CATALYTIC ASYMMETRIC SYNTHESIS

Third Edition

Edited by
IWAO OJIMA

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A JOHN WILEY & SONS, INC., PUBLICATION

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data

Catalytic asymmetric synthesis / [edited by] Iwao Ojima. – 3rd ed.
p. cm.
Includes index.
ISBN 978-0-470-17577-4 (cloth)
1. Asymmetric synthesis. 2. Catalysis. I. Ojima, Iwao, 1945–
QD262.C357 2010
547′.2–dc22

2009052132

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

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PREFACE

The first and second editions of *Catalytic Asymmetric Synthesis* published in the fall of 1993 and spring of 2000, respectively, were very warmly received by research communities in academia and industries, from graduate students, research associates, faculty, staff, senior researchers, and others. The first book was published at the very moment that the Food and Drug Administration (FDA) in the United States clarified the situation in "Chiral Drugs," the word "chirotechnology" was created, and chirotechnology industries were spawning in the United States and Britain. In the Preface of the first edition, I correctly positioned the significance and advancement of catalytic asymmetric synthesis as follows: "Extensive research on new and effective catalytic asymmetric reactions will surely continue beyond the year 2000, and catalytic asymmetric processes promoted by man-made chiral catalysts will become mainstream chemical technology in the 21st century." The second edition published in 2000 covered explosive development of catalytic asymmetric synthesis since 1993 by adding newly emerging reactions in that period, but keeping the historically important chapters in the first book. In 2001, the Nobel Prize in Chemistry was given to W. Knowles, K. B. Sharpless, and R. Noyori for their outstanding contributions to the advancement of catalytic asymmetric synthesis, pushing up this chemistry and chemical technology to a practical level for the benefit of mankind. Again, I wrote about their exceptional achievements in the Preface of the first edition as follows: "Among the significant achievements in basic research, (i) asymmetric hydrogenation of dehydroamino acids, a ground-breaking work by W. S. Knowles et al., (ii) the Sharpless epoxidation by K. B. Sharpless et al., and (iii) the second generation asymmetric hydrogenation processes developed by R. Noyori et al. deserve particular attention because of the tremendous impact that these processes have made in synthetic organic chemistry." In many cases, Nobel Prize in Chemistry is given to scholar(s) in a certain field of research that is fully matured. However, this Nobel Prize recognized the chemical science that was still very actively growing and expanding, hence significantly fueled further advances in this field. Accordingly, 8 years after the second edition, it became very clear that an updated and/or newer version of this book was necessary for the synthetic chemistry community. Thus, a third edition was planned.

This third edition, however, is organized in a manner different from that of the second edition. Since the chapters in the second edition are still very informative and the ingenious methodologies as well as innovative approaches described there are highly inspiring and stimulating even today, those chapters are regarded as "classics in catalytic asymmetric synthesis." Thus, I decided to edit essentially a new book, which would

become the most useful desktop reference and text, in addition to the "classics" in the second edition, for researchers at all levels, highlighting the most significant advances in catalytic asymmetric synthesis since 2000. Although the third edition does not aim to be comprehensive in nature, it covers the reactions most needed by today's practicing researchers and graduate students in synthetic organic, medicinal, and materials chemistry. New to the third edition, six new chapters focusing on novel approaches to catalytic asymmetric synthesis are introduced, including non-conventional media/conditions, organocatalysis, Lewis and Bronsted acids, CH activation, carbon-heteroatom bond forming reactions, and enzyme-catalyzed asymmetric synthesis (Chapters 1–6). I believe it is time for synthetic organic chemists to recognize and embrace the importance and power of "enzyme-catalyzed reactions" in asymmetric synthesis. Moreover, another very important reaction (metathesis, the subject of the 2005 Nobel Prize in Chemistry) for catalytic asymmetric synthesis is introduced as a new chapter (Chapter 8E) in the section of the carbon-carbon bond forming reactions. Updated chapters are on hydrogenation (Chapter 7), carbon-carbon bond forming reactions (conjugate additions, allylic alkylations, carbometallations and carbocyclizations, transition metal catalyzed ene reactions, and cycloadditions) (Chapter 8), hydrosilylation (Chapter 9), carbonylations (Chapter 10), oxidations (Chapter 11), amplifications and autocatalysis (Chapter 12), and polymerization (Chapter 13). It is obvious that these reactions and processes provide powerful methods for the highly efficient synthesis of enantio-enriched or enantiopure compounds of biological, medicinal, agrochemical, and materials/nano-science–related interests.

The authors of these chapters are all world leaders in this field, who provide systematic, in-depth state-of-the-art coverage of the basic principles, scope and limitations, strategies, and perspectives for future development of each reaction.

I sincerely hope that this book attracts the interests of broad range of synthetic organic, medicinal, and materials chemists, especially among the younger generation researchers in both academia and industry, who will introduce original and creative ideas into this fascinating field of research and advance catalytic asymmetric synthesis by highly innovative approaches in the years to come.

Iwao Ojima
November 2009

PREFACE TO THE SECOND EDITION

The first edition of *Catalytic Asymmetric Synthesis*, published in the fall of 1993, was very warmly received by research communities in academia and industries from graduate students, research associates, faculty, staff, senior researchers, and others. The book was published at the very moment that the Food & Drug Administration (FDA) in the United States clarified the situation in "Chiral Drugs," the word "chirotechnology" was created, and chirotechnology industries were spawning in the United States and Britain.

