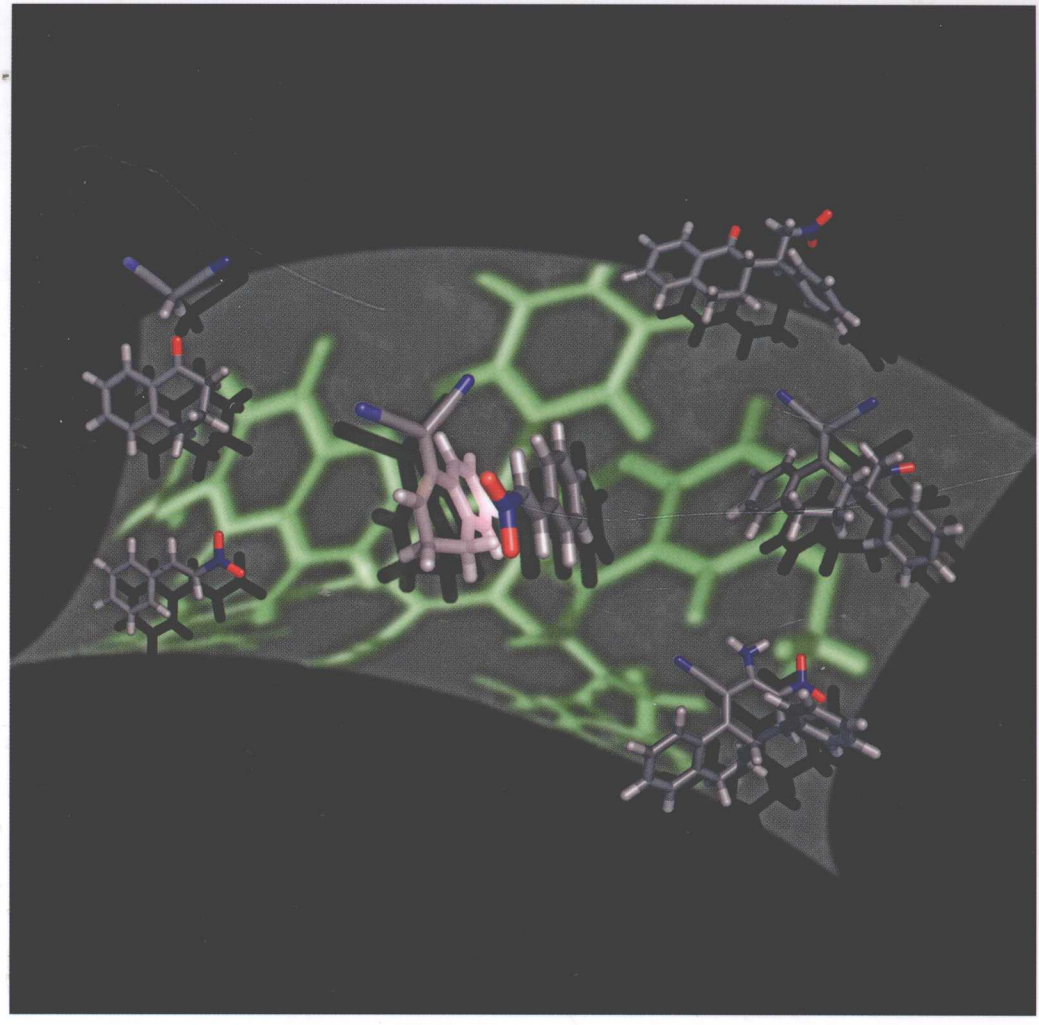
RSC Catalysis Series

Jose L. Vicario, Dolores Badía, Luisa Carrillo and Efraim Reyes

Organocatalytic Enantioselective Conjugate Addition Reactions

A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules



RSC Publishing

Organocatalytic Enantioselective Conjugate Addition Reactions

A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules

Edited by

Jose L. Vicario, Dolores Badía, Luisa Carrillo and Efraim Reyes
Department of Organic Chemistry II, University of the Basque Country, Bilbao, Spain

RSC Publishing

RSC Catalysis Series No. 5

ISBN: 978-1-84973-024-2
ISSN: 1757-6725

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

For further information see our website at www.rsc.org

Organocatalytic Enantioselective Conjugate Addition Reactions

A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules

RSC Catalysis Series

Series Editor:
Professor James J Spivey, *Louisiana State University, Baton Rouge, USA*

