Albrecht Berkessel, Harald Gröger

Asymmetric Organocatalysis –
From Biomimetic Concepts to
Applications in Asymmetric Synthesis
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Harald Gröger
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Asymmetric Organocatalysis –
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Contents

Preface xi

Foreword xiii

1 Introduction: Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis 1
References 8

2 On the Structure of the Book, and a Few General Mechanistic Considerations 9
2.1 The Structure of the Book 9
2.2 General Mechanistic Considerations 9
References 12

3 Nucleophilic Substitution at Aliphatic Carbon 13
3.1 α-Alkylation of Cyclic Ketones and Related Compounds 13
3.2 α-Alkylation of α-Amino Acid Derivatives 16
3.2.1 Development of Highly Efficient Organocatalysts 16
3.2.2 Improving Enantioselectivity During Work-up 25
3.2.3 Specific Application in the Synthesis of Non-natural Amino Acids 25
3.2.4 Synthesis of α,α-Dialkylated Amino Acids 28
3.2.5 Enantio- and Diastereoselective Processes – Synthesis of α-Amino Acid Derivatives with Two Stereogenic Centers 30
3.2.6 Solid-phase Syntheses 31
3.3 α-Alkylation of Other Acyclic Substrates 33
3.4 Fluorination, Chlorination, and Bromination Reactions 34
3.4.1 Fluorination Reactions 34
3.4.2 Chlorination and Bromination Reactions 38
References 41

4 Nucleophilic Addition to Electron-deficient C=C Double Bonds 45
4.1 Intermolecular Michael Addition 45
4.1.1 Intermolecular Michael Addition of C-nucleophiles 47
4.1.1.1 Chiral Bases and Phase-transfer Catalysis 47
4.1.1.2 Activation of Michael Acceptors by Iminium Ion Formation, Activation of Carbonyl Donors by Enamine Formation 55
4.1.1.3 Addition of C-nucleophiles to Azodicarboxylates 69
4.1.1.4 Cyclopropanation of Enoates with Phenacyl Halides 70
4.1.2 Intermolecular Michael Addition of N- and O-nucleophiles 71
4.1.3 Intermolecular Michael Addition of S- and Se-nucleophiles 73
4.2 Intramolecular Michael Addition 78
4.2.1 Intramolecular Michael Addition of C-nucleophiles 78
4.2.2 Intramolecular Michael Addition of O-nucleophiles 79
References 82

5 Nucleophilic Addition to C=N Double Bonds 85
5.1 Hydrocyanation of Imines (Strecker Reaction) 85
5.1.1 Chiral Diketopiperazines as Catalysts 85
5.1.2 Chiral Guanidines as Catalysts 86
5.1.3 Chiral Ureas and Thioureas as Catalysts 89
5.1.4 Chiral N-Oxides as “Catalysts” 95
5.2 The Mannich Reaction 97
5.2.1 Enantioselective Direct Mannich Reaction: Products with One Stereogenic Center 97
5.2.2 Enantio- and Diastereoselective Direct Mannich Reaction: Products with Two Stereogenic Centers 100
5.2.3 Proline-catalyzed Mannich Reaction: Process Development and Optimization 104
5.2.4 Enantioselective Mannich Reaction using Silyl Ketene Acetals 106
5.3 β-Lactam Synthesis 109
5.4 Sulfur Ylide-based Aziridination of Imines 119
5.5 Hydrophosphonylation of Imines 126
References 126

6 Nucleophilic Addition to C=O Double Bonds 130
6.1 Hydrocyanation 130
6.1.1 The Mechanism of the Reaction 132
6.2 Aldol Reactions 140
6.2.1 Intermolecular Aldol Reactions 140
6.2.1.1 Intermolecular Aldol Reaction With Formation of One Stereogenic Center 140
6.2.1.2 Intermolecular Aldol Reaction with Formation of Two Stereogenic Centers 154
6.2.2 Intramolecular Aldol Reaction 166
6.2.2.1 Intramolecular Aldol Reaction Starting from Diketones 166
6.2.2.2 Intramolecular Aldol Reaction Starting from Triketones 168
6.2.2.3 Intramolecular Aldol Reaction Starting from Dialdehydes 174
6.2.3 Modified Aldol Reactions – Vinylogous Aldol, Nitroaldol, and Nitrone Aldol Reactions 175
6.3 β-Lactone Synthesis via Ketene Addition 179
6.4 The Morita–Baylis–Hillman Reaction 182
6.5 **Allylation Reactions** 189
6.5.1 Chiral Phosphoramides as Organocatalysts 189
6.5.2 Chiral Formamides as Organocatalysts 197
6.5.3 Chiral Pyridine Derivatives as Organocatalysts 199
6.5.4 Chiral N-Oxides as Organocatalysts 199
6.6 Alkylation of C=O Double Bonds 205
6.7 The Darzens Reaction 205
6.8 Sulfur Ylide-based Epoxidation of Aldehydes 211
6.8.1 Epoxide Formation from Ylides Prepared by Means of Bases 212
6.8.2 Epoxide Formation from Ylides Prepared by Metal-catalyzed Carbene Formation 219
6.9 The Benzoin Condensation and the Stetter Reaction 227
6.9.1 The Benzoin Condensation 229
6.9.2 The Stetter Reaction 231
6.10 Hydrophosphonylation of C=O Double Bonds 234

