Albrecht Berkessel, Harald Gröger

Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis

WILEY-VCH Verlag GmbH & Co. KGaA

Albrecht Berkessel,
Harald Gröger

Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis

Further Reading from Wiley-VCH

A. de Meijere, F. Diederich (Eds.)

Metal-Catalyzed Cross-Coupling Reactions, 2^{nd} Ed., 2 Vols.

2004. 3-527-30518-1

R. Mahrwald (Ed.)

Modern Aldol Reactions, 2 Vols.

2004. 3-527-30714-1

M. Beller, C. Bolm (Eds.)

Transition Metals for Organic Synthesis, 2 Vols., 2^{nd} Ed.

Building Blocks and Fine Chemicals
2004. 3-527-30613-7

N. Krause, A. S. K. Hashmi (Eds.)

Modern Allene Chemistry, 2 Vols.

2004. 3-527-30671-4

J. Zhu, H. Bienaymé (Eds.)

Multicomponent Reactions

2005. 3-527-30806-7

Albrecht Berkessel, Harald Gröger

Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis

WILEY-VCH

WILEY-VCH Verlag GmbH & Co. KGaA

Prof. Dr. Albrecht Berkessel
Institut für Organische Chemie
Universität zu Köln
Greinstraße 4
50939 Köln
Germany

Dr. Harald Gröger
Service Center Biocatalysis
Degussa AG
Rodenbacher Chaussee 4
63457 Hanau-Wolfgang
Germany

Library of Congress Card No.: applied for
A catalogue record for this book is available from the British Library.
Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at http://dnb.ddb.de

Printed in the Federal Republic of Germany.
Printed on acid-free paper.

Typesetting Asco Typesetters, Hong Kong
Printing Strauss GmbH, Mörlenbach
Bookbinding J. Schäffer GmbH, Grünstadt

ISBN-13 978-3-527-30517-9
ISBN-10 3-527-30517-3

Contents

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

Foreword

"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

1
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].

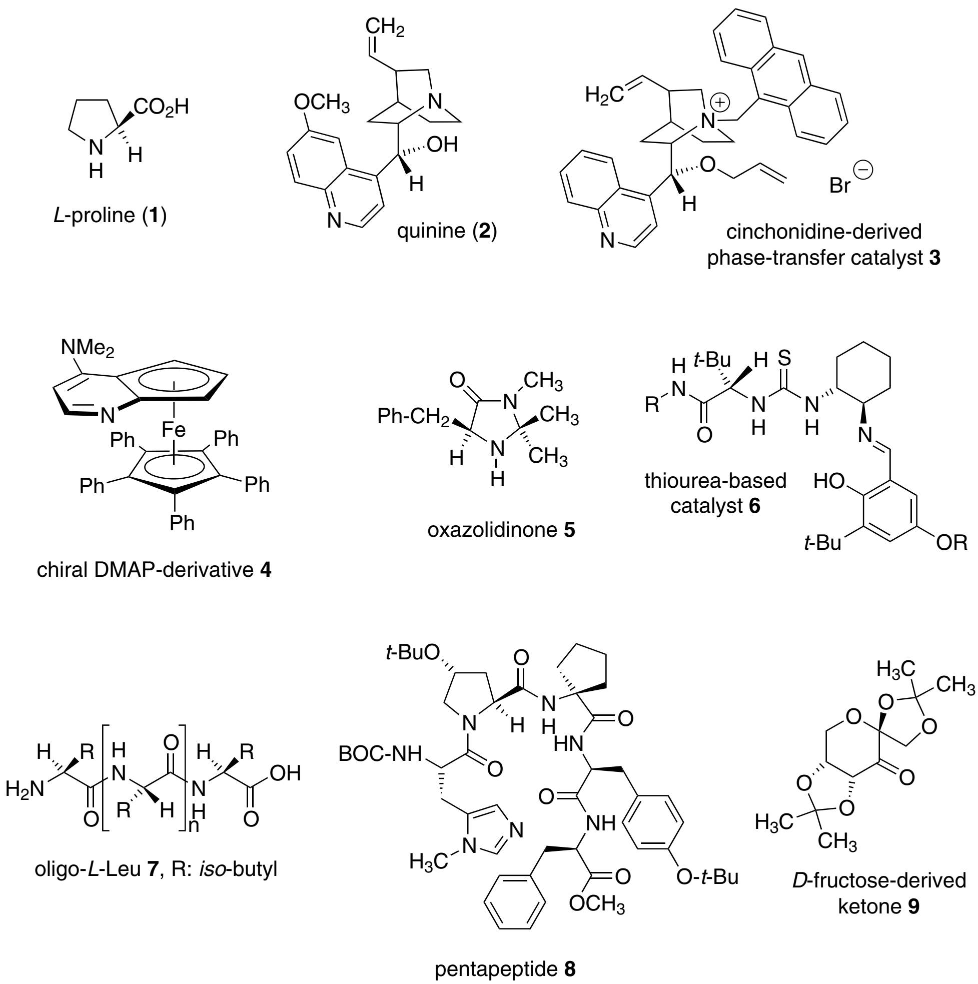
Until recently, the catalysts employed for enantioselective synthesis of organic compounds such as pharmaceutical products, agrochemicals, fine chemicals, or synthetic intermediates, fell into two general categories – transition metal complexes and enzymes. In 2001 the Nobel Prize in Chemistry was awarded 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 phosphorus. As opposed to organic ligands in transition metal complexes, the catalytic activity of organocatalysts resides in the low-molecular-weight organic molecule itself, 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 solvents, etc., are, in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation 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 catalysts. 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 nucleophilic 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 α,β-unsaturated aldehydes (oxazolidinone **5**) or the hydrocyanation of imines (thiourea **6**). Peptides, 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, Berkessel 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 D-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 chirality 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

