

TOPICS IN CURRENT CHEMISTRY

278

Volume Editor S. Bräse

Combinatorial Chemistry on Solid Supports

Combinatorial Chemistry on Solid Supports

Volume Editor: Stefan Bräse

With contributions by

A. G. Beck-Sickinger · S. Bräse · R. Breinbauer · K. Bromfield
B. Castagner · F. Debaene · M. Haack · F. Hahn · N. Jung · N. Kann
N. Ljungdahl · M. Mentel · Z. Pianowski · U. Schepers
P. H. Seeberger · M. Wiehn · N. Winssinger

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope of coverage includes all areas of chemical science including the interfaces with related disciplines such as biology, medicine and materials science. The goal of each thematic volume is to give the nonspecialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights are emerging that are of interest to a larger scientific audience.

As a rule, contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for *Topics in Current Chemistry* in English.

In references *Topics in Current Chemistry* is abbreviated *Top Curr Chem* and is cited as a journal. Visit the TCC content at springerlink.com

Library of Congress Control Number: 2007927309

ISSN 0340-1022

ISBN 978-3-540-72509-1 Springer Berlin Heidelberg New York

DOI 10.1007/978-3-540-72510-7

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable for prosecution under the German Copyright Law.

Springer is a part of Springer Science+Business Media

springer.com

© Springer-Verlag Berlin Heidelberg 2007

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Cover design: WMXDesign GmbH, Heidelberg

Typesetting and Production: LE-TeX Jelonek, Schmidt & Vöckler GbR, Leipzig

Printed on acid-free paper 02/3180 YL – 5 4 3 2 1 0

278

Topics in Current Chemistry

Editorial Board:

**V. Balzani · A. de Meijere · K. N. Houk · H. Kessler · J.-M. Lehn
S. V. Ley · S. L. Schreiber · J. Thiem · B. M. Trost · F. Vögtle
H. Yamamoto**

Topics in Current Chemistry

Recently Published and Forthcoming Volumes

Photochemistry and Photophysics of Coordination Compounds II

Volume Editors: Balzani, C., Campagna, S.
Vol. 281, 2007

Photochemistry and Photophysics of Coordination Compounds I

Volume Editors: Balzani, C., Campagna, S.
Vol. 280, 2007

Metal Catalyzed Reductive C–C Bond Formation A Departure from Preformed Organometallic Reagents

Volume Editor: Krische, M. J.
Vol. 279, 2007

Combinatorial Chemistry on Solid Supports

Volume Editor: Bräse, S.
Vol. 278, 2007

Creative Chemical Sensor Systems

Volume Editor: Schrader, T.
Vol. 277, 2007

In situ NMR Methods in Catalysis

Volume Editors: Bargon, J., Kuhn, L. T.
Vol. 276, 2007

Sulfur-Mediated Rearrangements II

Volume Editor: Schaumann, E.
Vol. 275, 2007

Sulfur-Mediated Rearrangements I

Volume Editor: Schaumann, E.
Vol. 274, 2007

Bioactive Conformation II

Volume Editor: Peters, T.
Vol. 273, 2007

Bioactive Conformation I

Volume Editor: Peters, T.
Vol. 272, 2007

Biominerallization II

Mineralization Using Synthetic Polymers and Templates
Volume Editor: Naka, K.
Vol. 271, 2007

Biominerallization I

Crystallization and Self-Organization Process
Volume Editor: Naka, K.
Vol. 270, 2007

Novel Optical Resolution Technologies

Volume Editors:
Sakai, K., Hirayama, N., Tamura, R.
Vol. 269, 2007

Atomistic Approaches in Modern Biology

From Quantum Chemistry
to Molecular Simulations
Volume Editor: Reiher, M.
Vol. 268, 2006

Glycopeptides and Glycoproteins

Synthesis, Structure, and Application
Volume Editor: Wittmann, V.
Vol. 267, 2006

Microwave Methods in Organic Synthesis

Volume Editors: Larhed, M., Olofsson, K.
Vol. 266, 2006

Supramolecular Chirality

Volume Editors: Crego-Calama, M.,
Reinhoudt, D. N.
Vol. 265, 2006

Volume Editor

Prof. Dr. Stefan Bräse

Institut für Organische Chemie
Universität Karlsruhe (TH)
Fritz-Haber-Weg 6
76131 Karlsruhe
Germany
braese@ioc.uka.de