Advisory Board:
Krijn P de Jong, *University of Utrecht, The Netherlands*, James A Dumesic, *University of Wisconsin-Madison, USA*, Chris Hardacre, *Queen's University Belfast, Northern Ireland*, Enrique Iglesia, *University of California at Berkeley, USA*, Zinfer Ismagilov, *Boreskov Institute of Catalysis, Novosibirsk, Russia*, Johannes Lercher, *TU München, Germany*, Umit Ozkan, *Ohio State University, USA*, Chunshan Song, *Penn State University, USA*

Titles in the Series:
1: Carbons and Carbon Supported Catalysts in Hydroprocessing
2: Chiral Sulfur Ligands: Asymmetric Catalysis
3: Recent Developments in Asymmetric Organocatalysis
4: Catalysis in the Refining of Fischer-Tropsch Syncrude
5: Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules

How to obtain future titles on publication:
A standing order plan is available for this series. A standing order will bring delivery of each new volume immediately on publication.

For further information please contact:
Book Sales Department, Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, CB4 0WF, UK
Telephone: +44 (0)1223 420066, Fax: +44 (0)1223 420247, Email: books@rsc.org
Visit our website at http://www.rsc.org/Shop/Books/

Preface

Asymmetric organocatalysis has experienced an impressive rebirth in the last few years, with a plethora of new methodologies developed for carrying out enantioselective transformations which up to that moment were only available under transition-metal catalysis. Given the operational and economical advantages associated with this methodology, together with the fact that organocatalysts are environmentally friendly, robust and very often commercially available reagents, many research groups worldwide have engaged in active research in this field. In this context, the conjugate addition reaction has attracted a particular interest by the synthetic organic chemists, which has led to an extraordinarily high number of reports dealing with enantioselective versions of this transformation carried out using small organic molecules as catalysts. Organocatalysts operating by very different mechanistic profiles have demonstrated their performance when applied to this reaction obtaining in many cases outstanding levels of chemical efficiency and stereoselectivity. The conjugate addition reaction is also a particularly interesting reaction because of its wide synthetic versatility due to the broad spectrum of donors and acceptors that may be employed on one hand and also because of its potential to be applied in tandem, domino or cascade reactions, resulting in an extremely powerful approach for the preparation of molecules of high complexity in a single step starting from readily available starting materials.

This book intends to cover a very hot topic in a rather comprehensive way, including the most recent research made in this field until 2009, presenting the advances in this field organized according to the mechanistic pathway involved in the activation of the reagents participating in the reaction by the organic catalyst. We hope that this book will provide a good state-of-the-art view to all organic chemists working in this field and also to all who wish to start projects in this area.

RSC Catalysis Series No. 5
Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules
By Jose L. Vicario, Dolores Badía, Luisa Carrillo and Efraim Reyes

Published by the Royal Society of Chemistry, www.rsc.org

Contents

RSC Catalysis Series No. 5
Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules
By Jose L. Vicario, Dolores Badía, Luisa Carrillo and Efraim Reyes

Published by the Royal Society of Chemistry, www.rsc.org

CHAPTER 1

Introduction

1.1 Organocatalysis: an Emerging Field

Chemistry is the science of matter and the changes it undergoes during chemical reactions. Behind this definition one can identify the ability of chemists to change the matter at will, in order to obtain new materials or compounds with novel or improved properties. As humans evolved toward modern societies, more and more complex chemical entities were required to satisfy their needs toward higher standards of life; chemists needed to develop new methods and reactions that allowed the preparation of the target compounds in a more efficient way. These two concepts, "efficiency" and "complexity", entail the major principles behind the activity of chemists dedicated to organic synthesis: a complex molecule, with many different types of functionalities located in different positions and with a certain three-dimensional orientation of all its atoms, has to be built up starting from simple and readily available starting materials by carrying out a set of transformations in the most efficient (economic) way. This means that reactions and synthetic methodologies have to be available for the organic chemist to carry out these transformations in the simplest way, with the highest possible yield and selectivity and with the minimum generation of waste. In this context, asymmetric synthesis represents the highest level with regard to selectivity control in a chemical reaction. If a chiral compound has to be prepared as a single enantiomer, the chemist has to control the exact trajectories in which the reagents approach to each other, which means that an exquisite control of all the events taking place in the reaction vessel has to be achieved.