A selection of typical organocatalysts:

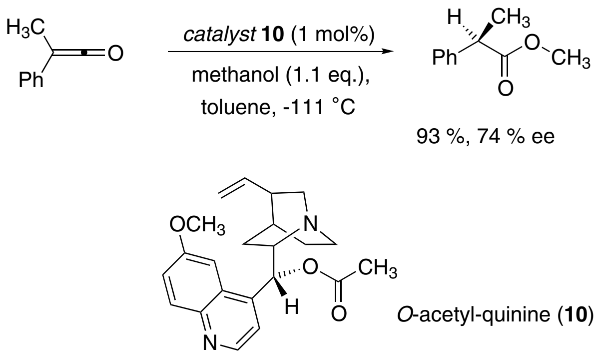


Scheme 1.1

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.

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 ≤ 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].

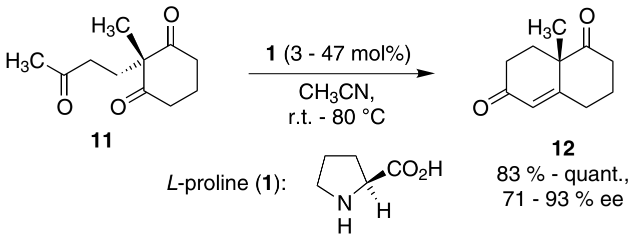
Alkaloid-catalyzed addition of methanol to a prochiral ketene by *Pracejus et al.* (ref. 11):



Scheme 1.2

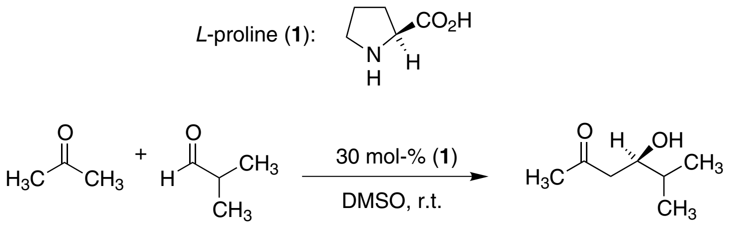
Further breakthroughs in enantioselectivity were achieved in the 1970s and 1980s. For example, 1971 saw the discovery of the Hajos–Parrish–Eder–Sauer–Wiechert reaction, i.e. the proline (**1**)-catalyzed intramolecular asymmetric aldol cyclodehydration of the achiral trione **11** to the unsaturated 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):



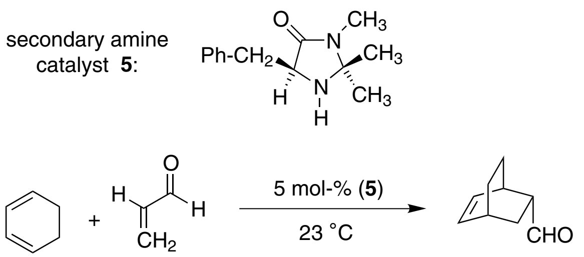
Scheme 1.3

Proline (**1**)-catalyzed intermolecular aldol reaction, *List et al.* (refs. 14,15):



