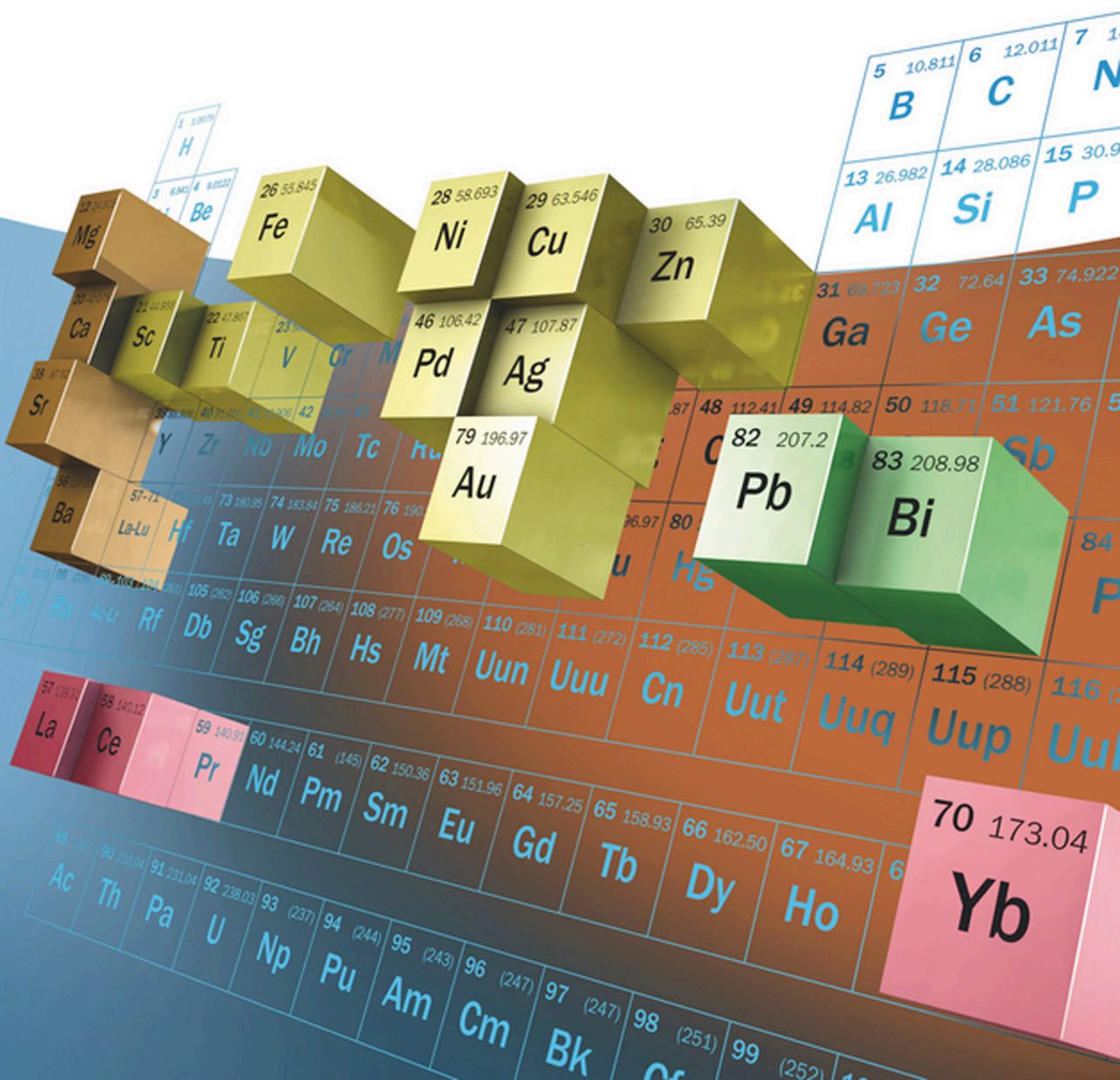


Edited by Jacek Mlynarski

Chiral Lewis Acids in Organic Synthesis



Chiral Lewis Acids in Organic Synthesis

Chiral Lewis Acids in Organic Synthesis

Edited by
Jacek Mlynarski

WILEY-VCH

Editor

Prof. Jacek Mlynarski
Jagiellonian University
Faculty of Chemistry
Ingardena 3
30-060 Krakow
Poland

■ All books published by **Wiley-VCH** are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

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>>.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Boschstr. 12, 69469 Weinheim, Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Print ISBN: 978-3-527-34129-0

ePDF ISBN: 978-3-527-80213-5

ePub ISBN: 978-3-527-80215-9

Mobi ISBN: 978-3-527-80216-6

oBook ISBN: 978-3-527-80214-2

Cover Design Formgeber, Mannheim, Germany

Typesetting SPi Global Private Limited, Chennai, India

Printing and Binding

Printed on acid-free paper

Contents

List of Contributors *xi*

Preface *xiii*

- 1 Alkaline-Earth Metal-Based Chiral Lewis Acids** *1*
Anna Domżalska, Artur Ulikowski and Bartłomiej Furman
- 1.1 Introduction *1*
- 1.2 General Properties of Alkaline Earth Metal Compounds *1*
- 1.3 Applications in Asymmetric Synthesis *2*
- 1.3.1 Cycloaddition Reactions *2*
- 1.3.2 Carbonyl and Imine Addition Reactions *8*
- 1.3.3 Conjugate Addition Reactions *14*
- 1.3.4 Other Reactions *21*
- References *23*
- 2 Titanium-Based Chiral Lewis Acids** *27*
Jun Wang and Xiaoming Feng
- 2.1 Introduction *27*
- 2.2 Asymmetric Addition of Carbon Nucleophiles to Carbonyl Compounds *27*
- 2.3 Asymmetric Cyanide Addition Reaction *30*
- 2.4 Asymmetric Epoxidation *31*
- 2.5 Asymmetric Darzens Reaction *35*
- 2.6 Asymmetric Ring-opening Reaction *36*
- 2.7 Asymmetric Sulfoxidation Reaction *39*
- 2.8 Asymmetric Hetero-Diels–Alder (HDA) Reaction *42*
- 2.9 Asymmetric Fluorination of 1,3-Dicarbonyl Compounds *44*
- 2.10 Asymmetric Sulfenylation of 1,3-Dicarbonyl Compounds *45*
- 2.11 Asymmetric Formal Intramolecular C(sp²)–H Insertion of *N*-Aryl α -Diazoamides *46*
- 2.12 Asymmetric Reduction of Ketones *46*
- 2.13 Asymmetric Hydroalkoxylation of Nonactivated Alkenes *47*
- 2.14 Asymmetric Titanium(III)-Catalyzed Reductive Coupling Reactions *47*
- 2.15 Asymmetric 1,3-Dipolar Cycloaddition of Nitron and Unsaturated Aldehyde *50*
- 2.16 Asymmetric Friedel–Crafts Alkylation Reaction *51*

