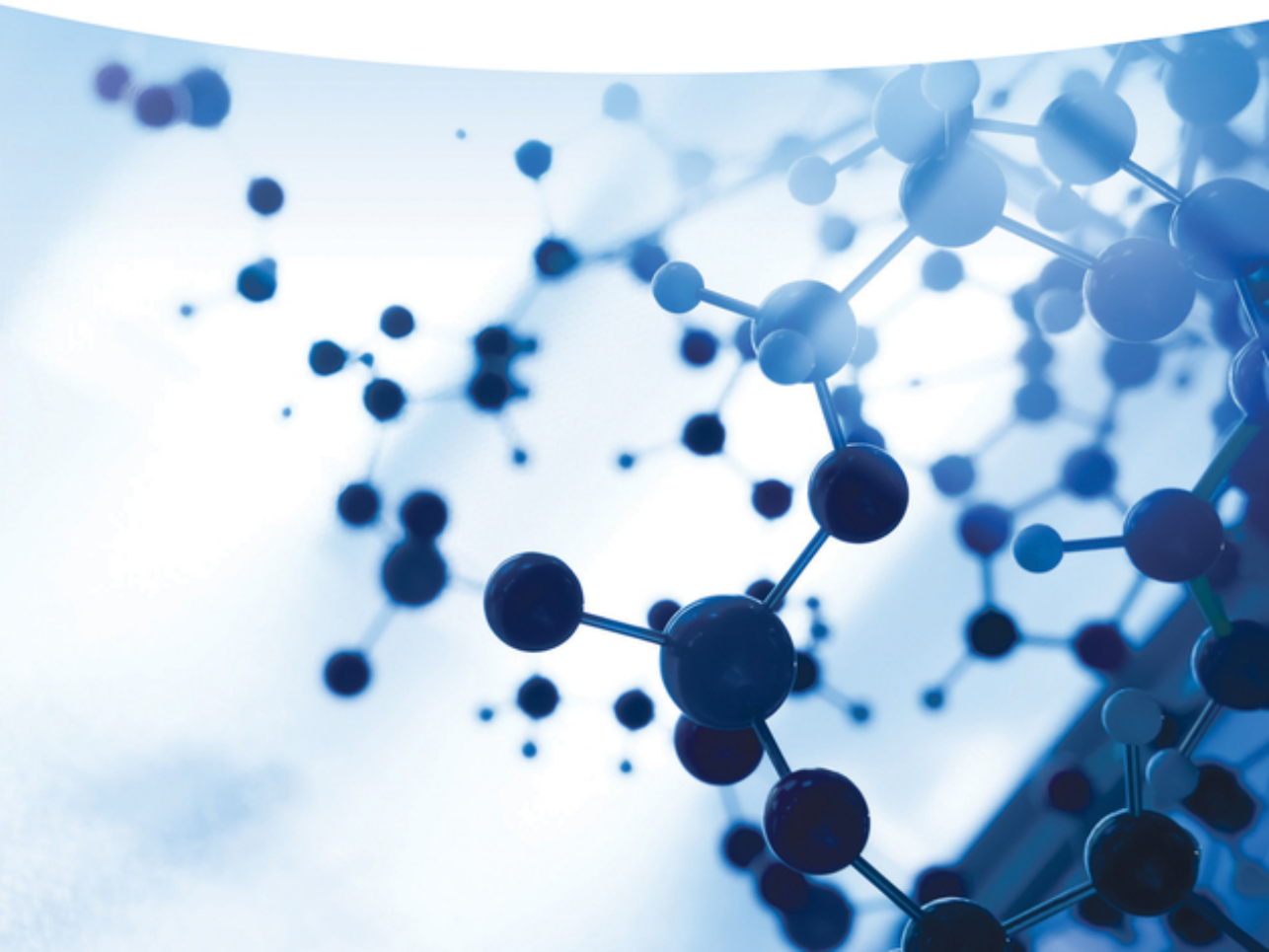
WILEY-VCH

Edited by Łukasz Albrecht, Anna Albrecht,
and Luca Dell'Amico

Asymmetric Organocatalysis

New Strategies, Catalysts, and Opportunities

Volume 1 & 2



Asymmetric Organocatalysis

Asymmetric Organocatalysis

New Strategies, Catalysts, and Opportunities

Volume 1

Edited by Łukasz Albrecht, Anna Albrecht, and Luca Dell'Amico

WILEY-VCH

Editors

Prof. Łukasz Albrecht
Lodz University of Technology
Institute of Organic Chemistry
Żeromskiego 116
90-924 Lodz
Poland

Prof. Anna Albrecht
Lodz University of Technology
Institute of General and Ecological Chemistry
Żeromskiego 116
90-924 Lodz
Poland

Prof. Luca Dell'Amico
University of Padova
Department of Chemical Sciences
Via Marzolo 1
53131 Padova
Italy

Cover Image: © alice-photo/Shutterstock

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-35125-1
ePDF ISBN: 978-3-527-83219-4
ePub ISBN: 978-3-527-83220-0
oBook ISBN: 978-3-527-83221-7

Typesetting Straive, Chennai, India

Dedicated to

*Professor **David W. C. MacMillan** and Professor **Benjamin List** for their outstanding contributions to the field of organocatalysis and to all the researchers around the world who contributed to the field of organocatalysis making it such an inspirational and meaningful area of research*

*In memory of Professor **Carlos F. Barbas III** (1964–2014) who passed away too soon*

Contents

Volume 1

Preface *xiii*

Part I New Catalysts and Activation Strategies in Asymmetric Organocatalysis *1*

1 New Developments in Enantioselective Brønsted Acid Catalysis with Strong Hydrogen Bond Donors *3*
Caroline Dorsch and Christoph Schneider
1.1 Introduction *3*
1.2 Chiral BINOL-Phosphoric Acids in Dehydration Reactions *5*
1.3 Chiral BINSA-Ammonium Salts *9*
1.4 Chiral Cyclopentadienyl-Based Brønsted Acids *12*
1.5 Combined Thiourea-Carboxylic Acids *14*
1.6 Disulfonimides *16*
1.7 Imidodiphoshoric Acids *19*
1.8 Imidodiphosphorimidates *25*
1.9 Silylium Asymmetric Counterion-Directed Catalysis *29*
1.10 Summary and Conclusions *37*
Acknowledgments *37*
References *37*

2 Organosuperbases – Moving Beyond Classical Brønsted Base Catalysis *43*
Azusa Kondoh and Masahiro Terada
2.1 Introduction *43*
2.2 Chiral Cyclopropenimine Catalysts *46*
2.3 Chiral Triaryliminophosphorane Catalysts *48*
2.4 Chiral P1-Phosphazene Catalysts *52*
2.5 Chiral Higher-Order Phosphazene Catalysts *58*
2.6 Other Chiral Strong Brønsted Base Catalysts *62*
2.7 Summary and Conclusions *64*
References *65*

