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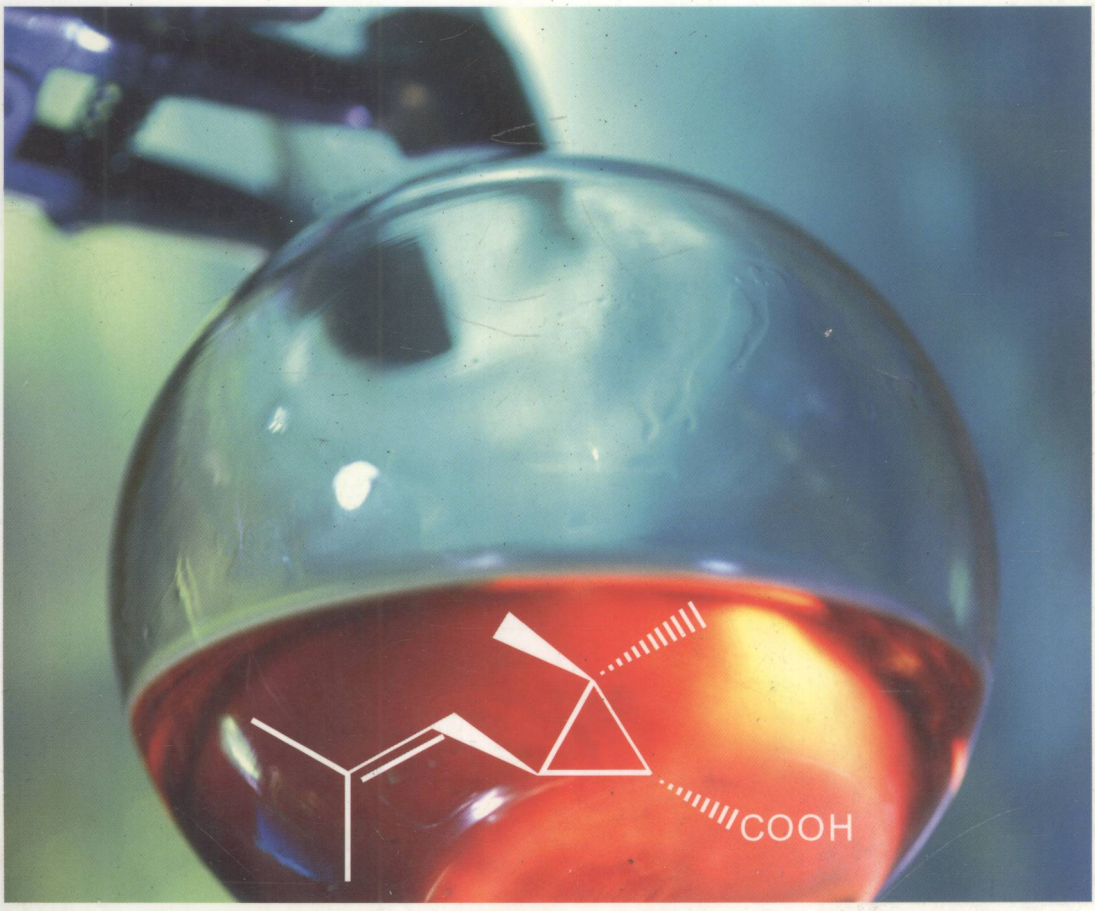
Reactions and Syntheses

in the Organic Chemistry Laboratory



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The Authors

Prof. Dr. Dr. h.c. Lutz F. Tietze
Institute of Organic and Biomolecular Chemistry
Georg-August-University
Tammannstr. 2
37077 Göttingen
Germany

Prof. Dr. Dr. h.c. Theophil Eicher
Saarland University
FR 8.1 – Organic Chemistry
66123 Saarbrücken
Germany

Prof. Dr. Ulf Diederichsen
Institute of Organic and Biomolecular Chemistry
Georg-August-University
Tammannstr. 2
37077 Göttingen
Germany

PD Dr. Andreas Speicher
Saarland University
FR 8.1 – Organic Chemistry
66123 Saarbrücken
Germany

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Reactions and Syntheses

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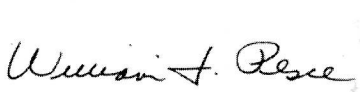

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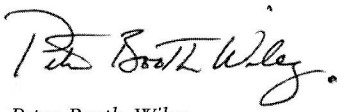

