Edited by
Dieter Enders and Karl-Erich Jaeger

WILEY-VCH

Asymmetric Synthesis with Chemical and Biological Methods

Foreword by Günter Helmchen

Asymmetric Synthesis with Chemical and Biological Methods

Edited by
Dieter Enders and Karl-Erich Jaeger

WILEY-VCH Verlag GmbH & Co. KGaA

The Editors

Prof. Dr. Dieter Enders
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Prof. Dr. Karl-Erich Jaeger
Institut für Molekulare Enzymtechnologie
der HHU Düsseldorf im FZ Jülich
52426 Jülich
Germany

Library of Congress Card No.:
applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.d-nb.de>.

Typesetting SNP Best-set Typesetter Ltd., Hong Kong
Printing betz-druck GmbH, Darmstadt
Binding Litges & Dopf GmbH, Heppenheim
Cover Design Adam Design, Weinheim
Wiley Bicentennial Logo Richard J. Pacifico
Printed in the Federal Republic of Germany

Printed on acid-free paper

ISBN: 978-3-527-31473-7

Asymmetric Synthesis with Chemical and Biological Methods

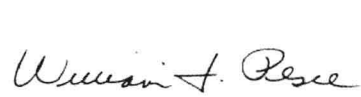
Edited by
Dieter Enders and Karl-Erich Jaeger

1807–2007 Knowledge for Generations

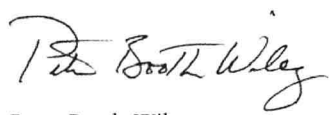
Each generation has its unique needs and aspirations. When Charles Wiley first opened his small printing shop in lower Manhattan in 1807, it was a generation of boundless potential searching for an identity. And we were there, helping to define a new American literary tradition. Over half a century later, in the midst of the Second Industrial Revolution, it was a generation focused on building the future. Once again, we were there, supplying the critical scientific, technical, and engineering knowledge that helped frame the world. Throughout the 20th Century, and into the new millennium, nations began to reach out beyond their own borders and a new international community was born. Wiley was there, expanding its operations around the world to enable a global exchange of ideas, opinions, and know-how.

For 200 years, Wiley has been an integral part of each generation's journey, enabling the flow of information and understanding necessary to meet their needs and fulfill their aspirations. Today, bold new technologies are changing the way we live and learn. Wiley will be there, providing you the must-have knowledge you need to imagine new worlds, new possibilities, and new opportunities.

Generations come and go, but you can always count on Wiley to provide you the knowledge you need, when and where you need it!



William J. Pesce
President and Chief Executive Officer



Peter Booth Wiley
Chairman of the Board

Foreword

Stereochemistry has been an important topic for more than a hundred years. Nevertheless, as far as the chemist's everyday life was concerned, it was mainly of interest to natural product chemists for most of the time. This changed in the 1950s when synthetic chemists, following the example of R. B. Woodward, G. Stork and others, began to boldly address complex natural product targets. At this time the racemic compound was targeted, i.e. it was diastereoselectivity that counted. In the 1970s it became increasingly clear that biological activities of enantiomers could differ to the extent that one member of a pair is toxic or generally harmful. In this respect, the Contergan disaster was a signal. Pharmacologic testing of both individual enantiomers rather than the racemic agent became a common practice.

Demand created interest in the development of new methods for syntheses of *enantiomerically pure compounds*, termed *EPC*-syntheses by Dieter Seebach. First auxiliary controlled, stoichiometric asymmetric synthesis began to flourish in the second half of the 1970s. Dieter Enders, the spiritus rector of this book, with his SAMP/RAMP method, was one of the pioneers of this field. At about the same time the potential of enzyme-catalyzed enantioselective reactions became more and more visible, not least through pioneering early work of the M. R. Kula/ C. Wandrey team in Düsseldorf/Jülich and of Hans-Joachim Gais in Darmstadt, later Aachen. In the 1980s, very few people dared to address transition metal catalyzed asymmetric synthesis. This changed in the 1990s after work of Kagan, Knowles, Sharpless, Noyori and others had shown that results useful for organic synthesis can be obtained.

Thus, in the early 1990s the stage was set for an Aachen/Jülich group of chemists to launch a collaborative program in the field of EPC synthesis that led to a prestigious Collaborative Research Center (Sonderforschungsbereich, SFB) "Asymmetric Syntheses with Chemical and Biological Methods", which was to become operative for 12 years (1994–2005). In this book the main results, obtained by ca. 20 research groups, are reviewed. A very large and colorful landscape of methods and applications is presented.

The first part of the book is devoted to auxiliary controlled reactions using the SAMP/ RAMP method (D. Enders) and metallated allylsulfoximines (H.-J. Gais).

