8.10.2.1 Reactions of nitrile oxides . . . 352
8.10.2.2 Reactions of nitrones . . . 353
8.10.2.3 Reactions of azomethine ylides . . . 353
8.10.2.4 Other [3+2]-cycloadditions . . . 353
8.10.3 [4+2]-cycloadditions . . . 353
8.10.3.1 Diels-Alder reactions . . . 353
8.10.3.2 Hetero-Diels-Alder reactions . . . 354

8.11 Transition metal catalyzed reactions
8.11.1 Palladium catalyzed reactions . . . 354
8.11.1.1 Suzuki reaction . . . 354

8.11.1.2 Stille reaction 355
8.11.1.3 Heck reaction 355
8.11.1.4 Sonogashira reaction 356
8.11.1.5 Other Palladium catalyzed reactions 356
8.11.2 Pauson-Khand reaction 357
8.11.3 Other transition metal catalyzed reactions 357

8.12 Radical reactions
8.12.1 Radical allylations 358
8.12.2 Radical additions 358
8.12.3 Cyclizations 358
8.12.4 Cleavage reactions 358

8.13 Reductions
8.13.1 Functional group conversions 358
8.13.1.1 Ester to alcohol 358
8.13.1.2 Carboxylic acid to alcohol 358
8.13.1.3 Carboxylic acid chloride to alcohol 358
8.13.1.4 Aldehyde to alcohol 358
8.13.1.5 Ketone to alcohol 358
8.13.1.6 Ketone to alkane 359
8.13.1.7 Thioester to aldehyde 359
8.13.1.8 Thioester to thiol 359
8.13.1.9 Thioester to alcohol 359
8.13.1.10 Amide to amine 359
8.13.1.11 Amide to aldehyde 359
8.13.1.12 Imine to amine 359
8.13.1.13 Carbamate to amine 359
8.13.1.14 Nitrile to amine 359
8.13.1.15 Oxime to hydroxylamine 359
8.13.1.16 Azide to amine 359
8.13.1.17 Aromatic nitro compounds to aromatic amines 359
8.13.1.18 Reduction of C=C and C≡C-bonds 359
8.13.1.19 Hydrogenation 360
8.13.1.20 Disulfide reduction 360
8.13.1.21 Other reductions 360
8.13.2 Reductive aminations 360
8.13.2.1 Amine + ketone 360
8.13.2.2 Amine + aldehyde 360

8.14 Oxidations
8.14.1 1° alcohol to aldehyde 361
8.14.2 2° alcohol to ketone 361
8.14.3 Aldehyde to carboxylic acid 362
8.14.4 Sulfide to sulfoxide 362

8.14.5 Sulfinamide to sulfonamide 362
8.14.6 Sulfide to sulfone 362
8.14.7 Selenide to selenoxide 362
8.14.8 Phosphite to phosphate 362
8.14.9 Kornblum oxidation of Merrifield resin to PS/DVB-CHO 362
8.14.10 Epoxidation 362
8.14.11 Ozonolysis 362
8.14.12 Hydroxylation 362
8.14.13 Other oxidation reactions 362

8.15 Formation of carbonyl compounds and derivatives thereof
8.15.1 Acetal formation/cleavage and related reactions 363
8.15.1.1 Acetal formation 363
8.15.1.2 Ketal formation 363
8.15.1.3 Acetal or ketal cleavage 363
8.15.1.4 Transacetalization 363
8.15.1.5 Transketalization 363
8.15.2 Enol ether formation 363
8.15.3 Imine formation and cleavage 363
8.15.3.1 Imine formation 363
8.15.3.2 Imine cleavage and related reactions 364
8.15.4 Enamine formation and cleavage 364
8.15.4.1 Enamine formation 364
8.15.4.2 Enamine cleavage 364
8.15.5 Oxime formation 364
8.15.6 Hydrazone formation 365
8.15.7 Carbonate formation 365
8.15.8 Carbamate formation 365
8.15.9 Urea formation 366
8.15.10 Thiourea formation 367
8.15.11 Guanidine formation 367
8.15.12 Carbodiimide formation 367
8.15.13 Acid chloride formation 367
8.15.14 Isocyanate formation 368
8.15.15 Isothiocyanate formation 368
8.15.16 Isonitrile formation 368
8.15.17 Nitrile oxide formation 368
8.15.18 Nitrone formation 368
8.15.19 Imidate formation 368
8.15.20 Other carbonyl derivatives 368

8.16 Formation of carbocycles
8.16.1 3-membered carbocycles 369
8.16.2 5-membered carbocycles 369
8.16.3 6-membered carbocycles 369

8.17 Formation of heterocycles
8.17.1 3-membered heterocycles 371
8.17.2 4-membered heterocycles 371
8.17.3 5-membered heterocycles (5-MH) 371
8.17.3.1 5-MH with 1 heteroatom 371
8.17.3.1.1 5-MH with 1 N 371
8.17.3.1.2 5-MH with 1 O 376
8.17.3.1.3 5-MH with 1 S 377
8.17.3.2 5-MH with 2 heteroatoms 378
8.17.3.2.1 5-MH with 2 N 378
8.17.3.2.2 5-MH with 1 N and 1 O 384
8.17.3.2.3 5-MH with 1 N and 1 S 387
8.17.3.3 5-MH with more than 2 heteroatoms 387
8.17.4 6-membered heterocycles (6-MH) 388
8.17.4.1 6-MH with 1 heteroatom 388
8.17.4.1.1 6-MH with 1 N 388
8.17.4.1.2 6-MH with 1 O 394
8.17.4.2 6-MH with 2 heteroatoms 395
8.17.4.2.1 6-MH with 2 N 395
8.17.4.2.2 Other 6-MH with 2 heteroatoms 400
8.17.5 7-membered heterocycles (7-MH) 401
8.17.5.1 7-MH with 1 heteroatom 401
8.17.5.1.1 7-MH with 1 N 401
8.17.5.2 7-MH with 2 heteroatoms 401
8.17.5.2.1 7-MH with 2 N 401
8.17.6 Other heterocycles 404

8.18 (De)protection, cleavage and hydrolysis reactions
8.18.1 (De)protection of alcohols 404
8.18.2 Other ether cleavage reactions 405
8.18.3 (De)protection of amines 405
8.18.4 Ester cleavage reactions 405
8.18.5 Silane cleavage and related reactions 406
8.18.6 Other cleavage reactions 406

8.19 Diazo chemistry
8.19.1 Diazonium ions 407
8.19.2 Diazo compounds 407

8.20 Rearrangements
8.20.1 Claisen rearrangement 407
8.20.2 Beckmann rearrangement 407
8.20.3 Hofmann rearrangement 407
8.20.4 Curtius degradation 407

8.21 Miscellaneous 408

References 409

Index 423

1 General Introduction

Willi Bannwarth

Within the pharmaceutical industry, one of the major aims is to increase the number of new chemical entities (NCEs) launched each year. Simultaneously, a reduction in development time of NCEs, together with a concomitant reduction in costs, is expected. One of the key disciplines by which this goal may be achieved is that of combinatorial chemistry, the emergence of which offers unprecedented rapid synthesis of compounds that may be monitored for their biological activity by using high-throughput screening formats. This, together with efficient data management and a constant influx of new biological targets, will undoubtedly lead to an acceleration in the process of drug discovery.

Combinatorial chemistry will, however, have a major impact on lead discovery, as well as on lead optimization. While in the past the initial focus in lead discovery has been on the rapid synthesis of highly complex mixtures comprising minute amounts of individual compounds, this strategy has now been largely substituted by the preparation of individual compounds in amounts of 5 mg to 50 mg, by the use of parallel synthesis. These new compounds are stored by pharmaceutical companies in their repositories, and serve as a valuable asset for lead finding. The repositories may contain a relatively large number of diverse compounds of high purity in order to produce reliable screening data, and it is in this area that computational methods for planning the diversity of the envisaged libraries will, in future, play a vital role.

During the developmental stages of combinatorial chemistry, it was believed that efficient synthesis was possible only by using solid-phase strategies. In part, this was influenced by the rapid and efficient synthesis of peptides and oligonucleotides by robots on solid support materials that has taken decades to develop to the current levels of performance.

The main advantage of solid-phase synthesis is that large excesses of reagents may be applied, thereby driving the reaction to completion. In this way, higher yields can be expected as compared to the same reaction performed in solution, and with equimolar amounts of reactants. Moreover, the excesses of reagents may be removed by simple filtration, thus avoiding time-consuming purification.

In solid-phase chemistry however, there is a major disadvantage in that two additional steps are involved, namely the attachment of the starting material, and the release of the product.

A major impact on combinatorial chemistry was made by the so-called "split and combine" procedure, which permits the synthesis of a multitude of individual compounds to be carried out on bead particles, each of which has only one defined compound attached to it, albeit in multiple copies. This approach minimizes the synthetic effort per compound, as compounds can be screened either while they remain attached to the solid support, or after being released from the bead into solution. The split and combine approach is ideal for the synthesis of minute amounts of a plethora of individual compounds, but it has one disadvantage in that it is a rather time-consuming, deconvoluted process that incorporates iterative rounds of resynthesis and screening of compound subsets in order to identify the active compound. The

danger exists that the originally identified activity is the sum of several moderate activities, so that invariably the original activity is lost during the deconvolution process. The split and combine approach has been applied mainly to peptide and peptide-like compound libraries.

As an alternative, tagging strategies have been developed in which the active molecule can be identified by placing a tag on the same bead. These procedures are rather tedious and, with the exception of radiofrequency tagging of small polypropylene reactors, have not fulfilled expectation.

Spatially addressed synthesis is yet another alternative. This does not play an important role in general combinatorial chemistry, but has been used successfully in biochip applications such as in DNA-probe technology.

If the solid-phase synthesis of peptides and nucleotides is to be extended to general organic synthesis, a few stumbling blocks become clear. Most notably, there is the need for a suitable linker molecule which allows for attachment of the starting material and which should guarantee an efficient release of the product after synthesis.

In peptide or nucleotide chemistry, the biopolymer sequence is assembled by repetitive cycles of identical chemical steps. In contrast, the synthesis of an organic compound usually involves different synthetic steps, each to be performed under specific conditions. The linker entity which represents the adapter between solid support and starting material, intermediate or final product, must withstand all these conditions and yet must allow for the efficient and specific release of the desired compound, without side reactions. Thus, it becomes clear that general organic synthesis on solid support requires the development of a huge array of different linker molecules that are suitable for the attachment of all types of functional groups, and thus permit all types of chemistries to be applied. In order to avoid the laborious development of linkers, alternative strategies were implemented which were mainly based on a release of the desired compounds by cyclization.

Another problem when embarking on synthesis on solid supports is the difficulty in analyzing compounds attached to that support. Methods exist to analyze compounds on individual beads, such as magic angle spinning-NMR or FT-infrared spectroscopy, but these are too demanding to be carried out on a routine basis on a multitude of beads.

A further limitation of general organic synthesis on solid support is the limited types of support materials available. These also restrict the use of different types of solvents, as only those solvents can be employed which lead to a sufficient swelling of the polymer and hence to an acceptable reaction rate. From the aforementioned restrictions it becomes clear that synthesis on solid support requires a somewhat careful and time-consuming optimization of reaction conditions. However, once properly developed – and with the scope of the pertinent reactions carefully evaluated – solid support synthesis offers high-speed preparation of compound libraries which can be carried out also by automated synthesizers.

Due to these difficulties, a number of solution chemistry approaches have emerged as alternatives to synthesis on solid support. These will be described in the chapter detailing multicomponent reactions and solid phase-supported solution chemistry.

The decision as to whether solution chemistry or chemistry on solid support should be applied to the preparation of a compound library depends also on whether the compounds produced are to be screened either for lead finding or lead optimization. In the latter case, an evaluation must be made as to whether analogs of the desired structure are best prepared in solution or by solid-phase approaches. On occasion, combinations between solution- and sol-

id-phase chemistry can be effective. It must be emphasized that lead optimization solely by combinatorial approaches is often not possible, and in these cases a combination of traditional medicinal chemistry and combinatorial approaches is the method of choice. However, the more reactions that are developed for combinatorial chemistry, the greater will be the impact in lead optimization.

Finally, it should be emphasized that the influence of combinatorial approaches will not be apparent only in medicinal chemistry. Were the entire periodic system to have been exploited, then of all the molecules that are theoretically possible, only a very small fraction have been synthesized and their properties explored to date. Thus, a vast array of as yet unknown properties can be expected to be found via combinatorial chemistry. This will have a particular impact in the material sciences, and perhaps most notably in the search for new catalysts.

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2 Combinatorial Chemistry in Solution

Willi Bannwarth

2.1 An Introduction to Solution Chemistry

When combinatorial chemistry first emerged, the initial focus was on solid-phase approaches due to the many advantages offered by this technology. Solution chemistry is not regarded as being suitable for combinatorial chemistry, as few reactions lead reliably to very high yields when equimolar amounts of reactants are employed. Thus, reactions in solution are usually followed by tedious isolation and purification procedures. Furthermore, for a specific reaction the difference in reactivity of building blocks becomes more obvious as compared with solid-phase chemistry when applying excesses of reagents. Hence, combinatorial chemistry in solution was centered around easily synthesized compound classes such as amides, sulfonamides, ureas and efficiently prepared heterocycles such as thiazoles. The high-yielding chemistry for the aforementioned substance classes was applied mainly to pharmacophore mapping in which templates of different consecutive reactivity (either rigid or with inherent flexibility) were used for the attachment of pharmacophore groups.

It seemed unlikely that the synthesis of compounds requiring several steps could be performed by combinatorial chemistry in solution. Nevertheless, in recent years a number of technologies have emerged for solution chemistry, so that in many cases this became an alternative to solid-phase synthesis.

Some multicomponent reactions can be carried out very efficiently and are suitable for the synthesis of compound libraries. Among those, the ones in which the final step in the formation of the product is irreversible proceed with high yields.

Often, a sufficient difference in the physical properties between starting material and product can be exploited for easy product purification. Thus, a great difference in pKa values can open up the possibility for an easy purification by ion-exchange resins.

A new area is that of solid phase-supported solution chemistry. This method allows for the application of excesses of reagents to drive reactions to completion. The excess can then be reacted with solid phase-bound functionalities and removed by an ensuing filtration step. Alternatively, intermediates or even final products can be trapped by suitably modified support materials.

Solid phase-bound reagents are another field of polymer-supported solution chemistry which is becoming increasingly important. An example is the use of solid phase-bound triphenylphosphine in Wittig-type reactions to avoid the cumbersome separation of the product from the triphenylphosphine oxide that is formed as a byproduct.

Recently, perfluorinated "pony tails" were proposed for the efficient solution synthesis of combinatorial libraries. This approach offers all the advantages of solution chemistry, and yet the compound carrying the fluorous tag can be extracted into a perfluorinated solvent and thus easily separated from other components. More recently, a number of articles have appeared describing this approach in combinatorial synthesis.

2.2 Multicomponent Condensations (MCCs)

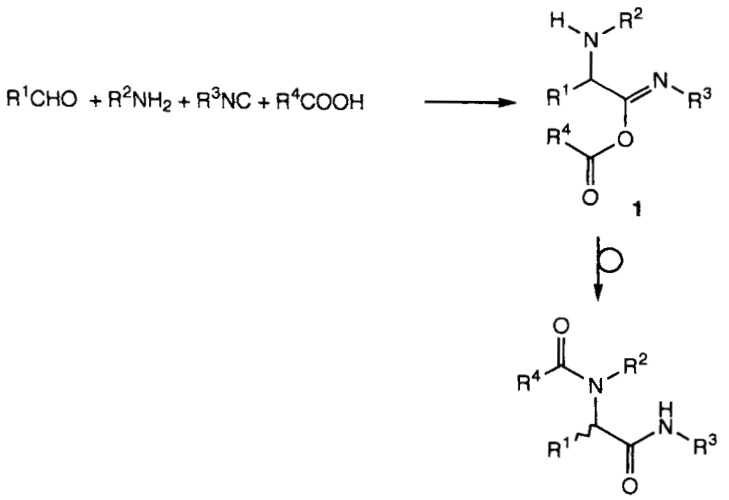
Willi Bannwarth

2.2.1 Introduction

Multicomponent condensations (MCCs) combine two important principles of organic synthesis: Convergence, and economics of atoms. They are of great value, especially in the identification of lead compounds. If the individual building blocks of such a reaction are available in great structural variety, then this approach allows for the synthesis of a vast number of individual products. A basic requirement is that the reactions must proceed in a reliable fashion, leading to high yields. In an ideal situation the multicomponent reaction should allow for an easy automation to exploit its full potential. The following chapter describes the MCCs already applied in combinatorial approaches. The main focus is on solution chemistry, though as some of these MCCs have been performed only on solid support, these have also been included.

2.2.2 MCC Reactions Involving Isonitriles

The classic example of a MCC which has been widely used in combinatorial chemistry is the Ugi four-component reaction [1, 2] (Scheme 1).



Scheme 1

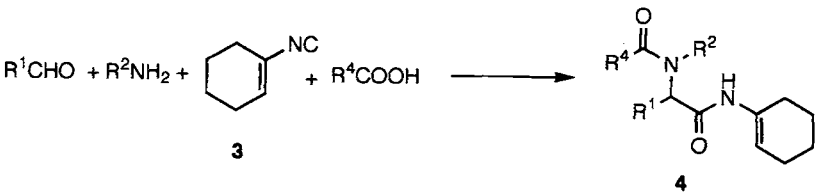
Reaction of an aldehyde, a primary amine, a carboxylic acid and an isonitrile leads to the formation of an α-acylamino carboxamide **2**. The initial step is the formation of a Schiff base as a result of the reaction of the aldehyde with the primary amine. This Schiff base is then attacked by the isonitrile, and acylation leads to intermediate **1**. The formation of **2** is driven by the irreversible acylation step leading from **1** to **2**. Thus, the Ugi reaction generally results in good yields over a broad range of building blocks and solvents. The preferred solvent is MeOH.

Due to the great variability of the individual building blocks the reaction leads to a great variety of structures and has found widespread application for the preparation of compound libraries for lead identification via general screening approaches.

Procedure [3]

The aldehyde (1.25 equiv.), the carboxylic acid (1.25 equiv.), and the amine (1.25 equiv.) were dissolved in methanol to an approximate concentration of 1 M in each component. This was kept for 10 min at rt and then added in one portion to a flask containing the isocyanide (1.0 equiv.). The resulting solution was stirred at rt for 12 h. The reaction was followed by TLC (1–5 % MeOH in DCM). On completion, the solvent was removed in vacuo, and the residue was purified (if desired) by flash chromatography on silica gel, eluting with a gradient of 0–5 % MeOH in DCM.

A restriction is the limited number of commercially available isonitriles. This problem was solved by the insertion of the universal isonitrile **3** derived from cyclohexene (Scheme 2). After insertion, this leads to the Ugi-product **4** which could be converted into different functionalities [3]. Thus, this approach allows for the synthesis of products which are not directly accessible by the original Ugi reaction.



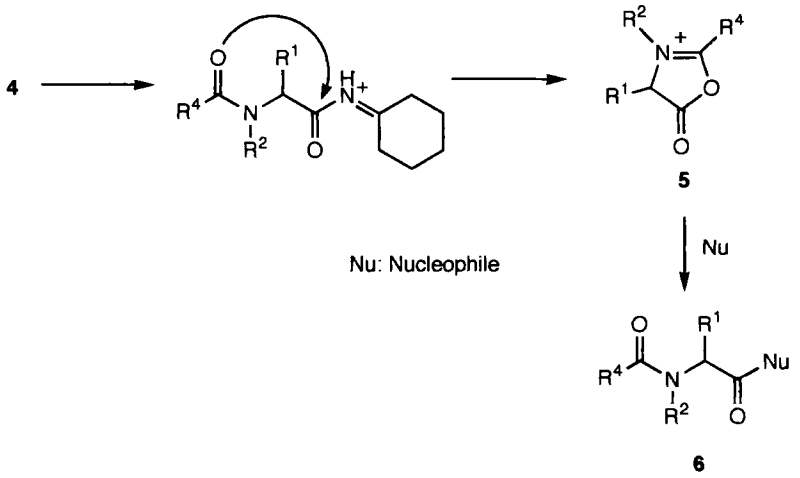
Scheme 2

The transformation of **4** into the desired compounds of type **6** proceeded under acidic conditions via an oxazolinium-5-one **5** (muenchnone) which was opened by a nucleophile, as illustrated in Scheme 3 [4].

The muenchnones were also applied to 1,3-dipolar cycloadditions, e.g., with acetylene dipolarophiles of which the products are pyrrole derivatives.

Procedure [3]

The cyclohexenamide product of the Ugi reaction carried out as described in the previous section (0.05 mmol) was azeotropically dried several times (toluene) and then dissolved in 1 mL of dry toluene. The acetylene component as dipolarophile (0.25 mmol) was added



Scheme 3

followed by HCl (3 equiv. as a 1.0 M solution in anhydrous ether). The capped flask was then heated for 4 h to 100° C. After cooling, the solvent was evaporated and the residue taken up in DCM and filtered. The filtrate was purified by preparative TLC using a gradient of 0–5 % MeOH in DCM.

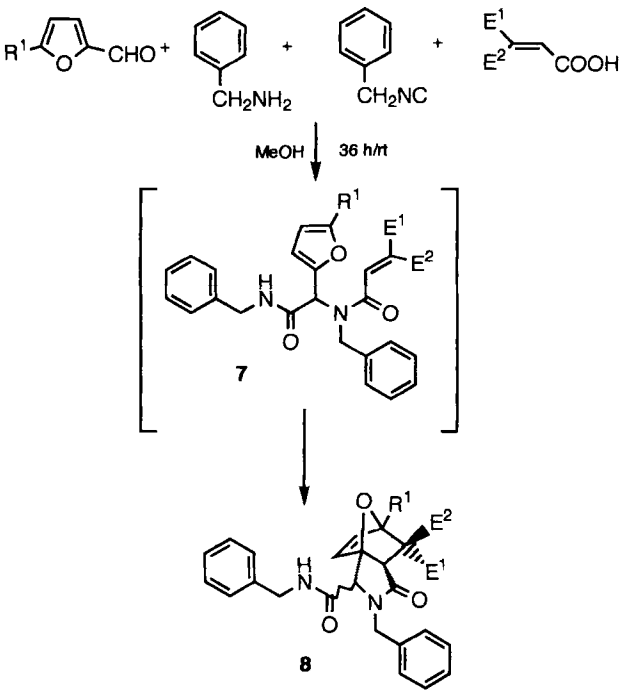
Furthermore, an intramolecular nucleophilic attack is also possible and was demonstrated in the synthesis of 1,4-benzodiazepine-2,5-diones [5] via the Ugi four-component condensation. The strategy of the convertible isonitrile was also used for the synthesis of diketopiperazine libraries [6].

By the incorporation of a furfurol aldehyde and an activated dienophile acid in the four-component reaction an intermediate **7** was formed which underwent a Diels–Alder reaction leading to tricyclic heterocycles of type **8** (Scheme 4) [7]. The reaction was performed in solution as well as with the resin-bound amine component.

As indicated already, the initial step in the Ugi reaction is the formation of a Schiff base resulting from the aldehyde and the amine component. This Schiff base is then attacked by the isonitrile. In the Passerini reaction, the amine is omitted so that the isonitrile reacts directly with the carbonyl function of the aldehyde which yields compounds of type **9** [8] (Scheme 5).

The reaction was applied in solution to create an array of azinomycin analogs, a class of antitumor compounds which bind to the major groove of double-stranded DNA and which leads to crosslinking of the two complementary single strands [9, 10]. In the same publication, the Passerini reaction contemplating azinomycin analogs was performed on a solid support whereby the acid component was attached before the synthesis via a photolabile linker to the solid support [10].

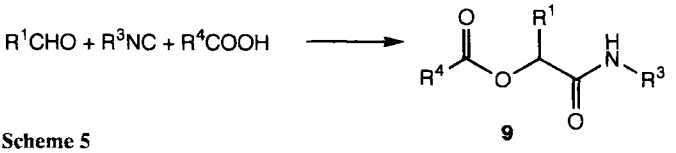
The diversity possibilities of multicomponent reactions can be further increased by prior functionalization of one of the components. This strategy, also dubbed "reagent explosion", was recently employed in a Passerini reaction in which methyl-β-(N,N-dialkylamino)-α-



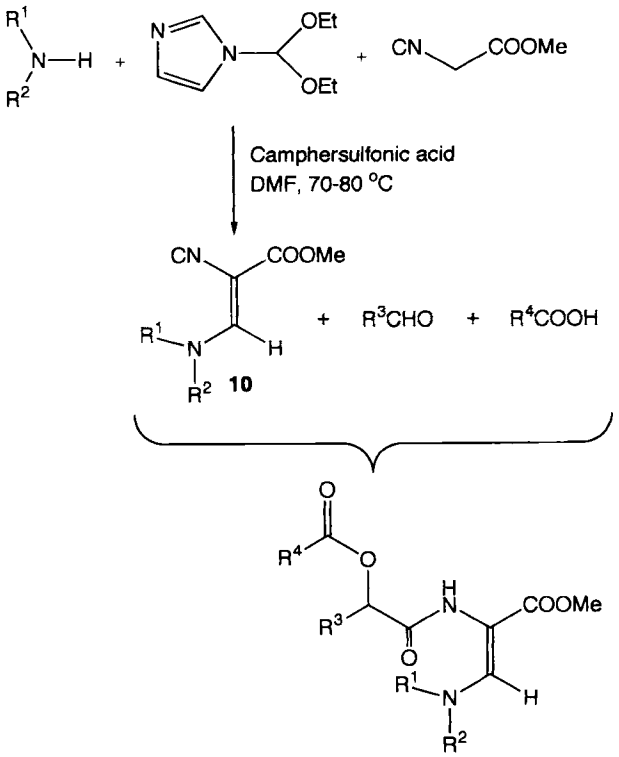
Scheme 4

isocyanoacrylates **10** were introduced as isocyanide component [11] (Scheme 6). The isocyanide derivatives were easily prepared from the reaction between various secondary amines, N-formylimidazole diethylacetal, and methyl isocyanoacetate as outlined in Scheme 6. Dipolar aprotic solvents such as dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were found to be superior in this multicomponent reaction, whereas the commonly applied methanol was not suitable. The authors have used this reagent explosion strategy for the synthesis of a 4620-member library consisting of compounds of type **11**.

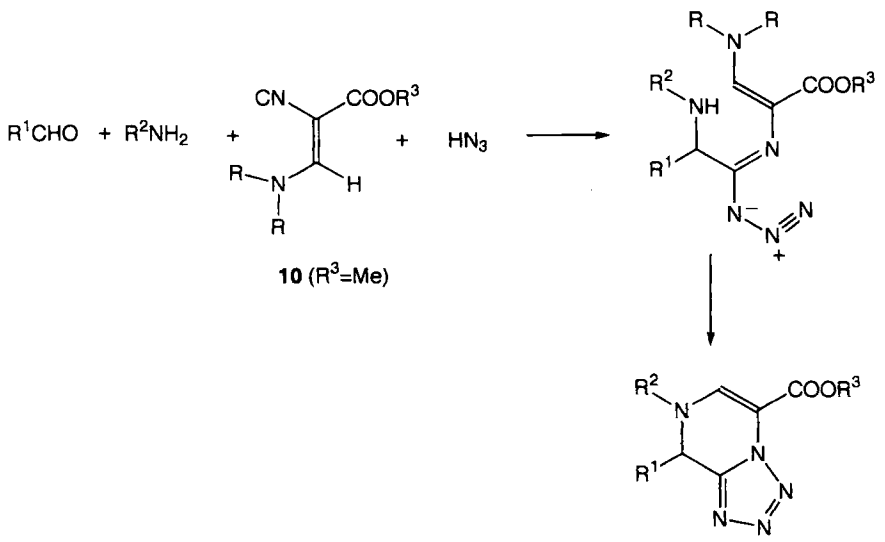
Methyl-β-(N,N dialkylamino)-α-isocyanoacrylates of structure **10** were also applied in a Ugi reaction in which the commonly used carboxylic acid component was replaced by hydrazoic acid [12]. This resulted in the formation of interesting bicyclic tetrazole derivatives **12**, as outlined in Scheme 7.



Scheme 5



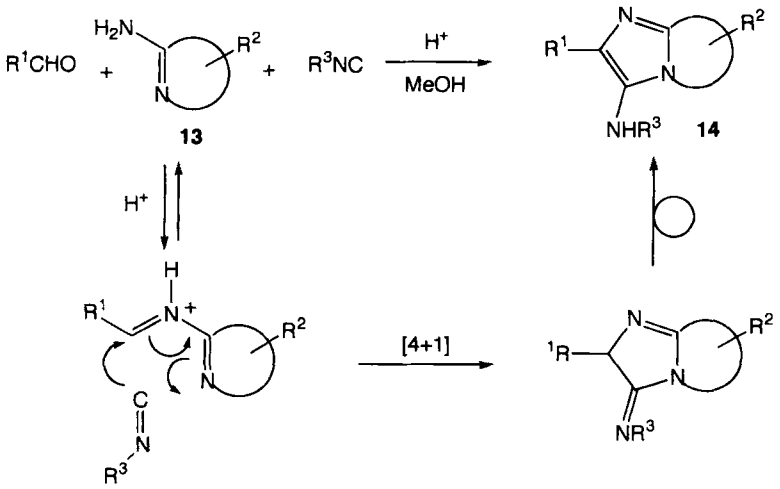
Scheme 6



Scheme 7

With respect to the aldehyde component, aliphatic, aromatic, and heteroaromatic ones were tolerated, and the reaction could even be extended to ketones as carbonyl entity. Aliphatic and aromatic amines were both suitable.

Recently, a new MCC reaction involving isonitriles was reported [13]. Heteroaromatic amidines **13** react with an isonitrile and an aldehyde in the presence of catalytic amounts of a protic acid. The reaction proceeds with high efficiency to yield 3-amino-imidazo [1,2-a] pyri(mi)dines of the general type **14**.



Scheme 8

The reaction proceeded well in methanol and was not sensitive to moisture or oxygen. With respect to the reactivity of aldehydes there was virtually no limitation. Very electron-poor amidines (e.g., adenine) did not react. With regard to the reaction mechanism, the authors assumed a nonconcerted [4+1]-cycloaddition, as outlined in Scheme 8. About 30 000 compounds of type **14** were synthesized by this route, either by parallel synthesis as individual compounds or as mixtures.

Procedure [13]

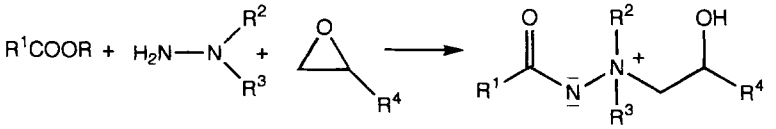
To a solution of 2-amino-5-picolin (0.415 g, 3.84 mmol) in MeOH (8 mL) pyridyne-2-carboxaldehyde (0.62 g, 5.79 mmol) and tert. butyl isonitrile (0.5 mL, 4.42 mmol) were added at rt. This was followed by the addition of 0.38 mL of 1 M $HClO_4$ solution in MeOH. After 18 h at rt the reaction mixture was diluted with DCM (50 mL) and extracted with water, saturated glutamine (pH 10, 20 mL) and saturated NaCl solution (50 mL). The organic layer was passed through $MgSO_4$ and concentrated. Addition of ether (3 mL) followed by slow addition of pentane (6 mL) led to crystallization. Yield: 0.821 g (76 %) of 3-tert. butylamino-2-(2-pyridyl)-6-methylimidazo [1,2-a] pyridine as slightly yellow crystals.

The same type of three-component reaction could also be mediated by scandium triflate [14]. A library of 3-amino-imidazo[1,2-a] pyridines and -pyrazines **14** was synthesized and purified by ion-exchange resin. Additionally, the amino function of compounds **14** was further modified by acylation and reaction with an isocyanate.

Procedure [14]
A 0.5 M solution of amine (1.5 mL) in $MeOH/CH_2Cl_2$ (1:3) was treated with 1.2 equiv. of aldehyde and 0.05 equiv. of scandium triflate. After 30 min, 1.2 equiv. of isonitrile was added and the solution was agitated for 72 h at ambient temperature. The reaction mixture was allowed slowly to adsorb onto 5 g of Dowex 50WX 2-200 acidic cation-exchange resin that had previously been equilibrated with MeOH–5 N HCl. The resin bed was washed with MeOH, DCM and MeOH. The 3 MCC product 14 was eluted from the resin using 2 M NH_3 in MeOH (10 mL), and the solvent evaporated. The products were analyzed by HPLC-MS. Purities were assessed from peak areas recorded with the UV-detector set at 280 nm.

2.2.3 Aminimides by Multicomponent Condensation

Another example of a MCC is the formation of aminimides of type **15** starting from N,N-dialkylhydrazine, an ester and an epoxide (Scheme 9). This reaction has been evaluated extensively for the preparation of the corresponding compound libraries [15].



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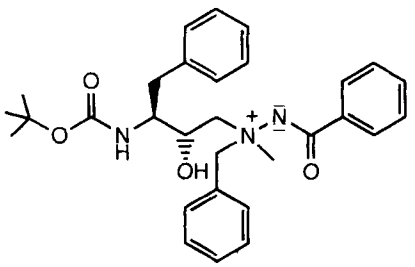
Scheme 9

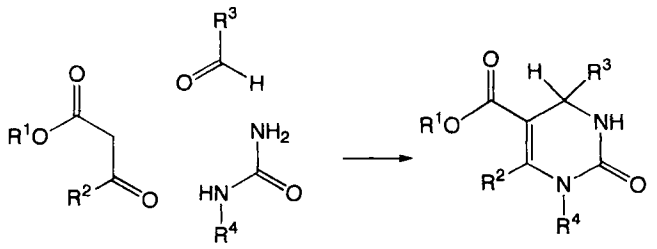
In such a library, the aminimide **16** was identified as a HIV protease inhibitor.



16 **Structure 16**

2.2.4 Biginelli More Component Reaction

A β-ketoester, an aryl aldehyde and a urea derivative, when refluxed in a protic solvent with catalytic amounts of acid, will result in 4-aryl-dihydropyrimidin-2-ones **17** (Scheme 10) [16]. This reaction was published for the first time by Biginelli in 1893.



Scheme 10 **17**

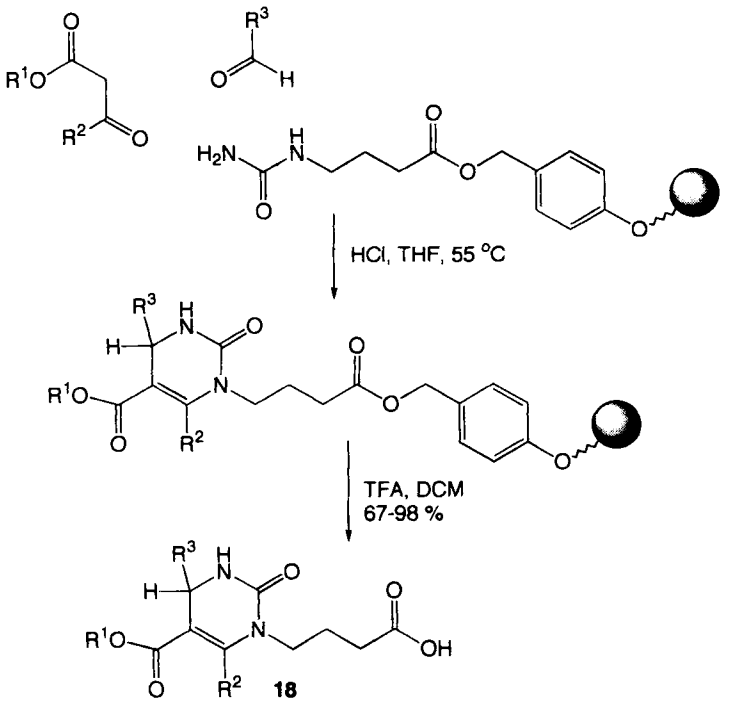
Compounds of this class are the basic backbone of several Ca-channel blockers, antihypertensive agents and α-1-a antagonists and thus, are of great interest in medicinal chemistry. The performance of this reaction has been improved significantly by the use of BF_3-Et_2O, CuCl and 10 mol % AcOH in THF, which leads generally to very high yields [17]. This was demonstrated for the synthesis of a whole array of compounds of type **17**.

Procedure [17]
A 50-mL three-neck, round-bottomed flask fitted with a thermocouple and reflux condenser was charged under N_2 with molecular sieve-dried THF (30 mL), β-ketoester (15.4 mmol), aryl aldehyde (15.4 mmol), urea (23.1 mmol), BF_3xOEt_2 (20.0 mmol), CuCl (1.54 mmol), and glacial acetic acid (1.54 mmol). The mixture was heated to reflux (at 65° C) for 8–18 h. The solution was cooled to rt and quenched with 10 % Na_2CO_3 (30 mL). EtOAc (30 mL) was added, the layers were separated, and the green aqueous solution was removed. The organic layer was distilled and replaced with toluene (c. 40 mL), cooled to rt, and stored overnight. The resulting suspension was filtered in vacuo, and the collected solid rinsed with toluene (10 mL) and dried in vacuo at 40° C to afford the desired product as crystalline solid. Yield: Generally 80–95 %.

A solid phase-based Biginelli reaction was also described recently in which the urea entity was linked to a Wang resin via a benzyl ester function [18] (Scheme 11). Cleavage from the resin by TFA yielded the dihydropyrimidinones of type **18**.

2.2.5 Hantzsch Pyridine Synthesis

The pyridine scaffold is a structural element of a number of different classes of pharmaceutical compounds. These drugs, derived from a pyridine template, comprise in essence antihis-



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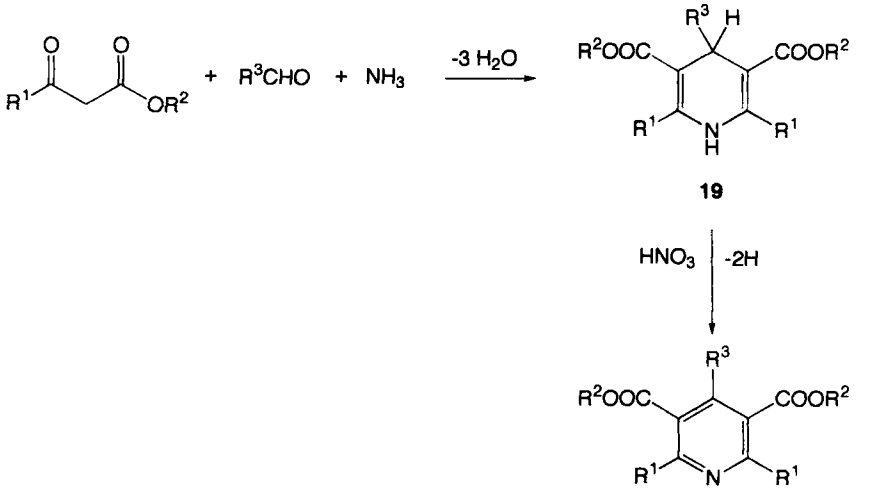
Scheme 11

tamines, antiseptics, and antirheumatics. The classical more component condensation for the preparation of pyridines is the Hantzsch synthesis [19], as outlined in Scheme 12.

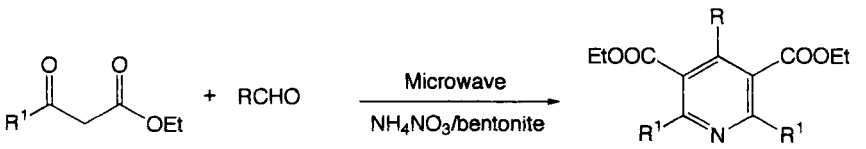


19

20

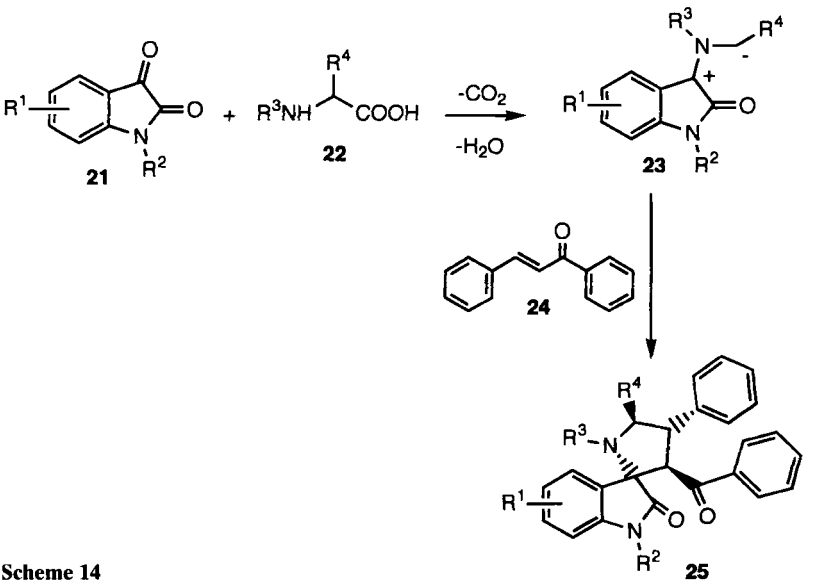
Scheme 12

The initial product of the condensation is a 1,4-dihydropyridine **19**, which can be oxidized to the corresponding pyridine derivative **20** [20]. Microwave-assisted combinatorial chemistry was recently applied to the high-throughput Hantzsch synthesis to create libraries of diverse substituted pyridines [21, 22]. The authors used a solvent-free approach in a 96-well plate format employing filter bottom plates. Bentonite clay was used as support and ammonium nitrate was applied as source of ammonia and oxidant [22], according to Scheme 13.



Scheme 13 **20**

After synthesis, the products were washed from the solid support with an appropriate solvent into a 96-well receiving plate. The authors have synthesized an entire array of pyridines using this approach.



Scheme 14

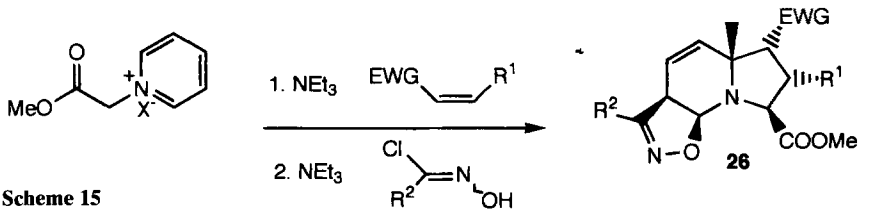
2.2.6 Three-Component Condensation Based on a 1,3-Dipolar Cycloaddition

An interesting library of spiro[pyrrolidine-2,3'-oxindoles] of type **25** was prepared by applying a three-component 1,3-dipolar cycloaddition reaction of isatins (**21**), α-amino acids (**22**) and trans chalcones (**24**) [23]. The isatin formed with the α-amino acid an azomethineylide (**23**) which was then trapped by the chalcone according to Scheme 14 to yield the final products. In this way, the authors have synthesized a library of 25 600 individual compounds of type **25**.

The reaction was performed in closed vials at 80° C. Isatines and chalcones were dispensed from 0.25 M solutions in dioxane while amino acids were added as 0.25 M aqueous solutions. The products were obtained as racemates in high purity directly after evaporation of the solvent. The trans chalcones used in the reaction were easily prepared from commercially available acetophenones and arylaldehydes.

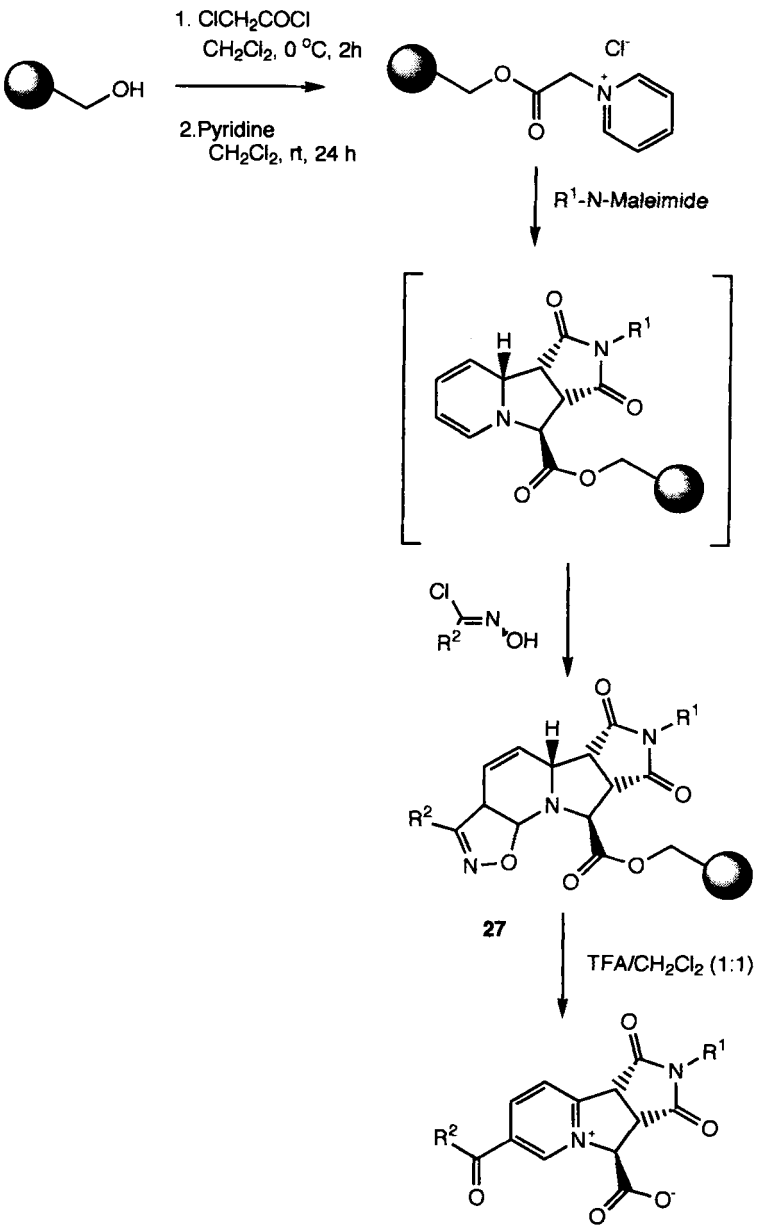
2.2.7 More Component Reaction Based on the Tsuge Reaction

A possibility leading to tricyclic templates is the reaction of dipolarophiles to pyridinium methylides, followed by in situ reaction with nitrile oxides; this leads to isoxazoline-fused tetrahydroindolizines **26** (Scheme 15) [24]. This is not a true more component reaction in which all partners react simultaneously. Nevertheless, it is mentioned here as the reaction occurs under mild conditions and has been applied successfully to the construction of a tricyclic compound library.



Scheme 15

The library was synthesized by a solid-phase strategy in which the pyridinium entity was directly prepared on Wang resin and the further reaction resulted in **27**. Cleavage from the solid support did not yield the desired compounds of type **26**, but compounds of type **28**. These were possibly the result of a fragmentation of the isoxazoline ring which was followed by oxidative formation of the pyridinium derivative and hydrolysis of the oxime (Scheme 16) [25]. The compounds **28** were obtained in good purities and yields.



Scheme 16

Procedure [25]

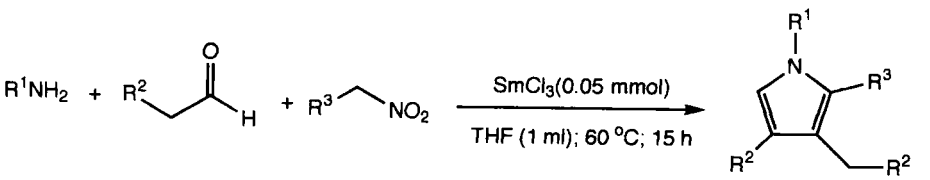
To a suspension of Wang resin (7 mmol) in dry DCM (100 mL) in a round-bottomed flask under argon and cooled to 0° C was added dropwise chloroacetyl chloride (14 mmol) and

the mixture stirred for 2 h. The resin was removed by filtration and washed with DCM (3 x 10 mL), THF and dioxane followed by diethyl ether (1 x 10 mL). The resin was suspended in dry DCM and pyridine (30 mmol) was added and the mixture shaken for 24 h at rt. The product was worked up as above.

To a suspension of the pyridinium-resin (0.032 mmol) in dry THF was added maleimide (0.16 mmol) followed by triethylamine (0.16 mmol) dropwise over 1 min. After 1 h shaking at rt the resin was filtered and resuspended in dry THF. Imidoyl chloride as nitrile oxide precursor (0.16 mol) was added, followed by triethylamine (0.16 mmol) dropwise over 5 min while shaking. After 2 h the resin was filtered and washed with DCM (3 x 10 mL), THF and dioxane followed by diethyl ether (1 x 10 mL) and dried. The cleavage of the compound was performed with 1 mL TFA/DCM (1:1).

2.2.8 A $SmCl_3$-Initiated Multicomponent Condensation

A three-component condensation of aldehydes, amines, and nitroalkanes in the presence of catalytic amounts of $SmCl_3$ as Lewis acid leads to the formation of highly substituted pyrroles of type **29** (Scheme 17) [26]. The reaction is considered to involve the coupling of α,β-unsaturated imines, which are provided by the Sm-catalyzed aldol-type condensation of imines generated from amines and aldehydes, with nitroalkanes. The yield was highly dependent on the nature of the different building blocks, and the products had to be purified by chromatography. Thus, the reaction may be of less importance for the routine synthesis of pyrrole libraries.

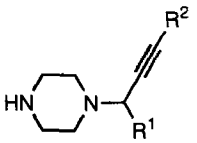


Scheme 17 **29**

2.2.9 Mannich Reaction

The Mannich reaction is another valuable more component reaction. Reaction of a secondary amine, an aldehyde, and a CH-acidic compound leads to an aminoalkylation of the latter compound. In solution chemistry this reaction has not gained importance in combinatorial approaches, but it has been applied successfully in solid-phase chemistry [27, 28]. The reaction on solid support can be carried out in various ways, as any participant of this three-component reaction can be immobilized on the resin, providing at the same time three different routes for the generation of diverse compound libraries.

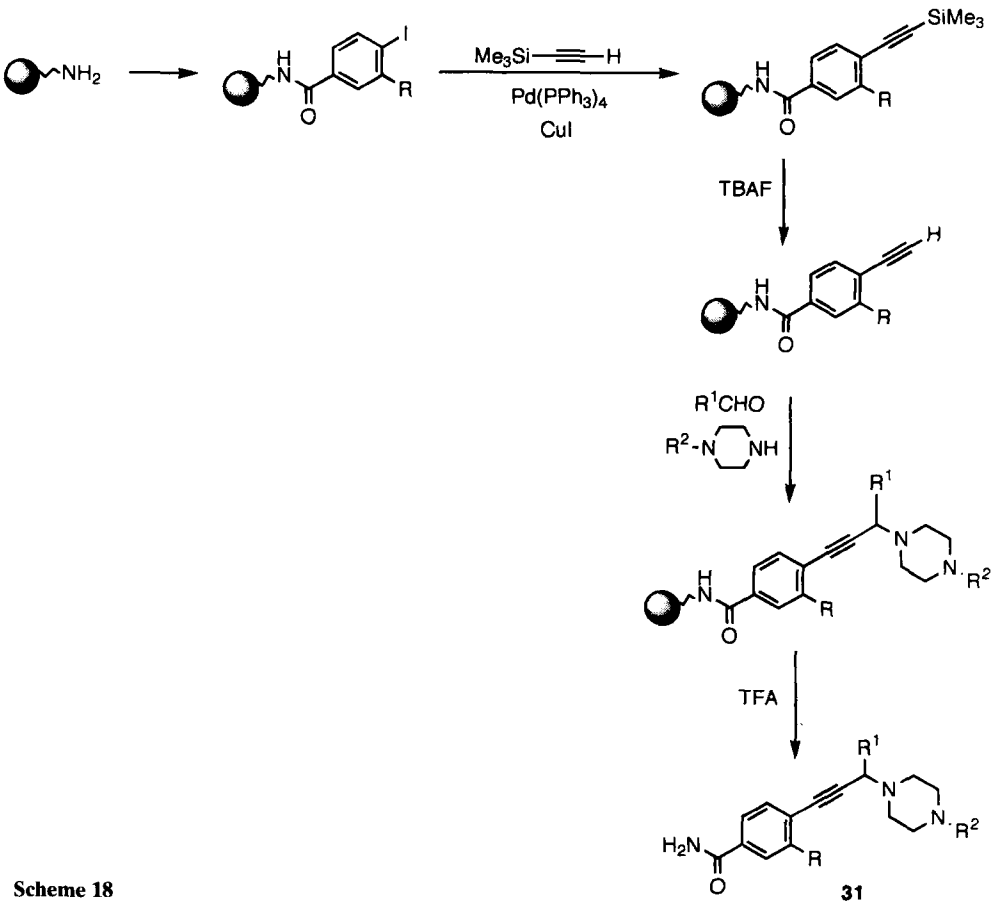
Very good results were obtained when the amines were attached to the solid support, preferably to a trityl linker (see Chapter 3.1.2.2.6, Scheme 15; including procedure). This led to compounds of type **30** (Fig. 2).



30

Figure 2

The alternative attachment of the aldehyde component led to much lower yields in the Mannich reaction on solid support. An aminomethylation on an indole moiety linked to a solid support was also reported [29].



Scheme 18

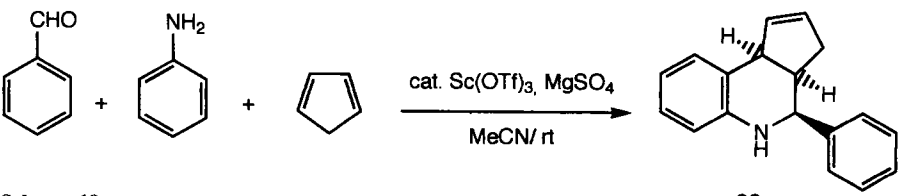
31

An extension of the application of the Mannich reaction with acetylides was achieved by combining it with a Sonogashira coupling [30]. The involvement of the Sonogashira reaction prior to the Mannich reaction greatly enhances the number of potential acetylenes available. The pertinent reaction sequence is outlined in Scheme 18.

The yield and the purity of the desired compounds **31** were reported to be excellent.

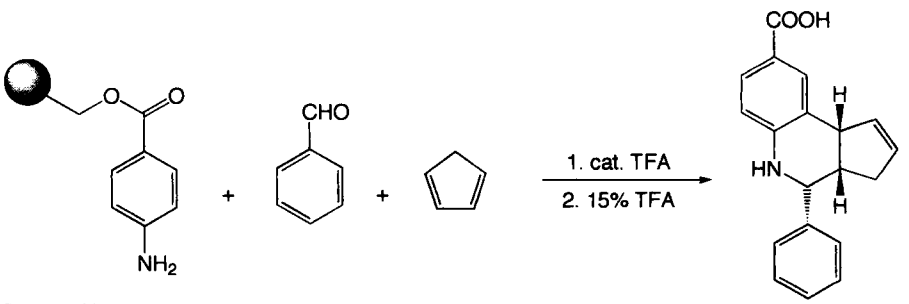
2.2.10 Grieco Three-Component Reaction

Diels–Alder-type reactions of imines with dienes (Aza Diels–Alder reactions) offer a useful means of preparing nitrogen-containing, six-membered heterocycles [31, 32]. Since the imine can be formed from an aldehyde and an amine component, the overall reaction can be performed as a three-component reaction (dubbed the Grieco three-component reaction). Initially, the reaction was performed under Mannich-like conditions. The performance of the reaction could be improved significantly by using $Sc(OTf)_3$ as Lewis acid catalyst [33]. The reaction allows for various combinations of aldehydes, amines and alkenes, and affords diverse tetrahydroquinoline derivatives of type **32** (Scheme 19). The reaction proceeds not in a concerted, but in a stepwise, fashion [33].



Scheme 19 **32**

The reaction can even be performed in aqueous solution and thus, a commercial formaldehyde/water solution can be employed as aldehyde component.



Scheme 20

Procedure [33]
To a suspension of $Sc(OTf)_3$ (0.05 mmol; 10 mol %) and MgSO4 (3.32 mmol, 400 mg) in MeCN (0.5 mL) was added benzaldehyde (0.5 mmol, 53.1 mg) and aniline (0.5 mmol) in MeCN (1.5 mL) and then cyclopentadiene (1.5 mmol) in MeCN (0.5 mL). The mixture was stirred at rt for 20 h. Water was added and the product was extracted with DCM. After usual work-up, the crude product was chromatographed on silica gel to afford the desired product.

Recently, a Grieco three-component condensation was reported to proceed also on a solid support [34] (Scheme 20).

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2.3 Purification Principles in High-Speed Solution-Phase Synthesis

Steffen Weinbrenner

2.3.1 Introduction

As discussed in Chapter 2.1, the benefits of solution-phase synthesis over solid-phase synthesis are the following. A great many more solution-phase reactions have been optimized and documented in the literature compared with currently available solid-phase reactions. A large number of protecting group reagents is available commercially, whereas the number of solid-phase synthesis resins, often used as solid-phase protecting reagents, is limited. Furthermore, in solution-phase chemistry the range of organic reactions is, in principle, very large, whereas on solid phase there are limitations, if one of the reagents or solvents used is not compatible with the support material.

Moreover, reaction progress as well as product identity and purity may be checked by well-established chromatographic and spectroscopic methods, and the time needed for chemistry development in the preparation of libraries in solution-phase approaches is much less than for solid-phase approaches.

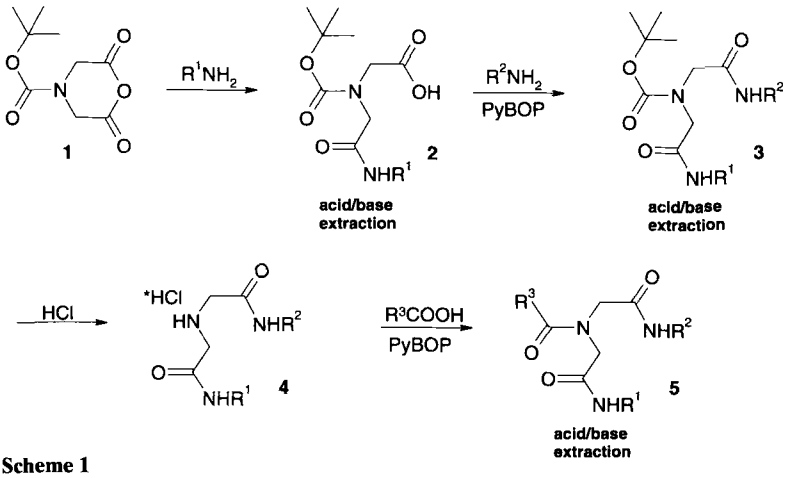
In contrast to the large number of advantages of solution-phase parallel synthesis there is one major disadvantage, the "purification problem". Given that solution- and solid-phase sample manipulation are both convenient and easily automated, the limitation to solution-phase parallel synthesis is the isolation of the desired compounds. So the throughput in automated solution-phase synthesis is directly related to the work-up procedures and to the purification process. Therefore, easy and efficient purification methodologies are required for high-speed solution-phase synthesis.

In this chapter an overview will be given of various purification strategies for automated solution-phase chemistry which have appeared recently in the literature.

2.3.2 Liquid–Liquid Extraction

2.3.2.1 Aqueous Work-Up

Aqueous work-up is a well-known purification method and is used extensively in traditional organic chemistry. The principle of this method is to use an aqueous- and an organic liquid phase, which are nonmiscible. Each particular substance has its partition coefficient between the two phases, and so it is possible to separate substances. For the generation of combinatorial libraries of individual compounds this purification principle was first used by Boger et al. [1, 2].



Scheme 1

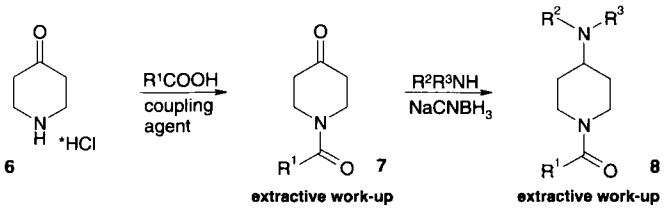
Starting with a protected anhydride scaffold **1** and adding amine, Boger and colleagues obtained the first sublibrary which was purified by acid/base extraction. The monoamides **2** were partitioned and the portions were treated with amine and coupling agent to afford diamides **3**. This second sublibrary was also purified by acid/base extraction and, after cleavage of Boc and partition, the last step of library synthesis was performed by coupling to various acids. To remove unreacted starting materials, reagents and the reaction byproducts, again aqueous acid and base extractions were used (Scheme 1).

Employing this methodology the authors were able to synthesize a library of 125 (5 x 5 x 5) amides of type **5** in high purity (>90 % by HPLC) and overall yields ranging from 32 % to 85 % (30–100 mg). Another 960-member amide library using this scaffold was synthesized with overall yields ranging from 10 % to 71 %, but no data were given about purity.

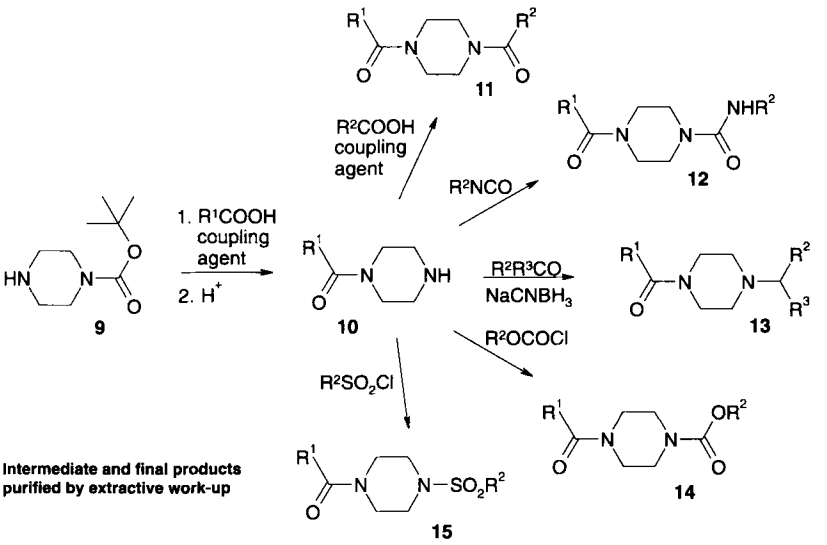
This method has also been extended to other anhydride scaffolds [2, 3] and to combinations of such scaffolds [4–7].

A similar approach [8] has been used for the synthesis of 7900 products derived from reactions of piperidone **6** (Scheme 2), 7500 compounds derived from a piperazine template **9** (Scheme 3), and 6000 products derived from 4-aminobenzylamine. Thus, over 20 000 compounds were synthesized by using solution-phase chemistry and liquid–liquid extraction work-up procedures. For acylations, the authors used a work-up procedure which typically involved robotically adding an aqueous solution of $NaHCO_3$ to the reaction vials, agitating and robotically removing the organic layer. Reductive aminations required a work-up that consisted of robotically adding dilute aqueous hydrochloric acid (to destroy excess $NaCNBH_3$), neutralizing with aqueous NaOH, extracting into dichloromethane, and removing the organic layer.

The purity of the intermediates was assessed by TLC, MS and ^{1}H-NMR, and intermediates that were identified as being less than 90 % pure were not used in subsequent reactions. Unfortunately, only a randomly chosen fraction (~5 %) of the final products was analyzed by MS and only a few products were analyzed by HPLC. So, there are no reliable data about identity and purity of the final products. Nevertheless, this work is an impressive example of



Scheme 2



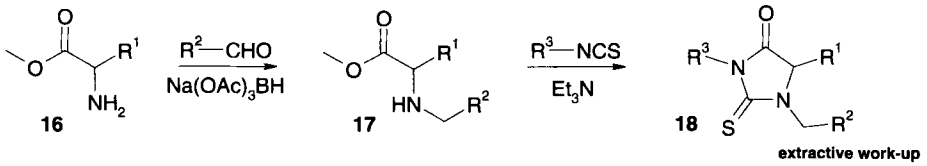
Scheme 3

solution-phase synthesis of a large combinatorial library and a purification strategy by automated liquid–liquid extraction.

A similar acid/base washing strategy has been employed for the synthesis of an aryl-piperazine library [9]. The synthesis was based on a nucleophilic aromatic substitution of nitro-fluoro aromatic compounds with Boc-piperazine and subsequent Schotten–Baumann acylation with acid chlorides. After each step the products were purified by extractive work-up.

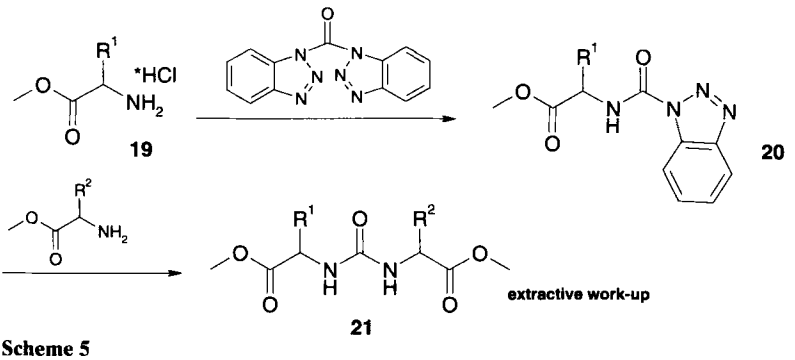
For the solution-phase synthesis of thiohydantoins, an efficient one-pot synthesis has been developed (Scheme 4) [10]. In the first step, amino acid esters **16** were alkylated by reductive alkyation, then isothiocyanate was added together with triethylamine, leading to thiohydantoin products **18**. The work-up procedure was performed by adding glycine as a quenching reagent (scavenger) and an aqueous extraction to remove the borate salts triethylamine and the water-soluble "scavenger-products".

Using this procedure, a library of over 600 discrete compounds on a 0.1 mmol scale was generated. Some 10 % of the library was checked by HPLC analysis and showed purities of 52 % to 98 %.



Scheme 4

For parallel synthesis of ureas based on amino acids, a solid-phase synthesis as well as solution-phase synthesis was used (Scheme 5) [11]. Solution-phase synthesis gave the desired compounds **21** in yields ranging from 80 % to 100 %, and purity between 71 % and 97 %. The work-up involved extraction of the benzotriazole formed in the coupling steps. Therefore an aqueous borax buffer (pH 9.2) was used and the separation of the CH_2Cl_2 layer from aqueous phase was performed in syringes equipped with a PTFE frit.



Scheme 5

Procedure: Preparation of **5** [1]

A solution of N-((*tert*-butyloxy)carbonyliminodiacetic acid (**1**) (0.349 g, 1.50 mmol) in dimethylformamide (DMF) (15 mL) was treated with N'-(3-dimethylamino-propyl)-N-ethyl-carbodimide hydrochloride (EDC) (0.294 g, 1.54 mmol) at 25° C. The mixture was stirred at 25° C for 1 h before the amine (1 equiv.) was added, and the solution was stirred for 20 h. The reaction mixture was poured into 10 % aqueous HCl (60 mL) and extracted with ethyl acetate (100 mL). The organic phase was washed with 10 % HCl (40 mL) and saturated aqueous NaCl (2 X 50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to yield the diacid monoamides **2**. Each of the diacid monoamides **2** was dissolved in anhydrous DMF (20 mL/mmol–1) and was divided into three equal portions in three separate vials. Each solution was treated with one of the three amines (1 equiv.), diisopropylethylamine (2 equiv.) and (benzotriazole-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (1 equiv.). The solution was stirred at 25° C for 20 h. The mixture was poured into 10 % HCl and extracted with ethyl acetate. The organic phase was washed with 10 % HCl, saturated aqueous NaCl, 5 % aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was

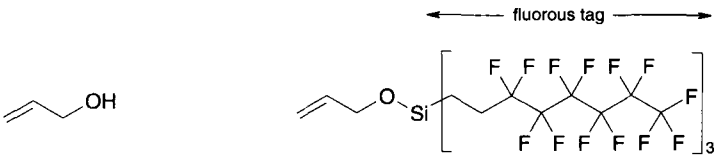
dried (Na_2SO_4), filtered and concentrated to yield the diamides **3**. Each of the diamides **3** was dissolved in 4 N HCl-dioxane (32 mL/mmol) and the mixture was stirred at 25° C for 45 min. The solvent was removed in vacuo and the residue dissolved in anhydrous DMF (28 mL/mmol), divided into three equal portions and placed in three separate vials. The solution was treated with one of three carboxylic acids (1 equiv.) followed by diisopropylamine (3 equiv.) and PyBOP (1 equiv.). The solution was stirred for 20 h. The mixture was poured into 10 % HCl and extracted with ethyl acetate. The organic phase was washed with 10 % HCl, saturated aqueous NaCl, 5 % aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to yield the final products **5**.

Procedure: Preparation of **21** [11]
A solution of amino acid methyl ester hydrochloride (**19**) (0.2 mmol, 1 equiv.) and diisopropylethylamine (1.1 equiv.) in DMF (1 mL) was added to 1,1'-carbonylbisbenzotriazole (1 equiv.) in dichloromethane (1 mL) and the resulting mixture was shaken overnight at rt. Then a solution of the second amino acid methyl ester (1 equiv.) and diisopropylethylamine (1.1 equiv.) in DMF (1 mL) was added and the resulting mixture was shaken overnight at rt. The samples were concentrated in vacuo, the residue was dissolved in dichloromethane, and transferred to syringes equipped with a PTFE frit, mounted on a VacMaster. The organic layer was washed with 2 x 2 mL borax buffer (0.1 M, pH 9.2) and 2 x 2 mL 0.2 M HCl. The organic layer was collected in pre-weighed tubes and concentrated in vacuo to yield the urea **21**.

2.3.2.2 "Fluorous Work-Up"

Another possibility of liquid–liquid extraction is the use of "fluorous" phase extraction. This methodology was first used by Horvath and Rabai [12], and has since been extended [13] to use in combinatorial chemistry.

Generally, the fluorous phase consists of perfluorohydrocarbons (e.g., perfluoro-hexanes (FC-72)) which are neither soluble in most organic solvents nor in water. To dissolve organic molecules in fluorous solvents, a fluorous tag is required; this consists of a large perfluorinated moiety which must be attached to one of the reactants or reagents. The purification strategy here is to separate fluorous molecules selectively from the rest of the components by a fluorous/organic (Fig. 1) or a fluorous/aqueous phase system. It is also possible to use a three-phase extraction (fluorous/organic/aqueous). A good partition coefficient between fluo-

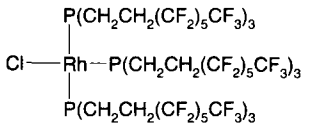


Organic
-soluble in organic phase

Fluorous
- soluble in fluorous phase

Figure 1

rous/organic and fluorous/aqueous phases is required to separate fluorous molecules from the rest of the components. This partition coefficient can be influenced by the number of fluorous atoms of the fluorous tag, as well as by the choice of the organic solvent [14]. The most effective fluorocarbon moieties are linear or branched perfluoralkyl chains with a high number of fluorine atoms. To achieve this high number of fluorine atoms, perfluoralkylated silicium-, tin-, or phosphorus compounds are most effective. It should be noted that the possibility of dipole–dipole interactions renders perfluoroaryl-containing reagents and catalysts more soluble in common organic solvents and therefore less useful as part of fluorous biphase systems [15]. The insertion of two or three methylene groups in front of the fluorous ponytail is necessary to decrease the strong electron-withdrawing effects of the fluorous ponytails – an important consideration if catalyst or reagent reactivity should not be influenced. The purification strategy is common for the use of fluorous catalysts (Fig. 2) [16], as well as for the use of fluorous reagents or fluorous reactants (Scheme 6; see also Scheme 8). As an example of a "fluorous phase strategy", the synthesis of isoxazolines is shown in Scheme 6 [17, 18].

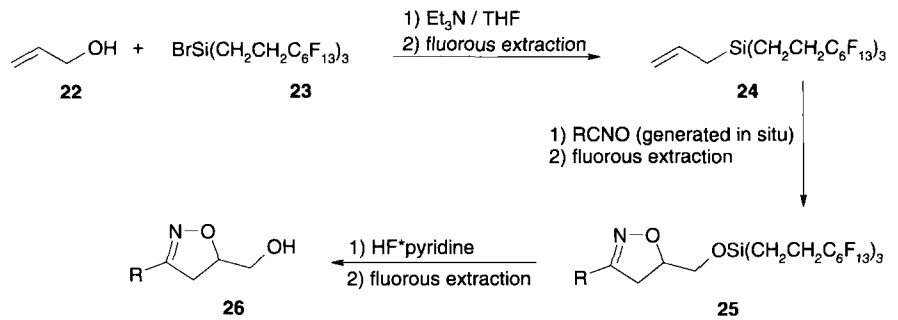


Fluorous analog of Wilkinson's catalyst for hydrogenation, hydroboration and hydrosilyation.

Figure 2

Procedure: Preparation of **26** [18]

Allyl alcohol **22** (0.91 mmol) and triethylamine (1 equiv.) were dissolved in dry THF (2 mL) under argon. A mixture of bromo tris(2-perfluorohexylethyl)silane **23** (0.25 equiv.) in THF (2 mL) was slowly added to the reaction mixture at 25° C. The solution was stirred at 25° C for 3 h. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (10 mL), dichloromethane (10 mL) and water (10 mL). The organic–aqueous biphase was additionally extracted twice with FC-72 (10 mL). After evaporation of the combined fluorous extracts, the residue was further purified by flash-chromatography (hexane:diethylether, 50:1) to yield a colorless oil.



Scheme 6

To a solution of this silyl ether **24** (0.1 mmol) in benzotrifluoride (BTF, 4 mL) were added a nitro alkane (0.99 mmol), phenyl isocyanate (1.98 mmol) and two drops of triethylamine. The reaction mixture was stirred at 25° C for 3 days. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (20 mL), benzene (20 mL) and water (20 mL). The combined fluorous extracts were evaporated to yield the isoxazolines **25**, which was dissolved in diethylether (3 mL) at 25° C. HF*pyridine (0.1 mL) was added and the solution was stirred for 1 h at 25° C. After removal of the solvent, the residue was dissolved in dichloromethane (20 mL). Saturated aqueous NH_4Cl (10 mL) was added and the organic–aqueous biphase was washed twice with FC-72 (10 mL). After separation of the layers, the aqueous phase was extracted twice with dichloromethane and the combined organic phases were dried ($MgSO_4$) and evaporated to yield the deprotected isoxazoline **26**.

2.3.2.3 Phase Separation Techniques

The traditional separation of two phases (in most cases organic/aqueous) can be performed in a parallel manner by several methods. One possibility is to use a robotic system with phase detection and liquid level detection (see Chapter 6.3). Another method is the use of adsorbent packing cartridges to adsorb the aqueous phase (Na_2SO_4, $MgSO_4$, alumina, EXtrelut®). Furthermore, a hydrophobic membrane or frit (PTFE) in a polypropylene cartridge can be used to separate a dichloromethane or chloroform phase from the aqueous phase (Fig. 3). The dichloromethane or chloroform phase is able to pass through the frit, and the aqueous phase remains on top of the filter.

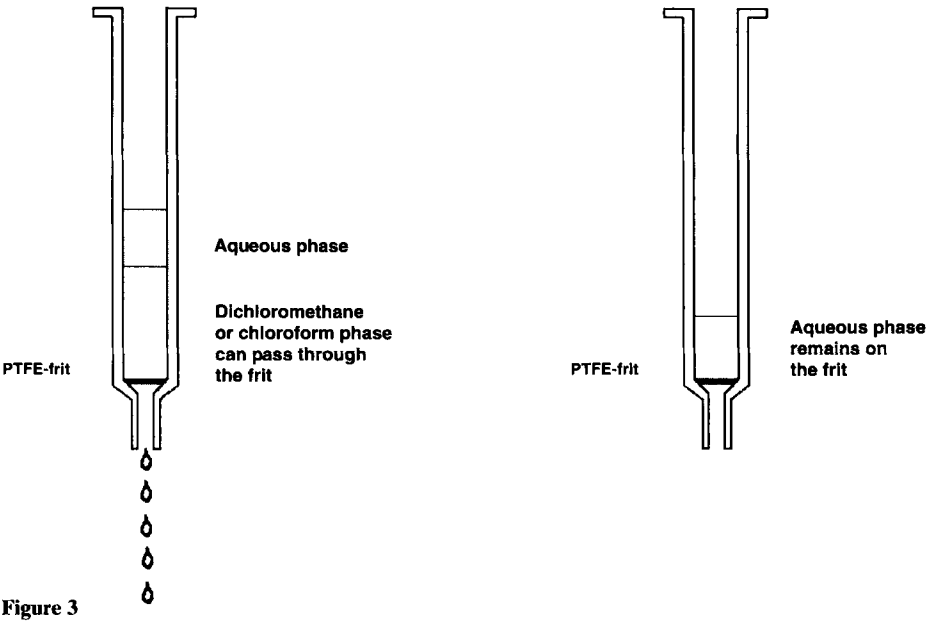


Figure 3

A novel separation method consists of cooling the organic/aqueous phase to -20° C in deep-well plates in the presence of pins. After the freezing process, the aqueous phase can be removed as ice attached to the array of pins, whereas the organic phase remains in the deep-well plate. In this way, 96 aqueous/organic mixtures can be easily separated using this "lollipop" method [19].

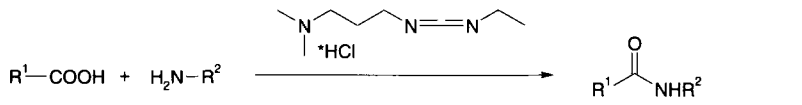
2.3.3 Solid-Phase Extraction

The principle of solid-phase extraction (SPE) or liquid–solid extraction (LSE) is similar to that of liquid–liquid extraction, involving a partitioning of compounds between two phases [20]. In SPE, the compounds to be extracted are partitioned between a solid and a liquid. The interactions responsible for the separation between liquid and solid phase are noncovalent (ionic, Van der Waals, hydrophobic), and those interactions can be modulated by the physical properties of the eluent (liquid phase) and the adsorbent (solid phase).

In principle, there are no major differences between solid-phase extraction and liquid–liquid extraction, but SPE can avoid or reduce some disadvantages of liquid–liquid extraction. SPE can handle small samples and very dilute solutions, it overcomes the formation of emulsions, and it can be easily automated. Furthermore, the sorbents which are commonly used are available commercially as cartridges. These sorbents are alumina, silica gel, reversed-phase silica gel, and various ion-exchange resins. It is also possible to pack different adsorbents in layers inside the same cartridge to give a "sandwich type" extraction column.

2.3.3.1 Silica Gel and Alumina

A large variety of inorganic salts can be very easily removed by SPE with silica gel or alumina, as in an aqueous work-up. Furthermore, it is possible to separate amine hydrochlorides or even an excess of amine or acid from the desired product by silica gel or alumina SPE. Even reagents (e.g., coupling agent EDC) can be separated by simple filtration of the reaction mixture through silica gel or alumina (Scheme 7).



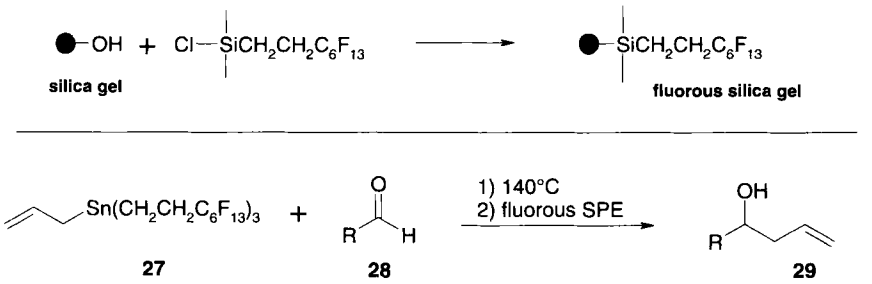
remove of unreacted amine or acid as well as excess of carbodiimide and formed urea by SPE with "sandwich column" of alumina and silica gel

Scheme 7

A large number of polar reagents, side products and impurities, removable by aqueous work-up can also be separated by SPE with alumina and/or silica gel. Thus, SPE based on these adsorbents provides an easily automated and inexpensive alternative to aqueous work-up.

2.3.3.2 Fluorinated Silica Gel

As by fluorous/organic liquid–liquid extraction, it is also possible to separate perfluorinated molecules from other organic molecules by fluorous solid-phase extraction (FSPE). Silica gel modified with dimethyl[2-(perfluorohexyl)ethyl]silyl chloride was used as solid adsorbent in the solid-phase extraction of fluorous tin byproducts (Scheme 8) [21].



Scheme 8

After addition of the fluorinated allyl tin reagent **27** to an aldehyde **28**, the crude reaction mixture was adsorbed on fluorous silica gel and then charged to a dry packed fluorous silica gel column. The column was eluted first with acetonitrile and then with hexane. Evaporation of the acetonitrile fraction provided the organic products **29**, whereas the fluorous byproducts remained adsorbed on the fluorous silica gel and were eluted with hexane. Using this reaction sequence the concept of fluorous silica gel extraction has been proved; future uses will demonstrate its applicability.

2.3.3.3 Ion Exchange

Ion-exchange resins, as well as ion-exchange silica gels, have been more commonly used for combinatorial applications than "traditional" adsorbent materials. The advantage of ion-exchange adsorbents is the possibility to influence – very selectively – the interaction between the adsorbent and the molecules. Ion-exchange adsorbents are able to differentiate charged molecules from neutral molecules, and species which can undergo a proton transfer can be retained by ionic interactions. These ionic processes are reversible and can be influenced by the ionic strength of the eluent (pH) as well as the ionic nature of the adsorbent.

A large number of ion-exchange adsorbents are available commercially, based on polystyrene polymers, as well as on silica gel. The advantage of the silica gel-based adsorbents is their much greater stability towards a very large number of organic reagents. Furthermore, they can be used with organic solvents without any problems, and even solvent changes between organic and aqueous solutions are possible without problems caused by swelling. These silica gel-based ion-exchange sorbents (Fig. 4) are available from various suppliers as

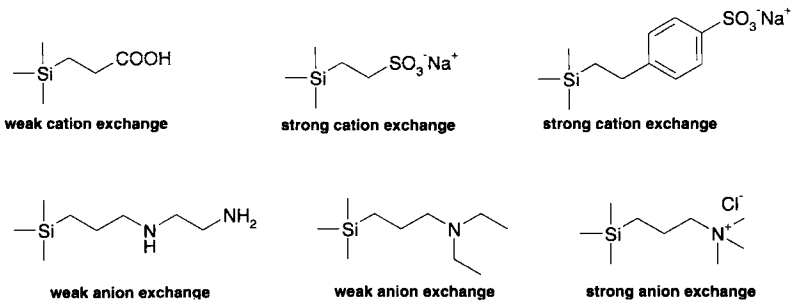
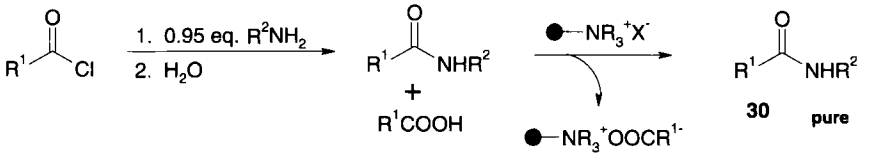


Figure 4 Silica gel-based ion-exchange sorbents.

prepacked polypropylene cartridges, filled with various amounts of sorbent. The capacity of the sorbents is given in mequiv. g^{-1} (normally ~0.7 mequiv. g^{-1}); thus it is easily determined how much material can be loaded onto the column.

Thus, products able to form ions can be purified by ion-exchange solid-phase extraction in automated solution-phase synthesis. Another possibility to purify a combinatorial solution-phase library is to separate selectively reagents, byproducts and impurities which are able to form ions from the product by ion exchange. Both methods have appeared in the literature, and a few examples will be given here.

For the purification of an amide library [22], a basic ion-exchange resin was used to separate an excess of unreacted acid chloride after addition of water to the reaction mixture (Scheme 9). The authors evaluated nine ion-exchange resins and three solvents, and obtained the best results using the weakly basic Amberlite® IRA-68 in combination with ethyl acetate. Using this method they obtained the desired products **30** in high yields (84-99 %) and purities (>95 %), but unfortunately only data of a nine-member library were given. Using this strategy, more than 4500 compounds were synthesized [23], starting from a series of substituted pyrimidine and benzene acid chlorides.

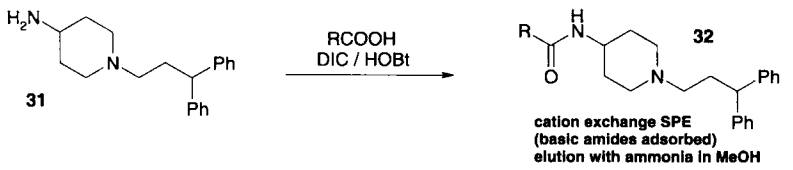


Scheme 9

To purify a library of amines generated by reductive amination, the use of strong cation-exchange adsorbents, based on silica gel was described [24]. An excess of aldehyde was used to ensure the completion of the reaction, and the crude reaction mixture was poured over a strong cation-exchange adsorbent. The column was rinsed with methanol to remove the excess of aldehyde and other neutral impurities, while the basic products remained on the sor-

bent. The adsorbent was then treated with a 2 M solution of anhydrous ammonia in methanol to elute the basic products in high purities.

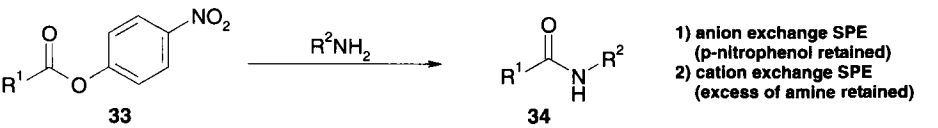
A similar approach to retain the product selectively on an ion-exchange adsorbent has been employed for the synthesis of a library of over 225 basic amides **32** (Scheme 10) and a neutral amide library of 150 compounds [25]. For the synthesis of the basic amide library, the authors used diisopropyl-carbodiimide (DIC) and 1-hydroxybenztriozole (HOBt) as coupling agent, because these reagents and the resulting byproducts are neutral and therefore compatible with the cationic SPE purification strategy. The reaction stoichiometry was optimized to ensure complete consumption of the basic diamine **31**, as separation of the unreacted diamine from the product amide **32** by cation exchange was not possible. Thus, in general the reactions were performed using 1.5 equiv. DIC and HOBt with 4 equiv. of acid.



After 24 h, the reaction mixture was loaded onto the cation-exchange column followed by washing with MeOH and 0.1 N ammonia in MeOH to remove the byproduct urea, excess acid and HOBt from the sorbent. The pure product was then eluted with 1 N ammonia in MeOH. Automation was performed using a commercially available liquid handler and a SPE workstation. HPLC and MS were used to determine the identity and purity of the products and an average yield of 70 % and an average HPLC purity of 90 % were given.

This robotic method was also applied to synthesize a neutral amide library (Scheme 11). Nucleophilic acyl substitution of nitrophenyl esters **33** with amines provided mixtures containing the product **34**, p-nitrophenol and excess amine. These products were purified by a dual ion-exchange SPE procedure. First, using an anion-exchange sorbent to remove the acidic p-nitrophenol, followed by a cation exchange to remove the excess of amine. The products were eluted with THF and dichloromethane, and obtained with average yields of 75 % and average purities of >90 %.

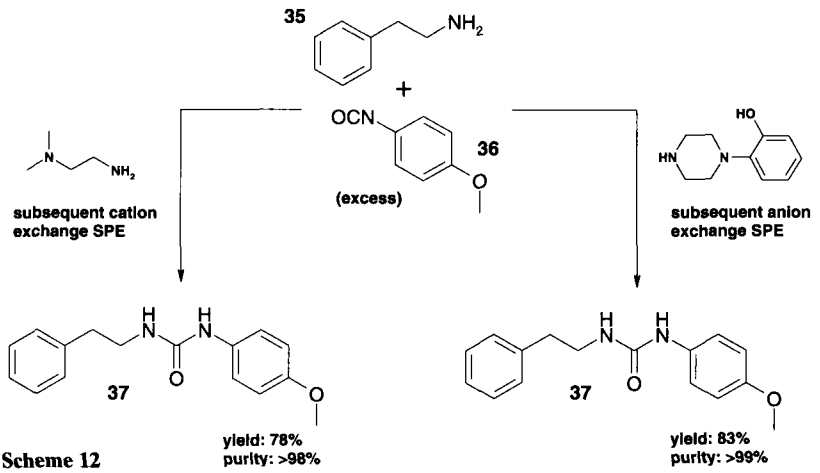
Both basic and neutral amide libraries were prepared in runs of 25 to 100 simultaneous reactions in quantities up to 0.4 mmol each (25–300 mg).



Scheme 11

For high-throughput synthesis and purification of ethanolamines, the method to retain selectively the basic products as ammonium sulfonate salts on strong cation-exchange sorbents was also used [26]. An 8 x 6 reaction array employing eight different amines and six different epoxides was performed, and the products were obtained with an average yield of 75 % and an average purity of >92 %.

If neither the desired product nor the reagents and impurities are ionizable, the ion-exchange methods shown above are not convenient. Nevertheless, the selective isolation of the desired compound using ion-exchange adsorbents can be performed using a "phase-switch" approach [24]. To achieve this, "phase-switch" quenching reagents were used to transform a neutral compound into an ionizable species that could be captured by an ion-exchange solid support. The principle is amenable to both anion- and cation-exchange chromatography, depending on the quenching agent employed. An illustration of the method is given in Scheme 12.



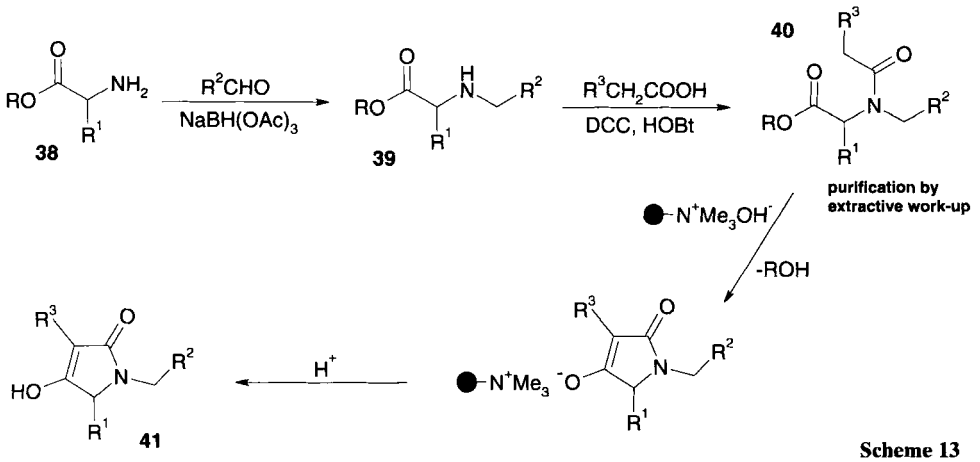
Scheme 12

Therefore, the authors used phenylethylamine **35** to react with 1.25 equiv. of 4-methoxyphenylisocyanate **36** to form a crude reaction mixture of product urea **37** plus excess isocyanate. Subsequently, the isocyanate impurity was removed by quenching either with N,N-dimethylaminoethylamine followed by cation exchange, or by quenching with 1-(2-hydroxyphenyl)piperazine followed by anion exchange.

Ion-exchange sorbents can also be used as activators or even reagents for chemical transformations, and in the area of combinatorial chemistry this principle has been applied first for the synthesis of combinatorial libraries of aryl and heteroaryl ethers [27].

Another approach combined the two applications and used an ion-exchange resin as reagent as well as the purification agent for the synthesis of tetramic acids [28] (Scheme 13). Starting from amino acid esters **38**, reductive amination and subsequent coupling with acids leads after extractive work-up to desired amide esters **40**. The Dieckmann condensation of these amide esters can be achieved using various bases, but the authors established that the cyclization can also be performed with Amberlyst A-26 resin (OH^- form) as base. After the

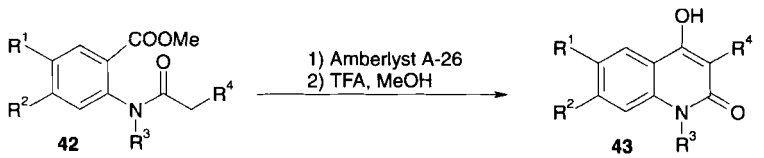
reaction, the tetramic acid binds to the resin, while the rest of the components (as well as impurities) are washed away. Subsequent acidification with trifluoroacetic acid in methanol then releases the product **41** in high yield (>70 %) and purity (87 % average).



Scheme 13

Furthermore, this ion-exchange strategy has been extended to an intramolecular Claisen-type condensation starting from substituted anthranilic acids **42** [29]. Employing Amberlyst A-26 resin (OH^- form) as base as well as purification sorbent, the authors were able to synthesize a library of 4-hydroxy-quinolin-2(1*H*)-ones **43** (Scheme 14).

The desired compounds were released again with trifluoroacetic acid in methanol, and the final products were obtained in yields of between 72 % and 97 %, and purities between 79 % and 99 %. The precursors were synthesized by reductive alkylation and subsequent acylation and were purified by extractive work-up.



Scheme 14

Procedure: Preparation of **30** [22]

To Amberlite® IRA-68 (approximately 0.05 g dried under vacuum overnight) was added the amine (0.0475 mmol) in ethyl acetate (0.6 mL) followed by the acid chloride (0.050 mmol) in ethyl acetate (0.6 mL). The reaction mixture was then shaken overnight. Water (0.1 mL) was added and the reaction shaken for an additional 30 min. Filtration and concentration of the filtrate provided the desired product **30**.

Procedure: Preparation of **32** [25]
The reaction set-up and product purification procedures were carried out using the Zymark Benchmate Robotic Workstation.
Reaction: The variable acid (4 equiv., 0.24–0.8 mmol) was manually added to each 16 mm x 100 mm tube and the tubes were loosely capped with a polypropylene cap. The liquid handler then carried out the following steps on each tube: 1) Added 500 µL (1.5 equiv., 0.092–0.3 mmol) of a solution of hydroxybenzotriazole in DMF. 2) Added 500 µL (1.5 equiv., 0.092–0.3 mmol) of a solution of diisopropyl carbodiimide in dichloromethane. 3) Added 500 µL (1 equiv., 0.061–0.2 mmol) of a solution of diamine **31** in dichloromethane. 4) Washed syringe with 3 mL of dichloromethane. 5) Mixed tube contents by vortexing at speed 3 for 15 s. After all additions were complete, the workstation cycled through the tubes five times, vortexing each tube for 20 s at speed 3. The reactions were allowed to proceed until all the reactions in the run were complete (19 h), as indicated by disappearance of diamine (monitored by TLC).
Purification: The workstation carried out the following steps for each tube: 1) Conditioned a SPE column (strong cation exchange, 0.5–1.5 g sorbent, 0.6 mequiv. g–1) with 10 mL of methanol. 2) Loaded reaction contents onto the column. 3) Washed column with 2 x 10 mL of methanol. 4) Washed column with 2 mL of 0.1 M ammonia in methanol. 5) Eluted column with 2–5 mL of 1 M ammonia in methanol and collected the effluent into a tared receiving tube. Aliquots (10–20 µL) were removed for HPLC and MS analysis. The product solutions were concentrated in vacuo and final solvent remnants were removed by further exposure to high vacuum to afford products **32**.

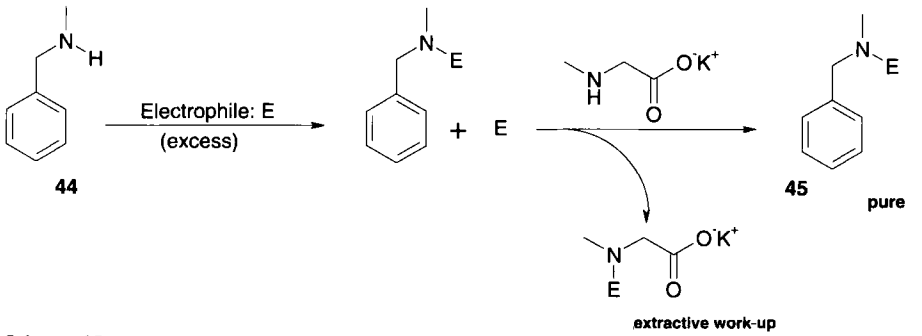
2.3.4 Covalent Scavengers

Another approach to remove unreacted excess starting material, reagents, and impurities is afforded by the option to use selective covalent derivatizations of these impurities after the synthesis. These quenching reagents are commonly named "scavenger" reagents or "scavengers". To allow easy separation of the desired products from the selectively formed byproducts, the scavenger reagent must be attached to suitable supports.

2.3.4.1 Solution Scavengers

One possibility is a support consisting of a functional group which is responsible for the "phase switch" of the impurities, so allowing subsequent separation of product and byproduct by aqueous extraction or simple filtration. This strategy has been employed as shown above (see Scheme 4) [10] for the synthesis of thiohydantoins **18**, as well as for synthesis of amides and ureas **45** (Scheme 15) [30]. Glycine or potassium sarcosinate were chosen as the quenching agents on the basis of their bifunctional nature. The amine end of the amino acid quenches the excess electrophile, while the carboxylic acid functionality renders the amino acid-bound impurity soluble in aqueous medium.

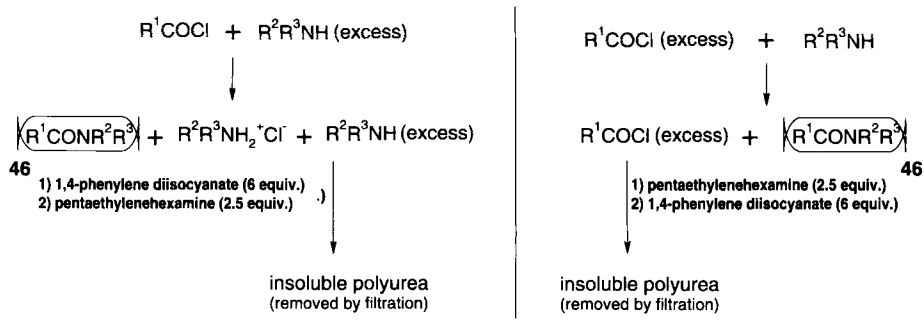
An excess (>1.5 equiv.) of electrophile (acid chloride or isocyanate) in the presence of triethylamine in dimethylformamide or THF was used. After stirring for 4 h, potassium sarcosi-



Scheme 15

nate (1 equiv.) was added and the reaction mixture was stirred for an additional 0.5 h. Water was then added and the product **45** was filtered or extracted in ethyl acetate. The ureas, as well as the amides, were obtained in high yields (>72 %); the purities were checked by ^{1}H-NMR and elemental analysis, but no discrete data on purity were given. This solution scavenger principle has been also used in combination with ion-exchange purification strategies, as shown in Scheme 12 [24].

A scavenger approach, based upon the annihilation of excess reactants by polymerization and simple filtration, was also employed to purify solution-phase libraries of amides and sulfonamides [31]. Co-polymerization of 1,4-phenylene diisocyanate and pentaethylene-hexamine was used to remove the excess amine as an insoluble filterable urea. An excess acyl or sulfonyl chloride can also be scavenged by polyamine and diisocyanate, depending on the order of addition (Scheme 16). The desired amides **46** and sulfonamides were obtained in good yield (>64 %) and purity (87 % average).



Scheme 16

Procedure: Preparation of **45** [30]

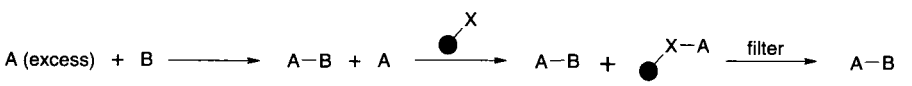
The amides and sulfonamides were synthesized by treating N-benzylmethylamine **44** (0.302 g, 2.5 mmol) with an acid chloride or sulfonyl chloride (3.5 mmol) in DMF (2 mL) and triethylamine (5 mmol). The reaction mixture was stirred for 4 h and was then quenched

with potassium sarcosinate (0.127 g, 1 mmol) and water (6 mL). The product **45** was isolated by filtration in the case of solids and extracted in ethyl acetate (10 mL) in the case of oils. The organic extract was pipetted out and evaporated to give the product.

Procedure: Preparation of **46** [31]
*Procedure for the formation of amides **46** or sulfonamides using an acid chloride or sulfonyl chloride respectively with an excess amine:* To a solution of acid chloride or sulfonyl chloride (0.1 mmol) in dichloromethane (1 mL) was added a solution of the amine (3 equiv.) in dichloromethane (1 mL). The mixture was stirred at rt for 30 min and a solution of 1,4-phenylene diisocyanate (6 equiv.) in dichloromethane (4 mL) was added. The mixture was stirred at rt for 40 min and a solution of pentaethylenehexamine (2.5 equiv.) in dichloromethane (4 mL) was added. After stirring for 1 h, the heterogeneous mixture was filtered. Evaporation of the solvent under reduced pressure afforded the expected amide **46** or sulfonamide.
*Procedure for the formation of amides **46** or sulfonamides using an amine with excess acid chloride or sulfonyl chloride respectively:* To a solution of amine (0.1 mmol) in dichloromethane (1 mL) was added a solution of the acid chloride or sulfonyl chloride (3 equiv.) in dichloromethane (1 mL) and polyvinylpyridine (100 mg). The mixture was stirred at rt for 40 min and a solution of pentaethylenehexamine (3 equiv.) in dichloromethane (4 mL) was added. The mixture was stirred at rt for 40 min and a solution of 1,4-phenylene diisocyanate (3 equiv.) in dichloromethane (4 mL) was added. After stirring for 1 h, the heterogeneous mixture was filtered. Evaporation of the solvent under reduced pressure afforded the expected amide **46** or sulfonamide.

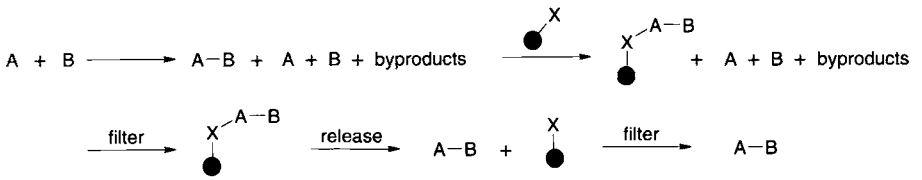
2.3.5 Polymer-Assisted Solution-Phase Chemistry (PASP)

Another possibility of performing the desired "phase switch" using a covalent scavenger approach consists of a resin-bound scavenger functionality. In this way the quenching proceeds via a covalent bond between the functionalized resin and the unreacted starting materials or other impurities. The resulting resin-bound reactants can be removed by simple filtration and rinsing (Scheme 17). Thus, an excess of one starting material can be utilized to drive the reaction to completion, without complicating the isolation and purification of the final product.



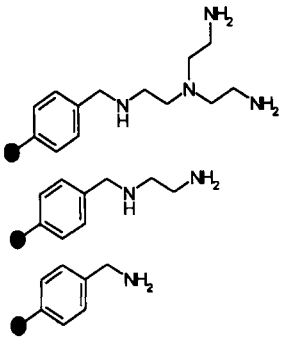
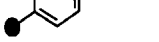
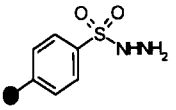
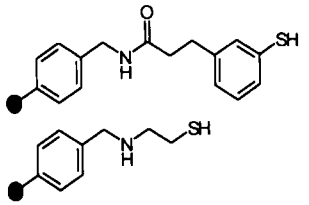
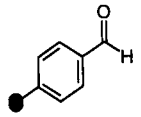
Scheme 17

In contrast to this method, another PASP strategy – known as resin capture – makes use of resins which transiently sequester solution-phase products, allowing solution-phase reactants, reagents, and byproducts to be filtered away from the resin-bound products. The products are subsequently released from the sequestering resin to afford the desired purified solution-phase products (Scheme 18).



Scheme 18

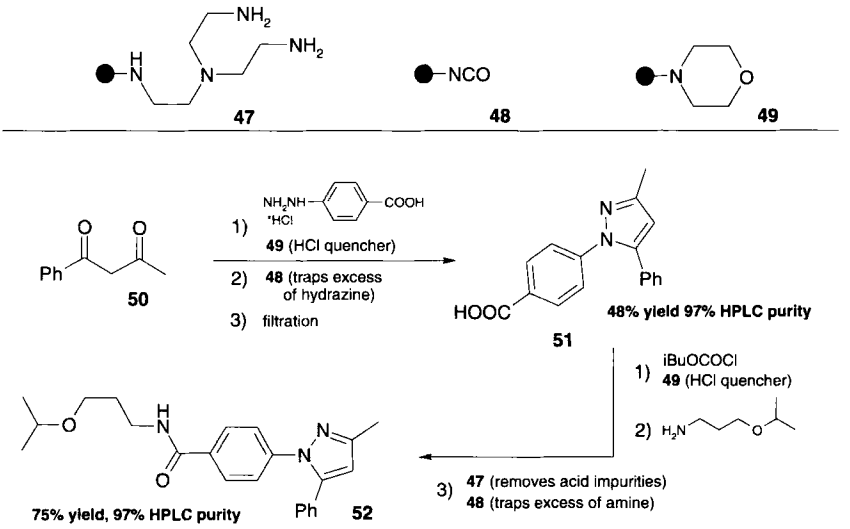
Table 1. Commercially available scavenger resins

Scavenger resin	Type of compound scavenged
	acid chlorides, sulfonyl chlorides, isocyanates
	amines, thioles, alkoxides, organometallics
	aldehydes, ketones
	halides, mesylates, tosylates, 1,2-unsaturated carbonyl compounds
	amines

2.3.5.1 Scavenger Resins

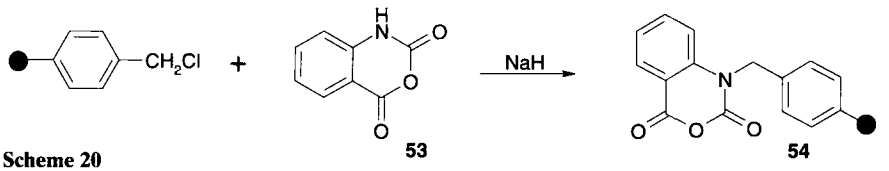
The concept of selective sequestration of nonproduct species has been first proved using solid-supported scavengers with electrophilic and nucleophilic character in amine acylation, amine alkylation and reductive amination protocols [32]. In the meantime, a wide range of scavenger reagents are available commercially from various suppliers. The structures and functions of these scavenger resins are shown in Table 1.

Recently, a number of scavenger resin approaches have appeared in the literature. For the synthesis of 4000 ureas (400 pools of 10-compound mixtures) [33], a solid-supported amino nucleophile was used to quench the excess of isocyanates, yielding the desired products in good purity. A similar concept was employed in the synthesis of 2-thioxo-4-dihydropyrimidinones [34] using aminomethylated polystyrene beads to quench isothiocyanates as well as aldehydes. For quenching an excess of amine in the synthesis of 2,6,9- trisubstituted purines [35], formyl polystyrene beads were used to form the corresponding polymer-bound imine, which was filtered off. Furthermore, a pyrazole synthesis with polymer-supported quench (PSQ) purification was described [36]. Primary amine **47**, isocyanate **48** and tertiary amine **49** supported on a polymer were used to quench an excess of acids, and an excess of hydrazine, as well as to trap HCl and acid impurities respectively. The synthesis, as well as the purification steps, are shown in Scheme 19.



Scheme 19

A very similar polymer-supported quench methodology has been used for the synthesis of dihydropyridones and derivatives of dihydropyridones [37]. Furthermore, the development of a new scavenger resin for amines has been published recently [38]. The author attached isatoic anhydride **53** to Merryfield resin by alkylation on its nitrogen, and used this resin **54** to remove excess of primary and secondary aliphatic amines (Scheme 20).



Scheme 20

Procedure: Preparation of **52** [36]
A solution of polymer-supported morpholine **49** (170 mg), 1-phenyl-1,3-butanedione **50** (0.5 mmol) and (4-carboxyphenyl)hydrazine hydrochloride (0.6 mmol) in methanol was shaken for 2.5 h. The methanol was removed by evaporation under a stream of nitrogen, dichloromethane (4 mL) and polymer-supported isocyanate **48** (350 mg) were added, and the reaction mixture was shaken for 16 h. An additional portion of polymer-supported isocyanate **48** (120 mg) was added. After 4 h, the resin was filtered and washed with dichloromethane (2 x 1.5 mL). The combined organic phases were concentrated in vacuo to give the desired product 4-(3-methyl-5-phenylpyrazol-1-yl)benzoic acid **51**. A portion (20 mg, 70 μmol) of this benzoic acid was dissolved in dichloromethane and the solution was treated with polymer-supported morpholine **49** (100 mg) and 0.1 M isobutyl chloroformate in dichloromethane (0.75 mL, 75 μmol). The resulting slurry was shaken under nitrogen at rt for 30 min and then treated with a solution of (3-isopropoxypropyl)amine (100 mg, 85 μmol) in dichloromethane (0.5 mL). The reaction mixture was shaken at rt for 2.5 h. Polymer-supported isocyanate **48** (75 mg) and polymer-supported tris(2-aminoethyl)amine **47** (100 mg) were added and the mixture was shaken for an additional 2 h. Resins were removed by filtration and rinsed with dichloromethane (2 x 2.5 mL). Combined filtrate and washings were evaporated and dried in vacuo, to yield product **52**.

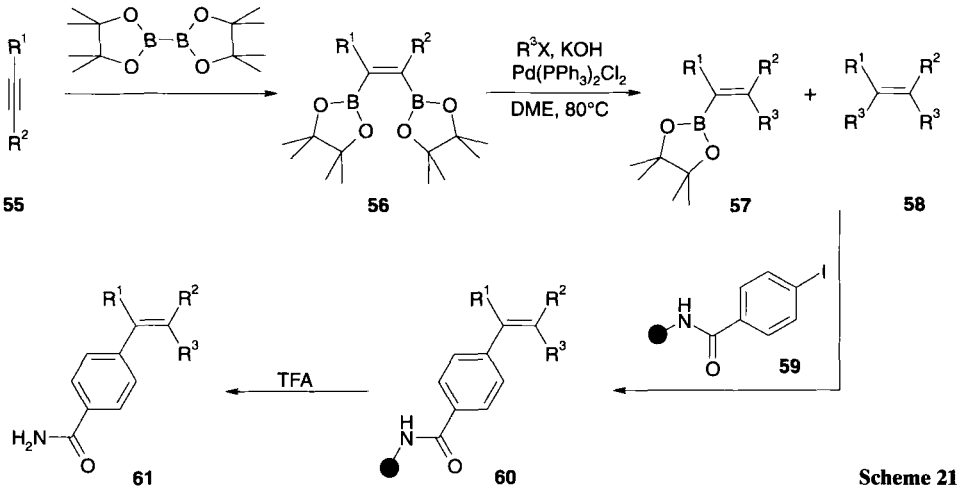
2.3.5.2 Resin Capture

As shown above, the second PASP strategy to purify a crude reaction mixture after the synthesis is to separate the desired product by selective covalent derivatization with a fuctionalized resin and subsequent filtration and rinsing. After formation of the product in solution, it reacts selectively with a solid support while impurities and unreacted substrate remain in solution and are washed away. This resin capture concept [39] has been introduced using the Ugi four-component condensation to prove this purification approach. After the condensation, the reactivity of the enamide allowed the specific reaction with Wang resin under anhydrous acidic conditions. The resin was then washed with methanol and dichloromethane, and the subsequent cleavage performed with trifluoroacetic acid in dichloromethane. The final carboxylic acids were characterized without further purification and were >95 % pure.

Another resin capture approach has been published in the synthesis of tetrasubstituted ethylenes via Suzuki coupling reactions [40, 41] (Scheme 21). A 25-member library was synthesized using five alkynes, five aryl halides, and a polymer-bound aryl iodide. The alkynes **55** were converted into bis(boryl)alkenes **56** in solution and the crude intermediates were used in Suzuki reactions with an excess of aryl halide. When all of the bis(boryl)alkene **56** was con-

sumed, the aryl iodide resin **59** was added to the reaction mixture and the reaction continued on solid support. Side reactions such as a double Suzuki reaction gave products **58** that remained in solution and were washed away. The compounds **60** were cleaved from the polymer using trifluoroacetic acid, and the products **61** obtained in >90 % purity.

The resin capture approach combines the ease of solution synthesis with the ease of solid-supported isolation and purification, but the unreacted starting materials and possible side products have to be inert to the capture.



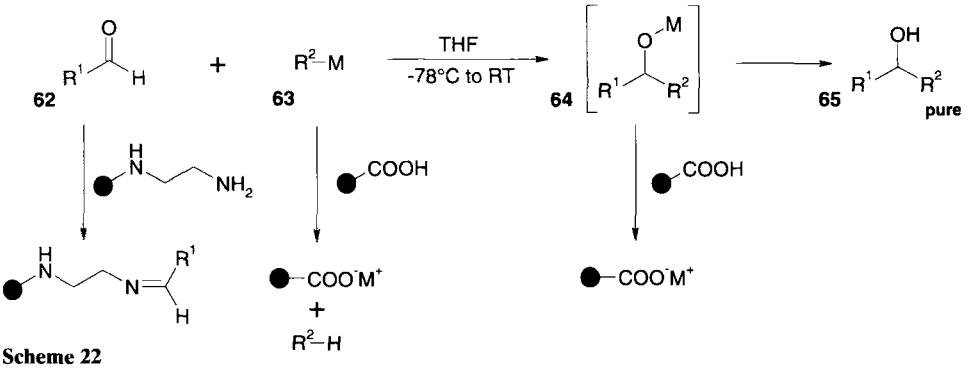
Scheme 21

Procedure: Preparation of **61** [40]
A small test tube was charged with **56** (10 equiv.), organohalide (15 equiv.), $Pd(PPh_3)_2Cl_2$ (0.3 equiv.), 3 M KOH (20 equiv.) and sufficient dimethoxyethane to bring the concentration of **56** to 0.5 M. The test tube was covered with a septum, flushed with N_2 and heated overnight. Another test tube was charged with 100 equiv. of KOH and 1 equiv. of **59** and flushed with N_2. The dimethoxyethane/KOH solution was syringed into the tube containing the polymer and heated overnight. The polymer was filtered from of the solution and washed successively with water, methanol, ethyl acetate and dichloromethane. The solid-bound products **60** were cleaved from the polymer with 30 % TFA in dichloromethane, to give **61**.

2.3.6 Complex Purification Strategies

Covalent scavenger and resin capture strategies use a covalent bond for the phase switch, whereas solid-phase extraction is based on noncovalent interactions between the product, the impurities, and the two phases. A combination of both methodologies has been introduced as a "complementary molecular reactivity and recognition" (CMR/R) purification approach [42]. The CMR/R approach allows for the rapid purification of products by incuba-

tion with various resins simultaneously, avoiding serial and more time-consuming purification procedures. By quenching all the undesired byproducts of the reaction mixture simultaneously, the desired product was obtained in solution after a simple filtration. This strategy has been illustrated with amine acylations, the Moffat oxidation, and the reaction of organometallics with carbonyl compounds. In case of amine acylation, commercially available aminomethyl polystyrene resin was utilized to react with excess of electrophile and Amberlyst A-21 or polyvinylpyridine was used to sequester HCl. The parallel Moffat oxidations of secondary alcohols to ketones were worked up by adding simultaneously sulfonic acid-substituted resin and tertiary amine-substituted resin. Simple filtration afforded the ketone products. The reaction of organo-metallics with carbonyl compounds and their CMR/R-work-up is illustrated in Scheme 22.

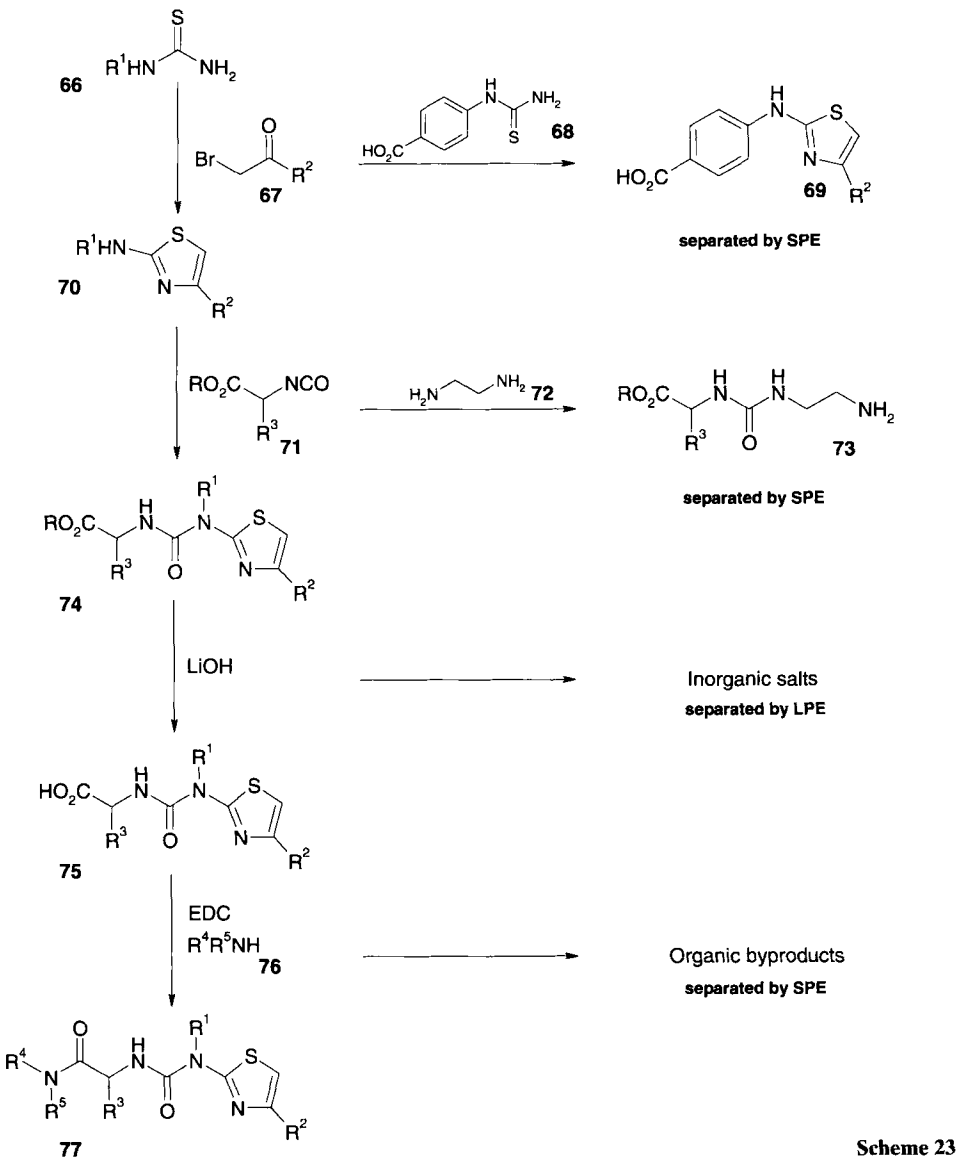


Scheme 22

Aldehydes **62** were reacted with an excess of either n-butyllithium or allylmagnesium chloride **63**, giving the metal alkoxides **64**, which were quenched with carboxylic acid functionalized resin. This resin also served a dual role in quenching excess of the organometallic reactant. Excess of carbonyl compound was quenched with primary amine-substituted resin and the products were obtained pure (>95 %). Other examples of the CMR/R strategy have also been published [43], and for the synthesis of heterocyclic carboxamides this strategy has been combined with the use of resin-bound reagents [44].

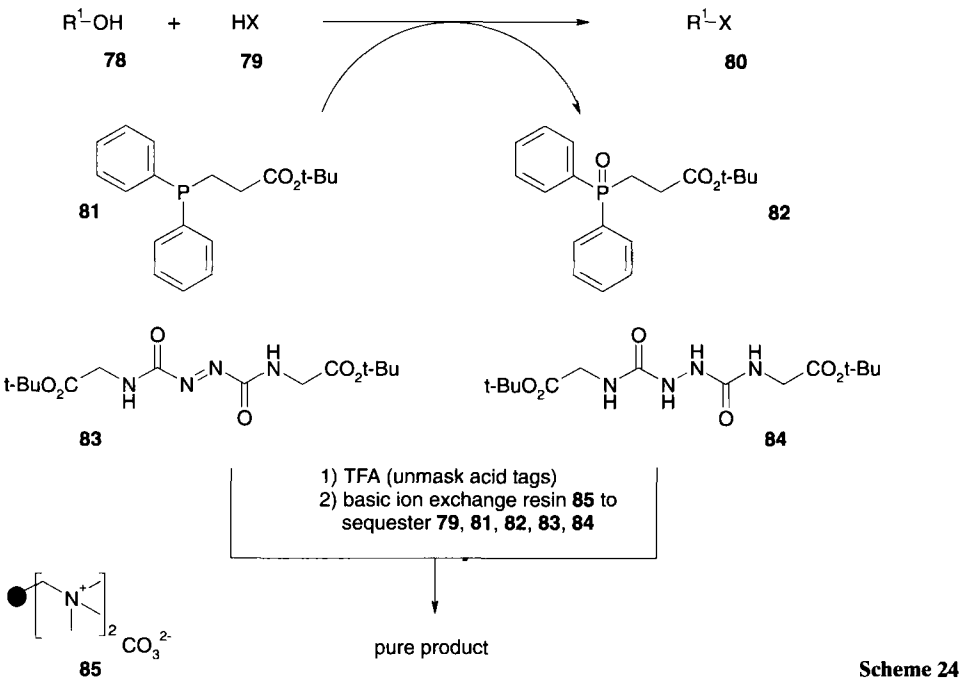
A combination of solid-phase extraction and liquid-phase extraction, as well as the use of solution scavengers, has been employed for the synthesis of thiazole libraries (Scheme 23) [45].

The synthesis is based on the Hantzsch condensation of thioureas **66** with 2-bromoketones **67** to give the 2-aminothiazoles **70**. The excess of **67** was trapped with N-(4-carboxyphenyl)thiourea **68** and removed by SPE. Subsequent treatment of the aminothiazoles **70** with a series of amino acid-derived isocyanates **71** gave the second generation of thiazoles **74**. Excess of **71** was quenched with 1,2-diaminoethane **72** and removed by SPE. Saponification gave the third generation of thiazole acids **75**, which were transformed into the corresponding amides **77** by using EDC and amine **76**. Again, all the excesses of reagents could be removed by SPE or LPE. Liquid-phase extractions were performed by the use of aqueous citric acid and all the solid-phase extractions were realized using neutral alumina [46].



Scheme 23

Another approach using chemically tagged reagents in combination with ion-exchange resin has recently been published [47] for high-throughput purification of Mitsunobu reactions. Masked carboxylic acid tags (t-butyl esters) were used for both Mitsunobu reagents so that, upon postreaction unmasking with trifluoroacetic acid, a base-functionalized ion-exchange resin **85** could be used to sequester the carboxy tagged reagents **81** and **83**, the carboxy-tagged byproducts **82** and **84**, as well as excess nucleophile **79**. An overview is given in Scheme 24.



Scheme 24

Procedure: Preparation of **65** [42]

Under conditions of parallel reaction synthesis, a solution of allylmagnesium chloride **63** (2.0 M solution in THF, 0.30 mL, 0.60 mmol) was added to each vial containing a solution of aldehyde **62** (0.5 mmol) in THF at –78° C and the resulting solution stirred at rt for 2.5 h. Amberlite IRC-50S (8–10 mmol, ~10 mequiv. g^{-1}) was added to each vial and the mixture was stirred for an additional 4 h. The mixture was filtered and the polymer was rinsed with THF.

The solvent was removed in vacuo to afford the carbinols **65**.

2.3.7 Conclusion and Outlook

A number of purification methods have been developed for high-speed solution-phase chemistry within a very short time. These methodologies offer valuable alternatives to the solid-phase approach. One of the major intentions of these product isolation strategies is to simplify the operation procedures in order to achieve a goal of automation. The phase switch of products or impurities, as well as the following phase separation, is the basis of automated purification. As documented above, this phase differentiation can be performed by various liquid–liquid extraction methods, as well as by liquid–solid extraction strategies. Most of the strategies mentioned here are in the preliminary phase of development, and so in the near future there will be rapid growth among the various purification strategies. In particular, the combination of covalent scavengers, resin capture, and solid-phase extraction may represent

a highly efficient and powerful tool for high-speed solution-phase synthesis. Furthermore, these strategies may be combined with resin-bound or chemically tagged reagents for the optimization of automated solution-phase synthesis.

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3 Solid Phase Chemistry

3.1 Linkers for Solid-Phase Organic Synthesis (SPOS) and Combinatorial Approaches on Solid Support

Willi Bannwarth

3.1.1 General

Synthesis on solid support involves three key elements: The solid support, the linker element, and the compound attached to the linker. The solid support should be stable to a wide range of reaction conditions and allow for reactions in different types of solvents and at elevated temperature. The need for linkers arises from the fact that the range of suitable functionality available on resins is severely restricted, and so consequently is the range of functional groups that are directly attachable to the solid support. The linker unit connects the support with the third element, which is either a starting material, an intermediate, or the target molecule (Fig. 1).

Unfortunately, there is no clear terminology regarding linker units in the literature. Sometimes, the term linker includes a further spacer molecule, or even the solid support. Moreover, if the actual linker molecule is attached to the support, this might change its structural features. In this context, I would like to apologize for the occasional confusion created by the lack of proper terminology.

An apology may be made here that, on occasion, confusion may be created within the text of this chapter by variation in terminology used, but perhaps in time this may be rectified by the chemical fraternity.

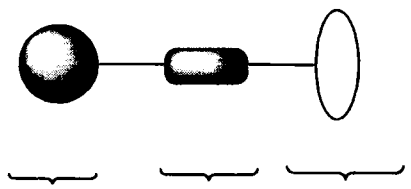


Figure 1

In general, synthesis on solid support involves two additional steps as compared with synthesis in solution. First, the starting material must be attached to the linker unit before synthesis; and second, the final compound must be released from the support after the synthesis.

The main challenge in the design of appropriate linker molecules lies in that they must be adapted to the type of chemistry to be performed. This chemistry should not cause the linker unit to be modified, neither should it result in cleavage from the linker entity during the chemical steps leading to the final product being still linked (via the linker) to the support. Yet, it should be possible for the product to be released from the support with high efficiency when the synthesis is complete. Preferably, this cleavage step should be carried out by a volatile reagent, but the use of a releasing reagent that leads to impurities appearing in the final product should be avoided. Otherwise, such impurities must be removed before the compound is submitted for screening.

The yield of the release step should not depend on the synthesized structure. This is of particular concern if equimolarity of the released products is required.

Finally, it should be mentioned that synthesis of the linker unit – if this is not available commercially – should be straightforward, and that coupling of the starting material should proceed without great difficulty.

This chapter is organized in such a way that section 3.1.2 describes linkers for the attachment of particular functional groups, while subsequent sections describe principles applied during the attachment and release of compounds, for example metathesis.

3.1.2 Linkers for Functional Groups

3.1.2.1 Linkers for Carboxyl Functions

Most of the linkers applied for attachment of carboxylic acids originated from peptide chemistry. These linkers are modified hydroxy-, amino- or trityl-units. Thus, after cleavage from the linker, the final products contain either a carboxyl or a carboxamide function. Depending on the type of linker, cleavage usually proceeds with the TFA concentration varying from 1 % to undiluted ("neat") TFA. As TFA is volatile, evaporation of the solution applied for the release yields the product without impurities. These linkers are described in great detail in the peptide chemistry literature, and most are available commercially.

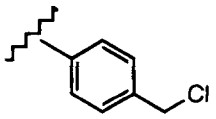
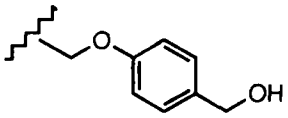
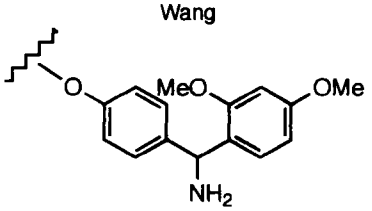
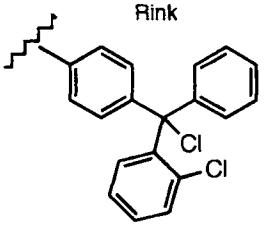
Some polymer supports may be purchased with the linkers already attached to them. The most prominent linkers of this type are outlined in Table 3.1, together with the pertinent key references of their application in combinatorial synthesis.

3.1.2.2 Linkers for Amino Functions

In order to extend the scope of the chemistries applied in the desired combinatorial approaches, an entire range of linker units for all types of functional groups and all sorts of chemistry must be developed. Most of the linkers reported to date in the literature are based on commonly used protecting groups for the pertinent functional units.

In peptide chemistry, two of the most common protecting groups for amino functions are the tert. butyloxycarbonyl group (Boc) and the benzyloxycarbonyl group (Z), both of which are cleaved under acidic conditions. These protecting groups for primary amino functions

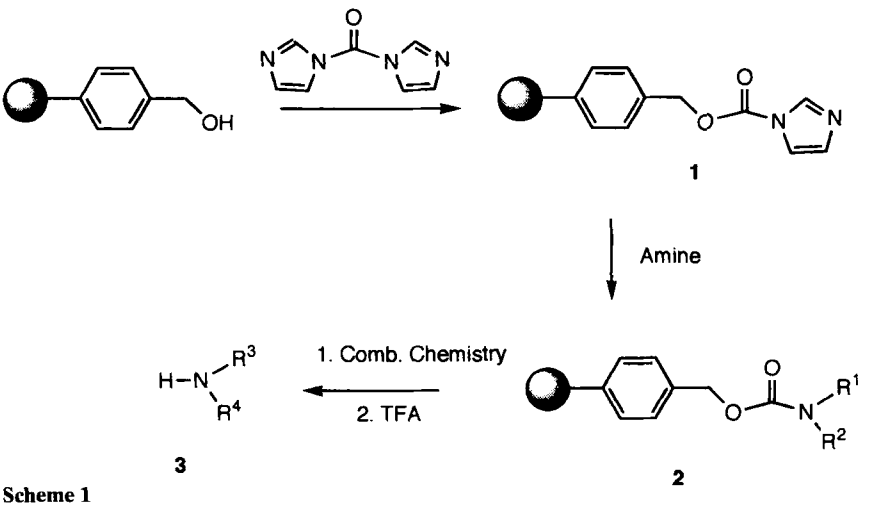
Table 1. Polymer support with pre-attached linkers

Linker	Type of bond	References
 Merrifield	Ester	[1–3]
 Wang	Ester	[4–6]
 Rink	Amide	[7–9]
 2-Chlorotrityl-	Ester	[10,11]

were modified in such a way that a linkage is introduced for the attachment of the group to the support material.

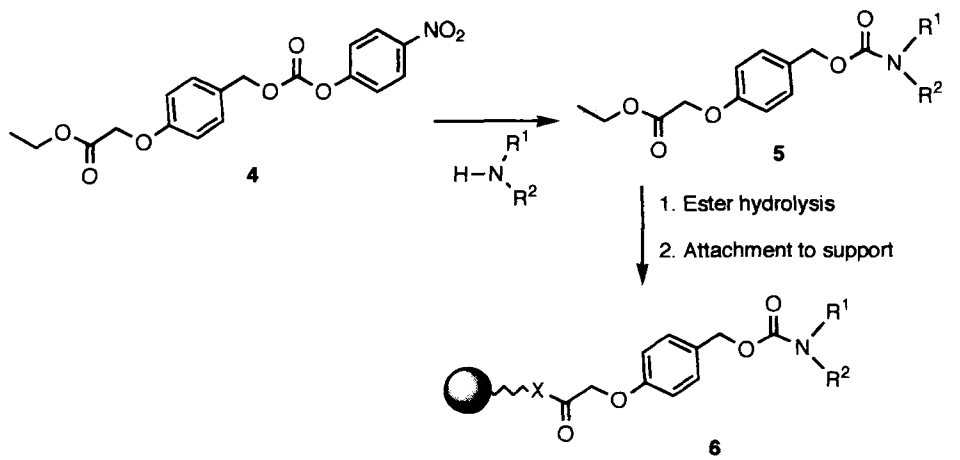
3.1.2.2.1 Linkers Based on Benzyloxycarbonyl (Z)

In order to allow attachment of an amine to a hydroxymethyl-modified support, the latter was reacted with carbonyl diimidazole (CDI) to create the activated support **1**. Polymer-bound amine **2** was obtained by treatment of **1** with HNR_1R_2. After combinatorial synthesis, the modified amine **3** was released under acidic conditions (TFA) (Scheme 1) [12].



Scheme 1

Procedure: Preparation of **1** and loading of amine to yield resin-bound amine **2** [12]
To Wang resin (Fluka, 0.6–0.8 mmol g^{-1}, 1.0 g) suspended in 15 mL THF under N_2 was added 1,1-carbonyl diimidazole (CDI, 3.5 mmol, 567 mg) and the slurry was stirred for 2 h. The resin was filtered, washed (2 x 10 mL) twice THF, Et_2O, THF, Et_2O and dried under vacuum to give 1.57 g of activated resin 1. Resin 1 (500 mg, 0.35 mmol) was resuspended in 5 mL THF and 5 mL N-methylpyrrolidinone. Phe-Val-Phe-OMe hydrochloride (1.75 mmol, 807 mg) was added followed by 1 mL N-methylmorpholine. The stirred mixture was heated under N_2 in a 60° C oil bath for 4 h. The resin was filtered, washed (2 x 10 mL) with DCM, MeOH, THF, Et_2O, THF, Et_2O and dried under vacuum to give 607 mg of resin **2**.

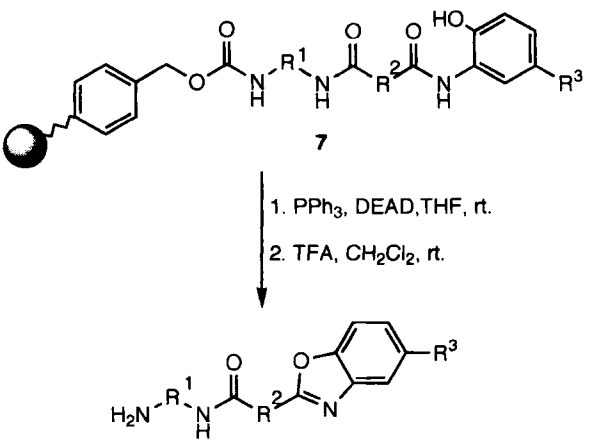


Scheme 2 X=NH,O

Procedure: Cleavage of 2 to yield the amine 3
Loaded resin **2** (35 μmol, 50 mg) was stirred with 1 mL DCM and 1 mL TFA at room temperature. After 3 h, 1 mL MeOH was added, and the resin was filtered and washed (2 x 2 mL) with MeOH, DCM, and MeOH. The filtrate was concentrated in vacuum to give 13 mg (85 % yield at 0.8 mmol g–1 loading) of a white solid, which was identical to authentic Phe-Val-Phe-OMe (**3**) by IR, MS and HPLC.

As an alternative, the strategy outlined in Scheme 2 could also be used. Reaction of the activated linker unit **4** with the amine yielded an amine-linker conjugate **5** which was attached after selective hydrolysis of the ester function onto the solid support via an ester or an amide bond to yield polymer-bound amine **6** [13].