13, 97 %, 96 % ee

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

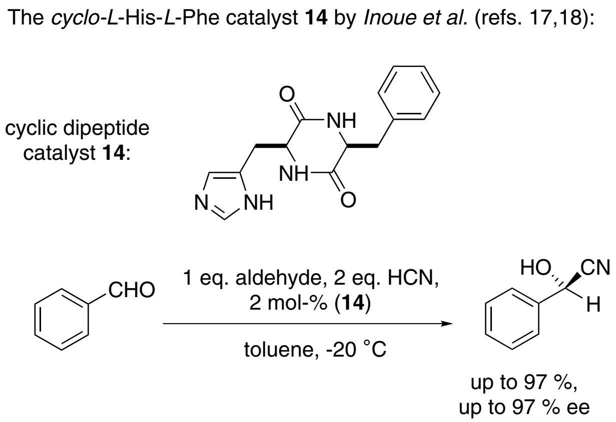


82 %, 94 % ee
(*end/exo* 14:1)

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 *inter*molecular 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 α,β-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.

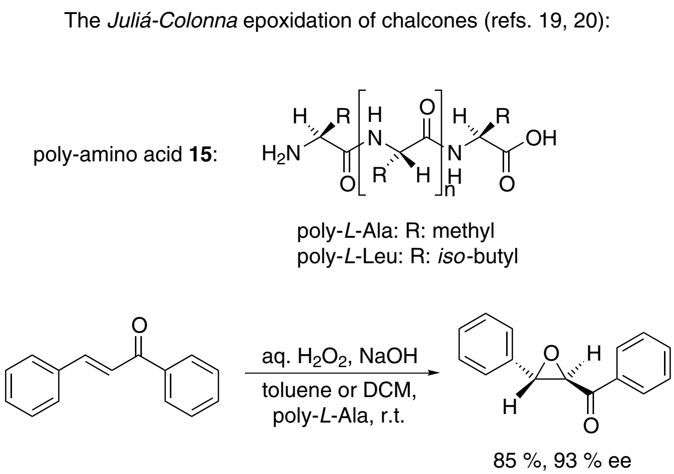
A similarly remarkable event was the discovery of the cyclic peptide **14** shown in Scheme 1.5. In 1981 this cyclic dipeptide – readily available from L-histidine and L-phenylalanine – was reported, by Inoue et al., to catalyze the addition of HCN to



Scheme 1.5

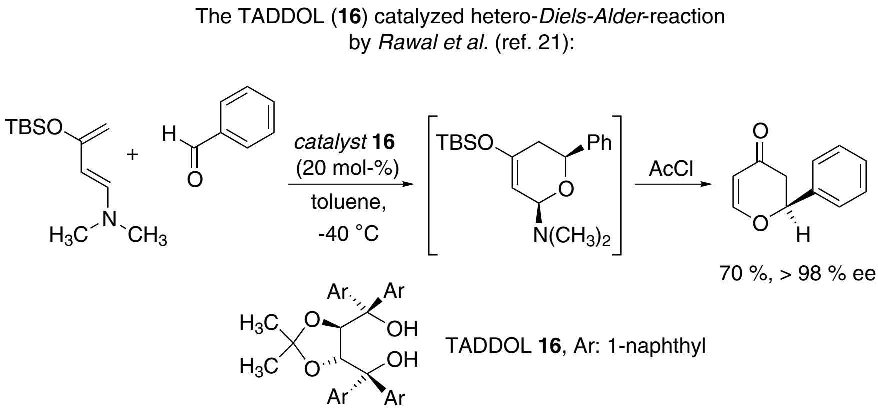
benzaldehyde with up to 90% ee [17, 18] (Scheme 1.5). Again, this observation sparked intensive research in the field of peptide-catalyzed addition of nucleophiles to aldehydes and imines.

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).



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 hydrocyanantion 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].



Scheme 1.7

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 synthesis [22]. 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

1 B. M. Trost, *Science* **1991**, *254*, 1471–1477.

2 B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

3 (a) M. T. Reetz, *Enzyme Functionality* **2004**, 559–598; (b) K. Drauz, H. Waldmann (eds), *Enzyme Catalysis in Organic Synthesis*, Wiley–VCH, Weinheim, 2002.

4 (a) T. Eggert, K.-E. Jaeger, M. T. Reetz, *Enzyme Functionality* **2004**, 375–390; (b) M. T. Reetz, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5716–5722; (c) M. Bocola, N. Otte, K.-E. Jaeger, M. T. Reetz, W. Thiel, *ChemBioChem* **2004**, *5*, 214–223; (d) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292–320; *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310; (e) S. Brakmann, K. Johnsson (eds), *Directed Molecular Evolution of Proteins*, Wiley–VCH, Weinheim, 2002.