As accurately predicted in the preface of the first edition, extensive research on new and effective catalytic asymmetric reactions has been continuing, in an explosive pace, and it is now obvious that these catalytic asymmetric processes promoted by man-made chiral catalysts will be the mainstream chemical technology in the 21st century. About five years from the publication of the original book, there was a clear demand in the synthetic community for an updated version of this book because advances in the field were accelerated during this period. Accordingly, I have agreed with the publisher to edit a second edition of this book.

In the second edition, I intended to incorporate all important reaction types that I am aware of, while keeping the monumental discovery and initial development of certain processes from the first edition, and highlighting recent advances in this field. The original book had 13 chapters (9 general-reaction types), which covered most of the important developments at that time. However, the second edition has 21 chapters (11 general-reaction types) (a total of 21 chapters for the 21st century is intriguing, isn't it?), reflecting the tremendous expansion in the scope of catalytic asymmetric synthesis in the past several years. In addition to the nine general-reaction types covered in the original book, the second edition includes "Asymmetric Carbometallations" (Chapter 4), "Asymmetric Amplification and Autocatalysis" (Chapter 9), and "Asymmetric Polymerization" (Chapter 11). "Cyclopropanation" in the original book has been replaced with "Asymmetric Carbene Reactions" (Chapter 5), which now includes powerful asymmetric intramolecular carbene insertion to C–H bonds. As the Table of Contents shows, there has been significant expansion and development in the asymmetric carbon–carbon bond-forming reactions (Chapter 8). Thus, this section consists of eight chapters dealing with cycloaddition reactions, aldol reactions, ene reactions, Michael reactions, allylic substitution reactions, cross-coupling reactions, and intramolecular Heck reactions. These processes provide very useful methods for the highly efficient synthesis of enantio-enriched or enantiopure compounds of biological, medicinal, agrochemical, and material science related interests.

Once again, the authors of these chapters are all world-leaders in this field, who outline and discuss the essence of each catalytic asymmetric reaction. Because the separate list of the chiral ligands in the original book was very well received, a convenient list of the chiral ligands with citation of relevant references appears in this book as an Appendix.

This book will, once again, serve as an excellent reference book for graduate students as well as chemists at all levels in both academic and industrial laboratories.

Iwao Ojima

PREFACE TO THE FIRST EDITION

Biological systems, in most cases, recognize a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. The sad example of thalidomide is well-known. It is the responsibility of synthetic chemists to provide highly efficient and reliable methods for the synthesis of desired compounds in an enantiomerically pure state, that is, with 100% enantiomeric excess (% ee), so that we shall not repeat the thalidomide tragedy. It has been shown for many pharmaceuticals that only one enantiomer contains all of the desired activity, and the other is either totally inactive or toxic. Recent movements of the Food & Drug Administration (FDA) in the United States clearly reflect the current situation in "Chiral Drugs," that is, pharmaceutical industries will have to provide rigorous justification to obtain the FDA's approval of racemates. Several methods are used to obtain enantiomerically pure materials, which include classical optical resolution via diastereomers, chromatographic separation of enantiomers, enzymic resolution, chemical kinetic resolution, and asymmetric synthesis.

The importance and practicality of asymmetric synthesis as a tool to obtain enantiomerically pure or enriched compounds has been fully acknowledged to date by chemists in synthetic organic chemistry, medicinal chemistry, agricultural chemistry, natural products chemistry, pharmaceutical industries, and agricultural industries. This prominence is due to the explosive development of newer and more efficient methods during the last decade.

This book describes recent advances in catalytic asymmetric synthesis with brief summaries of the previous achievements as well as general discussions of the reactions. A previous book reviewing this topic, *Asymmetric Synthesis, Vol. 5—Chiral Catalysis*, edited by J. D. Morrison (Academic Press, Inc., 1985), compiles important contributions through 1982. Another book, *Asymmetric Catalysis*, edited by B. Bosnich (Martinus Nijhoff, 1986) also concisely covers contributions up to early 1984. In 1971, an excellent book, *Asymmetric Organic Reactions*, by J. D. Morrison and H. S. Mosher, reviewed all earlier important work on the subject and compiled nearly 850 relevant publications through 1968, including some papers published in 1969. In the early 1980s, a survey of publications dealing with asymmetric synthesis (in a broad sense) indicated that the total number of papers in this area of research published in the 10 years after the Morrison/Mosher book, that is, 1971–1980, was almost the same as that of all the papers published before 1971. This doubling of output clearly indicates the attention paid to this important

topic in 1970s. Since the 1980s, research on asymmetric synthesis has become even more important and popular when enantiomerically pure compounds are required for the total synthesis of natural products, pharmaceuticals, and agricultural agents. It would not be an exaggeration to say that the number of publications on asymmetric synthesis has been increasing exponentially every year.