2.17	Conclusions	52
	Acknowledgments	53
	References	53
3	Iron-based Chiral Lewis Acids	59
	<i>Thierry Ollevier</i>	
3.1	Introduction	59
3.2	Chiral Iron Porphyrins	59
3.3	Chiral Iron Bipyridines	62
3.4	Chiral Salen–Salan Lewis Acid Catalysts	66
3.4.1	Chiral Schiff-based and Salen Lewis Acids	66
3.4.2	Chiral Salan Lewis Acids	69
3.5	<i>Bis(oxazoline)</i> Lewis Acid Catalysts	72
3.6	Pyridine <i>Bis(oxazoline)</i> Lewis Acid Catalysts	75
3.7	Diamine-derived Lewis Acid Catalysts	80
3.8	Diphosphine-derived Lewis Acid Catalysts	84
3.9	Binaphthyl-derived Lewis Acid Catalysts	91
3.10	Other Iron Lewis Acids	93
3.11	Conclusions	95
	Acknowledgments	95
	References	96
4	Copper-based Chiral Lewis Acids	103
	<i>Karthikeyan Iyanar and Mukund P. Sibi</i>	
4.1	Introduction	103
4.2	Conjugate Additions	104
4.2.1	Michael Addition	104
4.2.2	Mukaiyama–Michael Addition	107
4.3	Mannich-Type Reaction	107
4.4	Aldol-Type Reactions	109
4.4.1	Asymmetric Aldol Reaction	109
4.4.2	Nitro-aldol Reaction	109
4.4.3	Aza-Henry Reaction	109
4.4.4	Mukaiyama Aldol Reaction	112
4.5	Asymmetric Friedel–Crafts Alkylation	112
4.6	Cycloadditions	113
4.6.1	Diels–Alder Reaction	113
4.6.2	1,3-Dipolar Cycloaddition	116
4.6.3	[3+2]-Cycloaddition	117
4.6.4	[4+1] Cycloaddition	118
4.6.5	[6+3] Cycloaddition	118
4.7	Cyclization Reactions	119
4.7.1	Intramolecular Cyclization	119
4.7.2	Intermolecular Cyclization	120
4.7.3	Reductive Cyclization	121
4.7.4	Ring-Opening Cyclization	122
4.8	Kinetic Resolution	123

- 4.9 Desymmetrization 123
- 4.10 Trifluoromethylation 124
- 4.11 Halogenation 125
 - 4.11.1 Enantioselective Chlorination 125
 - 4.11.2 Asymmetric Chloro/Fluorination 125
- 4.12 Reductions 126
 - 4.12.1 Hydrosilane Reduction 126
 - 4.12.2 Hydrosilylation of Allene 126
 - 4.12.3 Amination Reaction 126
- 4.13 Other Reactions 127
 - 4.13.1 Aziridination 127
 - 4.13.2 Annulation Reaction 128
 - 4.13.3 Amino Lactonization 128
 - 4.13.3.1 Arylation of Ketone 129
 - 4.13.5 Allylic Oxidation 129
 - 4.13.6 Carbenoid Insertion 130
 - 4.13.6.1 C–H Insertion 130
 - 4.13.6.2 Phenolic O–H Insertion 131
 - 4.13.7 Alkynylation 131
- 4.14 Conclusions 132
- References 133

- 5 Zinc-based Chiral Lewis Acids 137**
Sebastian Baś, Marcin Szewczyk and Jacek Mlynarski
- 5.1 Introduction 137
- 5.2 Zinc Abundance in Nature 137
- 5.3 Carbon–Carbon Bond Formation 138
 - 5.3.1 Direct Aldol Reaction 138
 - 5.3.2 Mannich Reaction 144
 - 5.3.3 Michael Addition 147
 - 5.3.4 Addition to Carbonyl Group 151
 - 5.3.5 Cycloaddition 153
 - 5.3.6 Friedel–Crafts Reaction 157
 - 5.3.7 Other Reactions 162
- 5.4 Carbon–Hydrogen Bond Formation 162
 - 5.4.1 Reduction of Ketones 162
 - 5.4.2 Reduction of Imines 165
- 5.5 Carbon–Oxygen Bond Formation 169
- 5.6 Carbon–Phosphorus Bond Formation 171
 - 5.6.1 Phospha-Michael Addition 172
 - 5.6.2 Hydrophosphonylation 174
- References 176

- 6 From Noble Metals to Fe-, Co-, and Ni-based Catalysts: A Case Study of Asymmetric Reductions**
Jadwiga Gajewy, Daniel Łowicki and Marcin Kwit
- 6.1 Introduction 183

6.2	Brief Historical Background – “From the Golden Age to the Iron Age”	184
6.3	Development of New Methods for Asymmetric Reduction	189
6.4	Some Mechanistic Considerations	190
6.5	Reduction of C=C Bond – Asymmetric Hydrogenation	196
6.5.1	Noble Metal Catalysts	196
6.5.1.1	Rhodium-based Catalysts	196
6.5.1.2	Ruthenium-based Catalysts	198
6.5.1.3	Iridium-based Catalysts	198
6.5.1.4	Palladium-, Platinum- and Gold-based Catalysts	199
6.5.2	Non-noble Metal Catalysts	199
6.5.2.1	Titanium- and Zirconium-based Catalysts	200
6.5.2.2	Cobalt-based Catalysts	200
6.5.2.3	Nickel- and Iron-based Catalysts	201
6.6	Asymmetric Reductions of C=O bonds	201
6.6.1	Asymmetric Hydrogenation of Ketones	201
6.6.1.1	Iron-based Catalysts	201
6.6.1.2	Copper-based Catalysts	203
6.6.1.3	Nickel-based Catalysts	204
6.6.1.4	Osmium-based Catalysts	204
6.6.2	Asymmetric Transfer Hydrogenation of Ketones	206
6.6.2.1	Iron-based Catalysts	206
6.6.2.2	Nickel-based Catalysts	207
6.6.2.3	Cobalt-based Catalysts	208
6.6.2.4	Copper-based Catalysts	208
6.6.3	Asymmetric Hydrosilylation of Ketones	208
6.6.3.1	Copper-based Catalysts	209
6.6.3.2	Iron-based Catalysts	210
6.6.3.3	Zinc-based Catalysts	212
6.7	Conclusions	212
	References	214
7	Chiral Complexes with Carbophilic Lewis Acids Based on Copper, Silver, and Gold	223
	<i>Matej Žabka and Radovan Šebesta</i>	
7.1	Introduction	223
7.2	Enantioselective Copper Catalysis	223
7.2.1	Conjugate Additions	223
7.2.2	Allylic Substitutions	232
7.2.3	Other Reactions	238
7.3	Enantioselective Gold Catalysis	240
7.3.1	Chiral Gold Catalysts as σ -Acids: Aldol, Mannich, and Related Reactions	241
7.3.2	Chiral Gold Catalysts as π -Acids: Enyne Cycloisomerizations, Cycloadditions, and Rearrangements	243
7.3.3	Gold-catalyzed Functionalizations of Alkynes and Allenes	246
7.4	Enantioselective Silver Catalysis	250

- 7.4.1 Nucleophilic Additions to Carbonyl Compounds and Imines 250
- 7.4.2 Reactions of Azomethine Ylides 253
- 7.5 Conclusions 254
- References 255
- 8 Chiral Rare Earth Lewis Acids 261**
Helen C. Aspinall
- 8.1 Introduction 261
- 8.1.1 The Rare Earth Elements 261
- 8.1.2 Key Aspects of the Chemistry of the Rare Earth Elements 262
- 8.1.3 Variation of Ionic Radius and Lewis Acidity 262
- 8.2 Monofunctional Lewis Acid Catalysis 263
- 8.2.1 Rare Earth Triflates 263
- 8.2.1.1 Binaphthyl-Derived Ligands 264
- 8.2.1.2 Pybox Ligands 266
- 8.2.1.3 *N,N'*-Dioxide Ligands 272
- 8.2.1.4 Schiff Base Ligands 276
- 8.2.1.5 Enantioselective Catalysis by Ln(OTf)₃ Complexes in Aqueous Media 276
- 8.2.2 Rare Earth Phosphonates 280
- 8.2.3 Bifunctional Catalysts: Monometallic and Homometallic 281
- 8.2.4 Rare Earth Alkoxides 282
- 8.2.4.1 Enantioselective Epoxidation Reactions 282
- 8.2.4.2 Enantioselective Cyanation Reactions 283
- 8.2.5 Rare Earth Dialkylamides 284
- 8.2.6 Rare Earth Chlorides for Enantioselective Cyanation Catalysis 288
- 8.3 Heterobimetallic Catalysts 290
- 8.3.1 Alkali Metal Rare Earth Binaphtholates M₃[Ln(binol)₃] 290
- 8.3.1.1 Lewis Acid–Brønsted Base Catalysis 292
- 8.3.1.2 Lewis Acid–Lewis Acid Catalysis 294
- 8.3.2 Transition Metal–Lanthanide Schiff Base Catalysts 294
- 8.4 Conclusions 295
- References 296
- 9 Water-compatible Chiral Lewis Acids 299**
Taku Kitanosono and Shū Kobayashi
- 9.1 Discovery of Water-compatible Lewis Acids 299
- 9.2 Definition and Fundamentals of Water-compatible Lewis Acids 299
- 9.3 Chiral Induction by Lewis Acid in Aqueous Environments 303
- 9.4 1,2-Addition to C=O Double Bond 303
- 9.4.1 Mukaiyama Aldol Reactions 303
- 9.4.2 Direct-type Aldol Reactions 313
- 9.4.3 Allylation Reactions 317
- 9.4.4 Reduction 319
- 9.5 1,2-Addition to C=N Bond 320
- 9.5.1 Mannich-type Reactions 320
- 9.5.2 Alkyne Addition Reactions 321

