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Comprehensive Asymmetric Catalysis I–III

With contributions by numerous experts



Springer

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ISBN 3-540-14695-4 Springer-Verlag Berlin Heidelberg New York

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Printed in Germany

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Typesetting: Data conversion by MEDIO GmbH, Berlin
Cover: E. Kirchner, Heidelberg

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Preface

The title of this collection is an accurate reflection of the goals we defined at the outset of the project. Our intention was to bring together all important aspects of the field of asymmetric catalysis and to present them in a format that would be most useful to a wide range of scientists including students of chemistry, expert practitioners, and chemists contemplating the possibility of using an asymmetric catalytic reaction in their own research.

This project was initiated by Joe Richmond, who was one of many to recognize the need for an exhaustive and current treatment of the field of asymmetric catalysis, but was unique in being willing and able to get such an ambitious effort started. Considering that it is a field that is evolving in parallel in laboratories throughout the world, he sought to select editors who were not only authoritative, but also as geographically distributed as the field itself. He approached each of us separately, and in the end we were compelled equally by the significance of the project, and by the exciting prospect of working together.

Given the dramatic growth of activity in the field of asymmetric catalysis over the past few years in particular, it was apparent from the start that a comprehensive treatment would be a ambitious task, especially if we were to succeed in capturing the excitement and challenges in field, as well its basic principles. The field is interdisciplinary by its nature, incorporating organic synthesis, coordination chemistry, homogeneous catalysis, kinetics and mechanism, and advanced stereochemical concepts all at its very heart. We realized that the project would require authors who would be willing not only to commit the effort of writing definitive and compelling chapters, but who would also be capable of analyzing their topic with absolute authority. At a hotel near the Frankfurt airport in the Fall of 1996, we got together and constructed an exhaustive list of topics in asymmetric catalysis, and then we devised a “dream list” of contributors. These were individuals who contributed in defining ways to the topics in question. That this dream list came true hopefully should be evident by surveying the names of the contributing authors. If we have succeeded to any extent in our effort to put forth a comprehensive and useful analysis of the field of asymmetric catalysis, it is thanks to them.

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July 1999

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Chapter 1

Introduction

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In Morrison and Mosher's classical book 'Asymmetric Organic Reactions', which covered the literature up to 1968, asymmetric catalysis did not fill more than a few pages and no special chapter was devoted to it. Apart from enzymatic processes, only a few examples of enantioselective catalytic reactions were known at that time, and in view of the generally low enantiomeric excesses, many chemists doubted that synthetic chiral catalysts would ever play an important role in asymmetric synthesis. Shortly after, the situation changed dramatically as spectacular progress was made in the rhodium-catalyzed enantioselective hydrogenation of olefins, culminating in the famous Monsanto process for L-dopa. Since then, asymmetric catalysis has undergone explosive growth, especially during the last decade. Today, it has its standard place in the repertoire of asymmetric synthesis and the increasing number of industrial applications clearly demonstrates its practicality. Although the remarkable development of this still relatively young area has been documented in many excellent books and review articles, an up-to-date comprehensive overview is lacking. This makes it difficult for the newcomer, and even the specialist, to gather all the relevant information on a particular method or catalyst.

With 'Comprehensive Asymmetric Catalysis' we hope to fill this gap. 'Comprehensive' means that all important classes of enantioselective catalytic transformations are covered but it does not imply an extensive lexicographic compilation of examples. The aim was a concise and readable overview of the field, providing a clear picture of the state of the art. The reader should be able to recognize the scope and limitations of a specific catalyst or method and find the pertinent references for a more detailed bibliographic study. The electronic version with reaction and substructure search options should be particularly useful for this purpose.

Although enzymes are an important class of enantioselective catalysts, a systematic coverage of biocatalysis was beyond the scope of this work. However, the reader should be aware that biocatalysts can be an attractive alternative to synthetic chiral catalysts and in many chapters, references to related enzymatic transformations are given. An important new addition to biocatalysis are catalytic antibodies and their use for enantioselective transformations is summarized in chapter 40.

The wide variety of chiral catalysts and the impressive number of enantioselective reactions that are listed in this reference work might lead to the impression that for most organic transformations efficient enantioselective catalysts have been developed. However, a more critical evaluation reveals that the number of truly useful enantioselective catalysts is still limited, especially catalysts that can be employed in an industrial process. In addition to high enantioselectivity, there are other criteria that count, such as catalytic efficiency (turnover number and frequency), application range, reliability, accessibility of the catalyst, and functional group tolerance. In this respect, many of the current methods still need to be improved and the search for new and more efficient catalysts will continue. We feel that 'Comprehensive Asymmetric Catalysis' will allow one to recognize the gaps and weak points of current methodology and, in this way, serve as a basis for future research.

It is interesting to compare and categorize the various catalysts discussed in the individual chapters. Most enantioselective catalysts are metal complexes containing chiral organic ligands. Obviously, the choice of a suitable chiral controller ligand is a crucial step in the development of a new catalyst. While originally chiral diphosphines dominated the field, an impressive variety of mono-, bi-, and multidentate ligands with P, N, O, and other coordinating atoms is used today. However, compilation of the most efficient ligands reveals that most of them belong to a relatively small number of structural classes. Examples are binaphthyl and other biaryl derivatives such as BINOL and BINAP, bisoxazolines, salens and the tartrate-derived TADDOLS, which are all C_2 -symmetric. However, there are also important classes of non-symmetric ligands such as ferrocenylphosphines, phosphinooxazolines and cinchona alkaloid derivatives.

The concept of C_2 symmetry, introduced by Kagan in the early seventies with the diop ligand, had an important impact on the course of research in asymmetric catalysis. This is reflected in the remarkably high number of C_2 -symmetric ligands developed so far. C_2 symmetry is attractive because it reduces the number of possible catalyst-substrate arrangements and, consequently, the number of competing reaction pathways by a factor of two. This can have a beneficial effect on the enantioselectivity and, moreover, facilitates a mechanistic analysis and identification of the factors responsible for enantiocontrol. However, there is no fundamental reason that nonsymmetrical ligands should necessarily be less effective and, indeed, there are many examples where nonsymmetrical ligands are the better choice.

An ideal chiral ligand should not only be easily accessible but it should also be possible to modify its structure systematically. In this way the catalyst structure can be optimized for a specific application or substrate structure. Therefore, it is not surprising to see a clear trend toward modular ligands that can be readily assembled from a large selection of simple precursors. Good examples of such modular ligands are salens, phosphinooxazolines or TADDOLS, which are derived from inexpensive chiral diamines, amino alcohols and tartrate, respectively.

In general, the current approach to finding new catalysts is still rather empirical. Chance and intuition as well as systematic screening play an important role.

Although we can see a trend toward a more rationally based catalyst design, our present, still limited mechanistic understanding and the complexity of most catalytic processes prevents a purely rational approach. Nevertheless, for certain reactions such as rhodium-catalyzed hydrogenation or palladium-catalyzed allylic substitution, the mechanism and the structure of intermediates in the catalytic cycle are known in detail so that an at least semi-rational development of new ligands seems possible (cf. chapters 5 and 24). Because rational design is so difficult, an alternative approach based on combinatorial strategies has been proposed. However, in contrast to biology or medicinal chemistry, where combinatorial chemistry is already well-established, the situation in asymmetric catalysis is rather different. Screening of large catalyst libraries for enantioselectivity and reactivity is much more difficult than testing for biological activity or for binding to a specific receptor. Therefore, future progress in 'combinatorial catalysis' will crucially depend on the development of suitable high-throughput screening methods. Nevertheless, first steps in this direction have been taken and, in some cases, promising results have been obtained (cf. chapter 39).

It was our goal to find for each chapter an author who has been personally involved in the research described therein so that he would be able to provide an insider's view and a critical analysis of the state of the art. We are grateful to all our colleagues who agreed to contribute to this ambitious project, despite their busy schedules and many other obligations. The result, more than 40 chapters written by well-known experts, is more than satisfying. We feel that this reference work is not only an authoritative up-to-date treatment of the field but, in addition, provides a lively view on the many fascinating aspects of asymmetric catalysis, the remarkable and often unexpected developments, as well as current and future trends. We hope that 'Comprehensive Asymmetric Catalysis' will be a useful tool for the practicing chemist and, at the same time, serve as a source of inspiration for the specialists as well as those who are planning to enter this dynamic area of research.

Chapter 2

Historical Perspective

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Keywords: Asymmetric catalysis, Asymmetric hydrogenation, Catalytic antibodies, Chiral Lewis acids, Chiral ligands, Enzymes, Organometallic catalysts, Organic catalysts, Nonlinear effects, History

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1

Introduction

Catalysis is a process which was recognized early in the last century. It seems that Michael Faraday was one of the first scientists to study a catalytic reaction, namely the reaction of hydrogen and oxygen on platinum. This work was pub-

lished in 1834. Faraday understood that in this case of heterogeneous catalysis, the platinum surface was involved and he explained the activity of platinum by adsorption of the reactants on the surface. Apparently, this investigation originated from his association with sir Humphrey Davy who contributed to the development of the miner's safety lamp in 1818. A year before Davy found that a platinum or palladium wire became incandescent in a mixture of coal gas and air. In 1823 in Germany Döbereiner set up a porous platinum which catalyzed the combination of hydrogen and oxygen at room temperature. It was this experiment which became known to Faraday and encouraged him to study catalysis over platinum. In 1835, Berzelius also investigated some catalytic reactions such as gas combustion and coined the word "catalysis", derived from an ancient Greek word meaning dissolution, destruction or end. This choice of word is quite unfortunate as catalysis is most of the time very productive, and in fact the opposite of destruction. Berthelot studied many cases of catalysis in organic transformations. In 1902, Ostwald defined catalysts as agents which accelerate chemical reactions without affecting the chemical equilibrium. This definition applies to reversible systems and excludes autocatalytic reactions. P. Sabatier (Nobel laureate in Chemistry in 1911) defined catalysis as a mechanism whereby some compounds are intimately involved in the process of generating or accelerating chemical reactions without being products of the reaction.

Catalysis may be divided into three branches:

1. Heterogeneous catalysis (chemical).
2. Homogeneous catalysis (chemical).
3. Enzymatic catalysis.

Historically, heterogeneous catalysis had a strong impact on the concept of catalysis (vide supra). It also gave powerful tools to the chemical industry and to organic synthesis.

It is interesting to recall that the first catalytic asymmetric reaction was performed on a racemic mixture (kinetic resolution) in an enzymatic reaction carried out by Pasteur in 1858. The organism *Penicillium glauca* destroyed (*d*)-ammonium tartrate more rapidly from a solution of a racemic ammonium tartrate [1]. The first use of a chiral non-enzymatic catalyst can be traced to the work of Bredig and Fajans in 1908 [2]. They studied the decarboxylation of camphorcarboxylic acid catalyzed by nicotine or quinidine, and they established the basic kinetic equations of kinetic resolution.

In this chapter, we intend to restrict the expression "asymmetric catalysis" to the specific case of an enantioselective reaction controlled by a chiral catalyst. We will not consider the diastereoselective reactions on a chiral substrate involving a chiral catalyst (double asymmetric induction with matched and mismatched pairs).

The concept itself of asymmetric synthesis, stoichiometric or catalytic, took a long time appear. One important step was the investigations of Fischer in 1894–1899 on the structure and stereochemistry of sugars [3, 4, 5]. He observed the formation of diastereomers on addition of HCN to the aldehyde function of

some sugars. He also recognized that enzymes acted as catalysts either in a living organism or as an isolated species and proposed the “lock and key” analogy for explaining the stereospecificity of the enzymes. Marckwald [6] gave, in 1904, a definition of asymmetric synthesis which is still acceptable today, although it has been modified since by Morrison and Mosher in order to include the various cases of asymmetric induction [7].

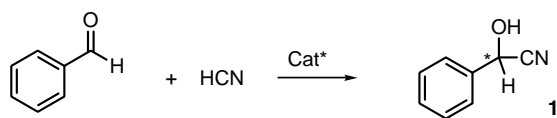
2 Some Early Examples of Bioorganic Enantioselective Catalysis

It is difficult to localize in the literature the initial reports on enantioselective reactions. After Pasteur’s discoveries, many people tried to prepare optically active compounds from inactive precursors, though without making much distinction between racemic or prochiral starting materials. These attempts to generate enantiomerically enriched products were most of the time carried out by fermentation in presence of a microorganism. The synthesis of optically active mandelonitrile by addition of HCN to benzaldehyde, catalyzed by an isolated enzyme, emulsin from almonds, was reported by Rosenthaler in 1908 [8]. It was clearly recognized by the author as a case of asymmetric synthesis as defined by Marckwald. Another early example of bioorganic catalysis is the work of Hayashi in 1929, who rearranged phenylgloxal (hydrate) into mandelic acid (95% ee) in the presence of *B. proteus* [9].

3 The First Examples of Non-enzymatic Enantioselective Catalysis

Bredig, in a pioneering investigation in 1908, was able to prepare mandelonitrile **1** from benzaldehyde and HCN in the presence of an alkaloid (quinine or quinine) as catalyst (Scheme 1) [10]. The enantioselectivities were less than 10%, however this work was conceptually important, though it did not lead to developments in other laboratories. It was only in 1955 that Prelog and Wilhelm reinvestigated this system and proposed a mechanistic picture [11].

Asymmetric catalysis in oxidation reactions by molecular oxygen with a chiral cobalt catalyst was studied by Shibata et al. in 1931 for the kinetic resolution



Cat* : emulsin Rosenthaler, 1908 [8]
Cat* : alkaloids Bredig, 1912 [10]

Scheme 1

of a racemic mixture [12]. This interesting work will not be detailed here since it is outside of the scope of this chapter.

Another approach to asymmetric catalysis was proposed in Japan in the late 1950s by Akabori, Izumi et al. [13]. It was based on heterogeneous catalysis, a metal being modified by a chiral environment. The first attempt made was to impregnate silk with palladium dichloride which was subsequently reduced with hydrogen. The resulting colloidal palladium being deposited on the silk. Asymmetric hydrogenation of some dehydroaminoacid derivatives gave rise to appreciable ee's, for example phenylalanine was obtained in 25% ee. Unfortunately, the experiments were not reproducible.

Izumi et al. then developed another type of catalyst, Raney nickel modified by tartaric acid [14]. Using this, methyl acetoacetate could be hydrogenated into methyl β -hydroxybutyrate with an ee of up to 80%. Unfortunately, only some specific substrates were reduced enantioselectively. However, some interesting developments were later realized (*vide infra*).

4

Enantioselective Catalysis Until 1980

4.1

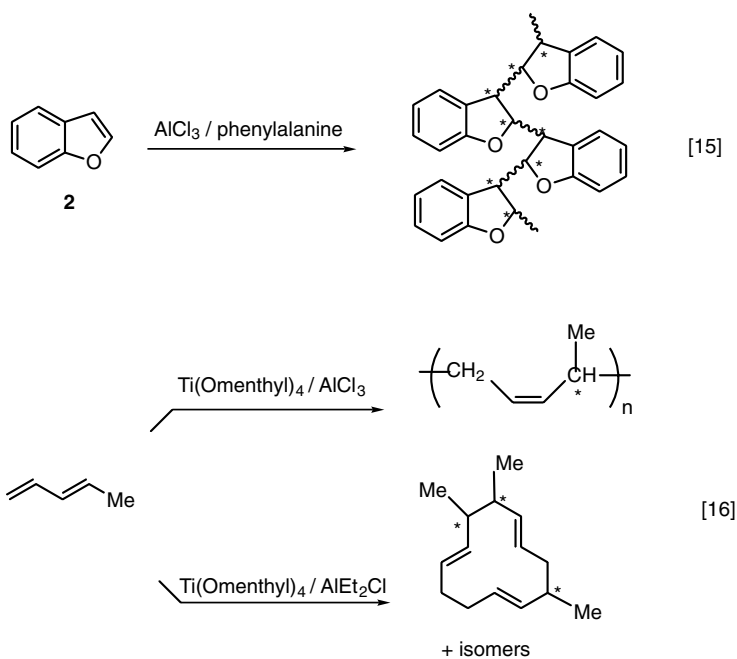
Organometallic Catalysis

4.1.1

Asymmetric Polymerization

Organometallic catalysis was stimulated by industrial research, especially in Germany before and during the last world war. Of course, there were no projects devoted to asymmetric synthesis.

The discovery of the stereoregular polymerization of alkenes by Ziegler-Natta catalysis opened a possible route to optically active polymers by a suitable modification of the catalyst. Indeed, Natta, in 1961, succeeded in polymerizing benzofurane 2 (Scheme 2) under the influence of a catalyst obtained by a combining of AlCl_3 and phenylalanine. Optical activity was detected for the polymer [15]. This reaction seems the first example of homogeneous asymmetric catalysis by a metal complex, however it is difficult to estimate the efficiency of the process from the specific rotation of the polymer. The asymmetric polymerization of 1,3-pentadiene was also studied by Natta et al. in 1963 [16]. The chiral catalysts used were prepared by the combination of titanium tetrachloride with either AlEt_3 or AlEt_2Cl . In both cases optically active polymers were isolated.