The agrochemical and pharmaceutical industries are fields in which chirality and stereochemical control are of special relevance. Drug chirality is now a major theme in the design, discovery, development, launching and marketing of

RSC Catalysis Series No. 5
Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules
By Jose L. Vicario, Dolores Badía, Luisa Carrillo and Efraim Reyes

Published by the Royal Society of Chemistry, www.rsc.org

new drugs and, therefore, stereochemistry is an essential dimension to be taken into account. The thalidomide case in the 1960s is a paradigmatic example of this behavior. This drug was prescribed in Europe in a racemic form to pregnant women to alleviate sickness but, while one of the enantiomers had sedative and antiemetic activities, the opposite enantiomer had teratogenic effects. This tragedy led to a new awareness of the importance of stereoselective pharmacodynamics and pharmacokinetics, enabling the differentiation of the relative contributions of enantiomers to overall drug action. When one enantiomer is responsible for the activity of interest, its paired enantiomer could be inactive, be an antagonist of the active enantiomer or have a separate activity that could be desirable or undesirable. Considering these possibilities, there appear to be major advantages in using enantiomerically pure drugs, such as a reduction of the total administered dose, enhanced therapeutic window and a more precise estimation of dose–response relationships. These factors have led to an increasing preference for single enantiomers in both industry and regulatory authorities. Regulatory control of chiral drugs began in the United States with the publication in 1992 of formal guidelines on the development of chiral drugs and was followed in the European Union in 1994 by a document entitled *Investigation of Chiral Active Substances*. Applicants must recognize the occurrence of chirality in new drugs, attempt to separate the stereoisomers, assess the contribution of the various stereoisomers to the activity of interest and make a rational selection of the stereoisomeric form that is proposed for marketing.

Among the strategies available in the synthetic organic chemist's toolbox for controlling the stereochemical outcome of a given reaction, catalysis has become the option of choice in the last 20 years. The true advantages displayed by catalytic enantioselective methods compared to the chiral auxiliary methodology justify this situation: catalytic methods constitute a more direct and atom-economic approach than the use of chiral auxiliaries because the requirement of stoichiometric quantities of the chirality source and the need for additional synthetic steps for the attachment/removal of the auxiliary are avoided. As a consequence of this, a huge number of different research groups worldwide have engaged in the development of enantioselective versions of almost all the organic reactions known up to date. In this context, the catalytic methodologies typically employed for the enantioselective preparation of chiral compounds have been considered for many years to lie in two main categories, namely metal catalysis and enzymatic methods. In fact, metal-catalyzed reactions have prevailed for many years above the enzymatic methods, reaching an exceptional level of sophistication. Proof of the paramount importance of transition-metal-mediated enantioselective transformations is the 2001 Nobel Prize in chemistry, which was awarded to William R. Knowles, Ryoji Noyori and K. Barry Sharpless for the development of important metal-catalyzed enantioselective reductions and oxidations. On the other hand, enzymatic methodologies, although a well-known method even used by living cells to produce their own metabolites, normally chiral compounds in enantiomerically pure form, have been considered for many years as a more limited strategy, due

to the extremely high specificity shown by enzymes toward the substrate structure. This situation has been overcome in recent years with the advances in biotechnology, which allow the preparation of modified enzymes from genetically modified organisms.

However, in the last decade a new branch of knowledge has opened up in the interface between these two methodologies. The fact that small chiral organic molecules that do not contain metal atoms in the structure (organocatalysts) can catalyze certain chemical transformations in a stereoselective way has experienced an impressive rebirth in the chemical community, which has led to the coining of a new term, "asymmetric organocatalysis", to define this new methodological alternative for carrying out a reaction in a catalytic and enantioselective way. Organocatalysts are (purely) organic molecules, composed of (exclusively) hydrogen, carbon, silicon, nitrogen, phosphorous, oxygen, sulfur, selenium, tellurium and halides and arise as the "opposite" to metal complexes, in which the metal is the main thing responsible for the catalytic activity in the reaction. However, there are some organocatalysts which do incorporate some metal elements in their structure (for example, several chiral DMAP derivatives containing a ferrocene unit) but in which the metal atom does not participate in the catalytic cycle, remaining as a simple architectural element of the catalyst.