Editorial Board

Prof. Vincenzo Balzani

Dipartimento di Chimica „G. Ciamician“
University of Bologna
via Selmi 2
40126 Bologna, Italy
vincenzo.balzani@unibo.it

Prof. Dr. Armin de Meijere

Institut für Organische Chemie
der Georg-August-Universität
Tammanstr. 2
37077 Göttingen, Germany
ameijer1@uni-goettingen.de

Prof. Dr. Kendall N. Houk

University of California
Department of Chemistry and
Biochemistry
405 Hilgard Avenue
Los Angeles, CA 90024-1589
USA
houk@chem.ucla.edu

Prof. Dr. Horst Kessler

Institut für Organische Chemie
TU München
Lichtenbergstraße 4
86747 Garching, Germany
kessler@ch.tum.de

Prof. Jean-Marie Lehn

ISIS
8, allée Gaspard Monge
BP 70028
67083 Strasbourg Cedex, France
lehn@isis.u-strasbg.fr

Prof. Steven V. Ley

University Chemical Laboratory
Lensfield Road
Cambridge CB2 1EW
Great Britain
Svl1000@cus.cam.ac.uk

Prof. Stuart L. Schreiber

Chemical Laboratories
Harvard University
12 Oxford Street
Cambridge, MA 02138-2902
USA
sls@slsiris.harvard.edu

Prof. Dr. Joachim Thiem

Institut für Organische Chemie
Universität Hamburg
Martin-Luther-King-Platz 6
20146 Hamburg, Germany
thiem@chemie.uni-hamburg.de

Prof. Barry M. Trost

Department of Chemistry
Stanford University
Stanford, CA 94305-5080
USA
bmtrost@leland.stanford.edu

Prof. Dr. Hisashi Yamamoto

Department of Chemistry
The University of Chicago
5735 South Ellis Avenue
Chicago, IL 60637
USA
yamamoto@uchicago.edu

Prof. Dr. F. Vögtle

Kekulé-Institut für Organische Chemie
und Biochemie
der Universität Bonn
Gerhard-Domagk-Str. 1
53121 Bonn, Germany
voegtle@uni-bonn.de

Topics in Current Chemistry Also Available Electronically

For all customers who have a standing order to Topics in Current Chemistry, we offer the electronic version via SpringerLink free of charge. Please contact your librarian who can receive a password or free access to the full articles by registering at:

springerlink.com

If you do not have a subscription, you can still view the tables of contents of the volumes and the abstract of each article by going to the SpringerLink Homepage, clicking on "Browse by Online Libraries", then "Chemical Sciences", and finally choose Topics in Current Chemistry.

You will find information about the

- Editorial Board
- Aims and Scope
- Instructions for Authors
- Sample Contribution

at springer.com using the search function.

Preface

The modern billion-dollar drug-discovery process strongly relies on both high-throughput synthesis and screening methods. Whereas the latter is based on molecular biological methods, the efficient and reliable generation of compound collections often makes use of combinatorial chemistry. Discovered in the 1980s, this methodology was explored extensively in the 1990s by groups in academia and in industry. Without any doubt, combinatorial chemistry changed the whole drug-discovery process and found many applications in crop science and the material sciences.

However, since its implementation, solution- and solid-phase techniques have been competing with each other, and although many companies started their combinatorial chemistry program with solid-phase techniques, solution-phase combinatorial methods have taken over and now account for approximately 25% of all combinatorial efforts.

The syntheses of complex, non-polymeric structures, discovered in the 1960s by the late Bruce Merrifield, was largely ignored in the context of solid supports, mainly due to the fact that appropriate synthesis techniques were not available.

Since solid-phase chemical methodology strongly differs from traditional solution-phase chemistry, two chapters deal with this topic. The Bräse group (Jung, Wiehn, Bräse) gives an overview of multifunctional linkers, which can be used for the generation of diversity-oriented collections, simply by cleavage from resins.

Still in its infancy, solid-phase reactions employ “simple” amide chemistry in most cases due to their high-yielding, reliable protocols. Ljungdahl, Bromfield, and Kann address solid-phase organometallic chemistry, which is now one of the great challenges in reliable solid-phase organic synthesis.