**References** 236

7 **Nucleophilic Addition to Unsaturated Nitrogen** 245
7.1 Nucleophilic Addition to N=N Double Bonds 245
7.2 Nucleophilic Addition to N=O Double Bonds 249

**References** 254

8 **Cycloaddition Reactions** 256
8.1 [4 + 2]-Cycloadditions – Diels–Alder Reactions 256
8.1.1 Diels–Alder Reactions Using Alkaloids as Organocatalysts 256
8.1.2 Diels–Alder and hetero-Diels–Alder Reactions Using (S)-Amino Acid Derivatives as Organocatalysts 258
8.1.3 Diels–Alder and hetero-Diels–Alder Reactions Using C2-symmetric Organocatalysts 261
8.2 [3 + 2]-Cycloadditions: Nitrone- and Electron-deficient Olefin-based Reactions 262

**References** 267

9 **Protonation of Enolates and Tautomerization of Enols** 269
9.1 Enantioselective Protonation of Enolates formed in situ from Enolate Precursors 270
9.2 Enantioselective Tautomerization of Enols Generated in situ 271
9.3 Enantioselective Protonation of Enolates Generated in situ from Conjugated Unsaturated Carboxylates 274

**References** 275

10 **Oxidation** 277
10.1 Epoxidation of Olefins 277
10.1.1 Chiral Dioxiranes 277
10.1.2 Chiral Iminium Ions 287
10.2 Epoxidation of Enones and Enoates 290
10.2.1 Chiral Dioxiranes 290
10.2.2 Peptide Catalysts 290
10.2.3 Phase-transfer Catalysis 299
10.3 Sulfoxidation of Thioethers 303
10.4 Oxidation of Alcohols 306
10.4.1 Kinetic Resolution of Racemic Alcohols 306
10.4.2 Desymmetrization of meso Diols 308
References 309

11 Reduction of Carbonyl Compounds 314
11.1 Borane Reduction Catalyzed by Oxazaborolidines and Phosphorus-based Catalysts 314
11.2 Borohydride and Hydrosilane Reduction in the Presence of Phase-transfer Catalysts 318
11.3 Reduction with Hydrosilanes in the Presence of Chiral Nucleophilic Activators 319
References 321

12 Kinetic Resolution of Racemic Alcohols and Amines 323
12.1 Acylation Reactions 323
12.2 Redox Reactions 342
References 345

13 Desymmetrization and Kinetic Resolution of Anhydrides; Desymmetrization of meso-Epoxides and other Prochiral Substrates 347
13.1 Desymmetrization and Kinetic Resolution of Cyclic Anhydrides 347
13.1.1 Desymmetrization of Prochiral Cyclic Anhydrides 349
13.1.2 Kinetic Resolution of Chiral, Racemic Anhydrides 352
13.1.2.1 Kinetic Resolution of 1,3-Dioxolane-2,4-diones (\(\alpha\)-Hydroxy Acid O-Carboxy Anhydrides) 352
13.1.2.2 Kinetic Resolution of N-Urethane-protected Amino Acid N-Carboxy Anhydrides 355
13.1.3 Parallel Kinetic Resolution of Chiral, Racemic Anhydrides 358
13.1.4 Dynamic Kinetic Resolution of Racemic Anhydrides 358
13.1.4.1 Dynamic Kinetic Resolution of 1,3-Dioxolane-2,4-diones (\(\alpha\)-Hydroxy acid O-Carboxy Anhydrides) 359
13.1.4.2 Dynamic Kinetic Resolution of N-protected Amino Acid N-Carboxy Anhydrides 360
13.2 Additions to Prochiral Ketenes 363
13.3 Desymmetrization of meso-Diols 366
13.3.1 Desymmetrization of meso-Diols by Acylation 367
13.3.2 Desymmetrization of meso-Diols by Oxidation 371
13.4 Desymmetrization of meso-Epoxides 374
13.4.1 Enantioselective Isomerization of meso-Epoxides to Allylic Alcohols 374
13.4.2 Enantioselective Ring Opening of meso-Epoxides 381
13.5 The Horner–Wadsworth–Emmons Reaction 383
13.6 Rearrangement of O-Acyl Azlactones, O-Acyl Oxindoles, and O-Acyl Benzofuranones 385
References 389