9.5.3	Allylation Reactions	322
9.6	Cycloadditions	323
9.6.1	Diels–Alder Reactions	323
9.6.2	Kinugasa Reaction	325
9.7	Addition to Epoxides	326
9.7.1	Addition of N,O,S-Nucleophiles	326
9.7.2	Addition of C-nucleophiles	327
9.8	Conjugate Additions	328
9.8.1	Thia-Michael Additions	328
9.8.2	Epoxidations	328
9.8.3	1,4-Addition of C-nucleophiles	329
9.8.4	Boron Conjugate Additions	332
9.8.5	Silyl Conjugate Additions	333
9.8.6	Protonations	334
9.9	Conclusions	335
	References	335
10	Cooperative Lewis Acids and Aminocatalysis	345
	<i>Samson Afewerki and Armando Córdoba</i>	
10.1	Introduction	345
10.1.1	Combined Enamine and Metal Activations	346
10.1.1.1	α -Allylic Alkylation of Aldehydes and Ketones	346
10.1.1.2	Merging Lewis Acid and Aminocatalysis for the Reactions with Alkynes	352
10.1.1.3	Merging Lewis Acid and Aminocatalysis for the Reactions with Allenes	362
10.1.1.4	Merging Lewis Acid and Aminocatalysis for the α -Functionalization of Aldehydes	363
10.1.1.5	Merging Lewis Acid and Aminocatalysis in Miscellaneous Reactions	364
10.1.2	Combined Iminium and Lewis Acid Catalysts	366
10.2	Conclusions	368
	References	370
	Index	375

List of Contributors

Samson Afewerki

Mid Sweden University
Department of Natural Sciences
SE-851 70 Sundsvall
Sweden

Helen C. Aspinall

University of Liverpool
Department of Chemistry
Crown Street
Liverpool L69 7ZD
UK

Sebastian Baś

Jagiellonian University
Ingardena 3
30-060 Krakow
Poland

Armando Córdoba

Mid Sweden University
Department of Natural Sciences
SE-851 70 Sundsvall
Sweden

Anna Domzalska

Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw
Poland

Xiaoming Feng

College of Chemistry
Sichuan University
Key Laboratory of Green Chemistry
& Technology, Ministry of Education
Chengdu
China

Bartłomiej Furman

Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw
Poland

Jadwiga Gajewy

Adam Mickiewicz University
Department of Chemistry
Umultowska 89B
61 614 Poznan
Poland

I. Karthikeyan

North Dakota State University
Department of Chemistry and
Biochemistry
Dunbar Hall 354, 1231 Albrecht Blvd.
Fargo, ND 58108-6050
USA

Taku Kitanosono

The University of Tokyo
Department of Chemistry
School of Science
Hongo, Bunkyo-ku
Tokyo 113-0033
Japan

Shu Kobayashi

The University of Tokyo
Department of Chemistry
School of Science
Hongo, Bunkyo-ku
Tokyo 113-0033
Japan

Marcin Kwit

Adam Mickiewicz University
Department of Chemistry
Umultowska 89B
61 614 Poznan
Poland

Daniel Łowicki

Adam Mickiewicz University
Department of Chemistry
Umultowska 89B
61 614 Poznan
Poland

Jacek Mlynarski

Jagiellonian University
Faculty of Chemistry
Ingardena 3
30-060 Krakow
Poland

Thierry Ollevier

Université Laval
Département de Chimie
Pavillon Alexandre-Vachon 1045
avenue de la Médecine
Québec
Canada G1V 0A6

Radovan Šebesta

Comenius University
Department of Organic Chemistry
Mlynska dolina, Ilkovicova 6
84215 Bratislava
Slovakia

Mukund P. Sibi

North Dakota State University
Department of Chemistry and
Biochemistry
Dunbar Hall 354, 1231 Albrecht Blvd.
Fargo, ND 58108-6050
USA

Marcin Szewczyk

Jagiellonian University
Ingardena 3
30-060 Krakow
Poland

Artur Ulikowski

Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw
Poland

Jun Wang

School of Chemistry
Sun Yat-Sen University
Xingang West Road 135
Guangzhou 510275
P. R. China

Matej Žabka

Comenius University
Department of Organic Chemistry
Mlynska dolina, Ilkovicova 6
84215 Bratislava
Slovakia

Preface

Metal catalysis still lies at the heart of modern chemistry. Application of chiral metal complexes for asymmetric synthesis has become a key activity for organic chemists in the past 20–30 years. Particularly, the second half of the twentieth century documented vast progress in the development of transition metal-based asymmetric synthesis. The Nobel Prize was awarded for this tremendous effort in 2001 to William S. Knowles and Ryoji Noyori “for their work on chirally catalysed hydrogenation reactions” and to K. Barry Sharpless “for his work on chirally catalysed oxidation reactions.” On the other hand, enantioselective organocatalysis has recently become a field of central importance for the asymmetric synthesis of chiral molecules. Since the ground-breaking work of, for example, B. List and D. W. C. MacMillan in the early 2000s, this field has grown at an extraordinary pace from a small collection of reactions to a flourishing area of transformations. The use of metal complexes, however, never ceased to be an important area of research. Parallel to the organocatalysis, application of chiral Lewis acids is still the most important field of research. Moreover, there are many important classes of synthetic transformations for which application of chiral metal-based Lewis acids are essential.

Now, after many years of academic endeavor the stereocontrol in organic synthesis has become also a major issue for the chemical industry. The basic criteria for such applications, efficiency, economy, and ecology are equally well met by purely organic molecules as well as by asymmetric metal-based reagents. In fact, many transformations have been discovered or recently reinvented under asymmetric control by using chiral Lewis acids while industrial application of organocatalysis is still at an early stage.

This book was thought of as a panorama of modern chiral Lewis acid-type catalysts and their broad applications. We tried to emphasize the most recent contributions in the field as well as more prominent directions of development. The first chapters venture into various parts of the periodic table, giving insight into extensive application of alkaline metals, as well as classical Lewis acids such as titanium, iron, copper, and zinc. Recently prepared chiral alkaline earth metal complexes (calcium, strontium, and barium) showed that their strong Brønsted basicity and mild Lewis acidity are useful for construction of chiral catalysts for various carbon–carbon bond forming reactions (Chapter 1). Alkaline earth metal catalysis is undoubtedly also an important topic from the viewpoint of green sustainable chemistry. The next chapters demonstrate broad application

and growing interest in some of the most abundant metals on Earth: titanium (Chapter 2) and iron (Chapter 3). The major advantages of titanium chemistry are the possibility of adjusting reactivity and selectivity by ligands and the relative inertness toward redox processes. Iron salts, on the other hand, are cheap, less harmful, and benign. Chapters 4 and 5 detail the broad utility and application of copper- and zinc-based Lewis acids in organic transformations for the synthesis of important classes of compounds. Chapter 6 deals with growing interest in non-noble metal catalysts useful for asymmetric reduction, while Chapter 7 provides insight into coinage metals copper, silver, and gold, which can be considered as prominent examples of carbophilic Lewis acids. Such compounds displaying affinity towards carbon–carbon double or triple bonds are important in a wide range of chemical reactions. The last three chapters provide information on recent *hot topics* in the area: application of chiral lanthanide complexes (Chapter 8), water-compatible Lewis acids (Chapter 9), and cooperative application of chiral metal complexes and aminocatalysis (Chapter 10).