The next four chapters address the construction of designed and native complex structures, such as polyamines (Hahn and Schepers), natural products (Mentel and Breinbauer) and peptides, with a focus on identification of bioactive hormone structures (Haack and Beck-Sickinger). Furthermore, the automated synthesis of carbohydrates is addressed in detail by Castagner and Seeberger.

Finally, Winssinger, Pianowski, Debaen give an overview of array techniques that are suitable for solid-phase chemistry.

In this volume, state-of-the-art solid-phase synthesis is presented from different angles. Ranging from methodology development to application in the synthesis of complex native and designed structures, a complete overview is presented.

We are confident that addressing the fascinating interface between chemistry and biology is only possible by innovative methods in both disciplines. Combinatorial chemistry is surely one of these.

The editor thanks the editorial staff of *Topics in Current Chemistry*, in particular Mrs. Kollmar-Thoni and Dr. Marion Hertel for their professional support.

Karlsruhe, April 2007

Stefan Bräse

Contents of Volume 254

Organic Solid State Reactions

Volume Editor: Fumio Toda

ISBN: 978-3-540-22982-7

Thermal and Photochemical Reactions in the Solid State

F. Toda

**Crystal Engineering of Organic Cocrystals
by the Solid State Grinding Approach**

A. V. Trask · W. Jones

**Intra-Solid and Inter-Solid Reactions of Molecular Crystals:
a Green Route to Crystal Engineering**

D. Braga · D. D'Addario · S. Giaffreda · L. Maini · M. Polito · F. Grepioni

Organic Solid-State Reactions with 100% Yield

G. Kaupp

The Mechanochemical Solid-State Reaction of Fullerenes

K. Komatsu

Photochemical Aspects of Thiocarbonyl Compounds in the Solid-State

M. Sakamoto

**Asymmetric Induction in Organic Photochemistry
via the Solid State Ionic Chiral Auxiliary Approach**

J. R. Scheffer · W. Xia

Reactions of 1,3-Diene Compounds in the Crystalline State

A. Matsumoto

Contents

Multifunctional Linkers for Combinatorial Solid Phase Synthesis N. Jung · M. Wiehn · S. Bräse	1
Solid Phase Organometallic Chemistry N. Ljungdahl · K. Bromfield · N. Kann	89
Solid Phase Chemistry for the Directed Synthesis of Biologically Active Polyamine Analogs, Derivatives, and Conjugates F. Hahn · U. Schepers	135
Combinatorial Solid Phase Natural Product Chemistry M. Mentel · R. Breinbauer	209
Multiple Peptide Synthesis to Identify Bioactive Hormone Structures M. Haack · A. G. Beck-Sickinger	243
Automated Solid Phase Oligosaccharide Synthesis B. Castagner · P. H. Seeberger	289
Probing Biology with Small Molecule Microarrays (SMM) N. Winssinger · Z. Pianowski · F. Debaene	311
Author Index Volumes 251–278	343
Subject Index	355

Multifunctional Linkers for Combinatorial Solid Phase Synthesis

Nicole Jung · Matthias Wiehn · Stefan Bräse (✉)

Institute for Organic Chemistry, University of Karlsruhe (TH), 76131 Karlsruhe,
Germany
braese@ioc.uka.de

1	Introduction	4
2	Ester-Type Linkers	6
2.1	Esters Type A	6
2.1.1	Cleavage Yielding Carboxylic Acids	8
2.1.2	Cleavage Yielding Ketones, Aldehydes and Alcohols	10
2.1.3	Traceless Cleavage	12
2.1.4	Cleavage Yielding Primary and Secondary Amides	13
2.1.5	Cleavage Yielding Alkyl-O- and S-Esters	15
2.1.6	Cleavage Yielding Hydroxamates	15
2.1.7	Ring-Forming Strategies	16
2.2	Esters Type B	17
2.2.1	Allylic Esters	18
3	Amide Linkers	20
4	Carbamate and Carbonate Linkers	24
4.1	Carbamate Type A	24
4.2	Carbamates Type B	28
4.3	Carbonate Linkers	29
5	Weinreb Derivatives and Hydroxamates	30
6	Triazene Linkers	33
6.1	The Triazene T1 Linker	34
6.2	The Triazene T2 Linker	39
7	Hydrazone Linkers	40
8	Benzotriazole Linkers	42
9	Phosphonium Linkers	42
10	Sulfur Linkers	44
10.1	Cleavage of Non-Diversified Thioether Linkers	45
10.2	Cleavage via Sulfonium-Ions	48
10.3	Cleavage via Oxidation to Sulfones/Attachment of Sulfones	49
10.4	Cleavage via Sulfoxide-Linkers	54
11	Sulfonyloxy Linkers	56