14 Large-scale Applications of Organocatalysis 393
14.1 Introduction 393
14.2 Organocatalysis for Large-scale Applications: Some General Aspects and Considerations 393
14.2.1 Economy of the Catalyst (Price/Availability) 394
14.2.2 Stability of the Catalysts and Handling Issues 395
14.2.3 Recycling Issues: Immobilization of Organocatalysts 395
14.2.4 Enantioselectivity, Conversion, and Catalytic Loading 396
14.3 Large-scale Organocatalytic Reaction Processes (Selected Case Studies) 398
14.3.1 Case Study 1: Julia–Colonna-type Epoxidation 398
14.3.2 Case Study 2: Hydrocyanation of Imines 401
14.3.3 Case Study 3: Alkylation of Cyclic Ketones and Glycinates 402
14.3.4 Case Study 4: The Hajos–Parrish–Eder–Wiechert–Sauer Reaction 405
References 406

Appendix: Tabular Survey of Selected Organocatalysts: Reaction Scope and Availability 409
I Primary and Secondary Amine Catalysts 410
II Tertiary Amine and Pyridine Catalysts 413
III Phosphanes 417
IV Phosphoramidites, Phosphoramides and Formamides 418
V Ureas, Thioureas, Guanidines, Amidines 420
VI Ketones 422
VII Imines, Iminium Cations and Oxazolines 423
VIII Diols 424
IX Sulfides 425
X N-Oxides and Nitroxyl Radicals 427
XI Heterocyclic Carbenes (Carbene Precursors) 429
XII Peptides 430
XIII Phase Transfer Catalysts 433

Index 436
Preface

What is the incentive for writing a book on “Asymmetric Organocatalysis”? Why should chemists involved in organic synthesis know about the current state and future perspectives of “Asymmetric Organocatalysis”? First of all, efficient catalytic processes lie at the heart of the atom-economic production of enantiomerically pure substances, and the latter are of ever increasing importance as pharmaceuticals, agrochemicals, synthetic intermediates, etc. Until recently, the catalysts employed for the enantioselective synthesis of organic compounds fell almost exclusively into two general categories: transition metal complexes and enzymes. Between the extremes of transition metal catalysis and enzymatic transformations, a third general approach to the catalytic production of enantiomerically pure organic compounds has now emerged: *Asymmetric Organocatalysis*, which is the theme of this book. *Organocatalysts* are purely “organic” molecules, i.e. composed of (mainly) carbon, hydrogen, nitrogen, oxygen, sulfur and phosphorus.

In fact, the historic roots of organocatalysis date back to the first half of the 20th century and the attempt to use low-molecular weight organic compounds to both understand and mimic the catalytic activity and selectivity of enzymes. Before the turn of the century, only a limited number of preparatively useful applications of organocatalysts were reported, such as the proline-catalyzed synthesis of the Wieland-Miescher ketone (the Hajos-Parrish-Eder-Sauer-Wiechert process in the 1970s), and applications of chiral phase-transfer-catalysts in e.g. asymmetric alkylations. The second half of the 20th century saw tremendous progress in the development of transition metal-based catalysis – ultimately culminating in the award of Nobel Prizes to Sharpless, Noyori and Knowles in 2001 – but comparatively little attention was paid to the further development of the promising early applications of purely organic catalysts for asymmetric transformations.

Now, triggered by the ground-breaking work of e.g. Denmark, Jacobsen, List, MacMillan and many other researchers in the 1990s and early 2000s, the last decade has seen exponential growth of the field of asymmetric organocatalysis: iminium-, enamine- and phosphoramide-based organocatalysis now allows cycloadditions, *Michael* additions, aldol reactions, nucleophilic substitutions (and many other transformations) with excellent enantioselectivities; new generations of phase-transfer catalysts give almost perfect enantiomeric excesses at low catalyst loadings; chiral ureas and thioureas are extremely enantioselective catalysts for the addition of...
various nucleophiles to aldehydes and imines, and so forth. Organocatalysis, by now, has definitely matured to a recognized third methodology, of potential equal status to organometallic and enzymatic catalysis.

Again: Why take the effort to write a book on “Asymmetric Organocatalysis”? Both authors are deeply committed to the development of novel catalytic methodology, within the academic and the industrial environment, respectively. They both consider asymmetric organocatalysis as a methodology that should be taught to students in up-to-date academic curricula, and should be present in the methodological toolbox of “established” chemists dealing with organic synthesis, both in fundamental research and in industrial applications.