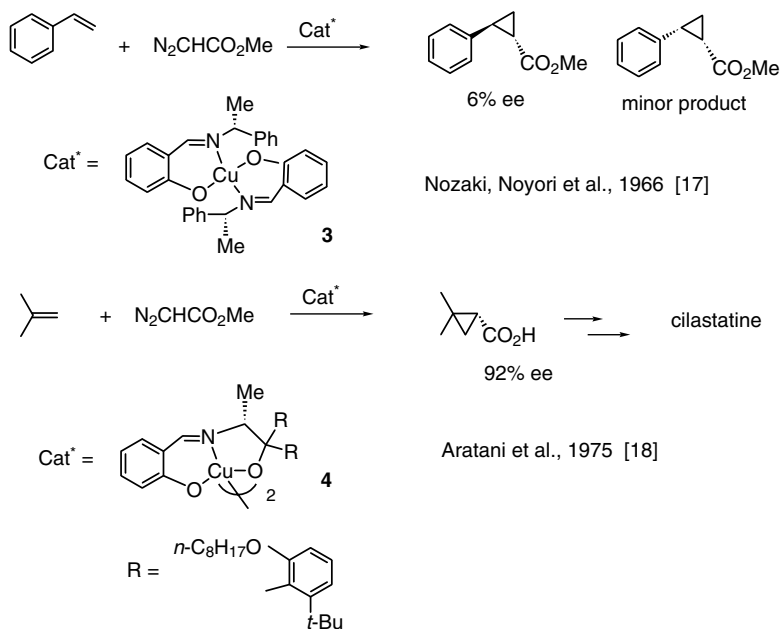
Early examples (1961–1963) of enantioselective polymerization of alkenes

Scheme 2

4.1.2

Asymmetric Cyclopropanation

The first example of asymmetric organometallic catalysis outside the area of polymer chemistry was the cyclopropanation of alkenes as described by Nozaki, Noyori et al. in 1966 [17]. The chiral catalyst used was a salen-copper complex **3** (Scheme 3), giving a maximum enantioselectivity of 10% ee. These low but well-established values initiated further research in this area. Later, Aratani et al. initiated the tuning of the structure of the copper catalyst at Sumitomo [18]. They were able to reach quite high level of enantioselectivity with copper catalyst **4**. For example, 2,2-dimethyl-cyclopropane carboxylic acid was obtained in 92% ee, and subsequently used in a process to prepare cilastatine.



Scheme 3

4.1.3

Asymmetric Hydrogenation

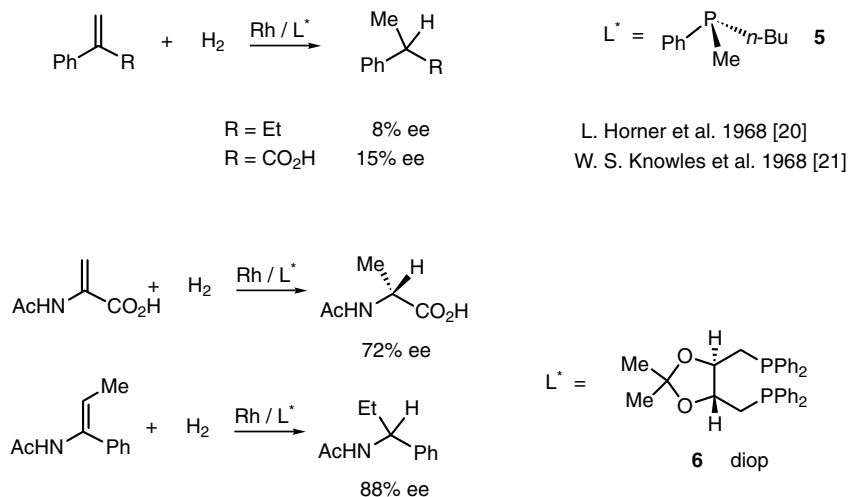
4.1.3.1

Early Stages (1968–1972)

In this section the first five years of asymmetric hydrogenation are described.

The landmark paper of Wilkinson et al. in 1966 [19] established the feasibility of homogeneous hydrogenation of alkenes with $\text{RhCl}(\text{PPh}_3)_3$ as the catalyst precursor. It destroyed the dogma that molecular hydrogen could only be activated and transferred to alkenes by a metallic surface. The mechanism for the Wilkinson catalytic systems was reasonably well-established, showing that two phosphines remain coordinated to rhodium. Moreover, the experimental data showed that the reaction rates were sensitive to the steric hindrance of the substrates. This paper gave the idea to several groups, including ourselves, of looking at asymmetric hydrogenation as a reasonable target.

The most obvious approach was to introduce chiral ligands around rhodium. Horner et al. [20] and Knowles et al. [21], in 1968, independently selected monophosphine **5** as the chiral auxiliary. Phosphorus itself was the center of chirality, located in close proximity to the alkene coordinated to rhodium. Unfortunately, the asymmetric induction was very small, not over 10% ee (Scheme 4). Nevertheless, these experiments established the possibility of transforming the Wilkin-



H. B. Kagan, T. P. Dang, 1971 [22], 1972 [23]

Scheme 4

son catalyst into a chiral rhodium catalyst, although there remained a question mark: what would be the maximum level of enantioselectivity be reached in these systems?

In 1971 [22] and 1972 [23], we showed that the chelating diphosphine **6**, named diop, provided an excellent rhodium catalyst, able to give enantioselectivities of up to 88% ee. We chose to synthesize ligands devoid of asymmetric phosphorus and easily prepared from precursors from the chiral pool. In order to enhance the asymmetric induction we decided to synthesize chelating diphosphines, hoping that a chiral conformation of the chelate ring would induce a preferential chiral array of the phenyl rings on phosphorus. We also wanted to minimize the formation of the number of diastereomers around rhodium. For that reason we selected C₂-symmetric diphosphines with two equivalent phosphorus (a highly dissymmetric C₁-symmetric diphosphine will equally fulfill these conditions). This was the first example of the use of a C₂-symmetric ligand. This approach has been widely used since then (for a review see Ref. [24]) and many chiral diphosphines of C₂-symmetry have been subsequently prepared (vide infra). The easy access to diop stimulated the study of enantioselective catalysis in various reactions, such as hydroformylation [25], hydrosilylation [26] and allylic substitution [27, 28].

Some chiral monophosphines were also prepared during the period 1971–1973. Camp (cyclohexyl *o*-anisyl methyl phosphine) led to a quite high ee (up to 90%) in asymmetric hydrogenation of *N*-acetyl dehydrophenylalanine [29] and neomenthyl diphenyl phosphine gave modest ee's in the reduction of various conjugated acids [30].

4.1.3.2

The Period 1973–1979

The continuous efforts of various groups in the area of enantioselective hydrogenation is well reflected by the synthesis of new generations of chiral diphosphines of improved efficiency.

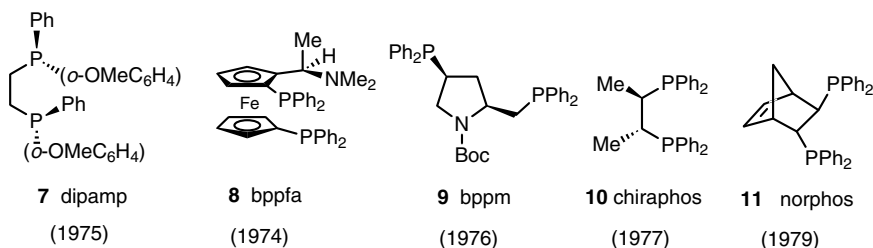
One of the early and important achievement was the preparation, in 1975, of dipamp **7** at Monsanto by Knowles et al. [31]. This chiral diphosphine combines the good properties of a C_2 -symmetric chelating system with the simultaneous presence of two asymmetric phosphorus. It was efficient in the asymmetric hydrogenation of dehydroaminoacids (ee's of up to 90–95%), allowing the preparation of (*S*)-DOPA on an industrial scale from the mid-1970s. This was the first industrial asymmetric synthesis.

Knowles et al. also investigated the X-ray structures of various rhodium complexes involving chelating diphosphines. They proposed an empirical rule (the “edge-face rule”) correlating the absolute configuration of the chiral arrays of P-phenyl groups to the absolute configuration of the aminoacid which is produced in the hydrogenation [32].

A very simple C_2 -symmetric diphosphine **10** was prepared by Bosnich and Fryzuck in 1977 [33]. Hydrogenation of *N*-acetyldehydrophenylalanine gave *N*-acetylphenylalanine with an ee close to 99%. The authors proposed that the asymmetric induction originated from the twist conformation of the chelate ring (λ or δ configuration), locked by the diequatorial orientation of the two methyl substituents.

C_1 -symmetric diphosphines such as bppfa **8** [34, 35], bppm **9** [36] or norphos **11** [37] were synthesized, some of which gave excellent results in asymmetric hydrogenation (Scheme 5).

The mechanism of asymmetric hydrogenation of dehydroaminoacids has been studied by a combination of kinetic and spectroscopic methods, mainly by Halpern et al. [38] and Brown et al. [39]. It was proved that the substrate bound by both the double bond and the amide group. It was surprising to see that the major diastereomeric rhodium-alkene complex detected in solution was the less reactive one towards hydrogen. This showed the inaccuracy of previous models of the “lock and key” type between the prochiral double bond and the chiral



Scheme 5

complex. The stereodetermining-step was believed to occur during the oxidative addition of hydrogen to rhodium.

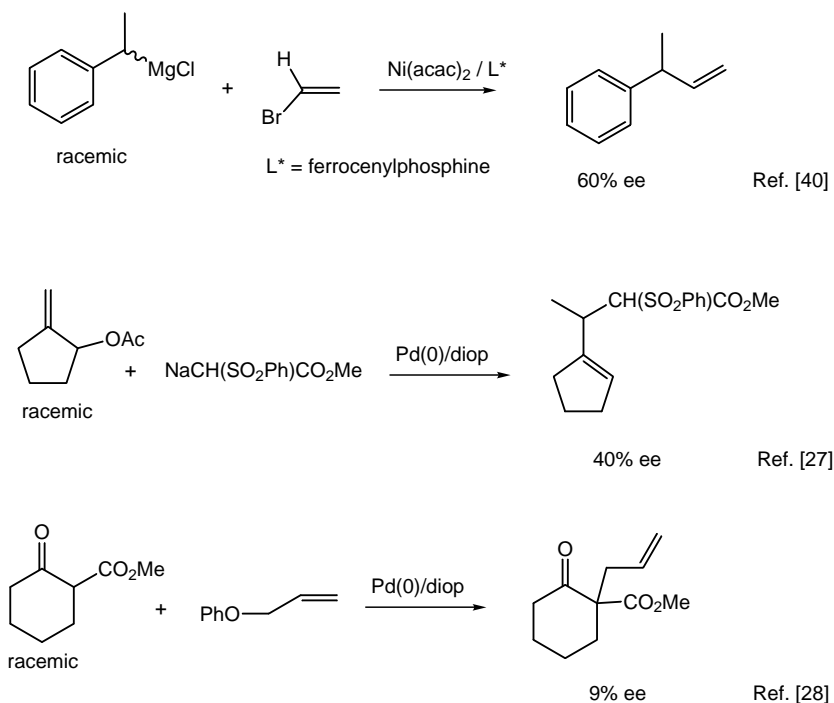
4.1.4

Miscellaneous

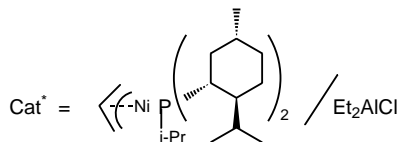
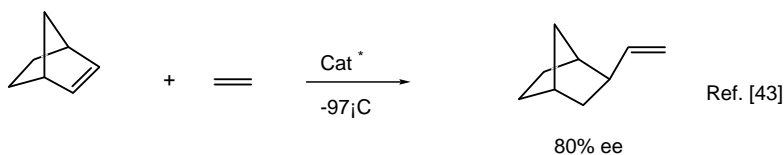
Asymmetric hydroformylation was studied in depth by Pino et al. from a fundamental point of view, but the enantioselectivities remained modest [25]. *Asymmetric hydrosilylation* of ketones gave alcohols with ee's of up to 85%, using mainly diop as a ligand [26]. *Asymmetric C-C coupling* between a Grignard reagent and a vinylic halide was pioneered by Kumada and Hayashi [40]. Substantial enantioselectivities were achieved by the use of ferrocenyl mono- or diphosphines such as bppfa **8** or analogs (Scheme 6). The beginning of asymmetric *allylic substitution* catalyzed by palladium complexes can be traced to 1977–1978 [27, 28] (Scheme 6).

The first asymmetric *Wacker-type oxidation* of alkenes using a chiral Pd(II) complex was described by Hosokawa and Murahashi [41]. A copper salt catalyzed the air reoxidation of Pd(0) to Pd(II).

Asymmetric codimerization between 1,3 dienes and alkenes catalyzed by nickel/phosphine complexes was discovered in the Max-Planck-Institut für Kohlen-



Scheme 6



Scheme 7

forschung in Mülheim in the late 1960s. Wilke, Bogdanovic et al. in 1972 found that 1, 3-cyclooctadiene and ethylene gave 3-vinylcyclooctene in 70% ee [42]. This was the first example of catalytic asymmetric C-C formation with such a high enantioselectivity. Norbornene and an excess of ethylene gave also in good yield *exo*-vinylbornane in 90% ee (Scheme 7) [43]. The reaction temperature was -97°C and the chiral ligand used was isopropyl dimethyl phosphine. An investigation of the mechanism led to a proposition to explain the origin of asymmetric induction.

A *Diels-Alder reaction* catalyzed by a chiral Lewis acid was described for the first time in 1979 by Koga et al. [44]. The catalyst was prepared by action of *(-)*-menthol on EtAlCl_2 and gave 72% ee (later revised to 55% ee) in the formation of the *exo*-cycloadduct between cyclopentadiene and methacroleine.

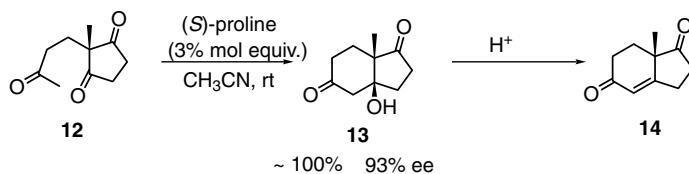
4.2 Organic Catalysts in Enantioselective Synthesis

There were many attempts to modify well-established base-catalyzed reactions, mostly with limited success.

From 1960, Pracejus studied the base-catalyzed methanolysis of ketenes in depth [45]. Using *O*-acetylquinine as a catalyst, he obtained (*S*)-methyl hydratropate in 74% ee at -110°C from methyl phenyl ketene. An inversion of absolute configuration occurred on raising of the temperature.

Wynberg popularized and systematically investigated the use of *alkaloids* (e.g. quininium benzylchloride: quibec) as chiral catalysts in various base-catalyzed reactions [46, 47]. The best result (56% ee) was obtained in the Michael addition.

Asymmetric phase-transfer catalysis had a very slow development, although the principle is quite simple. A two-phase system is involved, usually liquid/liquid (water:organic solvent), with a water-soluble base and reactants in the organic phase. A phase-transfer catalyst such as a quaternary ammonium salt with a good balance of hydrophilicity and hydrophobicity transfers the base to the or-



Catalytic intramolecular aldol reaction (1971) [51, 52]

Scheme 8

ganic phase and triggers the start of the reaction (alkylation, Michael addition etc.). The first attempts were made with an ephedrinium salt as the phase-transfer catalyst for the asymmetric alkylation of β -ketoesters [48] or epoxide formation from aldehydes and sulfonium salts [49]. The enantioselectivities were detectable but very small, making this approach not very appealing (a cautionary and pessimistic note in 1977: see ref. [50]).

A most surprising discovery came in the early seventies from the independent investigations at Hoffmann-La-Roche [51] and Schering Berlin [52]. (S)-Proline (3% mol equiv.) catalyzes the *intramolecular aldolization* of triketone **12** (Scheme 8) in good yield, giving ketol **13** in 93% ee. This ketol was dehydrated into diketone **14**, which is a starting material in the total synthesis of steroids and 19-norsteroids. The Hajos-Parrish-Wiechert reaction was extended to various diketones, and became in the seventies one of the first catalytic reactions of practical usefulness in synthetic organic chemistry. At that time the mechanism was unknown and the origin of asymmetric induction could not be determined.

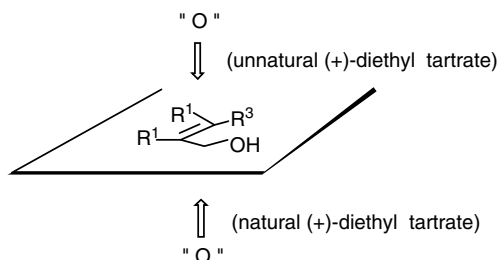
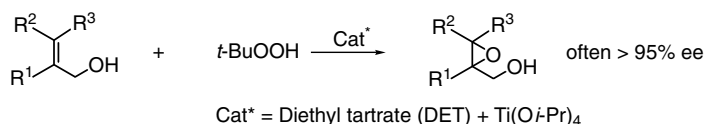
5**Enantioselective Catalysis Between 1980 and 1990**

The period 1980–1990 was a decade of impressive achievements in asymmetric catalysis, giving birth to new synthetic methods. Most of the progress came from organometallic catalysts.

5.1**Organometallic Catalysis**

Two breakthroughs were published in 1980, making the year a pivotal date in the development of asymmetric catalysis.