All chapters are thoroughly well written by experts in the respective fields. It is my personal pleasure to express gratitude to all contributors to this book for their effort to join this editorial enterprise. I am also grateful to the Wiley-VCH team who made this project real.

Jacek Mlynarski
Krakow 2016

1

Alkaline-Earth Metal-Based Chiral Lewis Acids

Anna Domżalska, Artur Ulikowski and Bartłomiej Furman

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

1.1 Introduction

Catalysis based on transition metal compounds has received considerable attention over the years. In this field, asymmetric catalysis based on chiral Lewis acids is broadly recognized as a significant tool for the preparation of optically active compounds. However, from the perspective of green sustainable chemistry, it is highly preferred to find environmentally friendly processes and catalysts. In contrast to most transition and noble metal complexes, chiral alkaline-earth metal-based catalysts offer high efficiency and stereoselectivity but also less toxicity and less potential for harm. That is why the studies of asymmetric transformations with the use of these novel catalytic systems are attracting ever-growing interest.

1.2 General Properties of Alkaline Earth Metal Compounds

In alkaline-earth metal-catalyzed reactions, the amphoteric acid/base character of the complexes is of extreme importance. The strong Brønsted basicity allows for the abstraction of acidic protons, such as the α -protons of carbonyl compounds. On the other hand, the significant Lewis acidity is used for stereocontrol of the reaction [1–5]. These unique properties of alkaline earth metal complexes are due to the chemical properties of Group II metals. Both the Brønsted basicity and the Lewis acidity are directly connected to the electronegativity of the metals [1, 2, 5]. For this reason, the calcium compounds are weaker Brønsted bases and stronger Lewis acids than barium and strontium complexes when coupled with similar counterions [1, 2, 5]. However, the smaller ionic radius and smaller coordination number of calcium makes it more amenable to chiral modifications than strontium or barium [1, 4, 6]. Moreover, the character of the ligand exerts an influence not only on the asymmetric environment construction but also on the amphoteric acid/base character of the alkaline earth metal compounds.

Taking into account the character of ligands and the type of bonds between the metal and the ligand, chiral alkaline earth metal complexes have been classified into three types (Figure 1.1) [1, 2, 5].

In the first type of complexes, the metal is tightly connected to the anionic chiral ligands through covalent bonds. Since these ligands act as Brønsted bases, it is difficult to control the basicity of the catalyst. However, when anionic chiral ligands are bonded to the metal by a combination of one covalent and further coordinative bonds (type II), the Brønsted basicity can be controlled by changing the remaining free counterion [1, 2, 5]. Thanks to the presence of a covalent bond in both type I and type II complexes, there is a possibility for strict control of the asymmetric environment [1, 2, 5].

On the other hand, the construction of chiral alkaline earth metal complexes by attaching a ligand through only coordinative bonds (type III) is also possible [1, 2, 5]. The metal center interacts efficiently with Lewis bases, such as neutral coordinative ligands, owing to its significant Lewis acidity [1, 2, 5]. In such complexes, the two remaining anionic ligands act as effective Brønsted bases. Moreover, the Brønsted basicity of the whole compound should be enhanced by electron donation of the ligands to the metal center [1, 2, 5].

1.3 Applications in Asymmetric Synthesis

Scientists all around the world still carry out research into highly stereoselective reactions including asymmetric transformations which target optically active compounds [1]. One of the most popular approaches in this regard is organocatalysis based on heavy transition metal compounds. However, there is a necessity to find environmentally friendly catalytic systems from the viewpoint of green sustainable chemistry [1, 2, 5, 7]. An alternative path is the use of the chiral alkaline earth metal catalysts [1, 2, 5]. This approach also allows for enantiomeric or diastereomeric enrichment, which is crucial for asymmetric synthesis, but is less environmentally damaging [1–5]. Moreover, the unique chemical properties of Group II metals, such as amphoteric acid/base character, divalent stable oxidation state, and the high coordination numbers to the metal center allow to obtain three types of chiral alkaline earth metal complexes, which collectively find applications in a number of organic reactions [1, 2, 5]. We review many of these applications below.

1.3.1 Cycloaddition Reactions

Some of the fundamental processes in organic chemistry that have been developed over the years are cycloaddition reactions. This type of pericyclic process

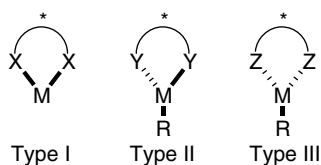


Figure 1.1 Types of alkaline earth metal complexes.

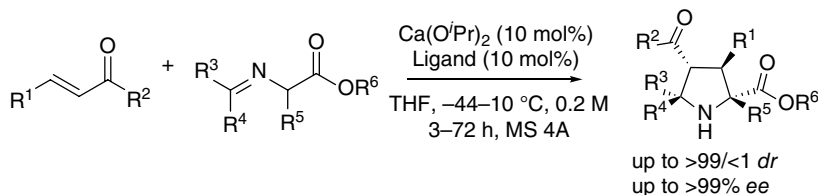
can be used to obtain cyclic adducts and asymmetric versions of such transformations are extremely useful methods to construct highly functionalized derivatives in an optically active form. For instance, asymmetric 1,3-dipolar cycloaddition reactions are some of the most efficient and often used tactics to synthesize five-membered heterocyclic rings, in regio- and stereocontrolled fashion [1, 6, 8, 9]. In particular, [3+2] cycloaddition reactions are a useful method for synthesizing chiral pyrrolidine derivatives, which are important building blocks in the syntheses of many natural products and pharmaceuticals [1, 4, 6]. Several enantioselective metal catalyst systems have been employed to these reactions, but most of these systems require additional bases [1, 10]. This inspired Kobayashi and Yamashita's investigation of asymmetric [3+2] cycloaddition reactions using chiral calcium catalysts [4, 10–13]. They successfully applied chiral Box–calcium complexes to reactions of glycine Schiff bases with β -substituted α,β -unsaturated esters, such as methyl crotonate (Scheme 1.1), and obtained the desired chiral pyrrolidine derivatives with high yields, complete diastereoselectivities, and excellent enantioselectivities (Table 1.1) [10–12].

However, the results of their research indicate that the size and character of the substituent in the aldehyde part of the imine could play an important role in the enantioselectivity of the Box–calcium complex-catalyzed [3+2] cycloaddition reactions [1, 3, 5]. In comparison with glycine Schiff bases that are prepared from aromatic aldehydes (Table 1.1, entries 1–10; Table 1.2, entries 1–10), aliphatic aldehyde derivatives (Table 1.2, entries 11–12) are less stable. This stems from possible tautomerization processes which lead to the formation of enamines. These competitive processes could be crucial in Kobayashi's group research. Moreover, aromatic substituents form better stabilized carbocations, which shifts the equilibrium of the reaction toward the formation of the cyclic adducts and induces higher enantioselectivity.

These catalytic systems have performed well in the constructing of highly substituted contiguous chiral carbon centers using amino acid derivatives containing an α -alkyl group and α,β -unsaturated carbonyl compounds (Table 1.3) [1, 4, 5].