Among the types of asymmetric reactions, the most desirable and the most challenging is *catalytic* asymmetric synthesis because one chiral catalyst molecule can create millions of chiral product molecules, just as enzymes do in biological systems. Among the significant achievements in basic research: (i) asymmetric hydrogenation of dehydroamino acids, a ground-breaking work by W.S. Knowles et al.; (ii) the Sharpless epoxidation by K. B. Sharpless et al.; and (iii) the second-generation asymmetric hydrogenation processes developed by R. Noyori et al. deserve particular attention because of the tremendous impact that these processes have made in synthetic organic chemistry. Catalytic asymmetric synthesis often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. In fact, a number of catalytic asymmetric reactions, including the "Takasago Process" (asymmetric isomerization), the "Sumitomo Process" (asymmetric cyclopropanation), and the "Arco Process" (asymmetric Sharpless epoxidation) have been commercialized in the 1980s. These processes supplement the epoch-making "Monsanto Process" (asymmetric hydrogenation), established in the early 1970s. This book uncovers other catalytic asymmetric reactions that have high potential as commercial processes. Extensive research on new and effective catalytic asymmetric reactions will surely continue beyond the year 2000, and catalytic asymmetric processes promoted by man-made chiral catalysts will become mainstream chemical technology in the 21st century.

This book covers the following catalytic asymmetric reactions: asymmetric hydrogenation (Chapter 1); isomerization (Chapter 2); cyclopropanation (Chapter 3); oxidations (epoxidation of allylic alcohols as well as unfunctionalized olefins, oxidation of sulfides, and dihydroxylation of olefins) (Chapter 4); hydrocarbonylations (Chapter 5); hydrosilylation (Chapter 6); carbon–carbon bond-forming reactions (allylic alkylation, Grignard cross-coupling, and aldol reaction) (Chapter 7); phase-transfer reactions (Chapter 8); and Lewis acid-catalyzed reactions (Chapter 9). The authors of the chapters are all world-leaders in this field, who outline and discuss the essence of each catalytic asymmetric reaction. (In addition, a convenient list of the chiral ligands appearing in this book, with citation of relevant references, is provided as an Appendix.)

This book serves as an excellent reference for graduate students as well as chemists at all levels in both academic and industrial laboratories.

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March 1993

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1

CATALYTIC ASYMMETRIC SYNTHESIS IN NONCONVENTIONAL MEDIA/ CONDITIONS

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1.1. INTRODUCTION

Conventionally, catalytic asymmetric synthesis has been carried out in organic solvents, because most organic materials are not soluble in other solvents. However, asymmetric catalysis in other solvents (nonconventional solvents) is now of interest for many reasons. First and most significantly, the negative characteristics of organic solvents have come to the fore recently; many organic solvents are volatile, flammable, sometimes explosive, and have a damaging effect on human health (e.g., mutagenic or carcinogenic) or on the environment. On the other hand, recovery and reuse of catalysts is crucial in organic synthesis not only from an economical aspect but also from an environmental point of view. Use of nonconventional solvents often enables the recovery and reuse of catalysts.

In this chapter, water, fluorous solvents, supercritical fluids (SCFs), and ionic liquids (ILs) are discussed as nonconventional solvents, and characteristic features of asymmetric catalysis are surveyed. Microwave-assisted catalytic asymmetric synthesis is also described.

1.2. CATALYTIC ASYMMETRIC SYNTHESIS IN WATER

Water is remarkable in nature; indeed, nature chooses water as a "solvent." Many elegant *in vitro* reactions, mainly catalyzed by enzymes, are carried out in an aqueous

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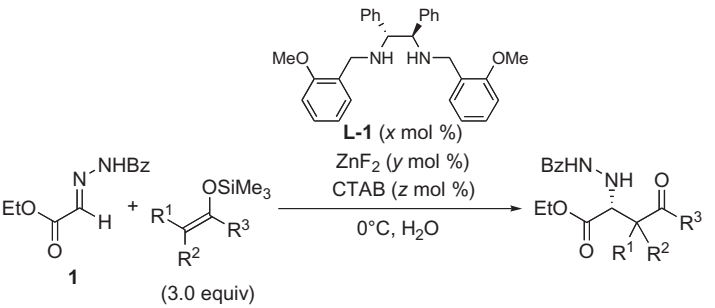
Catalytic Asymmetric Synthesis, Third Edition, Edited by Iwao Ojima

environment in our bodies. Given that nature so gracefully exploits water, why should mankind not perform synthesis in water too?

1.2.1. Chiral Lewis Acid Catalysis in Water

In general, the formation of chiral Lewis acid complex is much more difficult in water than in organic media, since a chiral ligand competes with water in coordination with Lewis acid. Although there are successful reports to realize chiral Lewis acid catalyzed asymmetric reactions in *aqueous media*, it is still very challenging to use *water as sole solvent* [1,2].

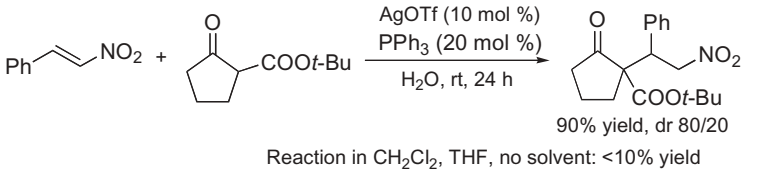
1.2.1.1. Mannich-Type Reaction in Water Asymmetric Mannich reactions provide useful routes for the synthesis of optically active β-amino ketones and esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing biologically important compounds [3]. Diastereo- and enantioselective Mannich-type reactions of α-hydrazono ester **1** with silicon enolates in aqueous media can be successfully achieved with a ZnF_2–chiral diamine **L-1** complex (Scheme 1.1) [4]. This complex enables reactions in water without any organic cosolvents or additives to proceed smoothly, affording the corresponding products in high yields and high stereoselectivities (Conditions A) [5]. In the reaction of α-monosubstituted ketone-derived silyl enol ether with **1**, cetyltrimethyl ammonium bromide (CTAB) is necessary to accelerate the reaction. It is also noted that, in contrast to most asymmetric Mannich-type reactions, either syn- or anti-adducts are stereospecifically obtained from (E)- or (Z)-silicon enolates in the present reaction (Conditions B). Moreover, the amount of ZnF_2 and **L-1** can be successfully reduced to 10 and 5 mol %, respectively, maintaining the same level of result (Conditions C).