Sharpless and Katsuki described a very general method for the *asymmetric epoxidation of allylic alcohols* (Scheme 9) [53]. The titanium alcoholate was initially used in stoichiometric amounts, though it was subsequently found it was possible to run the reaction catalytically in the presence of molecular sieves [54]. This method soon became a routine reaction in synthesis, because of its gener-



Sharpless epoxidation of allylic alcohols (1980) [53, 54]

Scheme 9

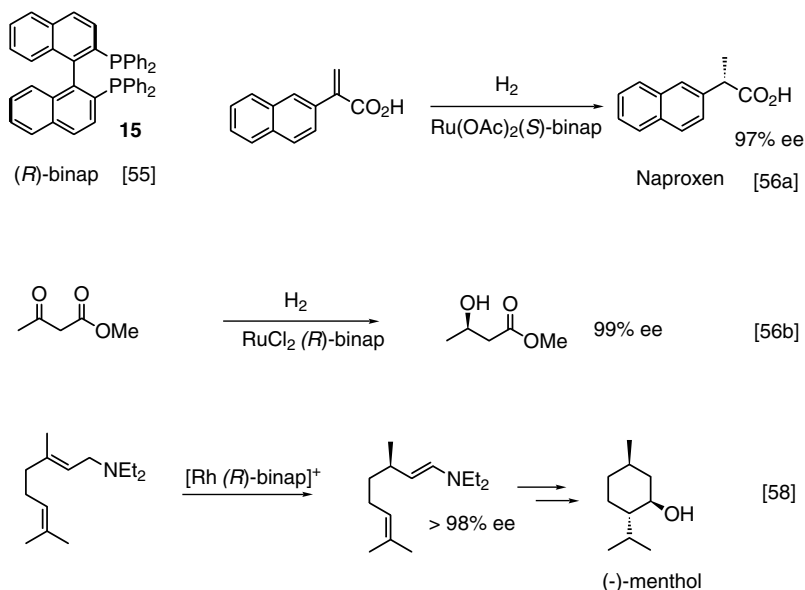
ality, broad scope, high ee's and the predictability of configurations by the mnemonic rule of Scheme 9.

Asymmetric hydrogenation was boosted towards synthetic applications with the preparation of binap 15 by Noyori et al. [55] (Scheme 10). This diphosphine is a good ligand of rhodium, but it was some ruthenium/binap complexes which have found spectacular applications (from 1986 up to now) in asymmetric hydrogenation of many types of unsaturated substrates (C=C or C=O double bonds). Some examples are listed in Scheme 10. Another important development generated by binap was the isomerization of allylamines into enamines catalyzed by cationic rhodium/binap complexes [57]. This reaction has been applied since 1985 in Japan at the Takasago Company for the synthesis of (-)-menthol (Scheme 10).

A new family of chelating diphosphines, where phosphorus is part of a five-membered ring containing two asymmetric centers, was developed at Du Pont by Burk et al. in 1990 [58a]. These C_2 -symmetric ligands (duphos and derivatives) gave excellent rhodium catalysts for asymmetric hydrogenation of many types of unsaturated systems.

Pfaltz et al. performed enantioselective reduction of α,β -unsaturated esters by sodium borohydride in ethanol in the presence of semicorrin 16- CoCl_2 catalyst (Scheme 11), with some enantioselectivities reaching 96% ee [58b].

Asymmetric dihydroxylation of isolated C=C was achieved by Sharpless et al. [59] using OsO_4 in catalytic amounts in the presence of a chiral amine in an organic solvent and water, a tertiary amine *N*-oxide being the secondary oxidant. The chiral catalyst is *O*-protected dihydroquinine or dihydroquinidine, which binds to osmium by the quinuclidine nitrogen. The enantioselectivity is the highest with *trans*-stilbene or *trans*-1-phenylpropene (85% ee and 65% ee respec-



Binap (Noyori et al. 1980) and some applications in asymmetric catalysis (1980-87)

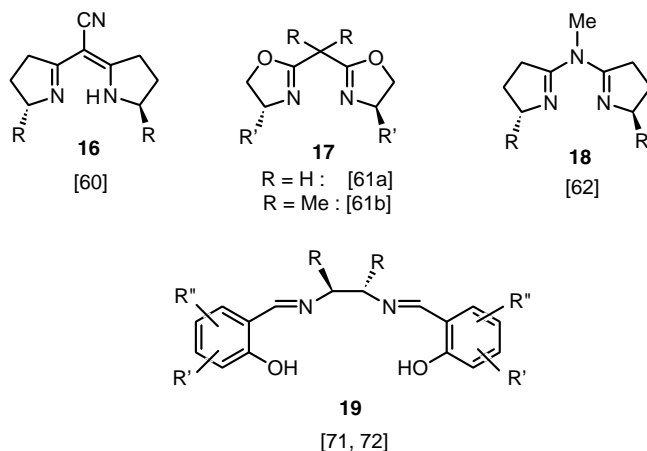
Scheme 10

tively), it is lower for a monosubstituted alkene such as styrene (56% ee). Mechanistic investigations and ligand engineering quickly allowed the definition of new experimental conditions and new ligands, specific for a given class of alkenes. This optimization culminated in the following decade by making this second Sharpless reaction a highly useful technology in organic synthesis.

Cyclopropanation of alkenes was greatly improved by the use of a new generations of chiral copper complexes [60–62]. Some of the ligands (16–18) are indicated in Scheme 11. Chiral complexes of rhodium (II) started to be developed by Doyle et al. [63], later giving enantioselectivities up to 89–90% ee in many cases.

Catalysis by palladium complexes was actively developed during this decade. Allylic substitution gave excellent results in some cases, thanks to a good fit between the structures of catalyst and substrate. There were significant improvements in the enantioselectivities of the reactions and understanding to some extent of various mechanistic details (for example see [64, 65, 66]). Most of the time the product was formed with one or several asymmetric centers. In rare cases axial chirality may be created, too [67].

The first cases of an asymmetric Heck reaction were reported in 1989 by Shibasaki et al. [68] and Overman et al. [69]. The authors selected suitable substrates, choosing intramolecular ring forming reactions.



Some polydentate nitrogen ligands prepared during 1980-1990 decade

Scheme 11

Asymmetric epoxidation of alkenes is a key reaction in organic synthesis. Most of the approaches have been inspired by the mechanism of biological oxidations involving P-450 cytochrome. The first positive results were given using a chiral iron porphyrine as the catalyst and PhIO as the oxygen donor, according to a publication by Groves and Meyer in 1983 [70]. The enantioselectivity was low (51% ee) for the epoxidation of *p*-chlorostyrene, and the method was not practical. In 1990, chiral salen Mn complexes **19** (Scheme 11) were successfully used by Jacobsen et al. [71] and Katsuki et al. [72] for catalytic epoxidation of alkenes, enantioselectivities reaching 90% ee. This approach was developed in the following years into a useful method (ee's up to 98%), especially by Jacobsen et al. who used cheap oxygen sources such as sodium hypochlorite.

In the 1980s, *chiral Lewis acids* became a new area of fast development for asymmetric catalysis. In 1983 Danishefsky et al. described hetero Diels-Alder reactions of aldehydes and activated dienes catalyzed by the lanthanide catalyst $\text{Eu}(\text{hfc})_3$, which gave a moderate enantioselectivity (58% ee) [73]. In 1986 Narasaka et al. [74] and Reetz et al. [75] used catalytic amounts of $(\text{RO})_2\text{TiCl}_2$ (binolate or taddolate respectively) in the Diels-Alder reaction of cyclopentadiene with some simple dienophiles. Narasaka et al. reached an enantioselectivity close to 90%. Kauffman et al. [76] found in 1987 that a chiral boron reagent RBBr_2 (R = pinanyl) was a catalyst for the Diels-Alder reaction, giving a modest ee. In 1988, Yamamoto et al. initiated research on a new family of chiral boron catalysts, easily obtained from action of controlled amounts of diborane to a derivative of tartaric acid (leading presumably to the $\text{RCOO-OBR}'_2$ species) [77]. Reaction of cyclopentadiene and acrylic acid using such catalysts gave the *endo*-adduct in 78% ee. In 1990, Helmchen [78] and Yamamoto [79] extended the synthesis of chiral

catalysts by taking *N*-sulfonyl derivatives of α -amino acids instead of tartaric acid derivatives.

Because of lack of space it is impossible to describe the many reports on Lewis acids acting as catalyst in Diels-Alder or hetero Diels-Alder reaction, most of the results prior 1990 may be found in the review of Ref. [80].

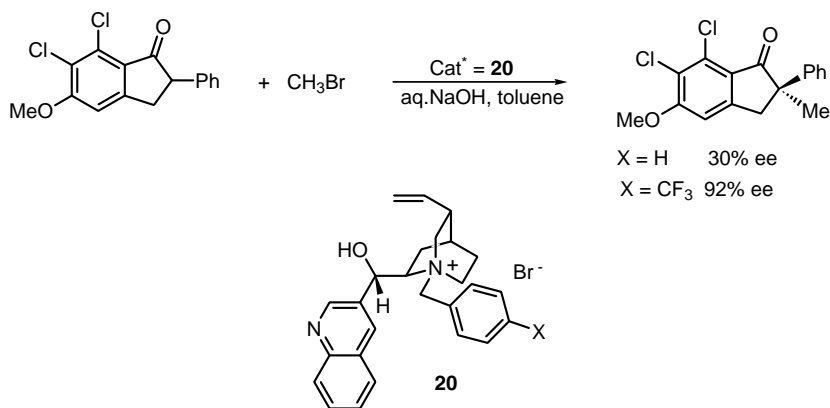
The carbonyl ene-reaction between isobutene and methyl glyoxylate gave a good yield of β -hydroxyester in 95% ee when the catalyst is a dichlorotitanium-binolate [81].

The Mukaiyama aldol reaction has been successfully catalyzed by a tin complex prepared from $\text{Sn}(\text{OTf})_2$ and a chiral diamine [82]. The diastereoselectivity and the enantioselectivity may be remarkably high, both close to 99%.

5.2

Organic Catalysis

Enantioselective *phase transfer catalysis* was stagnant for many years. It emerged suddenly as a preparative method, after the discovery at Merck in 1984 that asymmetric alkylation of some aromatic ketones was possible in ee's of higher than 90%, Scheme 12 [83a]. The authors reached this high level of stereoselectivity by a careful optimization of the experimental conditions and after a detailed mechanistic study [83b]. The key factor is the diastereoselective formation of an ion pair between the enolate of the initial ketone and the catalyst **20**. There is a good fit between complementary aromatic portions of the two components, moreover a hydrogen bond involving the enolate oxygen and the hydroxyl of **20** helps in the formation of the ion pair. By varying the nature of the *para* substituent, X, in the catalyst **20**, it was concluded that the benzyl group of



First example of phase-transfer catalysis reaching 90% ee (1984) [83]

Scheme 12

20 faces the phenyl group of the enolate because of charge transfer towards the benzyl group. The highest ee's occurred with X=electron-withdrawing substituents.

Aminoalcohols or peptides were used as catalysts in various reactions, sometimes with remarkable success.

Asymmetric epoxidation of chalcone, in basic conditions, by hydrogen peroxide may be catalyzed by poly-(*S*)-alanine [84], giving ee's of up to 97%. The system may be considered as a case of phase-transfer catalysis. The scope of this reaction is however not very broad.

β -Aminoalcohols are excellent catalysts for the enantioselective addition of diorganozincs to aromatic aldehydes (enantioselectivities of up to 90–98% ee). This reaction was discovered by Oguni et al. in 1983 [85]. In a sense it may be considered as a case of organometallic catalysis since zinc alcoholates are involved in the catalytic cycle [86].

Prolinol or diphenylprolinol were found by Corey et al. [87] and Itsuno et al. [88] to catalyze the enantioselective diborane reduction of many ketones. Corey et al. developed this new route greatly, often called CBS reduction (from the names of the authors of Ref. [87]). An oxazaborolidine which is either formed in situ or can be preformed, is the actual catalyst. A mechanistic picture has been proposed [87].

As a final example of organic catalysis it is interesting to mention the catalytic addition of HCN to an aromatic aldehyde [89]. This old reaction of hydrocyanation of benzaldehyde, pioneered by Bredig in 1912 [10], was revisited in 1981 by Inoue et al. [89]. Impressive enantioselectivities (of up to 90% ee) could be reached by using a cyclic dipeptide as the catalyst. The catalyst is the diketopiperazine formed between (*S*)-histidine and (*S*)-phenylalanine. The mechanistic details of this remarkable reaction are still not well understood, but it has been demonstrated by Danda et al. at Sumitomo that the high enantioselectivity is associated with the colloidal state of the catalyst in the organic solvent [90].

5.3

Nonlinear Effects

The use of enantioimpure catalysts was studied by Kagan, Agami et al. in 1986 [91]. It was established for several examples that it was possible to observe some departure from the expected proportionality between the enantiomeric excess of the catalyst and the enantiomeric excess of the product. Nonlinear effects (NLE) are categorized as a positive nonlinear effect ((+)-NLE) if the curve $ee(\text{product}) = f(ee(\text{catalyst}))$ is above the straight line characterizing the expected proportionality between $ee(\text{product})$ and $ee(\text{catalyst})$. The (+)-NLE has also been named asymmetric amplification [92]. A negative nonlinear effect ((-)-NLE) means that the experimental curve $ee(\text{product}) = f(ee(\text{catalyst}))$ lies below the straight line of the linear correlation. The departure from linearity reflects the formation of diastereomeric species (catalytically active or not) which perturb the predictions based only on mixture of enantiomeric catalysts and the

proportions expected from the initial ee. For example, a ML_2 (or $(ML)_2$) model has been proposed to explain some cases [91]. If the three catalytic complexes ML_RL_R , ML_SL_S and ML_RL_S are formed, an asymmetric amplification will be observed when the *meso* complex is of low activity with respect to the homochiral complexes. Spectacular asymmetric amplifications were observed in 1988 and 1989 [92, 93]. Many cases of (+)- or (-)-NLE are presently known, see Chapter 4.1, this volume for a review on nonlinear effects.

6 Epilogue

In this chapter we have not tried to cover the last decade (1990–2000) because of the exceptional number of new results. Only some general trends will be discussed.

The synthetic value of asymmetric catalysis has been greatly improved by the possibility to reach, in many cases, enantioselectivities in the range of 95–99% ee, with a broad scope. Some books have been specially devoted to asymmetric catalysis, most of the results concerning the period 1980–1994 may be found in Refs. [94, 95]. Many new enantioselective reactions have been discovered, for example, aminohydroxylation [96], aziridination [97, 98], alkene methathesis [99] or alkene chlorohydroxylation [100]. Asymmetric hydrogenation is subject to constant development thanks to the synthesis of new generations of chiral ligands or of new catalysts. Consequently, some industrial processes have started to use asymmetric hydrogenation [101]. Similarly enantioselective allylic substitution, catalyzed by palladium complexes, may give enantioselectivities close to 98% ee thanks to new families of ligands (for example see Refs. [102, 103]). Chiral Lewis acids are of increasing efficiency, although often needing low temperatures to achieve high enantioselectivities. Catalytic enantioselective Mukaiyama aldol condensation has been greatly developed (review: Ref. [104a]). Impressive results both in catalytic loading (0.5 mol %) and enantiomeric excess (99%) have been achieved by Evans et al. with C_2 -symmetric Cu(II) complexes [104b].

Some reactions are still not satisfactory from the point of view of enantioselectivity, such as hydroformylation or allylic hydroxylation (recent review: Ref. [105]).

The accurate measurement of enantiomeric excesses has been helped greatly by technological progress. Before 1970–1975, most enantiomeric excesses were evaluated by polarimetry, with errors in many cases because of contaminants or of the use of incorrect values of specific rotations for references. Nowadays chromatographic or spectroscopic methods are used routinely.

There is a need in asymmetric catalysis to combine high enantioselectivity and high catalytic activity (TOF and TON). This will facilitate the transfer of asymmetric catalysis towards industrial applications. Until now, only a very few industrial processes have taken advantage of asymmetric catalysis.

One can hope that the optimization of asymmetric catalysts or the discovery of new chiral ligands will be accelerated by combinatorial chemistry methods

and by fast-screening methodologies (for a recent review see Ref. [106]). However, breakthrough discoveries will surely remain based on the imagination and the sense of innovation of chemists.

Concepts and mechanistic considerations are often considered in the search for new, efficient enantioselective catalysts. For example, interactions other than steric repulsions are of growing importance in the analysis of competing transition states. Attractive noncovalent secondary interactions between substrate and catalyst are now taken into account in various enantioselective catalytic reactions [107–111]. Corey et al. have discussed transition states, considering an hydrogen bond between the C-hydrogen of an aldehyde group and various hydrogen bond acceptors [112]. Electronic effects of substituents on the catalyst or substrate may also influence the enantioselectivity of the process. Calculations relating to hypothetical competing transition states should be of increasing help to devise more efficient enantioselective catalysts.

Bimetallic catalysts and multifunctional catalysis, whereby activation of substrate and reactant occurs simultaneously at Lewis acid and Brønsted base sites, is an approach for giving more organization to the transition state and a higher stereocontrol [125].

Catalytic antibodies, since the seminal contributions of Lerner and Schulz in the mid 1980s, have appeared as a fascinating way to construct artificial enzymes, specific for a given reaction. Some applications have appeared in asymmetric catalysis, for example Ref. [113]. However, it is too early to predict if this approach will develop into a useful methodology.