The chiral Lewis acids that were developed by Kobayashi and co-workers, prepared from calcium alkoxides with chiral bisoxazoline ligands bearing active methylene moieties, were classified as type II [3].

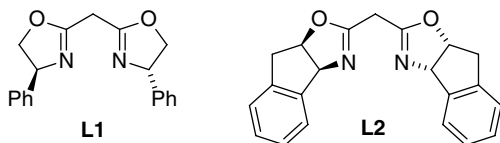
During the preparation of these catalysts, an anionic bidentate Box ligand is produced by deprotonation. The chiral ligand is then bound to the metal by a combination of covalent and coordinate bonds, assisted by the mild Lewis acidity of alkaline earth metals (Figure 1.2) [3].



Scheme 1.1 A Box–calcium complex-catalyzed [3+2] cycloaddition reaction of amino acid Schiff bases with α,β -unsaturated carbonyl compounds [1, 4].

Table 1.1 Asymmetric [3+2] cycloaddition of a glycine ester Schiff base with α,β -unsaturated carbonyl compounds [1].

Entry	R ¹	R ²	Ligand	Time (h)	Yield (%)	ee (%)
1	MeO	Me	1	3	Quant.	>99
2	EtO	Me	1	3	98	98
3	^t BuO	Me	1	3	77	87
4	MeO	Et	2	24	Quant.	95
5	MeO	ⁱ Bu	2	24	Quant.	99
6	MeO	ⁿ Heptyl	2	48	97	>99
7	NMe ₂	H	1	12	83	95
8		H	1	24	76	98
9	H	H	1	24	84	97
10	^c Hex	H	1	24	93	91



This type of bonding opens up the opportunity for strict control of the effective asymmetric environment. Furthermore, the Brønsted basicity of such complexes can be controlled by changing the remaining free counterion [3].

While chiral Box–calcium complexes prepared from calcium isopropoxide worked well in asymmetric [3+2] cycloaddition reactions, further investigations showed that stronger Brønsted bases such as calcium amides (e.g., Ca(HMDS)₂) could be employed successfully in these types of reactions (Scheme 1.2). Moreover, they exhibit higher solubility in many solvents when compared with calcium alkoxides, which makes them more suited to organic synthesis [1, 3–5].

Examination of the chiral alkaline earth metal complexes has shown that these Lewis acids are useful catalytic systems in Diels–Alder cycloadditions as well. For years, the [4+2] cycloaddition reaction has been one of the best methods for the preparation of six-membered rings and Lewis acid-catalyzed asymmetric Diels–Alder reactions have been widely reviewed to date [13, 14]. It has been

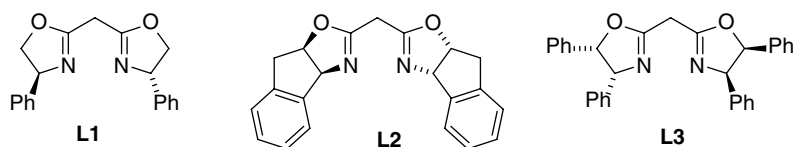
Table 1.2 Asymmetric [3+2] cycloaddition of a Schiff base of a glycine ester with *t*-butyl crotonate [1].

Ca(O'Pr)₂ (10 mol%)
L (10 mol%)
THF, temp., 0.2 M
Time, MS 4A

(1.2 equiv.)

Entry	R	Ligand	Time (h)	Temperature (°C)	Yield (%)	ee (%)
1	Ph	1	3	10	86	86
2	<i>p</i> -ClC ₆ H ₄	2	8	-20	92	82
3	<i>p</i> -BrC ₆ H ₄	1	3	10	95	86
4	<i>p</i> -MeC ₆ H ₄	3	12	-30	92	87 ^a
5	<i>m</i> -MeC ₆ H ₄	2	12	-20	Quant.	91
6	<i>o</i> -MeC ₆ H ₄	1	3	10	86	78
7	3,5-Me ₂ C ₆ H ₃	1	12	10	Quant.	94
8	2-Naphtyl	1	3	10	97	92
9	<i>p</i> -MeOC ₆ H ₄	1	12	10	76	86
10	2-Furyl	3	12	-30	97	90 ^a
11	^t Bu	2	12	-20	80	38
12	Cy	2	12	-20	97	29

a) The absolute configuration of the product was reversed.



frequently reported that the reaction rate and selectivity depends on the Lewis acidity of the metal and the Lewis basicity of the counterion [2]. Moreover, the HOMO–LUMO energy gap plays an important role in the pericyclic reactions. Classic Lewis acids promote these types of reactions by coordinating to the dienophile and lowering the LUMO energy. On the other hand, investigations of Shibasaki *et al.* have shown that the reaction of a silyloxydiene with fumarate is likely promoted through a HOMO-raising mechanism. This reaction catalyzed by chiral barium complexes yields a precursor for the synthesis of optically active oseltamivir (Tamiflu) (Scheme 1.3) [3, 13].

The catalytic cycle of the Diels–Alder type reaction postulated by Shibasaki and co-workers is based on the formation of a chiral barium-activated diene (Figure 1.3) [13].

First, the silyloxydiene is activated by the fluoride cocatalyst, which facilitates the formation of a barium dienolate through transmetalation with the barium

Table 1.3 Asymmetric [3+2] cycloaddition of a Schiff base of α -amino esters with α,β -unsaturated carbonyl compounds [1].

Entry	R ¹	R ²	R ³	R ⁴	Ligand	Time (h)	Temperature (°C)	Yield (%)	ee (%)
1	H	^t Bu	Me	Me	1	12	10	Quant.	90
2	H	^t Bu	Me	Et	1	3	10	Quant.	91
3	H	^t Bu	Me	Bn	1	3	10	93	90
4	H	^t Bu	ⁱ Pr	Me	1	3	10	32	59
5	H	^t Bu	Et	Me	2	12	-30	82	96
6	H	^t Bu	Bn	^t Bu	2	12	-30	90	92
7	H	^t Bu	ⁿ Bu	Me	2	12	-20	94	94
8	H	^t Bu	ⁱ Bu	Me	2	12	-30	98	87
9	H	^t Bu	CH ₂ CH ₂ SMe	Me	2	12	-20	81	81
10 ^a	H	^t Bu	CH ₂ O ^t Bu	^t Bu	2	12	-20	80	93
11	Me	Me	Me	Me	2	12	0	79	96
12	Et	Me	Me	Me	2	12	0	64	96
13 ^b	ⁿ Bu	Me	Me	Me	2	18	0	81	98
14	Me	Me	Et	Me	2	24	-20	42	89
15 ^b	Me	Me	ⁿ Bu	Me	2	72	-30	50	93
16 ^b	Me	Me	Bn	^t Bu	2	72	-30	98	85
17 ^a	Me	Me	CH ₂ O ^t Bu	^t Bu	2	24	10	80	97
18 ^{a,b}	ⁱ Bu	Me	CH ₂ O ^t Bu	^t Bu	2	24	0	87	95

a) L-Amino acid was used.

b) 20 mol% of catalyst was used.

alkoxide. This achiral diene is reactive enough to produce the barium alkoxide intermediate with the dienophile in a concerted or stepwise manner. Finally, the free oxygen electron pair attacks the trimethylsilyl group that is attached to the ligand, leading to catalyst regeneration and formation of an optically active silylated cyclohexane derivative [3, 13].

Investigations of Shibasaki *et al.* have proved that asymmetric Diels–Alder reactions with ketone-derived silyoxydienes do not depend on acid catalysis. Moreover, unlike chiral barium catalytic systems, calcium, strontium, and magnesium complexes were not effective (Table 1.4). Only Lewis acids prepared from a barium alkoxide and a chiral diol bearing a phosphine oxide moiety gave the expected product [13]. This result shows the importance of the metal Brønsted basicity for the development of effective metal catalysis [1].