12	Sulfamate Linkers	61
13	Selenium Linkers	62
14	Bismuth Linkers	65
15	Silyl Linkers	66
16	Germanium Linkers	71
17	Stannane Linkers	72
18	Boron Linkers	73
19	Olefinic Linkers	75
	References	79

Abstract This review covers recent results in the area of multifunctional linkers for solid phase synthesis during the period 2000–2006.

Keywords Diversity-oriented synthesis · Linkers · Solid phase synthesis

Abbreviations

AA	amino acid
Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitril
AM	aminomethyl
AMB	α -methyl benzyl
BAL	backbone amide linker
9-BBN	9-borabicyclo[3.3.1]nonane
BHA	benzhydramine
BME	β -mercapto ethanol
Bn	benzyl
Boc	<i>t</i> -butyloxycarbonyl
BOP	benzotriazole-1-(<i>y</i> loxy) tris-(dimethylamino) phosphonium hexafluorophosphate
BPO	benzoylperoxide
BSA	bovine serum albumin
BTC	<i>bis</i> -trichloromethyl carbonate
CAN	cerium ammonium nitrate
Cbz	carbobenzyloxy
CDI	carbonyl diimidazole
CSA	camphor sulfonic acid
DBU	diazabicyclo[5.4.0]undecane
DCC	dicyclohexyl carbodiimide
DCH	1,3-dichloro-5,5-dimethylhydantoin
DDQ	dichlorodicyanobenzoquinone
DEAD	diethylazodicarboxylate

DEAM	diethanolaminomethyl
DEPEC	diethyl phosphorocyanidate
DIBAL	diisobutylaluminumhydride
DIC	diisopropyl carbodiimide
DIEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DNA	desoxyribonucleic acid
DOS	diversity-oriented synthesis
dppe	1,3-bis(diphenylphosphino)ethane
dppf	1,3-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DSC	<i>N,N</i> -disuccinimidyl carbonate
DVB	divinylbenzene
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimid
Fmoc	9-fluorenylmethyloxycarbonyl
FMP	4-formyl-3-(methoxyphenoxy)methyl-PS
Gly	glycin
HASC	heteroatom-substituted carbonyl linker
HAL	hypersensitive acid-labile
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisiloxane
HMPA	hexamethylphosphoramide
HMPB	4-hydroxymethyl-3-methoxyphenoxy-butyric acid
HOAt	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazol
LDA	lithiumdiisopropylamide
MAMP	Merrifield α -methoxyphenyl
MBHA	methylbenzhydramine
<i>m</i> CPBA	<i>m</i> -chlorperbenzoic acid
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMM	<i>N</i> -methyl morpholine
NMP	<i>N</i> -methyl pyrrolidone
NPCF	4-nitrophenylchloroformate
NpSSM ^{pact}	2-methoxy-5-[2-((2-nitrophenyl)dithio)-1-oxopropyl]phenylacetic acid
Nu	nucleophile
PAC	peptide acid linker
PAM	phenylacetamidomethyl
PEG	polyethylene glycol
PEGA	polyethylene glycolpoly-(<i>N,N</i> -dimethyl-acrylamide)
PFS	perfluoroalkylsulfonyl
PPF	1,1'-bis(diphenylphosphino)ferrocene
PPTS	<i>p</i> -pyridinumtoluene sulfonic acid
PNA	peptide nucleic acid
PS	polystyrene
PTMSEL	(2-phenyl-2-trimethylsilyl)ethyl
Py	pyridine