Conditions A: $x = 10$, $y = 100$, $z = 0$, $R^1 = R^2 = H$, 20 h
Conditions B: $x = 10$, $y = 100$, $z = 2$, 20 h
Conditions C: $x = 5$, $y = 10$, $z = 2$, 40 h

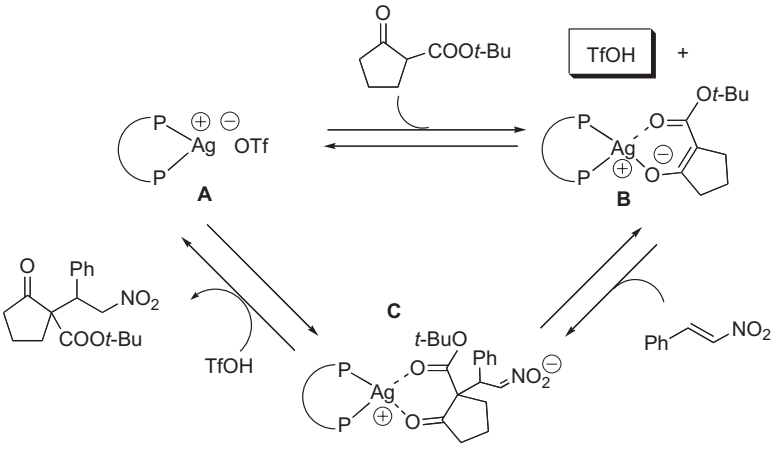
Scheme 1.1.

1.2.1.2. Michael Reaction in Water AgOTf–PPh_3 complex-catalyzed Michael additions of β-ketoesters to nitroalkenes proceed efficiently only in water but not in organic solvents (Scheme 1.2).



Scheme 1.2.

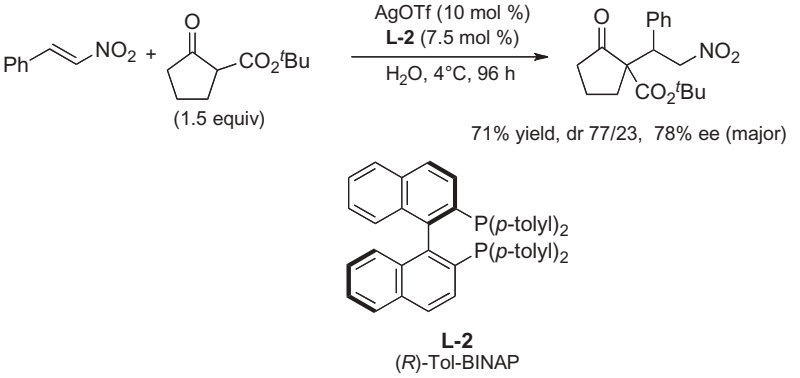
Based on these results, a plausible mechanism is shown in Scheme 1.3. In the formation of metal enolate B, TfOH is generated and the reaction mixture becomes heterogeneous, where metal enolate B stays in organic phase, while TfOH is excluded to water phase because of the difference of hydrophobicity between them. On the other hand, in the case of a normal organic solvent system, the reaction mixture becomes homogeneous, leading the reverse reaction from B to A fast. As a result, metal enolate B does not make contact with TfOH, and the reverse reaction from B to A is suppressed. Metal enolate B and nitrostyrene would thus combine in high concentration, and the Michael addition step (B to C in Scheme 1.3) may proceed smoothly. Moreover, this reaction system can be applied to catalytic asymmetric synthesis in water (Scheme 1.4) [6,7].



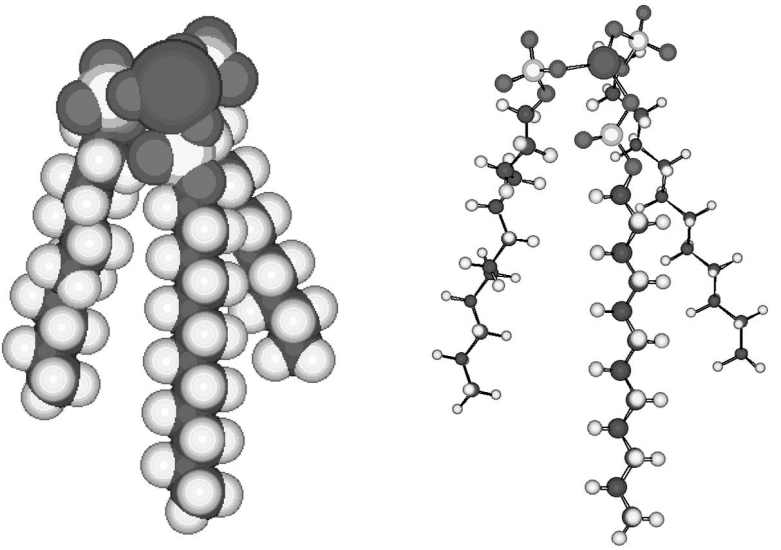
Scheme 1.3.