3 Asymmetric Phase-Transfer Catalysis – From Classical Applications to New Concepts *71*
Jan Otevrel and Mario Waser
3.1 Introduction *71*
3.2 Classes of Asymmetric PTCs *73*
3.2.1 Chiral Cation-Based Catalysts *74*
3.2.2 Chiral Anion-Based Catalysts *78*
3.2.3 Uncharged PTCs *80*
3.3 Applications of Chiral PTCs *81*
3.3.1 "Classical" Applications of Quaternary (Amm)-Onium Salts *82*
3.3.2 S_NAr Reactions *83*
3.3.3 Umpolung of Imines *84*
3.3.4 Utilization of Allenoates *86*
3.3.5 Intramolecular Carbo- and Heterocyclization Approaches *87*
3.3.6 Intermolecular Carbo- and Heterocyclization Approaches *89*
3.3.7 Utilization of O-, N-, and S-Nucleophiles *94*
3.3.8 Electrophilic α-Heterofunctionalization Reactions *99*
3.3.9 PTC-Controlled Reactivity of F^+ and F^- Species *101*
3.3.10 Ammonium (Hypo)-Iodite Catalysis *105*
3.3.11 PTCs in Combination with Photochemistry *106*
3.3.12 Bisguanidinium Salt-Catalyzed Oxidations Using Permanganate, Tungstate *107*
3.3.12.1 PTCs in Combination with Transition Metal Catalysis *108*
3.3.13 Synopsis *108*
References *109*

4 Asymmetric Ion-Pairing and H-Bonding Catalysis *121*
Esteban Matador, Rosario Fernández, José M. Lassaletta, and David Monge
4.1 Introduction *121*
4.2 Ion-Pair with Chiral Catalyst-Bound Spectator Anions *122*
4.2.1 Reactions Involving Oxygen-Stabilized Cations *122*
4.2.2 Reactions Involving Nitrogen-Stabilized Cations *126*
4.2.3 Reactions Not Involving Heteroatom-Stabilized Carbocations *132*
4.3 Ion-Pair with Chiral Catalyst-Bound Reactive Ions *134*
4.3.1 Catalyst-Bound Anion Acting as Nucleophile *134*
4.3.2 Catalyst-Bound Oxy-Allyl Cation Acting as Electrophile *136*
4.4 Anion-Binding Catalysis Combined with Other Activation Modes *137*
4.4.1 Merging Anion-Binding with Nucleophilic Catalysis *137*
4.4.2 Merging Anion Binding with Aminocatalysis *140*
4.4.3 Merging Anion Binding with Photochemical Activations *142*
4.5 Summary and Conclusions *143*
References *144*

5 Isothiourea Catalysis – New Opportunities for Asymmetric Synthesis *151*
Alastair J. Nimmo, Claire M. Young, and Andrew D. Smith
5.1 Introduction *151*

5.2 Acyl Transfer Reactions *154*
5.2.1 Acylative Kinetic Resolutions of Alcohols *154*
5.2.2 Acylative Desymmetrization of Diols *158*
5.2.3 N-Acylation *159*
5.2.4 Kinetic Resolutions of Chiral Carboxylic Acid Derivatives *161*
5.2.5 Dynamic Kinetic Resolutions *162*
5.2.6 Enantioselective O–C Acyl Transfer *163*
5.3 Silyl Transfer Reactions *165*
5.4 α,β-Unsaturated Acyl Ammonium Intermediates *166*
5.4.1 Michael Addition-Annulation *166*
5.4.2 Cascade Reactions *170*
5.4.3 Cycloadditions *174*
5.4.4 Catalyst Turnover by Aryloxide *175*
5.5 C(1)-Ammonium Enolates *177*
5.5.1 Surface Modification *180*
5.5.2 Catalyst Turnover by Aryloxide *181*
5.6 Diastereo- and Enantioselective [2,3]-Sigmatropic Rearrangements *188*
5.7 Solid-Supported Catalysis *190*
5.8 Summary and Conclusions *193*
References *193*

6 Halogen-Bonding Organocatalysis – New Opportunities for Asymmetric Synthesis *203*
Mikk Kaasik and Tõnis Kanger
6.1 Introduction *203*
6.2 XB Donors as Organocatalysts *204*
6.3 Solely XB Catalytic Activation in Combination with Asymmetric Counterion-Directed Catalysis *207*
6.4 Asymmetric Catalysis through Solely XB Catalytic Activation *209*
6.5 Bifunctional Catalysts and Co-Catalytic Systems Utilizing XB Activation in Asymmetric Catalysis *211*
6.6 Topics Related to Asymmetric XB Catalysis *215*
6.7 Future Perspectives *217*
6.8 Summary and Conclusions *219*
References *220*

7 Merging Organocatalysis with Light – New Opportunities for Asymmetric Synthesis *225*
José Alemán, Leyre Marzo, Jose A. Fernández-Salas, and Alberto Fraile
7.1 Introduction *225*
7.2 Covalent Catalysis *227*
7.2.1 Dual Amine-Photoredox Catalysis *228*
7.2.1.1 Dual Catalysis: Enamine-Based Strategy *228*
7.2.1.2 Dual Catalysis: Iminium-Based Strategy *233*
7.2.2 Amines as Organo-Photocatalysts *235*
7.2.2.1 Enamine Photo-Organocatalysis *235*

7.2.2.2 Iminium Photo-Organocatalysis *238*
7.2.3 Dual Photoredox-*N*-Heterocyclic Carbene Catalysis *240*
7.3 Asymmetric Photocatalysis Mediated by Non-Covalent Organocatalysis *241*
7.3.1 Stereoinduction in the Ground State *241*
7.3.1.1 Hydrogen Bond Activation *241*
7.3.1.2 Ion Pair Activation *245*
7.3.1.3 Lewis Base Activation *246*
7.3.2 Stereoinduction in the Excited State *247*
7.3.2.1 Hydrogen Bond Activation *247*
7.3.2.2 Ion Pair Activation Mode *249*
7.4 Conclusions *250*
References *250*

8 Asymmetric Electrochemical Organocatalysis: New Opportunities for Synthesis *259*
Yingdong Duan, Qifeng Lin, and Sanzhong Luo
8.1 Introduction *259*
8.2 Organocatalysis in Asymmetric Electrochemical Reactions *260*
8.2.1 Natural Alkaloids *260*
8.2.2 β-Cyclodextrins *261*
8.2.3 Iminium Salts *262*
8.2.4 Aminocatalysts *263*
8.2.5 Hydrogen-Bonding Catalysts *267*
8.3 Summary and Outlook *268*
References *269*

9 Synergistic Organo-Organocatalysis *271*
Fabio Pesciaioli, Valeria Nori, Arianna Sinibaldi, and Armando Carlone
9.1 Introduction *271*
9.1.1 Enamine in Synergistic Organocatalysis *272*
9.1.2 Iminium Ion in Synergistic Organocatalysis *279*
9.1.3 Hydrogen Bonding in Synergistic Organocatalysis *286*
9.1.4 Acids and Bases in Synergistic Organocatalysis *293*
9.1.5 Phase-Transfer Catalysis in Synergistic Organocatalysis *298*
9.1.6 *N*-Heterocyclic Carbenes in Synergistic Organocatalysis *299*
9.2 Summary and Conclusions *309*
References *309*

10 Merging Organocatalysis with Metals – New Opportunities for Asymmetric Synthesis *319*
Ramon Rios
10.1 Introduction *319*
10.2 Metal and Enamine Catalysis *320*
10.3 Combination of a Metal Catalysis and Iminium Chemistry *328*