This book is in part meant as an introduction to organocatalysis, revealing its historical background, and mostly as a state-of-the-art summary of the methodology available up to early/middle 2004. Organocatalysis has entered the state of a “gold rush”, and at short intervals, new “gold mines” are being discovered and reported in the literature. The reader may forgive the authors if one of his/her favorite catalysts has not made it to the press in time.

Both authors wish to thank Dr. Elke Maase of Wiley-VCH, Weinheim for excellent and most enjoyable collaboration in the course of the preparation of this book!

Cologne and Hanau,  
December 2004  

Albrecht Berkessel  
Harald Gröger
“Organocatalysis: the word.” In the spring of 1998 I became very interested in the notion that small organic molecules could function as efficient and selective catalysts for a large variety of enantioselective transformations. Inspired directly by the work of Shi, Denmark, Yang, Fu, Jacobsen, and Corey, I became convinced of the general need for catalysis strategies or concepts that revolved around small organic catalysts. In that same year we developed an enantioselective organocatalytic Diels Alder reaction based on iminium-activation, to the best of our knowledge a new catalysis concept we hoped would be amenable to many transformations. During the preparation of our Diels Alder manuscript I became interested in coining a new name for what was commonly referred to as “metal-free catalysis”. My motivations for doing so were very simple: I did not like the idea of describing an area of catalysis in terms of what it was not, and I wanted to invent a specific term that would set this field apart from other types of catalysis. The term “organocatalysis” was born and a field that had existed for at least 40 years acquired a new name. More importantly, with the pioneering work of researchers such as Barbas, List, Jacobsen, and Jørgensen, this field began to receive the attention it had always deserved and the “organocatalysis gold rush” was on.

“Organocatalysis: the field.” Over the last ten years the field of organocatalysis has grown from a small collection of chemically unique or unusual reactions to a thriving area of general concepts, atypical reactivity, and widely useful reactions. Although the modern era of organocatalysis remains in its infancy, the pace of growth in this field of chemistry has been nothing short of breathtaking. Indeed, a day hardly passes without a new organocatalytic reaction hitting the electronic chemistry newsstands. It is, therefore, important and timely to have a major text that summarizes the most important developments and concepts in this booming area of catalysis. In this regard, Albrecht Berkessel and Harald Gröger have produced a highly valuable resource for students and researchers in all laboratories working on catalysis and chemical synthesis.

This book is logically presented and lends itself to effortless reading. Because the organization of content has been carefully handled, it is straightforward for the reader to locate and retrieve information. The authors have, moreover, paid considerable attention to providing many of the historical details associated with this
renaissance field. As a result, the readers are provided with a highly accessible text that is as readable as it is educational.

This book will be found both in libraries and on the bookshelves of chemists who enjoy catalysis, chemical synthesis, and the history of our field. Berkessel and Gröger’s “Asymmetric Organocatalysis” is the first book to be published in this area and it is likely to be the best monograph in the field for a long time. I hope the authors intend to revise this volume throughout the many exciting times that lie ahead in the field of organocatalysis.

Caltech, September 2004

David MacMillan
Introduction: Organocatalysis – From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis

“Chemists – the transformers of matter”. This quotation, taken from the autobiography “The Periodic Table” by Primo Levi, illustrates one of the major goals of chemistry – to provide, in a controlled and economic fashion, valuable products from readily available starting materials. In organic chemistry “value” is directly related to purity; in most instances this implies that an enantiomerically pure product is wanted. In recent years the number of methods available for high-yielding and enantioselective transformation of organic compounds has increased tremendously. Most of the newly introduced reactions are catalytic in nature. Clearly, catalytic transformation provides the best “atom economy”, because the stoichiometric introduction and removal of (chiral) auxiliaries can be avoided, or at least minimized [1, 2].

Until recently, the catalysts employed for enantioselective synthesis of organic compounds such as pharmaceutical products, agrochemicals, fine chemicals, or synthetic intermediates, fell into two general categories – transition metal complexes and enzymes. In 2001 the Nobel Prize in Chemistry was awarded to William R. Knowles and Ryoji Noyori “for their work on chirally catalyzed hydrogenation reactions”, and to K. Barry Sharpless “for his work on chirally catalyzed oxidation reactions”. Could there be a better illustration of the importance of asymmetric catalysis? For all three laureates the development of chiral transition metal catalysts was the key to success. It has been a long-standing belief that only man-made transition metal catalysts can be tailored to produce either of two product enantiomers whereas enzymes cannot. This dogma has been challenged in recent years by tremendous advances in the field of biocatalysis, for example the discovery of preparatively useful enzymes from novel organisms, and the optimization of enzyme performance by selective mutation or by evolutionary methods [3, 4]. The recently issued Wiley–VCH book “Asymmetric Catalysis on Industrial Scale” (edited by H. U. Blaser and E. Schmidt) [5] vividly illustrates the highly competitive head-to-head race between transition metal catalysis and enzymatic catalysis in contemporary industrial production of enantiomerically pure fine chemicals. At the same time, the complementary character of both types of catalyst becomes obvious.