1.2.1.3. Epoxide Ring-Opening Reaction in Water Scandium trisdodecylsulfate ($Sc(DS)_3$) was designed as a Lewis acid as well as a surfactant as illustrated in Scheme 1.5. In the model reaction of benzaldehyde with the silyl enol ether derived from propiophenone in water, $Sc(DS)_3$ catalyzes the reaction smoothly, while the reaction proceeds sluggishly when $Sc(OTf)_3$ is used as a catalyst (Scheme 1.6).

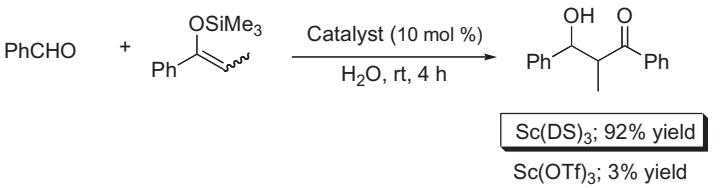
A key to the success in this system is assumed to be the formation of stable emulsions. Physical property of the droplets was investigated, and transmission electron microscopy (TEM) analysis revealed that only about 0.08 mol % of $Sc(DS)_3$ is sufficient to form



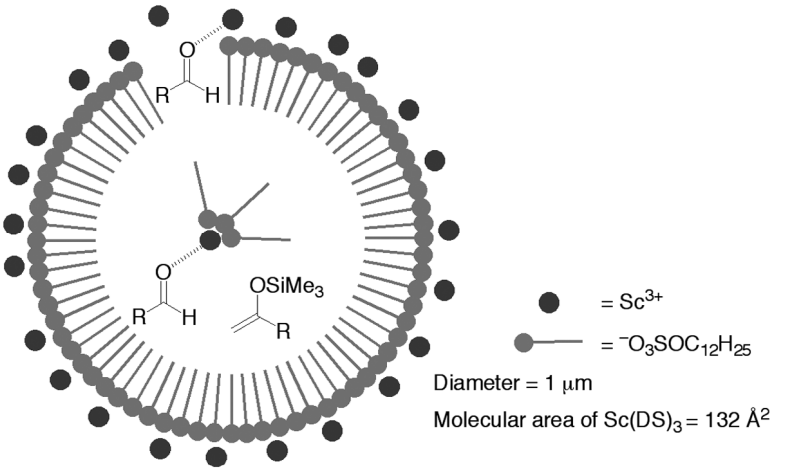
Scheme 1.4.



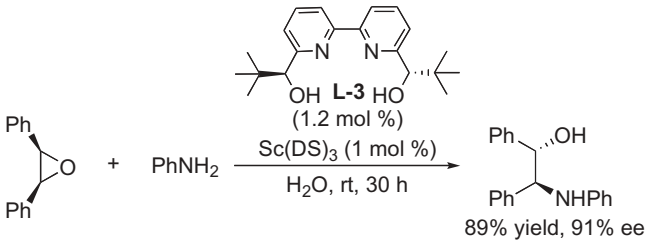
Scheme 1.5.



Scheme 1.6.



Scheme 1.7.



Scheme 1.8.

monolayers (Scheme 1.7). Based on these results, it is expected that highly hydrophobic environment is formed inside of the emulsion.

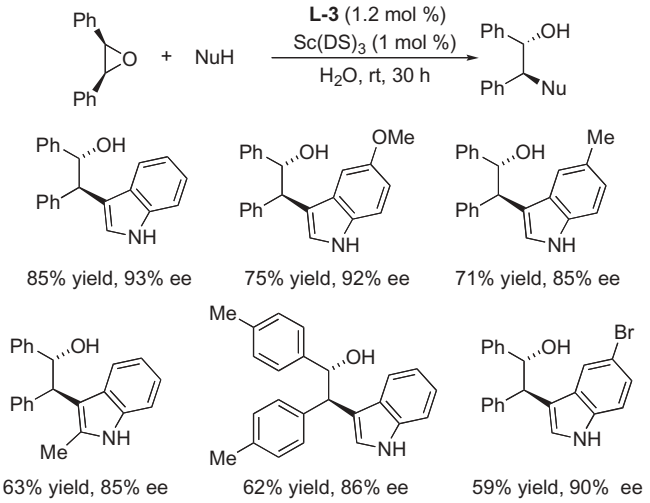
To explore this catalyst further, chiral $Sc(DS)_3$ catalyst has been investigated. The complex $Sc(OTf)_3$•**L-3** was found to be effective in asymmetric hydroxymethylation using aqueous formaldehyde solution in DME (1,2-dimethoxyethane)/H_2O cosolvent condition [8,9]. Therefore, there was a possibility that $Sc(DS)_3$ could form chiral complex with **L-3** in water. First, the asymmetric ring opening of *cis*-stilbene oxide with aniline in water was investigated.

