Asymmetric Synthesis with Chemical and Biological Methods

Edited by
Dieter Enders and Karl-Erich Jaeger

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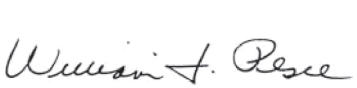

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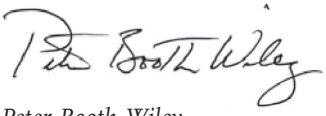

Peter Booth Wiley
Chairman of the Board

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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

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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).

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 arenechromiumtricarbonyl 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

Contents

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

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

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

1
Stoichiometric Asymmetric Synthesis

1.1
Development of Novel Enantioselective Synthetic Methods

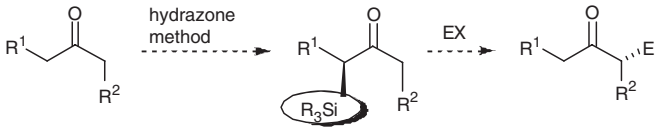
Dieter Enders and Wolfgang Bettray

1.1.1
Introduction

Since the pioneering times of the mid-1970s, when the first practical and generally applicable methods in asymmetric synthesis [1] were developed, such as the oxazoline method of Meyers [2] and the SAMP/RAMP hydrazone method [3], there has been a tremendous growth in this research field. One major driving force for this rapid development is of course the different biological activities of enantiomers and thus the need for enantiopure compounds. In this chapter we describe the development of some efficient synthetic methods for asymmetric carbon–carbon and carbon–heteroatom bond formation, which have been carried out within the frame of the "Sonderforschungsbereich 380" (1994–2005) and employing the concept of stoichiometric asymmetric synthesis.

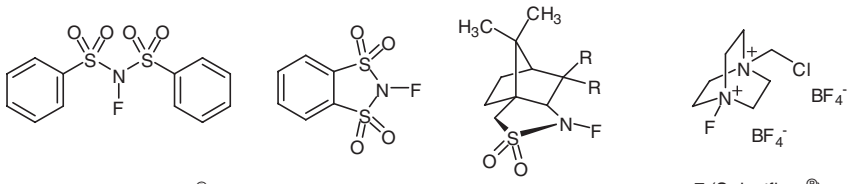
1.1.2
α-Silyl Ketone-Controlled Asymmetric Syntheses

Electrophilic substitutions with carbon and hetero electrophiles α to the carbonyl group of aldehydes and ketones are among the most important synthetic operations. Such regio-, diastereo-, and enantioselective substitutions can be carried out efficiently with the SAMP/RAMP hydrazone methodology [3]. For cases where virtually complete asymmetric inductions could not be attained, an alternative approach based on α-silylated ketones **2** was developed [4]. They can be prepared easily from ketones **1** in high enantiomeric purity (*ee* > 98%) by asymmetric carbon silylation employing the SAMP/RAMP hydrazone method (Fig. 1.1.1). After the introduction of various electrophiles via classical enolate chemistry with excellent asymmetric inductions, the desired product ketones **3**



1 **2** (*ee* > 98%) **3** (high *ee*'s)

Fig. 1.1.1 α-Silyl-controlled asymmetric synthesis (the "silyl trick").



4 (NFSI, Accufluor®) **5** (NFOBS) **6** (Davis, R=H, Cl) **7** (Selectfluor®)

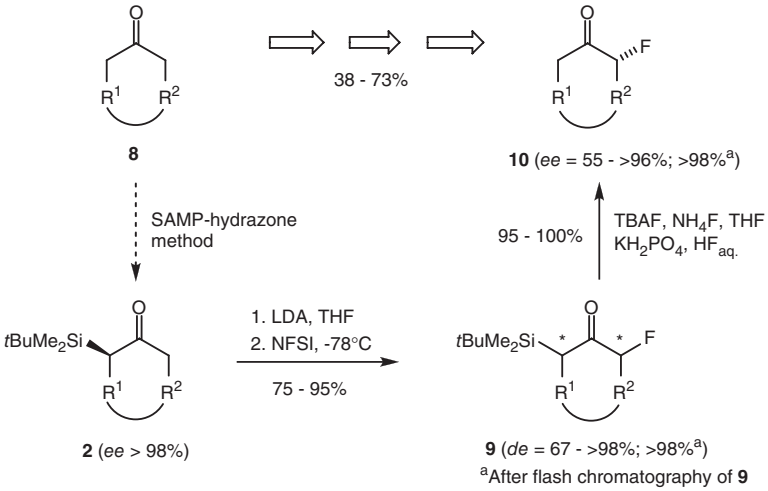
Fig. 1.1.2 NF-reagents for electrophilic fluorination.

are obtained by removal of the "traceless" silyl directing group with various sources of fluoride.

1.1.2.1 Regio- and Enantioselective α-Fluorination of Ketones

Due to the unique properties of organofluorine compounds and their rapidly increasing practical usage in plant protection, medicine, and many other areas, the scientific and economic interest in organofluorine coumpounds has grown immensely over recent decades. With the availability of user-friendly NF reagents such as **4** (NFSI, Accufluor®), **5** (NFOBS), **6** (Davis et al.) and **7** (Selectfluor®) (Fig. 1.1.2), for electrophilic fluorination [5], the efficient synthesis of α-fluorinated ketones, aldehydes, and esters has become possible. However, the asymmetric inductions in enantioselective α-fluorinations of ketones reached no practical values (*ee* = 10–75%) until the mid-1990s. We were therefore pleased to see that our α-silyl ketone-controlled approach led for the first time to the target α-fluoro ketones in high yields, few steps, and very good enantiomeric excesses [6].