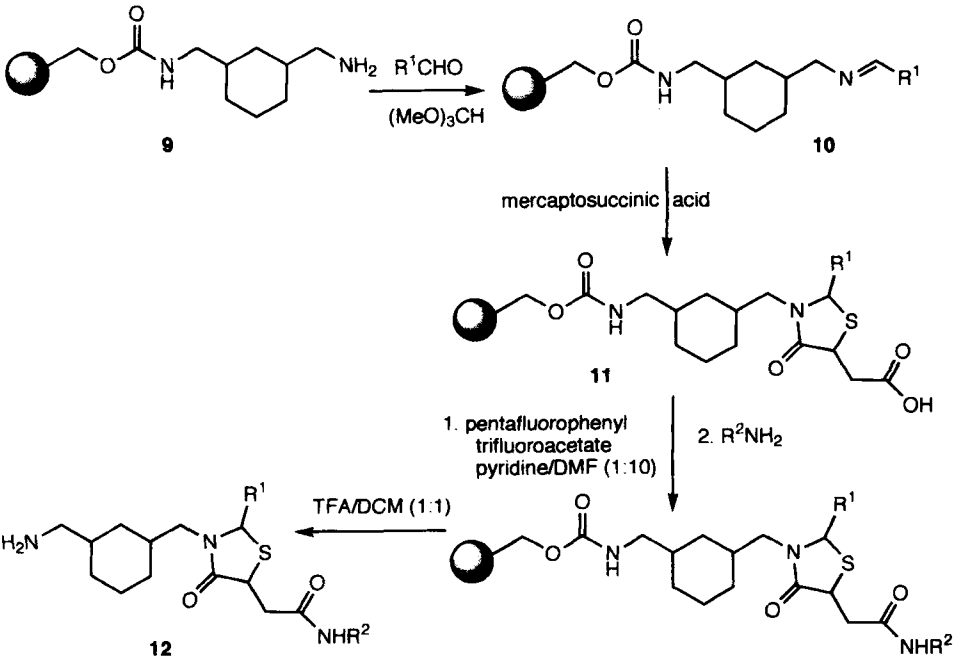
This type of linker was recently applied to the synthesis of a library of benzoxazoles **8** via cyclization of 2-amido phenols **7** under Mitsunobu conditions [14]. The final products were obtained after TFA-mediated release (Scheme 3).



Scheme 3

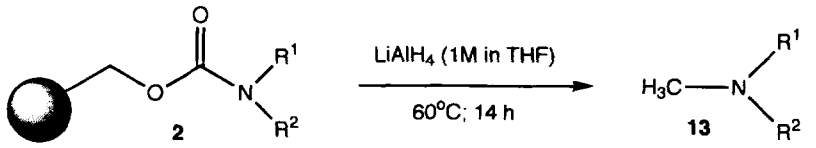
The acid-labile carbamate linkage of type **2** was also applied to the parallel synthesis of a thiazolidinone library **12** according to Scheme 4. At the start of the synthesis, an excess of an unprotected symmetrical diamine was incorporated directly onto the carbonyl imidazole-activated support **1** to yield **9**. Reaction with an aldehyde led to Schiff base **10**, which was then reacted with mercaptosuccinic acid to heterocycle **11**, the carboxyl function of which was used to introduce further diversity via amide formation. Cleavage from the support yielded finally the desired compounds of type **12** [15].

Application of trityl-based resins (see section **3.1.2.2.6.**) for this reaction sequence was not possible as the trimethylorthoformate used for the preparation of the Schiff base resulted in poor swelling of the resin.



Scheme 4

Starting from carbamates of type **2**, N-methylamines (**13**) by $LiAlH_4$-reduction can also be prepared according to Scheme 5. Although the yield varied from moderate to high, the compounds were obtained in high purity [16].



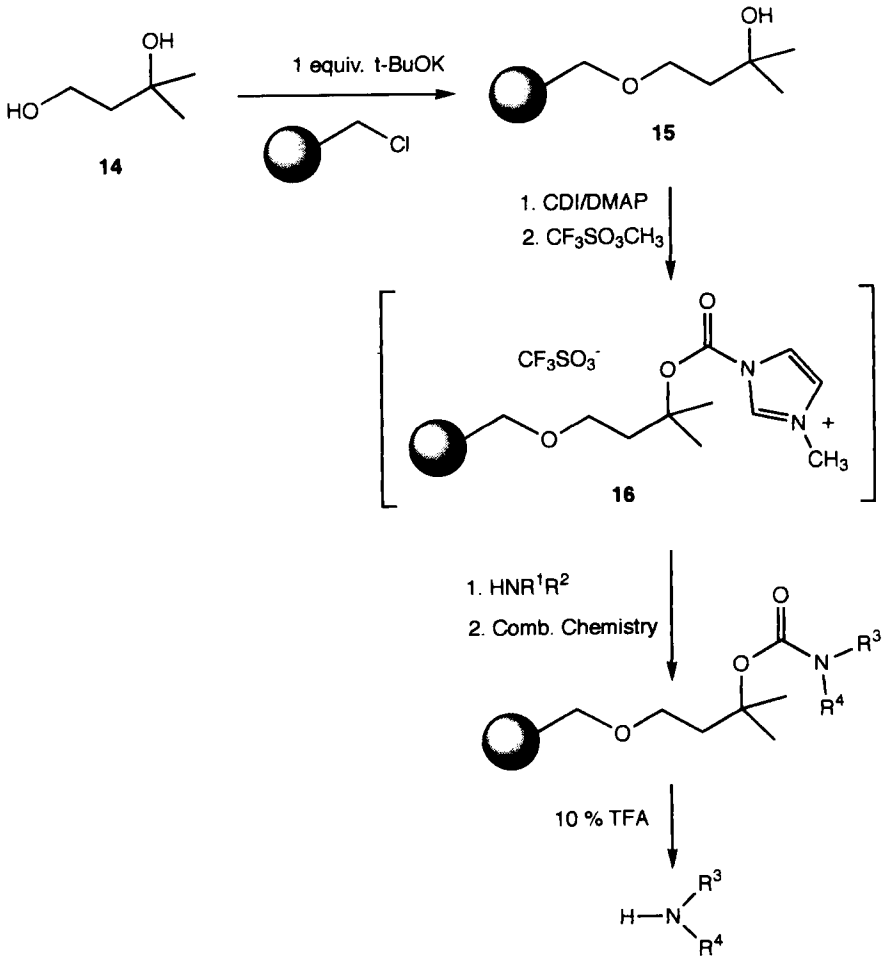
Scheme 5

Procedure: Preparation of **13** by reduction of resin-bound carbamates **2** with $LiAlH_4$
Resin **2** (1 equiv.) was suspended in a solution of $LiAlH_4$/THF (10 equiv.) and heated at 60 ° C with shaking for 14 h. The reaction was quenched by sequential addition of water, 15 % NaOH, and water (38 µL, 38 µL and 114 µL, respectively, per mmol of $LiAlH_4$). The solid was washed with DCM and the filtrate concentrated. The yield varied from 48 % to 90 %. To remove traces of aluminum salts, the compounds were further purified by SPE over C-18 reversed-phase cartridges with acetonitrile/water (80:20) containing 0.1 %TFA as eluent.

3.1.2.2.2 Linker Based on Tert.-Butoxycarbonyl (Boc)

The synthesis of a Boc-like linker outlined in Scheme 6 was performed in a straightforward manner. Commercially available 3-methyl-1,3-butanediol **14** was reacted with one equivalent of potassium tert.-butoxide, and the resulting monoalkoxide was coupled to chloromethyl support to create the solid support-bound tert. alkyl alcohol **15** which was activated with CDI. In order to enhance the acylating reaction, the imidazole intermediate was methylated before the addition of the amine which resulted in **16**. The release of the amine **17** was performed by 10 % TFA.

The linker is stable towards strongly alkaline conditions as well as strong nucleophiles [17].



14 **15** **16** **17**

Scheme 6

Procedure: Preparation of resin-bound amine **16**

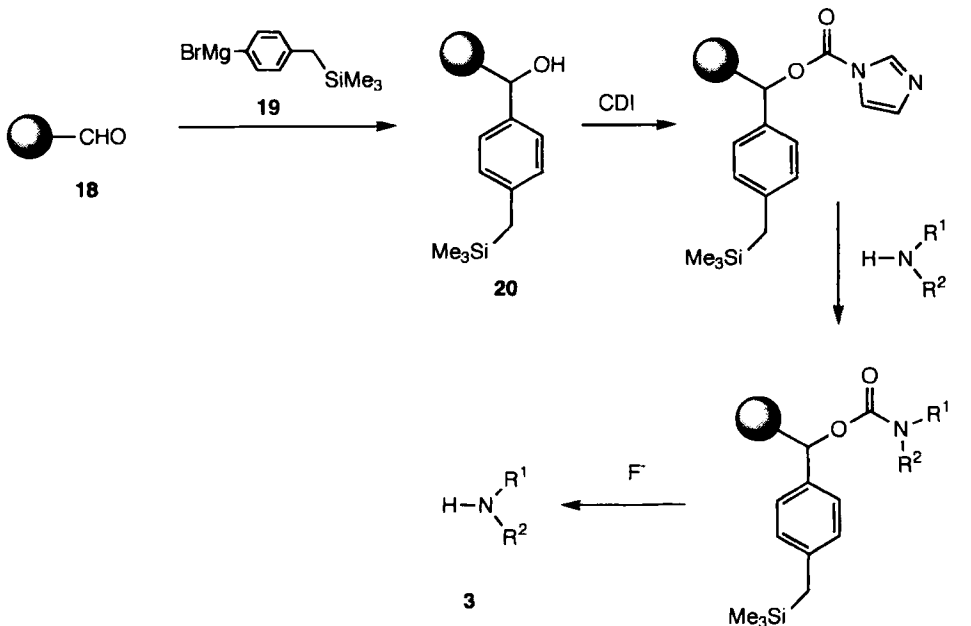
A 1 M t-BuOK/THF (300 mol %) solution was added to a solution of diol **14** (300 mol %) in dry THF (2.5 mL/mmol), cooled at 0° C. The solution was stirred at 0° C for 45 min and for 3 h at rt. Merrifield resin (100 mol % of chlorine sites, loading: 1.35 mmol g) was added, and the suspension was shaken for 3.5 days at rt. After filtration, the resin-bound tert.-alkyl alcohol **15** was washed with THF (4 times), 1/1 DMF/water (twice), DMF (twice), THF (twice), and DCM (twice) and dried.

DMAP (50 mol %) and CDI (400 mol %) were added to a suspension of resin **15** (100 mol %) in dry DMF (4.5 mL/mmol). The mixture was shaken for 24 h at rt and filtered. The support was washed with DCM (three times), THF (three times), DCM (three times) and dried.

Methyl triflate (170 mol %) was added to a suspension of the resin (100 mol % of carbonylimidazole sites) in dry 1.2-DCE (16 mL/mmol), cooled at 10° C. The mixture was stirred for 15 min at this temperature and for 5–10 min while being warmed to rt. After addition of Et_3N (500 mol %), stirring was continued for an additional 5 min. A secondary amine was added (600 mol %, neat or as a solution in DCM or DMF) and the mixture was shaken for 3.5 h at rt. and filtered. Polymer-bound carbamate was washed with THF (three times), THF/MeOH 1/1 (three times), THF (three times) and DCM (three times) and dried. The product was characterized by IR and CHN analysis.

Procedure: Cleavage of **16** to yield amine **17**

Resin **16** was treated with 10 % TFA/DCM (2.5 mL per 100 mg resin) for 4.5 h and filtered. The resin was rinsed with DCM (three times), MeOH (twice) and the filtrates were evapo-



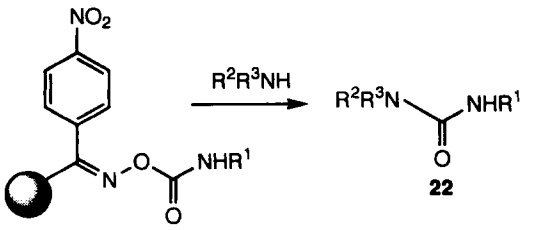
Scheme 7

rated and dried to give the amine **17** as a TFA salt. The ^{1}H-NMR spectra of the cleaved amines were identical with those of authentic samples.

3.1.2.2.3 A Urethane Linker to be Cleaved by Fluoride Ions

This recently reported linker was synthesized starting from commercially available aldehyde-modified support **18** [18]. After reaction with Grignard compound **19**, alcohol **20** was obtained which was then transformed with CDI to the activated species ready for the attachment of the amine to yield **21**. The desired amine **3** was liberated by fluoride ions (Scheme 7). The linker is versatile in that it can be used not only for the attachment of amines but also for the attachment of carboxylic acids and alcohols.

Primary amines attached to the solid support via an oxime carbamate were used for the preparation of diverse ureas of type **22** according to Scheme 8. In this respect, further diversity could be introduced, leading at the same time to a release from the support [19].



Scheme 8

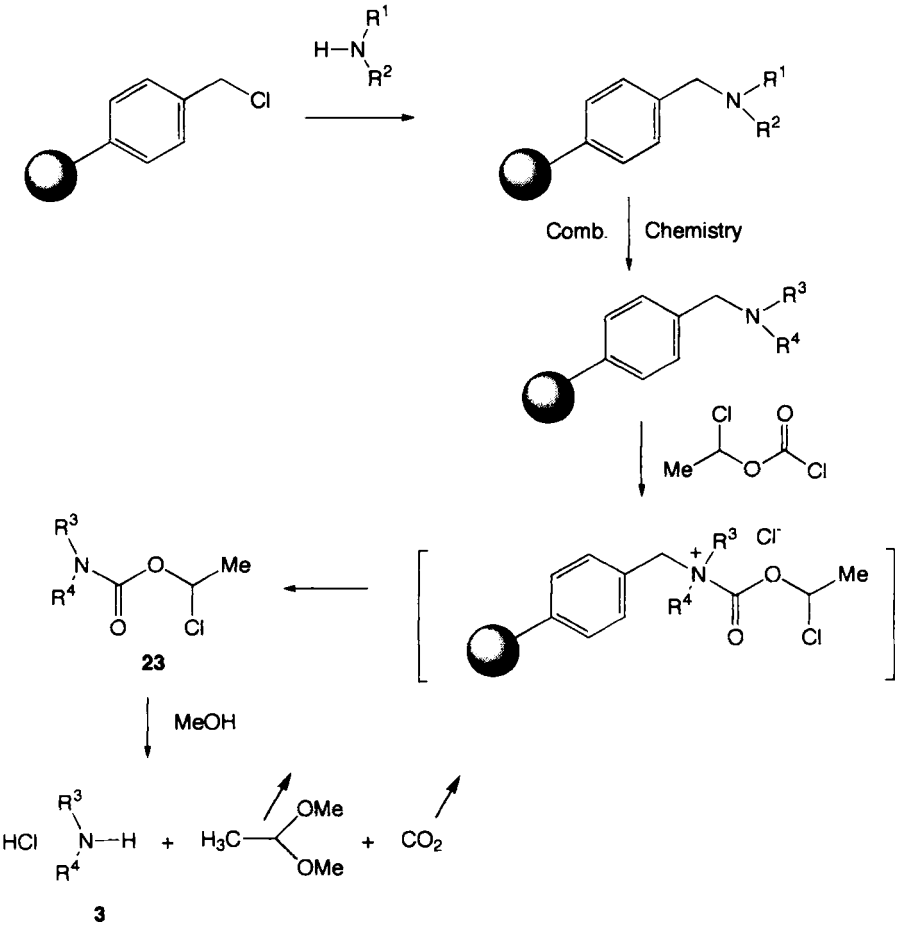
3.1.2.2.4 Benzyl-Linked Approaches for Secondary Amines

An elegant approach for the preparation of secondary amines is outlined in Scheme 9. The method is based on the efficient cleavage of N-benzyl-linked tert. amines from solid support by treatment with α-chloroethyl chloroformate/MeOH [20].

Attachment of a secondary amine as starting material to the chlorobenzyl group of Merrifield resin proceeded with high efficiency. After combinatorial synthesis, treatment with α-chloroethyl chloroformate released the intermediate **23**, which decomposed in refluxing methanol to yield the secondary amine **3**.

Procedure: Cleavage of N-benzyl-linked tert. amines from the support by α-chloroethyl chloroformate/MeOH to yield sec. amines **17**

An excess of an amine was first coupled to the Merrifield resin in a suspension of DMF (if the amine was added as hydrochloride, then 20 equiv. of DIPEA were added). The mixture was stirred for 17 h at 50° C. The substitution level was >0.6 mmol/g (>85 %). To a suspension of the resin in 1,2-dichloropropane, 10 equiv. of α-chloroethyl chloroformate was added and the suspension was stirred for 3 h at rt. The resin was filtered off and the filtrate evaporated to dryness. The residue was dissolved in MeOH and the solution refluxed for

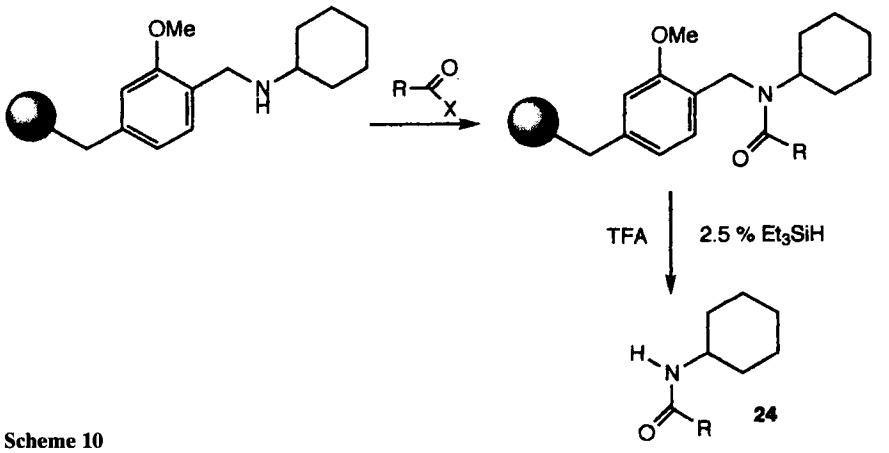


Scheme 9

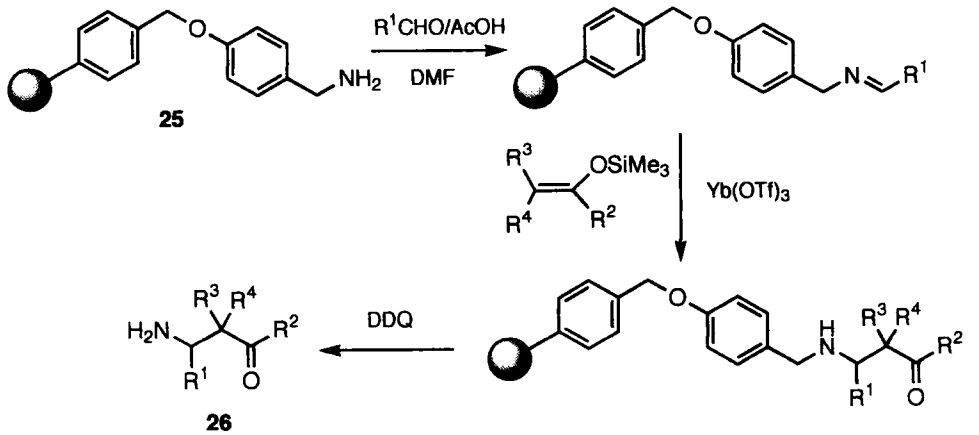
3 h. Evaporation yielded the secondary amine **17** as hydrochloride. The isolated yield varied from 70 % to 95 %, depending on the type of amine.

Another benzyl-based method was developed for the preparation of secondary amides on solid support. Release of the product after treatment with TFA required an electron-rich benzyl linker (Scheme 10). The secondary amides **24** were obtained quantitatively, and in high purity [21].

As a further example of a benzyl-based attachment of amines, the p-benzyloxybenzylamine resin (**25**) was prepared and applied to the synthesis of compounds of type **26** [22]. The reaction involved the formation of a Schiff base as well as a $Yb(OTf)_3$-catalyzed addition of silyl enolates. The cleavage from the support was achieved by a DDQ-oxidation (Scheme 11).

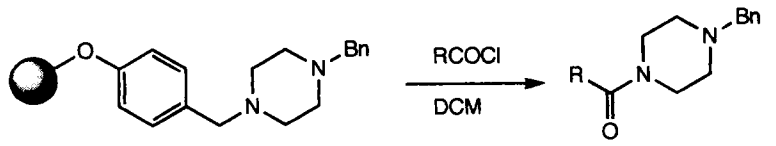


Scheme 10



Scheme 11

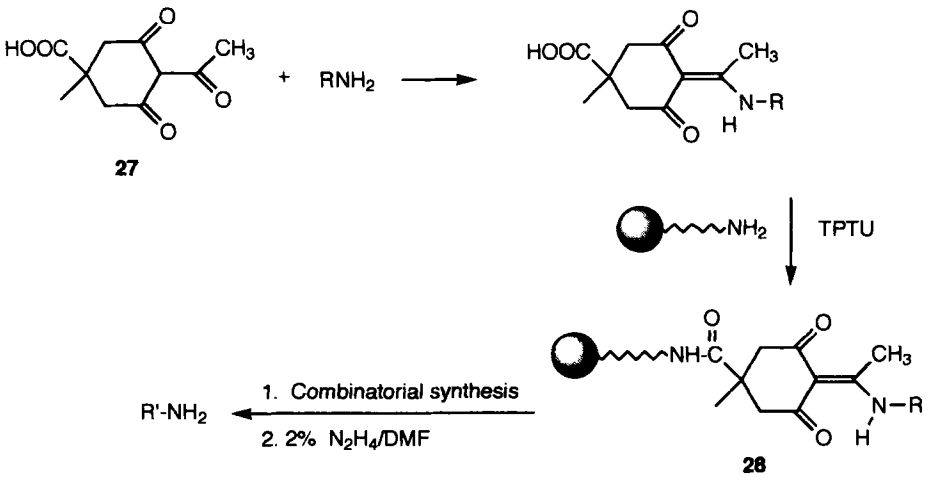
Benzyl-linked secondary amines can also be cleaved from the support to yield amides [23]. This opens up a way to transform solid phase-bound tertiary amines to amides (Scheme 12). The reaction was carried out with several acid chlorides. The resulting amides were obtained in moderate to good yields with high purity.



Scheme 12

3.1.2.2.5 Linkers Based on Acetyldimedone

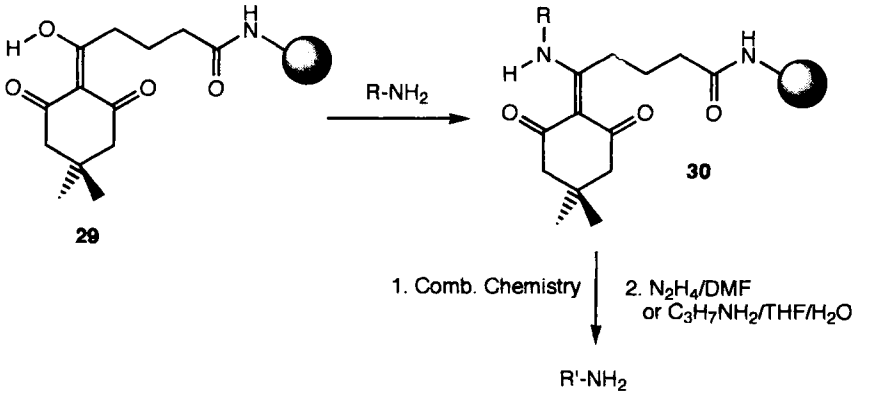
These linkers are based on the acetyldimedone (Dde) protecting group for amines originally developed by Bycroft et al. [24]. Linker **27** can be coupled to an amino-modified support, and the attachment of the amine to give **28** proceeds without activating reagent. Alternatively, the linker can first be coupled to the amine, after which the adduct is attached to the solid support. The linker is stable towards acidic conditions as well as moderately basic conditions, but the amine can be cleaved from the linker by a 2 % hydrazine solution in DMF (Scheme 13). Evaporation of the cleavage solution yields the desired compounds directly [25]. This linker is now available commercially (Fluka, Bachem, Lipomed).



Scheme 13

Procedure: Preparation of **28** and cleavage from the support to yield the primary amine
The linker **27** (1.0 equiv.) and the primary amine (1.0 equiv., L-phenylalanine methyl ester) were reacted in DMF at rt to form the desired vinylogous amide. This vinylogous amide (2.5-fold excess relative to the loading of the support) was attached with TPTU as activating agent to aminomethyl polystyrene.
For the cleavage of the amine (L-phenylalanine methyl ester), **28** was treated with a 2 % hydrazine hydrate solution in DMF for 5 min under argon. The support was filtered off and washed several times with DMF. Complete recovery of L-phenylalanine methyl ester was observed after evaporation of the combined DMF solutions.

An alternative Dde-based linker (**29**) also for application to primary amines was reported very recently (Scheme 14). A notable feature is that, from **30**, the amine can be removed not only by 2 % hydrazine in DMF but also by a transamination by n-propylamine which is sufficiently volatile to be removed from the products without difficulty [26].



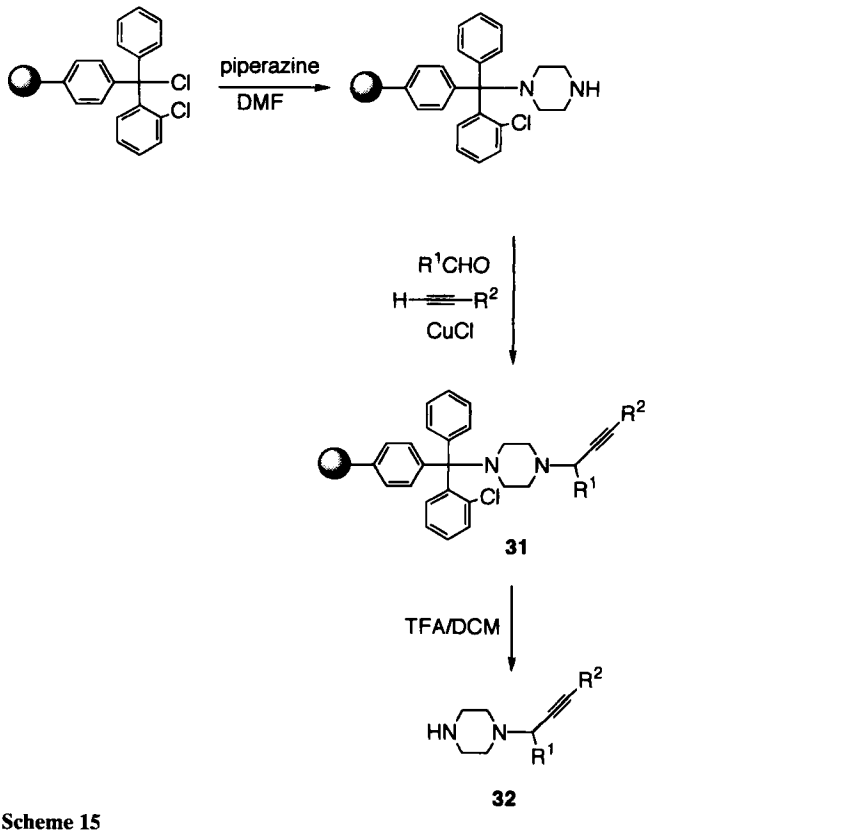
Scheme 14

3.1.2.2.6 Trityl Linker

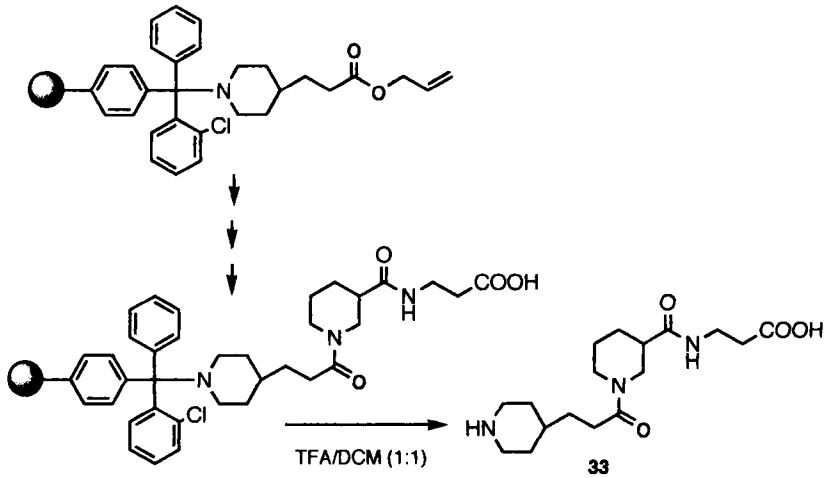
In addition to the linkers mentioned above, the chlorotrityl linker commonly applied for the binding of carboxylic acids can also be used for the attachment of secondary amines [27]. An example is the binding of piperazine as the amine component in a Mannich reaction on solid support (Scheme 15). Reaction of an aldehyde with the resin-bound amine, followed by addition of acetylide, led to solid phase-bound intermediates of type **31** from which the final compounds **32** were obtained by acid-mediated cleavage.

Procedure:
Commercially available 2-chlorotrityl chloride resin was treated with piperazine and washed with DMF (three times), MeOH (three times), THF (three times), and DCM (three times) and dried.
For the Mannich reaction, a screw-capped fritted glass reaction vessel was charged with the resin (0.3 g, 0.75 mmol g^{-1}), Cu(I)Cl (0.45 mmol, 45 mg) and benzaldehyde (1.57 mmol, 0.16 mL). After shaking for 0.5 h, phenylacetylene (1.57 mmol, 0.173 mL) was added to the mixture, and the reaction vessel was heated to 85° C with shaking for 3 h. The resin was filtered hot and washed thoroughly with dioxane (once), DMF (three times), 20 % aqueous HOAc (once), DMF (once), 7 M NH_4OH (once), DMF (once), MeOH (three times), THF (three times), and DCM (three times).
Cleavage of the desired product from the solid support was accomplished by treatment of the resin with TFA/DCM (1:1) for 5 min. After filtration, it was washed as above. Evaporation of the solvents under nitrogen gave the desired Mannich adduct as an oily bis-TFA salt (98 mg, 86 %).
A secondary amine can be attached to the 2-chlorotrityl resin in the presence of Huenig's base [28].

The 2-chlorotrityl linker was used recently also for the synthesis of peptidomimetics libraries of type **33** [28, 29]. The actual synthesis is outlined in Scheme 16.

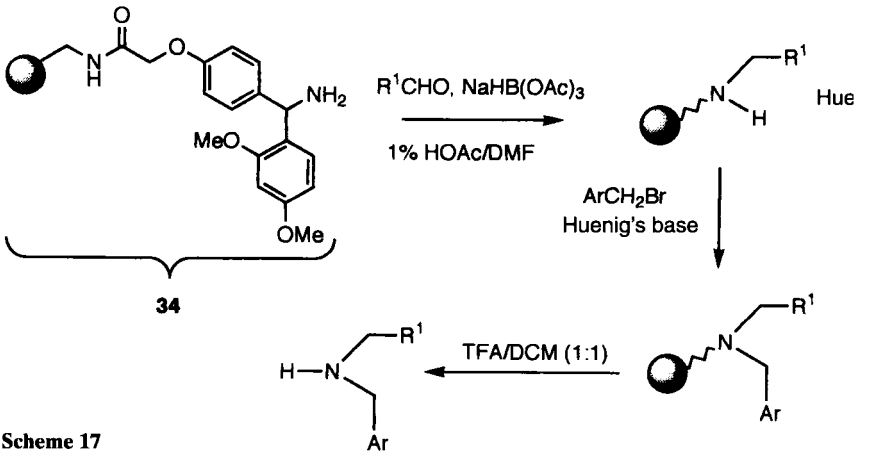


Scheme 15



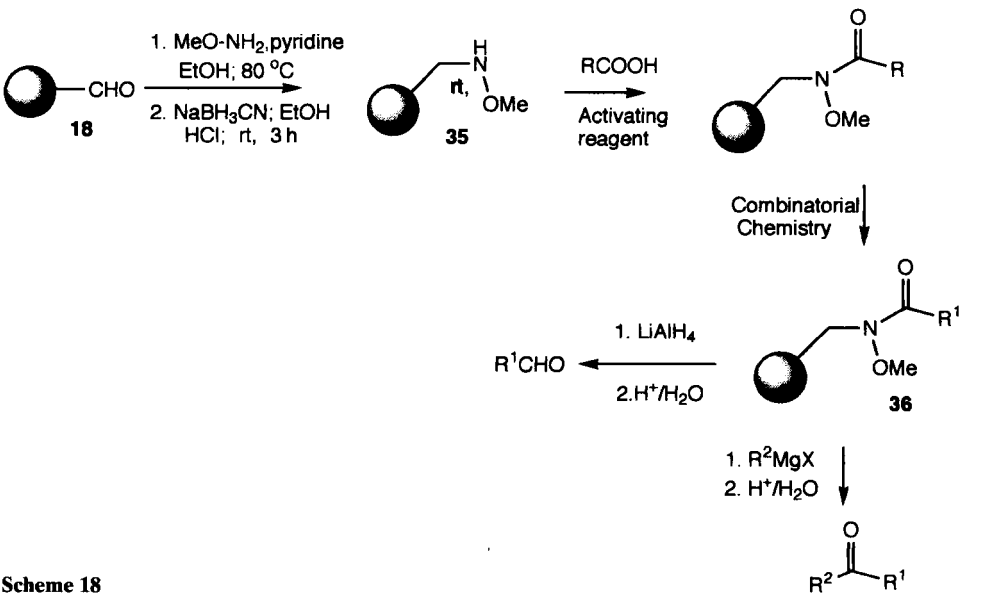
Scheme 16

Benzhydril-derived linker **34** (Advanced Chem Tech), which is applied in peptide chemistry for the attachment of carboxylic acids and allows for a cleavage under weakly acidic conditions, can also be used for the synthesis of amines. The method is especially useful for the preparation of unsymmetrical secondary amines [30].



Scheme 17

The reaction sequence (Scheme 17) starts with an alkylation of the resin via Schiff base formation and reduction. After the second alkylation the products can be cleaved off the support with TFA/DCM (1:1) in high purity.



Scheme 18

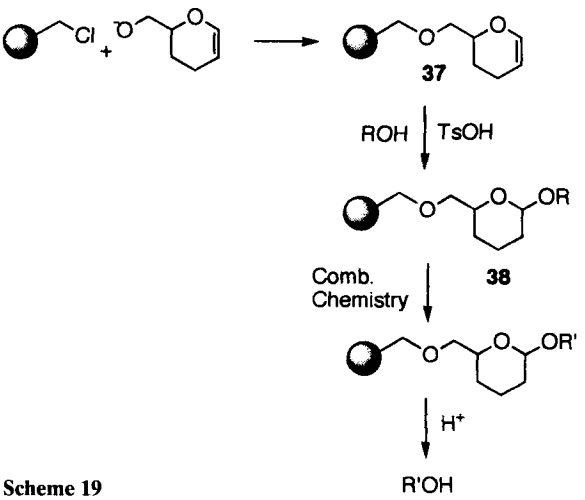
3.1.2.2.7 Hydroxylamine Linker for the Formation of Weinreb Amides

Aldehyde-modified support **18** was applied to the binding of hydroxylamine according to Scheme 18 to yield **35**. By acylation with carboxylic acids, Weinreb amides (36) were obtained – these are valuable intermediates for combinatorial approaches. Treatment with DIBAH or $LiAlH_4$ finally released the desired aldehydes. Reaction with Grignard reagents led to the corresponding ketones [31, 32].

3.1.2.3 Linker for the Attachment of Alcohols or Phenols

3.1.2.3.1 Linker Based on the Tetrahydropyranyl (THP) Group

Hydroxymethyl dihydropyrane was coupled to chloromethyl resin via an ether linkage to yield **37** (Scheme 19) [33]. The alcohol was then attached as THP ether (**38**). After combinatorial synthesis, the alcohol was released under acidic conditions.



Scheme 19

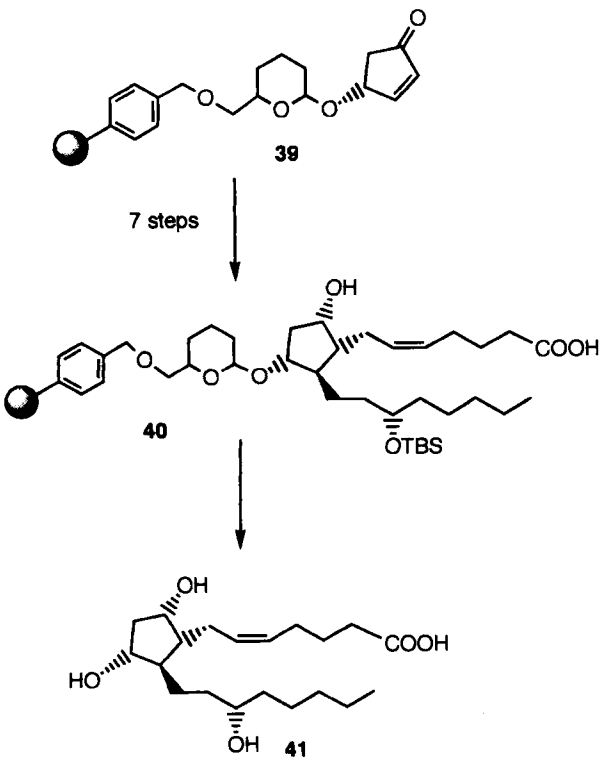
Procedure: Attachment of alcohols to the THP-based linker **37** and release from the linker 3,4-Dihydro-2H-pyran-2-ylmethoxymethyl polystyrene **37** is commercially available (Novabiochem). Alcohols (5 equiv.; 0.4 M in DCE) were loaded onto **37** in the presence of 2 equiv. of PPTS at 80° C for 16 h. Alternatively, the coupling is also possible with p-TsOH at 0° C for 16 h.

Procedure: Cleavage from **38**
0.74 mmol (1 g of support **38**) in 20 mL of a mixture of DCE/butanol (1:1) and 1.48 mmol (370 mg) PPTS in a closed flask were heated to 60° C for 16 h. After filtration, the solution

was evaporated. The product can be separated from PPTS or p-TsOH by extraction or chromatography. Alternatively, the cleavage can be performed with TFA/water (95:5).

Several examples have appeared in the literature applying this linker to combinatorial chemistry strategies. Thus, it has been used for a Pd-mediated three-component coupling strategy for the solid-phase synthesis of tropane derivatives [34], for the solid-phase synthesis of aspartic acid protease inhibitors [35], for the attachment of a cholic acid as template for a combinatorial approach [36] and, more recently, for the solid-phase synthesis of pyrrolidines via 2-azaallyl anion cycloadditions with alkenes [37].

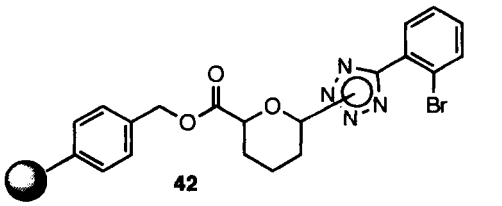
An impressive total synthesis of prostaglandin $F_{2\alpha}$ was achieved on this linker [38]. The starting material **39** was transformed in a multistep synthesis to the polymer-bound target molecule **40**. Compound **41** was then released in good yield and high purity with 48 % aqueous HF/THF (3:20; v/v) (Scheme 20).



Scheme 20

A variant of the THP-linker in which the THP-unit was attached via an ester function onto the solid support was applied to the synthesis of biphenyl tetrazole derivatives **43**, as outlined in Scheme 21 [39]. A bromophenyl tetrazole was attached to polymer-bound dihydropyrane

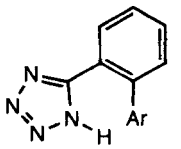
to yield **42**. This step was followed by Suzuki coupling and acid-catalyzed release from the support to yield the desired compounds **43**.



42

1) Ar-B(OH)$_2$
Pd(PPh$_3$)$_4$
Na$_2$CO$_3$

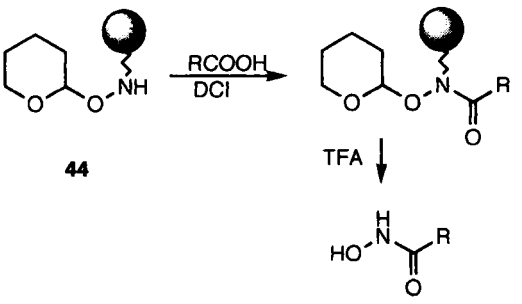
2) 3 % HCl in MeOH



43

Scheme 21

The THP-based linker can be modified in such a way as to allow the synthesis of hydroxamic acids **45**, as outlined in Scheme 22. Linker **44** plays a role in the solid-phase synthesis of matrix metalloproteinase inhibitors [40]. Alternative linkers which yield hydroxamic acids after release were used in connection with peptide chemistry, as well as for the preparation of combinatorial compounds [41–46].



44

RCOOH
DCI

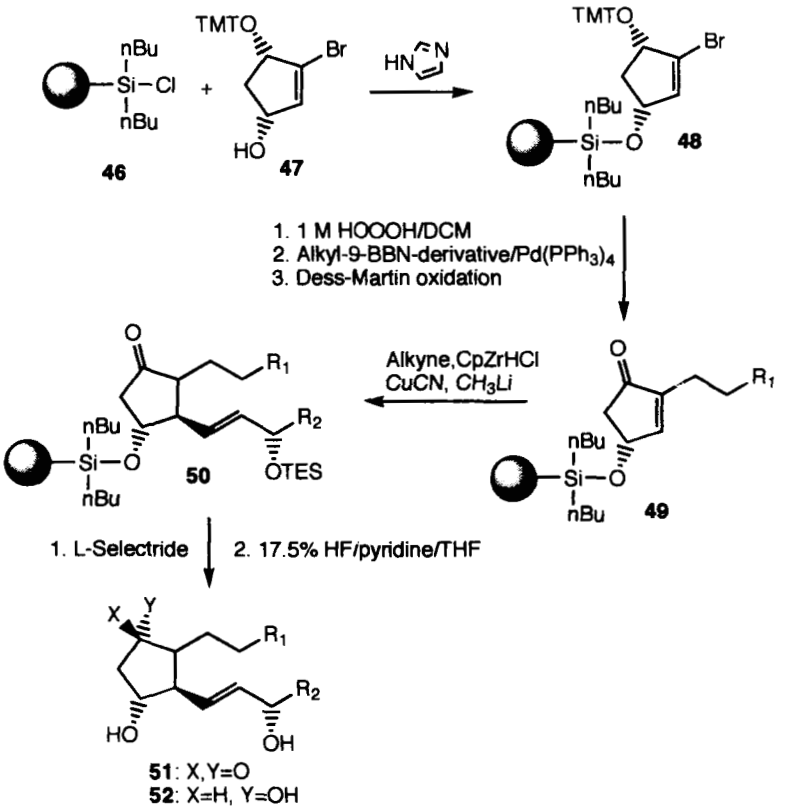
TFA

45

Scheme 22

3.1.2.3.2 Silyl Linker for the Attachment of Alcohols

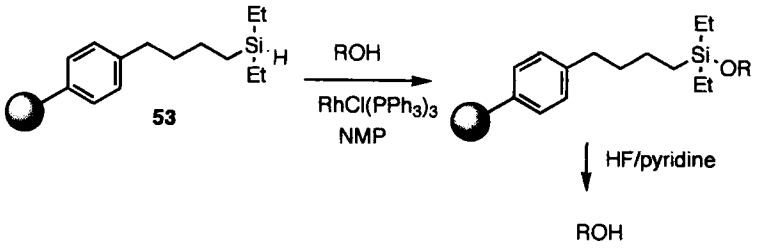
A support material carrying a silyl linker (**46**) can be prepared from polystyrene according to Farrall and Frechet [47]. This was successfully applied to the synthesis of diverse prostaglandins [48]. One example of such a synthesis is outlined in Scheme 23.



Scheme 23

Alcohol **47** was attached to the silyl-modified support **46** in the presence of imidazole. The trimethoxytrityl group (TMT) of **48** was cleaved off using formic acid in DCM. The loading was estimated by spectroscopic quantitation of the released TMT-cation and was in a range of 0.35–0.45 mmol/g. The first element of diversity was introduced by a Suzuki crosscoupling. This step was followed by Dess–Martin oxidation to afford intermediate **49**. Diversity was introduced again in the next step by the addition of a vinyl cuprate. Reduction of the keto function of **50** is performed by L-Selectride. The cleavage from the support can be carried out before or after this reduction to yield **51** or **52**, respectively. Alternatively, the cleavage can be performed with a 2 mM solution of TBAF in DCM for 5 h, followed by treatment with water.

Recently, details were published of the new silyl linker **53** for the attachment of alcohols [49]. This attachment was reported to proceed directly in the presence of a Rh-catalyst (Scheme 24). Thus, a transfer of **53** into the corresponding silyl chloride as in a previously published example of the same authors could be omitted [50]. Linker **53** allowed also for the attachment of ketones via hydrosilylation. Cleavage of the final product proceeded as in the application of linker **46** by HF/pyridine/THF with $MeOSiMe_3$ as scavenger.



Scheme 24

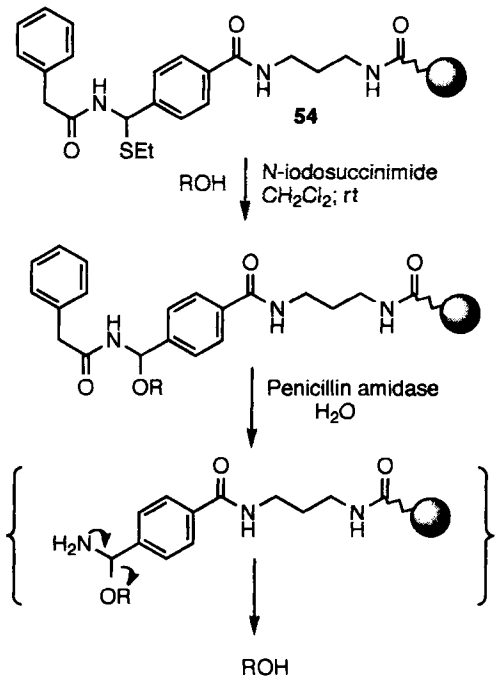
Procedure: Direct loading of primary alcohol to polystyrene diethyl silane [50]
To a solution of 1.7 mg Rh-catalyst in a 10 mL round-bottomed flask under argon was added 200 mg of resin **53**. Then 66 mg of (S)-(-)-1-(2-methoxybenzoyl)-2-pyrrolidine in ethanol were added, and the reaction mixture was stirred at rt for 3 h. The mixture was then filtered and the resin washed with DCM (three times), toluene (twice) THF/water (1:1, twice), and THF (three times).
Treatment with AcOH/THF/water (6:6:1) at 50° C for 4 h. released the alcohol from the support. The filtrate was concentrated to obtain the alcohol in a yield of 99.3 % (GC).

3.1.2.3.3 Miscellaneous Linkers for Alcohols

Alcohols can be immobilized directly as p-alkoxybenzylethers on Wang resins. The latter are stable to a variety of reaction conditions, and the final compounds are cleaved by mild acid treatment [51]. As a further alternative, alcohols can also be linked to a solid support by a trityl linker [52]. Release of the alcohol proceeds with 1 N HCl at rt.

A 9-phenylfluoren-9-yl-based linker can also be used for the attachment of alcohols. This linker shows an improved acid stability compared with the trityl linker. The linker was applied to the synthesis of a peptide alcohol [53].

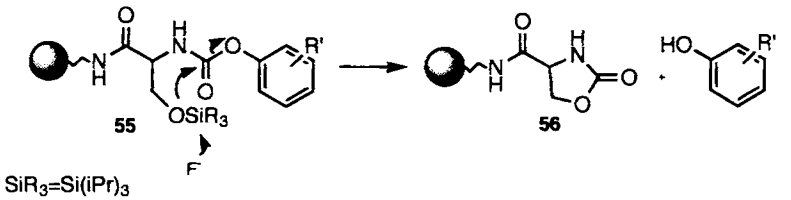
An additional linker **54** for the immobilization of alcohols on solid support was published recently [54]. The linker is activated with N-iodosuccinimide for the attachment of the alcohol. The alcohol is released by the action of penicillin amidase or by mild acid treatment, as outlined in Scheme 25. The yield of the enzymatic cleavage (25–50 %) is strongly dependent on the resin used.



Scheme 25

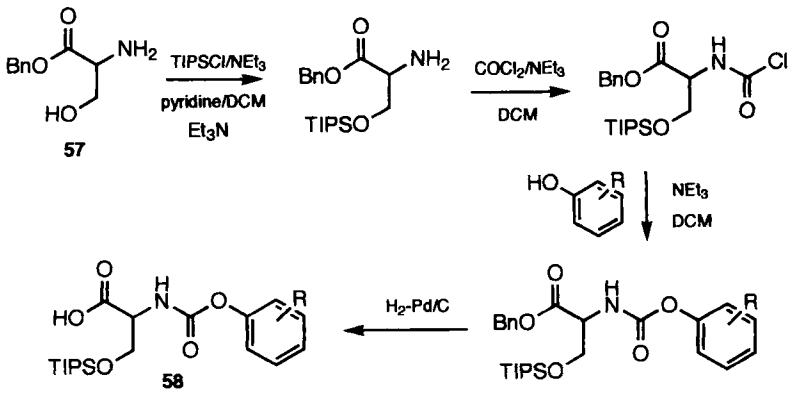
3.1.2.3.4 Serine-Based Linker for Phenols

This linker unit, when coupled to an amine-modified support as in **55**, is stable towards acids such as TFA as well as towards bases. The phenol can be released by fluoride ions [55]. The driving force for the cleavage is the intramolecular formation of the oxazolidinone ring system **56** (Scheme 26).



Scheme 26

The application of the linker was demonstrated in connection with Pictet–Spengler cyclizations and Knoevenagel reactions. In a preliminary example it was also demonstrated that the linker might also be useful for alcohols.



Scheme 27

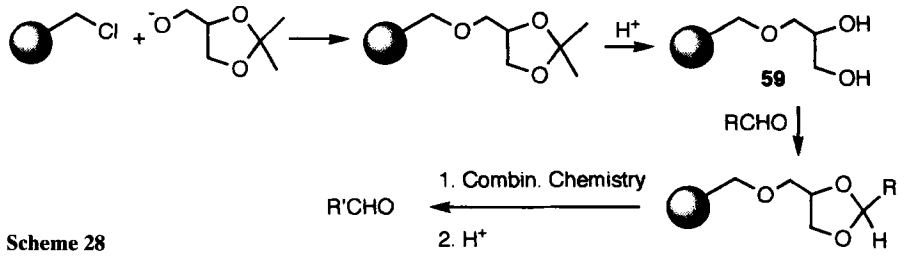
The linker was prepared starting from serine benzyl ester **57** according to Scheme 27. First, the hydroxyl function was protected as silylether. The amino group was then reacted with phosgene to allow for the further reaction with a substituted phenol (the educt). Finally, the benzylester was hydrogenolyzed, yielding unit **58** that carried a carboxylic acid function for attachment to the solid support to yield **55** ready for use in combinatorial synthesis.

3.1.2.3.5 Carboxy Functionalized Resins for the Attachment of Phenols

Polystyrene was modified with carboxyl groups to allow for an attachment of phenols via an ester bond [47]. Hence, the insertion of a special linker unit was not necessary. After combinatorial synthesis the phenol was released under basic conditions. A typical example was the preparation of a bis benzamidophenol library by this approach [56].

3.1.2.4 Acetal Linker for the Preparation of Aldehydes

This linker was originally developed by Leznoff and colleagues [57, 58]. Its preparation is outlined in Scheme 28. Commercial Merrifield resin was functionalized with the sodium



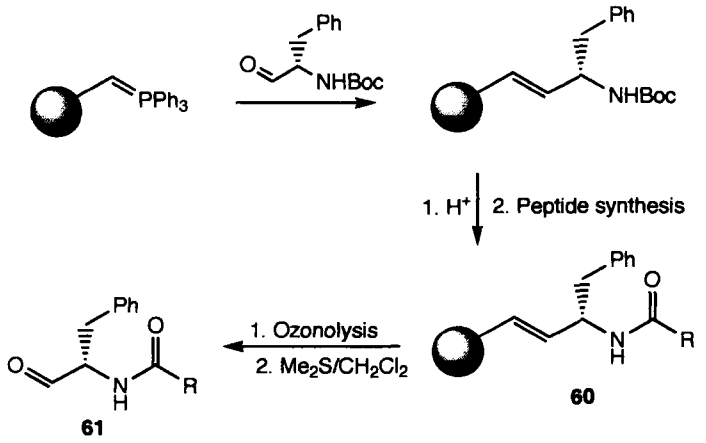
Scheme 28

alkoxide of isopropylidenglycerol. Hydrolysis of the acetonide yielded the desired entity **59**, to which an aldehyde was coupled as starting material for a combinatorial synthesis. The final product carrying an aldehyde function was released by mild acid treatment. The linker was applied successfully in Suzuki–Miyaura cross-couplings to yield biaryl and heterobiaryl aldehydes as products [59].

Procedure: Attachment of aldehyde to resin **59** [57]
Anhydrous resin **59** was suspended in 60 mL of anhydrous dioxane. Excess terephthalaldehyde (2.0 g) and 0.1 g of m-benzenedisulfonic acid as catalyst were added as well as 2.0 g of anhydrous sodium sulfate to absorb the liberated water. The mixture was stirred at rt for 48 h under exclusion of moisture. The resin was filtered, neutralized with anhydrous pyridine and re-filtered. The resin was then washed twice with pyridine/water (1:1), with water (10 times), ethanol (three times) and with ether (three times).
For cleavage of the aldehyde, the resin (3.43 g) was stirred with 40 mL of a 1:1 mixture of dioxane and dilute HCl for 48 h at rt. The resin was filtered and washed with water (six times), acetone (once), ethanol (three times) and ether (three times). The aqueous filtrate was extracted three times with ether. The combined ether extracts were washed with water, dried over Na_2SO_4 and evaporated to give a solid which upon preparative TLC yielded 86 % of the desired aldehyde.

Aldehydes could also be attached to resin-bound serine or threonine via oxazolidine formation [60]. This linker was used for the preparation of peptide aldehydes. The cleavage occurred with mild aqueous acid at 60° C.

A further aldehyde linker was constructed using Wittig chemistry [61]. The olefin **60** created by the Wittig reaction was cleaved via ozonolysis, followed by subsequent work-up with dimethyl sulfide yielding the aldehyde **61**. The principle was demonstrated for the synthesis of a library of peptide aldehydes.



Scheme 29

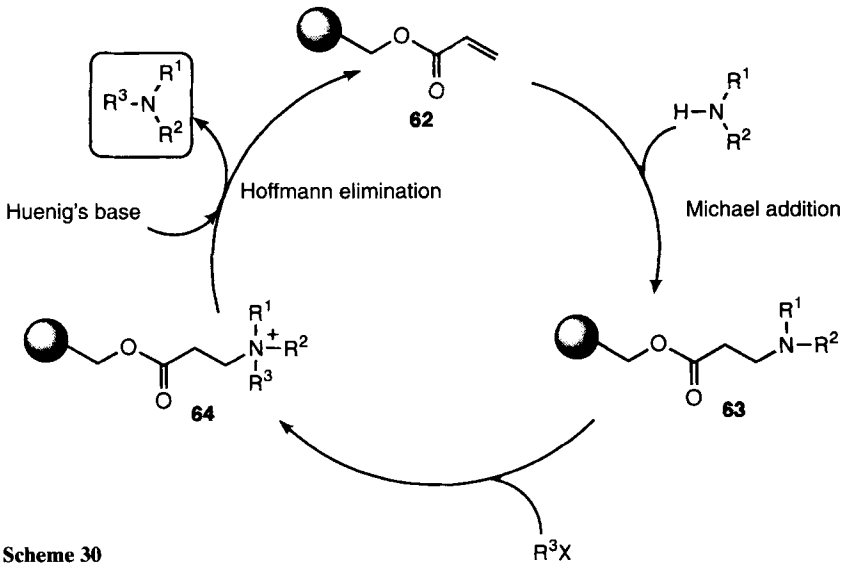
3.1.3 Traceless Linker Systems

The salient feature of these linkers is in that they do not yield a functional group in the final products after cleavage from the support. This can be a major advantage as most of the currently applied linkers produce carboxylic acids, amides, esters, hydroxy or amino functions in the final product. These relatively polar groups often influence bioavailability, and should be introduced only if these groups contribute significantly to the binding of the compound to the pertinent target protein. Hence, there is a high demand for such traceless linkers.

3.1.3.1 Application of Hofmann Elimination in the Linker Design

Tertiary amines are a very important class of pharmacophores, as about one-quarter of all registered drugs contain tertiary amines. Among drugs applied to the central nervous system, the proportion of tertiary amines is even higher. The design of the synthesis of tertiary amines on solid support is performed in such a way that the Hofmann elimination, which is commonly used for the synthesis of olefins, has been applied to the synthesis of tertiary amines [62, 63]. The basic principle is outlined in Scheme 30.

Acrylic acid was first attached via an ester bond to the hydroxymodified solid support to yield **62**. This was followed by a Michael addition which gave the tertiary amine **63**. Alkylation lead to the quaternary ammonium salt **64** that is prone to β-elimination induced by Huenig's base, thereby yielding the required tertiary amine.



Scheme 30

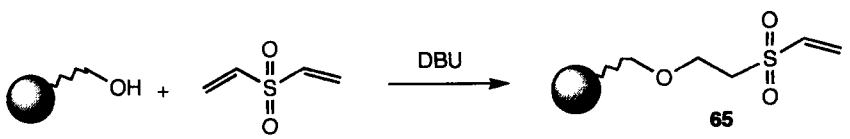
The system has the advantage that lability of the ester linkage to the solid support is of no concern. No special entity needed to be placed between the hydroxymethyl polystyrene and the acryl unit. The ester bond was stable towards mildly basic and acidic conditions.

According to the authors, a further advantage was that the modified resin **62** was regenerated during the elimination process and could be reused several times without loss of efficiency. The purity of the products obtained by this synthetic procedure was reported to be consistently high.

Procedure: Attachment of amine to resin **62** [62]
Resin **62** (0.17 mmol, 0.3 g) was taken up in a mixture of DMF (4 mL) and the secondary amine (3 mmol) and reacted under shaking for 18 h at rt to yield **63**. The resin was then washed with DMF (three times) DCM (three times) and MeOH (twice) and dried under vacuum. For quaternization, the resin was suspended in a solution of the alkylating agent R^3X (1.5 mmol) in 4 mL of DMF and reacted under shaking for 18 h at rt to yield **64**. The resin was washed with DMF (three times), DCM (three times), and MeOH (twice) and dried under vacuum.

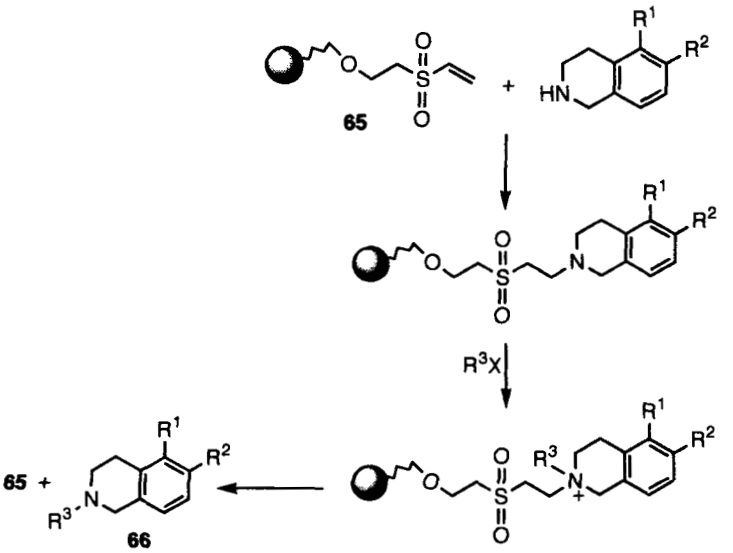
Procedure: Hofmann elimination from resin **64**
The resin was taken up in 4 mL DMF containing 0.6 mmol (106 µL) DIEA and shaken at rt for 18 h. The resin was washed with DMF (three times), DCM (three times), and MeOH (twice) and the filtrate was evaporated. The resulting white solid was distributed between EtOAc (2 mL) and 5 % aqueous Na_2CO_3 solution (2 mL). The organic layer was removed and the aqueous layer was washed with EtOAc (twice).
The combined organic layers were dried and evaporated. The base-line material was removed by SPE, employing 40 % ether in heptane as solvent.

An alternative approach (**65**, Scheme 31) was recently reported which was based on vinylsulfone groups [64]. These linkers were stable to a wider range of conditions as compared with the original acryl system as the attachment to the support was mediated via an ether linkage.



Scheme 31

This linker was applied to the synthesis of a library of N-alkylated 5- and 6-alkoxy-1,2,3,4-tetrahydroisoquinolines **66** involving the following steps: Michael addition, acid-catalyzed removal of a THP group, Mitsunobu etherification, quaternization of the nitrogen and Huenig's base-catalyzed elimination to result in the final products [65] (Scheme 32).



Scheme 32

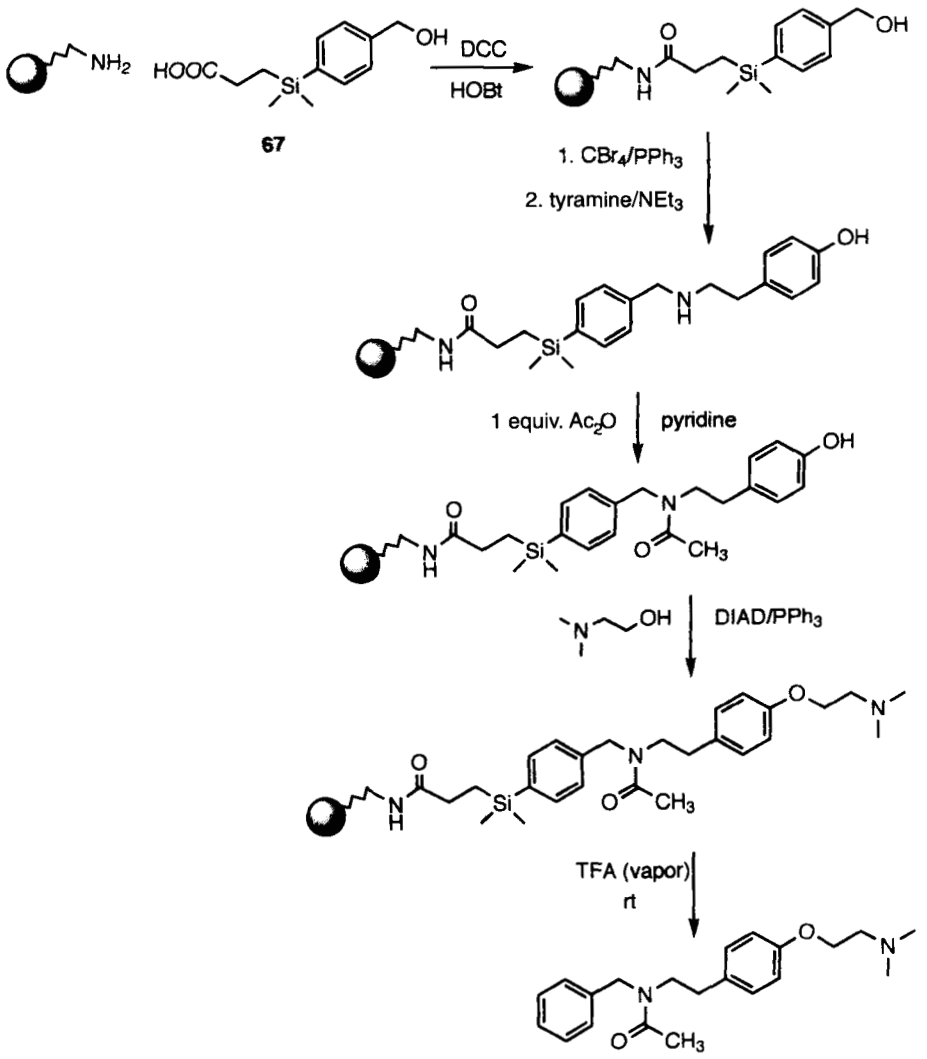
An interesting variant of Hofmann elimination on solid support was reported which involves two resins [66]. Besides the solid support for synthesis, an ion-exchange resin (Amberlite) was applied to promote the Hofmann elimination in the presence of a catalytic amount of triethylamine.

3.1.3.2 Traceless Linkers Based on Silylfunctionalization

Silicon-based linkers can be applied to the immobilization of aromatic and heteroaromatic entities onto a solid support. Protodesilylation procedures used to cleave off the combinatorial compounds leave no functional groups on the final products [67–69]. One limitation of this can be the relatively complicated and multistep synthesis of the actual linker unit. Usually, the starting material must be bound to the linker unit first, after which the resulting construct is attached to the support material. In addition, the conditions for the protodesilylation depend on the substitution on the arene ring.

Newly developed silicon linkers such as **67** (Scheme 33) were synthesized using fewer steps as compared with the earlier reported traceless linkers based on silylfunctionalization. They allow for an easy binding to the support before performing the combinatorial synthesis [70, 71].

The linker was used in combination with alkylation, acylation, and Mitsunobu reaction according to Scheme 33, and the Si-phenyl bond was cleaved with either TFA vapor, neat TFA [70] or TFA/DCM (1:1) [71].

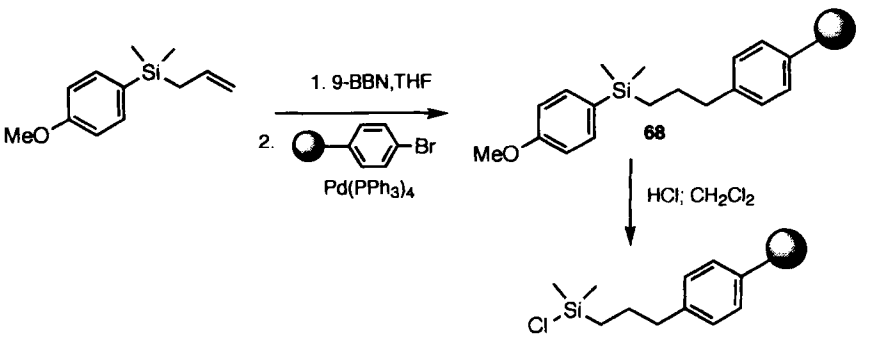


Scheme 33

A silicon linker (**68**) which allows for the direct loading of the aromatic compound to the solid support has also been developed (Scheme 34).

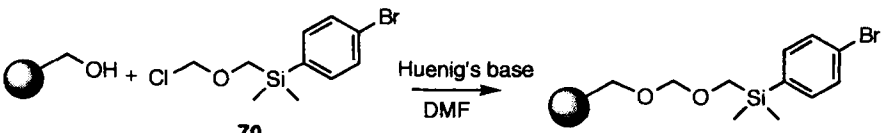
The system has the advantage that **68** can be stored indefinitely, but can be activated with HCl to form **69** before use. The utility of the linker was demonstrated in the synthesis of pyridine-based tricyclic structures [72].

A method for the attachment of haloarylsilanes to a polymer support via the intermediate **70** also led to a traceless system (Scheme 35). The polymer-bound arylhalides were used in a



Scheme 34

Suzuki reaction with a variety of arylboronic acids, and the final products were cleaved from the support by different electrophiles (including H^+) [73].



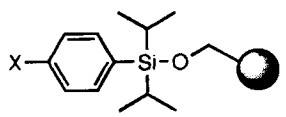
Scheme 35

Procedures for cleavage

Cleavage is generally performed as protodesilylation. The conditions very much depend on the nature of the aromatic system, as well as on the substitution. Either neat TFA, TFA vapor or TFA/DCM can be used. Electron-poor aromatic systems require treatment with CsF in DMF/water (4:1) at 110° C.

In the traceless system outlined in Scheme 35 an electrophilic cleavage, either iododesilylation (ICl in DCM) or bromodesilylation (Br_2/pyridine in DCM) is required after the Suzuki coupling. These methods of electrophilic cleavage were found to be superior to protodesilylation.

A variant of a silyl linker contains a silyloxy linkage rather than a silylalkyl linkage (**71**). The diisopropylsilyloxy linkage in this type of linker (which is commercially available with different substituents on the phenyl ring) is stable to a wide range of reagents such as strong bases or moderately strong acids, yet it can be cleaved under mild conditions using TBAF in THF. It is important to note that the cleavage conditions may be highly influenced by substitution on the aryl ring [74].

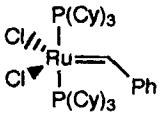


71

Procedure
For loading onto the resin, (hydroxymethyl)polystyrene (6.00 g, 6 mmol) and imidazole (36 mmol, 2.45 g) were taken up in 40 mL of DMF. The arylchlorosilane (24.1 mmol, 6.92 g) was added to the suspension and the mixture was kept at rt with shaking for 45 h. The resin was filtered and washed with DMF (three times), THF (three times), and DCM (three times), after which the resin was dried. Repetition of the above procedure enhanced the loading. For cleavage after solid-phase synthesis starting from **71**, the resin (0.209 g) in 2 mL of DMF was treated with 1 mL of TBAF in THF (1 M), and the mixture was heated at 65° C for 1 h with shaking. After cooling to rt, the mixture was diluted with water (10 mL), filtered and washed with Et_2O (three times). The organic layer was washed with water (10 mL) and brine (10 mL), dried and evaporated. The residue was taken up in $CHCl_3$ followed by SPE on basic Al_2O_3. Evaporation of the solvent yielded the desired product.

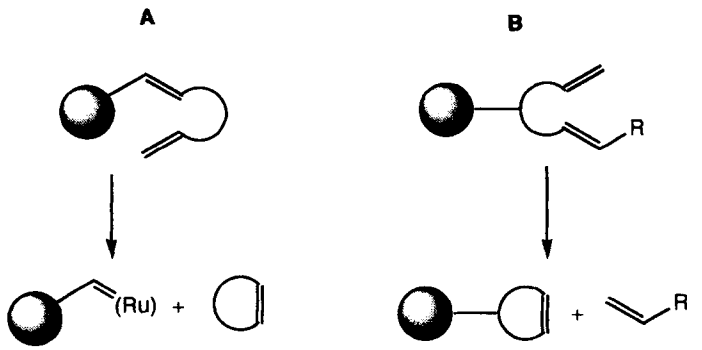
3.1.3.3 Traceless Linkers Based on Olefin Metathesis

Recently, it was shown that bis(tricyclohexyl phosphine) benzylidene ruthenium dichloride (**72**) [75, 76] was also able to catalyze olefin metathesis on a solid support [77]. Thus, if the re-



72

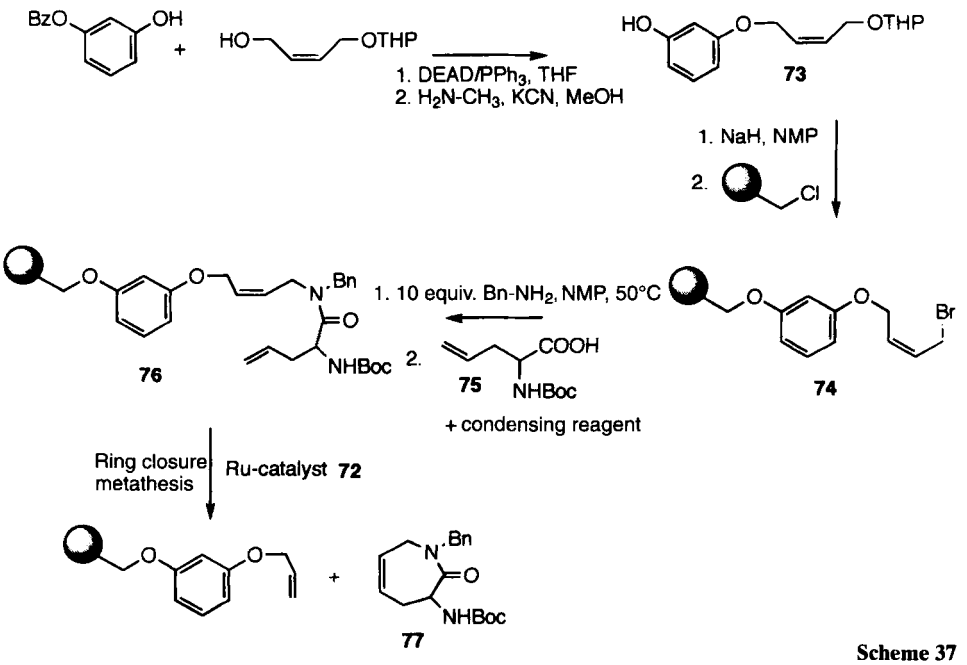
action were to be performed as ring closure metathesis, this offered another possibility for a traceless release of combinatorial compounds from solid supports. As only the desired products were cleaved off during the reaction, these were obtained in high purity. The method is compatible with a whole variety of different functionalities such as carboxylic acids, carboxylic acid anhydrides, amides, aldehydes, ketones, alcohols and sulfonamides.



Scheme 36

Furthermore, the reaction proceeded under very mild and neutral conditions. Hence, the concept was found to be very extremely versatile. For the release of the compounds after ring closure metathesis on the support there exist in principle two alternatives, as outlined in Scheme 36 [78].

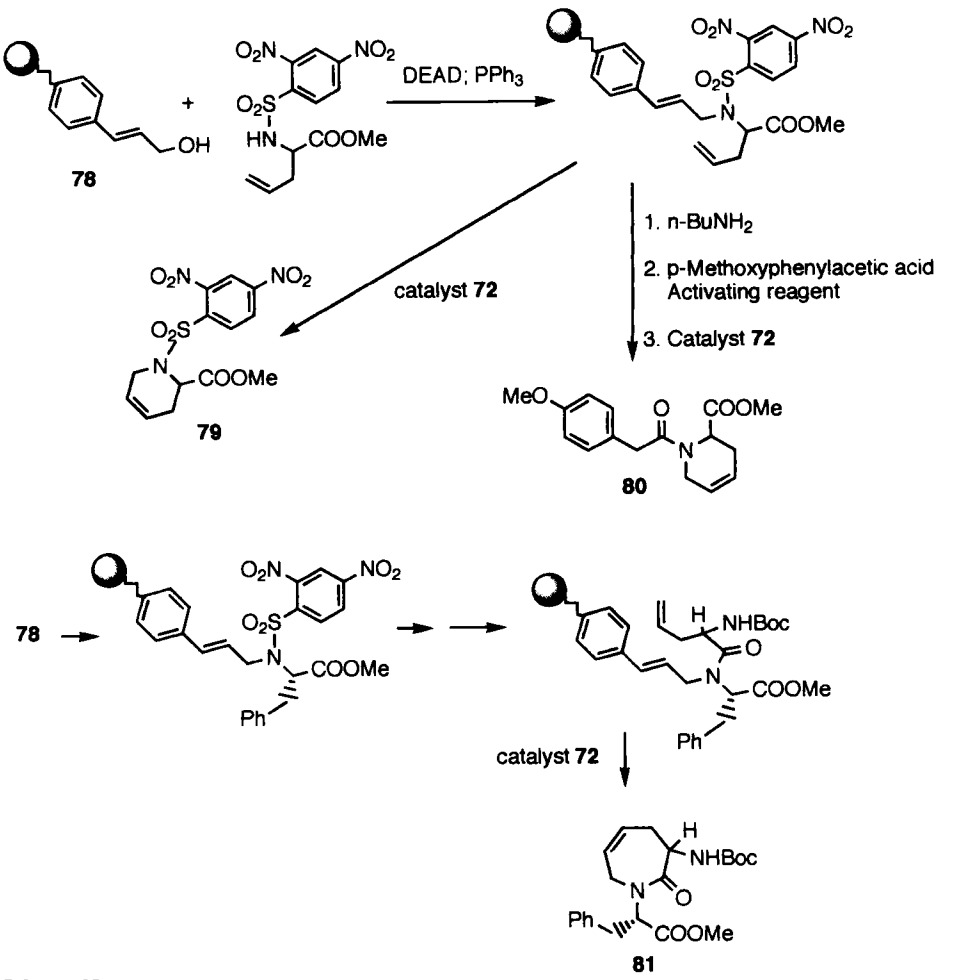
The strategy outlined in concept A leads to a release of the cyclized product. At the same time, the Ru-complex is immobilized on the support. Thus, ethylene or octene were added to re-liberate the Ru-complex in a metathesis reaction from the support. The strategy was successfully applied to the synthesis of a seven-membered lactame [79] (Scheme 37).



Scheme 37

The first step consisted of the Mitsunobu etherification of an allyl alcohol with the mono resorcinol ester, which afforded **73**. Cleavage of the benzoyl protecting group released the phenol which was then attached to the solid support. One-step cleavage of the THP-group and bromination was achieved with PPh_3/Br_2 to furnish **74**. Nucleophilic substitution of the bromide by benzylamine was followed by acylation of the secondary amine with N-Boc-allylglycine **75**, which resulted in the precursor **76** ready for the metathesis reaction performed with catalyst **72** to yield the final product **77**. Either 1-octene or ethylene were applied to generate **72**.

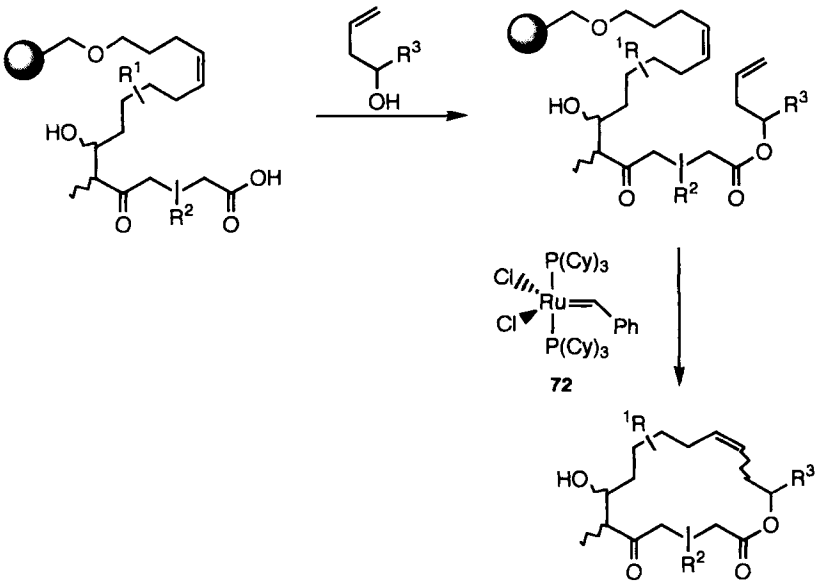
The same strategy starting from **78** yielded by metathesis of α,ω-dienes dihydropyranes, pipecolic acid derivatives (**79, 80**) and Freidinger lactams (**81**) [80] (Scheme 38).



Scheme 38

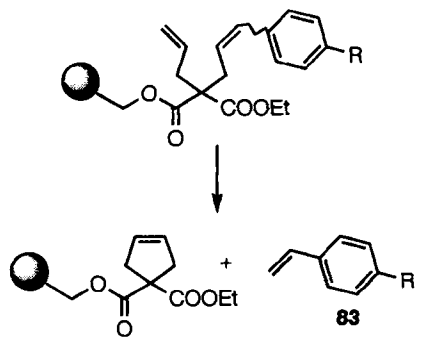
Recently, the approach to the Freidinger lactam was modified, using a novel variant of the Fukuyama–Mitsunobu process [81]. The salient features of the new method were its simplicity and its versatility [82]. The concept is not restricted to six- or seven-membered rings [83]. Excellent examples of the formation of larger rings were reported recently for the combinatorial synthesis of epothilones of the general structure **82** in which ring closure metathesis with concomitant release from the support was a key step in the overall synthetic strategy [84] (Scheme 39).

Concept B in Scheme 36 involves also a metathesis reaction on the solid support, but this time the formed ring remains attached to the solid support and an olefin is released. The Ru-complex is generated during the formation of the support-bound cycloolefin, and thus the entire reaction can be performed with catalytic amounts of Ru-complex. The concept was ap-



Scheme 39 **82**

plied as outlined in Scheme 40 to result in compounds of type **83**. The driving force for the reaction is the energetically favorable formation of the five-membered ring [78].



83

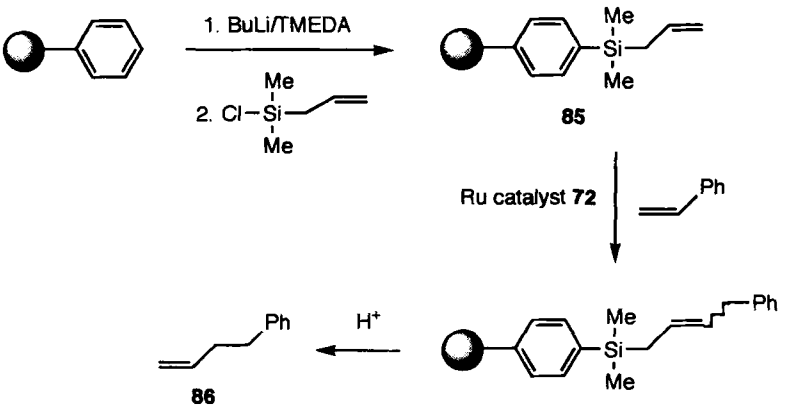
Scheme 40

Prodecure for metathesis [78]

Resin (400 mg; loading 0.52 mmol/g) was suspended in 3 mL of dry DCM (Argon, glovebox), and 5 mg (6.08 (mol, 3 mol %) of catalyst 72 was added. The mixture was stirred for 12 h at rt and then passed through a glass filter. The resin was washed with DCM. The crude product was obtained by evaporation of the filtrate and purified by silica gel chro-

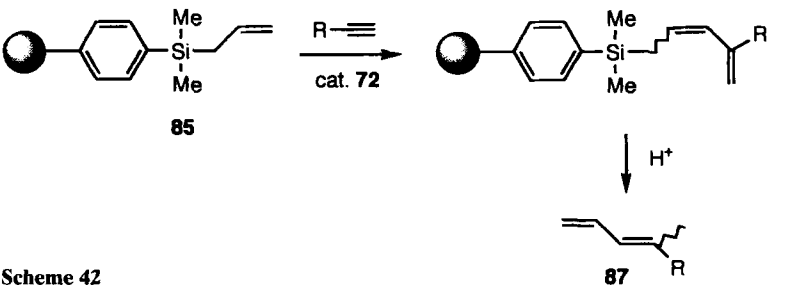
matography, whereupon 23 mg (44 %) of **83** were obtained. When the resin was exposed a second time to the same conditions, a second batch of **83** (6 mg, 11 %) was obtained.

The metathesis concept on solid support was extended to the so-called cross-metathesis, whereby one of the reacting olefins was attached to the solid support and a terminal olefin was present in solution [85]. During metathesis, this terminal olefin becomes immobilized on the resin. The reaction conditions were optimized in such a way that the possible formation of macrocycles could be prevented. The allyl-dimethylsilyl polystyrene **85** used in the reaction was synthesized according to Scheme 41. The release after metathesis is possible by scission of the Si-C bond mediated by appropriate nucleophiles (Sakurai conditions) to yield terminal olefins **86**.



Scheme 41

The reaction was carried out with an entire range of olefins carrying various functional groups. Besides obtaining terminal olefins, this linker can also be used to obtain hydroxyl or carboxyl functions in the final product. As the electrophilic attack may also occur intramolecularly, the synthesis of cyclic compounds was also possible using this route. Recently, the methodology was extended to cross-coupling metathesis between terminal alkynes and linker **85** (Scheme 42). Dienes **87** are obtained by such a process after electrophilic cleavage [86].

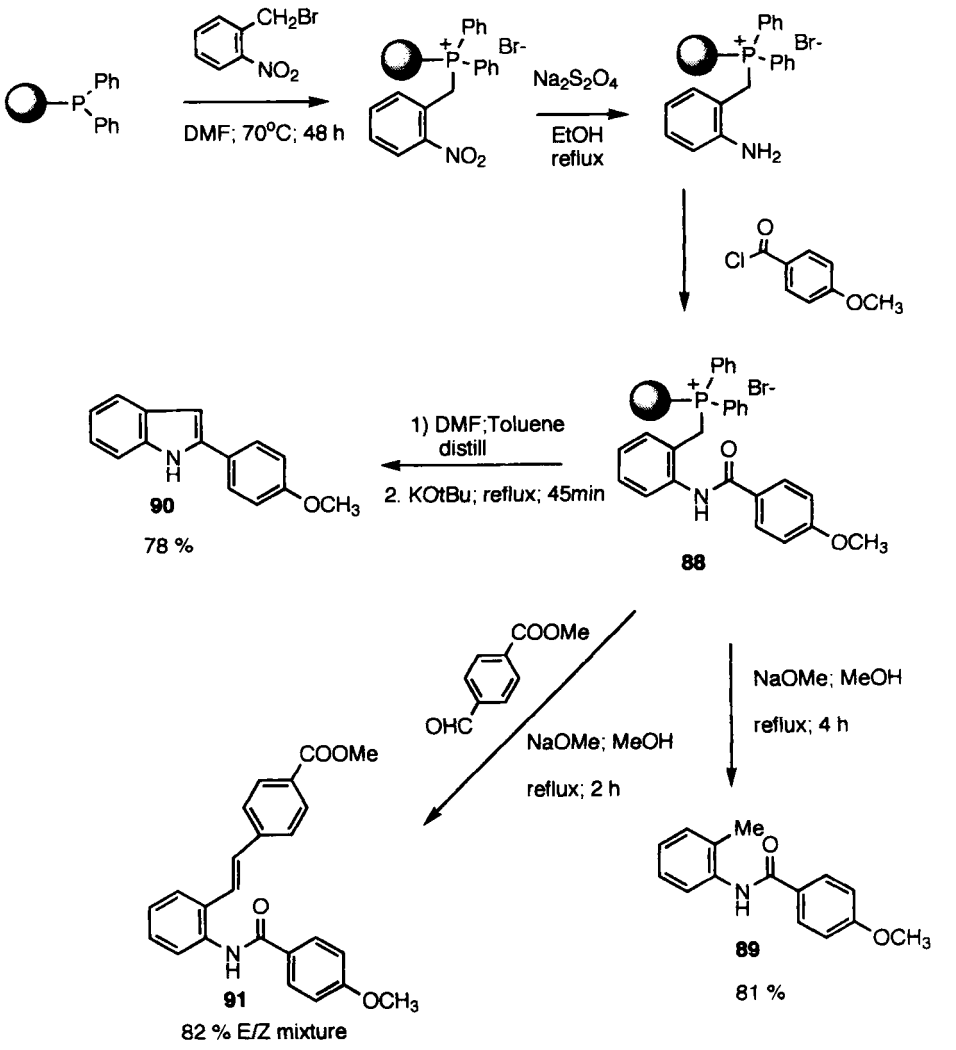


Scheme 42

3.1.3.4 Traceless Synthesis by Using Polymer-Bound Triphenylphosphine

The Wittig reaction on solid support offers the advantage that the phosphine oxide formed as byproduct remains bound to the solid support and can thus be separated from the olefinic product by filtration.

A phosphonium salt was prepared from commercially available polymer-bound triphenylphosphine. This phosphonium salt is compatible with a whole range of functionalities and reaction conditions. Depending on the conditions, different types of final product can be synthesized from the same precursor molecules (Scheme 43).



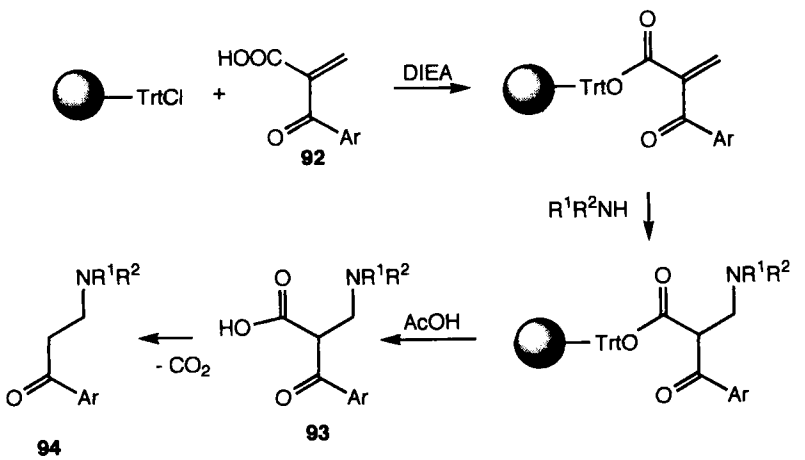
Scheme 43

Treatment of key intermediate **88** with methoxide led to a toluene-type compound **89**. An intramolecular Wittig reaction can also be achieved to yield 2-substituted indole **90**. The addition of an aldehyde resulted in a stilbene, e.g., **91** [87].

Procedure: Transformation of phosphonium salt **88** into Wittig product **91**:
The polymer-bound phosphonium bromide **88** (500 mg, 1.53 mmol/g) in dry MeOH (15 mL) was treated with 0.9 mL of a 2 M sodium methoxide solution followed by addition of methyl 4-formylbenzoate (1.8 mmol, 295 mg). This was heated under reflux for 2 h, cooled and then treated with glacial acetic acid (0.5 mL) and (carboxymethyl)trimethylammonium chloride hydrazide (2.7 mmol, 452 mg). After stirring overnight at rt (reaction with excess of aldehyde), the mixture was filtered over Kieselguhr and washed with DCM. The filtrate was washed with water (three times) and brine, dried over Na_2SO_4 and evaporated to yield a 3:1 mixture of (E)- and (Z)-stilbenes (82 %).

3.1.3.5 Decarboxylation-Based Traceless Linking

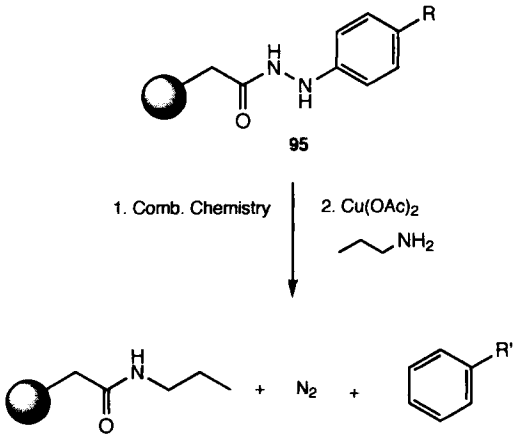
This concept is based on the decarboxylation of β-keto carboxylic acids. Commercially available 2-aroyl acrylic acid **92** as starting material was coupled to trityl-modified resin. This step was followed by a Michael-type addition of indolines [88]. Upon cleavage, the released intermediates **93** are decarboxylated to afford the desired β-indolinyl propiophenones **94** (Scheme 44).



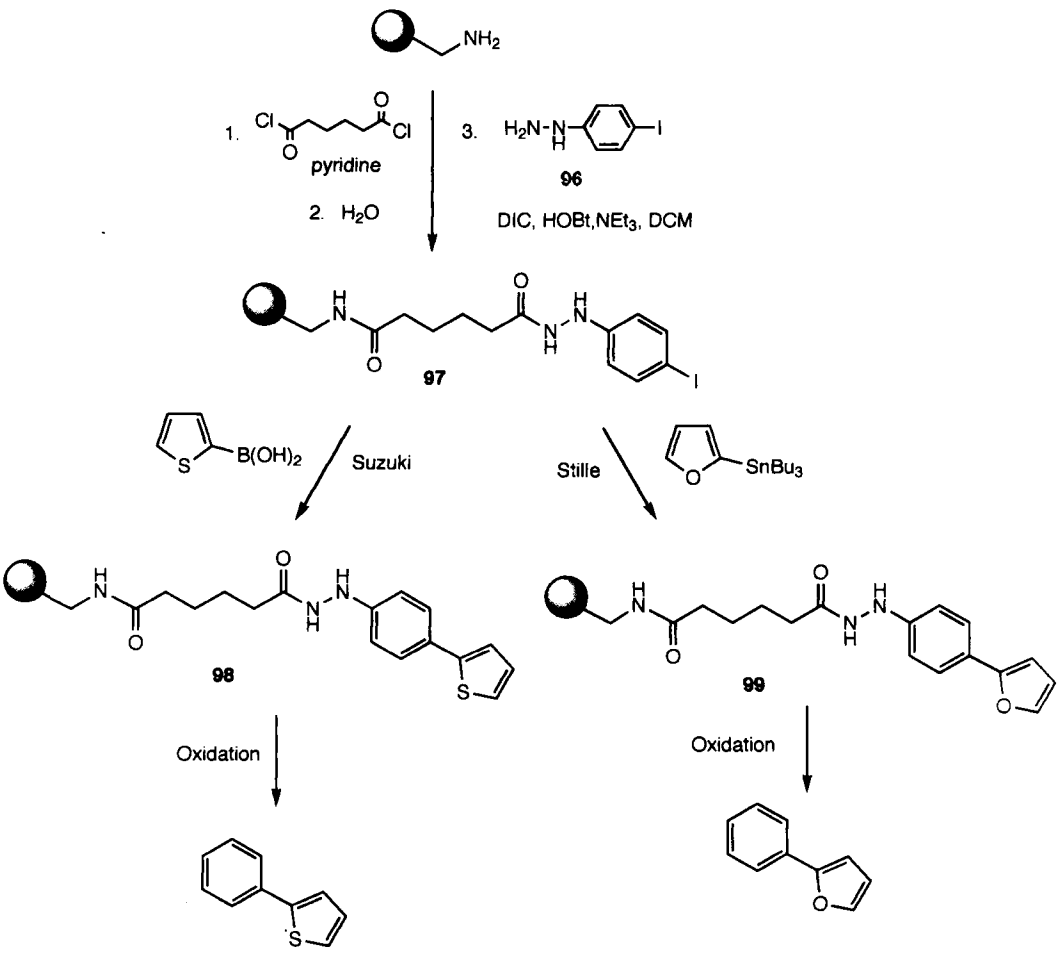
Scheme 44

3.1.3.6 Traceless Linker Based on Arylhydrazide

The principle of this linker is based on an oxidative cleavage of aryl hydrazides, and it has been used successfully in the synthesis of peptides [89]. The linker system is stable under



Scheme 45

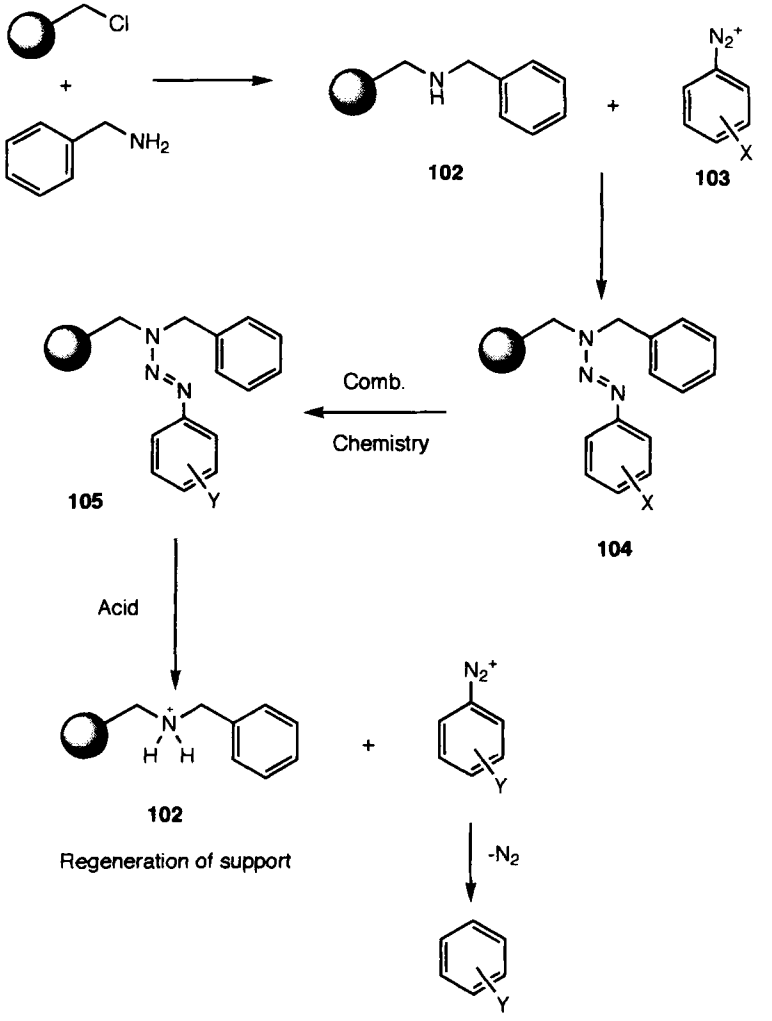


Scheme 46 100 101

acidic and basic conditions, and may be modified as for **95** so as to allow the synthesis of combinatorial compounds in a traceless manner, as outlined in Scheme 45 [90].

Meanwhile, the same concept was applied to Pd-mediated CC-couplings according to Scheme 46. Tentagel, Argo Pore and Polystyrene were applied as solid supports [91].

The amino-modified support was reacted with adipinic acid dichloride and, after hydrolysis, was coupled to 4-iodo phenyl hydrazine **96** to yield the immobilized iodobenzene **97**. Intermediate **97** was then applied to Pd-mediated CC-couplings (Stille, Heck, Suzuki, Sonogashira) to yield for example compounds **98** and **99**. The final products **100** and **101** were obtained in good to excellent yields by oxidation of **98** and **99**.

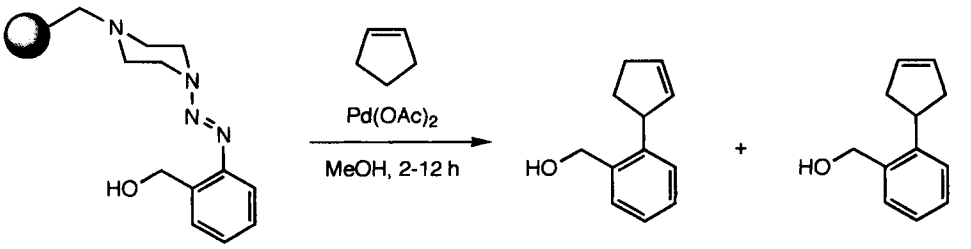


Scheme 47 **106**

3.1.3.7 Triazene-Based Traceless Linker

The principle of this linker system is outlined in Scheme 47. Reaction of a diazonium salt **103** with the amino group on the resin (**102**) yields the triazene **104**. These triazenes are stable under basic conditions, but are prone to cleavage under acidic conditions. Thus, after synthetic manipulations leading to **105** the triazene was cleaved; this resulted in regeneration of the initial support **102** and the desired product **106**. The loss of activity after regeneration was less than 10 %, and therefore **102** could be re-used [92]. The potential of this traceless system was demonstrated for Heck couplings and Diels–Alder reactions.

The system was also applied to Pd-mediated CC cross-coupling reactions directly at the cleaving step in which the diazonium salt is the reacting partner for the olefin. An example of a Heck reaction performed in this fashion is outlined in Scheme 48 [93].



Scheme 48

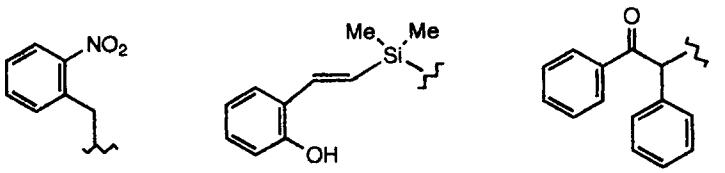
95 % 5 %

The triazene linker system may also be reversed to be used as linker for aliphatic amines [94].

3.1.4 Photolabile Linker Units

3.1.4.1 Introduction

Photolabile linkers are stable under a great number of other reaction conditions in organic synthesis, and they also allow for release under neutral conditions. Photolabile linking groups for hydroxy and amino functions can be divided into three different basic entities, as shown in Fig. 2.



o-nitrobenzyl- [95] o-hydroxystyryl dimethylsilyl- [96] 2-oxo-1,2-diphenylethyl (Desyl) [97]

Figure 2

For an application in combinatorial synthesis, photolabile linkers must be modified to allow for an attachment to the solid support, and must be further modified to adjust the cleavage step after combinatorial synthesis to the requirements of the photolytic removal of the target molecules from the support (modulation of photolytic cleavage kinetics). For combinatorial synthesis, only the o-nitrobenzyl-derived linkers have found wider applications, whereas the Desyl-derived linker has been used mostly in photolithographic DNA synthesis.

3.1.4.2 Linkers Based on o-Nitrobenzyl

The different o-nitrobenzyl-based linkers are outlined in Fig. 3, together with the acyl unit to which it is attached. Upon photolytic cleavage, the o-nitrobenzyl unit is transformed into an o-nitroso benzaldehyde unit, resulting in concomitant release of the combinatorial compound.

The linker designed in [101] was recently further optimized so that it is stable towards acid, base and Lewis acid/amine combinations [104].

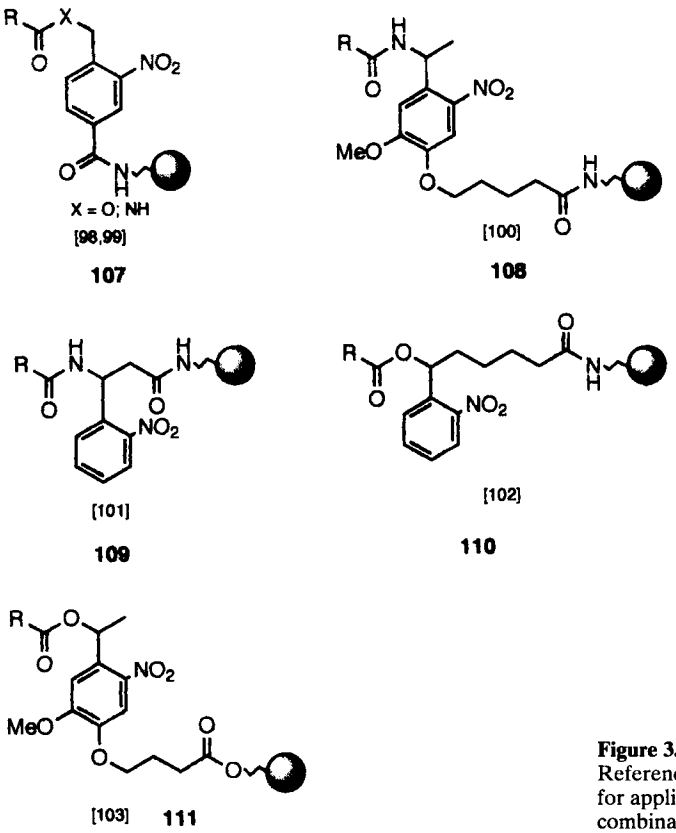
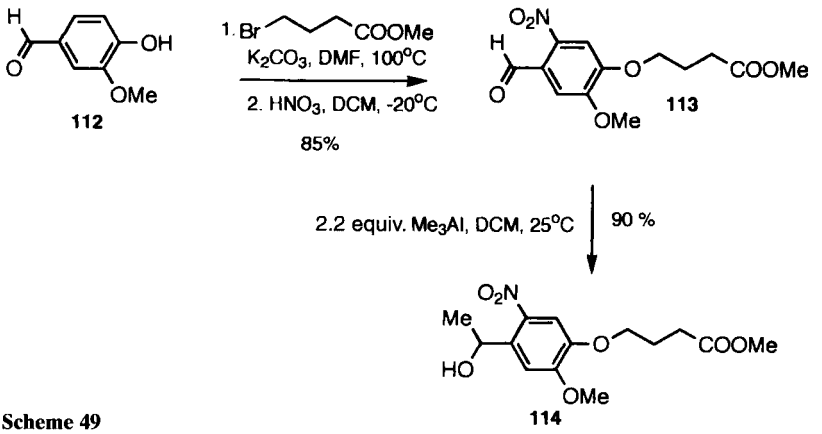


Figure 3. *o*-Nitrobenzyl-based linkers. Reference numbers indicate citations for application of these linkers in combinatorial chemistry.

Procedure

The conditions for the photolytic cleavage to mediate release of the products are highly dependent on the nature of the linker, so that a general procedure cannot be outlined. It is therefore recommended that the specific conditions for each individual linker be identified in the pertinent literature reference.

A straightforward synthesis of the linker unit **111** applied in [105] was reported recently (Scheme 49) [106].

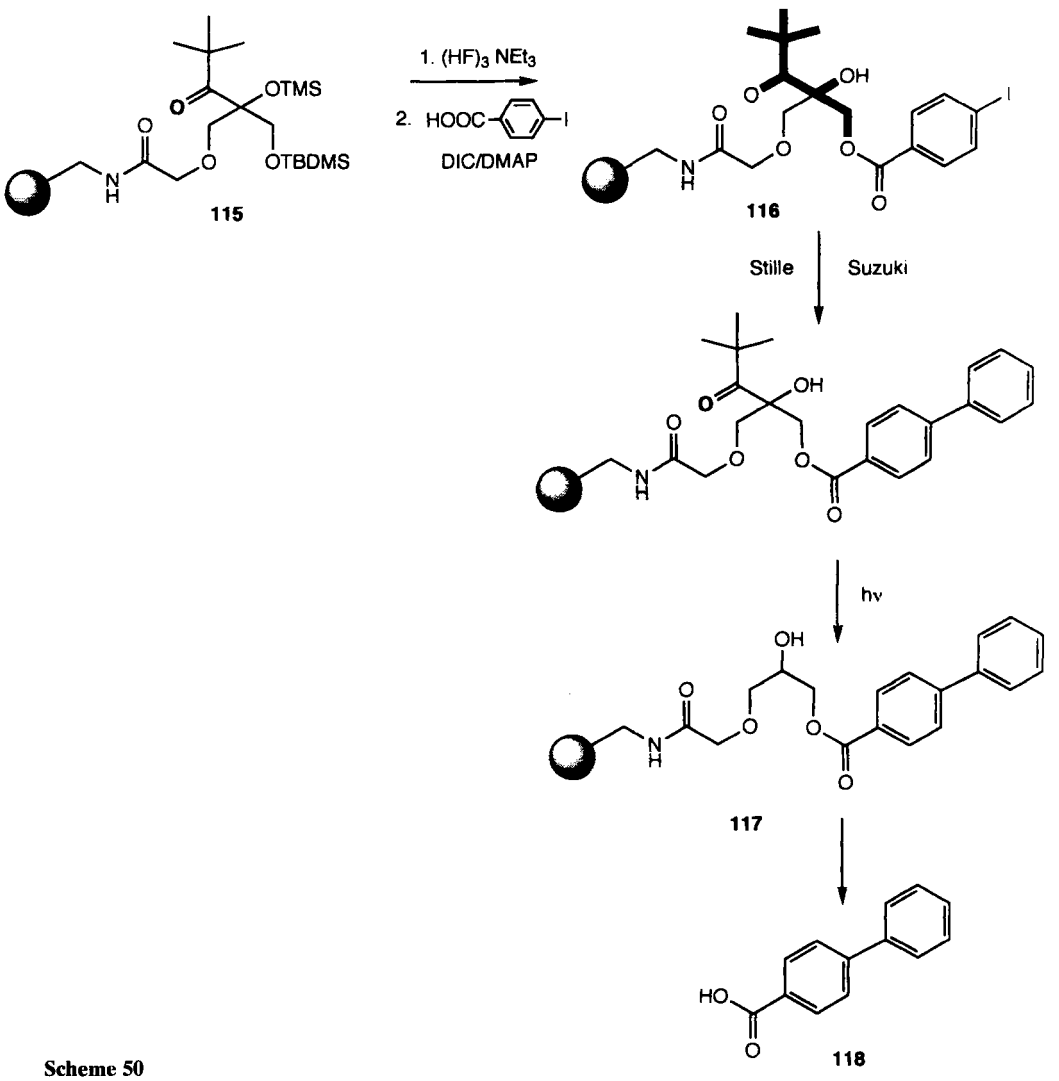


Scheme 49

Alkylation of vanillin **112** with methyl 4-bromobutyrate, followed by nitration afforded **113**. Addition of the methyl group to the aldehyde was performed with the commercially available $AlMe_3$ to yield **114**; this could be crystallized directly from the crude, three-step reaction mixture. After hydrolysis, the corresponding acid may be attached to a hydroxymodified support as an ester. After acylation, this results in the desired construct **111**.

3.1.4.3 Photocleavable Linker Based on Pivaloylglycol

Recently, a new type of photolabile linker **115** for the attachment of carboxylic acids was reported [107]. The linker is based on pivaloylglycol (the bold structure in Scheme 50). Cleavage of the silyl groups was followed by attachment of the iodobenzoic acid to give **116** ready for CC-couplings. The photolytic cleavage proceeded via a two-step process. The reaction was initiated by the formation of a radical center **117**, which was followed by a spontaneous β-C,O-bond scission to yield the final product **118**. The photolytic cleavage proceeded rapidly and produced high yields of released acids. The system proved to be compatible with many reagents and reactions, and its utility was demonstrated in peptide synthesis, in Stille and Suzuki couplings (Scheme 50), and epoxidations.



Scheme 50

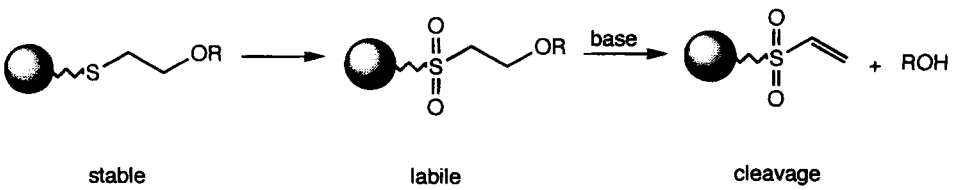
Procedure: Deprotection of the silyl groups from **115**:
1 g of **115** (0.28–0.29 mmol) was suspended in 4 mL of THF and 1 mL of $(HF)_3$ x NEt_3 was added. After 24 h, the resin was washed with THF, DCM and dried to yield 1.01 g of the support ready for the attachment of the aromatic carboxylic acid.
To a suspension of the linker prepared above (200 mg, 58 μmol) was added 4-iodobenzoic acid (2 equiv.), DMAP (0.2 equiv.), and DIC (1.2 equiv.), and the mixture was shaken for 18 h at rt. Washing (THF and CH_2Cl_2) and drying afforded **116**.
Suzuki coupling with resin **116**: To a degassed suspension of resin **116** (100 mg, 28 μmol) in DMF were added $PhB(OH)_2$ (14 mg, 112 μmol), $PdCl_2(dppf)$ (4 mg, 6 μmol), and NEt_3

(39 µL, 0.28 µmol). After 18 h at 65° C, the reaction mixture was washed with DMF and DCM and dried to afford the resin ready for the photolysis.

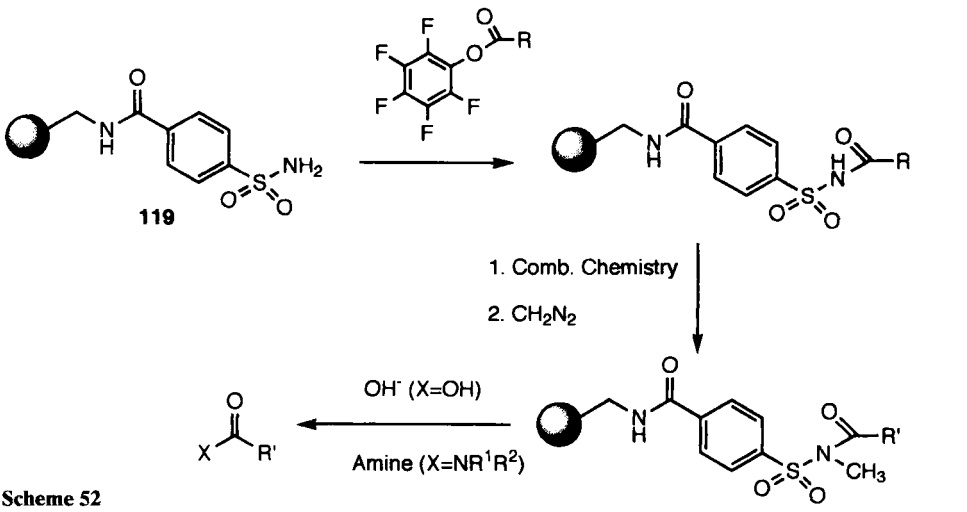
Photolysis: The photolysis in quartz cells (1-cm path length, equipped with stir bar) were conducted with 2–8 mg of resin suspended in 3 mL of solvent in the beam of a 500 W Hg high-pressure lamp fitted with a 280–400 nm dichroitic mirror and a 320 nm cut-off filter. The power level was adjusted by a collimating lens between 50 and 1000 mW cm^{-2}. The cells were maintained at 20° C and irradiated horizontally with gentle mixing of the beads by means of a magnetic stirrer. After photolysis, the supernatant was analyzed by UV spectroscopy and reversed-phase HPLC. Alternatively, the photolysis can also be performed directly in microtiter plates.

3.1.5 Safety Catch Linkers

One of the potential problems with linker units can be a partial or even a complete release of the compound attached to the support during combinatorial synthesis of the desired products. To avoid this danger, one can aim for very robust linker units which may be transformed,



Scheme 51



Scheme 52

after synthesis of the product, to a labile version which allows for release under mild conditions. Such a basic principle is outlined in Scheme 51.

The first safety catch linker (**119**) was developed for peptide chemistry [108] and later adapted to combinatorial approaches [109]. The linker is compatible with a number of reaction conditions. The activation for the release step proceeds via an alkylation of the imide nitrogen. Nucleophilic attack leads then to the desired cleavage according to Scheme 52.

Cleavage using aqueous base afforded the carboxylic acids. If the release step is performed with an amine, the corresponding carboxamide is obtained. Thus, by the latter version one can introduce further diversity during the cleavage step.

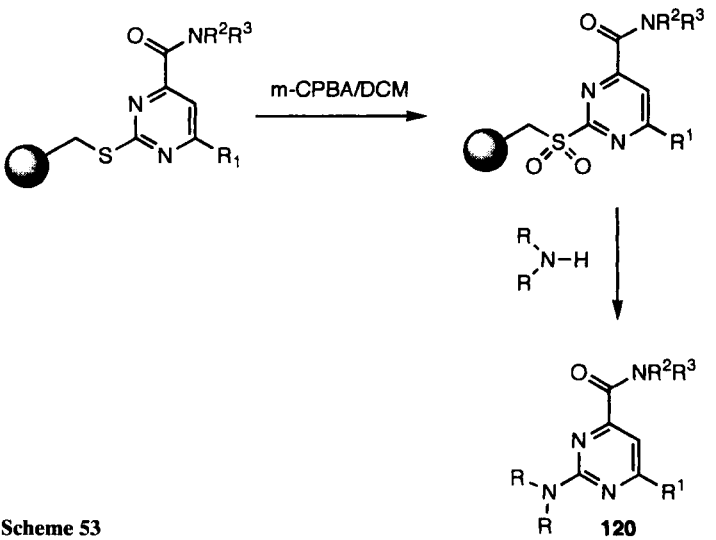
If less nucleophilic amines are to be used for the cleavage step, then prior alkylation with bromo- or iodo-acetonitrile is necessary [110].

Procedure

Loading onto the sulfonamide resin: Resin **119** was acylated by using the pentafluorophenylester of the carboxylic acid to be attached. Alternatively, the attachment can also be performed with the carboxylic acid anhydride prepared in situ by DIC.

To 3-(3,4,5-trimethoxyphenyl) propanoic acid (36 mmol, 8.6 g) was added 18 mmol (2.8 g) of DIC and after addition of 60 mL of DCM the mixture was stirred for 8 h at rt. After cooling in an ice bath, the urea was filtered off. The filtrate was added to a 250 mL round-bottomed flask which was followed by resin **119** (3.9 mmol, 10 g), DMAP (0.36 mmol, 44 mg), DIEA (12 mmol, 2.1 mL), and DCM (10 mL). After stirring for 39 h the suspension was filtered, and the resin was washed with THF, 5 % TFA in THF, THF, and MeOH. The resin was dried on the rotary evaporator and then under high vacuum for 24 h.

Cleavage to provide amides: To 500 mg (0.17 mmol) of acylated resin was added DMSO (4 mL), DIEA (0.85 mmol, 136 µL), and bromoacetonitrile (4 mmol). After stirring for 24 h, the resin was filtered and washed with DMSO (five times) and THF (three times). To the resin



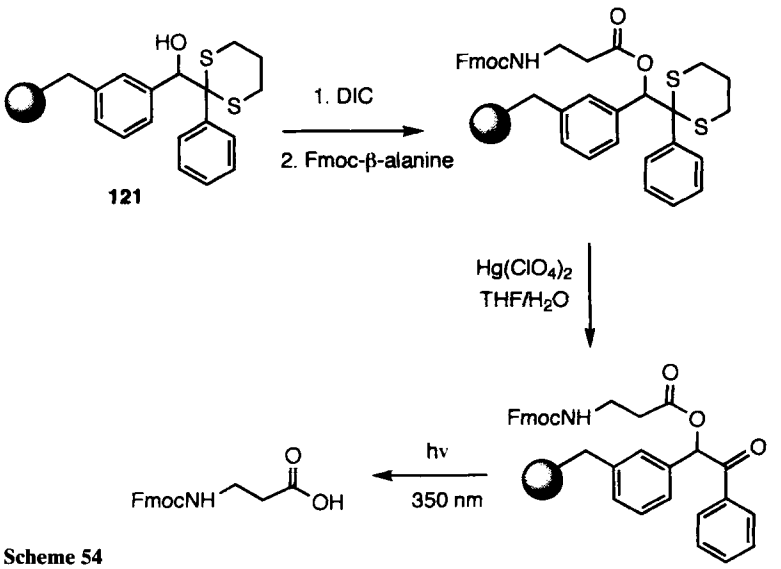
Scheme 53

was then added THF (3 mL) and the amine (3 mmol) and the suspension was stirred for 12 h. Then the support was removed by filtration and washed with DCM (three times). The filtrate and the DCM-washes were combined, washed with 1 N HCl (twice), dried over Na_2SO_4, filtered and evaporated. Particles from the solid support were removed by SPE. Treatment with limiting amounts of amine resulted in pure amides.
Alternatively, the resin can be treated with 0.5 N NaOH (1 equiv.) to form the corresponding carboxylate. Hydrolysis with 0.5 N ammonia in dioxane yielded the carboxamide.

Recently, the linker was used for the preparation of arrays of 2'-amido-2'-deoxyadenosine derivatives [111]. The products were obtained ready for biological testing without need for chromatographic purification.

Another example of the safety catch principle in which the cleavage step is used to introduce further diversity, is outlined in Scheme 53. Aminopyrimidines of type 120 were synthesized by using this approach [112, 113].

A further safety catch linker is based on a dithiane-protected benzoin (**121**). This can be activated for cleavage by photolysis according to Scheme 54 by removal of the dithiane protection [114]. It can be applied to the attachment and leads to the release of alcohols and carboxylic acids. A disadvantage is that if activation is performed with a Hg(II) salt, then this must be removed completely in order to avoid problems in assays using proteins as biological targets.



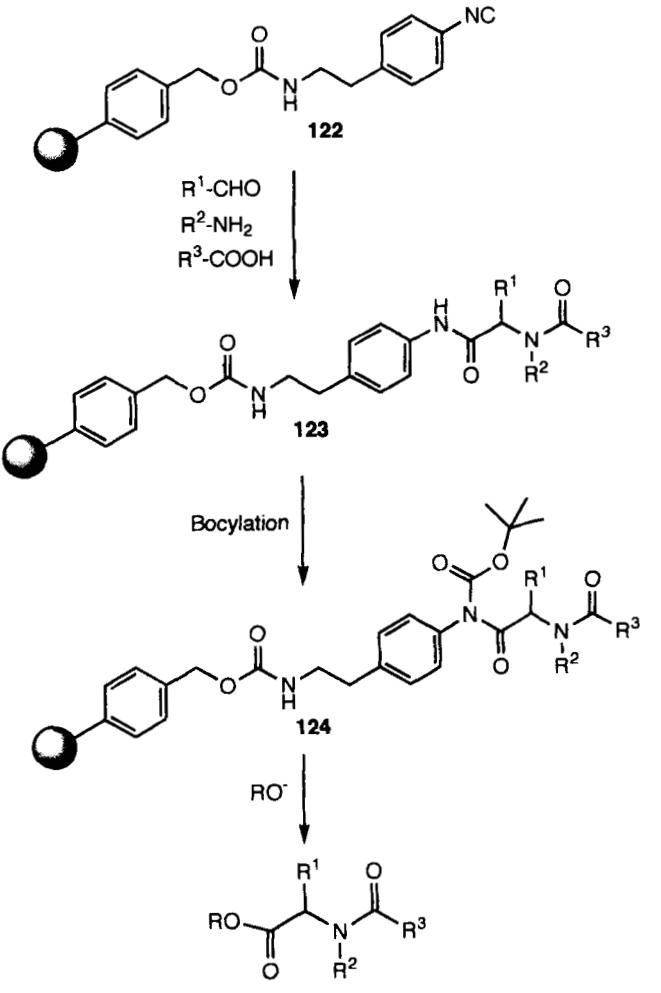
Scheme 54

Procedure

Attachment and cleavage: To resin **121** were added 3 equiv. of DIC, Fmoc-β-alanine (3 equiv.), DIPEA (3 equiv.), DMAP (catalyst), HOBt (catalyst) in DMF. Esterification yield was 32 % as checked by the release of the Fmoc-group from an aliquot.

The removal of the dithiane group proceeded either with $Hg(ClO_4)_2$ in THF or bis [(trifluoroacetoxy) iodo]benzene or periodic acid (4 equiv.) in THF/water at rt for 18 h. The conversion was in the range of 95 %. After Irradiation at 350 nm in THF/MeOH (3:1), the release of Fmoc-β-alanine was followed by HPLC, and was maximal after 120 min.

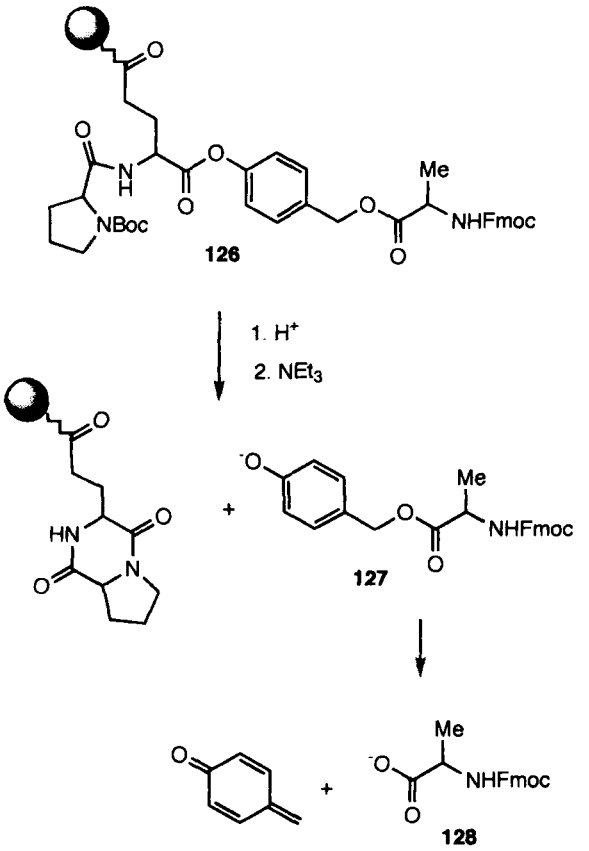
A very elegant safety catch linker was activated by attachment of a Boc group to a benzamide. The compounds could then be released by various nucleophiles, which in turn led to different heterocyclic systems [115]. The linker was developed in connection with the Ugi four-component condensation, for which the starting isonitrile had been formed directly on the solid support **122** (Scheme 55).



Scheme 55

The solid phase-bound isonitrile **122** yielded (in the Ugi reaction) the derivative **123**; this was converted into **124** by Bocylation. This intermediate was now amenable to a nucleophilic attack to yield the desired compounds of type **125**; depending on R^2,R^3, these can undergo cyclizations to yield diketopiperazines, 1,4-benzodiazepine-2.5-diones, ketopiperazines, or dihydroquinoxalinones.

A further safety catch linker is outlined in Scheme 56. This linker allows for efficient compound release into buffered aqueous solutions [116]. The activation of linker **126** under acidic conditions was followed by a base-mediated diketopiperazine formation, leading to intermediate **127**. This undergoes a 1,6-elimination process to yield the desired product **128**. As yet, the linker has only been applied in connection with amino acids and small peptides.



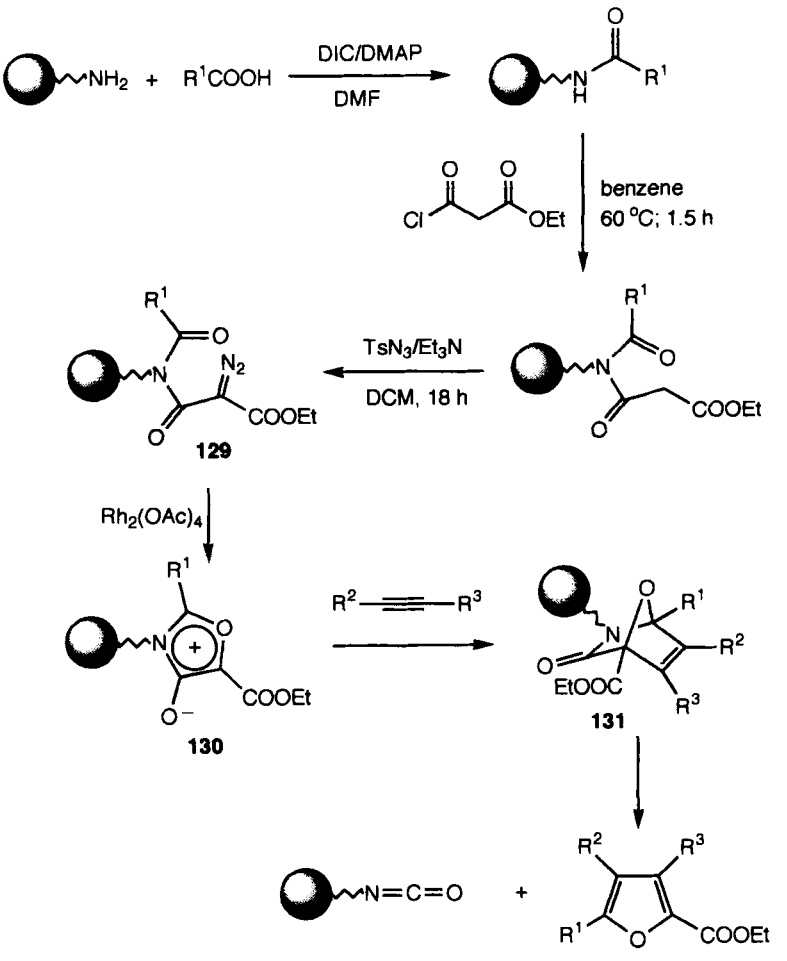
Scheme 56

The safety catch concept was also realized for the development of a traceless linker which led, after an oxidation–reduction sequence, to the release of molecules containing an aliphatic C-H bond [117, 118].

3.1.6 Traceless Concept Based on Cycloaddition–Cycloreversion

A new concept of traceless solid-phase synthesis is based on cycloaddition–cycloreversion. Cycloadditions are synthetically useful reactions with a wide scope for the construction of rigid templates of different ring sizes. Due to the versatility and the variation of substituents of the components for cycloadditions, this allows an efficient introduction of diversity.

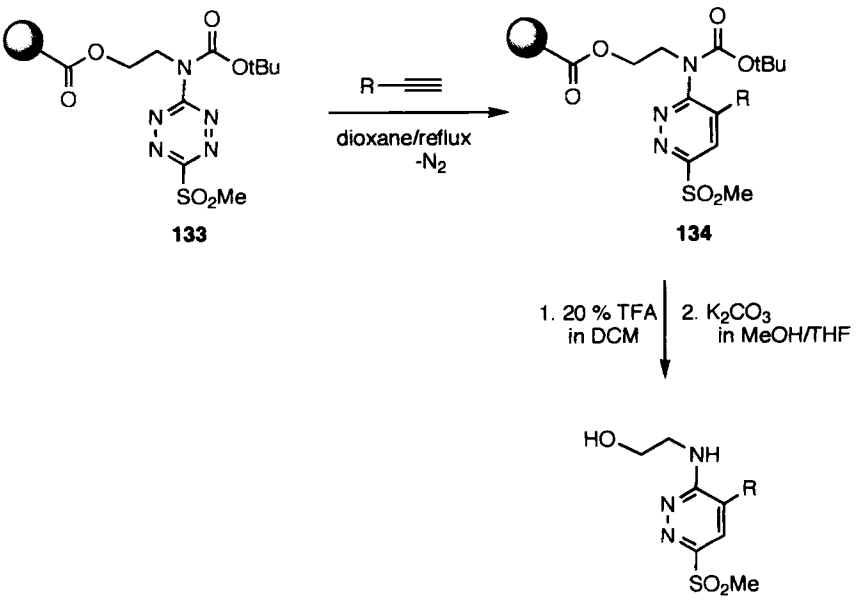
An example is illustrated in Scheme 57. The sequence can be performed directly on amino-modified resin without a special linker unit. α-Diazo carbonyl compounds of type **129** were reacted with a Rh (II)-catalyst to form highly reactive Rh (II) carbenoids which yielded isomuenchnones **130**. These underwent [2+3] cycloadditions with acetylenes to form bicyclic intermediates **131**. Thermolytic cycloreversion led to the desired furans **132** in high purity [119, 120].



Scheme 57

A related approach was used for the synthesis of 1,2-diazines of type **135** according to Scheme 58 [121]. After cycloaddition to tetrazine **133**, nitrogen is released with the formation of functionalized 1,2-diazines. The system has the further advantage that these 1,2-diazines bear a leaving group (SO_2Me) which should be useful for introduction of further diversity.

Thus, the reaction of **133** with acetylenes yielded polymer-bound intermediates **134**. The release of the final products was performed in two steps. After cleavage of the Boc-group under acidic conditions, the products **135** were cleaved from the support under basic conditions. In addition to acetylenes, other dienophiles such as enolethers were employed.



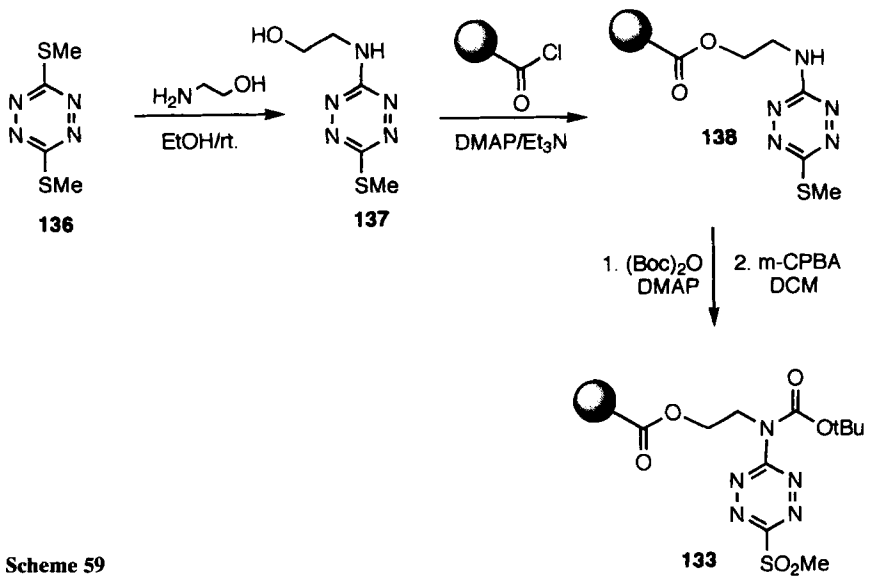
133 **134** **135**

Scheme 58

Procedure

The Diels–Alder reaction between **133** (50 mg, 74 μmol) and 10–20 equiv. of the dienophile in 4.0 mL of dioxane was performed for 16 h at reflux. The Boc-group was removed by stirring **134** in an excess of TFA/DCM (1:4) for 1 h. The product was released from the support by washing with DCM (three times), MeOH/THF (twice) and treatment with K_2CO_3 in MeOH/THF for 12 h. After filtration, the filtrate was extracted with EtOAc. After evaporation, the organic layer yielded the product **135**.

For the synthesis of the solid phase-bound tetrazines (Scheme 59), the readily available 3,6-bis methylthio-1,2,4,5-tetrazine **136** was monosubstituted with aminoethanol to yield **137**. This was then coupled to carboxylated polystyrene to afford the immobilized tetrazine **138**. Boc-protection and oxidation provided diene **133** ready for the Diels–Alder reaction.



Scheme 59

3.1.7 Summary and Outlook

With the emergence of combinatorial chemistry, the solid-phase synthesis of small molecules has become an intensive field of research. Synthesis on solid support has been shown not only to provide an efficient means of preparing compounds, but also to provide them in highly pure form. However, although such advantages are significant, the design of suitable linker molecules must be approached with great care. As yet, those linkers which have been developed are by no means sufficient to exploit the potential offered by solid-support reactions. It follows that, therefore, that in the near future a major effort will be necessary in order to design innovative linker units that will complement the techniques of combinatorial chemistry.

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3.2 Cyclative Cleavage: A Versatile Concept in Solid-Phase Organic Chemistry

Josef Pernerstorfer and Thomas Krämer

3.2.1 Principles

Solid-phase chemistry often suffers from the problem that synthetic techniques developed and optimized for solution-phase chemistry must be adapted to solid-phase chemistry. In contrast, the cyclization–cleavage strategy uses the special characteristics of solid-phase chemistry and offers advantages that are not possible in solution phase. In general, the precursors for this cyclization–cleavage approach are linked to the solid phase by a leaving group for the cyclization (e.g., an ester bond). Another group in the molecule (e.g., an amine as a nucleophile) provides the ring closure by displacing the leaving group (Fig. 1).

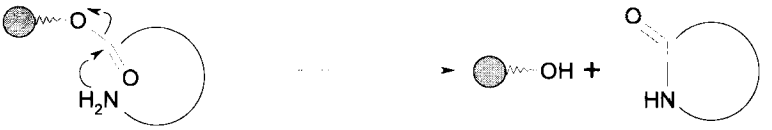


Figure 1. The principle of cyclative cleavage exemplified by the formation of a lactam from a solid phase-bound amino acid ester.

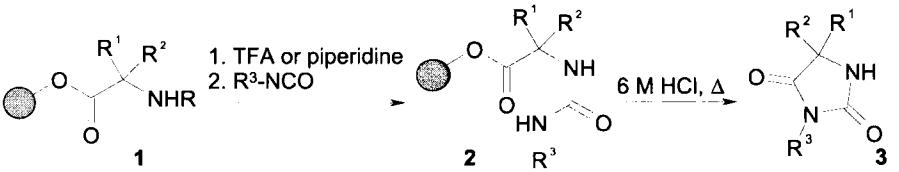
This strategy provides an additional purification step in the synthesis, as only the cyclized products are released from the solid phase. Precursors which do not have both moieties necessary for cyclization (which may occur, if the reactions leading to the precursors were incomplete), remain bound to the solid phase. In addition, products of intermolecular reactions remain bound to the polymeric support and, therefore, can simply be filtered off. This effect makes the method especially prone for macrocyclizations: in solution-phase chemistry, undesired oligomeric byproducts are often obtained from intermolecular rather than intramolecular reactions of the chain ends. However, high dilution of the substrates can reduce the amount of di- and oligomerized byproducts. Similarly, a low loading of the resins provides the same effect for solid-phase chemistry. This strategy also provides a "traceless" way of cleaving from the solid phase, as the linkage to the solid phase becomes an endocyclic moiety after cleavage. Furthermore, solid-phase chemistry normally requires strategically useless steps, as the binding to and cleavage from the solid phase do not increase the complexity of the molecule. In contrast, the cyclative cleavage approach combines the cleavage with a ring closure.