10.4 Transition Metal and Organocascade (Iminium/Enamine) Activation *331*
10.5 Merging the NHC and Metal Catalyses *339*
10.6 Summary and Conclusions *343*
References *343*

Volume 2

Preface *xv*

11 Immobilized Organocatalysts for Enantioselective Continuous Flow Processes *349*
Carles Rodríguez-Escrich and Miquel A. Pericàs

12 Mechanochemistry and High-Pressure Techniques in Asymmetric Organocatalysis *393*
Rafał Kowalczyk

13 Organocatalytic Reactions Under Nontraditional Conditions *433*
C. Gabriela Ávila-Ortiz, Alberto Vega-Peñaloza, and Eusebio Juaristi

Part II New Organocatalytic Synthetic Methodologies *455*

14 Merging Organocatalysis with Vinylogy – New Opportunities for Asymmetric Synthesis *457*
Claudio Curti, Andrea Sartori, Lucia Battistini, and Franca Zanardi

15 Organocatalytic Umpolung Strategies: Beyond Classical Reactivity Patterns *497*
Sayan Shee, Arghya Ghosh, and Akkattu T. Biju

16 Dearomative Organocatalytic Strategies *539*
Xue Song, Zhi-Chao Chen, Wei Du, and Ying-Chun Chen

17 From Organocatalytic Cycloadditions to Asymmetric Higher-Order Cycloadditions *577*
Karl Anker Jørgensen and K. N. Houk

18 Asymmetric Organocatalysis – From a Process Development Perspective *601*
Hao Jiang, Björn Gschwend, and Yang Li

Part III Mechanisms of Organocatalytic Reactions *633*

19 Computational Studies – A Useful Tool in Elucidation of Mechanisms of Organocatalytic Reactions *635*
Simarpreet Singh, Jorge Dourado, and Rebecca L. Davis

20 A Tutorial on Kinetic-Assisted Mechanistic Analysis in Asymmetric Aminocatalysis *657*
Jordi Burés, Alan Armstrong, and Donna G. Blackmond

21 Mayr Linear Free Energy Relationship: A Powerful Tool for Understanding Aminocatalyzed Reactions *679*
Sami Lakhdar

Index *701*

Preface

Catalysis is one of the most fundamental techniques to promote and kinetically control chemical reactions. Many industrial processes in chemical, pharmaceutical, agrochemical, polymer, and petroleum industries are based on catalysis. The main benefits of catalysis are associated with the high efficiency and atom economy of catalytic processes since catalysts are used in sub-stoichiometric amounts. Furthermore, catalytic technologies save energy and reduce waste generation, time, and costs required to access the intended products. Therefore, such an approach to chemical reactions provides important economic and environmental benefits when compared to classical stoichiometric solutions, placing catalysis among the 12 principles of *green chemistry*. The importance of catalysis has been acknowledged by the Nobel Prize Committee already in 1909, when Ostwald received the Nobel Prize for his pioneering work on catalysis, chemical equilibria, and reaction velocities. Furthermore, since the turn of the millennium three Nobel Prizes in Chemistry have been awarded to scientists developing new concepts in catalysis (2001 – Knowles, Noyori, Sharpless – catalytic asymmetric hydrogenations and oxidations; 2005 – Chauvin, Grubbs, Schrock – development of new catalysts for metathesis reactions; 2010 – Heck, Negishi, Suzuki – transition metal-catalyzed cross-coupling reactions).

On 6 October 2021, by the decision of the Royal Swedish Academy of Sciences, David W. C. MacMillan (Princeton University, United States) and Benjamin List (Max-Planck Institut für Kohlenforschung, Germany) joined this elite group of chemists and were awarded the Nobel Prize "*for the development of asymmetric organocatalysis*." In their justification for the award, the Nobel Committee recognized the Laureates for the conceptual and experimental development of a new tool for the construction of molecules with a well-defined three-dimensional arrangement. Organocatalysis has had an enormous impact on our everyday life, from the development of pharmaceuticals and agrochemicals to the design of new drugs, while making chemistry cheaper and more environmentally friendly.

For many years, the field of asymmetric catalysis has been dominated by transition metal-based catalysts and enzymes. However, in the past 22 years, the catalysis mediated by small organic molecules, commonly known as organocatalysis, has shown its great potential becoming complementary to the existing methods. Organocatalysis is in principle biomimetic, where small organic molecules mimic

chemical and stereochemical behavior of enzymes, without the need of such a complex supramolecular architectures. The field of organocatalysis has grown exponentially becoming a powerful tool for the construction of a broad range of enantiomerically enriched complex scaffolds including many universal synthons, biologically active compounds, and natural products. Over the past years, organocatalysis proved particularly well-suited for large-scale industrial applications. This trend was boosted by its high chemical and stereochemical efficiency, diversity, and the high availability of the organocatalysts that are characterized by relatively low toxicity, as well as air and moisture stability.

We believe that this book collecting contributions prepared by the leading experts in the field of organocatalysis will provide a comprehensive overview of the most important advancements in the area of asymmetric organocatalysis that occurred within the past 10 years. Owing to the implementation of new concepts and ideas such as merging organocatalysis with metal catalysis, photocatalysis, electrocatalysis, or biocatalysis, novel reaction have been developed manifolds. Due to the inspiring nature of these findings, we believe that our contribution will be of interest to all researchers in the field of catalysis, within both academia and industry at different stages of their careers, providing them with detailed information on what has been achieved in the field and indicating the areas of research that still need scientific efforts. We hope that this book will serve to set the principles and become inspiration for the development of the sustainable chemistry for tomorrow.

Łódź, Poland
Padua, Italy
August 2022

Anna Albrecht
Luca Dell'Amico
Łukasz Albrecht

Part I

New Catalysts and Activation Strategies in Asymmetric Organocatalysis

1

New Developments in Enantioselective Brønsted Acid Catalysis with Strong Hydrogen Bond Donors

Caroline Dorsch and Christoph Schneider

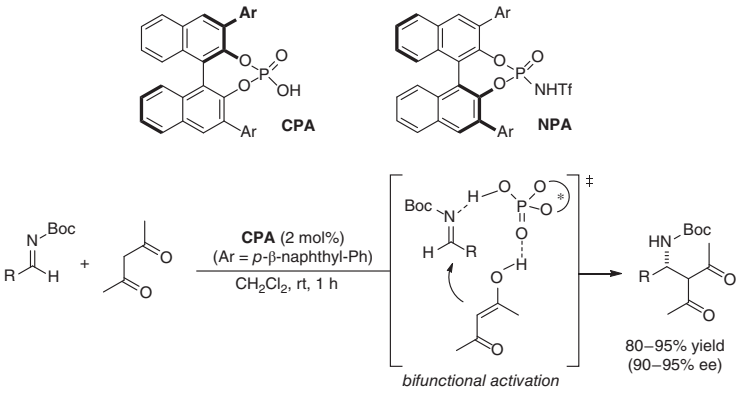
Department of Chemistry, University of Leipzig, Leipzig, Germany