Between the extremes of transition metal catalysis and enzymatic transformations, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – organocatalysis. Organocatalysts are purely “organic”
molecules, i.e. composed of (mainly) carbon, hydrogen, nitrogen, sulfur and phos-
phorus. As opposed to organic ligands in transition metal complexes, the catalytic
activity of organocatalysts resides in the low-molecular-weight organic molecule it-
self, and no transition metals (or other metals) are required. Organocatalysts have
several advantages. They are usually robust, inexpensive and readily available, and
non-toxic. Because of their inertness toward moisture and oxygen, demanding
reaction conditions, for example inert atmosphere, low temperatures, absolute sol-
vents, etc., are, in many instances, not required. Because of the absence of transi-
tion metals, organocatalytic methods seem to be especially attractive for the prepa-
ration of compounds that do not tolerate metal contamination, e.g. pharmaceutical
products. A selection of typical organocatalysts is shown in Scheme 1.1. Proline
(1), a chiral-pool compound which catalyzes aldol and related reactions by iminium
ion or enamine pathways, is a prototypical example (List et al.). The same is true
for cinchona alkaloids such as quinine (2), which has been abundantly used as a
chiral base (Wynberg et al.) or as a chiral nucleophilic catalyst (Bolm et al.) and
which has served as the basis for many highly enantioselective phase-transfer cata-
lysts. The latter are exemplified by 3 (Corey, Lygo et al.) which enables, e.g., the
alkylation of glycine imines with very high enantioselectivity. The planar chiral
DMAP derivative 4 introduced by Fu et al. is extremely selective in several nucleo-
philic catalyses. Although it is a ferrocene it is regarded an organocatalyst because
its “active site” is the pyridine nitrogen atom.

Amino acid-derived organocatalysts such as the oxazolidinone 5 introduced by
MacMillan et al. or the chiral thiourea 6 introduced by Jacobsen et al. have enabled
excellent enantioselectivity in, e.g., Diels–Alder reactions of \( \alpha,\beta \)-unsaturated alde-
hydes (oxazolidinone 5) or the hydrocyanation of imines (thiourea 6). Pepti-
des, such as oligo-l-leucine (7) have found use in the asymmetric epoxidation of
enones, the so-called Juliá–Colonna reaction (recently studied by Roberts, Berkes-
sel et al.). Peptides are ideal objects for combinatorial optimization/selection, and
the pentapeptide 8 has been identified by Miller et al. as an artificial kinase that
enables highly enantioselective phosphorylation. The chiral ketone 9 introduced
by Shi et al. is derived from \( \delta \)-fructose and catalyzes the asymmetric epoxidation
of a wide range of olefins with persulfate as the oxygen source. This small (and by
no means complete) selection of current organocatalysts is intended to illustrate
the wide range of reactions that can be catalyzed and the ready accessibility of the
organocatalysts applied. With the exception of the planar chiral DMAP derivative 4,
all the organocatalysts shown in Scheme 1.1 are either chiral-pool compounds
themselves (1, 2), or they are derived from these readily available sources of chirali-
ity by means of a few synthetic steps (3, 5–9).

The historic roots of organocatalysis go back to the use of low-molecular-weight
compounds in an attempt both to understand and to mimic the catalytic activity
and selectivity of enzymes. As early as 1928 the German chemist Wolfgang Langenbeck published on “Analogies in the catalytic action of enzymes and definite
organic substances” [6]. The same author coined the term “Organic Catalysts”
(“Organische Katalysatoren”) [7] and, in 1949, published the second edition (!) of
the first book on “Organic Catalysts and their Relation to the Enzymes” (“Die
organischen Katalysatoren und ihre Beziehungen zu den Fermenten’) [8]. It is fascinating to see that, for example, the use of amino acids as catalysts for aldol reactions was reported for the first time in 1931 [9]. Refs. [6]–[9] also reveal that the conceptual difference between covalent catalysis (called ‘primary valence catalysis’ at that time) and non-covalent catalysis was recognized already and used as a means of categorization of different mechanisms of catalysis. As discussed in Chapter 2, this distinction between ‘covalent catalysis’ and ‘non-covalent catalysis’ is still viable and was clearly a farsighted and revolutionary concept almost 80 years ago.