Asymmetric organocatalysis has become a very rapidly growing field of research, as a result of both the novelty of the concept and the high efficiencies and selectivities attained by many organocatalytic transformations.[1,2] One of the main advantages of this methodology is the fact that organocatalysts and the intermediate species participating in the catalytic cycle are usually inert toward water or oxygen, and therefore reactions do not require special care with regard to the use of an inert atmosphere or dry solvents. This turns into a high operational simplicity when running the reaction, compared with the typical specific equipment and expertise required when carrying out most of the transition metal-catalyzed reactions. In addition, the fact that the presence of hazardous metals is precluded in the reaction scheme makes this methodology even more interesting from the environmental point of view and this is of special relevance in the production of chemicals for human consumption which do not tolerate the presence of metal contaminants even at the trace level. All these practical and economical advantages, together with the fact that organocatalysts are very often commercially available reagents, have contributed significantly to the rapid growth of the field, leading many research groups to engage in the development of novel organocatalytic procedures for performing transformations which were typically run using transition-metal catalysis. This has made organocatalysis a rapidly changing field, which has experienced an impressive growth especially in the last few years, as can be seen from the evolution of the publications in this area as shown in Figure 1.1, with several very important research groups involved. As a consequence of this, organocatalysis has also become a very competitive field, which in some cases has led to multiple publications appearing almost simultaneously and covering similar reactions or reporting similar

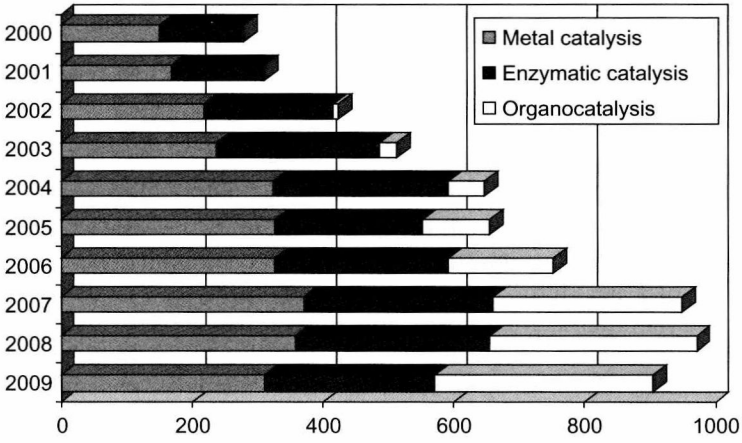


Figure 1.1 Evolution of publications in the field of asymmetric catalysis (2000–2009).[4]

results. This competitiveness and the rush for publication has also in some cases resulted in a rather superficial treatment of the experimental results obtained and a lack of a deep research into the consequences of these results and the knowledge which could be acquired thereof. In fact, many organocatalytic reactions like enamine and iminium catalysis or the reactions *via* H-bonding interactions or with *N*-heterocyclic carbenes proceed *via* mechanisms which are closely related to those operating in many enzymatic processes, although this connection has very often been underestimated during the research process.[3] A global vision on the field, and possible new advances and future directions, could have been complicated by such a fragmented way of reporting the huge amount of information gathered in many different laboratories worldwide.

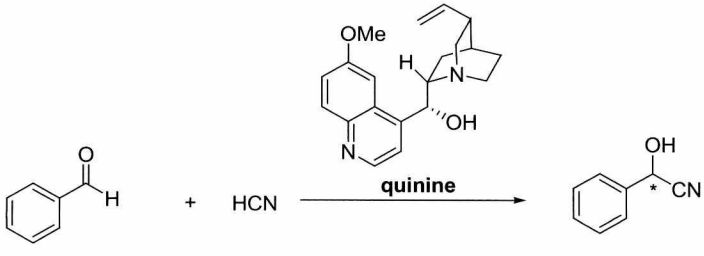
However, despite the impressive advance gained in this field in the last years, many issues still remain unsolved. Some reactions have remained elusive to organocatalysis and, therefore, transition-metal catalysis stands as the only available synthetic tool. Another issue which has to be underlined is the fact that organocatalytic reactions typically require very high catalyst loadings (5–20 mol%), which at the moment is very far from the extremely high efficiencies achieved in this context by transition-metal catalytic methodologies and makes the application of the methodology to large-scale synthesis much more difficult. In fact, the application of organocatalytic asymmetric methodologies to industrial production is still to be developed. Finally, the application of organocatalytic reactions in total syntheses of complex molecules also remains rather unexplored,[5] although there is a significant tendency observed in the last years which indicates that chemists working in total synthesis are starting to seriously consider organocatalytic methodologies as a potent alternative in their chemical reactions toolkit.