Enzymes have high potential in organic synthesis. Applications have been until now mainly based on kinetic resolution, but many opportunities exist to use enzymatic catalysis for enantioselective syntheses. Recently, it was shown by Reetz et al. that a combination of genetic engineering and mutagenesis can easily provide modified enzymes of greatly improved stereoselectivity for the transformation of a given substrate [114]. This concept should find wide applications in catalyzed enantioselective reactions.

Nonlinear effects is becoming very common (see Ref. [115] for a review) and is often a mechanistic tool. Asymmetric amplification has been discovered in many different kinds of catalytic reactions (for a recent review, see Ref. [116]). It has also been very useful in the devising of efficient asymmetric autocatalytic systems [117].

Organic catalysts are of growing interest. A breakthrough occurred in 1998 in phase-transfer catalysis when modified quaternary ammonium salts of alkaloids were used as chiral catalysts [118, 119]. Thus, Schiff bases of glycine esters could be alkylated to give aminoesters (98% ee). Small peptides or organic molecules with a nitrogen acting as an efficient chiral base gave excellent results in various cases of asymmetric catalysis [120, 121].

Various processes (asymmetric protonation or asymmetric deprotonation) which are in principle strictly stoichiometric with respect to the chiral reagent have been transformed into catalytic processes by the addition of an achiral reagent or an achiral ligand.

If an asymmetric catalyst acts perfectly well from the point of view of enantioselectivity and activity, there remains one difficulty to overcome, namely the recovery and the reuse of the catalyst. This can be achieved by asymmetric heterogeneous catalysis. This old approach, where a metal was modified by a chiral additive [12, 14], has been reappraised recently, giving interesting results, but the scope of the reaction remains very narrow (see the review in Ref. [122]).

Another possibility is to covalently graft a chiral catalyst to the surface of an insoluble material (organic or inorganic polymers or sol-gel materials). This approach is not new. We described, in 1973, the first example with the synthesis of a rhodium/diop catalyst bound to a Merrifield resin [122]. Since that time many examples have been published, with moderate success. There is a renewal of interest in this technology, which combines the high enantioselectivity of homogeneous catalysis with the ability to recycle the catalyst. The major limitations to be addressed are a decrease of the catalytic activity and the often encountered problem of partial leaching of the metal. An alternate method is to retain the catalyst in one of the two phases of a biphasic system (for example as a water-soluble catalyst). Some promising results have been obtained for such systems..

In conclusion, asymmetric catalysis is emerging as an almost mature field, after a quarter of a century of active investigations. Asymmetric catalysis is the topic of many international meetings [124] and is periodically reviewed in many journals and books. The continuous interest of the academic and the industrial communities in enantioselective catalysis will be, without any doubt, a strong driving force for new developments in the near future.

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Chapter 3

Basic Principles of Asymmetric Synthesis

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Keywords: Stereogenic reactions, Mechanism control, Substrate and reagent control, Stereoselectivity, Simple diastereoselectivity, *exo-endo*-Diastereoselectivity, Double stereodifferentiation, Chiral catalysts, Chiraphor and catalaphor, Hybrid catalysts, Chiral auxiliary

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1

Introduction

One of the central fields of organic chemistry is that of EPC (enantiomerically pure compound)-synthesis [1], which can be achieved in three different ways:

- (i) by derivatization of a chiral natural product (“ex-chiral pool approach”),
- (ii) by optical resolution, and
- (iii) by asymmetric synthesis.

This article will deal exclusively with the last-mentioned aspect. We define asymmetric synthesis as the act of generating stereogenic units, which may be elements of central, axial, or facial chirality, in a defined configuration. This article will only describe the generation of *stereogenic centers* and leave the synthesis of facially or axially chiral molecules to other review articles [2]. If the substrate is achiral, asymmetric synthesis will generate one out of two *enantiomers* (*enantioselective synthesis*). If the substrate already contains other stereogenic units, or if the reaction generates more than one stereogenic center in one act in an achiral substrate, the asymmetric synthesis creates one out of several possible *diastereomers* (*diastereoselective synthesis*). A special way of generating enantiomers from achiral substrates containing stereogenic units in a *meso* arrangement is desymmetrization [3]; this method is not covered in this article.

In the first section of this article reactions generating new stereogenic centers will be discussed with respect to their reliability and practicability. In a second section syntheses of specific chiral molecules will be described to show how the methodology presented in the first section is used in practice for simple molecules containing just one stereogenic center, for molecules of moderate complexity (two to five stereogenic centers) and for complex molecules with acyclic and polycyclic structures containing many stereogenic centers.

2

Survey of Stereogenic Reactions

2.1

Mechanism Controlled Reactions

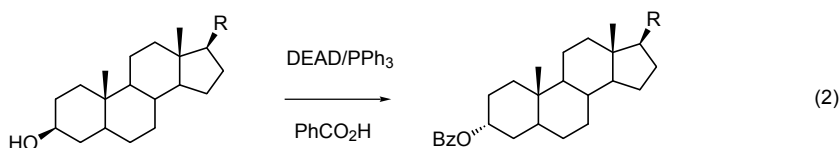
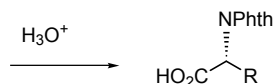
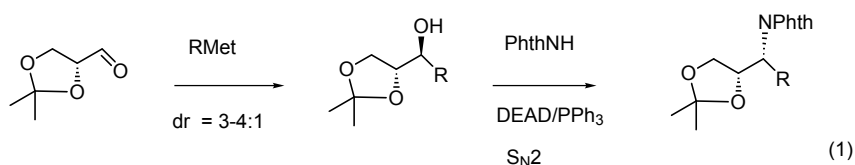
As the central feature, the substrate contains a configurationally pure stereogenic center, which is sacrificed during the process (“self-immolative reaction”) The reaction itself transfers chirality *intramolecularly* from the existing stereogenic center to a new one via an unambiguous stereochemical pathway which is

controlled by stereoelectronic factors only. The other stereogenic centers or substituents in the substrate have only an accelerating or retarding influence. Examples of such mechanism-controlled reactions are S_N2 displacements, sigmatropic rearrangements, and 1,2-migrations of the Wagner-Meerwein type.

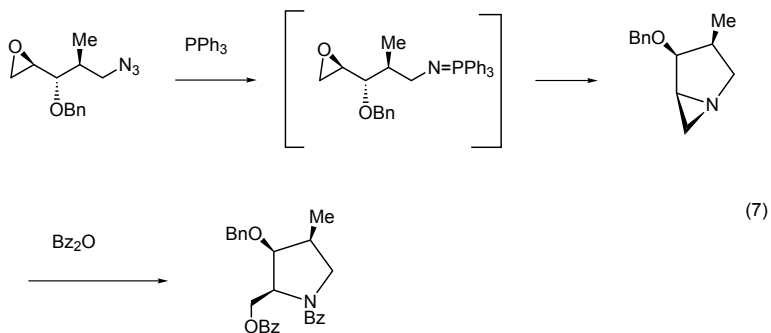
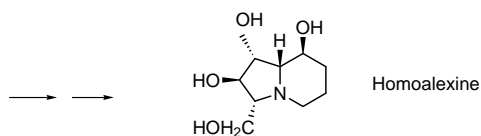
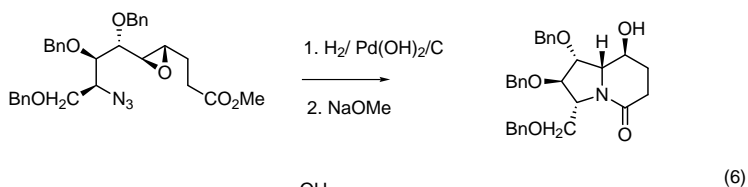
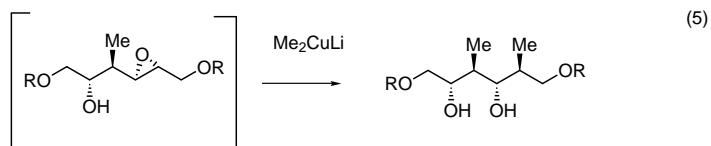
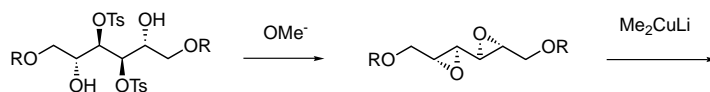
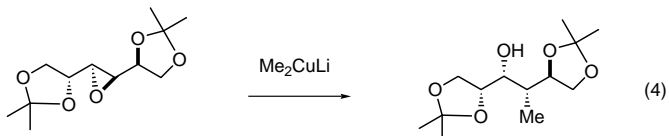
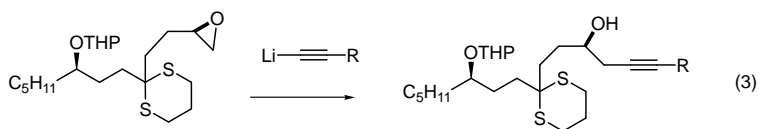
2.1.1

S_N2 -Displacements

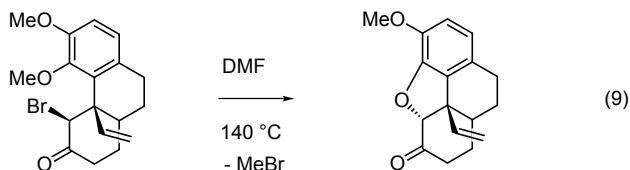
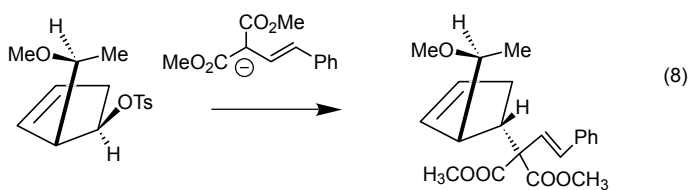
These reactions are particularly important for the introduction of heteroatoms such as nitrogen in polyalcohols in a stereounambiguous manner. Reaction (1) (Scheme 1) shows how this strategy is used for generating amino acids and amino alcohols from (R)-isopropylidene glycerinaldehyde [4]. Also important are the inversion of configuration at secondary hydroxy functions [e.g., Mitsunobu inversion, reaction (2) in Scheme 1] [5] and the opening of epoxides with cuprate reagents. The latter reaction is useful for the stereounambiguous generation of secondary alcohols, if primary epoxides are used [reaction (3) in Scheme 2] [6] or the incorporation of carbon appendages [reaction (4) in Scheme 2] [7], particularly, if performed in a tandem fashion [reaction (5) in Scheme 2] [8]. Azides may be used as amine precursors in S_N2 -type epoxide ring openings. This is demonstrated in an elegant synthesis of indolizidine alkaloids [reaction (6) in Scheme 2] [10]. As shown in reaction (7) in Scheme 2 [11] epoxyazides undergo an S_N2 -type cyclization under Staudinger conditions to form a bicyclic aziridine, which is then opened by a second S_N2 -reaction regioselectively at the primary position to give a monocyclic prolinol derivative as final product. If BOC-anhydride is used in place of benzoic acid anhydride the S_N2 -attack occurs at the secondary position of the aziridine to form the piperidine derivative. Classical S_N2 -



Scheme 1



Scheme 2



Scheme 3

reactions of stabilized carbanions with secondary tosylates or bromides are normally unreliable and low-yielding. An exception is formulated in reaction (8) (Scheme 3) [9]. In a suitable geometric array phenolic methyl ethers undergo S_N2 -ring closure under concomitant demethylation [reaction (9) in Scheme 3] [12].

2.1.2

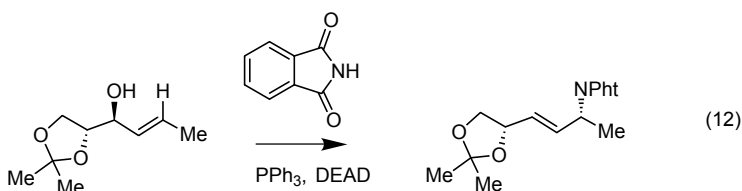
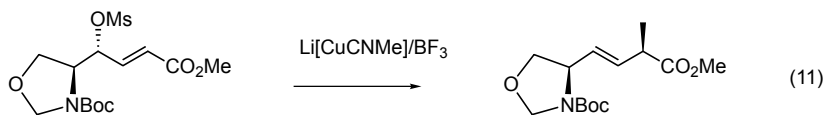
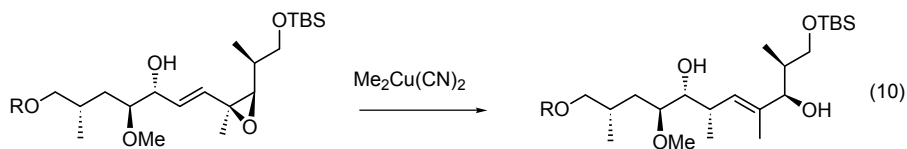
S_N2' -Displacements

Although the stereochemical courses of these displacements are basically also mechanism-controlled, the predictions are not as reliable as in the case of the S_N2 reactions. However, cuprates have been shown to undergo S_N2' -displacements with vinyl epoxides [reaction (10) in Scheme 4] [13] and γ -mesyloxy- α,β -enoates [reaction (11), Scheme 4] [14] with extremely high stereocontrol. A Mitsunobu-type S_N2' -displacement is shown in reaction (12) (Scheme 4) [15].

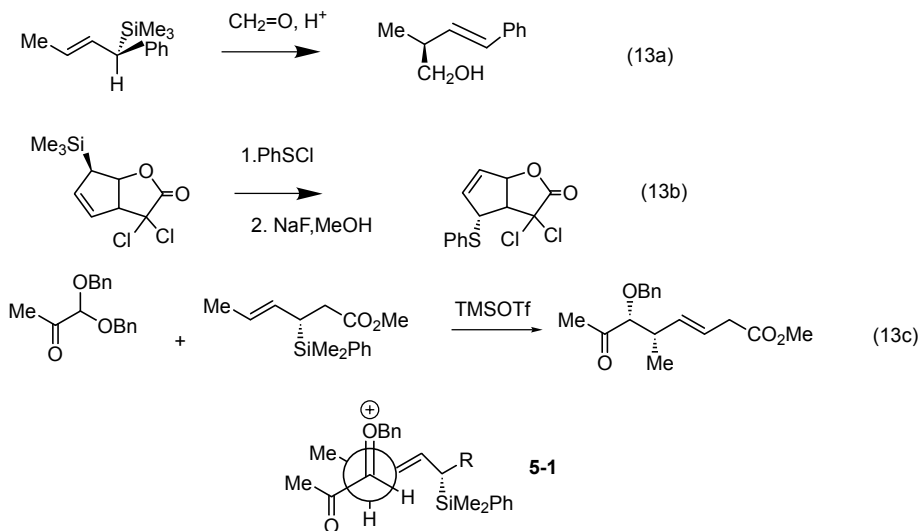
2.1.3

S_E2' -Displacements

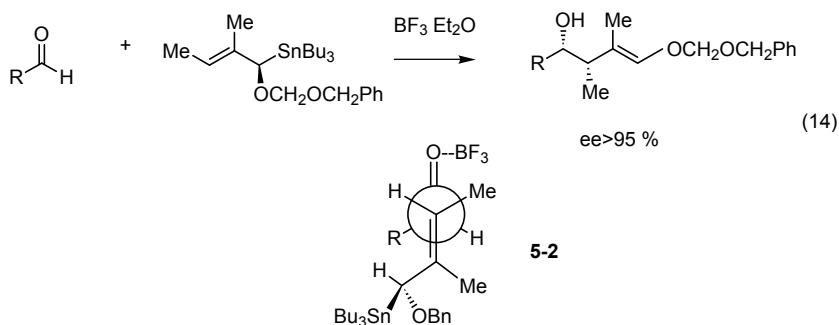
These reactions are typical of allylsilanes and proceed under mechanism-controlled *anti*-addition of electrophiles such as aldehydes and pseudo-halides [reactions (13a, b, c), Scheme 5] [16] and reaction (14) (Scheme 5)[17, 18]. In reaction (13c) a closed transition state 5-1 has been assumed. A very interesting, highly stereocontrolled example is given in reaction (14). An open transition state 5-2 has been postulated with an *anti*- S_E2' attack at the chiral allylstannane [19].



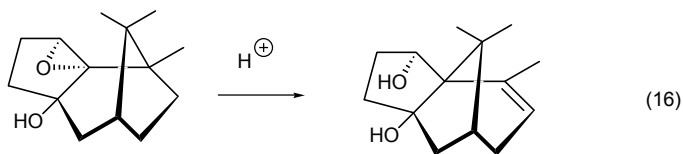
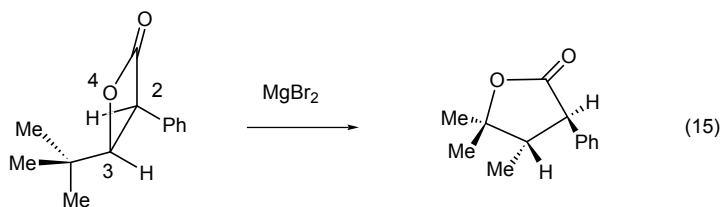
Scheme 4



Scheme 5



Scheme 5 (continued)



Scheme 6

2.1.4

Wagner-Meerwein-Type 1,2-Migrations

These migrations occur in compounds which have a leaving group {such as *O*-acyl in reaction (15) in Scheme 6 [20] or epoxide in reaction (16) in Scheme 6 [21], but cannot undergo an E2-elimination due to a lack of β -hydrogens or due to stereoelectronic constraints. For instance in reaction (15) the 2-H is orthogonal to the *O*-acyl bond and in reaction (16) there is no β -H at all. In such cases a C-C-bond undergoes a 1,2-migration under inversion of configuration. The carbenium ion which is generated by this migration is quenched by adding a nucleophile [reaction (15)] or proton elimination to form an olefin [reaction (16)].