Scheme 1.1

A selection of typical organocatalysts:
The first example of an asymmetric organocatalytic reaction was reported by Bredig and Fiske as early as 1912, i.e. ca. 90 years ago [10]. These two German chemists reported that addition of HCN to benzaldehyde is accelerated by the alkaloids quinine (2) and quinidine and that the resulting cyanohydrins are optically active and of opposite chirality. Unfortunately, the optical yields achieved in most of these early examples were in the range \( \leq 10\% \) and thus insufficient for preparative purposes. Pioneering work by Pracejus et al. in 1960, again using alkaloids as catalysts, afforded quite remarkable 74\% ee in the addition of methanol to phenylmethylketene. In this particular reaction 1 mol\% \( O \)-acetylquinine (10, Scheme 1.2) served as the catalyst [11].

![Alkaloid-catalyzed addition of methanol to a prochiral ketene](image)

Alkaloid-catalyzed addition of methanol to a prochiral ketene by Pracejus et al. (ref. 11):

Further breakthroughs in enantioselectivity were achieved in the 1970s and 1980s. For example, 1971 saw the discovery of the Hajos–Parrish–Eder–Sauer–Wiechert reaction, i.e. the proline (1)-catalyzed intramolecular asymmetric aldol cyclodehydration of the achiral trione 11 to the unsaturated Wieland–Miescher ketone 12 (Scheme 1.3) [12, 13]. Ketone 12 is an important intermediate in steroid synthesis.

The Hajos-Parrish-Eder-Sauer-Wiechert-reaction (refs. 12,13):

![Hajos-Parrish-Eder-Sauer-Wiechert-reaction](image)
Proline (1)-catalyzed intermolecular aldol reaction, List et al. (refs. 14,15):

\[
\text{L-proline (1):} \quad \begin{array}{c}
\large \text{O} \\
\text{N} \\
\text{H} \\
\text{H}
\end{array}
\]

\[
\text{CH}_3\text{C} = \text{CH}_3 + \text{CH}_3\text{O} \rightarrow \begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{H}
\end{array}\text{CH}_3\text{C} = \text{CH}_3
\]

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C}
\end{array}\text{OH} \quad 30 \text{ mol-% (1)} \quad \begin{array}{c}
\text{DMSO, r.t.}
\end{array}
\]

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C}
\end{array}\text{OH} \quad 13, 97 \%, 96 \% \text{ ee}
\]

Secondary amine 5-catalyzed Diels-Alder reaction, MacMillan et al. (ref. 15):

\[
\text{secondary amine catalyst 5:} \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{H}
\end{array}\text{Ph-CH}_2
\]

\[
\begin{array}{c}
\text{C} \\
\text{H}_2
\end{array}\text{CHO} + \begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{H}
\end{array}\text{H} \rightarrow \begin{array}{c}
\text{C} \\
\text{H}_2
\end{array}\text{CHO}
\]

\[
5 \text{ mol-% (5)} \quad 23 \text{ °C}
\]

\[
82 \%, 94 \% \text{ ee} \quad (\text{end/exo} 14:1)
\]

Scheme 1.4

Surprisingly, the catalytic potential of proline (1) in asymmetric aldol reactions was not explored further until recently. List et al. reported pioneering studies in 2000 on intermolecular aldol reactions [14, 15]. For example, acetone can be added to a variety of aldehydes, affording the corresponding aldols in excellent yields and enantiomeric purity. The example of iso-butyraldehyde as acceptor is shown in Scheme 1.4. In this example, the product aldol 13 was obtained in 97% isolated yield and with 96% ee [14, 15]. The remarkable chemo- and enantioselectivity observed by List et al. triggered massive further research activity in proline-catalyzed aldol, Mannich, Michael, and related reactions. In the same year, MacMillan et al. reported that the phenylalanine-derived secondary amine 5 catalyzes the Diels–Alder reaction of \( \alpha,\beta \)-unsaturated aldehydes with enantioselectivity up to 94% (Scheme 1.4) [16]. This initial report by MacMillan et al. was followed by numerous further applications of the catalyst 5 and related secondary amines.

A similarly remarkable event was the discovery of the cyclic peptide 14 shown in Scheme 1.5. In 1981 this cyclic dipeptide – readily available from \text{l}-histidine and \text{l}-phenylalanine – was reported, by Inoue et al., to catalyze the addition of HCN to
benzaldehyde with up to 90% ee [17, 18] (Scheme 1.5). Again, this observation sparked intensive research in the field of peptide-catalyzed addition of nucleophiles to aldehydes and imines.