5 H. U. Blaser, E. Schmidt (eds.), *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, 2004.

6 W. Langenbeck, *Angew. Chem.* **1928**, *41*, 740–745.

7 W. Langenbeck, *Angew. Chem.* **1932**, *45*, 97–99.

8 W. Langenbeck, *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten*, 2nd ed., Springer, Berlin, 1949.

9 (a) F. G. Fischer, A. Marschall, *Ber.* **1931**, *64*, 2825–2827; (b) W. Langenbeck, G. Borth, *Ber.* **1942**, *75B*, 951–953.

10 G. Bredig, W. S. Fiske, *Biochem. Z.* **1912**, 7.

11 (a) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22; (b) H. Pracejus, H. Mätje, *J. Prakt. Chem.* **1964**, *24*, 195–205.

12 U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497.

13 Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

14 B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

15 B. List, *Tetrahedron* **2002**, *58*, 5573–5590.

16 K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

17 J. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.* **1981**, 229–230.

18 J.-I. Oku, N. Ito, S. Inoue, *Macromol. Chem.* **1982**, *183*, 579–589.

19 S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317–1324.

20 S. Juliá, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929.

21 Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.

22 For recent reviews on asymmetric organocatalysis, see: (a) *Acc. Chem. Res.* **2004**, *37*, issue 8; (b) *Adv. Symth. Catal.* **2004**, *346*, issue 9+10; (c) P. I. Daiko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

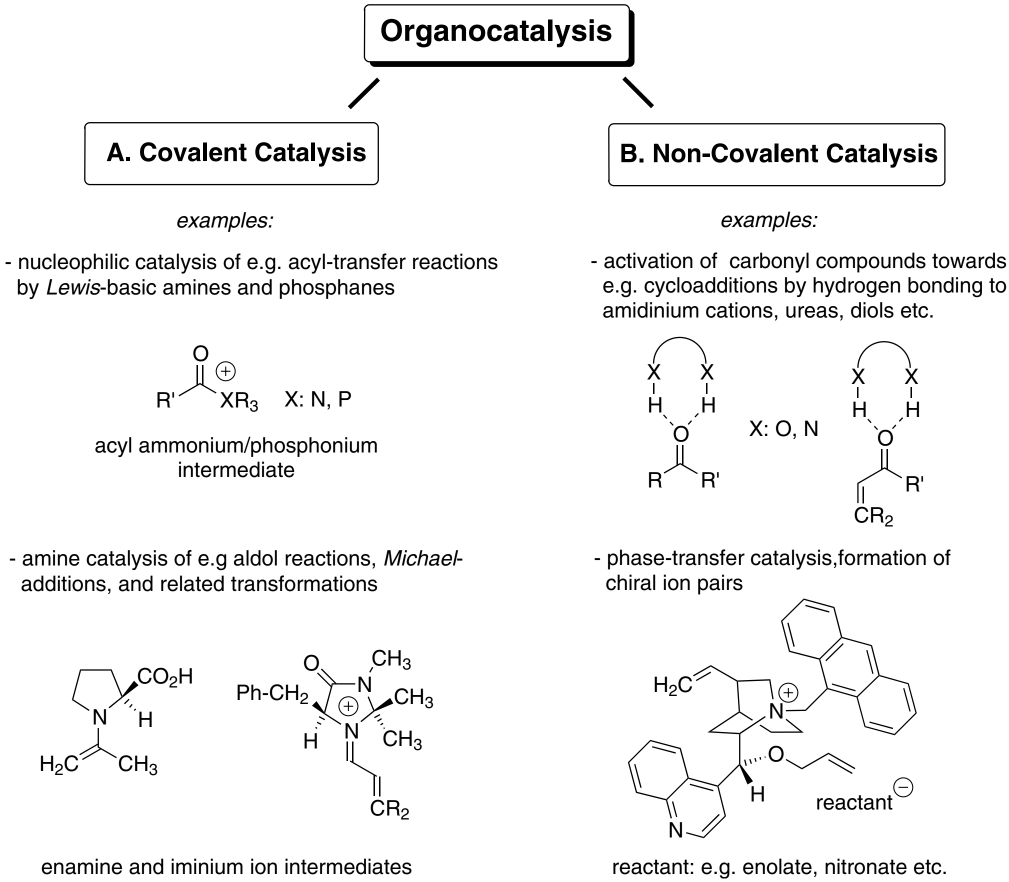
2
On the Structure of the Book, and a Few General Mechanistic Considerations