1.1 Introduction

Brønsted acid catalysis, the acceleration of organic reactions with hydrogen bond donors, is a fundamental principle in organic chemistry. It is based upon the protonation to a Brønsted basic substrate upon which its lowest unoccupied molecular orbital (LUMO) orbital is lowered and thus activated toward nucleophilic attack. Early on, it was shown that carbon–carbon bond-forming processes can as well be accelerated by Brønsted acid catalysis like in aldol and Diels–Alder reactions. Quite surprisingly, however, the development of enantioselective Brønsted acid catalysis with chiral hydrogen bond donors is a relatively new field of little more than the last two decades. In 1998, Jacobsen reported the Strecker reaction of aldimines and hydrogen cyanide catalyzed by a bifunctional, chiral thiourea catalyst [1]. This seminal report laid the foundation for the development of a broad range of enantioselective, thiourea-catalyzed carbon–carbon bond-forming reactions [2]. In 2003, Rawal established the capacity of chiral diols to act as hydrogen bond donors for enantioselective hetero Diels–Alder (HDA) and Mukaiyama aldol reactions [3]. Subsequently, chiral, bifunctional squaramides were introduced as hydrogen bond donors with a defined distance of the two hydrogen bonds relative to each other in close analogy to the thioureas [4].

The earlier mentioned chiral catalysts display rather weak Brønsted acidity with pK_a values (in dimethyl sulfoxide [DMSO]) ranging between 12 (squaramides) and 18 (diols) and are proposed to catalyze the respective reactions via hydrogen bonding. On the other hand, much stronger and hence more active chiral Brønsted acids have been developed recently that activate the substrates through protonation and formation of mostly hydrogen-bonded ion pairs. In groundbreaking work published independently by Akiyama [5] and Terada [6] in 2004, the preparation and the first use of 1,1′-bi-2-naphthol (BINOL)-derived, chiral phosphoric acids (CPA) in Mannich reactions have been documented (Scheme 1.1). Their higher Brønsted acidity (pK_a = 3.4 (DMSO), 13.3 (MeCN)) and the rigid chiral BINOL backbone make them powerful chiral catalysts, in particular, for imine addition

Asymmetric Organocatalysis: New Strategies, Catalysts, and Opportunities, First Edition.
Edited by Łukasz Albrecht, Anna Albrecht, and Luca Dell'Amico.

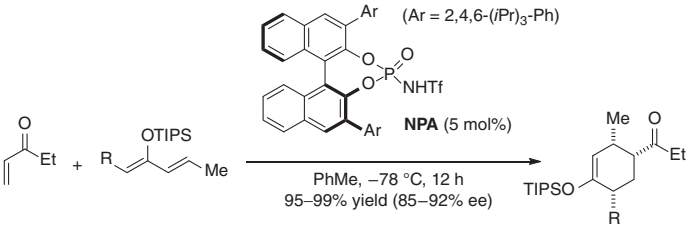


Scheme 1.1 BINOL-based phosphoric acid-catalyzed Mannich reaction [6].

reactions. In addition to the acidic OH moiety, the Brønsted basic phosphoryl oxygen atom provides the opportunity for bifunctional activation due to additional hydrogen bonding of the nucleophile resulting in a highly ordered transition state assembly of nucleophile and electrophile. These seminal reports have provided the basis for a wealth of subsequent applications of these catalysts [7].

It is important to emphasize here the role of the bulky 3,3′-aryl groups within the backbone of the catalyst, which extends the C_2-symmetry of the BINOL architecture into space and thereby creates an enlarged chiral pocket in which the reaction takes place with high enantiofacial control. Due to their basicity, imines are ideal substrates in that respect, which are readily protonated and form closely associated ion pairs composed of iminium cations hydrogen bonded to chiral phosphate anions.

In order to also activate less basic substrates such as carbonyl compounds, the phosphoric acid catalysts have been modified into more acidic *N*-triflyl phosphoramides (NPA) ($pK_a = -3.4$ (DMSO), 6.4 (MeCN)). With NPAs in hand, Yamamoto was able to catalyze the Diels–Alder reaction of silyloxy dienes and α,β-unsaturated ketones with excellent enantioselectivity, low catalyst loading, and at a low temperature (Scheme 1.2) [8].



Scheme 1.2 *N*-triflyl phosphoramide-catalyzed Diels–Alder reaction [8].

This class of strongly acidic Brønsted acids has later been routinely employed as an alternative to the classical phosphoric acids whenever higher Brønsted acidity was required [9]. Further modification of the phosphoryl oxygen moiety into the

corresponding thiophosphoryl and selenophosphoryl groups is easily possible and results in yet enhanced Brønsted acidity of the *N*-triflyl phosphorthioamides and *N*-triflyl phosphorselenoamides, respectively, e.g. for protonation and Mukaiyama aldol reactions [10].

In this chapter, we will focus on select newer applications of these catalysts in recent years as well as further developments toward yet stronger and more refined chiral Brønsted acids. For ease of understanding, we will use the abbreviation CPA for chiral phosphoric acids and NPA for *N*-triflyl phosphoramides and specify only the different 3,3′-aryl groups (Ar) employed in the individual reactions. Due to limited space, this chapter cannot possibly be comprehensive and therefore reflects more a personal selection of the authors. For more detailed information on the characteristics and applications of BINOL-phosphoric acids and amides as Brønsted acid catalysts and further developments in the field, the reader is referred to excellent review articles that have appeared recently [7 and 9].

1.2 Chiral BINOL-Phosphoric Acids in Dehydration Reactions

The early focus of CPA catalysis was the activation of imines, aldehydes, and ketones. In recent years, other substrates have been studied as well that are prone to Brønsted acid activation. For example, benzyl alcohols are easily dehydrated into benzyl cations under Brønsted acid catalysis and may subsequently be reacted with a broad range of nucleophiles. The principal difference in comparison to the earlier mentioned substrates concerns the nature of the ion pair. Whereas iminium and oxonium phosphate ion pairs are closely connected through a strong hydrogen bond, the benzyl phosphate ion pair is only loosely held together by purely electrostatic interactions lacking any directional interaction through a hydrogen bond. Thus, it is anything but easy for the chiral anion to provide an effective chiral environment that results in high enantioselectivity of the ensuing reaction.

To overcome this problem, an *ortho*-phenol moiety has been introduced into the benzyl alcohol and substrates such as **1** have been investigated. Upon Brønsted acid-catalyzed dehydration, the resulting cation may be hydrogen bonded to the chiral phosphate anion X* through the adjacent phenol moiety (Figure 1.1). The prevailing resonance structure of this cation is the corresponding *ortho*-quinone methide **2** connected to the chiral phosphate anion X* via a hydrogen bond [11].