Asymmetric Synthesis with Chemical and Biological Methods. Edited by Dieter Enders and Karl-Erich Jaeger

ISBN 978-3-527-31473-7

Syntheses of an impressive array of natural products, including medicinally interesting alkaloids, underline the usefulness of these methods. The following part deals with enantioselective reactions catalyzed by transition metal complexes. Chiral ligands with a modular make-up are of crucial importance here and many new classes are described: phosphines containing an arenechromium-tricarbonyl moiety ("Daniphos" ligands, A. Salzer), phosphaferrocenes (C. Ganter), sulfoximine-based N,N- and P,N-ligands (C. Bolm), P,C- and N,O-ligands containing a [2,2]paracyclophane skeleton (C. Bolm, S. Bräse) and phosphines based on dihydroquinolines ("Quinaphos" ligands, W. Leitner). Catalyst immobilization on or in a zeolite matrix was much debated in the SFB; finally, W. F. Hoelderich's group has been able to obtain highly active, reusable hydrogenation as well as Jacobsen type epoxidation catalysts.

The next part of the book deals with enzyme catalysis and bioorganic synthesis. An important aim of this research has been the preparation of enantiomerically pure small molecules that are useful in general organic synthesis and as intermediates in drug process synthesis. It is apparent that there has been fruitful and remarkably successful collaboration between ca. 10 groups, led by established as well as junior group leaders. The first three articles, with authors from the groups of K.-E. Jaeger, M.-R. Kula, M. Pohl, M. Müller and G. A. Sprenger, deal with applications of techniques of enzyme biochemistry, for example site-directed mutagenesis and directed evolution based on recombinant DNA technology. The following articles describe asymmetric syntheses of a large variety of chiral alcohols using *R*-specific alcohol dehydrogenases (W. Hummel), aldolases and related types of C-C bond forming enzymes (W.-D. Fessner) as well as sucrose synthase I (L. Elling). An article naming 17 authors on asymmetric synthesis of 1,3-diols and propargylic alcohols concludes the section.

An asset of the Aachen/Jülich bioorganic synthesis approach is technology transfer, which is testified by no less than five start-up companies. Scale-up requires stable and highly efficient enzymes as well as appropriate reaction technology. The development of membrane reactors has been a key to success. Reaction technology is outlined by C. Wandrey and co-workers in the final article.

Reading this book is worthwhile for anybody seeking an impression of the state of the art of the entire field of asymmetric synthesis. A lot of interesting material is offered to the expert from academia or industry as well as to the student looking for an interesting field of graduate research.

Günter Helmchen

Preface

After the pioneering work of Louis Pasteur and Emil Fischer in the middle and at the end of the nineteenth century, respectively, it still took more than fifty years before chemists started to discuss transition state models together with polar and steric effects to gain more insight into the phenomenon of asymmetric induction. Even first observations in organic synthesis of enantioselectivities comparable to those of enzymes in the late fifties and sixties of the 20th century did not convince the chemical community and the term "asymmetric synthesis" was regarded a mechanistic curiosity rather than a practical way to synthesize compounds of high enantiomeric purity.

In the mid-seventies, with the development of generally applicable stoichiometric asymmetric syntheses, especially the Meyers oxazoline methodology as the first one, the scientific community began to believe that asymmetric synthesis really worked resulting in an explosive growth of this new field. Later on, and mainly driven by the fact that the biological activity of enantiomers is usually different, dozens of new chemical companies were founded all over the world in a newly created area called "chirotechnology".

Around that time and after intensive discussions several professors of the RWTH Aachen University and the nearby Jülich Research Center decided to apply at the German Research Council for a so-called Collaborative Research Center on the topic of asymmetric synthesis. Looking back, it was truly a seminal event when the Professors D. Enders, W. Keim, M.-R. Kula, H. Sahm and C. Wandrey stopped their cars at the highway station Köln-Frechen and nailed down the proposed research topic as "Asymmetric Synthesis with Chemical and Biological Methods". After Professor E. Winterfeldt, as an advisor, saw this new initiative "under a good star", indeed the new "Sonderforschungsbereich 380" was funded and started in 1994.

From the very beginning of this long term research endeavor, the aim has been to cover *all* aspects of the *entire* field of asymmetric synthesis including stoichiometric and catalytic asymmetric syntheses with chemical and biological methods as well as the development of new reaction technologies. The interdisciplinary cooperation among the areas of classical organic and inorganic chemistry as well as technical chemistry (RWTH Aachen University) and the various fields of

Asymmetric Synthesis with Chemical and Biological Methods. Edited by Dieter Enders and Karl-Erich Jaeger

ISBN 978-3-527-31473-7

enzyme technology and biotechnology (Research Center Jülich, HHU Düsseldorf) resulted in efficient asymmetric syntheses of synthetic building blocks, fine chemicals, natural products and biologically active compounds in general. Mechanistic and theoretical aspects, organic synthesis, organometallic chemistry, homogeneous and heterogeneous transition metal catalysis, microbiology, enzyme- and biotechnology were all employed and used for stereoselective C-H-, C-C-, and C-heteroatom bond formations.