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



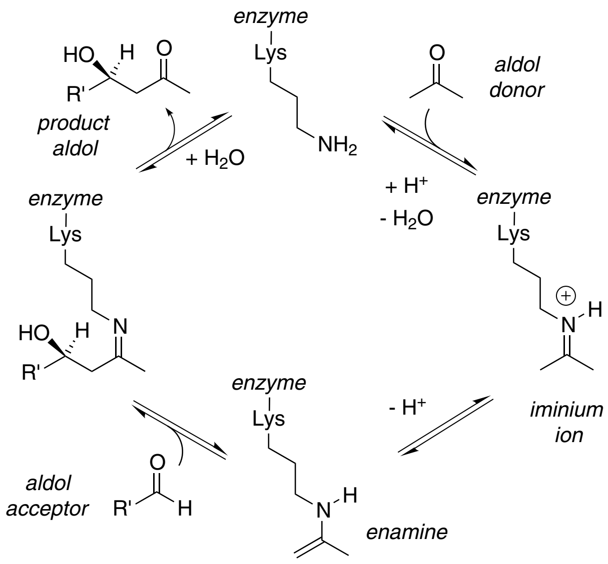
Scheme 2.1

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).

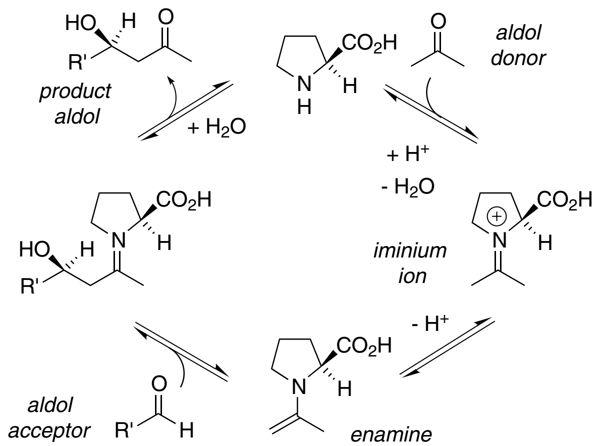
The formation of covalent substrate–catalyst adducts might occur, e.g., by single-step Lewis-acid–Lewis-base interaction or by multi-step reactions such as the formation of enamines from aldehydes and secondary amines. The catalysis of aldol reactions by formation of the donor enamine is a striking example 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

1 For a very early account on enzymatic catalysis and organocatalysis, and their analogies, see: W. Langenbeck, *Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten (Organic Catalysts and their Relation to the Enzymes)*, 2nd ed., Springer, Berlin, 1949.

2 M. Page, A. Williams, *Organic and Bio-Organic Mechanisms*, Longman, Harlow, 1997.

3 H. Dugas, *Biorganic Chemistry: A Chemical Approach to Enzyme Action*, 3rd edn, Springer, New York, 1991.

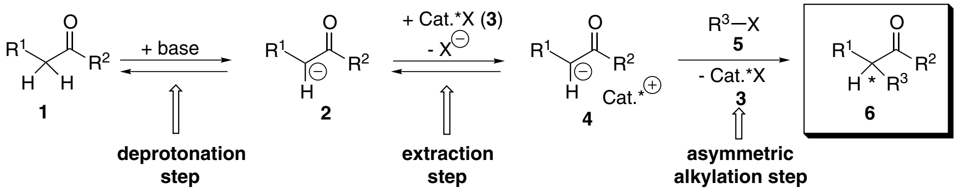
4 A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed.* **1996**, *35*, 707–724.

5 R. Breslow, *Chem. Biol.* **1998**, *5*, R-27–R-28.

6 R. Breslow, *J. Chem. Educ.* **1998**, *75*, 705–718.

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 an 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].

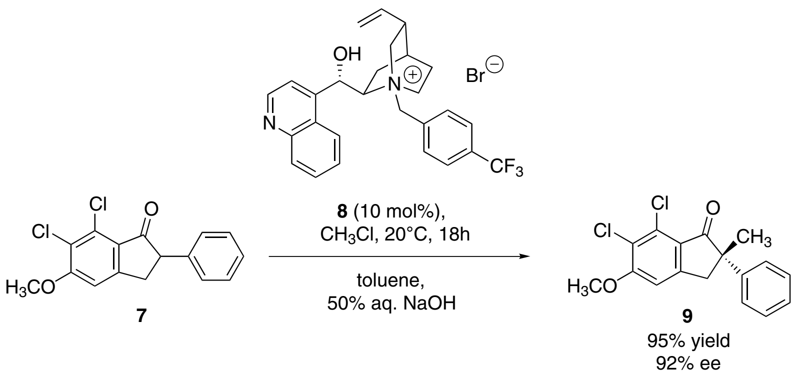


Scheme 3.1

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 α-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
α-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



Scheme 3.2

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