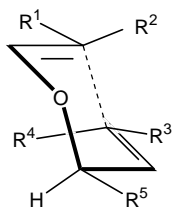
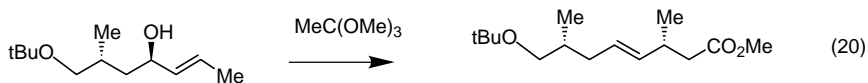
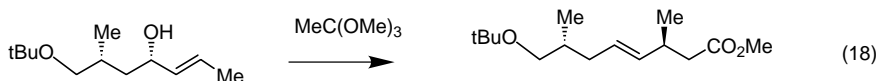
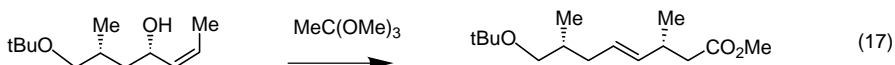
2.1.5

Sigmatropic Rearrangements

2.1.5.1

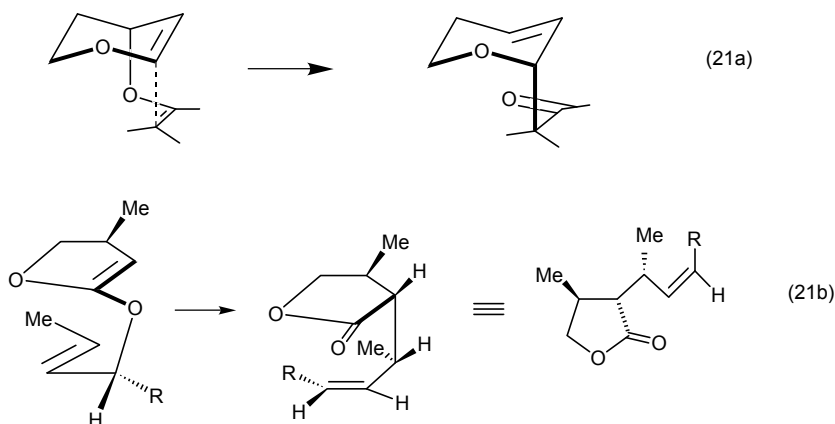
Claisen-Rearrangements

In the Claisen-Johnson or Claisen-Eschenmoser variation, this reaction is a standard method for elongating a carbon chain by a terminally functionalized C₂-fragment (normally from an orthoester or orthoamide). The preparative value lies in the mechanism-controlled transformation of *O*-chirality to *C*-chirality under allylic transposition [reactions (17 to 20) in Scheme 7] [22]. As the rear-



7-1

Scheme 7



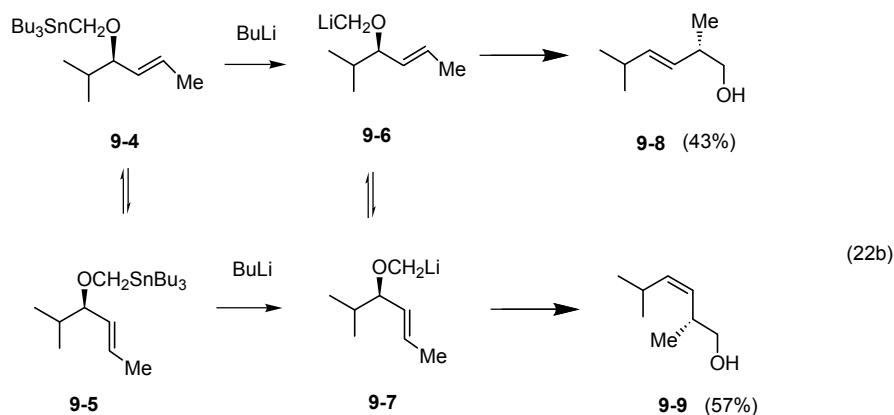
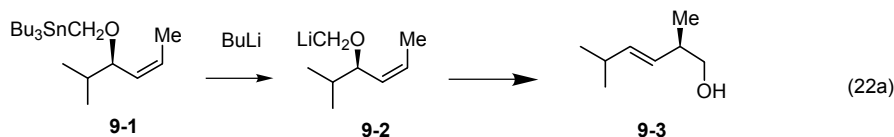
Scheme 8

rearrangement of acyclic allylic systems reliably proceeds via a chairlike six-centered transition state 7-1 the 1,3-chirality transfer occurs suprafacially with respect to the nodal plane of the olefin. For secondary allylic alcohols the substituent R^5 adopts an equatorial position. As shown in reactions (17 to 20) the configuration of the newly created stereogenic center depends on the configuration of the corresponding allylic-OH-function and the (*E/Z*)-geometry of the double bond. If both stereodescriptors are inverted as in reactions (17) vs. (20) or (18) vs (19) the stereochemical result is the same. If only one stereodescriptor is changed, the configuration at the new stereogenic carbon is reversed [reactions (17/18) or (17/19) or (18/20) or (19/20)]. If the allylic alcohol is part of a ring boat like transition states are frequently preferred [reactions (21a) [22] and (21b) [23] in Scheme 8}. The change from chair to boat does not change, however, the suprafacial nature of the 1,3-chirality transfer.

2.1.5.2

[2,3]-Wittig Rearrangement

This rearrangement is generally performed in the variation by Still using tributylstannyl ethers which undergo α -lithiation on treatment with *n*-butyllithium. Olefin 9-1 is conformationally stabilized due to the allylic 1,3-strain phenomenon discussed later. Thus 9-2 is formed which undergoes the sigmatropic rearrangement at temperatures below -60°C and produces stereochemically pure homoallylic alcohol 9-3 [reaction (22a) in Scheme 9]. By contrast, the (*E*)-olefin 9-4 is in a mobile conformational equilibrium with 9-5, so that 9-6 and 9-7 are generated after lithiation which both undergo suprafacial [2,3]-shifts to form alcohols 9-8 and 9-9 in comparable amounts [reaction (22b)] [24].



Scheme 9

2.2 The Problem of Stereoselectivity

Mechanism-controlled reactions do not have stereochemical problems as the stereochemical course of the reaction is unambiguous. Contrary to that there is a large body of reactions where the mechanism does not solely determine the stereochemical outcome. Rather it depends on the substrate and the reagent which one of two enantiomers or diastereomers will be formed. This creates the problem of stereoselectivity.

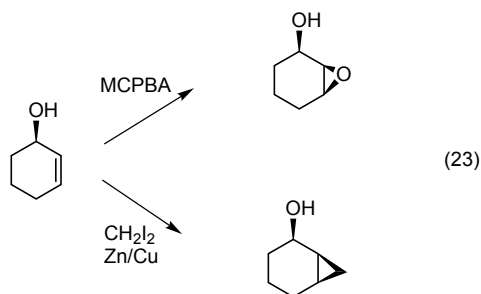
2.2.1 Substrate Controlled Reactions

The vast majority of new stereogenic centers is generated by additions to prosterogenic sp^2 carbons under the influence of preexisting stereogenic centers in the substrate which may exert a stereodirecting influence in two ways: either *passively* by steric shielding of one of the two diastereotopic faces of the reactive center or *actively* by binding the reagent in form of non-covalent interactions and directing it towards one of the diastereotopic faces.

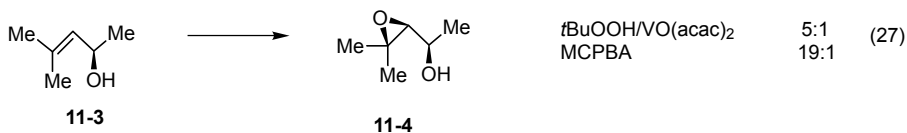
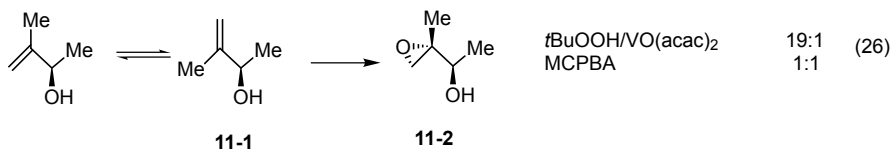
2.2.1.1

Active Substrate Control

The standard situation is well illustrated by Henbest's classical epoxidation of 2-cyclohexenol with MCPBA [reaction (23), Scheme 10] [25]. The OH-function acts

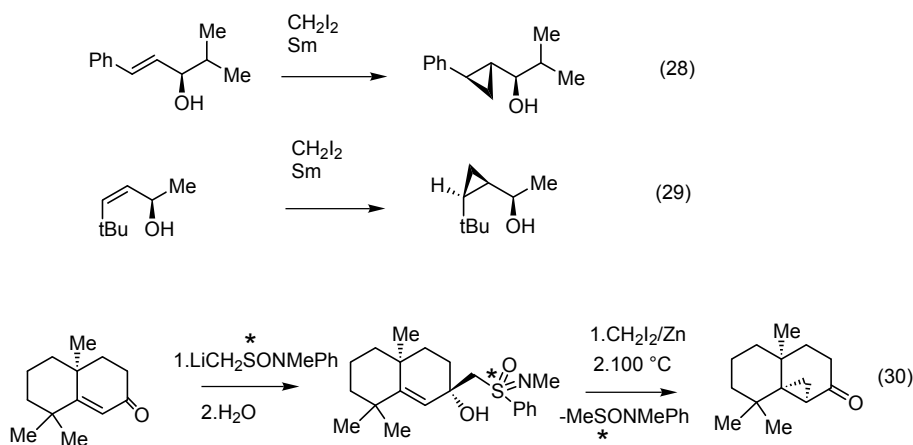


R=R'=H > 25:1
 R=H, R'=Bn 6:1
 R=Bn, R'=H >25:1
 R=R'=Bn 1:1



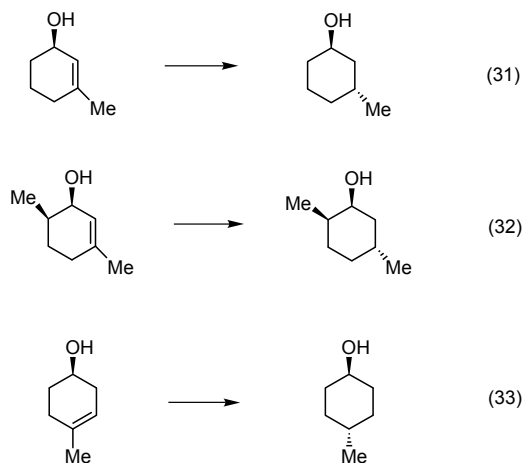
Scheme 10

as an anchor for the peracid by hydrogen bridging and directs it towards the *syn* face of the double bond. The same mechanism, now by means of ionic O-Zn-interactions, operates in the Simmons-Smith cyclopropanation of the same substrate. In acyclic substrates the stereocontrol is less reliable although high diastereoselectivities are observed in favorable cases. In reaction (24) in Scheme 10 [26] it is demonstrated that free hydroxy functions are required in allylic alcohol systems to acquire high stereoselection. In many cases the anchor function of a free OH-function is utilized to bind a transition metal, preferably vanadium or molybdenum to direct and activate the peroxide for epoxidation. The reaction is *syn* to the OH-function within the reactive conformation. This is clearly the *cis*-ring face in cyclic allylic and homoallylic alcohols [reaction (25), Scheme 10] [27], whereas in acyclic substrates the stereochemical outcome depends on A^{1,2}- and A^{1,3}-strain effects around the double bond (*vide infra*). For instance, in reaction (26) (Scheme 10) the A^{1,2}-strain exerted by the two adjacent methyl groups leads to a reactive conformation 11-1 with minimized steric repulsion and the *anti*-epoxide 11-2 is produced. Alternatively, in reaction (27) (Scheme 10) the A^{1,3}-strain leads to the reactive conformation 11-3 from which the *syn*-epoxide 11-4 is formed [28]. In both reactive conformations the epoxidating agent is directed to the *syn*-face of the double bond via OH-complexation. Similar *syn*-OH-stereodirecting effects in the reactive conformation are observed in the samarium-induced Simmons-Smith cyclopropanation. In reaction (28) (Scheme 11) the substrate adopts an extended conformation, whereas in reaction (29) (Scheme 11) the A^{1,3}-strain effect is operative [29]. In cyclic hydroxysulfoximides, which are obtained by the addition of the corresponding sulfoximine carbanion to the cyclic ketone, the cyclopropanation is again directed *syn* to the OH-group. After the addition the sulfoximine is eliminated by thermolysis [reaction (30), Scheme 11] [30]. Homogeneous catalytic hydrogenations can also be performed under the directing effect of free hydroxy functions (Scheme 12).



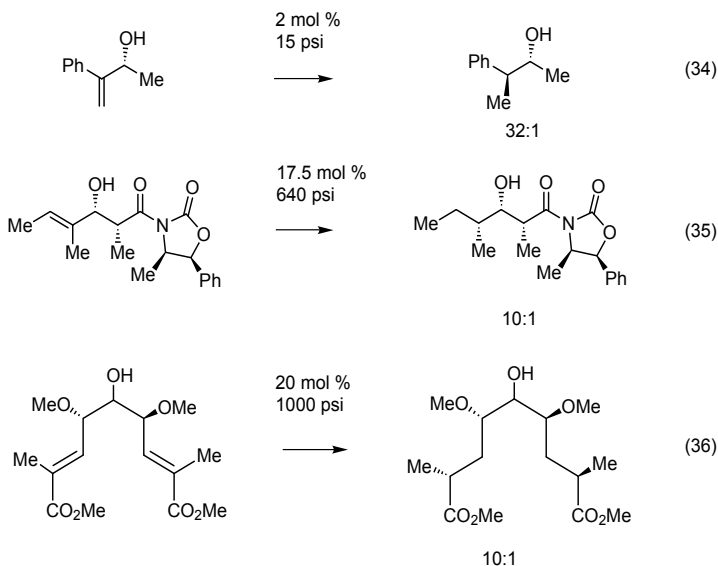
Scheme 11

With the Ir-catalyst noted in reactions (31 to 33), Scheme 12 [31] the hydrogenation of cyclohexenols is totally *syn*-controlled. In acyclic systems such as reaction (34) [31] and reactions (35 and 36) in Scheme 13 [32] a Rh-catalyst is employed which has a *syn* directing effect in reaction (34) whereas reactions (35



Conditions in reactions (31-33): H_2 / catalyst $[\text{Ir}(\text{cod})\text{py}(\text{PCy}_3)]\text{PF}_6$ 2-20 mol %

Scheme 12

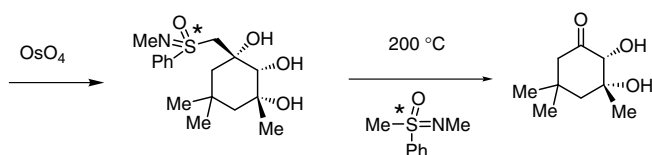
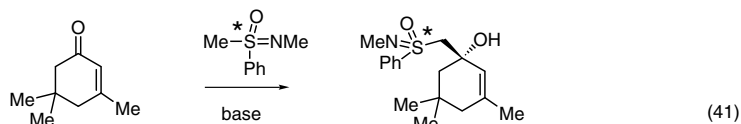
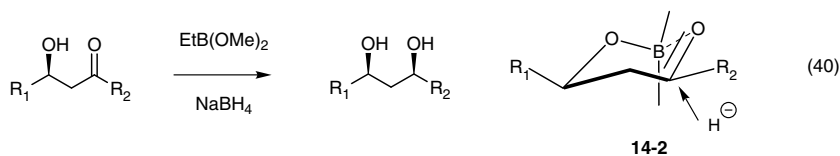
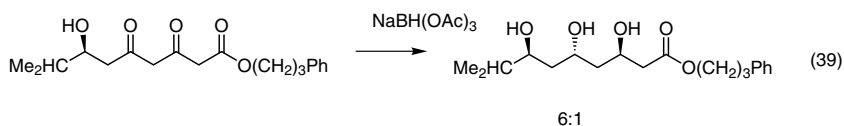
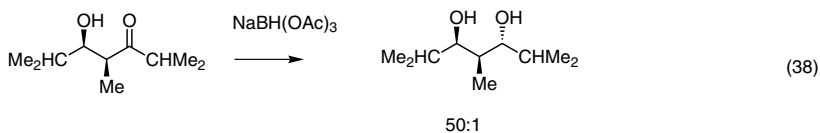
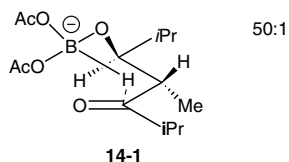
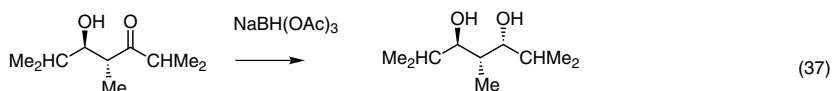


Conditions in reactions (34,35,36): $[\text{Rh}(\text{nbd})(\text{diphos-4})]\text{BF}_4$, catalyst concentration, H_2 -pressure

Scheme 13

and 36) formally show *anti*-direction which however may be due to other substituents present in the molecules.