On occasion, it is difficult to differentiate between the cyclative cleavage reaction and a classical cleavage from the solid phase which is accompanied by cyclization of the substrate. In the following discussion, the examples are arranged by the resulting products rather than by mechanisms.

3.2.2 Carbon-Hetero Bond Formation

3.2.2.1 Hydantoins

The formation of hydantoins represents an early application of the cyclative cleavage strategy. The group of Hobbs DeWitt presented a synthesis starting from Merrifield resin-bound amino acid derivatives **1** (Scheme 1). These were N-deprotected and subsequently converted to ureas **2** by reaction with an isocyanate. Treatment with 6 M HCl (85–100° C, 2 h) gave hydantoins **3** in yields of 4 % to 81 %, with two dimensions of diversity [1].

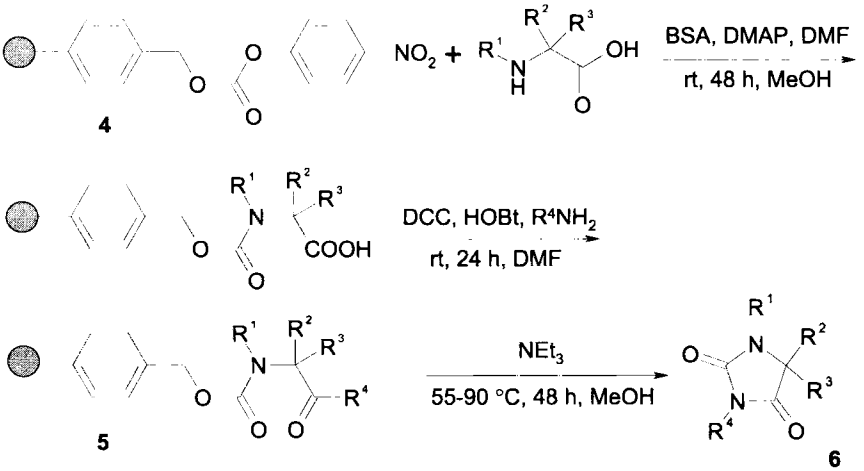


OH = Merrifield resin

R = Fmoc or *t*Boc

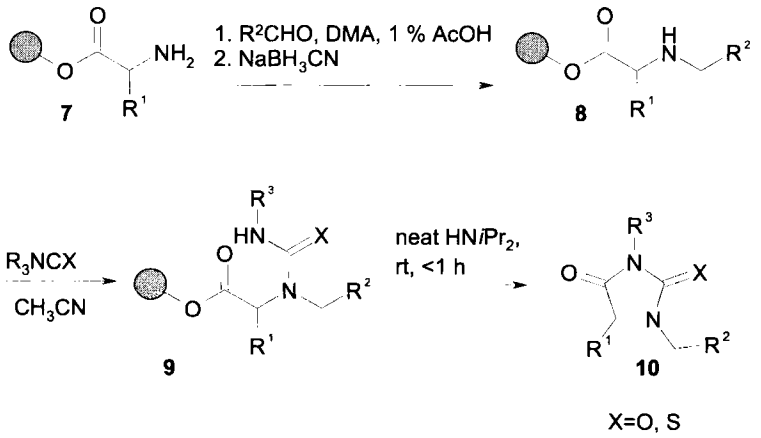
Scheme 1. Synthesis of hydantoins by cyclative cleavage of an ester bond on Merrifield resin.

Another approach to hydantoins is outlined in Scheme 2. Twenty different amino acids were N-terminally bound to a carbamate linker **4** and coupled to 80 primary amine building blocks to give amides **5**. The cyclization was performed under basic conditions with triethylamine to produce 800 hydantoins **6**. The HPLC purities ranged from 65 % to 99 %, and the yields were satisfactory, varying from 24 % to 74 %. The major advantage of this approach is that primary amines are more easily available building blocks than isocyanates [2].



Scheme 2. Synthesis of hydantoins by cyclative cleavage of a carbamate linker.

A third dimension of diversity for the generation of hydantoins can be introduced as shown in Scheme 3. After coupling an Fmoc-amino acid to Wang resin and N-deprotection to give **7**, a reductive alkylation sequence using aromatic aldehydes was performed (**8**) before the coupling of an isocyanate (**9**, X = O). The cleavage conditions (undiluted diisopropylamine, rt) to produce hydantoins **10** are reported to be exceptionally mild [3]. Other cleavage conditions reported are a refluxing mixture of $CHCl_3$/triethylamine [4].



Scheme 3. Synthesis of hydantoins with three dimensions of diversity.

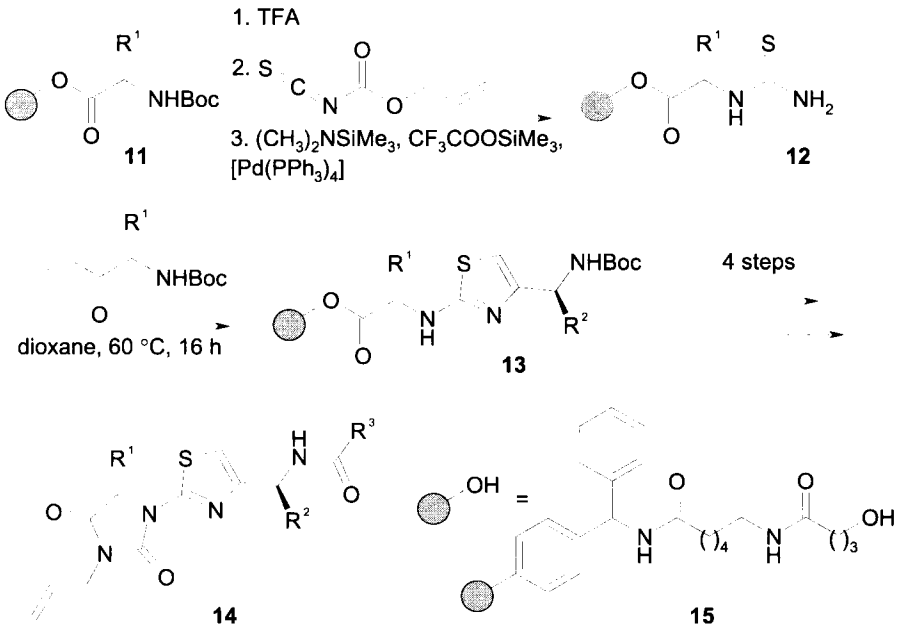
Procedure

Resin **9** (188 mg, 0.164 mmol, R^1 = Bn, R^2 = H, R^3 = substituted alkyl, X = O) was swollen in $CHCl_3$ (2 mL) / triethylamine (0.229 mL, 1.64 mmol). The mixture was heated at reflux for 72 h. The mixture was filtered and repeatedly washed with acetonitrile and CH_2Cl_2. The combined organic washes were evaporated and the residue was dried in vacuo to provide 60.8 mg (100 %) of crude product. The compound was purified by chromatography (hexane/EtOAc, 1:5) to provide 19.6 mg (32 %) **10** as a white solid [4].

Using phenylisothiocyanate in the second step (X = S) generated thioureas which cyclized slowly at room temperature without added base or preferentially at reflux in acetonitrile/ $CHCl_3$ to give thiohydantoins **10** (X = S) [4].

Scheme 4 shows another impressive example for intrinsic purification by cyclative cleavage: structurally complex thiazolylhydantoins were synthesized starting from N-protected amino acids which were bound to 6-aminohexanoic acid-derivatized benzhydrylamine resin **15**. The conjugates **11** were transformed into thiuoreas **12** which were treated with α-bromoketones to produce thiazoles **13** on the solid phase. The hydantoins **14** were prepared in four further steps by cyclative cleavage as described above. At the end of this nine-step sequence, almost **20** products were obtained, with purities generally exceeding 95 %. Cleavage conditions in this case were a mixture of dioxane/triethylamine at 60° C for 6 h [5].

Other groups also synthesized hydantoins by cyclative cleavage [6–11].



Scheme 4. Approach to complex thiazolylhydantoins.

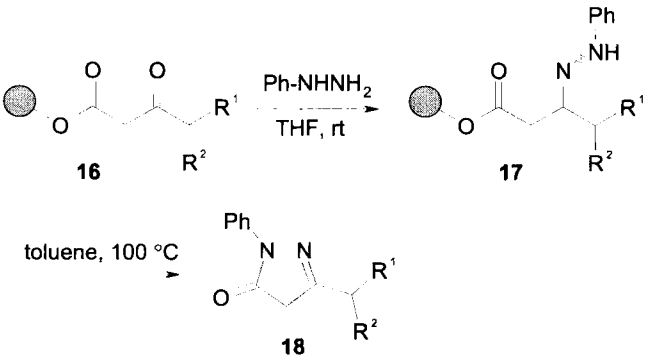
3.2.2.2 Pyrazolones

The group of Tietze described syntheses of variously substituted pyrazolones **18** starting from solid phase-bound β-ketoesters. Single or iterative alkylation of the dianion of immobilized acetoacetate with allyl-, benzyl- or alkylhalides produced a set of γ-substituted ketoesters **16** which could be transformed to the phenylhydrazones **17**. Treatment of these intermediates in toluene at 100° C produced 1-phenylpyrazolone derivatives **18** in 40–75 % yield (Scheme 5) [12].

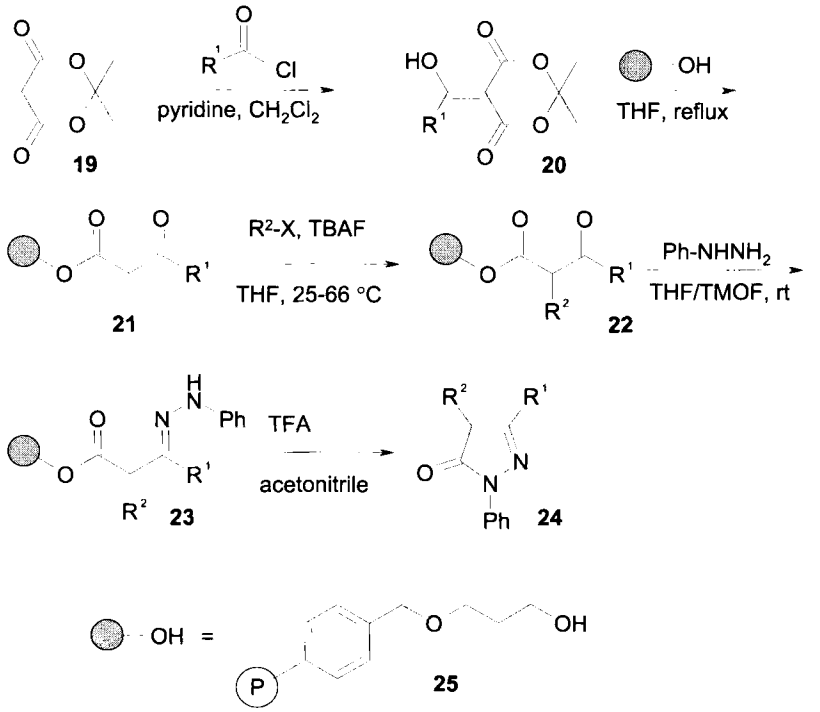
The same group reported an approach to trisubstituted pyrazolones beginning with a solution-phase acylation of Meldrum's acid **19** and resin-capturing of the intermediates **20** with the acid-insensitive resin **25**. The products **21** were α-alkylated using tetrabutylammonium fluoride (TBAF) and primary alkyl halides under strict exclusion of moisture, as the yields dropped dramatically otherwise. Treatment of the products **22** with phenylhydrazines produced the corresponding hydrazones **23**, which were cleaved from the solid phase by cyclization using 2 % TFA in acetonitrile at room temperature (Scheme 6) to form pyrazolones **24** [13].

Procedure

Resin-capturing: Acyl Meldrum's acid **20** (5 equiv.) was heated with the spacer modified polystyrene-resin **25** in THF at reflux for 4 h to give the polymer-bound β-ketoester **21**.



Scheme 5. Cyclative cleavage of pyrazolones from the solid phase.



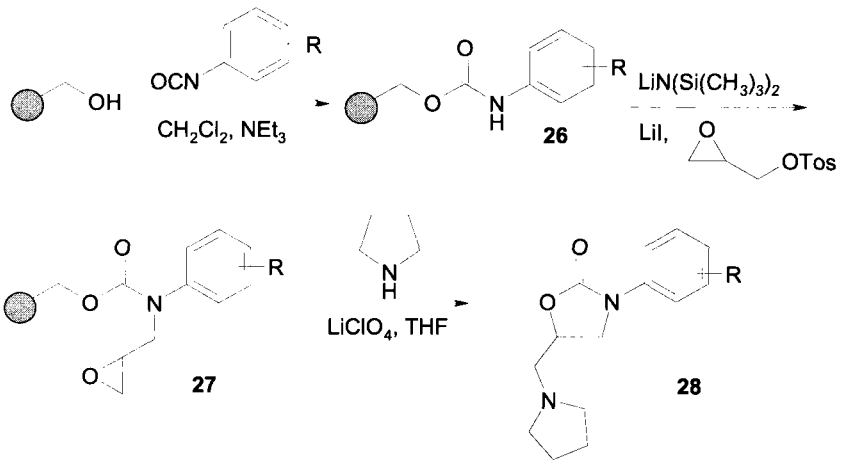
Scheme 6. Synthesis of 4,5-disubstituted pyrazolones by cyclative cleavage.

Alkylation: β-ketoester **21** was reacted with a primary bromo- or iodoalkane (36 equiv.) in the presence of 1 M TBAF in THF (26 equiv.) at rt for 3 h to give **22**. Traces of water decrease the yield dramatically and have, therefore, to be excluded.

Hydrazone formation and cyclative cleavage: Phenylhydrazine (20 equiv.) was added to a suspension of **22** in THF/trimethylorthoformiate (TMOF) (1:1) and stirred for 3 h at room temperature. The products **23** were treated with 2 % TFA/acetonitrile at room temperature for 0.5 h to give pyrazolones **24** in purities of 85–95 % and yields of 52–95 %.

3.2.2.3 Oxazolidinones

Scheme 7 outlines an approach to 3,5-substituted 1,3-oxazolidinones **28** by an interesting ring opening–recyclization–cleavage procedure. The precursors were built up on Wang resin which was transformed to carbamates **26** with aromatic isocyanates. The carbamates were N-alkylated using glycidyl tosylate and a catalytic amount of lithium iodide (**27**). The epoxide rings were opened with pyrrolidine as an exemplary example for a secondary amine and lithium perchlorate as a Lewis acid catalyst. The amino alcohols which formed cyclized spontaneously, accompanied by cleavage from the resin to give **28** [14].



Scheme 7. Approach to oxazolidinones by a ring-opening–recyclization–cleavage procedure.

Procedure

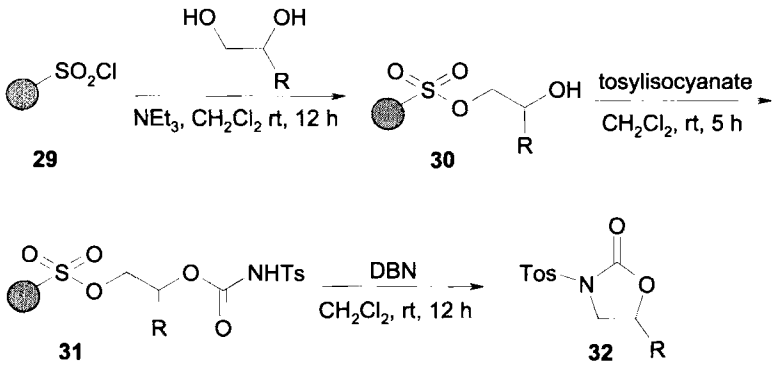
Resin-bound carbamate: To a suspension of Wang resin (1 g, 1.11 mmol/g) in dry CH_2Cl_2 (8 mL) phenyl isocyanate (6 equiv.) and a catalytic amount of triethylamine were added. The reaction mixture was stirred for 6.5 h. The resins **26** were filtered and washed with DMF (five times), DMF/CH2Cl2 (1:1, three times) and CH_2Cl_2 (five times) and dried.

Alkylation: Resin **26** (1 g, based on Wang resin, 1.11 mmol/g), lithium iodide (1 equiv.) and glycidyl tosylate (10 equiv.) were suspended in dry NMP (8 mL) and stirred for 10 min at ambient temperature under an argon atmosphere. Lithium bis(trimethylsilyl)amide (2 equiv., 1 M in THF) was added dropwise and the reaction mixture was stirred overnight.

The resin **27** was filtered and washed with DMF (10 times), DMF/CH_2Cl_2 (1:1, five times) and CH_2Cl_2 (five times) and dried under vacuum.

Cyclative cleavage: Resin **27** (R = H, 150 mg, 0.14 mmol) and lithium perchlorate (5 equiv.) were suspended in dryTHF (1.5 mL) and stirred for 5 min at ambient temperature. Pyrrolidine (58 µL, 0.7 mmol) was added and the reaction mixture stirred over night. The resin was filtered and washed with CH_2Cl_2 several times. The combined filtrates were washed with water, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give 34 mg (94 %) of **28** (R = H).

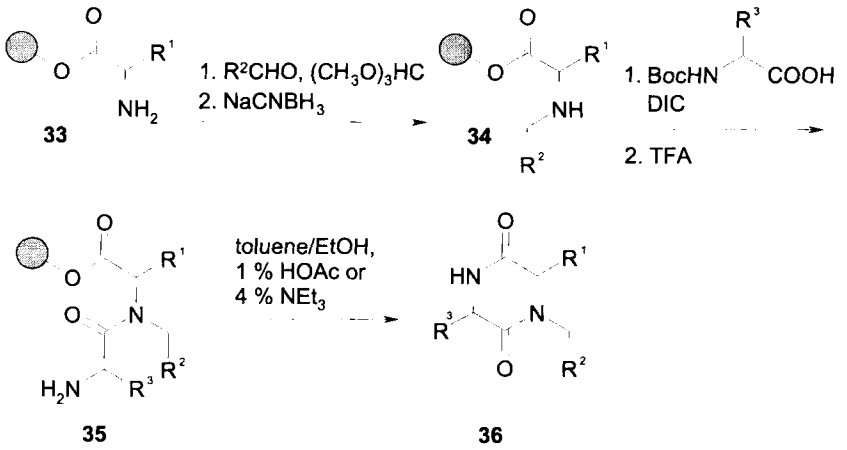
Another approach to oxazolidinones is shown in Scheme 8. 1-Alkylated 1,2-diols were bound to chlorosulfonylated resin **29** to produce hydroxy sulfonates **30**. Treatment with tosyl isocyanate gave carbamates **31**, which were cyclized with DBN (1,5-diazabicyclo [4.3.0]non-5-ene) at room temperature yielding the oxazolidinones **32**. The base was finally removed by filtration over silica [15].



Scheme 8. Synthesis of N-sulfonylated oxazolidinones.

3.2.2.4 Diketopiperazines

The synthesis of diketopiperazines by cyclative cleavage is a well-established and often-used procedure. One approach is outlined in Scheme 9. The sequence started from TentaGel S-OH (Rapp Polymere) or PAM (NovaBiochem) resin-bound amino acids **33**, which were N-alkylated by a standard sequence of imine formation with an aliphatic or aromatic aldehyde in TMOF and subsequent reduction of the imine using $NaCNBH_3$ and methanol (aliphatic aldehydes) or acetic acid (aromatic aldehydes) as proton sources. These resins **34** were coupled to a second N-tBoc amino acid. Deprotection with trifluoroacetic acid gave the precursors **35** for cleavage. Cyclization was performed under acid or base catalysis. This synthetic sequence was used to synthesize a library of more than 1300 diketopiperazines **36**, of which some proved to be a new class of inhibitors of matrix metalloproteinases [16, 17].



33 34 35 36

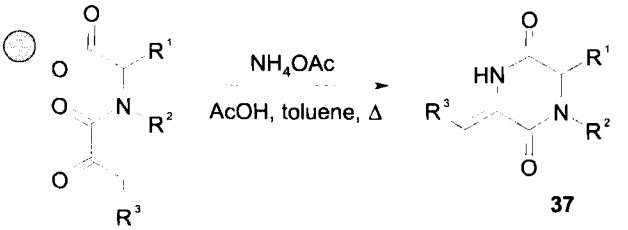
Scheme 9. Synthesis of diketopiperazines.

Procedure

*Cyclative cleavage:*The resin **35** (200 mg) was shaken in toluene or toluene/ethanol (1:1; 2 mL) in the presence of 1 % acetic acid or 4 % triethylamine at room temperature for several hours (8–12 h for acidic conditions, 2–5 h for basic conditions).The resin was washed several times with ethanol, the combined filtrates were concentrated to give **36** [16].

In a similar strategy, α-hydroxy acids were bound to substituted amino acids via a Ugi reaction. Cyclative cleavage resulted in the formation of diketomorpholines after cyclative cleavage with triethylamine/CH_2Cl_2 [16]. Similar concepts were also presented by other groups [18].

Introducing an α-ketoacid instead of a second amino acid moiety afforded almost planar 3-alkylidene-2,5-dioxopiperazines **37** after cyclization in toluene/acetic acid with ammonium acetate as source of ammonia (Scheme 10) [19].

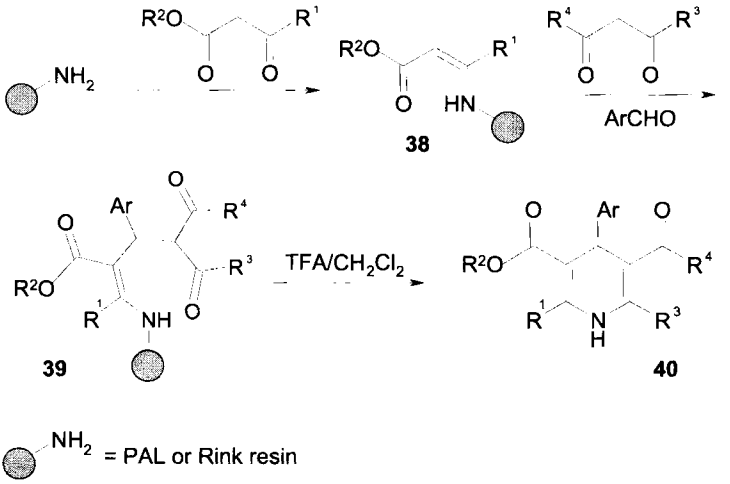


37

Scheme 10. Synthesis of virtually planar 3-alkylidene-diketo-piperazines.

3.2.2.5 Dihydropyridines

A synthesis of biologically highly potent dihydropyridines (DHPs) is shown in Scheme 11. β-Ketoesters were bound to PAL or Rink resin to give the corresponding enamines **38**. Reaction with aromatic aldehydes and β-diketones or β-ketoesters (R^4 = OR) gave the precursors for cyclization **39**. Cyclative cleavage was performed in a mixture of TFA/CH_2Cl_2. The authors assumed that the products **40** were formed by a cyclization of the precursors with a subsequent cleavage from the resin, although they did not exclude that cleavage from the resin might also occur before cyclization [20].



Scheme 11. Approach to dihydropyridines.

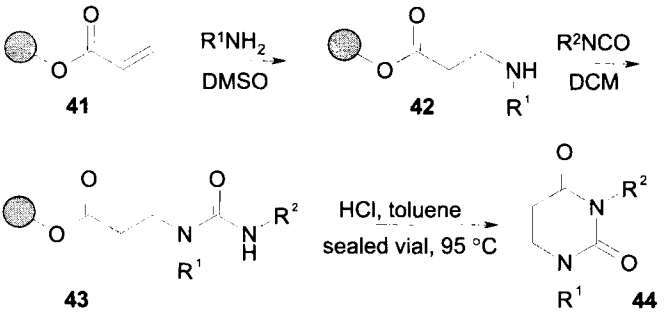
Procedure

*Preparation of enamino esters **38**:* A free amino PAL or Rink resin (0.23 mmol) was shaken with an appropriate β-ketoester (6.9 mmol) and 4 Å molecular sieves (1 g) in CH_2Cl_2 (4 mL) for 3 days at rt. The product **38** was filtered and washed three times each with $CHCl_3$, ethyl acetate and diethyl ether and dried in vacuo.

Preparation of DHPs: Enamino ester **38** (0.023 mmol) and an appropriate β-ketoester (1 mmol) (or acetylacetone; 1 mmol) and 4-nitrobenzaldehyde (1 mmol) and 4 Å molecular sieves (250 mg) in dry pyridine (0.75 mL) were stirred at 45° C under argon in a sealed vial for 24 h. The resin was filtered and washed four times each with methanol and ethyl acetate and dried in vacuo. The resulting resin **39** was stirred under argon with 3 % TFA/CH_2Cl_2 (1 mL, 45 min, Rink resin) or 95 % TFA/THF (1 mL, 1.5 h, PAL resin). Degassed acetonitrile (4 mL) was added and the supernatant layer separated and quickly evaporated in vacuo with addition of toluene to ensure complete TFA removal to yield the DHP **40**.

3.2.2.6 5,6-Dihydropyrimidine-2,4-diones

These core structures are accessible as shown in Scheme 12. Michael addition of primary amines to Wang resin-bound acrylic acid **41** produced β-aminoesters **42**, which were reacted with isocyanates to give precursor ureas **43** for cyclization. Treatment of **43** with TFA/water (19:1) at room temperature cleaved mainly the noncyclized precursors, whereas cyclized products **44** were formed by treatment under rather harsh conditions (toluene saturated with HCl, sealed vial, 95° C) and isolated in yields varying from 13 % to 76 % [21].



Scheme 12. Synthesis of 5,6-dihydropyrimidine-2,4-diones.

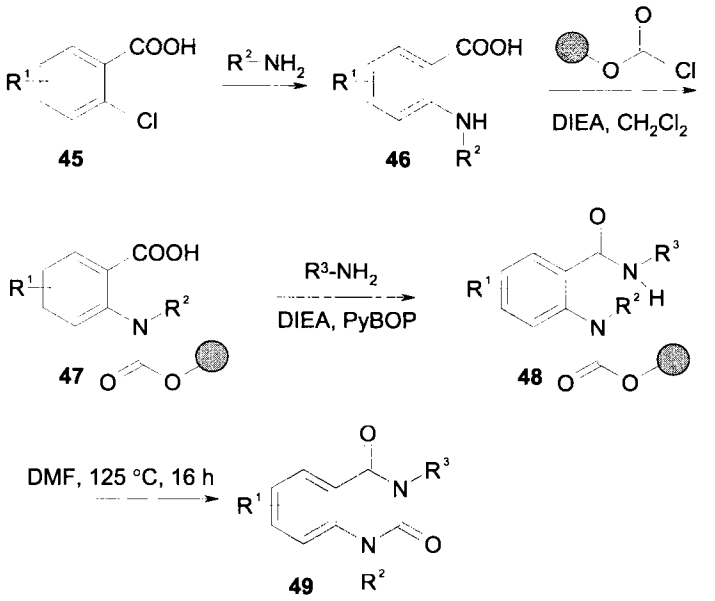
Procedure

A suspension of Wang resin (0.5 g, 0.88 mmol/g) in 4 mL of dry CH_2Cl_2 was treated twice with triethylamine (200 µL) followed by acryloyl chloride (100 µL) and allowed to stir for 2 h at rt. After filtration, the resin **41** was washed three times each with the following solvents: CH_2Cl_2, methanol, DMF, methanol, DMSO. The resin **41** was treated with DMSO (2 mL) and benzylamine (0.28 g, 2.6 mmol) and allowed to stir for 24 h. The resin **42** (R^1 = Bn) was washed three times each with DMSO, methanol, CH_2Cl_2 and dried. The resin **42** (0.42 g, 0.31 mmol) was suspended in CH_2Cl_2 (3 mL) and reacted with phenyl isocyanate (0.1 g, 0.8 mmol) at room temperature for 4 h and washed three times each with CH_2Cl_2, methanol, CH_2Cl_2 and diethylether to afford **43**. This resin was placed in a glass vial with 4 mL of a saturated solution of HCl in toluene, capped and heated to 95° C for 4 h. The resin was filtered and washed three times with methanol and CH_2Cl_2. The combined filtrates were concentrated, the crude product was purified by silica gel chromatography (diethylether/CH_2Cl_2, 1:1) to afford 39.7 mg (46 %) of **44** (R^1 = Bn, R^2 = Ph).

3.2.2.7 2,4(1H,3*H*)-Quinazolinediones

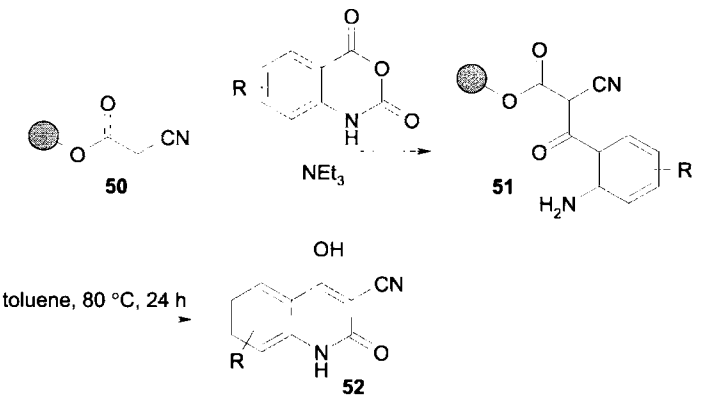
The synthesis of this scaffold requires a set of diverse anthranilic acids **46** of which only a few are available commercially. A variety of these was prepared by nucleophilic substitution of 2-

chlorobenzoic acid **45** with a range of primary amines (alkyl, benzyl, phenyl). These anthranilic acids **46** were bound to a polystyrene/ triethyleneglycol chloroformate resin via the amine group (**47**). Amidation of the carboxylic acid function gave **48** and reaction at 125° C in DMF gave the cyclized product **49** (Scheme 13) [22].



Scheme 13. Synthesis of 2,4(1*H*,3*H*) quinazolinediones.

Other cleavage conditions reported were methanol/triethylamine at 60° C to give quinazolinediones in purities of >80 % [23].



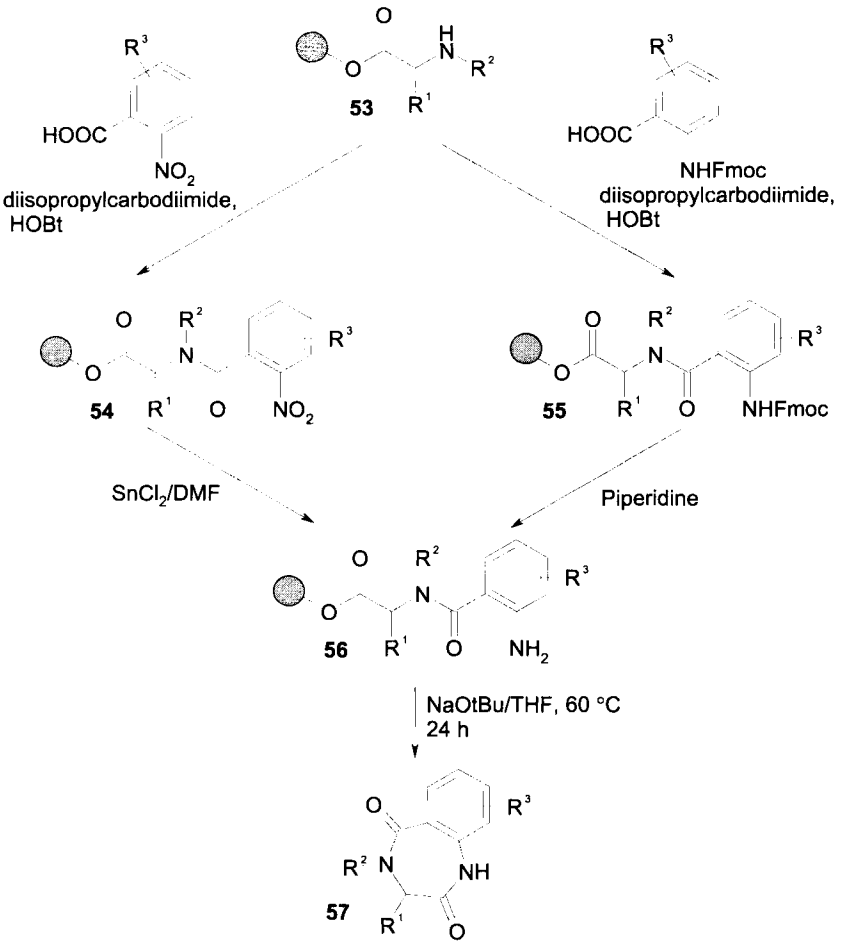
Scheme 14. Synthesis of 4-hydroxyquinolin-2(1*H*)-ones.

3.2.2.8 4-Hydroxyquinolin-2(1*H*)-ones

Wang resin-esterified cyano acetic acid **50** is an appropriate precursor for the synthesis of these scaffolds. C-Acylation with a number of isatoic anhydrides provided a set of intermediates **51**, which cyclized on heating in toluene to give hydroxyquinolinones **52** in yields of 22 % to 65 %, and purities of 72 % to 97 % (Scheme 14) [24].

3.2.2.9 1,4-Benzodiazepine-2,5-diones

The approach to these heterocycles was achieved using two similar strategies. Fmoc amino acid-derivatized Wang resins were N-deprotected (**53**) and coupled with either o-nitroben-

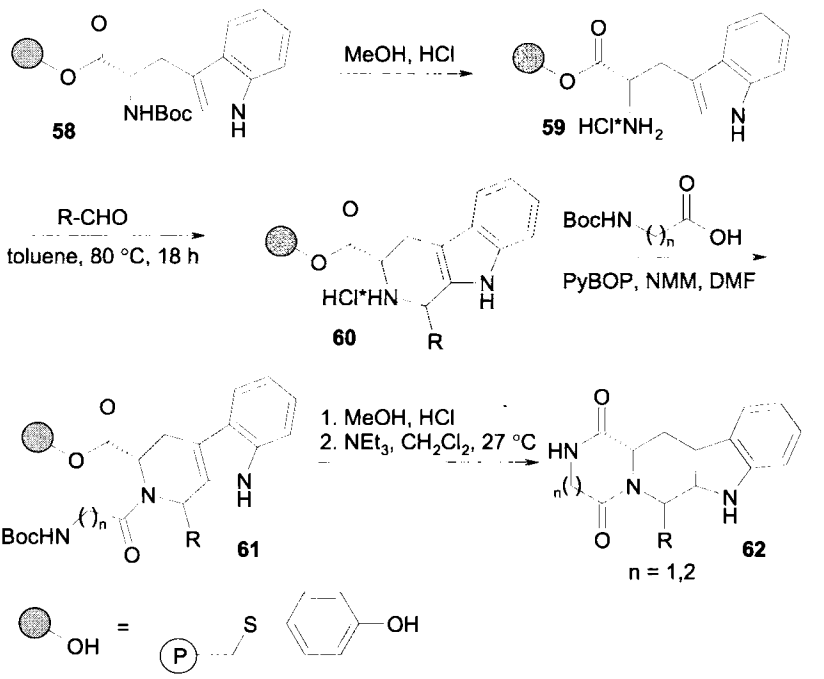


Scheme 15. Synthesis of 1,4-benzodiazepine-2,5-diones.

zoic acid or N-Fmoc anthranilic acid (**54** and **55**). Reduction of the nitro group with 2 M $SnCl_2$/DMF or Fmoc-cleavage with piperidine/DMF, respectively, produced **56** which was cyclized with NaOtBu/THF at 60° C. Extraction of the raw materials yielded 11 different 1,4-benzodiazepine-2,5-diones **57** in 45–80 % yield and an average purity of 90 % (Scheme 15) [25].

3.2.2.10 Tetrahydro-β-Carboline Derivatives

As outlined in Scheme 16, t-Boc-tryptophan linked to acid stable phenyl thioether resin **58** proved to be a suitable starting material for the synthesis of tetracyclic β-carboline derivatives. The t-Boc group was cleaved with MeOH/HCl to give **59**. Reaction with various aldehydes (aliphatic, aromatic without electron-donating groups in the 2- or 4-position of the ring which would reduce the electrophilicity of the intermediate) gave the corresponding imines which immediately cyclized to the tetrahydro-β-carbolines **60** under the reaction conditions (toluene, 80° C) in a Pictet–Spengler reaction. Coupling of a further glycine or β-alanine moiety produced **61**, removal of the Boc protective group and treatment with triethylamine in dichloromethane at room temperature gave six- and seven-membered bis-lactams annellated to the β-carbolines, **62** [26].



Scheme 16. Synthesis of annellated tetrahydro-β-carbolines.

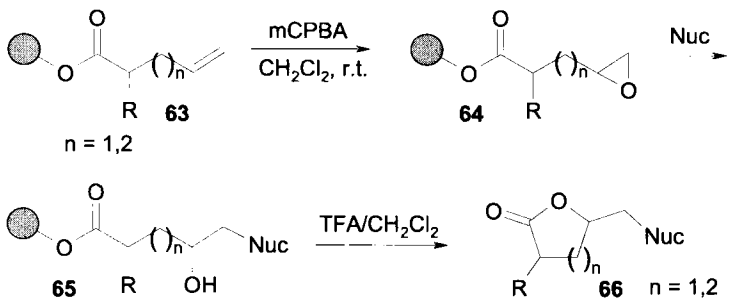
Procedure

Formation of β-carbolines ***60****:* A solution of 3-benzyloxybenzaldehyde (1.62 g, 7.7 mmol) in toluene (10 mL) was reacted with **59** (1.7 g, 1.3 mmol) at 80° C for 18 h. The mixture was cooled to rt, filtered and washed with CH_2Cl_2 to yield **60** (R = 3-BnO-Ph).

Synthesis of lactams ***62****:* Resin **60** (R = 3-BnO-Ph, 0.15 g, 0.11 mmol) was suspended in dry DMF (0.15 mL) and treated with NMM (49 μL, 0.45 mmol), Boc-β-alanine (64 mg, 0.34 mmol) and PyBOP (0.23 g, 0.45 mmol). The mixture was shaken at 27° C for 18 h, filtered, washed thoroughly with DMF and CH_2Cl_2, then allowed to react with 3 % methanolic HCl (1.2 mL) at 27° C for 4 h. The resin was rinsed with CH_2Cl_2 and then shaken with 50 % triethylamine/CH_2Cl_2 at 27° C for 4 h. The resin was filtered and washed with CH_2Cl_2. The combined washings were concentrated in vacuo to provide **62** (25 mg, 66 %, R = 3-BnO-Ph, n = 2) as a white solid.

3.2.2.11 Lactones

Lactones are common subunits in natural products and are therefore of high biological relevance. An approach to γ- and δ-lactones starts from Merrifield resin-bound w-alkenoic acids **63** (Scheme 17). Epoxidation and nucleophilic ring opening of the oxiranes produced the hydroxy acids **65**, which cyclized on treatment with trifluoroacetic acid to give five- and six-membered lactones **66**. Treatment of the epoxides **64** with trifluoroacetic acid provided the lactone **66** (Nuc = OH) [27].



Scheme 17. Synthesis of variably substituted lactones.

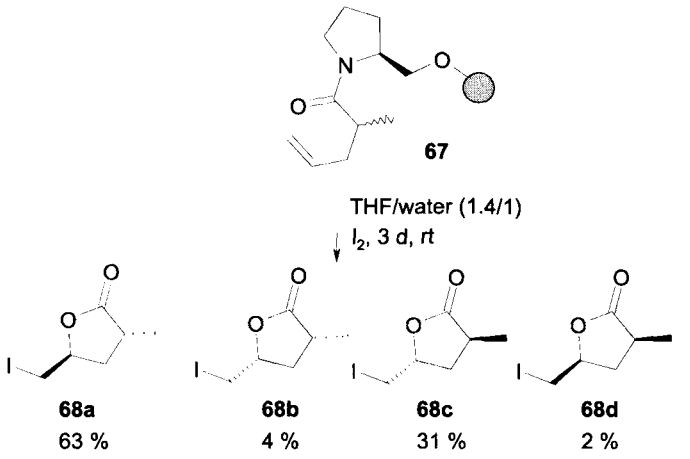
Procedure

A solution of mCPBA (5 equiv.) in dry CH_2Cl_2 (15 mL) was slowly added to a suspension of resin **63** (R = H,Me, n = 1,2) (600 mg, approx. 1.02 mmol) in dry CH_2Cl_2 (3 mL) at room temperature under inert gas. After shaking for 48 h, the reaction mixture was filtered and the resin **64** was repeatedly washed and dried.

Phenylthiomethyl lactones: PhSNa (3 equiv.) (generated by treatment of NaH in dry DMF with an excess of PhSH) was added to resin **64** (n = 1, R = H, 600 mg, 1.02 mmol) in dry DMF (8 mL) at 0° C and the mixture was shaken for 12 h at rt. After cleavage with

TFA/CH_2Cl_2, (1:1, 16 mL, rt, 2 h) the solution was filtered from the resin, concentrated to dryness and analyzed by GC. Purification of the residue by silica gel chromatography (CH_2Cl_2/EtOAc, 4:1) gave **66** (Nuc - = PhS -, R = H, n = 1) (67 %).
Hydroxymethyl lactones: TFA/CH_2Cl_2 (1:1, 16 mL) was added to resin **64** (R = H, n = 1) and shaken for 2 h. The resulting solution was filtered from the resin and concentrated to dryness. Purification of the residue by silica chromatography (CH_2Cl_2/EtOAc, 1:4) gave **66** (Nuc - = OH -, R = H, n = 1) (57 %).

A diastereoselective approach to γ-butyrolactones is presented in Scheme 18. 4-Pentenoic acid was coupled to Merrifield resin via prolinol as a chiral linker unit. α-Methylation and treatment of the amides **67** with iodine in THF/water mixtures liberated substituted (butyrolactones **68 a–d** as mixture of mostly *trans*-diastereomers [28].

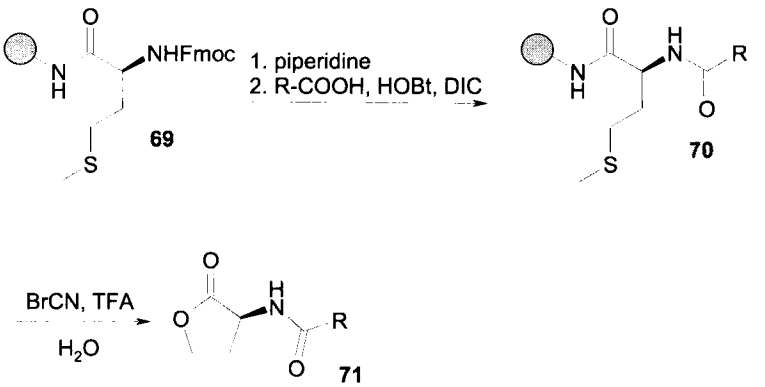


Scheme 18. Diastereoselective synthesis of γ-lactones.

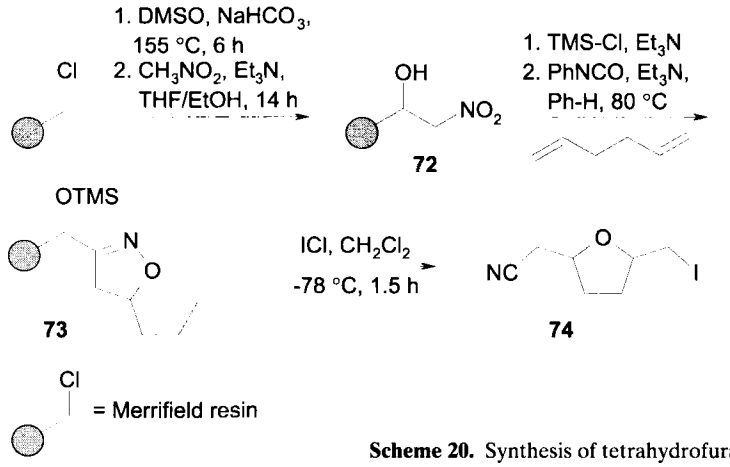
A synthesis of homoserine lactones is shown in Scheme 19. Fmoc-methionine was coupled to aminomethylated polystyrene (**69**). Fmoc-cleavage and derivatization with a variety of acids produced a set of nine compounds **70**. Cyclization was effected with cyanogen bromide/TFA/$CHCl_3$/H_2O to give homoserine lactones **71** in 32–53 % yield [29].

3.2.2.12 Tetrahydrofurans

An approach to 2,5-disubstituted tetrahydrofurans is outlined in Scheme 20. Solid phase-bound 2-nitroethanol **72** was synthesized in two steps from Merrifield resin. TMS protection and reaction with phenylisocyanate in the presence of 1,5-hexadiene gave the dihydroisoxazoles **73** in a 1,3-dipolar cycloaddition of the nitriloxide formed by dehydration of the nitroalkane. Treatment with ICl at –78° C introduced a "ring closing–ring opening" sequence (electrophilic cyclization) which resulted with cleavage from the resin under formation of tetrahydrofuran **74** in 40 % yield as a mixture of diastereomers [30, 31].



Scheme 19. Synthesis of enantiomerically pure homoserine lactones.



Scheme 20. Synthesis of tetrahydrofurans.

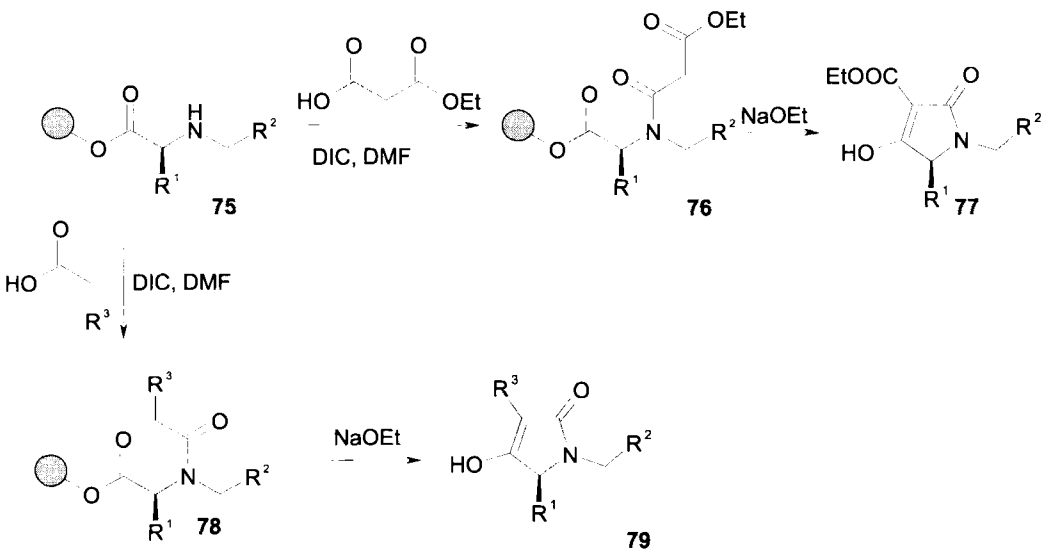
3.2.3 Formation of C-C Bonds

Unlike carbon-hetero bonds, carbon-carbon bonds do not show obvious retrosynthetic cuts; hence, formation of the latter enhances significantly the (structural) complexity of a molecular scaffold. The methods presented in the following sections combine the formation of carbon-carbon bonds with the cyclative cleavage approach.

3.2.3.1 Tetramic Acids

Tetramic acids are substructures of natural products with antimicrobial activity. An access to these structures starts from Wang resin-bound Fmoc-protected amino acids which were de-

protected and reductively alkylated. These intermediates **75** were transformed into amides, for example with malonic acid monoesters or arylacetic acids (**76** and **78**, respectively). Cyclative cleavage was induced with 0.1 M NaOEt at 85° C and gave substituted tetramic acids **77** and **79** in yields and purities of generally >95 % (Scheme 21) [32].



Scheme 21. Synthesis of tetramic acids.

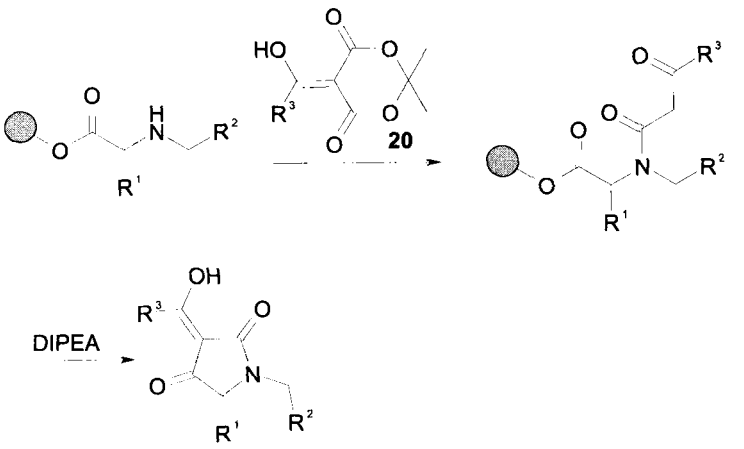
Procedure

Cyclative cleavage: To resins **76** or **78** (0.108 mmol) was added 0.1 M NaOEt (2.1 mL, 0.216 mmol) and the material was heated with vigorous shaking at 85° C for 24 h. The mixtures were cooled to rt and filtered, and the resins were repeatedly washed with ethanol and CH_2Cl_2. The combined washings were evaporated and the crude residue was dissolved in methanol (2 mL) and eluted through a COOH ion-exchange column with MeOH to yield **77** and **79** (100 %).

When N-acylation of the amino acid derivatives was performed with acylated Meldrum's acid **20**, the products were 3-acyl-tetramic acids **80**. The best conditions for cleavage in this case are DIPEA/dioxane (3:7) at 80° C (Scheme 22) [33].

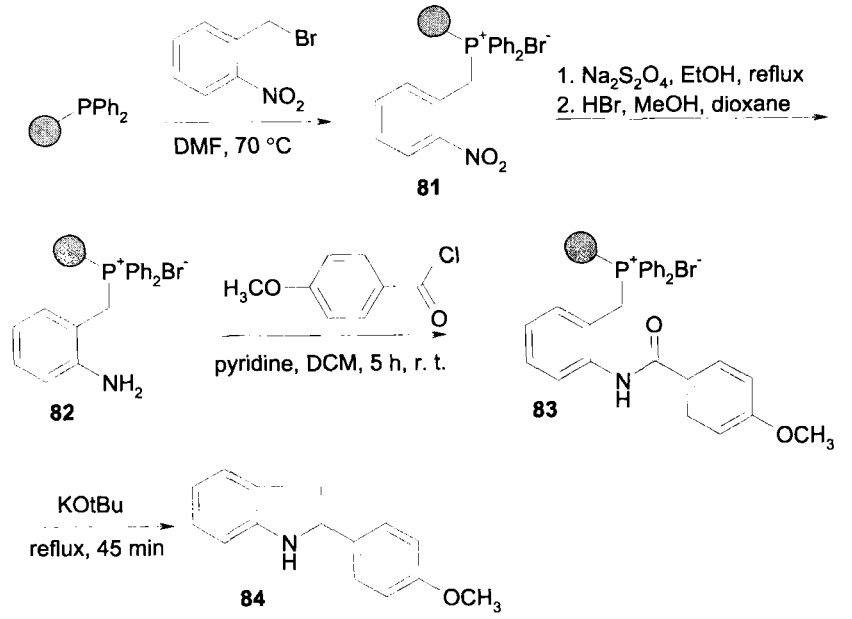
3.2.3.2 Wittig-Type Reactions

The formation of phosphor moieties able to couple to carbonyl groups turned out to be a versatile method for the cyclative cleavage approach under formation of C-C double bonds. The stoichiometric phosphine oxide byproducts which must be separated from the products when performing the reaction in solution phase remain bound to the solid phase and can, there-



Scheme 22. Synthesis of 3-acyl tetramic acids.

fore, simply be filtered off. As shown in Scheme 23, polymer-bound triphenylphosphine was transformed into the phosphonium salt **81** with 2-nitrobenzyl bromide. Reaction with $Na_2S_2O_4$ in ethanol afforded the corresponding aniline **82** which was treated with HBr to restore the bromide counter ion. The aniline **82** was acylated with 4-methoxybenzoylchloride to give the amide **83**. Treatment with KOtBu under strict exclusion of moisture produced the indole **84** with concomitant cleavage from the solid phase [34].

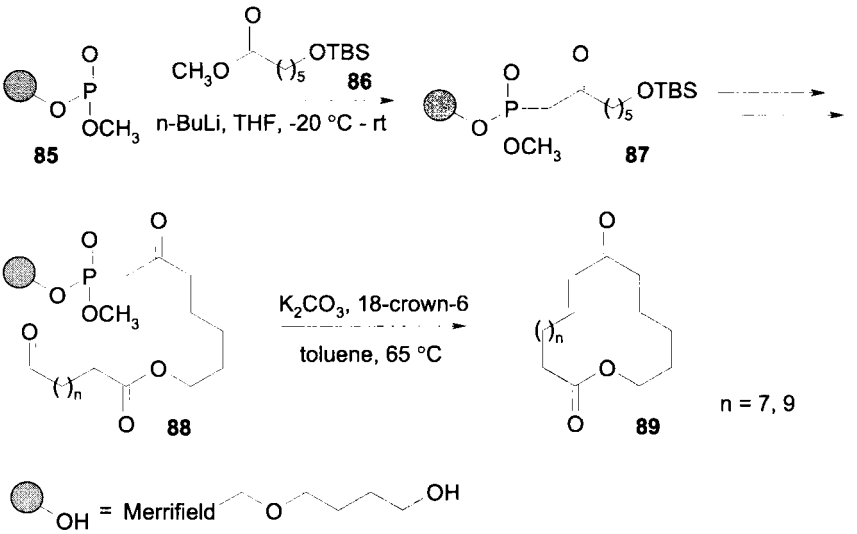


Scheme 23. Synthesis of indoles by cleavage from solid support via the Wittig reaction.

Procedure

Formation of indoles by intramolecular Wittig reaction: A suspension of **83** (500 mg) in toluene (25 mL) and DMF (5 mL) was distilled until approx. 5 mL distillate was collected. KOtBu (134 mg, 1.2 mmol) was added and the mixture was heated under reflux for 45 min. After cooling, the mixture was acidified with 2 N HCl, filtered through Kieselguhr, and the polymer washed well with CH_2Cl_2. The filtrate was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness to yield **84** (135 mg, 78 %).

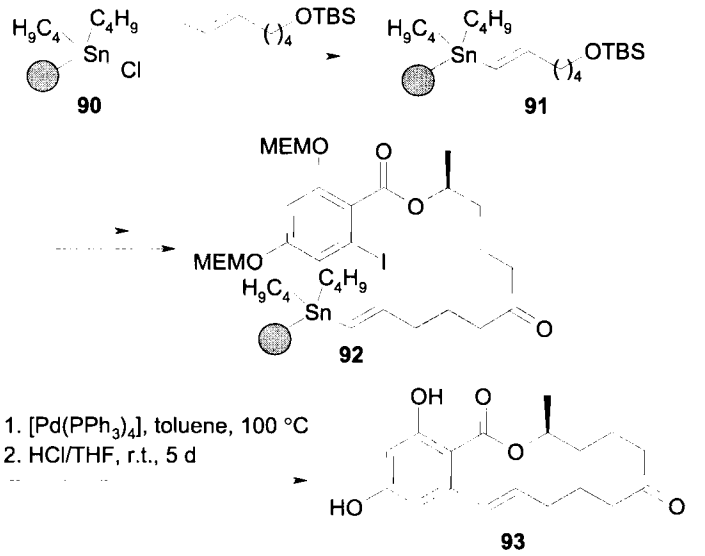
Nicolaou presented the synthesis of 18- and 20-membered macrocycles **89** from solid phase-bound phosphonate **85**. Condensation with ester **86** produced the intermediate **87** which was converted to the precursors **88** for cyclization in a fivestep sequence. Reaction of **88** with K_2CO_3 gave the macrocycles **89** in 58 % and 62 % yield, respectively (Scheme 24) [35].



Scheme 24. Synthesis of macrocycles by cleavage from solid support via the Wittig reaction.

3.2.3.3 Stille Reactions

The Stille reaction is extremely useful to form diene and stilbene moieties, but suffers from the drawback of requiring poisonous tin compounds. Once again, the polymeric support provides the opportunity to eliminate the tin moieties simply by filtration. Nicolaou demonstrated the synthesis of the 14-membered macrocycle (S)-Zearalenon **93** which started from solid phase-bound tin chloride **90**. Coupling to a vinyl lithium compound generated **91**, and two more steps produced the precursors for cyclization **92**. Cyclative Stille coupling finally gave Zearalenon **93**. Remarkably, only the E-isomers came off the solid phase by cyclization, whereas the Z-isomers did not cyclize and remained bound to the solid phase (Scheme 25) [36].



Scheme 25. Cleavage from solid support by a Stille coupling reaction.

3.2.3.4 Ring Closing Metathesis

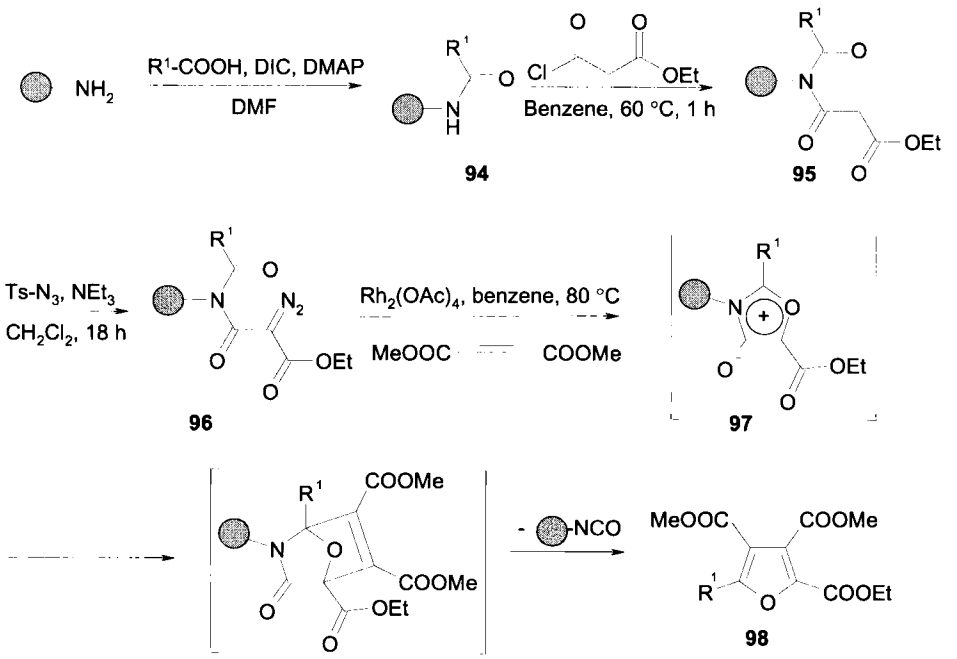
The contribution of W. Bannwarth in this book (Chapter 3.1.3.3) provides a good review of cyclative cleavage using olefin metathesis; therefore, this reaction is not described in detail here.

3.2.4 Miscellaneous

Some of the concepts of cyclative cleavage follow a multi-bond-formation-breaking strategy in the essential cyclization step and thus were not included in the preceding sections.

3.2.4.1 Furans

A rhodium-mediated carbene addition is the key step in a synthesis of furans. The precursors were synthesized on TentaGel-NH_2 resin, which was transformed into an amide **94**. Subsequent formation of imides **95** with malonylchloride and reaction with tosylazide gave solid phase-bound diazoimides **96**. Reaction with $Rh_2(OAc)_4$ in presence of electron-deficient acetylenes produced substituted furans **98** via the intermediate isomünchnone **97** and a sequence of a [2+3]-cycloaddition to the acetylene and an subsequent cycloreversion sequence. The yields of the reaction varied from 50 % to 70 % (Scheme 26) [37].



Scheme 26. Synthesis of furans via isomuenchnone intermediates.

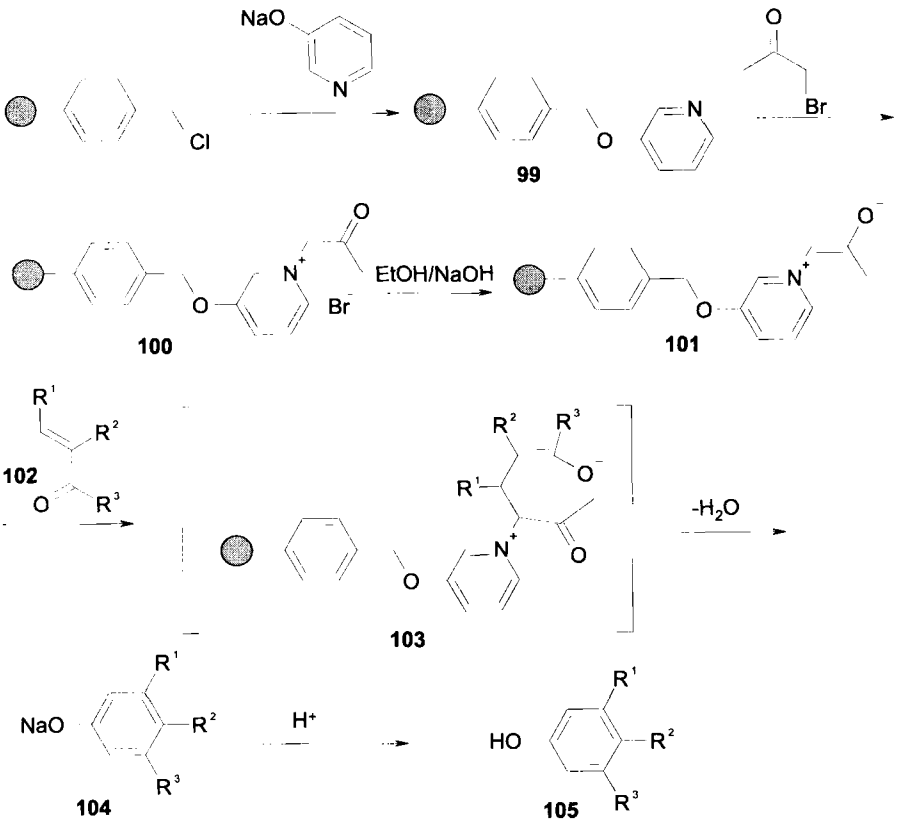
3.2.4.2 Phenols

An approach to carbocyclic arenes by cyclative cleavage was presented only recently [38]. Merrifield resin was etherified with 3-hydroxypyridine (**99**), and the pyridine moiety was quaternized with bromoacetone to yield **100**. Formation of an ylide **101** with NaOH/ethanol and subsequent reaction with a chalcone **102** produced the intermediates **103** after a Michael addition. A subsequent condensation reaction released the phenolates **104** from the solid phase under restoration of the pyridine moiety. Acidic work-up and filtration furnished 3,4,5-trisubstituted phenols **105** in yields varying from 52 % to 85 % (Scheme 27). Examples are shown in Table 1.

Procedure

*Preparation of **100**:* A solution of the sodium salt of 3-hydroxypyridine (22 g, 188 mmol) in DMA (100 mL) was added to Merrifield resin (20 g, 2.91 mmol/g) and stirred at 60–70° C for 12 h. The resin **99** thus obtained was filtered and repeatedly washed with THF, THF/water (1:1), THF, CH_2Cl_2, and dried. Resin **99** (24.7 g) was added to the solution of 2-bromoacetone (16 g, 116 mmol) in acetonitrile (200 mL) and stirred at 70–78° C for 40 h. Resin **100** was washed as described above.

*Preparation of phenols **105**:* Resin **100** (600 mg) and the corresponding chalcone **102** (0.29 mmol) were added to the solution of NaOH (14 mg) in EtOH (10 mL) and the mixture was stirred under reflux for 1 h. The resin was filtered off and washed as described



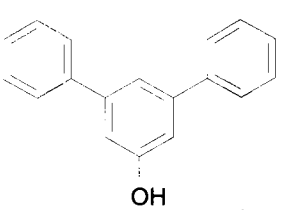
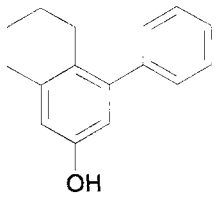
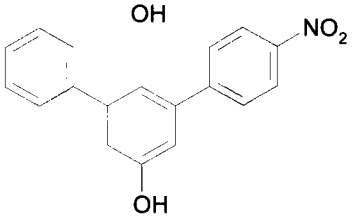
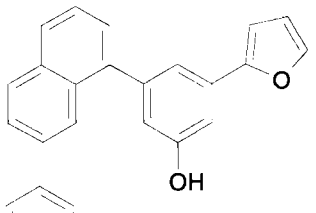
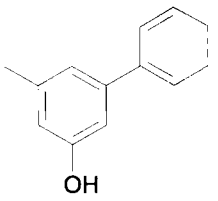
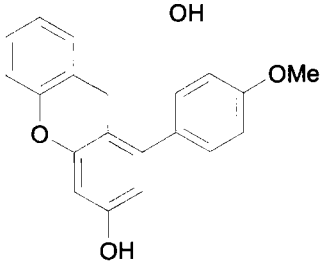
Scheme 27. Synthesis of homoaromatic phenols by cyclative cleavage.

above. The combined organic layers were acidified (10 % aqueous HCl) to pH 3–4, the organic layer was washed with $NaHCO_3$, water, and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by silica chromatography (hexane/EtOAc) to yield pure **105**.

3.2.5 Summary

The approach of cyclative cleavage represents a highly versatile tool in solid-phase organic chemistry as it permits the synthesis of a large variety of molecular scaffolds, while its intrinsic purification properties provide the ability to synthesize highly pure compounds, even after a large number of synthetic steps. Furthermore, even macrocyclic systems can be synthesized in high purity and not be contaminated by oligomeric byproducts, as these remain bound to the solid phase.

Table 1. Examples of phenols synthesized. a) Isolated yield; b) Determined by gas chromatography/ mass spectrometry

Yield[a] (Purity[b])		Yield (Purity)	
	85 (94)		52 (79)
	63 (97)		61 (99)
	80 (94)		53

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3.3 C-C Bond-Forming Reactions

Wolfgang Brill

3.3.1 General

A major effort of combinatorial chemistry development over the past few years has been devoted to synthetic methodology for the preparation of nonpeptidic entities by multiparallel synthesis schemes on solid supports. In particular, the development of reliable procedures with a wide scope for the formation of C-C bonds is of great importance. The following chapter presents some standard key transformations requiring special experimental know-how.

The described reaction types could be grouped as:
1) Transition metal-mediated vinylations and arylations (Section 3.3.2)
2) Reactions involving Grignard reagents, organolithium and organozinc reagents (Section 3.3.3)
3) Olefin metathesis (Section 3.3.4)
4) Generation of carbanions on solid phase (Section 3.3.5)
5) Radical reactions on solid phase (Section 3.3.6)
6) The Pauson–Khand reaction (Section 3.3.7)

The examples for these key transformations may serve as a starting point in reaction optimization efforts directed to more complex molecules. Applications of some of these key transformations are seen in other sections of the book as an integral part of more complex synthetic tasks.

3.3.2 Transition Metal-Mediated Vinylations and Arylations

Very attractive sets of C-C bond-forming reactions are those mediated by transition metals. The biaryl synthesis, being extensively reviewed [1, 2], has been of great importance for combinatorial libraries, due to the large number of biologically active compounds bearing biaryl moieties. In particular, methods involving transition metal catalysts as integral part of rather complex "reagent cocktails" are receiving great attention.

3.3.2.1 Suzuki Couplings

One of the most popular C-C bond-forming reactions is the Suzuki reaction, which has been the subject of recent reviews [2]. Here, an aromatic iodide [3–12], bromide [4–7, 13–19], chloride [17, 20, 21], tosylate [22], triflate [23, 24] fluorosulfonate [24], diazonium salt [25–28] or iodoso species is allowed to react with an arylboronate or arylboronate ester [3, 4, 7, 22, 23]. The Suzuki coupling has also been performed with vinylboronic esters or 9-alkyl 9-borabicy-

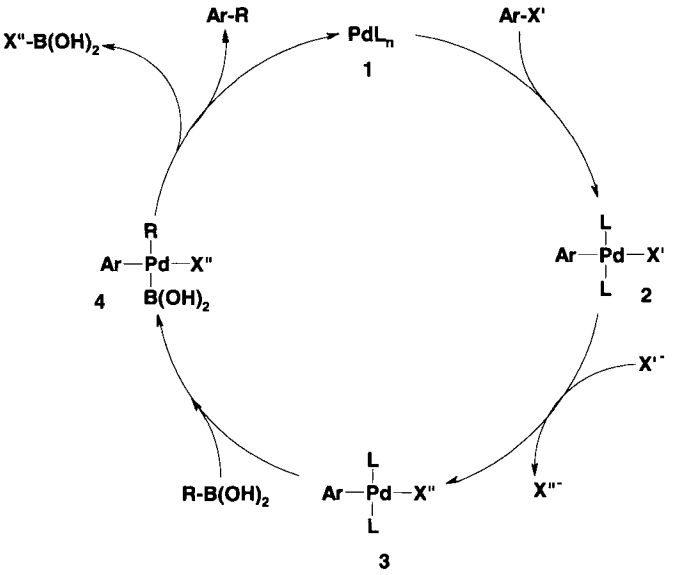
clononanes [9, 23, 29]. The reaction usually requires palladium catalysis. In case of aromatic tosylates [22] or arylchlorides, Ni catalysts have been used [20, 21] where Pd catalysts were found to be less effective. Some chloro substituents of aromatic heterocycles, known to be displaced readily by nucleophiles such as in aminochloro pyrimidines, may also allow Pd-mediated aryl displacement. The aromatic halides display the following order of reactivity in Pd-catalyzed Suzuki cross-couplings $Ar\text{-}N_2^+BF_4^- > Ar\text{-}I >> Ar\text{-}Br \geq Ar\text{-}OTf >> Ar\text{-}Cl$ [28–30]. Thus, chloro iodoaryls may be substituted selectively on the iodo moiety in almost quantitative yields. Among the catalysts used, $Pd(PPh_3)_4$ and the air-stable $Pd(OAc)_2$ are the most widely used. Various bases have been used as co-catalysts, among them being aqueous Na_2CO_3 [8, 16], K_2CO_3 [9, 10, 31], $KHCO_3$ [31], $Ba(OH)_2$ [28], NEt_3, CsF [32], TBAF, [33], KF [9] and K_3PO_4 [7, 9, 20, 21, 23]. If aryl iodides are used, KF and K_3PO_4 are in particular very attractive bases. Their presence is tolerated by hydrolytically labile moieties such as carboxylic esters. Surprisingly, the latter base is even effective in coupling reactions involving a three-phase system with the aryl halide on a polystyrene support, dioxane as a liquid phase, and the base as second solid phase. Diazonium salts react with arylboronates in alcohol without additional base, but these couplings may follow a different mechanism [25, 27, 28, 34].

Some limitations of the Suzuki coupling lie in the availability or the synthesis of the boronate starting materials. The classical method to synthesize boronates is to react an aryl-Grignard or aryllithium compound with triisopropylborate. (Trimethylborate is difficult to purify to an extent suitable for transmetallations.) The resulting boronates have a tendency to oligomerize, thus giving hardly interpretable NMR spectra. In turn, their pinacol esters may be readily obtained and easily characterized [35]. A perhaps more attractive method may be the conversion of an arylhalide with commercially available bis-pinacolato-diboron [36]. This method was even used to generate boronates from aryl iodides on polymeric supports, where the classical method remained unsuccessful [7]. Alkyl and vinylboronic esters are accessible through hydroboration.

The Suzuki coupling is thought to follow in principle the pathway originally proposed by Suzuki et al. [37]. The cycle is initiated by oxidative addition of an aromatic halide Ar-X' to a stabilized Pd(0) species **1**. In a subsequent ligand exchange reaction the halide X' is replaced by a suitable nucleophile X", which is usually provided by the Lewis basic co-catalyst. The resulting Pd-complex **3** undergoes a transmetallation where the Ar' group is transferred from the metal boron to the metal palladium to generate an intermediate **4** having Ar, Ar', $B(OH)_2$ and X" in the coordination sphere of the palladium. Two reductive elimination steps follow, yielding Ar-Ar', X"-$B(OH)_2$ and regenerating the Pd(0) species. This cycle, though similar to cycles proposed for cross-couplings induced by other metals such as Mg [38, 39], Zn [40] and Sn [41, 42], differs by the step where the base X" is introduced in the coordination sphere of the Pd-atom. As a result the mineral base, providing X" becomes essential for the success of the cross coupling.

Four problems may be encountered in Suzuki cross-couplings:

1. The coupling of an arylboronic acid with a phenyl group of a triphenylphosphine ligand, if it is part of the Pd catalyst [43].
2. Homodimerization of boronic acids [44–46].
3. Homodimerization of arylhalides.
4. Precipitation of Pd metal and Pd-species, insoluble in organic or neutral aqueous environments even in presence of chelating agents.



Scheme 1. Catalytic cycle for Suzuki couplings. X' and X" are the leaving groups at the aromatic or vinylic coupling partner such as I, OTf or Br; MX" is a metal carbonate, hydroxide, fluoride or hydrogen phosphate added as promoter. L is a ligand, which is provided by the solvent or a phosphine.

The first problem may be circumvented by using $Pd(OAc)_2$ as catalyst [31]. This method has been shown to provide consistently high coupling yields with a variety of substrates [9, 10, 31]. Phosphine free-catalysts such as $Pd(OAc)_2$ have also been shown to be more than an order of magnitude more active than phosphine-containing complexes such as $Pd(PPh_3)_4$ [31]. A drawback of $Pd(OAc)_2$ is the somewhat greater formation of "black" Pd-species that are insoluble in organic or neutral aqueous solutions.

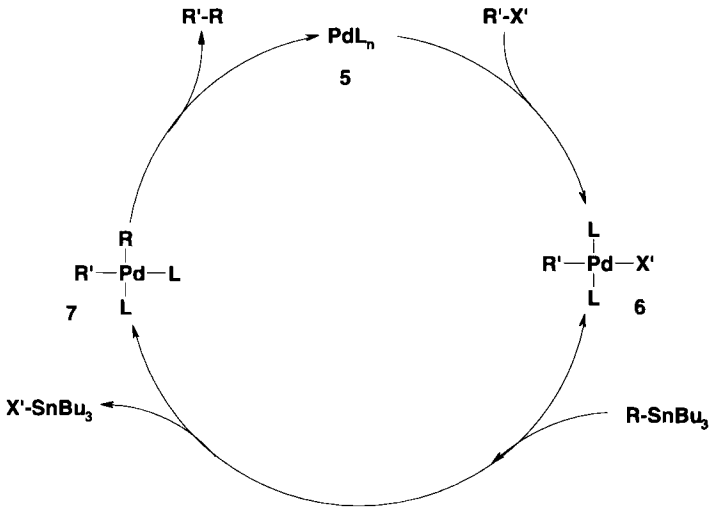
The self-coupling of boronates is a reaction which is promoted by the presence of oxygen and is thought to proceed via a catalytic cycle [47, 48]. The rigorous exclusion of oxygen limits the extent of this side reaction.

The homocoupling of aryl halides is caused by oxygen contaminant in the reaction medium. In reactions where the aryl halide is bound to a polymeric support, homocoupling may occur in spite of the site isolation effect of the polymer. Rigorous exclusion of oxygen in the coupling medium suppressed this side reaction efficiently.

The precipitation of Pd-species, which are insoluble in organic solvents containing chelating agents and neutral or basic aqueous media, are a serious problem. Unfortunately, these precipitates are soluble in 20 % TFA in dichloroethane, which is often used to liberate products from polymeric supports after combinatorial syntheses. Usually dissolution of the dried down cleavage products in neutral solvents and subsequent filtration (pore size 40 μm) removes most of the precipitates. Another method is to introduce of trioctylphosphine oxide (TOPO) into the coupling reaction, which allows solubilization of Pd-metal as colloid [49] and results in the formation of precipitates of larger particle size, effectively filterable through a P5-frit. Chromatography is inevitable to obtain metal-free material.

3.3.2.2 Stille Coupling

The Stille coupling [50] is the reaction of a trialkylaryl stannane or a trialkylvinyl stannane with an aromatic iodide, bromide or triflate. Its mechanism differs from that of the Suzuki coupling in that OH^-, RO^-, CO_3^{2-} or F^- is not required for the progression of the catalytic cycle (Scheme 2).



Scheme 2. Stille coupling. R and R' are aromatic or vinylic residues. L is a ligand provided by the solvent or an added arsine or phosphine.

This reaction allows the cross-coupling of an aryl halide with an aryltrialkyl stannane, even in the presence of a boronic ester. The latter remains unreactive because it would need a suitable nucleophile as co-catalyst [51, 52]. The Stille conditions proved very useful to afford many aryl-aryl [1, 5, 53–55] vinyl-aryl [10, 54, 56–58] and also alkyl-aryl [59] compounds bearing hydrolytically labile moieties. The reactivity order of aryl or vinyl halide components reflects the order in the Suzuki coupling, e.g., I(OH)OTs >> I > Br >> Cl [60]. Diaryl iodonium salts were reported to couple with various stannanes at room temperature under CuI catalysis. They therefore have a reactivity similar to other formal I(I) species [29]. An extremely effective catalysts is $Pd_2dba_3CHCl_3$ (dba = dibenzylidene acetone) in conjunction with $AsPh_3$ [5, 10, 11, 42, 61, 62]. In turn, other co-catalysts such as trifurylphosphine or PPh_3 were much less effective [42, 62]. Coupling reactions promoted by cuprous thiophenecarboxylate were also reported to take place at, or below, room temperature at high rates. However, they seem to be restricted to aryl halides with ortho NO_2-groups [63].

Most Stille couplings on solid phase were performed with tributylstannyl derivatives as coupling components. The trimethylstannyl derivatives are more reactive, but are also more

toxic and therefore unpleasant to work with on a daily basis. Aryl and vinyl stannanes are readily obtained from alkenyl or aryl halides using hexamethyl [64] or hexabutyl distannane [65]. The use of polyfluorinated alkyl groups around the Sn-atom allows the use of fluorinated solvents to extract the stannyl species from a reaction mixture composed either of aqueous or organic environments. This may be of great value for solution-phase aryl-aryl or aryl-vinyl cross-couplings [53, 66, 67]. Monoalkyl or monoaryl halo bis (hexamethyldisilazanyl) stannanes have been also shown to be useful precursors for aryl-aryl, vinyl-aryl, allyl-aryl and even alkyl-aryl coupling reactions. Apart from their broad scope as coupling precursors, they allow facile extraction of water-soluble Sn-species from the hydrophobic coupling products [59].

Problems associated with Stille couplings are:

1. Greater oxygen sensitivity than Suzuki reactions.
2. Alkyl scrambling due to transfer of the wrong alkyl group from the stannyl derivative onto the aryl-species.
3. Hydrogenation of the halide component.
4. Dimerization of stannanes.

The greater oxygen sensitivity relative to the Suzuki couplings is reflected in unsuccessful attempts to couple the polymer bound with various tributyl vinyl or aryl stannanes. Only impure products due to multiple Ph_2AsO-adducts on the peptide were obtained.

Alkyl scrambling has been reported to occur more frequently with trimethylstannyl than with tributylstannyl derivatives [62].

Hydrogenation of the halide function of the aryl component may be the result of hydrolysis of an aryl-palladium species.

Oxidative dimerization of vinyltrimethyl stannanes was reported recently to be effectively catalyzed by CuCl. This reaction requires oxygen, as does the dimerization of boronates, and can be suppressed by oxygen exclusion [68]. As in the previously described Suzuki couplings, great attention must be paid to the presence of Sn, As and Pd impurities in the product mixture. The use of acetic acid in dichloromethane (DCM,1:5, v:v) was found to provide a versatile means of removing the Sn-impurities. Unfortunately, formerly mentioned Ph_2AsO-adducts on peptides cannot be removed by washing procedures. Problems associated with residual Pd-catalyst have already been mentioned in the preceding section on Suzuki couplings. Thus, low levels of metal impurities (ppm amounts) may only be achievable by HPLC.

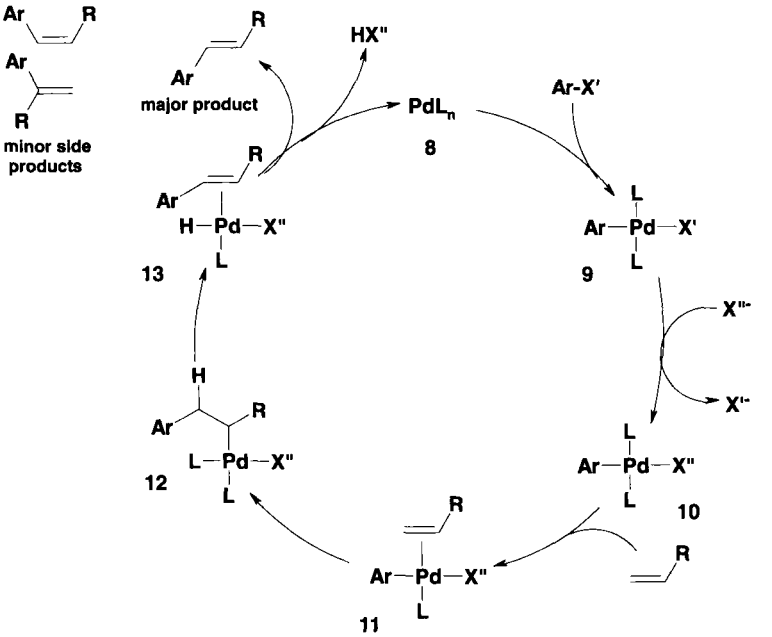
3.3.2.3 The Heck Reaction

The Heck reaction [69–71] is a reaction with an alkene, an aryl, or a vinyl halide. It has been widely employed on solid phase in various intra- [72–76] and intermolecular [28, 29, 73, 77–85] versions. It is the coupling of an aryl or vinyl chloride [79] bromide [75, 79, 82, 84–86], iodide [72–74, 76, 78, 80–83, 86], triflate [77], iodonium salt [29, 87] or diazonium salt [28] with an alkene.

The catalyst cocktails contain a Pd-source, a ligand to stabilize the Pd species throughout the catalytic cycle, an assisting nucleophile, and a base. The most commonly used Pd source is the conveniently stable $Pd(OAc)_2$. [72, 73, 76, 78, 81, 83, 88] However, Pd sources such as

$PdCl_2(PhCN)_2$ [88] $Pd(PPh_3)_2Cl_2$ [74], and $Pd(PPh_3)_4$ [75] have been used. The Pd-salts or complexes then form Pd(0) species **8**, being the starting point of the catalytic cycle (Scheme 3). This Pd(0) species undergoes oxidative addition to the aryl or alkyenyl halide or triflate. The resulting complex **9** may be converted into **10** where a halogen or hydroxy ligand X" is believed to determine the reactivity in steps further along the catalytic cycle [77]. The Pd-aryl or alkenyl complex bearing an X"-group **10** then reacts with the incoming olefin initially by co-ordination to its π-system. In a subsequent rearrangement of the Pd-complex **12**, the aryl functionality, stemming from the aryl or alkenyl halide adds onto the olefin. The presence of water or Cl^- was found beneficial in this step. Bu_4NCl^- is a commonly used Cl^- source due to its solubility in organic solvents. The resulting Pd-alkyl specie undergoes β-elimination to form the Pd alkene **13** complex. The product alkene will be released, if displaced by appropriate ligands to reconstitute the initial Pd catalyst.

Various acid quenchers have been used to sequester the HX" produced after the β-H-elimination step. Triethylamine [73–75, 78, 81], phosphines [72, 76], K_2CO_3 [78] and NaOAc [83] have been employed for this purpose. Often, a phosphine is used to facilitate ligand exchange and also to stabilize the active Pd-species. The stabilization effect was well demonstrated by Herrmann et al. who achieved high TON (turnover number) in their catalytic system with the appropriate ligand [79]. In the case of phosphine-free couplings, the solvent (DMA) takes over the role of a ligand [83]. During the reaction of styrene with an arylbromide, not only the E-stilbene is formed, as substantial amounts (>5 %) of 1,1-diarylethenes



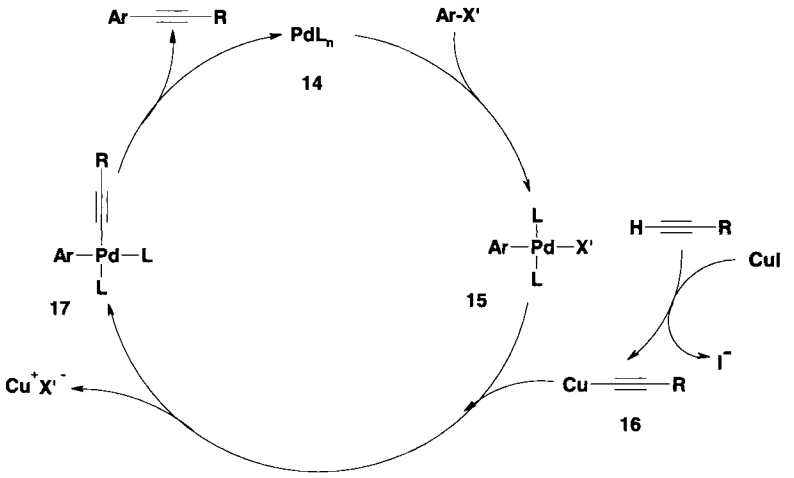
Scheme 3. Mechanism of the Heck reaction. X" may be the OH– or Cl– which is the co-catalyst used. L is a ligand provided by the solvents or a phosphine added to the reaction.

and Z-stilbenes are often formed. The formation of these byproducts may be suppressed in many solvents using N, N-dimethylglycine (DMG) as co-catalyst [88]. If DMG is used, halides are not required for the reaction to take place [88]. DMG is also reported to boost the TON of the catalytic system without need of expensive phosphine ligands [79]. The Heck reaction can also be used in sequence with other Pd-mediated coupling reactions. During the synthesis of a collection of tropane derivatives, Koh et al. performed first a Heck reaction on a tropene derivative, where the progress of the β-H-elimination was retarded due to steric constrains of the bicyclic system. The Pd-complex was then allowed to undergo Suzuki and Sonogashira couplings, as well as a transfer hydrogenation to afford the target tropane derivative [89].

3.3.2.4 The Sonogashira Coupling

Sonogashira et al. [90–93] described cross-couplings between aryl halides and monosubstituted acetylenes catalyzed by a Pd(0)-Cu(I)-system. This reaction has been used on a solid phase where aromatic bromides, iodides [10, 83, 94, 95] or triflates were immobilized on a solid phase and allowed to react with various acetylenes in solution. In turn, good yields were also reported, when the alkyne was immobilized on the solid phase and diaryl or arylalkenyliodonium tetrafluoroborates were in solution [96]. The reactivity order with respect to the halogen bonded to the sp^2-carbon is I > Br > Cl, and with respect to the sp^2-center is vinylic > allenic > heteroaromatic > aromatic [97]. In our experience, consistently good results were obtained with $Pd(PPh_3)_2Cl_2$ as Pd source, CuI as co-catalyst, dioxane as solvent, and with NEt_3 or Heunig's base. However, some heterocyclic triflates are reported to undergo high-yielding Sonogashira couplings with other Pd-sources and without Cu additives [98]. The catalytic cycle is initiated by oxidative addition of an aromatic halide Ar-X' to a stabilized Pd(0) species **14**; attack of an acetylide **16** follows. In many reactions copper acetylides, which are generated from the acetylene and CuI in presence of an amine base give superior results (Scheme 4).

The amine base may not only provide basic conditions to deprotonate the acetylene and facilitate the formation of the Cu acetylide, it might also act as a reducing agent for the Pd(II) salt added to the reaction mixture. The role of the copper is to enhance the nucleophilicity of the acetylene towards Ar-Pd-X species (Scheme 4). However, R-Pd-OTf (where R are imines or pyridines) are readily attacked by ammonium or alkaline acetylides themselves [97, 98]. The aryl alkynyl Pd-complex then may undergo a rearrangement similar to that proposed in the case of the Heck reaction. Subsequent elimination of CuX" may follow, facilitated by the addition of an I^--source readily soluble in the organic solvent. Thus the addition of KI or Bu_4NI enhanced the coupling reaction [99]. Bu_4NOTf was also found to be effective, as it allows the generation of soluble I^- through salt exchange with CuI. In turn, the presence of LiCl was found to inhibit the reaction [99]. In the case of sluggish reactions, where air poisoning of the catalyst often causes the reaction to come to a standstill, multiple couplings might help to drive the reactions to completion. If Sonogashira couplings are performed on a support bound aryl halide, the acid lability of the formed acetylenes must influence the solid phase linker selection. Thus, acetylenes formed in the coupling reaction may decompose to a ketone in presence of aqueous TFA.



Scheme 4. Sonogashira coupling. L is a ligand provided by the solvent or a phosphine added.

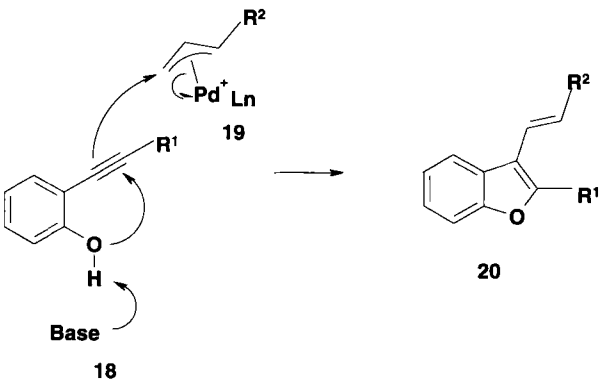
Alkynylation products of o-iodo phenols readily undergo cyclization to give benzofuran derivatives [82, 100]. This reactivity has been exploited in tandem reactions, where cationic Pd-allyl complexes serve as electrophiles [101, 102].

Analogously, o-alkynylation products of trifluoroacetylated anilines form indoles [94].

3.3.3 Remarks on Pd-Mediated Couplings on a Polymeric Support

In view of the previously mentioned side reactions, having one component immobilized on the solid phase offers the advantage of using certain reagents in excess to compensate for their potential losses. In most cases the aryl halide is chosen to be bound to the support. Note that cross-couplings involving polymer-bound aryl halides may also be driven to completion using multiple coupling strategies mentioned later. In turn, the extent of proteo dehalogenations and halide-OH exchange reactions is limited, especially if oxygen is carefully excluded [48, 103]. The homo-coupling of aryl-halides in the presence of oxygen was found to be the most prominent side reaction with swellable polystyrene supports. Here, a coupling of two different resin-bound aryl groups probably localized adjacent to one another in the swollen resin are coupled. As mentioned earlier, thorough exclusion of oxygen eliminates this problem.

Further limitations of Pd-couplings are implied by the nature of the resin. Many combinatorial syntheses are performed on swellable, low-cross-linked polystyrene supports initially designed for peptide chemistry. The accessibility of functional groups on the polymer must be maintained throughout the reaction by the use of solvents or solvent mixtures, which allow sufficient swelling. In our hands, mixtures of dioxane-water have been found very useful for 1 %-cross-linked polystyrene resins. Some coupling reactions involving electron-rich aryl halides are sluggish and may not go to completion due to the poisoning of the catalyst, main-



Scheme 5. Tandem reaction involving cyclization of an o-alkynylphenol and trapping of the carbanion intermediate with an allyl-Pd electrophile.

ly by oxygen impurities diffusing into the reaction mixture over long periods of time. In case the aryl halide is bound on a polymeric support, those reactions may still be driven to completion using multiple couplings. Here, the resin bearing the incompletely converted residue is filtered off; a second coupling is then performed with the residue on the washed resin. In our experience, up to three coupling runs were necessary to convert poorly reactive 1-alkoxy-4-iodo benzene.

Another strategy is to develop immobilized catalysts and to use product or impurity specific extraction methods or chromatography to separate wanted from unwanted compounds. Advantages of this approach might be easier handling of the catalyst and minimization of heavy-metal impurities in the product [19, 80, 85, 87, 104].

Thus, the Heck reaction was performed with the Pd-catalyst immobilized via its phosphine ligands on a zirconium phosphite-based support. According to the authors, no Pd-leaching form the solid was observed [80]. A polymeric substitute for $Pd(PPh_3)_4$, being a potent catalyst for Suzuki couplings, was described by Fenger et al. [19] This catalyst is prepared by treatment of Merrifield resin with $LiPPh_2$, followed by immobilization of Pd(0) through ligand exchange with $Pd(PPh_3)_4$. The resulting catalyst was reported to be considerably more stable to air than free $Pd(PPh_3)_4$, and could be re-used several times without loss of activity.

3.3.4 Experimental approach

3.3.4.1 Materials and Methods

The Pd-catalysts ($Pd(OAc)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$) were handled under oxygen-free argon, though, in contrast to $Pd(PPh_3)_4$, they appear to be air-stable, as no discoloration occurs. In the following experiments, deionized water generated by a Millipore, Milli-Q water system was degassed by three-fold application of 100 mbar and subsequent re-establishment of ambient pressure with oxygen-free argon. Dioxane, tetrahydrofuran (THF) and ethylene glycol

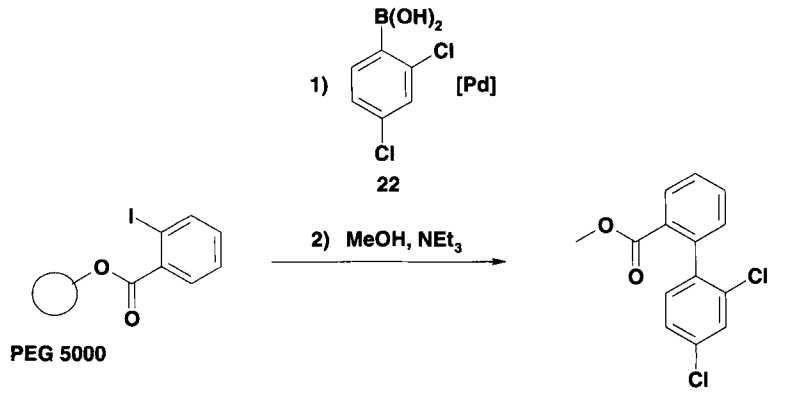
dimethylether (diglyme) were distilled over sodium, and benzophenone under an argon atmosphere. Dichloromethane (DCM) was distilled over NaPb (E. Merck) or passed through alumina. All other solvents were reagent grade and used directly. It is desirable to use a higher quality of argon for the Pd-mediated coupling reactions; however, if only technical quality argon is available, it may be passed through oxygen-quenching systems such as diglyme/Na/benzophenone. The boronic acids and stannylenes were purchased from different suppliers and used directly.

All described reactions were performed in a "glass frit reactor", unless specified otherwise. The top of the reactor was sealed with a rubber septum, connected to an argon-filled balloon. The bottom contained a P3-glass frit, leading to a narrow outlet, which could either be sealed by a tight screw cap, a small septum or a rubber stopper, or fastened tightly onto a PTFE valve to perform washing procedures. This "frit reactor" could be placed on a heating block that was mounted on an orbital shaker to allow agitation of the resin during the reactions. Washings were performed in a "flow-through" manner when the reactor was mounted on a PTFE valve. Argon flushes were performed by introducing the gas via a syringe-type outlet through either the bottom or the top septum of the reactor. In either case, a syringe needle pinched through the top septum acted as the gas release.

3.3.4.2 Suzuki Couplings

Procedure: General Procedure to Perform a Suzuki Coupling on a Soluble PEG 5000-Support (Scheme 6) [8]

1 g of monomethoxy PEG 5000 polymer esterified with o-iodobenzoic acid (approx. 0.19 mmol) was dissolved in distilled DMF (5 mL). 2,4-Dichlorophenylboronic acid (73 mg, 0.38 mmol, 2 equiv.), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.05 equiv.) and 2 M sodium carbonate solution (0.25 mL, 0.5 mmol, 2.5 equiv.) was added. The mixture was stirred under argon at 110° C for 10 h in a screw-cap culture tube. Toluene was added and insoluble material re-



Scheme 6

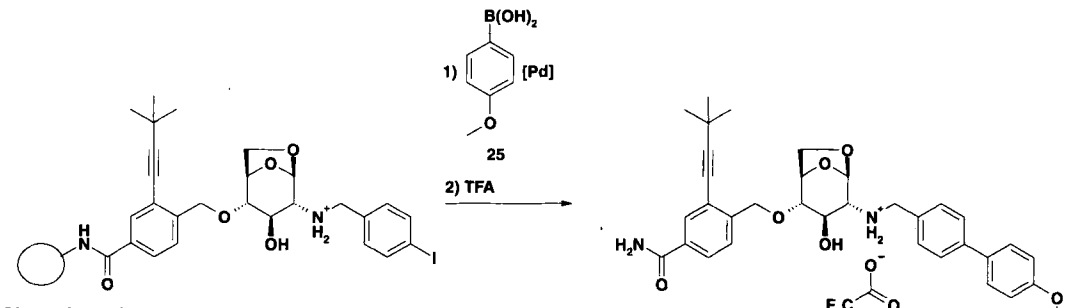
moved by centrifugation. The volume of the solution was reduced in vacuo and subsequently poured into ice-cold tert.-butyl methylether (MTBE) for precipitation. The precipitate was filtered and washed with ice-cold ethanol. The polymer was taken up in DCM, precipitated into MTBE and washed with ethanol twice (Note: MTBE is a less volatile, low price substitute for diethyl ether).

Cleavage of the product by transesterification: The polymer bearing the biaryl was dissolved in 10 mL of dry NEt_3:MeOH (1:4, v:v) and stirred in a screw-cap culture tube under argon at 85° C for 2 days. The mixture was dried in vacuo, taken up in DCM (4 mL) and precipitated into MTBE, redissolved and precipitated as above. The combined filtrates were evaporated under reduced pressure. The crude product was purified by column filtration using EtOAc:iso-hexane (4:1, v:v) (Rf: 0.68) to give a colorless oil in 93 % yield.

Procedure: General Procedure for a Suzuki Cross-Coupling on a 2 % Cross-Linked Polystyrene Support (Scheme 7):

K_2CO_3 (537 mg, 3.88 mmol) were dissolved in distilled, degassed water (1.23 mL). This solution was added to dioxane (7.4 mL). The resulting emulsion was used without further phase separation. To 300 mg of Rink-amide resin bearing 0.216 mmol of the iodine containing carbohydrate was added under a blanket of argon the dioxane-H_2O-K_2CO_3-solution and 4-methoxy benzeneboronic acid (263 mg, 1.727 mmol). To these components of the reaction mixture a steady stream of argon was passed for 10 min to minimize oxygen contaminants. Subsequently $Pd(OAc)_2$ (10 mg, 0.044 mmol) was added to the reaction mixture and the reactor was sealed with a septum carrying an argon balloon. The reaction mixture was then agitated on a heating block at 100° C for 24 h. The reactor was emptied and the resin again subjected to K_2CO_3-solution, boronic acid and $Pd(OAc)_2$ as in the first coupling round described above. The reaction mixture was agitated in a heating block at 100° C for 24 h. The resin was then washed as follows:

6 x 0.5 mL dioxane, 2 min
6 x 0.5 mL H_2O, 2 min
3 x 0.5 mL EtOH:H_2O (1:1, v:v), 2 min
3 x 0.5 mL EtOH, 2 min
6 x 0.5 mL dioxane, 2 min
6 x 0.5 mL DCM, 2 min
6 x 0.5 mL ether, 2 min



Scheme 7

The product was then liberated from the resin by 10 successive 2-min treatments each with 0.5 mL of 20 % TFA in dichloroethane. To the combined product solutions was added 2 mL of toluene to avoid a large increase in TFA concentration during the evaporation process, which would lead to a scission of the glycosidic bond of the product. The product was dried down in vacuo over P_4O_{10}/KOH and obtained in 90 % isolated yield based on ^{1}H-NMR and MS.

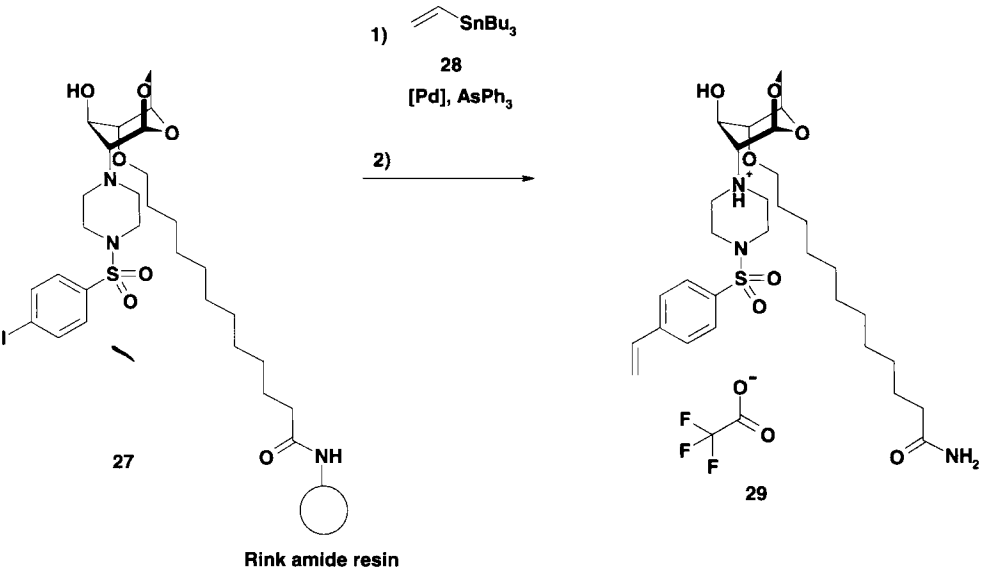
Procedure: General Procedure for a Suzuki Cross-Coupling on a 2 % Cross-Linked Polystyrene Support using Aqueous KF as Base

The coupling was performed with the same substrate as in the previous example. K_2CO_3 was replaced by 337 mg (5.8 mmol) of KF. The KF was dissolved in distilled, degassed water (1.8 mL). This solution was added to dioxane (11 mL). The resulting emulsion separates phases slowly. The separation of the phases before the coupling does not seem to be important for the progress of the reaction. The product was obtained after double Pd-coupling using $Pd(OAc)_2$ (29 mg, 0.13 mmol) for each run. The yield after work-up as described above was quantitative.

3.3.4.3 Stille Couplings

Procedure: General Procedure for a Stille Coupling on a 2 % Cross-Linked Polystyrene Support (Scheme 8).

To 250 mg 2 %-cross-linked polystyrene resin bearing 0.075 mmol of the levoglucosan derivative was added under a blanket of argon tris(dibenzylideneacetone)dipalladium (complex with chloroform) (=Pd_2dba_3·$CHCl_3$) (6.9 mg, 0.0075 mmol), triphenylarsine (9.2 mg



Scheme 8

0.03 mmol), and freshly distilled dioxane (6 mL). The reactor was sealed and a steady stream of argon was passed for 10 min to minimize oxygen contaminants. Subsequently, vinyltributyl stannane (71.3 mg, 65.7 µL, 0.225 mmol) was introduced into the reactor. The reaction mixture was then agitated for 22 h at 50° C. The reactor was emptied and the resin was washed 10 times using 0.5 mL of dioxane per wash with each wash lasting 2 min. A second coupling cycle was then performed using identical conditions. After the second coupling, the resin was washed as follows:

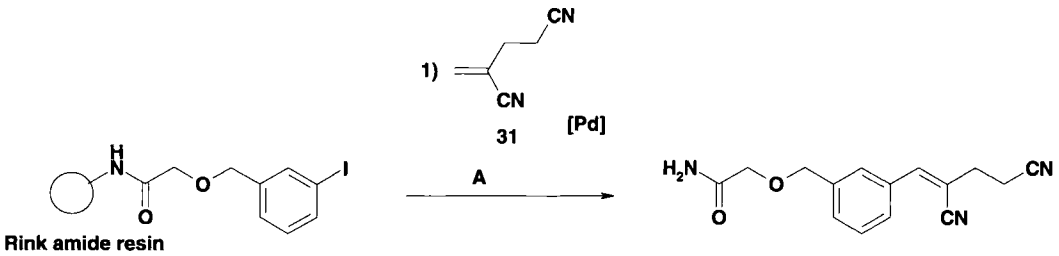
1) 10 x 0.5 mL dioxane, 2 min
2) 10 x 0.5 mL HOAc:DCM (1:5, v:v), 2 min
3) 5 x [a) 2 mL MeOH, 2 min; b) 2 mL DCM, 2 min]
4) 5 x 2 mL EtOEt, 2 min

(Note that the weak acid treatment is necessary to remove Sn contaminants from the support)

The product was then liberated from the resin by 10 successive 2-min treatments with 20 % TFA in dichloroethane (0.5 mL each). To the combined product solutions was added toluene (2 mL) to avoid a large increase in TFA concentration during the evaporation process, which would lead to a scission of the glycosidic bond of the product. The product was dried in vacuo over P_4O_{10}/KOH and obtained in 85 % isolated yield.

3.3.4.4 Heck Reaction

Procedure: General Procedure for a Heck coupling on a 2 % Cross-Linked Polystyrene Support (Scheme 9) [83]



Scheme 9

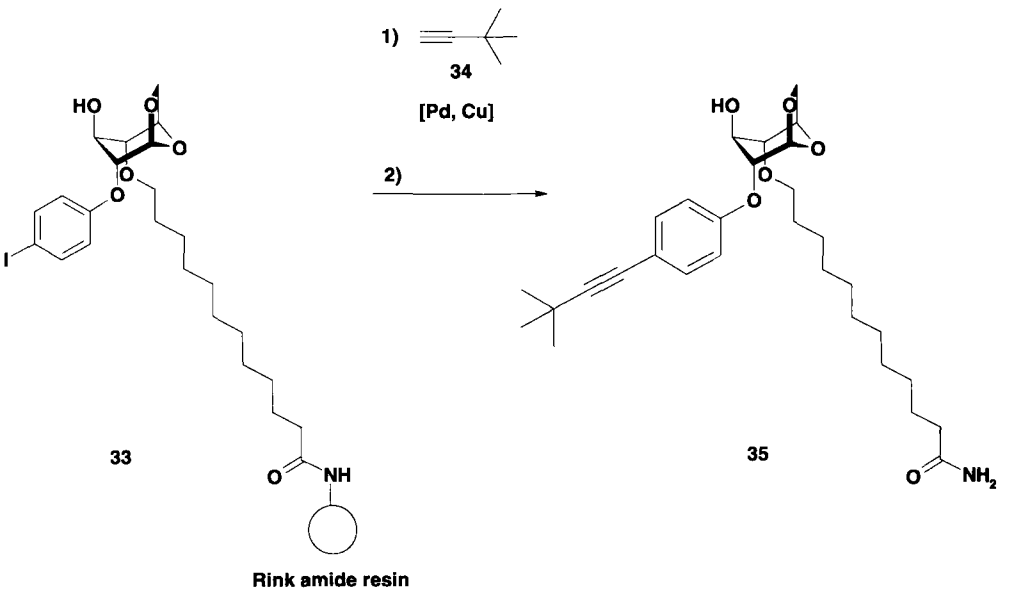
To 200 mg 2 %-cross-linked polystyrene resin bearing aryl iodide (0.094 mmol, 1 equiv.) were added DMA (4.7 mL), NaOAc (23.2 mg, 0.283 mmol, 3 equiv.), Bu_4NCl (55.6 mg, 0.188 mmol, 2 equiv.), and methyleneglutaronitrile (79.8 mg, 82 mL, 0.752 mmol, 8 equiv.) under a blanket of argon. A stream of argon was passed through the mixture for 15 min, then $Pd(OAc)_2$ (5.27 mg, 0.0235 mmol, 0.2 equiv.) was added under a blanket of argon and the reaction mixture was shaken for 24 h at 100° C. The following washes were performed:

1) 6 x 5 mL dioxane, 1 min
2) 6 x 5 mL H_2O, 1 min
3) 6 x 5 mL EtOH:H_2O (1:1, v:v), 1 min
4) 3 x 5 mL EtOH, 1 min
5) 6 x 5 mL dioxane, 1 min
6) 6 x 5 mL DCM, 1 min
7) 6 x 5 mL Et_2O, 1 min

The resin was then resubjected to the coupling procedure and the washes as described above, dried in vacuo, and subjected to TFA cleavage. The product was liberated from the resin by five successive 1-min treatments with 20 % TFA in dichloro ethane (0.5 mL each). The crude product was dried in vacuo over P_4O_{10}/KOH and obtained with a purity of 90 % (NMR) in 86 % yield. Major impurities were tetrabutylammonium salts.

3.3.4.5 Sonogashira Coupling

Procedure: General Procedure for a Sonogashira Coupling onto an Electron-Rich Aromatic System on a 2 % Cross-Linked Polystyrene Support (Scheme 10).



Scheme 10

The reaction was performed in a reactor as described previously. To the resin bearing a levoglucosan derivative (400 mg, 0.072 mmol) was added 3,3-dimethyl-butyne (61 µL, 0.5 mmol) and CuI (5.2 mg, 0.027 mmol). Subsequently, dioxane (6 mL) and NEt_3 (3 mL) were

added. A constant stream of argon was allowed to flow through the resulting solution for 10 min to remove oxygen traces. Addition of $Pd(PPh_3)Cl_2$ (20 mg, 0.028 mmol) followed under a blanket of argon. The reaction mixture was shaken in the dark for 24 h at rt. The resin was then washed as follows:

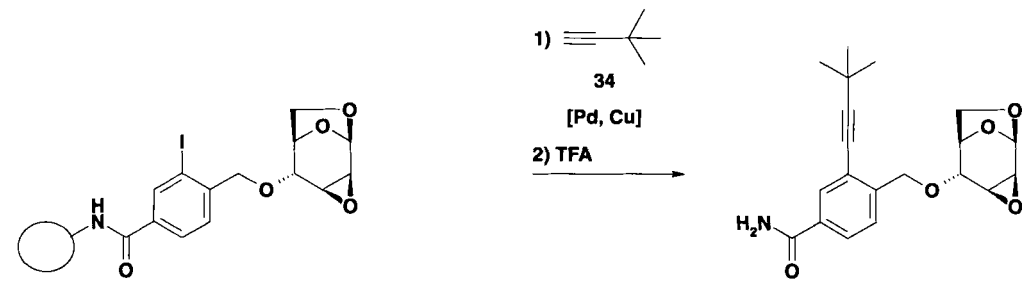
1) 6 x 0.5 mL dioxane
2) 6 x 0.5 mL H_2O
3) 6 x 0.5 mL EtOH:H_2O (1:1, v:v)
4) 6 x 0.5 mL EtOH
5) 6 x 0.5 mL dioxane

After the wash two more 24-h couplings and washes followed as described above. After the wash, and following the third coupling procedure, the resin was washed as follows:

6) 6 x 0.5mL DCM
7) 5 x [a) 0.5 mL MeOH, 2 min; b) 0.5 mL DCM, 2 min]
8) 5 x [a) 0.5 mL DCM, 2min; b) 0.5 mL n-pentane, 2 min]

The product was then liberated from the resin by 10 successive 2-min treatments each with 0.5 mL of 20 %TFA in dichloroethane. To the combined product solutions was added 2mL of toluene to avoid a large increase in TFA concentration during the evaporation process, which would lead to a scission of the glycosidic bond of the product. The product was dried down in vacuo over P_4O_{10}/KOH and obtained in 95 % isolated yield. The purity of the product was 90 % yield based on the HPLC trace at 215 nm and ^{1}H-NMR.

Procedure: Sonogashira Coupling (Scheme 11)



Rink amide resin **36** **37**

Scheme 11

To 400 mg of resin bearing a levoglucosan derivative (0.072 mmol) was added 3,3-dimethylbutyne (61 µL, 0.5 mmol) and CuI (5.2 mg, 0.027 mmol). Subsequently, dioxane (6 mL) and NEt_3 (3 mL) were added. A constant stream of argon was allowed to flow through the resulting solution for 10 min to remove oxygen traces. Addition of $Pd(PPh_3)_2Cl_2$ (20 mg, 0.028 mmol) followed under a blanket of argon. The reactor was shaken in the dark for 91 h at rt. The resin was then washed as follows:

1) 6 x 0.5 mL dioxane, 2 min
2) 6 x 0.5 mL H_2O, 2 min

3) 3 x 0.5 mL EtOH:H_2O (1:1, v:v)
4) 3 x 0.5 mL EtOH, 2 min
5) 6 x 0.5 mL dioxane, 2 min
6) 6 x 0.5 mL DCM, 2 min
7) 6 x 0.5 mL Et_2O, 2 min

The product was then liberated from the resin by 10 successive 2-min treatments each with 0.5 mL of 20 % TFA in dichloroethane. To the combined product solutions was added 2 mL of toluene to avoid a large increase in TFA concentration during the evaporation process, which would lead to a scission of the glycosidic bond of the product. The product was dried down in vacuo over P_4O_{10}/KOH and obtained in 92 % isolated yield.

3.3.5 Reactions Involving Grignard Reagents or Organozinc Reagents

3.3.5.1 Grignard Reagents, Lithium and Organozinc Reagents

Grignard reagents and lithium organyls are very versatile carbanion sources used in the synthesis of acyclic [105–107] heterocyclic [108] and carbocyclic compounds [109]. They are more susceptible to water than zinc organic reagents, and react with water to the corresponding alkane and with oxygen to the hydroperoxide. For reactions on solid phase, the ester, ketone or aldehyde component is much more stable towards small amounts of oxygen or water impurities, and is therefore immobilized on a resin during reactions on the solid phase. Side reactions are minimized by:

1. Rigorous drying of the resin, if one reagent is immobilized on a solid phase.
2. Use of large excess of Grignard reagent.

In general, the procedures involving reactions with Li, Zn and Mg organyls are very similar. However, Zn [110] and Mg reagents often require ambient temperature, or even heating for the conversions. This is particularly advantageous in reactions involving the gel phase of a swellable resin. Here, low temperatures such as –78° C may lead to "frozen" gelphase and poor interactions with the substrate on the solid phase.

Synthetically useful is the Weinreb procedure for the reductive coupling of an N-alkyl-N-methoxy amide with a Grignard reagent to afford a ketone. This method has been applied frequently on the solid phase by several authors [105, 106, 111]. The product recovery of reactions involving Grignard addition may sometimes be modest if the reaction vessels are not sufficiently dry.

3.3.5.2 Pd-Mediated Couplings with Organozinc Reagents

Organozinc reagents are very versatile for alkyl-alkyl, alkyl-aryl and aryl-aryl couplings [40]. Arylzinc bromides and benzylzinc iodides may serve as more reactive substitutes of boronates or stannanes in Pd-mediated couplings. They also tolerate many functional groups. Thus, aryl iodides have been shown to react selectively with alkyl zinc iodides in the presence

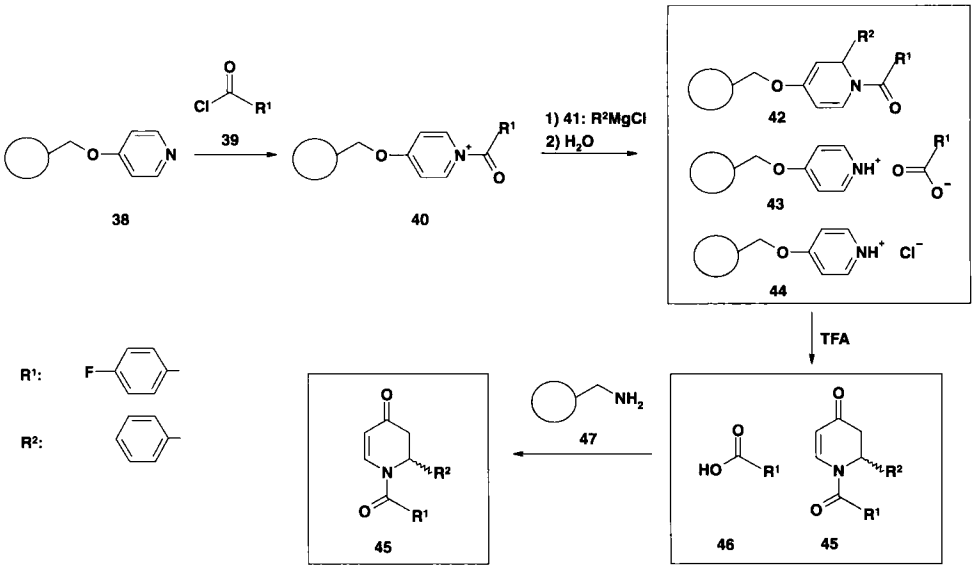
of boronate esters in Pd-mediated couplings [112]. In turn, aryl or benzylic zinc halides display high selectivity for C-C bond formations with aryl iodides over aryl triflates. These features were successfully exploited in several aryl-aryl and aryl alkyl couplings involving polystyrene-bound aryl halides and aryl or benzyl zinc halides in solution [113]. The couplings were catalyzed by $Pd_2(dba_3)$ and tri-o-furylphosphine (tfp) in THF. Couplings involving aryl iodides were carried out at room temperature, while those with triflates required a temperature of 65–70° C [113]. In the case of o-iodoaryl triflates, Zn-insertion occurs in both the C-OTf and the C-I bond, and therefore generates a reagent which may perform two aryl-aryl couplings with another aryl iodide at adjacent carbon atoms [114]. The main drawback of zinc organyls is their lability towards water, as many synthesis supports are often difficult to dry.

3.3.5.3 General Remarks on Preparations Involving Water-Sensitive Reagents

These include reactions such as those with Grignard reagents, lithium or zinc organyls on solid phase. Dryness of the resin is essential for the outcome of such reactions. One way to predry polystyrene is by co-evaporation with dry toluene. This process is best suited for bulk amounts of polymer and requires a rotary evaporator that may be flooded by a dry inert gas such as argon. A "bump trap" or a P-2 frit may have to be used during the evaporation as resins that are almost dry have a tendency to "bump". Small resin samples may be well dried upon excessive washings (10–20 consecutive washings) with a dry hygroscopic solvent. If polystyrene resins are used, a solvent should be taken which allows swelling of the support. Dry THF, DMA, NMP or dioxane are very useful for this purpose. They are very hygroscopic, may be easily dried, and are even available in dry form from commercial sources. The inner surfaces of glass reactors are a major source of water contamination. Polypropylene or PTFE reactors or reactor blocks are more readily dried. Throughout these reactions the amount of precipitations must be minimized – especially if resin beads are used as polymeric support in conjunction with frit reactors. Hydroxide and carbonate precipitates readily cause clogging of frits. It is advisable to transfer Grignard reagents or other organyls from their storage bottles or flasks into a graduated cylinder via a cannula fitted with a frit, in order to remove any precipitate from the reagent. Custom-made Grignard reagents may also be filtered through a Schlenk frit under dry argon before use. The precipitate-free reagent may then be transferred via a gas-tight syringe or cannula to the reactors. Crowns (Chiron Technologies) are substantially larger than beads and are more easily subjected to co-evaporations with toluene in large, round-bottomed flasks. They may be fastened on pins while immersed into organometallic reagents, and can also be filtered off through a wide polypropylene mesh. As problems of clogging frits are therefore nonexistent using crowns, the latter may be preferred over beads if poorly filterable precipitates are unavoidable. In Grignard and many other reactions, inorganic salts that are insoluble in most neutral organic solvents may be distributed over polymeric supports. Washes consisting of an aqueous buffer or acid and an organic component allowing the swelling of a support should be considered during the work-up.

3.3.5.4 Experimental: Grignard on Solid Phase

Procedure: Synthesis of a 2-Substituted Dihydropyridone on Wang Resin [108]



Scheme 12. The polymer-bound pyridinium salts resulting from the Grignard reaction of **43** leads to salt impurities occurring in the crude product. These salts are removed by ion exchange with resin **47**. Note that the greater lability of the enol ether **42** to acid allows its selective cleavage.

To a suspension of Wang resin bearing 4-oxo-pyridine (100 mg, 0.075 mmol based on loading of 0.75 mmol g^{-1}) in anhydrous THF (1 mL) in a 3-mL polypropylene tube fitted with a frit was added a solution of 4-fluorobenzoyl chloride (0.015 g, 0.096 mmol) in anhydrous THF (1 mL). The resulting slurry was agitated for 30 min and then treated with a solution of phenylmagnesium chloride (1.0 M in THF, 0.3 mL, 0.3 mmol). The mixture was agitated for 1–2 h and then filtered. The resin was washed as follows:

1) 3 x 1 mL THF:0.1 M HOAc (2:1, v:v)
2) 3 x 1 mL H_2O
3) 3 x 1 mL MeOH
4) 3 x [a) 1 mL MeOH; b) 1 mL DCM]
5) 3 x 1 mL THF

The product was then liberated from the resin by treatments with a solution of 2 mL THF:aqueous 1 M TFA (2:1, v:v) for 2 h. The mixture was then filtered and the resin was washed as follows:

6) 2 x 1 mL THF:1 M aqueous TFA (2:1, v:v)
7) 2 x 1 mL THF

The filtrate and the combined washings were concentrated and dried in vacuo. The resulting residue was dissolved in THF (3 mL) and treated with aminomethyl polystyrene RS

resin (200 mg, loading 0.8 mmol g^{-1}). In this purification step, the carboxylic acid **45** resulting from hydrolysis of the polymer-bound acylpyridinium salt **40**, which had not reacted with the Grignard reagent was removed from the product solution. The mixture was agitated for 48 h and then filtered. The resin was washed with THF (2 x 1 mL). The combined filtrate and washings were concentrated to yield the desired product.

3.3.6 Olefin Metathesis

There have been a number of applications of olefin metathesis to solid-phase synthesis of small molecules and peptide analogs [115–123]. Three types of cross-metathesis reactions have been performed:

The linear elongation of an olefin. Here, an olefin in solution is allowed to react with an olefin on the support. It is advisable that both reaction partners have terminal alkene residues. Cross-metathesis will then also afford ethene, which will escape the reaction due to its volatility. Alternatively, a 1,2-disubstituted Z-alkene bearing the same substituent in positions 1 and 2 may be used as the solution component.

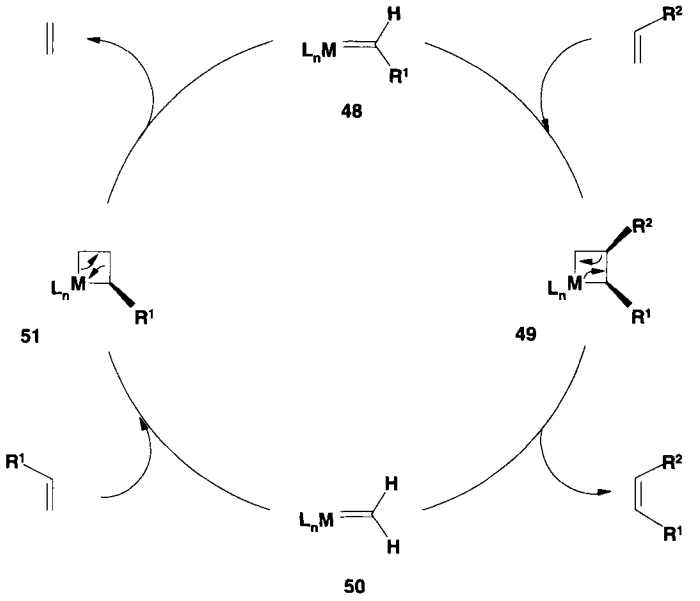
Ring-closing metathesis. Here, a resin-bound molecule bearing two alkene moieties is allowed to cyclize. Terminal alkenes are desirable for the ring-closing metathesis because the reaction is then driven by ethylene generation.

The ring-opening metathesis. Here, a resin-bound cyclic olefin reacts with an alkene in solution to give a product bearing two alkene residues. This reaction is favored due to the release of ring strain. If the reaction partners do not have a mirror plane perpendicular to the double bond, undergoing the cross-metathesis, a mixture of regioisomers may be obtained. The composition of the mixture is heavily dependent on the reaction conditions, the reactants, and the catalyst.

A general problem of alkene cross-metathesis is the formation of self-metathesis products from the starting alkenes. On solid phase, dimerization of polymer–bound olefin should be minimized by the use of excess of the solution olefin combined with the effective dilution of the resin-bound olefin by the site isolation effect (see Section 3.3.2.1). Homocoupled products of the solution-phase olefin are simply washed off during the resin washes.

3.3.6.1 Mechanism

The catalytic cycle begins when an alkene or adds to a metal carbene complex **48** or **50** being the active catalyst, to form a metallacyclobutane **49** or **51**. The initial metal carbene complex **48** may be added directly to the reaction mixture or is afforded rapidly upon displacement of suitable ligands on the metal center by the alkene. The intermediacy of metallacyclobutanes of early transition metals in olefin metathesisis is well-ascertained, but the role of such putative intermediates by late transition metals is more speculative [124]. The metallacyclobutanes [125] may then decompose to afford metallacarbenes complexes and alkenes (Scheme 13). Other decomposition patterns of the metallacyclobutanes are also known and have been reviewed recently [126].

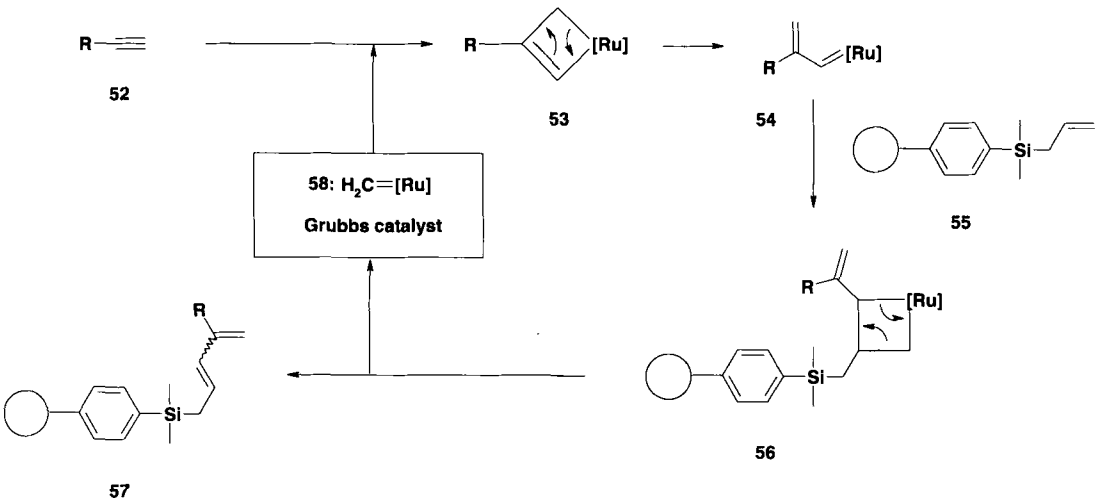


Scheme 13. Mechanism of a cross-metathesis reaction with two primary alkenes. The driving force of the reaction is the formation of ethylene, which escapes from the reaction mixture. M may be a metal with little Z-E scrambling such as Ru as in the Grubbs catalyst.

The major breakthrough of olefin metathesis came with the availability of catalysts that allow this reaction to take place in many solvents (including water) at low temperatures, including room temperature. Commonly, the Grubbs catalyst ($(Cy_3P)_2Cl_2Ru{=}CHPh$) is used; this is both robust and commercially available [116, 123, 127, 128]. If substituted alkenes are used, the stereochemistry of the reaction is most likely determined by the geometry of the metallayclobutane intermediate. In the presence of Mo and Cr catalysts, starting alkenes with one relative configuration leads to products with predominantly one relative configuration. In turn, W catalysts lead to complete Z-E scrambling [129] of the olefin. A special type of olefin metathesis is the reaction of an alkene with an alkyne to give a diene. Thus, a reaction between a terminal acetylene and a terminal alkene leads to a 1,3-diene. One of the alkene residues is a methylidene group; the other is a mixture of Z and E alkene residues [116]. In the case of propargyl-allylamides, an intramolecular reaction can occur, leading to cyclization to afford vinyl pyrrolines [130].

On solid phase, alkene metathesis has been applied to bind terminal alkynes onto polymer-bound allyl silanes. The resulting polymer-bound 1,3-dienes may then undergo Diels–Alder reactions with alkenes bearing electron-withdrawing groups [131] (Scheme 14).

The ring-closing metathesis has been used to synthesize various macrocycles, which were cleaved from the support in the ring-closing reaction [132]. Here, the spacer length between the polymeric support and the internal alkene bond involved in the metathesis appears to be crucial for the product purity. A spacer length of eight CH_2-units was found to be superior over that of one CH_2 group [132].



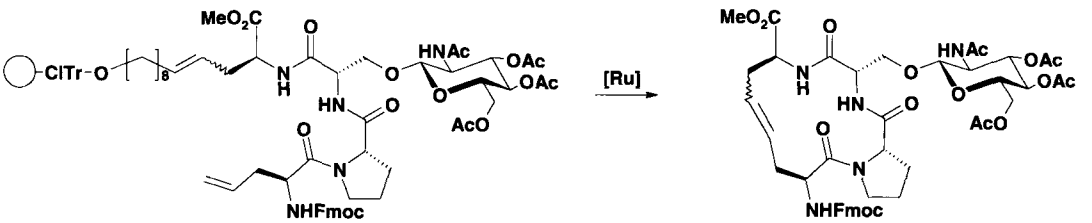
Scheme 14. Synthesis of 1,3-dienes on polystyrene support using metathesis.

3.3.6.2 Experimental: Metathesis on Solid Phase

Procedure: Synthesis of a Tetrapeptide Bearing Two Alkene Residues on a Polymeric Support [132]

The following reaction is performed with polystyrene resin bearing a chlorotrityl linker to allow monitoring of byproducts by cleaving the acid-labile trityl ether bond.

Polymer (200 mg) was suspended in DCM (1.5 mL) and refluxed after addition of $Cl_2(PCy_3)_2Ru{=}CHPh$ (Cy = cyclohexyl) (9 mg, 0.011 mmol). After 17 h, the resin was filtered off and washed twice with DCM. The contents of the filtrate were analyzed by analytical HPLC. A SEDEX 55 (ERC, Germany) Evaporative-Light-Scattering Detector (ELSD) was employed to ensure comparable mass response for different analytes. Cyclic products formed were purified by semipreparative HPLC and characterized by 1H NMR spectroscopy and high-resolution MS (HRMS). They formed E/Z mixtures, as indicated by HPLC



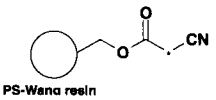
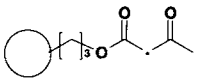
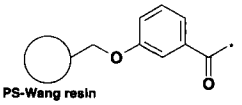
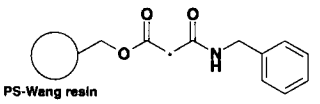
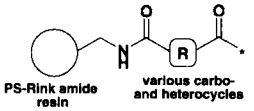
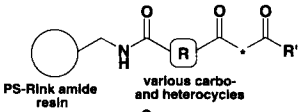
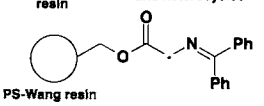
Scheme 15. Ring-closing metathesis on a polymeric support. (ClTr: chlorotrityl support linker).

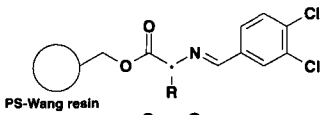
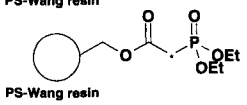
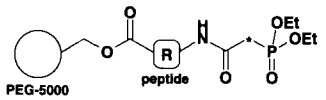
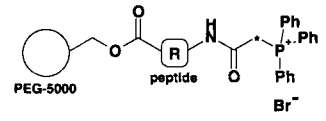
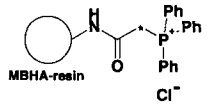
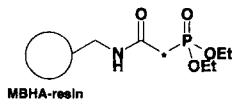
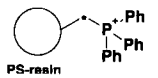
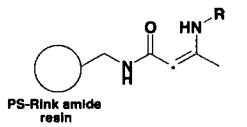
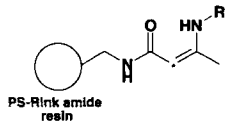
and ^{1}H NMR spectroscopy. The desired peptide was obtained in 30 % yield with a purity of 85 %.

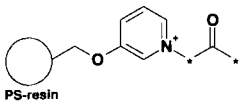
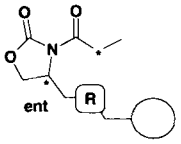
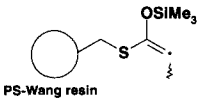
3.3.7 Generation of Carbanions and their Equivalents on the Solid Support

As an alternative to the reaction of a dissolved carbanion equivalent with an electrophile bound to a polymeric support, the opposite arrangement has a carbanion equivalent generated on the support and the electrophile in solution. The generation of boronates and stannanes from the corresponding aryl halides has been described [7, 109]. More common is the generation of stabilized carbanions, which are often the starting point of syntheses of heterocycles. A list of stabilized carbanions and their method of generation is provided in Table 1.