As shown in Scheme 1.1.1, symmetric and unsymmetric ketones (control of regioselectivity) as well as cyclic and acyclic ketones **8** were first converted to the corresponding virtually enantiopure α-silyl ketones **2** (*ee* > 98%) employing the SAMP/RAMP hydrazone methodology. Metallation with LDA and treatment of the enolates with the *N*-fluorosulfonamide **4** (NFSI) afforded the α-fluoro-α′-silylated ketones **9** with moderate to excellent diastereomeric excesses. Finally, the racemization-free removal of the sterically demanding silyl directing group was carried out with fluoride sources in almost quantitative yields, leading to the desired α-fluoroketones **10** (*ee* 55 to >96%). Especially in the case of cyclic ketones almost complete asymmetric inductions could be achieved. As the epimeric



Scheme 1.1.1 Asymmetric synthesis of α-fluoroketones.

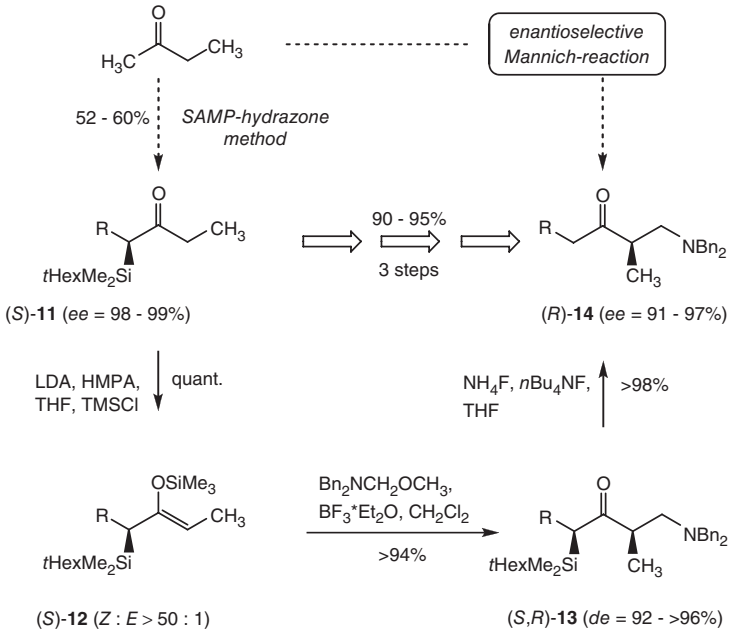
fluorinated silyl ketones **9** can be separated easily by flash column chromatography, various enantiopure α-fluoroketones **10** could be obtained in this way.

Although efficient organocatalytic methods for the electrophilic α-fluorination of aldehydes and ketones have recently been developed [7], high enantiomeric excesses can only be reached with aldehydes so far. The asymmetric inductions in the case of ketone fluorinations have remained low (*ee* ≤ 36%) [7a]. Thus, the α-silyl ketone-controlled stoichiometric asymmetric synthesis of α-fluoroketones **10** (Scheme 1.1.1) still constitutes a practical method.

1.1.2.2 α-Silyl Controlled Asymmetric Mannich Reactions

The Mannich reaction, in which an aminomethyl group is introduced in the α-position of the carbonyl function, has been the subject of investigations since the early 20th century [8]. In 1985 our research group, in close cooperation with Steglich and coworkers, developed a first asymmetric Mannich reaction [9]. Some ten years later, with the enantiopure α-silylated ketones **2** in hand, we reported a first practical procedure for the regio- and enantioselective α-aminomethylation of ketones taking advantage of the excellent asymmetric inductions with the help of the "traceless" silyl control group [10].

As depicted in Scheme 1.1.2, the silyl ketones (*S*)-**11** of high enantiomeric purity were converted into the *Z*-configured silyl enol ethers (*S*)-**12**, which were used in the aminomethylation step by treatment with dibenzyl(methoxymethyl)amine in the presence of a Lewis acid. The silylated Mannich bases (*S,R*)-**13** were obtained in excellent yields and diastereomeric excesses (*de* = 92–96%). Finally,



Scheme 1.1.2 Enantioselective synthesis of β-dibenzylamino ketones.

the silyl directing group was removed tracelessly by employing a fluoride source. In this way, the α-substituted β-amino ketones (*R*)-**14** were obtained in three steps with superb overall yields of 90–95% and, most importantly, with very high enantiomeric excesses *ee* of 91–97%. To explain the almost complete diastereofacial selectivity of the Mannich key step, two transition states can be discussed: a closed one along the lines of the Zimmerman–Traxler model, and an open one with the iminium ion formed in situ, explaining in both cases the *R* configuration at the newly generated stereocenter (Scheme 1.1.3).

After the successful asymmetric synthesis of α-substituted β-amino ketones (*R*)-**14**, we envisaged the diastereo- and enantioselective synthesis of α,β-disubstituted Mannich bases. As shown in Scheme 1.1.4, we were able to use benzaldehyde-*N*-phenylimine [11] as well as α-alkoxycarbonylaminosulfones [12] as Mannich electrophiles to synthesize in good overall yields and high *de*- and *ee*-values the *anti*-configured β-amino ketones (*R,S*)-**15** and (*R,S*)-**16**, respectively [13].