A well-established procedure to obtain *anti*-1,3-diols is the stereocontrolled reduction of 3-hydroxyketones via a complexation of the OH-function with the reagent (Scheme 14). In this way a cyclic transition state such as 14-1 [reaction



Scheme 14

(37), Scheme 14] is adopted in which the hydride is delivered *syn* to the hydroxy function. This stereochemistry is independent of additional stereogenic centers in the 2-position [reactions (37 vs 38), Scheme 14]. It also works in a relay fashion to create all-*anti*-1,3,5-triols [reaction (39), Scheme 14] [33]. The application of a different borohydride reagent ($\text{Et}_2\text{BOME}+\text{NaBH}_4$) results in the formation of complex 14-2 and, hence, in an *anti*-attack of the hydride to generate *syn*-1,3-diols [reaction (40), Scheme 14] [34]. The *syn*-directing effect of the OH-function in cyclic systems is also utilized in dihydroxylation reactions with osmium tetroxide [reaction (41) in Scheme 14]. The methodology introduced in reaction (30) (Scheme 11) is applied to convert the achiral cyclohexenone 14-3 into the enantiomerically pure diol 14-4 [35].

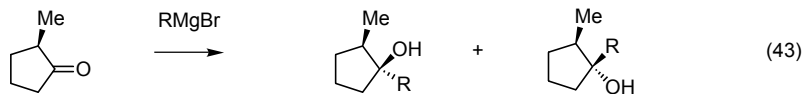
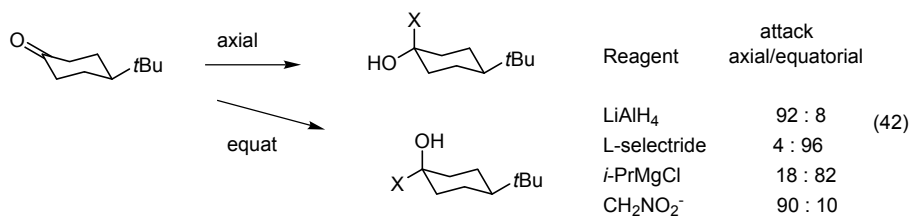
2.2.1.2

Passive Substrate Control

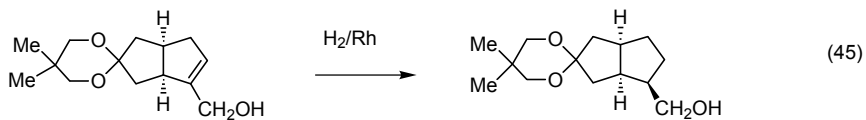
This can be done by conformational and steric effects, which have to serve two objectives. Firstly, as in the previous section, a defined reactive conformation has to be fixed by substituent effects and, secondly, one of the two diastereofaces has to be shielded by the steric repulsion of the substituents. These effects are different in cyclic and acyclic systems as in the former ones the conformation is normally controlled by the more or less rigid geometry of the ring.

Cyclic Substrates (Scheme 15). In reaction (42) [36] the classical case of axial vs. equatorial attack of nucleophilic reagents on a conformationally locked cyclohexanone is described. Although the issue is not totally settled yet, it appears that for “small” nucleophiles such as lithium aluminum hydride or the nitromethane anion the axial attack is preferred for stereoelectronic reasons. For bulkier reagents the equatorial attack prevails. In cyclopentanones vicinal substituents direct the incoming nucleophile into the *trans*-position [reaction (43), Scheme 15] [37]; a similar effect is observed for cuprate additions to cyclohexenones [reaction (44), Scheme 15] [38], although in this specific example the stereochemical course of the reaction is strongly influenced by the nature of a remote protective group (high stereocontrol for TBDMS, low stereocontrol for benzoate). A reliable stereocontrol is exerted by the bicyclo[3.3.0]octane skeleton which, due to the ring strain, exists in the *cis*-fused geometry. The addition to *endo*- and *exo*-double bonds within the ring system selectively occurs from the convex-face, i.e., *cis* to the hydrogens on the ring fusion {reactions (45) [39] and (46), Scheme 15 [40]}.

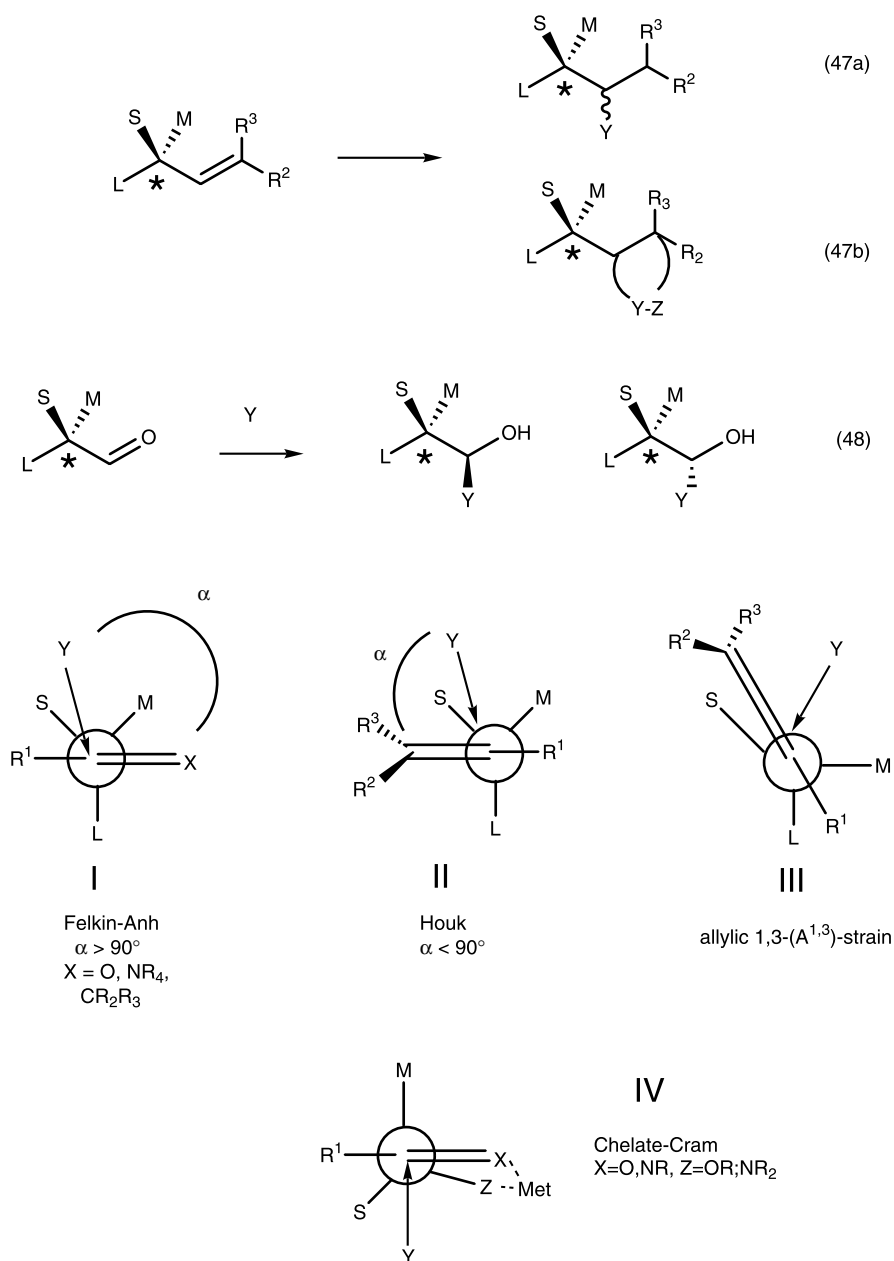
Acyclic Substrates. The situation in acyclic systems is much more complicated than in cyclic ones as high stereocontrol for additions to prostereogenic double bonds [reactions (47a,b), Scheme 16] or carbonyl groups [reaction (48), Scheme 16] can only be achieved if the molecule adopts a definite reactive conformation in which one of the two diastereofaces is efficiently shielded by the steric effects of the substituents (Scheme 16) [41]. This means that these substituents have to be of different sizes and may be classified as small (S), medium



R = Me 60 : 40, Et 75 : 25, Ph 99 : 1

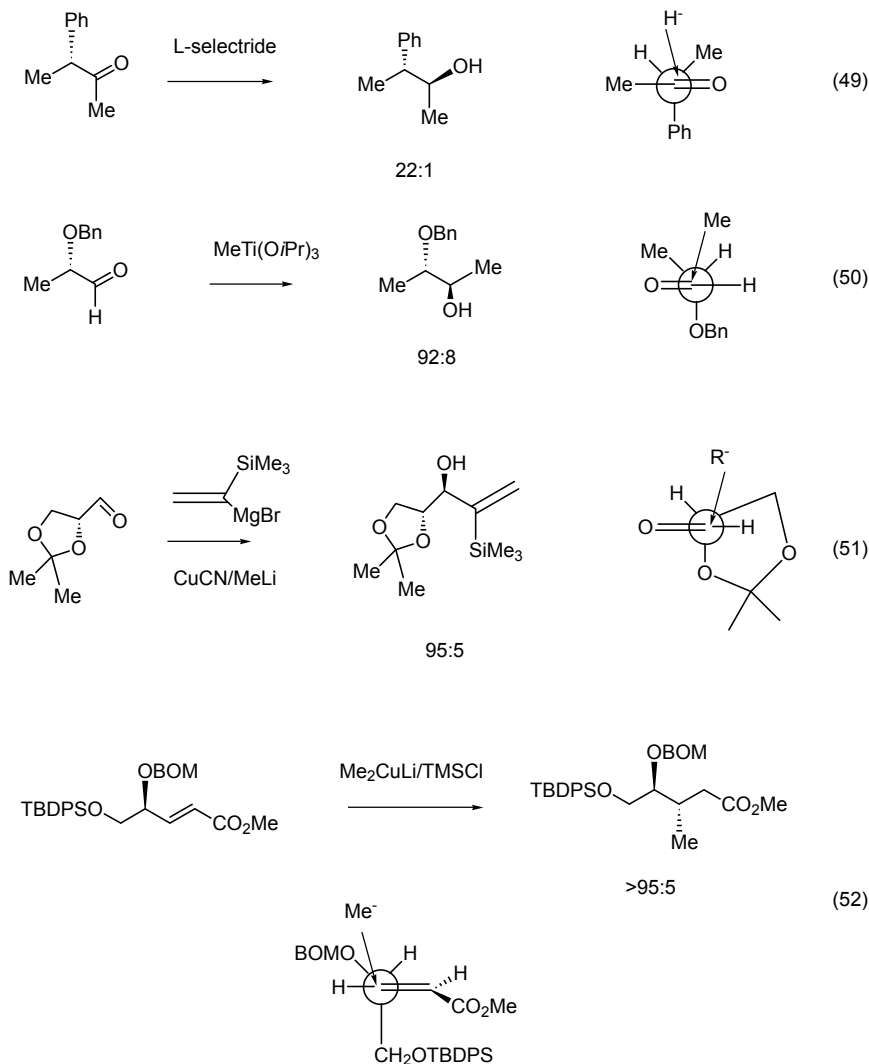


Scheme 15



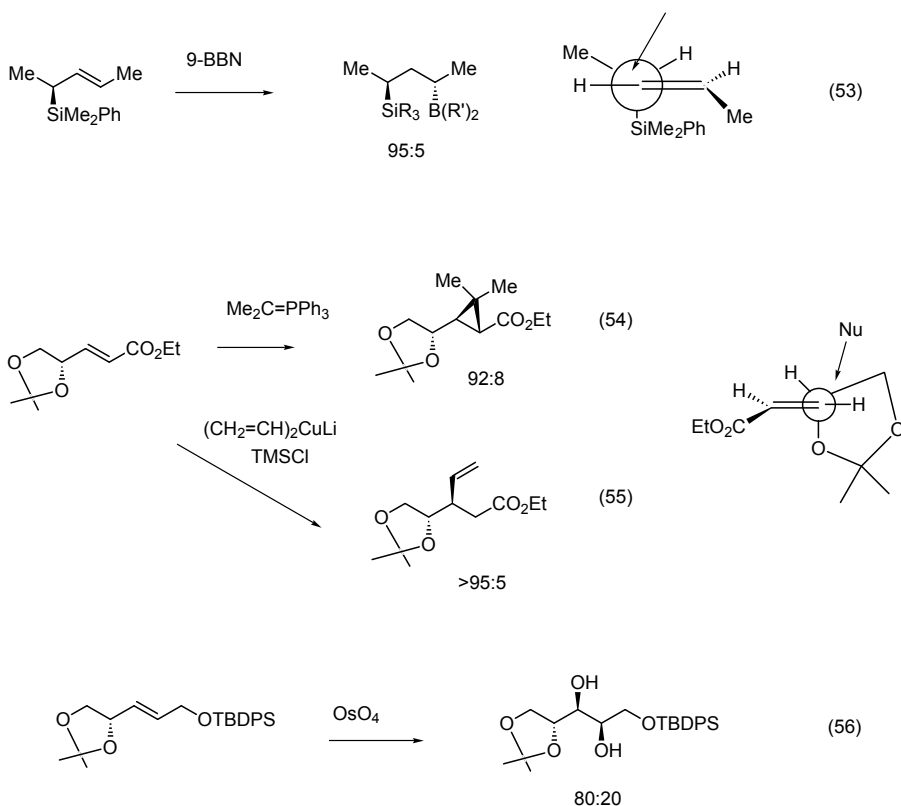
Scheme 16

(M), and large (L). With respect to the reactive conformations four possibilities I to IV (Scheme 16) are discussed depending on the angle which is formed by the trajectory of the reagent and the olefinic or carbonyl plane. For obtuse angles (carbonyl additions) the Felkin-Anh transition state I applies whereas for acute angles (hydroboration, most cycloadditions, conjugate 1,4-enone-additions) the Houk geometry II is favored. In the specific case that a di- or trisubstituted olefin bears a substituent R^3 *cis* to the stereogenic center the allylic 1,3-strain ($A^{1,3}$ -strain) model III applies. For carbonyl additions which proceed via a preformed

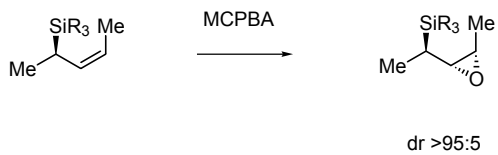
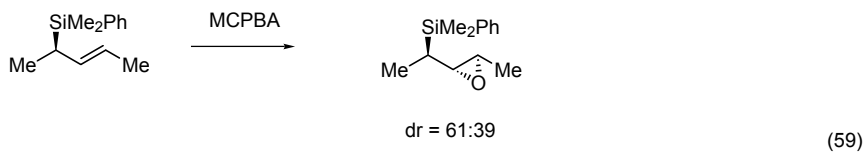
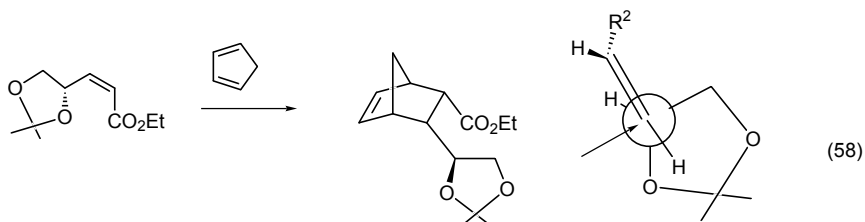
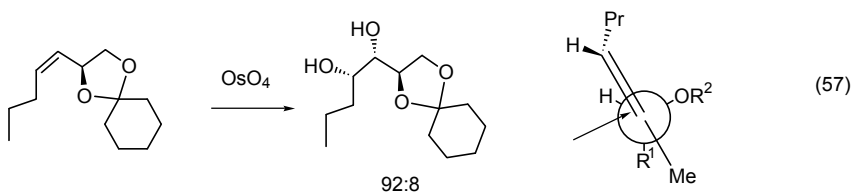


Scheme 17

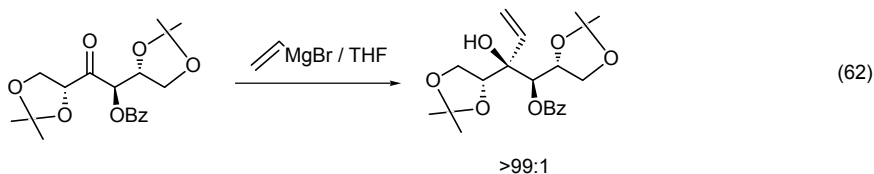
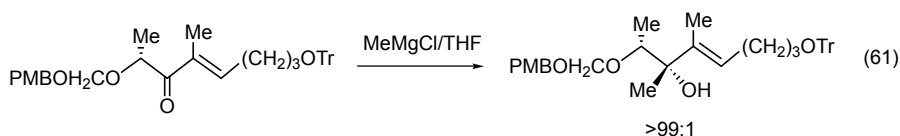
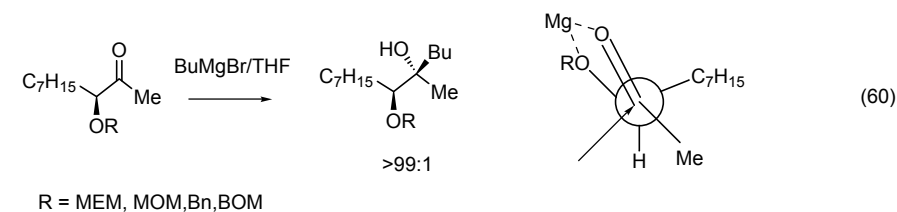
chelate complex the chelate-Cram model IV seems appropriate. Models III and IV are the most reliable ones with respect to the stereoselectivity and lead to predictable diastereomeric ratios (dr's) of >90:10. For normal Felkin-Anh-type additions, however, a combination such as S=H, M=Me, and L=Ph leads to a diastereoselectivity of no more than 3 or 4:1 for a variety of carbonyl or olefinic additions. Higher selectivities (Scheme 17) may be achieved for particularly selective reagents {for instance L-selectride, reaction (49), Scheme 17 [42]} or if the steric effect is superimposed by a stereoelectronic effect (*anti*-periplanar effect) by placing an OR- or NR₂-ligand into the position of the L-substituent {reactions (50 to 52), Scheme 17 [42, 43, 44, 45]}. A similar stereoelectronic effect for silicon or OR-ligands in the L-position is observed for Houk-type additions [Scheme 18; reactions (53 to 56)] [46, 47, 48, 49]. The A^{1,3}-strain model proves its reliability in hydroboration, Diels-Alder-cycloaddition, and epoxidation reactions [Scheme 19, reactions (57 to 59)] [50, 51, 52]. The same is true for the chelate-Cram model (Scheme 20) which is particularly efficient for Grignard additions to ketones [reactions (60 to 62), Scheme 20] [53, 54, 55].