Besides the scientific success of this Collaborative Research Center as measured in publications, patents and foundation of start-up companies, it should be mentioned that a high percentage of the younger scientific members received and accepted calls for full professorships including D. Vogt (Eindhoven), W.-D. Fessner (Darmstadt), U. Kragl (Rostock), A. Liese (Hamburg), S. Bräse (Karlsruhe), G. Sprenger (Stuttgart) and M. Müller (Freiburg) and also associate professorships as C. Ganter (Düsseldorf), L. Elling (Aachen), M. Ansorge-Schumacher (Berlin) and M. Pohl (Privatdozent, Düsseldorf). A highlight during the twelve years of funding was the "Deutsche Zukunftspreis" awarded by the Federal President of Germany to Prof. Kula and Dr. Pohl and presented in a spectacular nationwide television show broadcasted from Berlin in 2002. Professor Maria-Regina Kula, herself being a chemist, was always aware of the necessity to combine biological and chemical catalytic methods. As her 70th birthday coincides with the appearance of this book, the editors would like to express their warm congratulations and best wishes for her future.

We thank the German Research Council ("Deutsche Forschungsgemeinschaft") for the generous financial support of the Collaborative Research Center "Sonderforschungsbereich, SFB 380" over a period of twelve years. In particular, we are thankful to Dr. H. H. Lindner and Dr. A. Pollex-Krüger as well as Dr. W. Rohe, Dr. P. Schmitz-Möller and Dr. H. Schruff for their organizational help during the course of the priority programme. In addition, on behalf of all participants of the Collaborative Research Center, we would like to thank the scientific referees, the Professors M. Ballauff (Bayreuth), J. E. Bäckvall (Stockholm), A. Böck (München), H. Brunner (Regensburg), H. Buchholz (Erlangen-Nürnberg), W. Buckel (Marburg), G. Dziuk (Freiburg), F. Effenberger (Stuttgart), H. Eschrig (Dresden), H. Fischer (Konstanz), W. Francke (Hamburg), G. Gottschalk (Göttingen), H. Griengl (Graz), G. Helmchen (Heidelberg), U. Kazmaier (Saarbrücken), H. Kessler (München), H. Kunz (Mainz), E. P. Kündig (Genf), J. Mulzer (Wien), H.-U. Reißig (Berlin), K. Sandhoff (Bonn), G. Schulz-Eckloff (Bremen), H. Simon (München), W. Spiess (Mainz), J. Thiem (Hamburg), H. Tschesche (Bielefeld), H. Vahrenkamp (Freiburg), and H. Waldmann (Dortmund) for their help, advice and the many fruitful discussions.

We hope that this book will be useful and a source of inspiration for all those interested in the chemical, biological and technical aspects of asymmetric synthesis in general and will stimulate new ideas and research activities among the young scientists in this rapidly growing field.

Aachen / Jülich, December 2006

Dieter Enders
Karl-Erich Jaeger

List of Contributors

Prof. Dr. Marion-B. Ansorge-Schumacher
Technische Universität Berlin
Institut für Chemie / Enzymtechnologie
Straße des 17. Juni 124
10623 Berlin
Germany

Melinda Batorfi
Institut für Brennstoffchemie und Physikalisch-chemische Verfahrenstechnik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Dr. Wolfgang Bettray
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Silke Bode
Lehrstuhl für Pharmazeutische und Medizinische Chemie
Institut für Pharmazeutische Wissenschaften
Albert-Ludwigs-Universität Freiburg
Albertstr. 25
79104 Freiburg
Germany

Prof. Dr. Carsten Bolm
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Prof. Dr. Stefan Bräse
Institut für Organische Chemie
Universität Karlsruhe (TH)
Fritz-Haber-Weg 6
76131 Karlsruhe
Germany

Dr. Wolfgang Braun
Institut für Anorganische Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Asymmetric Synthesis with Chemical and Biological Methods. Edited by Dieter Enders and Karl-Erich Jaeger

ISBN 978-3-527-31473-7

Dr. Holger Breithaupt
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Annabel Cosp
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Adrian Crosman
Institut für Brennstoffchemie
und Physikalisch-chemische
Verfahrenstechnik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Dr. Jairo Cubillos
Institut für Brennstoffchemie
und Physikalisch-chemische
Verfahrenstechnik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Prof. Dr. Ayhan S. Demir
Department of Chemistry
Middle East Technical
University
06531 Ankara
Türkei