Chiral β-amino alcohol units can be found in many biologically active compounds and chiral auxiliaries/ligands used in asymmetric reactions [10]. Catalytic enantioselective synthesis of these chiral building blocks mainly relies on the asymmetric ring opening of *meso*-epoxides. Indeed, several examples using a chiral catalyst (typically a chiral Lewis acid) are reported in literature [11]; however, all these reactions proceeded in organic solvents. It is probable that epoxides are readily decomposed under acidic conditions in water.

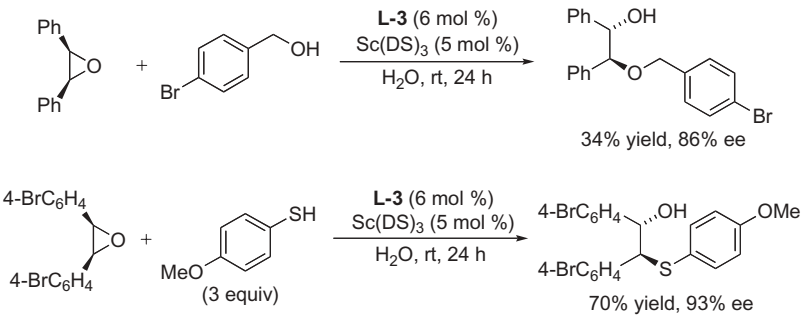
Using 1 mol % of $Sc(DS)_3$ and 1.2 mol % of **L-3** in water, the reaction proceeded smoothly in high yield with high enantioselectivity (Scheme 1.8). It is noted that the

ring-opening reaction proceeded smoothly in water, and that no diol formation was observed. This is to date the first example of an asymmetric epoxide ring opening in water as a sole solvent [12,13].

Moreover, catalytic asymmetric ring-opening reactions of *meso*-epoxides with indoles, alcohols, and thiols proceed smoothly in the presence of catalytic amounts of $Sc(DS)_3$ and chiral bipyridine ligand **L-3** in water to afford β-amino alcohols in high yields with high enantioselectivities (Schemes 1.9 and 1.10) [14,15]. These results suggest that an excellent asymmetric environment is created in water.



Scheme 1.9.



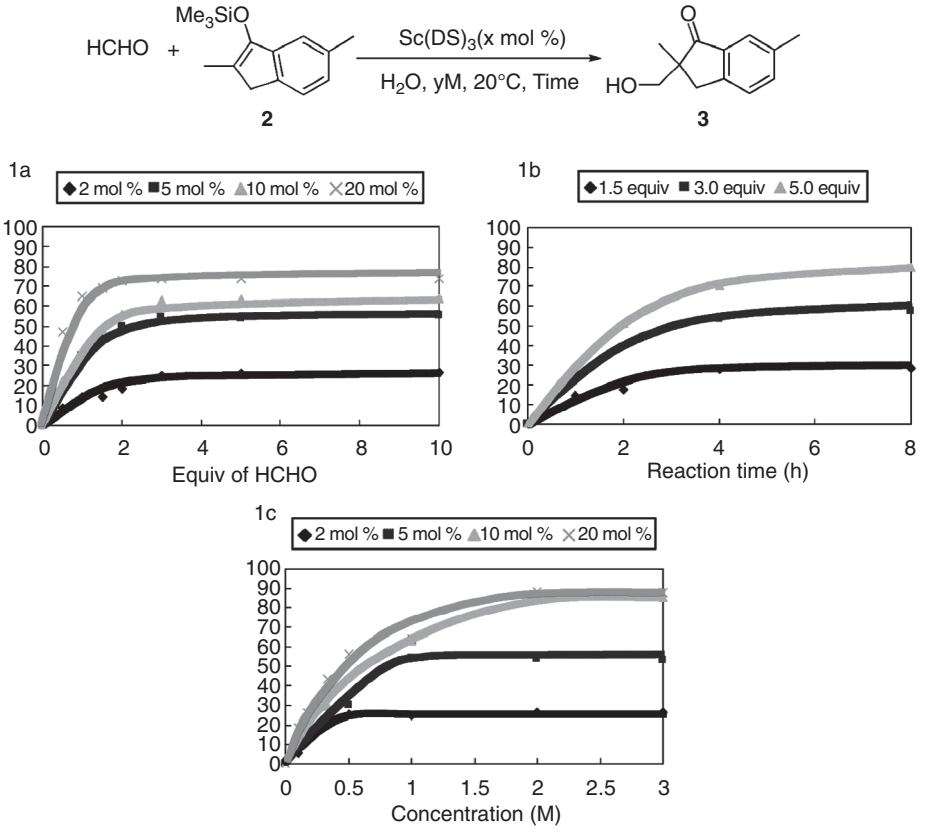
Scheme 1.10.

1.2.1.4. Hydroxymethylation in Water Several asymmetric organic reactions have been achieved in water without any organic cosolvents. These reactions proceeded smoothly by creating hydrophobic areas in water to stabilize and concentrate organic substrates or by suppressing the undesired pathway in the reaction mechanism by water.

One of the key factors for these successes is hydrophobicity of substrates. Therefore, asymmetric reactions in water with hydrophilic substrates are far more challenging.