Scheme 18



Scheme 19

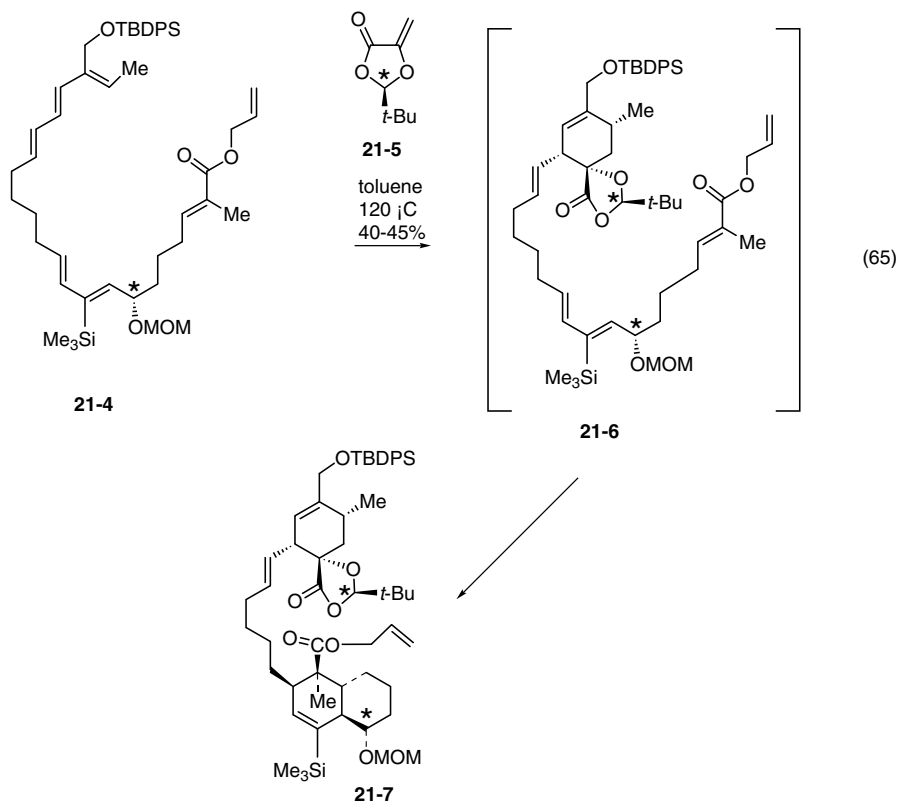
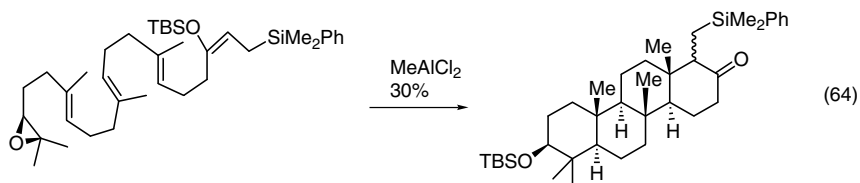
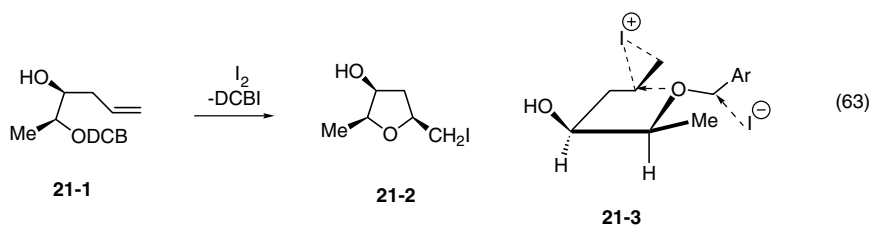


Scheme 20

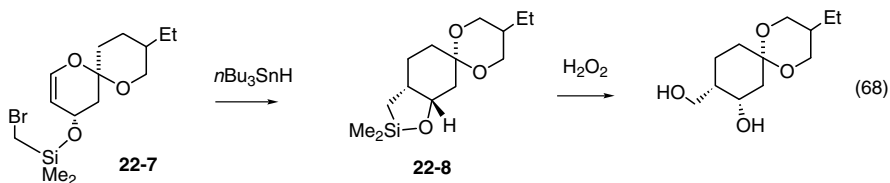
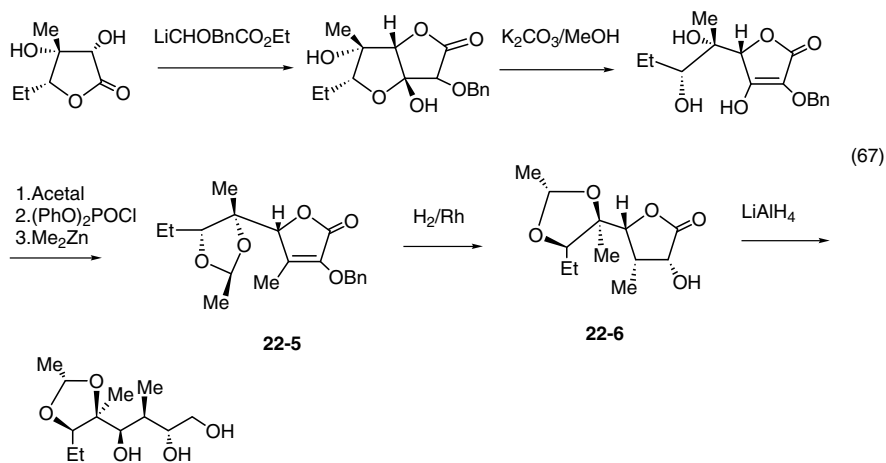
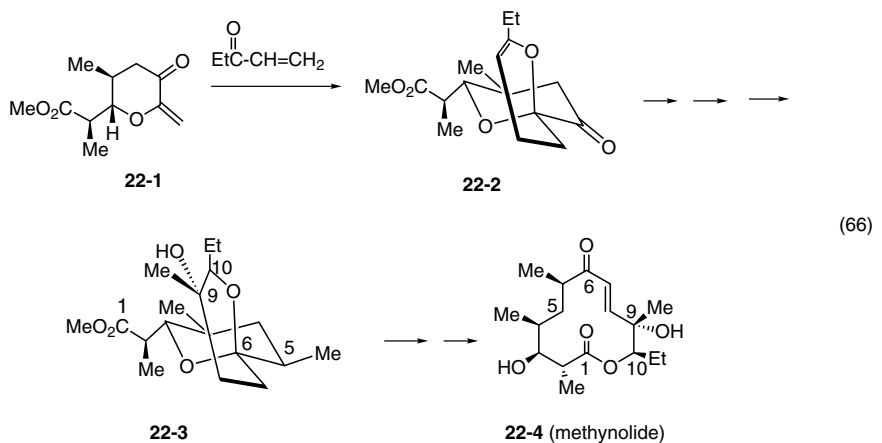
2.2.1.3

Enhanced Substrate Control via Cyclic Transition States

It is a general and frequently used strategy to enhance the stereocontrol in a substrate-controlled addition by intramolecular reactions which lead to cyclic intermediates. Either these are preserved if the desired product is cyclic or they are disconnected to form an acyclic product. In this case the ring formation is used as a temporary stereocontrolling tool. The first-mentioned strategy is illustrated in Scheme 21. The formation of halohydrins **21-2** from an acyclic olefin **21-1** [reaction (63), Scheme 21] proceeds totally regio- and stereocontrolled if a tetrahydrofuran ring is closed. The *cis*-diastereoselectivity originates from the diequatorial arrangement of both carbon appendages in transition state **21-3** [56]. In reaction (64) in Scheme 21 the initial S_N2 -opening of the epoxide determines the relative and absolute configurations at centers 3 and 5 of the homosteroid system formed [57]. In consequence all other stereogenic centers are formed via *trans*-additions of carbenium ions to the olefinic double bonds from the less hindered face so that an all-*trans* ring fusion results from this polycyclization. In reaction (65), Scheme 21, the initial step is an intermolecular Diels-Alder addition between diene **21-4** and dienophile **21-5** which is stereodirected by the stereogenic center in the acetal. The second intramolecular Diels-Alder addition,



Scheme 21



Scheme 22

21-6to 21-7, is stereocontrolled by the OMOM-unit at the adjacent stereocenter [58].

Temporary ring formations are the topic of Scheme 22. In reaction (66) a spiroketal is generated by a hetero-Diels Alder addition in the first step (22-1 to 22-2) of the sequence. By means of the anomeric effect the spiroketal prefers the diaxial arrangement of the oxygens at C-6 which rigidifies the bicyclic system in 22-2 and exerts a stereodirecting effect on the stereogenic transformations at C-9/10 and C-5 to form 22-3, which is finally disconnected to give 22-4 [59]. Similarly, in reaction (67), Scheme 22 two temporary five-membered rings are formed to control the catalytic hydrogenation step 22-5 to 22-6 after which the cyclic structure is disrupted [60]. Reaction (68), Scheme 22 finally illustrates the principle of the “silicon tether” by which the radical addition 22-7 to 22-8 proceeds intramolecularly with high stereocontrol as a *cis*-annelation after which the silicon is excised via Baeyer-Villiger type oxidation [61].

2.3

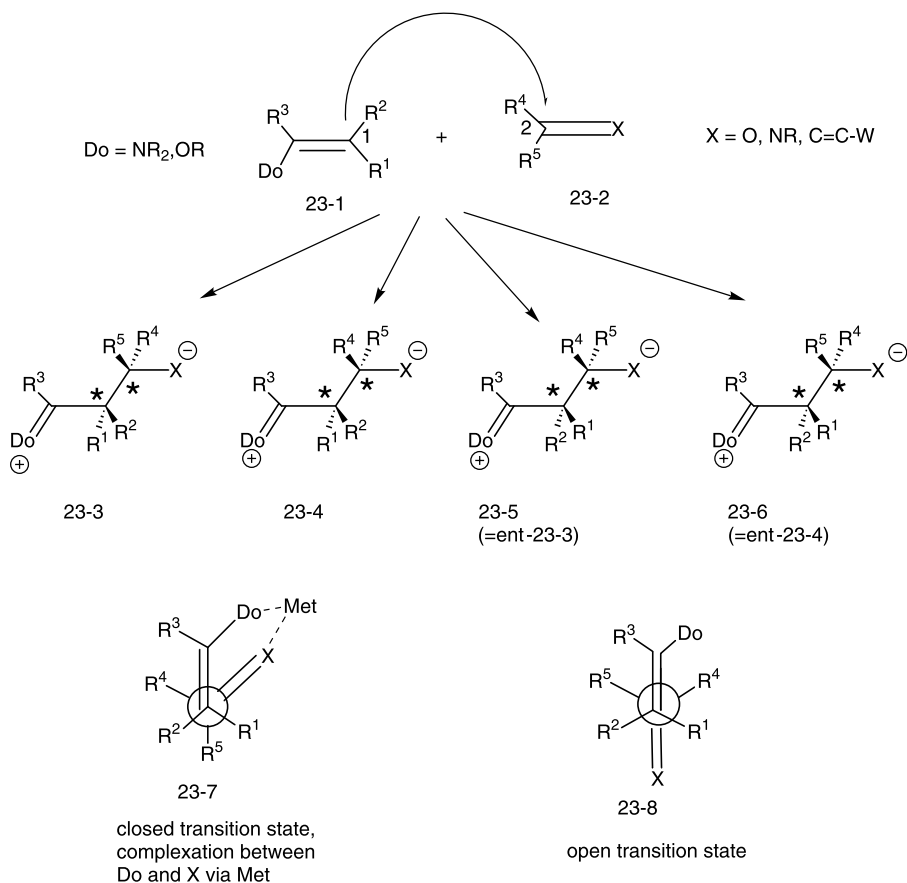
Substrate Plus Reagent Controlled Reactions

In these types of stereocontrolled reactions both the substrate and the reagent by means of their mutual geometric interaction dictate the stereochemical outcome of the reaction. Two types are particularly widespread and important: the “*simple diastereoselection*”, which is primarily observed in aldol-type- and ene-reactions and the “*exo-endo-selectivity*” which is characteristic of cycloadditions.

2.3.1

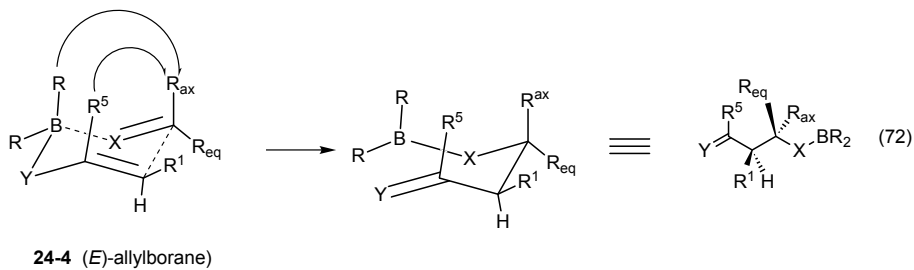
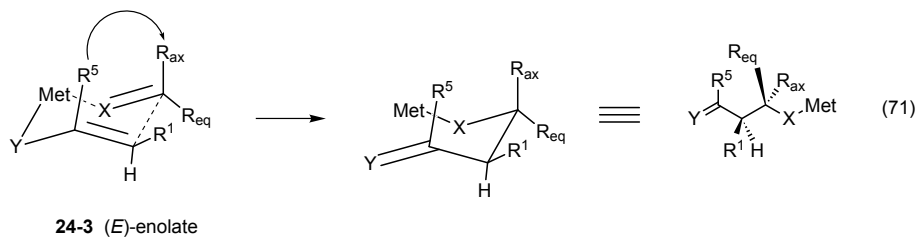
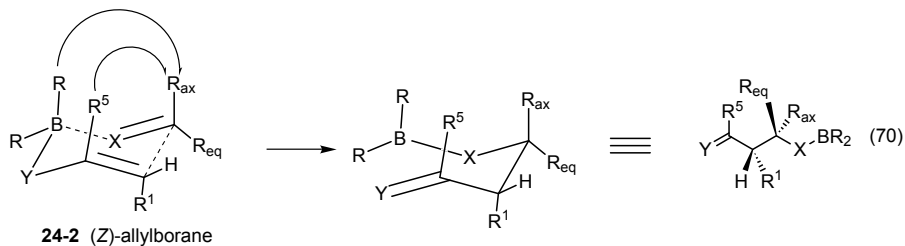
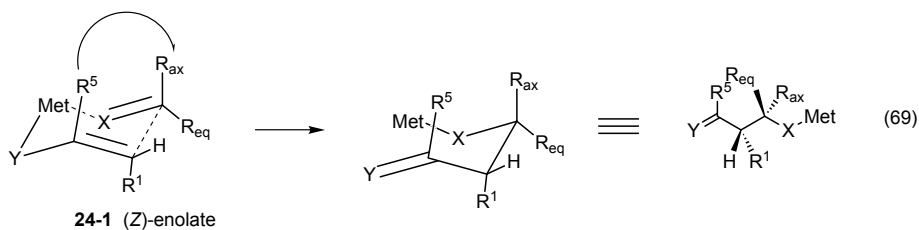
Simple Diastereoselection

Scheme 23 shows how four possible diastereomers can arise from the combination of two sp^2 -carbon centers C-1 and C-2 in a donor component 23-1 and an acceptor component 23-2. Species 23-3 and 23-4 are two diastereomers and 23-5 and 23-6 are their enantiomers. The problem of “simple diastereoselection” is the control of the diastereomer ratio 23-3+23-5/23-4+23-6. The enantiocontrol of 23-3 vs 23-5 or of 23-4 vs 23-6 cannot be achieved by simple diastereoselection; in this case an external source of chirality has to be applied, for instance a chiral catalyst or the incorporation of stereogenic units in one of the components. Simple diastereoselection can be exerted in terms of closed and open transition states, depending on the mutual interaction of the termini X and Do, respectively. If these termini are linked via a six-membered chelate, a closed (“Zimmerman-Traxler”) transition state 23-7 with synperiplanar olefinic units is formed. On the other hand, if the termini have a repulsive interaction an open transition state 23-8 with an antiperiplanar arrangement of the olefinic units is adopted. Efficient stereocontrol via Zimmerman-Traxler transition states 24-1 to 24-4 is observed in aldol-type and allylborane carbonyl additions (Scheme 24). The crucial stereodifferentiating interaction is the diaxial repulsion between Rax and R⁵, which must be kept as low as possible. Only small substituents (nor-