1.2 Historical Evolution of Asymmetric Organocatalysis

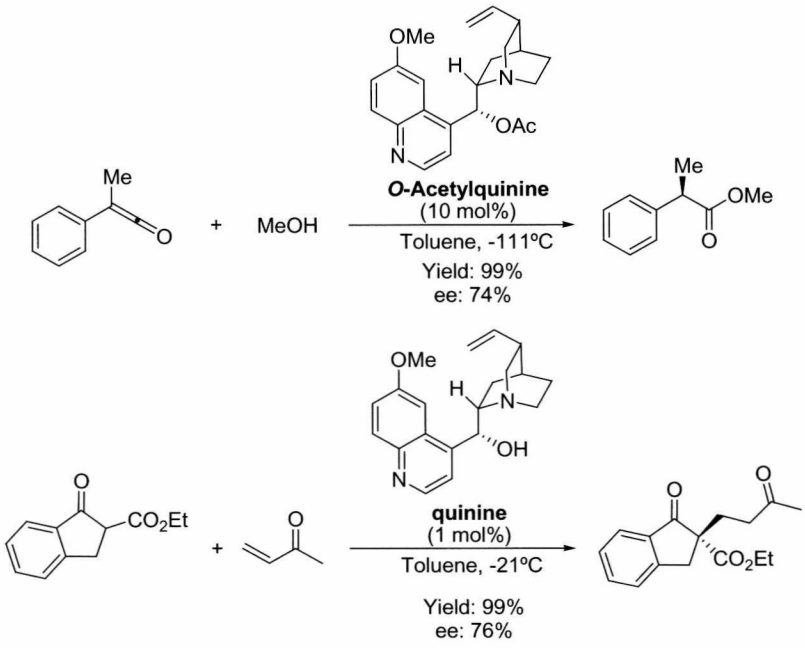
The possibility that small organic molecules could catalyze organic transformations in a stereoselective way can even be considered as a key element in the origins of life, as it is widely accepted that the source of homochirality in biological systems should be attributed to the presence of enantiomerically enriched α-amino acids in meteorites,[6] and especially once it was demonstrated that these α-amino acids were able to catalyze aldol reactions in a stereoselective way under prebiotic conditions conducing to sugar-type products.[7]

However, the first attempts in the field were carried out when trying to understand the mechanism of several enzymatic transformations, the small chiral organic molecule being intended to operate as a model mimicking the enzyme behavior. For example, in 1908, Georg Bredig, who was indeed interested in the origin of the enzyme activity, found that the thermal decarboxylation of optically enriched camphorcarboxylic acid in the presence of (+)- or (−)-*limonene* proceeded with an enhancement of optical purity of the final product[8] and, as an extension of this work, he subsequently studied the same decarboxylation reaction in the presence of natural alkaloids like nicotine or quinidine.[9] It was also G. Bredig who reported the first enantioselective C–C bond-forming reaction under metal-free conditions, when he demonstrated that the addition of HCN to benzaldehyde in the presence of quinine or quinidine also proceeded with some degree of enantioselection (Scheme 1.1).[10] Although the observed ee was too low for preparative purposes, the proof of principle was clearly established for future advances in the field.