An aqueous formaldehyde solution, or formalin, is one of the most important C1 electrophiles as well as a representative of hydrophilic substrates. Asymmetric hydroxymethylation using an aqueous formaldehyde solution has been investigated in water-organic cosolvent systems [16,17]. Since the hydrophobicity of a substrate is an important factor, it is assumed that hydrophilic substrates are very difficult to handle in water.

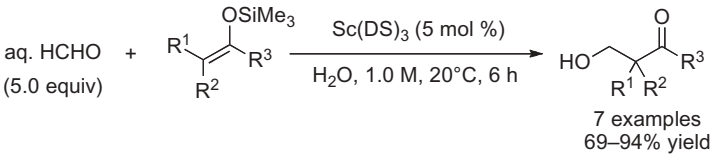
Hydroxymethylation of silicon enolate **2** with 36% aqueous formaldehyde solution (aq. HCHO) was studied in detail. The yield of **3** was improved when the amount of formaldehyde was increased from 1 to 5 equiv with a catalyst loading dependency (Scheme 1.11, **Part 1a**) and for an 8-h reaction (**Part 1b**). The concentration of aq. HCHO also affected the yield of **3** (**Part 1c**). With an Sc loading level (10 and 20 mol %) in the presence of 5 equiv of aq. HCHO, the yields were improved to >80% as the concentrations increased up to 2.0 M; however, no improvement was observed by further



Scheme 1.11. Part 1a. Hydroxymethylation of **2** (catalyst loading and HCHO equiv, reaction concentration was 1.0 M, reaction time was 1 h). **Part 1b.** Hydroxymethylation of **2** (reaction time and HCHO equiv, reaction concentration was 1.0 M). **Part 1c.** Hydroxymethylation of **2** (catalyst loading and concentration, reaction time was 8 h).

increasing the concentration. In the cases of the lower Sc loading level (2 and 5 mol %), the yields leveled off at much lower concentrations, 0.5 and 1.0 M, respectively. These results indicated that $Sc(DS)_3$ might be saturated by aq. HCHO. Based on the experiments, it can be said that, in spite of the extreme solubility of HCHO in water, *the population of HCHO in the hydrophobic environment increases in the presence of $Sc(DS)_3$ due to Lewis acid–Lewis base interaction between $Sc(DS)_3$ and HCHO*, and therefore, the reaction of HCHO with silicon enolate **2** can proceed smoothly even in water.

Furthermore, the hydroxymethylation of various silyl enol ethers proceeded smoothly (Scheme 1.12). Consequently, these experiments suggest that Lewis acid-surfactant combined catalyst (LASC) reaction system can be applied to hydrophilic substrates as well as hydrophobic substrates.

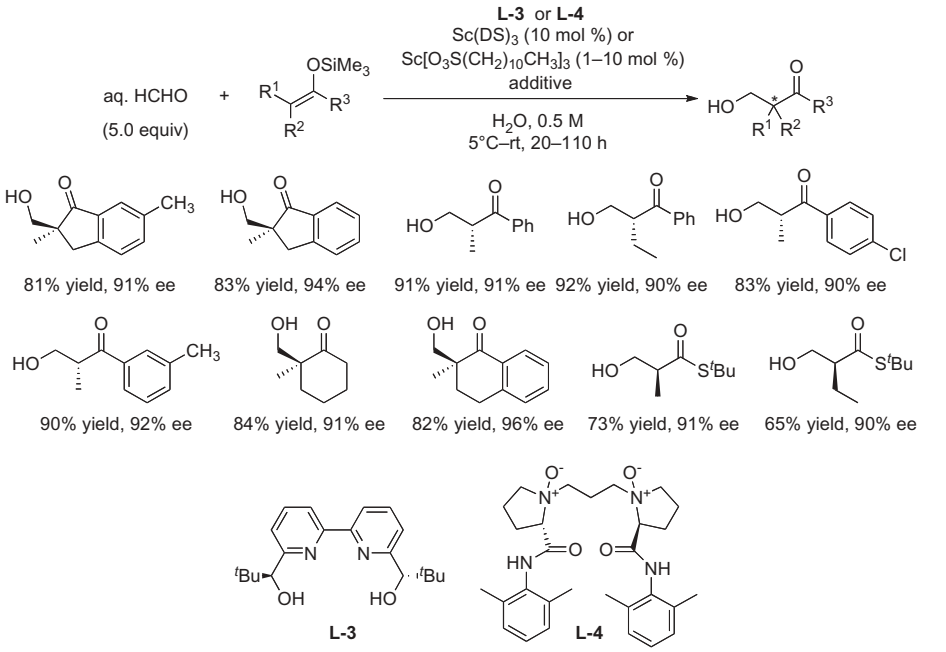


Scheme 1.12.

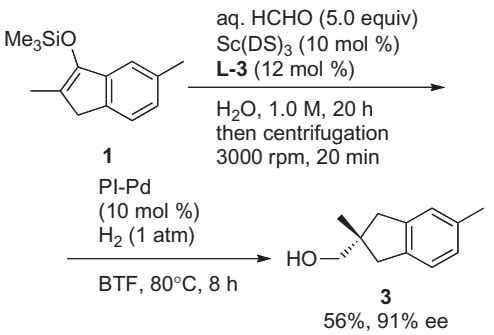
Lewis acid-catalyzed asymmetric reactions in water using hydrophilic substrates are recognized as highly challenging [18], considering the importance of *Lewis acid–Lewis base interactions*, since Lewis acids lose their acidity upon coordination from chiral ligands. Additionally, chiral ligands compete with substrates and water molecules for coordination with Lewis acids. Therefore, the development of chiral Lewis acid-catalyzed hydroxymethylation using aq. HCHO with water as the sole solvent would make a great impact in the field.