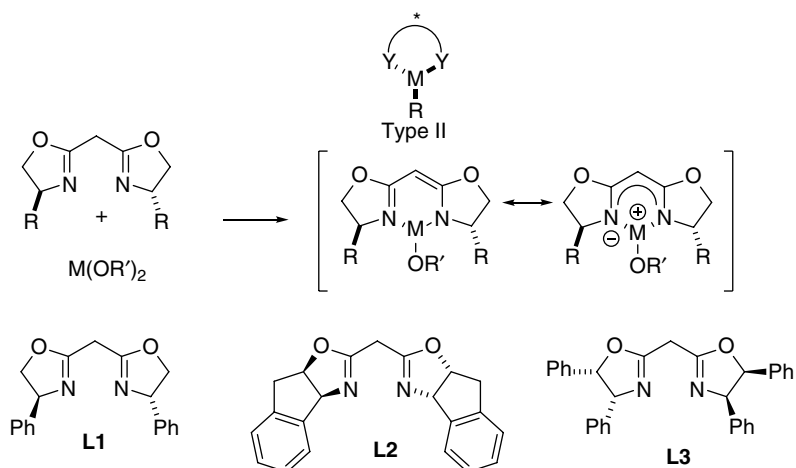
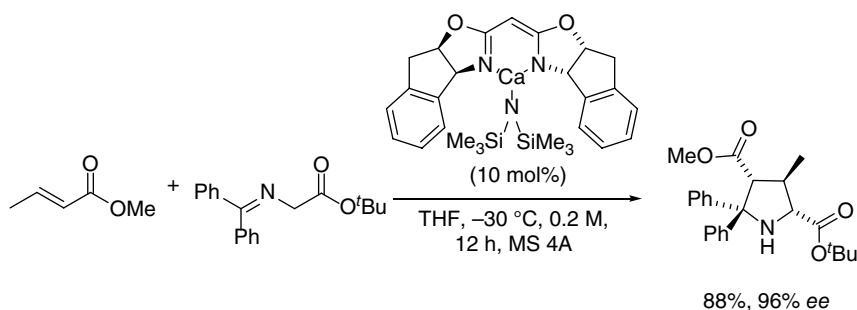
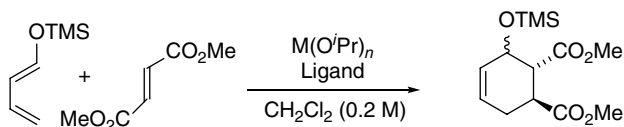


Figure 1.2 Type II chiral alkaline earth metal complexes. Alkaline earth metal–chiral bisoxazoline complexes [1, 3].



Scheme 1.2 Catalytic [3+2] cycloaddition reaction using a Box–calcium complex prepared from calcium amide and bisoxazoline derivative.



Scheme 1.3 Asymmetric Diels–Alder reaction of a silyloxydiene with fumarate catalyzed by chiral alkaline earth metal complexes.

A great deal of attention has been given to hetero-Diels–Alder reactions [2, 15] because of their potential for efficiently constructing functionalized six-membered heterocyclic rings in an enantioselective fashion. Despite many developments in this field and the large number of catalytic systems that have been developed, many groups still carry out research focused on this powerful method of heterocycle synthesis. The investigations of Zhu *et al.* on the enantioselective construction of dihydropyran derivatives are an excellent example. Working toward an effective

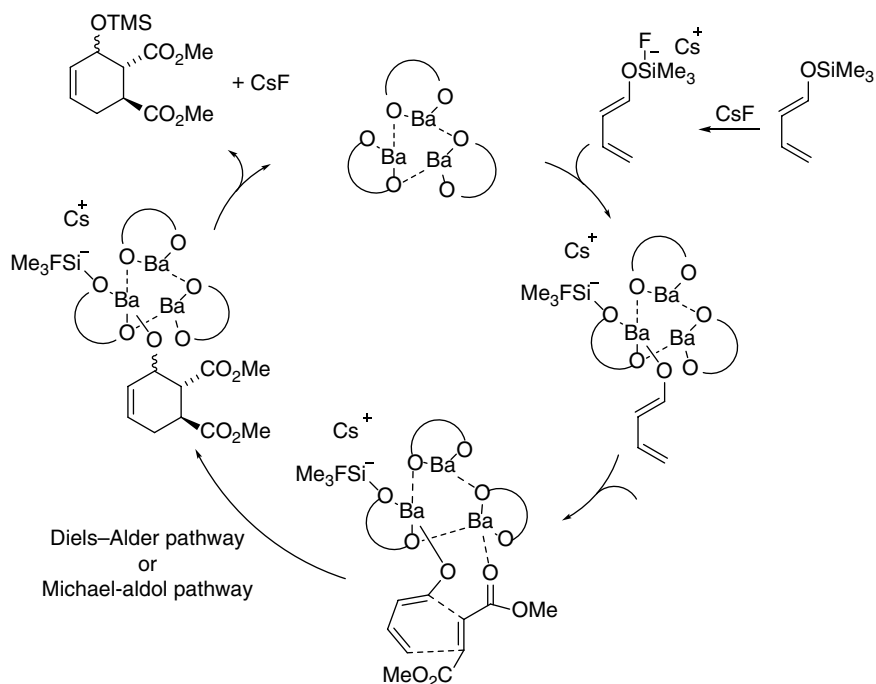


Figure 1.3 The catalytic cycle of asymmetric Diels–Alder-type reaction postulated by Shibasaki.

method for the construction of optically pure oxygen-containing cycloalka[2,3-b]indoles, they have reported that chiral calcium phosphate catalytic systems could be successfully employed in the reaction of oxindole heterodienes with vinyl ethers (Scheme 1.4) [3, 15].

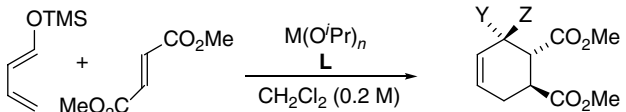
The results of Cheng's group have shown the importance of Lewis acid heterodiene activation in achieving the desired product formation [3]. Moreover, the screening of catalysts for the hetero-Diels–Alder reactions revealed that strontium and barium compounds could also catalyze this class of reactions [15]. However, the lower yields and enantioselectivities that were obtained from strontium- and barium-based catalysts, versus calcium-based ones, indicate that the Lewis acidity of the metal plays an important role in this type of catalysis.

1.3.2 Carbonyl and Imine Addition Reactions

However, chiral strontium catalysts proved to be successful in Mannich-type reactions. This approach is the first example of this kind of catalytic reaction on sulfonylimides and provides the desired addition product, of *N*-Boc-imines to the ester surrogate, with good yields and moderate enantioselectivity (Table 1.5) [16, 17].

Moreover, further works have revealed that high enantioselectivity could be induced using a combination of $\text{Sr}(\text{O}^i\text{Pr})_2$ and a bis(sulfonamide) chiral ligand which bears a diphenylethylenediamine backbone (Scheme 1.5). In this catalytic system, the strontium complex coordinates to the nitrogen of the sulfonylimide and increases the acidity of the α -proton of the sulfonylimide, allowing deprotonation by Et_3N [16, 17].

Table 1.4 Influence of the alkaline earth metal complexes on the enantio- and diastereoselectivity of the asymmetric Diels–Alder reaction.