Table 1. Stabilized carbanions and their method of generation

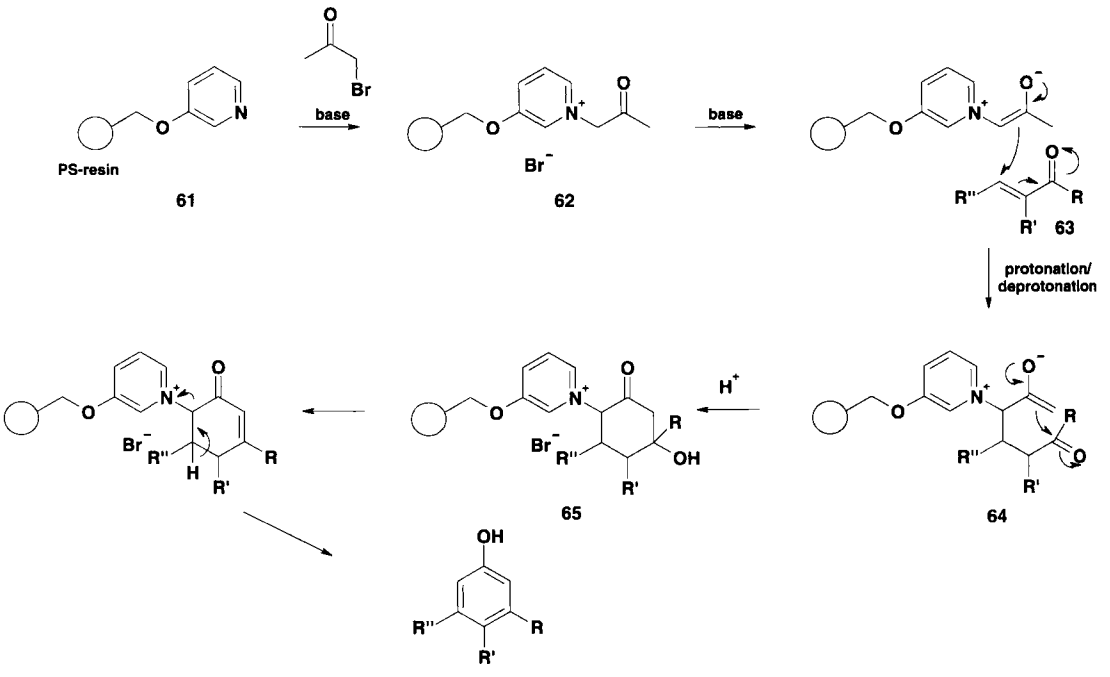
Entry	Structure to be deprotonated	Conditions	Electrophile	Reference
1		5 % NEt_3 in DMF	acid anhydride	133
2		0.2-0.4 equiv. piperidinium acetate DCM, 20 °C, 3 h	aldehydes	134, 135
3		1) preswell the resin with THF. 2) Add 0.1 M NaOMe in MeOH (12 equiv.)	aldehydes	136
4		0.25 equiv. piperidinium acetate toluene, 85 °C	aldehydes	137 further reference: 138
5		20 equiv. NaH (60 % suspension in oil, 0.66 mmol/ml DMA) DMA, 1 h, 90 °C	methyl esters ethyl esters	139
6		1) M Bu_4NF (10 equiv.) in THF, 2 h, 25 °C	alkyl bromides alkyl iodides	139
7		BEMP (2-10 equiv.), NMP, r.t.	alkyl bromides alkyl iodides alkyl chlorides	140

Entry	Structure to be deprotonated	Conditions	Electrophile	Reference
8		BEMP (2–10 equiv.), NMP, r.t.	alkyl bromides alkyl iodides	141
9		1) KHMDS or LiHMDS (4 equiv.) THF, 0 °C-r.t. 2) ketone (5 equiv.)	ketones	142
10		1) LiBr (11 equiv.) THF 2) 2) NEt_3 (11 equiv.), aldehyde (11 equiv.)	aldehydes	143
11		1) LiBr (11 equiv.), THF 2) NEt_3 (11 equiv.), aldehyde (11 equiv.)	aldehydes	143 other references: 144
12		1) n-BuLi (3 equiv.) THF 0 °C 2) Wash resin with DCM and THF 3) Aldehyde, 65 °C, 20 °C	chiral amino aldehyde (this procedure causes little epimerization)	145
13		NaH (3 equiv.), THF, r.t. 20 h	Amino aldehyde	145
14		NaHMDS	Amino-aldehyde	146
15		EtOH:DMF 1:1 (v:v), 60 °C, 2 h nitroalkene (5 equiv.)	nitroalkene	147
16		EtOH:DMF 1:1 (v:v), 70 °C, aldehyde (5 equiv.) nitro-methane (10 equiv.) triethyl-orthoformate (5 equiv.) piperidine (5 equiv. 5 h	nitromethane Mannich: imine made in situ: aldehyde + piperidine	147

Entry	Structure to be deprotonated	Conditions	Electrophile	Reference
17		EtOH chalcone (3 equiv.) NaOH (30 equiv.) 1 h, 75 °C	Generation of phenols: chalcone	148
18		1) LDA (2 equiv.) THF, 0 °C 2) BnBr (5 equiv.)	R-Br	149, 150
19		$Sc(OTf)_3$ (0.1 equiv.) amine (1.2 equiv.), Aldehyde (1.2 equiv.)	Mannich: imine made in situ: aldehyde + amine	151, 152

(*): C-atom to be alkylated; R: alkyl unless specified

Special attention has been given to the enantioselective alkylation using chiral auxiliaries on the solid support (entry 18 in Table 1) [149, 150]. Various resins and linkers have been investigated; thus, Wang resin was found superior to Merrifield and Tentagel resins, when a



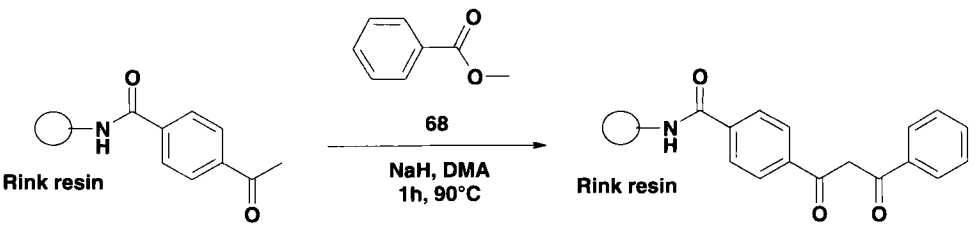
Scheme 16

phenyl spacer R = 1,4-phenylene was used. In turn, Merrifield resin with an ether linkage to the auxiliary (R = O) gave good stereoselectivities. The reaction time was also found to be important, as cleavage of the substrate from the resin was observed [150]. The loss of product may have been caused by take-up of water by the hygroscopic resin bearing the carbanion. Another approach to provide carbanion-like reactivities is the use of silylenolates (entry 9 in Table 1). Drierite was added to the reaction mixture to assure dryness.

Especially intriguing is the generation of a structure having two potential carbanionic centers on the solid phase (entry 17 in Table 1) (Scheme 16) [148]. Thus, a 1-(2-oxo-propyl)-pyridinium moiety was allowed to react with various chalcones to give 2-pyridinium cyclohex-5-enones, attached to the solid phase via their pyridinium substituent. Hoffmann elimination, driven by aromatization then rapidly occurs to liberate a set of phenols in high yields and purity.

3.3.7.1 Experimental Approach

Procedure: Claisen Condensation on an Acetyl Residue Bound to Polystyrene Support [139]



Scheme 17. Claisen condensation on a polymeric support.

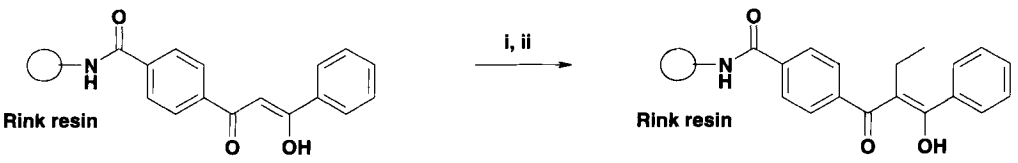
Resin bearing acetyl residues (50 mg, 0.0225 mmol) was suspended in a 1 M solution of carboxylic ester in DMA (0.675 mL, 0.675 mmol). Under inert gas, sodium hydride (60 % suspension in mineral oil, 18 mg, 0.450 mmol) was added to the reaction mixture, which was shaken well for 1 h at 90° C. The resin was filtered, washed as follows:

1) 5 x 1mL HOAc:H_2O (3:7, v:v)
2) 5 x 1 mL DMA
3) 5 x 1 mL DMSO
4) 10 x 1 mL iPrOH

Subsequently, the resin was dried under reduced pressure.

Procedure: Monoalkylation on Polystyrene Resin using Tetrabutyl Ammonium Fluoride (Bu_4NF, TBAF) [139]

Resin bearing 1,3 diketone (20 mg, 8.6 μmol) was treated with a 1 M solution of Bu_4NF in THF (86 mL) for 2 h at rt. After addition of 150 μL of a 2.5 M solution of the appropriate alky-



70 71

Scheme 18. (i) TBAF, THF, 2 h, rt.; (ii) CH_3CH_2I, 2 h, rt.

lating agent, here ethyl iodide, the reaction was continued for another 2 h. The resin was filtered off and washed as follows:

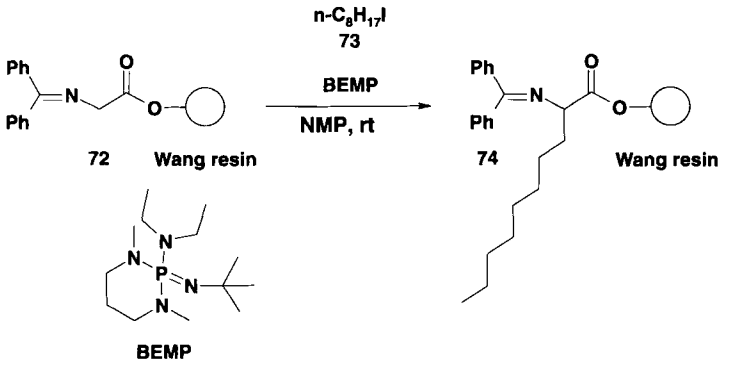
1) 10 x 0.5 mL THF, 2 min
2) 10 x 0.5 mL HOAc:DCM (1:5, v:v), 2 min
3) 5 x [a) 2 mL MeOH, 2 min; b) 2 mL DCM, 2 min]
4) 5 x 2 mL Et_2O

Procedure: Monoalkylation of an Amino Acid on a Polymeric Support using Schwesinger Base [140, 141]

(This reaction is also suitable for alkylating amino acids bearing an α-alkyl substituent so that dialkylation does occur. In this case the amino function must be protected as an aldimine.)

To 0.175 g of Wang resin bearing glycine benzophenone imine (0.1 mmol), suspended in NMP (0.85 mL) and 1.33 M 1-iodooctane solution in NMP (0.15 mL, 2 equiv.) was added 0.4 M BEMP solution in NMP (0.5 mL, 2 equiv.). The reaction mixture was mixed for 24 h at rt. The resin was filtered and washed as follows:

1) 3 x 3 mL DMF
2) 3 x 3 mL DCM



Scheme 19. Alkylation of amino acid imines with Schwesinger base.

3) 3 x 3 mL THF
4) 3 x 3 mL THF:H_2O (3:1, v:v)
This resin was then used in the next reaction step.
For the alkylation with some alkyl bromides or chlorides, Finkelstein exchange with I^- is required:
0.25 mL of a 0.35 M Bu_4NI/NMP solution (2 equiv.) was added before the base.
Some reactions require a large excess of halide, in cases where the latter is sequestered byelimination to an alkene. When adding 10 equiv. of reagents, only 0.25 mL of NMP was added followed by 0.75 mL of the R-X solution, 0.5 mL of a 2 M BEMP/NMP solution, and the Bu_4NI was added as a solid due to low solubility.

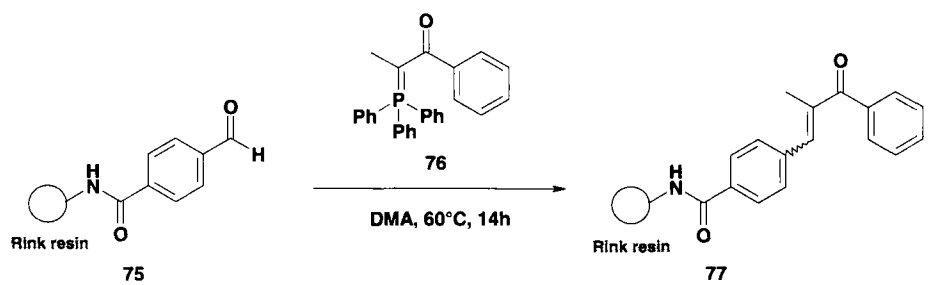
3.3.7.2 Comment on Reactions using Schwesinger Base

In some cases, when Schwesinger base is used in reaction sequences, the removal of polymer-associated base may be difficult. In this case, a five-fold wash with DCM:HOAc (4:1, v:v) may be employed. The loss of polymer-bound substrate, attached to a Rink-linker via amide, ester or amine functions is minimal during this treatment.

3.3.7.3 Wittig and Related Reactions

Wittig/Horner–Wadsworth–Emmons reactions sometimes lead to low yields, when the reactant bearing the stabilized carbanion is bound to the support by an ester linkage [143]. The presence of OH^- ions during the reaction or work-up may be responsible for the cleavage of product from the polymer.

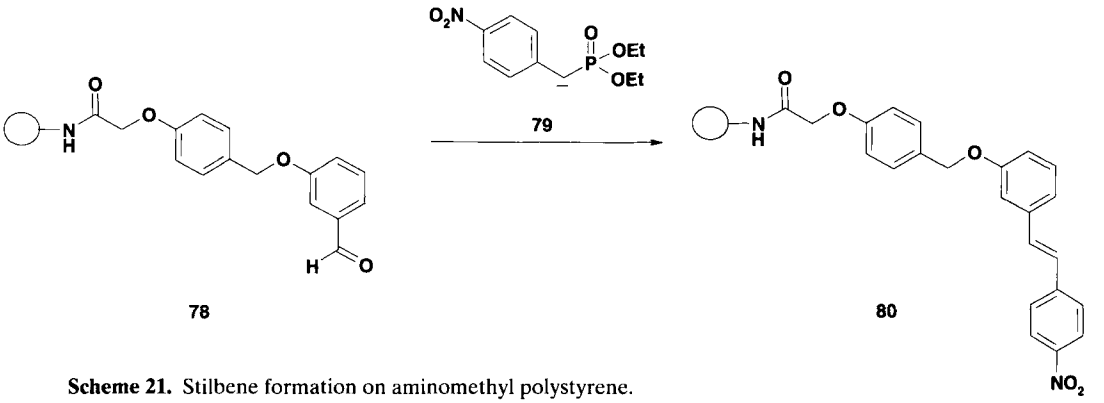
When chiral amino aldehydes were coupled to phosphorus ylides on a support, the "salt-free" Wittig procedure caused the least epimerization [145]. By contrast, the opposite methodology is very successful, where the ylide formed in solution is allowed to react with an aldehyde on the polymeric support [153–155].



Scheme 20. Wittig reaction on a solid support. The phosphorane is generated according to Dombrovskii et al. [155].

Procedure: Wittig on Rink Resin [154]
A 23.6 mL portion of a 0.25 M solution of 1-phenyl-2-(triphenyl-phosphanylidene)-propan-1-one 161 (5.91 mmol) in DMA was added to 2.0 g (788 μmol) of resin-bound 4-formyl-benzamide. The resulting mixture was shaken at 60° C for 14 h. The resin was filtered, washed with DMA and iPrOH and air-dried on the frit. Cleavage of the resin with 20 % (v/v) TFA/DCM for 15 min provided 4-(2-Methyl-3-oxo-3-phenyl-propenyl)-benzamide in 71 % yield.

Procedure: Horner–Emmons Condensation on Aminomethyl Polystyrene Resin with Various Spacers and Wang Linker [156]



Scheme 21. Stilbene formation on aminomethyl polystyrene.

Diethyl 4-nitrobenzylphosphonate [0.27 g, 23 mmol, previously prepared by the reaction of 4-nitrobenzyl bromide (5 g, 23 mmol) with triethyl phosphite (3.8 g, 23 mmol) at 100° C for 3 h] was dissolved in DMF (5 mL), treated with sodium methoxide (81 mg, 1.5 mmol), and stirred for 15 min. The bright-red solution was added to aminomethyl polystyrene resin, bearing a hydrophilic spacer and a Wang linker (200 mg) and was shaken overnight. The resin was isolated by filtration and washed as follows:
1) 5 x H_2O
2) 5 x DMF:H_2O (1:1, v:v)
3) 5 x DCM
4) 2 x MeOH.
From the resin dried in vacuo, the stilbene was liberated by treatment with TFA:H_2O (19:1, v:v) for 2 h. The filtrate was collected, evaporated and the crude product purified by flash chromatography [ethyl acetate:hexane gradient (3:7 to 1:0, v:v)] to give the desired product (68 mg).

The same reaction was optimized and performed in a 10 mL syringe reactor with 200 mg of various resins as follows. The resin was allowed to react with 2 mL of a solution of 4-nitrobenzyl diethylphosphonate (1.0 g, 3.7 mmol) and sodium methoxide (0.32 g, 5.9 mmol) in DMF (20 mL). The resin was shaken for 5 h and washed as follows:

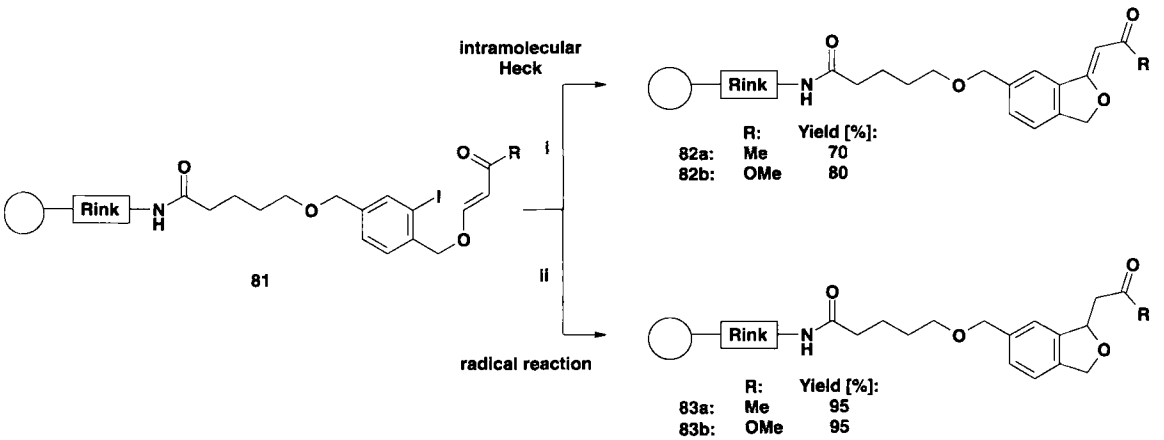
1) 5 x DMF
2) 5 x DMF:H_2O (1:1, v:v)
3) 3 x DCM
4) 3 x MeOH

From the resin, dried in vacuo, the product stilbene was liberated by treatment with TFA:H_2O (19:1, v:v) for 2 h. The filtrate was collected and evaporated to dryness.

3.3.8 Radical Reactions to Achieve C-C Bonds

Radical reactions were performed on the solid phase to achieve certain cyclization reactions. In these cases, a radical generated by a selective reaction is allowed to react with a nonradical, mainly a double bond. The radical character in such a reaction is not destroyed during the process; therefore, only catalytic amounts of radical initiator are required. The products coming from radical reactions are mostly not diffusion controlled and the selectivities are influenced strongly by the variation of the substituents [157], which is often in sharp contrast to the requirement of combinatorial syntheses to employ transformations that allow the introduction of a wide variety of substituents or functional groups.

When steric and electronic features of the radical intermediates do not allow the desired radical propagation steps to be sustained, the product yield may be low. In such a case more favorable – but often undesirable – processes such as H-abstraction from the solvent may become dominant [158]. Especially intriguing are scaffolds, where radical and ionic cyclizations lead to different products. Thus, Berteina et al. described the formation of 1-alkylidene-5-H-dihydrobenzofuran and 1-alkyl-5-dihydrobenzofuran from o-iodobenzyl vinylethers. The former product was formed by an intramolecular Heck reaction, while the latter was formed in high yields in a radical cyclization [159].



Scheme 22. Two methods of cyclization. (i) Heck reaction: 0.3 equiv. $Pd(OAc)_2$, 0.6 equiv. PPh_3, 2 equiv. nBu_4NCl, 4 equiv. K_2CO_3, DMA, 100° C, 27 h. (ii) Radical reaction: 3 equiv. nBu_3SnH, 0.6 equiv. AIBN, benzene, reflux, 48 h.

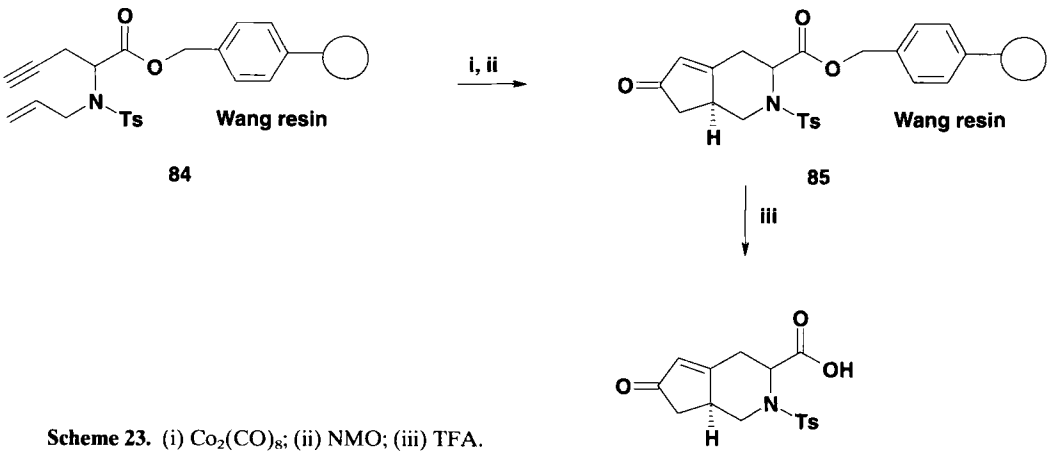
SmI_2 [160] and AIBN [158, 159, 161] have been used as initiators for radical reactions. A means of obtaining a clean product is described by Du and Armstrong [160], who selectively trap the final radical product by reduction to an organosamarium. The latter is then allowed to react with various polymer-bound electrophiles.

3.3.9 The Pauson–Khand Cyclization

The Pauson–Khand reaction [162–164] has been applied in combinatorial chemistry for some years [165–167]. Its mild reaction conditions, together with the improved accessibility of allylated amino acids through Pd-mediated allylations, might allow a greater applicability of this reaction type.

3.3.9.1 Experimental approach

Procedure: Intramolecular Pauson–Khand Reaction on Solid Phase [168]



Scheme 23. (i) $Co_2(CO)_8$; (ii) NMO; (iii) TFA.

To a suspension of Wang resin bearing a propargylated and allylated amino acid (0.53 g, 0.34 mmol, loading: 0.64 mmol g^{-1}) in DCM (10 mL) in a peptide shaker was added $Co_2(CO)_8$ (0.17 g, 0.51 mmol) The suspension was shaken under N_2 for 2 h with periodic venting. The solvent was filtered off and the resin washed with DCM (3 x 10 mL). The resin was suspended in DCM (10 mL) and N-methylmorpholine-N-oxide (NMO) (0.13 g, 1.11 mmol) was added. The mixture was shaken under N_2 with periodic venting for 1 h, and a second portion of NMO (0.13 g) was added. After shaking for another 1 h, the solvent was filtered off, and the resin was washed as follows:

1) 3 x 10 mL DCM
2) 3 x 10 mL HOAc:DCM (1:3, v:v)
3) 3 x 10 mL DCM

The resin was then shaken with TFA:DCM (1:1, v:v) (15 mL) for 1 h, filtered, and washed with DCM (3 x 10 mL). The combined filtrates were concentrated, taken up in DCM and reconcentrated twice, and then dried in vacuo to give 0.11 g of bicyclic amino acid.

3.3.10 Summary and Outlook

A survey of the recent literature suggests that almost all reaction types may, in principle, be adapted to solid phase. The use of many carbanion equivalents, when readily manipulated on solid phase, has been applied to numerous syntheses for diverse heterocycles, and some of these are discussed elsewhere in this book.

In some cases, as in transition metal-catalyzed C-C bond formation, the advantage of using large excesses of reagents, but without the accompaniment of severe problems when isolating the required product, has been advantageous. In the case of transition metal-catalyzed reactions, where the oxygen-mediated degradation of reagents may cause many reactions to slow or even stop, the use of excess reagents or multi-coupling protocols has been shown to allow high reaction yields. In addition, the development of more robust catalytic systems will broaden the scope of transition metal catalysis in combinatorial chemistry. However, equally important is the choice of robust linkage systems that are stable to reaction conditions involving either strong base and/or Lewis acids. And on a final note, chemically robust solid phases with high loading are called for, and not only for C-C bond-forming reactions.

Fortunately, when we consider the progress that has been made in this field within the past few years, and the ongoing investigations, it is clear that many of these present shortcomings will most likely be overcome within the near future.

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3.4 Combinatorial Synthesis of Heterocycles

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3.4.1 Introduction

The scope of combinatorial chemistry has broadened to a remarkable extent over the past years, ever since the preparation of a small benzodiazepine library [1] illustrated the applicability of combinatorial synthesis beyond chain-like, oligomeric structures. Although the concepts formulated by Furka in the 1980s [2, 3] appeared to possess broad validity, they were initially a domain of peptide and oligonucleotide chemistry. On one hand the immediate relevance for epitope mapping and mimotope generation [4] with peptidic compounds was apparent, as much as the utility for genetic engineering applications [5]. On the other hand, the assembly of bio-oligomers could rely on established, well-optimized protocols of solid-phase synthesis, making the preparation of large libraries immediately accessible to laboratories possessing the relevant skills. The ambition to apply the combinatorial principles to a much more extensive exploitation in drug discovery was a logical consequence of the enormous potential residing in combinatorial chemistry. It was envisaged that high-performing systematic schemes of compound library preparation and testing would contribute both to lead finding (for the identification of novel active dstructures in a given discovery target), as well as to lead optimization (for the rapid progress of activity profiles). Consequently, a key success factor for combinatorial chemistry was to develop the ability to efficiently prepare a large variety of structure types with drug-like features, and therefore to overcome existing limitations on the type of suitable chemistry.

In the years preceding the advent of combinatorial chemistry, the experiences made in transforming peptide leads into viable drug candidates indicated that such processes are sometimes feasible, but often too demanding in terms of resources and time requirements to become standard practice. For combinatorial chemistry to have a noticeable impact on drug discovery approaches, it is evidently a "must" to produce molecular entities which meet basic criteria of modern lead structures with regards to molecular weight ("small molecules") and the physico-chemical parameters compatible with an increased likelihood for superior bioavailability and pharmacokinetics in general. Nowadays such molecular features are often referred to as "compliance to the rule-of-five" [6].

In the mid 1990s, the missing piece for a straightforward establishment of combinatorial chemistry as a key discovery method was the general lack of methodologies for the high yield preparation of small molecules by solid-phase synthesis. This synthesis format was, and remains, instrumental for the efficient preparation of combinatorial libraries by "split-and-mix" [3, 7] or "sort-and-combine" [8] protocols. Also, the automation of synthetic processes greatly benefits from the uniform and predictable physical properties of intermediates grafted on the solid support, as well as from the ease of removing excess reagents by simple filtration and washes.

This chapter illustrates selected examples of solid-phase syntheses of heterocycles, which are based on combinatorial synthesis schemes developed in recent years. Heterocycles are

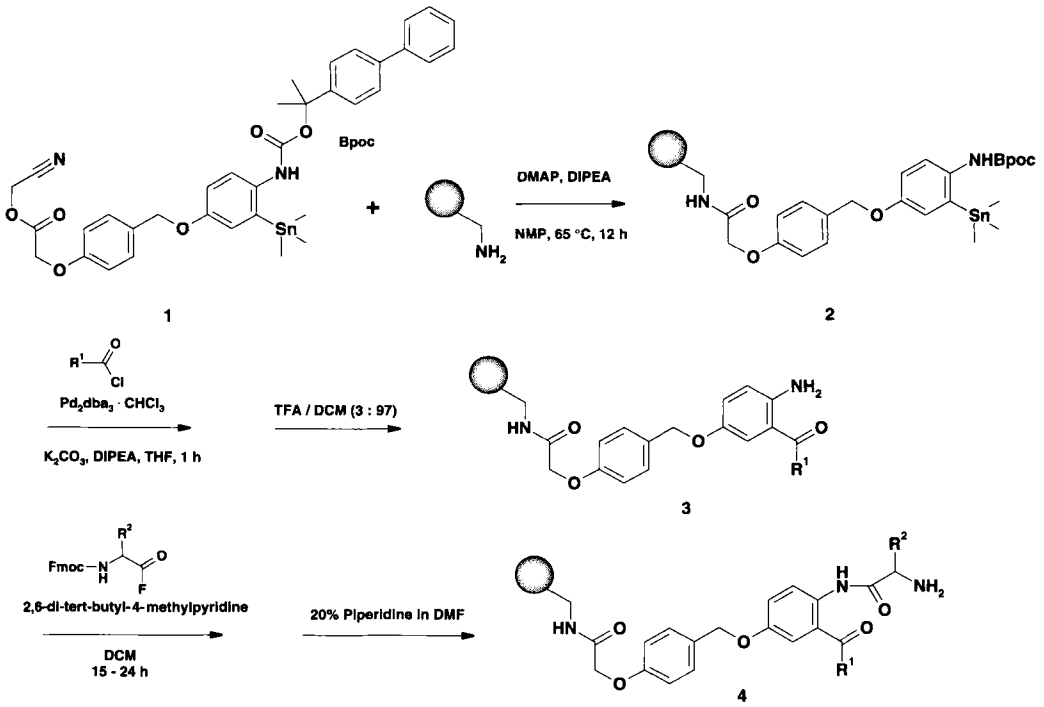
privileged molecules for assuming the role of attractive lead structures, giving access to a large diversity of conformationally constrained structures derived from stable low molecular weight templates. Computational studies assessing diversity measures of library components have indicated that one single low molecular weight template (with multiple substituent sites) may be used for generating a diverse collection of compounds, but that the common template structure also introduces a residual similarity [9]. It is therefore important to develop the capability to work with a variety of templates. The heterocyclic chemistry described in this chapter was selected specifically on the basis of its potential to be utilized for the efficient preparation of highly diverse combinatorial libraries by a sequence of consecutive steps. Usually, substitutions or modifications on more than two sites of each template are possible in these cases. This allows the systematic combining and reshuffling of synthons based on protocols validated by the original authors on whole sets of appropriate chemical building blocks (reactants). Many more heterocyclic systems were described in the literature, but often the potential for diversification remains modest, with one or two variable sites.

Meanwhile, the wealth of single transformations on solid phase can be grasped by consulting electronic databases such as SPORE (Molecular Design Ltd., San Leandro, USA) or SPS (Synopsys Scientific Systems, Leeds, UK). Obviously, only a small fraction of the heterocyclic chemistry described in solution has been "translated" into useful combinatorial reaction systems on solid phase. The "translation" of protocols from solution chemistry into validated solid-phase procedures is a nontrivial task, often requiring substantial development time. This is particularly the case when broad validation for a large variety of building blocks is sought. In general, diversity schemes combine large sets of building blocks (reactants) with each other, to such an extent that it is not possible to apply individually tailored reaction conditions for each combination. Thus, suitable conditions with general validity need to be identified in a more or less laborious and extensive "scope and limitations study", where a representative set of combinations are synthesized under systematically varied conditions. The difficulty to design a sequence of compatible reactions, to refine the experimental conditions, and to reach near-quantitative yields over multistep procedures is reflected by the proportionally modest number of mature chemical diversity systems, compared with the abundant number of described individual organic solid-phase reactions. The cases reported here begin with the benzodiazepine and hydantoin systems, which pioneered the field of combinatorial chemistry on small molecules, followed in loose order by systems with increasing scaffold complexity and similar scope.

3.4.2 Benzodiazepines

As mentioned previously, a new era of combinatorial chemistry was entered when one of the most important classes of bioavailable therapeutic agents was shown to be accessible through building block assembly on a solid phase [1]. A library of 1,4-benzodiazepines was prepared from three building block types: 2-aminobenzophenones or 2-aminoacetophenones, Fmoc-amino acid fluorides, and alkylating agents. A somewhat limiting aspect of this first account published by Bunin and Ellman [1] in 1992 was the small number of commercially available 2-aminoarylketones. From the same laboratory a similar synthesis method (illustrated here in Schemes 1 and 2) for 1,4-benzodiazepines was developed, with a broader scope [10]. A

high-yielding solid-phase synthesis procedure for 2-aminoarylketone derivatives that display diverse chemical functionality was directly incorporated into the approach for diverse benzodiazepine assembly. A palladium-mediated Stille coupling between an acid chloride and a support-bound N-protected (2-aminoaryl)stannane is the key bond-forming step because it proceeds under mild and generally applicable reaction conditions tolerant of a wide range of functionality. For the N-protection of the (2-aminoaryl)stannane the 2-(4-biphenylyl)-prop-2-oxycarbonyl (Bpoc) group was chosen, since it is stable to both basic and Stille coupling conditions, yet can be cleaved under very mild acidic conditions, to which the alkoxybenzylether linker is completely stable. Stille reactions are performed with the "ligandless" catalyst $Pd_2dba_3{\cdot}CHCl_3$, which provides a rapid reaction at room temperature, while coupling with $Pd(PPh_3)_4$ required elevated temperature causing some cleavage of the Bpoc group.

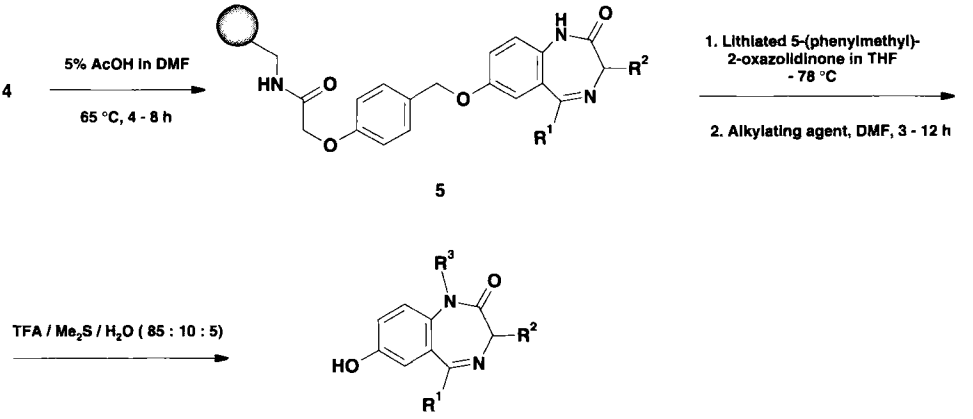


Scheme 1

Procedure

The generic building block **1** (cyanomethyl active ester) was coupled to aminomethylated polystyrene resin by reacting 2.0 g (1.04 mmol) of the solid phase with a solution of ester 1 (1.50 g, 2.10 mmol, 2 equiv.), DMAP (256 mg, 2.10 mmol, 2 equiv.), DIPEA (365 µL, 3.15 mmol, 3 equiv.) in N-methylpyrrolidone (NMP, 8 mL) at 65° C for 12 h. The resin **2** was rinsed with EtOAc (three times) and DCM (three times), then dried under vacuum.

Resin **2** (0.4 g, 0.15 mmol) was added to a dried Schlenk flask under nitrogen. Also $Pd_2dba_3{\cdot}CHCl_3$ (60 mg, 60 µmol), K_2CO_3 (10 mg), THF (4.0 mL) and DIPEA (40 µL, 0.20 mmol) were added. The resin was stirred for 3 min to ensure complete solvation, at which



Scheme 2

point the acid chloride (1.0 mmol, 6.67 equiv.) was added slowly. The reaction was allowed to proceed for 1 h, after which the mixture was transferred to a fritted (solid-phase) flask and rinsed with DCM (three times), DMSO saturated with KCN (once), MeOH (once), water, MeOH (three times) and DCM (three times). The resin was treated with DCM/TFA (97:3) for 5 min to provide support-bound 2-aminoacetophenone or 2-aminobenzophenone **3**. The resin was rinsed with DCM (five times), MeOH (five times) and dried under nitrogen. To support-bound 2-aminoacetophenone or 2-aminobenzophenone **3** was added 0.2 M Fmoc-protected amino acid fluoride and 0.2 M 2,6-di-tert-butyl-4-methylpyridine in DCM (at least eight-fold excess relative to the molar amount of resin **3**). After stirring for 15–24 h at rt, the solution was removed by filtration cannula and the anilide was washed with DCM (three times) and DMF (three times). The Fmoc protecting group was removed by incubation and repeated washings with 20 % piperidine in DMF over a period of 20–30 min (rt) or until no residual dibenzofulvene was detectable in the eluates. The solvent was removed and the resin was washed with DMF (three times) and with DCM (three times) to the deprotected anilide **4**.

The intermediate **4** was then taken up in with 5 % acetic acid in DMF or NMP and the slurry stirred at 60° C for 12 h to give **5**. The immobilized cyclic product was rinsed with DMF (three times), DCM (three times) and THF (three times). The reaction flask was sealed with a fresh rubber septum, and was flushed with nitrogen followed by cooling to 0° C. In a separate flame-dried 25 mL round-bottomed flask was added 12 equiv. (with respect to **5**) of 5-phenylmethyl-2-oxazolidinone. To the reaction flask was added freshly distilled THF (the appropriate volume to provide a 0.2 M solution of the 5-phenylmethyl-2-oxazolidinone). The resulting clear solution was then cooled to –78° C and 1.6 M n-butyl lithium in hexanes was added dropwise with stirring by syringe (10 equiv. with respect to **5**). The solution was stirred at –78° C for 15 min and then transferred by cannula to the solid support **5** with stirring at 0° C. The resulting slurry was stirred at 0° C for 1.5 h, at which point 15 equiv. of the appropriate alkyl halide was added by syringe followed by addition of anhydrous DMF to reach a final solvent ratio of approx. 70:30 THF/DMF. The slurry was allowed to warm to rt with stirring. After 3–12 h at rt, the solvent was removed by filtration cannu-

la. The support was then washed with THF (once), 1:1 THF/H_2O (twice), THF (twice) and DCM (twice).

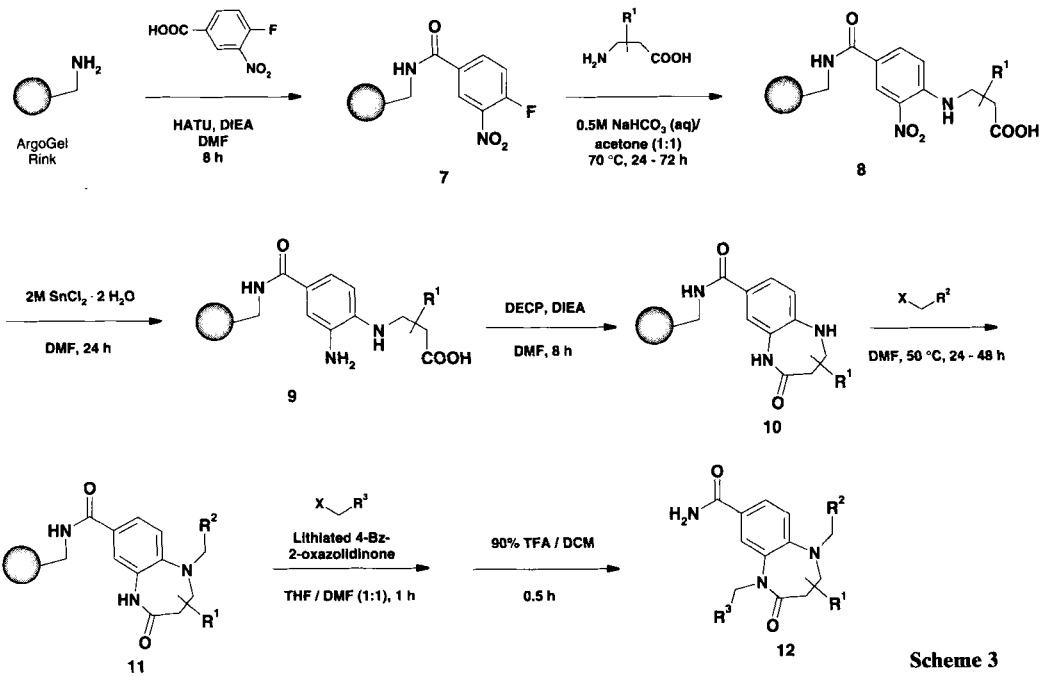
To the fully derivatized product on solid support was then added 15 mL TFA/H_2O/dimethylsulfide (95:5:10) and the mixture stirred for 12 h. The cleavage solution was removed by filtration cannula, and the resin was rinsed with an appropriate solvent (e.g., MeOH/DCM). Concentration of the combined filtrates then provided the crude product **6**. Products may be purified by silica gel chromatography with hexane/EtOAc 50–0/0.5–100 % as eluant to give purified products in yields of 52–82 %.

Palladium black precipitates on the resin during Stille coupling. After the reaction solution is removed and the resin rinsed, a brief treatment with dilute KCN in DMSO clears the precipitate from the resin.

While initially the main synthetic interest resided in 1,4-benzodiazepin-2-ones [1, 11–13] and 1,4-benzodiazepin-2,4-diones [14–18], another 1,5-benzodiazepin-2-one system was explored with a strategy outlined in Scheme 3 [19]. Of particular interest is the role 4-fluoro-3-nitrobenzoic acid, a common fundamental building block at the origin of all the structures aimed for. Accessing diversity through one or more simple reactants common to all members of a library has favorable practical consequences on the production phase of a combinatorial library.

The extension of this synthetic strategy to the preparation of 1,5-benzothiazepin-4-ones and 4-alkoxy-1,4-thiazin-3-ones by using suitably protected forms of cysteine and α-mercapto acids in nucleophilic aromatic substitution reactions of **7** has been envisaged by the authors.

Various other solid-phase syntheses of heterocycles made similar use of 4-fluoro-3-nitrobenzoic acid, e.g., for the preparation of quinoxalin-2-ones [20] or benzimidazolones [21].



Scheme 3

Procedure

From ArgoGel-Rink-resin (Argonaut, CA, USA) the Fmoc protecting group was removed by incubation and repeated washings with 20 % piperidine in DMF over a period of 20–30 min (rt) or until no residual dibenzofulvene was detectable in the eluates. The resin was rinsed thoroughly with DMF and allowed to react with 4 equiv. of 4-fluoro-3-nitrobenzoic acid, 4 equiv. of HATU, and 8 equiv. of DIEA in DMF. After appropriate washes with DMF (five times), DCM (three times) and MeOH (three times), 300 mg of the intermediate **7** were treated with 12 mL of a hot 0.17 M solution of an aliphatic β-amino acid (~ 20 equiv.) in a mixture (1:1) of acetone/0.5 M $NaHCO_3$ (aqueous) while agitating and heating to 70–75° C for 24 h. If anthranilic acids were used instead of β-amino acid ,the reaction time was prolonged to 3 days at a temperature of 75–80° C.

The immobilized nitroaromatic acid **8**, rinsed with DMF, was reduced to **9** by suspending and agitating the resin in 2 M $SnCl_2 \cdot 2H_2O$ in DMF for 24 h at rt. Following further washes with DMF, 4 mL of a 0.2 M solution of DIEA in DMF was added at rt and subsequently 0.8 mmol (~ 8 equiv.) diethylcyanophosphonate (DECP). After a reaction time of 8 h, the supernatant was removed and resin **10** was washed with DMF (five times), DCM (three times), MeOH (three times), DCM (twice) DMF (three times), DCM (three times) and dried in vacuo.

A first alkylation step was performed suspending **10** in a 2 M solution of a suitable alkyl halide in DMF and reacting at 50° C for 24–48 h. After thorough washing with DMF (three times), DCM (three times) andTHF (three times) intermediate **11** was subjected to the final alkylation. The reaction flask was sealed with a fresh rubber septum, and was flushed with nitrogen followed by cooling to 0° C. In a separate flame-dried 25 mL round-bottomed flask was added 12 equiv. (with respect to **11**) of 5-phenylmethyl-2-oxazolidinone. To the reaction flask was added freshly distilledTHF (the appropriate volume to provide a 0.2 M solution of the 5-phenylmethyl-2-oxazolidinone). The resulting clear solution was then cooled to –78° C and 1.6 M n-butyl lithium in hexanes was added dropwise with stirring by syringe (10 equiv. with respect to **11**). The solution was stirred at –78° C for 15 min and transferred by cannula to the solid support **11** with stirring at 0° C. The resulting slurry was stirred at 0° C for 1.5 h, at which point 15 equiv. of the appropriate alkyl halide was added by syringe followed by addition of anhydrous DMF to reach a final solvent ratio of approx. 70:30 THF/DMF. The slurry was allowed to warm to ambient temperature with stirring. After 3–12 h at rt, the solvent was removed by filtration cannula. The support was then washed withTHF (once), 1:1 THF/H_2O (twice),THF (twice) and DCM (twice).

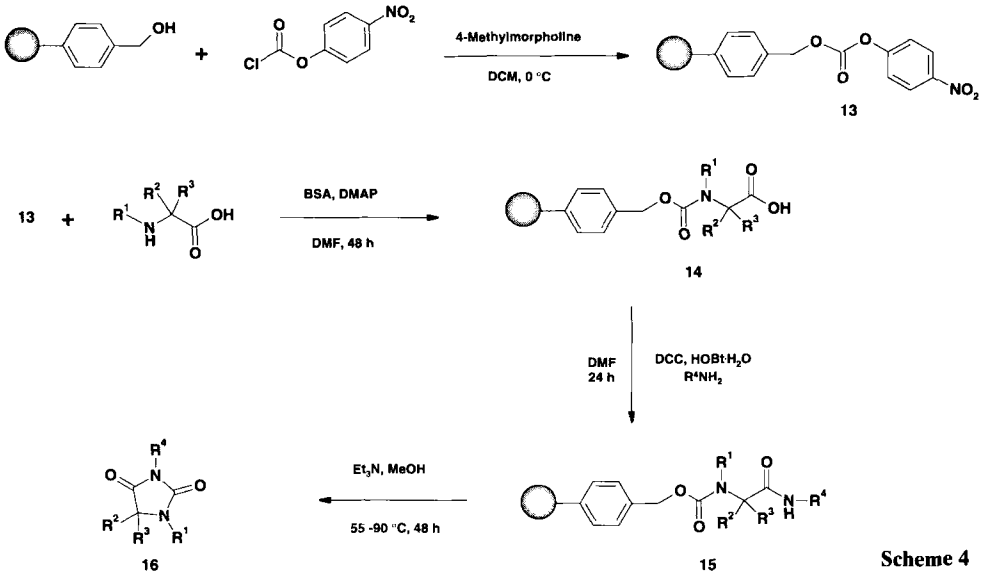
To the fully derivatized product on solid support was then added excessTFA/DCM (90:10) and the cleavage reaction allowed to continue for 0.5 h at rt . The cleavage solution was removed by filtration cannula, and the resin was rinsed with an appropriate solvent (e.g., MeOH/DCM). Concentration of the combined filtrates then provided the crude product **12** in yields of >80 % (56–67 % isolated, purified by RP-HPLC)

The same set of alkyl halides used for N^5-alkylation was found suitable also for N^1-alkylation, with the notable expansion to include other alkyl iodides beyond methyl and ethyl iodide. No evidence was found for C- or O-alkylation. Some "resin bleeding", not uncommon in the use of PEG-derived solid supports, was reported. This relates to the presence of PEG fragments (released during strong acid treatments) in the crude samples.

3.4.3 Hydantoins and Thiohydantoins

The hydantoin scaffold is among the earliest described diversity generation systems in combinatorial chemistry [12]. The first procedures were appropriate for syntheses of small arrays, but not suitable for large libraries. Practical limitations such as the small choice of required building blocks from commercial vendors, as well as conceptual limitations in the number of diversity sites modifiable directly on the solid phase, made it necessary to design improved approaches for a more extensive exploitation of this template's diversity potential.

A newer method [22] switched to N-terminal (rather than C-terminal) attachment of the amino acid building blocks and to base- (rather than acid-) catalyzed cyclative cleavage strategy. In contrast to the first published method for the solid-phase synthesis of hydantoins [12], which relied on isocyanates for derivatization at R^4, the route illustrated here utilizes primary amines and anilines, of which there are more than 3000 commercially available.



Scheme 4

Procedure

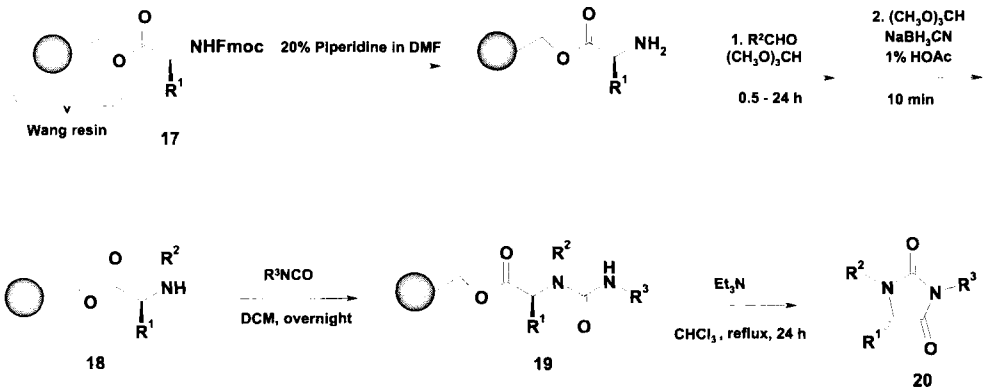
To a stirring solution of 1 % crosslinked hydroxymethylpolystyrene (3.26 g, 3.26 mmol) was added p-nitrophenyl chloroformate (1.31 g, 6.5 mmol, 2 equiv.) in one portion and N-methyl morpholine (659 mg, 6.5 mmol, 2 equiv.) in DCM at 0° C. The reaction mixture was warmed to rt, stirred overnight, filtered and washed with DCM. Drying overnight in a vacuum oven gave 3.28 g of light pink resin **13**.

An N-alkyl or N-aryl substituted amino acid (4 equiv.) was dissolved with gentle heating in DMF using N,O-bis(trimethylsilyl)acetamide (BSA; 10 equiv.) and then coupled with activated carbonate **13** in the presence of DMAP (2 equiv.) to obtain the free acid resin-bound intermediate **14** after 48 h at rt. The resin was washed extensively with DMF, then with MeOH and dried.

Following thorough washes with DMF, amide formation was carried out for 24 h using standard carbodiimide coupling conditions (DCC, 4 equiv., HOBt.H_2O, 4 equiv.) with an excess of a primary amine (4 equiv.) in DMF. Intermediate **15** was obtained after exhaustive washing in DMF, followed by MeOH.
Treatment of **15** with excess triethylamine (14 equiv.) in methanol for 48 h at temperatures between 55–90° C afforded hydantoin **16**, which was released into solution in purities of generally around 90 % and mass recoveries of 15–76 %.

Because of the wide range of reported therapeutic effects, new hydantoin derivatization strategies continue to attract the interest of medicinal chemists. An utmost pragmatic strategy, which is not uncommon in pursuing rapid generation of "small molecule" libraries for screening purposes, consists of applying much of the chemical diversification at exocyclic positions of the heterocyclic scaffold. This simplifies matters considerably in the validation phase for the production of new libraries, because many reactions steps remain unchanged from one diversity system to another, and may be carried over to a new reaction scheme. A new hydantoin derivatization scheme [23] was recently reported, where orthogonally protected diamino acids are bound to the solid support, thereby introducing two sites of diversity upfront (according to previously known procedures) before the five-membered hydantoin ring is built up with just one additional substituent.

While the procedure of Scheme 4 [22], like the original method, introduces much of the diversity (i.e., up to three variable positions) off the solid phase, thereby limiting the combinatorial potential available for "split-and-mix" protocols, another scheme described recently [24] builds up the diversity stepwise on solid phase, which simplifies the logistics for automated library production. Intermediates may also be used to access thiohydantoins (see Scheme 6).



Scheme 5

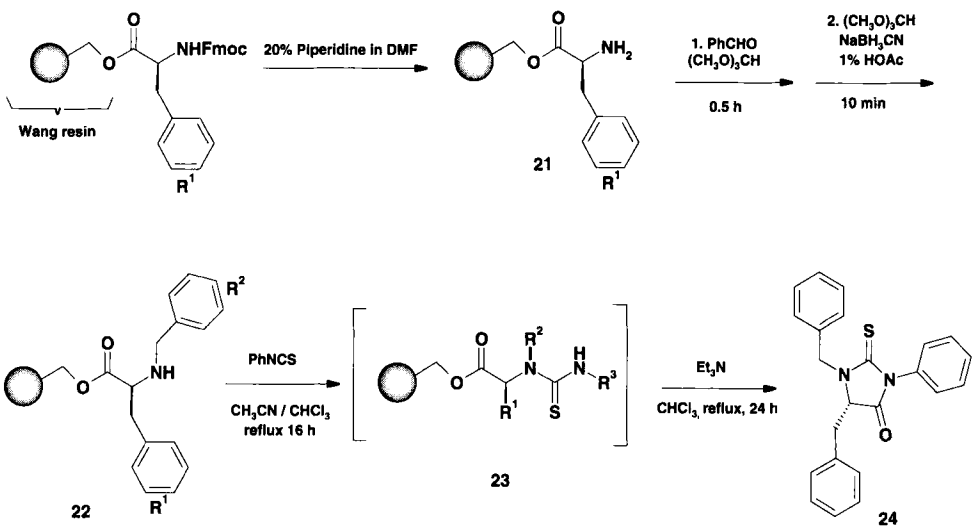
Procedure
To 0.284 mmol of an appropriate Amino acid Wang resin with a free α-amino group (e.g., Fmoc-Phe Wang 0.49 mmol g^{-1} repeatedly treated with 20 % piperidine in DMF: (2 x 5 min, 1 x 20 min), swelled in 6 mL trimethyl orthoformate (TMOF) was added the aldehyde build-

ing block (5.68 mmol, 20 equiv.) and the reaction was mixed at rt for 30 min (24 h if 3,4,5-trimethoxybenzaldehyde is used). $NaCNBH_3$ (5.68 mmol, 20 equiv.) dispersed in 3 mL trimethyl orthoformate (TMOF) was added, followed by HOAc (60 µL), and the reaction was mixed for an additional 10 min (if valeraldehyde is used, prior to the addition of $NaCNBH_3$ in TMOF the reaction mixture was drained and the resin washed with DMF, DCM and TMOF (3 x 6 mL each). The resin suspension was filtered and the resin washed with DMF, MeOH, 10 % Et_3N in DCM, MeOH, DCM, MeOH, and ether. Resin **18** was obtained after drying in vacuo.

Resin **18** (0.108 mmol, 1 equiv.) swelled in anhydrous DCM, was reacted with an appropriate isocyanate building block (1.08 mmol; 1 equiv.) and agitated at rt overnight. The resin was filtered and subsequently washed with DMF, MeOH, DCM, MeOH, ether, and dried in vacuo to provide intermediate resin **19**.

Resin 19 (0.108 mmol, 1 equiv.) was reswelled in $CHCl_3$ (1 mL) and triethylamine (1.08 mmol, 1 equiv.) was added. The reaction was heated at reflux for 24 h and then cooled to rt. After filtration, the eluate was collected. The resin was washed with MeCN and DCM several times, and the washes were combined with the first eluate collected previously. The combined organic washes were evaporated and the residue was dried at 50 ° C in vacuo. The residue **20** was purified by radial chromatography eluting with hexane/EtOAc (5:1). Isolated yields were in the range of 48–58 %.

In many literature procedures of reductive alkylations (of primary amines) concerns with the bis-alkylation side-reaction to the tertiary amine are evident. The claims are that this type of problem does not affect the procedures described above [24]. For the reactions with isocyanates, best results are obtained with a chlorinated solvent (DCM). The isothiocyanates give optimum yields when heated to reflux in acetonitrile.



Scheme 6

Procedure

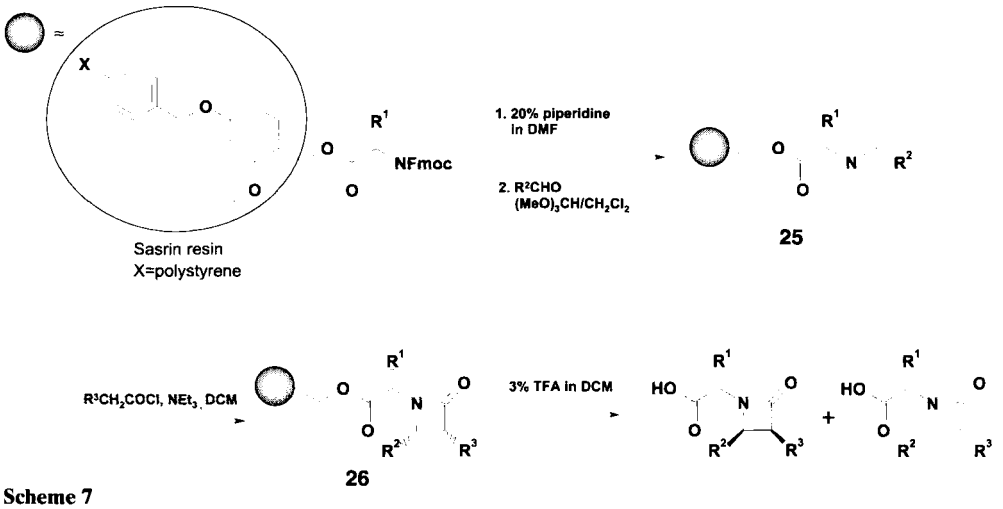
To 0.284 mmol of Fmoc-Phe Wang resin (0.49 mmol g^{-1} repeatedly treated with 20 % piperidine in DMF: (2 x 5 min, 1 x 20 min), swelled in 6 mLTMOF was added benzaldehyde (5.68 mmol, 20 equiv.) and the reaction was mixed at rt for 30 min. $NaCNBH_3$ (5.68 mmol, 20 equiv.) dispersed in 3 mLTMOF was added, followed by HOAc (60 μL), and the reaction was mixed for an additional 10 min. The resin suspension was filtered and the resin washed with DMF, MeOH, 10 % Et_3N in DCM, MeOH, DCM, MeOH, and ether. Resin **22** was obtained after drying in vacuo.

Resin **22** (0.132 mmol, 1 equiv.) was swelled in 2 mL MeCN/$CHCl_3$ (1:1) and phenyl isothiocyanate (0.092 mmol, 0.70 equiv.) and the reaction was heated to reflux for 16 h. Once filtered, the resin was washed further with MeCN and DCM several times. The combined organic washes were evaporated and the residue **24** was purified by radial chromatography using hexane/EtOAc (5:1) as the eluent. Isolated yield: 95 %.

3.4.4 β-Lactams (Azetidin-2-ones)

Azetidines are well studied, and in particular β-lactam derivatives such as the penicillins or cephalosporins, have received considerable attention for their antibacterial properties. A vast amount of research effort has gone into increasing their efficacy against resistant organisms. Among the variety of mechanisms that can provide resistance to β-lactam antibiotics in Gram-negative bacilli, the production of β-lactamase is the most important factor [25]. Due to changes in the resistance pattern and the limited spectra of activity of many currently available antimicrobials, new antimicrobials have been developed in the hope of improving therapy. Amoxillin and trimethoprim-sulfamethoxazole are examples of first-line agents. Lactams may also show other forms of biological activity, e.g., as antidepressants [26].

All reported solid-phase combinatorial syntheses of the lactam core utilize a [2+2] cycloaddition reaction of ketenes with resin-bound imines [27–34]. Because of the variability derived from the scaffold synthesis, not many attempts have been made for derivatizing the resin-bound lactam template [35]. One of the most detailed descriptions of a versatile β-lactam synthesis on resin employed amino acids tethered as esters on Sasrin resin [36]. After removal of the Fmoc protecting group, the resulting amines were condensed with alkyl, aromatic, or α,β-unsaturated aldehydes in trimethylorthoformiate/methylene chloride at room temperature to provide quantitatively the resin-bound imines. As presented in Scheme 7, Staudinger reactions were performed by treatment of the resin-bound imines with a large excess of acid chlorides in the presence of triethylamine in methylene chloride at 0° C. Under these optimized reaction conditions, a wide range of ketenes afforded the cycloaddition product, even with sterically hindered amino acids. The lactams were released from the resin by treatment with 3 % (v:v) TFA/DCM and purified by preparative HPLC; 23 examples were purified in 55–97 % isolated yields and a purity of typically >90 %. Although the cycloadditions were highly *cis*-selective, only modest levels of stereoinduction from the asymmetric center of the amino acid was observed.



Scheme 7

Procedure

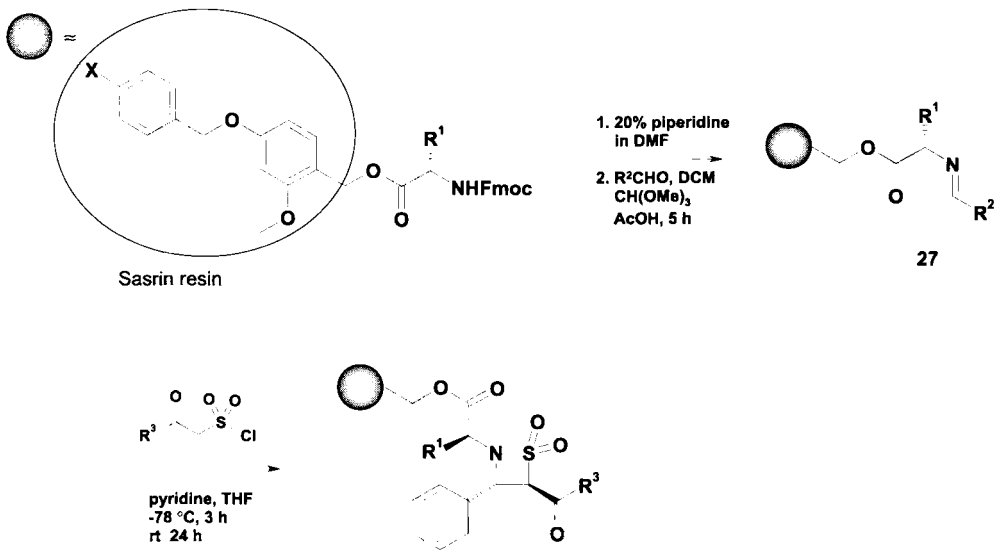
Sasrin resin [loaded with an N-Fmoc-protected amino acid (0.165 mmol, i.e., 0.3 g of resin, loading 0.55 mmol g^{-1})] was treated with a solution of 30 % (v:v) piperidine in N-methylpyrrolidone (NMP) for 45 min, in a standard peptide synthesis vessel. The resin was rinsed sequentially with NMP or DMF, DCM, MeOH, Et_2O, and dried under vacuum. The resin was suspended in a mixture of DCM (1.5 mL), and the aldehyde (2.3 mmol, 13.9 equiv.) was added. After agitating for 3 h, the resin was rinsed with DCM, MeOH, Et_2O, and dried under reduced pressure. The resin **25** was transferred to a glass vial, suspended in DCM (3 mL), and cooled at 0° C. To the suspension was added triethylamine (460 µL, 3.3 mmol) followed by slow addition of the acid chloride (2.5 mmol, 15.2 equiv.). The reaction mixture was maintained at 0 °C for 5 min and agitated overnight at rt . The resin **26** was filtered, rinsed as above (DMF, DCM, MeOH, Et_2O) and dried under vacuum. The product was cleaved from the support by treating the resin with a solution of 3 % (v:v) TFA in DCM for 45 min. For products derived from amino acids requiring acid-labile side chain protection, the crude material was subjected to a second TFA treatment (50 % (v:v) TFA in DCM) to remove these protecting groups. The solution was filtered, and, after removal of the solvent, the crude product was purified by preparative HPLC.

3.4.5 β-Sultams

Because of their structural similarity to the β-lactams, the solid-phase synthesis of β-sultams (1,2-thiazetidine-1,1-dioxides) is of relevance. However, in spite of their structural analogy to the β-lactams, very little is known about the biological activity of β-sultams. Thus far, the (-sultams examined have shown disappointingly weak β-lactamase inhibition activity [37], although by using combinatorial technologies this may change, as more diverse analogs are tested. A study of β-sultam-mediated inhibition of cholesterol absorption indicated an atten-

uated activity of β-sultams as compared with their β-lactam counterparts [38]. In addition, sultams bearing a dimethylpyrimidinyl urea moiety have been reported as plant growth regulators and broad-spectrum herbicides [39].

In analogy to the previously described β-lactam synthesis on solid support, the key step of the synthetic sequence is a [2+2] cycloaddition. The stepwise cyclization of 2-aminoalkanesulfonic acid derivatives is a complementary route to the cycloaddition known in solution-phase chemistry [40]. On solid phase, an amino acid immobilized on Sasrin resin (as a first point of diversity) is treated with an aldehyde in the presence of trimethyl orthoformate and a catalytic amount of acetic acid to provide a resin-bound imine (Scheme 8). Reaction of the imine with (chlorosulfonyl)acetate as a reactive sulfene precursor and pyridine (as the base) in THF afforded usually two *trans* diastereomeric support-bound sultams after 3 h at –78 ° C. Characterization of the resulting products after mild acid cleavage (1–2 % TFA in DCM) demonstrated the reliability of this synthetic sequence. The compatibility with high-throughput screening methodologies (e.g., cell lawn assays) was addressed by developing a photocleavable linker methodology allowing a direct release under nonacidic conditions. Utilizing TentaGel resin, derivatized with an α-methyl-6-nitroveratryl alcohol-based photolabile linker, the β-sultams were released by photolysis in *i*-PrOH at 365 nm. The large differences in yield (19 % to 90 %, 14 examples with TFA release, two examples with photocleavage) and purity (58 % to 95 %) are attributed to the sensitivity of the thiazetidine ring formation to steric hindrance.



Scheme 8

Procedure

An appropriate N-Fmoc-protected amino acid resin (100 mg, c. 0.06 mmol) on Sasrin support (method A) or TentaGel S NH_2 resin (150 mg, c. 0.03 mmol), functionalized with α-

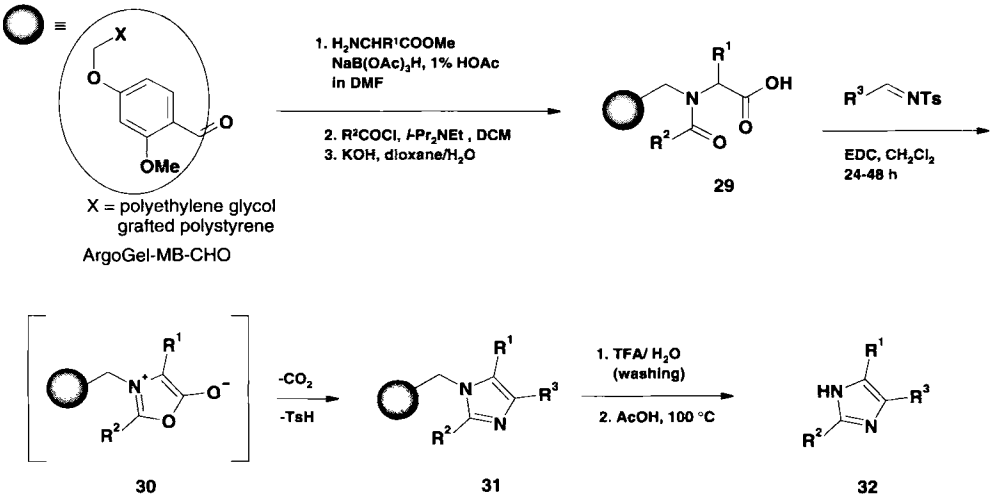
methyl-6-nitroveratryl alcohol photolinker (method B), was deprotected with 20 % (v:v) piperidine in DMF for 30 min. The resin was filtered, washed liberally with DMF, MeOH, and DCM, and dried under vacuum. The deprotected resin was suspended in a solution of an appropriate aldehyde (1 mmol) in DCM (0.5 mL), and trimethylorthoformate (0.5 mL, 4.57 mmol) with catalytic AcOH (10 μL) were added, and the mixture was agitated by gentle shaking for 5 h. The resulting imine resin **27** was filtered, washed with DMF, MeOH, and DCM, and dried under vacuum. Anhydrous pyridine (0.080 mL, 1.0 mmol) was added, under inert atmosphere, to a suspension of the above imine. THF (2.0 mL) precooled to –78° C was added, followed by dropwise addition of an appropriate chlorosulfonylacetate (0.86 mmol) in THF (0.4 mL). The mixture was stirred at –78° C for 3 h, and allowed to warm to rt over ~ 24 h. MeOH (~ 5 mL) was added and the resin **28** was filtered off, washed with MeOH and DCM, and dried under vacuum. Photolinker-tethered compounds were released by photolysis (365 nm, 12 h) in *i*-PrOH (2.0 mL). Sasrin-supported sultams were cleaved with 2 % (v:v) TFA in DCM (~ 2 mL, rt, 20 min). In the latter case, MeCN (7 mL) and toluene (~ 3 mL) were added (to prevent concentration of the labile products in TFA), and the solvent was removed under high vacuum.

3.4.6 Imidazoles

Five-membered ring heterocycles are common in numerous pharmaceuticals. In particular, the imidazole core structure, an element of histidine and its decarboxylation metabolite histamine, is often found [41]. The exceptional properties and wide applicability of the imidazole pharmacophore is due to its hydrogen bond donor acceptor capabilities and its high affinity for metals (present in many protein active sites, e.g., Zn, Fe, Mg) [42–46]. In addition, peptide-based protease inhibitors with improved pharmakokinetics and bioavailability have been obtained by replacing an amide bond with an imidazole [47].

The chosen example of imidazole synthesis on solid support relies on a new linking method, where attachment is achieved through an imidazole core nitrogen [48]. The key reaction of the sequence utilizes a münchnone [3+2]-cycloaddition, as shown in Scheme 9 [49]. Adaptation of this chemistry to polystyrene-poly(ethyleneglycol) grafted copolymer resin ArgoGel-MB-CHO includes a standard reductive alkylation protocol with an amino acid methyl ester. The resin-bound amino ester was acylated with a carboxylic acid chloride in the presence of Huenig base. KOH hydrolysis afforded the caboxylic acid **29**. Treatment of the resin-bound acid under modified conditions with EDC and tosylimine led initially to the intermediate münchnone **30**. Subsequent cycloaddition of the münchnone with the tosylimine, followed by elimination of toluenesulfinic acid and CO_2, afforded the polymer-bound imidazole **31**. Interestingly, the yield of the corresponding reaction in solution is generally low, which is (at least in part) due to self-condensation of münchnones [50]. It is well known that immobilization on a solid support can reduce the potential for self-condensation. The authors took advantage of the high stability of the 4-alkoxy-2-methoxybenzylic type linkage by washing the resin with 90 % (v:v) TFA/H_2O for 1 h to remove unreacted starting materials and non-imidazole byproducts. During this purification step the desired imidazole was not cleaved from the resin. The actual cleavage was achieved by treatment with glacial acetic acid

at 100° C for 2 h. The synthesis proceeds in high overall yields (49–99 %; 12 examples) and excellent purity (94–98 %).



Scheme 9

Procedure for the preparation of tosylimines

To 100 mL of toluene was added 52.4 mmol of the appropriate carboxaldehyde, p-toluenesulfonamide (7.47 g, 43.6 mmol) and p-toluenesulfonic acid monohydrate (1 g, 5.27 mmol). The reaction flask was fitted with a Dean–Stark trap and heated to 115° C for 16 h. Upon cooling to rt, the reaction was filtered, and the filtrate concentrated under vacuum. The concentrated filtrate was washed with ether and dried under vacuum to give the corresponding tosylimine.

Procedure: Imidazole synthesis on solid-support

ArgoGel™-MB-CHO resin (0.6 g, 0.246 mmol) was swollen in 1 % (v:v) HOAc in DMF (6 mL). To the reaction tube was added sodium triacetoxyborohydride (417 mg, 1.97 mmol, 8 equiv.). The reaction mixture was treated with the corresponding amino acid methyl ester (1.97 mmol, 8 equiv.), and the capped tube was agitated by shaking at rt for 12 h. The reaction mixture was then filtered and the resin was washed sequentially with DMF (3 x 10 mL), methanol (3 x 10 mL), and DCM (3 x 10 mL). A portion of the resin was then removed and checked by the dinitrophenylhydrazine test. This test indicates, by the absence of red coloured resin, that the reaction has gone to completion. The resin from the first step (400 mg, 0.164 mmol) was suspended in DCM (2 mL) and treated with DIEA (343 µL, 12 equiv.). The resin was then treated with the appropriate acid chloride (1.64 mmol, 10 equiv.). The reaction was agitated at rt for 12 h. The resin was then washed sequentially with DCM (5 x 10 mL), methanol (3 x 10 mL), and DMF (3 x 10 mL). The resin from step 2 was treated with a degassed solution of potassium hydroxide (92.0 mg, 1.64 mmol, 10 equiv.) in 3 mL of dioxane/water (v:v = 3:1). The reaction mixture was degassed with argon for 10 min, capped, and agitated at rt for 12 h. The resin was then washed sequentially with dioxane

(3 x 5 mL), water (3 x 5 mL), methanol (5 x 10 mL), DMF (5 x 10 mL), and DCM (5 x 10 mL). The resin **29** from step 3 (200 mg, 0.082 mmol) was suspended in 2 mL of DCM and treated with EDC (158 mg, 0.82 mmol, 10 equiv.). Subsequently, to the resin was added the appropriate tosylimine (0.82 mmol, 10 equiv.). The reaction was agitated at rt for 12 h. The resin was washed sequentially with DCM (5 x 10 mL), methanol (5 x 10 mL), DCM (5 x 5 mL), and ether (5 x 10 mL). The washed resin was dried under vacuum for 3 h and weighed. The resin **31** was then suspended in 3 mL of 9:1 (v:v) TFA/H_2O for 30 min. The reaction was drained and the procedure repeated as above. The resin was then washed with acetic acid (3 x 5 mL) at rt. Finally, the resin was placed in a glass tube (13 x 100) and treated with glacial acetic acid (2.5 mL). The reaction was heated to 100° C for 2 h, cooled to rt and the reaction mixture filtered. The resin was washed with acetic acid (2 x 1 mL) and all the filtrates were collected in preweighed vials and concentrated under vacuum to give the final imidazole **32**.

Imidazoles have also been prepared by a three-component or a four-component reaction in a one-pot procedure [51]. The structures of imidazoles obtained after cleavage from the resin with TFA/DCM are depicted in Fig. 1.

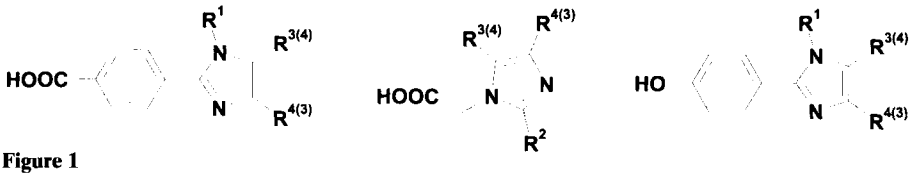


Figure 1

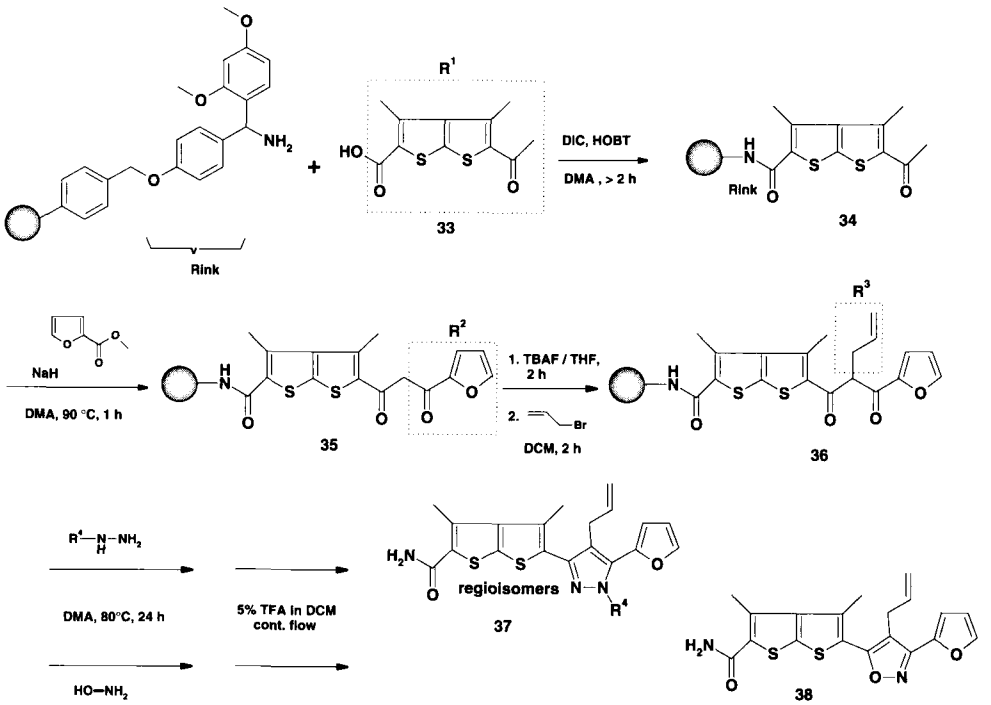
The cyclic urea moiety provides structural rigidity as well as hydrogen bonding possibilities similar to that of the imidazoles described above. The corresponding 2-imidazolidones have been prepared on solid phase by tandem aminoacylation of a resin-bound allylic amine with an isocyanate, followed by intramolecular Michael addition [52]. However, due to the scarce data presented on characterized compounds and the brief experimental procedure, the synthesis is not discussed in detail. Likewise, we mention a patent application on cyclic urea derivatives [53].

3.4.7 Pyrazoles and Isoxazoles

Small heterocycles are viewed as an attractive means to display diverse chemical functionality in space through systematic combinatorial rearrangement of substituents. The limited size of the scaffold leaves little residual similarity among the various components of a library, while the substituents have a more prominent impact on the overall characterisics of a compound [9]. The relatively low level of upfront structural bias is therefore suited for the design of large libraries for lead finding in multiple targets. To this end, practical combinatorial syntheses of pyrazoles and isoxazoles on solid phase have been envisaged early on. Initially, the isoxazole group was built into the side chains of peptoids. In this strategy isoxazoles were formed through [3+2] cycloaddition reaction of nitrile oxides with alkyne side chains of

N-substituted (oligo)glycines [54]. The more versatile role as an actual diversity scaffold was introduced soon thereafter, and a scope and limitation study for a divergent combinatorial pathway, also giving access to pyrazoles, was reported [55]. An example is described in Scheme 10 and in the following experimental procedure. In this diversity generation scheme, four sequential reaction steps were validated, including the loading of the support with an acetyl-bearing moiety, a Claisen condensation with esters, an α-alkylation, and a cyclization of a β-diketone with monosubstituted hydrazines. The α-alkylation is a critical step, but generally works well under the conditions described, i.e. in the presence of TBAF. This reagent shields the oxygen atoms of the β-dicarbonyl intermediate, thus inhibiting O-alkylation as a side reaction and furthermore increasing the nucleophilicity of the compound. The alkylation yield range is relatively wide, mostly depending on the structure of residues of the diketone intermediate. For this reason, in the construction of a complex library [56], this step was omitted, as it is not a prerequisite for the heterocycle formation. Furthermore, the cyclization kinetics of non-alkylated intermediates of type **35** is more rapid.

Similarly, the condensation of β-dicarbonyl compounds with hydrazines was used for accessing pyrazolones [57, 58], which have a long history of application in the pharmaceutical chemistry.



Scheme 10

Procedure: Resin deprotection

The Rink Amide resin (4-(2′,4′-dimethoxyphenyl-fmoc-aminomethyl)-phenoxy resin) with a loading of approx. 450 μmol g^{-1} was subjected to repeated washes with 20 % piperi-

dine/DMA until no UV absorption from cleaved dibenzofulvene derivatives was detected in the eluate.

Unless otherwise specified, after each reaction, the resin was thoroughly washed by sequential treatments with DMA, DMSO and *i*-PrOH. Previous to each reaction, traces of isopropanol were washed away with the corresponding dry solvent.

Coupling procedure: The NH_2-linker group was acylated with a 0.3 M solution of the carboxylic acid reactant **33** (3 equiv. in DMA) at rt (preactivation 40 min with 3.3 equiv. DIC and 3.3 equiv. HOBt) until the Kaiser test [59] was negative.

Claisen condensation: 1000 mg (460 μmol) of resin **34** were suspended in a solution of 13.8 mmol carboxylic ester (30 equiv.) in 13.5 mL DMA. Under inert gas 180 mg (4.6 mmol, 10 equiv.) of NaH (60 % dispersion) were added and the mixture was well shaken under argon at 80° C for 1 h. The resulting mixture was filtered, washed with 30 % (v:v) acetic acid/H_2O, DMA, DMSO, and *i*-PrOH and dried under vacuo. A 95 % conversion to the diketone resin **35** is typical.

Alkylation (optional low yield step): A 1 M solution of TBAF in THF (4.5 mL, 4.5 mmol, 10 equiv.) was added to 1.08 g (0.45 mmol) of the resin-bound diketone **35** at rt and the mixture was shaken for 1 h and then treated with 779 μL (9 mmol, 2 equiv.) of allyl bromide. The mixture was shaken for another 2 h, followed by filtration, washing with DCM, DMA, DMSO, and *i*-PrOH and air-drying to yield the resin-bound **36**. Only approx. 40 % conversion was observed at this stage.

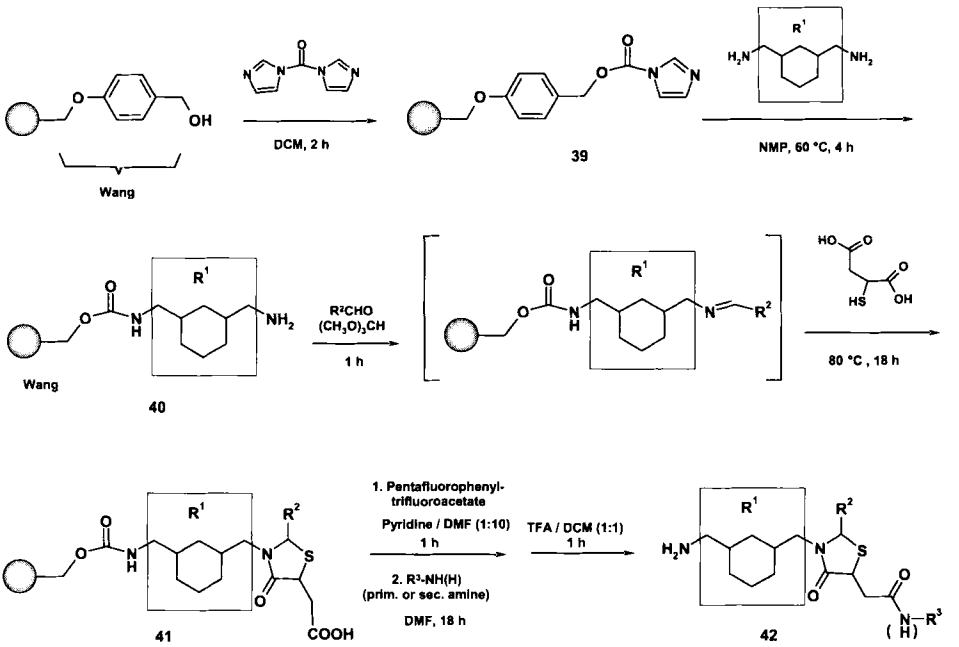
Cyclization to pyrazole or isoxazole derivative: Cyclization of **36** was performed using 1 mL hydrazine hydrate or a monosubstituted hydrazine in 4 mL DMA. The mixture was heated at 80° C for 24 h. The resulting mixture was filtered, washed with DMA, DMSO, and *i*-PrOH and dried under vacuo to give **37** in a yield of 95 % for this step. Analogously, if hydroxylamine was used instead of a hydrazine derivative, the isoxazole derivative of type **38** was obtained.

Cleavage: Cleavage from the support was carried out with diluted TFA according to a procedure described by Rink [60]. This avoided contamination of crude cleavage eluates with linker fragments. The treatment consisted of a continuous flow of 5 % TFA in DCM for 60 min. Subsequent solubilization of the cleaved product with DMF is recommended.

3.4.8 Thiazolidinones

Recently, an efficient solid-phase synthesis route for thiazolidinones was developed [61]. The methodology is the result of a goal-oriented design, which takes into account the requirements for high-speed synthesis of large compound collections. To this end, the ambition fully to resolve diastereomeric structures or to define the exact isomeric composition of final ring structures has no priority over the exploitation of diversity generation. Implicitly one relies on the ability and efficiency to provide full analytical characterization directly or after resynthesis of any sample which shows interesting biological activity.

A positive aspect of this combinatorial scheme is typical for approaches with broad practical utility. Special building blocks (i.e. reactants belonging to a distinct chemical class with few commercially available analogs – in this case mercaptosuccinic acid) are used in a crucial



Scheme 11

role, namely for enabling the insertion of a diversity branch point allowing numerous subsequent derivatizations.

Procedure

Wang (benzyloxybenzyl-OH) polystyrene resin was swelled in DCM and treated with carbonyldiimidazole (CDI) (4 equiv.) for 2 h. Once filtered, the resin was washed with DCM (twice), DMF (three times), DCM (twice) and NMP (twice). Activated resin **39** was heated for 4 h to 60° C with a concentrated solution of the appropriate symmetrical diamine (4 equiv.) in NMP. Once filtered, the resin was washed with NMP (twice), DMF (three times), DCM (twice), MeOH (twice) and dried in vacuo to provide **40**.

Resin **40** was swelled in TMOF and reacted with a suitable aldehyde building block (3 equiv.) in TMOF for 1 h. Subsequently, mercaptosuccinic acid (6 equiv.) was added as a solid and the reaction was heated to 80° C for 18 h. Once filtered, the resin was washed with TMOF (twice), DMF (three times), DCM (twice), MeOH (three times) and dried in vacuo to provide **41**.

Resin **41** was swelled in pyridine/DMF (1:10) and reacted with first pentafluorophenyl trifluoroacetate (6 equiv.) in pyridine/DMF (1:10) for 1 h. Once filtered, the resin was washed with DMF, then subjected to an 18 h treatment with an appropriate amine building block (6 equiv.). Once filtered, the resin was washed with DMF (five times), DCM (twice), MeOH (three times) and dried in vacuo to provide the product grafted on solid support.

Final products of type **42** were obtained by cleavage with TFA/DCM (1:1) for 1 h and subsequent rinsing with appropriate solvents. The cleavage solution and all organic washes

were combined and evaporated. Crude yields were in the range of 65–85 % of the desired component.

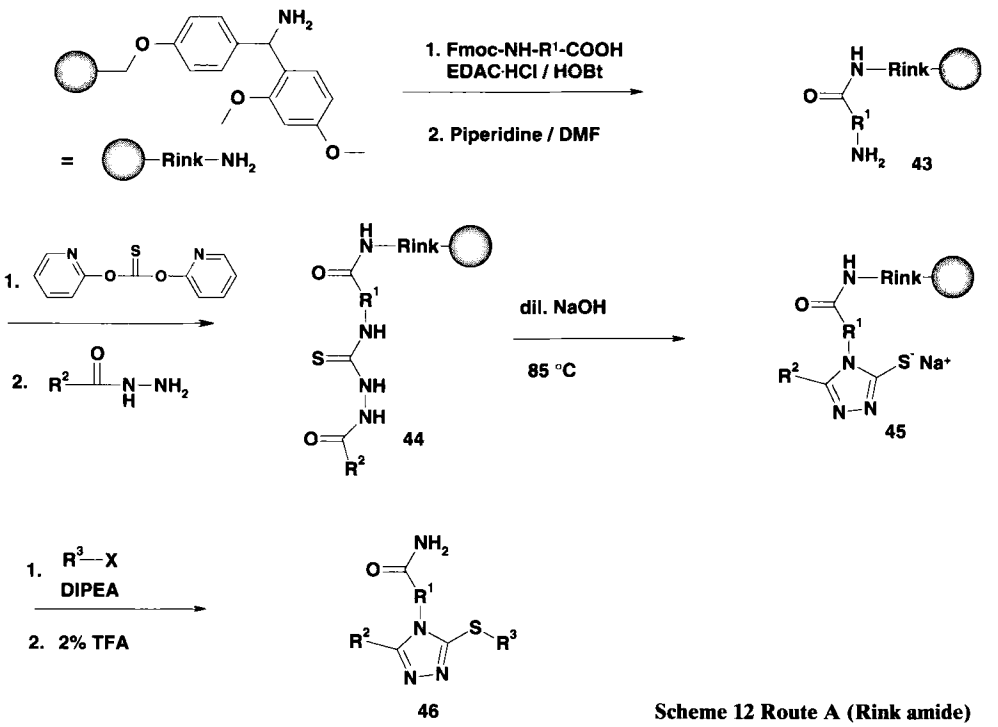
Commercially available diamine functionalized trityl-based resins were found to be unsuitable starting materials due to their poor swelling in trimethylorthoformate, the solvent of choice for imine formation.

In spite of the excess ofprotected diamine building block in the first derivatization step, usually less than 5 % resin crosslinking was observed. This obviates the tedious selective solution phase mono-protection of the symmetrical diamines.

Some problems were observed with thiophene and furan-based aldehydes, pyridyl-containing precursors, and when aliphatic aldehydes were used (especially with sterically encumbered groups).

3.4.9 Thiotriazoles

With a simple scaffold of limited topology an ingenious pathway to maximize the exploitation of a diversity system was developed by providing multiple alternatives for starting material sets and solid support derivatives [62]. The 3-thio-1,2,4-triazole scaffold was chosen due to the robust and high-yielding procedures known in solution chemistry [63]. The adaptation of this chemistry to solid-phase synthesis was designed in a way that the use of two different



Scheme 12 Route A (Rink amide)

linkers facilitated the expansion of product diversity by bringing into play different classes of building blocks and reagents. The first synthesis route employs Rink amide resin [64], the second route a tert.-alkyl carbamate resin ("Boc resin") [65]. Based on these two strategies, mutually exclusive libraries of triazoles with distinct Tanimoto coefficient distribution can be prepared [62].

Procedure: Route A

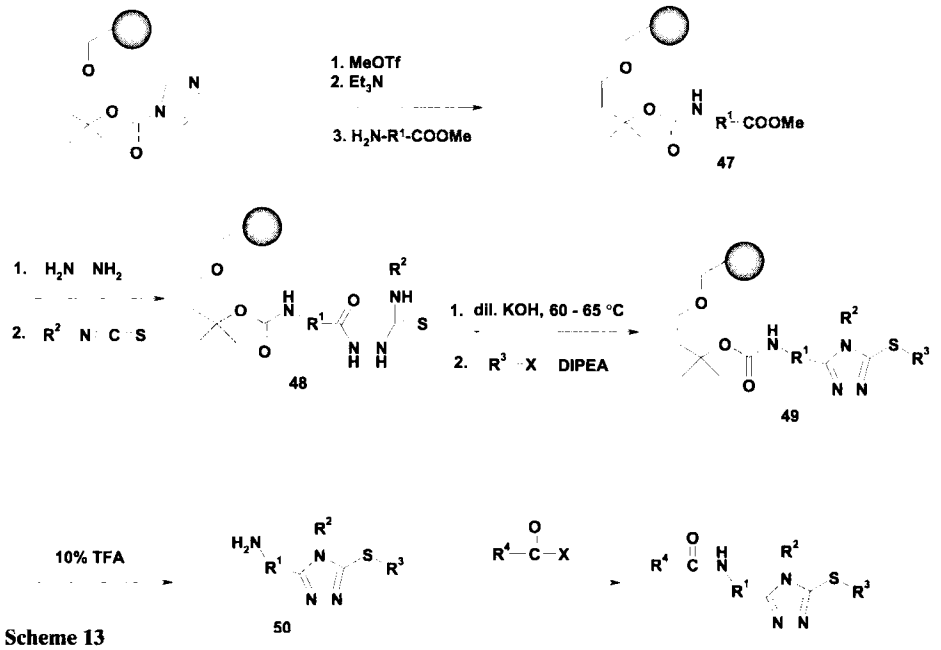
Introduction of R^1. Resin-bound 4-aminomethylbenzamide: To Rink resin (2.0 mmol) Fmoc-protected 4-aminomethyl-benzoic acid (8.0 mmol, 4 equiv.), EDAC·HCl (8.0 mmol, 4 equiv.) and HOBT (8.0 mmol, 4 equiv.) were added in a volume of 30 mL DMF and the mixture was agitated at rt overnight. The resin was filtered and washed successively with DMF (2 x 50 mL), DCM (2 x 50 mL), Et_2O (2 x 50 mL), and DCM (2 x 50 mL). The resulting resin (dried overnight in a vacuum oven at rt) gave a negative ninhydrin test. A portion of this resin (100 mg, ~0.07 mmol) was treated with 30 mL of a 20 % solution of piperidine in DMF and agitated for 20 min. After filtering, it was washed once with 30 mL DMF and then re-treated with 20 % piperidine in DMF for 20 min. Finally, the deprotected resin was filtered and washed consecutively with DMF (2 x 5 mL), DCM (2 x 5 mL), Et_2O (2 x 5 mL) and DCM (2 x 5 mL) to afford **43** (R^1 = Bn).

Introduction of R^2. Resin-bound thio-semicarbazide: Resin **43** obtained above was treated with 0.14 M solution of di-(2-pyridyl)-thionocarbonate in DMF (5 mL, 0.7 mmol, 10 equiv.) and agitated for 1 h at rt. The resulting resin was filtered and washed consecutively with anhydrous DMF (2 x 5 mL), DCM (2 x 5 mL) and anhydrous THF (2 x 5 mL). This intermediate isothiocyanate resin was suspended in anhydrous DMF (5 mL) , treated with butyric acid hydrazide (0.15 g, 1.5 mmol, 21.4 equiv.) and agitated overnight. The resin was washed consecutively with DMF (2 x 5 mL), DCM (2 x 5 mL), Et_2O (2 x 5 mL) and dioxane (2 x 5 mL). After drying overnight in a vacuum oven **44** (R^1 = Bn, R^2 = C_3H_7) was obtained.

Introduction of R^3. Resin-bound thio-triazole: Resin **44** obtained above was treated with a solution composed of dioxane (3 mL), MeOH (1 mL), and 1N NaOH (1 mL, 1 mmol, 14.3 equiv.). The resulting suspension was heated to 85° C for 4 h. After cooling to rt, the resin was filtered and washed consecutively with MeOH/H_2O (1:1, 2 x 5 mL), MeOH (2 x 5 mL) and THF (2 x 5 mL) to afford the intermediate thiolate salt **45** (R^1 = Bn, R^2 = C_3H_7). This resin was treated with a solution of 0.2 M benzyl bromide in dioxane (5 mL, 1 mmol, 14.3 equiv.). Diisopropylamine (2 drops) was added and the mixture was agitated for 1 h. Following filtration, the resin was washed repeatedly with DCM (10 x 2 mL). After drying at rt overnight in a vacuum oven, resin-bound product was obtained.

Cleavage from resin: The resin obtained above was treated with 2 % TFA in DCM (5 mL) agitating for 20 min. The resulting resin was filtered and re-exposed to the acid treatment twice. The acidic filtrates were combined and concentrated at 40° C to dryness. The residue was dissolved in $CHCl_3$ and filtered through a SPE column loaded with silica gel (230–400 mesh, 1 g). The elution was carried out first with $CHCl_3$ (4 mL) to remove non-polar impurities and then with a step gradient of 2, 3, 4, 5 and 10 % MeOH in $CHCl_3$ (3–4 mL at each step) to provide 12.8 mg of **46** (R^1 = Bn, R^2 = C_3H_7, R^3 = Bn) (50 % overall yield) upon evaporation of solvent from fractions containing product detected by TLC.

Alpha-amino acids are incompatible with this synthetic route as they give rise to byproducts, possibly due to undesired cyclizations in the isothiocyanate-forming step.



Scheme 13

Procedure: Route B

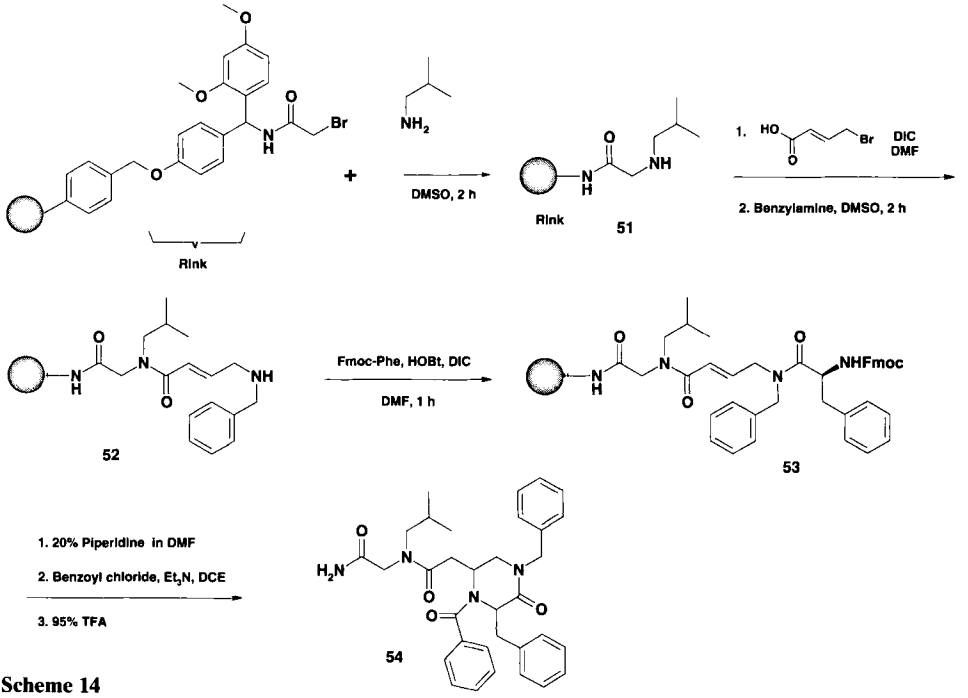
Introduction of R^1. Resin-bound amino acid ester and hydrazide: To a suspension of resin-bound N-(tert-alkoxycarbonyl)-leucine methyl ester [65] **47** (2.07 g, 1.49 mmol) in n-butanol (8 mL), anhydrous hydrazine (2.0 mL) was added and the mixture was shaken at rt for 6.5 h. After filtration, the resin was washed alternately with THF and MeOH (4 portions each). After rinsing three times with DCM and drying, the resin-bound acid hydrazide (1.95 g) was obtained.

Introduction of R^2, ring formation and derivatization with R^3: The resin-bound acid hydrazide (110 mg, 0.079 mmol) and a solution of benzyl isothiocyanate (57 mg, 0.38 mmol, 4.81 equiv.) in DMF (3 mL) were mixed and shaken at rt overnight. After draining off the solution, the resin was washed with DMF (3 x 2 mL), DCM (3 x 2 mL), THF (3 x 2 mL) and dried to afford the thiosemicarbazide resin **48** (R^2 = Bn). A 3 mL volume of KOH solution (0.25 M KOH/dioxane, 2:3) was added to this resin and the mixture was heated to approx. 65 ° C for 3 h. After filtration, the resin was washed with THF (3 x 2 mL), MeOH (3 x 2 mL), THF (3 x 2 mL) and dried to afford a triazole thiolate resin. To a suspension of this resin in a 0.16 M DIPEA/dioxane solution (1 mL) a 0.4 M methyl iodide/dioxane solution (1 mL) was added and the mixture was shaken at rt for 3 h. The reagent solution was drained off and the resin was washed with THF (3 x 2 mL), MeOH (3 x 2 mL), THF (3 x 2 mL), DCM (3 x 2 mL) and dried to give the S-alkyl triazole resin **49** (R^2 = Bn, R^3 = Me). This resin was treated with 10 % TFA/DCM (2.5 mL) at rt for 4.5 h and filtered. The resin was rinsed with DCM (2 x 3 mL), MeOH (2 x 3 mL) and the filtrates were evaporated and dried to afford the trifluoroacetate salt of **50** (30 mg, 93 % crude yield from resin **47**). This product may be acylated in solution, as indicated in Scheme 13.

With most methyl esters the hydrazinolysis occurs at room temperature; however resin-bound methyl 3-aminobenzoate, ethyl nipecotate, and proline methyl esters require heating (45–50° C) for 7–8 h.

3.4.10 Piperazinones

Piperazinones (oxopiperazines) readily meet some of the combinatorial chemist's favourite criteria in designing diversity systems for lead finding. The low molecular weight scaffold is amenable to a high degree of straightforward derivatization and allows the incorporation of a richness of amino acid side chains into structurally well-defined heterocyclic products. The oxopiperazine ring can be viewed as a means to constrain the torsion angle of an amino acid's backbone bonds in a dipeptide mimick. An ethylene bridge links the nitrogen atoms of adjacent amino acids and consequently restricts the conformational freedom of the linear parent molecule. This principle was illustrated with the synthesis of a constrained enkephalin analog, including a novel route to the piperazinone ring structure [66]. In a follow-up study, the possibility to synthesize pentasubstituted oxopiperazines [67] was reported as a further elaboration of a previously published method described in more detail [68]. The main difference consists of an elegant tandem SN2 displacement/Michael addition for the cyclization step. The original method [68] emphasized practical aspects by allowing the use of easily accessible aminoacid building blocks at that stage. Independently from the actual substitution



Scheme 14

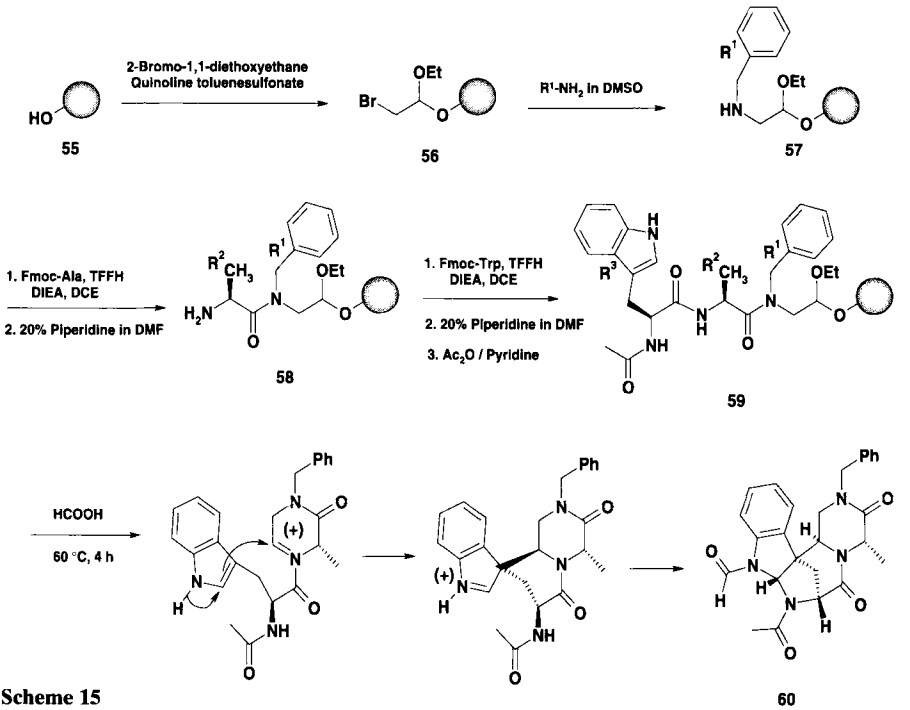
pattern of a library, *trans*-4-bromobutenoic acid is required as a special reactant. This building block can also be used for the construction of unsaturated peptoids [69].

Procedure

In a 250 mL fritted reaction vessel (under argon), agitated on an orbital shaker at 200 rpm, the Fmoc protection of 5.7 g Rink amide resin (2.907 mmol, 0.51 mmol g^{-1}) was removed by first swelling the resin in DMF, draining, then treating with 20 % piperidine in DMF (1 x 50 mL) for 5 min and again for 30 min (1 x 50 mL). The resin was washed well with DMF, then treated with a solution of bromoacetic acid (30 mmol, 10.32 equiv.) and diisopropyl carbodiimide (DIC) (30 mmol, 10.32 equiv.) for 2 x 30 min in 50 mL DMF. The resin was washed well with DMF, then treated with a 2.0 M solution of isobutylamine (34.4 equiv.) in DMSO (50 mL) for 2 h at rt. The resin **51** was again washed with DMF and treated with 4-bromo-2-butenoic acid (30 mmol, 10.32 equiv.) and DIC (30 mmol, 10.32 equiv.) in 50 mL DMF for 2 x 30 min. The resin was washed with DMF, then treated for 2 h with a 2.0 M solution of benzylamine (34.4 equiv.) in DMSO (50 mL). After thorough washing with DMF and DCM the resin **52** was dried overnight in vacuo at rt.

A portion of the obtained resin **52** (1.5 g, approx. 0.67 mmol) was swelled in DMF, drained and treated with a solution of Fmoc-Phe (15 mmol, 22.4 equiv.), HOBt (15 mmol, 22.4 equiv.) and DIC (15 mmol, 22.4 equiv.) in DMF (25 mL) for 1 h. The resin was then washed and dried as before.

Of the obtained resin **53**, a portion of 190 mg (approx. 0.066 mmol) was swelled in DMF for 5 min, then treated with 20 % piperidine in DMF (1 x 5 min, 1 x 30 min, 5 mL). The resin



Scheme 15

was washed well with DMF and then with 1,2-dichloroethane (DCE). The resin was treated with a mixture of 1.0 M benzoyl chloride in DCE (2 mL, 30.3 equiv.) and 1.0 M Et_3N in DCE (2 mL, 30.3 equiv.) for 2 x 30 min. After thorough washing of the resin with DMF and DCM, the linker was cleaved with TFA/H_2O (95:5) for 20 min at rt to give crude **54** as a mixture of diastereomers (Note: to avoid contamination of crude cleavage eluates with linker fragments, a milder treatment with 5 % TFA in DCM in a continuous-flow mode for 60 min and subsequent solubilization of the cleaved product with DMF was recommended [60]).

Mixtures of diastereomers arise, but the ratio of these is not determined. In addition, in generating R^2, anilines or hindered amines should be avoided because subsequent aminoacylation may fail.

A particularly effective strategy for the design of new heterocyclic libraries employs a tandem N-acyliminium ion cyclization/nucleophilic addition for ring-forming processes [70] (Scheme 15). The methodology described provides access to bi-, tri- and tetracyclic derivatives of 1-acyl-3-oxopiperazines. The bicyclic variants in particular represent an interesting probe for a constrained type I β-turn motif with potential for combinatorial diversification.

Procedure: (2-Bromo-1-ethoxyethan-1-oxy)-linked TentaGel resin **(56)**
To remove remaining poly(ethylene glycol) from the commercially available TentaGel HL-OH resin (130 μm, 0.41 mmol OH g^{-1}), a suspension of the resin (100 g, 41 mmol) in formic acid (500 mL, 13.3 mol) was stirred at 60 ° C for 14 h. The mixture was filtered and the resin was thoroughly washed with dioxane (1.5 L) followed by treatment with 1 M NaOH (300 mL, 300 mmol). After 4 h, the resin was washed with water (1 L), MeOH (1.5 L), and dioxane (1.5 L) to give the PEG-free solid support.
A suspension of dry, PEG-free TentaGel resin **55** (see above) and quinoline toluenesulfonate (25 g, 83 mmol, 2.02 equiv.) in 1,2-dichloroethane (DCE) (1.5 L) was heated to reflux while continuously removing the solvent and traces of water. After removing about 500 mL of the distillate, a solution of 2-bromo-1,1-diethoxyethane (50 mL, 332 mmol, 8.1 equiv.) in 1,2-dichloroethane (500 mL) was added and the mixture was held at reflux for 4 h with continuous removal of EtOH/DCE, after which the resin was washed with DMF (500 mL) and dioxane (500 mL) followed by lyophilization to give the desired product **56** (98 g). The loading level was determined by quantitation of bromine with elemental analysis (approx. 0.31 mmol g^{-1}).

Procedure: Attachment of primary amines (Resin **57**)
A solution of primary amine in DMSO (5 mL, 2 M, 66.7 equiv.) was added to the resin **56** (0.5 g, 0.15 mmol, 1 equiv.) and the suspension was shaken (vortexed) at 60 ° C for 15 h. Alternatively, comparable results were obtained when the resin **56** was treated twice with the same solutions of amines at rt overnight. The resin was filtered, washed with DMSO (3 x 7 min), and dried in vacuo overnight. The loading level of secondary amines was approximately 0.30 ± 0.02 mmol g^{-1}, measurable by an ion-selective electrode technique [71].

Procedure: Fmoc-amino acid coupling (Resin **58**)
A solution of Fmoc-amino acid (1.5 mmol, 10 equiv.), TFFH (1.5 mmol, 10 equiv.), DIEA (3.0 mmol, 20 equiv.) in dry DCE (7 mL) was added to the resin **57** (0.50 g, 0.15 mmol, 1 equiv.) and the suspension was shaken at rt for 2 days. The progress of the reaction was moni-

tored by using a modified chlororanil test [72]. The resin was then filtered and washed with DCM (2 x 7 mL), DMF (3 x 7 mL), and DCM (3 x 7 mL), to give the desired product **58**. The loading level was determined by Fmoc-reading (UV-active piperidine-dibenzofulvene adduct) after Fmoc deprotection with 20 % piperidine in DMF (2+20 min). In the next step, coupling of Fmoc-amino acids and 2-fluoro-5-nitrobenzoic acid to the previous amino acid was performed under the same reaction conditions, except for the shorter reaction time (24 h).

Procedure: N-Capping of terminal amino groups (e.g. linked to a resin of type **59**)
A solution of acylating reagent – e.g., acetic anhydride/pyridine (1:1) – was added in large excess to a resin of the type obtained above, bearing the free amino group (0.50 g, 0.15 mmol) after Fmoc deprotection. At least 5 equiv. of acylating agent were used in an appropriate solvent (DMF if reagent solubilization was necessary). The suspension was shaken at rt for 2 h. The progress of the reaction was monitored using a modified chloranil test [72]. The resin was then filtered and washed with DCM (2 x 7 mL), DMF (3 x 7 mL) and DCM (3 x 7 mL), to give resin-bound compounds of the type **59**.

Procedure: General method for nucleophilic displacement (by primary amines) of fluoroaromatic substituents to introduce a nucleophile into precursors (at R^3) of the acyliminium cyclization (not applicable in Scheme 15)
A solution of primary amine in DMSO (5 mL, 2 M, 66.7 equiv.) was added to the resin bearing the fluoroaromatic substituent (0.5 g, 0.15 mmol, 1 equiv.) and the suspension was shaken (vortexed) at ambient temperature for 16 h. The resin was then filtered and washed with DCM (2 x 10 mL) and DMF (3 x 10 mL) to give the desired product.

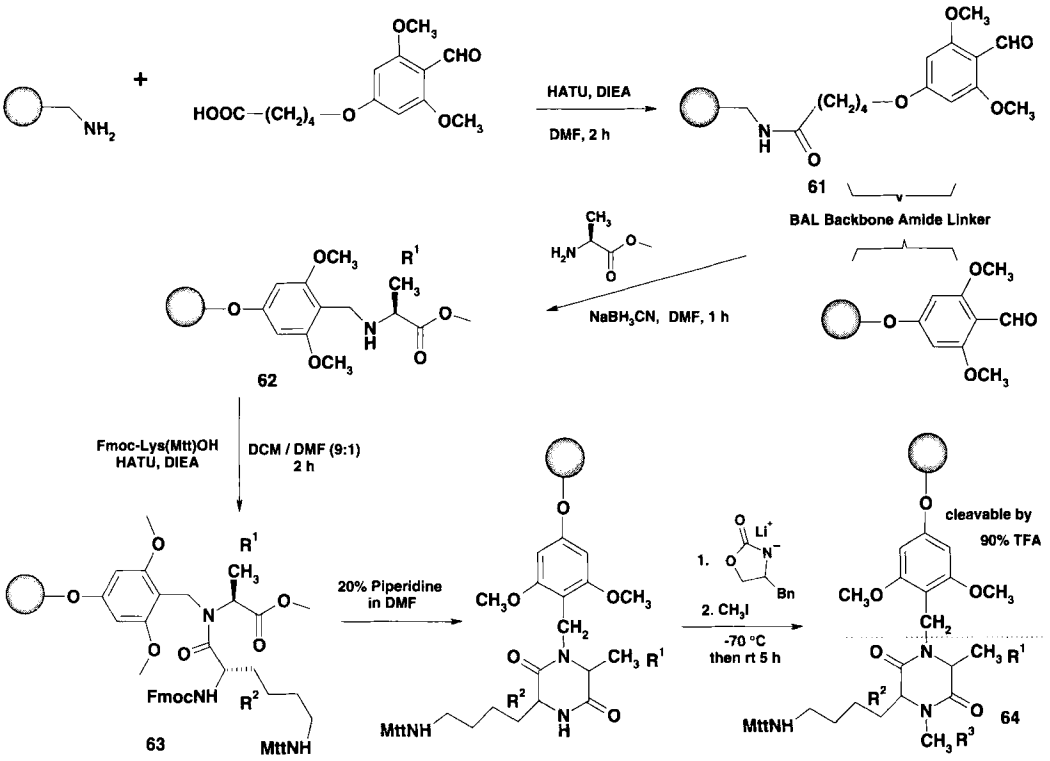
Procedure: General method for acyliminium-ion cyclization (e.g., **59** to **60**)
The resin bearing the nucleophilic substituent ready for cyclization (e.g., **59**) (0.50 g, 0.15 mmol) was stirred with formic acid (7 mL) for 3–4 h at rt (typical case) or for 4 h at 60° C in case of **59**, which requires harsher conditions for complete cleavage. The supernatant was then separated and evaporated in vacuo. The resulting crude product was further purified by chromatography (silica, 40 % EtOAc/$CHCl_3$) to give pure product (e.g., **60**) as an oil.

3.4.11 Piperazine-diones (Diketopiperazines)

Piperazine-2,5-diones (diketopiperazines) are a long known side product observed at the dipeptidic stage of peptide synthesis, as a consequence of intramolecular cyclization by aminolysis [73]. More recently, a number of studies have pointed out the attractive features of this heterocyclic scaffold from a combinatorial chemist's perspective. On one hand, there is ample precedence documenting the potential for biological and therapeutic activity within this class of compounds, considering recent reports on inhibitors of mammalian cell cycle [74], plasminogen activator-1 [75], topoisomerase I [76], and on competitive antagonists of Substance P at the neurokinin-1 receptor [77], to name just a few. On the other hand, the synthetic accessibility is straightforward while there is enough room for the development of original combinatorial derivatization patterns. Three systems are illustrated in Schemes 16 [78], 17 [79] and 18 [80]. An outline for the preparation of unsaturated 3-alkylidene-2,5-piperazinediones has recently been published [81].

3.4.11.1 Diketopiperazines via Backbone Amide Linker (BAL) [78]

Although originally, the BAL linker was developed for facilitating the preparation of cyclic peptides [82], it transpires that this linker is particularly useful (in a combinatorial chemistry context) if diketopiperazine formation is intentionally promoted rather than suppressed. The linker is introduced to an amino-functionalized solid support by coupling with the carboxylic acid function of the bifunctional molecule 5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid [83], the aldehyde being the actual anchoring group for the heterocycle to be assembled. This linker is compatible with orthogonally protected residues; thus, examples were described with Lys-ε-amino groups protected with allyloxycarbonyl or 4-methyltrityl (Mtt) residues. Carboxyl groups may be protected with allyl. Once deprotected, further derivatization of the residues is possible. Selective alkylation of the diketopiperazine amide bond must be carried out before formation of new amides in the side chains.



Scheme 16

Procedure

Linker attachment: An amino-functionalized polystyrene or PEG-polystyrene resin may be used as starting material. First, 5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid (PALdehyde) [83] (4 equiv.) and HATU [84] (4 equiv.) were dissolved in DMF, then DIEA (8 equiv.)

was added and, after 1 min of preactivation, this solution was added to the resin (1 equiv.). Coupling was allowed to proceed at 25° C for 2 h, at which time the Kaiser ninhydrin test [59] was negative.

General procedure: A mixture of amino acid methyl ester hydrochloride (10 equiv.) and $NaBH_3CN$ (10 equiv.) in DMF was added to the PALdehyde resin **61** (1 equiv.). The reaction was allowed to proceed for 1 h at 25° C, after which the resin was washed with DCM and MeOH, and finally dried.

The Fmoc-amino acid (10 equiv.), HATU (10 equiv.) and DIEA (20 equiv.) in DCM/DMF (9:1) were added to the aminoacyl ester resin **62** and allowed to react for 2 h at 25° C. After washing with DMF and DCM the coupling was repeated with fresh reagents, again for 2 h. The resulting resin **63** was washed with DMF and DCM , then treated with Ac_2O/DMF (1:9) for 20 min, and washed thoroughly with DMF.

Repeated treatments with 20 % piperidine in DMF (3 x 1 min, then 3 x 5 min) was followed by extensive washing with DMF (Kaiser ninhydrin test remains negative). The diketopiperazine remains grafted on the support.

An optional alkylation of the unsubstituted amide bond may be carried out by the following steps under argon atmosphere in a screw-cap tube with a Teflon-lined cap, a sintered glass frit, a stopcock, and a jacket where acetone at –70° C circulates during metalation. Lithiated oxazolidinone in THF was freshly prepared from 5-phenylmethyl-2-oxazolidinone (10 equiv.) plus 2.0 M n-BuLi in hexane (10 equiv.), then added to the diketopiperazine resin. After 90 min at –70° C, the alkylating agent (15 equiv.) was added, followed by DMF to reach a final solvent ratio of THF/DMF (7:3). The resin was allowed to warm to 25° C and after 5 h it was filtered and washed with THF, then THF/H_2O (1:1), again with THF, and finally with DCM [1].

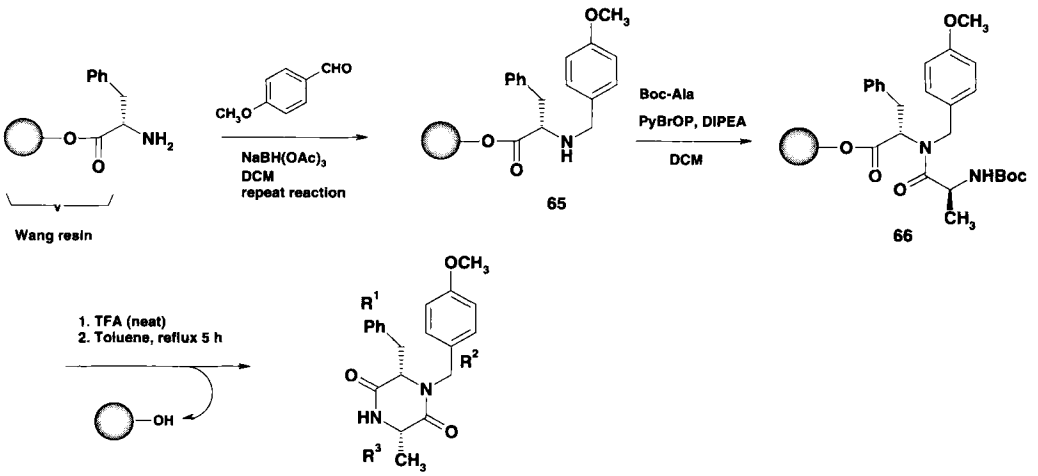
The trisubstituted diketopiperazine **64** was cleaved into solution with TFA/H_2O (9:1) for 2 h and isolated from the eluate and the combined washes (using appropriate solvents to solubilize the product).

Diketopiperazine libraries prepared according to the scheme above are suitable for both on- and off-resin screening. The heterocycle formation occurs while the product is grafted on the solid support, whereas alternative schemes described in the literature [79, 80] involve cyclative cleavage, with ring formation leading to concomitant release of the product into solution.

The chemistry described was also successful for amino acid esters other than methyl esters. Ring formation rates and yields with methyl, allyl, and benzyl esters were shown to be very similar.

3.4.11.2 Piperazine-diones by Acid Cyclative Cleavage. Method A including Reductive Alkylation

This method [79] was used for the preparation of a prototype combinatorial library of 1000 piperazine-diones. The key step of this experimental procedure resides in the reductive alkylation step with sodium triacetoxyborohydride, which was thoroughly validated for the solid-phase reaction format.



Scheme 17

Procedure

Reductive alkylation: Fmoc amino acids on resin (Wang polystyrene, 0.2 mmol) are suitable starting materials, protected for long-term storage. Before alkylation, the Fmoc group was cleaved to liberate the amino function on the resin. Such resin was suspended in DCM (0.5 mL). An aldehyde component (0.24 mmol, 1.2 equiv.) dissolved in DCM (0.5 mL) was added. The vessel was sonicated in an ultrasound bath for 20 min followed by addition of a pre-sonicated solution of sodium triacetoxyborohydride (0.28 mmol, 1.4 equiv.) in DCM (0.5 mL). The reactor was sonicated for 5 min, then stirred vigorously for 16 h. The resin was filtered, washed (H_2O, aqueous $NaHCO_3$, H_2O, THF, 3 x 2 mL each), dried and the reductive alkylation procedure repeated.

Coupling: The solution of a Boc-amino acid component (0.2 mmol, 1.1 equiv.) in DCM (0.5 mL plus DMF as needed to solubilize) was added to the resin **65** obtained above (previously resuspended in 3 mL DCM). Also a solution of PyBrOP (0.2 mmol, 1.1 equiv.) in DCM (0.5 mL) was added, followed by DIPEA (0.4 mmol, 2.2 equiv.). The reaction was stirred for 24 h, then filtered, washed (DMF, H_2O, THF), dried and the coupling process repeated.

Cleavage from resin: The resin **66** was suspended in TFA (1 mL) for 3 h with occasional agitation, then filtered and washed with DCM (5 mL). The filtrate was concentrated, the residue dissolved in toluene and concentrated once more to remove any residual TFA.

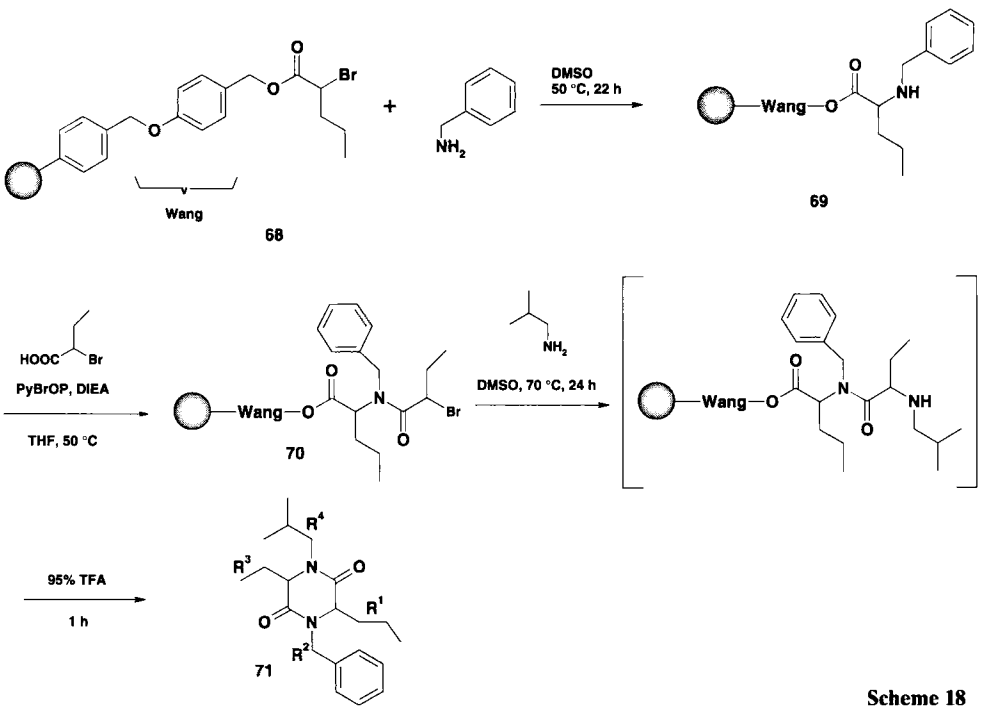
Cyclization: The residue was dissolved in toluene (10 mL) and stirred under reflux for 5 h, then evaporated to dryness to yield the crude diketopiperazine product **67**.

In this reaction, partial racemization of some homochiral amino acids was observed. In addition, the combination of hindered amino acids and electronically deactivated aldehydes may cause low yields. Bis-alkylation side-reactions of aliphatic aldehydes may generate between 1 % and 10 % tertiary amines.

3.4.11.3 Piperazine-diones by Acid Cyclative Cleavage. Method B, including SN2 Displacement

This method [80] differs from the procedure of [79] mainly with respect to the preparation of the solid-phase grafted N-alkylated amino acid. Rather than reductive alkylation, the bromine displacement by primary amines [85] (a widely used principle for the synthesis of oligomeric N-substituted glycines) is applied in the context of this heterocycle synthesis. While relying on this established and robust reaction type is an advantage on one hand, the requirement for α-bromo-substituted carboxylic acid building blocks (of which only a dozen are readily available commercially) reduces the choice of residue functionality for that position. An initial concern that the high concentrations of amine used would promote aminolysis of the ester linkage to the solid phase turned out to be a minor issue. This side reaction is not prominent, and is relatively insensitive to the steric nature of the amine component.

Electronically deactivated amines react very slowly. Here, cyclization of the acyclic peptoid dimer occurs mainly during the TFA post-treatment.



Scheme 18

Procedure

1-N-benzyl-3-ethyl-4-N-(2-methyl)propyl-6-propyl-2,5-dioxo-1,4-piperazine: To a slurry of (Wang) hydroxymethyl resin (5.0 g, having a loading of 0.50 mmol g^{-1}, 2.50 mmol) in DMF (50 mL) was added α-bromovaleric acid (0.984 mL, 7.50 mmol, 3 equiv.) and DMAP (30 mg,

0.25 mmol, 0.1 equiv.). DIC (1.17 μL, 7.50 mmol, 3 equiv.) was added in one portion to the reaction mixture, which was agitated at rt for 30 min, after which the resin was drained and the acylation repeated. The resin was filtered and washed with DMF (2 x 10 mL) and DCM (2 x 10 mL).

This resin (**68**; R^1 = propyl; ~2.5 mmol) was treated with a solution of benzylamine in DMSO (50 mL of a 2 M solution, 40 equiv.) at 50° C for 22 h. The resin was filtered and washed with DCM (2 x 10 mL), MeOH (2 x 10 mL) and DCM (2 x 10 mL) to afford resin **69** (R^1 = propyl, R^2 = benzyl). A ninhydrin test [59] was used to confirm the presence of amine on the resin.

To a slurry of a portion of this resin (**69**; R^1 = propyl, R^2 = benzyl; 0.20 g, ~0.10 mmol) in THF (2 mL) was added 2-bromobutyric acid (107 μL, 1.0 mmol, 10 equiv.) and DIEA (348 μL, 2.0 mmol, 20 equiv.). PyBrOP (466 mg, 1.0 mmol, 10 equiv.) was added in one portion to the reaction mixture, which was subsequently agitated at 50° C until a ninhydrin test confirmed the completion of acylation (~18 h). The resin was filtered and washed with DMF (2 x 10 mL) and DCM (2 x 10 mL).

This resin (**70**; R^1 = propyl, R^2 = benzyl, R^3 = ethyl; ~0.10 mmol) was treated with isobutylamine in DMSO (1 mL of a 2M solution, 20 equiv.) for 24 h at 70° C. The resin was drained and washed with DCM (3 x 10 mL) and the eluents were concentrated on a rotary evaporator. At this point, only a trace of diketopiperazine (DKP) was detectable, while most of the material remained on the support. The resin was treated with 95 % TFA/5 % H_2O for 1 h. After filtration, the TFA eluent was evaporated to afford the desired (crude) product **71** as an oil.

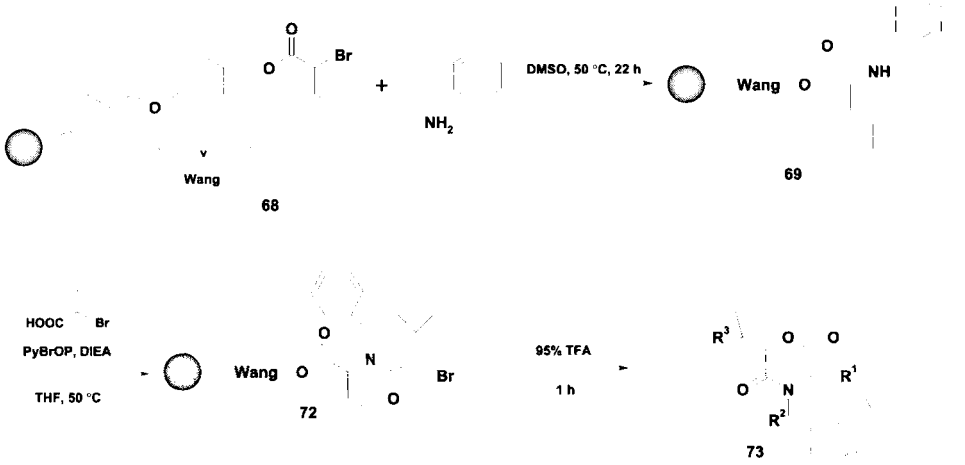
Two routes to cyclization were observed in various examples. In some cases intramolecular cyclization occurred to afford the product directly after in situ release from the solid support. In other cases, after draining the eluent, it was necessary to induce cyclization with TFA.

This method lends itself to the preparation of trisubstituted morpholines if the bromo-substituted intermediate is cleaved by TFA without previous treatment with an amine building block.

3.4.12 Diketomorpholines

The method of piperazinedione synthesis [80] illustrated above (Scheme 18) is an example of scaffold proliferation by branching out from common intermediate structures ("divergent library design"). Resin-bound bromides like **70** are suitable for bromine displacement with primary amines to obtain acyclic precursors of piperazinediones, but direct treatment with TFA also induces cyclization, leading effectively to analogous morpholine derivatives. The intramolecular displacement of bromine by the carboxylate seems to occur in the cleavage solution, once the linear intermediate is released from the solid support.

Although less well studied than diketopiperazines, biologically active compounds containing a diketomorpholine ring system are also known (e.g., Lateritin, an inhibitor of acyl-CoA-cholesterol acyltransferase [86]).



Scheme 19

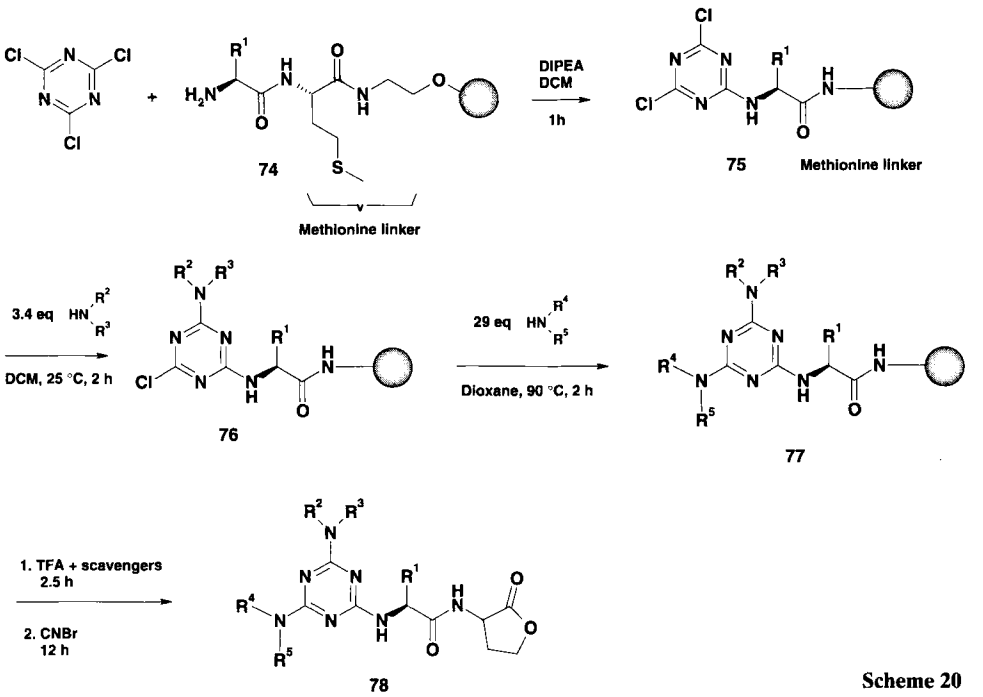
Procedure

3-Propyl-4-N-benzyl-6-(1-methyl)ethyl-2,5-dioxo-1,4-morpholine: To a slurry of resin **69** prepared as described in the previous section (R^1 = propyl, R^2 = benzyl; 1.50 g, ~0.75 mmol) in THF (15 mL) was added (+)-2-bromo-3-methylbutyric acid (1.36 g, 7.5 mmol, 10 equiv.) and DIEA (2.6 mL, 15 mmol, 20 equiv.). PyBrOP (3.5 g, 7.5 mmol, 10 equiv.) was added in one portion to the reaction mixture, which was then agitated at 50° C until a ninhydrin test confirmed the completion of the acylation (~18 h). The resin was filtered and washed with DMF (2 x 10 mL) and DCM (2 x 10 mL). The resin (**72**) was treated with a solution of 95 %TFA/5 % H_2O for 1 h. After filtration, the TFA eluent was evaporated to afford the desired (crude) product **73** as an oil.

3.4.13 Triazines

The three symmetrically positioned electrophilic centers of trichlorotriazine enable the selective introduction of diversity positions through the successive substitution of the chlorine atoms. This feature of trichlorotriazine is well known and widely utilized, e.g., in the chemistry of dyestuffs. The principle was applied for the preparation of a 12 000-membered library [87] to be used in both solid-phase and solution assays, with a selectively cleavable linker stable to the TFA treatment necessary for the deprotection of displayed functional groups. Methionine was used as a suitable linker between the library and the resin. This type of linkage to the support was used earlier for release of the compounds for mass spectrometric analysis [88]. Both the first and second chlorine atoms of the triazine scaffold can be substituted at room temperature, but the kinetics of both reactions are sufficiently different, so that the use of a large excess of trichlorotriazine in combination with the amine attached to the solid support enables the selective substitution of only the first chlorine atom. Crosslinking seems not

to be an issue. The second diversification step consists of the substitution of the second chlorine with primary or secondary amines. This step is also performed at room temperature, but, unlike in the previous step, an excess of amine is used in order to drive the reaction to completion. For this step it is important to select amines which yield clean, monosubstituted products without dialkylated side products [87]. The third chlorine is substituted under elevated temperature. As the molecule is symmetrical, the sequence selection of amines for the second or third randomization has no influence on the composition of the created library. The use of more reactive amines (piperidine, indoline) may therefore be reserved for the third step.



Scheme 20

Procedure

Linker (methionine) attachment: The solid support (18 g PEG-PS·HCl, substitution 0.58 mmol g^{-1}, 10.44 mmol, size 220 µm, Perseptive) was swollen in DMF (120 mL) for 20 min, followed by treatment with 10 % DIEA in DCM (2 x 120 mL, 2 min). The solid support was washed with DCM (2 x 100mL), DMF (1 x 100mL) and 5 % HOBt in DMF (1 x 100 mL). To a solution of Fmoc-L-methionine (11 g, 30 mmol, 2.87 equiv.) and HOBt (4 g, 30 mmol, 2.87 equiv.) in DMF (100 mL), DIC (4.7 mL, 30 mmol, 2.87 equiv.) was added and the mixture was stirred for 20 min at rt. The activated methionine was added to the resin, and the suspension was agitated with nitrogen for 1 h at rt or until the ninhydrin test [59] was negative, indicating complete coupling. The solid support was washed with DMF (2 x 100 mL), DCM (1 x 100 mL) and DMF (1 x 100 mL). The Fmoc group was removed by treatment with

50 % piperidine in DMF (2 x 50 mL) for 30 min, and the resin washed with DMF (4 x 100 mL). The substitution with methionine, determined by UV measurement of the dibenzofulvene-piperidine adduct (λ_{max} 302 nm) formed during the deprotection was approx. 0.49 mmol g^{-1}.

Aminoacylation: A portion of the resin was transferred into a Wheaton glass vial (0.9 g, 0.44 mmol). To a solution of a protected Fmoc-amino acid (1.5 mmol) and HOBt (203 mg, 1.5 mmol, 3.41 equiv.) in DMF (5 mL), DIC (237 µL, 1.5 mmol, 3.41 equiv.) was added, and the reaction mixture was shaken for 20 min at rt. The activated amino acid solution was added to the resin and shaken at rt for 3 h, or until the ninhydrin test was negative. The resin was then washed with DMF (twice), DCM (once), and DMF (once). The Fmoc group was removed by treatment with 50 % piperidine in DMF (twice, 1 + 15 min), and the resin was washed with DMF (four times). The substitution with amino acid, determined by UV measurement of dibenzofulvene-piperidine adduct (λ_{max} 302 nm) formed during the deprotection, was approx. 0.41 mmol g^{-1}.

Scaffold (trichlorotriazine) attachment: The resin **74** was washed with DCM (twice) and cooled to 2° C for 30 min. A solution of cyanuric chloride (0.29 g, 1.57 mmol, 3.56 equiv.) in DCM (5 mL) was added to the resin, followed by dropwise addition of DIEA (0.275 mL, 1.57 mmol) in DCM (1 mL). The suspension was agitated with nitrogen at rt until the ninhydrin test was negative (c. 1 h). The resin was washed with DCM (three times).