In the last years, the Schneider group investigated this concept in detail and developed a broad range of cycloaddition reactions using hydrogen-bonded *ortho*-quinone methides as transient intermediates [12]. Thus, a broad variety of benzannulated

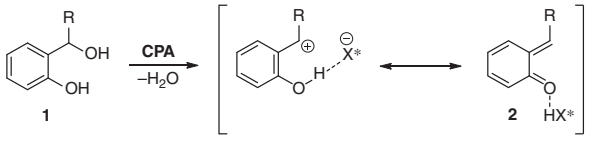
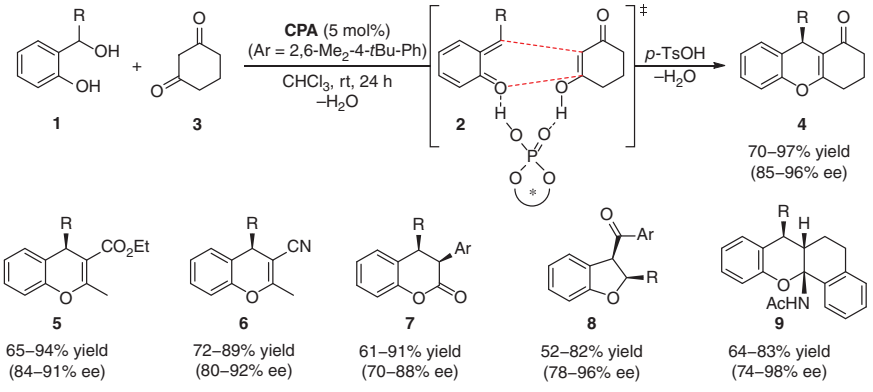


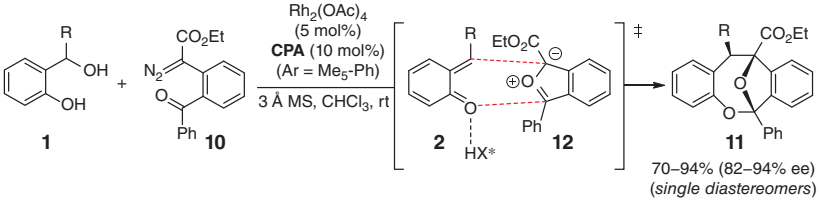
Figure 1.1 Dehydration of *ortho*-hydroxy benzyl alcohols 3 to *ortho*-quinone methides 2.

oxygen heterocycles **4**–**9** have been prepared in a highly straightforward fashion with excellent enantioselectivity starting from *ortho*-hydroxy benzyl alcohols **1** and enol-rich β-diketones **3**, aldehydes as well as enamides and α-diazo ketones (Scheme 1.3). The dihydrocoumarins **7** and dihydrofurans **8** were obtained with good *cis*-diastereoselectivity as well, whereas the acetamidotetrahydroxanthenes **9** were isolated even as single diastereomers.



Scheme 1.3 Phosphoric acid-catalyzed cycloadditions of *ortho*-quinone methides [12].

The earlier depicted reaction with 1,3-cyclohexane dione **3** (Scheme 1.4) has been investigated in detail by thorough kinetic, spectroscopic, and theoretical studies providing a detailed mechanistic picture. After a rate-determining dehydration event to furnish the hydrogen-bonded *ortho*-quinone methide **2**, the cycloaddition took place in a concerted, yet highly asynchronous manner with the C–C-bond formation preceding the C–O-bond formation. It proved to be mandatory for reactivity as well as enantioselectivity that the dienophile carried an acidic proton capable of hydrogen bonding to the phosphoric acid catalyst in accord with the assumption of a bifunctional activation of both reaction partners in a highly ordered transition state.



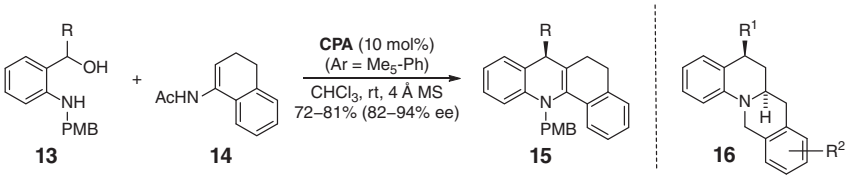
Scheme 1.4 Cooperative Rh-/phosphoric acid-catalyzed cycloaddition with diazo esters [13].

This concept was subsequently merged with transition metal catalysis. Thus, it was shown that a cooperative Rh-/phosphoric acid-catalyzed reaction of *ortho*-quinone methides with diazo esters **10** delivered densely substituted and highly functionalized chromanes and oxa-bridged dibenzooxacines **11** with good yields,

excellent enantioselectivity, and complete diastereoselectivity (Scheme 1.4) [13]. It is noted that both transient intermediates, the *ortho*-quinone methide **2** and the carbonyl ylide **12**, are generated in only catalytic amounts in two separate catalytic cycles that are merged in the stereoselectivity-determining (4+3)-cycloaddition.

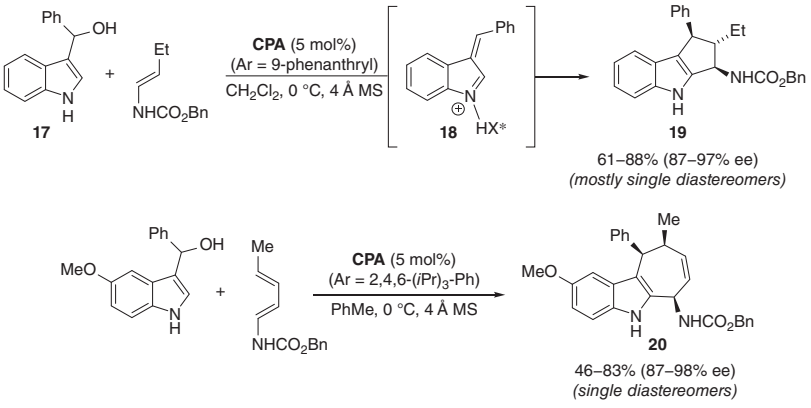
Sterically, more hindered β, β-disubstituted *ortho*-quinone methides were shown by Sun to undergo transfer hydrogenation with Hantzsch esters under CPA catalysis to produce 1,1-diaryl ethanes with good enantioselectivity [14]. In addition, highly enantioselective Diels–Alder reactions were reported with simple alkenes by Rueping and 2-vinyl indoles by Shi [15]. In the former case, it was unexpected that high enantioselectivity was obtained by single-point activation of merely the *ortho*-quinone methide.

This strategy was successfully extended to transformations of transient *ortho*-quinone methide imines (or aza-*ortho*-quinone methides), which are readily available from the corresponding anilines likewise. The reaction of *ortho*-amino benzyl alcohol **13** with enamides **14** under phosphoric acid catalysis delivered tetrahydroacridines **15** with good chemical yields and enantioselectivity (Scheme 1.5) [16]. The reaction could as well be run in an intramolecular fashion to assemble benzannulated quinolizidines **16** with an NPA as catalyst [17]. As the preparation of the aniline was accomplished through reductive amination under Brønsted acid catalysis, it could be elegantly coupled to the actual aza-Diels–Alder reaction in a one-pot process.