Carola Dresen
Lehrstuhl für Pharmazeutische und
Medizinische Chemie
Institut für Pharmazeutische
Wissenschaften
Albert-Ludwigs-Universität Freiburg
Albertstr. 25
79104 Freiburg
Germany

Dr. Pascal Dünkelmann
Lehrstuhl für Pharmazeutische und
Medizinische Chemie
Institut für Pharmazeutische
Wissenschaften
Albert-Ludwigs-Universität Freiburg
Albertstr. 25
79104 Freiburg
Germany

Dr. Thomas Dünnwald
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Dr. Thorsten Eggert
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Prof. Dr. Lothar Elling
Lehr- und Forschungsgebiet
Biomaterialien
Institut für Biotechnologie und
Helmholtz-Institut für
Biomedizinische Technik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Prof. Dr. Dieter Enders
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Prof. Dr. Felice Faraone
Dipartimento di Chimica
Inorganica, Chimica Analitica e
Chimica Fisica
Università degli studi di
Messina
Salita Sperone 31 (vill. S. Agata)
98166 Messina,
Italy

Ralf Feldmann
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Prof. Dr. Wolf-Dieter Fessner
Institut für Organische Chemie
und Biochemie
TU Darmstadt
Petersenstr. 22
64287 Darmstadt
Germany

Dr. Giancarlo Franciò
Institut für Technische und
Makromolekulare Chemie
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Prof. Dr. Hans-Joachim Gais
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Prof. Dr. Christian Ganter
Institut für Anorganische Chemie der
HHU Düsseldorf
Universitätsstr. 1
40225 Düsseldorf
Germany

Petra Geilenkirchen
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Dr. Petra Heim
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Prof. Dr. Wolfgang Hölderich
Institut für Brennstoffchemie und
physikalisch-chemische
Verfahrenstechnik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Prof. Dr. Werner Hummel
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Hans Iding
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Tomoyuki Inoue
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Prof. Dr. Karl-Erich Jaeger
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Sandra Johnen
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Bettina Juchem
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Doris Kolter-Jung
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Prof. Dr. Udo Kragl
Institut für Chemie
Universität Rostock
Albert-Einstein-Str. 3a
18059 Rostock
Germany

Prof. em. Dr. Maria-Regina Kula
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Prof. Dr. Walter Leitner
Institut für Technische und
Makromolekulare Chemie
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Prof. Dr. Andreas Liese
Institut für Technische Biokatalyse
Technische Universität
Hamburg-Harburg
Denickestr. 15
21073 Hamburg
Germany

Dr. Bettina Lingen
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Stephan Lütz
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Prof. Dr. Michael Müller
Lehrstuhl für Pharmazeutische und
Medizinische Chemie
Institut für Pharmazeutische
Wissenschaften
Albert-Ludwigs-Universität Freiburg
Albertstr. 25
79104 Freiburg
Germany

Adam Nitsche
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Priv. Doz. Dr. Martina Pohl
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Prof. Dr. Hermann Sahm
Institut für Biotechnologie I
Forschungszentrum Jülich
52425 Jülich
Germany

Prof. Dr. Albrecht Salzer
Institut für Anorganische
Chemie
RWTH Aachen
Landoltweg 1
52074 Aachen
Germany

Dr. Ulrich Schörken
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Dr. Thomas Schubert
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Dr. Martin Schürmann
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Dr. Melanie Schürmann
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Dr. Carmen Schuster
Institut für Brennstoffchemie und
Physikalisch-chemische
Verfahrenstechnik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Dr. Petra Siegert
Institut für Molekulare
Enzymtechnologie der HHU
Düsseldorf im FZ Jülich
52426 Jülich
Germany

Prof. Dr. Georg A. Sprenger
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Gerda Sprenger
Institut für Mikrobiologie
Universität Stuttgart
Allmandring 31
70550 Stuttgart
Germany

Dr. Hans-Hermann Wagner
Institut für Brennstoffchemie und
Physikalisch-chemische
Verfahrenstechnik
RWTH Aachen
Worringerweg 1
52074 Aachen
Germany

Lydia Walter
Lehrstuhl für Pharmazeutische und Medizinische Chemie
Institut für Pharmazeutische Wissenschaften
Albert-Ludwigs-Universität Freiburg
Albertstr. 25
79104 Freiburg
Germany

Prof. Dr. Christian Wandrey
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Dr. Andrea Weckbecker
Institut für Molekulare Enzymtechnologie der HHU Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Marion Wendorff
Institut für Molekulare Enzymtechnologie der HHU Düsseldorf im FZ Jülich
52426 Jülich
Germany

Dr. Michael Wolberg
Institut für Biotechnologie II
Forschungszentrum Jülich
52425 Jülich
Germany

Contents

Asymmetric Synthesis with Chemical and Biological Methods. Edited by Dieter Enders and Karl-Erich Jaeger

ISBN 978-3-527-31473-7