Introduction of scaffold substituents: A resin portion (**75**) was transferred into a Wheaton glass vial (0.6 g, 0.25 mmol). A solution of the amine reactant (0.85 mmol, 3.4 equiv.) in DCM (5 mL) was added to the resin and the suspension was shaken for 2 h at rt. After draining the reaction mixture, the resin was washed with DCM (three times) and 1,4-dioxane (once).

A portion of resin **76** (0.45 g, 0.18 mmol) was treated with a solution of an amine or hydrazine (5.2 mmol, 28.9 equiv.) in dry 1,4-dioxane (6 mL), and shaken for 2 h at 90° C. The resin was then transferred to a syringe equipped with a polypropylene frit at the bottom. The syringe was washed with DCM (5 x 4 mL).

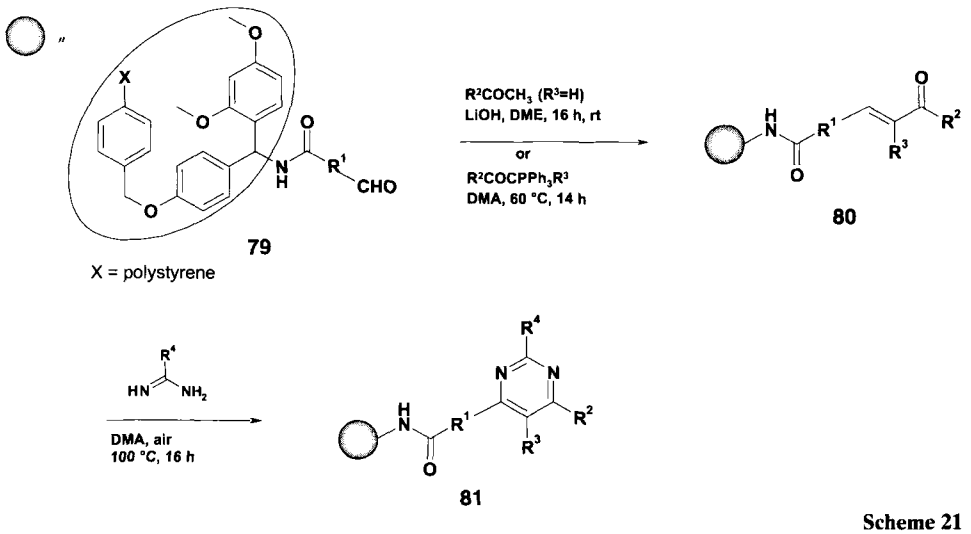
Side chain deprotection: In order to remove side chain protections of the tert. butyl type (or trityl and Pmc protections), the resin **77** was treated with 4 mL TFA containing 5 % thioanisole, 2.5 % 1,2-ethanedithiol and 5 % water for 2.5 h at rt, washed with TFA (2 x 4 mL), DCM (5 x 4 mL), DMF (1 x 4 mL), MeOH (3 x 4 mL), and dried under vacuum for 12 h. The dry resin was stored at 5° C.

Release of compound from resin: Resin containing the methionine linker (0.9 g resin) was treated with 4 mL cyanogen bromide solution (20 mg mL^{-1} in 0.1 N HCl) at 25° C for 12 h in the darkness. The reaction was stopped by freezing and lyophilization. The crude product **78** was extracted with methanol.

3.4.14 Pyrimidines

The nucleic acid components uracil, thymine, and cytosine are the most important naturally occuring pyrimidines. Many pharmaceuticals have been developed from pyrimidine nucleoside analogues, *e.g.*, Idoxuridine for the treatment of herpes infections of the eye, and AZT, a widely used anti-AIDS drug [89].

Focusing here on pyrimidine syntheses where the core structure has been assembled from a variety of building blocks, the derivatization of α,β-unsaturated ketones to form pyrimidines with a number of amidines has been reported [90]. Apart from their use in pyrimidine synthesis, α,β-unsaturated ketones are key intermediates for the combinatorial assembly of different templates on solid phase, namely dihydropyrimidinones, pyridines, and pyrazoles [90]. Reactive intermediates useful for the assembly of different templates are of particular value, as the search for new valuable drug candidates not only demands that numerous structural subunits (building blocks) are combined on a particular backbone or template, but also that a rich variety of such scaffolds is accessible. This takes into account that the core structure of a compound class contributes substantially to the pharmacological profile, in addition to the effects it mediates by directing the spatial arrangement of the various pharmacophoric substituents.



79

X = polystyrene

80

81

Scheme 21

4-Carboxybenzaldehydes immobilized on Rink resin are easily obtained by standard amide coupling protocols utilizing DIC and HOBt. Also, other aldehydes with furan or thiophene moieties, are suitable for further derivatization, representing a first variable site R^1 for diversity generation. Best results were obtained with LiOH in DME at room temperature for the subsequent Claisen-Schmidt reaction. Under these specific conditions, no Michael adduct was formed. Access to R^3-derivatized α,β-unsaturated ketones is possible by Wittig reaction of the appropriate aldehyde with the corresponding triphenylphosphonium bromide in the presence of NaOEt at 60° C in dimethylacetamide (DMA). The resin-bound vinyl ketones were treated with a 0.5 M solution of the appropriate amidine in DMA at 100° C for 16 h under an air atmosphere. Subsequent treatment with 20 % TFA in dichloromethane, cleavage from the support, and evaporation of the cleavage reagent gave the corresponding pyrimidines. The reported yields of the nine fully characterized examples were between 38 % and 98 % [90].

Procedure

Fmoc-protected 4-[(2',4'-dimethoxyphenyl)aminomethyl-phenoxymethyl resin (Rink amide resin) (5 g, 2.25 mmol) was subjected to repeated washes with 20 % (v:v) piperidine/DMA until the UV absorption at 299 nm in the eluates reached baseline level. An additional five washes (50 mL) were carried out with pure DMA. Rink resin, with the amino group of the deprotected linker, was acylated with a 0.3 M solution of a carboxyaldehyde (22.5 mL, 6.75 mmol) at rt (preactivation 40 min with 3.3 equiv. of DIC (7.23 mmol) and 3.3 equiv. of HOBt (7.23 mmol)) for at least 4 h, until the Kaiser test [59] was negative. The resulting solid-phase-grafted aldehydes **79** were utilized for the following derivatizations.

Claisen-Schmidt reaction on solid phase: To a glass vial containing 250.0 mg of aldehyde resin **79** (0.1 mmol) in anhydrous dimethoxyethane (5.0 mL) were added $LiOH.H_2O$ (48.0 mg, 2.0 mmol, 20 equiv.) and the appropriate methylketone (2.0 mmol, 20 equiv.). The capped vial was shaken for 16 h at rt. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and DCM consecutively and dried under vacuum.

Wittig reaction: A 0.25 M solution of the appropriate triphenylphosphorane (23.6 mL, 5.91 mmol, 7.5 equiv.) in DMA was added to 2.0 g (788 μmol) of resin-bound aldehyde **79**, and the resulting mixture was shaken at 60° C for 14 h. The mixture was filtered, washed with DMA and *i*-PrOH, and air-dried to provide resin-bound α,β-unsaturated ketones **80**.

Pyrimidines: To a solution of the corresponding amidine hydrochloride (96 μmol, 10 equiv.) in DMA (96 μL) was added NaOEt in DMA (96 μL of a 1 M suspension, 10 equiv.). Free amidines were used without NaOEt treatment. The suspension was sonicated for 5 min and centrifuged. The resulting solution was added to the resin-bound chalcone derivative of type **80** (9.6 μmol) in a vial, and the suspension was vigorously stirred at 100° C overnight under an air atmosphere. The resin was washed sequentially with glacial acetic acid, DMA, *i*-PrOH and DCM and dried under vacuum. Cleavage with 20 % (v:v) TFA/DCM for 15 min afforded pyrimidines **81**.

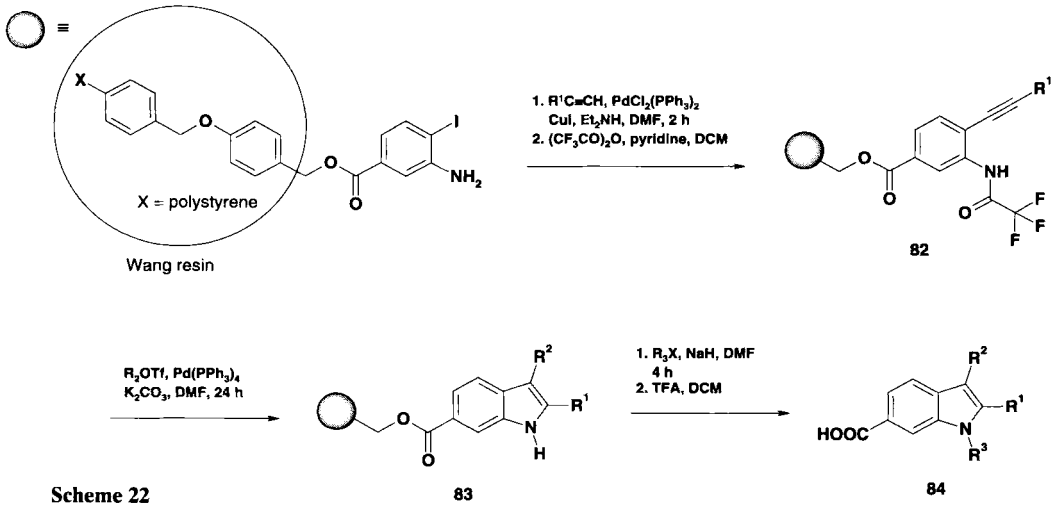
3.4.15 Indoles

The synthesis of indoles on solid support has been driven by the wide range of indole derivatives which occur in nature [91–93], and by the biological activity of many indole derivatives of both natural and synthetic origin [94]. The indole scaffold appears in the amino acid tryptophan, the metabolites of which are important in the biochemistry of both plants and animals. In addition, the indole ring appears in many compounds which have found use as drugs, e.g., indometacin [95], sumatriptan [96], and pindolol [97].

Palladium catalysis for C-C bond formation and reactions in which a heterocycle is formed are of particular importance for the synthesis of small molecules for drug research. One approach has been described employing asymmetrical alkynes with a wide variety of substituents in indole ring closure reactions starting from 4-amino-3-iodobenzoic acid coupled to Rink resin [98]. Generally, the more sterically demanding group ends up in the 2-position. In a similar synthesis, tetramethylguanidine has been used as the base ensuring complete in-situ cyclization of the initially formed crosscoupling product [99]. However, these syntheses offer only one point of diversity. The Fischer indole synthesis – the most widely used of all indole syntheses – has also been adapted to the solid phase [100]. In this approach, a variety of

phenylhydrazines can be incorporated, the exceptions being the electron-deficient 4-nitro and 4-carboxyphenylhydrazines. Indoles have also been synthesized by cleaving a phosphonium salt with an intramolecular Wittig reaction involving a relatively unreactive amide carbonyl group (one example) [101].

Starting with 2-ethinylaniline, some 2-aryl and 2-cycloalkenyl-indoles have been prepared by coupling and subsequent cyclization utilizing Pd-catalyzed reactions in solution phase [102, 103]. Transfer of the reaction sequence to the solid phase was first reported in [99]. Since the authors introduced only one diversity point in their synthesis, a later publication with three independently variable residues is discussed here [104]. Interestingly, Pd-catalyzed heteroannulation of terminal acetylenes has been similarly used for the solid-phase synthesis of benzofurans by utilizing ortho-hydroxy aryl iodides [105].



Scheme 22

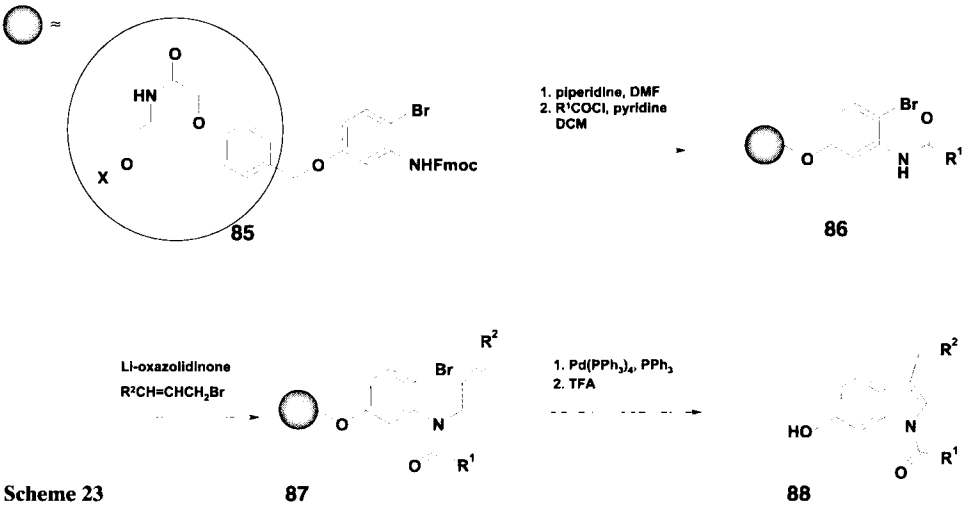
Commercially available Wang resin, modified to chloro Wang resin by treatment with MsCl, LiCl, and collidine in DMF, was coupled with the cesium salt of 3-amino-iodobenzoic acid [104, 106]. The reaction mixture was heated in DMF at 50° C for 24 h without a protecting group on the nitrogen (Scheme 22). Coupling of a terminal alkyne, according to the procedure of Sonogashira [107], followed by trifluoroacetylation, provided the polymer-bound alkyne **82**, which cyclized with the incorporation of a vinyl group from a vinyl triflate [108] to the 2,3-derivatized indole **83**. Optional alkylation in the presence of NaH with methyliodide or bromo acetic acetate gave the trisubstituted indoles **84** after cleavage from the resin with 50 % TFA in DCM. The yields range from 34 % to 76 % (six examples) for the nonalkylated indoles, and from 33 % to 73 % (12 examples) for the alkylated indoles.

Procedure

3-Amino-iodobenzoic acid coupled to modified Wang resin (3 g, 1.8 mmol) was suspended in DMF (40 mL). Alkyne (9.0 mmol, 5 equiv.), Et_2NH (30 mL), $PdCl_2(PPh_3)_2$ (0.29 mmol, 0.16 equiv.), and CuI (0.525 mmol, 0.29 equiv.) were added and the mixture was stirred at

rt for 2 h. The resin was filtered and washed sequentially with DMF and DCM. Trifluoroacetylation with TFAA (2.6 mL, 1 equiv.), pyridine (1.5 mL), and DCM (50 mL) afforded the alkyne substituted resin **82** (3.05–3.07 g). A 100 mg portion of the alkyne derivatized resin was suspended in DMF (1 mL), and K_2CO_3 (70 mg, 8.5 equiv.) was added. 2-Carbomethoxy-1-cyclopentenyl triflate (55 mg, 3.5 equiv.) and DMF (1 mL) containing $Pd(PPh_3)_4$ (15 mg) were added. The mixture was stirred for 24 h at rt, filtered, and washed to provide the polymer-bound indole **83**. The product was either cleaved with 50 % (v:v) TFA/DCM or alkylated: to a suspension of the indole resin in DMF (1.5 mL) was added NaH (30 mg, 0.75 mmol, 12.5 equiv. 60 % dispersion in oil). After 30 min, an alkyl halide (0.3 mmol, 5 equiv.) was added and stirring was continued for 4 h at rt. After filtration and washing, the N-substituted indole **84** was cleaved from the resin with 50 % (v:v) TFA/DCM (2 mL).

An indole synthesis with two diversity points utilizing the Heck reaction has been reported [109]. The indole core structure was synthesized via a 5-exo-trig transition state, which provided the exocyclic double bond that then underwent exo to endo double bond migration. The anthranilate building block was prepared in solution and immobilized by a method previously described for the loading of 2-aminobenzophenones [1]. After Fmoc cleavage, the resulting 4-bromo-3-aminophenyl ether was treated with acid chlorides and pyridine in DCM. As outlined in Scheme 23, alkylation of the anilide with substituted allyl bromides was achieved in the presence of lithium benzyloxazolidinone in THF. The reaction mixture was treated with base for 1 h and an allylic halide was added and vortexed for 6 h at room temperature. The alkylation reactions were routinely repeated to ensure complete alkylation. The Heck reaction was performed under N_2 at 85–90° C using tetrakistriphenylphosphine palladium, triphenylphosphine, and triethylamine. It was found that an inert atmosphere was essential as Pd(0) is oxidized in air at elevated temperatures, resulting in reductive debromination of the starting materials. After repetition of the procedure the indole analogs were cleaved from the resin with 95 % (v:v) TFA in H_2O. In all other cases examined (seven examples), the product was the 3-alkylindole isomer. Indolinones were synthesized by a modification of this synthesis [110].



Scheme 23

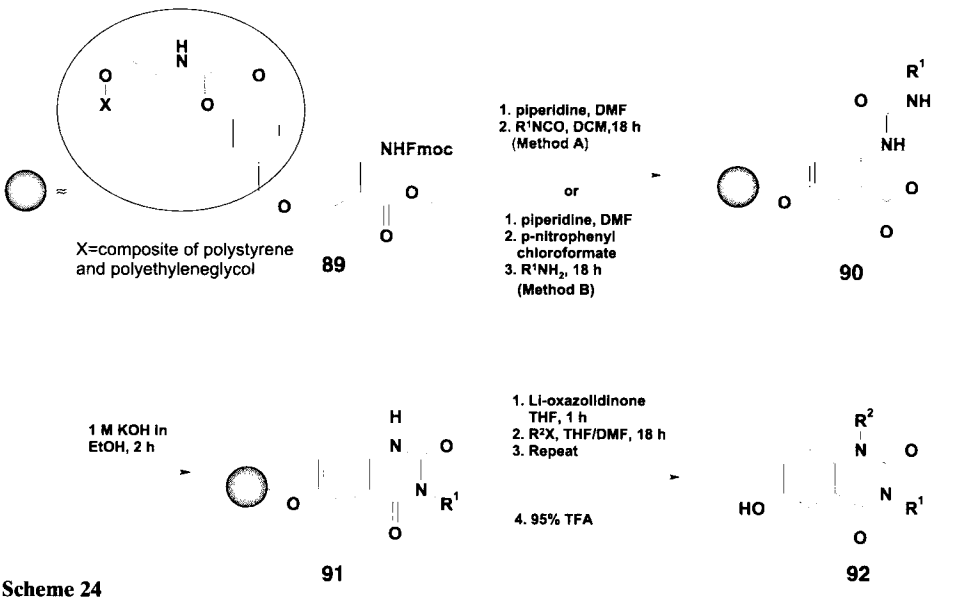
Procedure

4-Bromo-3-fmoc-aminophenyl ether attached to 4-hydroxymethylphenoxyacetic acid linker on PEG-resin (**85**) was suspended in 20 % piperidine in DMF and vortexed for 30 min. The resin was washed sequentially with DMF and DCM and treated with the acid chloride (5 equiv.) together with pyridine (7 equiv.) in DCM for 32 h. The resin **86** was washed sequentially with DMF, *i*-PrOH, and DCM and then slurried in DMF. A solution of lithium benzyloxazolidinone (15 equiv.) in THF was added to the reaction mixture. The reaction was vortexed at rt for 1 h followed by addition of the allylic halide (30 equiv.). After 6 h of vortexing, the alkylation procedure was repeated. The resin **87** was rinsed sequentially with DMF, *i*-PrOH, and DCM. Then $Pd(Ph_3)_4$ (0.5 equiv.), PPh_3 (2 equiv.), NEt_3 (13 equiv.), and DMA were added to the derivatized resin. The reaction tube was evacuated, sealed under N_2, and heated at 85–90 ° C for 5 h. This procedure was repeated. The resin was then rinsed with DMF, and with a solution of $Et_2NCS_2Na{\cdot}3\ H_2O$ in DMF (0.2 M). The resin was washed sequentially with DMF, *i*-PrOH, and DCM. Cleavage with 95 % (v:v) TFA in H_2O for 3 h provided the indole analogs **88**. An analytically pure sample is obtained by flash chromatography.

3.4.16 Quinazolines

The quinazoline moiety is present in a variety of biologically active compounds known to interact with G-protein-coupled receptors and enzymes [111–115]. Quinazolines are often used as tyrosine kinase inhibitors [112]. In general, the quinazoline template is synthesized starting from polymer-bound anthranilic acids. After diversity generation, the template is normally cleaved by a cyclative release mechanism; this cleavage is directed by either amide or carbamate cyclization. In one reported example, the quinazoline synthesis by N-acylation of anthranilic acid derivatives with the chloroformate of hydroxymethylpolystyrene proceeds via coupling of the free acid group with a primary amine, followed by subsequent release by heating in DMF [116, 117].

Syntheses based on a non-cyclative release mechanism have also been reported. Dialkyl quinazolinones were synthesized from an anthranilate immobilized on solid support through a ((4-hydroxymethyl)phenoxy)acetic acid, as depicted in Scheme 24. Although the carboxylic acid to be immobilized was not available commercially, it was readily obtained from 5-hydroxyanthranilate via a three-step synthesis. Urea formation was either achieved by removal of the Fmoc group and subsequent addition of isocyanate, or by reaction of the anthranilate with 4-nitrophenylchloroformate, to afford a reactive carbamate that gave the urea upon reaction with a primary amine. Subsequent cyclization was achieved by treatment with ethanolic KOH. Treatment of the product obtained (**91**) with lithium oxazolidinone followed by addition of an activated alkylating agent, e.g. alkyl iodides, benzylic or allylic bromides, provided di-alkyl quinazolines. Ultimately, the title products were detached from the support using 95 % TFA. Quinazolines bearing alkyl, alkenyl, haloaryl, alkylaryl and heteroaryl substituents on both nitrogen atoms were prepared from isocyanates or primary amines and alkyl halides. The syntheses proceeded in high overall yields (82–95 %; 15 examples) [118].



Scheme 24

Procedure

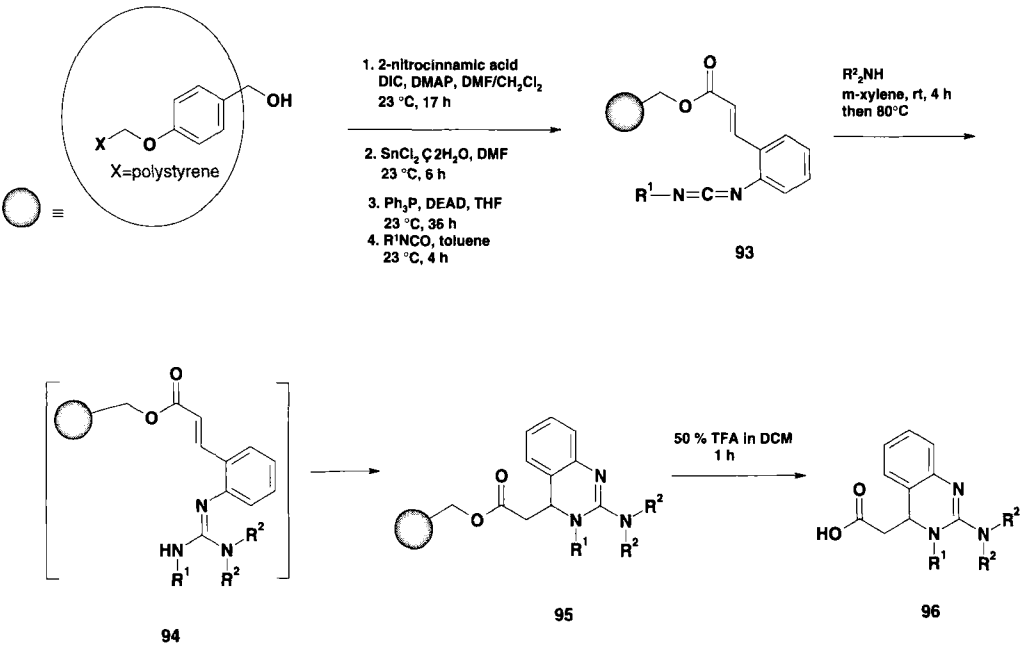
The Tentagel S-NH_2 supported anthranilic acid derivative **89** (0.20 g, 0.06 mmol) was slurried in 2 mL DMF. Piperidine (0.5 mL) was added, and the reaction flask was shaken for 1 h.

Method A: The resin was rinsed with DMF, followed by DCM (2 mL) and the isocyanate (1.16 mmol, 20 equiv.) was added. The reaction mixture was shaken for 18 h. The resin **90** was rinsed with DCM and EtOH.

Method B: To the free amine was added 0.5 M p-nitrophenyl chloroformate (8.3 equiv.) and 0.5 M triethylamine in THF/DCM (v:v = 1:1, 2 mL) and the reaction mixture was shaken for 18 h. The resin was rinsed with DCM, and a primary amine (2 mL of a 0.5 M solution in DCM, 16.7 equiv.) was added. The reaction mixture was shaken for 18 h. The immobilized urea 90 was rinsed with DCM and EtOH. To resin **90** 1 M KOH in EtOH (2 mL) was added, and the mixture was shaken for 1 h. The resin **91** was rinsed with EtOH and THF. THF (1 mL) was added followed by lithium benzyloxazolidinone (3 mL, 0.3 M in THF, 0.90 mmol, 15.5 equiv.). The reaction mixture was shaken for 1.5 h. An alkylating agent (2.32 mmol, 40 equiv.) was added, followed by DMF (1 mL), and the reaction mixture was shaken for 18 h. The resin was filtered and addition of lithium benzyloxazolidinone and alkylating agent was repeated as described above to give the immobilized dialkyl quinazoline. The resin was rinsed with THF, THF/H_2O, then THF again. TFA (95 % in water, 2 mL) was added to the resin and the mixture was shaken for 1 h. The resulting solution was filtered from the resin, diluted with water, and lyophilized to provide the corresponding quinazoline **92**.

Syntheses of 3,4-dihydroquinazolines were achieved by aza-Wittig coupling, to form the carbodiimide, and subsequent addition of a secondary amine inducing an intramolecular

Michael addition [119]. Elements of diversity are therefore added by treating the iminophosphoranes with isocyanates or thioisocyanates, and with the subsequent reaction of the carbodiimide with an excess of a secondary amine.



Scheme 25

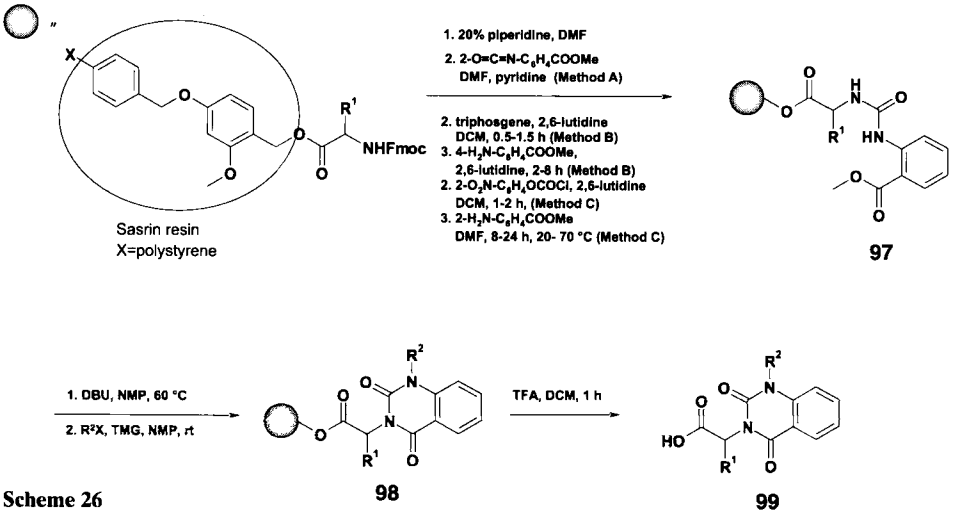
As shown in Scheme 25, the commercially available 2-nitrocinnamic acid was attached to Wang resin by a standard coupling method, followed by reduction of the nitro group with $SnCl_2 \cdot 2H_2O$ in DMF. Treatment of the immobilized aminobenzoic acid derivative under Mitsunobu reaction conditions [120] provided the iminophosphorane. The key step in the synthtetic pathway is the aza-Wittig reaction of the iminophosphoranes with isocyanates in toluene at room temperature. Treatment of the reactive intermediate with an excess of secondary amine in anhydrous m-xylene at room temperature for 2 h provided the guanidine **94**. Depending on the nature of the secondary amine the guanidine underwent partially intramolecular Michael addition to provide dihydroquinazoline **95**. The reaction was driven to completion by heating at 80° C for 4 h. Release of the dihydroquinazolines was obtained by treatment with TFA/DCM. With reactive aryl isocyanates, high yields and purities were reported (yield 87–100 %, nine examples).

Procedure

To the Wang resin (0.10 g, 0.80 mmol g^{-1} substitution) was added 2-nitrocinnamic acid (77 mg, 0.40 mmol, 5 equiv.) in 1 mL DMF/DCM (v:v = 1:1) followed by DIC (63 µL, 0.40 mmol, 5 equiv.) and DMAP (10 mg, 0.08 mmol). After shaking for 17 h at 23° C, the resin was washed with DMF, DCM, and MeOH, and was added to 1 mL of 2 M $SnCl_2 \cdot 2H_2O$ in DMF,

then shaken at 23° C for 6 h. The resulting resin was washed with DMF, DCM , MeOH, and dried under vacuum. To the mixture of resin and PPh_3 (105 mg, 0.40 mmol, 5 equiv.) in anhydrous THF (1 mL) was added dropwise DEAD (63 µl, 0.40 mmol, 5 equiv.) at 23° C. The mixture was shaken at rt for 36 h. The mixture was washed with dry THF and DCM. After drying under vacuum, the resin was treated with an isocyanate (0.40 mmol, 5 equiv.) in anhydrous toluene (1 mL) for 4 h at 23° C. The resulting resin-bound carbodiimide **93** was filtered and washed sequentially with anhydrous DCM and ethyl ether under nitrogen. To the resin was added the secondary amine (0.40 mmol, 5 equiv.) in anhydrous m-xylene (1 mL), and the mixture was shaken for 2 h at 23° C followed by heating at 80° C for 4 h. After undergoing sequential washes with DMF, DCM, and MeOH, the resin was dried under high vacuum, and treated with a solution of 50 % (v:v) TFA in DCM at 23° C for 1 h to release the 3,4-dihydroquinazoline **96**. Removal of the volatile components under a stream of nitrogen was followed by lyophilization with 50 % CH_3CN in water to afford the pure compounds as powders.

A patent application describes the synthesis of 2,4-quinazolinediones from immobilized amine reagents or immobilized isocyanates, respectively [121]. Utilizing the amine route (Method A in Scheme 26), an Fmoc-protected amino acid immobilized on Sasrin resin [122] was treated with piperidine to provide the free amine derivative. Reaction of a resin-bound amino acid with 2-carboxymethyl phenylisocyanate and cyclization of the resulting urea upon treatment with DBU afforded a support-bound 2,4-quinazolindione. Treatment of the resin with a reactive alkylating agent in the presence of DBU for 10–48 h at 20–70° C provided the N^1-alkylated quinazolinedione. The compounds were released from the resin with TFA/DCM.



Scheme 26

A second route (Method B in Scheme 26) involves the reaction of triphosgene with the deprotected terminal amine, providing chloroformamides that lose HCl to give isocyanates. A urea derivative is formed by adding an anthranilate or an anthranilic acid derivative. Alter-

natively, an activated carbamate can be produced from 4-nitrophenyl chloroformate as the reactive intermediate (Method C in Scheme 26).

In addition, by treatment of the immobilized isocyanate or carbamate with a heterocyclic anthranilate or a heterocyclic anthranilic acid, a variety of other core structures were synthesized, e.g., pyrimidopyrimidinediones, pyridopyrimidinediones, 2,4-pteridinediones, or azolopyrimidinediones. Again, the cyclization occurs in the presence of DBU. Finally, the compounds are released by the addition of dilute TFA. Ala, Val, Ile, Met, Phe, Tyr(tBu), Asp(tBu), Glu(tBu), Arg(Mtr), Lys(Boc), Trp(Boc) -derivatized 2,4 quinazolinediones without N^1-alkylation were synthesized in this manner. The following alkylating agents were utilized for the preparation of Phe-derivatized quinazolinediones: MeI, $BrCH_2CH_2OCH_2CH_2OMe$, $ClCH_2Ph$, $ICH_2(CH_2)_4Me$, 2-$BrCH_2$-naphthalene, N-($BrCH_2CH_2CH_2$)-phthalimide, 4-$MeOC_6H_4CH_2Br$, 2-cyano-$C_6H_4CH_2Br$, $BrCH_2COO_2{}^tBu$, and $BrCH_2CONH_2$. The HPLC purity of the 10 alkylated heterocycles was reported to be between 75 % and 99 %.

Procedure: Method A

An appropriate N-Fmoc-protected aminoacid resin (100 mg, 0.06 mmol for the Sasrin support-immobilized amines) was deprotected by treatment with 20 % piperidine in DMF for 30 min. The resin was filtered, washed liberally with DMF, MeOH, and DCM, and dried under vacuum. The amine resin was suspended with an appropriate isocyanate or 4-nitrophenylcarbamate (0.2–0.5 mmol, 3.3–8.3 equiv.) in 10 % (v:v) pyridine/DMF (1–2 mL), and agitated at room temperature until a negative ninhydrine test indicated the absence of a free amine on the solid phase (typically, 0.5–3 h for reactions with isocyanates, or 1–24 h for reactions with p-nitrophenylcarbamate). The resulting urea resin **97** was filtered, washed with DMF, MeOH, and DCM, and dried under vacuum. Immobilized urea derivatives thus obtained were further cyclized into 2,4-quinazolinediones by agitation at 40–80° C (preferably at 50–65° C) with an organic base (such as 2–10 % DBU or tetramethylguanidine in DMF) or an inorganic base (such as 1–10 % lithium, sodium or cesium carbonate in DMF or NMP) for 2–24 h. The resin **98** (R^2= H) was filtered, washed sequentially with liberal amounts of DMF, MeOH, and DCM, and dried under vacuum. The resulting 2,4-quinazolinediones were cleaved from the support with 1–40 % TFA in DCM for 0.5–2 h. The Sasrin resin-immobilized products were typically released from the support with 1 % TFA in DCM (30 min). When necessary, amino acid side chain functionalities were further deprotected with mixtures of TFA and additives (scavengers: thiols, phenols, or trialkylsilanes), such as 5 % triethylsilane – 40 % TFA in DCM (0.5–4 h, depending on the nature of the protecting groups). The crude products were lyophilized and analyzed by NMR, MS, and HPLC.

Alkylation-procedure. Method (a): An appropriate N^1-H quinazolinedione resin **98** (R^2 = H), prepared as discussed above (~ 100 mg Sasrin support, 0.06 mmol), was agitated with an appropriate alkylating agent (1.2 mmol, 40 equiv.) and an organic base (such as tetramethylguanidine, DBU, 1.2 mmol, 40 equiv.) in NMP (1.75 mL) for 10–48 h at 20–70° C (typically 18 h at rt). The resulting resin 98 ($R^2 \neq$ H) was filtered, washed with liberal amounts of DCM, MeOH, and dried under vacuum (rt, 0.5 Torr). Cleavage and isolation of the N^1-alkylated quinazolinediones **99** was performed as described above for preparations of N^1-H quinazolinediones.

Alkylation-procedure. Method (b): An appropriate N^1-H quinazolinedione resin **98** (R^2 = H) (~ 100 mg Sasrin support, 0.06 mmol) together with an appropriate alcohol (2.4 mmol, 80

equiv.), a trisubstituted phosphine (such as triphenylphosphine, 0.472 g, 1.8 mmol, 30 equiv.), and a dialkyl diisopropylazodicarboxylate (0.283 mL, 1.8 mmol, 30 equiv.) in 1,4-dioxane (3.6 mL) was agitated at rt for 4–24 h (typically overnight). The resulting resin **98** ($R^2 \neq H$) was filtered, washed with liberal amounts of DCM, MeOH, and dried under vacuum (rt, 0.5 Torr). Cleavage and isolation of the N^1-alkylated quinazolinediones **99** was performed as described above for preparations of N^1-H quinazolinediones (see Method A).

Procedure: Method B
An appropriate resin (such as an immobilized amino acid reagent, see above, Method A; ~ ~ 100 mg for Sasrin support, 0.06 mmol) was agitated with triphosgene (0.19 mmol, 3.2 equiv.) and an organic base (such as 2,6-lutidine, 0.3 mL) in DCM (1.5 mL) for 0.5–1.5 h (until a negative ninhydrin test indicated the absence of a free amine on solid phase). The resulting isocyanate resin was washed liberally with DCM. Subsequently an appropriate amine (such as methyl anthranilate, 1 mmol, 16.7 equiv.) together with 2,6 lutidine (0.2 mL) in DCM (2 mL) was added. The mixture was agitated at rt until the reaction was completed (typically, 2–8 h). The resin was filtered, washed liberally with DMF, MeOH, and DCM, and dried under vacuum. The resultant immobilized ureas **97** were further converted into fused 2,4-quinazolinediones as described in Method A.

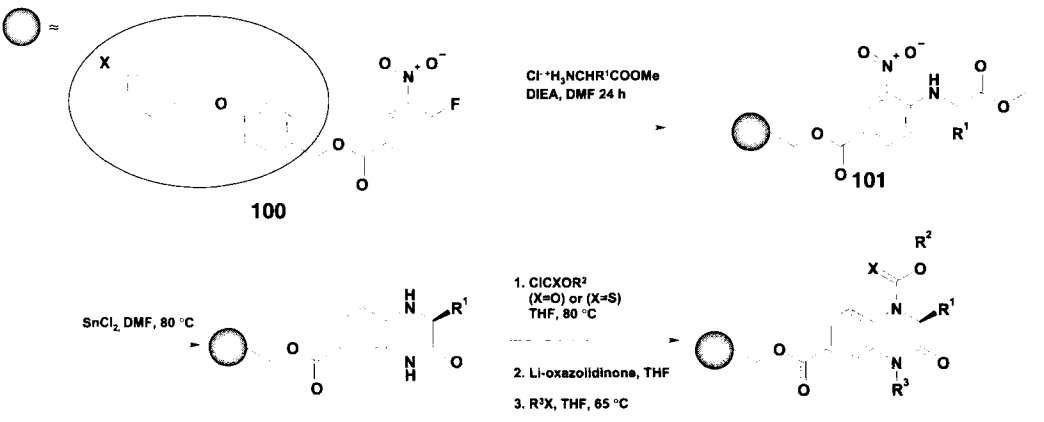
Procedure: Method C
An appropriate amine resin (such as immobilized amino acid reagents, see above, Method A; ~ 100 mg for Sasrin support, 0.06 mmol) was agitated with p-nitrophenyl chloroformate 202 mg (1.0 mmol, 16.7 equiv.) and an organic base (such as 2,6-lutidine, 0.3 mL) in DCM (1.5 mL) for 1–2 h (until a negative ninhydrin test indicated the absence of a free amine on a solid phase). The resulting p-nitrophenylcarbamate resin was filtered, washed with liberal amounts of DCM, and dried under vacuum (rt, 0.5 Torr). An appropriate amine (such as methylanthranilate, 1 mmol, 16.7 equiv.) and a solution of an organic base such as 10 % (v:v) pyridine or 2,6-lutidine in DMF (2 mL) was added, and the mixture was agitated at 20–70° C for 8–24 h (typically, this reaction with methyl anthranilates was essentially complete overnight at rt). The resin was filtered, washed with liberal amounts of DMF, MeOH, and DCM, and dried under vacuum. The resulting immobilized ureas **97** were further converted into fused 2,4-quinazolinediones as described in Method A.

3.4.17 Benzopiperazinones

Although benzopiperazinones (1,2,3,4-tetrahydroquinoxalin-2-ones) are structurally related to benzodiazepines, their use in drug discovery is less established. Examples of biological activity of benzopiperazinones include inhibitors of aldose reductase [123], partial agonists of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex [124, 125], and angiotensin II receptor antagonists [126]. In addition, derivatives with antiviral activity associated with HIV have been reported [127, 128].

Two very similar routes for the synthesis of the heterocycle have been reported. The quinoxalinones reported in an earlier publication have two diversity points, (N^4 and C^3) [129], whereas a later publication described a sequence incorporating four diversity points including the amino acid attachment of the template to the support [130]. Focusing here on the

latter publication (Scheme 27), 4-fluoro-3-nitrobenzoic acid was loaded onto Wang resin via an ester linkage employing DCC and a catalytic amount of DMAP in dichloromethane or by coupling to bromomethyl Wang resin [131] using CsI in DMF at room temperature (Scheme 27). The subsequent ipso-fluoride displacement [132–135] with amino acid ester hydrochloride salts in the presence of 5 % DIEA/DMF provided polymer-bound 3-nitro-4-aniline benzoates **101** after agitation for 24 h. Complete reduction of the nitro group was achieved by treatment with an aqueous 2 M $SnCl_2$ solution in DMF at 80° C. The reaction was performed in deoxygenated solvents to avoid formation of an oxidized byproduct. The resulting anilines cyclized to afford immobilized benzopiperazinones **102** without any trace of precursor material. Upon cleavage with TFA, a considerable amount of racemization was detected by chiral HPLC analysis. It transpired that a further advantage of derivatizing the aniline site (N^4 position) consists of a greatly decreased racemization extent during the acid cleavage. Treatment of the benzopiperazinone resin **102** with chloroformates and thiochloroformates in the presence of $NaHCO_3$ at 80° C under an argon atmosphere provided the N^4-derivatized quinoxalinone resin. Further diversity generation at the anilide site was achieved by alkylation using 4-benzyl-2-oxazolidinone and benzyl bromide in anhydrous THF at 60–65° C under argon to produce benzopiperazinones with an ee >99 % upon TFA cleavage. For even more variability, different amino acids can be used as linker between the aromatic carboxylic acid unit of the scaffold and the solid-support (not presented in Scheme 27). In that case, the appropriate Fmoc-protected amino acids were attached to the solid support via an ester linkage, and deprotected with 20 % piperidine solution in DMF. Subsequent coupling of 4-fluoro-3-nitrobenzoic acid through an amide linkage gave an amino acid-derivatized resin, suitable for further modification. Unfortunately, no examples were reported where all four variable residues are introduced. The yield of the reported examples including C^3 and N^4 substitution ranges from 34 % to 69 %. Six examples, including the ipso-fluoride displacement, provided the benzopiperazinones in 17 % to 50 % isolated yield.



Scheme 27

Procedure

A 1-L single-necked, round-bottomed flask was charged with Wang resin (50.0 g, 36.5 mmol), DMF (500 mL), triphenylphosphine (47.9 g, 5 equiv.), and carbon tetrabromide

(60.5 g, 5 equiv.). The flask was shaken for 2.5 h at rt, and the resin was then filtered, washed sequentially (300 mL volumes) with DMF (twice), DCM (twice), DMF (twice), DCM (twice), and *i*-PrOH (twice), and dried by bubbling air through the resin. The resin was suspended in DMF and reacted with 4-fluoro-3-nitrobenzoic acid (13.5 g, 2 equiv.), cesium iodide (18.96 g, 2 equiv.), and DIEA (9.43 g, 2 equiv.) at rt overnight. The final yellow resin was filtered, washed thoroughly (300 mL volumes) with water (twice), DMF (twice), DCM (twice), *i*-PrOH (twice), water (twice), DMF (twice), DCM (twice), *i*-PrOH (twice), and dried, first by bubbling air through it and then in an oven (70° C) under reduced pressure overnight to afford a 3-nitro-4-aniline benzoate resin **100** with the theoretical loading of 0.698 mmol g^{-1}.

A 50-mL single necked, round-bottomed flask was charged with the 4-fluoro-3-nitrobenzoic acid loaded resin **100**, the amino acid ester hydrochloride salts (2 equiv.), and 5 % DIEA/DMF. The mixture was agitated at rt for 24 h, filtered, washed with DMF (three times), DCM (three times), *i*-PrOH (three times) in that order twice, and dried to afford enantiomerically pure aniline intermediate **101**.

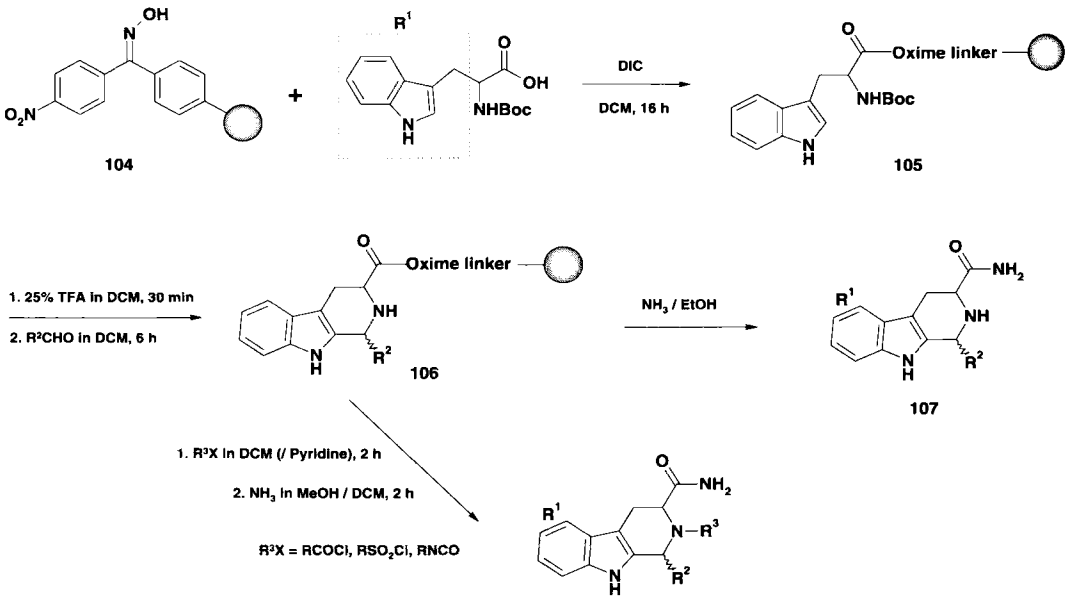
The intermediate resin **101** (150 mg) was treated with oxygen-free 2 M $SnCl_2$ (20 equiv.), and oxygen-free DMF (1.5 mL). The reaction vessel was purged with argon for 1 min , sealed, and agitated overnight in a pre-heated heating block (80° C). The resin was then filtered and washed thoroughly (1.5–2.0 mL volumes) with water (three times), *i*-PrOH (three times), DCM (three times), *i*-PrOH (three times), and $CHCl_3$ (three times) and dried to afford the benzopiperazinone resin **102**.

Introduction of N^4 acyl groups was achieved by treatment of the N^4-unsubstituted benzopiperazinone resin **102** (150 mg) with $NaHCO_3$ (10 equiv.), and chloro- or thiochloroformate (10 equiv.) in anhydrous THF (1.5 mL). The reaction vessel was purged with argon for 1 min , sealed, and agitated overnight in a pre-heated heating block (80° C). The resin was then filtered and washed thoroughly (1.5–2.0 mL volumes) with water (three times), *i*-PrOH (three times), DCM (three times), *i*-PrOH (three times), and $CHCl_3$ (three times) and dried to provide the resin-bound N^4-substituted benzopiperazinone resin **103**.

3.4.18 Tetrahydro-β-carbolines

The combinatorial chemist's considerable interest in the tetrahydro-β-carboline scaffold (1,2,3,4-tetrahydropyrido [3,4-b]indoles) is already reflected by various published reports on the efforts to derivatize this compound class efficiently on solid phase. Tetrahydro-β-carbolines are a key structural motif common to a large class of tryptophan-derived natural product alkaloids, and have been shown to have the potential to interact with biological targets. The spectrum of pharmacological properties is broad within this compound class, and includes the modulation of central nervous system targets [136]. For instance, compounds inhibiting monoamine oxidase A or binding with serotonin receptors are known [137]. Binding with the GABAA receptor ion channel and the modulation of anxiety control mechanisms, convulsion and sleep have also been reported [138, 139]. In principle, β-carbolines possess sufficient sites for functionalization in order to allow the production of diverse combinatorial libraries. Mostly, it is the chemistry of the Pictet–Spengler [140] reaction that was used in developing solid-phase synthesis protocols. This reaction, based on the intramolecular inter-

action between an iminium ion and an aromatic C-nucleophile, utilizes tryptophan analogs and aldehydes (or ketones) to afford β-carboline derivatives that can be further functionalized with acid halides, isocyanates, and sulfonyl chlorides. On the other hand, the reported low reactivity of the position-2 nitrogen seems to preclude broad systematic derivatization [141]. Nonetheless, with the availability of a wide variety of aldehydes and ketones, as well as a number of substituted tryptophan derivatives, a reasonably large number of β-carbolines may be aimed for. For the solid phase, a linker which will withstand the acid Pictet–Spengler conditions is required. The Wang linker [142] used by Mayer et al. [141] (Scheme 29), although acid-cleavable, is sufficiently stable, and the Kaiser linker employed in Scheme 28 [143] is also entirely unaffected at higher acid concentrations. A 4-hydroxythiophenol linker proposed in [144] (Scheme 30) is useful for the incorporation of additional diversity during the cleavage from the solid support by aminolysis of the ester linkage with a primary amine. Alternatively, acylation at the carboline 2-position with Boc-protected α- or β-amino acid derivatives, followed by deprotection and neutralization, results in an intramolecular cyclization and cleavage to afford six- and seven-membered bis-lactams.



Scheme 28

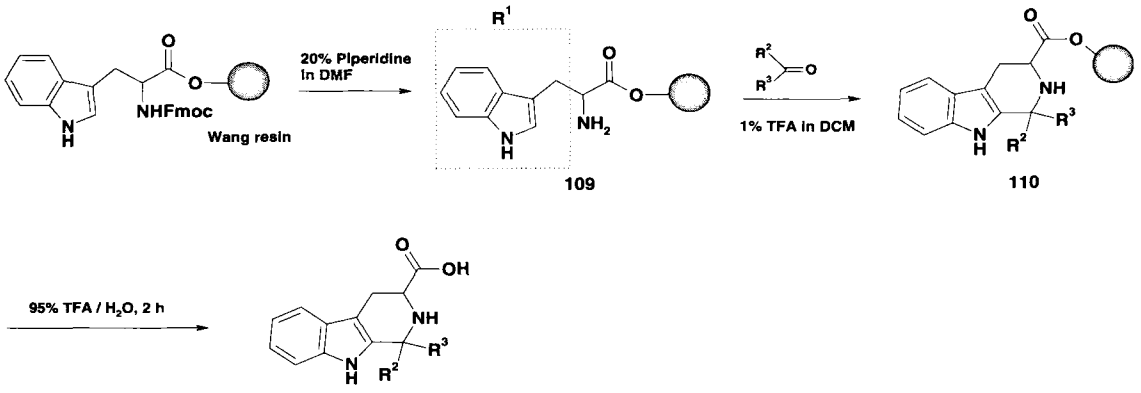
Procedure

Oxime resin **104** (6.0 g, 0.38 mmol g^{-1}, 2.28 equiv.) suspended in 50 mL DCM was shaken for 15 min. Boc-L-Tryptophan (1.1 g, 3.5 mmol, 1.54 equiv.) was added followed by DIC (548 µL, 3.5 mmol, 1.54 equiv.). The resin was shaken for 16 h, washed with DCM (3 x 50 mL), isopropanol (3 x 50 mL) and DCM (3 x 50 mL).

Resin **105** (0.4 mmol) was washed with DCM (3 x 3 mL). 25 % TFA in DCM (3 mL) was added and the resin was shaken for 1 min, then flushed free of the TFA solution with nitrogen. An additional 3 mL of 25 % TFA in DCM was added and the resin shaken for 30 min.

The resin was flushed free of the TFA solution. Fresh TFA (25 % in DCM, 3 mL) was added followed by the aldehyde reactant (6 mmol, 15 equiv., 2 M final concentration). The reaction was shaken for 6 h. The resin was then flushed free of the liquids, washed with DCM (3 x 4 mL), followed by DMF (3 x 4 mL) and DCM (3 x 4 mL). Once dried, this resin **106** could be used for subsequent reactions (see below) or treated with excess volume saturated NH_3 in EtOH to obtain the N^2-unsubstituted tetrahydro-β-carboline **107**.

To resin **106** (0.067 mmol) in DCM (0.5 mL) was added pyridine (0.20 mL of 1 M solution in DCM) followed by the acid chloride or sulfonyl chloride (0.20 mL of 1 M solution in DCM, 3 equiv.). In case of the isocyanate, the pyridine was omitted. The resin was shaken for 2 h, flushed and washed sequentially with DCM , DMF, and again DCM. The resin was then treated with 2 mL of a 1:1 (v:v) mixture of DCM and saturated NH_3 in MeOH for 2 h. The resin was filtered, the filtrate collected and evaporated to afford the tetrahydro-β-carboline **108** as a solid.



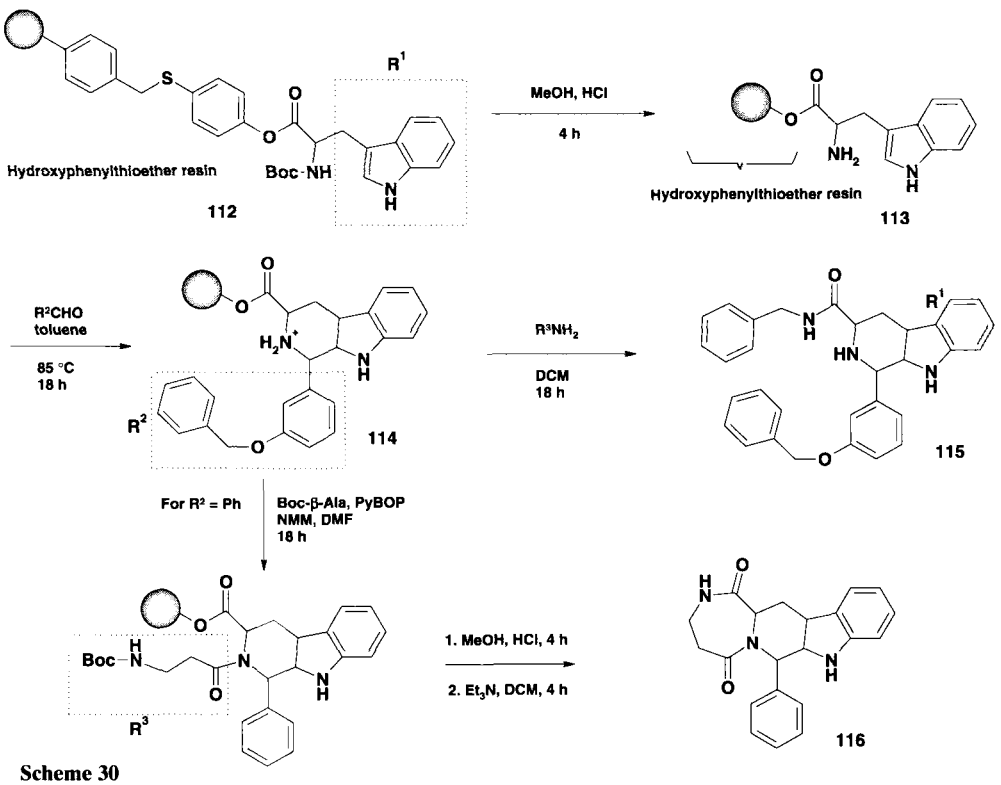
Scheme 29

Procedure: Synthesis on Wang resin and usage of ketone (or aldehyde) reactant

Commercially available Fmoc-L-Tryptophan-Wang resin (1 g, 0.5–0.7 mmol) was treated with two portions of 20 % piperidine in DMF to remove the Fmoc protecting group. The resin **109** was then washed several more times with DMF followed by DCM .The ketone (or aldehyde) reactant (4 equiv.) was added in a 1 % solution of TFA. The reaction vessel was agitated at rt for 48–72 h (or 2–4 h in the case of aldehydes). The reaction progress was monitored by the Kaiser [59] method. Cleavage from the support was accomplished by suspending and stirring the resin **110** in neat TFA for 2 h at rt, and the product **111** was recovered by filtering the suspension and concentrating the filtrate. Purity 46–97 %; mass recovery 85–99 %.

Procedure: Synthesis on 4-hydroxyphenylthioether resin

To a slurry of 4-hydroxythiophenol-linked Merrifield resin [145] (15 g, 11.3 mmol) in DMF (60 mL) was added Boc-L-tryptophan (6.85 g, 22.5 mmol, 2 equiv.) followed by HOBt (3.04 g, 22.5 mmol, 2 equiv.), DMAP (0.14 g, 1.13 mmol, 0.1 equiv.) and DIC (3.52 mL, 22.5 mmol, 2 equiv.). The slurry was shaken for 24 h at 27° C, filtered, and the resin **112** washed thoroughly with DMF and DCM.



Scheme 30

Resin **112** obtained above was suspended in 3 % methanolic HCl (50 mL) and shaken for 4 h at 27° C, filtered, and thoroughly rinsed with MeOH and DCM to obtain **113**.

A solution of the aldehyde reactant (3-benzyloxybenzaldehyde, 1.62 g, 7.7 mmol, 5.92 equiv.) in toluene (10 mL) was allowed to react with **113** (1.7 g, 1.3 mmol, 1 equiv.) for 18 h at 85° C. The mixture was cooled to rt, filtered and washed with DCM to obtain **114**. Solid-supported **114** (1 mmol) was washed with 50 % Et_3N/DCM , then with DCM. It was then resuspended in DCM (5 mL) and allowed to react with substoichiometric amounts of benzylamine (56 µL, 0.5 mmol, 0.5 equiv.) for 18 h at rt. The slurry was filtered, rinsed with DCM and the combined solutions were concentrated to afford **115** (120 mg, 0.25 mmol, 50 % yield).

Bis-lactams through cyclative cleavage: A suspension of **114** (R^2 = Ph) (0.15 g, 0.11 mmol) in dry DMF (0.15 mL) was treated with NMM (49 µL, 0.45 mmol, 4.09 equiv.), Boc-β-alanine (64 mg, 0.34 mmol, 3.09 equiv.) and PyBOP (0.23 g, 0.45 mmol, 4.09 equiv.). The mixture was shaken for 18 h at 27° C, filtered, washed thoroughly with DMF and DCM , then allowed to react with 3 % methanolic HCl (1.2 mL) at 27° C for 4 h. The deprotected material was then rinsed with DCM and shaken with 50 % Et_3N/DCM at 27° C for 4 h. The resin was filtered, washed well with Et_3N/DCM and the combined washings concentrated in vacuo to provide **116** (25 mg, 0.07 mmol, 66 % yield).

A low reactivity of nitrogen at position-2, is noticeable as pointed out in [146] (failure to acylate with Fmoc-Gly) and [141] (derivatization with alkylating reagents such as α-bromomethyl acetate achieved no validation of the reaction with a wide series of substrates).

In addition, mixtures of diastereomers are obtained (position-1). Further substitutions could be realized by using bromo or hydroxy-substituted tryptophan, followed by palladium-mediated cross-coupling or Mitsunobu reactions, respectively.

3.4.19 Outlook

While the methodology for high-yield, solid-phase peptide and nucleotide synthesis is the result of decades of optimization, the analogous synthesis mode for heterocycles is a young field in a vast, unexplored territory, that is challenging both developers and application scientists alike. Nonetheless, the foundation of past experiences in related fields is likely to accelerate the process of method development. The efforts invested in establishing a good skill base in combinatorial chemistry are likely to translate into more efficient progress achievements in the early phases of drug discovery.

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4 Polymer-Supported Reagents: Preparation and Use in Parallel Organic Synthesis

Berthold Hinzen

4.1 Introduction

The use of polymer-supported reagents (PSRs) [1–3] can combine the benefits of solid-phase chemistry [4–7] with the advantages of solution-phase synthesis. The most important advantage of these reagents is the simplification of reaction work-up and product isolation, these processes being reduced to simple filtrations (Figure 1). In addition, PSRs can be used in excess without a drawback in the purification step. By using this technique, reactions can be driven to completion more easily than in conventional solution-phase chemistry.

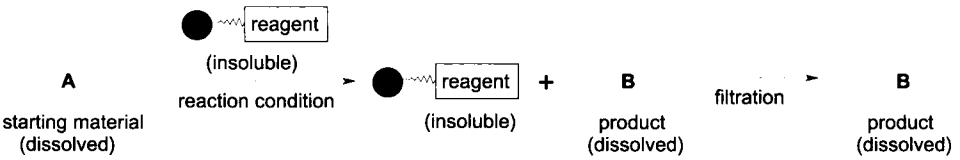


Figure 1. Polymer-supported reagents (PSR) for the transformation of dissolved reactants. The product is purified by filtration.

Other advantages include the potential of recyclization, of higher stability, of reduced toxicity, of simple reaction monitoring by TLC, and of simplified automation. The possibility of combining several PSRs in one pot to achieve multistep procedures is another appealing aspect, and this will be discussed in detail. The term "clean technology" has been created by Ley to characterize the concept of PSRs [8].

Some disadvantages of PSRs must be mentioned, however. Supporting the active moiety might reduce its activity due to unfavorable electronic and steric interactions with the support. This effect might be relevant with highly crosslinked polymer supports and can lead to long reaction times and poor yields. Furthermore, the loading of PSRs is in general low. This is an important difference between organic and inorganic supports, the loading capacities of the former being generally lower [9]. Large-scale reactions involving stoichiometric amounts of PSRs are therefore not practicable.

Critical requirements for PSRs include the absence of leaching of any impurities or side products. In addition, well-defined synthetic transformations should be performed with high fidelity. The loading on the polymer should be high (~1 mmol g^{-1}), and the stability and practical properties reasonable (ready to use from the shelf).

Potential supports include not only organic polymers but also inorganic materials such as alox, clay, zeolithes and silica [10]. Immobilization on the latter is done in most cases by adsorption processes. Depending on the reaction conditions and the solvents used, leaching of only weakly associated reagents into the solution and the resulting contamination of the product is a major problem. Therefore, these reagents can only be used in clean technology processes by way of exception, and are excluded from this review. A support in the current context is a linear or crosslinked organic polymer. The latter are also described as resins and are easily solvated by solvents such as dichloromethane or N,N-dimethylformamide (DMF), but remain macroscopically insoluble. The preference for beads has largely limited the monomeric precursors to styrene and acrylates due to the preparation method (suspension polymerization). Resins can be classified into three groups [1–3,11,12]:

1. Gel-type resins. These are prepared from vinyl monomers and a difunctional vinyl comonomer, without the use of a solvent. The properties of the resin are strongly dependent on the degree of crosslinking. In practice, 1–2 % crosslinking provides a good compromise between mechanical stability and diffusional properties, allowing sufficient penetration of the polymer by the liquid reaction medium. The most important characteristic of gel-type resins is their good swelling behavior in many solvents, giving highly porose phases that are accessible to soluble reactants.
2. Macroporous resins. In contrast to gel-type resins, these are prepared by polymerization in an unreactive solvent which defines the pore structure. The functionality is largely restricted to the pore surface and is accessible even to solvents and liquid reaction media that are not good swelling solvents.
3. Macroreticular resins. These are obtained from polymerizations in the presence of a solvent which readily solvates the monomers, but precipitates the polymer. The structure and volume of these materials is independent of the solvent and resins. The reaction sites are located at the internal surfaces of the pore.

4.2 Preparation and Use of PSRs

Polymer-supported reagents [1–3] have been prepared by one of the following methods: (i) formation of a covalent bond between the active/activating moiety and the support, e.g., immobilization of a carbodiimide group to achieve condensation reactions; (ii) polymerization of monomers carrying the active group or precursors thereof; and (iii) ion-exchange enabling the attachment of an ionic active species to immobilized ions, e.g., the quaternary ammonium ions of common anion-exchange resins (Figure 2).

Various types of PSRs will be described in the following sections. However, rather than classify these reagents by the type of support or by functionality, a classification by the way of their preparation will be used here. Furthermore, rather than providing an exhaustive list of all PSRs described in the literature, the aim of this chapter is to provide an understanding of the principles of preparation and application of such reagents, with a special focus on important reactions and on the combination of several PSRs in one synthetic sequence or, if possible, in one pot. The latter aspect is rather novel and highly interesting for combinatorial chemistry applications.

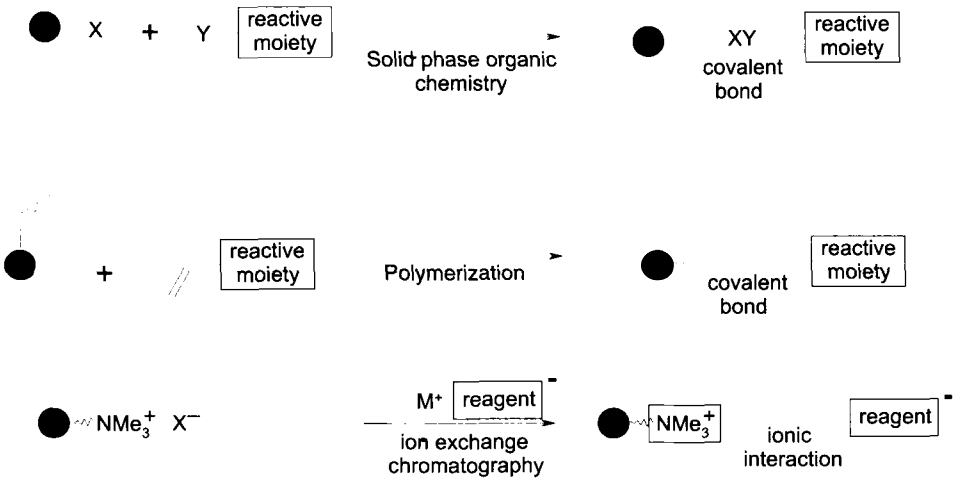


Figure 2. General methods for the preparation of PSRs.

4.2.1 Covalent Linkage Between the Active Species and Support

4.2.1.1 PSR Prepared by Solid-Phase Chemistry

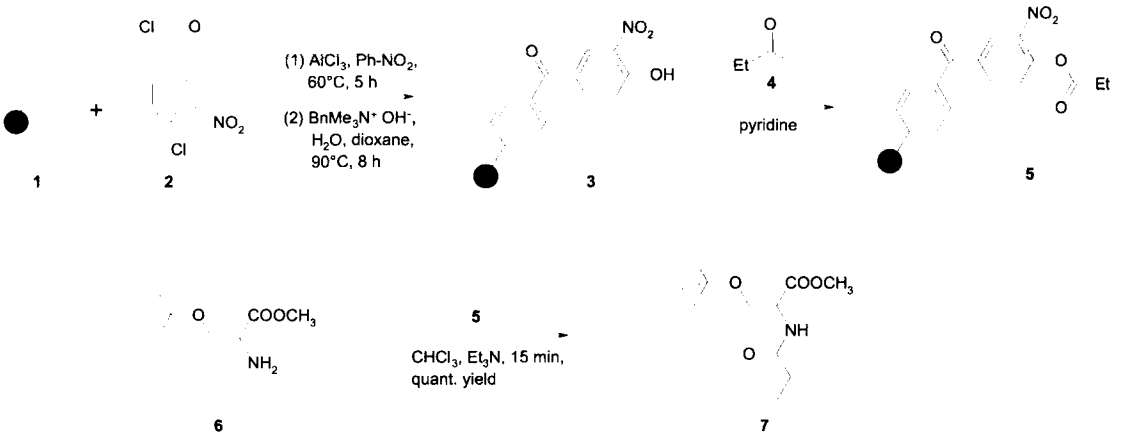
A covalent linkage between the active moiety and the support guarantees (under most chemical reaction conditions) a nonleaking reagent, and thus fulfills one of the most important requirements for PSR technology applications. Solid-phase organic chemistry is used for the preparation of reactive functionalities on the support. These moieties are ready to use in the chemical transformation of molecules in solution.

Activators for Amide Couplings

Amides and esters are often formed from activated esters and the corresponding nucleophiles. A side product in these coupling reactions is the leaving group of the activated esters, e.g., the pentafluorophenol or hydroxybenzotriazole moiety. The immobilization of these activators on a solid support would remove the most dominant side product from the reaction mixture, and would therefore in most cases obligate further purification steps. This concept was realized with the preparation of polymer-bound active esters of o-nitrophenol, N-hydroxybenzotriazole and 4-hydroxy-3-nitrobenzophenone [13–15]. The first was easily prepared by Friedel–Crafts acylation of polystyrene with 4-hydroxy-3-nitrobenzoyl chloride in the presence of $AlCl_3$, but reactions of the active esters with amines were slow [13]. N-hydroxy benzotriazole-derived activated esters were highly reactive but too moisture-sensitive to be useful PSRs. Active esters of 4-hydroxy-3-nitrobenzophenone showed reasonable acylating activities and were stable reagents (Scheme 1). They were prepared via Friedel–Crafts acylation of polystyrene **1** with 4-chloro-3-nitrobenzoyl chloride (**2**) using $AlCl_3$ or $FeCl_3$ as catalyst (Scheme 1). Replacement of fluoride with hydroxide and coupling

the resulting phenol **3** to a variety of acids or acid chlorides, e.g., **4** using standard coupling protocols generated the corresponding activated nitro phenyl esters **5**. The loading of the polymer was determined by its increase of weight, by titration with benzylamine, or by reaction with excess benzylamine and weighing the resulting amide. Polymeric activated esters with loadings of 0.9–1.2 mmol g^{-1} of resin were obtained from Boc-phenylalanine, Boc-glycine, and Boc-(*O*-benzyl)-tyrosine [13]. Coupling of amines, e.g., side chain-protected serine methyl ester (**6**) with the supported activated ester **5** was performed in chloroform in the presence of triethylamine. Amide **7** was isolated in quantitative yield after 10–15 min. Longer reaction times were required for more hindered amines and activated esters [13].

The polymeric phenols **3** were recyclable. A sample was reactivated for three reaction cycles using benzoyl chloride **2** as acylating agent. Coupling with benzylamine was used to determine the loading, which was found to be virtually identical for all three cycles [13].



Scheme 1. Preparation and use of polymer-supported activated esters for the synthesis of amides.

Procedure

Preparation of the polymer [13]: To a mixture of macroreticular polystyrene **1** (50 g, 0.48 mmol) and 4-chloro-3-nitrobenzoyl chloride (**2**) (100 g, 0.22 mol) a solution of aluminum trichloride (25 g, 0.18 mol) in dry nitrobenzene (200 mL) was added. The mixture was stirred mechanically at 60° C for 5 h, then poured onto a mixture of ice, DMF, aq. HCl (conc.) and finally filtered. The beads were washed with DMF, dichloromethane and methanol. The dried polymer weighed 82 g (36 %) corresponding to a loading of 2.10 mmol g^{-1}.

Hydrolysis was carried out with a mixture of 40 % benzyltrimethylammonium hydroxide in water, water (130 mL) and dioxane (260 mL) at 90° C for 8 h. The polymer **3** was filtered and the process repeated. The beads were finally washed with dioxane, acetic acid and dichloromethane:methanol (2:1).

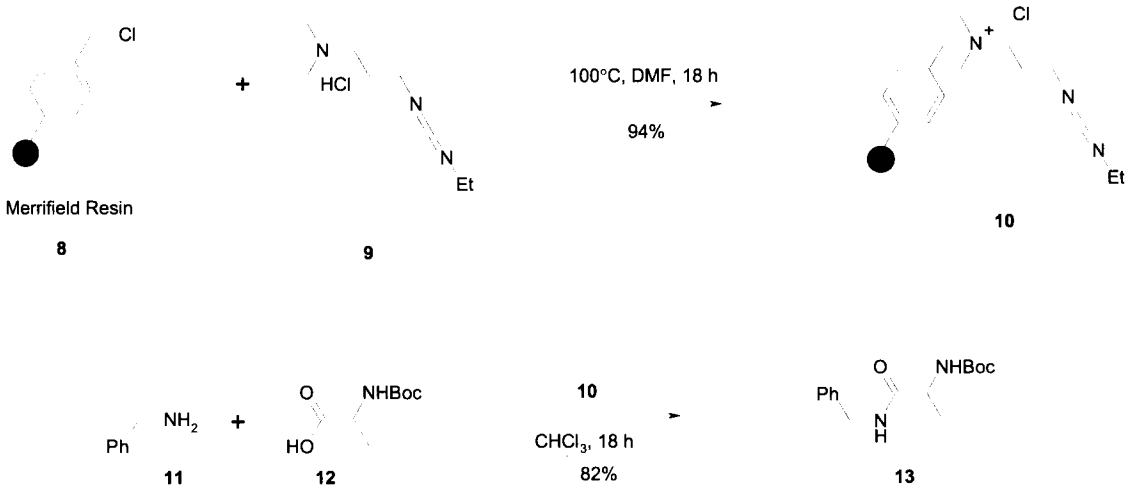
Esters of simple acids were prepared from the acid chlorides and pyridine following standard procedures. Active esters of Boc-protected amino acids were prepared by the symmetric anhydride method [13].

Peptide synthesis [13]: ATFA salt of a peptide was dissolved in chloroform (10 mL $mmol^{-1}$). The polymeric activated ester of the amino acid to be coupled, in 40 % excess and 2 equiv. of dry triethylamine were added. Shaking was continued until complete disappearance of the starting material as determined by TLC. The polymer was washed with chloroform and the combined washings were extracted with aqueous sodium bicarbonate and dried.

Another example of a polymer-bound phenolic leaving group has been reported by Huang et al. [16]. Supported 8-acyloxyquinolines were shown to readily acylate primary and secondary amines and anilines at room temperature. A neighboring group participation was proposed for the quinoline nitrogen atom.

The concept described for the hydroxy-substituted leaving group of activated esters was also applicable to the immobilization of the carbodiimide moiety used as dehydrating functionality in the condensation reaction of a carboxylic acid and an amine to yield an amide [17, 18]. Alkylation of Merrifield resin **8** using commercially available EDC hydrochloride (**9**) gave the supported reagent **10** (Scheme 2). Several resins have been examined for their properties and loadings. Best coupling results were obtained with a 2 % crosslinked polystyrene-divinylbenzene resin (200–400 mesh) with a rather low loading (0.8 mmol g^{-1}). The reagents derived from resins with higher loadings resulted in reduced swelling which had an detrimental effect on the coupling reaction [17]. Consequently, the choice of solvent was essential for good couplings reactions. Diethylether and tetrahydrofuran (THF) slowed down the reaction considerably due to the reduced swelling of the polymer.

Stirring the PSR **10** (2 equiv.) with a mixture of an aniline or amine, e.g., benzylamine (**11**), and a carboxylic acid, e.g., Boc-protected alanine (**12**), overnight at room temperature gave the amide **13** in good to excellent yields. A slight excess of the acid can be employed without a loss of purity of the product after filtration since the excess acid remains bound to the support.



Scheme 2. Preparation and use of a polymer-supported carbodiimide moiety for the coupling of amines and carboxylic acids to yield amides.

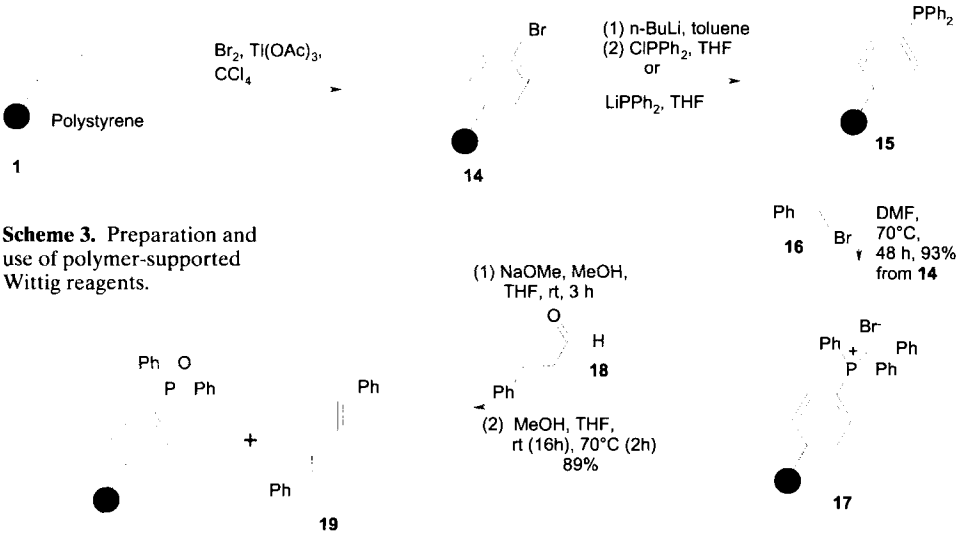
Procedure

Preparation of the reagent [17]: To a stirred solution of EDC (**9**) (15.7 g, 100.9 mmol) in DMF (800 mL) was added Merrifield resin (**8**) (2 % crosslinked, 105 g, 80.72 mmol, 0.76 mmol g^{-1}). After stirring at 100° C overnight, the mixture was cooled to room temperature and filtered. The polymer beads **10** were washed with DMF, THF and ether and dried under reduced pressure to give the product **10** (117.9 g, 94 % yield, 0.72 mmol g^{-1}).

Procedure for coupling [17]: To a suspension of polymer-supported carbodiimide **10** (650 mg, 0.5 equiv.) in chloroform (4 mL) N-tert-Boc-α-alanine **12** (42 mg, 0.22 mmol) and benzylamine **11** (22 mg, 0.20 mmol) were added. After the reaction was shaken over night at rt, the mixture was filtered. The resin was washed with chloroform and the combined filtrates were evaporated to dryness to yield the product **13** (46 mg, 82 %).

Wittig Reagents

Polymer-supported Wittig reagents were first prepared more than 20 years ago [19]. It has been shown that the success of the reaction depends strongly upon: (i) the preparation of the reagent by bromination and phosphination of crosslinked polystyrene rather than by copolymerization using styryldiphenyl phosphine; and (ii) upon the generation of the phosphorane with a base/solvent system that swells the phosphonium sites in the polymer network (Scheme 3) [20]. Thus, bromination of polystyrene **1** yielded phenylbromide **14** and was followed by phosphination with n-butyl lithium and chlorodiphenylphosphine or with lithium diphenylphosphide to give **15** – a compound which is now available commercially (Scheme 3). Treatment of the phosphine resin **15** with alkyl bromides, e.g., **16**, gave in excellent yields the corresponding phosphonium bromide **17**. The formation of the phosphorane was described as a crucial step for which the transport of the base to the phosphonium site within the polymer was essential. Various bases, e.g., sodium hydride, potassium tert.-butoxide in



Scheme 3. Preparation and use of polymer-supported Wittig reagents.

THF or n-butyl lithium in dioxane have been employed. Good results for the formation of the ylide were obtained with a mixture of sodium methoxide, methanol and THF, and more recently sodium bis(trimethyl)silylamide in THF [21, 22]. After the addition of aldehyde **18** and stirring over night the product **19** was isolated cleanly by simple filtration in excellent yield (95 %).

Procedure

Preparation of the supported phosphonium salt [20]: Benzylbromide **16** (7.18 g, 42 mmol, 5 equiv.) was added dropwise to a suspension of commercially available diphenylphosphine-derivatized polystyrene **15** (10 g) [21] in DMF (70 mL). The mixture was stirred for 48 h at 70° C cooled, filtered, washed and dried to give the supported phosphonium salt **17** in a yield of 13.5 g (93 %).

Formation of the olefin [20]: To the supported phosphonium salt **17** (1.97 g, 2.42 mmol) in THF (30 mL) at –10° C a solution of sodium methoxide in methanol (2.03 M solution, 1.2 mL, 2.44 mmol) was added dropwise and the mixture was stirred for 3 h at room temperature. After cooling the reaction mixture to –10° C the aldehyde **18** (0.25 g, 2.5 mmol) was added. The mixture was stirred for 16 h at room temperature and then 2 h at reflux. After filtration, washing of the resin with THF and removal of the solvent by evaporation the product **19** was isolated in 89 % yield.

Polymer-Supported Triphenylphosphine and Pd-Complexes

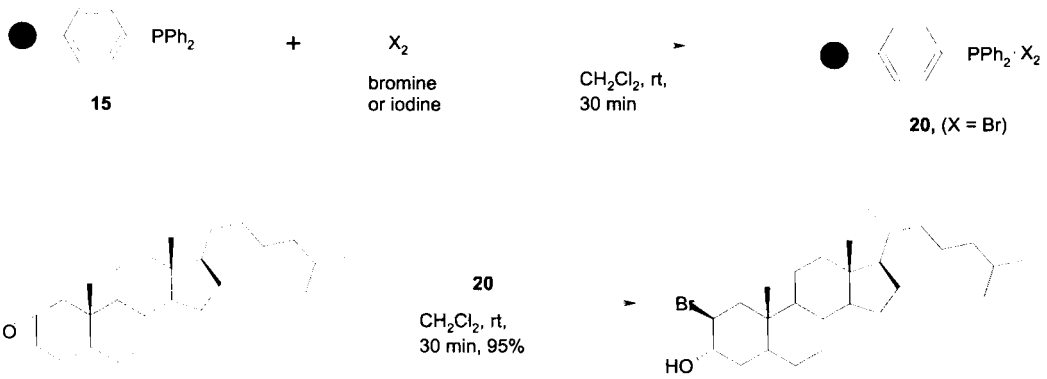
Polymer-supported triphenylphosphine was used not only for the preparation of polymer-supported Wittig reagents but also as a reagent for Mitsunobu esterifications [23]. The synthetic procedure consists of the addition of the carboxylic acid (1 equiv.) and the alcohol (1 equiv.) to the solvent (THF)-swollen polymer (1.8 equiv.), followed by the addition of the DEAD (1.4 equiv.). At room temperature, the reaction is generally complete in minutes, although longer reaction times should be employed to ensure maximum yields, particularly with more hindered secondary alcohols. If necessary, an excess of one of the two coupling components can be used for complete conversion of one of the reactants, as these excesses remained bound to the support after the reaction was complete and the product isolated by filtration. The phosphine oxide byproduct of the reaction also remained bound to the support and was removed by filtration. The other side product, the highly polar sym-dicarboxyethylhydrazine, was separated from the product by short-path silica gel filtration. The reaction was reported to work well for primary and secondary alcohols [23], but tertiary alcohols were too hindered to react properly with the bulky reagent. The oxidized reagent can be recycled by reduction with trichlorosilane and triethylamine, although a decrease of reactivity of the recycled reagent was observed [23].

A library of aryl ethers was prepared via Mitsunobu etherification by stirring a mixture of polymer-bound triphenylphosphine (1.5 equiv.), DEAD (1.5 equiv.), the alcohol (1.5 equiv.) and a phenol (1 equiv.) in dichloromethane at room temperature for 4–12 h [24]. The resin was filtered off, the solvent evaporated, and the DEAD-derived side product removed by a short-path silica gel column.

The use of polymer-bound triphenylphosphine has also been described in combination with carbon tetrachloride for the condensation of carboxylic acids with primary amines to

give amides via the corresponding in-situ-formed mixed phosphinic anhydride, and for the conversion of aliphatic alcohols to the corresponding alkyl chlorides [25].

Caputo et al. described the use of polymer-supported triphenylphosphine halogen complexes for the clean conversion of epoxides to halohydrins [26]. The reagents, e.g. **20**, were prepared by simply mixing a suspension of polymer-supported triphenyl phosphine **15** in dichloromethane with a solution of the halogen (bromine or iodine) in the same solvent (Scheme 4). The halogen was consumed almost immediately and the formed complex was used either directly or after washing with dichloromethane. Epoxides, e.g. **21**, were opened to give halo hydrines, e.g. **22**, by adding a solution of the epoxide to a slurry of the reagent in dichloromethane. The reaction was complete within minutes and the product **22** was isolated cleanly and in good yield by filtration [26].



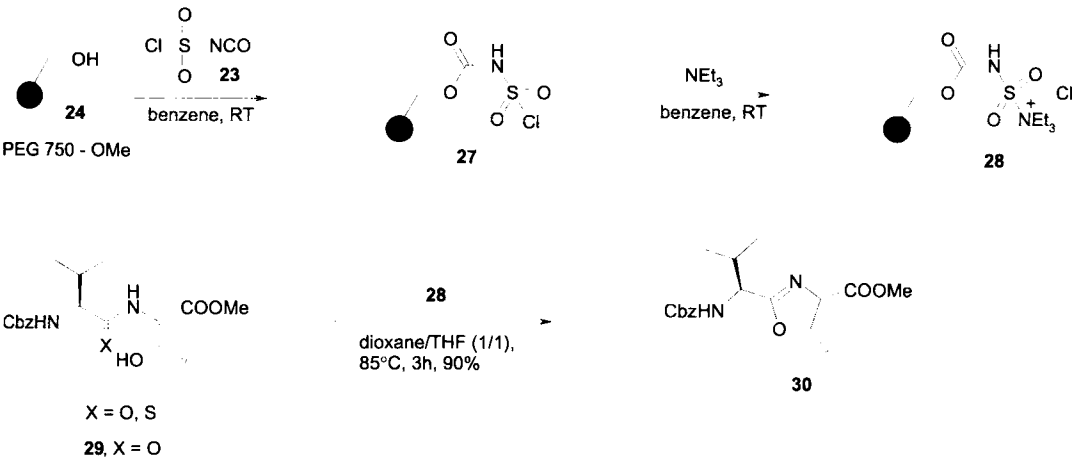
Scheme 4. Preparation of halohydrins from epoxides using polymer-supported halogen-triphenyl phosphine complexes.

Recently, a polymer-supported Pd-complex was described in which the metal is coordinated to a polymer-bound triphenylphosphine moiety [27]. This catalyst can be used for Suzuki couplings and other Pd-catalyzed C-C bond-forming reactions.

Polymer (PEG)-Supported Burgess Reagent

The cyclodehydration of N-(hydroxyethyl)-amides and -thioamides using Burgess reagent [28] is an important reaction for the preparation of oxazolines, thiazolines, oxazoles, and thiazoles. However, the commercially available Burgess reagent is prone to oxidation and moisture and should thus be stored at low temperature; even then, it has only a very limited shelf-life. To overcome these problems the reagent was attached to a solid support [29]. Coupling chlorosulfonyl isocycanate **23** to dry PEG monomethylether **24** (MW = 750) and then treating the polymer **27** with triethylamine produced the desired reagent **28** (Scheme 5). Cyclodehydration of, for example, threonine-derived amide **29** in hot dioxane/THF occurred cleanly and provided oxazoline **30** in 15 % higher yield than the standard Burgess reagent [29]. On

completion of the reaction, the product was obtained cleanly by simple filtration through a short plug of silica to remove the polymer-bound reagent.



Scheme 5. Preparation of polymer-supported Burgess reagent for cyclodehydration reactions.

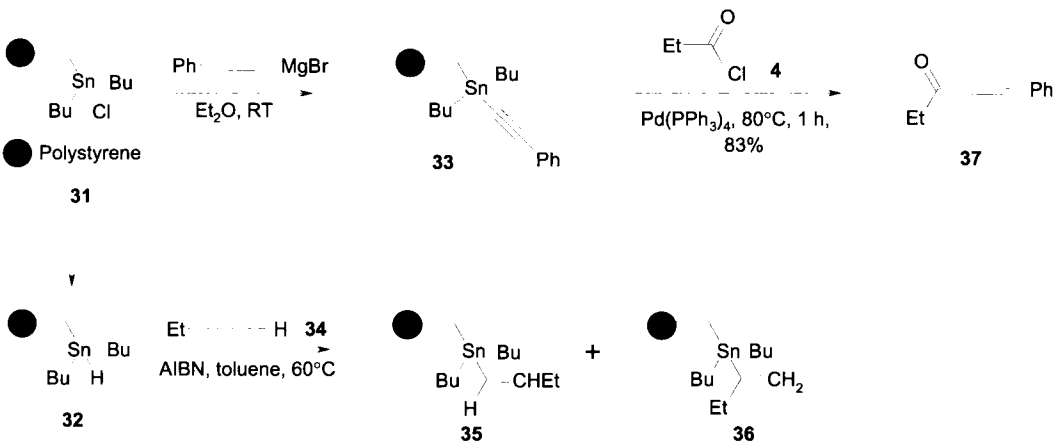
Procedure

Preparation of the reagent [29]: A solution of PEG monomethylether (MW = 750) **24** (5.88 g, 7.8 mmol) in benzene (20 mL) was dried azeotropically for 24 h in a Dean–Stark trap and subsequently added dropwise to a solution of chlorosulfonylisocyanate (**23**) (1.10 g, 7.8 mmol) in dry benzene (20 mL). The mixture was stirred at room temperature for 1 h, then concentrated and dried. A solution of this residue in benzene (35 mL) was added dropwise to a solution of triethylamine (2.5 mL, 17.3 mmol) in benzene (15 mL). The mixture was stirred for 30 min at room temperature then filtered and dried to yield polymer-supported Burgess reagent **28** (6.2 g, 82 %).

Cyclodehydration [29]: A solution of Cbz-Val-Thr-OMe **29** (100 mg, 0.28 mmol) in dioxane/THF (1:1) (1.5 mL) was treated with PEG-Burgess reagent **28** (400 mg, 0.41 mmol) and heated at 85° C for 3 h. The reaction mixture was concentrated and filtered through SiO_2 to yield the product 30 (85 mg, 90 %).

Organotin Reagents

The high toxicity of organotin compounds renders their immobilization, and thus simple separation from the product, a very interesting alternative to solution-phase chemistry. As solid-supported analogs of tributyltin chloride and tributyltin hydride, the immobilized tin reagents **31** and **32** (**31** being the precursor for **32**) (Scheme 6) were prepared by solid-phase chemistry [30]. These intermediates were transformed to polymer-supported Stille reagents either via a Grignard reaction giving **33** or via hydrostannation of a terminal alkyne, e.g., **34** to give **35** and **36** [30]. The resulting reactive polymer **33** was then crosscoupled with organic



Scheme 6. Polymer-supported organotin reagents as useful intermediates for C-C bond-forming reactions.

electrophiles, e.g., acid chloride **34**. Product **37** was obtained in good yield, although the reaction time was considerably longer than in solution.

Procedure

Hydrostannation of a terminal alkyne [30]: 2 equiv. of the alkyne **34** and 0.08 equiv. of AIBN were added to the tin hydride resin **32** in dry toluene under argon. The mixture was slowly stirred for 20 h at 60° C. Every 2.5 h, portions of AIBN (4 (0.08 equiv.)) were added. The polymer was separated from the solvent in an argon frit, washed several times with dry toluene and ether and dried.

Grignard reaction [30]: The dry tin halide resin **31** was swollen under argon in dry ether at 0° C for 30 min. The Grignard reagent (5 equiv.) was dissolved in dry ether and added to the suspension of resin **31** over 1 h. After 15 h at ambient temperature, the polymer was filtered off and washed with ether and water. The polymer was then extracted with refluxing THF:water (2:1) for 8 h, with refluxing ether for 4 h and then dried in vacuo.

Stille reaction [30]: To phenylethyltin resin **33** (1.33 g, 2.0 mmol) in dry toluene (8 mL) were added $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and propionyl chloride **4** (0.28 g, 2.9 mmol). The mixture was stirred and heated to 80° C for 1 h. Filtration and washing of the resin gave the clean product **37** (83 %).

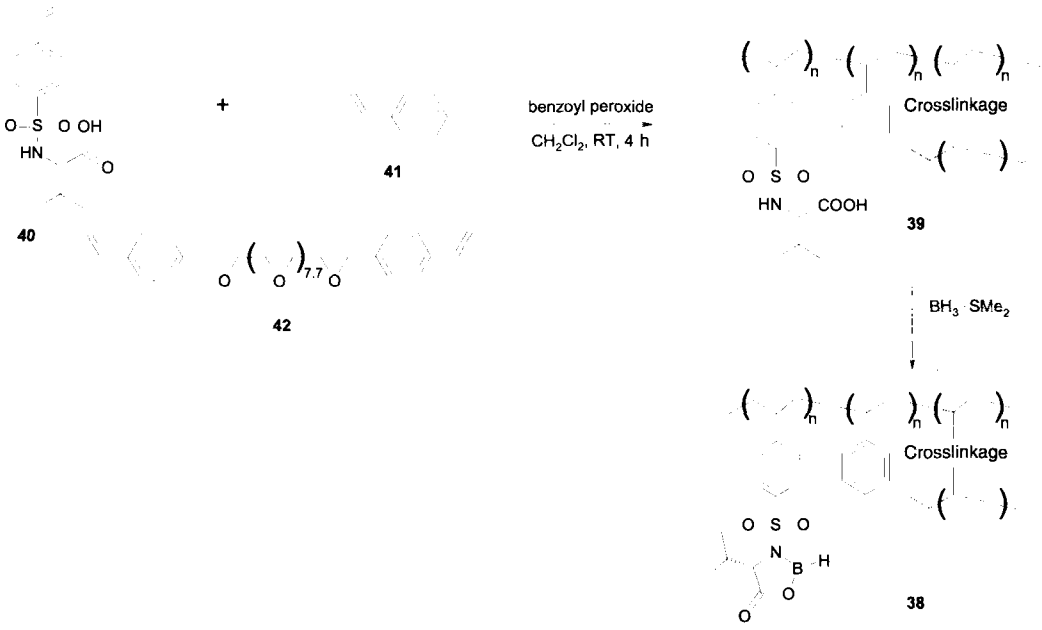
4.2.1.2 PSR Prepared by Polymerization

The covalent linkage between the support and the reactive moiety can be built up not only by solid-phase chemistry (as described in Section 4.2.1.1), but also by co-polymerization of, e.g., divinylbenzene and a co-monomer carrying the reactive moiety used for the chemical transformation of a molecule in solution (see Fig. 2). The latter method has often been used for the immobilization of chiral catalysts. Three groups of supported catalysts are described

in the following section: borane amino alcohol complexes for asymmetric Diels–Alder reactions; quinine-derived systems for the asymmetric dihydroxylation reaction; and polymer-bound (salen)-complexes for the enantioselective epoxidation of olefins.

Supported Borane Amino Alcohol Complexes and other supported Lewis Acids

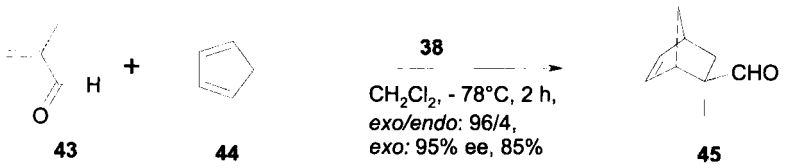
Itsuno et al. have reported the use of polymer-supported oxazaborolidinone **38** as chiral catalysts for asymmetric Diels–Alder reactions (Scheme 7) [31]. The catalyst was synthesized from borane dimethylsulfide and a chiral polymer bearing N-sulfonylamino acid **39**. The latter was prepared by co-polymerization of chiral sulfonamide **40** with styrene **41** and the crosslinking agent **42** in the presence of benzoyl peroxide as radical initiator.



Scheme 7. Preparation of polymer-supported borane amino alcohol complexes as catalyst for asymmetric Diels–Alder reactions.

The cycloaddition reaction occurs smoothly, even at –78° C, by the addition of a mixture of methacroleine **43** and cyclopentadiene **44** in dichloromethane to a slurry of the freshly prepared catalyst (Scheme 8). The catalyst's performance was strongly dependent on its crosslinking structure, due to the specific microenvironment created by the ethylene glycol chains. High exo/endo selectivities (up to 96:4) were achieved with enantiomeric excesses up to 95 % ee (Scheme 8) [31]. This is comparable with the selectivity obtained for the unsup-

ported catalyst in solution (up to 86 % ee) [32]. The catalyst was recovered and could be used several times without loss of activity – an observation which triggered investigations into continuous flow processes. Rinsing a catalyst-filled column with a mixture of methacrolein **43** and cyclopentadiene **44** in dichloromethane at –30° C allowed the isolation of the (R)-product **45** with 71 % ee at a scale of up to 138 mmol [31].



Scheme 8. Diels–Alder reaction catalyzed by an immobilized Lewis acid. This process can be run in a continuous-flow mode.

Procedure

Preparation of polymer [31]: Suspension co-polymerization of styrene derivative **40** (1.41 g, 5 mmol), styrene **41** (4.16 g, 40 mmol), and crosslinking agent **42** (3.23 g, 5 mmol) gave polymer **39**. The chiral catalyst **38** was generated in situ by stirring borane methyl sulfide complex in dichloromethane (1.0 M solution, 1.5 mL, 1.5 mmol) and the polymer precursor **39** suspended in 30 mL dichloromethane for 4 h at room temperature. Generation of hydrogen ceased during this period.

Cycloaddition [31]: Methacroleine **43** (0.83 mL, 10 mmol) and cyclopentadiene **44** (1.20 mL, 12 mmol) were added to the above suspension of the catalyst at –78° C. The mixture was stirred for 2 h at this temperature and then quenched with aqueous sodium hydrogen carbonate. Filtration, washing of the resin and evaporation gave the product **45** (1.16 g, 85 %).

Other polymer-supported catalysts for the asymmetric Diels–Alder reaction include aluminum and titanium complexes of chiral amino alcohols [33].

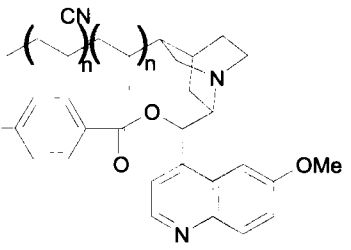
Polymer-bound borane complexes derived from polymer-bound amino acids and borane were also described [34]. These Lewis acids promoted the aldol reaction of benzaldehyde with a silyl ketene acetal in THF in a similar enantioselectivity as was observed for the corresponding soluble counterpart. The enantioselectivity was strongly dependent on the solvent, with THF giving the best results – presumably due to its favorable support-swelling properties. Interestingly, the enantioselectivity of the reaction was increased when higher reaction temperatures were employed: the authors suggested that the polymer-bound intermediates are conformationally more adequate for the enantiodifferentiating process at –10° C than at –78° C – the temperature commonly employed for the corresponding solution phase reaction [31, 35].

Polymer-supported chiral oxazoborolidines have also been used for the reduction of prochiral ketones. Enantiomeric excesses of 98 % ee were obtained for the reduction of acetophenone using borane dimethylsulfide as stoichiometric reducing agent [39, 40].

Another polymer-supported Lewis acid was described by Kobayashi et al. [36–38]. To ensure sufficient solubility in an organic solvent, polyacrylonitrile was used as the support. Poly-(allylscandiumtrifyl)-amide ditriflate (PA-Sc-TAD) was prepared from polyacrylonitrile which was first reduced with borane to give the corresponding polyamine. Subsequent reaction with triflic anhydride and scandium triflate gave, under basic conditions, the PSR which was partially soluble in dichloromethane–acetonitrile mixtures. Using this reagent as catalyst for a three-component condensation reaction involving an aldehyde, an aromatic amine and an alkene, a library of tetrahydroquinolines can be prepared. The reaction gave the product in good yield and purity, and the reagent could be recycled. Other supports for scandium species were also described [37, 38].

Polymer-Supported Quinine-Based Catalysts

In addition to the immobilization of boron-derived catalysts, other commonly used homogenous catalysts have been supported on a polymer. Sharpless and others [41–46] prepared various quinine-based catalysts to achieve asymmetric dihydroxylations of olefins. Initial studies were performed with catalyst **46** obtained by co-polymerization of 9-(p-chlorobenzoyl)quinidine with acrylonitrile [41].



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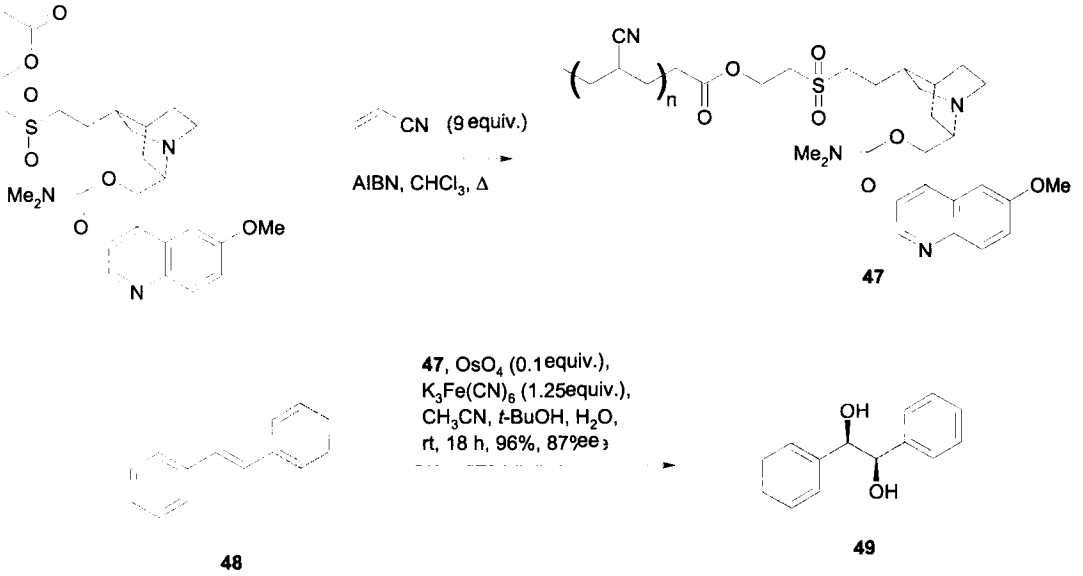
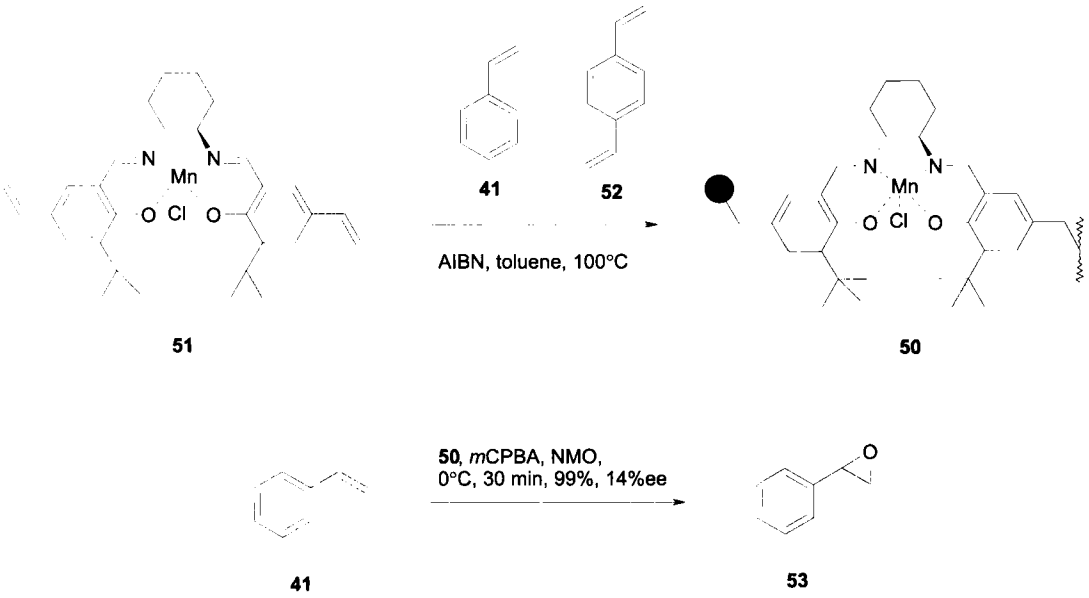
However, the dihydroxylation reaction proceeded only slowly, presumably due to steric congestion resulting from the alkaloid being too close to the polymer backbone. Polymers with longer spacer groups between the alkaloid and the polymer backbone were investigated, and good to excellent asymmetric inductions were obtained with catalyst **47** using potassium ferricyanide, $K_3Fe(CN)_6$, as secondary oxidant (Scheme 9). Dihdroxylations were performed by mixing a solution of OsO_4 in acetonitrile and a suspension of the alkaloid polymer, $K_3Fe(CN)_6$ and potassium carbonate in tert.-butanol and water. After stirring for 10 min, trans-stilbene **48** was added and the product **49** isolated after 24–48 h in excellent yield (96 %) and good enantioselectivity (87 % ee) [41].

Enantioselectivities comparable with those obtained in solution phase were also described using polymer-bound bis-hydroquinylpyridazine catalysts [45, 46].



Scheme 9. Polymer-supported quinine-type catalysts for asymmetric dihydroxylation reactions.



Scheme 10. Polymer-supported (salen) complexes for asymmetric epoxidation reactions.

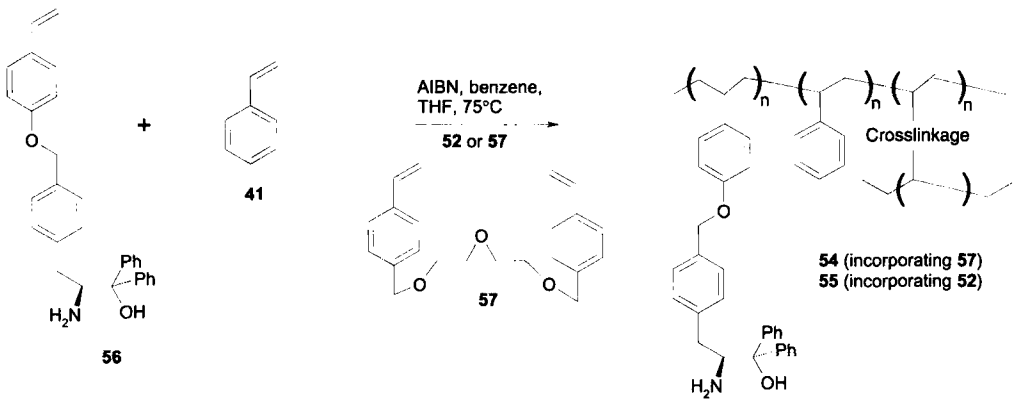
Supported (Salen) Complexes

Asymmetric epoxidation of unfunctionalized olefins catalyzed by chiral (salen) Mn(III) complexes has proven to be a useful solution-phase reaction [47]. To simplify product isolation and to avoid degradation of the Mn-(salen) complex via formation of μ-oxo-manganese (IV) dimers by spatial distribution, the polymer-supported catalyst **50** was prepared by co-polymerization of complex **51**, styrene **41**, and divinylbenzene **52** (Scheme 10) [48]. As stoichiometric oxidant, a combination of meta-chloroperbenzoic acid (mCPBA) and N-methyl morpholine-N-oxide (NMO) in acetonitrile is used. Yields and rates of conversion were satisfactory for the epoxidation of styrene **41** (to give **53**) and of methyl styrene, but only low enantioselectivities were obtained. However, the catalyst preserves its efficiency in terms of yields and enantioselectivities after repetitive use. Similar results have been described by others [49].

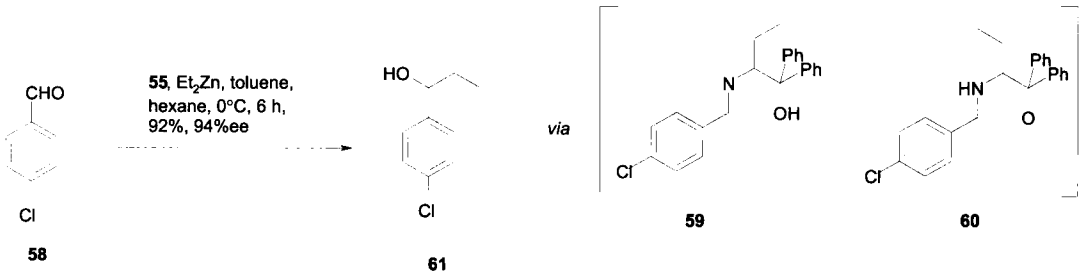
Polymer-Supported Schiff Base Zinc Complexes

The addition of diethylzinc to aldehydes produces secondary alcohols. This process can be stereoselectively catalyzed by chiral amino alcohols which form Schiff base–zinc complexes with the aldehyde and the metal. With the aim of simplifying the work-up of these reactions and to use continuous flow processes, the polymer-supported amino alcohols **54** and **55** were synthesized (Scheme 11) [50]. The polymers were obtained by co-polymerization of the chiral monomer **56** and styrene **41** in the presence of divinylbenzene **52** or crosslinking agent **57** containing a flexible oxyethylene chain. The latter was used to ensure sufficient flexibility within the crosslinked network of the polymer and to further activate the nucleophile by coordination of the oxyethylene chain to the metal.

Treatment of an aldehyde, e.g. **58**, with one of the polymeric reagents in toluene resulted in the formation of the intermediate Schiff base **59** and oxazolidine **60**, as was confirmed by analytical data (Scheme 12) [50]. Subsequent addition of diethylzinc to the reaction mixture af-



Scheme 11. Preparation of polymer-supported amino alcohols.



Scheme 12. Addition of diethyl zinc to aldehydes is stereoselectively catalyzed by polymer-supported amino alcohol–zinc complexes. The addition proceeds via the intermediates **59** and **60**.

forded cleanly the product **61** after stirring for 6 h at 0° C. The yields of the products were high (92 %) and the enantioselectivities were good (94 % ee). Best results were obtained in mixtures of hexane and toluene. The polymer can easily be separated from the reaction mixture and recycled after washing. This process was also used in continuous-flow applications: diethylzinc and the aldehyde were added slowly into an ice-cooled jacketed column containing polymer **55**. A solution of the product could then be eluted continuously. Thus, a column containing 5 mmol of the catalyst is able to produce about 90 mmol of (*S*)-1-(p-chlorophenyl)-propanol (**61**) with 94 % ee. Such a continuous-flow system is advantageous over common batch applications of the polymer as it eliminates the need for stirring, which can cause destruction of the polymer beads. Similar results were described by others [51].

4.2.2 Immobilization Using Ionic Interactions

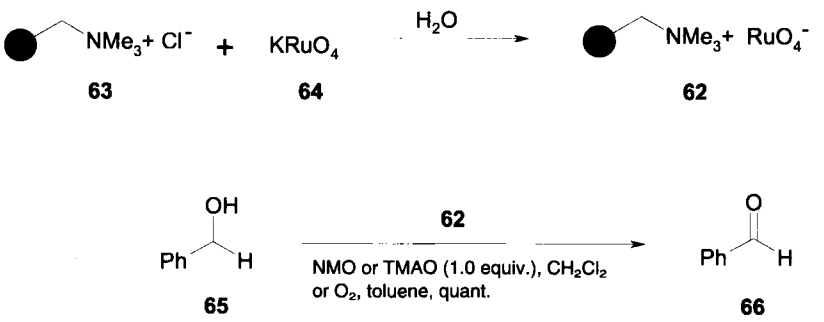
Many organic transformations are based on ionic reagents. These ions can easily be immobilized by ion-exchange chromatography using ionic interactions between the active ion and a polymer-bound counterion (see Fig. 2). This principle is especially useful for the immobilization of anionic species on anion-exchange resins carrying quaternary ammonium ions. However, to obtain clean products after filtration, not only the reactive species itself but also the corresponding side products must be ions in order to remain bound to the support after completion of the reaction. If such conditions are fulfilled, this method of immobilization is surely one of the easiest ways to prepare a solid-supported reagent.

4.2.2.1 Oxidants

Immobilized oxidants were some of the earliest examples of PSRs [1–3]. This is due to the sometimes tedious work-up protocols required for oxidation reactions carried out in homogeneous solution. To support the active moieties, most often inorganic ions such as RuO_4^-, $HCrO_4^-$, CrO_4^{2-} or MnO_4, and ionic interactions between the polymer and the reagent can be used. Consequently, the reagents were prepared by ion-exchange chromatography. Early

examples of solid-supported redox systems include chromic acid on anion-exchange resins [52] for the oxidation of alcohols to aldehydes and ketones or poly(vinylpyridinium) chlorochromate or dichromate [53, 54]. The latter was prepared from a poly(vinylpyridine) resin with a slight excess of chromium trioxide in water at room temperature. The product was ready for use and the nature of the supported active species was confirmed by infra-red spectroscopy. The loading was estimated by titration to be ~2.3 mmol g^{-1}. Oxidation reactions were performed with stoichiometric amounts of the wet reagent in apolar solvents such as cyclohexane, and at elevated temperatures [53, 54]. However, while the yields for benzylic alcohols were good within 4 h, oxidation of secondary, nonactivated alcohols proved to be difficult, and only moderate yields were obtained after 24 h. Reactions with primary alcohols were clean, with only filtration being required to obtain pure products, as not only the active species but also the inorganic side products remained bound to the support.

The difficulties associated with the chromium reagents (stoichiometric amounts required, harsh conditions, selectivity) [52–54] led to the development of polymer-supported perruthenate **62** by Ley et al. [55]. These efforts rely on a large body of experience with soluble salts of the perruthenate ion, e.g., tetrapropylammonium perruthenate (TPAP) [56, 57]. The reagent **62** is prepared by washing an anion-exchange resin (**63**) extensively with an aqueous solution of potassium perruthenate **64**.



Scheme 13. Polymer-supported perruthenate for the oxidation of alcohols to carbonyl compounds.

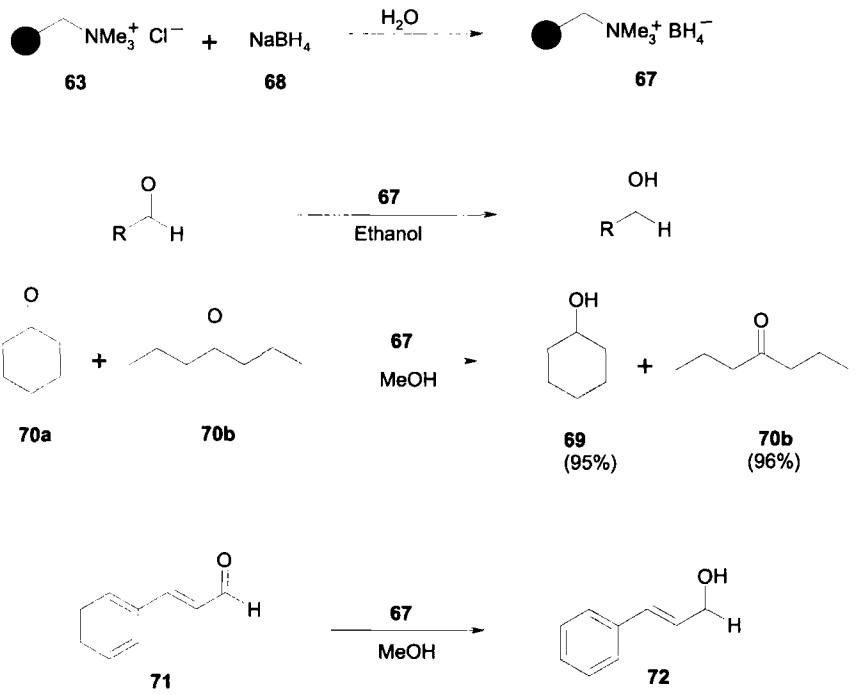
First experiments using an excess of the reagent produced satisfactory results: benzylic alcohols, e.g. **65**, were oxidized quantitatively, while less activated alcohols were oxidized in slightly lower yields. The oxidation was a clean process; products (e.g. **66**) were obtained as pure compounds after filtration [55]. However, in solution-phase chemistry, the oxidation can be performed catalytically with respect to the perruthenate moiety TPAP, and NMO is used as the secondary oxidant in stoichiometric amounts [56]. Following this route, it was shown that the polymer-supported perruthenate species can also be used catalytically (10 mol %) in combination with either NMO or trimethyl amine N-oxide (TMAO) as co-oxidants [55]. These catalytic oxidation reactions give similar yields when compared with the stoichiometric transformations, although the amount of co-oxidant used must be accurately monitored in order to obtain the product in pure form after filtration. A major simplification, and an elegant solution, of this problem was the use of molecular oxygen as the stoichiometric oxidant

[58]. As described for the other polymer-supported perruthenate (PSP) systems, oxidations of benzylic alcohols gave quantitative yields within 30 min. The oxidation of nonactivated primary alcohols and secondary alcohols gave the corresponding products in 80–92 % yield [58].

Procedure

Preparation of the reagent [55]: A concentrated aqueous solution of $KRuO_4$ **64** (approx. 20 mg (0.1 mmol) $KRuO_4$ in 100 mL water, after treatment with ultrasound) is filtered through a column filled with Amberlyst anion-exchange resin **63** (1.0 g) (IR 27). Subsequently, the resin **62** is thoroughly washed with distilled water and acetone and dried in vacuo.

Oxidation reactions [55]: The alcohol was added to a mixture of the PSR **62** (0.1 equiv., 0.1 mmol g^{-1}) and the co-oxidant (NMO or TMAO, 1.0 equiv.) in dichloromethane (2.0 mL per 100 mg catalyst). The oxidation with oxygen a co-oxidant was performed in toluene (2.0 mL per 100 mg catalyst) in an oxygen atmosphere provided by a balloon. The mixture was stirred at rt for 16–36 h, and the product isolated by filtration and evaporation.



Scheme 14. Preparation and use of polymer-supported borohydride. Using this reagent, high chemoselectivities are observed.

4.2.2.2 Reducing Agents

Following the same concept as described for the preparation of supported oxidants, anion-exchange resins carrying quaternary ammonium groups were also used for the immobilization of a variety of borohydride species. Borohydride was immobilized on an anion-exchange resin to give **67** by simply stirring the resin **63** with a two- to three-fold excess of an aqueous solution of sodium borohydride **68** (Scheme 14). Reduction of aldehydes can readily be realized using this reagent, although the reductions are at least 25 times slower than the corresponding reactions with sodium borohydride (**68**) [59]. The reagent is highly chemoselective: aldehydes can be reduced in the presence of ketones, and it is possible to differentiate between ketones, e.g., preparation of **69** from **70a** [60]. The use of supported borohydride was also reported for the reduction of α,β-unsaturated ketones to the corresponding allylic alcohols in various solvents, e.g., synthesis of **72** from **71** [61] (see also [66]). Reaction times in aprotic solvents were in general longer than in protic solvents; yields were excellent, within reaction times of a few hours.

Using the same reagent, the reduction of nitro alkenes to the corresponding nitro alkanes in methanol was reported [62]. Again, filtration of the reaction mixture gave the clean product. ^{11}B NMR spectroscopy of the methanolic solution of the product revealed no boron impurities in the solution [62]. In addition, the reagent has also been used for the reduction of alkyl halides to the corresponding hydrocarbons [63], the reduction of acid chlorides to the aldehydes [64], and the reduction of aryl azides to the corresponding amines [65]. The broad scope [66], the high yields, and the absence of any leaking renders polymer-supported borohydride **67** one of the most useful immobilized reagents. This aspect will be further discussed in Chapter 4.4.

Procedure

Preparation of the reagent [59]: Wet Amberlite IRA 400 anion resin **63** (20 g) was slurry-packed in a 100 mL sintered glass funnel. A 0.5 M aqueous $NaBH_4$ **(68)** solution (200 mL) was then slowly passed through the resin over a period of 60 min. The resulting resin **67** was washed thoroughly with distilled water. The borohydride exchange resin was then dried in vacuo at 65° C for 2 h. The loading was estimated by acidification to be 2.5 mmol g^{-1}.

Reduction of α,β-unsaturated carbonyl compounds [61]: A solution of the carbonyl compound **71** (1.0 mmol) in methanol (20 mL) was added to the resin (0.5 g, 1.25 mmol). After completion of the reaction, the resin was filtered and washed. The product **72** was isolated by concentration of the washings.

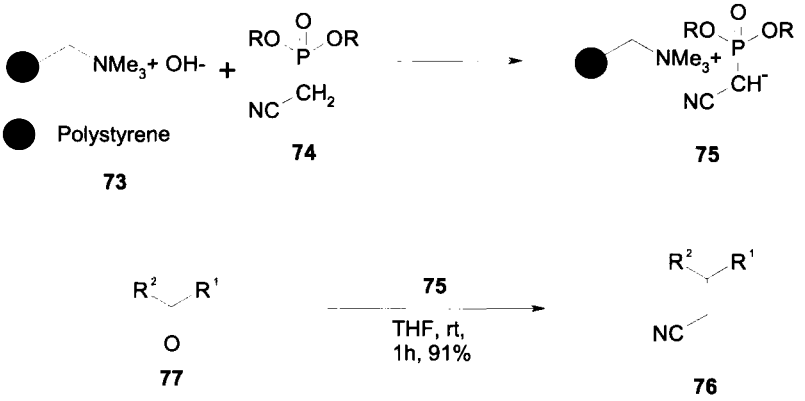
4.2.2.3 Alkoxides Bound to a Polymer Support

The basicity of common anion-exchange resins in the OH– form is sufficiently high to deprotonate phenols and aromatic hydroxy heterocycles ([67]; see also [68]). Thus, the corresponding anions can be immobilized by a simple acid–base neutralization reaction. Circulating a solution of a phenol through a column filled with an anion-exchange resin (OH– form) effectively immobilized the phenoxide ion on the support. The reactivity of these nucle-

ophiles was increased due to the ionic nature, and thus the formation of an ether linkage via reaction with an alkyl bromide works with good yields and purities, especially when an excess of the PSR was used. This method was applied to the preparation of libraries of aryl and hetaryl ethers [68].

4.2.2.4 Horner–Emmons Reagents on Support

Cainelli et al. described a similar approach towards the preparation of polymer-supported Horner–Emmons reagents [69]. The C-H acidity of phosphonates bearing an electron-withdrawing substituent (nitrile or ester) is in the pKa range of 6–9. This allows their deprotonation by a conventional ion-exchange resin **73** in the OH– form. Simple filtration of a solution of the phosphonate (e.g., **74**) through a column filled with anion-exchange resin led to the production of supported phosphonates **75** (Scheme 15).



Scheme 15. Polymer-supported Horner–Emmons reagents.

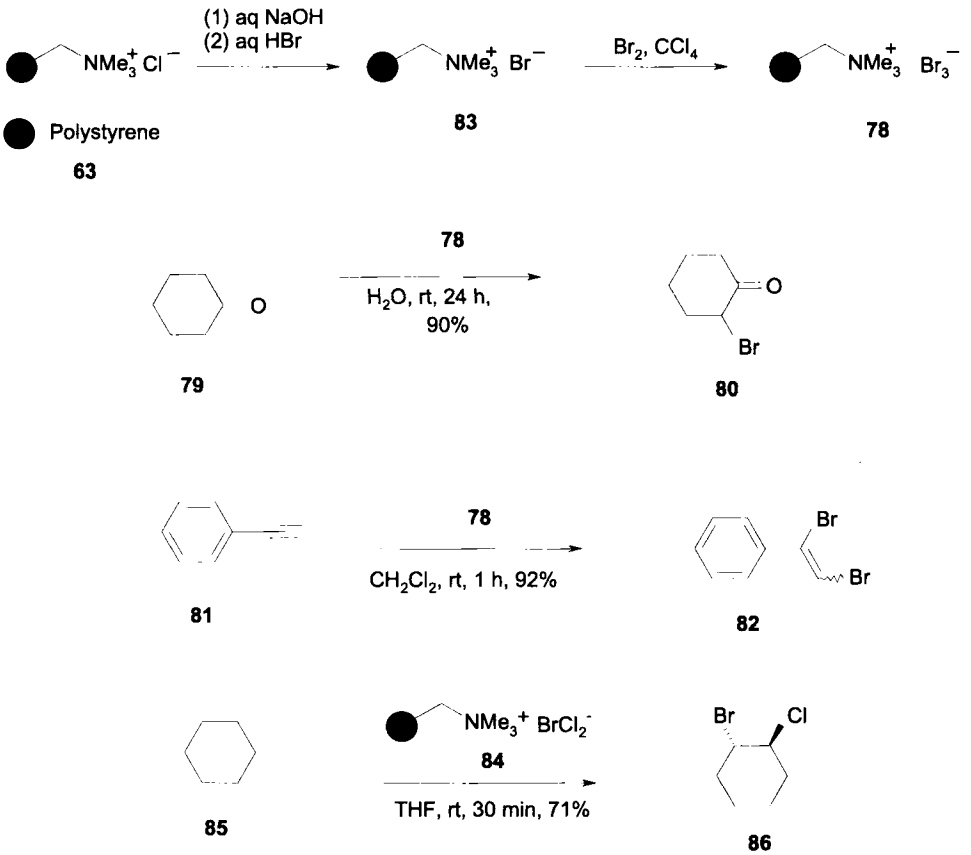
The capacity of the resin **75** was calculated to be in the range of 3.4 mmol g^{-1} [69]. However, the stability of the reagent is limited, and it should be prepared immediately before use. Using 2 equiv. of the phosphonate resin, olefins **76** were prepared from the corresponding carbonyl compounds **77** in good yields within 1 h at room temperature simply by stirring the mixture in THF. Alternatively, a solution of the carbonyl compound can be percolated through a column packed with the supported phosphonate [69]. This, together with the possibility of recycling the resin by washing and reloading steps, enables continuous-flow processes.

4.2.2.5 Halogenating Agents

Alkyl and aryl halides are highly attractive intermediates in multistep syntheses. Thus, their preparation by solid-supported reagents is very interesting. Polymer-supported chloro- and bromoimides [70, 71] have been used for the halogenation of aromatic and olefinic com-

pounds. The polymer backbone of these reagents, poly-maleimide, is prepared by free radical polymerization of maleimide in the presence of divinylbenzene as crosslinking agent. The backbone is then chlorinated or brominated by a solution of the halogen in tetrachloromethane under basic conditions.

However, due to drastic reaction conditions and only limited selectivity, these reagents are less practicable than perbromide on ion-exchange resin **78**, which is by far the most dominant polymer-supported halogenating agent (Scheme 16). This reagent can be used very efficiently for the α-bromination of carbonyl compounds, e.g., conversion of **79** to **80**, and for the addition of bromine to alkenes and alkynes, e.g., **81** to **82** [72–74]. A 50 % excess of the reagent at room temperature is commonly employed for the α-bromination of ketones. The reagent is available commercially, and can easily be prepared from an anion-exchange resin Br– form (**83**) and a solution of bromine in tetrachloromethane. The content of active bromine is approximately 2.5 mmol g^{-1} (evaluated by iodometry) [74], and only a small decrease is observed after 3 months' storage at room temperature. As the side product of the reaction **79** to **80**, hydrogen bromide, can be removed by using polymer-supported bases, this reaction is clean and is thus an ideal transformation in a multistep reaction sequence.



Scheme 16. Polymer-supported perbromide and chlorobromide.

Procedure

Preparation of the reagent [72, 74]: Amberlyst A26-Cl-form (35 g) was washed with aqueous sodium hydroxide and water. The polymer was then suspended in 1 M aqueous HBr (200 mL), stirred overnight, filtered and washed with water, acetone and ether. The dried resin(14.9 g) was suspended in tetrachloromethane (160 mL) and a solution of bromine (2.8 mL) in tetrachloromethane (28 mL) was added slowly. After 7 h, the resin was filtered off and washed extensively with tetrachloromethane, THF and ether to give 22.3 g of **78**.

α-Bromination of a ketone [72]: To a stirred solution of cholestan-3-one (500 mg, 1.29 mmol) in THF (5.0 mL) the polymer-supported reagent (1.0 g, 1.50 mmol) was added and the mixture stirred at rt for 30 min. The resin was filtered off and washed with ethyl acetate. The combined organic phases were washed with aqueous sodium hydrogen carbonate solution and dried. The product, 2α-bromocholestan-3-one, was isolated in good yield (470 mg, 78 %).

Using the same strategy, Cainelli et al. [74] supported chlorobromide ion by stirring ion-exchange resin Amberlyst A26 bromide form with a solution of chlorine in dichloromethane. A loading in the range of 2.5 mmol g^{-1} is achieved, and the reagent **84** (Scheme 16) stores well at room temperature. Chlorobromination reactions of alkenes or alkynes are performed at room temperature by treating the organic substrate, e.g. **85**, with a 50 % excess of the reagent to give the product **86** cleanly (Scheme 16).

Fluorine can be introduced into alkenes and alkynes by hydrofluorination or by substitution of the hydroxy group of secondary and tertiary alcohols by using polyvinylpyridinium-supported poly(hydrogen fluoride) (PVPHF) as described by Olah et al. [75]. The reagent was conveniently prepared either by adding condensed anhydrous hydrogen fluoride or by condensing anhydrous HF into a bottle containing 2 % crosslinked poly-4-vinylpyridine cooled to –78° C [75]. Hydrofluorinations of alkenes and alkynes with the reagent (60 weight % of HF) were carried out at atmospheric pressure in polyethylene bottles under nitrogen in dichloromethane, at or below room temperature. The yields of the products were good. Fluorination of tertiary alcohols proceeded satisfactorily with this reagent, but secondary alcohols were transformed only with limited success. Fluorosulfonic acid and sulfur dioxide have been used to modify the reagent and have improved the yields of fluorination of secondary alcohols [75]. Recovered PVPHF can be readily regenerated by washing with water, drying, and retreatment with hydrogen fluoride. Low HF-containing polymer can be prepared by reacting calculated amounts of condensed anhydrous HF with polyvinyl pyridine beads. The corresponding reagent does not corrode laboratory glassware.

4.3 Support-Bound Sequestering and Scavenging Agents

Polymer-supported reagents can be used in excess to drive a reaction to completion, without a penalty in terms of purification. However, in many coupling reactions, it is not only an excess of coupling reagent, e.g., a carbodiimide moiety such as **10** (Scheme 2) that is required to drive the reaction to completion, but also an excess of one of the coupling partners. Consequently, new methods were developed to separate these excess quantities by simple filtration processes from the product (Fig. 3). These techniques are described in more detail in Chapter 2.3.

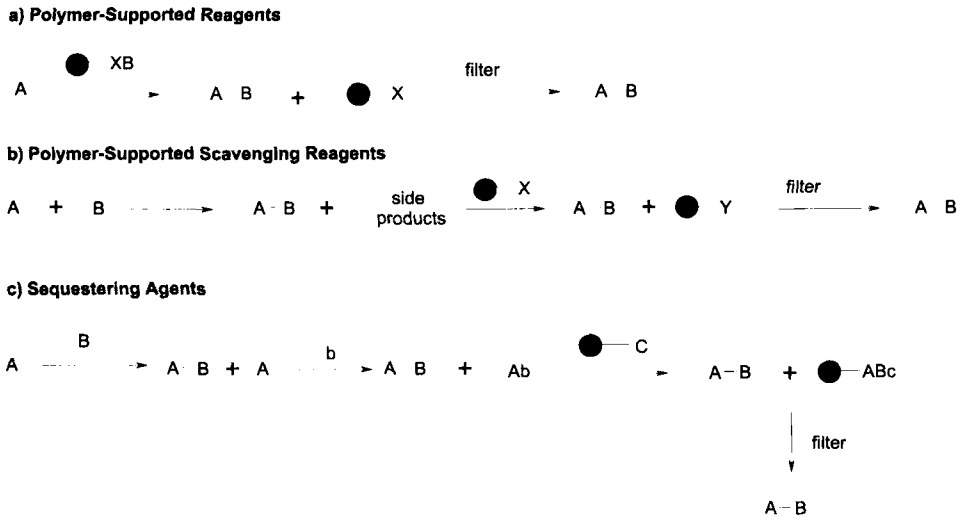
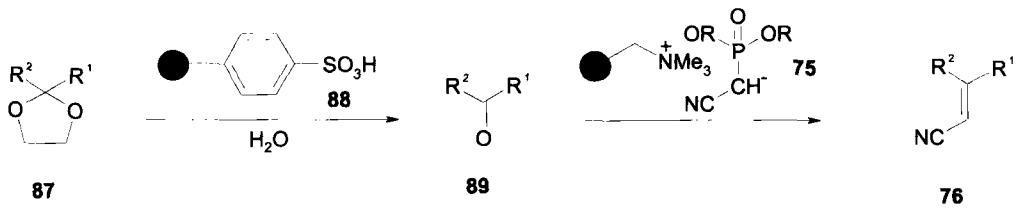


Figure 3. Scavenging reagents used for the removal of excess starting materials and other reactive impurities from the reaction mixture.

4.4 Combination of PSRs

The use of PSRs as described in the earlier sections of this chapter was restricted to one-step transformations. However, a highly interesting application of PSRs was first described by Cainelli and colleagues [74] in 1980, and further developed by both Parlow [76] and especially by Ley et al. [77–80]. These groups described the use of several PSRs within one reaction sequence. Reactive species such as oxidants and reducing agents do not react with each other when they are polymer-supported; consequently, one-pot transformations are possible which cannot be realized in conventional solution-phase chemistry.

Dioxolans **87** can be considered as masked carbonyl functionalities, and are cleaved under acidic conditions. In solution, the olefination of a dioxolan-protected ketone would therefore be a two-step transformation consisting of deprotection and olefination. Using polymer-supported acids, e.g., strongly acidic Amberlyst resin **88** and polymer-supported phosphonates **75** (Scheme 15), the two-step transformation involving the carbonyl compound **89** as intermedi-

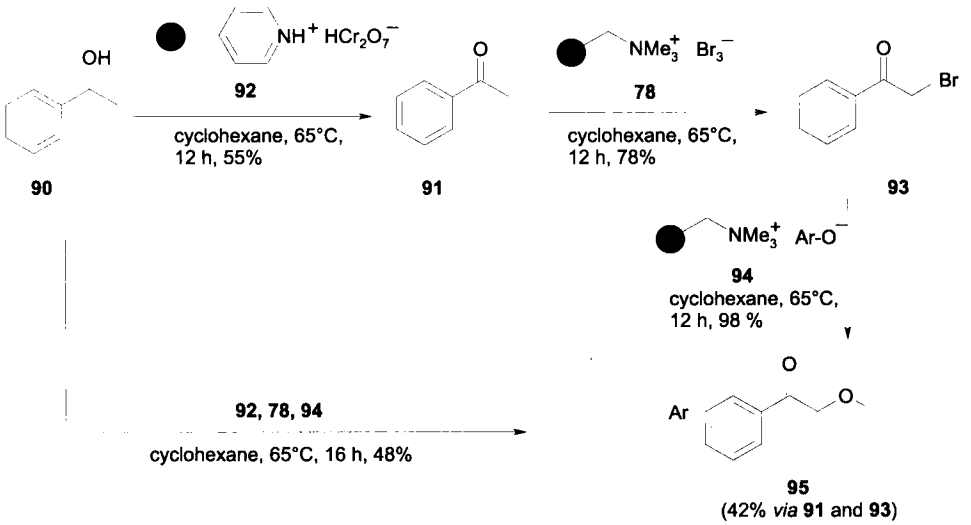


87 **89** **76**

Scheme 17. Olefination of protected carbonyl compounds. This procedure would not work in solution because the one-pot-acidic catalyst would immediately quench the basic phosphonate resin.

ate was performed simultaneously in one pot (Scheme 17) [69]. The product **76** was isolated by filtration. This procedure would not work as a one-pot sequence in solution because the acidic catalyst would immediately quench the basic phosphonate resin.