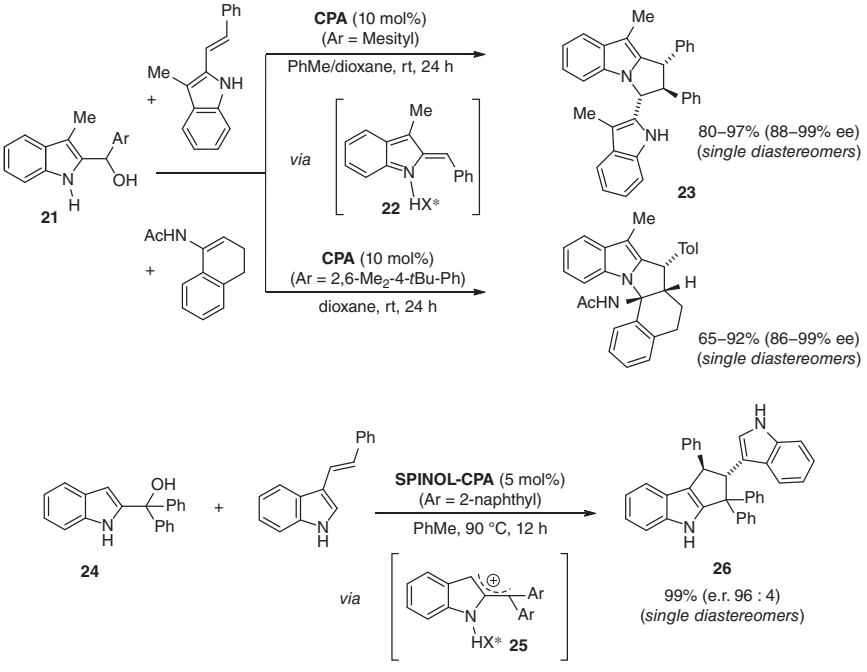
Scheme 1.5 Phosphoric acid-catalyzed cycloaddition of *ortho*-quinone methide imines [16].

Electron-rich heteroaryl carbinols such as indolyl-3-carbinols **17** have been employed in the same reaction manifold [18]. Again, the mesomeric effect of the nitrogen lone pair helps stabilize the transient cation in the form of a 3-alkylidene indoleninium cation **18** and provides an excellent binding opportunity for the CPA catalyst. At the same time, the nucleophile can be coordinated to the bifunctional catalyst via a second hydrogen bond. Gong and Rueping first showed that enamides can be employed as nucleophiles in the course of a highly enantioselective conjugate addition under phosphoric acid catalysis [19]. Later, You, Peng, and Shi established similar protocols with different substrates and nucleophiles [20]. Building on this precedence, Masson developed a very elegant (3+2)-cycloaddition of 3-alkylidene 3*H*-indoles and enecarbamates to produce amino-substituted cyclopenta[b]indoles **19** with excellent enantioselectivity and perfect diastereoselectivity (Scheme 1.6) [21]. More recently, Masson was able to extend this scheme to highly enantioselective (4+3)-cycloadditions with 1-amino-substituted butadienes toward the synthesis of cyclohepta[b]indoles **20** [22].



Scheme 1.6 Phosphoric acid-catalyzed cycloadditions of 3-alkylidene 3H-indoles [21, 22].

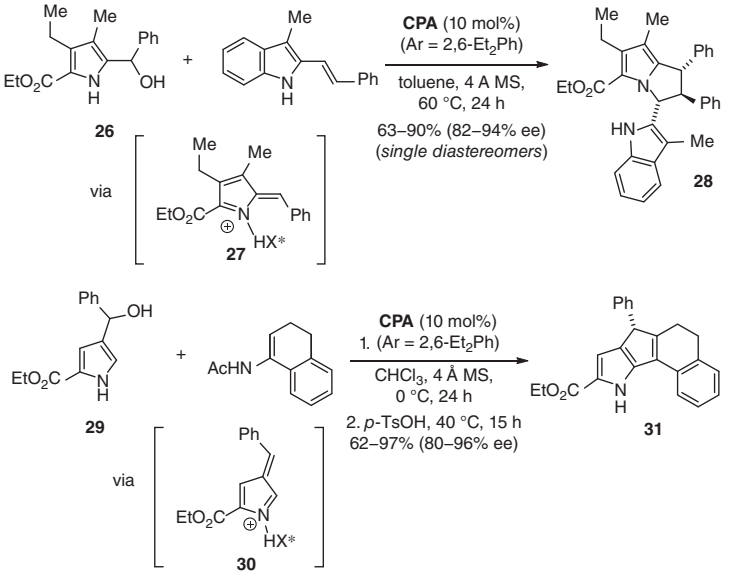
Indolyl-2-carbinols **21** have been shown to also participate in cycloaddition reactions via the corresponding hydrogen-bonded 2-alkylidene 2*H*-indoles **22** [18]. Building upon the first precedence established by Han [23], Schneider disclosed a phosphoric acid-catalyzed (3+2)-cycloadditions with 2-vinyl indoles and enamides to produce complex pyrrolo[1,2-a]indoles **23** with excellent yields and stereocontrol (Scheme 1.7, top) [24].



Scheme 1.7 Phosphoric acid-catalyzed cycloadditions of 2-alkylidene 2H-indoles [24].

An elegant, highly stereoselective (3+2)-cycloaddition of indolyl-2-diaryl carbinols **24** with 3-vinyl indoles to furnish cyclopenta[b]indoles **26** was developed by Shi [25] (Scheme 1.7, bottom). This reaction exploits the electrophilic character of the delocalized and 3-unsubstituted 2-alkylidene indoleninium cation **25** so that the 3-vinyl indole first adds to the now electrophilic indole-3-position followed by cyclization via the now nucleophilic exocyclic 2-alkylidene indole.

More recently, this strategy was extended to reactions of electronically fine-tuned, phosphoric acid-bound 2-alkylidene-2*H*-pyrroles **27** that were obtained by acid-catalyzed dehydration of the corresponding pyrrolyl-2-carbinols **26**. When treated with 2-vinyl indoles at elevated temperatures, 2,3-dihydro-1*H*-pyrrolizines **28** were isolated as single diastereomers, with good yields and enantioselectivity (Scheme 1.8) [26a]. Likewise, cyclopenta[b]pyrroles **31** were successfully obtained in a (3+2)-cycloaddition with enamides from pyrrolyl-3-carbinols **29** via the corresponding 3-alkylidene-3-pyrroles **30** after an acid-mediated elimination of acetamide [26b].



Scheme 1.8 Phosphoric acid-catalyzed (3+2)-cycloaddition of 2- and 3-alkylidene pyrroles [26].

1.3 Chiral BINSA-Ammonium Salts

While a phosphoric acid is ideally suited to be incorporated into a rigid BINOL backbone to form a monobasic, CPA diester, other Brønsted acids have emerged in recent years as well as chiral organocatalysts. Ishihara and coworkers have worked extensively on the development and applications of chiral 1,1′-binaphthyl-2,2′-disulfonic acids (BINSAs) [27]. In independent work, the List group has pioneered the use of this catalyst architecture for their disulfonyl imides and employed it mainly for

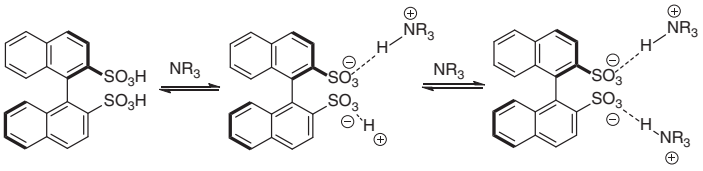
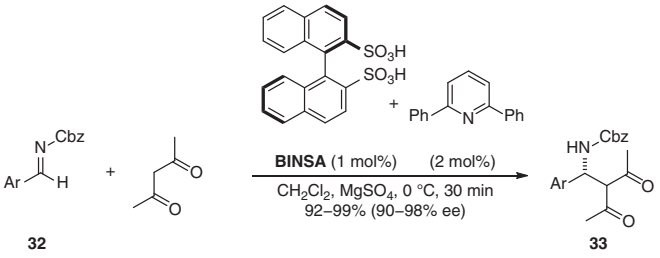


Figure 1.2 Chiral BINSA-ammonium salts.