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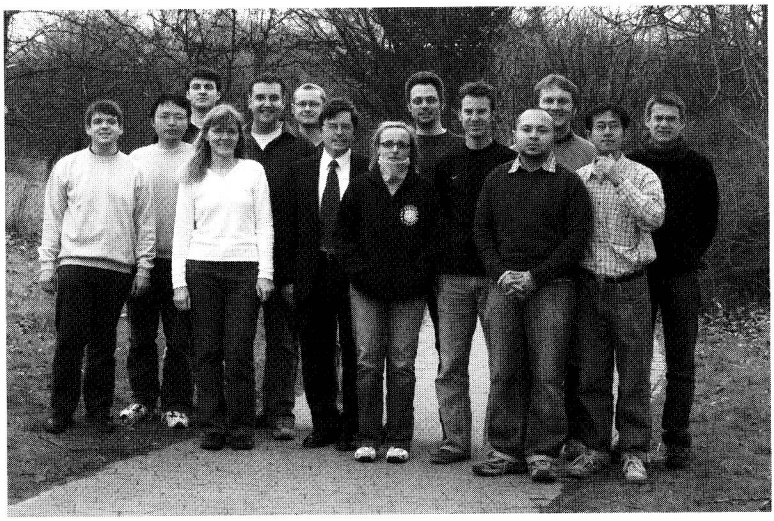
The three research groups in Göttingen and Saabrücken participated in equal parts in the preparation of the experimental sections of the syntheses presented in this book. The following collaborators were engaged in checking, testing and elaborating the selected literature procedures:

The *Tietze* group



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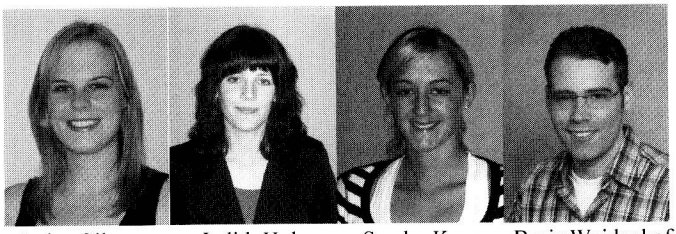
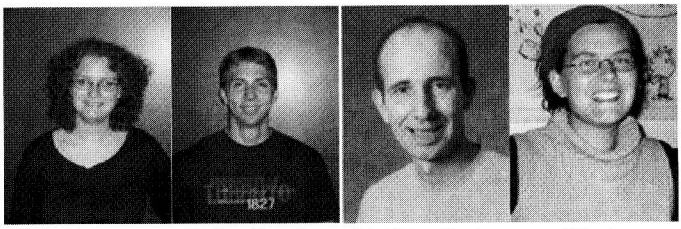
The *Speicher* group

Timo Backes Sabrina Bleif Mandy Döring Matthias Groh



Luisa Gilmore Judith Holz Sandra Kern Boris Weidenhof

The *Diederichsen* group



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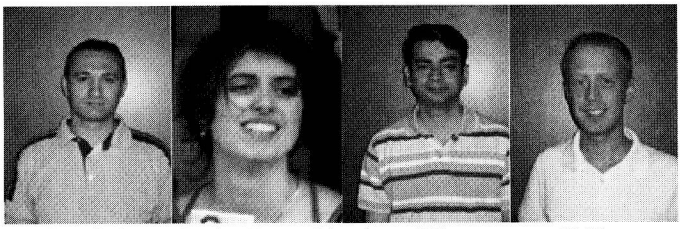

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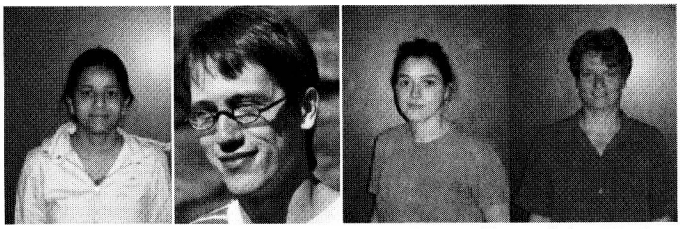

Ratika Srivastava | Thorsten Stafforst | Angelina Weiß | Brigitte Worbs

Abbreviations and Symbols

General abbreviations and symbols

g	gram
mg	milligram
L	liter
mL	milliliter
mol	mole
mmol	millimole
min	minute(s)
h	hour(s)
d	day(s)
°C	degrees Celsius
%	percent
mp	melting point
bp	boiling point
n_D^{20}	refractive index at Na D line (at 20°C)
$[\alpha]_D$	specific rotation
ee	enantiomeric excess
ds	diastereoselectivity
TLC	thin-layer chromatography
HPLC	high-performance liquid chromatography
ca.	approximately
ref.	literature reference
p.	page
ed.	edition
Ed(s).	editor(s)
cf.	compare
dec.	decomposition
M_r	relative mass
rt	room temperature

Spectroscopic abbreviations

IR	infrared spectrum
$\tilde{\nu}$	wave number (in cm^{-1})
^1H NMR	proton nuclear magnetic resonance spectrum
^{13}C NMR	^{13}C nuclear magnetic resonance spectrum
δ (ppm)	chemical shift relative to tetramethylsilane ($\delta_{TMS} = 0$)
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
dt	doublet of triplets
q	quartet
quint	quintet
sext	sextet
sept	septet
m	multiplet
br	broad
Hz	Hertz
J	coupling constant
UV/VIS	ultraviolet/visible spectrum
nm	nanometer
λ_{max} (log ε)	wavelength of the absorption maximum (molar extinction coefficient)

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Abbreviations for substituents...