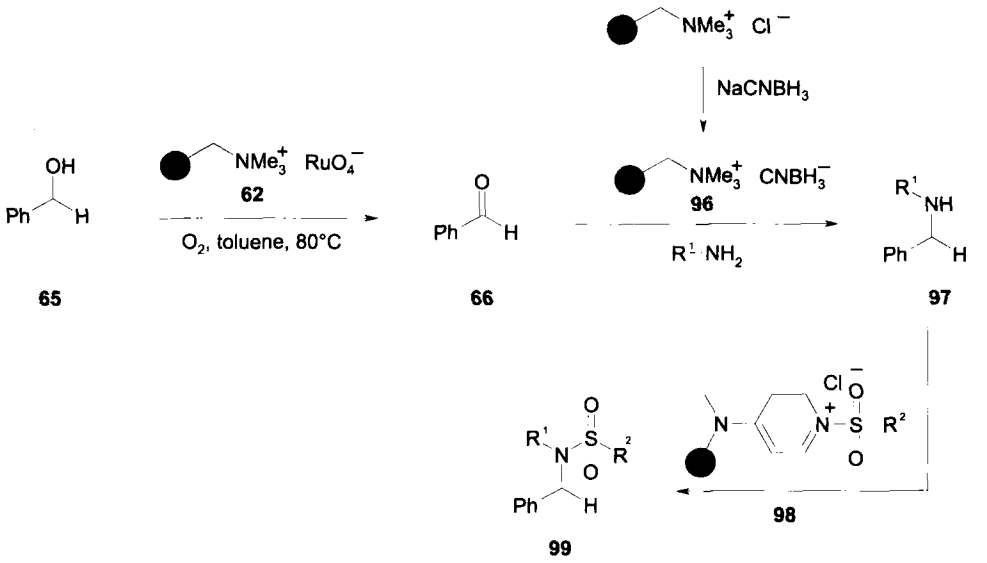
Another process was described by Parlow [76] in which sec-phenethyl alcohol **90** was oxidized to acetophenone **91** using poly(4-vinylpyridinium dichromate) **92**. This intermediate was subsequently α-brominated to give **93** using polymer-supported perbromide on an anion-exchange resin (**78**). In the third step, the halogen was substituted using a polymer-supported phenoxide anion **94**. Consequently, ether **95** was isolated by simple filtration. This three-step synthesis can be performed sequentially, with an overall yield of 42 % [76]. However, the same synthesis can be run more efficiently and in higher yield in one pot by using a mixture of all three PSRs (48 %). As was observed in the previous reaction, incompatibility of the reagents in a homogeneous solution would not have resulted in product formation.



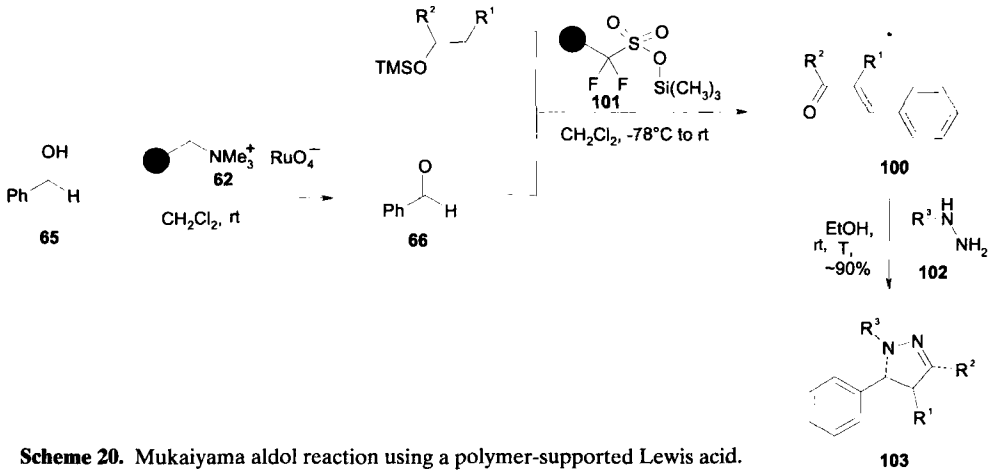
Scheme 18. Three-step, one-pot preparation of arylethers: products are formed because the reagents are polymer-supported.

Ley et al. described a combination of an oxidant, polymer-supported perruthenate **62**, and of a reducing agent, polymer-supported cyano borohydride **96**. Readily available alcohols **65** as a primary feedstock were oxidized to intermediate **66** and further reacted with amines to afford higher substituted amines, e.g., **97** (Scheme 19) [77]. These were further sulfonylated using polymer-supported sulfonylpyridinium ion **98** to give sulfonamides **99** [77].

A variety of other sequential, clean, multistep transformations solely based on PSRs have been described. Starting from alcohols **65**, which were oxidized to the corresponding carbonyl compounds (**66**), α,β-unsaturated ketones **100** were prepared in a Mukaiyama aldol condensation using Nafion-TMS **101** as silylating agent and Lewis acid [78]. The resulting enones were treated with hydrazines **102** to give clean final products, 4,5-dihydro-^{1}H-pyrazoles **103** [78].



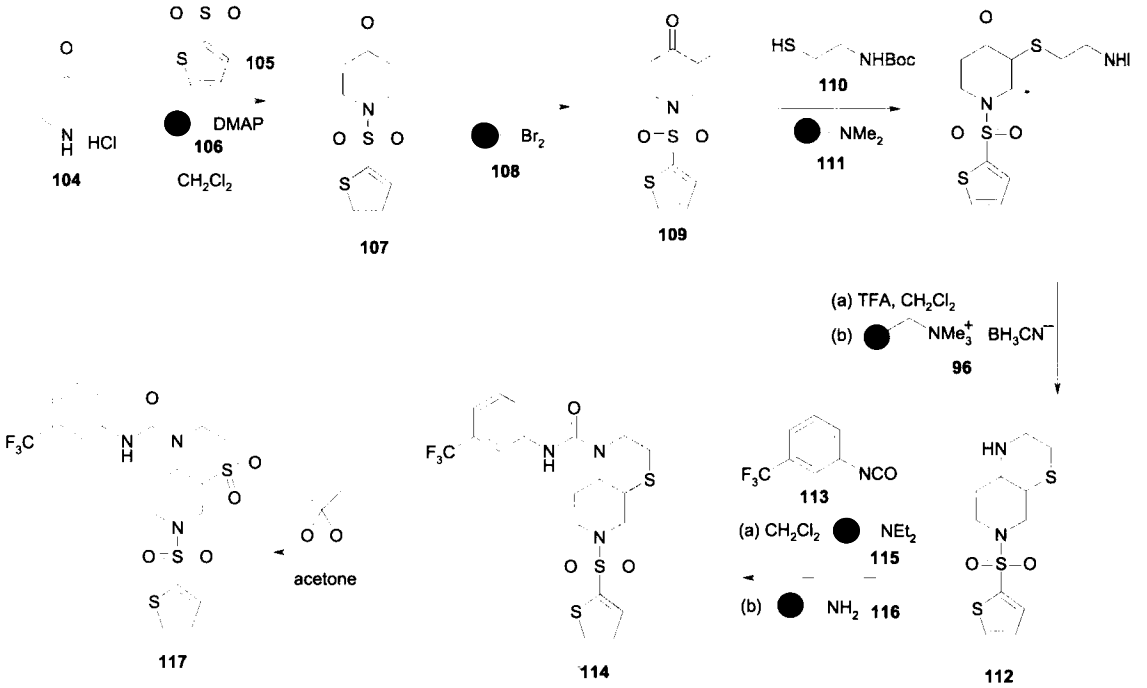
Scheme 19. Preparation of sulfonamides from alcohols using orchestrated polymer-supported reagents.



Scheme 20. Mukaiyama aldol reaction using a polymer-supported Lewis acid.

The combined use of PSRs in multistep sequences was further demonstrated by Ley et al. in the preparation of libraries of piperidino-thiomorpholines **117** (Scheme 21) [79]. Starting from 4-piperidone (**104**), the amine was derivatized with a range of sulfonyl chlorides, e.g. **105**, using polymer-supported dimethylaminopyridine **106** as base to give **107**. Selective monobromination α to the carbonyl group was achieved by using polymer-supported pyridinium perbromide **108**. Displacement of the bromine in **109** by N-Boc-protected 1-amino-2-thiols such as **110** using polymer-supported base **111** (Amberlyst A21) and deprotection with TFA in DCM yielded the corresponding imines directly. These could then be reduced with

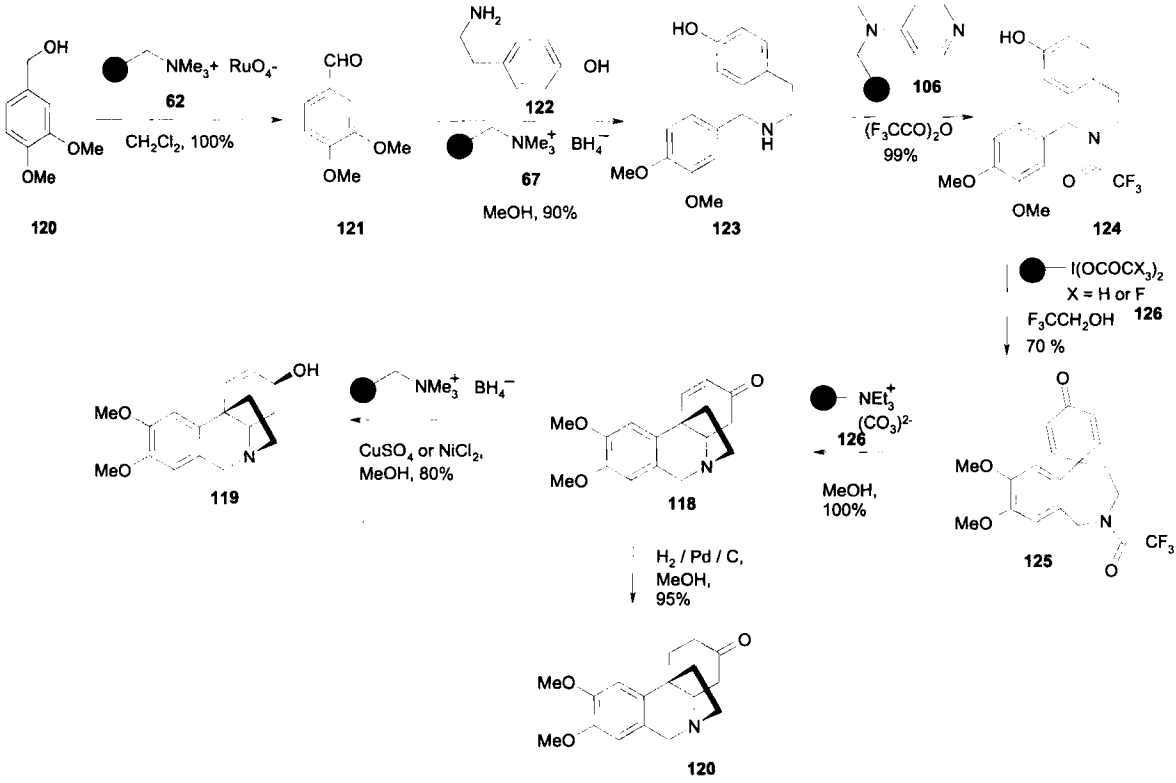
polymer-supported borohydride **96** to give the corresponding thiomorpholine derivatives **112**. The amino function of the thiomorpholine unit was further elaborated with a range of isocyanates, e.g. **113**, and isothiocyanates to give the corresponding ureas, e.g. **114**, and thioureas. This reaction was catalyzed by a polymer-bound base, diethylaminomethylpolystyrene **115**. The excess quantities of the electrophiles were scavenged with aminomethyl polystyrene **116**. Products were then either isolated by filtration and evaporation or further oxidized to sulfones **117** (Scheme 21) [79].



Scheme 21. Six-step synthesis of a piperidino-thiomorpholine library.

As a final example for the combined use of PSRs in synthetic sequences, the preparation of two natural products, (±) oxomaritidine **118** and (±)-epimaritidine **119** is described (Scheme 22) [80]. The first step employed polymer-supported perruthenate **62** for the conversion of alcohol **120** into aldehyde **121** in quantitative yield. This aldehyde was reacted with the primary amine **122** under reductive amination conditions to generate the norbelladine derivative **123**. The best conditions for this step involved the addition of polymer-supported borohydride **67** to a solution of the pre-formed imine. Subsequently, trifluoracetylation of amine **123** was effected by treatment with trifluoroacetic anhydride using polymer-bound dimethylamino pyridine to give the amide **124** in 99 % yield. The intramolecular phenolic oxidative cyclization of **124** to the spirodienone **125** was best achieved using polymer-supported (diacetoxyiodo)benzene **126** in trifluoroethanol. This oxidation reaction gave the desired

ortho-para coupled product in 70 % yield, with no other products being detected by liquid chromatography–mass spectrometry following filtration and evaporation. Treatment of **125** with polymer-supported carbonate **126** in methanol resulted in rapid deprotection and spontaneous intramolecular 1,4-addition to give (±)-oxomaritidine **118** in 98 % yield. Reduction of the carbonyl group in **118** using polymer-supported borohydride **67** in methanol provided access to (±)-epimaritidine **119** in high yield [80]. By hydrogenation of **118**, the saturated analog **120** was also accessible.



Scheme 22. Synthesis of two natural products (±) oxomaritidine **118** and (±)-epimaritidine **119** by Ley *et al.* based on the combined use of polymer-supported reagents.

4.5 Summary and Conclusion

Polymer-supported reagents represent a versatile addition to solid-phase organic synthesis and parallel solution-phase chemistry. They can be prepared by a variety of methods which ensure clean, non-leaking properties. However, although the "orchestration" [8] of these reagents offers exciting possibilities, the synthetic chemist is far from being the conductor of a large symphony orchestra!

Although the "instruments" described in this chapter are both interesting and fascinating, they do not yet enable the chemist to exploit all synthetic routes that he or she might consider. Thus, there is a clear requirement for advanced solid-supported reagents which, in the future, will undoubtedly lead to exciting developments in the field of combinatorial chemistry.

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5 Encoding Strategies for Combinatorial Libraries

Berthold Hinzen

5.1 Introduction

The tagging of chemical compounds first arose as a relevant topic when large numbers of compounds were prepared and conventional and convenient methods, e.g., writing with waterproof pens on reaction flasks and vials, became no longer appropriate.

One of the most obvious methods for the encoding of chemical compounds is spatial or positional tagging/encoding. The structure of a compound or its synthetic history is encoded by the position of the corresponding reactor, in most cases in a spatially fixed, two-dimensional matrix. However, a number of alternatives exist to encode for a chemical structure: chemical tags consisting of peptides, nucleotides, or aromatic compounds; graphical encoding methods; or perhaps the advanced and most useful technique, radiofrequency encoding [1]. However, before discussing these methods in more detail, some of their key requirements must be summarized.

As a large number of chemical entities is involved in combinatorial chemistry, manual handling is either very tedious or simply not possible; therefore, the tags should be readable by technical devices. Furthermore, for the efficient characterization of compound libraries, it is much more efficient to encode the planned structures before the synthesis than afterwards. The latter would require extensive analysis of the products using advanced techniques, and this again is either extremely tedious or impossible.

In order to encode, the tag must invariably be connected to the compound of choice at all times; that is, either on the compound itself (such as a protecting group) or via the reactor/polymer on which the product is being synthesized. Thus, another requirement arises, namely that the tags need to be chemically inert under the reaction conditions. Like a good protecting group, the tag must be orthogonal to the applied chemical conditions. Furthermore – and again like a good protecting group – the synthesis of the compound should not be affected by the presence of the tag. As some compounds are screened for biological activity in the presence of the tag, neither should the latter affect the product's biological properties.

5.2 Positional Encoding

Spatial or positional encoding is one of the most obvious and simple methods to encode for a chemical structure. It is also the method that is used by most robotic synthesizers. Furthermore, it is one of the oldest and best described methods for chemical encoding. Geysen's ear-

ly preparation of a polypeptide library relied on the spatial positions (in a two-dimensional array) of plastic pins which carried the compounds during synthesis [2]. Similarly, Affymax prepared a library of 1024 peptides [3], with each product being positioned in a 50 μm x 50 μm unit and with its position being related to its structure. However, this example demonstrates already the limitation of this method: space is limited. Either only very small amounts of a large number of substance can be prepared, or only a very limited number of products can be encoded by its position. In particular, when automated handling is envisaged, the workspace of robotic systems and handling of small amounts of solutions is difficult and might be a serious limitations. For solution-phase applications, positional encoding remains the method of choice, and although other methods may be possible (e.g., chemical encoding), these seem to be of only limited use. In most cases, this is most likely due to the rather small number of compounds.

5.3 Graphical/Barcode Encoding

Barcodes are among the best known codes for a large variety of items. Many libraries rely on barcodes for the automated storing and tracking of books, and most repositories of pharmaceutical companies use barcodes to encode their test compounds. Therefore, it is not surprising that this technique has also been used for the encoding of chemical/structural information during synthesis.

Houghton was the first to apply graphical techniques in combination with his teabag method, although attempts to automate the handling were not undertaken [4]. This approach was realized later when a 500 000-compound library was prepared on tubes carrying barcodes which also enabled automated sorting [5]. More recently, the use of 2D-barcodes was described for the preparation of an oligonucleotide library on square aluminum plates carrying a polystyrene layer as synthesis support [6].

5.4 Chemical Encoding

Encoding of chemical compounds as described above is based on the difficulties of determining the structure of each library member individually by analytical methods. For most organic compounds, this would require one- or multi-dimensional NMR techniques that are not suitable for large numbers. Moreover, analysis would also require a sufficient amount of material. An alternative approach is based on the preparation of the product simultaneously with the synthesis of a tagging compound that can be analyzed more easily than the original product. This approach was first discussed on the basis of oligonucleotides as chemical tags in which individual nucleotides serve as increments of the tag [7, 8]. Analogously, peptides have been used as chemical tags [9–11]. Both biopolymers are decoded by sequencing, and the sequence is related to the structure of the product. A limitation of these coding strategies is the possibility that not only the product but also the tag displays some biological activity, and thus can cause false-positive screening hits. Another limiting factor is the orthogonality of the tagging method and the chemical reaction conditions used to prepare the library. A solution

to this latter problem however was described recently: a library of hexapeptides was chemically tagged using polyhalogenated phenoxyalkyl derivatives which were covalently attached to the polystyrene backbone [12, 13]. The analysis/decoding of these tags was performed after cleavage from the support by electron capture gas chromatography. However, the problem of chemical orthogonality and different cleavage conditions may cause problems.

A related approach uses mono-amides of iminodiacetic acid as molecular tags [14]. The tags are attached to the support via the free carboxylic acid group and a free amino group bound to the support. The imino nitrogen group of the first part of the codon serves as attachment point for the carboxylic acid group of the next iminodiacetic acid mono amide. Due to the amide structure, the tags are chemically inert. Cleavage and conversion to the corresponding dansyl derivatives allow their characterization by HPLC and fluorimetry.

All chemical tagging strategies are greatly limited by the additional synthetic transformations required to build up not only the product but also the tag. Consequently, this encoding method is only used exceptionally for the production of libraries [15–17].

5.5 Mass Spectroscopic Encoding

Chemical encoding strategies rely on the assumption that the chemical analysis of a given member of the library is more difficult than the analysis of a chemical tag. In most cases this assumption is valid and justifies the described technique. Some libraries have been prepared and characterized by individual mass spectroscopic analysis of each member of the library. However, to obtain unambiguous results, the following criteria must be fulfilled:

1. Each member of the library must have a different molecular weight.
2. The compounds must ionize, without destruction into the gas phase.

These requirements seem to be rather limiting, but a synthetic linker to a solid support was recently described which enhances ejection of the product upon laser irradiation in the MALDI instrument [18]. Another approach relies on isotopically different reagents [19].

Due to the aforementioned limiting factors, spectroscopic encoding is not broadly applicable and is used only rarely for the encoding of libraries.

5.6 Radiofrequency Encoding

The most general method of encoding a chemical library is based on a small device which, upon activation, emits a given radiofrequency (rf). This device needs to be attached to the synthetic platform (beads, resins, tubes, etc.) on/in which the synthesis of products takes place. The device (which is ~8 mm x 1 mm in size) contains three components: first a memory for alphanumeric codes; second a rectifying circuit which absorbs radiofrequency energy and converts this energy into electrical energy. The latter is used by the third component, an antenna, to transmit the code to an external receiver that is linked to a computer.

This encoding method was commercialized for example by the IRORI group, which also produces small polypropylene reactors, "Kans". These act in the same manner as Houghton's teabags but contain the rf tag in addition to the resin. The advantages of rf encoding are nu-

merous: "split-and-pool" syntheses can easily be realized, the tags are chemically inert under the reaction conditions, and are also readable using technical devices [20].

5.7 Conclusion

Several possibilities exist for the encoding of combinatorial libraries. The limitations of one of the earliest and most general methods, spatial encoding, are overcome by the more advanced rf encoding, which appears to be the method of choice in the preparation of large libraries, whereas spatial encoding is used for smaller libraries and solution-phase applications.

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6 Automation and Devices for Combinatorial Chemistry and Parallel Organic Synthesis

Christian Zechel

Abbrevations

mtp	microtiter plate
rv	reaction vessel
wv	working volume

6.1 Introduction

In order to exploit fully the potential of combinatorial organic synthesis, it is important to automate or at least parallelize all or part of the individual steps. A typical workflow as it is encountered in automated organic (solid-phase) synthesis is shown in Fig. 1.

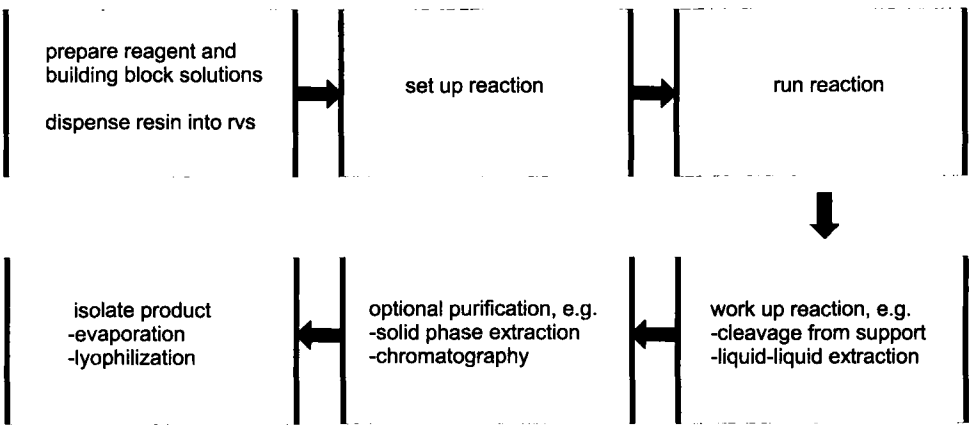


Figure 1. Typical combinatorial synthesis workflow.

Before a library synthesis can be performed automatically on a robot ("production stage"), the corresponding chemistry must be validated, i.e. its scope and limitations must be determined ("rehearsal stage").

For the actual run, solutions of common reagents and building blocks must be prepared, and the solid support dispensed into the correct reaction vessels (rvs). The reactions must then be set up under the proper conditions, run, and subsequently worked-up in an appropriate manner. This is followed by optional purification steps and, finally, isolation of the product. For all of these steps equipment is available that helps to achieve high throughput. The challenge is to devise a strategy which integrates all these separate devices as seamlessly as possible. This applies to both hardware and software.

It is clear that for consistently high throughput, all bottlenecks must be addressed. That does not necessarily mean that the whole process from start to finish has to be automated. This can be very costly – and is not even necessary. Rather, one should look carefully at which steps to automate, and avoid automating rare events that would require only infrequent manual intervention. It is the repetitious steps – such as washing procedures or addition of solvents – that benefit most from being automated.

Combinatorial organic synthesis can be performed both on solid phase and in solution. It is obvious that solid-phase synthesis is less difficult to automate, as work-up usually consists only of simple filtration steps. Solution-phase synthesis requires automation of work-up procedures such as liquid–liquid extraction or isolation and purification of intermediates. Strategies and devices designed for automating solution-phase synthesis have been dealt with in Chapter 2.1. In this chapter, the emphasis will therefore be on approaches to automate solid-phase organic synthesis.

6.2 Synthesis

6.2.1 General Remarks

Efficient parallel synthesis of large numbers of single defined compounds plays an ever more important role in drug research. While it is possible to synthesize manually mixtures of large numbers of compounds employing the split-mix method, in parallel single compound synthesis a number of reaction vessels equal to the number of desired final products has to be handled[1]. This latter approach clearly benefits from, or even requires assistance by, some sort of robotic equipment/devices. It is of course possible to start with a relatively small number of larger reaction vessels containing larger amounts of resin-bound intermediates which in subsequent steps are divided in ever smaller portions until the final products are obtained. This has been referred to as the split-only or split-split-technique (e.g. P. Brooking, A. Doran, P. Grimsey, N. W. Hird, W. S. MacLachlan, M. Vimal, "Split-split. A multiple synthesiser approach to efficient automated parallel synthesis", *Tetrahedron Lett.*, **1999**, *40*, 1405–1408; V. Krchnák, "Semi-Automated High Throughput Combinatorial Solid Phase Organic Synthesis", *Biotechnol. Bioengineering (Combinatorial Chemistry)*, **1999**, *61*, 135–141).

1 Obvious exceptions to this are compound libraries generated on beads by the split-mix technique which are subsequently tested in single bead assays. Here, the amount of compound obtained after cleavage from a single bead is sufficient to perform the biological assay. This is the classical one bead – one compound situation, where resin-bound compounds are synthesized in mixtures and sequestered before cleavage. In cases where these small amounts of material are sufficient, one gets the best of both worlds, i.e. large numbers of **single** compounds.

Early organic synthesizers were mostly derived from multiple peptide synthesizers (even those can still be used for relatively undemanding room temperature organic chemistry). Compared to the rather specialized and mild conditions employed in solid-phase peptide synthesis, however, the range of reaction conditions encountered in organic solid-phase chemistry is much wider. This means in practice: reaction temperatures lower as well as higher than ambient, the requirement of an inert atmosphere for many reactions, the handling of moisture or air sensitive reagents, and the use of aggressive chemicals. All these requirements are met by today's organic synthesizers. Issues such as reliable handling of solid reagents are still more or less unresolved, while for reactions involving reactive gases solutions are beginning to emerge.

In the meantime, equipment for carrying out reactions in an automated or parallel fashion has become available that should fit virtually all requirements and budgets. Broadly speaking, this equipment can be categorized as follows:

- Reaction blocks and manual systems: manual addition of solvents and reagents, simultaneous emptying of reaction vessels via bottom filtration
- Semiautomated systems: manual addition of reagents, automated addition of solvents, i.e. automated washing steps
- Fully automated systems: automated addition of both solvents and reagents, top and bottom filtration

As mentioned above, solid-phase synthesis lends itself to being automated because all phase separation steps occurring in the course of an organic synthesis can be reduced to filtration steps. To accomplish this, all reaction blocks and most semi- or fully automated instruments rely on bottom filtration, i.e. they use reaction vessels with a frit at the bottom. This allows complete draining of the reaction vessel (with the obvious exception of the amount of solvent that is retained within the resin beads). Top filtration is less common, and is practical only in fully automated equipment. One commercially available synthesizer does not employ filtration steps at all: on the COMPAS 768.2 (Spyder Instruments) the solid-phase synthesis is performed in microtiter plates and removal of liquids is achieved by the technique of "tilted centrifugation" see Section 6.2.4).

Several manufacturers offer both "full" and "light" versions of their equipment: in some cases it is possible to upgrade manual reaction blocks to semiautomated synthesizers by adding, e.g. a pipetting robot or custom wash station (see tables). In addition, some fully automated machines are available in a manual or also a semiautomated version. Mettler Toledo Myriad offer a product line consisting of the Myriad Core System and a range of "Personal Synthesizers". The latter can be used for chemistry development and small libraries. They use the same software and hardware as the core system, and so permit easy transfer of synthetic protocols. The same applies to Advanced ChemTech "Venture"/"Vantage", Argonaut "Trident", Zinsser SOPHAS, Chemspeed and MultiSynTech Syro.

In the following, an overview of equipment that is currently available commercially is presented. Especially in the early days of combinatorial chemistry, when little was available commercially, a significant number of companies designed and built their own robotic equipment. These proprietary solutions, as well as peptide synthesizers, are not listed.

The data that comprise the tables below are taken from company brochures and flyers, websites or from personal contacts at conferences, exhibitions, etc. This compilation reflects

the state of affairs as of September 1999. For details which are beyond the scope of this review and to obtain the most up-to-date information, the reader is advised to visit the manufacturers' websites (see Section 6.6).

6.2.2 Manual Systems

It is possible to perform combinatorial synthesis in standard microplates or filterplates with frits at the bottom as they are available from, e.g. Millipore, Matrix, Polyfiltronics (Whatman), or Porvair. In its simplest form, synthesis is carried out by adding solvents and reagents manually with a (multichannel) pipette. If filterplates are used simultaneous emptying of the wells or collection of products can be achieved in conjunction with appropriate collection plates.

Various reaction blocks especially designed for organic synthesis also have the footprint of a microtiter plate (Fig. 2). In most cases they have 48 or 96 reaction cavities with a pitch compatible with that of a microtiter plate (see Table 1) so that product collection, for example, can be performed using standard microtiter plates. The reaction blocks themselves are either solid blocks made of various chemically resistant materials or contain single separable reaction vessels. They are usually equipped with a frit at the bottom of each reactor (bottom filtration). Inadvertent drainage of the reaction vessels is prevented by using either sealing covers and clamping plates or by built-in proprietary valve assemblies. Agitation is generally achieved by placing the reaction plates on an orbital shaker. In some cases a custom heat/cool shaker or oven is available which makes it possible to run reactions at temperatures other than ambient. While in the basic version addition of both reagents and solvents must be performed manually, an upgrade is often possible, for example by adding a pipetting robot. Some suppliers offer custom wash stations which add solvent to all wells simultaneously and provide simultaneous emptying of all wells.

The currently available solid-phase synthesis reaction blocks with other footprints than the microtiter plate are listed in Table 2. Larger footprints allow higher reaction volumes (Chemglass, J-Kem). The CSPS Multiblock offers a simple means to perform split-mix synthesis.

Many companies offer reaction blocks which find their use primarily in solution-phase synthesis (Table 3, Fig. 3) as the reaction vessels normally used are (round-bottomed) glass vials, tubes or bottles. These devices can basically replace a number of magnetic stirplates and in addition to their making more efficient use of hood space offer features like common temperature control and inert atmosphere. In many cases, temperature ramps can be programmed and/or an interface for remote control from a PC is provided.

Agitation of the reaction mixture is provided by either built-in magnetic stirring or orbital shaking. These blocks also offer electric heating. Unless otherwise indicated, cooling is possible if an external chiller is used. Frequently an additional cooling layer or condenser enables real reflux conditions. For the Büchi Syncore and the J-Kem solid-phase reactor, block concentrator covers are available which effectively convert these devices into parallel evaporators.

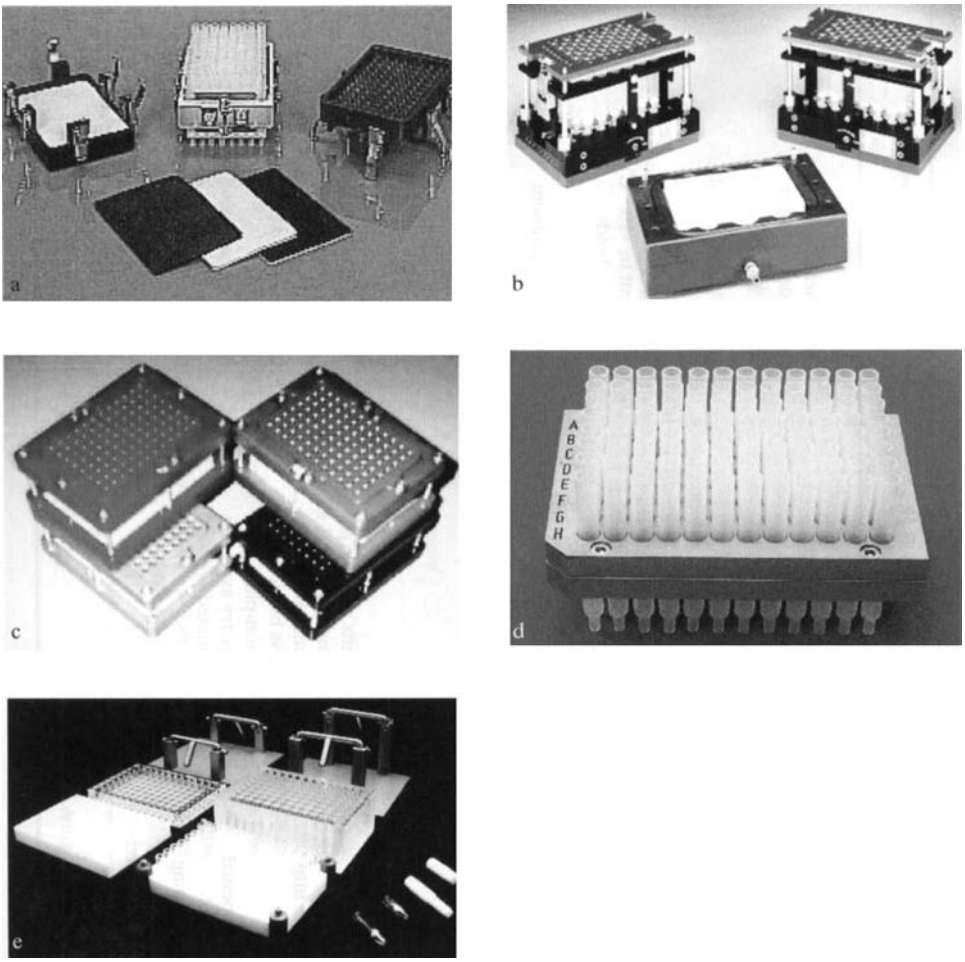


Figure 2. Reaction blocks in the microtiter plate format: Robbins Scientific (a), Bohdan Miniblock (b), Charybdis Technologies Calypso (c), MultiSynTech MicroBlock (d) and Rapp Polymere SYREM (e).

Many of these reaction blocks can also be integrated with (custom) robotic equipment so that the user has the possibility to begin with a completely manual system which later can be converted into a semi or fully automated system.

In comparison to reaction blocks, manual synthesizers (Table 4; Fig. 4) provide additional features such as simultaneous emptying of reaction vessels or in case of the "light" versions of automated equipment parallel evaporation or facile product collection in custom blocks after cleavage from the support.

It is obviously possible (but not very practical) to run reactions under inert atmosphere on any standard reaction blocks or manual synthesizers if the reaction vessels are, e.g. septum-covered. Much more efficient is the use of special covers or other means that provide an in-

Table 1. Reaction blocks in mtp format (or with mtp footprint)

	Bohdan MiniBlock	**Charybdis Technologies Calypso**	**MultisynTech MicroChem**
Reaction vessels *Material/shape*	Teflon block holding polypropylene syringes with frit	glass or glass-filled PTFE block with cavities (with or without frits)	block holding polypropylene syringes with frit
Number/volume	48/4.5 ml, 24/12 ml, 12/20 ml, 6/40 ml	24/10 ml, 48/5 ml, 96/2 ml	48/4 ml or 96/1.2 ml
Agitation	orbital shaking, heating/vortexing stations available (hold 2 or up to 6 blocks)	heating/vortexing station available (holds 4 blocks)	heating/rotating oven (ambient to +100 °C) available, holds 4 blocks
Temperature range	–20 to 80 °C	–80 to 180 °C	oven from ambient to 100 °C
Inert atmosphere in rv	+		+ –
Integration with robotic equipment	+		+ +
Special features/ comments	• products from *two* blocks may be collected in *one* mtp • septum cover available • all rvs can be opened and closed simultaneously by turning *one* knob • SPE can be performed with two Mini Blocks on top of each other	• permits reactive gas chemistry (up to 2 at pressurization/well) • fritless blocks for solution-phase chemistry available • automated system Iliad PS^2 available (see Table 6)	• cleavage station, 96-well solvent dispenser and automated wash system for 4 blocks available • proprietary valve plate available

Table 1 (continued)

	Robbins Scientific	**Rapp SYREM**	**Torviq Domino block**
Reaction vessels *Material/shape*	polypropylene block with cavities (with frits)	Teflon block holding single glass reactors with frit	Teflon block holding polypropylene syringes with frit
Number/volume	48/5.5 ml or 96/3 ml	96/150 µl or 450 µl	12/20 ml, 24/2.5 or 5 ml
Agitation	heating/rotating oven available	none (mixing effected solely by adding solvents/reactants)	orbital shaking (external shaker)
Temperature range	depends on gasket used, oven from ambient to 99° C	ambient	ambient
Inert atmosphere in rv		–	–
Integration with robotic equipment	+	+	+
Special features/ comments	• 96-well solvent dispenser (HYDRA 96) available		• block is a solvent and distribution manifold rather than a regular reaction block

Table 2. Reaction blocks especially designed for solid-phase synthesis

	Chemglass DIVERSOMER	**CSPS Multiblock**	**J-Kem Solid Phase Synthesis Reactor**
Reaction vessels			
Material/shape	glass pins	Teflon block holding polypropylene syringes with frit	polypropylene syringes with frit
Number/volume	8/2 ml (model 8–100), 40/2 ml (model 40–100), 10/30 ml (model 10–800) wv	42/2 ml wv	48 or 96/15 ml
Agitation	orbital shaking (external shaker)	orbital shaking (external shaker)	gas bubbling
Temperature range	custom heat/cool shakers available, covering a temperature range from –60 to 200°C	ambient	ambient and higher (custom heater available)
Inert atmosphere	+	–	+
Reflux capability	+	–	+
Custom blocks possible		–	
Interface for remote control	optional	–	–
Integration with robotic equipment	+	+	+
Special features/ comments	• synthesis takes place *in* the pin • rvs septum covered	• glass cover for randomization of resin (split–mix synthesis) available	• septum cover for rvs available • block for collection of products available • concentrator cover for evaporation from collection block available

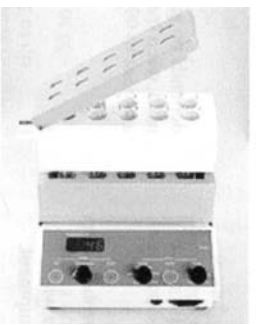
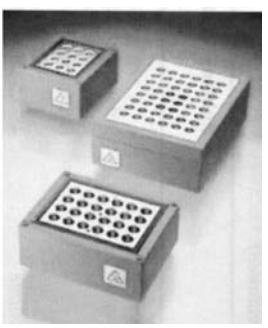




Figure 3. The Radleys reaction block (left) mounts on a standard stirplate. Reaction blocks by STEM (center) and H+P (right) are available in numerous sizes and can provide heating/cooling as well as magnetic stirring in each position. A reflux option is also available.

Table 3. Reaction blocks for parallel organic synthesis

	Büchi Syncore	**H+P Variomag**	**J-Kem RB/RBC/RBR**	**J-Kem KEM-Prep**
Reaction vessels *Material/shape*	glass vials, held in aluminum block	preferably glass tubes, vials or bottles, held in aluminum block	glass vials, held in aluminum block	glass vials
Number/volume	4/500 ml wv, 6/250 ml wv, 24/25 ml wv or 96/10 ml wv	various hole sizes available allowing the use of rvs from 6/250 ml to 96/6 ml	RB series: 96/2 ml, 4 ml,8 ml; 81/20 ml RBC series: 70/2.4 or 8 ml; 63/20 ml RBR series: 70/2 or 4 ml; 63/8 or 20 ml wv	24/5 or 10 ml
Agitation	orbital shaking	magnetic stirring	orbital shaking	orbital shaking
Temperature range	–20 to 150 °C	–80 to 200 °C	RB: ambient to 140 °C RBC: –120 to 140 °C RBR: ambient to 150 °C	–100 to 130 °C
Reflux capability	–	optional	+ (RBR series)	+
Custom blocks possible	+	+	+	–
Interface for remote control	–	RS 232	–	–
Integration with robotic equipment	+	+ (special versions available)	+	+
Special features/ comments	• can be converted to parallel evaporator, see also section 6.5 and Table 7 • temperature/time programs possible	• septum covers or self-closing flaps for rvs available • temperature/time programs possible • inert atmosphere in rv possible (comes with reflux option)	• built–in timer can turn heating on/off at specified time	• inert atmosphere in rv • rvs septum covered • built–in timer can turn heating on/off at specified time

Table 3 (continued)

	Radleys Carousel	**Robosynthon MultiReactor**	**STEM RS (heat/stir)**	**STEM (chill/stir)**	**STEM RS 6000 series**
Reaction vessels *Material/shape*	glass vials or tubes held in aluminum block	glass vials or tubes held in aluminum block	glass tubes/vials (16, 20 or 24 mm diam.) held in aluminum block	glass tubes/vials (16, 20 or 24 mm diam.) held in aluminum block	glass vials/tubes(16 mm diam.) or mtps held in exchangeable (aluminum) blocks
Number/volume	12 (24 x 150 mm) or 24 (16 x 100 mm)	24/10 or 18 ml	10, 25, 50	10, 25, 50	96 vials/tubes or up to 4 mtps
Agitation	magnetic stirring[a]	magnetic stirring	magnetic stirring	magnetic stirring	orbital shaking
Temperature range	ambient (PTFE block) or up to 160 °C (aluminum block)	–60 to +200 °C	30 to +150 °C	–30 to + 50 °C	ambient +5 to 150 °C
Reflux capability	+	condenser available	optional (air or water cooling)	–	–
Custom blocks possible				–	+
Interface for remote control	–	–	–	RS 232/485	RS 232/485
Integration with robotic equipmen	–	–	+	+	+
Special features/ comments	[a]mounts on a standard stirring hotplate • inert atmosphere in rv • permits reactive gas chemistry • PTFE caps with septum	• block temperature and agitation speed programmable from separate unit, dedicated PC-software also available • filtration rv for solid phase synthesis available	• reflux cover (also providing inert atmosphere in rv) available • septum cover for rvs available • Model RS 1000H has extended temperature range (30 to 300 °C)	• cooling with dedicated refrigerated gas chiller • septum cover for rvs available	

Table 4. Manual synthesizers

	Advanced ChemTech PLS 6	**Advanced ChemTech PLS 4 x 4**	**Advanced ChemTech PLS 4 x 6**	**Advanced ChemTech PLS 24**
Reaction vessels *Material/shape*	Teflon tubes with frit	Teflon tubes with frit	Teflon tubes with frit	Teflon tubes with frit
Number/volume	6/70 ml (adapters for other rvs available)	16/1 to 40 ml (adapters for other rvs available)	24/1 to 10 ml (adapters for other rvs available)	24/10 ml (adapters for other rvs available)
Agitation	orbital shaking	orbital shaking	orbital shaking	orbital shaking
Temperature range	–80 to 150 °C	rt to 150 °C (temperatures can be set individually in 4 zones)	rt to 150 °C (temperatures can be set individually in 4 zones)	–80 to 150 °C
Inert atmosphere in rv	–	–	–	–
Reflux capability	–	–	–	–
Integration with robotic equipment	–	–	–	–
Special features/ comments	• based on IKA shaker with programmable timer (0 to 56 min) • cooling with cold nitrogen generated from liquid nitrogen	• based on IKA shaker with programmable timer (0 to 56 min)	• based on IKA shaker with programmable timer (0 to 56 min)	• based on IKA shaker with programmable timer (0 to 56 min) • cooling with cold nitrogen generated from liquid nitrogen

Table 4 (continued)

	Advanced ChemTech Labtech I	**Advanced ChemTech Labtech II**	**AdvancAdvanced ChemTech Labtech III**	**Advanced ChemTech Labtech IV**
Reaction vessels				
Material/shape	Teflon block with cavities (solid phase version with fritted cavities)	Teflon block with cavities (solid phase version with fritted cavities)	Teflon block with cavities (solid phase version with fritted cavities)	Teflon block with cavities (solid phase version with fritted cavities)
Number/volume	96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)	96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)	96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)	96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)
Agitation	orbital shaking	orbital shaking	orbital shaking	orbital shaking
Temperature range	ambient	ambient to 150 °C	–70 to 150 °C	–70 to 150 °C
Inert atmosphere in rv	+	+	+	+
Reflux capability	–	–	–	
Integration with robotic equipment	–	–	–	–
Special features/ comments			• cooling with cold nitrogen generated from liquid nitrogen	• cooling with cold nitrogen generated from liquid nitrogen

Table 4 (continued)

	Chemspeed Manual System	**MultiSynTech SMS**	**Rapp Polymere APOS 1200**
Reaction vessels *Material/shape*	glass reactors with frit	Teflon block holding polypropylene or glass syringes with frit	glass tubes with frit
Number/volume	128/5 ml, 128/13 ml, 64/27 ml, 32/75 ml, 32/100 ml, 16/130 ml	40/10 ml, 60/5 ml, 96/2 ml	12/3 ml wv
Agitation	orbital shaking	magnetic levitation stirring	gas bubbling
Temperature range	–70 to + 150 °C/up to 8 different zones, external chiller(s) required	–30 °C (or –60 °C) to 150 °C	–60 °C to 150 °C
Inert atmosphere in rv	+	+	+
Reflux capability	+	–	+
Integration with robotic equipment	+	+	+
Special features/ comments	• fully enclosed • reagent/solvent addition under agitation possible • parallel evaporation on the instrument • liquid-liquid extraction tool • parallel filtration (vessel to vessel) • push-button or PC control • this is an upgradable "light" version of the fully automated Chemspeed ASW 2000 (see Table 6)	• cleavage from support on the instrument, collection of products in custom block • reagent/solvent addition under agitation possible • this is a "light" version of the fully automated SYRO II (see Table 6)	• temperature/time programs possible • automated version available (see Table 6)

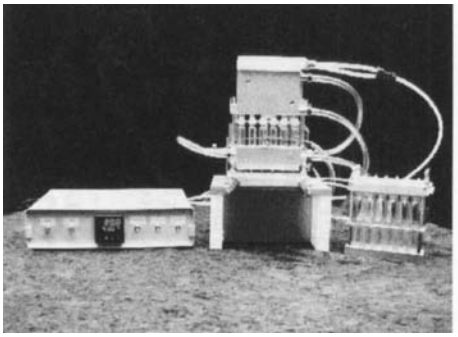


Figure 4. The modular manual synthesizer APOS 1200 (Rapp Polymere) accommodates an unlimited number of reaction units (each containing 12 rvs). An automated version is also available.

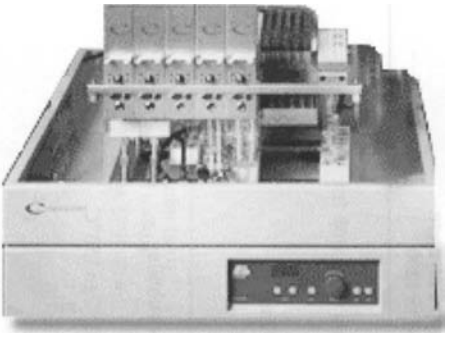


Figure 5. Chemspeed's Manual Synthesis Workstation offers special features like vessel-to-vessel filtration and parallel evaporation. It can be upgraded to a fully automated system.

ert atmosphere for all reaction vessels simultaneously. This feature is available for, or is already incorporated into, some standard reaction blocks and manual synthesizers, in particular those with built-in cooling devices for reactions under real reflux conditions (see Tables 3 and 4; Fig. 5).

6.2.3 Semiautomated Systems

These robots perform wash procedures in an automated fashion, while reagents have to be added manually. Generally, three to six online solvents are available. To accelerate wash cycles some instruments use multichannel pipettes or solvent delivery heads. For details, see Table 5.

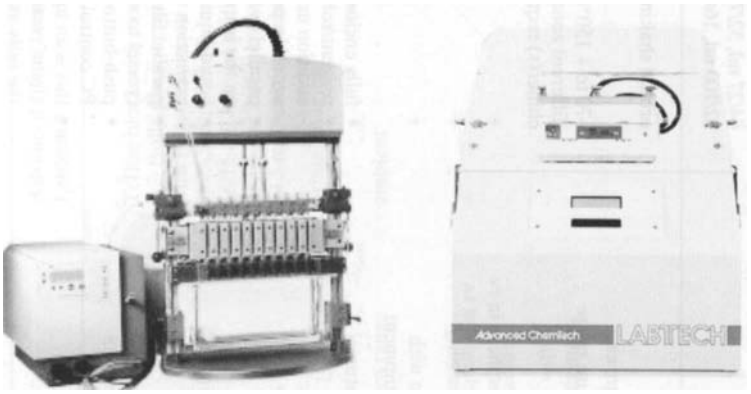


Figure 6. Semi-automated synthesizers QUEST 210SLN (Argonaut) and LabTech (Advanced ChemTech)

Table 5. Semiautomated synthesizers

	Advanced ChemTech LabTech V	**Advanced ChemTech Vanguard**	**Advanced ChemTech ReacTech**	**Argonaut Trident Workstation**
Reaction vessels				
Material/shape	Teflon block with cavities (solid phase version with fritted cavities)	Teflon block, cavities with frits	Teflon block, cavities with frits	round bottom glass vessels
Number/volume	96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)	40/6 ml wv, 96/2 ml wv, 384/0.5 ml wv	40/8 ml	48/5 or 10 ml
Agitation	orbital shaking	orbital shaking	orbital shaking	orbital shaking
Temperature range	–70 to 150 °C	–70 to 150 °C	–70 to 150 °C	–40 to 150 °C
Inert atmosphere in rv	+	+	+	+
Reflux capability	+	–	–	sealed rv
Online solvents	up to 6	up to 6	3	4
Special features/ comments	• rvs septum-covered • multichannel (up to 8) pipette for solvent delivery available • cooling with cold nitrogen generated from liquid nitrogen	• reactive gas chemistry possible (rv can be pressurized up to 150 psi) • multichannel pipette for solvent delivery	• rvs septum-covered • 40 channel solvent delivery head • cooling with cold nitrogen generated from liquid nitrogen	• septumless rvs with Teflon valve cap • top filtration • this is a "light" version of the fully automated Trident (see Table 6)

Table 5 (continued)

	Argonaut Quest 205	**Argonaut Quest 210 ASW/SLN**	**MultiSynTech SAS**	**Spyder COMPAS 768.2**
Reaction vessels *Material/shape*	disposable Teflon tubes with frit	disposable Teflon tubes with frit	polypropylene or glass syringes with frit	up to 8 microplates in centrifuge rotor
Number/volume	10/100 ml	20/5 ml or 10 ml	96/2 ml, 60/5 ml, 40/10 ml	
Agitation	vertically moving magnetic bar (gas driven)	vertically moving magnetic bar (gas driven)	magnetic levitation stirring	"stop and go" motion
Temperature range	–25 to 130 °C (2 temperature zones)	–40 to 130 °C (2 temperature zones)	–30 to 150 °C	ambient
Inert atmosphere in rv	+	+	+	–
Reflux capability	–	–	condenser plate optional	–
Online solvents	4	4	6	6
Special features/ comments	• limited reactive gas chemistry possible • on board work up possible (filtration, SPE, liquid–liquid extraction)	• limited reactive gas chemistry possible • on board work up possible (filtration, SPE, liquid–liquid extraction)	• reagent/solvent addition under agitation possible • this is a "light" version of the fully automated SYRO II (see Table 6)	• separation of solid and liquid phases achieved by "tilted centrifugation" (see text) • solvent must have lower density than solid support • solvent delivery via 96 channel distributor • also available as automated version (see Table 6)

6.2.4 Automated Systems

Fully automated synthesizers perform both addition of reagents and work-up procedures such as solvent washes automatically. Both self-contained benchtop systems and modular systems are available (Table 6). If really high throughput, versatility and expandability are required, then modular synthesizers are the robots of choice. In these systems a central processing unit is in charge of setting up and working-up reactions. This central unit can be surrounded by an (in principle) unlimited number of dedicated modules such as incubators, cleavage or liquid–liquid extraction devices (Fig. 7). A setup like this is expandable – whenever the user for example needs more incubator capacity or wishes to automate a new method, then another module can be added to the system.

Another advantage is that the pipetting robot is used more efficiently: In a simple benchtop system the robot platform would be idling and used more or less as an expensive stirrer or shaker during the reaction. In a modular system, the reaction vessels would be transferred to an incubator module where they remain for the duration of the reaction. In this way the robot is not tied up and can be used to set up a new reaction, thus allowing a much higher throughput. This was recognized by several instrument companies who in consequence developed remote shakers/stirrers for off-line incubation which can be attached to a benchtop synthesizer.

Among the modular systems, the high-throughput Mettler Toledo Myriad core system (Fig. 8) most closely resembles an assembly line, as so-called "minitrays" each holding 12 reaction vessels are automatically transferred to remote incubators and back to the processing

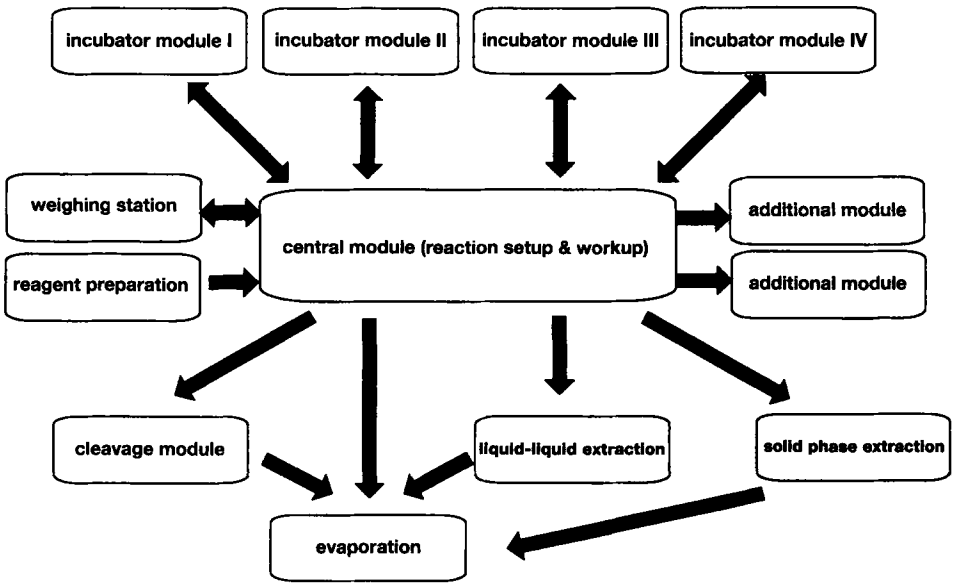


Figure 7. Modular system for automated organic synthesis.

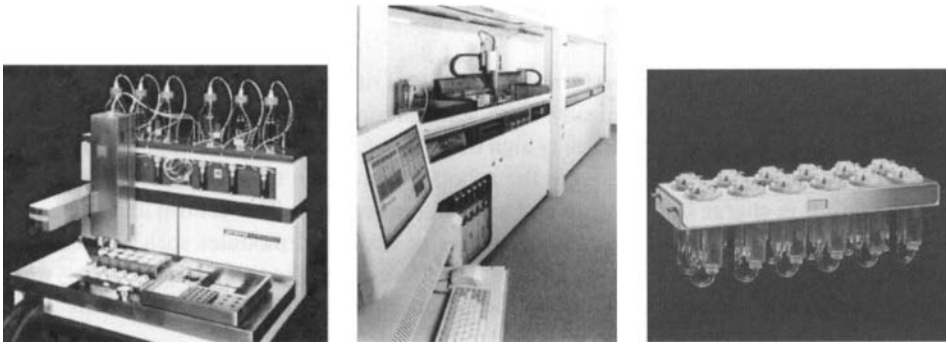


Figure 8. The Myriad Personal synthesizer (left) and Core System (center) (Mettler Toledo Myriad) use minitrays each holding 12 reaction vessels with novel twist caps (right).

module by a conveyor belt located on the back of the system. The SOPHAS (Zinsser) is also capable of moving reaction blocks with a mtp footprint around (within the limits of the platform).

Accelab offers a complete fully automated high-throughput synthesis laboratory (Fig. 9) which includes synthesizer, solid-phase extraction module, balance, vortexer, liquid–liquid extraction, and a vacuum centrifuge. A robot arm is in charge of all vessel transfers.

Most fully automated synthesizers rely on pipetting/autosampler technology for dispensing reagents and solvents. Pipetting is normally performed using (multichannel) steel cannulas or in the case of the Mettler Toledo Myriad robots using displacement pipettes (reusable within and disposable after the run) which help to prevent cross-contamination and facilitate the handling of viscous reagents. In contrast, the automated machines from Argonaut are closed systems where solvents and reagents are delivered to the reaction vessels through permanently connected tubing.

The reaction volumes most frequently encountered are in the range of several ml, which in solid-phase organic synthesis permits the preparation of several tens of milligrams of compound per reaction vessel. While some suppliers also offer larger volumes (up to 50 ml) volumes on the order of 1 ml or smaller become increasingly interesting because smaller amounts of precious building blocks are needed and high-throughput screening in the life sci-

Figure 9. Accelab offers a complete high-throughput synthesis laboratory.

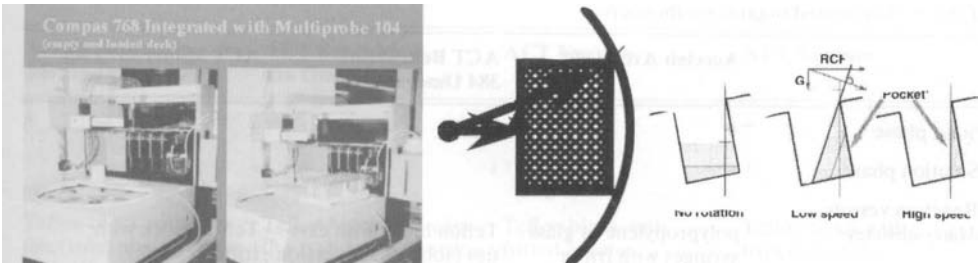


Figure 10. The COMPAS 768 (Spyder) uses "tilted centrifugation" to separate solid and liquid phases.

ences does not require large amounts of test compound anyway. Special reagent vials are no longer an issue, as today automated synthesizers are able to accommodate all sorts of different vial formats for building blocks and common reagents so that there are virtually no serious limitations anymore with regard to reagent number and volume.

An interesting approach towards the separation of solid and liquid phases (which in principle allows very high throughput) is taken by Spyder Technologies (Fig. 10). Here, the synthesis takes place in standard microtiter plates which are placed on the rotor of a centrifuge. Under certain conditions (tilt angle, speed, rotor diameter) it is possible to remove the liquid from the wells by centrifugation. It could be shown that cross-contamination is not a problem (this is attributed to the ribs around each well of a microplate). An obvious limitation is that only solvents can be used which have a lower density than the solid support.

High-throughput synthesizers with a large number of more conventional reaction vessels are available from Advanced Chemtech ("Venture") and Argonaut ("Trident") (Fig. 11). The "Venture" can accommodate up to several thousand reaction vessels in the 384-well micro plate format, is capable of performing reactive gas chemistry and liquid–liquid extraction in the reaction vessel. The glass reaction vessels of the "Trident" are organized in removable "reaction cassettes" of 48 and possess rotatable Teflon valve caps.

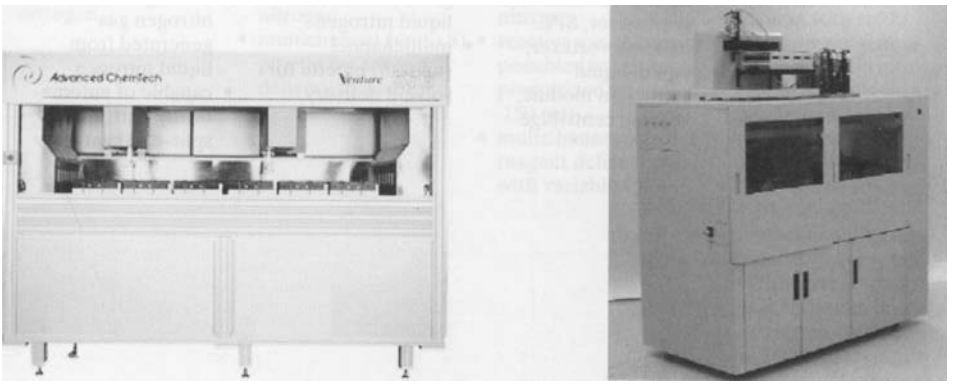


Figure 11. The high-throughput synthesizers Advanced ChemTech "Venture" (left) and Argonaut "Trident" (right).

Table 6. Automated organic synthesizers

	Accelab Arcosyn98	**ACT BenchMark 384 Omega**	**ACT Model 357 FBS**
Solid phase	+	+	+
Solution phase	+	+	–
Reaction vessels			
Material/shape	polypropylene or glass syringes with frit or custom vessels/reaction blocks	Teflon block with cavities (solid phase version with fritted cavities)	Teflon block with fritted cavities
Number/volume	up to 100/5 ml (with above standard syringes)	4 blocks of 96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)	36/5 ml wv
filtration mode	bottom	bottom	bottom
Online solvents	min. 6	4	2
Agitation	magnetic levitation stirring	orbital shaking	orbital shaking, gas bubbling
Temperature range	–80 to 160 °C	–70 to + 150 °C	ambient
Inert atmosphere in rv	+	+	+
Reflux capability	+	+ (solution phase reaction block)	–
Waste segregation	+	+	–
Fully enclosed	+	+	+
Special features/ comments	• complete high-throughput organic chemistry stand with synthesizer, SPE, balance, vortexer, liquid–liquid extraction module, vacuum centrifuge	• cooling with cold nitrogen gas generated from liquid nitrogen • multichannel (up to 8) pipette for solvent delivery	• designed primarily for peptide synthesis • cooling with cold nitrogen gas generated from liquid nitrogen • capable of automatically performing split–mix synthesis

ACT = Advanced Chem Tech

ACT BenchMark 440 Omega	ACT BenchMark 496 Omega	ACT Vantage	ACT Venture
+	+	+	+
+	+	+	+
Teflon block with cavities (solid phase version with fritted cavities)	Teflon block with cavities (solid phase version with fritted cavities)	Teflon block with fritted cavities	Teflon block with fritted cavities
40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 40/14.5 ml (solution phase)	96/3.5 ml, 40/9 ml, 16/15 ml, 8/30 ml (solid phase) or 96/6 ml, 40/14.5 ml (solution phase)	384/0.5 ml wv, 96/2 ml wv, 40/6 ml wv	multiples of 384/0.5 ml wv, 96/2 ml wv or 40/6 ml wv
bottom	bottom	bottom	bottom
up to 3	4	min. 4	min. 4
orbital shaking	orbital shaking	orbital shaking	orbital shaking
–70 to 150 °C	–70 to 150 °C	–70 to 150 °C	–70 to 150 °C
+	+	+	+
+ (solution-phase-reaction block)	+ (solution phase-reaction block)	+	+
+	+	+	+
+	+	+	+
• cooling with cold nitrogen gas generated from liquid nitrogen	• cooling with cold nitrogen gas generated from liquid nitrogen • multichannel (up to 8) pipette for solvent delivery available	• cooling with cold nitrogen gas generated from liquid nitrogen • reactive gas chemistry possible (rv can be pressurized up to 150 psi) • multichannel solvent/reagent delivery head with variable span	• expandable, customizable (up to 10 000 reactions simultaneously) • cooling with cold nitrogen gas generated from liquid nitrogen • reactive gas chemistry possible (rv can be pressurized up to 150 psi) • TFA can be used as system fluid • multichannel solvent/reagent delivery head with variable span • built-in liquid–liquid extraction capability with conductometric detection of phase boundary

Table 6 (continue)

	Argonaut Nautilus	**Argonaut Trident**	**Bohdan RAM/ Neptune**
Solid phase	+	+	+
Solution phase	(+)	(+)	+
Reaction vessels *Material/shape*	glass/Teflon round-bottom vessels	glass vessels organized in "reaction cassettes" of 48	glass tubes (solid phase version with frit)
Number/volume	24/5, 8, 15, 23 ml	up to 192/5 or 10 ml	48/7 ml wv (solution phase), 48/5 ml wv (solid phase)
Filtration mode	top	top	bottom
Online solvents	min. 4	min. 7	4 aqueous, 8 organic
Agitation	rocking motion	orbital shaking	magnetic stirring (solution phase), orbital shaking (solid phase)
Temperature range	–40 to 150 °C	–40 to 150 °C	–20 to 80 °C (solid phase block), –70 °C to 150 °C (solution-phase block)
Inert atmosphere in rv	+	+	+
Reflux capability	sealed vessel	sealed vessel	–
Waste segregation	+	+	+
Fully enclosed	+	+	+
Special features/ comments	• closed system • on-line sampling through vessel side port • temperature can be set for each reaction vessel individually • reagent vials in autosampler	• rvs sealed with rotatable Teflon valve • temperature can be set for each "reaction cassette" individually • "light" version Trident workstation available	• off-line incubation possible

Charybdis Technologies Iliad PS[2]	Chemspeed ASW 2000	MTM Personal Synthesizer	MTM Core system
+	+	+	+
+	+	+	+
Calypso reaction blocks (see Table 3)	glass vessels with frit	glass vessels (solid-phase version with frit) organized in minitrays with 12 rvs each	glass vessels (solid-phase version with frit) organized in minitrays with 12 rvs each
up to 4 blocks with up to 96 wells each	128/5 ml, 128/13 ml, 64/27 ml, 32/75 ml, 32/100 ml, 16/130 ml	24/10 ml	192/10 ml (expandable basic version)
bottom	bottom	bottom	bottom
6	up to 15	6/11	up to 10
orbital shaking	orbital shaking	magnetic stirring, gas bubbling	magnetic stirring, gas bubbling
	–70 to + 150 °C/up to 8 different zones, external chiller(s) required	–60 or –30 to 150 °C (chiller-dependent)	–60 to 150 °C
+	+	+	+
–	+	closed rvs with overpressure valve	closed rvs with overpressure valve
–	+	–	+
–	+	–	–
• Calypso reaction blocks available separately (see table 3)	• reagent/solvent addition under agitation possible • parallel evaporation on the instrument • liquid–liquid extraction tool • parallel filtration (vessel-to-vessel) • off-line incubator available • manual version available (see Table 4)	• septumless rvs with novel twist cap • reagent/solvent addition under agitation possible • remote incubator available with 4 independent temperature zones for 12 rvs each • "light" version of MTM core system	• septumless rvs with novel twist cap • reagent/solvent addition under agitation possible • modular, expandable system • rv minitrays are moved between modules via conveyor belt

MTM = Mettler Toledo Myriad

Table 6 (continue)

	MultiSynTech SYRO II	**Perkin–Elmer Solaris 530**	**Spyder COMPAS 768.2**
Solid phase	+	+	+
Solution phase	–	(+)	–
Reaction vessels *Material/shape*	polypropylene or glass syringes	glass round-bottomed flasks	up to 8 microplates in centrifuge rotor
Number/volume	96/2 ml, 60/5 ml or 40/10 ml	48/10 ml	
Filtration mode	bottom	top	filtration replaced by "tilted centrifugation"
Online solvents	6	6	6
Agitation	magnetic levitation stirring	orbital shaking	"stop and go" motion
Temperature range	–60 to 150 °C	–30 to 150 °C	Ambient
Inert atmosphere in rv	+	+	
Reflux capability	+	+	–
Waste segregation	+	+	
Fully enclosed	+	+	–
Special features/ comments	• reagent/solvent addition under agitation possible	• off-line incubator available	• separation of solid and liquid phases achieved by "tilted centrifugation" (see text) • solvent must have lower density than solid support • solvent delivery via 96 channel distributor • centrifuge also available as semiautomated stand alone version (see Table 5)

Zenyx Magellan	Zinsser SOPHAS
+	+
(+)	–
glass tubes	Teflon, glass vessels
96/10 ml	up to 9 aluminium reaction blocks (mtp footprint) with 4,8,16,24,48 or 96 positions/1 to 50 ml
top (96 channel filtration head)	top
up to 8	6
orbital shaking	orbital shaking
ambient to +150 °C	–80 to 150 °C
–	+
–	optional
+	optional
–	+
• all components barcoded • off-line incubation possible	• 3 work-table widths available • reaction vessels are moved between functional units on work plate • liquid–liquid extraction and SPE on board possible • off-line incubator available • "light" version with 1 reaction block available

6.2.5 Special Applications

6.2.5.1 Process Development

Process development is a multiparameter optimization problem. It is not surprising, therefore, that now that the technology is available to parallelize and automate organic synthesis, it is applied in this field.

Three systems designed for solution-phase synthesis and especially process development are currently available: Anachem SK233, Argonaut Surveyor and BOHDAN (Table 7). The latter two are especially designed for the process chemist who wishes to evaluate different reaction conditions such as temperatures, solvents, etc. The BOHDAN instrument offers the possibility to set the temperature individually for each reaction vessel.

Table 7. Equipment for parallel process development

	Argonaut Surveyor	**Bohdan Process optimization workstation**	**Gilson Anachem SK 233**
Reaction vessels *Material/shape* *Number/volume*	 Teflon vessels up to 10/75 ml (wv 15–45 ml)	 glass tubes up to 12/20 ml wv	 glass tubes up to 20/ca. 10 ml wv
Reagent vials *Number/volume*	up to 28/40 ml + bulk reagents	• 16/40 ml stirred, ambient • 16/40 ml stirred (–10 to 50 °C) • common reagents 2/125 ml, stirred (–10 °C to 50 °C) • slurry 2/125 ml, stirred	up to 28/40 ml
online solvents	min. 4	6	3/250 ml each
Agitation	vertically moving magnetic bar	magnetic stirring	magnetic stirring
Temperature range	–40 to 150 °C	–20 to 140 °C (temperature can be set individually for each vessel)	–30 to 150 °C
Inert atmosphere	+	+	+
Reflux capability	+	–	+
waste segregation	–	+	–
On line sampling	+	+	+
Fully enclosed	–	+	–

6.2.5.2 Equipment for Parallel Reactive Gas Chemistry

Zinsser SOPHAS, Argonaut Quest, ACT Vantage/Venture, Chemspeed as well as the Calypso reaction blocks already possess (limited) reactive gas chemistry capabilities. Recently, instruments dedicated to perform pressurized gaseous reactions have appeared: Bohdan developed a high-pressure synthesizer which is capable of running 12 reactions (30 ml total volume each) simultaneously at pressures up to 13 atm (200 psi). Argonaut Technologies have devised a high-pressure synthesizer named "Endeavor". This machine allows up to eight reactions to be performed at pressures up to 500 psi and temperatures up to 200° C. The reaction vessel working volume is 5 ml (total volume 15 ml). Gas uptake and pressure changes over time can be monitored.

6.3 Liquid–Liquid Extraction

Phase separations are a crucial step in every work-up procedure. While it is relatively straightforward to automate a filtration step to separate a solid and a liquid phase, automated liquid–liquid extraction is more difficult to achieve. This is essential for automating multistep solution synthesis, but can also be advantageous in solid-phase chemistry, as it is then possible to use nonvolatile cleavage agents and remove them conveniently (e.g. to cleave products from the support via saponification and remove the salts that were formed during the reaction).

Probably the simplest approach to automate liquid–liquid extraction is to perform the phase separation by volume. Known volumes of wash or extraction solvent and organic phase are mixed, the phases are allowed to separate, and then only e.g. 90 % of the organic phase is retracted to make sure that no aqueous phase is withdrawn. Obviously this step can be repeated to optimize recovery. This procedure can be carried out on most synthesizers with essentially no change to the hardware.

Another inexpensive approach which can be automated with the aid of a standard pipetting robot is to use cartridges equipped with a hydrophobic membrane which allows the organic phase to pass but retains the aqueous phase (Whatman). It is even possible to separate emulsions. These membrane materials are also available in bulk and various shapes (1 PS Phase Separator). Varian offer "Chem Elut" cartridges filled with a hydrophilic matrix that can be "conditioned" with an aqueous solution of the product which can subsequently be extracted with an organic solvent.

The ingenious "Lollipop"-method (Fig. 12) was invented by a summer student at Glaxo, and has been commercialized by Radleys. The organic and aqueous phases are mixed in polypropylene containers (two array sizes are available: 96 x 1.2 ml and 24 x 7 ml), and allowed to separate. An array of polymer pins is then immersed into the two-phase solution, which is subsequently cooled in a dry ice/acetone bath. After 3–10 min, the aqueous phase is frozen and, by retracting the pin array can be removed like a lollipop, while the organic phase is left behind.

Figure 12. The "Lollipop" phase separation method.

The automated liquid–liquid extraction module ALLEX (Mettler Toledo Myriad) uses a flow-through cell to monitor conductivity and thereby detect the phase boundary. The system is able to divert the upper and lower phase (and if the separation is not complete, in a second step the rag layer as well) into individual vessels. It can perform up to 60 separations per hour, the total volume is on the order of 10–15 ml (Fig. 13).

Advanced ChemTech's high-throughput synthesizer "Venture" has on-board liquid–liquid extraction facilities (conductometric detection of the phase boundary). Accelab has announced a liquid–liquid extraction module based on a fiberoptical sensor for detecting the phase boundary (this module is part of their automated synthesis system, but will also be available separately).

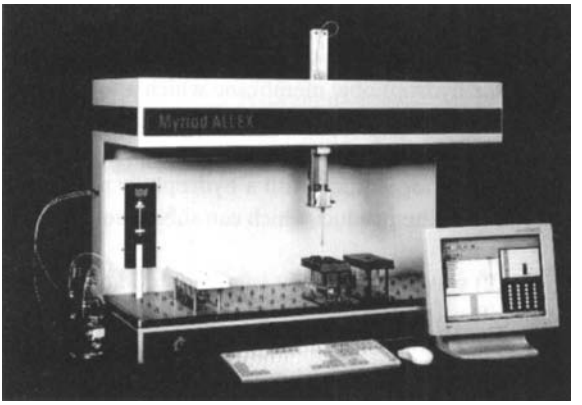


Figure 13. The ALLEX liquid–liquid extraction module.

6.4 Equipment for High-Throughput Evaporation

For high-throughput evaporation, vacuum centrifuges are currently the devices which are in most widespread use. Recently, equipment using orbital shaking as an alternative has come to the fore.

Key issues in both cases are efficient heat transfer to the samples to achieve good evaporation performance, and resistance against the chemicals usually encountered in organic synthesis.

To address the first issue, the current centrifuge models manufactured by Savant, Christ and Genevac use IR-lamps which are located in the walls of the vacuum chamber, or in the lid in case of the shakers (Hettlab IR-dancer). The Büchi Polyvap is different from all other vacuum evaporation equipment mentioned above in that each vessel is (and needs to be) sealed and evacuated individually to avoid cross-contamination. As no heat transfer through vacuum is required, a regular heating block is sufficient.

Generally, the sample or rotor temperature is monitored to prevent overheating of precious samples. It is possible to run pressure/temperature/time programs which is very useful, e.g. for evaporation of solvent mixtures. Even poorly volatile solvents such as NMP, DMF or DMSO can be removed efficiently.

Chemical stability (e.g. stability against trifluoroacetic acid – which is probably one of the most frequently used reagents in solid-phase organic synthesis) is much less of a problem now than it was just a few years ago. All equipment listed below has been especially designed or modified for use in organic synthesis and according to the manufacturers' specifications has the required chemical resistance. The Christ and Genevac centrifuges have been integrated with a robot for automatic loading/unloading of samples (Fig. 14).

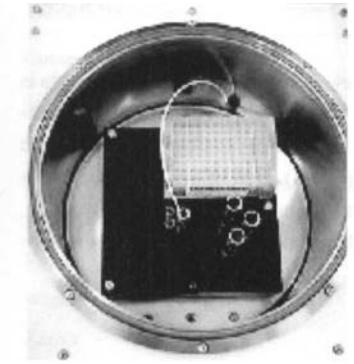
Centrifuge rotors are available for a large variety of vessels and can also be made according to the customers' specifications. Special swing-out rotors permit evaporation directly from (deep-well) microtiter plates or from vials held in racks with a microtiter plate footprint. Vacuum centrifuges are offered in various sizes up to machines which can handle 12 deep-well microplates or more (Table 8).

Shakers such as the IR-Dancer (Hettlab) or the Polyvap from Büchi (Fig. 15) offer the advantage that, as opposed to centrifuges, it is not necessary to balance moving parts. A variety of sample trays is available, and other vessel formats can be accommodated with custom-made holders.

Figure 14. Vacuum centrifuges: Genevac's Mega Series and CHRIST's Beta RVC. Both have been integrated with robotic systems.

Table 8. Equipment for high-throughput evaporation

	Capacity	**Comments**
Christ Alpha RVC >>IR<<	Single, double or triple-decker (e.g. max. 240 Eppendorf tubes) rotors or 2 sample swings for deep-well mtp	Rotor chamber diameter 305 mm, rotor diameter 260 mm, custom rotors possible
Christ Beta RVC	Single, double or triple-decker (e.g. max. 270 Eppendorf tubes) rotors or 8 sample swings for deep-well mtp	Rotor chamber diameter 395 mm, rotor diameter 350 mm, custom rotors possible
Genevac HT4	4 sample swings for deep-well mtp or racks with mtp Footprint	Proprietary "Cole pump" is offered, custom rotors possible
Genevac HT8	8 sample swings for deep-well mtp or racks with mtp Footprint	Proprietary "Cole pump" is offered, custom rotors possible
Genevac HT12	12 sample swings for deep-well mtp or racks with mtp Footprint	Proprietary "Cole pump" is offered, custom rotors possible
Genevac Mega systems		For larger sample numbers/sizes
Savant SC 250 DDA	4 sample swings each holding up to 2 deep-well or 5 standard micro-titer plates	Various integrated systems complete with pump, cold trap and cart available
Hettlab IR–Dancer	sample tray size 200 * 200 mm, min. 4 mtp	2 models available (chamber diameter 300 or 360 mm), custom vial holders possible
Büchi Syncore Polyvap	4 to 96 samples from 1 to 500 ml	Interconvertable with reaction block Syncore



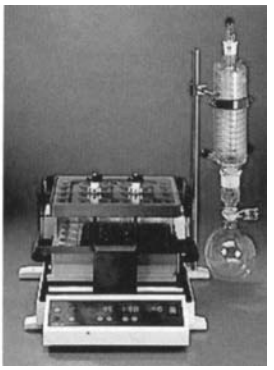


Figure 15. IR-Dancer (Hettlab, left) and Polyvap (Büchi, right).

6.5 Automated Resin Dispensing

Before any solid-phase synthesis, the appropriate amount of solid support must be dispensed into each reaction vessel. With increasing numbers of reaction vessels, this becomes quite labor-intensive and tedious. While it is possible to use a pipet(ting) robot and suspensions of resin in isopycnic solvent mixtures, other methods and devices for "dry dispensing" have recently come to the fore.

Argonaut Technologies offer the "Argoscoop", which is a calibrated spoon. They also sell so-called "Argocaps", i.e. prefilled polycarbonate capsules containing a specified amount of resin. Two different sizes are currently available containing 40 to 70 or 100 to 160 mg of resin, respectively. The capsule dissolves in many organic solvents and so can be washed away before the synthesis. Custom filling with supports provided by the customer is possible.

Both Zinsser (REDI; Fig. 16) and Anachem (RPD-1) market automated resin dispensers which employ powder dispensing technology borrowed from the pharmaceutical industry. Based on a standard pipetting robot they use a vacuum pipette with adjustable tips which are available in various sizes. Both suppliers specify a typical reproducibility of ±2 % for 50 mg and ±1 % for 150 mg of support. With one tip, resin can be dispensed for example into the 96 wells of a microtiter plate within about 15 min.

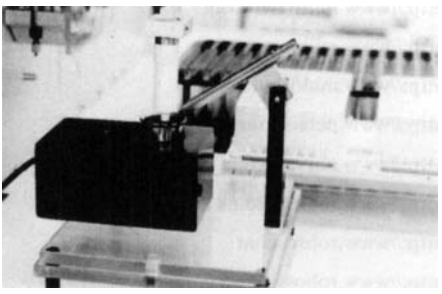


Figure 16. The resin dispenser REDI (Zinsser).

6.6 Suppliers

Essentially all instrument suppliers are present in the internet. As combinatorial synthesis is a fast-moving field, the internet is the information source of choice. Unfortunately the manufacturers' web pages do not always provide sufficient detail or are not sufficiently up to date (occasionally even less so than already available printed material!). But in any case the website at least represents a good starting point before contacting a manufacturer directly.

Very useful websites which offer many links to equipment manufacturers' and other websites relevant to combinatorial chemistry are:

- 5z.com
- combinatorial.com
- combichem.net

Table 9 lists instrument companies mentioned in the text in alphabetical order together with their web addresses.

Table 9. Suppliers of equipment for combinatorial synthesis

Company	Website
Accelab	http://www.accelab.de
Advanced Chemtech (ACT)	http://www.peptide.com
Argonaut Technologies	http://www.argotech.com
BOHDAN Automation	http://www.bohdan.com
Büchi	http://www.buchi.com
Charybdis Technologies	http://www.charybtech.com
Chemspeed	http://www.chemspeed.com
Christ	http://www.martinchrist.de
Genevac	http://www.genevac.com
Hettlab[a]	http://www.prolab.ch
H+P	http://www.hp-lab.de
J-Kem	http://www.jkem.com
Matrix	http://www.matrixtechcorp.com
Mettler Toledo Myriad	http://www.mtmyriad.com
Millipore	http://www.millipore.com
MultiSynTech	http://www.multisyntech.com
Perkin Elmer	http://www.pebio.com
Porvair	http://www.porvair.com
Radleys	http://www.radleys.co.uk
Robbins Scientific	http://www.robsci.com
Robosynthon	http://www.robosynthon.com

Table 9 (continued)

Company	Website
Savant	http://www.savec.com
Spyder Technologies	http://www.5z.com/spyder
Stem (Electrothermal Engineering)	http://www.stemcorp.com
Torviq	http://www.torviq.com
Varian	http://www.varianinc.com
Whatman	http://www.whatman.com
Zenyx	http://www.zenyx.com
Zinsser	http://www.wheatonsci.com

[a]Hettlab: in Germany the IR-dancer is distributed by TecConsult & Trading, Frühlingstr. 5, D–81325 Eggstätt, e-mail: tecconsult@ibm.net

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7 Computer-Assisted Library Design

Andreas Dominik

7.1 Introduction

7.1.1 Optimizing Combinatorial Libraries

Combinatorial chemistry is able to provide the screening laboratories of pharmaceutical companies with a vast number of new chemical compounds and novel scaffolds for drug discovery. For that reason, combinatorial chemistry has rapidly become widespread among medicinal chemistry departments such that today, it is one of the most important sources of new lead structures in the drug development process [1–3].

To speed up the lead-finding process, the design of specialized libraries that comply with many different requirements has become increasingly important:

1. The resulting chemical structures should show a certain degree of "drug-likeness", so that biologically active compounds can be further developed into drug candidates.
2. Structural novelty is also demanded for the structures of a library.
3. The region of covered chemical space should be populated steadily, without clusters or gaps.
4. The region of chemical space covered by the chemical structures of a screening library must be as large as possible. This implies a maximum of diversity for the structures of the combinatorial library.
5. The diversity of a focused library should be small. However, the chemical space in the region of active compounds must be populated steadily.
6. The need for matrix synthesis and use of robots for the synthetic steps limits the variety of applicable chemical reactions.

All of these demands require comparison of molecules, and therefore computation of molecular similarity is a major task in library design. When combinatorial chemistry started to become an important tool in medicinal chemistry, library design was focused mainly on synthetic accessibility, but today, all aspects of library optimization must be taken into consideration [4, 5].

The methods of computational chemistry and molecular modeling can help the combinatorial chemist to satisfy all these requirements. In this way, the basic concepts of combinatorial chemistry (to synthesize large numbers of compounds – i.e., drug discovery by random screening) and rational drug design are combined. The resulting combinatorial libraries comprise a high number of rationally designed compounds for screening, as well as for lead optimization (Table 1) [6–8].

Table 1. Applications of combinatorial chemistry and typical requests to the library design.

Application	Requests to library design
Library for repository expansion and high-throughput screening (HTS) (lead finding)	Maximum diversity of single library. Maximum diversity within a set of libraries. Find gaps in the represented chemical space.
Focused library, based on HTS results	Medium diversity. Similarity to HTS hits. Include structure information from biochemical or biological data. Diversity of structures should allow the derivation of structure – activity relationships.
Focused library, based on detailed pharmacological data	Small diversity. High degree of drug-likeness.
Focused libraries, based on 3-D information of target structure	Focus not on diversity! Every single structure optimized for best fit.

7.1.2 A Computer-Assisted Design Strategy

The fundamental strategy of computer-assisted library design is shown in Fig. 1. The set-up of the reaction scheme and building block selection lead to the virtual combinatorial library. Due to the virtual character of this library its size is not limited by experimental restrictions, and depends mainly on the number of available building blocks.

In the next step, computational algorithms are applied to derive numerical descriptors that describe structural properties of all compounds in the library [9]. These descriptors are used for the following comparison of all molecules and the subsequent selection of building blocks for synthesis.

Combinatorial libraries designed this way promise to combine the main advantages of small (highly specialized) as well as of large (diverse and uniform) combinatorial libraries. The huge virtual library comprises thousands or millions of structures, and therefore addresses diversity. The comparatively small final library consists of only of a small percentage of the total number of molecules and ensures synthetic accessibility [10].

The selection algorithm is responsible for the quality of this final library that – hopefully – satisfies the given requests as well as the entire virtual one [12, 13].

A brief introduction into the computer-assisted design strategy is given in Section 7.2. Basic theory and methods applied to the different steps of library design are described in the following sections in more detail:

- **Descriptors** and their applicability are presented in Section 7.3.
- **Compound selection methods** are shown in Section 7.4.
- **Strategies compound selection and library design** are described in Section 7.5.

How the computer-aided design strategy can be applied to different problems is shown in the Sections 7.6 and 7.7. The following is an introduction into the theory of diversity and basics of the computational chemistry methods, when applied to combinatorial chemistry problems.

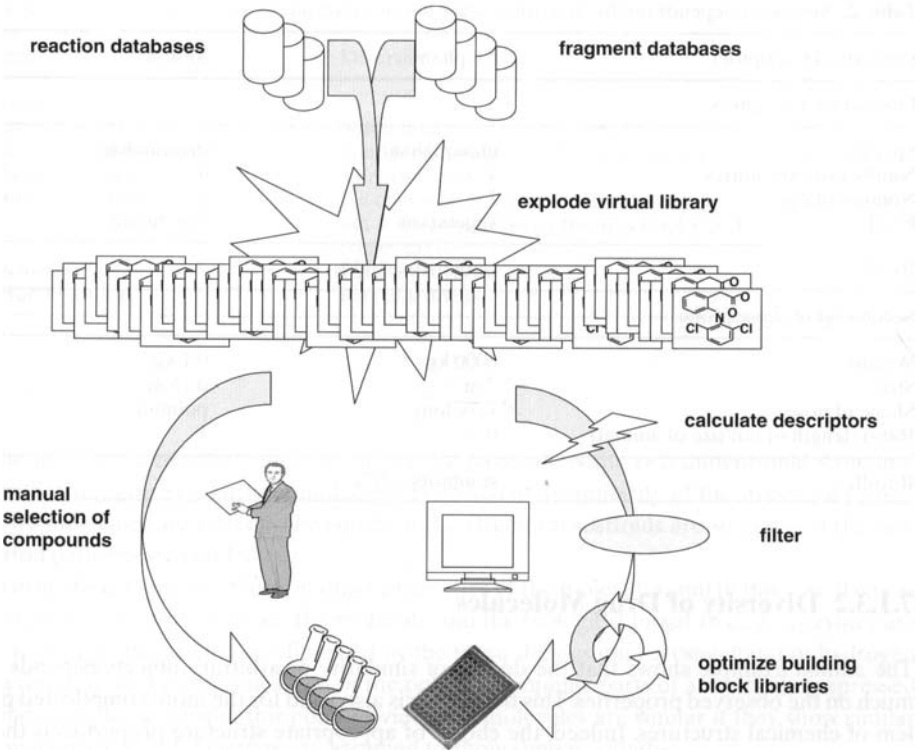


Figure 1. Computer-assisted design strategy. At best, building blocks are selected by optimizing the enumerated virtual library (product-based selection).

7.1.3 What is Diversity?

All chemists engaged in combinatorial chemistry must come to terms with the concept of "diversity", although it is not yet possible to give a reliable answer to the question of what 'diversity' is.

7.1.3.1 First Examples

As a first illustrative example, two animals are to be compared. Each time things are compared, some selected properties of the test objects must be examined. Animals may be classified by properties such as species, number of extremities, or number of eyes. Table 2 shows the results of the diversity examination of an elephant and a mouse; 100 % similarity or 0 % diversity are found. Just looking for other typical characteristics such as weight, shape of nose or the ratio (length of tail/size of animal) will give quite different results: 0 % similarity or 100 % diversity for this example.

Table 2. Similarity depends on the descriptor sets.

Property (Descriptor)	Elephant	Mouse
First set of descriptors:		
Species	mammalian	mammalian
Number of extremities	4	4
Number of eyes	2	2
Food	vegetarian	vegetarian
Result:	similarity = 100%	
Second set of descriptors:		
Weight	6000 kg	0.1 kg
Size	7 m	0.15 m
Shape of nose	very long	pointed
Ratio (length of tail/size of animal)	0.2	1
Result:	similarity = 0%	

7.1.3.2 Diversity of Drug Molecules

The animal example shows that the degree of similarity of arbitrary objects depends very much on the observed properties. This trivial rule is also valid for the more complicated problem of chemical structures. Indeed, the choice of appropriate structure properties is the essential problem involved in describing diversity, since the competence of the properties is not as obvious as in the simple animal example above.

Fig. 2 shows a set of molecular structures. Which of these molecules are similar? Which subsets are diverse? Table 3 shows possibilities for more detailed examinations. Also in this example the answer depends heavily on the properties observed. In analogy to the animal example, there is no general answer to the "diversity question" in connection with molecules.

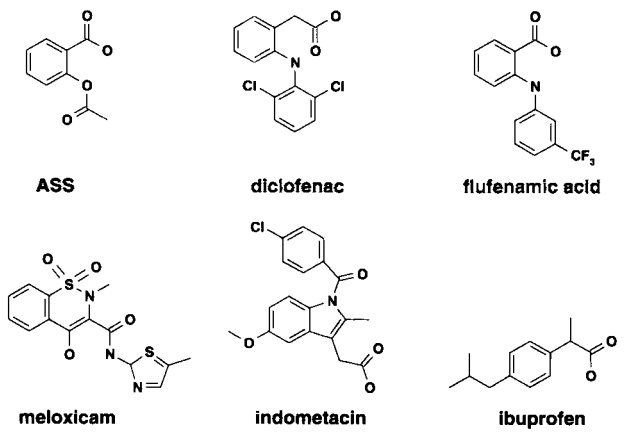


Figure 2. Are these molecules diverse?

Table 3. Diversity examination of the molecules of Fig. 2.

Property	Diversity
Structure	?
Structure formula	Some similarity between upper row
Physico-chemical properties	Similar pK_A-value (acids), more variation of lipophilicity
Synthetic accessibility	Very different!
Pharmacological properties	All compounds are anti-inflammatory drugs (low diversity) but different selectivity towards the COX-1 and COX-2 coenzymes
Molecular weight	Partially diverse
Structural patterns	Partially diverse

The most usual representation of an organic molecule is the two-dimensional structural formula. Therefore, similarity of molecules is looked at as similarity of the structural formulas. Two molecules are stated to be similar if the structural scaffolds are similar and the substitution patterns are similar.

In drug design, one must look at other properties of the molecules, and in this case the possibilities of interaction between the molecule and the biological target (e.g., an enzyme) are important. This interaction is influenced by the three-dimensional arrangement of hydrogen bond donor or acceptor groups, and of the polar or lipophilic parts of a molecule (expressed as pharmacophores). From this point of view, two molecules are similar if they show similar pharmacophores and then they are assumed to show similar activities.

The pharmacophore necessary for a drug molecule is obviously defined by the biological target molecule. Therefore similarity of two molecules is not a constant, but depends on the target. The same set of molecules may show a diverse behavior in one biochemical assay (i.e., a broad range of activities or binding affinities) and a high similarity (i.e., same or similar activities) in another one [6, 13].

For this reason the appropriate molecular representation for diversity or similarity examination of a combinatorial library varies and depends on the purpose of library (e.g., general screening library, lead evaluation library, lead optimization library, etc.).

7.1.3.3 Diversity and Similarity

The simple animal example above addresses the problem of diversity by just looking at missing similarity. Strictly speaking, similarity can be defined based on a limited number of properties of a limited number of objects. In contrast, the nature of diversity is more formal and always more uncertain, because diversity refers to all possible appearances of the objects. Diversity is a more fundamental principle and is not limited to the objects observed. Two objects may be called dissimilar – but to call them diverse one must know how dissimilar they can be theoretically.

When analyzing libraries of molecular structures, it is normally not possible to obtain a general idea of the entire chemical space comprising all structural possibilities. This entire

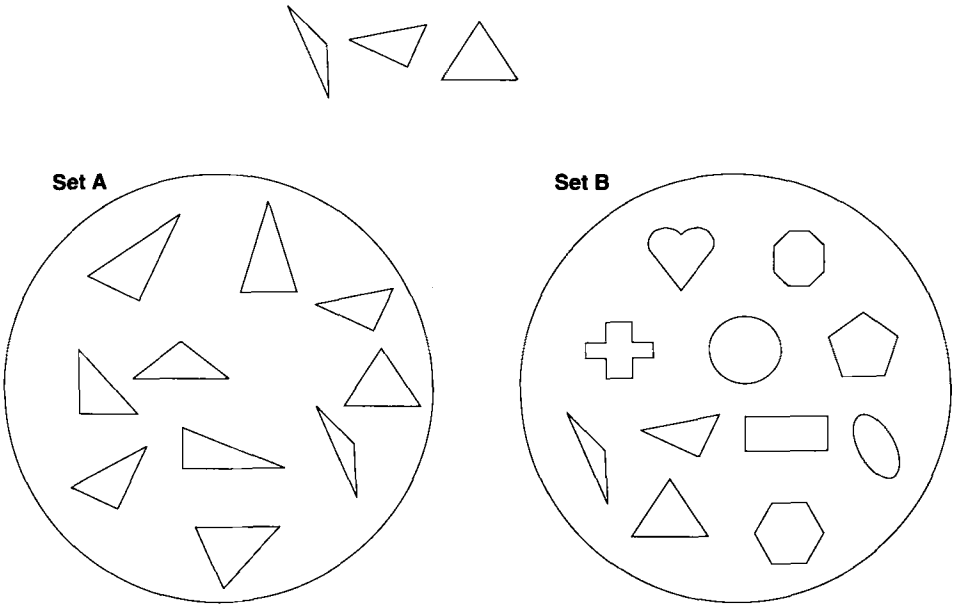


Figure 3. Diverse or not diverse? The three selected figures are a highly diverse selection from set **A**, but a low diversity selection from set **B**.

chemical space comprises a huge number of compounds. Only a very small fraction of these compounds is known and characterized (see Table 4).

Table 4. Size of the chemical space to which the diversity of a combinatorial library refers [10].

Number of molecules	Chemical space
10^{180}	Possible drugs
10^{18}	Likely drugs
10^{7}	Known compounds
10^{6}	Commercially available compounds
10^{6}	Compounds in a corporate database
10^{4}	Compounds in drug databases
10^{3}	Commercial drugs
10^{2}	Profitable drugs

Diversity is therefore always regarded as a local phenomenon and limited to a certain part of the structural space. Extent and localization of the region covered has to be defined previously – otherwise it is impossible to define the diversity of a subset.

In order to obtain a pragmatic and useful base for diversity computations, diverse chemical structures are compared with a known part of chemical space. This approach is applicable when the library described in terms of diversity is a small fraction of the entire dataset.

Consequently, the generation of huge virtual libraries is necessary in order to define the visible chemical space and form a virtual mesh in this space. Distances, similarities, or even diversity can be measured by referring to this virtual mesh.

7.2 How Do We Compute Diversity?

7.2.1 An Overview

As explained in Section 7.1.3, a universal definition of similarity or diversity of a set of molecules is not possible. For this reason, the diversity computation algorithm is split into several computational steps, and every step must be adapted to the given problem (see Fig. 4). The major steps are:

- Choice of descriptors.
- Calculation of descriptor values.
- Calculation of similarities in the descriptor space.
- Mapping or classifying the descriptors.
- Selection of compounds.

Every particular study looks at just some of the structural properties and neglects others. To ensure that the initial aim of the library design is achieved, a critical interpretation of the results is essential.

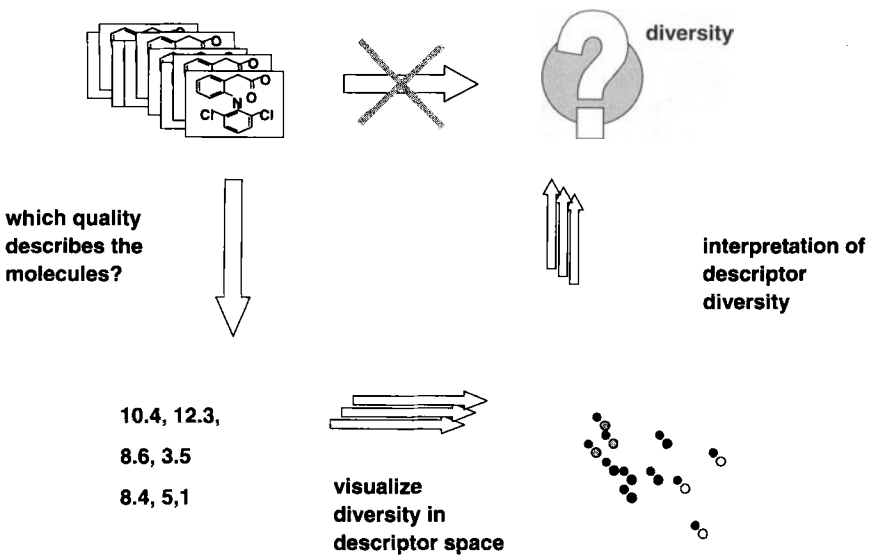


Figure 4. The diversity computation bypass. A direct description of molecular diversity is not possible – therefore diversity and similarity are assessed in numerical descriptor space.

7.2.2 Descriptors

The first and most important step is to choose properties that describe the molecules as numerical values. In the following text these numerical representations of some molecular properties will be denoted as "descriptors". The use of numeric descriptors prepares the problem for subsequent computer processing (Fig. 5). All subsequent steps of a study look at the descriptors instead at the molecules themselves. Therefore, diversity or similarity is defined in the descriptor space instead of the chemical space. The relevance of descriptor similarity for the similarity of the molecules must be ensured by a appropriate choice of the descriptor set [14, 15]. Obviously, it is very important to know the characteristics and applicability of various descriptor sets.

The total number of descriptor values needed to describe a molecule depends on the problem given and the size of the virtual library. Small datasets may be described with only few descriptors – huge virtual libraries may need hundreds of descriptors to work out typical similarities or differences of all the chemical structures.

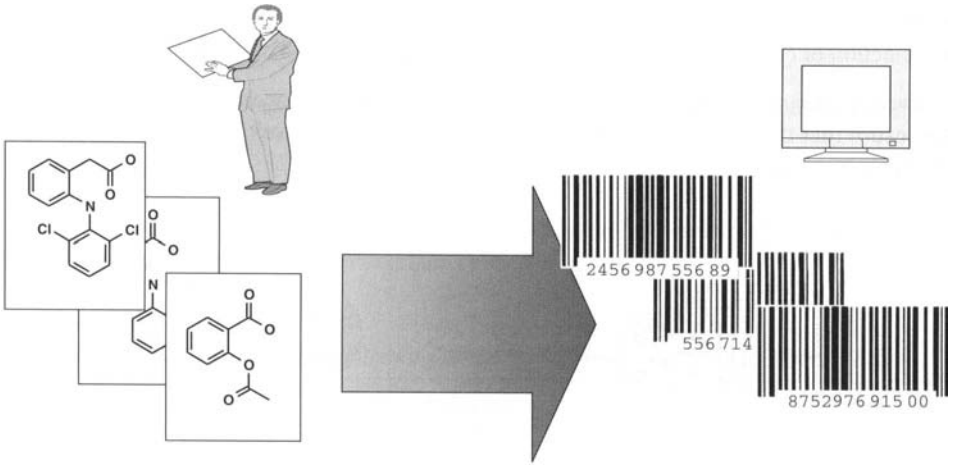


Figure 5. Structural formulas are the best representation of molecules for chemists – numerical descriptors are preferred by computers.

7.2.3 Classification and Mapping

The second step of the algorithm is the comparison of descriptor values. Several different methods are applicable to the problem, most of which are adopted from pattern recognition or statistical sciences.

For a manual interpretation of the diversity behavior of a dataset, the descriptors are usually mapped or projected into a two-dimensional map. Similar molecules are identified due to their proximity on the map (see figures in Section 7.2.5 for examples). These maps are very helpful tools for the visualization of the distribution of structures of a library in terms of di-

versity. A common problem is that of mapping errors that arise because it may be geometrically impossible to project all inter-molecule distances into a two-dimensional map correctly (see Fig. 14).

Purely numerical methods such as hierarchical clustering or the minimal spanning tree compute the similarity of molecules directly in the high-dimensional descriptor space. The results promise higher accuracy (no mapping errors), but their interpretation is less intuitive.

The chemist can select compounds for synthesis from the maps or clustering results with the possibility of additional optimization such as use of preferred building blocks or functional groups in the molecules.

In general, it is not necessary for the user to understand the theory of classification methods in detail. The decision as to which method is to be used depends mainly on technical aspects, such as size or dimension of the dataset or complexity of the problem. The classification results do not depend heavily on the method used, but especially cluster borders will differ slightly. Classification software will work out and visualize the information already included in the descriptors.

7.2.4 Interpretation of Results: Summary

The final step in the diversity computation algorithm must be a very thorough and careful interpretation of the resulting similarities [16]. It is very important to keep in mind that the result is based only on the information that was included in the descriptor set. No interpretation is possible beyond this base.

For example, it is not possible to identify similarity or diversity of bioavailability – that depends on lipophilicity – if no lipophilicity descriptor was included in the dataset. As already mentioned, it is most important to use the appropriate descriptors for every inquiry and to know the limits of the descriptors when interpreting the results. Every diversity classification describes diversity of descriptor values – not diversity of molecules. Classification and selection algorithms can be applied as black boxes. In contrast, every scientist who uses diversity or similarity computation software must have a comprehensive knowledge about the properties of applied descriptor sets.

7.3 Descriptors

Most important for a successful diversity description of a combinatorial library is the appropriate choice of the descriptor set. Thus far, a large number of different descriptor sets are published or implemented in software packages sold commercially or available in the public domain. Every descriptor set is able to represent certain properties of molecules. An overview is shown in Table 5. Some descriptor values can be calculated quickly (e.g., tens of thousands per second), while others require enormous amounts of computer time (minutes or hours!) for every single structure [17, 18].

For some problems, simple and easily computable descriptors are sufficient. Increasingly complicated descriptors might be necessary to describe a library appropriately. The level of

accuracy and the total effort in computation time needed depends on the size of the library and on the information that is to be included in the descriptor set.

1. Simple descriptors are knockout filters that are used to remove obviously unwanted compounds from a library. Most of these filters can be calculated very quickly and are therefore the first method used for downsizing a library.
2. Filter functions are combinations of the simple filters or are already derived from a small descriptor set.
3. Descriptors from topology include more or less simple representations of two-dimensional structural patterns of the molecules. The presence or absence of functional groups, atom types or scaffolds are described. Recurrent patterns are identified.
4. Pharmacophore descriptors include possible interaction sites between drug molecules and targets. Pharmacophores are defined from two- or three-dimensional molecular structures.
5. If available, any additional information on structure–activity relationships can be utilized as a descriptor.

Table 5. Types of descriptors for assessment of diversity.

Structural information required	Descriptor	Represented property	Computation time per structure
1D	Simple filter	Simple molecular properties (e.g., molecular weight, molecular volume, element composition, etc.)	10^{-3} to 1 s
2D	Complex filter	Molecular properties that are more complicated to compute (basicity, acidity, drug-likeness, etc.)	0.1 to 10 s
	Fingerprints	Atom types and substructures in a binary representation	0.1 to 1 s
	Physico-chemical properties	Lipophilicity, $p\mathrm{K}_A$-values	0.1 to 1 s
	Substructure descriptors	Patterns of substructures (functional groups, atom types, chains, ring systems, etc.)	0.1 to 10 s
	Topological indices	Topology, branching, general shape	0.1 to 10 s
	Autocorrelation coefficients	General shape, distribution of atomic properties	1 to 100 s
3D	Quantum chemical descriptors	Charge distribution in the molecules, molecular interaction fields	10 to 10^2 s
	Feature – feature distances	Representation of certain pharmacophore patterns	1 to 10^2 s
	Three-dimensional pharmacophore patterns	Target interaction sites (hydrogen bonds, electrostatic or lipophilic interactions, etc.). Similarities between different chemical classes and scaffolds can be recognized.	10 to 10^2 s
	Structure – activity relationship-patterns	Pharmacological activity	10 to 10^2 s
	Autocorrelation coefficients	Similarity of shape and similarity of possible interaction sites. Similarities between different chemical classes.	10^2 to 10^3 s
	Virtual screening	Pharmacological activity	10^2 to 10^3 s

6. Descriptors based on the three-dimensional structure of molecules are applied when sets of structurally diverse compounds must be compared. The time needed for the calculations may exceed several minutes or even hours.
7. If the three-dimensional structure of the biological target (an enzyme or receptor that is to be affected by the hypothetical drug molecule) is known, it might be informative to test every structure of the library for a steric fit to this target. Such calculations take at least a few minutes for each structure and are therefore only feasible for relatively small virtual libraries.

a)

```
00001000 00100000 00000000 00100000 00100000 00000000 00000000 00000000 00000010 00001000
00000100 00000000 00000010 00000000 10000000 01001000 00000000 00000000 00000000 00010000
00000000 00000000 00100110 10000000 01000100 00001010 00000000 10100000 00000100 01010000
00000000 10000100 10001101 00010000 10000000 01000000 00000001 00010100 00000000 10000000
00000011 00000000 00000000 00100000 10000000 00000000 10000000 00000000 00000000 01100100
00011100 00000000 00000000 00100010 00000000 00000000 10001000 10000000 00010000 01000000
00000000 00000000 00000000 00000001 00000000 00000000 00001000 00000000 00000000 00100000
00100000 00100000 10100000 00000000 00000000 00000001 00000000 00100000 00000000 11001000
00000100 00010100 01010001 00100000 10000000 10000110 00000011 01000000 00100000 00100000
00000010 00000000 00000100 10100101 00000000 00010010 00010000 00001000 00000010 00000001
00001000 00000000 00000000 00000000 01000001 00010000 01000100 00001000 00001000 00000000
01000000 00100000 00000000 00000100 01010000 00101111 11000000 10000000 00011000 00000000
11000111 00000001 10000001 10000000
```

b)

```
0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 7 1 4 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 5
1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0
0 0 0 0 0 0 0 0 1 0 0 0 0 0 2 0 0 0 0 0 0 0 0 5 0 0 0 0 0
```

c)

```
0.558331  0.282134 -0.0212569 -0.273807 -0.326727 -0.276843 -0.206716   -0.0772396 0.0100203
0.043421  0.038305  0.0191716  0.006473  0.001468  0.000125  1.0268e-06  0          0
0         0
```

Listing 1. Examples for descriptor sets of the drug molecule diclofenac. **a)** Molecular fingerprints [19]. **b)** Substructure descriptors [20]. **c)** Autocorrelation coefficients, based on the three-dimensional interaction potential of the molecule [21].

7.3.1 Simple Filters

The most simple filters are calculated directly from the molecular formula, from the element composition, or from an extended description of the atom types of a molecule. Extended atom types are notations of atoms that include more information than just the element name (e.g., level of hybridization, membership in a certain functional group, etc.). Many molecular properties are usable as filter descriptors [22–25].

1. The *molecular weight* can be calculated very quickly and used to restrict the range of molecular size in the library.

2. The *element composition* of a molecule is also easily derived from the molecular formula.
3. Simple *substructure searches* enable us to remove molecules containing unwanted functional groups or structural patterns. Unwanted molecules may contain reactive groups, unstable groups or functional groups that might cause problems in the synthesis of the final library.

7.3.2 Physico-chemical Constants

Estimated physico-chemical constants are also used as filters to remove unwanted compounds from a library. Suitable limits can be found by statistical analyses of a large number of on-market drug molecules [30, 31].

Although the estimation of the constants might be inaccurate, they are very effective tools for downsizing a library.

7.3.2.1 Estimation of log*P* Values

The hydrophobicity or lipophilicity of compounds is described as estimated 1-octanol/water partition coefficient (log*P*) [11, 14]. Lipophilicity is a very important property of a drug compound, because to penetrate a cell membrane passively the drug's log*P*-value must be within a narrow range.

Most frequently, the log*P* values are calculated based on extended atom types or on fragmental codes [11, 26–29]. A lipophilicity parameter is assigned to every atom type or fragment. The parameters are optimized based on a statistical analysis of experimental log*P* data. The parameter table consists of more than 100 different fragments or types. The increments for all included atoms or fragments are used to calculate the log*P* for a molecule.

Different computer programs use different parameter tables, and thus differ in their results. Nevertheless, most of the existing software packages for log*P* calculation arrive at satisfactory results.

7.3.2.2 Estimation of pK_A Values

Basicity or acidity are estimated by using topology-based increment systems. No software package is available so far that is able to predict basicity precisely for arbitrary structures. Basicity is a very important drug property, and therefore also a very rough estimation of pK_A values is useful in describing a library.

Because of the charge distribution, especially pK_A predictions of mesomeric and heterocyclic structures are difficult and often incorrect. Unfortunately, most drug-like molecules contain these structural elements.

Current computer programs use huge databases of experimental data to obtain more reliable results.

7.3.3 Drug-Likeness

Combinatorial libraries are one of the starting points of the drug development process that comprises a number of phases and lasts many years in total.

After synthesis, the compounds are screened in vitro against biological targets. This results in a certain number of so-called "hits" for each target. Lead structures are selected from the hits and optimized to only a few drug candidates. These will go into the clinical phases of drug development. In every phase of this process a compound or lead structure can drop out for a variety of reasons.

Because of the very high cost of the entire process, it is desirable to identify compounds that will fail to become a drug as soon as possible. Analyses of candidates cancelled in clinical studies show that many of them do not even pass the very basic filters. Millions of dollars can be saved if these molecules are eliminated earlier. At best, the non drug-like compounds are already removed from the virtual library before the start of synthesis [32].

Unfortunately, it is impossible to predict the basic parameters, such as log$P$ or pK_A with high precision. In addition, a universally valid definition of drug-likeness is not yet known, and thus preliminary methods must be used.

Several methods of drug-likeness prediction are published, based on different descriptor sets (physico-chemical constants [33], fingerprints [34], substructure descriptors [35, 36], and drug-like fragments [37]).

7.3.3.1 The Rule of 5

Lipinski et al. used the USAN (United States Adopted Name) and the INN (International Non-proprietary Name) lists to derive a database of compounds that entered phase II studies [33] and therefore should not show major solubility or permeability problems.

They then analyzed this database for the four simple filters of molecular weight (MW), Clog$P$, number of hydrogen bond acceptors, and number of hydrogen bond donors. They found that only 11 % of the compounds has a MW >500, about 10 % have a Clog$P$ >5, only 8 % have more than five hydrogen bond donors, and about 12 % have more than 10 hydrogen bond acceptors. Less than 10 % of the compounds have two of the parameters outside the desirable ranges (see Table 6).

The 'rule of 5' states that poor absorption or permeation are more likely when two or more of these parameters are out of range. Exceptions are compounds that are substrates for biological transporters. A compound for which all parameters are within the ranges shows simi-

Table 6. "Rule of 5". Problems with poor intestinal absorption or solubility become more likely if two or more of the given parameters are out of range.

Rule	Limit
Molecular weight	MW ≤ 500
Lipophilicity	Clog$P$ ≤ 5
Number of hydrogen bond donors	$n^{hbD} \leq 5$
Number of hydrogen bond acceptors	$n^{hbA} \leq 10$

lar physico-chemical properties as typical drug molecules and is therefore drug-like (in terms of the physico-chemical properties considered).

With this rule it is not possible to discriminate between compounds that are bioavailable and compounds that are not bioavailable. However, the filters allow us to select the more drug-like compounds from a virtual combinatorial library.

7.3.3.2 Artificial Neural Networks

A more sophisticated procedure is based on a larger number of simple descriptors such as atom types, topology, physico-chemical constants, or typical patterns of substructures. This descriptor set is used as input for an artificial neural network (ANN) that analyzes the descriptors by means of pattern recognition to select the compounds that are drug-like or not drug-like. The ANN is trained with a huge number of on-market drugs as well as typical non-drugs, and thus learns to recognize typical differences in the descriptor sets of drugs and non-drugs [34, 35].

The neural network outputs a drug-likeness score for every compound (e.g., between 0 and 1; Fig. 6). The actual limit for a drug-like molecule must be found by experience, or may depend on the total number of chemical structures that are to be removed or selected from the library.

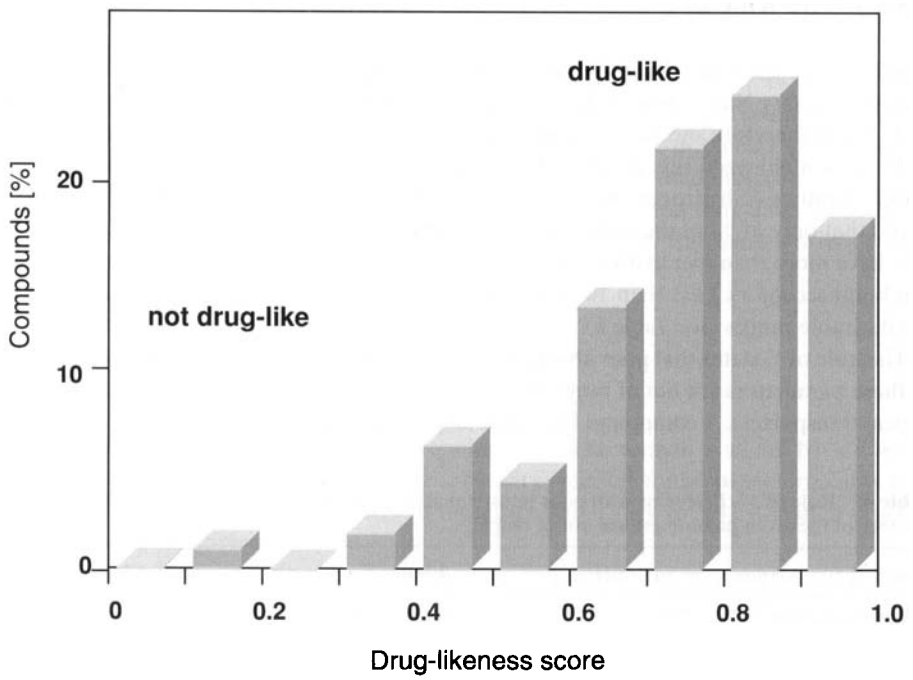


Figure 6. Drug-likeness profiling of a combinatorial library. High scores denote high drug-likeness.

7.3.3.3 Further Improvements of Drug-Likeness Prediction

Both methods presented are based on statistical analyses of a large set of several thousands of proven drug molecules. Therefore, both methods are only able to identify probable drugs by identifying their similarity to drug molecules already in existence. Unfortunately, most of these were developed many years ago, which is why current trends in drug development are missed. Shifts in the composition of drugs, such as use of other structural patterns or functional groups, are not considered. On the other hand, using newly developed drugs exclusively would restrict the size of the dataset for training.

Some characteristics, such as the increase of the mean molecular weight of new drug candidates, can be included easily by relaxing the ranges for these properties. (However, in so doing, the computational chemist abandons the solid statistical base!)

7.3.4 Molecular Fingerprints

Descriptors, expressing atom types, and the presence or absence of certain substructures are not only usable for filtering, but also for measuring similarity. To obtain the descriptor set each compound of the virtual library is analyzed and the presence of every fragment is noted [38].

Molecular fingerprints (FP) store the presence or absence of molecular fragments in a binary format. Because of the large number of fragments that are necessary to describe all molecules, the number of bits in the FP is very high (see Listing 1).

The length of the FP can be reduced by folding the bits of the FP into a smaller bit string (e.g., from a length of 1000 to a length of 100). A single bit of this FP can represent several fragments. Although there is some loss of information, these compressed fingerprints (hashed fingerprints) are still usable, because similar molecular structures gives similar fingerprints [15, 39].

The FP originate from molecular structure database software where they are used to speed up substructure searches. For this reason, routines to calculate FP are implemented in many commercial software packages and play an historically important role as a first attempt to describe diversity. Even though their applicability as descriptors is limited, the use of FP in library design is still widespread (see Section 7.7 for examples and comparison with other descriptors). In particular, similarity searches in huge databases can be performed very quickly using FPs.

7.3.5 Substructure Descriptors

More information about a molecular structure is held in the descriptor if the exact number of occurrences of all represented substructures is stored. The resulting array of numbers (the substructure descriptor, SSD) is a far better description of the corresponding structure as the FP.

The entire descriptor set typically consists of several hundred atom type and substructure fragment descriptors. The total number of fragments determines the length of the SSD.

The SSDs include different kinds of fragment descriptors:

1. **Simple atom types:** *"aromatic carbon", "carbon sp3 hybridized" or "any oxygen"*, etc. Between 10 and 20 atom types are used.
2. **Extended atom types** contain information about the element and the neighborhood of the atom. Examples are *"carbon in a methyl-group", "carbon bonded to oxygen"*, etc. The neighborhood can include atoms at a distance of one, two, or more chemical bonds. Depending on the distance analyzed, the number of extended atom type descriptors is between 100 and 200.
3. **Substructure patterns** include core fragments such as *"cyclohexane-ring", "saturated chains of different length", or "heterocyclic ring systems"*, as well as *functional groups"*. Several hundred patterns of this kind can be found in drug molecules and should be taken into consideration.

Substructure descriptors describe the two-dimensional structural formulas and are therefore very valuable formal representations of chemical structures. About 0.1 to 1 s is needed to compute a SSD for one compound. They can thus be applied to huge virtual libraries.

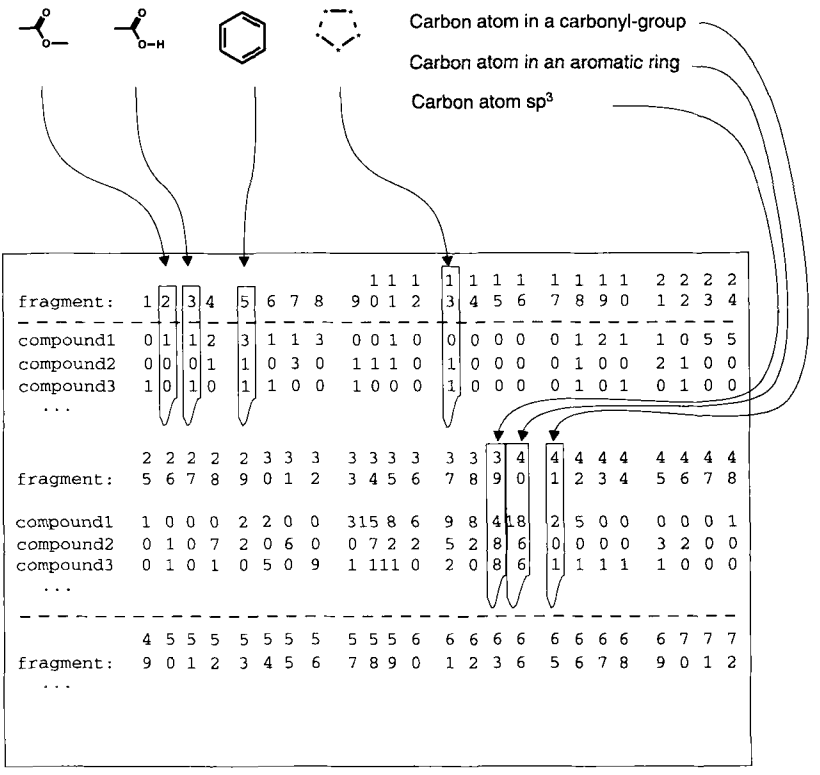


Figure 7. Definition of substructure descriptors. The number of occurrences of all defined substructures in a molecule is stored in a high-dimensional vector (several hundred substructures are needed).

7.3.6 Single Atom Properties

Sets of atom properties, such as point charges, atomic lipophilicity parameters or any other atom properties, can be used to describe properties of molecules. However, the use of such single atom properties as descriptors requires an atom-to-atom mapping of all atoms considered of all compounds of the dataset. This is not possible in most cases and therefore, it is necessary to compute more general descriptors from these parameters:

1. Reduce the number of parameters to some *typical atoms* that are common to all structures considered.
2. Summarize the parameters for *common groups* which are present in all structures considered.
3. Summarize the parameters for the compounds (e.g., calculate log*P-values* or *dipole moments*).
4. Calculate *autocorrelation* or crosscorrelation coefficients to work out typical patterns of parameter arrangement in the compounds.

7.3.6.1 Atom Charges

Atom charges of molecules without extended π-electron systems are described very well and quickly by empirical methods [40]. Only milliseconds are needed to compute the charges for one molecule.

For molecules with large mesomeric parts, in which charges can shift over a distance of more than one or two bonds, the quantum-chemical methods have to be used [41, 42]. The computation time of one molecule then ranges from 0.1 s (e.g., semi-empirical method) to several hours (high-precision, ab-initio calculation).

7.3.6.2 Atomic Lipophilicity Parameters

Most of the methods that are used to predict logP-values of molecules depend on fragmental codes or lipophilicity increments based on extended atom types. Obviously, it is possible to assign lipophilicity increments directly to every atom of a structure as an atomic property. The distribution of lipophilic and hydrophilic properties in a molecule can be described this way [43].

7.3.7 Topological Indices

The substructure descriptors compare every structure with a limited set of predefined substructures. To include every important structural element, the number of substructures considered must be very high.

Other topological descriptors do not display this disadvantage, because their definition is more general and it is possible to describe arbitrary structural patterns with the same de-

scriptors. All topological descriptors are calculated based on the connectivity matrix of a molecule. This matrix includes all information about all atom–atom bonds (the so-called topology).

7.3.7.1 Atom Indices

Atom indices describe atoms of a molecule, based on their neighborhood as well as their electronic and physical properties. The notation "topological" clearly indicates that such an index includes information about the molecular structure – and is thus more than a simple atom parameter. Commonly used indices are topological state indices and electrotopological state indices.

The *topological state index* (T_i) of an atom represents the position of the atom in the scaffold of the molecular structure in relation to all other atoms of the molecule (but based on topology, i.e., on the connectivity and not on the three-dimensional structure) [44]. Chemically and topologically equivalent atoms have identical indices.

The *electrotopological state index* (S_i) is an extension of the purely topological index [45]. Electronic properties (i.e., the charge distribution in the molecule) are also considered. Atoms with identical T_i may differ in their S_i. Electrotopological state indices have been used successfully to predict physico-chemical data, such as basicity (pK_A) or lipophilicity ($\log P$), as well as for quantitative structure–activity relationship (QSAR) studies.

The atom indices are typical single atom properties and are thus not suitable for a direct comparison of molecules in general (see Section 7.3.6). Normally they have to be transformed into more general representations (e.g., by calculating autocorrelation or crosscorrelation coefficients), or the molecule topological indices – which, however, include less information – have to be used.

7.3.7.2 Molecule Indices

Molecule indices describe structural features of entire molecules. The *molecular connectivity index* (also called χ-index) encodes total size, branching, unsaturation, heteroatom content and cyclicity in only one descriptor for a given bond path length [46, 47].

The *molecular shape indices* (also called $^1\kappa$, $^2\kappa$, $^3\kappa$-index) represent the overall molecular shape in three values based on counts of one-bond, two-bond, and three-bond fragments [48, 49]. Local topology (e.g., tetrahedral or planar coordination) as well as atom types are considered using parameter tables, including information such as valence radii and connectivity of the atoms.

Molecule indices are able to discriminate between general types of molecular structures. Due to of the small number of values (χ,$^1\kappa$, $^2\kappa$, $^3\kappa$ for different path lengths) the description of the structure is relatively rough, but still important. The molecule indices are therefore normally used together with other descriptors.

7.3.8 Topological Autocorrelation and Crosscorrelation Coefficients

Autocorrelation coefficients are used to transform a pattern of atom properties into a representation that allows comparison of molecules without need of finding the correct atom-by-atom superposition [50, 51]. Any atom property P (atomic charge, lipophilicity parameter, topological or electrotopological index, etc.) can be used as input.

The *autocorrelation coefficient* A^i describes the correlation of any atomic property of atoms pairs *(a,b)* with a distance of *i* bonds *((a,b),d = i)*. The products of the properties of all atom pairs are with the same distance i are summarized and result in one autocorrelation coefficient:

$$A^i = \sum_{(a,b),d=i} P(a) \cdot P(b)$$

A^i -values may be calculated for every distance $i = 0, 1, 2, ..., j$ in a molecule, where j is the maximum distance in the molecule (Fig. 8).

The set of all computed Ai-values is a descriptor with the ability to identify typical patterns of properties in a molecule, e.g., *the distance of two polar functional groups or the distance of lipophilic groups*. Due to the importance of functional groups as interaction sites of drug molecules, the autocorrelation coefficients are very helpful in classifying or describing drugs.

Because the autocorrelation function uses the number of bonds to describe the distance between two atoms in a molecule, autocorrelation coefficients are topological descriptors. In addition to the topology information, however, they include the atom properties considered.

The same procedure is used to compute *crosscorrelation coefficients* C^i which correlate two different properties, e.g., electrostatic and lipophilic single atom parameters. Every C^i-value describes typical distances of regions in a molecule with the two different properties (e.g., *the distance of a polar functional group from a lipophilic center*). Due to the high number of different possible crosscorrelation transformations (depending on the variety of calculated atom properties) the total number of crosscorrelation coefficients is very high.

7.3.9 Descriptors from a Pharmacophore Model

Most important for a probable drug molecule is its capability to interact with a biological target (e.g., an enzyme or receptor). Not all atoms of a molecule are able to build up these interactions. Therefore the substructures of the molecule can be divided into two classes:

1. Groups with target interaction (i.e., hydrogen bond acceptors, hydrogen bond donors, positively charged centers, aromatic rings, hydrophobic centers) are the pharmacophore centers [52].
2. Spacer fragments that are necessary to bring the functional groups into a correct relative orientation.

The pharmacophore is defined as the critical geometric arrangement of molecular fragments required for binding [53] (Fig. 9). Pharmacophore descriptors are derived by analyzing distances between pairs or triples of pharmacophore centers [18, 54–56].

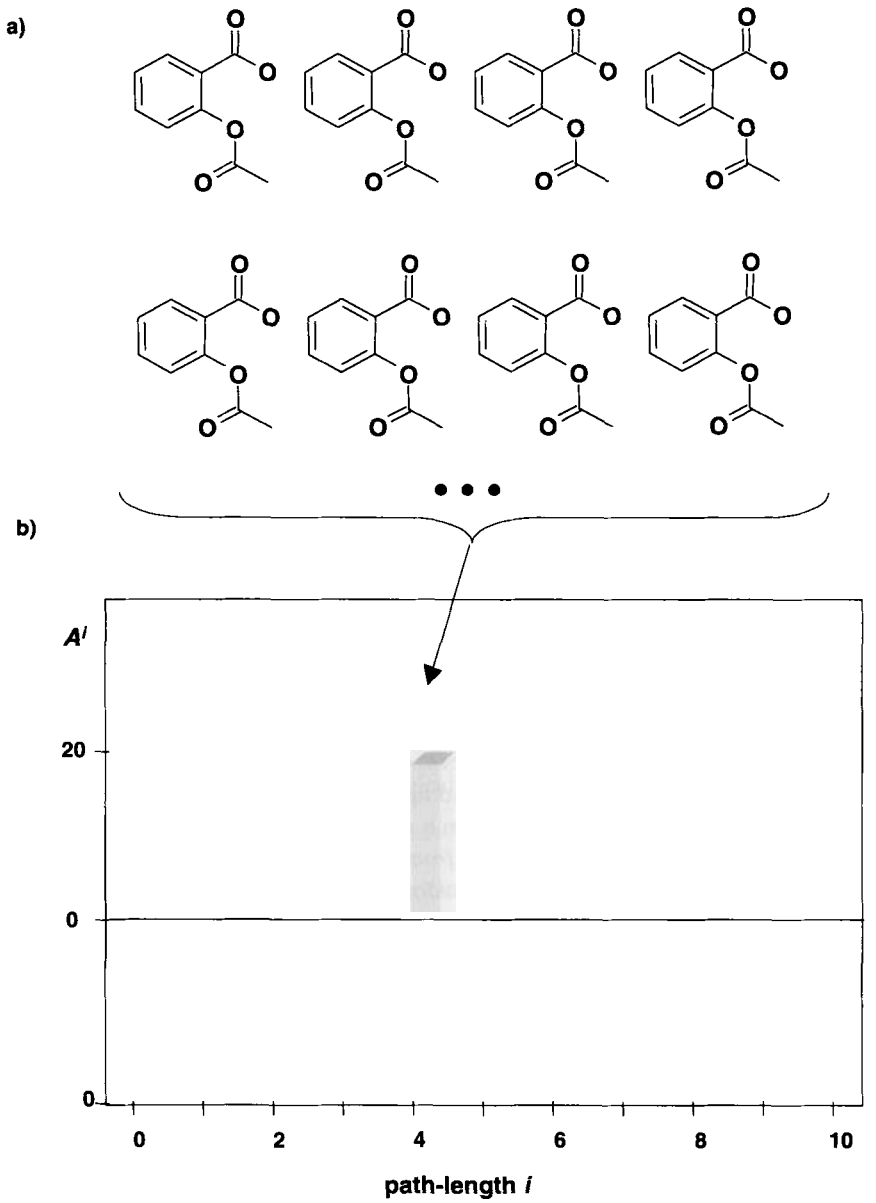


Figure 8. Calculation of topological autocorrelation coefficients as molecular descriptors. **a)** Some examples for a distance of i = 4. **b)** the sum over all possible paths *(i = 4)* gives the A4 value.

Pharmacophore centers (PCs) can be used instead of atoms to describe a molecular structure. PCs derived from a three-dimensional structure include the direction of interaction, and are vectors.

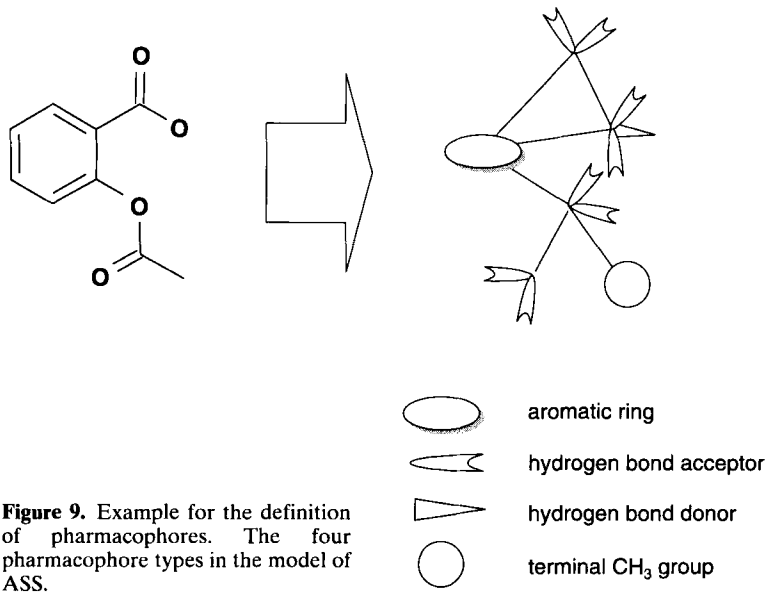


Figure 9. Example for the definition of pharmacophores. The four pharmacophore types in the model of ASS.

To illustrate the relevance of PCs, Fig. 10 shows two ways of superimposing a dihydrofolate and a methotrexate molecule. Both compounds bind to the dihydrofolate reductase enzyme. Dihydrofolate is the natural substrate, methotrexate is a potent inhibitor. Atom-by-atom mapping leads to the first superposition. By looking on pharmacophore centers and the direction of interactions a quite different superposition, in which a part of the molecule is rotated by 180°, is found. Indeed, this is the orientation found by X-ray analyses of the enzyme–ligand complexes [57].

7.3.10 Stereochemistry

Stereochemistry and chirality are very important molecular properties in drug design. The most simple way to consider stereochemistry is by adding an 'R/S'-flag or a '+/–'-flag to the descriptor set. However, this only makes sense for diversity optimization of huge screening libraries where no other methods are applicable. These flags cannot be used to design focused libraries, or to carry out similarity searches.

This is because stereochemistry nomenclature is merely a formal description of the real molecular structure. The correct spatial shape of the pharmacophore is not represented at all. A correct description of stereochemistry is possible with descriptors based on the three-dimensional structure only. Molecules can show the *same* pharmacophore (i.e., same three-dimensional arrangement of pharmacophore centers) but *different* chirality according to chirality nomenclature.

Moreover, stereochemistry in a drug-design sense is not a discrete (R or S) but a continuous variable. Obviously, in some cases chirality has only a small effect on the activity of a

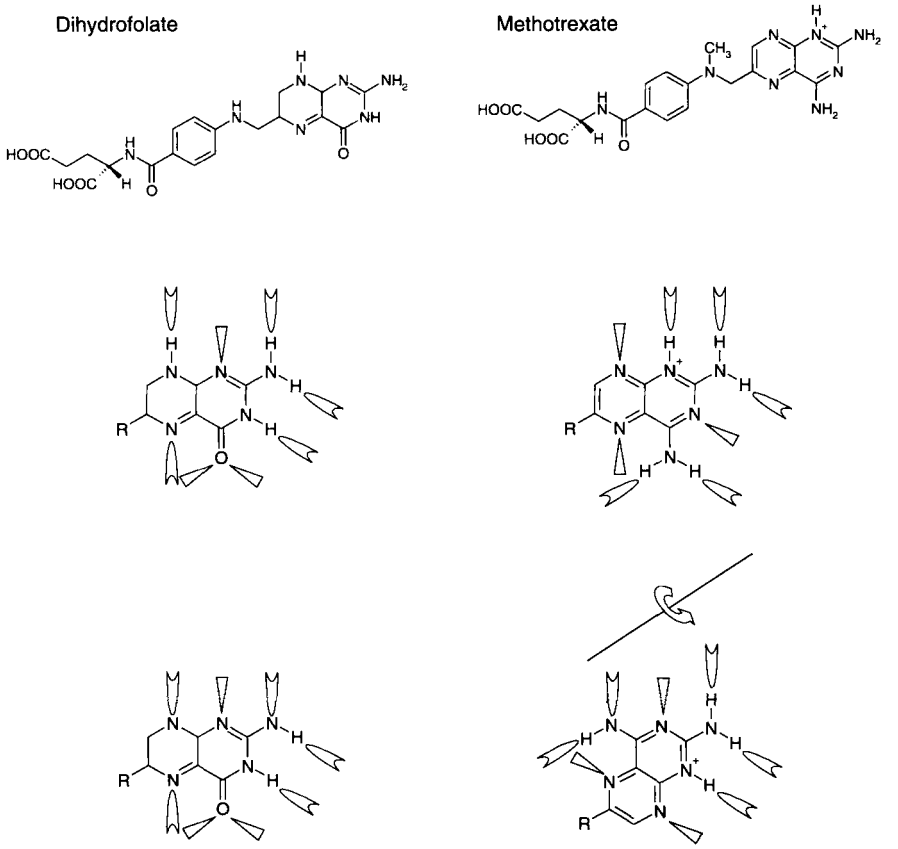
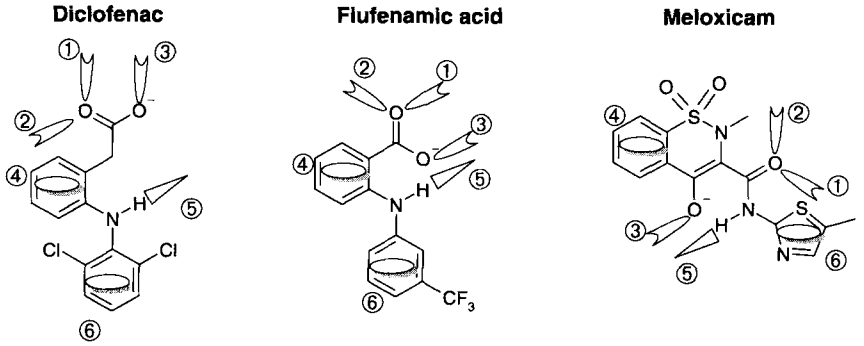


Figure 10. Use of pharmacophore descriptors in order to find the correct superposition of dihydrofolate and methotrexate [57] (see legend of Fig. 9 for the pharmacophore types). **a)** According to the structural formula the molecules are very similar and can be superimposed easily. **b)** However, visualization of hydrogen bonding acceptor and donor sites turns up major differences in the hydrogen bonding pattern. **c)** One-by-one mapping of the pharmacophore vectors leads to a different superposition; the heterocyclic ring system of methotrexate is rotated to reproduce the pharmacophore of dihydrofolate.

compound, in other cases the effect is more important. Therefore, *quantified chirality* can be used as a stereochemical descriptor which is computed by measuring the extent of differences between a chiral molecule and a hypothetical, nonchiral one [58, 59]. Even QSARs have been derived from these descriptors.