PyBrOP	bromo-tris-pyrrolidino phosphoniumhexafluorophosphate
RAM	Rink amide
RCM	ring-closing metathesis
RRTR	resin-to-resin transfer reaction
SAC	silyl acid
SASRIN	super acid sensitive resin
SCAL	safety catch acid labile
SEC	2-alkylsulfonyl ethyl carbamate
SPPS	solid phase peptide synthesis
TBAF	tetrabutylammoniumfluoride
TBDPS	<i>t</i> -butyldiphenylsilyl
TBTU	<i>O</i> -(benzotriazole-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TEA	triethylamine
THF	tetrahydrofuran
Tf	trifluoromethylsulfonyl
TFA	trifluoro acetic acid
TFAA	trifluoro acetic acid anhydride
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
TMG	2- <i>t</i> -butyl-1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Trt	trityl
XAL	xanthenylamide linker
XAN	9-xanthenyl linker
XPHOS	2-dicyclohexylphosphino-2',4',6'-triisopropyl-biphenyl

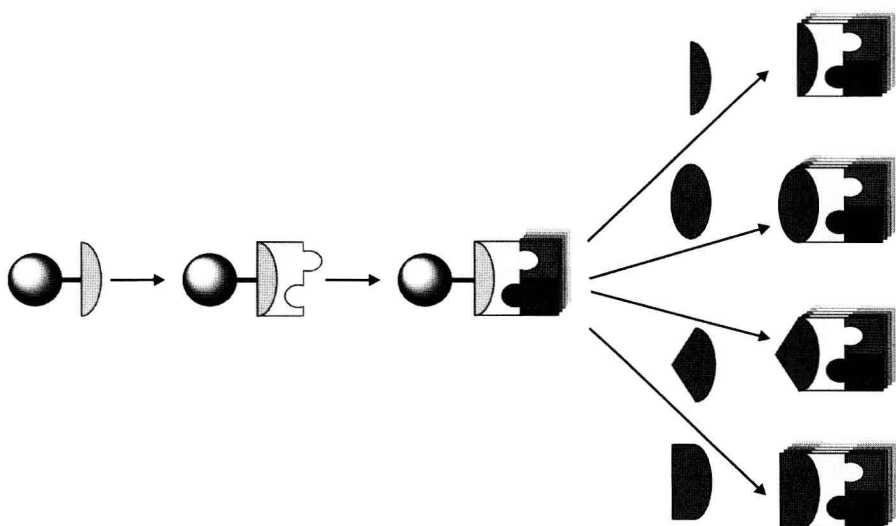
1

Introduction

The advent of combinatorial chemistry being implemented in the modern drug discovery process in the 1990s [1] has reinitiated the use of solid phase synthesis originally developed by the late Bruce Merrifield [2]. While in the early stages of solid phase synthesis, first peptides and later nucleic acids were favorably synthesized using this technique due to the ease of automation [3], small molecular entities obeying the Lipinski rules have been prepared in the last decades with the notable exception by Frechet and others [4, 5]. In particular, the invention of the split-and-mix-technique by Furka [6] and later the technological platforms derived from this, e.g. the IRORI techniques [7], triggered the design and preparation of large compound libraries with more than 2 000 000 compounds [8]. Diversity-oriented synthesis (DOS), originally proposed by S. L. Schreiber [9, 10], is today used by many laboratories both in academia and industry. In particular solid phase synthesis has served as a technology platform and allows the rapid assembly of building blocks to generate quite complex structures in few synthetic steps. A crucial point in the design of compound libraries is the careful choice of the appropriate

linker attaching the molecule to the solid support [11, 12]. Linkers do not only serve as the point of attachment, they also control the chemistry being allowed during the assembly stage and importantly are directing the functional group being generated upon cleavage. While peptide synthesis requires more or less the detachment of carboxylic acids and amides, diversity-oriented synthesis strongly relies on the cleavage of various functional groups in order to avoid constraints. Thus, a high number of various linkers have been prepared and discussed in a number of reviews.

Linkers allowing the cleavage of one certain functional group have been named mono-functional linkers [13]. However, an attachment being cleavable to generate more than one functional group is named a multifunctional linker [14–16] (Scheme 1).



Scheme 1 Solid phase synthesis and multifunctional cleavage

We will define *multifunctional linkers as attachments which allow the generation of more than one functional group upon cleavage from a solid support either with or without implementation of building blocks.*

Linkers which allow cleavage of reactive functional groups that in turn can be reacted with added building blocks in a one-pot method are also called multifunctional.

In this review we will discuss the multifunctional linkers in terms of assembly on solid supports, stability towards reaction conditions, and finally the issue of introduction of multifunctionality.