Ac	$-COCH_3$	acetyl	*i*Bu	$-CH_2CH(CH_3)_2$	*iso*-butyl
Ar		aryl	*s*Bu	$-CH(CH_3)CH_2CH_3$	*sec*-butyl
Me	$-CH_3$	methyl	*t*Bu	$-C(CH_3)_3$	*tert*-butyl
Et	$-CH_2CH_3$	ethyl	Mes	$-SO_2CH_3$	methanesulfonyl
Pr	$-CH_2CH_2CH_3$	propyl	Ph	$-C_6H_5$	phenyl
*i*Pr	$-CH(CH_3)_2$	*iso*-propyl	Tf	$-SO_2CF_3$	trifluoromethanesulfonyl
*n*Bu	$-(CH_2)_3CH_3$	*n*-butyl	Tos	$-SO_2C_6H_4CH_3$	*p*-toluenesulfonyl

...and commonly used compounds...

AIBN	azoisobutyronitrile
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[4.3.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	dichlorodicyano-*p*-benzoquinone
DIBAL	diisobutylaluminum hydride
Diglyme	diethylene glycol dimethyl ether
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMSO	dimethyl sulfoxide
Et_2O	diethyl ether
EtOH	ethanol
LAH	lithium aluminum hydride
MeOH	methanol
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
PPA	polyphosphoric acid
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran

...and retrosynthesis

disc	bond disconnection
FGI	functional group interconversion
FGA	functional group addition

Preface

(1) Background

The book "Reactions and Syntheses in the Organic Chemistry Laboratory" was first published in German in 1981, with a second edition in 1991, and was translated into Japanese in 1984 (2nd edition 1995), English in 1989, Chinese in 1999, Russian in 2000, and Korean in 2002. The intention was

- to associate classes of compounds and functionalities with reaction types and mechanisms,
- to offer a great number of reliable preparative procedures of general importance,
- to show usefulness and robustness of the offered procedures for the synthesis of selected interesting compounds of relevance in biology, pharmacy, and medicine.

Since the last German edition, many new preparative procedures have been developed showing high chemo-, regio-, diastereo-, and enantioselectivity, which frequently approach the selectivity of enzymatic transformations with the advantage of a lower substrate specificity. In addition, new methods such as combinatorial chemistry, solid-phase chemistry, high-pressure chemistry, and the use of microwaves for heating have been introduced. Moreover, the efficiency of a synthesis, which can be defined as the increase in complexity per transformation, the avoidance of toxic reagents as well as solvents, and the preservation of resources are important issues in modern preparative organic chemistry. Significant developments in the last years have been realized in transition metal catalysis, organocatalysis, and domino reactions. This progress has been impressively documented in "Classics of Total Synthesis" [1], "Organic Synthesis Highlights" [2], and "Domino Reactions in Organic Synthesis" [3].

As a consequence, we now present the book „Reactions and Syntheses in the Organic Chemistry Laboratory"

(a) in a new form with respect to its concept and organization,

(b) extensively renewed with respect to its content.

- Basic units as well as main objectives are *syntheses* (up to multi-step syntheses with > 5 steps) of interesting and instructive target molecules from various fields of Organic Chemistry. Each synthesis is centred around one ore more methods and reactions principles of general synthetic relevance.
- As before, the users of the new book are provided with carefully elaborated experiments, which are described in preparative and analytical detail. However, experiments and syntheses are accompanied throughout in concentrated form by the required general, theoretical and mechanistic background and explanations. Special attention is given to retrosynthetic analysis and alternative approaches of synthesis for a given target molecule.
- To allow the inclusion of a representative and qualified spectrum of contemporary synthetic methods, more than 70 % of the contents of the former book have been replaced by more recent and more relevant experimental examples. The remaining (elder) syntheses have been „updated" with respect to description of their general background.

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Considering the various types of potential users of the book in the past, there has been a definite and broad acceptance among chemists and pharmacists on a more advanced level, besides graduate students and researchers at universities and in industry. From these considerations, the following consequences have emerged for the 3rd edition:

- General laboratory information, such as safety, first aid, performance of chemical reactions, instrumentation and standard apparatus, isolation and purification of products, has been omitted. Methods for the formation and transformation of basic functional groups in organic compounds, regarded as being important for the elementary education level in organic laboratory practice, are not described. These topics are comprehensively covered in other qualified textbooks [4–6].
- The deletion of these elementary aspects of organic chemistry has allowed us to describe more of the advanced synthetic methods and to include mechanistic aspects as well as to incorporate total syntheses and retrosynthetic analyses.