7.3.11 Descriptors from the Three-Dimensional Structure

Descriptors derived from the three-dimensional structure of a drug molecule are able to represent properties such as binding affinity or activity. Preliminary calculations are necessary to



Diclofenac

	①	②	③	④	⑤	⑥
①	0					
②	0	0				
③	0.23	0.23	0			
④	0.37	0.37	0.50	0		
⑤	0.29	0.29	0.38	0.28	0	
⑥	0.43	0.43	0.36	0.48	0.28	0

Flufenamic acid

	①	②	③	④	⑤	⑥
①	0					
②	0	0				
③	0.22	0.22	0			
④	0.37	0.37	0.38	0		
⑤	0.27	0.27	0.42	0.28	0	
⑥	0.34	0.34	0.46	0.48	0.28	0

Meloxicam

	①	②	③	④	⑤	⑥
①	0					
②	0	0				
③	0.32	0.32	0			
④	0.58	0.58	0.37	0		
⑤	0.23	0.23	0.34	0.59	0	
⑥	0.26	0.26	0.49	0.80	0.25	0

Figure 11. Distance matrices of drug molecules based on pharmacophore pseudo atom types. Distances are calculated from three-dimensional structures and given in nm. Such matrices can be used to obtain a uniform description of a diverse set of molecular structures (see legend of Fig. 9 for the definition of pharmacophore types).

obtain the three-dimensional structure of the molecule. For molecules with high flexibility, a conformation analysis must be performed to arrive at a set of molecular conformations that are all included into the dataset [60, 61].

Descriptors can be computed from atom coordinates, from the molecular surface [62–64], or from molecular interaction potentials [15, 65, 66].

7.3.12 Distance Matrix

The distance matrix describes the distances between all atoms (or functional groups) of a molecule. It is the three-dimensional counterpart of the molecular topology. A direct comparison of distance matrices is normally not possible because of size and appearance of the matrix depends on the atom numbering in the molecules.

If the matrix is restricted to a subset of atoms, functional groups or pharmacophore centers shared by all molecules considered the matrices can be compared automatically by computer programs [67] (Fig. 11). However, this implies an atom-by-atom superposition of all atoms (or groups, or PCs) that are part of the matrix.

7.3.13 Autocorrelation Coefficients

Autocorrelation descriptors (ACDs) based on spatial data are a preferred way of describing drug molecules. Classification of autocorrelation descriptors arrives at a high level of pharmacophore recovery.

Major advantage of autocorrelation coefficients are:

1. Pharmacophore-like representation of molecular properties such as charge distribution, pattern of hydrogen bonding acceptors or donors, etc.
2. Invariance to rotation and translation of the molecules. Therefore it is not necessary to superimpose structures to be compared.

A major disadvantage is the time required for the computation. The entire algorithm (generation of 3-D structure, conformation analyses, property calculation, property mapping on surface or field and autocorrelation transformation) needs between 100 and 100 000 s for one molecule. With today's computer technology, using multi-processor compute servers and highly vectorized software, it is possible to calculate up to several thousand three-dimensional autocorrelation descriptors within a day (Table 7).

Another important disadvantage is the insufficient representation of stereochemistry: enantiomers show exactly the same autocorrelation descriptor values.

7.3.13.1 Based on Atom Coordinates

The most simple way is using the same single atom properties, as for the topological autocorrelation descriptors. The distance now is not measured as the number of bonds between the two atoms in consideration, but as the real distance between the atoms. The distances are as-

signed to classes (e.g., distance between 0.1 nm and 0.2 nm) in order to get a limited number of descriptors (e.g., 20), and the coefficient is calculated for each class [68].

7.3.13.2 Based on Surface Properties

More time-consuming computations are needed to obtain autocorrelation coefficients based on molecular surface properties [69, 70]. Atom properties (such as charge, lipophilicity, etc.) or interaction potentials (electrostatic interaction, van der Waals interactions, hydrogen bonding donor or acceptor sites, etc.) are mapped to the surface of the molecule. In the next step, autocorrelation coefficients are calculated to represent the patterns of these properties on the surface. The descriptor includes information like: "*two negative regions with a distance of 0.9 nm*" or "*a hydrogen bond acceptor and a lipophilic group with 0.6 nm diameter in 1.8 nm distance*", etc.

7.3.13.3 Based on Potential Fields

Autocorrelation coefficients are also calculated on the basis of three-dimensional molecular interaction fields (e.g., MIP, CoMFA-field or CoMSIA-field). These fields are generated by mapping of atom properties to the spatial neighborhood of the molecule [21]. Distances between grid points located in the space around the molecules are used as input for the autocorrelation algorithm.

Because potential fields describe the pharmacophore of a molecule rather than its topology, they are applicable to sets of molecules with diverse chemical scaffolds.

The invariance to translation and rotation is achieved by integration over all five independent modes of motion (i.e., translational movement in the x, y or z directions and rotation around two independent axes). The autocorrelation coefficient $F(r)$ is calculated from all pairs of points x and y with a distance of r and the properties $f(x)$ or $f(y)$:

$$F(r) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(\bar{x}) \cdot \left[\int_{0^\circ}^{360^\circ} \int_{0^\circ}^{360^\circ} F(\bar{y}) \cdot d\theta \cdot d\varphi \right] \cdot d\bar{x}$$

$$y_1 = x_1 + r \cdot \sin\theta \cdot \cos\varphi$$
$$y_2 = x_2 + r \cdot \sin\theta \cdot \sin\varphi$$
$$y_3 = x_3 + r \cdot \cos\theta$$

7.3.14 Virtual Screening

Virtual screening or "in-silico" screening is used for the design of targeted libraries. All information about the target or known active compounds can be used to remove unfavorable structures from the library [71, 72].

Three-dimensional structural constraints are derived from analyses of structure–activity relationships or from high-throughput screening results. However, the best starting point for a three-dimensional 'in-silico' screening is a *three-dimensional target structure* from X-ray or NMR-analysis. All compounds of the virtual library are screened against this target structure and the results are used as a binary filter or for scoring of the compounds [8, 73].

Table 7. Computation times for autocorrelation descriptors, using the fastest and most precise methods.

Task	Time (s) (simple method)	Time (s) (best method)
Generation of three-dimensional structure	0.1	0.5
Conformation analyses	100	1000
Refinement of geometry	1.0	1000
Calculation of single atom properties	0.1	1000
Mapping of properties to surface or three-dimensional field	0.1	0.5
Autocorrelation transformation	180	600
Total CPU-time	300	∞

7.4 Clustering and Mapping Algorithms

Once the chemical structures are encoded by an appropriate descriptor set, the similarities of descriptors must be calculated. Descriptor similarities are the base for a selection of compounds according to diversity or similarity [74]. Diversity selection techniques fall into four classes:

1. Dissimilarity-based selection.
2. Mapping-based selection.
3. Cluster-based selection.
4. Partition-based selection.

7.4.1 Distance Metric

The most commonly used methods for calculation of descriptor similarities are the Tanimoto coefficient, the Euclidean distance, and the Mahalanobis distance (Fig. 12).

7.4.1.1 Tanimoto Coefficient

Similarity of binary molecular FP is described by calculating simple similarity coefficients [75]. The most often used Tanimoto coefficient $T(a,b)$ is defined as the number of bit positions set in both individual bitstrings normalized by the number of substructures in common:

$$T(a,b) = \frac{N(a,b)}{N(a) + N(b) - (a,b)}$$

$T(a,b)$ represents the similarity between the FP of molecule a and b. $N(a,b)$ denotes the number of common substructures, $N(a)$ denotes the number of substructures which appears in molecule a, and $N(b)$ denotes the number of substructures present in molecule b.

The Tanimoto coefficient is 1.0 for identical FP, and 0.0 if the molecules a and b have no substructure in common. Two molecules are marked as "similar" if the Tanimoto coefficient of their fingerprints is greater than 0.85 [76].

7.4.1.2 Euclidean Distance

To compute Euclidean distances, any descriptor of n components is looked at as a vector in n-dimensional space. The dissimilarity is defined as the distance between the points addressed by the vectors (e.g., descriptors consisting of three values $\bar{a} = (a_1, a_2, a_3)$ for each molecule refer to points in three-dimensional space. The dissimilarity of two vectors $\bar{a}$ and $\bar{b}$ is given by the distance between the two corresponding points in space).

Dissimilarities $S(a,b)$ between two molecules described by high-dimensional descriptors are calculated the same way:

$$S^2(a,b) = \sum_{i=1}^{num} (a_i - b_i)^2$$

a_i denotes the component i of the descriptor of molecule a and *num* the number of components of the descriptor. The distance $S(a,b)$ can be computed for arbitrary descriptors.

7.4.1.3 Nonlinear Distance Scaling

Quality of distance measurements can be improved by nonlinear scaling (Gaussian-type or exponential functions) of the distances $S(a,b)$.

Often, not only the similarity between two molecules is of interest, but also the similarity between one compound and a set of compounds (e.g., all pre-selected structures from a library). This problem can be addressed by summing all scaled $S(a,b)$ values for all interesting molecule pairs [21].

7.4.1.4 Mahalanobis Distance

A more general way to describe the similarity of one molecule and a predefined set is calculation of the so-called Mahalanobis distance [77, 78]. This forms an elliptical similarity region that fits the real shape of a group of molecules in the chemical space much better than the Euclidean distance.

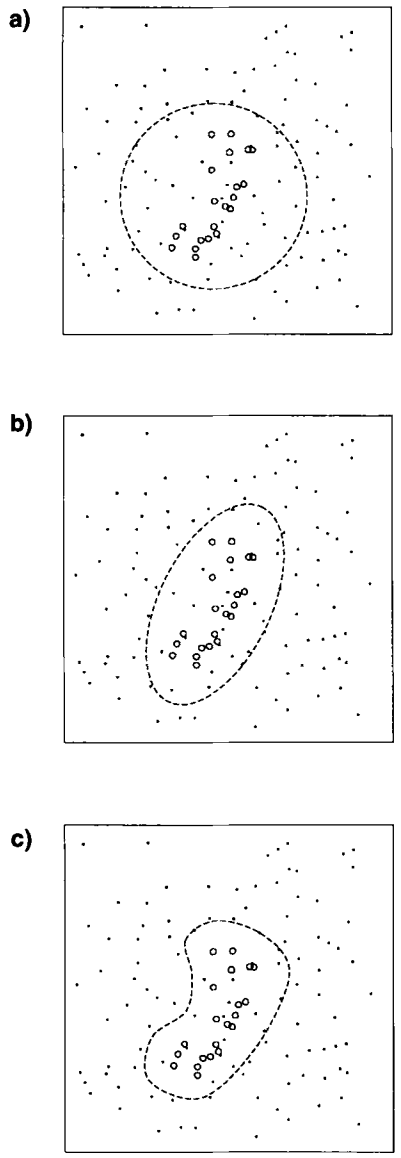


Figure 12. Regions of a two-dimensional descriptor space defined by different similarity computation methods. The small circles show positions of a predefined set of molecules (e.g., cluster of active compounds). Similar compounds are found in the marked regions. The dissimilarities are calculated as: **a)** Euclidean distances to the cluster center; **b)** Mahalanobis distances to each molecule of the predefined set; and **c)** sum of all nonlinearly scaled Euclidean distances.

7.4.2 Dissimilarity-Based Selection

A number of different algorithms have been proposed to select a maximally diverse subset from a set of descriptors. Normally, the diverse subset is generated by selecting an initial molecule at random from the database, and then repeatedly selecting that molecule that is as different as possible from those that have already been selected [79–82].

The method can be improved by removing all compounds from the dataset that are similar to already selected ones in each iteration [83].

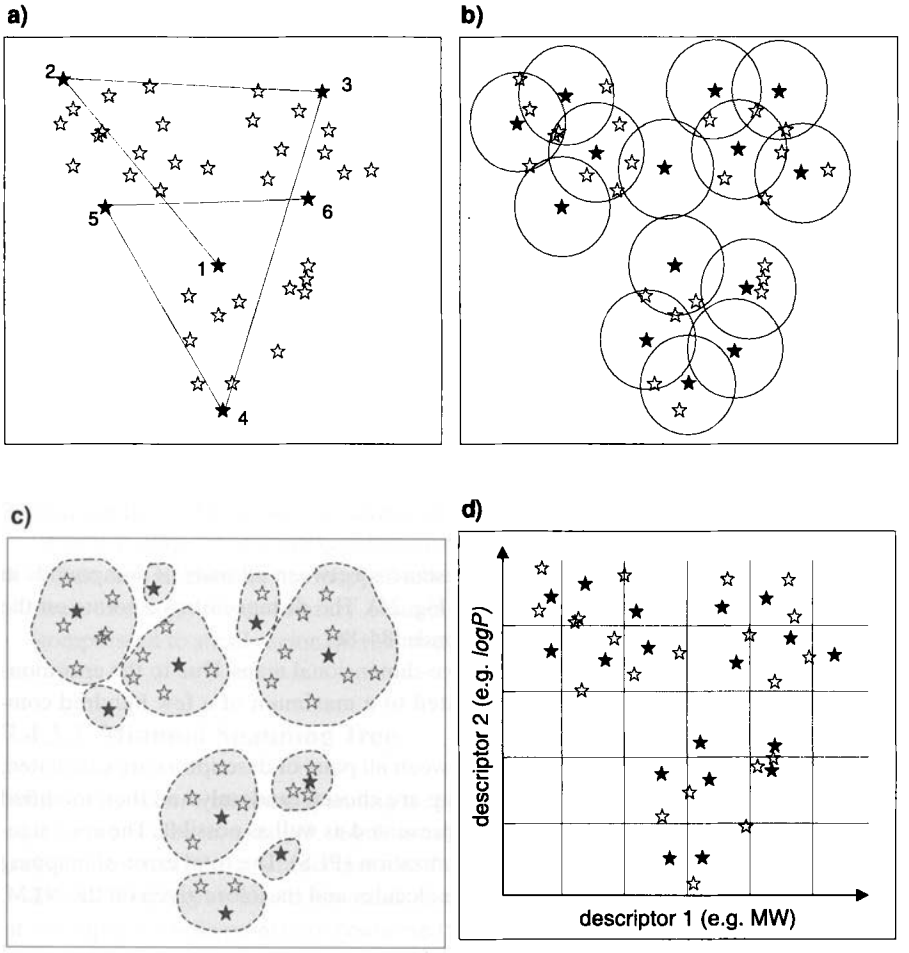


Figure 13. Selection of compounds from a virtual combinatorial library. **a)** First six steps of a maximum dissimilarity selection. **b)** Selection by excluding similar compounds. **c)** Maximum diversity selection as a result of clustering. **d)** Grouping by partitioning of descriptor space.

7.4.3 Mapping-Based Selection

In the mapping method, compounds are arranged on a two-dimensional map in a way that the relative similarity of all pairs of descriptors (i.e., molecules) is displayed as correct as possible. The resulting map is illustrative and helps the chemist in assessing a library. However, all mapping methods suffer from mapping errors that distort the result (Fig 14).

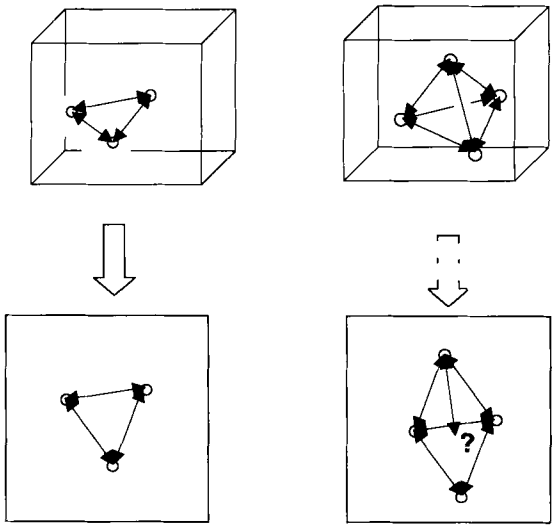


Figure 14. Mapping errors of projections from three dimensions into a two-dimensional map. **a)** Any arrangement of three points can be projected into a two-dimensional map correctly. **b)** In general, arrangements of points in a three- or higher-dimensional space cannot be mapped into a two-dimensional map without mapping errors.

7.4.3.1 Nonlinear Mapping

Nonlinear maps (NLMs) represent all relative distances between all pairs of compounds in descriptor space in a two-dimensional map (see Fig. 24). The distance of two points on the map directly reflects the similarity of the compounds [84–86].

Nonlinear maps are preferably calculated as two-dimensional maps. Due to the enormous demand for computer power, the method is limited to a maximum of a few hundred compounds.

To compute a nonlinear map, the distances between all pairs of descriptors are calculated. The initial positions of the compounds on the map are chosen randomly and then modified in an iterative algorithm until all distances are represented as well as possible. The core algorithm of NLM is a partial least square error minimization (PLS). The total error of mapping must be smaller than the distances between the molecules and therefore given on the NLM, e.g., as sum of error squares, E^2.

7.4.3.2 Self-Organizing Maps

Self-organizing maps (also called SOMs, Kohonen feature maps, or kmaps) are special kinds of artificial neural networks (ANNs) that are able to represent sets of descriptors into a low-dimensional map [87–89], and are increasingly applied for mapping of various molecular data in the fields of analytical chemistry and drug design [70, 90, 91].

The algorithm of an ANN imitates the information processing in the human brain whose capabilities in image processing are undefeated so far. The self-organizing map consists of artificial neurons that are characterized by weight vectors with the same dimensionality as the descriptor set. The artificial neurons are connected by a distance dependent function.

In an unsupervised (so-called cognitive) training algorithm the neurons self-organize until their pairwise neighborhoods represent the correct topology of the original dataset. The training requires a huge number of training cycles (e.g., 10^5 cycles).

In the trained map, every neuron stands for a typical description vector and thus represents the properties of a hypothetical compound. After completion of training, a molecule can be mapped by comparing its description vector with all weight vectors. The neuron with the most similar weight vector is called "the winner", and defines the position of the molecule on the SOM.

SOMs are a very powerful method for dividing up 100 000 structures without problems into a defined number of groups. Even higher numbers are possible; however, the times for training of the maps are very high. Some points must be considered when interpreting a SOM:

1. The SOM is optimized for local topology conservation. Similar compounds are mapped into the same neuron – dissimilar compounds are mapped into distant neurons. However, it is impossible to quantify the dissimilarity as in nonlinear maps (i.e., a double distance on the map does not mean double dissimilarity).
2. A SOM tends to utilize as many neurons as possible for describing the similarities in the descriptor set. Therefore, any library will cover almost the entire map (except if the number of compounds is smaller than the number of neurons).
3. Gaps in the SOM are *undefined regions*, and even small gaps can include huge parts of the chemical space (that is not covered by the mapped library).
4. When several libraries are mapped into one SOM they must compete for the space on the map. The most diverse library occupies most of the neurons. Less diverse libraries are compressed to small region on the map.

7.4.3.3 Minimal Spanning Tree

Formally spoken, a minimal spanning tree (MST) is the shortest way to indirectly interconnect all molecules in a set [92, 93]. It is calculated in the high-dimensional descriptor space and can be visualized as a branched tree (see Fig. 23b).

The MST interprets all n compounds of the library as points in the high-dimensional space of descriptors. These points are connected by $n-1$ edges, so that exactly one path from each point to every other point is generated and the sum of all edge lengths is minimal.

7.4.4 Cluster-Based Selection

Cluster-based approaches try to divide molecules into groups or clusters of similar molecules. During the clustering process the intracluster similarity is maximized and the similarity between the clusters is minimized. From the resulting clusters, sets of compounds can be obtained by selecting one or more representatives from each cluster [60, 94, 95].

7.4.4.1 Hierarchical Clustering Analysis

Clustering methods such as hierarchical clustering analysis (HCA) are able to find clusters of similar molecules in a dataset (see Fig. 23a). The calculation is based on the descriptors, and thus no mapping errors occur [96, 97].

The algorithm is limited to a maximum of about 100 000 compounds, because long computation times and huge amounts of computer memory are needed. The clustering algorithm starts by combining the two most similar compounds to a first cluster. A new descriptor is derived for the cluster. The two compounds are then removed from the dataset and replaced by the newly created cluster. This procedure is repeated until all compounds are merged to one cluster, or until a termination criterion is reached (e.g., minimum number of clusters).

7.4.5 Partition-Based Selection

The simplest and fastest technique for grouping molecules are partitioning methods. Every molecule is represented by a point in a n-dimensional space, the axes of which are defined by the n components of the descriptor vector. The range of values for each component is then subdivided into a set of subranges (or bins). As a result, the entire multidimensional space is partitioned into a number of hypercubes (or cells) of fixed size and every molecule (represented as a point in this space) falls into one of the cells [18, 98–100].

Partition-based selection is much faster then clustering, mapping, or dissimilarity methods because no similarities of pairs of molecules have to be calculated. The computational complexity is only linearly proportional to the number of compounds that need to be processed. For this reason the method can be used for rapid grouping of compounds in huge databases or libraries. The method becomes impractical if the number of dimensions in the descriptor set is too high (about seven dimensions or grouping parameters are the limit).

7.5 Strategies for Compound Selection

The previous section introduced methods to group molecules based on the descriptor set. Strategies for selecting compounds from these groups or clusters depend on properties that are to be optimized. Objectives of compound selection are to:

- maximize overall diversity
- minimize local similarity
- minimize redundancy to existing databases
- maximize similarity to lead compounds
- control the number of building blocks from each educt library
- maximize the hit rate.

In most cases, maximum diversity selection is wanted for high-throughput screening libraries, assuming that the possibility of finding a lead structure is higher if a larger part of the chemical space is screened. However, it is not clear whether the total hit rate of a screening collection can be improved by diversity design. Theoretically, any subset (of the same size)

from a random set of compounds has the same change of containing active compounds. A designed library with optimized diversity will contain more different compounds, but not necessarily more actives [98, 101]. On the other hand, combinatorial libraries are not random selections from the chemical space but normally highly clustered ones. Therefore, an increase in hit rates is possible for such libraries.

Nonetheless, the quality of a screening library will improve if it is expanded by designed libraries that are optimized for small redundancy and high internal diversity. A noticeable increase of hit rates can also be expected if the library design is integrated in the drug design cycle.

Only small numbers of products can be synthesized individually, and are therefore selected individually in terms of maximum diversity. In the design of combinatorial libraries not only the diversity but also the selection of building blocks is to be optimized. This leads to different optimization strategies:

1. Optimization based on the diversity of building blocks.
2. Optimization based on the diversity of product libraries.
3. Optimization of the screening library by selection or rejection of complete libraries (library selection).
4. Optimization based on activities (evolutionary design circle).

7.5.1 Optimization Based on Diversity of Building Blocks

The same algorithms that are applied to virtual libraries can be used to generate optimized educt libraries. Diverse and highly drug-like educt libraries contain generally optimized sets of building blocks that are selected from all available reactants of a certain class [5]. Usage of such designed libraries of building blocks implies some important advantages.

7.5.1.1 Advantages of Educt-Based Optimization

The library can *easily be reused* every time educts of this chemical class are needed. The entire educt library is stored as a database, including structures, descriptors, mapping coordinates, cluster memberships, etc., and availability information such as supplier or price. The chemist can retrieve optimized subsets of different sizes from this database.

Computational methods applied in diversity computations for building blocks can be much more complicated and *more precise*, because the number of processed structures is much smaller. If a combinatorial library utilizes three building block libraries which contain 50, 100 and 200 reactants, the virtual library consists of one million structures. To describe the entire virtual library, one million descriptor vectors are needed. In contrast, the sum of building blocks to be described is just 350.

7.5.2 Optimization Based on Diversity of Product Libraries

Optimization based on diversity of products is the method of choice, although this is computationally expensive (see Section 7.5.1 for the disadvantages of educt-based design). Normal-

ly, library design is not the rate-limiting step in combinatorial synthesis, so that there is no necessity to apply the fastest computational methods.

7.5.2.1 Advantages of Product-Based Optimization

Diverse sets of building blocks do not lead necessarily to an optimized diversity of the resulting library. The *properties of the assembled final molecules are not a simple sum of the fragment properties.* Especially physico-chemical constants (e.g., lipophilicity, basicity, etc.) depend very much on interactions between structural fragments. It has been shown that assessing the diversity of the enumerated library leads to significantly more diverse libraries than from assessing merely the diversity of the reactants [102, 103].

Once the huge virtual library is enumerated and described, it delivers very *valuable knowledge* about the properties of the included compounds and about the accessible chemical space.

The first screening library can be designed in terms of maximum diversity and high drug-likeness (drug-like educts are no guarantee for drug-like products!).

If active compounds are identified in the library by high-throughput screening, *focused libraries* can be easily designed from the same virtual library. In this case the compounds are no longer selected by diversity maximization, but by looking for similarity to the hit compounds.

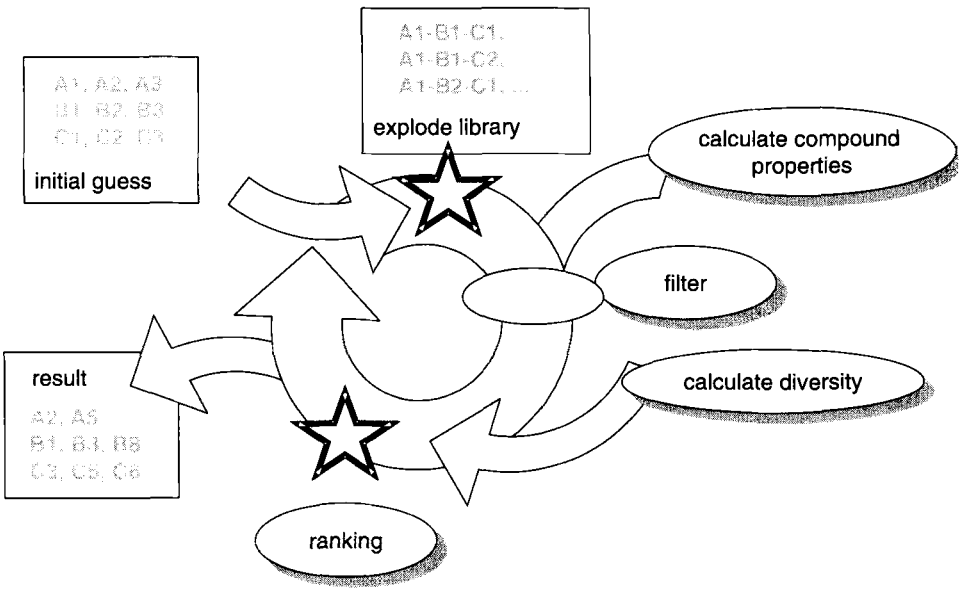


Figure 15. Derived building blocks from a clustered virtual library by an iterative algorithm (e.g., a genetic algorithm). The cycle must be repeated until the final library satisfies the required criteria.

Selection algorithms must be able to select building blocks in a way that an optimized set of products is generated by combinatorial explosion. Genetic or evolutionary algorithms are most commonly used for this optimization step [56, 74, 82, 103].

The algorithm starts with a so-called "initial guess" for the building blocks. This set of educts is then optimized under the competing constraints that are optimized in parallel:

- small educt libraries
- preferred numbers of building blocks from each educt library (e.g., 4, 8, 16, 24, etc.)
- high diversity of products
- high drug-likeness of products
- the educts should be similar in terms of reactivity but diverse in their possibilities to interact with target enzymes or receptors.

The resulting final building block libraries are as small as possible, and nevertheless generate a highly diverse set of products (Fig. 15).

Listing 2 shows parts of the results of an evolutionary library optimization. The software suggests different libraries, characterizes all of them, and lists the needed building blocks. A major advantage of this method is that several proposals for optimized libraries are made. The chemist can decide which library will be synthesized or which demand is most important for this specific library (e.g., high diversity, high hit rate, numbers of building blocks from each educt library, etc.). Libraries designed this way show a significantly higher diversity compared with random libraries (Fig. 16).

```
Library no. 1:
  fitness:                    44.86
  number of molecules:        180
  number of building blocks: 9 1 5 4
  matched molecules:          77 (of 180 [rate = 42.8%])
  matched clusters:           44 (of preferred 47 [rate = 93.6%])
                                 (of populated 104 [rate = 45.2%])
  numbers of building blocks in libs:
  BB library  1: A4 A5 A9 A11 A12 A16 A19 A21 A24
  BB library  2: B1
  BB library  3: C1 C4 C5 C13 C14
  BB library  4: D2 D6 D9 D14

Library no. 2:
  fitness:                    44.84
  number of molecules:        180
  number of building blocks: 9 1 5 4
  matched molecules:          76 (of 180 [rate = 42.2%])
  matched clusters:           44 (of preferred 47 [rate = 93.6%])
                                 (of populated 107 [rate = 43.9%])
  numbers of building blocks in libs:
  BB library  1: A4 A5 A9 A11 A12 A15 A19 A21 A24
  BB library  2: B1
  BB library  3: C1 C4 C5 C13 C14
  BB library  4: D6 D9 D12 D14

Library no. 3:
  fitness:                    44.83
  number of molecules:        192
  number of building blocks: 8 2 6 2
  ...
  ...
```

Listing 2. Result of an evolutionary library optimization. Several different libraries are suggested and characterized. The given information includes total numbers of molecules, numbers and names of building blocks of each BB library, rate of molecules in preferred clusters, rate of preferred clusters populated, etc.

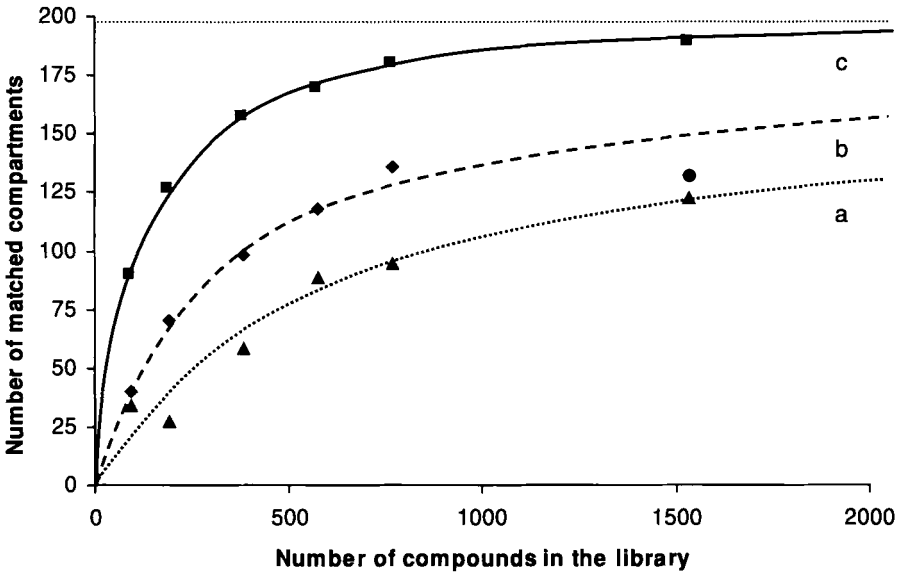


Figure 16. Comparison between random and designed combinatorial libraries of different sizes. **a)** Random choice of building blocks. **b)** Diverse selection of building blocks. **c)** Building block selection based on diversity of the products. A higher number of different matched compartments marks higher diversity of the library. The library set-up for this example is described in more detail in Section 7.7.

7.5.3 Library Selection

Every pharmaceutical company already has access to many thousands, or even millions, of screening compounds. Newly synthesized combinatorial libraries shall fill the significant gaps in chemical space that are not covered by existing compounds. Besides this, the redundancy to existing structures must be minimized.

Virtual libraries can be mapped together with already existing libraries in order to visualize redundancy or complementary properties. From huge libraries, only the new scaffolds are selected. Small libraries are accepted or rejected (Fig. 17).

Self-organizing Kohonen maps are a preferred method for visualization of these redundancies. Product-based library selection is a powerful tool to select fractions of a virtual library in order to complete a homogeneous covering of the chemical space.

7.5.4 Evolutionary Design Circle

All strategies described so far tend to optimize computed compound properties in the descriptor space. Another possibility is to utilize the biological response to guide the selection of compounds in a successive process of synthesis and biological evaluation. In fact, evolutionary algorithms can be applied for controlling the drug discovery cycle. The method is suitable for very large virtual libraries.

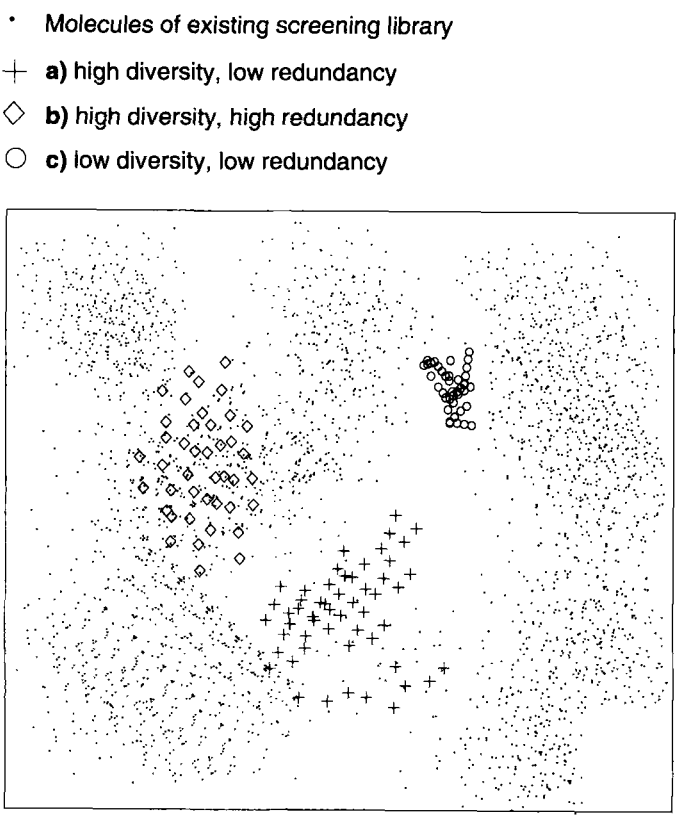


Figure 17. Selection of libraries in terms of completion of a screening library. Diversity and redundancy must be considered.

Only a small number of compounds is chosen for synthesis in the first step randomly. The compounds are then tested in a biochemical or biological assay, and the design algorithm selects a new set of compounds from the virtual library automatically [104, 105].

Obviously this method requires a very close co-operation between design, synthesis and biochemistry groups to achieve a rapid run through the circle. However, several examples are published which demonstrate the power of this strategy (e.g., only 300 compounds from a 64 000 000-hexapeptide library were synthesized in [104]).

7.6 Comparison of Descriptors and Selection Methods

A first and very simple example illustrates the influence of different types of descriptor sets on classification results and similarity measurements. Twenty well-known drug molecules are described by different types of descriptors (topological descriptors and descriptors derived from spatial physico-chemical patterns).

All compounds of the test dataset are nonsteroidal anti-inflammatory drugs (NSAIDs) and are thus relatively similar in terms of their pharmacological properties (Fig. 18). The

compounds are: 1, acetylsalicylic acid; 2, diclofenac; 3, flufenamic acid; 4, flubiprofen; 5, ibuprofen; 6, indometacin; 7, ketoprofen; 8, meclofenamic acid; 9, mefenamic acid; 10, naproxen; 11, piroxicam; 12, sulindac sulfide (active metabolite of sulindac); 13, tenoxicam; 14, meloxicam; 15, cgp 28238; 16, DuP-697; 17, L-745-337; 18, 6-methoxy-2-naphtylacetic acid (active metabolite of nabumeton); 19, NS-389; 20, SC 58125.

All compounds inhibit the enzyme cyclo-oxygenase (COX), but show significant differences in the pharmacological profiles. Most of the compounds are inhibitors of both known

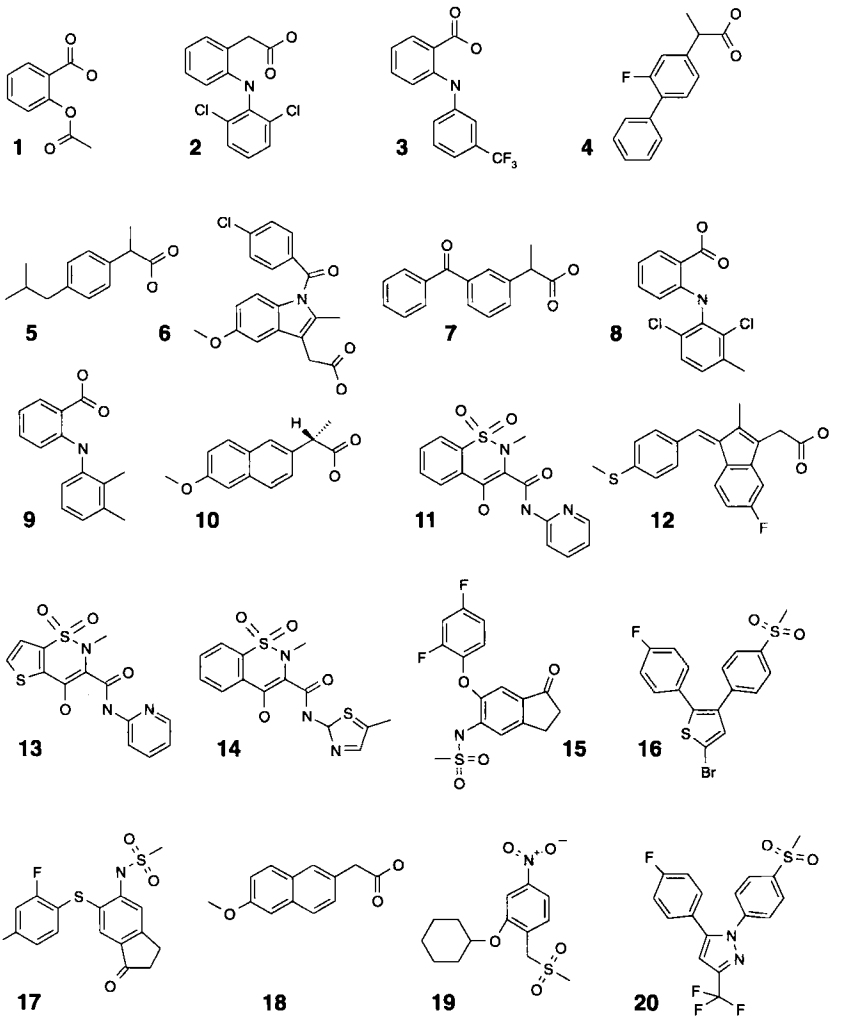


Figure 18. NSAID dataset that is used for evaluation of descriptors and similarity measurements: 1, acetylsalicylic acid; 2, diclofenac; 3, flufenamic acid; 4, flubiprofen; 5, ibuprofen; 6, indometacin; 7, ketoprofen; 8, meclofenamic acid; 9, mefenamic acid; 10, naproxen; 11, piroxicam; 12, sulindac sulfide (active metabolite of sulindac); 13, tenoxicam; 14, meloxicam; 15, cgp 28238; 16, DuP-697; 17, L-745-337; 18, 6-methoxy-2-naphtylacetic acid (active metabolite of nabumeton); 19, NS-389; 20, SC 58125.

COX co-enzymes, though only some drugs show selectivity towards the COX-2 enzyme (i.e., 15, 16, 17, 19, 20).

This small dataset is used to visualize molecular properties such as chemical scaffold, functional groups, pharmacological profile, etc. that are recognized and interpreted by the diversity computation algorithms.

7.6.1 Topological Descriptors

The first descriptor set includes simple topological descriptors and substructure descriptors (312 structural elements). Based on the similarities of these descriptors, the drugs are clustered by means of a self-organizing Kohonen map (Fig. 19). As already explained, similar molecules (respectively similar descriptor sets!) are mapped close to each other on the map.

Obviously, the neural network is able to display molecules with similar structural scaffolds or common patterns of functional groups (Fig. 20). The clustering based on the topological descriptors follows the same (or similar) rules that would be applied by a chemist in order to organize the molecule structures. For this reason, manual clustering would give similar results for this small dataset.

The example shows that the automated clustering works in a similar way as a chemist's intuition, but that it can be applied to huge datasets (e.g., virtual libraries) that contain too many structures for a manual examination to be performed.

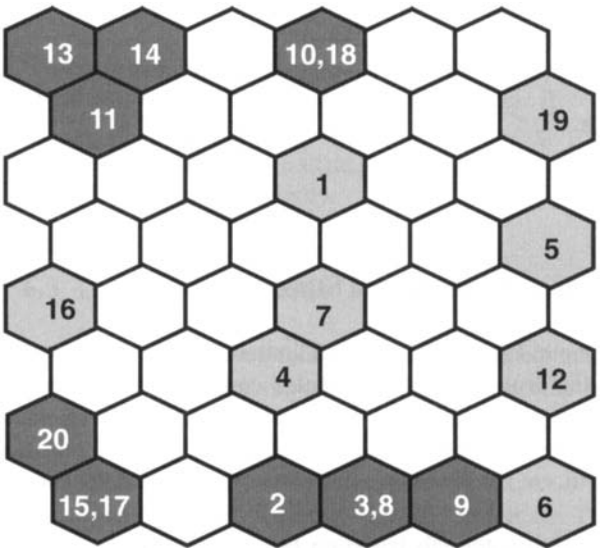


Figure 19. Kohonen map of NSAIDs based on substructure descriptors. White neurons are empty (no compound is mapped to these neurons). Different shades of gray are used to visualize identified classed of compounds.

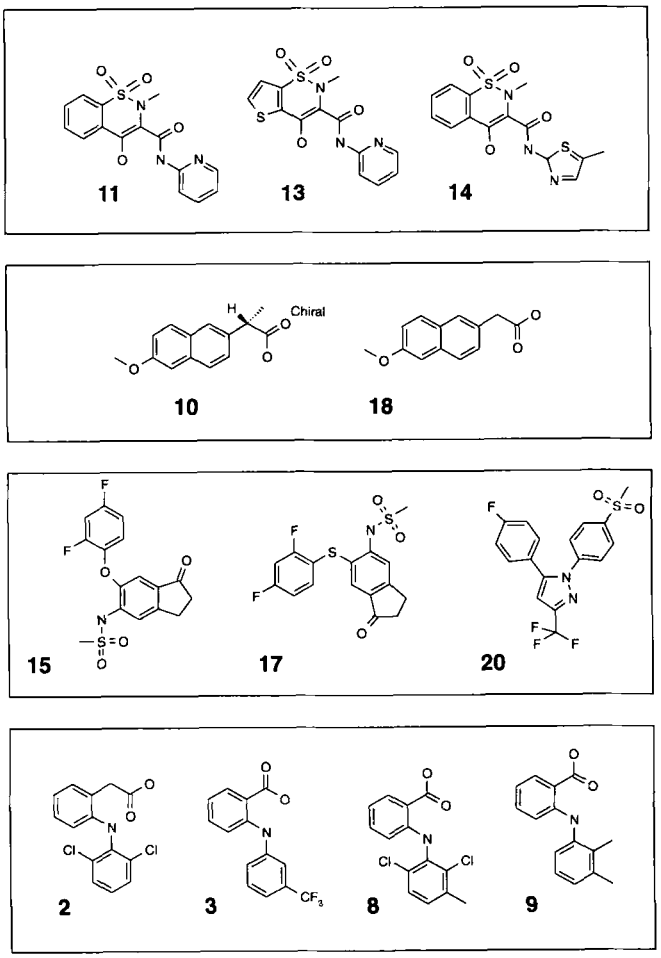


Figure 20. Classes of "similar" structures in the NSAID dataset as displayed in the Kohonen map of Fig. 19.

7.6.2 Descriptors Based on Three-Dimensional Structure

On the other hand, the Kohonen map in Fig. 20 allows only a limited view on similarity because pharmacological profiles of the drugs are not represented correctly. This is because pharmacological properties are not represented by the topological descriptor set. Descriptors based on three-dimensional structures and molecular interaction potentials (hydrogen bonds, lipophilic interactions, steric fit, etc.) are indispensable to describe these properties of molecules.

For this reason, molecular interaction potentials based on three-dimensional structures are calculated for the compounds of the test dataset. The potentials include all possibilities of interaction between the small molecule and the enzymes, as well as the shape of the molecule. Twenty autocorrelation coefficients are derived from these potentials for each molecule

and used as descriptor set. The new descriptors are mapped in the same way as the topological descriptors by means of self-organizing map.

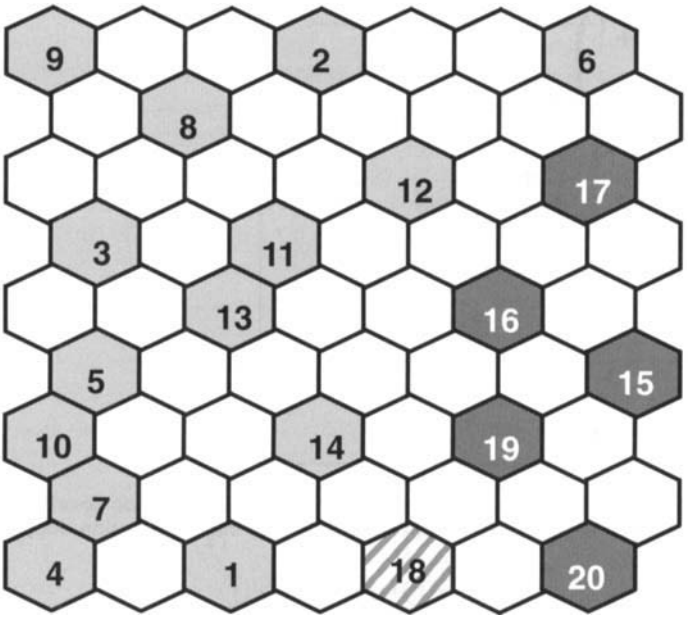


Figure 21. Self-organizing map (SOM) of the NSAID dataset from descriptors based on three-dimensional molecular structure. Dark gray cells contain selective COX-2 inhibitors.

This map (Fig. 21) displays a completely different picture. Now, the molecules are grouped by their pharmacological behavior instead of their structural scaffold. The COX-2-selective drugs (15, 16, 17, 19, 20) are grouped at the same region of the map. Compounds 14 (meloxicam) and 18 (6-mna) show a slight selectivity for COX-2 and are located between the regions of selectivity and nonselectivity.

7.6.3 Clustering Methods

In the third part of the method evaluation with the NSAID dataset, different clustering and mapping algorithms are compared. The Kohonen map calculated from the autocorrelation coefficients (Fig. 21) is used as a reference. The same dataset is processed with nonlinear mapping (NLM), hierarchical clustering (HCA) and with the minimal spanning tree algorithm (MST) as described in Section 7.4.

Figs 22 and 23 show the results of these calculations. The grouping does not depend mainly on the method used. Selective and nonselective COX inhibitors are well separated on the nonlinear map. Hierarchical clustering analyses forms a single branch for the selective group of molecules, and also in the visualization of the minimal spanning tree compounds are lined up in the same way.

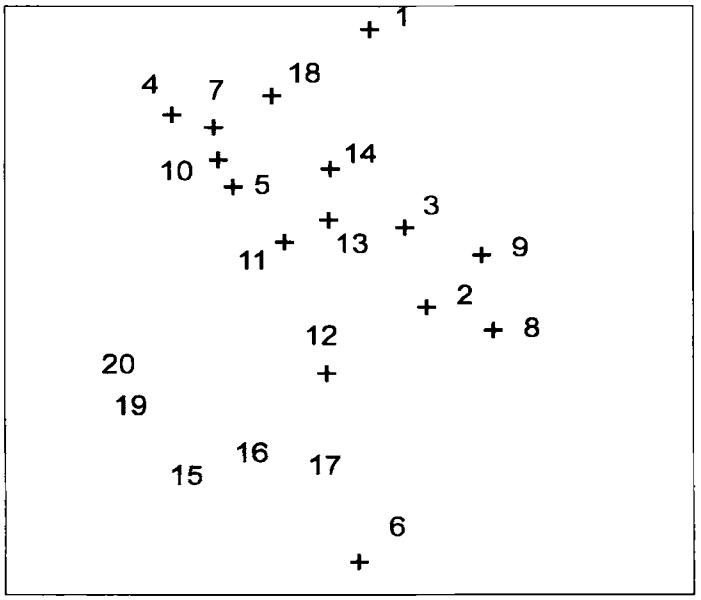


Figure 22. Classification of the NSAID dataset based on three-dimensional autocorrelation descriptors: Nonlinear map. The regions marked indicates classes of compounds. The dark gray region displays COX-2-selective drugs.

7.6.4 Summary

The simple NSAID example shows which decisions and parameters influence the result of similarity or diversity examinations. Most important is the choice of the descriptors set which defines the molecular properties considered. The method used for classification and any further computation has only a small effect on the result.

Topological descriptors can be computed very quickly for a huge number of compounds. These descriptors are able to reproduce the intuitive classification of structural formulas. For this reason, topological descriptors are a good choice to describe diversity of huge virtual libraries in an automated way.

Classification based on three-dimensional molecular structures requires more time-consuming computations, but results in more reliable information. These descriptors are able to identify different pharmacological profiles of compounds and thus provide the chemist with novel information that is often not recognizable from the structural formulas directly.

7.7 Example Library of Thrombin Inhibitors

A recently published combinatorial library of thrombin inhibitors [106] is examined by means of different computational methods in this section. The library is enumerated and

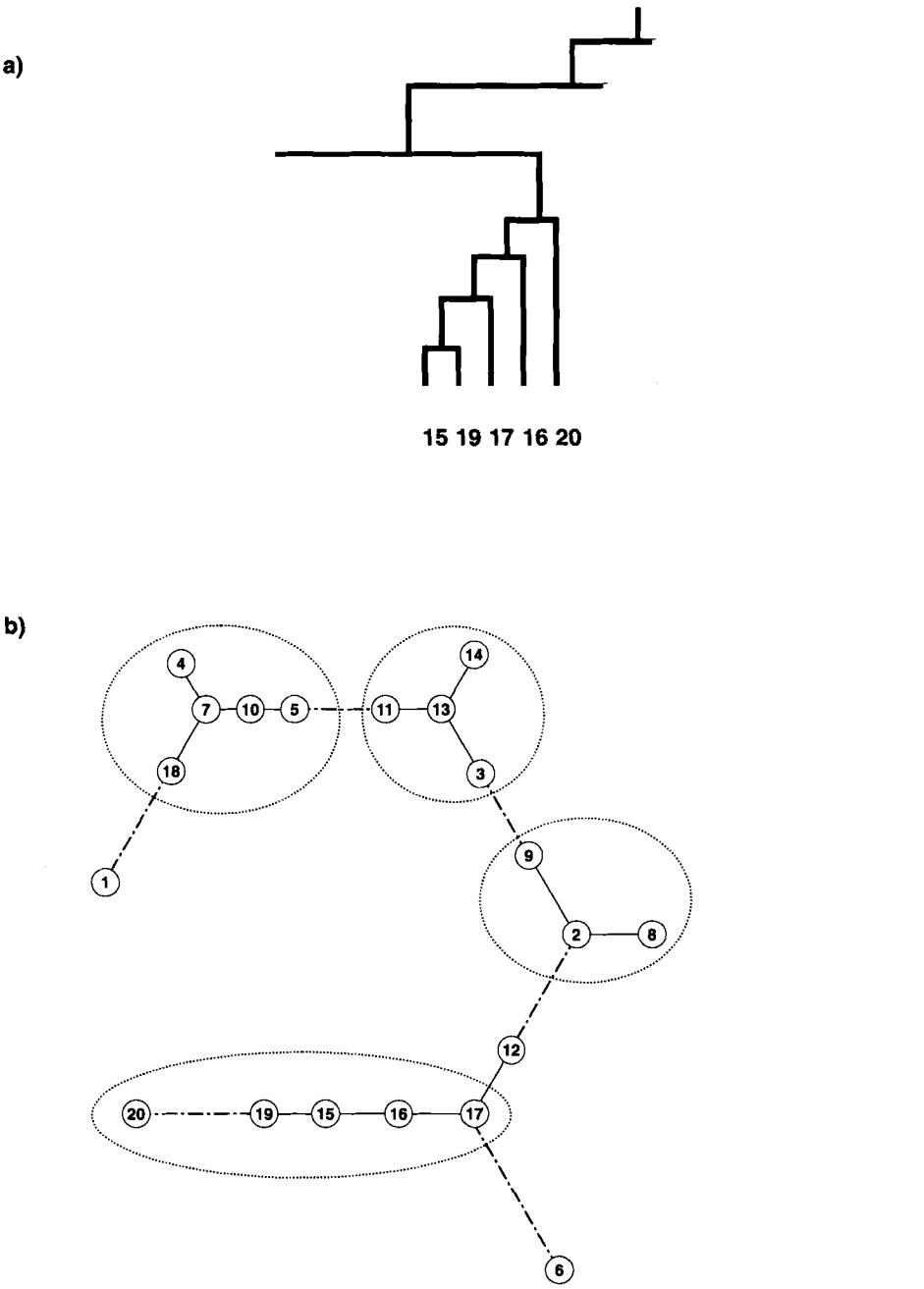


Figure 23. Classification of the NSAID dataset based on three-dimensional autocorrelation descriptors. **a)** Hierarchical clustering analysis (HCA). The dark gray cluster includes the COX-2-selective drugs. **b)** visualization of the minimal spanning tree (MST). The longest connections are drawn as dotted lines in order to derive classes of compounds.

grouped with the help of a self-organizing map. Screening hits are marked on the map and the cells containing hits are identified. "In-silico" screening is used in order to increase the number of screening hits [107, 108] and to generate an HTS-like dataset.

Different descriptor sets are calculated and used for building block selection in order to derive small and diverse sublibraries. As many hits as possible shall be recovered with a minimum number of synthesized compounds.

The design of the libraries is carried out with the product-based building block selection algorithm described in Section 7.5. An evolutionary strategy is used to find optimized sets of building blocks. All results are discussed and validated by comparing them with random selections.

7.7.1 Virtual Library Design

The virtual library consists of three sublibraries: an amide; a sulfonamide; and a urea library. High-throughput parallel synthesis strategies for the sublibraries are given elsewhere [106]. The schematic set-up of the virtual library is shown in Fig. 24. Examples of building blocks are given in Fig. 25.

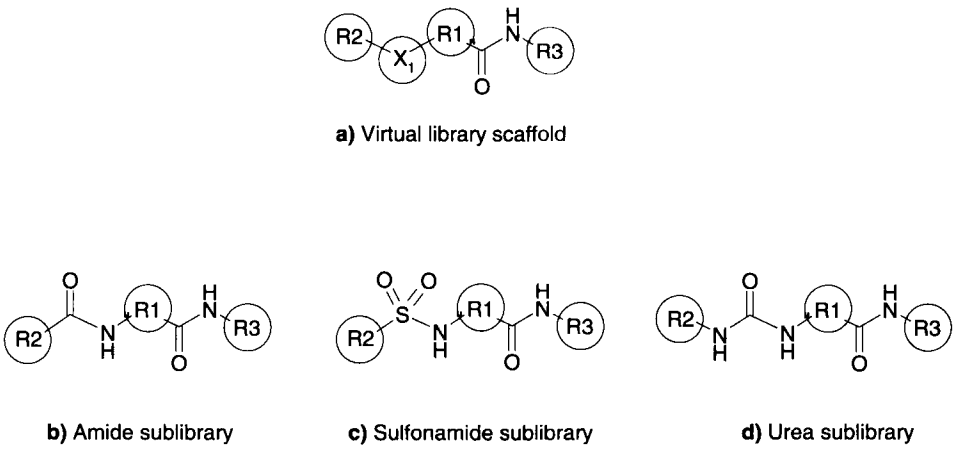


Figure 24. Schematic set-up of the virtual library of thrombin inhibitors, and the three sublibraries.

Three scaffolds (an amide, a sulfonamide, and a urea) are decorated with the same variable residues, *R*. The educt libraries include 26, 15 respectively 14 different reactants which leads (combined with the three scaffolds) to a virtual library that comprises 16 380 compounds in total. In addition, 2779 high-potential thrombin inhibitors are identified (17 %) by screening and virtual screening.

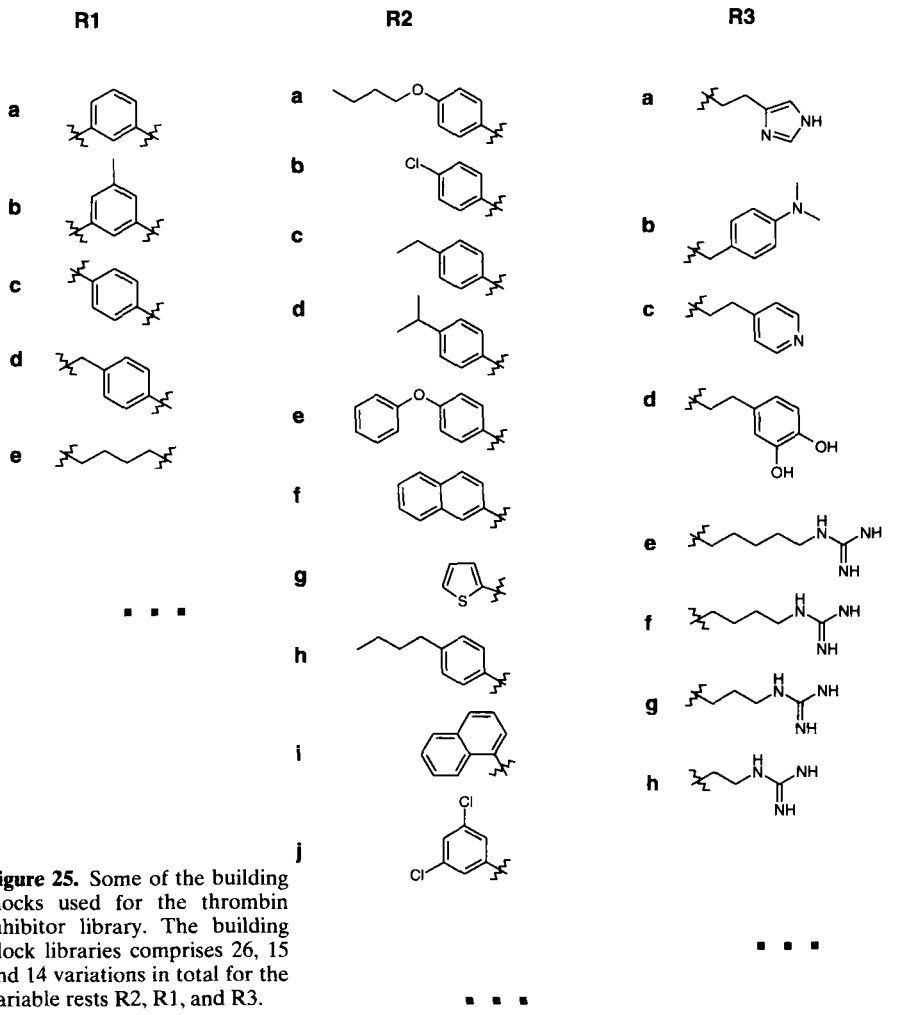


Figure 25. Some of the building blocks used for the thrombin inhibitor library. The building block libraries comprises 26, 15 and 14 variations in total for the variable rests R2, R1, and R3.

7.7.2 Final Library Design

Computer-assisted library design can provide optimized libraries for different applications. In this example, a high overall hit-rate from an unknown library is desirable. A two-step method is used.

7.7.2.1 Maximum Diversity Library

A screening library is designed as a maximally diverse subset of the virtual library in order to explore the entire chemical space and to identify compartments of hits or highly potent scaf-

folds. An increased hit rate is not necessary, and not even expected in this first design step, because the selected set of compounds is evenly distributed in the entire chemical space defined by the virtual library.

7.7.2.2 Targeted Library

The screening results of the first library are used for subsequent design of targeted sublibraries. The purpose of these libraries is a more detailed examination of the regions where the screening hits were found.

Again, product-based building block selection tools are used. Design strategy now is not directed to a highly diverse distribution, but to a high similarity to the screening hits.

7.7.2.3 Descriptor Sets

All calculations of this example study are done with three descriptor sets in parallel:

1. A simple set of 992 fingerprints.
2. A combined set of 312 substructure descriptors, topological autocorrelation coefficients and physico-chemical properties.
3. A set of 15 autocorrelation coefficients, calculated from three-dimensional molecular interaction potentials.

The computation times needed to derive the descriptor values for all 16 380 compounds of the virtual library are given in Table 8.

Table 8. Computation times for calculation of the descriptor sets for the 16 380 compounds of the virtual library.

Descriptors	Number of descriptors	Time
Fingerprints	992	150 s
Substructure descriptors and properties	312	15 h
Autocorrelation coefficients	15	120 h

7.7.3 Comparison of the Libraries

Table 9 gives the hit rates for all example libraries, as well as the numbers of neurons matched by the compounds of the library.

The number of recovered hits in the *screening libraries* varies, and depends on a fortunate selection. Fig 26 shows the coverage of the descriptor space by the three designed libraries. The chemical space defined by fingerprints shows gaps, whereas genes and autocorrelation descriptors define a space that is homogeneously filled by the 768 selected compounds. The average density on the maps is four compounds per compartment.

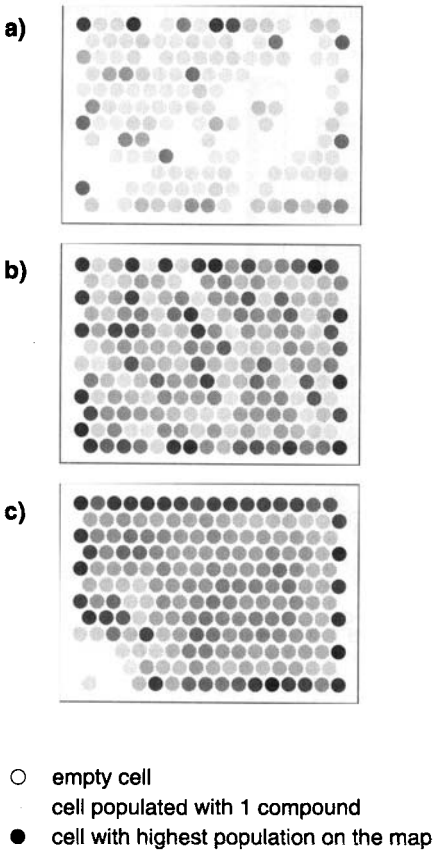


Figure 26. Kohonen maps of the diverse screening libraries. Gray levels indicate the population of a cell. Light gray cells contain only one compound; black cells indicate the highest population for each map (a: 141, b: 12, c: 8). The chemical space on the maps is defined by **a)** fingerprints, **b)** substructure descriptors, and **c)** autocorrelation coefficients (from three-dimensional structure).

Second-generation *targeted libraries* are designed to explore the chemical space near the hits in more detail. This is achieved by selecting compounds from the cells containing hits. The hit rates in the new libraries represent the capabilities of the different descriptor sets.

In case of the fingerprints, the hit rate is only slightly higher compared with the screening library or a random library. This shows that the population of active compounds in the hit neurons is not significantly higher than in any other region of the chemical space defined by the fingerprints. The fingerprint descriptor set therefore describes the structures of the compounds in a way that does not correspond to biological activity.

In contrast, the library designed on the basis of substructure descriptors as well as the autocorrelation-based library show a significant increase of hit rates. These descriptor sets can be used for identification of pharmacophore patterns and are applicable for selection of active compounds from a virtual library.

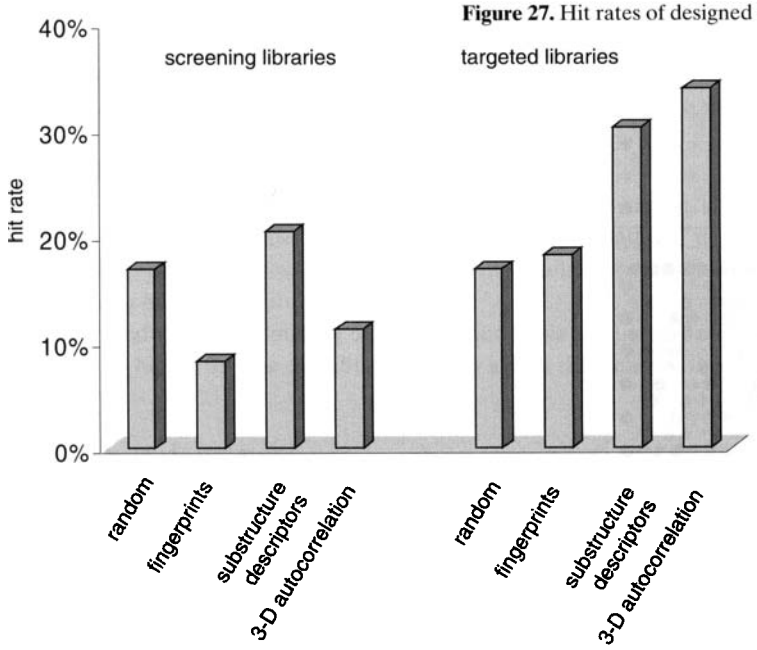


Figure 27. Hit rates of designed and random libraries.

Table 9. Diversity and hit rates of the example libraries.

Library	Number of compounds (of preferred)	Number of matched clusters (of preferred)	Number of hits	Hit rate (%)
Screening libraries:				
Fingerprints	768 (768)	131 (192)	62	8.1
Substructure descriptors	768 (768)	191 (192)	157	20.4
3-D -autocorrelation	768 (768)	185 (192)	86	11.2
Random library	768 (768)	–	130	16.9
Targeted libraries:				
Fingerprints	192 (192)	30 (31)	35	18.2
Substructure descriptors	189 (192)	75 (90)	57	30.2
3-D -autocorrelation	180 (192)	44 (47)	61	33.9
Random library	192 (192)	–	32	16.9

7.7.4 Summary

The examples demonstrate opportunities of computer-assisted optimization in library design. The quality of combinatorial libraries can be improved by computing similarities of vir-

tual compounds or by estimation of activities [7, 109]. However, high diversity and high hit rates are usually not attainable in one library, and must be addressed in different design steps.

The examples also show that the benefit of a theoretical investigation depends on the methods used –the choice of descriptors is especially crucial. Different descriptors must be applied for different design tasks, and all scientists who use computer-assisted library design methods should know the characteristics of basic descriptor sets.

On the other hand, differences in mapping and clustering algorithms have only a minor influence on the result, and may be applied as "black boxes". The results of diversity assessment and similarity computation can provide valuable information about combinatorial libraries at an early stage (even before synthesis). This information helps the chemist to select certain building blocks or libraries.

Last, but not least, the importance of a close co-operation between the computational and the medicinal chemist is to be highlighted. Only the combination of theoretical investigations and experience of medicinal chemists allows goal-directed design of optimized combinatorial libraries.

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8 Organic reactions on solid phase – A survey of the literature from 1970 to 1998

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8.1 Introduction

With the advent of combinatorial chemistry, solid phase organic synthesis (SPOS) is currently enjoying a renaissance, one of the main reasons for which is the (relative) ease with which reactions on solid phase can be performed in a (semi)automated fashion on robotic equipment. Solid phase organic chemistry began in the early 70s when an impressive body of work was carried out, mainly by the groups of Leznoff, Frechet, Rapoport, Camps and Patchornik. These first efforts focused on polymer modification (e.g. reaction of metalated polystyrene/divinylbenzene with various electrophiles, reaction of Merrifield resin with a variety of nucleophiles, monoprotection of bifunctional compounds, etc.). But even at this time quite a few other organic reactions like Wittig reactions, epoxidations, reductions and Diels-Alder reactions were carried out using solid phase chemistry. This early work has been dealt with in several reviews (1-4).

The last few years have witnessed an increasing number of publications in this area. A number of review articles (5-19) and books (20, 21) explicitly dedicated to solid phase organic chemistry have appeared. Regularly updated lists of articles on solid phase organic chemistry are available on the internet (22). Some company catalogs are also valuable sources of information (23-25).

This compilation lists most papers in solid phase organic chemistry published from the 1970s up to December 1998. In line with the objectives of this book only papers which contain enough preparative detail (like stoichiometry, reaction times, temperatures etc.) so that someone "skilled in the art" should be able to repeat the work described have been included. Work reported in patents has not been incorporated. This is also true for reactions using polymer bound reagents or articles on oligomers like peptides, carbohydrates or nucleotides. Very well established reactions from peptide chemistry, like the formation of amide bonds with the aid of coupling agents, have not been included unless they were conducted under non-standard conditions. This also applies to the use of standard N-protecting groups like Boc, Z, Fmoc, as well as their equivalents for the protection of the carboxylic acid group.

Although every reasonable effort was made, it is virtually impossible to cover this area comprehensively, given the enormous amount of data and the fact that particularly the early work from the 70s and 80s is widely scattered throughout the literature. The authors of this survey apologize for any omissions and misrepresentations.

The tables are organized according to reaction types. Notable exceptions are the sections on carbocycle and heterocycle formation. In these sections figures are used for the sake of better readability.

When a published procedure was used with essentially no change generally only the reference for this first publication is given. To specify which of the reactants is linked to the solid phase the prefix "sb" (= "support bound") is used wherever appropriate. If the substrate is released from the support in the course of the reaction, this is indicated by "w.c.s." (="with concomitant cleavage from the support").

Abbreviations

acac	acetylacetonate
ADDP	1,1'-Azodicarbonyl-dipiperidine
AIBN	azoisobutyronitrile
Alk	alkyl
AMEBA	Acid sensitive MEthoxy BenzAldehyde
Ar	aryl
BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
BOBA	*p*-benzyloxybenzylamine
BSA	N,O-bis(trimethylsilyl)-acetamide
BSTFA	N,O-bis(trimethylsilyl)-trifluoracetamide
Bt	benzotriazolyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CDI	carbonyldiimidazole
CPBA	chloroperbenzoic acid
CSA	(+/-)-campher-10-sulfonic acid
CSI	chlorosulfonylisocyanate
DABCO	1,8-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPC	diethyl phosphorocyanidate
DIAD	diisopropyl azodicarboxylate
DIBAH	diisobutylaluminium hydride
DIC	N,N'-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(N,N-dimethylamino)pyridine
DME	dimethoxyethane
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide

DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppb	1,4-bis-(diphenylphosphino)butane
dppf	bis-(diphenylphosphino)ferrocene
DSC	di-(N-succinimidyl)carbonate
DVB	divinylbenzene
EDC	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide
EWG	electron withdrawing group
Fmoc	9H-9-fluorenylmethoxycarbonyl
gen.	generated
HetAr	heteroaryl
HMPT	hexamethyl phosphoric triamide
HOBt	N-hydroxybenzotriazole
IBX	1-hydroxy-1,2-benziodoxol-3(1H)-one
*i*Pr	isopropyl
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MCR	multicomponent reaction
MH	membered heterocycle
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MTDA	methyltrimethylsilyl dimethylketene acetal
Mukaiyama's reagent	2-chloro-1-methyl-pyridinium iodide
NBS	N-bromosuccinimide
2-NBSCl	2-nitrobenzenesulfonyl chloride
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NEM	N-ethylmorpholine
NMM	N-methylmorpholine
NMO	N-methylmorpholine N-oxide
NMP	N-methylpyrrolidinone
PG	prostaglandin
pfbm	perfluorobutyramidate
Pfp	pentafluorophenyl
PhFl	9-phenylfluoren-9-yl
PMB	4-methoxybenzyl
PPTS	pyridinium p-toluenesulfonate
PS	polystyrene
PTC	phase transfer catalysis
PTSA	*p*-toluenesulfonic acid
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy) aluminium hydride
sb	support bound
st. aq. cond.	standard aqueous conditions

st. cond.	standard conditions
Su	succinimidyl
TBAF	tetrabutylammonium fluoride
TBDMS	*t*butyldimethylsilyl
TBDPS	*t*butyldiiphenylsilyl
TCD	thiocarbonyldiimidazole
TCEP	triscarboxyethyl phosphine
TEOF	triethyl orthoformate
TIPS	triisopropylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMAD	N,N,N',N'-tetramethylazodicarboxamide
TMG	tetramethylguanidine
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
Tol	toluyl
TPAP	tetra-*n*propylammonium perruthenate
Trs	2,4,6-trisisopropylbenzenesulfonyl
Trt	trityl
Ts	*p*-toluenesulfonyl
unsat.	unsaturated
w.c.s.	with concomitant cleavage from the support

8.2 Nucleophilic aliphatic substitution reactions

8.2.1 N-alkylation

8.2.1.1 Alkylation of amines (amine + RX)

sb amine	sb 1° amine + TrtCl, DIEA/DCM/DMF	[26]
	+ propargyl bromide, Cs_2CO_3/DMF	[27]
	sb 2° amine + allyl or benzyl bromide, DMF	[28]
	+ allyl bromide, Schwesinger base/dioxane	[29]
	+ benzyl bromide, DBU/DMSO	[30]
	+ benzyl bromide, DIEA/DMF/acetone	[31]
	+ benzyl chloride, NEt_3	[32]
	sb 2° or 3° amine + alkyl halide, DMF	[33]
	sb 3° amine + allyl or benzyl bromide, DMF	[34]
	+ alkyl halide, DMF	[35]
	sb ArNHR + benzyl bromide, DIEA/DMF	[37]
	proton sponge/DMSO	[38]
	sb indole + alkyl halide, NaH/DMF	[39]
	sb tetrahydroisoquinoline + alkyl halide (Br or I), DMF	[40]
	sb xanthine + alkyl halide, NEt_3	[36]
	sb pyridine + bromoacetamide derivative, DMF	[41]
	+ 2-bromoacetone, acetonitrile	[42]
	sb amine + allyl methyl carbonate/$Pd(PPh_3)_4$/toluene or DMF	[43]
sb RX (X=Cl)	sb 1-alkyl-4-chlorouracil + benzylamine, DMF	[36]
	sb α-chloroacetamide + amine, NaI/NMP	[44]
	sb $ArCH_2Cl$ + allylamine, NaH/DMF	[45]
	+ $BuNH_2$, NBu_4Br/NEt_3	[29]
	sb chloroacetate + py/DCM	[46]
Merrifield resin	+ ephedrine, DMF	[47]
	+ amine, DMF	[48]
	+ *n*-propylamine (neat)	[49]
	+ piperazine, dioxane	[50]
	+ 2° amine, NMP	[51]
	+ oxazoline derivative, NaH/THF/DMF	[48]
trityl chloride resin	+ diaminobutane, DCM	[52]
	+ propargylamine, DMF	[53]
Rink chloride resin	+ 1° amine or aniline, DIEA/DCE	[54]
other base resins	chlorinated Wang resin + aniline, proton sponge/NaI/DMF	[55]
	α-OMe-phenyl-Merrifield resin (MAMP) + 2-thiophenemethylamine, NMP	[44]
sb RX (X=Br)	sb allyl bromide + allylglycine derivative, DIEA/KI/NMP	[32]
	+ 1° amine, DMSO	[56]
	sb alkyl bromide + 1° or 2° amine, DMF	[57]
	sb benzyl bromide + *n*-butylamine, DCM	[58]
	+ tyramine, NEt_3/DMF	[59]
	sb α-bromocrotonate + *o*-I-aniline, DIEA/DMF	[37]

	sb α-bromoamide + 1° amine, DMSO	[60–67]
	+ 1-alkyl-4-chlorouracil, NEt_3/DMF	[36]
	+ hydroxylamine · HCl, DIEA/DMF	[68]
	sb α-bromoester + 1° amine, DMSO	[64]
	+ pyridine	[69]
	+ polyamine, DCM	[70]
	sb α-bromoacetal + 1° amine, DMF	[71]
	sb alkyl bromide + 2° amine, DMF	[28]
sb RX (X = I)	sb alkyl iodide + 1-(TMS)-imidazole, AgOTf/DMF	[72]
	sb benzyl iodide + *n*-butylamine, DCM	[58]
sb RX (X = OSO_2R')	PS/DVB-CH_2CH_2OTs + various N-nucleophiles	[73]
	+ pyrrolidine, py	[74]
	sb tosylate + 1° amine, NMP	[75]
	sb mesylate + 1° amine, NMP	[76]
	DCM/MeCN	[77]
	DMF	[78]
	+ *n*-butylamine, DCM	[58]
	+ propargylamine, THF	[79]
	+ 2° amine, DMF	[28]
	sb triflate (gen. in situ from sb α-hydroxyester + $(CF_3SO_2)_2O$/lutidine) + O-benzylhydroxylamine	[80]
sb RX (X = OAc etc.)	sb allyl acetate + amine, $Pd(acac)_2$/dppb	[43]
	sb allyl ester + amine, $Pd(PPh_3)_4$/THF, w.c.s.	[81]
	N-benzyl piperazine from sb benzyl 4-F-benzoate + neat piperazine	[82]
	PS/DVB-CH_2O-*p*-C_6H_4-SO_2OR + 1°, 2° amine or imidazole	[83]
8.2.1.2 Alkylation of amides	1,5-benzodiazepin-2-one + alkyl halide (alkylation at N5), DMF	[84]
	sb quinoxalinone + RCH_2Br, K_2CO_3/acetone	[85]
	sb amide + alkyl halide, LiO*t*Bu	[26]
	, LiO*t*Bu/DMSO	[86]
	sb ArCONHR[1] + 2-butynyl mesylate, LiO*t*Bu/THF/DMSO	[87]
	sb amide + alkyl halide, lithiated acetanilide or N-*t*Bu-benzanilide	[88]
	1,4-benzodiazepine-2,5-dione + alkyl halide, Li-acetanilide	[89, 90]
	sb amide + methyl iodide, NaH/DMSO (permethylation of peptides)	[91]
	sb benzimidazolone + alkyl halide, NaH/DMF	[92]
	sb ArNHCOR + benzyl bromide, lithiated 5-(phenylmethyl)-2-oxazolidinone	[93]
	sb quinazoline-2,4- dione + alkyl halide, lithiated 5-(phenylmethyl)-2-oxazolidinone	[94]
	sb diketopiperazine + alkyl halide, lithiated 5-(phenylmethyl)-2-oxazolidinone	[95]
	1,4-benzodiazepine + alkyl halide, lithiated 5-(phenylmethyl)-2-oxazolidinone	[96–101]
	1,5-benzodiazepin-2-one + alkyl halide (alkylation at N1), lithiated 5-(phenylmethyl)-2-oxazolidinone	[84]
	sb amide + alkyl halide, 4-benzyl-2-oxazolidinone/*n*BuLi	[102]
	sb quinazoline-2,4-diones + alkyl halide, TMG/NMP	[103]
	+ 1° alcohol, PPh_3/DIAD/THF	[103]

8.2.1.3 Alkylation of carbamates	sb carbamate + glycidyl tosylate, LiHDMS/LiI	[104]
8.2.1.4 Alkylation of sulfonamides	sb sulfonamide + benzyl bromide, KO*t*Bu	[105]
	sb $ArSO_2NHR$	
	+ $Br-(CH_2)_2-Br$, K_2CO_3/DMF	[106]
	+ methyl *p*-nitrobenzenesulfonate, MTBD/DMF	[107]
	+ methyl nosylate, MTBD/DMA	[108]
	+ allyl methyl carbonate, Pd_2dba_3/PPh_3	[108]
	sb N-acylsulfonamide	
	+ CH_2N_2, Et_2O	[109, 110]
	+ $BrCH_2CN$ or ICH_2CN, DIEA	[110]
	+ $BrCH_2CN$, DIEA/NMP	[111]
	sb allyl ester + sulfonamide, $Pd(PPh_3)_4$/THF, w.c.s.	[81]
under Mitsunobu conditions	sb $ArSO_2NHR$	
	+ 1° alcohol, PBu_3/ADDP	[112]
	+ 1° alcohol, PPh_3/DEAD/THF	[113]
	+ 1° alcohol (intramolecular), PPh_3/DEAD or PPh_3-sulfonamide betaine	[114]
	+ 1° alcohol, PBu_3/various azo reagents	[115]
	+ MeOH, PPh_3/DEAD/THF	[116]
	+ 3-PyridylCH_2OH, PBu_3/TMAD	[117]
	+ 2° alcohol, DEAD/PPh_3	[118]
	sb 1° alcohol + $ArSO_2NHR$, PPh_3/DEAD	[32, 119]
	sb 1° alcohol + $BocNHSO_2Ar$, PPh_3/DEAD	[118]
8.2.1.5 Alkylation of azides	sb monosaccharide + NaN_3/DMF, w.c.s.	[120]
	sb benzyl bromide + NaN_3/DMF	[121]
	+ NaN_3/DMSO	[122]
	sb alkyl iodide + NBu_4N_3, DMF	[72]
	sb nosylate + NaN_3, DMF	[123]
	sb $C{\equiv}C-CH_2OH$ + DPPA/PPh_3/DEAD	[124]
	sb 1° alcohol + DPPA/PPh_3/DEAD	[125]
8.2.1.6 Other N-alkylations and substitutions	N-9 alkylation of purines, PPh_3/DEAD/THF/DCM	[126]
	amine exchange, sb dimethylformamidine + 2° amine	[127]
	+ 2° amino alcohol	[128]
	hydrazine formation, sb RNH_2 + N-Boc-3-(4-cyanophenyl)-oxaziridine)	[129]
	sb bis-Boc thiopseudourea + 1° or 2° alcohol, PPh_3/DIAD	[130]
	For other N-alkylation reactions see sections 8.5.2.2 and 8.13.2	

8.2.2 N-acylation

8.2.2.1 Acylation of amines		
sb acylating agent	amides from sb RCOOH (activation with $CF_3CO_2C_6F_5$) + 2° amine	[131, 132]
	amides via acyl transfer, sb N-acylpyridinium salt + amine or aniline	[133]
	sb carboxylic ester + 1° or 2° amine, $AlCl_3$/DCM, w.c.s.	[57]
	+ 1° amine, $AlMe_3$/DCM/toluene, w.c.s.	[134]
	sb quinic acid lactone + $BnNH_2$, Me_3Al	[125]

	Asn, Asp and Gln amides via ring opening of sb oxazolidinones with 1° amines/MeOH or DMF	[135]
	RCOO-Merrifield resin + ethylamine, THF, w.c.s.	[136]
	RCOO-polymer + hydroxylamine, THF, w.c.s.	[137]
	RCOS-polymer + 2° amine, $AgNO_3$, w.c.s.	[138]
	N-alkylacylsulfonamide + amine, THF	[110]
	N-alkylacylsulfonamide + amine, THF or dioxane	[109]
	Reissert complex formation from sb RCOCl + isoquinoline/TMSCN	[139, 140]
sb amine	β-ketoamides from sb 2° amine + 5-acyl Meldrum's acids	[141, 142]
	acetoacetamides from Rink resin + diketene	[143]
	sb pyridine + acid chloride, DCM, THF	[133, 144]
	sb Ar-NH_2 + $(CF_3CO)_2O$, py	[39]
	formamides from sb aniline + HCOOH/Ac_2O	[145]
8.2.2.1 Acylation of amides	imide from sb amide + malonyl chloride, benzene	[146, 147]
	sb oxazolidinone + acid chloride, *n*BuLi/THF	[148]
	Evans auxiliary + propionic anhydride, DMAP	[149]
8.2.2.3 Acylation of sulfonamides	sb sulfonamide + RCOOPfp, DMAP	[109]
	+ $(RCO)_2O$, DMAP	[110]
8.2.2.4 Other N-acylations	amides from sb azide + carboxylic acid, PPh_3/EDC/HOBt	[150]

8.2.3 N-sulfonation and sulfination

sb amine (aliphatic)	sb 1° amine + $ArSO_2Cl$, NMM/DCM	[117]
	, DIEA/DCM	[114]
	sb amino acid ester + $ArSO_2Cl$, NEt_3/DCM	[151, 152]
	+ 2-NBSCl, DIEA/THF	[116]
	sb Rink amine resin + RSO_2Cl, py/DCM	[105]
	sb amino acid amide + 2-NBSCl, collidine/DCM	[107]
	sb amino acid ester + $BocNHCHRCH_2SO_2Cl$, NMM/DCM	[153]
	sb glycine ester + $BocNHCHRCH_2SO_2Cl$, MTDA/DMAP	[154]
	+ Boc-NHCHRCH=$CHSO_2Cl$, DBU/DMAP/DCM	[155]
	sb 2° amine + $ArSO_2Cl$, NMM/DCM	[58]
	+ $ArSO_2Cl$, DIEA/DCM	[156]
	+ RSO_2Cl, DMAP/DIEA	[157]
	+ $ArSO_2Cl$, py	[158]
	+ RSO_2Cl, py/DMF	[63]
	+ TsCl, py	[159]
	sb 3-amino-2-pyrazoline + TsCl, py	[160]
	sulfinamides from sb 1° amine + $BocNHCHRCH_2SOCl$, NMM	[161]
sb amine (aromatic)	sb aniline + $ArSO_2Cl$, DMAP/py	[55, 162]
	+ $MeSO_2Cl$, py	[163]
	sb 5-(NH_2)-pyrazoles + $ArSO_2Cl$, DMAP/py	[164]
sb sulfonyl chloride	sb $ArSO_2Cl$ + 1° amine, py	[165]
	+ 1° diamine, py /DMF	[166]
others	sb carbamates + $ArSO_2Cl$, NaH/DMA or LiHMDS/THF	[167]
	sb chlorosulfonyl carbamate + 1° or 2° amine	[168]

8.2.4 N-phosphination

iminophosphorane formation	sb ArN_3 + PPh_3/THF	[169]
	+ PBu_3/toluene	[62]
	sb $ArCH_2N_3$ + PPh_3/THF	[121]
	sb $ArNH_2$ + PPh_3/DEAD/THF	[170]

8.2.5 O-alkylation

8.2.5.1 Alkylation of alcohols (ROH + R'X, X=Cl, Br)	sb phenol + $BrCH_2COR$, DIEA/NMP	[171]
	+ alkyl halides, DBU/DMSO	[172]
	+ allyl halides, Schwesinger base	[173]
	+ $R^1CH{=}CHCH_2Br$, Schwesinger base	[174]
	PS/DVB-*p*-C_6H_4-OH	
	+ 2-(chloromethyl)benzimidazole, NaH	[175]
	+ 2-(chloromethyl)benzimidazole, K_2CO_3/18-crown-6	[175]
	sb 1° alcohol + TrtCl, py	[176]
	sb 2° alcohol + Ar_2CH_2X, NaH	[127]
	sb levoglucosan derivative + RX, KO*t*Bu	[177]
	sb alkyl bromide + alcohol, NaH/Bu_4NI/18-crown-6	[123]
	+ Na-phenolate	[178]
	+ phenol, K_2CO_3/KI	[77]
	sb RCH_2Br + *o*-I-phenols, DIEA/DMF	[37]
	sb benzyl chloride + *o*-F-phenol, DBU/MeCN	[179]
	sb propargyl chloride (gen. in situ from propargyl alcohol + chloroenamine) + phenol, Schwesinger base/Bu_4NBr	[174]
R'X = (2-Cl-)Trityl resin	2-Cl-TrtCl resin + 4-hydroxybenzaldehyde, py/THF	[180]
	TrtCl resin + symmetrical diol, py (monoprotection)	[181–184]
	+ 1,4-butanediol, py (monoprotection)	[185, 186]
	+ furan or thiophene methanol, DMAP /DMF	[187]
	2-Cl-TrtCl resin + N-hydroxyphthalimide, NEt_3/DMF	[188]
	TrtCl resin + N-hydroxyphthalimide, NEt_3/DMF	[189]
	2-Cl-TrtCl resin + Fmoc-hydroxylamine, DIEA	[190]
R'X = Merrifield resin	+ phenol, K_2CO_3/KI/DMF	[166]
	+ 3-hydroxy-acetophenone, Cs_2CO_3/NaI/DMF	[191]
	+ phenol, NaOH	[192, 193]
	, NaOMe	[194]
	+ 3-bromo-4-hydroxybenzoate, NaOMe/DMA	[195]
	+ phenol, KO*t*Bu/DMSO	[196]
	, KO*t*Bu/18-C-6/NBu_4I/DMF	[197]
	+ 4-OH-2,6-$(OMe)_2$-benzaldehyde, NaH/DMF	[89]
	+ phenol, NaH	[90, 198–201]
	+ 1° alcohol, NaH	[202]
	+ 1,3-propanediol, NaH	[203]
	+ 1,4-butanediol, NaH/NBu_4I/DMF	[124, 204]
	+ PEG200, NaH	[205]
	+ diol, KO*t*Bu	[206]
	+ NaOR, THF	[207]
	+ NaI, then alcohol, KO*t*Bu	[48]
	+ 4-$(HOCH_2)$-2,4-Me_2-2-oxazoline, NaH	[208]
	+ 4-$(HOCH_2)$-oxazolidinone, KH/18-C-6/DMF	[149]

	+ 6-($NaOCH_2$)-3,4-dihydro-2H-pyran, DMA	[209]
	+ HO-R-N=CH-NMe_2, NaH/15-C-5	[128]
	+ Na salt of 3-hydroxypyridine	[42]
R'X = other resins	PhFlCl resin + phenol, NMM/DMF	[210]
	Rink chloride resin + 1° alcohol, DIEA	[54]
8.2.5.2 Mitsunobu reactions	sb $PhCH_2OH$ + phenol, PBu_3/TMAD/THF/DCM	[211]
	sb 1° alcohol + phenol, DIAD/PPh_3/NEM	[212]
	, preformed sulfonamide betaine	[213]
	, PBu_3/TMAD	[214]
	sb RCH_2OH + phenol, PPh_3/DEAD	[215]
	sb phenol + 1,5-pentanediol, PBu_3/TMAD	[214]
	sb phenol + alcohol, PPh_3/DEAD/THF	[59, 216]
	sb phenol + alcohol, PPh_3/DIAD/THF	[217, 218]
	, PPh_3/DIAD/NMM	[159]
	sb phenol + RCH_2OH, PPh_3/DEAD	[219]
	sb phenol + alcohol, PBu_3/TMAD/THF/DCM	[211]
	, PBu_3/ADDP	[40]
	, preformed sulfonamide betaine	[220]
	sb phenol + alcohol, PPh_3/DEAD/NEt_3/THF (MIMOTOPES pins^R used as solid support)	[221]
	sb phenol (on silica gel or molecular sieves) + alcohol, PPh_3/DIAD	[222]
	PS/DVB-CH_2OH + phenol, PPh_3/DEAD	[148]
	, PPh_3/DEAD/NMM	[223]
	Wang and TentaGel resins + phenol, PPh_3/DEAD	[197]
	Wang resin + phenol, PPh_3/DIAD	[224]
	, PPh_3/DEAD	[225]
	+ 2,5-dihydroxybenzaldehyde, PPh_3/DEAD/THF	[38, 226]
	+ 4-hydroxybenzaldehyde, PPh_3/DIAD/NEM/ultrasound	[227]
	+ HetArOH, PPh_3/DEAD	[144]
	+ N-hydroxyphthalimide, PPh_3/DEAD/THF	[63]
	intramolecular, benzoxazoles from sb 2-amidophenols, PPh_3/DEAD/THF	[228]
8.2.5.3 Other O-alkylations		
ether formation	sb phenol, CH_2N_2/THF	[229]
	sb 1,4-butanediol + 3° alcohol, PPTS	[124]
	Wang resin trichloroacetimidate + 1°, 2° or 3° alcohol and diols, $BF_3 \cdot Et_2O$	[230]
	PS/DVB-CH_2OH + 2° alcohol via trichloroacetimidate	[231]
	PS-PEG resin from 2-(1-methyl)hydroxyethyl polystyrene + ethylene oxide, KOH	[232]
	mesylated Wang resin + N-hydroxyphthalimide, Cs_2CO_3/NMP	[233]
	sb diazoketone + alcohol, $[Rh(OAc)_2]_2$ cat. carbene OH-insertion	[234]
	iodoetherification, sb $ArCH_2OH$ + NIS/$ArCH{=}CH_2$/triflic acid	[72]
	, sb RCH_2OH + NIS/RCH=CHR'/triflic acid	[235]
ester formation	sb RCOOH, CH_2N_2/DCM	[236]
	sb $ArSO_2Li$ + allyl bromide	[237]
	PS/DVB-CH_2CH_2OTs + (3-nitro)$PhCO_2K$	[73]
	For other O-alkylations see section 8.5.2.4.	

8.2.6 O-acylation

8.2.6.1 Ester formation	PS/DVB-CH=CHCOOH + HCl/EtOH	[238]
	PS/DVB-COCl + $ArCH_2OH$, NEt_3	[220]
	+ diol, py	[176, 239]
	+ dihydroxylated phenyl derivative, py	[229]
	PS/DVB-CH_2OH + diacid chloride	[240, 241]
	sb cyclohexeneamide + alcohol, AcCl	[242]
	resin capture of cyclohexeneamide derivative with Wang-resin, HCl/THF	[243]
	sb 1° alcohol + malonic acid monomethylester chloride, DIEA/DCM	[244]
	Wang resin trichloroacetimidate + RCOOH, $BF_3 \cdot Et_2O$	[245]
	β-ketoesters from Wang resin + diketene	[246]
	+ Meldrum's acid	[247]
8.2.6.2 Mitsunobu reactions	sb alcohol + Fmoc-glycine, PPh_3/DEAD	[248]
	sb R^1CHR^2OH + ArCOOH, PPh_3/DIAD	[249]
	sb R^1OH + R^2COOH, PPh_3/DEAD	[250]
	Wang resin + RCOOH, PPh_3/DEAD	[251]
	TentaGel resin + RCOOH, PPh_3/DEAD/THF	[217]
	+ benzoic acid, PPh_3/DEAD	[252]
	+ RCOOH, PPh_3/DEAD/THF	[218]
	sb C=C-COOH + alcohol, PPh_3/DEAD	[124]
	sb R^1COOH + R^2OH, PPh_3/DIAD/THF	[217]
8.2.6.2 Transesterification	RCOO-polymer to RCOOMe, MeOH/DMF/NEt_3	[250]
	, NEt_3/MeOH/KCN	[253]
	, CH_3CH_2COOMe/$Ti(OEt)_4$	[244]
	, Triton B/MeI	[254]
	β-ketoester from sb alcohol + β-keto-*t*Buester	[255]
	Wang resin + $RCOCH_2COOEt$/DMAP	[256]

8.2.7 O-phosphonation

	sb 2° alcohol + RPOOMeOH, $(4\text{-Cl-Ph})_3P$/DIAD/DIEA/THF	[257, 258]

8.2.8 O-phosphorylation

	sb 2° alcohol + $ClPO(OC_6F_5)_2$	[201]

8.2.9 O-sulfonation

	1° alcohol + $MeSO_2Cl$, py	[28, 182]
	, py/C_6H_6	[181, 259]
	, py/DCM	[77]
	, NEt_3	[78, 79]
	Wang or TentaGel resin + $MeSO_2Cl$, NMM	[58]
	alcohol + NosCl, 4-pyrrolidinopyridine	[123]
	+ 4-NO_2-$PhSO_2Cl$, py	[260]
	phenol + $PhSO_2Cl$, DIEA/DCM	[172]
	vinyl triflate from sb cyclohexenone + Tf_2NPh, $KN(TMS)_2$	[261]
	sb $ArSO_2Cl$ + alcohol	[83]
	PS/DVB-SO_2Cl + 1,2-diol, NEt_3	[262]
	PS/DVB-CH_2CH_2-OH + TsCl, diisopropylamine	[73, 74]

8.2.10 P-alkylation

phosphonium salt formation	sb alkyl bromide + molten PPh_3	[182]
	sb alkyl iodide + PPh_3	[204]
	sb benzyl bromide + PPh_3	[263]
	sb crotyl bromide + PBu_3	[248]
	sb α-bromoketone + PPh_3/NaOH	[264]
	sb α-bromoamide + PPh_3	[248]
	sb α-chloroamide + PPh_3	[265]
	sb mesylate + molten PPh_3	[182, 236]
	Merrifield resin + PPh_3	[238, 266]
	sb PPh_3 + alkyl halide	[267]
	+ 2-nitrobenzyl bromide	[268]
	+ neat benzyl chloride	[269]
	phosphorane formation, sb RCH_2I + 1. PPh_3, 2. LiHMDS	[124]
other P-alkylation reactions	PS/DVB-CH_2CH_2OTs + $LiPPh_2$, DMSO	[73]

8.2.11 S-alkylation

sb α-chloroacetophenone + thiol	[270]
α-bromoamide + thiol, TMG (intramolecular)	[60, 271]
, NMM (intramolecular)	[272]
sb alkyl bromide + thiol, DIEA/DMF	[57]
sb $ArCH_2Cl$ + RCH_2COSK, DMF	[273]
sb allyl acetate + 2-$HOOCC_6H_4SH$, $Pd(acac)_2$/dppb	[43]
+ 4-$MeOC_6H_4SO_2H$, $Pd(acac)_2$/dppb	[43]
Merrifield resin + thiophenol	[274]
+ mercaptoethanol, Cs_2CO_3/DMF	[28]
+ thiourea	[130, 275, 276]
Rink chloride resin + thiol, DIEA	[54]
Wang resin trichloroacetimidate + thiol, $BF_3 \cdot Et_2O$	[245]
PS/DVB-CH_2CH_2OTs + butanethiol, K_2CO_3/hexadecyltributylphosphonium bromide	[73]
PS/DVB-CH_2O-*p*-C_6H_4-SO_2OR^1 + R^2SNa to R^2SR^1	[83]
thioester from sb benzenesulfonate + $KSC(O)CH_3$	[277]
sulfonium salt from PS/DVB-SCH_2R + RX	[278]
PEG-thiol resin + 2-chloropyrimidine derivative, NEt_3	[279]
sb thioamide + α-halo ketone, 5% HOAc/DMF	[280]
sb cyclic thiourea + RCH_2Br, DIEA	[281]
isothiourea from sb thiourea + CH_3I	[282]
sb 1,2,4-triazole-3-thiolate + alkyl halide, DIEA	[283]
sb thiol + 4-phenylbenzyl bromide, DIEA/DMF	[270]
sulfones from PS/DVB-sulfinate + alkyl halide, NaOH/PTC	[284]
sb α,β-unsat. ketone + thiol, NaOMe	[285]
For other S-alkylations see section 8.5.2.3.	

8.2.12 S-acylation

thioesters from sb RCOOH + thiol, DCC	[286]

8.2.13 C-alkylation

sb imine	α-methylation of cyclohexanone imine, CH_3I, LDA	[287]
	α-alkylation of sb glycine benzophenone imine, activated halide, BEMP/NMP	[288]
	alkyl halide, BEMP/NMP/Bu_4NI	[289]
	α-monoalkylation of sb glycine benzophenone imine, alkyl halide, BEMP/py	[290]
	α-alkylation of sb α-iminoester, allyl or aralkyl halide, BEMP	[291]
sb amide	α-alkylation of sb amide, alkyl halide, LDA	[292]
	, benzyl bromide, LDA	[149]
	α-dialkylation of sb ketopiperazine, benzyl chloride, LiHMDS/THF	[293]
	α-alkylation of sb N-propionylated oxazolidinone, alkyl halide, LDA	[197]
	sb $RCH_2CONHSO_2Ar$, alkyl halide, LDA	[109]
sb nitrile	α-alkylation of sb nitrile, $ClCH_2CN$, NaOH/PTC	[294]
sb 1,3-dicarbonyl compound	sb β-ketoesters + alkyl halide, TBAF/THF	[295]
	sb β-diketone + alkyl halide, TBAF	[296]
	first γ-alkylation of sb β-keto ester + alkyl halide, LDA	[255]
	second γ–alkylation of sb β-keto ester + alkyl halide, BuLi	[255]
	sb β-ketoesters or β-diketones + allylic acetates, carbonates and chlorides, Pd $(PPh_3)_4$ + various additives and/or base	[297]
sb ester	α-alkylation, alkyl halide, TrtLi	[298]
	, benzyl bromide or allyl iodide, KHMDS	[125]
	, sb glycine benzophenone imine, activated halide, Schwesinger base	[288]
	, alkyl halide, BEMP/NMP/Bu_4NI	[289]
	α-monoalkylation of sb glycine benzophenone imine, alkyl halide, BEMP/py	[290]
	α-alkylation of sb α-iminoester, alkyl halide, KHMDS or P_4-*t*Bu	[290]
	, BEMP	[291]
sb alkyl halide or sulfonate	Merrifield resin + sodium cyclopentadienylide	[299]
	+ malodinitrile, NaOH/NBu_4OH	[294]
	+ diethylmalonate, NaH/DMF	[300]
	+ KCN, NBu_4Cl	[73]
	α-alkylation of diimine derivative, PS/DVB-CH_2Br, LDA	[301]
	sb nosylate + $NaCpMe_3Et$, THF	[260]
	sb mesylate + Li-acetylide, HMPT/THF	[181]
	+ Li-alkynes, HMPT/THF	[182, 259]
other C-alkylation reactions	sb allyl ester + β-dicarbonyl derivative, $Pd(PPh_3)_4$/THF, w.c.s.	[81]
	α-alkylation of cyanohydrin (intramolecular), $ArSO_3R$, LiHDMS, w.c.s.	[120]
	sb dithian, BuLi, alkyl halide	[277]
	α-dialkylation of sb $ArSO_2CH_2CH{=}CH_2$ + alkyl halide, BuLi	[237]
	sb α-bromoester + allyltributylstannanes, AIBN	[302]
	sb Reissert complex of isoquinoline + alkyl halide, LDA	[139, 140]
	sb Mannich base of indole + KCN or ethyl 2-nitroacetate	[163]

alkylation of 2-alkyloxazolines + alkyl halide, BuLi [208]
sb alkyne +*n*BuLi or *t*BuLi/THF/HMPT, then RBr [182]

8.2.14 C-acylation

sb cyanoacetate + isatoic anhydrides, NEt_3 [303]
sb cyanoacetate or EWG-CH_2COO-polymer + RCOOH, DEPC/NEt_3/DMF [304]
sb cyanoacetate + RNCS, DIEA/DMF [305]
thioamides from sb isothiocyanate + EWG-CH_2CN, DBU/DMF [280]
For other C-acylations see also section 8.7.

8.2.15 Epoxide opening

lithiated PS/DVB + ethylene oxide [73, 74, 306, 307]
sb epoxide + NaN_3/NH_4Cl or PhSNa [308]
+ $TMSN_3$, [(salen)CrN_3], asymmetric [250]
+ benzyl- or 2° amine [200]
+ alcohol, $Yb(OTf)_3$ [201]
sb levoglucosan derivative + alcohol or phenol, KO*t*Bu or BEMP [177]
+ thiol or thiophenol, DBU or LiHMDS [177]
+ 2° amine, $LiBPh_4$/2,6-lutidine [177]
oxazolidinones from sb epoxide + pyrrolidine, $LiClO_4$ cat., w.c.s. [104]
PS/DVB-(-CH-CH_2-O-) + $HNMe_2$ [266]

8.2.16 Halogenation

8.2.16.1 Chlorination

ROH to RCl

Wang or SASRIN resin + MsCl/DIEA/DMF [309]
Wang resin + $SOCl_2$ [55]
sb $ArCH_2OH$ + $Me_2C{=}C(NMe_2)Cl$/DCM [29]
sb TrtOH + AcCl [310]
+ $SOCl_2$ [311]
Trityl-OH resin, AcCl [184, 186]

RSO_3H to RSO_2Cl

sb RSO_3H + $SOCl_2$/DMF [262]
sb $ArSO_3H$ + PCl_5/DMF [166]

other chlorination reactions

sb oxime + NCS [180]
PS/DVB-$(CH_2)_3$-$SiMe_2Ar$ to PS/DVB-$(CH_2)_3$-$SiMe_2Cl$, HCl/DCM [88]

8.2.16.2 Bromination

ROH to RBr

sb RCH_2OH + PBr_3 [28]
Wang resin + $SOBr_2$ [55]
Wang or TentaGel resin + Ph_3PBr or Ph_3P/CBr_4 [58]
Wang resin + PPh_3/CBr_4/DCM [123]
sb $ArCH_2OH$, PPh_3/CBr_4/THF [59]
PS/DVB-CH_2OH + PPh_3/CBr_4 [263]
ROMs + NaBr/HMPT [182]
THP-protected alcohol to RBr, PPh_3Br_2/DCM [32]

other bromination reactions

α-bromination of ketones: RCOMe + Py · HBr · Br_2 [264]
PS/DVB-CH_2CH_2OTs + $MgBr_2$ [73]
SeMe to SeBr, Br_2 [312]

8.2.16.3 Iodination	sb $ArSO_3R$ + NaI/DMF, w.c.s.	[120]
	1° alcohol + NaI/Me_3SiCl	[73]
	ROMs + NaI /HMPT	[182]
	RCH_2OH, PPh_3/I_2/imidazole	[124, 204]
	Wang or TentaGel resin + Ph_3PI_2 or Ph_3P/DIAD/CH_3I	[58]
8.2.16.4 Halogen exchange	Cl to I, Merrifield resin + NaI	[48]
	SiF to SiCl, sb trialkylfluorosilane + BCl_3/DCM	[313]

8.3 Nucleophilic aromatic substitutions

8.3.1 N-nucleophiles

reactions with ArF	sb nitroarylfluorides + piperazine, NMP	[314]
	sb 3-fluoro-4-nitrophenol + 1° amine, DMSO	[315]
	sb 4-fluoro-3-nitrobenzamide + ethyl 3-aminopropanoate, DIEA/DMF	[316]
	+ amino acid ester, DIEA/DMF	[85]
	+ 1° amine/DMF	[281]
	+ β-amino acid, $NaHCO_3/H_2O$/acetone	[84]
	+ aniline, DIEA/DMSO	[317]
	sb 4-fluoro-3-nitrobenzoate + amino acid ester, DIEA/DMF	[93]
	+ 1° amine/DMSO	[92]
	sb 4-fluoro-3-nitrobenzoate or – benzamide + 1° amine, DIEA/NMP	[318]
	sb 4-fluoro-benzoate + piperazine, NMP	[82]
	sb *o*-difluoroquinolone + piperazine, NMP	[256]
	sb trifluoropyridine + 1° or 2° amine, NMP	[319]
	quinolone derivative from sb trifluoroaryl-enamide (intramolecular), TMG/DCM	[256]
reactions with ArCl	sb dichloropurine, 1. + 1°, 2° amine or aniline, *n*BuOH/NEt_3, 2. 1° amine, neat, 150° C	[320]
	sb 2-acylamino-6-chloropurine + 1° or 2° amine, DMSO/DMF	[321]
	sb dichlorotriazine, 1. + amine, DCM /RT, 2. + amine, dioxane/90° C	[322]
	sb dichloropurine + benzenesulfonamide, NaH/DMA (*no* 2nd substitution)	[320]
reactions with $ArSO_nR$ (n = 1,2)	sb RSO_2-pyrimidine + amine or azide, w.c.s.	[275]
	sb RSO_2-pyrimidine derivative + amine, w.c.s.	[279]
	sb MeSO-pyrimidine + amine, w.c.s.	[276]

8.3.2 O-nucleophiles

	sb ArF + ArOH/K_2CO_3	[323]
	sb dichloropurine + benzylalcohol, NaH/THF (no 2nd substitution)	[320]
	sb ArOH + tetrafluoropyridine, NaH/DMF	[319]

8.3.3 S-nucleophiles

	3-fluoro-4-nitrobenzamide + thiol, DBU/DMF (intramolecular)	[324]
	sb ArF + ArSH, K_2CO_3	[323]

8.3.4 Other nucleophilic aromatic substitutions

2-substitution of sb quinoline-N-oxide, 1. BzCl, 2. various N- and C-nucleophiles	[325]
PS/DVB-CO-*p*-(3-nitro)C_6H_4X + $BnNMe_3OH$, 90° C (X = F, Cl, OMe)	[326]
For Pd-catalyzed aromatic substitution reactions see section 8.11.1.5	

8.4 Electrophilic aromatic substitutions

8.4.1 Halogenation

8.4.1.1 Chlorination	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then C_2Cl_6	[327]
8.4.1.2 Bromination	poly(p-hydroxystyrene)resin + Br_2/NBu_3	[328]
	PS/DVB + $Br_2/Tl(OAc)_3$, $TlCl_3$ or $FeCl_3$	[306]
	PS/DVB + $Br_2/Tl(OAc)_3$	[307]
	sb thiophene + NBS/DMF	[329]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then CBr_4	[327]
8.4.1.3 Iodination	conversion of Ar-triazenes to ArI, MeI	[202]
	sb tyrosine derivative + $IPy_2 \cdot BF_4$	[330]

8.4.2 Formation and reactions of metalated aromatic compounds

8.4.2.1 Epoxide opening	PS/DVB-Br + *n*BuLi, then ethylene oxide	[73, 74, 306, 307]
8.4.2.2 Addition to carbonyl compounds	PS/DVB + *n*BuLi/TMEDA, then fluorenone	[210]
	, then Ph_2CO	[184]
	PS/DVB-Br + *n*BuLi, then Ph_2CO	[306]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then PhCHO	[327]
	sb furan or thiophene, C-2-lithiation with *n*BuLi, then (Het)ArCHO	[187]
	sb 2,4-substituted thiophene, C-5-lithiation with *n*BuLi, then *p*-MeC_6H_4CHO	[187]
	PS/DVB + *n*BuLi/TMEDA, then CO_2	[331]
	PS/DVB-Br + *n*BuLi, then CO_2	[306]
8.4.2.3 Acylation reactions	sb *p*-(CH_3OCH_2O)phenylsilane, ortho-lithiation with *n*BuLi/TMEDA, then DMF	[171]
	PS/DVB-Br + *n*BuLi, then DMF	[306]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then DMF	[327]
	sb furan or thiophene, C-2-lithiation with *n*BuLi, then DMF	[187]
	, then DMA	[187]
	sb 2,4-substituted thiophene, C-5-lithiation with *n*BuLi, then DMA	[187]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then PhCOCl	[327]
	PS/DVB-Br + *n*BuLi, then PhNCO	[306]
8.4.2.4 Alkylation reactions	PS/DVB-Br + *n*BuLi, then $BrCH_2CH_2Br$	[306]
	PS/DVB + *n*BuLi/TMEDA, then RBr	[260]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then MeI	[327]
	sb furan or thiophene, C-2-lithiation with *n*BuLi, then MeI	[187]
	, then allyl bromide	[187]

8.4.2.5 Silylation	PS/DVB + *n*BuLi/TMEDA, then $Me_2ClSiCH_2CH{=}CH_2$	[332]
	PS/DVB-Br + *n*BuLi, then Me_2SiCl_2	[306]
	sb $RSiMe_2Cl$ + Li-3-pyridyl derivative	[88]
	sb furan or thiophene, C-2-lithiation with *n*BuLi, then TMSBr	[187]
8.4.2.6 Sulfide/selenide formation	PS/DVB-Br + *n*BuLi, then RCH_2SSCH_2R	[278]
	PS/DVB-Br + *n*BuLi, then MeSSMe	[306]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then MeSSMe	[327]
	sb 1-hydroxyimidazole, ortho-lithiation with *n*BuLi, then PhSSPh	[327]
	PS/DVB + *n*BuLi/TMEDA, then MeSeSeMe	[312]
8.4.2.7 Sulfinate formation	PS/DVB-Br + *n*BuLi, then SO_2	[284]
	PS/DVB + *n*BuLi/TMEDA, then SO_2	[237]
8.4.2.8 Boronate formation	PS/DVB + *n*BuLi/TMEDA, then $B(OMe)_3$	[333]
	PS/DVB-Br + *n*BuLi, then $B(OMe)_3$	[306]
8.4.2.9 Other reactions of metalated aromatic compounds	sb ArBr or ArI + *n*BuLi, then di(iPr)squarate	[334]
	PS/DVB-Br + *n*BuLi, then PPh_2Cl	[306]
	, then S_8	[306]

8.4.3 Friedel-Crafts acylation

PS/DVB, various acid chlorides, $FeCl_3$/DCM	[335]
, 5-phenylvaleryl chloride, $AlCl_3/CS_2$	[273]
, isobutyryl chloride, $AlCl_3/CS_2$	[336]
, 4-nitrobenzoyl chloride, $AlCl_3$/DCM	[337]
, 3-nitrobenzoyl chloride derivative, $AlCl_3/PhNO_2$	[326]

8.4.4 Friedel-Crafts alkylation

PS/DVB + propylene oxide, $SnCl_4$ or $AlCl_3$	[232]
+ N-(chloromethyl)phthalimide, $FeCl_3$/DCM	[335]
macroporous resin + $SnCl_4/CH_3OCH_2Cl$	[338]
sb phenylalkyl derivative, $SnCl_4/CH_3OCH_2Cl$	[273]

8.5 Addition reactions

8.5.1 Grignard and related reactions

8.5.1.1 with aldehydes	sb arom. aldehyde + PhMgBr	[336, 339]
	+ (4-BrMg)benzyltrimethylsilane	[198]
	+ RMgBr	[340]
	sb RCH_2CH_2CHO + RCH_2MgBr	[249]
	sb aldehyde + PhMgBr	[186]
	PS/DVB-CHO + (4-BrMg)benzyltrimethylsilane	[198]
8.5.1.2 with ketones	sb ketone + PhMgBr	[341]
	+ PhLi	[236]
	lithiated PS/DVB + ketone	[184]
	sb dihydropyridones + ArMgX, $CeCl_3$	[342]
	sb cyclohexenone + RMgBr or RLi	[261]

	piperidine-4-ones via 1,4-addition of RMgCl/CuI/$BF_3 \cdot Et_2O$ to sb dihydropyridone	[343]
8.5.1.3 with imines	sb imine + RMgX or RLi	[344]
	+ allylMgBr	[159]
	+ allyllithium	[345]
8.5.1.4 with Weinreb amides	ketone from sb Weinreb amide + RMgX	[123, 346]
	+ MeMgCl	[347]
	+ RMgBr	[115]
	ketone from sb RCOOEt + RMgX/HN(OMe)Me · HCl (via in situ gen. sb Weinreb amide)	[348]
8.5.1.5 with esters	3° alcohol from sb methyl ester + RMgBr	[349]
	+ MeMgCl	[125]
	ketones from sb thioesters + RMgBr, w.c.s.	[350]
8.5.1.6 with acid chlorides	ketones from sb RCOCl + PhCdCl	[351]
	3° alcohols from sb RCOCl + RMnI	[351]
8.5.1.7 Reactions with sb Grignard reagents	sb ArI or HetArBr + *i*PrMgBr,then RX, TsCN, PhSSPh or benzaldehyde/CuCN · 2 LiCl	[352]
	Merrifield resin + Mg-anthracene complex, then CO_2	[353]
8.5.1.8 Other Grignard reactions	trisubstituted alkenes from sb allylic sulfones + RMgX/CuI/THF, w.c.s.	[237]
	dihydropyridones from sb carbamoylpyridinium derivative + RMgX	[343]
	N-acyl-2-substituted-dihydro-4-pyridones from sb N-acylpyridinium derivative + RMgX	[144]

8.5.2 Michael and related reactions

8.5.2.1 C-nucleophiles	sb $RCH_2N{=}CPh_2$ + α,β-unsat. carbonyl compound, BEMP	[354]
	sb N-propionyl Evans auxiliary + acrylonitrile, $TiCl_3$(O-*i*Pr)/DIEA	[148]
	tandem-Michael-addition, sb acrylate + cyclohexenone, LDA	[355]
	sb α,β-unsat. ketone + vinyl cuprate (from terminal alkyne/Cp_2ZrHCl/CuCN/MeLi)	[111]
	sb 3-alkylidene-2-oxindole + $(COOEt)_2CH_2$, NEt_3	[356]
	ring opening of sb N-protected alkenylaziridines with RCu(CN)Li	[357]
	piperidine-4-ones via 1,4-addition of RMgCl/CuI/$BF_3 \cdot Et_2O$ to sb dihydropyridone	[343]
8.5.2.2 N-nucleophiles	sb acrylate + 1° amine	[358, 359]
	+ 1° or 2° amine	[360]
	+ 2° amine	[33–35, 361]
	acrylate derivative + 2° amine/NaOMe (intramolecular)	[78]
	sb squarate + 1° or 2° amine	[334]
	sb α,β-dehydroamino acid + 1,2,4-triazole or pyrazole, K_2CO_3	[251]
	sb vinyl ketone + $PhCH_2NH_2$	[264]
	sb vinylsulfone + tetrahydroisoquinoline	[40]
	sb 2° amine + activated alkyne	[29]
	sb piperazine + propargyltriphenylphosphine	[50]

8.5.2.3 S-nucleophiles

sb $ArCH_2SH$ + 3-butenone [264]
sb thiol + maleimide [362]
sb 3-alkylidene-2-oxindole + thiol, NEt_3 [356]
sb α,β-unsat. ketone + thiol, NaOMe [285]
sb α,β-unsat. ketone + thiophenol, NaOMe [185]
, *n*BuLi [363]
sb maleimide + thiol [362]

8.5.2.4 O-nucleophiles

sb nitroalkene + alcohol, KH [364]
sb $ArCH_2OH$ + C≡C-COR, NMM [29]
Wang resin + divinylsulfone, DBU [40]

8.5.3 Other 1,2-additions

8.5.3.1 Additions to alkenes and alkynes

sb alkene + bromine [365]
PS/DVB-SeBr + alkene [312]
hydrosilylation of PS/DVB-$CH{=}CH_2$, $HSiR^1R^2Cl$, $Co_2(CO)_8$ [313]
hydroboration, PS/DVB-$CH{=}CH_2$+ 9-BBN, then H_2O_2/NaOH [366]
, sb alkyne + disiamylborane, THF [181]
, sb alkyne + 9-BBN, THF [182]

8.5.3.2 Additions to imines

sb imine + allyllithium [345]
+ allylMgBr [159]
+ trimethylsilyl enolate, $Yb(OTf)_3$ [192]
+ $HP(OSiMe_3)_2$ [367]
sb silyl enol ether + imine, $Sc(OTf)_3$ [273, 368]
α-aminophosphonates from sb H-phosphonate + imine, Lewis acid or ultrasound [369]

8.5.3.3 Additions to carbonyl groups

aldehydes

sb arom. aldehyde + p-lithiated anisole [171]
sb aldehyde + CH_3NO_2 [364, 370, 371]
sb arom. aldehyde + acetophenone, K_2CO_3 [134]
+ silyl ketene acetal, $BF_3 \cdot H_2O$ [372]
+ 2-phenyl-1,3-dithian, *n*BuLi/THF [199]
sb aldehyde + chiral boron enolate [372]
+ boron enolate of N-propionyl-Evans auxiliary [286]
+ δ-keto acid, LDA/THF [204]
+ crotylsilane derivative, TMSOMe/TMSOTf [373]
RCH_2COO-polymer + arom. aldehyde, LDA/$ZnCl_2$ [374]
sb silyl enol ether + aldehyde, $Sc(OTf)_3$ [375]
sb acylated Evans auxiliary + 1. $(n\text{Bu})_2BOTf/NEt_3$ 2. PhCHO [148]
+ 1. $(n\text{Bu})_2BOTf$/DIEA, 2. aldehyde, 3. H_2O_2 [376]
sb ketone + CH_2O, KOH [336]
sb crotylsilane derivative + aldehyde, TMSOMe/TMSOTf [373]
+ acetal, TMSOTf [373]
sb formamidine + aldehyde, *t*BuLi [127]
α-hydroxyphosphonates from sb H-phosphonate + aldehyde, DBU [377]

ketones

sb ketone + PhLi [236]
lithiated PS/DVB + ketone [184]

acid chlorides

ketones from sb RCOCl + PhCdCl [351]
3° alcohols from sb RCOCl + RMnI [351]

8.5.4 Radical additions

sb $RCH{=}CH_2$ + $n Bu_2SnHCl$ (in situ from $n Bu_2SnH_2/n Bu_2SnCl_2$/AIBN) [249]
sb $RCH_2Sn(n Bu)_2H$ + alkyne, AIBN [249]
sb thiol + alkene, AIBN [378]

8.6 Elimination reactions

8.6.1 Hofmann eliminations

3° amines from sb quaternized sulfonylethyl amines
+ NEt_3, w.c.s. [35, 40]
+ DIEA, w.c.s. [28]
3° amines from sb quaternary ammonium salts
+ NEt_3, w.c.s. [34]
Amberlite promoted, w.c.s. [33]

8.6.2 Other eliminations

oxidative

dehydroalanine derivatives from sb cysteine derived benzyl sulfones + DBU [379]
PS/DVB-CH_2-SO_2-CH(NHR^1)$COOR^2$ + DBU, w.c.s. [380]
alkenes from sb SeR + $NaIO_4$ [331]
alkenes $CH_2{=}CHR$ from PS/DVB-$SeCH_2CH_2R$ + H_2O_2, w.c.s. [312]

reductive

alkenes $CH_2{=}CHR$ from PS/DVB-$SeCH(CH_2Br)R$ + $n Bu_3SnH$/AIBN, w.c.s. [312]
alkanes CH_3-CH_2R from PS/DVB-$SeCH_2CH_2R$ + $n Bu_3SnH$/AIBN, w.c.s. [312]
PS/DVB-Se-alkyl to alkane, $n Bu_3SnH$/AIBN/toluene, w.c.s. [381]

8.7 Condensation reactions

8.7.1 Aldol condensation

sb acetophenone + arom. aldehyde, NaOMe [191]
sb aldehyde + acetophenone, NaOMe [339]
+ CH_3NO_2, NH_4OAc/HOAc [364]
sb arom. aldehyde + RCOMe, LiOH/DME [382]
PS/DVB-CHO + malonic acid, piperidine [238]

8.7.2 Knoevenagel condensation

sb β-ketoester + aldehyde, piperidine [246]
sb malonate + aldehyde, piperidine/HOAc [247]
+ arom. aldehyde, piperidine/py [383]
+ aldehyde, piperidinium acetate [244]
sb malonamide + aldehyde, piperidine/HOAc [247]

sb acetoacetate + aldehyde, piperidinium acetate [384]
sb oxindole + arom. aldehyde, pyrrolidine [385]
sb cyanoacetamide + aldehyde, piperidine [386]
+ arom. aldehyde, piperidine/DMF/MeOH [387]
quinolin-2(1H)-ones from sb N-malonylaminophenones, piperidine/py (intramolecular) [388]

8.7.3 Dieckmann condensation

N-acetoacetylamino acid esters + DIPEA, w.c.s. [142]
+ KOH/MeOH, w.c.s. [141]
pimelates + KOR [389]

8.7.4 Claisen condensation

sb R^1COCH_3 + R^2COOR^3, NaH [296]

8.7.5 Benzoin condensation

sb aldehyde + benzaldehyde, NaCN [339]

8.8 Multicomponent reactions

8.8.1 Ugi reaction

sb amine

Rink amine resin + ArCOOH/RCHO/RNC, MeOH/$CHCl_3$ [390]
+ RCOOH/RCHO/RNC, MeOH/DCM [391]
+ RCOOH/RCOMe/RNC [392]
+ 4-[(diethoxyphosphinyl)difluoromethyl] benzoic acid/RCHO/RNC [393]
+ RCOOH/RCHO/Weinreb amide isonitrile, MeOH/DCM [347]
sb amine + RCOOH/RCHO/PhNC or 2-pyNC, MeOH/$CHCl_3$/py [394]
+ RCOOH/RCHO (either one a C-glycoside)/RNC, MeOH/DCM [395]
sb amino acid ester + RCOOH/RCHO/RNC, MeOH [396]

sb acid

sb pyrimidine carboxylic acid + RNH_2/RCHO/RNC, dioxane/MeOH [275]

sb isonitrile

α-(N-acyl-N-alkylamino)-β-ketoamides from sb RNC + ArCOCHO/RNH_2/RCOOH [397]
5- and 6-membered lactams from sb RNC + $RCO(CH_2)_nCO_2H$/RNH_2 [398]
sb ArNC + RCHO/RNH_2/RCOOH, MeOH/THF [145]
hydantoin-4-imides from sb RNC + RCHO/RNH_2, py · HCl/KOCN/H_2O [399]
thiohydantoin-4-imides from sb RNC + RCHO/RNH_2, py · HCl/KSCN/H_2O [399]
5-(1'-aminoalkyl)tetrazoles from sb R^1NC + R^2CHO/R^3R^4NH, py · HCl/NaN_3/H_2O [399]
hydantoin-4-imides from sb RNC + RCHO/RNH_2/KOCN [400]

8.8.2 Mannich reaction

	tandem Mannich-Michael reaction of sb aldimine + Danishefsky's diene, $Yb(OTf)_3$	[225]
	sb silyl enol ether + aldehyde/aniline, $Sc(OTf)_3$	[401]
	sb alkyne + 2° amine/paraformaldehyde, CuCl/dioxane	[53]
	+ aldehyde/2° amine, CuCl	[402]
	sb arom. aldehyde + alkyne/2°amine, CuCl	[403]
	sb 2° amine + alkyne/aldehyde, CuCl	[403]
	sb indoles + paraformaldehyde/2° amine, HOAc	[163]

8.8.3 Baylis-Hillman reaction

	sb acrylate + arom. aldehyde, 3-HQN/DMF	[361]
	+ aldehyde, DABCO or 3-HQN	[360]
	+ arom. aldehyde/$ArSO_2NH_2$, DABCO/dioxane	[404]

8.8.4 1,3-dipolar cycloadditions

as one-pot reactions, with in situ formation of nitrone	sb hydroxylamine + aldehyde/alkene	[68]
	sb arom. aldehyde + hydroxylamine/alkene	[68]
	sb acrylates + aldehyde/CH_3NHOH	[68]
	tandem-Diels-Alder-reaction/1,3-dipolar cycloaddition (nitrostyrene + enol ether + sb acrylate)	[253]

8.8.5 Other multicomponent reactions

Grieco 3-component reaction	tetrahydroquinolines from sb aniline/aldehyde/alkene, cat. TFA	[405]
	from aniline/aldehyde/alkene, cat. TFA, either sb alkene or sb aldehyde	[224]
	from sb aniline/aldehyde/alkene, cat. $Yb(OTf)_3$	[406]
Hantzsch type reaction	1,4-dihydropyridines from sb enamine + β-ketoester/aldehyde	[407]
Doebner reaction	quinolines from sb α-ketoamide + aniline/aldehyde	[408]
Biginelli condensation	dihydropyrimidines from sb urea derivative+ β-ketoester/aldehyde	[409]
	thiazolidinones from sb amine, aldehyde and thiol	[410]

8.9 Olefination reactions

8.9.1 Wittig and related reactions

sb phosphonium salt or phosphonate	PS/DVB-$P(CH_2Ph)Ph_2Cl$ + 1. KO*t*Bu or NaH, 2. benzaldehyde, w.c.s.	[269]
	PS/DVB-CH_2-PPh_3Cl + formaldehyde, NaOH/Bu_4NOH	[266]
	PS/DVB-CH_2-PPh_3Cl/*n*BuLi, $ClCH_2CHO$	[238]
	PS/DVB-CH_2-PPh_3Br + 1. NaHDMS, 2. aldehyde	[263]
	PS/DVB-CH_2-PPh_3Cl + aldehyde, *n*BuLi/THF	[119]
	PS/DVB-$P(CH_2$-*p*-$C_6H_4NHCOR)Ph_2Cl$ + arom. aldehyde, NaOMe/MeOH, w.c.s.	[268]

	PS/DVB-P(CH_2-*p*-C_6H_4NHCOR)Ph_2Cl + KO*t*Bu/DMF/toluene (intramolecular with amide-CO)	[268]
	sb phosphonium salt + 1. *n*BuLi/THF, 2. aldehyde	[182]
	+ 1. *t*BuLi/THF, 2. aldehyde	[236]
	+ aldehyde, KO*t*Bu/THF	[50]
	, NaHMDS/THF/DMSO	[204]
	, LiBr/NEt_3/THF	[248]
	, LiHDMS/THF	[124]
	, NaOH/MeOH	[264]
	, various bases	[265]
	sb $RCH_2PO(OEt)_2$ + aldehyde, LiBr/NEt_3	[411]
	sb $RCOCH_2PO(OEt)_2$ + 2-formylaziridine, KO*t*Bu/THF	[357]
	+ aldehyde, LiCl/NEt_3/THF	[248]
	, various bases	[265]
	sb $R^1COCHR^2PO(OEt)_2$ + ketone, KHMDS or LiHMDS	[363]
sb aldehyde or ketone	sb arom. aldehyde + $PhCH_2PPh_3Br$, NaOMe/DMF	[215, 339]
	+ RCH_2PPh_3Br, NaOMe	[207]
	+ $PhCH_2PPh_3Cl$, NaOMe/DMF	[336]
	sb aldehyde + *n*-pentylPPh_3X, *n*BuLi/THF	[182]
	+ RCH_2PPh_3Br, *n*BuLi/dioxane	[412]
	+ PPh_3CH_3Br, NaHDMS/THF	[413]
	sb arom. aldehyde + Ph_3P=CHMe, THF	[224]
	+ R^1COC-$(PPh_3)R^2$, DMA	[382]
	sb aldehyde + Ph_3P=CHCOR, THF	[185]
	+ Ph_3P=CHR, THF	[285, 414]
	+ Ph_3P=CH_2, THF	[249]
	+ Ph_3P=CH-$(CH=CH)_n$-Ph, DMF	[207]
	sb RCH_2CHO + Ph_3P=$CHCO_2t$Bu, toluene	[32]
	sb arom. aldehyde + $(OEt)_2POCH_2CN$, NaH	[160]
	+ $ArCH_2PO(OEt)_2$, NaOMe/DMF	[415]
	sb aldehyde + $(OEt)_2POCH_2COOR$, *n*BuLi/THF	[413]
	+ $(OEt)_2POCH_2COOR$, LiBr/DIEA/MeCN	[414]
	sb ketone + $(OEt)_2POCH_2COOR$, KHDMS/THF or LiBr/DBU	[414]
phosphorylide formation	sb phosphonium salt + NaH or KOtBu	[269]
	sb RCH_2I + 1. PPh_3, 2. LiHMDS	[124]
phosphonium salt hydrolysis	sb PPh_2CH_2RBr to H_3CR, NaOMe/MeOH, w.c.s.	[268]

8.9.2 Metathesis reactions

8.9.2.1 cross metathesis		
ene-ene cross metathesis	sb alkene + alkene, $[Cl_2(PCy_3)_2Ru$=CHPh]	[332, 345]
	sb alkene + dodec-1-ene, $[Cl_2(PCy_3)_2Ru$=CHPh]	[416]
yne-ene cross metathesis	sb alkyne + alkene, $[Cl_2(PCy_3)_2Ru$=CHPh]	[81, 417]
ring opening cross metathesis	sb bicyclic alkene + styrene derivative, $[Cl_2(PCy_3)_2Ru$=CHPh]	[418]
	sb norbonene derivative + styrene, $[Cl_2(PCy_3)_2Ru$=CHPh]	[419]
8.9.2.2 ring closing metathesis	sb diene + $[Cl_2(PCy_3)_2Ru$=CHPh], with cleavage of styrene derivatives from support	[215]

formation of heterocycles

pyrrolines from sb yne-enes + $[Cl_2(PCy_3)_2Ru{=}CHPh]$, w.c.s. [87]
pyrrolines and tetrahydropyridines from sb dienes, $[Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2]$ or $[Cl_2(PCy_3)_2Ru{=}CHPh]$, w.c.s. [345]
dihydropyrans, tetrahydropyridines and 7-membered lactams from sb dienes + $[Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2]$, w.c.s. [119]
azepines and 7-membered lactams from sb dienes + $[Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2]$, w.c.s. [32]
7-membered lactams from sb dienes + $[Cl_2(PCy_3)_2Ru{=}CHPh]$, w.c.s. [118]
7-membered lactams from sb dienes + $[Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2]$, w.c.s. [420]

formation of macrocycles

cyclic peptides from sb dienes + $[Cl_2(PCy_3)_2Ru{=}CHPh]$ [421]
macrolactones from sb dienes + $[Cl_2(PCy_3)_2Ru{=}CHPh]$, w.c.s. [204]

8.9.3 Other olefination reactions

vinyl-PS/DVB from Merrifield resin + $Me_3S^+I^-$/*n*BuLi/LiI [366]

Tebbe olefination

RCOO-polymer to $RC(=CH_2)O$-polymer, $(Cp)_2TiCH_2/ClAlMe_2$ [365]

8.10 Cycloadditions

8.10.1 [2+2]-cycloadditions

β-lactams
- from ketene and sb imine [422]
- from sb imine + ketene [423]
- from sb aldimine + phenoxy ketene (gen. in situ from phenoxyacetylchloride + NEt_3) [424]

β-sultams from sb imine + sulfene (gen. in situ from $RCOCH_2SO_2Cl$/py) [425]

8.10.2 [3+2]-cycloadditions

8.10.2.1 Reactions of nitrile oxides

isoxazolines
- from sb nitrile oxide (gen. from nitroalkane) + alkene [364, 370, 371]
- from sb nitrile oxide (gen. from hydroximoyl chloride) + alkene [180]
- from sb nitrile oxide (gen. from aldoxime) + alkene [426]

isoxazoles from sb nitrile oxide (gen. from hydroximoyl chloride) + alkyne [180]
isoxazolines from sb alkene + nitrile oxide (gen. from nitroalkane) [139, 140, 331, 427, 429, 430]
isoxazolines/isoxazoles from sb alkene/alkyne + nitrile oxide (gen. from nitroalkane) [79]
isoxazoles from sb alkyne + nitrile oxide (gen. from nitroalkane or oxime) [427]
isoxazoles from sb alkyne + benzonitrile oxide (gen. in situ from benzohydroximoyl chloride) [428]

8.10.2.2	Reactions of nitrones	isoxazolidines	
		from sb cyclohexenol derivative + nitrone carboxylic acid	[431]
		from sb nitrone + α,β-unsat. carbonyl derivative, $Yb(OTf)_3$-cat.	[193]
		from sb hydroxylamine + aldehyde + alkene	[68]
		from sb arom. aldehyde + RNHOH + alkene	[68]
		from sb acrylate + aldehyde + CH_3NHOH	[68]
8.10.2.3	Reactions of azomethine ylides	pyrrolidines	
		from sb azaallyl anion (gen. in situ from α-imino stannane + *n*BuLi) + alkenes	[432]
		from sb pyridinium methide + maleimide	[46]
		from sb azomethine ylide (gen. from imine/ $AgNO_3/NEt_3$) + α, β-unsat. carbonyl derivative	[433]
		from sb α,β unsat. ketone + azomethine ylide (gen. from imines/LiBr/DBU)	[191]
		from sb imine + maleimides	[434]
		from sb arom. aldehyde + amine + *N*-phenylmaleimide	[226]
		via intramolecular reaction of azomethine ylide (gen. from imine) + alkene	[45]
		via intramolecular reaction of azomethine ylide (gen. from imine and DIEA/$AgNO_3$) + alkenes	[203]
		pyrroles from sb azomethine ylide (via sb münchnone) + acetylenedicarboxylate	[242]
		pyrroles from sb münchnone and alkyne	[394]
		imidazoles from sb münchnone + tosylimine	[435]
8.10.2.4	Other [3+2] -cycloadditions	furans from sb isomünchnone + alkyne	[146]
		furans from sb isomünchnone (gen. in situ from diazo imides with $Rh_2(pfbm)_4$) + DMAD, then cycloreversion	[436]
		furans from sb α-diazoester + alkyne, $Rh_2(pfbm)_4$	[147]