Mukaiyama-type reactions of silicon nucleophiles (vide infra) [28]. Synthetically, BINSA catalysts are available from the parent BINOLs by a microwave-induced Newman–Kwart rearrangement of the corresponding *O*-thiocarbamoyl derivatives and further modifications.

The enhanced Brønsted acidity associated with them ($pK_a = -9.1$, DMSO) allows for easy and flexible complexation with amines to furnish chiral ammonium salts that retain a good part of their original acidity depending on the number of complexed amines. One can assume that a dynamic equilibrium exists between mono- and diammonium salt formation and that the monoammonium salt is most likely the active catalyst in most cases due to its higher Brønsted acidity. At the same time, this acid–base complexation can enhance its solubility in nonpolar organic solvents. In terms of enantioselectivity, the amine components have been shown to successfully take the stereocontrolling role of the 3,3′-BINOL-substituents of the CPA's obviating the need to install them into the BINOL backbone in a lengthy procedure (Figure 1.2).

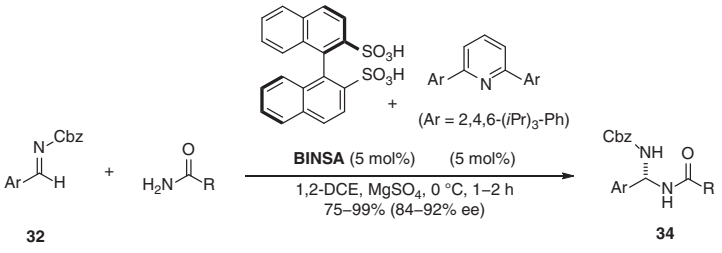
Thus, Ishihara and coworkers reported the Mannich reaction of acetylacetone with Cbz-protected imines **32** that was catalyzed by 1 mol% of the parent BINSA in combination with 2 mol% of 2,6-diphenyl pyridine. The reactions were completed within only 30 minutes at 0 °C in CH_2Cl_2 in the presence of $MgSO_4$. Excellent yields and enantioselectivities for the resulting β-amino diketones **33** were obtained across a broad range of aryl imines and β-diketones (Scheme 1.9) [27a]. In place of β-diketones, *N*-benzyl pyrroles have been employed as nucleophiles in aza-Friedel–Crafts reactions, which proceeded with moderate to good enantioselectivity [27b].



Scheme 1.9 BINSA-ammonium salt-catalyzed Mannich reaction [27a].

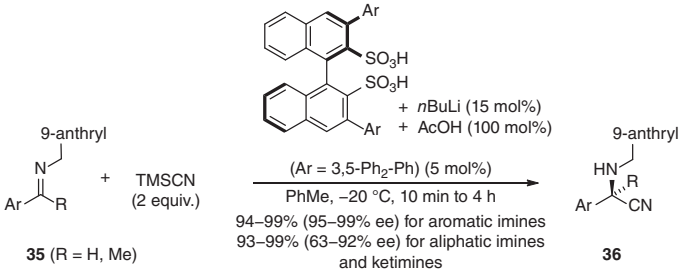
The reaction could be successfully extended to heteronucleophiles as well. The addition of amides and carbamates to Cbz-protected aryl imines proceeded under

BINSA-ammonium salt catalysis within a short reaction time at 0 °C and delivered aminals **34** with good yields and enantioselectivity (Scheme 1.10) [29]. Here, the BINSA-amine stoichiometry was just 1:1 pointing to a predominant chiral mono-ammonium salt as chiral catalyst.



Scheme 1.10 BINSA-ammonium salt-catalyzed aminal formation [29].

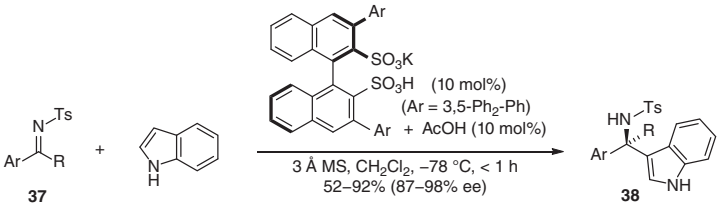
In subsequent studies, the Ishihara group found that Lewis acid-BINSA combinations furnished highly acidic chiral catalysts for otherwise difficult to realize carbon–carbon-forming reactions. After a first report on the $La(OPh)_3$-BINSA-catalyzed Strecker reaction of aldimines with trimethylsilyl cyanide (TMSCN) [30], they discovered that the dilithium BINSA-salt was able to catalyze a very rapid Strecker reaction of both aldimines and ketimines **35** with TMSCN in combination with acetic acid to deliver α-amino nitriles **36** with exceptional yields and enantioselectivities (Scheme 1.11) [31]. A pentacoordinate lithium cyano silicate was proposed as the catalytically active species that transfers the cyanide to the imine in an acid–base cooperative pathway. For this reaction, the authors had to employ a BINSA-backbone with sterically encumbered 3,3′-substituted aryl groups to achieve high enantioselectivity. Aromatic imines gave rise to consistently greater than 95% ee, whereas aliphatic aldimines and ketimines furnished products with 63–92% ee depending mainly on the steric bulk of the alkyl group.



Scheme 1.11 BINSA-dilithium salt-catalyzed Strecker reaction [31].

Following the concept of Lewis acid-activated chiral Brønsted acids originally formulated by Yamamoto [32], Ishihara and coworkers developed a BINSA-monopotassium salt-catalyzed Friedel–Crafts reaction of tosyl imines and indoles. Unlike previous examples, this process features the first application of nonactivated

ketimines **37** as reaction partners that gives rise to products **38** carrying a quaternary stereogenic center with excellent yields and enantioselectivities across a wide range of aromatic and heteroaromatic imines [33]. The addition of acetic acid had a beneficial effect on the rate of the reaction most likely through supporting the turnover of the catalytic cycle. Aliphatic ketimines, however, were not generally applicable in this reaction (Scheme 1.12).



Scheme 1.12 BINSA-mono potassium salt-catalyzed indole addition [33].

Moreover, a cycloaddition between *N*-Boc-imines and styrenes was successfully catalyzed with a chiral Mg-K-BINSA-cluster in close analogy to the previous work of Ishihara to provide oxazinanones from simple substrates with high yields and excellent enantio- and diastereocontrol in a one-step process [34].