In the same line with these pioneering reports, the German chemist Wolfgang Langebeck made several decisive contributions to the field, in particular, coining for the first time the term "organic catalyst" to define those reactions promoted exclusively by organic compounds.[11] In fact, the origins of the research by Langebeck were strongly multidisciplinary; he dedicated most of his efforts to the identification and explanation of enzymatic processes by using simple amino acids or small peptides in order to mimic the behavior of natural enzymes.[12] In 1949, Langebeck published his book "*Organic Catalysts and Their Relations with Enzymes*",[11] in which, for example, mechanistic



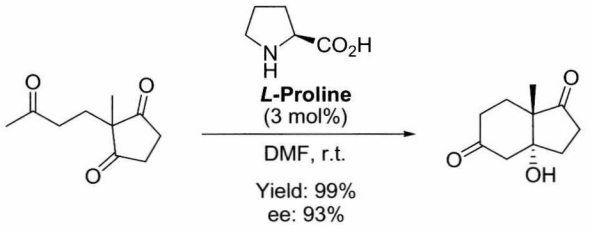
Scheme 1.1 Enantioselective addition of HCN to benzaldehyde reported by Bredig.



Scheme 1.2 The enantioselective addition of MeOH to methyl phenyl ketene reported by Pracejus and the quinine-catalyzed enantioselective Michael reaction reported by Wynberg.

implications related to the way organic catalysts and enzymes participate in promoting a reaction were discussed.

Probably the first organocatalytic asymmetric reaction furnishing high levels of enantioselection was the addition of methanol to methyl phenyl ketene in the presence of *O*-acetylquinine reported by Pracejus in 1960 (Scheme 1.2).[13] This reaction also formed the basis for the extension of this chemistry to the use of cinchona alkaloid-based catalysts in other reactions, by considering their implication in the reaction as a chiral Lewis base and it is in this context in which the first report on organocatalytic conjugate additions can be found in the literature. Initially, Bergstrom and Langström reported the Michael addition of β-keto esters to acrolein using 2-hydroxymethylquinuclidine as catalyst and, although the enantioselectivity was not determined, the authors reported that the final products had optical activity.[14] Subsequently, Wynberg and co-workers carried out extensive research in the use of cinchona alkaloids as promoters for conjugate additions (see the first example reported by the group in Scheme 1.2)[15] and additionally observing that natural cinchona alkaloids were superior catalysts to those in which the C-9 OH group had been modified, which led to the proposal that the cinchona alkaloids played the role of bifunctional catalysts in which the quinuclidine tertiary amine and the free



Scheme 1.3 The Hajos–Parrish–Eder–Sauer–Wiechert reaction.

9-OH groups were participating in the activation of the reagents and facilitating their orientation for achieving high stereocontrol. These works also indicated that H-bonding interactions could be a good element for the activation of molecules without the need for metal-centered Lewis acids.

One of the milestones in the development of organocatalysis is the intramolecular aldol reaction catalyzed by proline developed independently by two industrial research groups at Hoffmann-La Roche[16] and Schering[17] (Scheme 1.3). This reaction, also known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction, was reported in 1971 and is based on the foundations of stoichiometric enamine chemistry by Stork and the mechanistic conclusions driven by Langebeck himself on some enzymatic reactions, and outlines for the first time the reversible formation of a nucleophilic enamine as the key intermediate participating in the catalytic cycle.

Some other very important events in the historic development of asymmetric organocatalysis appeared between 1980 and the late 1990s, such as the development of the enantioselective alkylation of enolates using cinchona-alkaloid-based quaternary ammonium salts under phase-transfer conditions[18] or the use of chiral Brønsted acids by Inoue[19] or Jacobsen[20] for the asymmetric hydrocyanation of aldehydes and imines respectively. These initial reports acted as the launching point for a very rich chemistry that was extensively developed in the following years, such as the enantioselective catalysis by H-bonding activation or the asymmetric phase-transfer catalysis. The same would apply to the development of enantioselective versions of the Morita–Baylis–Hillman reaction,[21] to the use of polyamino acids for the epoxidation of enones, also known as the Julià epoxidation[22] or to the chemistry by Denmark in the phosphoramide-catalyzed aldol reaction.[23]

It was in 2000 that Barbas and List reported their well-known proline-catalyzed enantioselective intermolecular aldol reaction (Scheme 1.4),[24] as the culmination of a research which started in the 1990s with the use of aldolase antibodies as catalysts for the aldol reaction.[25] Trying to provide a mechanistic rationale for understanding these reactions, and with the evidence of enamine intermediates participating in the reaction in hand, they developed the proline-catalyzed intermolecular aldol reaction in an attempt to mimic the enzyme's behavior. Another important landmark in this context was the introduction of the iminium catalysis concept by MacMillan, related to the enantioselective