8.10.3 [4+2]-cycloadditions

8.10.3.1	Diels-Alder reactions	cyclohexeneamines from sb 2-aminobutadiene + maleimide or nitrostyrene	[437]
		C_{60}-annellated norbonene from sb cyclopentadiene derivative + C_{60} fullerene	[299]
		oxabicycloheptene derivatives from sb furan + methyl acrylate	[438]
		isoindolines from sb diene + maleimide	[87]
		cyclohexenes from sb diene + various dienophiles	[365]
		annellated cyclohexenes from sb diene + maleimide or naphthoquinone	[200]
		sb diene + divinylketone, $ZnCl_2$	[254]
		sb *o*-quinodimethane (gen. in situ from benzocyclobutenol) + various dienophiles, w.c.s.	[231]
		sb acrylate + butadiene derivatives	[428]
		sb acrylate + butadiene derivatives, $TiCl_4$, $TiCl_3(OiPr)$ or $TiCl_2(OiPr)_2$ catalyzed	[439]
		sb acrylate + bisdiene	[254]

	norbonene derivatives from sb crotonate + cyclopentadiene, Et_2AlCl-cat.	[440]
	norbonene derivatives from sb cinnamate + cyclopentadiene	[441]
	sb α,β-unsaturated ketone + 1,3-pentadiene, $ZnCl_2$	[254]
	tandem-Diels-Alder-1,3-dipolar cycloaddition, sb acrylate + enolether + nitrostyrene (at 15 kBar)	[253]
8.10.3.2 Hetero-Diels-Alder reactions	pyridoxines from sb alkene + oxazole derivative	[442]
	pyridazines from sb azadiene + electron rich alkene or alkyne	[443]
	3,4-dihydro-2H-pyrans from sb oxabutadiene + enol ether	[384]
	sb diene + 3,5-pyrazolinedione (gen. in situ from 3,5-pyrazolidinedione with $PhI(TFA)_2$)	[444]
	+ 1,2,4-triazolinedione (gen. in situ from urazole with $PhI(TFA)_2$)	[444]
	sb *o*-quinodimethane (gen. in situ from benzocyclobutenol) + arom. aldehydes, tosylimines or Cl_3CCN	[231]

8.11 Transition metal catalyzed reactions

8.11.1 Palladium catalyzed reactions

8.11.1.1 Suzuki reaction

sb aryl derivatives

sb ArBr	+ $ArB(OH)_2$, $Pd(PPh_3)_4/K_2CO_3/DMF/H_2O$ (= st.aq.cond.)	[89, 109, 159, 445]
	+ $RB(OH)_2$, st.aq.cond.	[195, 210, 310, 446, 447]
	sb 1,4-bromobenzodiazepine-2,5-dione + $ArB(OH)_2$, $[PdCl_2(dppf)]/Cs_2CO_3/DMF/THF/H_2O$	[90]
	+ in situ formed boronic acid (from alkene after hydroboration), st.aq.cond.	[88]
sb ArBr or ArI	+ $RB(OH)_2$, st.aq.cond.	[448, 449]
	, microwave, st.aq.cond.	[450]
	+ $PhB(OH)_2$, $[PdCl_2(dppf)]/NEt_3/DMF/H_2O$	[424]
sb ArI	+ $RB(OH)_2$, st.aq.cond.	[115, 139, 177, 451]
	+ $PhB(OH)_2$, $[PdCl_2(dppf)]/NEt_3/DMF$	[452]
	resin capture, tandem Suzuki with bis(borylalkenes), $[PdCl_2(dppf)]/KOH/DME/H_2O$	[453]
	$[Pd(PPh_3)_2Cl_2]/KOH/DME/H_2O$	[212]
	+ $RB(OH)_2$, $Pd(OAc)_2/K_2CO_3$/dioxane/H_2O	[454]
	+ $RB(OH)_2$, $Pd(OAc)_2/K_2CO_3/THF/H_2O$ (MIMOTOPES^R pins used as solid support)	[455]
	+ RBR'_3, st.aq.cond. or $Pd(dba)_3$ or $[PdCl_2(dppf)]$	[451]
	+ $RB(OR')_3$, st.aq.cond. or $Pd(dba)_3$ or $[PdCl_2(dppf)]$	[451]
sb ArOTf	+ $ArB(OH)_2$, st.aq.cond.	[261]
sb HetArBr	sb bromopyridine + $ArB(OH)_2$, st.aq.cond.	[41]
sb alkenyl bromides	sb vinyl bromide + $RB(OH)_2$, $Pd(OAc)_2/K_2CO_3$/dioxane/H_2O	[200]
	sb bromocyclopentenols + alkyl-9-BBN derivatives, st.aq.cond.	[111]

sb boron derivative

sb Ar-B(OR)$_2$ + ArBr, $Pd(PPh_3)_2Cl_2$/KOH/DME/H_2O [334]
+ ArX, $Pd(PPh_3)_4/K_3PO_4$/DMF/H_2O [456]
, st.aq.cond. [451]

8.11.1.2 Stille reaction

sb aryl derivatives

sb ArI
+ vinyl or aryl stannane, $Pd_2dba_3/AsPh_3$/NMP [457]
+ ethoxyvinyl stannane, $Pd_2dba_3/AsPh_3$/NMP [105]
+ aryl stannane, $Pd_2dba_3/AsPh_3$/NMP [452, 458]
, $Pd_2dba_3/AsPh_3$/NMP (microwave) [450]
+ stannane, $Pd_2dba_3/AsPh_3$/dioxane [177]
+ vinyl or heteroaryl stannane, $Pd_2dba_3/AsPh_3$/dioxane [454]

sb ArBr or ArI
sb ArX + tributyltinsquarate, $Pd(PPh_3)_2Cl_2$/CuI/DMF [334]
sb ArI, ArBr or HetArBr + vinyl or aryl stannane, $Pd(PPh_3)_4$/DMF or $Pd_2dba_3/(2\text{-furyl})_3P$/DMF [459]

sb HetAr-Br
sb bromothiophene + thiophene stannane, $Pd(PPh_3)_2Cl_2$/DMF [329]

sb alkenyl bromides

sb vinyl bromide + vinyl or heteroarylstannane, $Pd(PPh_3)_4$/dioxane [200]
+ vinyl stannane, $Pd_2dba_3/AsPh_3$/NMP [248]

sb stannanes

+ RX
sb aryl stannane + ArI or ArOTf, Pd_2dba_3/PPh_3/LiCl/NMP [458]
+ O-methyl-5-I-vanillin, $Pd_2dba_3/AsPh_3$/DMA [446]
vinyl stannane-vinyl bromide derivative + $Pd(PPh_3)_4$/toluene, intramolecular, w.c.s. [249]

+ RCOCl
sb aryl stannane + RCOCl, Pd_2dba_3/K_2CO_3/DIEA/THF [97, 98, 100]
sb stannane + RCOCl, Pd_2dba_3/K_2CO_3/DIEA/THF (MIMOTOPES pins^R used as solid support) [99]

8.11.1.3 Heck reaction

acyclic products
sb ArX + alkene, $Pd(OAc)_2/PPh_3/NEt_3$/DMF [441]
sb ArI + alkene, $[PdCl_2(dppf)]/NEt_3/NBu_4I/H_2O$/DMF [424]
+ α,β-unsat. carbonyl deriv., $Pd(OAc)_2/PPh_3/NEt_3$/NBu_4Cl/H_2O [460]
, $Pd(OAc)_2/NBu_4Cl$/NaOAc/DMA [461]
+ acrylate, $Pd(OAc)_2/NBu_4Cl/NEt_3$/DMF [105, 463]
, $Pd(OAc)_2/P(o\text{-Tol})_3/NEt_3$/DMF [462]
, $Pd_2(dba)_3/P(o\text{-Tol})_3$/DMF [125]
+ alkyne, $Pd(OAc)_2/NBu_4Cl/NEt_3$/DMF
or $Pd_2(dba)_3/P(o\text{-Tol})_3/NEt_3$/DMF [463]
sb styrene derivative + ArX, $Pd_2(dba)_3/P(o\text{-Tol})_3/NEt_3$/DMF
or $Pd(OAc)_2/NBu_4Cl/NEt_3$/DMF [463]

cyclic products
benzo[c]furans from sb Ar-I-enol ether, $Pd(OAc)_2/PPh_3/NBu_4Cl/K_2CO_3$/DMA [29]
benzofurans from sb O-allyl-*o*-I-phenol derivatives, $Pd(PPh_3)_2Cl_2/NEt_3/NBu_4Cl$/DMF/$H_2O$ [37]
indoles from sb N-allyl-*o*-I-aniline derivatives,

	$Pd(PPh_3)_2Cl_2/NEt_3/NBu_4Cl/DMF/H_2O$	[37]
	indoles from sb R^1-C=C-CH_2NR^2ArBr, $Pd(PPh_3)_4/PPh_3/NaOAc/DMA$	[102]
	3-alkylidene-2-oxindoles from sb 3-I-4-(NRCOC=CR)Ar derivatives, $Pd(OAc)_2/PPh_3/Ag_2CO_3/DMF$	[356]
	isoquinolinones from sb ArI-acrylamide, $Pd(PPh_3)_4/PPh_3/NaOAc/DMA$	[56]
	di- and tetrahydroisoquinolines from sb Ar-I-enamines or sb Ar-I-allylamines, $Pd(OAc)_2/PPh_3/NBu_4Cl/K_2CO_3/DMA$	[28]
	macrocycles from sb ArI-acrylamide, $Pd(OAc)_2/PPh_3/NBu_4Cl/DMF/H_2O/NEt_3$	[464, 465]

8.11.1.4 Sonogashira reaction

sb aryl derivatives

acyclic products	sb ArI + R-C≡CH, $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$/CuI/DMF	[431]
	, $Pd(PPh_3)_2Cl_2$/CuI/NEt_3/dioxane	[461]
	+ TMS-C≡CH, $Pd(PPh_3)_4$/CuI/NEt_3/THF	[402]
	+ propargyl alcohol, $Pd(PPh_3)_2Cl_2$/CuI/NEt_3/dioxane	[174]
	sb ArI (levoglucosan derivative) + R-C≡CH, $Pd(PPh_3)_2Cl_2$/CuI/NEt_3/dioxane	[177]
	sb *o*-I-aniline + R-C≡CH, $Pd(PPh_3)_2Cl_2$/CuI/NEt_3/DMF	[163]
	, $Pd(PPh_3)_2Cl_2$/CuI/Et_2NH/DMF	[39]
cyclic products	benzofurans from sb *o*-I-phenol + R-C≡CH, $Pd(PPh_3)_2Cl_2$/CuI/TMG/DMF	[466]
	indoles from sb 2-$NHSO_2Me$-ArI + R-C≡CH, $Pd(PPh_3)_2Cl_2$/CuI/NEt_3/DMF	[163]
	from sb *o*-I-aniline + R-C≡C-R, $Pd(PPh_3)_2Cl_2$/TMG/DMF	[467]
	from sb 2-NHAc-ArI + R-C≡CH, $Pd(PPh_3)_2Cl_2$/CuI/TMG/dioxane	[252]
	from sb *o*-I-aniline + R-C≡C-R, $Pd(OAc)_2/PPh_3$/base/DMF, base: LiCl/K_2CO_3 or Na_2CO_3/NBu_4Cl or KOAc/NBu_4Cl	[468]

sb alkinyl derivatives

acyclic products	sb Ar-C≡C + (TMS-C≡C)-Ar-I, $Pd(dba)_2$/CuI/PPh_3/NEt_3	[202]
	sb propiolyl hydroxamate + 5-iodouridine, $Pd(PPh_3)_4$/CuI/NEt_3/DMF	[189]
cyclic products	indoles from sb 3-F_3CCONH-4-alkyne-benzoic acid + ROTf, $Pd(PPh_3)_4/K_2CO_3$/DMF	[39]

8.11.1.5 Other Paladium catalyzed reactions

coupling reactions

Suzuki-type	sb Ar-$B(OR)_2$ from sb ArI + diboron pinacol ester, $PdCl_2$(dppf)/KOAc/DMF	[456]
Sonogashira-type	oligoacetylenes from sb acetylene + alkynyl iodide, $Pd_2(dba)_3$/CuI/PPh_3/TEA	[49, 469]
Ar-Ar cross-coupling	sb ArI + ArZnBr or BnZnBr, Pd_2 $(dba)_3/PPh_3$ or dppf/THF	[470]
	sb ArBr + ArZnBr, [$PdCl_2$(dppf)]	[471]

others	sb alkene, alkyne or boronate + hypervalent aryliodonium salt, $Pd_2(dba)_3/P(o\text{-}Tol)_3$	[472]
	sb tropane derivative + 1. ArBr, $Pd(PPh_3)_4$/THF 2. $ArB(OH)_2$, PPh_3/Na_2CO_3/THF or Ph-C≡C, CuI/Bu_4NCl/DMF or HCOOH, NEt_3/PPh_3/DMF	[473]
aromatic substitutions		
C-arylation	sb ArI + KCN, $Pd_2(dba)_3$/dppf/NMP	[461]
N-arylation	sb ArBr + Ar-NR^1R^2, $Pd_2(dba)_3$/various phosphines/NaO*t*Bu	[474]
	+ R^1R^2NH, $Pd_2(dba)_3$/P(o-tolyl)$_3$ or BINAP/NaO*t*Bu	[475]
S-arylation	sb ArI + RSH, $Pd_2(dba)_3$/dppf/DIPEA/DMA	[454]
	sb ArI + RSH, $Pd_2(dba)_3$/dppf/DIPEA/DMA (MIMOTOPES pins^R used as solid support)	[455]
nucleophilic aliphatic substitutions		
N-alkylation	sb allyl ester + amine, $Pd(PPh_3)_4$/THF, w.c.s.	[81]
	sb amine + allylic carbonate or acetate, $Pd(PPh_3)_4$	[42]
	sb sulfonamide + allyl methyl carbonate, $Pd_2(dba)_3/PPh_3$/THF	[108]
	sb allyl ester + sulfonamide, $Pd(PPh_3)_4$/THF, w.c.s.	[81]
C-alkylation	sb allyl ester + β-dicarbonyl derivative, $Pd(PPh_3)_4$/THF, w.c.s.	[81]
8.11.2 Pauson-Khand reaction		
intermolecular	sb alkyne + norbornadiene, $Co_2(CO)_8$/benzene	[476]
	+ bicyclic alkene, $Co_2(CO)_8$/benzene	[477]
intramolecular	azabicyclo[4.3.0]nonen-8-ones from sb N-allyl-yne derivative, $Co_2(CO)_8$/NMO	[478]
	hexahydro-1H-[2]pyrindinones from sb N-allyl-yne derivative, $Co_2(CO)_8$/NMO	[27]
8.11.3 Other transition metal catalyzed reactions		
acylcarbene insertion (tagging)	PS/DVB + diazoketone tags, $Rh_2(CF_3CO_2)_4$	[479, 480]
hydroformylation	sb R^1R^2=CH + $Rh(acac)(CO)_2/H_2/CO$	[481]
metallocene catalyst formation	sb cyclopentadiene + 1. MeLi 2. $CpTiCl_3$	[260]
Cadiot-Chodkiewicz reaction	sb haloalkyne + alkyne, $CuCl/NH_2OH \cdot HCl$	[482]
Stille type reaction	sb ArI + aryl, alkenyl or alkinyl stannanes, CuI/NaCl/NMP	[483]
boronate formation	sb ArI + bis-(pinacolato)diboron, $Pt(PPh_3)_4$/KOAc/DMSO	[212]

8.12 Radical reactions

8.12.1 Radical allylations

sb R_3CBr + allyltributylstannanes, AIBN	[302]

8.12.2 Radical additions

sb RSH + alkene, AIBN	[378]
sb $RCH{=}CH_2$ + $n Bu_2SnHCl$ (in situ from $n Bu_2SnH_2$/ $n Bu_2SnCl_2$), AIBN	[249]
sb $RCH_2Sn(n Bu)_2H$ + alkyne, AIBN	[249]

8.12.3 Cyclizations

furans and benzofurans from sb iodoacetylenic ethers, $n Bu_3SnH$/AIBN	[235]
sb *o*-I-benzyl enol ether, $n Bu_3SnH$/AIBN	[29, 174]
sb 4-allyloxy-*m*-I-phenyl acetate, 1. SmI_2/HMPT/THF, 2. electrophile	[484]
ArI + alkene, SmI_2/HMPT	[173]

8.12.4 Cleavage reactions

PS/DVB-$SeCHRCH_2Br$ to alkene $RCH{=}CH_2$, $n Bu_3SnH$/AIBN/toluene, w.c.s.	[312]
PS/DVB-Se-alkyl to alkane, $n Bu_3SnH$/AIBN/toluene, w.c.s.	[312, 381]

8.13 Reductions

8.13.1 Functional group conversions

8.13.1.1	Ester to alcohol	RCOOMe to RCH_2OH, DIBAH [125]
		, $NaBH_4$ [310]
		ArCOOR to $ArCH_2OH$, $LiAlH_4$ [195]
		malonate to diol, $LiAlH_4$ [300]
		RCOO-polymer to RCH_2OH, DIBAH, w.c.s. [244, 297]
		PS/DVB-$CH{=}CHCOOEt$ to PS/DVB-$CH{=}CHCH_2OH$, $LiAlH_4/AlCl_3$ [238]
8.13.1.2	Carboxylic acid to alcohol	PS/DVB-CH_2COOH to PS/DVB-$(CH_2)_2OH$, $LiAlH_4$ [73]
		PS/DVB-$CH{=}CHCOOH$ to PS/DVB-$CH{=}CHCH_2OH$, $LiAlH_4/AlCl_3$ [238]
8.13.1.3	Carboxylic acid chloride to alcohol	$NaBH_4$ or $NaBH_3CN$ [241]
8.13.1.4	Aldehyde to alcohol	arom. aldehyde to $ArCH_2OH$, $NaAl(CH_3OCH_2CH_2O)_2H_2$ [339]
		, $NaBH_4$ [196, 215, 336, 340]
		aldehyde to RCH_2OH, $NaBH_4$/sonication, with lactonisation [125]
8.13.1.5	Ketone to alcohol	$ArCOCH_2R$ to $ArC(OH)HCH_2R$, $NaBH_4$ [31, 128]
		ArCOMe to $ArCH(OH)Me$, $NaBH_4/NaHCO_3$ [485]
		steroidal ketone to steroidal alcohol, $NaBH_4$ or KBH_4 [486]
		PG-ketone to PG-alcohol, L-Selectride [111]
		$R^1CH_2COCHR^2$ to $R^1CH_2C(OH)HCHR^2$, $Zn(BH_4)_2$ [123]

8.13.1.6 Ketone to alkane	$ArCOCH_2R$ to $Ar(CH_2)_2R$, $LiAlH_4/AlCl_3$	[273]
8.13.1.7 Thioester to aldehyde	DIBAH	[375]
8.13.1.8 Thioester to thiol	$LiBH_4$	[264, 273]
	$LiAlH_4$	[277]
8.13.1.9 Thioester to alcohol	RCOS-polymer to RCH_2OH, $LiBH_4$, w.c.s.	[368, 375, 401]
	RCOSBn to RCH_2OH, 1. TIPSOTf, 2,6-lutidine, 2. $LiBH_4$	[286]
8.13.1.10 Amide to amine	RCONHR' to RCH_2NHR', $BH_3 \cdot THF$	[487]
	RCONHR' to RCH_2NHR', 1. $BH_3 \cdot THF$, 2. NEt_3	[488]
	N-acylated dipeptide to 3°/2° triamine, $BH_3 \cdot THF$	[86]
	$BH_3 \cdot THF/B(OH)_3/B(OMe_3)_3$	[489]
	$ArCONH_2$ to $ArCH_2NH_2$, $BH_3 \cdot DMS$	[192]
8.13.1.11 Amide to aldehyde	Weinreb amide to aldehyde, $LiAlH_4$ or DIBAH	[346]
8.13.1.12 Imine to amine	ArCH=NR to $ArCH_2NHR$, $LiBH_4$	[344]
	, $NaBH_4$	[194]
	dihydroisoquinoline to tetrahydroisoquinoline, $NaBH_3CN$	[490]
	dihydroisoquinoline iminium salt to tetrahydroisoquinoline, $NaBH_4$	[77]
	ketimine to amine, $NaBH_3CN$/HOAc/DMA	[491]
8.13.1.13 Carbamate to amine	sb carbamate to 3° N-methylamine, $LiAlH_4$/THF, w.c.s.	[492]
	, Red-Al	[349]
8.13.1.14 Nitrile to amine	ArCN to $ArCH_2NH_2$, $BH_3 \cdot DMS$	[51]
8.13.1.15 Oxime to hydroxylamine	ArC=NOH to $ArCH_2NHOH$, $BH_3 \cdot Py$	[193]
8.13.1.16 Azide to amine	$R^1R^2CHN_3$, $SnCl_2$/PhSH/NEt_3	[75, 123]
	RCH_2N_3, $SnCl_2$/PhSH/NEt_3	[72, 493]
	ArN_3, $SnCl_2$/PhSH/NEt_3	[88]
	$R^1R^2CHN_3$, 1. PMe_3, 2. THF/H_2O	[494]
	RCH_2N_3, PPh_3/H_2O	[124]
8.13.1.17 $ArNO_2$ to $ArNH_2$	$SnCl_2 \cdot 2H_2O$/DMF, RT	[162, 356]
	$SnCl_2$/DMF, 80° C	[93]
	$SnCl_2 \cdot 2H_2O$, NMP, 50° C	[317]
	$SnCl_2 \cdot 2\ H_2O$/EtOH/DCM, reflux	[134]
	$SnCl_2 \cdot H_2O$/DMF/EtOH, 70° C	[323]
	$Na_2S_2O_4$/EtOH, reflux	[268]
	$NaBH_4/Cu(acac)_2$/DMF/EtOH, RT	[315]
	$LiAlH_4$	[364]
8.13.1.18 Reduction of C=C and C≡C-bonds	alkyne to alkene, disiamylborane/THF	[181]
	, 9-BBN/THF	[182]
	cyclopentenone to cyclopentanone, $[(PPh_3)CuH]_6$/toluene	[27]
	alkene or alkyne to alkane, with diimide generated in situ from $PhSO_2NHNH_2$	[495]
	dehydropeptide + H_2/chiral Rh-cat. (asymmetric)	[496]
	steroid + $H_2/Rh(PPh_3)_3Cl$	[486]

8.13.1.19 Hydrogenation		
alkene to alkane	dehydropeptide + H_2/chiral Rh-cat. (asymmetric)	[496]
	steroid + $H_2/Rh(PPh_3)_3Cl$	[486]
benzyl ester cleavage	cleavage of peptide benzyl ester, $Pd(OAc)_2$/DMF	[497, 498]
8.13.1.20 Disulfide reduction	β-mercaptoethanol	[270]
	PBu_3	[60, 271]
	TCEP, w.c.s.	[76, 499]
	$NaBH_4$	[500]
8.13.1.21 Other reductions	diazonium salt to hydrazine, $SnCl_2$/HCl	[501]
	epoxide to 2° alcohol, $LiBH_4$	[413]
	RSnCl to RSnH, $LiBH_4$	[249]
	SeBr to SeLi, $LiBH_4$	[312]

8.13.2 Reductive aminations

8.13.2.1 Amine + ketone		
sb ketone	$NaBH(OAc)_3$, ultrasound	[355]
	1. $Ti(OiPr)_4$ 2. $NaBH(OAc)_3$	[502]
	$NaBH_3CN$ (MIMOTOPES pins^R used as solid support)	[503]
	sb α-ketoester, $NaBH_3CN$	[504]
sb amine	$BH_3 \cdot py$	[505]
	+ β-ketoacid, $BH_3 \cdot py$	[506]
	Rink amine resin + ketone, $NaBH_3CN$/THF/H_2O	[507]
8.13.2.2 Amine + aldehyde		
sb aromatic aldehyde	+ α-amino acid ester, $NaBH(OAc)_3$/1% HOAc in DMF	[89, 90, 435]
	+ arom. amine, $NaBH(OAc)_3$/1% HOAc in DMF	[126]
	+ $ArCH_2NH_2$, $NaBH(OAc)_3$/DCM	[159]
	AMEBA resin + (4-OMe)-phenethylamine, $NaBH(OAc)_3$/DCE	[156]
	+ cyclopropylamine 1. Na_2SO_4/AcOH, 2. $NaBH(OAc)_3$/THF	[446]
	+ benzylamine or arom. amine, $NaBH(OAc)_3$	[340]
	+ $ArNH_2$, $NaBH_3CN$/1% HOAc in DMA	[38]
	1. TMOF, 1° amine, 2. $NaBH_3CN$/1% HOAc in DMF	[215]
	+ tyramine, $NaBH_3CN$/HOAc /MeOH	[59]
	+ α-amino acid ester, $NaBH_3CN$/DMF	[95]
	+ benzylamine, $NaBH_3CN$/HOAc/DMF/DCM	[508]
	sb indole-3-aldehyde + amine: 1. $Me_4NBH(OAc)_3$/DCE, 2. $NaBH_3CN$/MeOH	[157]
	+ 4-aminoproline, TMOF /MeOH/$BH_3 \cdot$ py/1% HOAc	[114]
	+ 1° amines, 1. TMOF/MeOH, 2. $BH_3 \cdot$ py/HOAc	[213]
sb aliphatic amine	Knorr amine resin + 4-F-PhCHO, $NaBH(OAc)_3$/1% HOAc in DMF	[31]
	Rink amine resin + aldehyde, $NaBH_3CN$/THF/H_2O	[507]
	+ arom. aldehyde, 1. TMOF, 2. $NaBH_3CN$/1% AcOH	[387]
	sb amino acid ester + aldehyde, $NaBH(OAc)_3$/DCM/sonication	[509]
	$NaBH_3CN$/ 1% HOAc/DMF	[65]
	$NaBH(OAc)_3$/HOAc/DCM	[510]

	$NaBH_3CN$/TMOF/1% HOAc	[512]
	$NaBH_3CN$/TMOF/MeOH/(HOAc)	[396, 511, 513]
	1. TEOF, 2. $NaBH(OAc)_3$	[217]
sb amino acid + arom. aldehyde,		
	$NaBH_3CN$/TMOF/HAOc/MeOH	[396, 511, 513]
	1. 1% HOAc in DMA, 2. $NaBH_3CN$	[514]
	1% HOAc in DMF/$NaBH_3CN$	[515]
	$NaBH(OAc)_3$/DCM	[516]
	1. TMOF (2 x), 2. $NaBH_3CN$/HOAc (2 x)	[142]
	$NaBH_3CN$/TMOF	[517]
sb amine + aldehyde, $NaBH_3CN$/DMA/HOAc		[518]
+ arom. aldehyde or HetArCHO, $NaBH_3CN$		[272]
+ arom. aldehyde, $NaBH_3CN$/TMOF		[488]
sb 1° amine + PhCHO, $NaBH_3CN$/TMOF		[519]
+ aldehyde, $NaBH_3CN$/HOAc/TMOF		[141]
sb 2° amine + aldehyde, $NaBH(OAc)_3$/HOAc		[33]
+ aldehyde, $BH_3 \cdot Py$/DMF/EtOH		[505]
sb piperazine + aldehyde, $NaBH(OAc)_3$/MeOH/DCM		[82]
sb tropane derivative + aldehyde, 1% HOAc in DMF/$NaBH(OAc)_3$		[473]
Leuckart reaction	methylation of sb amine with CH_2O/HCOOH	[48]
sb aromatic amine	+ arom. aldehyde, 1% HOAc in DMA/$NaBH_3CN$	[30]
sb ArNHR + 2-hydroxybenzaldehyde, 1% HOAc in DMA/mol. sieves/$NaBH_3CN$ or $NaBH(OAc)_3$		[38]
+ aldehyde, $NaBH(OAc)_3$/sonication		[356]

8.14 Oxidations

8.14.1 1° alcohol to aldehyde	py · SO_3/NEt_3/DMSO	[185, 186, 285, 286]
	py · SO_3/NEt_3/DMSO/DCM	[413]
	benzyl alcohol to benzaldehyde, Py · SO_3/NEt_3/DMSO/DCM	[156]
	TPAP/NMO	[520]
	benzyl alcohol to benzaldehyde, TPAP/NMO	[521]
	$(COCl)_2$/DMSO/NEt_3/DCM	[45]
	$(COCl)_2$/DMSO/NEt_3	[204]
	DMP/$NaHCO_3$/py/DCM	[124]
	DMP/DCM	[286]
	IBX/DMSO/THF	[432]
	NCS/Me_2S/NEt_3	[249]
	CrO_2Cl_2/*t*BuOH/py	[182]
8.14.2 2° alcohol to ketone	py · SO_3	[128]
	TPAP/NMO	[520]
	DMP/DCM	[111]
	IBX/DMSO/THF	[171]
	NCS/Me_2S/NEt_3	[249]
	pyridinium dichromate (MIMOTOPES pins^R used as solid support)	[503]

8.14.3 Aldehyde to carboxylic acid	$NaClO_2/NaH_2PO_4$	[124]
	$NaClO_2/NH_2SO_3H$/2-methyl-2-2-butene/DCM/H_2O	[323]
8.14.4 Sulfide to sulfoxide	*m*-CPBA	[276, 522, 523]
8.14.5 Sulfinamide to sulfonamide	OsO_4/NMO, nBu_4N oxone or $NaIO_4/RuCl_3 \cdot H_20$	[161]
8.14.6 Sulfide to sulfone	*m*-CPBA	[28, 264, 275, 279, 363, 379, 380, 443, 523]
	m-CPBA, linker activation for cleavage	[165]
8.14.7 Selenide to selenoxide	$NaIO_4$	[331]
8.14.8 Phosphite to phosphate	NMO	[524]
8.14.9 Kornblum oxidation of Merrifield resin to PS/DVB-CHO	$NaHCO_3$/DMSO	[238, 370, 371, 525]
	K_2CO_3/DMSO	[249]
8.14.10 Epoxidation	sb alkene, *m*-CPBA	[308, 413]
	sb styrene derivative, *m*-CPBA	[452]
	sb cholesterol, *m*-CPBA	[486]
	sb alkene + dimethyldioxirane	[200]
8.14.11 Ozonolysis	sb alkene to aldehyde, 1. O_3/DCM/MeOH, 2. DMS	[373]
	, 1. O_3/DCM, 2. PPh_3/sonication	[526]
	, O_3/py/DCM	[125]
	, 1. O_3/DCM, 2. PPh_3	[372]
	, 1. O_3/DCM, 2. DMS, w.c.s.	[263]
	$R^1NHCHR^2CH{=}CHCONHR^3$ to R^1NHCHR^2CHO, 1. O_3/DCM, 2. thiourea	[265]
	sb alkene to 1° alcohol, 1. O_3/DCM, 2. $NaBH_4$/sonication	[526]
	sb alkene to carboxylic acid, 1. O_3/DCM/HOAc, 2. O_2	[526]
8.14.12 Hydroxylation	Sharpless asymmetric dihydroxylation of sb trans-cinnamate	[441, 527]
	Sharpless asymmetric dihydroxylation of sb alkenes	[528]
8.14.13 Other oxidation reactions	1,4-dihydropyridines to pyridines, CAN	[246]
	quinolines to quinoline-N-oxides, *m*-CPBA	[325]
	dihydroquinazolinone to quinazolinone, $KMnO_4$/acetone	[529]
	styrene derivative to $ArC(O)CH_3$, cat. $PdCl_2/CuCl_2$	[338]
	oxidative cleavage of sb $ArCH_2NHR$ to H_2NR, DDQ	[192]
	oxidative cleavage of sb aryl hydrazide with CuOAc/$nPrNH_2$	[530]
	sb $ArCOC(=Ph_3P)COOR$ to ArCOCOCOOR, oxone	[531]
	sb hydrazone to acetoxyazo derivative, $Pb(OAc)_4$	[532]

8.15 Formation of carbonyl compounds and derivatives thereof

For the formation of esters see sections 8.2.5.3 and 8.2.6.1

8.15.1 Acetal formation/cleavage and related reactions

8.15.1.1 Acetal formation	sb propanediol derivative + terephthalaldehyde, PTSA/Na_2SO_4 (monoprotection)	[336]
	sb propanediol + *m*- or p-$Ph(CHO)_2$, *m*-benzenedisulfonic acid/Na_2SO_4 (monoprotection)	[339]
	sb propanediol + 2,7-$(CH_3)_2$-2,4,6-octatriene-1,8-dial, *m*-benzenedisulfonic acid/Na_2SO_4 (monoprotection)	[412]
	sb 1,3-diol + 1-naphthaldehyde/PTSA/reflux azeotropically	[300]
	sb aldehyde + TMOF/PPTS	[373]
	PS/DVB-CHO + D-glucose derivative/PTSA	[533]
8.15.1.2 Ketal formation	sb ArCOMe + TMOF/CSA	[200]
	sb diol + symmetrical diketone, PTSA/TEOF or $BF_3 \cdot Et_2O$ (monoprotection)	[341]
	ketene aminals from sb thioamides + 1° or 2° amines, EDC	[305]
	dithian formation, sb dithiol + aldehyde, $BF_3 \cdot Et_2O$ or Me_3SiCl	[277]
8.15.1.3 Acetal or ketal cleavage	sb $RCH_2CH(OEt)_2$, PTSA/acetone/NMP	[32]
	HCOOH/$CHCl_3$, cleavage of arom. aldehyde from support	[336]
	HCl/H_2O/dioxane, cleavage of arom. aldehyde or Me_2CO from support	[207]
	HCl/H_2O/dioxane, cleavage of arom. aldehyde from support	[339, 447]
	TFA/H_2O, cleavage of aldehyde from support	[534]
	HCl/THF, cleavage of apocarotenals from support	[412]
	PPTS/dioxane, cleavage of 1-naphthaldehyde from support	[300]
	sb oxazolidine to RCHO, HOAc/H_2O, w.c.s.	[535]
	dithian cleavage, sb dithian + H_5IO_6 or $Hg(ClO_4)_2$	[277]
	+ $PhI(TFA)_2$, $Hg(ClO_4)_2$ or HIO_4/THF (/H_2O)	[199]
	cyanoacetamidines via cleavage of sb ketene aminals, TFA/DCM	[305]
8.15.1.4 Transacetalization	PEG-OH resin + $BrCH_2CH(OEt)_2$/quinoline toluenesulfonate	[71]
8.15.1.5 Transketalization	sb $ArC(OMe)_2Me$ + 3,5-cyclohexadiene-1,2-diol, PPTS	[200]

8.15.2 Enol ether formation

PS/DVB-$Si(iPr)_2Cl$ + furanone derivative/KHDMS	[438]
PS/DVB-CH_2SCH_2R + TMSOTf/NEt_3/DCM	[368]
PS/DVB-CH_2OH + 1,3-cyclohexanedione, cat. CSA	[261]

8.15.3 Imine formation and cleavage

8.15.3.1 Imine formation		
sb amine	sb amino acid ester + arom. aldehyde,	
	TMOF	[433, 536]
	TMOF/DCM	[422, 424]
	TMOF/DCM/cat. AcOH	[425]

	reflux azeotropically	[410]
	Na_2SO_4/DCM	[423]
	dry DCM or toluene	[434]
	sb glycine + arom. aldehyde, TMOF /THF	[203]
	sb aminoxanthene + aldehyde, 1% HOAc in DMF	[367]
	BOBA amine resin + aldehyde, 1% HOAc in DMF	[192]
	sb 1° amine + salicylaldehyde derivative, DMF or MeOH	[537]
	sb dipeptide + salicylaldehyde, DMF	[538]
	sb amino alcohol + PhCHO, MeOH (MIMOTOPES crowns^R used as solid support)	[535]
	sb glycine + benzophenone imine, AcOH/NMP	[288, 354]
	ketimine formation via transimination, sb 1° amine + ketimine	[491]
	sb $R^1R^2CH\text{-}NH_2$ + cyclohexanone, molecular sieves	[287]
sb aldehyde	sb arom. aldehyde	
	+ $PhCH_2NH_2$, toluene	[159]
	+ amino acid ester, TMOF (2x)	[536]
	+ 1° amine, TMOF/THF	[194]
	+ amine, TMOF	[225]
	+ 1,2-diaminocyclohexane, dioxane/reflux	[539]
	+ $HetArNH_2$, $Sc(OTf)_3$/MeOH/DCM	[540]
	sb aldehyde + α-amino stannanes, TMOF	[432]
sb 1,2-diketone	+ anilines/$TiCl_4$	[301]
8.15.3.2 Imine cleavage and related reactions	sb α-iminoester + $NH_2OH \cdot HCl$/THF	[291]
	sb benzophenone imine + $NH_2OH \cdot HCl$/THF	[289]
	+ $NH_2OH \cdot HCl$/THF/H_2O	[354]
	+ $NH_2OH \cdot HCl$ or HCl	[288]
	+ HCl/THF	[290]
	sb diimine to sb diketone, oxalic acid	[301]

8.15.4 Enamine formation and cleavage

8.15.4.1 Enamine formation		
enamino esters	Rink amine resin + β-ketoester, mol. sieves	[407, 541]
enamino amides	sb β-ketoamide + amine/TMOF	[542]
	+ amine/TMOF/2,6-di-tert-butyl-pyridine	[143]
enamides	sb β-ketoester + 1. $(OMe)_2CHNMe_2$/THF, 2. cyclopropylamine	[256]
enamine nitriles	sb $ArCH_2CN$ + *t*BuOCH $(NMe_2)_2$ (Bredereck's reagent)	[543]
8.15.4.1 Enamine cleavage	enamine nitrile to aldehyde nitrile, HCl	[543]
	ketones from sb enamines, TFA/DCM, w.c.s.	[50]

8.15.5 Oxime formation

sb arom. aldehyde + $NH_2OH \cdot HCl$/py	[180, 306, 336, 339]
+ $NH_2OH \cdot HCl/NEt_3$	[426]
+ $NH_2OH \cdot HCl$/py/EtOH	[193]
sb benzophenone + $NH_2OH \cdot HCl$/py/EtOH	[337]

8.15.6 Hydrazone formation

sb ArCOR + $PhNHNH_2 \cdot HCl$, py	[544]
sb β-ketoesters + $PhNHNH_2$, TMOF/THF	[295]
sb arom. aldehyde + Trs-$NHNH_2$	[545]
sb arom. aldehyde or ArCOR + dansylhydrazine, HOAc/DMF	[521]
sb hydrazine + aldehyde, DIEA/DMF	[546]
+ ketone, HOAc/EtOH	[546]

8.15.7 Carbonate formation

PS/DVB-CH_2OH + 4-nitrophenyl chloroformate, NMM/DCM	[547]
Wang resin + 4-nitrophenyl chloroformate, py/DCM	[386, 548]
, NMM/THF	[145]
sb benzyl alcohol + 4-nitrophenyl chloroformate, py/DCM	[549]
, DIEA/THF/DCM	[319]
sb ArOH + 4-nitrophenyl chloroformate, NMM/DCM	[274]
sb allyl alcohol + 4-nitrophenyl chloroformate/ 2,6-dimethyl-pyridine	[550]
sb imidazolyl carbonate + 3-nitrobenzyl alcohol, DBU/DCM	[198]

8.15.8 Carbamate formation

sb amine	2° amine + 4-nitrophenyl carbonate derivative, HOBt/DIEA/THF	[487]
	1° amine + 4-nitrophenyl chloroformate/NMM	[519]
	amino acid ester + 4-nitrophenyl chloroformate, py/DCM	[551]
	$PhCH_2NH_2$ + 4-nitrophenyl chloroformate, DIEA/THF/DCM	[552]
	1° amine + phenyl chloroformate, DIEA	[553]
	1° amine + ROCOOSu, DIEA	[75]
	2° amine + ClCOOR, DMAP/DIEA,	[157]
	amino acid ester + ROCOOBt, DIEA	[554]
	carbazate from sb hydrazine + 4-nitrophenyl chloroformate	[546]
sb alcohol	1° alcohol + $ClSO_2PhNCO$, dibutyltin laureate	[165]
	2° alcohol + 1. CDI/py, 2. 1° amine/py	[198]
	2° alcohol + tosylisocyanate, DCM	[262]
	Wang resin + CSI	[168]
	+ RNCO, NEt_3 cat.	[104]
	+ 1. CDI 2. diamine	[555]
sb oxime	oxime carbamates from sb oxime + 1. $COCl_2$ 2. amines	[337]
sb acylating agent		
4-nitrophenyl carbonate	+ 1°amine	[167]
	+ 1° or 2° amine	[274]
	+ 2° amine	[492]
	+ $ArCH_2NH_2$, HOBt/DIEA	[151]
	+ diamine	[519, 556]
	+ N-Trt-1,5-diaminopentane, DIEA	[550]
	+ amino acid ester, BSA/DMAP	[547]
	+ cyclohexylamine derivative, DIEA	[548]
	+ 2-(4-amino phenyl)ethylamine	[145]
	+ piperazine/DMF	[386]
	+ piperazine/DCM	[549]

	+ arom. amine, HOBt/DIEA	[557]
	+ amidine derivative	[319]
other acylating agents	sb N-methyl-imidazolinium triflate (gen. from sb imidazoles + 1. MeOTf/DCE, 2. NEt_3) + 1° or 2° amines	[206]
	sb chloroformate + arom. amine	[558]
	acylpyridinium complex from sb Wang chloroformate + 4-OMe-pyridine	[343]

8.15.9 Urea formation

sb acylating agent	sb 4-nitrophenyl carbamate + amine, DIEA/DMF	[559]
	+ diamine, NEt_3/DMF	[552]
	+ aniline, py/DMF	[103]
	sb phenyl carbamate + 1° or 2° amine	[553]
	sb oxime carbamate + amine, w.c.s.	[115, 337]
	sb 4-nitrophenyl carbamate + S-Me-isothiourea, NEt_3/DMF	[551]
	aminosulfonyl ureas from sb sulfonylcarbamate + amine, w.c.s.	[168]
	sb 4-nitrophenyl carbazate + amine, DIEA/DMF	[546]
	sb amino acid derived isocyanate + aniline, py/DMF	[103]
	sb ArNCO + 1° amine, DCM	[205]
	bisureas from diisocyanates (linked to oxime resin) + amine	[560]
sb aromatic amine	sb 1° arom. amine + allyl isocyanate, DCM	[323]
	sb 2° arom. amine + isocyanate, DCM	[94, 162]
	sb HetAr-NHR^1 + allyl isocyanate, dioxane	[561]
sb aliphatic amine	sb amine + isocyanate, DIEA, NMP	[562]
	sb 1° amine + isocyanate, DCM	[430, 491, 563]
	, DMF	[564]
	sb 1° amine + isocyanate (gen. in situ from amine + triphosgene/NEt_3/DCM)	[565]
	sb 1° amine + phenylisocyanate, DCM	[429, 519]
	sb 2° amine + isocyanate, DCM	[157, 158, 358, 512]
	, DMF/toluene	[514]
	, DMF	[518]
	+ phenylisocyanate, DCM	[203]
	+ *p*-tolylisocyanate, DMF	[114]
	+ 4-F-phenylisocyanate, DCM	[488]
	N-alkoxyureas from sb alkoxyamines + arylisocyanate, DCE	[80]
	sb amine + 4-nitrophenyl carbamate derivative, DIEA/DCM	[493]
2-step	sb 1° amine + 1. 4-nitrophenyl chloroformate, 2. amine	[566]
	sb 2° amine + 1. triphosgene/NEt_3/DMAP, 2. 1° amine	[75]
	sb piperidine + 1. $COCl_2$/DIEA, 2. amine/py	[567]
	sb piperazine + 1. triphosgene, 2. benzylamine	[82]
	sb amine, 1. $COCl_2$/2,6-di-tert-butylpyridine/toluene/DCM or 4-nitrophenyl chloroformate, 2. anthranilic acids, 10% py/DMF	[568]
	sb amine + 1. 4-nitrophenyl chloroformate, 2. diamine	[537]
	+ 1. 1,1-carbonylbisbenzotriazole, 2. amine	[569]
	sb Ar^1NH_2, 1. CDI, 2. Ar^2NH_2	[570]
	sb 2° arom. amine, 1. 4-nitrophenyl chloroformate/NEt_3/ THF/DCM, 2. 1° amine/DCM	[94]

8.15.10 Thiourea formation

	sb 1° amine + allyloxycarbonyl isothiocyanate, toluene	[561]
	+ isothiocyanate	[571]
	sb amino ester + benzyl isothiocyanate, DCM	[122]
	sb amine + aryl isothiocyanate	[572]
	sb 2° amine + isothiocyanates, MeCN	[512]
	sb 2° amine + Fmoc-NCS	[573]
	sb aniline + Fmoc-NCS, DCM	[282]
	thiosemicarbazide formation from sb $R^1NCS + R^2CONHNH_2$	[283]
2-step	sb 1° amine, 1. thiocarbonyl diimidazole 2. diamine	[537]
	biscarbamoylthioureas from 1. N-imidazolylcarbonyl-Wang resin + thiourea, NaH, 2. $(Boc)_2O$	[574]

8.15.11 Guanidine formation

sb 1° amine + N-bis-Boc-amidinium-3,5-dimethylpyrazole, DIEA/DMF	[575]
+ thiourea derivatives, EDC/DMF	[122]
+ N,N-bis-Boc-S-ethylthiourea or 2-(3,5-dimethylpyrazolyl)-4,5-dihydroimidazole · HBr	[576]
+ N,N'-bis-Boc-thiourea, Mukaiyama's reagent/NEt_3	
sb 1°, 2° amine and 1° arom. amine + N,N'-bis-Boc-thiourea or N,N'-bis-Boc-1-guanylpyrazole	[577]
sb 2° amine + $(BocNH)_2CS$/DIC	[157]
sb carbodiimide + N-phenylpiperazine/DMSO (MIMOTOPES crowns^R used as solid support)	[121]
sb diaryl carbodiimide + 2° amine, *m*-xylene	[170]
N-acyl-N'-carbamoylguanidines from sb 4-nitrophenyl carbamates + 1. S-methyl isothiourea, 2. acid cloride, 3. amine/$HgCl_2$	[551]
sb biscarbamoylthiourea + aniline, Mukaiyama's reagent/NEt_3	[574]
+ 1° or 2° amine, NEt_3	[574]
sb alkylated bis-Boc-thiopseudourea + NH_3/MeOH/DMF or 1° alkyl amine/DMF	[130]
sb methyl isothiourea + 1° or 2° amine	[282]

8.15.12 Carbodiimide formation

sb azide + PPh_3/phenyl isothiocyanate	[121, 122]
sb iminophosphorane + aryl isocyanate	[170]
+ isocyanate	[169]

8.15.13 Acid chloride formation

PS/DVB-COOH + oxalyl chloride/benzene	[220, 373]
+ oxalyl chloride/toluene	[486]
+ $SOCl_2$/benzene/DMF	[525]
+ $SOCl_2$/DMF	[331]
Rink acid resin + PPh_3/C_2Cl_6	[54]

8.15.14 Isocyanate formation

ArCOOH + DPPA/NEt_3, then 90° C	[205]
1° amine + diphosgene/DIEA	[578]
amino acid esters + phosgene or triphosgene/2,6-lutidine	[103]

8.15.15 Isothiocyanate formation

1° amine + Cl_2S/DIEA	[578]
+ $(2\text{-PyrO})_2CS$	[283]
+ CS_2/DIEA/TsCl or $CSCl_2$/DIEA	[280]

8.15.16 Isonitrile formation

ArNCHO + $PPh_3/CCl_4/NEt_3$	[145]
RNCHO + $PPh_3/CCl_4/NEt_3$	[397]

8.15.17 Nitrile oxide formation

aldoxime + NaOCl or Chlorox bleach	[426]
+ 1. NCS, 2. NEt_3	[180]
See also section 8.10	

8.15.18 Nitrone formation

sb $ArCH_2NHOH$ + aldehyde, TMOF	[193]
See also sections 8.8 and 8.10	

8.15.19 Imidate formation

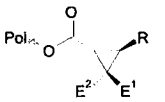
Wang resin trichloroacetimidate from Wang resin	
+ CCl_3CN/DBU/DCM	[230]
+ $CCl_3CN/KOH/Bu_4NHSO_4$	[245]
trichloroacetimidate formation, PS/DVB-CH_2OH + NaHDMS, then CCl_3CN	[231]

8.15.20 Other carbonyl derivatives

peracid formation, PS/DVB-COCl, $NaO_2/H_2O_2/MgSO_4$	[525]

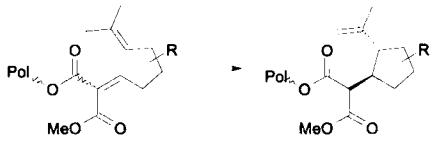
8.16 Formation of carbocycles

8.16.1 3-membered carbocycles

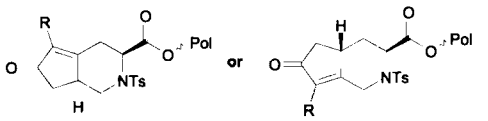


cyclopropanes via 1. Michael addition of pyridinium ylides to activated alkenes, 2.elimination of pyridine [69]

8.16.2 5-membered carbocycles

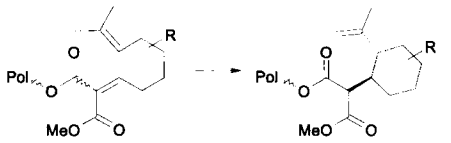


cyclopentane derivatives via Domino-Knoevenagel-ene-reaction [244]

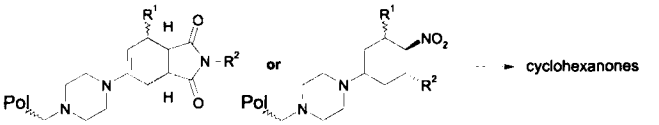


azabicyclo[4.3.0]nonen-8-ones via Pauson-Khand reaction [27, 478]

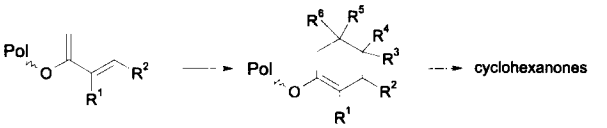
8.16.3 6-membered carbocycles



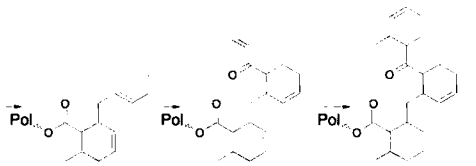
cyclohexanes via Domino-Knoevenagel-ene-reaction [244]



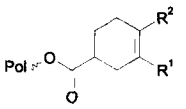
cyclohexeneamines via [4+2]-cycloaddition [437]



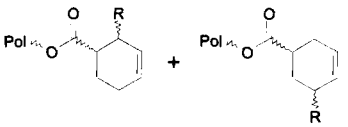
cyclohexanones via [4+2]-cycloaddition [365]



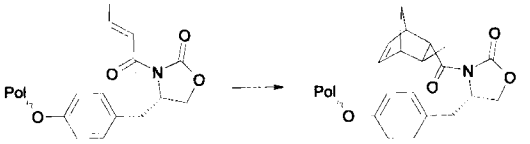
cyclohexenes via [4+2]-cycloaddition [254]



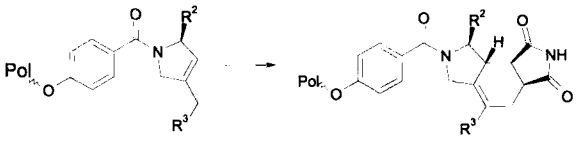
[439]



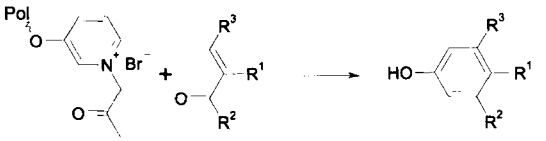
cyclohexenes via [4+2]-cycloaddition [428]



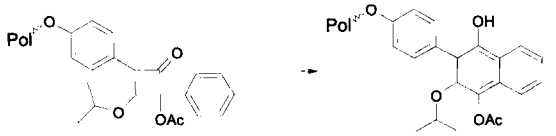
norbonenes via [4+2]-cycloaddition of sb N-crotonyl oxazolidinone + cyclopentadiene, Et_2AlCl-cat. [440]



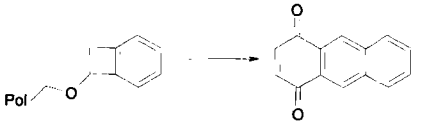
hexahydroisoindoles via [4+2]-cycloaddition [87]



phenols from α,β-unsat. ketones via 1. tandem Michael addition/annellation reaction, 2. elimination, 3. rearrangement [42]



naphthyl derivatives from squaric acid precursors via 1. thermolysis, 2. oxidation [334]

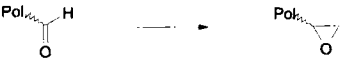


naphthalene derivatives via [4+2]-cycloaddition, w.c.s. [231]

8.17 Formation of heterocycles

8.17.1 3-membered heterocycles

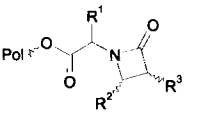
oxiranes



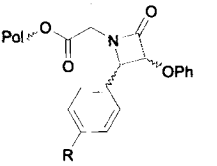
PS/DVB-CHO + $(CH_3)_3S^+Cl^-$/BnNEt$_3$Cl [266]

8.17.2 4-membered heterocycles

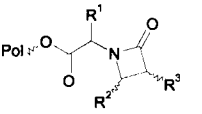
β-lactams



[422]

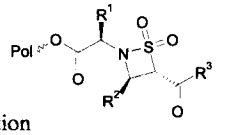


[424]



via [2+2]-cycloaddition [423]

β-sultams



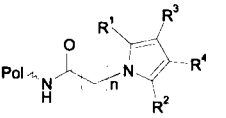
via [2+2]-cycloaddition [425]

8.17.3 5-membered heterocycles (5-MH]

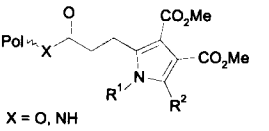
8.17.3.1 5-MH with 1 heteroatom

8.17.3.1.1 5-MH with 1 N

pyrroles

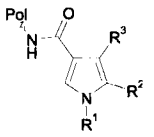


[394]

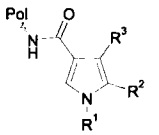


via 1,3-dipolar cycloaddition [242]

pyrroles (ctd)

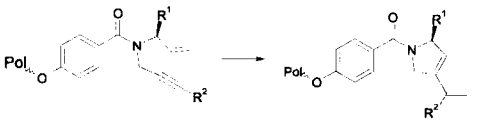


rom sb enaminone + nitroalkene, or nitroalkane + arom. aldehyde (with in situ Henry reaction) [579]



from sb enaminone + α-bromoketone (Hantzsch pyrrole synthesis) [143]

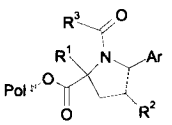
pyrrolines



[87]

via ring closing metathesis [345]

pyrrolidines



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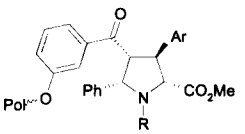

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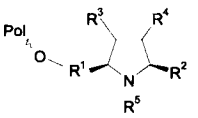

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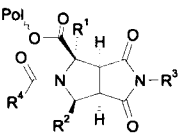
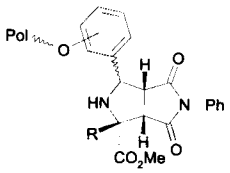
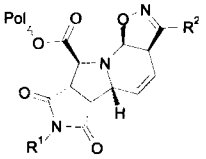


via 1,3-dipolar cycloaddition [434]

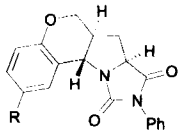
pyrrolidines (ctd)



[226]



via 1,3-dipolar cycloaddition [46]



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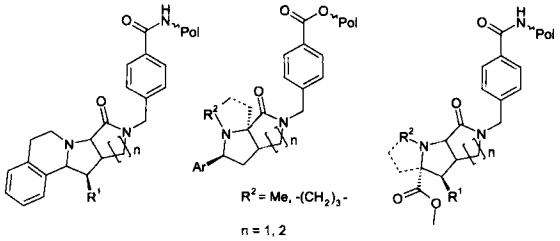
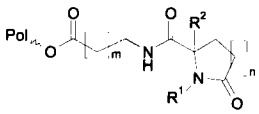


via intramolecular 1,3-dipolar cycloaddition [45]

lactams



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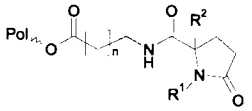
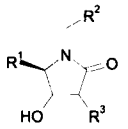


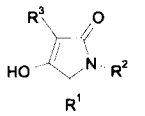
via Ugi reaction [398]

tetramic acids

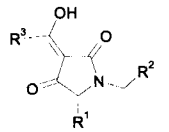


from N-ArCH$_2$CO-N-alkylamino ester + NaOEt, w.c.s. [517]

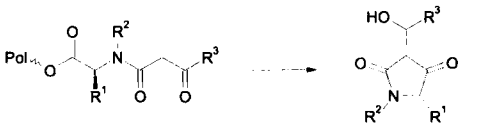
tetramic acids (ctd)



from N-RCH_2CO-N-alkylamino ester + Bu_4NOH, w.c.s. [516]

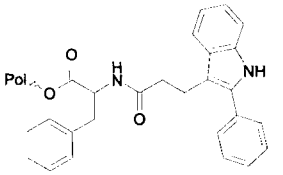


[142]

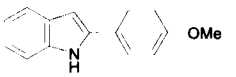


3-acyl tetramic acids via Dieckmann condensation [141]

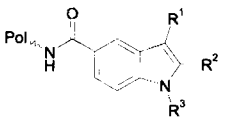
indoles and related heterocycles



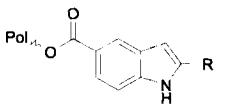
via Fischer indole synthesis from sb ketone [544]



via intramolecular Wittig reaction from sb anilide phosphonium salt, w.c.s. [268]



[468]



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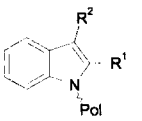
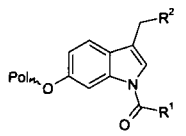
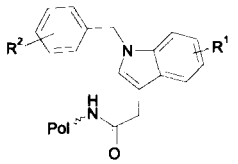


via Sonogashira reaction [467]

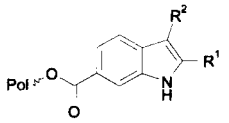
indoles and related heterocycles (ctd)



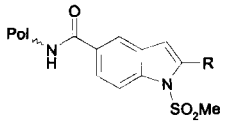
[102]



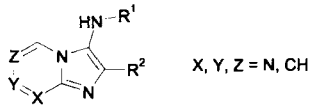
via intramolecular Heck reaktion [37]



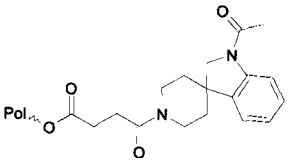
via Pd-cat. cyclization [39]



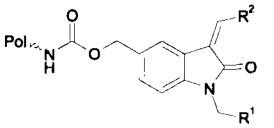
from sb *o*-$MeSO_2NH$-ArI + alkyne, Pd-cat. [163]



3-aminoimidazo[1,2-a]azines via $Sc(OTf)_3$-cat. multicomponent reaction of arom. aldehyde + $HetArNH_2$/RNC - any starting material may be sb [540]

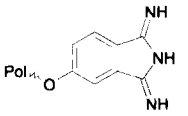


spiroindolines via Fischer indole synthesis from sb aldehyde + arylhydrazine, 1. TFA/DCM, 2. $NaB(OAc)_3H$, 3. Ac_2O/NEt_3/DMAP [580]



3-alkylidene-2-oxindoles via intramolecular Heck reaction [356]

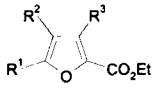
indoles and related heterocycles (ctd)



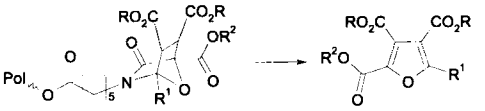
diiminoisoindolines from sb phthalodinitrile + NH_3/NaOMe [581, 582]

8.17.3.1.2 5-MH with 1 O

furans

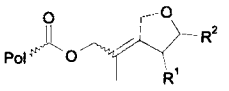


[146]

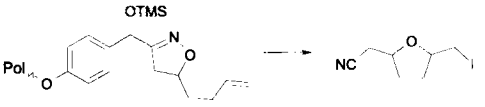


via 1,3-dipolar cycloaddition/thermal cycloreversion [147, 436]

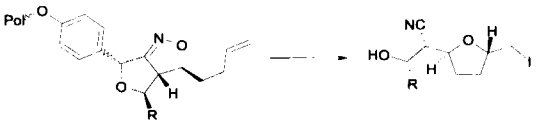
tetrahydrofurans



via radical cyclization [235]

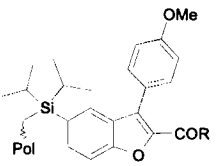


[370, 371]

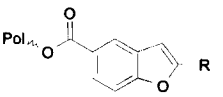


via electrophilic cyclization from sb isoxazoline + ICl [364]

benzofurans

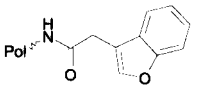


via intramolecular aldol condensation [171]

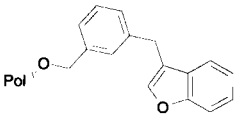


via Sonogashira reaction [466]

benzofurans (cid)

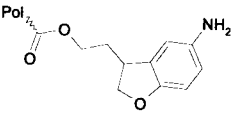


via intramolecular Heck reaction [37]

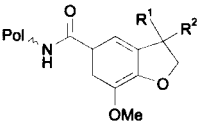


via radical cyclization [174]

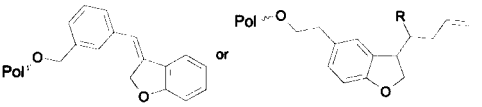
benzodihydrofurans



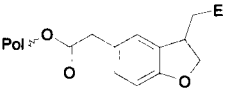
[235]



[173]

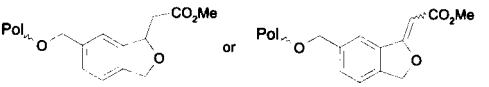


via radical cyclization [174]



via radical cyclization/electrophilic capture [484]

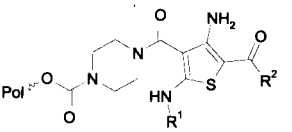
benzo[c]furans



via intramolecular Heck reaction/radical cyclization [29]

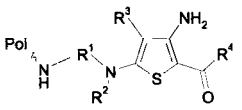
8.17.3.1.3 5-MH with 1 S

thiophenes



3-aminothiophenes from sb cyanoacetamide + 1. RNCS/DBU, 2. α-haloketone/HOAc [583]

thiophenes (ctd)

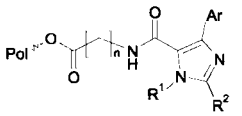


3-aminothiophenes from sb S-alkylated cyanothioacetamide + DBU [280]

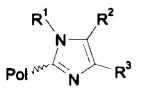
8.17.3.2 5-MH with 2 heteroatoms

8.17.3.2.1 5-MH with 2 N

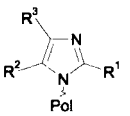
imidazoles and related heterocycles



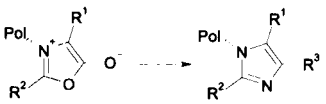
from sb α-(*N*-acyl-*N*-alkylamino)-β-ketoamide + NH_4OAc [397]



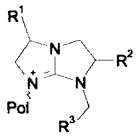
from sb arom. aldehyde + $R^1NH_2/R^2COCOR^3/NH_4OAc$ [227]



from sb R^1NH_2 + $R^2CHO/R^3COCOR^4/NH_4OAc$ [227]

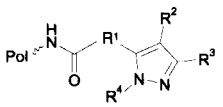


via 1,3-dipolar cycloaddition involving an isomünchnone [435]

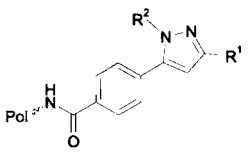


bicyclic guanidines from sb triamine + TCD [489]

pyrazoles

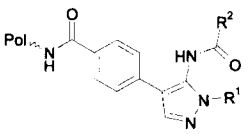


[296]

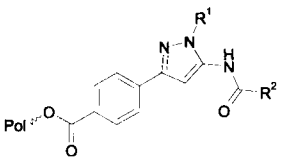


from sb α,β-unsat. ketone + $ArNHNH_2$ [382]

pyrazoles (ctd)

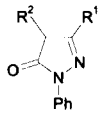


5-aminopyrazoles from sb aldehyde nitrile + hydrazine [543]

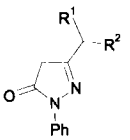


5-aminopyrazoles from sb β-ketonitrile + hydrazine [164]

pyrazolones

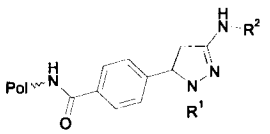


from sb phenylhydrazone + TFA, w.c.s. [295]



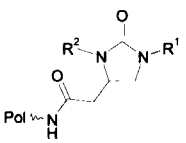
1-phenylpyrazolones from sb β-ketoesters + hydrazine, w.c.s. [255]

pyrazolines

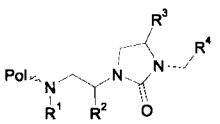


3-amino-2-pyrazolines from sb α,β-unsat. nitrile + hydrazine/NaOEt [160]

cyclic ureas or thioureas

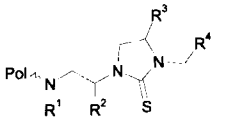


2-imidazolidones from sb $R^1COCH{=}CHCH_2NHR^2 + R^3NCO$ [584]



cyclic ureas from polyamine + CDI [86]

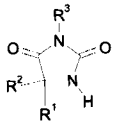
cyclic ureas or thioureas (ctd)



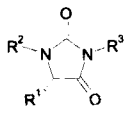
cyclic thioureas from polyamine + TCD [86]

hydantoins

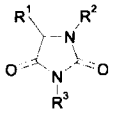
from sb N-ureido α-amino acid esters



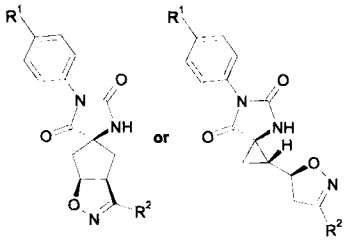
+ 6 M HCl, 85-100°C, w.c.s. [564]



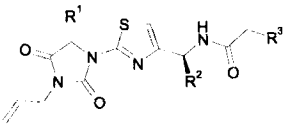
+ $NEt_3/CHCl_3$, reflux, w.c.s. [512]



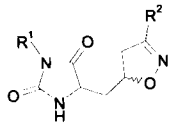
+ NEt_3/MeOH, w.c.s. [562]



+ NEt_3/THF, 60° C, w.c.s. [429]

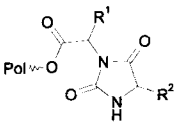


+ NEt_3/dioxane, 60° C, w.c.s. [561]

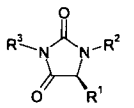


+ NaOEt/EtOH, w.c.s. [430]

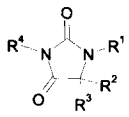
hydantoins (ctd)



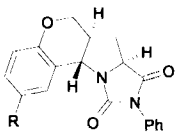
+ NaOMe/THF/MeOH [566]



+ neat isopropylamine, w.c.s. [491]
+ neat diisopropylamine, w.c.s. [518]

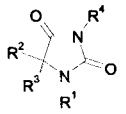


+ neat diisopropylamine, w.c.s. [514]

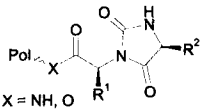


from N-ureido-proline deritative + DIEA/DMF, 100° C, w.c.s. [203]

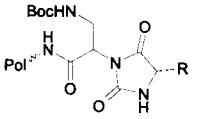
from other precursors



from sb N-carbamoyl α-amino acid amide + NEt_3/MeOH, 55-90° C, w.c.s. [547]

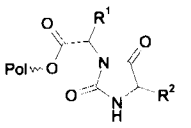


from sb N-phenylcarbamoyl dipeptide + DIEA or DBU/DMF [553]

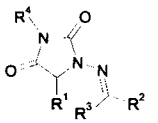


from sb dipeptide + triphosgene or CDI [585]

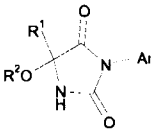
hydantoins (ctd)



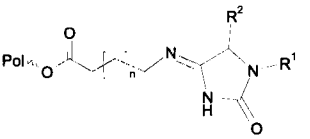
from sb dipeptide isocyanate/toluene, 70° C [578]



1-aminohydantoins from sb N-ureido α-hydrazino ester + BSTFA/1,2-DCE, 70-80° C, w.c.s. [546]

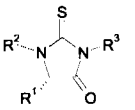


5-alkoxyhydantoins from sb N-hydroxyureido α-amino acid esters + R^2OH/KOtBu, w.c.s. [80]

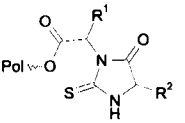


hydantoin-4-imides via Ugi reaction [399, 400]

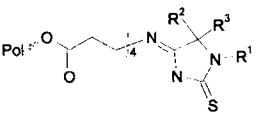
thiohydantoins



sb N-thioureido α-amino acid ester/MeCN/$CHCl_3$, reflux, w.c.s. [512]

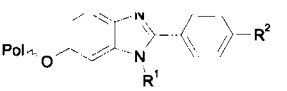


sb dipeptide isothiocyanate/toluene, 70° C [578]



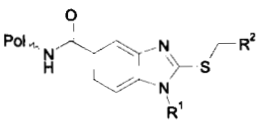
thiohydantoin 4-imides via Ugi condensation [399]

benzimidazoles and related heterocycles

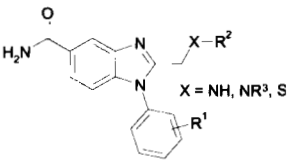


from sb *o*-phenylenediamine + ethyl benzimidate [315]

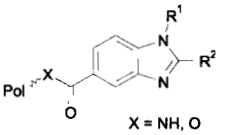
benzimidazoles and related heterocycles (ctd)



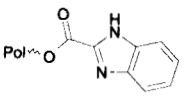
from sb *o*-phenylenediamine + TCD, with subsequent S-alkylation [281]



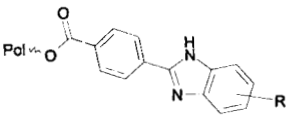
from sb N-acylated *o*-phenylenediamine + TFA, w.c.s. [317]



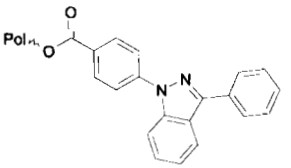
from sb *o*-phenylenediamine + aldehyde/DDQ [318]



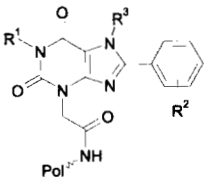
from PS/DVB-CHO + *o*-phenylenediamine/$FeCl_3/O_2$ [175]



from sb aromatic aldehyde + *o*-phenylenediamine derivative/nitrobenzene [586]

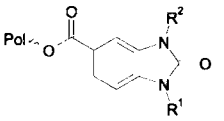


indazoles from sb α-arylazobenzhydryl ester + $BF_3 \cdot Et_2O$ [532]



xanthines from sb 6-alkylamino-5-nitrosouracils [36]

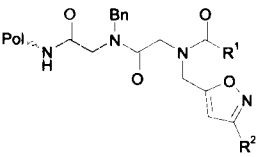
benzimidazoles and related heterocycles (ctd)



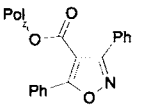
benzimidazolones from sb *o*-phenylenediamine + DSC [92]

8.17.3.2.2 5-MH with 1 N and 1 O

isoxazoles



[427]



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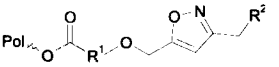

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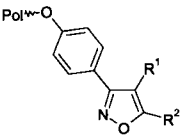
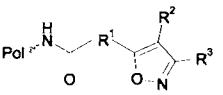
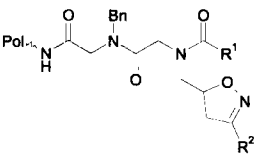


via 1,3-dipolar cycloaddition [180]



from sb β-diketone + hydroxylamine [296]

isoxazolines



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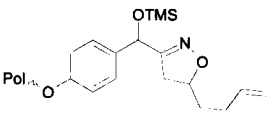
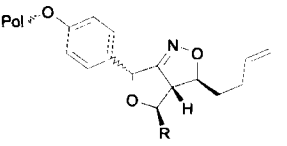


via 1,3-dipolar cycloaddition [370, 371]

isoxazolines (ctd)



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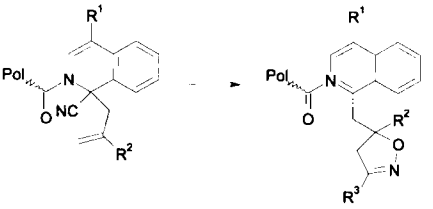

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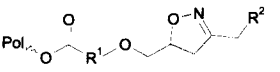

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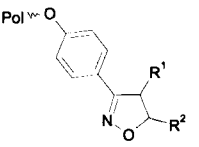

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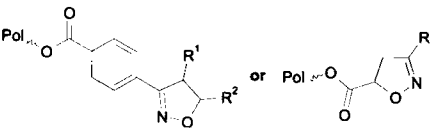

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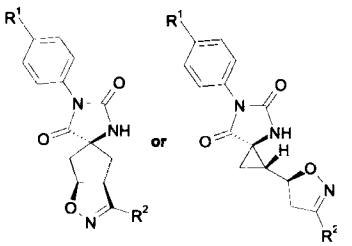

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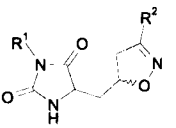
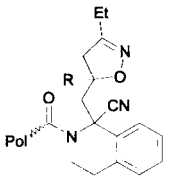
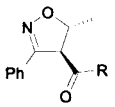


via 1,3-dipolar cycloaddition [430]

isoxazolines (ctd)

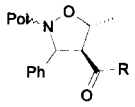


via 1,3-dipolar cycloaddition [139]



from 2-isoxazolidine + DDQ, w.c.s. [193]

isoxazolidines



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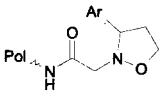
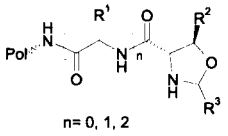


via 1,3-dipolar cycloaddition [68]

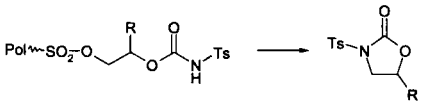
oxazolidines



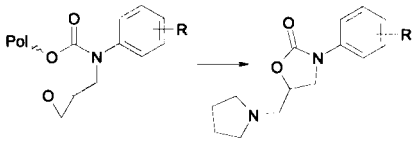
n= 0, 1, 2

via cyclisation of imino alcohol derivatives [535]

oxazolidinones

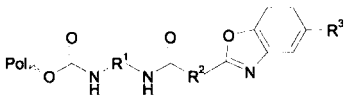


1,3-oxazolidin-2-ones from sb carbamates, w.c.s. [262]



1,3-oxazolidin-2-ones from sb amino alcohols generated in situ [104]

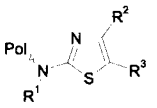
benzoxazoles



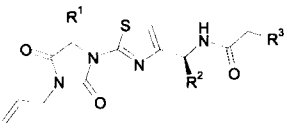
via intramolecular Mitsunobu reaction of 2-amidophenols [228]

8.17.3.2.3 5-MH with 1 N and 1 S

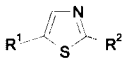
thiazoles



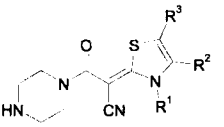
from sb thiourea + α-bromoketone [573]



from sb thiourea + α-bromoketone, w.c.s. [561]

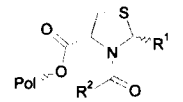


from sb dibromoether + thiourea, w.c.s. [365]



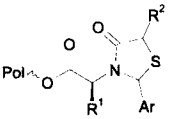
2-methylene-2,3-dihydrothiazoles from sb cyanoacetamide + 1. RNCS/DBU, 2. α-haloketone/HOAc [583]

thiazolidines

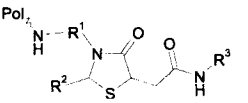


from sb cysteine + aldehyde [522]

thiazolidinones



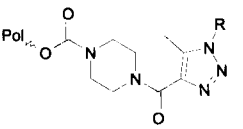
from sb amine + arom. aldehyde/thiol [410]



from sb amine + arom. aldehyde/mercaptosuccinic acid [555]

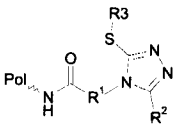
8.17.3.3 5-MH with more than 2 heteroatoms

triazoles



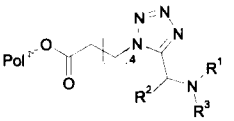
1,2,3-triazoles from sb eneamides + TsN_3 [542]

triazoles (ctd)



3-thio-1,2,4-triazoles from sb thiosemicarbazide + NaOH [283]

tetrazoles



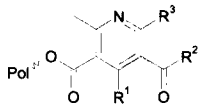
5-(1'-aminoalkyl)tetrazoles via Ugi condensation [399]

8.17.4 6-membered heterocycles (6-MH]

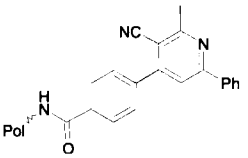
8.17.4.1 6-MH with 1 heteroatom

8.17.4.1.1 6-MH with 1 N

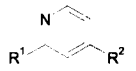
pyridines



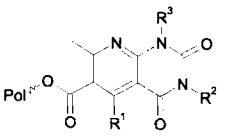
via CAN-oxidation of dihydropyridines [246]



from sb α,β-unsat. ketone + 1° enamine/KOtBu [382]

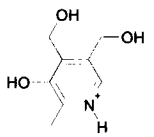


from sb dihydropyridone + ArMgX, $CeCl_3$, w.c.s. under oxidative conditions [342]



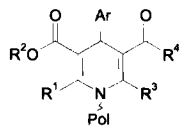
pyrido[2,3-d]pyrimidines via Hantzsch reaction of sb β-ketoester + 6-amino uracil [246]

pyridoxines

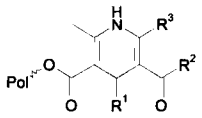


via Diels-Alder reaction and subsequent elimination of EtOH, w.c.s. [442]

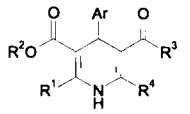
dihydropyridines



1,4-dihydropyridines from sb enamino ester + β-ketoester/aldehyde/molecular sieves [541]

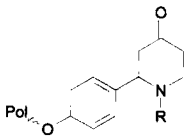


1,4-dihydropyridines via Hantzsch reaction of sb β-koesters + $H_2NCR^1{=}CHCOR^2$ [246]

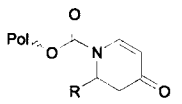


1,4-dihydropyridines from sb enamine + aldehyde + β-ketoester or β-diketone, w.c.s. [407]

dihydropyridones

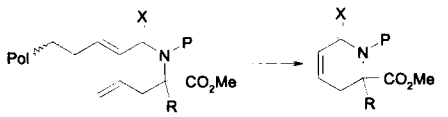


via tandem Mannich-Michael reaction [225]



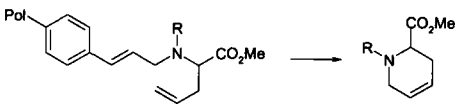
via Grignard reaction with sb acylpyridinium derivative [144, 343]

tetrahydropyridines



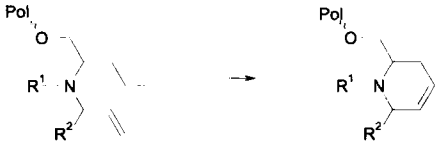
X = CH_2, O; P = Bz, Bn, SO_2Ar, PMB

[32]

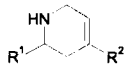


via ring closing metathesis, w.c.s. [119]

tetrahydropyridines (ctd)

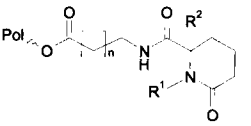


via ring closing metathesis [345]

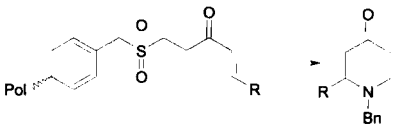


from sb dihydropyridone + ArMgX, $CeCl_3$, w.c.s. under reductive conditions [342]

piperidinones

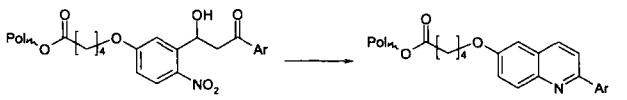


piperidin-2-ones via Ugi condensation [398]

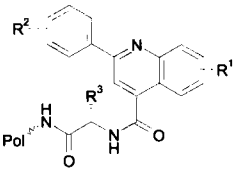


piperidin-4-ones from sb sulfonyl vinyl ketones, w.c.s. [264]

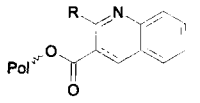
quinolines



via reductive cyclization: 1. $SnCl_2$, 2. $TiCl_3$ [134]

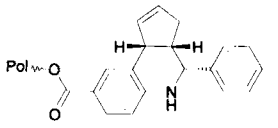


from sb pyruvic amide + arom. aldehyde/aniline (Doebner reaction) [408]



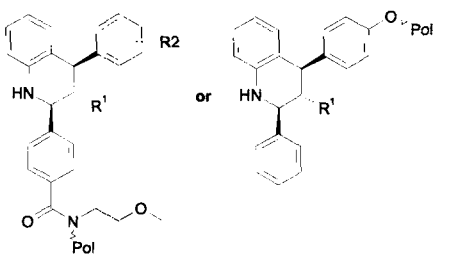
from sb quinoline-N-oxides + 1. BzCl, 2. nucleophile [325]

tetrahydroquinolines

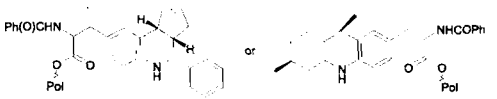


via Grieco 3-component reaction [405]

tetrahydroquinolines (ctd)

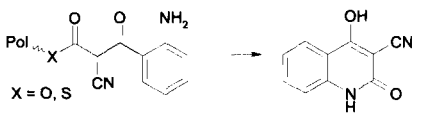


via Grieco 3-component reaction [224]

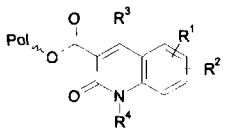


from sb aniline + aldehyde/alkene, $Yb(OTf)_3$-cat. [406]

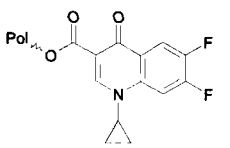
quinolones



4-hydroxyquinolin-2(1H)-ones via Claisen-type condensation, w.c.s. [303]

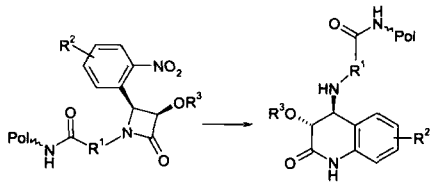


quinolin-2(1H)-ones via intramolecular Knoevenagel condensation of malonylaminophenone [388]



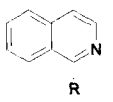
4-quinolones from sb enamide + TMG [256]

dihydroquinolones



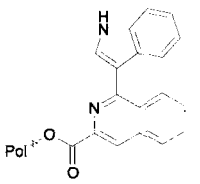
4-amino-3,4-dihydro-2-quinolones via rearrangement of sb β-lactam [423]

isoquinolines

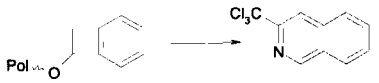


from sb Reissert complexes of isoquinoline, w.c.s. [139, 140]

isoquinolines (ctd)

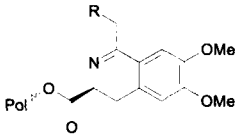


from sb isoquinoline-N-oxide + 1. BzCl, 2. indole [325]

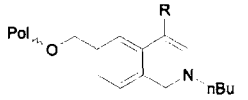


via Hetero-Diels-Alder reaction, w.c.s. [231]

dihydroisoquinolines

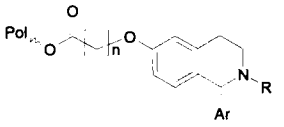


from acylphenylalanine derivative, 1. $POCl_3$ 2. $NaBH_3CN$ [490]

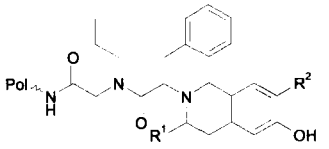


via intramolecular Heck reaction/oxidation [29]

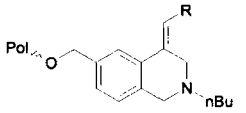
tetrahydroisoquinolines



via Bischler-Napieralski reaction [77]

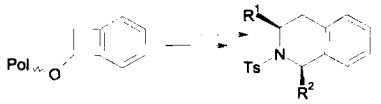


from sb arylethylamines + arom. aldehyde [587]



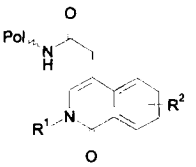
via intramolecular Heck reaction/oxidation [29]

tetrahydroisoquinolines (ctd)



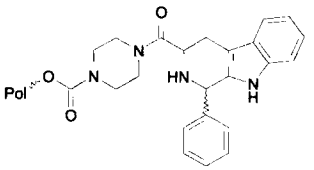
via Hetero-Diels-Alder reaction and subsequent reaction with C-nucleophile/Lewis acid [231]

isoquinolones

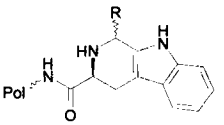


1(2H)-isoquinolones via intramolecular Heck reaction [56]

tetrahydro-β-carbolines

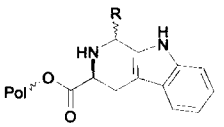


via Pictet Spengler reaction of sb tryptophane derivative + aldehyde/molecular sieves [549]



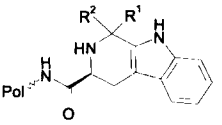
via Pictet-Spengler reaction of sb tryptophane derivative + aldehyde [158]

via Pictet-Spengler reaction of sb tryptophane derivative + aldehyde/TFA [136]



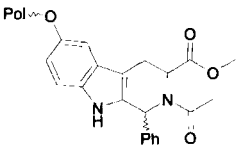
via Pictet-Spengler reaction of sb tryptophane derivative + aldehyde [588]

via Pictet-Spengler reaction of sb tryptophane derivative + aldehyde/molecular sieves [589]

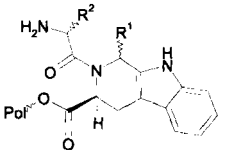


via Pictet-Spengler reaction of sb tryptophane derivative + aldehyde or ketone/TFA [590]

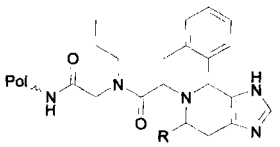
tetrahydro-β-carbolines (ctd)



via Pictet-Spengler reaction of sb tryptophane analogs + aldehyde/Ac_2O [385]

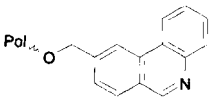


via Pictet-Spengler reaction of sb tryptophane derivative + aldehyde or ketone/TFA [591]



tetrahydro-3H-imidazo[4,5-c]pyridines from sb histamines + aldehyde [587]

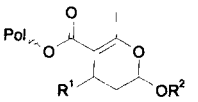
phenanthridines



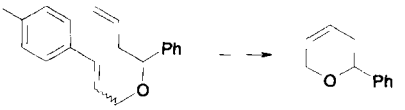
via intramolecular Heck reaction/oxidation [29]

8.17.4.1.2 6-MH with 1 O

dihydropyranes

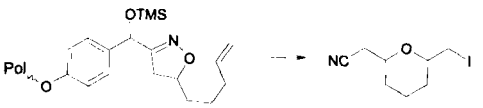


3,4-dihydro-2H-pyranes via hetero-Diels-Alder reaction [384]



via ring closing metathesis, w.c.s. [119]

tetrahydropyranes

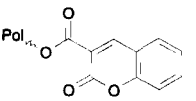


via electrophilic cyclization of sb isoxazoline, ICl [371]

tetrahydropyranes (ctd)

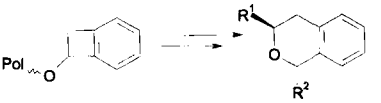
via electrophilic cyclization of sb isoxazoline, ICl, IBr or NIS [364]

coumarins



from sb malonate + 2-hydroxybenzaldehyde/piperidine/py [383]

benzodihydropyrans

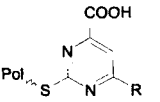


via Hetero-Diels-Alder reaction and subsequent reaction with C-nucleophile/Lewis acid [231]

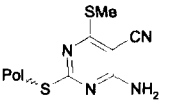
8.17.4.2 6-MH with 2 heteroatoms

8.17.4.2.1 6-MH with 2 N

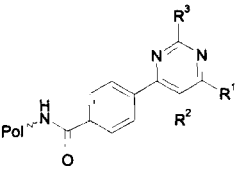
pyrimidines



from sb thiouronium salt + acetylenic ketone [275]

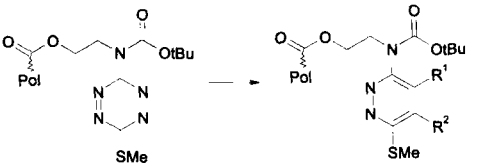


from sb thiouronium salt + $(MeS)_2C{=}C(CN)_2$ or $EtOCH{=}C(CN)_2$ [276]



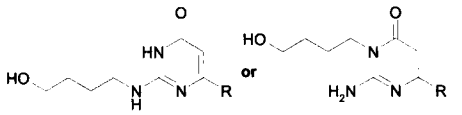
from sb α,β-unsat. ketone + amidine [382]

pyridazines



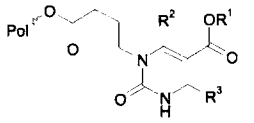
1,2-pyridazines via hetero-Diels-Alder reaction [443]

pyrimidinones



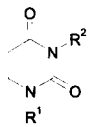
from sb guanidines + β-ketoesters [592]

dihydropyrimidines



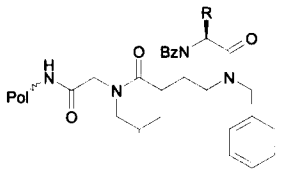
via Biginelli condensation of sb urea + β-ketoester/aldehyde [409]

dihydropyrimidinediones

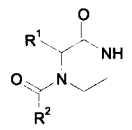


5,6-dihydropyrimidine-2,4-diones from sb β-ureido-β-alanines + HCl, w.c.s. [358]

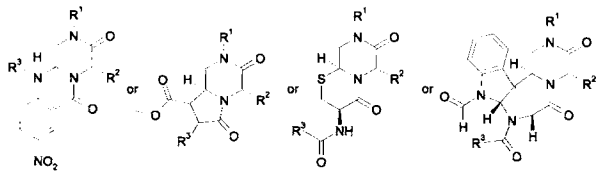
ketopiperazines



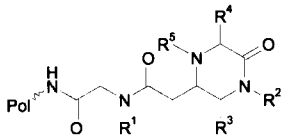
2-oxopiperazines from α,β-unsaturated peptoids + trimethylsulfoxonium iodide/NaH [593]



from dipeptides obtained via Ugi reaction [145]

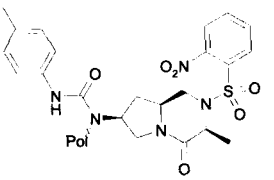


1-acyl-3-oxopiperazines via acyliminium ion cyclization [71]

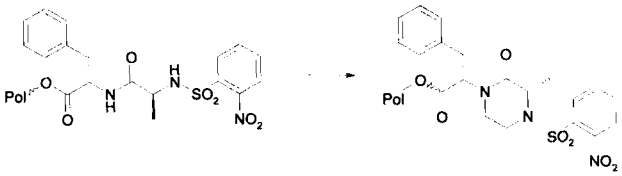


2-oxopiperazines via tandem S_N2/Michael addition of sb α,β-unsat. peptoid + amine [67]

ketopiperazines (ctd)

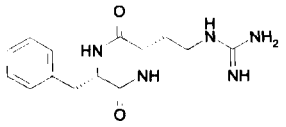


1,4-diazabicyclo[3.4.0]nonan-2-ones via intramolecular Mitsunobu sulfonamide N-alkylation [114]

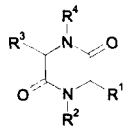


2-oxopiperazines from sb NBS-dipeptides + Br-$(CH_2)_2$-Br [106]

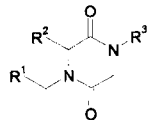
diketopiperazines



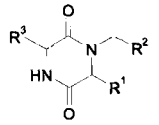
from sb dipeptide + HOAc/toluene, 90° C, w.c.s. [575]



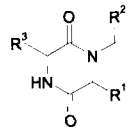
from sb N-bromoacetyl α-amino ester + R^4NH_2, DMSO, 70° C, w.c.s. [64]



from sb N-alkylated dipeptide ester + HOAc/2-BuOH, 110° C, w.c.s. [65]

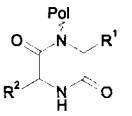


from sb N-alkylated dipeptide ester + HOAc/toluene/EtOH or NEt_3/toluene/EtOH, w.c.s. [396]

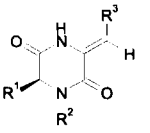


from sb N-alkylated dipeptide ester + HOAc/MeOH, w.c.s. [513]

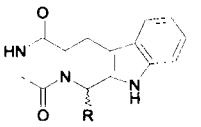
diketopiperazines (ctd)



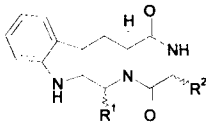
from sb N-Fmoc-protected N'-alkylated dipeptide ester + piperidine/DMF [95]



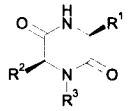
from sb $R^3CH_2COCONR^2CHR^1COO$-polymer + NH_4OAc/HOAc/toluene, 100° C, w.c.s. [510]



from sb N-aminoacyltetrahydro-β-carboline + NEt_3/DCM, w.c.s. [588]

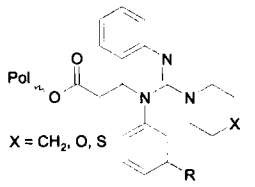


from sb N-Fmoc-protected N-aminoacyltetrahydro-β-carboline + piperidine/THF, w.c.s. [591]



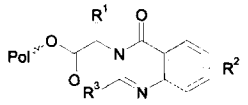
from sb N-alkylated dipeptide ester + DIEA/AcOH/DCM, w.c.s. [594]

dihydroquinazolines



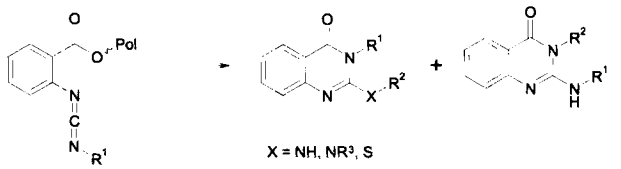
from sb carbodiimide, via guanidine formation and intramolecular Michael addition [170]

quinazolinones



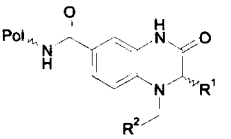
from sb anthranilic amide + aldehyde/1. HOAc, 2. $KMnO_4$ [529]

quinazolinones (ctd)

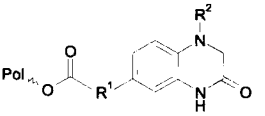


3H-quinazolin-4-ones from sb carbodiimide + amine, w.c.s. [169]

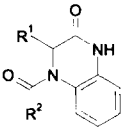
dihydroquinoxalin-2-ones



from N-(2-aminophenyl)-amino ester, subsequent alkylation [85]

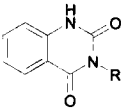


from N-(2-aminophenyl)-amino ester [93]

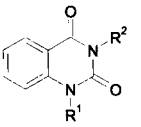


from dipeptide generated by Ugi reaction, w.c.s. [145]

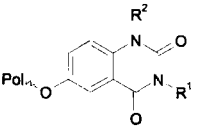
quinazoline-2,4-diones



[557]

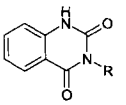


from sb anthranilic acid amide, w.c.s. [558]

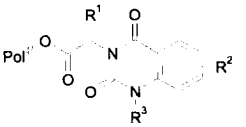


from sb N-ureido-anthranilic ester [94]

quinazoline-2,4-diones (ctd)

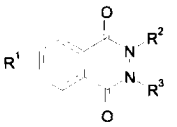


from sb N-ureido-anthranilic ester, w.c.s. [205]



from sb N-ureido-anthranilic acid derivative [103]

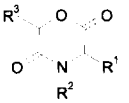
phthalhydrazides



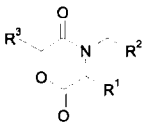
from sb phthalimide + hydrazine, w.c.s. [595]

8.17.4.2.2 Other 6-MH with 2 heteroatoms

diketomorpholines

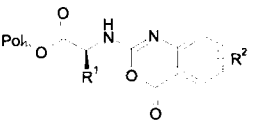


from α-bromodipeptide, w.c.s. [64]



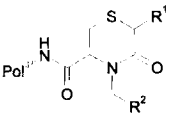
from sb hydroxyacetyl α-amino acid ester derivative
+ NEt_3/DCM, w.c.s. [396]

benzoxazinones



3,1-benzoxazine-4-ones from sb N-ureido anthranilic acid derivatives [568]

thiomorpholinones

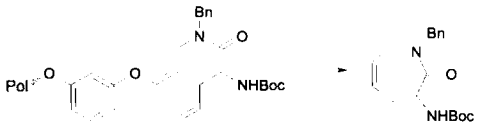


thiomorpholin-3-ones from sb N-(α-bromoacyl)cysteine derivatives [272]

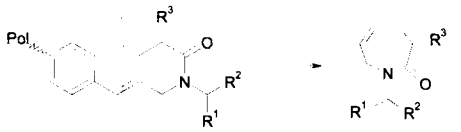
8.17.5 7-membered heterocycles (7-MH]

8.17.5.1 7-MH with 1 heteroatom

8.17.5.1.1 7-MH with 1 N
tetrahydroazepine-2-ones



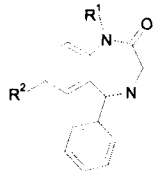
[420]



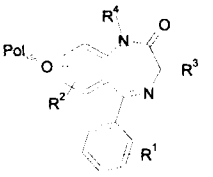
Freidinger lactams via ring closing metathesis, w.c.s. [118, 119]

8.17.5.2 7-MH with 2 heteroatoms

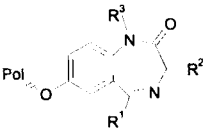
8.17.5.2.1 7-MH with 2 N
dihydro-1,4-benzodiazepine-2-ones



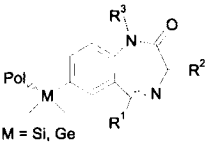
from in situ generated sb aminobenzophenone imine + py, w.c.s. [596]



from sb aminoacyl-aminobenzophenone, HOAc/DMF [96]

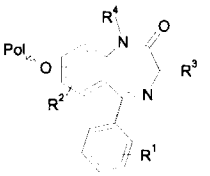


[98, 99]

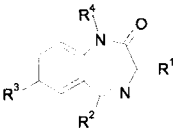


from sb aminoacyl-aminobenzophenone or acetophenone derivative, HOAc/DMF [97, 100]

dihydro-1,4-benzodiazepine-2-ones (ctd)

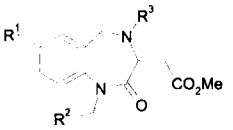


from sb aminoacyl-aminobenzophenone derivative, HOAc/DMF [101]

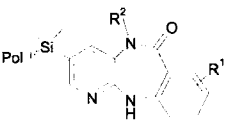


from sb aminobenzophenone imine + TFA, w.c.s. [564]

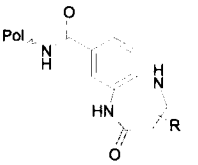
tetrahydrobenzodiazepine-2-ones



tetrahydro-1,4-benzodiazepine-2-ones via cleavage/ intramolecular conjugate addition, w.c.s. [78]

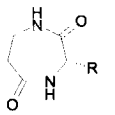


tricycles from sb *o*-azidobenzoylamidopyridine derivatives via reduction/rearrangement [88]



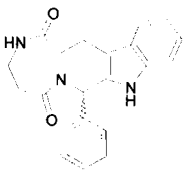
tetrahydro-1,5-benzodiazepine-2-ones from sb *o*-NH_2-Ar-$NH(CH_2)_2COOH$ via lactam formation with DECP/DIEA [84]

perhydrodiazepine-2,5-diones

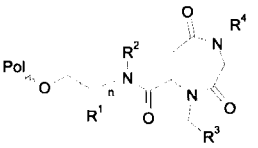


from sb N-alkylated dipeptide ester + DIEA/AcOH/DCM, w.c.s. [594]

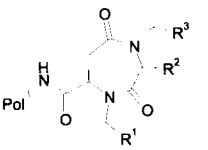
perhydrodiazepine-2,5-diones (ctd)



2,3-bislactams via intramolecular aminolysis, w.c.s. [588]

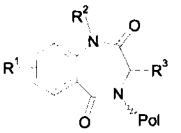


perhydro-1,4-diazepine-2,5-diones from Xxx-Asp-dipeptide derivative, DPPA/DIEA [66]

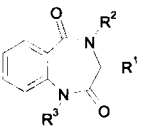


perhydro-1,4-diazepine-2,5-diones from Xxx-Asp-dipeptide derivative, HATU/DIEA/DMF [515]

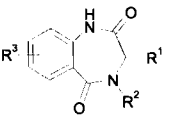
1,4-benzodiazepine-2,5-diones



from sb *N*-anthranoyl amino acid ester, lithiated acetanilide/ DMF/THF [89, 90]

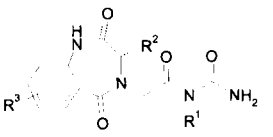


from sb anthranoyl peptide derivatives, TFA/dioxane/H_2O, w.c.s. [597]



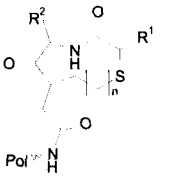
from sb anthranoyl amino acid ester + NaO*t*Bu/THF, w.c.s. [598]

1,4-benzodiazepine-2,5-diones (ctd)

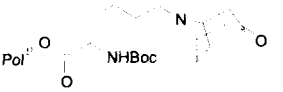


from sb *o*-azidobenzamide via intramolecular aza-Wittig reaction, w.c.s. [62]

8.17.6 Other heterocycles



β-turn-mimetics via intramolecular S-alkylation [271]



tropane derivatives from sb 1° amine + succinic dialdehyde/1,3-acetonedicarboxylic acid [599]

8.18 (De)protection, cleavage and hydrolysis reactions

8.18.1 (De)protection of alcohols

For other protection reactions of alcohols see section 8.2.5.1

formation of THP-ethers	sb DHP + alcohol/PPTS/DCE	[209]
	sb DHP + 2° alcohol/PPTS/DCE	[75, 348, 349]
	sb DHP + 2° alcohol/PTSA/DCM	[209, 473]
	sb 1° alcohol + DHP/*m*-benzenedisulfonic acid/dioxane	[176]
cleavage of THP-ethers	sb RCH_2OTHP + PTSA/DME/MeOH	[32]
	sb PhOTHP derivative + TFA/MeOH/DCM	[40]
formation of silyl ethers	PS/DVB-CH_2OH + $ArSi(iPr)_2Cl$/imidazole/DMF	[171]
	2° alcohol + TIPSOTf/lutidine	[286]
	PS/DVB-$(CH_2)_2$ SiR_2Cl+ R'OH/py or NEt_3	[313]
cleavage of silyl ethers	RO-TBDMS + TBAF/HOAc/THF	[600]
	RO-TBDMS + HCl/THF	[204]
	RO-TBDPS + TBAF/HOAc/THF	[520]
	RO-TIPS + TBAF/THF	[385]
	ArOTBDMS + TBAF/HOAc /THF	[220]
	$ArCH_2OTBDPS$ + TBAF/HOAc/dioxane	[29]
	PS/DVB-$Si(iPr)_2OR$ + TBAF/THF, w.c.s.	[438]
	PS/DVB-$(CH_2)_2$ SiR_2OR + HF/H_2O/MeCN, w.c.s.	[313]
formation of boronates	PS/DVB-$B(OH)_2$ + diol/py	[333]
	PS/DVB-$B(OH)_2$ + diol/benzene	[601]
	PS/DVB-$B(OH)_2$ + triol/py, benzene or toluene	[602]

cleavage of boronates	PS/DVB-B(OR)$_2$ + acetone/H$_2$O	[601, 602]
	PS/DVB-B(OR)$_2$ + acetone/H$_2$O or THF/H$_2$O	[333]
	For other protection reactions see section 8.2.5	

8.18.2 Other ether cleavage reactions

hydroxamic acids from sb hydroxamic acid Wang ethers + TFA/*i*Pr$_3$SiH/DCM or TFA/anisole, w.c.s.	[233]
hydroxamic acids from sb hydroxamic acid (2-Cl)-tritylethers + 5% TFA/DCM, w.c.s.	[189, 190]
hydroxamic acids from sb hydroxamic acid trityl ethers + HCO$_2$H/THF, w.c.s.	[188]
RSTrt + TFA/(*i*Bu)$_3$SiH/DCM	[272]
PS/DVB-CH$_2$OAr + TMSOTf, w.c.s.	[192]
PS/DVB-CH$_2$OR + SnCl$_4$, w.c.s.	[201]
MOM-ether + 5% TFA/DCM	[171]
sb benzylthioether (photochemical cleavage), w.c.s.	[270]

8.18.3 (De)protection of amines

Teoc removal	TBAF/THF	[152, 473, 518]
Alloc removal	[PPh$_3$]$_2$PdCl$_2$, Bu$_3$SnH, w.c.s.	[550]
phthaloyl removal	preparation of hydroxylamine trityl resin, N$_2$H$_4$/THF	[188]
	preparation of hydroxylamine (2-Cl)-trityl resin, N$_2$H$_4$/THF	[189]
	preparation of hydroxylamine Wang resin, N$_2$H$_4$/EtOH	[233]
	, N$_2$H$_4$/THF/EtOH	[63]
	N$_2$H$_4$/MeOH	[548]
	N$_2$H$_4$/DMF	[565]
	H$_3$CNHNH$_2$/THF/EtOH	[603]
nitrobenzenesulfonyl removal	(2-NO$_2$)PhSO$_2$NRMe + HSCH$_2$CH$_2$OH/DBU/DMF	[107]
	+ PhSNa/DMF	[116]
	(2-NO$_2$)PhSO$_2$NR$_2$ + HSCH$_2$CO$_2$H/DBU/DMF	[114]
	(2,4-diNO$_2$)PhSO$_2$NR$_2$ + *n*BuNH$_2$/DCM	[118, 119]
N-protection reactions	sb DHP + 2,6-dichloropurine, CSA/DCE	[320]
	sb DHP + tetrazole/ TFA	[445]

8.18.4 Ester cleavage reactions

RCOO(CH$_2$)$_2$TMS + TBAF/DMF	[603]
RCOOMe + LiOH/THF/H$_2$O	[125, 151, 152]
RCOOMe + KOH/dioxane/H$_2$O	[435]
RCOOMe + KOTMS /THF	[604]
RCOOEt + KOTMS/THF	[605]
PS/DVB-COOR + NaOMe/THF/ MeOH, w.c.s.	[220]
penicillanic acids bound to Merrifield or Wang resin + AlCl$_3$/DCM/MeNO$_2$, w.c.s.	[523]
sb N-Boc-amino acid phenacyl esters + Me$_3$SnOH/DCM	[606]
sb RCOOallyl + (PPh$_3$)$_4$Pd/TMSN$_3$/DCE	[604]
sb ArOAc to ArOH, piperidine/DCM	[220]
PS/DVB-OAc + N$_2$H$_4$/dioxane	[328]

	photocleavage of sb pivaloylglycerol ester derivative, w.c.s.	[452]
	sb ArOAc to ArOH, lipase/buffer/MeOH	[589]
thioester cleavage	sb RCOSR' to sb R'SH, NaOMe/THF/MeOH	[76]
	sb RCOSR' to sb R'SH, NaOMe/THF/MeOH	[499]
phosphate ester cleavage	$ROPO(OC_6F_5)_2$ to $ROPO_3^-$, SnCl4	[201]

8.18.5 Silane cleavage and related reactions

silane cleavage	conversion of sb aryl silane to ArCl, ArBr or ArH with ICl, Br_2/py or TFA, w.c.s. (traceless linker)	[449]
	conversion of PS/DVB-$CH_2OSi(i\text{Pr})_2$Ar to ArH with TBAF/DMF, w.c.s. (traceless linker)	[171]
	conversion of sb aryl silane to ArH with anhydrous HF, w.c.s. (traceless linker)	[100]
	conversion of sb aryl silane to ArH with TFA/DCM, w.c.s. (traceless linker)	[446, 453]
	conversion of sb aryl silane to ArH with TFA, w.c.s. (traceless linker)	[159]
	sb allyl silane derivatives + TFA/DCM, w.c.s. (traceless linker)	[417]
germane cleavage	conversion of sb aryl germane to ArH with TFA or to ArBr with Br_2/DCM, w.c.s.(traceless linker)	[100]
alkyne deprotection	sb TMS-alkyne + TBAF	[49, 202, 402, 469]

8.18.6 Other cleavage reactions

	2° amines via cleavage of sb formamidines, N_2H_4/HOAc	[127]
	homoserine lactones from sb N-acyl methionine derivatives + BrCN/TFA/$CHCl_3$/H_2O	[607]
aryltriazene cleavage	conversion to aryl iodide with MeI, w.c.s.	[49, 202, 469]
	conversion to ArH with HCl/THF or H_3PO_2/$Cl_2HCCOOH$, w.c.s. (traceless linker)	[441]
amine dealkylation	PS/DVB-$CH_2NR^1R^2$ + α-chloroethyl chloroformate/MeOH, w.c.s.	[51]
	PS/DVB-$CH_2NR^1R^2$ to $R^3R^2R^1N$, R^3COCl, w.c.s.	[608]
hydrolysis of nitriles	PS/DVB-CH_2CN to PS/DVB-CH_2COOH, HOAc/H_2SO_4/H_2O	[73]
hydrolysis of amides	RCO-Evans auxiliary + LiOH/THF, cleavage of RCOOH from support	[148]
	RCO-Evans auxiliary + LiOH/THF /H_2O, cleavage of RCOOH from support	[149]
	RCO-Evans auxiliary to sb RCOOH, LiOH/H_2O_2/THF/H_2O	[286]
hydrolysis reactions	carboxylic acids via hydrolysis of sb N-alkylacylsulfonamides, NaOH	[109, 110]
	amino alcohols via hydrolysis of sb oxazolines, H_2SO_4/ EtOH/THF	[208]
	amino alcohols via hydrolysis of sb oxazolines, HCl	[48]
	hydrolysis of isoquinoline Reissert complex, KOH/THF/H_2O, w.c.s	[139, 140]

8.19 Diazo chemistry

8.19.1 diazonium ions

formation	sb arom. amine + $NaNO_2$/HCl	[501]
	sb amine + $NaNO_2$/HCl	[609]
	sb sulfonyl hydrazone + KOH/MeOH/THF	[545]
reactions	resin-Na^+ (Amberlite-IR-120) + ArN_2^+, then sodio indole	[610]
	sb $ArCH_2N_2^+$ to $ArCH_2OCOR$, RCOOH	[545]
	aryltriazene formation, sb 2°amine + ArN_2^+	[49, 441, 469]

8.19.2 diazo compounds

formation	diazo imide from malonyl imide derivative + TsN_3, NEt_3	[146]
	+ MsN_3/NEt_3	[147]
	diazo imide from sb malonic ester amide + MsN_3, NEt_3	[436]
	β-ketoamide + TsN_3, DIEA/DMF	[234]
reactions		
Arndt-Eistert homologation	sb amine + diazoketone, Ag benzoate/NEt_3/THF	[611]
cyclopropenation	sb diazoester + alkyne, $[Rh(OAc)_2]_2$	[609]
carbene insertion	sb diazoketone + alcohol, $[Rh(OAc)_2]_2$	[234]

8.20 Rearrangements

8.20.1 Claisen rearrangement

sb phenyl allylether, 225° C (silica gel or molecular sieves used as support)	[222]

8.20.2 Beckmann rearrangement

sb 23-isonitrososstrychnine + $SOCl_2$	[612]

8.20.3 Hofmann rearrangement

sb $RCONH_2$ to 1° amine, $PhI(TFA)_2$	[575]

8.20.4 Curtius degradation

1. sb R^1COOH to R^1CON_3, DPPA, 2. sb R^1CON_3 + R^2OH to $R^1NHCOOR^2$	[613]

8.21 Miscellaneous

	H-phosphonate salt formation from Wang resin + 1. 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one, DCM/py, 2. $NaHCO_3/NEt_3$	[369, 377]
Aza-Wittig reaction	intramolecular, sb iminophosphorane (gen. from sb ArN_3 and PBu_3) + RCOOR	[62]
	sb iminophosphorane + RNCO	[169]
	See also section 8.15.12 (carbodiimide formation) for other examples.	
Nitrosation	α-nitrosation of uracile derivatives	[36]
	α-nitrosation of aminoketone, isoamylnitrite	[612]

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Index

A
acetal linker 68
acetyldimedone linkers 58
acetyldimedone (Dde) protecting group 58
activators 211
active esters
– N-hydroxybenzotriazole 211
– 4-hydroxy-3-nitrobenzophenone 211
– of Boc-protected amino acids 212
– polymer bound: o-nitrophenol, 211
α-acylamino carboxamide 7
3-acyl-tetramic acids, synthesis 116
aldol-type condensation, Sm-catalized 18
algorithm, evolutionary 312
alkene cross metathesis 141, 142
alkene metathesis, on solid phase 142
alkoxides bound to a polymer 227
N-alkylated 5-alkoxy -1,2,3,4-tetrahydroisoquinolines 71
N-alkylated 6-alkoxy -1,2,3,4-tetrahydroisoquinolines 71
α-Alkylation 174, 175
3-alkylidene-diketopiperazines 106
alumina 29
amides 35–37
– synthesis of 212
2'-amido-2'-deoxyadenosine derivatives 90
amines
– acylation 39, 42
– amine alkylation 39
– from bound tertiary amides 57
– synthesis of 61
aminimides 12
amino acid fluoride, Fmoc protected 162
aminoalkylation 18
2-aminoarylketones 161
aminobenzylamine 23
3-amino-imidazo (1,2-a)pyrazines 12
3-amino-imidazo (1,2-a)pyri(mi)dines 11
3-amino-imidazo (1,2-a)pyridines 12
aminomethylation 19
aminopyrimidines 90
anhydride scaffold 23
anthranilate, immobilized 196
antihistamines 14
antihypertensive agents 13
antirheumatics 14
antiseptics 14
aqueous work-up 22
artificial neural network (ANN) 290,306
aryl ethers 33
aryl halides, homocoupling 125
arylations, transition metal-mediated 123
arylether library 215
aryl-piperazine library 24
aspartic acid protease inhibitors
– solid-phase synthesis of 63
asymmetric dihydroxylation of olefins 221
atom charges 293
autocorrelation
– coefficient A^i 295
– descriptors (ACDs) 300
automated
– liquid-liquid extraction 269
– organic synthesis 243, 259
– organic synthesizers 262
– resin dispensing 273
– solution-phase synthesis 45
– systems 245, 259
Aza Diels-Alder reactions 20
Aza-Wittig reaction 197
azetidin-2-ones see Beta-Lactams
azinomycin analogs 8
Azolopyrimidinediones 200

B
Backbone Amide Linker (BAL) 184
barcodes 240
basic amide library 32
benchmate robotic workstation 35
benchtop synthesizer 259
benzene acid chlorides 31
benzhydril-derived linker 61
1,4-benzodiazepine-2,5-diones 8
1,4-benzodiazepine-2,5-diones 92, 110
benzodiazepines 160
benzofuran dervatives 130
benzoin, dithiane-protected 90
benzopiperazinones 201
benzoxazole library 51
benzyl-linked
– approaches for secondary amines 55
– tert.amines, cleavage of 55
p-benzyloxybenzylamine resin 56
benzyloxycarbonyl group (Z) 48
– linkers based on 49

beta-Lactams 168
beta-Sultams 169
biaryl aldehydes 69
Biginelli more component reaction 13
biphenyl tetrazole derivatives 63
bis-benzamidophenol library 68
bis-hydroquinylpyridazine catalysts 221
bis-lactams 206
borane amino alcohol complexes, supported 219
borane complexes, polymer-bound 220
borohydride
- polymer-supported 226, 234
- species 227
boronates, self coupling 125
Bpoc, 2-(4-biphenylyl) –prop-2-oxycarbonyl 161
bromine displacement, by primary amines 187
α-bromo-substituted carboxylic acid 187
2-α-bromocholestan-3-one 230
bromodesilylation 74
building-block libraries 311
Burgess reagent polymer(PEG)-supported 216,217

C
Ca-channel blockers 13
Carbanion equivalents 153
carbanions and equivalents
- generation on solid support 144
- stabilized 144
carbodiimide moiety, polymer supported 213
β-Carbolines 203, 204
carbon-hetero-bond formation 100
carboxy functionalized resins 68
4-Carboxybenzaldehydes, immobilized 192
C-C bond
- formation 114
- forming reactions 123
CC-couplings, Pd-mediated 83
centrifuges 271, 272
chalcone 16
chemical
- encoding 240
- space 282
- tagging 240, 241
chiral catalysts 218
chiral oxazoborolidines, polymer supported 220
chirality 297
- quantified 298
chloranil test 183
chloro-and bromoimides, polymer supported 228
chromium reagents 225
Claisen condensation 147, 174, 175
Claisen-Schmidt reaction 192
Claisen-type condensation 34
classification 284
- algorithms 285
- software 285
clean technology 209
cluster-based selection 307
clustering
- algorithm 302, 308
- methods 317
CMR/R approach 41, 42
coding strategies 240
combinations of PSRs 231
combinatorial
- approaches on solid support 47
- combinatorial chemistry, microwave assisted 15
- combinatorial organic synthesis 243
- synthesis of heterocycles 159
Complexes, polymer-supported 222
compound selection strategies 308
computational chemistry 277
covalent scavanger approach 37
COX-2-selective drugs 319
crosscorrelation coefficients C^i 295
cross-metathesis 79
cyano borohydride, polymer-supported 232
cyclative cleavage 99, 120, 206
- acid 185
- of carbamate linker 100
[3+2]Cycloaddition 171,
- of nitrile oxides 173
[2+2]Cycloaddition reaction 170,
- of ketenes 168
[4+1]cycloaddition
- nonconcerted 11
cycloaddition-cycloreversion 93
cycloadditions, 1,3-dipolar 7,16
cyclodehydration reaction 217
cyclooxydation 220

D
descriptor set 285,287,291,318
descriptor types 286
descriptors 284
- based on three-dimensional structure 316
- comparison 313
- substructure 315
- topological 315,318
design strategy, computer assisted 278,279
1,2-diazines, synthesis 94
Dieckmann condensation 33
Diels-Alder reaction 84, 220
- asymmetric 219
4,5-dihydro-1H-pyrazoles 232
dihydrofolate 298
dihydropyranes 76
1,4-dihydropyridine 15
dihydropyridines (DHPs) 107
dihydropyridinones 39
5,6-dihydropyrimidine-2,4-diones, synthesis 108

dihydropyrimidinones 13, 192
dihydroquinazolines 198
dihydroquinoxalines 92
dihydroxylation reaction, asymmetric 219, 222
diketomorpholines 188
β-diketone 174
diketopiperazines, see also piperazine-diones 92
– by cyclic cleavage 105
– libraries 8, 105
dissimilarity based selection 304
distance matrix 299,300
distance scaling, nonlinear 303
divergent library design 188
diversity 279, 281
– *computation algorithm* 283, 285
– maximum diversity library 321
– of drug molecules 280
drug -likeness score, prediction 289-291
dry dispensing 273

E
electrotopological state index (S_i) 294
encoding
– graphical 240
– mass spectroscopic 241
– methods, strategies 239
– positional 239
– radiofrequency 239, 241
– spatial 239, 242
(±)-epimaritidine 234
epothilones 77
epoxidation of olefins, enantioselective 219
epoxidation reactions, asymmetric 222
epoxides opened 216
equipment
– for *combinatorial synthesis ,suppliers* 274
– for high-throughput evaporation 272
– for parallel process development 268
– for parallel reactive gas chemistry 269
ethanolamines 33
ethylenes, tetrasubstituted 40
Euclidean distance 303
evaporation, high-throughput 271

F
filters, simple 287
Fischer indole synthesis 193, 194
fluorination of secondary alkohols 230
4-fluoro-3-nitrobenzoic acid 163, 202
fluorous extraction 26, 27
fluorous ponytails 27
fluorous solid phase extraction (FSPE) 29
fluorous tag 5, 26
Freidinger lactams 76
Fukuyama-Mitsunobu process 77
fully automated systems, see automated furans 93, 118

G
goal-directed design 325
graphical encoding, see encoding
Grieco three component reaction 20, 21
Grignard reagents,
– on solid phase 139, 140
– reactions involving 138

H
halogenating agents 228
halogenation 228
halohydrines 216
Heck couplings 84
Heck reaction 127, 131, 135
– indole synthesis 195
– mechanism of 128
heteroannulation, Pd-catalyzed 194
heteroaryl ethers 33
heterobiaryl aldehydes 69
heterocyclic carboxamides 42
hierarchical clustering analysis (HCA) 308, 319
high-pressure synthesizers 269
high-speed solution-phase chemistry 44, 45
high-throughput
– synthesis laboratory 260
– synthesizers 261
HIV protease inhibitor 12
Hofmann elimination, linker design 70
homoserine lactones 114
Horner-Emmons reagents, polymer supported 228
Horner-Wadsworth-Emmons reactions 149, 150
hydantoins 100, 101, 165
hydrazinolysis 179
hydrofluorination
– of alkenes 230
– of alkynes 230
hydrostannation 218
N-(hydroxyethyl)-amides cyclodehydration 216
N-(hydroxyethyl)-thioamides cyclodehydration 216
hydroxylamine linker 62
4-hydroxyquinolin-2(1H)-ones 110
4-hydroxyquinolin-2(1H)-ones 34
4-hydroxyquinolin-2(1H)-ones, synthesis 109
hydroxy-substituted leaving group 213

I
imidazoles 171
imines, resin-bound 168
iminophosphorane 197
immobilization 224
immobilized oxidants 224
incubators 259
indoles 116, 130, 193
β-indolinyl propiophenones 81
in silico screening 301
iododesilylation 74

ion-exchange 30–33
– chromatography 224
– solid-phase extraction 31
ionic interactions 224
ipso-fluoride displacement 202
isocyanate, immobilized 199, 200
isocyanates 167
isomuenchnones 93
isonitriles 6, 7
Isothiocyanates 167
isoxaline ring, fragmentation 16
isoxalines 27
isoxazoles 173

K
Kaiser linker 204
Kaiser ninhydrin test 185
kans 241
ketones, α,β-unsaturated 192
ketopiperazines 92
Knoevenagel reactions 67
Kohonen maps 312, 323
– self-organizing 315

L
χ-lactones, diastereoselective synthesis 113
lead dicovery 1
lead finding 2
lead optimization 1, 2
Lewis acid, polymer-suported 221
libraries
– of arylethers 228
– of het-arylethers 228
– of peptide aldehydes 69
– of peptidomimetics 59
– of piperidino-thiomorpholines 233
– of pyrroles 18
– solution-phase 36
– targeted 323
library design, computer assisted 277, 324
library downsizing 288
library optimization 277
library selection 312
linker 47
linker unit, synthesis of 48
linkers
– for alkohols 66
– for amino functions 48
– for carboxyl functions 48
– pre-attached 49
liquid level detection 28
liquid-liquid extraction 22, 269
– automated 24
– devices 259
– methods 44
– module 270
liquid-phase extraction 42
liquid-solid extraction (LSE) 29, 44
lithium organyls on solid phase 139
lithium reagents, reactions involving 138
logP values 288, 293
lollipop method 29, 269
– phase separation method 270

M
macrocycles, cleavage from solid support 117
macrocyclizations 99
Mahalanobis distance 303
MALDI instrument 241
manual synthesis workstation 256
manual synthesizers 247, 253
manual systems 245, 246
mapping 284
mapping algorithms 302
mapping based selection 304
mapping, nonlinear 306
maps, self organizing (SOMs) 306, 307, 317
masked carboxylic acid tags 43
mass spectroscopic encoding 241
matrix metalloproteinase inhibitors 105
– solid phase synthesis of 64
maximum diversity library 321
metathesis see also cross-metathesis 78
– concept on solid support 79
– on solid phase 143
– ring closing 118
– ring-closing, on polymeric support 143
methotrexate 298
Michael addition, intramolecular 198
minimal spanning tree (MST) 307
Mitsunobu
– esterification 215
– reactions 43
Mn(III) complexes chiral 223
modular manual synthesizers 256
modular synthesizers 259
Moffat oxidation 42
molecular connectivity index 294
molecular fingerprints (FP) 291
molecular interaction field, three-dimensional 301
molecular modelling 277
molecular oxygen 225
molecular shape index 294
molecular surface properties 301
molecular tag 241
morpholines, trisubstituted 188
Mukaiyama aldol condensation, reaction 232, 233
multicomponent condensations (MCCs) 6
multistep procedures 209
Münchnone 171

N
N-acyliminium ion 182, 183
neutral amide library 32

Ninhydrin test see Kaiser ninhydrin test
nonsteroidal anti-inflammatory drugs (NSAIDs), dataset 313–317, 319

O
olefin formation 215
olefin metathesis 141, 142
olefin, linear elongation 141
olefination of protected carbonyl compounds 231
one-pot preparation, three-step 232
one-pot transformations 231
o-nitrobenzyl-based linkers 85
optimization
– educt-based 309
– evolutionary 311
– product-based 310
orchestrated polymer-supported reagents 233
organic polymer
– crosslinked 210
– linear 210
organic synthesizers 245
organotin reagents 217
organozinc reagents
– Pd-mediated couplings 138
– reactions involving 138
oxazolidinones
– 3,5 disubstituted 104
– N-sulfonylated 105
oxazolinium-5-one (muenchnone) 7
oxidation reactions 226
(±)-oxomaritidine 234
oxopiperazines see Piperazinones

P
palladium
– precipitates 163
– Pd-complex, polymer supported 216
– Pd- couplings, limitations 130
Pd-mediated couplings on a polymeric support 130
parallel evaporators 246
parallel synthesis 1, 44, 209, 244
PASP strategy 37, 40
Passerini reaction 8
Pauson-Khand cyclization 152
peptide aldehydes library 69
peptide synthesis 213
peptidomimetics library 59
perbromide on ion-exchange resins 229
perfluoralkylated
– phosphorus compounds 27
– silicium compounds 27
– tin compounds 27
perfluorohydrocarbons 26
perruthenate, polymer supported 225, 232, 234
pharmacophore 281
– centers (PCs) 296
– descriptors 295, 298
– mapping 5
phase detection 28
phase differentiation 44
phase separation 269
– techniques 28
phase switch 33, 35, 37, 44
phenolic leaving group, polymer bound 213
phenols
– attachment 68
– homoaromatic 120
– 3,4,5-trisubstituted 119
9-phenylfluoren-9-yl based linker 66
5-phenylmethyl-2-oxazolidinone 162, 185
phosphine resin 214
phosphorane 214
photocleavable linker, based on pivaloylglycol 86
photolabile linkers 84
photolysis 88
photolytic cleavage 85, 86
physico-chemical constants 288
Pictet-Spengler
– cyclizations 67
– reaction 203
pipecolic acid derivatives 76
piperazine template 23
piperazine-diones (Diketopiperazines) 183
piperazinones 180
piperidone 23
pipetting robots 259
piperidino-thiomorpholine library 234
pK_A values 288
poly(allylscandiumtriflyl)-amide ditriflate (PA-Sc-TAD) 221
poly(hydrogen fluoride) (PVPHF) polyvinylpyridium supported 230
polymer-assisted solution-phase chemistry (PASP) 37
polymer-supported
– isocyanate 40
– quench (PSQ) purification 39
– reagents 235
– tris(2-aminoethyl)amine 40
pony tails, perfluorinated 5
positional encoding 239
process development 268
product isolation strategies 44
prostaglandin $F_{2\alpha}$, total synthesis 63
prostaglandins, synthesis 65
protecting groups for amino functions 48
protodesilylation 74
PSR by polymerization, by co-polymerization 218
2,4-pteridinediones 200
purification methods 44
pyrazoles 39, 173, 191
pyrazolones 102
pyrazolones

- cyclic cleavage of 103
- 4.5 disubstituted 103
- trisubstituted 102
pyridine-based tricyclic structures 73
pyridines 192
pyridopyrimidinediones 200
pyrimidines 31, 191
pyrimidopyrimidinediones 200
pyrrole libraries 18
pyrroles, highly substituted 18
pyrrolidines, solid-phase synthesis of 63

Q
quenching agents 35
2,4-(1H,3H)quinazolidinones, synthesis 109
2,4-Quinazolindiones 199
quinazolines 196
quinine-based catalysts, polymer-supported 221, 222

R
radical reactions 151
radiofrequency encoding 239, 241
radiofrequency encoding 241
reaction blocks 245–251
- for parallel organic synthesis 251
- for solid phase synthesis 250
- in mtp format 248
reagents, polymer supported 209, 210, 231
redox systems 225
reducing agents 227
reduction of α,β-unsaturated carbonyl compounds 227
reductive alkylation 185, 186
reductive amination 23, 39
release 48
resin bound amine 54
resin capture 37, 44
- approach, strategies 41
- concept 40
resin dispensing, automated 273
resins
- gel-type 210
- macroporous 210
- macroreticular 210
restrictions 2
ring opening-recyclization cleavage 104
ring-closing metathesis, on polymeric support 143
robotic
- method 32
- system 28
rule-of-5 159

S
safety catch linkers 88–91
scandium triflate 12
scavanger
- approach 36
scavanger resins 39
- covalent 35, 41, 44
- solid-supported 39
solution 35
scavenging agents
- polymer supported 231
- support-bound 230
Schiff base zinc complexes, polymer supported 223
Schwesinger base 148, 149
selection
- algorithms 285
- cluster-based 307
- dissimilarity based 304
- mapping based 304
- methods, comparison 313
- partition-based 398
Self-condensation 171
semiautomated synthesizers 245, 256, 257
semiautomated systems 245, 256
sequestering agents 231
- support-bound 230
serine-based linker for phenols 67
side products, dialkylated 190
side reactions 41
- bis-alkylation 167, 186
- reductive debromination 195
silica gel 29
- fluorinated 30
- fluorous 30
silica gel-based
- adsorbents 30
- ion-exchange sorbents 31
silicon linkers 72
silyl linker 65
similarity 280, 281
single atom properties 293
SN2 displacement/Michael addition 180
solid-phase
- chemistry 99
- extraction (SPE) 29, 41, 42, 44
- organic synthesis (SPOS) 47
- synthesis 1, 22
synthesis of tropane derivatives 63
solution chemistry 5
- applications 240
- polymer-supported 5
solution-phase
- libraries 36
- parallel synthesis 22
synthesis 22, 268
Sonogashira coupling 20, 129, 130, 136, 137
Sonogashira reaction, indole synthesis 194
sort-and-combine 159
spatial encoding 239, 242
spatially addressed synthesis 2
SPE procedure, dual ion exchange 32

SPE see solid-phase extraction 42
SPE workstation 32
spiro(pyrrolidine-2,3'-oxindoles) 16
split and combine procedure 1
split-mix method 244
split-only technique 244
split-split technique 244
Staudinger reaction 168
stereochemistry 297
(E)-stilbenes 81
(Z)-stilbenes 81
Stille coupling 126, 161
– cyclative 117
– problems associated with 127
Stille reaction 117, 218
Stille reagents, polymer-supported 217
stoichiometric oxidant 225
strategy, reagent explosion 8, 9
styrene derivative co-polymerization 220
sublibraries, targeted 322
substituted lactones, synthesis 112
substructure descriptor (SSD) 291, 292
sulfonamides 232, 233
sulfonamides 36,37
sulfonylpyridinium ion, polymer-supported 232
supported phosphonium salt 215
Suzuki coupling 123, 132, 216
– catalytic cycle 125
– limitations 124
– reaction 40
Suzuki cross-coupling 124, 133
Suzuki reaction, double 41
Suzuki-Miyaura cross-couplings 69
symmetric anhydride method 212
synthesis, on solid support 95

T
tag 2, 239
– analysis 241
– chemically tagged reagents 45
– decoding 241
– tag 241
Tanimoto coefficient 302
target structure, three-dimensional 302
teabag method 240
3-tert. butylamino-2-(2-pyridyl)-6-methylimidazo (1,2-a) pyridine 11,12
tert.butyloxycarbonyl (Boc), linker based on 53
tert.butyloxycarbonyl group (Boc) 48
tertiary amines on solid support 70
tetrahydro-β-carboline derivatives 111
tetrahydro-β-carbolines 203
– synthesis of annellated 111
tetrahydrofurans
– 2,5-disubstituted 113
– synthesis 114
tetrahydroindolizines, isoxaline-fused 16
tetrahydropyranyl(THP) group linker 62
tetrahydroquinoline derivatives 20
tetramic acids 33, 114
– synthesis 115
tetrazole derivatives, bicyclic 9
thiazole libraries 42
thiazolidinone library 51
thiazolidinones 175
thiazolylhydantoins 102
thiohydantoins 5, 24, 165
thiotriazoles 177
2-thioxo-4-dihydropyrimidinones 39
thrombin inhibitors 318
thrombin inhibitors, virtual library 320
tin reagents immobilized 217
topological autocorrelation descriptors 300
topological descriptors 293
topological state index (Ti) 294
tosylimines 172
traceless linker
– based on arylhydrazide 81
– based on olefin metathesis 75
– based on silylfunctionalization 72
– decarboxylation based 81
– systems 70
– triazene-based 84
traceless solid phase synthesis 93
triacetoxyborohydride 185
triazines, scaffold, trichloro- 189–191
triazoles 177
triphenylphosphine polymer-supported 80, 215
trityl linker 59
tropane derivatives 129
Tsuge reaction 16

U
Ugi four component reaction 6,7
Ugi four-component condensation 40, 91
α,β-unsaturated ketones 232
ureas 35, 36, 37
– parallel synthesis 25
urethane linker, cleaved by fluoride ions 55

V
vacuum centrifuges see centrifuges 271
vinylations, transition metal-mediated 123
vinylsulfone groups 71
virtual library 278, 283
– design 320
– thrombin inhibitors, 320
– virtual mesh 283
virtual or "in silico" screening 301

W
Wang linker, chloro-Wang resin 194
wash procedures 256
washing strategy acid/base 24
web addresses 274

– manufacturers' web pages 274
Weinreb amides 62
Wittig reaction 149, 192
– intramolecular 117, 193
– on solid support 80
Wittig reagent, polymer supported 214, 215
Wittig, on Rink resin 150
Wittig-type reactions 5, 115

Z
(S)-zearalenon 117
zinc organyls, on solid phase 139