Y = OTMS, Z = H (*endo*: desired)
Y = H, Z = OTMS (*exo*: undesired)

Entry	M	Ligand	Time (h)	Yield (%)	<i>dr</i> (%) <i>endo/exo</i>	<i>ee</i> (%) <i>endo</i>
1	Mg	4	17	0	—	—
2	Ba	4	17	45	3/1	4
3	Sc	4	17	0	—	—
4	Gd	4	17	0	—	—
5	Ba	5	0.5	97	4/1	1
6	Ba	6	2.5	72	3/1	77
7	Ba	6	42	74	3/1	61
8	Ba	7	1.5	34	5/1	73
9	Ba	8	17	62	6/1	73
10	Ba	8	23	64	3/1	88

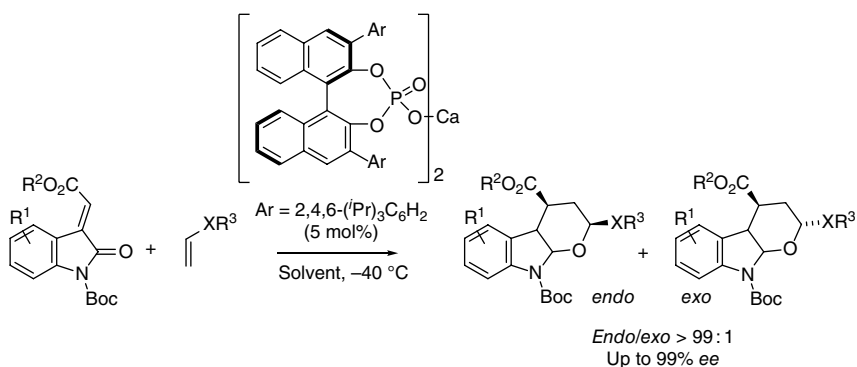
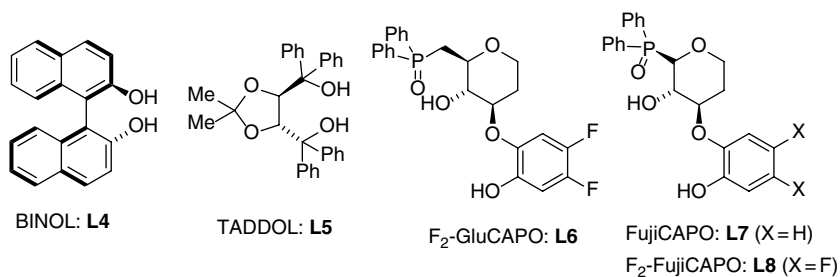
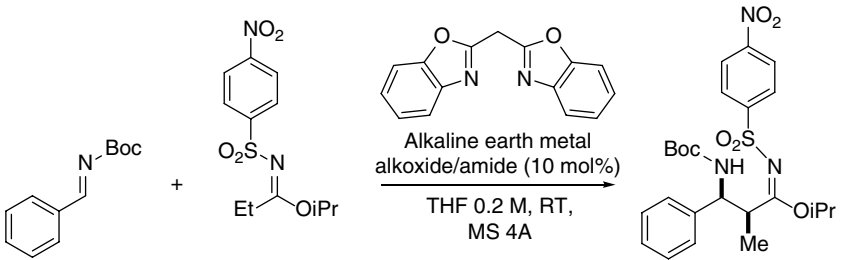
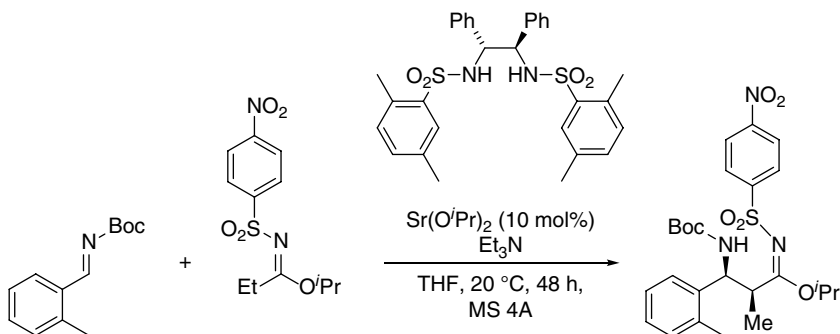
**Scheme 1.4** Asymmetric hetero-Diels–Alder reactions of heterodienes with vinyl ethers.

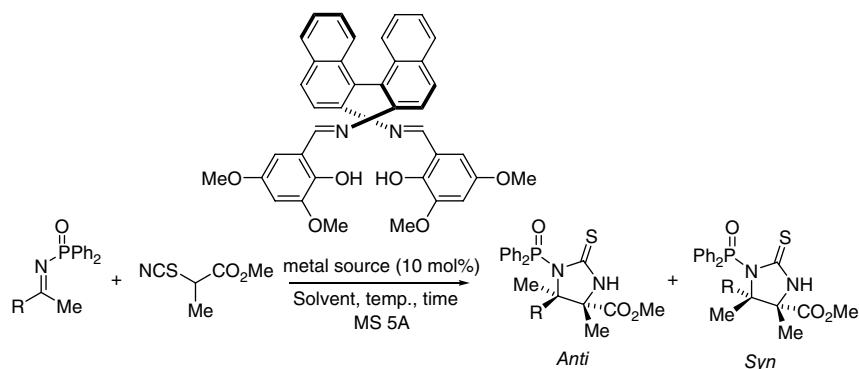
Table 1.5 Chiral alkaline earth metal complex-catalyzed catalytic Mannich reactions of sulfonylimidates with *N*-Boc-imines.


Entry	Catalyst	Time (h)	Yield (%)	<i>Anti/syn</i>
1	Ca(O ^{<i>i</i>} Pr) ₂	48	68	11/89
2	Sr(O ^{<i>i</i>} Pr) ₂	48	45	7/93
3	Ba(O ^{<i>i</i>} Pr) ₂	48	65	9/91
4	1/2[[Sr(HMDS) ₂] ₂]	24	92	7/93
5	1/2[[Sr(HMDS) ₂] ₂]	48	76	6/94
6	1/2[[Sr(HMDS) ₂] ₂]	72	65	6/94

**Scheme 1.5** Chiral strontium complex-catalyzed asymmetric Mannich reaction of sulfonylimidates.

Shibasaki *et al.* have also reported that chiral strontium complexes could be applied to asymmetric Mannich reactions. They found that, unlike Ca(O^{*i*}Pr)₂ and Ba(O^{*i*}Pr)₂, the use of Sr or Mg compounds as metal sources gives good results in asymmetric reactions of α -isothiocyanate esters with ketimines. Moreover, the obtained results have shown that the type of metal has an influence on the ratio of *syn* and *anti*-products. Compared with magnesium complexes, the application of strontium complexes reverses the diastereoselectivity and promotes the formation of *anti*-products (Table 1.6) [18].

Likewise, chiral barium complexes which are prepared from a barium alkoxide and optically active BINOL or aryloxy derivatives have been found to be effective

Table 1.6 Catalytic asymmetric Mannich reactions of α -isothiocyanate esters with ketimines.