1.4 Chiral Cyclopentadienyl-Based Brønsted Acids

The Lambert group has pioneered the development and first synthetic applications of cyclopentadienyl-based, chiral Brønsted acids. This work was undertaken under the consideration of the significant acidity of cyclopentadiene ($pK_a = 18$ in DMSO), which is the result of the stable, aromatic cyclopentadienyl anion. Adding five electron-withdrawing ester groups around the core of the cyclopentadiene, the Brønsted acidity was further increased to a remarkable value of $pK_a = 8.9$ (MeCN) which is about four orders of magnitude more acidic than the classic phosphoric acids. The synthesis of this new scaffold is straightforward and requires only a single synthetic step from dimethyl malonate and dimethylacetylene dicarboxylate. More importantly, simple transesterification with commercially available (–)-menthol produced the chiral pentacarboxymenthyl cyclopentadiene (PCCP) **39** (Figure 1.3) [35]. Both the crystal structure of the corresponding ammonium salt and DFT

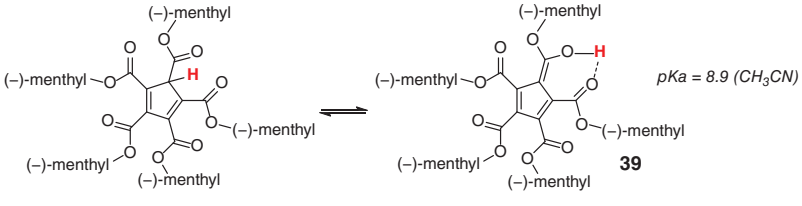
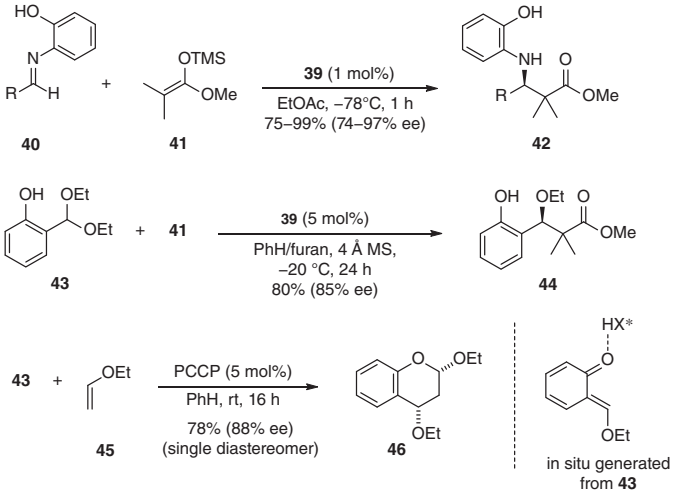


Figure 1.3 PCCP catalyst 39 [35].

calculations revealed a helical chiral arrangement of **39** with the five ester groups strongly geared to one another. Apparently, the central chirality of the five menthol groups has been efficiently transmitted to a powerful helical chirality, which is presumed to be responsible for the enantioselectivity of the ensuing reactions.

In direct comparison with the CPA-catalyzed Mukaiyama–Mannich reaction of imines **40** and silyl ketene acetal **41** developed by Akiyama [5], the new PCCP catalyst **39** displayed strongly enhanced activity while maintaining high enantioselectivity. Thus, Mannich product **42** was obtained in 97% yield and 97% ee after only 1 h at –78 °C with just 1 mol% of catalyst (Scheme 1.13, top). The catalyst loading could be further lowered to 0.01 mol% with no loss of enantioselectivity albeit after an extended reaction time of 48 hours. However, α-substituted, prostereogenic silylketene acetals were not viable substrates for this reaction as they did not provide good levels of additional diastereoselectivity.

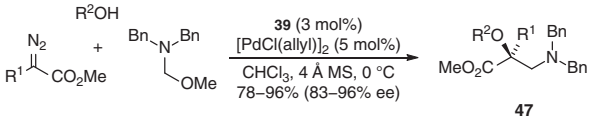


Scheme 1.13 PCCP-catalyzed Mukaiyama–Mannich-, oxonium-aldol, and oxa-Diels–Alder reactions [35, 36].

Likewise, the oxonium-aldol reaction between salicylaldehyde diethyl acetal **42** and silyl ketene acetal **41** provided aldol products **44** with good yields and good levels of enantioselectivity under PCCP catalysis (Scheme 1.13, middle). The additional hydrogen bonding capability of the phenol moiety as we had seen before in the *ortho*-quinone methides was essential to coordinate the chiral anion and establish a highly ordered transition state assembly.

Highly enantioselective oxa-Diels–Alder reactions of β-alkoxy-substituted *ortho*-quinone methides, generated in situ through acid-catalyzed dehydration of salicylaldehyde diethyl acetal **43**, and vinyl ethers **45** provided 2,4-dialkoxy chromans **46** with good levels of enantioselectivity and as mostly single diastereomers (Scheme 1.13, bottom) [36]. Here, a thoroughly optimized chiral PCCP catalyst derived from *trans*-2-*para*-methoxyphenyl-1-cyclohexanol was employed to achieve the optimal enantiocontrol.

In a cooperative approach, Hu and coworkers merged Pd and PCCP catalysis to assemble highly valuable α-alkoxy-β-amino esters **47** carrying a quaternary chiral center with excellent enantioselectivity (Scheme 1.14) [37]. The three-component reaction starting from a diazo compound, an alcohol, and α-aminomethyl ether proceeded via the intermediate generation of an enol intermediate from the diazoester and the alcohol, which was subsequently trapped by the methylene iminium ion in a hydrogen bonding network enabled by the chiral PCCP catalyst.



Scheme 1.14 Pd-/PCCP-cocatalyzed aminomethylation reaction [36].

1.5 Combined Thiourea-Carboxylic Acids

Although simple chiral carboxylic acids, from natural sources or handmade, are among the most obvious choices for chiral Brønsted acid catalysts, they have not been frequently employed for enantioselective transformations with the notable exception of the BINOL-derived dicarboxylic acids by Maruoka and his coworkers [38]. In most cases, their Brønsted acidity is lower than that of the examples discussed earlier so that only sufficiently basic substrates can be employed. In other cases, their synthesis just requires too many synthetic steps.

To address these shortcomings, the Seidel group has conceptualized a new approach. Drawing from precedence established by Jacobsen on the cocatalysis of thioureas with Brønsted acids [39], they designed a new bifunctional catalyst **48** that combines a simple brominated benzoic acid tethered to a thiourea moiety (Figure 1.4) [40]. The anion-binding ability of the thiourea helps stabilize the conjugate base of the benzoic acid internally, thus enhancing its acidity significantly. At the same time, a structurally well-organized substrate catalyst ion pair is formed with attenuated hydrogen bonding ability of the catalyst to the substrate, which increases the electrophilicity of the latter. A straightforward two-step synthesis has been developed to rapidly access this catalyst class that allows structural modifications easily. Moreover, the Brønsted acidity has been determined with $pK_a = 12.4$ (CH_3CN), which is about one order of magnitude more acidic than the classic CPAs [40e].

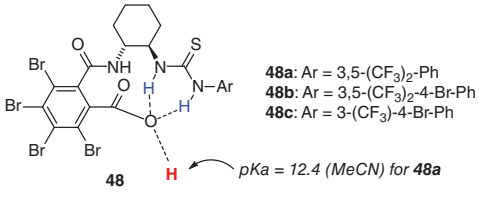


Figure 1.4 Combined thiourea-carboxylic acid 48 [40].