The investigation of asymmetric variants of hydroxymethylations using aq. HCHO revealed that the addition of a chiral ligand and a small amount of a surfactant suppressed the competitive hydrolysis of silicon enolates. Eventually, catalytic asymmetric hydroxymethylation reactions are successfully carried out in the presence of a catalytic amount of $Sc(DS)_3$, chiral ligand **L-3** [19], or **L-4** [20] in the presence of additives to afford the desired products in high yields with high selectivities. It is noteworthy that thioketene silyl acetals, which are known to be much less stable than silyl enol ethers (ketone-derived silicon enolates) in water, reacted smoothly under the conditions to afford the desired hydroxymethylated adducts in good yields with high enantioselectivities (Scheme 1.13).

This method could be applied to the synthesis of an artificial odorant (S)-(+)-**3** (Scheme 1.14) [12]. Hydroxymethylation of **1** was performed using $Sc(DS)_3$•**L-3** as a catalyst. After the reaction, the reaction mixture was centrifuged (3000 rpm, 20 min) to separate the colloidal white dispersion into three phases. The upper, middle, and bottom phases are water, surfactant, and organic layers, respectively. After the separation of organic phase, followed by hydrogenation with polymer incarcerated palladium (PI-Pd) [13] in benzotrifluoride (BTF), the compound (S)-(+)-**3** was obtained in 56% yield with 91% ee over two steps. It should be noted that the synthesis has been accomplished using a catalytic asymmetric reaction in water and a hydrogenation with an immobilized catalyst, which are suitable for green sustainable chemistry [3,14].



Scheme 1.13.

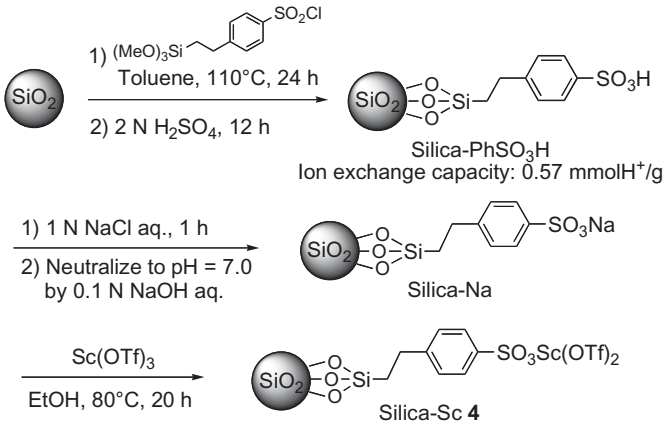


Scheme 1.14.

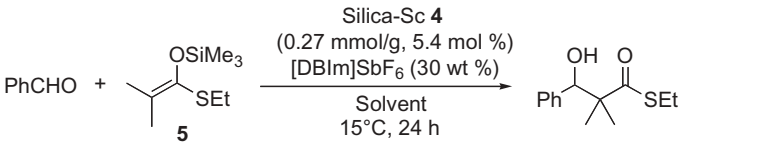
1.2.1.5. Silica Gel-Supported Scandium with Ionic Liquid (Silica-Sc-IL) A novel heterogeneous scandium catalyst system, Silica-Sc-IL, has been developed (Scheme 1.15) [21].

The catalyst **4** coated with an IL, $[DBIm]SbF_6$, works efficiently in Mukaiyama aldol reaction in water (Scheme 1.16). The reaction proceeds much faster in water than in organic solvents, without solvent or in the absence of IL.

These experiments clearly suggest that Silica-Sc-IL and IL forms hydrophobic reaction environments in water (Scheme 1.17). It should be noted that water-labile reagents

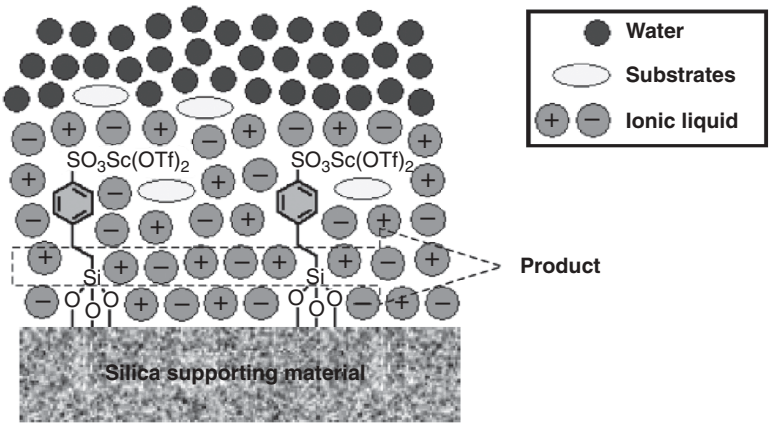


Scheme 1.15.



Solvent: Et_2O	22% yield
Hexane	26% yield
H_2O	97% yield
H_2O without Silica-Sc	0% yield
H_2O without IL	31% yield
neat	25% yield

Scheme 1.16.



Scheme 1.17.