Entry	Catalyst	R	Solvent	Temp (°C)	Time (h)	Yield (%)	<i>dr</i> syn/anti	<i>ee</i> (%)
1	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -BrC ₆ H ₄	CHCl ₃	r.t.	48	86	6/94	92
2	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -ClC ₆ H ₄	CHCl ₃	r.t.	48	82	10/90	87
3	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -FC ₆ H ₄	CHCl ₃	r.t.	48	71	6/94	90
4	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -CF ₃ C ₆ H ₄	CHCl ₃	r.t.	48	85	11/89	92
5 ^a	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -MeC ₆ H ₄	CHCl ₃ / THF	r.t.	20	97	6/94	95
6 ^a	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -MeC ₆ H ₄	CHCl ₃ / THF	r.t.	24	99	8/92	93
7 ^a	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -MeOC ₆ H ₄	CHCl ₃ / THF	r.t.	24	91	4/96	97
8 ^a	Sr(O ^{<i>i</i>} Pr) ₂	<i>p</i> -Me ₂ NC ₆ H ₄	CHCl ₃ / THF	r.t.	69	45	4/96	97
9 ^a	Sr(O ^{<i>i</i>} Pr) ₂		CHCl ₃ / THF	-5	47	76	6/94	95
10 ^a	Sr(O ^{<i>i</i>} Pr) ₂	2-Thienyl	CHCl ₃ / THF	0	48	70	13/87	90
11 ^a	Sr(O ^{<i>i</i>} Pr) ₂	3-Thienyl	CHCl ₃ / THF	-5	48	74	12/88	92
12 ^a	Sr(O ^{<i>i</i>} Pr) ₂	2-Furyl	CHCl ₃ / THF	-10	48	84	17/83	84
13	Bu ₂ Mg	<i>p</i> -BrC ₆ H ₄	CHCl ₃	-10	48	87	91/9	84
14	Bu ₂ Mg	<i>p</i> -ClC ₆ H ₄	CHCl ₃	-10	48	90	92/8	85
15	Bu ₂ Mg	<i>p</i> -FC ₆ H ₄	CHCl ₃	0	44	96	93/7	84
16	Bu ₂ Mg	<i>p</i> -MeC ₆ H ₄	THF	-25	48	99	90/10	82
17	Bu ₂ Mg		THF	-5	17	96	92/8	81

(Continued)

Table 1.6 (Continued)

Entry	Catalyst	R	Solvent	Temp (°C)	Time (h)	Yield (%)	dr syn/anti	ee (%)
18	Bu ₂ Mg	2-Naphtyl	CHCl ₃	0	48	99	93/7	95
19	Bu ₂ Mg	3-Thienyl	THF	-25	48	80	93/7	81
20	Bu ₂ Mg	2-Furyl	CHCl ₃	-5	48	70	93/7	80

a) CHCl₃/THF (2/1).

in reactions of β,γ -unsaturated esters with imines, leading to an aza-Morita–Baylis–Hillman-type product *via* isomerization of the initially formed Mannich adducts (Table 1.7) [19].

Alkaline earth metal catalysis have been widely investigated in recent years also by Ishihara *et al.* Their research has revealed that a chiral calcium phosphate, prepared from a calcium alkoxide and phosphoric acid bearing a chiral BINOL backbone, could be successfully applied in asymmetric Mannich reactions of 1,3-dicarbonyl compounds with *N*-Boc-imines. In particular, these Lewis acids were effective for enantioselective Mannich-type reactions with less acidic 1,3-dicarbonyl compounds, including β -ketoesters and thiomalonates (Table 1.8) [20–22].

Table 1.7 Chiral barium aryloxide-catalyzed Mannich reactions of β,γ -unsaturated esters with imines.

Entry	Ligand	R	Time (h)	Yield (%)	α/γ	ee (%)
1	(<i>S</i>)-BINOL	Ph	19	58	>15/1	14
2	(<i>S</i>)-Biaryldiol	Ph	17	69	9/1	77
3	(<i>S</i>)-Biaryldiol	<i>p</i> -MeC ₆ H ₄	19	78	>15/1	80
4	(<i>S</i>)-Biaryldiol	2-Thienyl	17	73	>15/1	78

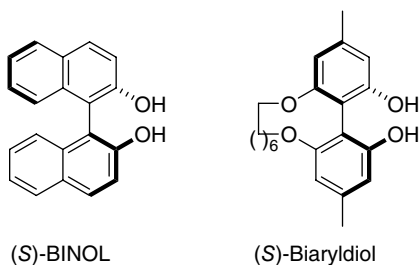


Table 1.8 Chiral calcium phosphate-catalyzed asymmetric Mannich reactions.

Ar = 4-(β-naph)-C₆H₄
(2.5 mol%)

Entry	Ar	R ¹	R ²	Yield (%)	ee (%)
1	Ph	Ac	Ph	>99	90
2	<i>p</i> -MeC ₆ H ₄	Ac	2,6-Xyl	>99	94
3	<i>p</i> -MeOC ₆ H ₄	Ac	2,6-Xyl	94	92
4	Ph	Ac	2,6-Xyl	>99 (>99) ^a	94 (98) ^a
5	<i>p</i> -ClC ₆ H ₄	Ac	2,6-Xyl	90	90
6	<i>p</i> -BrC ₆ H ₄	Ac	2,6-Xyl	99	91
7	1-Naphtyl	Ac	2,6-Xyl	88	97
8	3-Thionyl	Ac	2,6-Xyl	>99	96
9	Ph	2,6-Xyl	2,6-Xyl	94	95
10	<i>p</i> -MeOC ₆ H ₄	2,6-Xyl	2,6-Xyl	81	91
11	<i>p</i> -BrC ₆ H ₄	2,6-Xyl	2,6-Xyl	89	95

a) 0.5 mol% of the catalyst was used.

Rueping *et al.* confirmed that the BINOL-phosphoric acid calcium salt is a valuable catalytic system in asymmetric Mannich reactions. However, in contrast with the work of Ishihara *et al.*, their investigations have been based on using pyrone (Table 1.9) and 1,3-cyclohexadione (Table 1.10) as carbonyl donors. This approach yielded intermediates that are valuable in organic synthesis with high enantioselectivities [22].

Alkaline earth metals possess multiple coordination sites, which enables them to accept multidentate ligands; Kobayashi *et al.* used this concept to develop chiral calcium catalysts such as (PyBox)-calcium complexes with neutral ligands. They have reported that complexes constructed with a ligand that binds *via* only coordinate bonds are useful in the addition of malonates to imines (Table 1.11). However, only aromatic-substituted *N*-Boc imines yielded the Mannich-type product in high yields and with moderate-to-good enantioselectivities [23].

Table 1.9 Chiral calcium phosphate-catalyzed asymmetric Mannich reaction of *N*-Boc-imine with pyrone.

Ar = 2,4,6-(^tPr)₃C₆H₂
(5 mol%)
Solvent, -40 °C

Entry	Ar	Solvent	Yield (%)	ee (%)
1	<i>p</i> -MeC ₆ H ₄	Bu ₂ O	49	88
2	<i>p</i> -MeC ₆ H ₄	CHCl ₃	62	82
3 ^a	<i>p</i> -MeC ₆ H ₄	CHCl ₃	45	39
4	<i>m</i> -ClC ₆ H ₄	Bu ₂ O	43	76
5	<i>o</i> -BrC ₆ H ₄	Bu ₂ O	55	86
6	<i>o</i> -BrC ₆ H ₄	Bu ₂ O	43	73
7 ^a	<i>o</i> -BrC ₆ H ₄	CHCl ₃	67	84
8	Ph	Bu ₂ O	43	52

a) 10 mol% phosphoric acid **1** was added.

1.3.3 Conjugate Addition Reactions

Conjugate addition reactions are one of the most powerful carbon–carbon and carbon–heteroatom bond forming strategies known in organic chemistry. Numerous examples are known in the literature, some of which have been reviewed [24, 25]. Asymmetric Michael additions are crucial transformations in the syntheses of medically relevant compounds and natural products [26].

The first example of an asymmetric Michael addition catalyzed by a chiral alkaline earth metal complex was described by Kumaraswamy and co-workers in 2001 (Scheme 1.6). They developed an addition of malonates to α,β -unsaturated acyclic/cyclic ketones and aldehydes, catalyzed by a calcium–BINOL complex, and obtained the conjugate addition products with modest yields and enantioselectivities [27].

In the same report, thiophenol was used as a substrate, although furnishing a racemic product. Addition of ethanol was found to be advantageous, increasing the reaction rate and enantioselectivity.

In their next report, in 2003, the Kumaraswamy group proposed an asymmetric epoxidation of chalcones using ^tBuOOH as the oxidizer (Scheme 1.7). A similar calcium–BINOL complex was used in the reaction [28]. However, in contrast to the previous report, most additives were found to have a deleterious effect on