Also striking was the discovery, by Juliá, Colonna et al. in the early 1980s, of the poly-amino acid (15)-catalyzed epoxidation of chalcones by alkaline hydrogen peroxide [19, 20]. In this experimentally most convenient reaction, enantiomeric excesses > 90% are readily achieved (Scheme 1.6).

As discussed above, asymmetric organocatalysis is, in principle, an “old” branch of organic chemistry, with its beginnings dating back to the early 20th century (for example the first asymmetric hydrocyanation of an aldehyde in 1912). This
initial phase of organocatalysis was, however, mainly mechanistic/biomimetic in nature, and the relatively low enantiomeric excess achieved prohibited “real” synthetic applications. Isolated examples of highly enantioselective organocatalytic processes were reported in the 1960s to the 1980s, for example the alkaloid-catalyzed addition of alcohols to prochiral ketenes by Pracejus et al. (Scheme 1.2) [11], the Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 1.3) [12, 13], the hydrocyanation of aldehydes using the Inoue catalyst 14 (Scheme 1.5) [17, 18], or the Juliá–Colonna epoxidation (Scheme 1.6) [19, 20], but the field still remained “sub-critical”. Now, triggered by the ground-breaking work of List, MacMillan, and others in the early 2000s, the last ca. five years have seen exponential growth of the field of asymmetric organocatalysis. Iminium and enamine-based organocatalysis now enables cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions, and many other transformations with excellent enantioselectivity; new generations of phase-transfer catalysts give almost perfect enantiomeric excesses at low catalyst loadings; chiral ureas and thioureas are extremely enantioselective catalysts for addition of a variety of nucleophiles to aldehydes and imines; and so forth. Organocatalysis currently seems to be in the state of a “gold rush” and at short intervals new “gold mines” are discovered and reported in the literature. A very recent example is the finding by Rawal et al. that hetero-Diels–Alder reactions – a classical domain of metal-based Lewis acids – can be effected with very high enantioselectivity by hydrogen bonding to chiral diols such as TADDOL (16, Scheme 1.7) [21].

Compared with earlier approaches, both prospecting and exploiting of the fields is greatly aided and accelerated by advanced analytical technology and, in particular, by synergism with theoretical and computational chemistry. Overall, asymmetric organocatalysis has matured in recent few years into a very powerful, practical, and broadly applicable third methodological approach in catalytic asymmetric
This book is meant as a “mise au point” dated 2005; it is hoped it will satisfy the expectations of readers looking for up-to-date information on the best organocatalytic methods currently available for a given synthetic problem and those of readers interested in the development of the field.

References

2
On the Structure of the Book,
and a Few General Mechanistic Considerations

2.1
The Structure of the Book

Two similarly attractive possibilities were considered for ordering the many examples of organocatalytic processes reported in the literature – by the type of catalyst employed or by the type of reaction catalyzed. As mentioned in the introduction, Chapter 1, the major goal of this book is to provide up-to-date information about the organocatalytic methods currently available for solution of a given synthetic problem. Chapters 3–13 are, therefore, arranged according to the type of organocatalytic reaction, for example aldol reactions, cycloadditions, desymmetrization of meso anhydrides, etc. Each chapter ends with a “Conclusion”, a brief summary of the state of the art for the type of reaction under discussion. Most of the work reported and discussed in Chapters 3–13 originated from academic laboratories and these chapters deal mainly with “academic aspects” of synthesis and catalysis. Chapter 14, on the other hand, provides examples of organocatalytic processes applied in an industrial environment. Finally, the appendix lists prominent and frequently applied organocatalysts, together with the reaction types for which they have been used. Availability is commented on, and references to the corresponding chapters of this book are provided.

2.2
General Mechanistic Considerations

As discussed above, this book is ordered according to the different types of reaction being catalyzed. It should be noted, however, that there are only a rather limited number of “mechanistic categories” to which all these reactions can be assigned. The mechanisms by which metal-free enzymes (the majority of enzymes do not contain catalytically active metals) effect dramatic rate accelerations have been a major field of research in bioorganic chemistry for decades [1–6]. In many instances organocatalysts can be regarded as “minimum versions” of metal-free enzymes, and the mechanisms and categories of enzymatic catalysis apply to the action of organocatalysts also. In both cases the rate accelerations observed depend on typical interactions between organic molecules. A general distinction can be
made between processes that involve the formation of covalent adducts between catalyst and substrate(s) within the catalytic cycle and processes that rely on non-covalent interactions such as hydrogen bonding or the formation of ion pairs. The former interaction has been termed “covalent catalysis” and the latter situation is usually denoted “non-covalent catalysis” (Scheme 2.1).