(2) Organization of the book and directions for its use

The book is divided into four chapters with several subchapters:

Chapter **1** C–C Bond formation

Chapter **2** Oxidation and reduction

Chapter **3** Heterocyclic compounds

Chapter **4** Selected natural products

The subchapters (e.g. **1.1**, **1.2**, etc.) contain the different procedures and syntheses specified at the beginning of the section and in the Table of *Contents* (cf. p. II) and are organized as follows:

(a) In the general part (a) the *structural formula* of the target molecule and the *topics* of the presented synthesis (important for rapid information!) are given, which is followed by *introductory information* on the target molecule, *retrosynthesis* [7], and *planning of the synthesis* (possibilities, strategies, and synthetic alternatives; considerations on practicability for laboratory use).

(b) In part (b) the *synthesis of the target molecule* and the synthetic steps performed in the experimental part are described. This is accompanied by information about the mechanism(s), the stereochemical outcome, and the selectivity of the transformations (specific reaction principles). Finally, the number of steps performed and the yields obtained are summarized. In general, section (b) contains a complete *scheme of the synthesis* performed.

(c) In section (c) individual *experimental procedures* are described.

Each procedure has the following structure:

- An identification number, which characterizes the prepared compound according to chapter, subchapter, and synthesis (e.g. **1.1.1.1**, **1.1.1.2**, etc.); the identification number carries one or more asterisks (*, **, ***) according to the degree of difficulty of the procedure.
- Literature reference(s) for the prepared compound.
- A formula equation, which gives structures of reactants and products, and their relative molecular masses. In general, apparatus is not discussed in detail; however, in special cases, information about specialized equipment (photochemical, high-pressure, microwave, etc.) is given.

- Throughout, the procedures are presented in two parts. The first, describing the reaction, often includes additional notes about purification and characteristics of the substrates, such as toxicity and safety remarks. The second describes the work-up, isolation, and purification of the product, along with criteria of purity (mp, bp, n_D, TLC/R_f, $[\alpha]_D$), notes about characteristics of the product, and other crucial experimental details.
- Characterization of the product by spectral data (IR, UV/VIS, ^1H and ^{13}C NMR, MS). In selected cases, the preparation of derivatives together with their instrumental and chemical analysis is given.

(d) The presentation of each synthesis is concluded by a compilation of the *literature references* cited in the sections (a)–(c). They cover the primary literature on the synthesis, its steps and its topics, and refer to important collective articles, reviews, and textbooks of advanced organic chemistry [8].

[1] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1997**; K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, **2003**.

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[3] L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[4] *Organikum*, 21st ed., Wiley-VCH, Weinheim, **2001**.

[5] S. Hünig, P. Kreitmeier, G. Märkl, J. Sauer, *Arbeitsmethoden in der Organischen Chemie* (mit Einführungspraktikum), Verlag Lehmanns, Berlin, **2006**.

[6] R. C. Larock, *Comprehensive Organic Transformations* (A Guide to Functional Group Preparations), 2nd ed. Wiley-VCH, Weinheim, **1999**.

[7] Retrosynthesis is oriented toward the concepts and terminology of S. Warren, *Organic Synthesis – The Disconnection Approach*, John Wiley & Sons, New York, **1982**; S. Warren, *Designing Organic Syntheses*, John Wiley & Sons, New York, **1978**; E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**.

[8] For example: M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 6th ed., John Wiley & Sons, Inc., New York, **2007**; F. A. Carey, R. J. Sundberg, *Organische Chemie*, VCH, Weinheim, **1995**; G. Quinkert, E. Egert, Ch. Griesinger, *Aspekte der Organischen Chemie*, VCH, Weinheim, since **1995**; R. Brückner, *Reaktionsmechanismen* (Organische Reaktionen, Stereochemie, moderne Synthesemethoden), 3rd ed., Spektrum Akademischer Verlag, Heidelberg, **2004**; E. L. Eliel, S. H. Wilen, M. P. Doyle, *Basic Organic Stereochemistry*, John Wiley & Sons, New York, **2001**; J.-H. Fuhrhop, G. Li, *Organic Synthesis*, 3rd ed., Wiley-VCH, Weinheim, **2003**; P. J. Kocieński, *Protecting Groups*, 3rd ed., Georg Thieme Verlag, Stuttgart, **2005**; G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, *Houben-Weyl, Methods of Organic Chemistry, Stereoselective Synthesis*, Vol. E21, 4th ed., Georg Thieme Verlag, Stuttgart, **1996**; S. Hauptmann, G. Mann, *Stereochemie*, Spektrum Akademischer Verlag, Heidelberg, **1996**.

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Contents

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3 Heterocyclic compounds