The formation of covalent substrate–catalyst adducts might occur, e.g., by single-step Lewis-acid–Lewis-base interaction or by multi-step reactions such as the formation of enamines from aldehydes and secondary amines. The catalysis of aldol reactions by formation of the donor enamine is a striking example of common mechanisms in enzymatic catalysis and organocatalysis – in class-I aldolases lysine provides the catalytically active amine group whereas typical organocatalysts for this purpose are secondary amines, the most simple being proline (Scheme 2.2).

In many instances non-covalent catalysis relies on the formation of hydrogen-
Catalytic mechanism of class I aldolases:

Proline-catalysis of aldol reactions:

Scheme 2.2
bonded adducts between substrate and catalyst or on protonation/deprotonation processes. Phase-transfer catalysis (PTC) by organic phase-transfer catalysts also falls into the category “non-covalent catalysis”. It is, however, mechanistically unique, because PTC promotes reactivity not only by altering the chemical properties of the reactants but also involves a transport phenomenon. It is tempting to speculate whether “covalent forms” of PTC might also be feasible.

Specific mechanistic information on the organocatalytic processes discussed in this book is given in the individual chapters.

References


3
Nucleophilic Substitution at Aliphatic Carbon

Enantioselective catalytic alkylation is a versatile method for construction of stereogenic carbon centers. Typically, phase-transfer catalysts are used and form a chiral ion pair of type 4 as a key intermediate. In a first step, an anion, 2, is formed via deprotonation with an achiral base; this is followed by extraction in the organic phase via formation of a salt complex of type 4 with the phase-transfer organocatalyst, 3. Subsequently, a nucleophilic substitution reaction furnishes the optically active alkylated products of type 6, with recovery of the catalyst 3. An overview of this reaction concept is given in Scheme 3.1 [1].

An important issue is the right choice of substrate 1 which functions as an anion precursor. Successful organocatalytic conversions have been reported with indanones and benzophenone imines of glycine derivatives. The latter compounds are, in particular, useful for the synthesis of optically active $\alpha$-amino acids. Excellent enantioselectivity has been reported for these conversions. In the following text the main achievements in this field of asymmetric organocatalytic nucleophilic substitutions are summarized [1, 2]. The related addition of the anions 2 to Michael-acceptors is covered by chapter 4.

3.1
$\alpha$-Alkylation of Cyclic Ketones and Related Compounds

The first example of the use of an alkaloid-based chiral phase-transfer catalyst as an efficient organocatalyst for enantioselective alkylation reactions was reported in 1984 [3, 4]. Researchers from Merck used a cinchoninium bromide, 8, as a catalyst.
in the methylation of the 2-substituted indanone 7. The desired product, 9, a key intermediate in the synthesis of (+)-indacrinone was formed in 95% yield and with 92% ee (Scheme 3.2) [3]. After detailed study of the effects of solvent, alkylating agent, temperature, and catalysts, improvement of enantioselectivity up to 94% ee was achieved [5].

The catalyst concentration, which was varied between 10 and 50 mol%, controlled the rate of the reaction but did not have a significant effect on enantioselectivity [3]. Use of methyl chloride as methylating agent resulted in higher enantioselectivity than methyl bromide or iodide. In general, non-polar solvents, e.g. toluene, resulted in higher enantioselectivity than polar solvents. In addition, higher ee values were obtained after greater dilution of the reaction mixture [3]. Kinetic and mechanistic studies [5] revealed several unusual features. For example, depending on the concentration of sodium hydroxide (50% or 30%) a solid sodium enolate can be formed in the initial stage [5]. The high enantioselectivity was rationalized in terms of formation of a tight ion pair between the catalyst and the indanone enolate.

The broad substrate range, in particular with regard to the alkyl halide component, led to numerous interesting applications of this asymmetric phase-transfer-catalyzed alkylation using alkaloids as catalyst [6–18]. Selected examples are described below.

When the reaction is performed using 1,3-dichloro-2-butene as the alkyl halide, the indanone derivative 11 is formed in excellent yield (99%) and with high (92%) ee (Scheme 3.3, Eq. 1) [6]. Products of type 11 are interesting intermediates for preparation of optically active tricyclic enones, which are obtained after hydrolysis and Robinson annelation [6].

Organocatalytic asymmetric alkylation methodology has also been efficiently applied in a practical multi-gram synthesis of pharmaceutically interesting, optically active (-)-physostigmine analogs [7]. In the presence of 15 mol% of the catalyst 13 alkylation of the oxindole substrate 12 with chloroacetonitrile furnished the desired product 14 in 83% yield and 73% ee (Scheme 3.3, Eq. 2). The counter-ion of the