Scheme 23

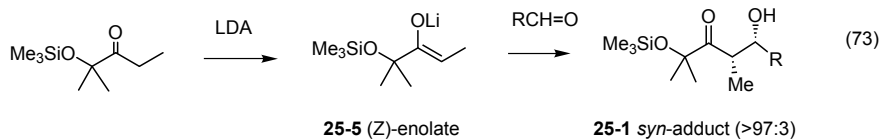
mally H) are tolerated in the R_{ax} position. Consequently the stereochemical outcome of the addition is dictated by the relative position of the R¹ substituent and, hence, the (*E*)/(*Z*)-geometry of the enolate-or allylborane moiety (Scheme 24). Scheme 25 illustrates four examples [reactions (73 to 76)] [62, 63, 64, 65] for reactions (69) and (70) of Scheme 24. By insertion of the substituents in the transition states 24-1 and 24-3 the *syn*- and *anti*-configurations of the adducts 25-1 to 25-4 can easily be derived. The (*E*) and (*Z*)-geometry of the enolate species 25-5 to 25-8 are dictated by the deprotonation. In the allylborane and allylboronate carbonyl additions [reactions (70), (72) in Scheme 24, and (77a,b) in Scheme 26) the boron is bound to have one axial substituent; this enhances the steric pressure exerted on R_{ax}, and, hence, the demand of placing a small ligand in this position. These additions have a distinctly higher simple diastereoselectivity than the normal aldol-type addition. In consequence, as shown in Scheme 26 [65], (*Z*)-crotylboronates 26-1 generate the *syn*-adduct with aldehydes [reac-



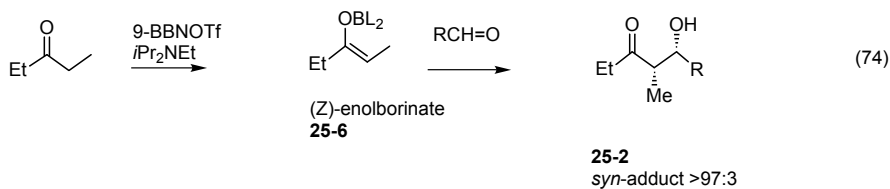
Y = O (enolate), CH₂ (allylborane), X = O; NR,
adduct stereochemistry depends on enolate or allylborane *E/Z*-geometry

Scheme 24

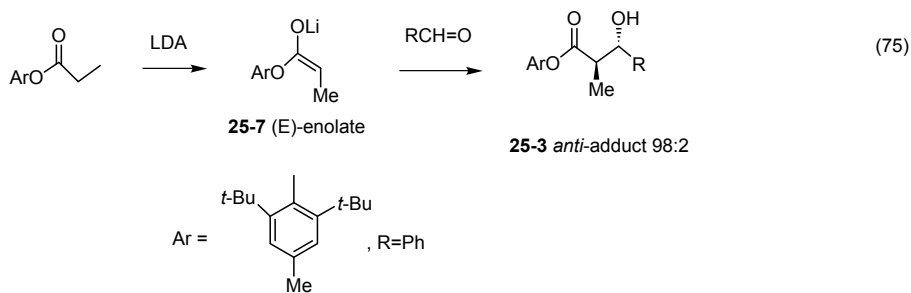
1. Reaction (69) : $Y=O$, $Met=Li$, $R^5=CMe_2OSiMe_3$, $R^1=Me$, $R_{ax}=H$, $R_{eq}=R$



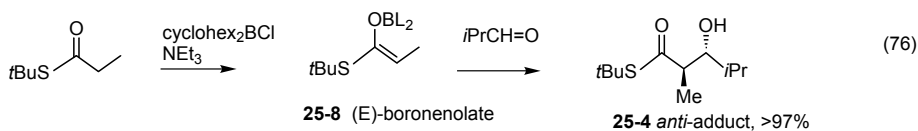
2. Reaction (69) : $Y=O$, $Met=BL_2$, $R^5=ethyl$, $R^1=Me$, $R_{ax}=H$, $R_{eq}=R$



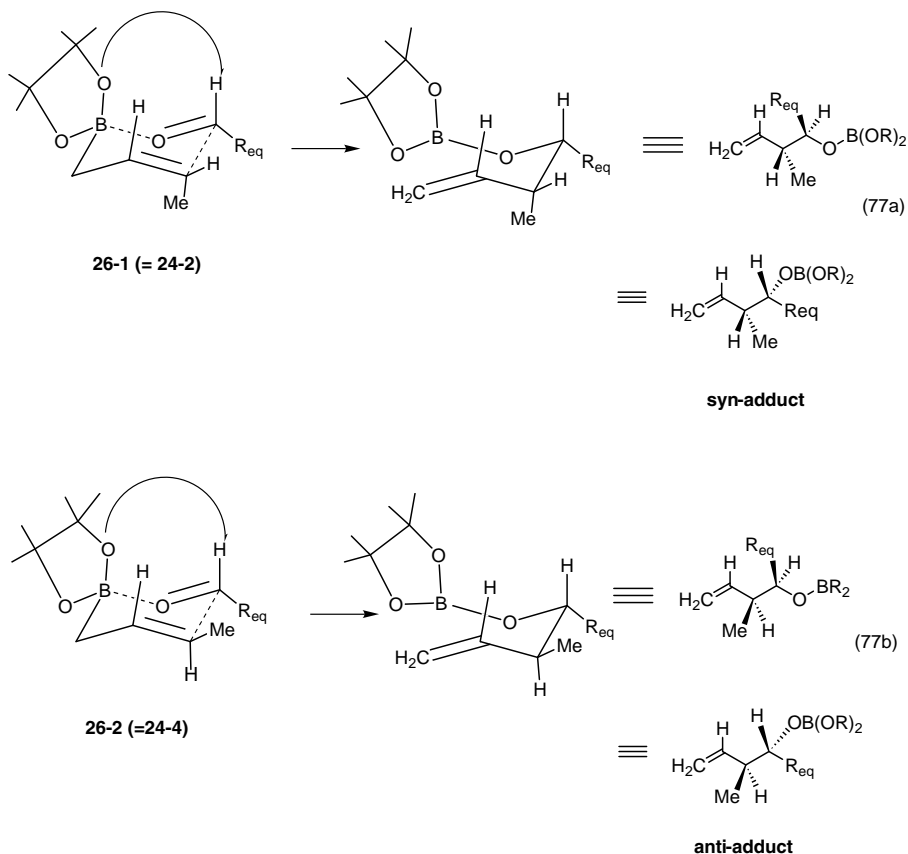
3. Reaction (71) : $Y=O$, $Met=Li$, $R^5=OAryl$, $R^1=Me$, $R_{ax}=H$, $R_{eq}=R$



4. Reaction (71) : $Y=O$, $Met=BL_2$, $R^5=StBu$, $R^1=Me$, $R_{ax}=H$, $R_{eq}=R$



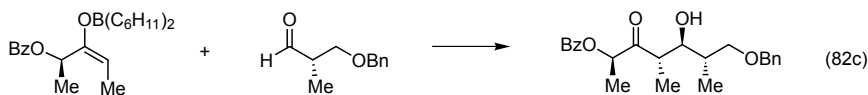
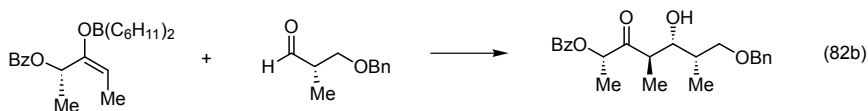
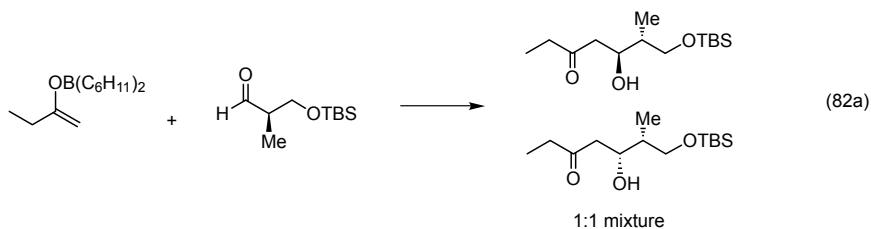
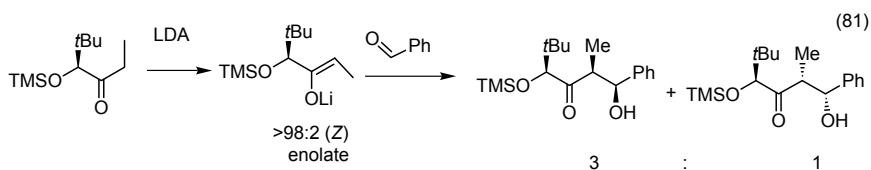
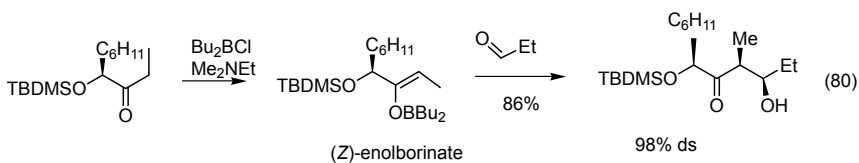
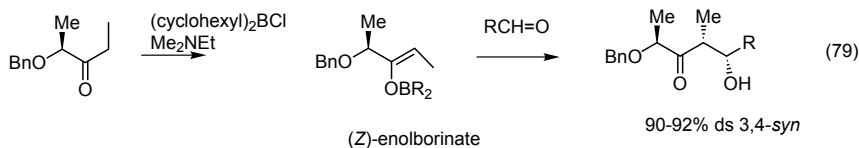
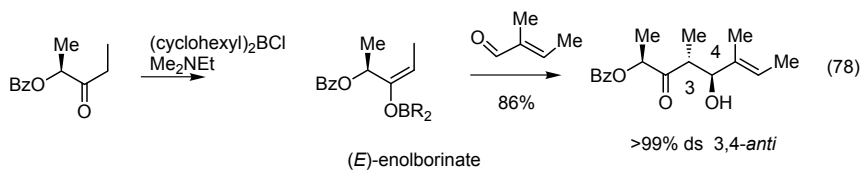
Scheme 25



Scheme 26

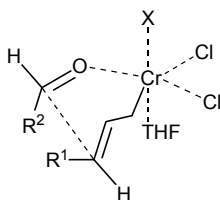
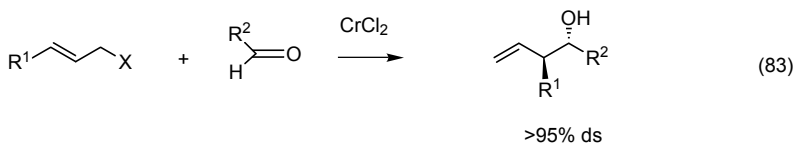
tion (77a), Scheme 26], and (*E*)-crotylboranes **26-2** the *anti*-adduct [reaction (77b), Scheme 26].

The simple diastereoselection may be combined with considerable substrate-induced diastereoselectivity if one of the components contain a stereogenic center proximal to the reactive site. In Scheme 27 this is demonstrated for α -chiral enolborinates which are generated in situ from the ketone and a dialkylchloroborane [reactions (78), (79), and (80)] [67, 68]. Depending on the conditions either the (*E*)- or the (*Z*)-enolborinate may be generated and, due to the Zimmerman-Traxler transition state the *anti*-adduct is formed from the (*E*)- and the *syn*-adduct from the (*Z*)-enolborinate. In the case of “normal” lithium enolates the induced diastereoselectivity is significantly lower [reaction (81), Scheme 27] [69]. At any rate, the selectivities are low if the stereogenic center is incorporated in the aldehyde [reaction (82a), Scheme 27] [70]. If stereogenic centers are in both components the one in the enolborinate dominates as shown in reactions (82b) and (82c), Scheme 27 [70].



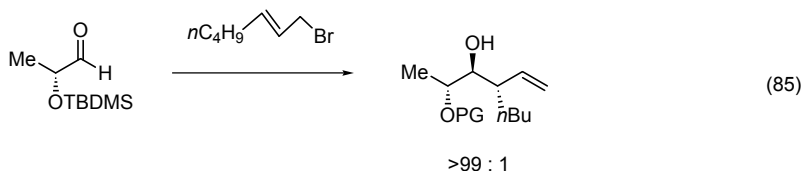
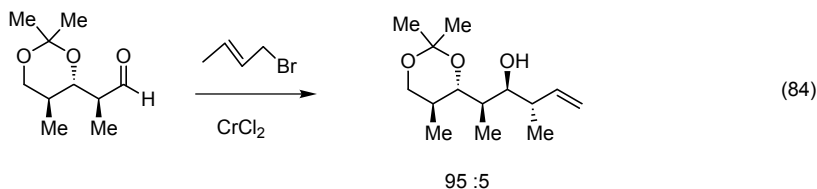
Scheme 27

An entirely different closed transition state is postulated for the addition of allyl- and crotylchromium(II) species to aldehydes (Scheme 28), (Hiyama-Nozaki reaction) [71]. In this case an *anti*-arrangement of R¹ and OH is found in the product, resulting from a chromium complex in which the R¹ and R² substituents are *anti* to each other with respect to the newly created single bond [reaction (83), Scheme 28]. Substrate induced diastereoselectivities may be significant in suitable cases [reactions (84) [72] and (85) [73], Scheme 28], but typically they do not exceed ratios of 3 to 4 :1. In contrast the induction resulting from stereogenic units in the allyl component is high and dominates over the induction exerted from the aldehyde as shown in reactions (86) to (88), Scheme 28 [74]. The crotylstannane case (Scheme 29) is unique as the stereochemical outcome depends on the presence [*syn*-adduct, reaction (89)] or absence of a Lewis acid [*anti*-adduct, reaction (90)] [75]. This is interpreted by assuming that the



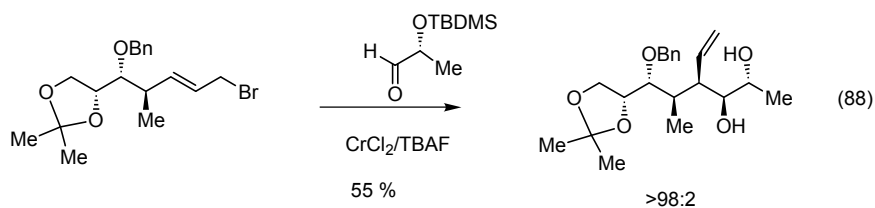
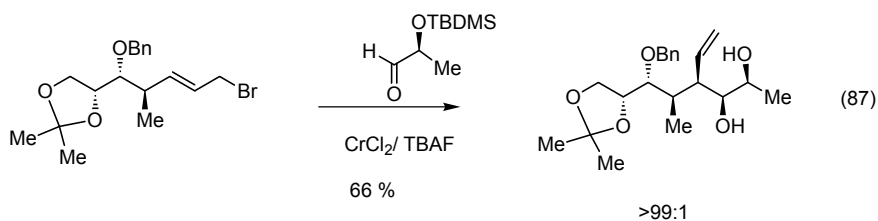
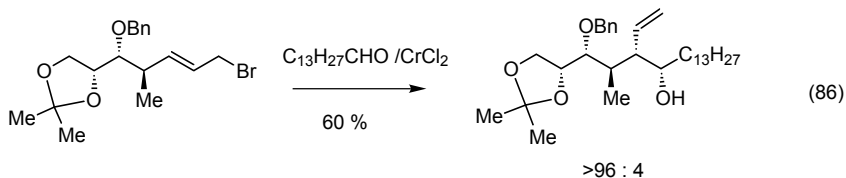
Substrate-Induced Diastereoselectivity :

1. from the aldehyde

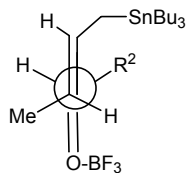
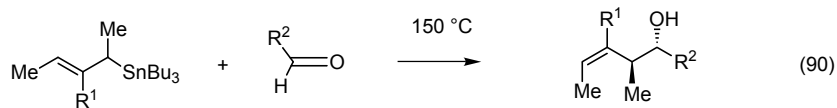


Scheme 28

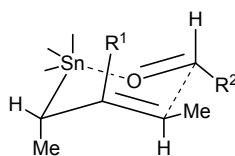
2. from the allylic component



Scheme 28 (continued)



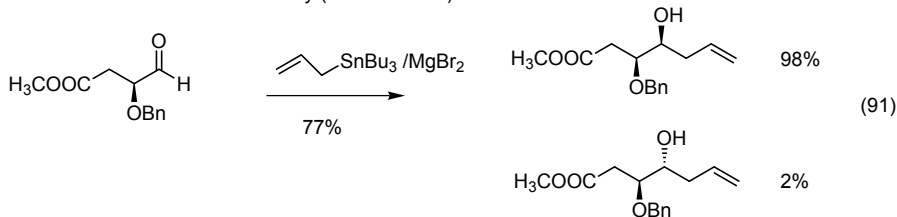
open transition state
for Lewis acid catalysis
[reaction (89)]



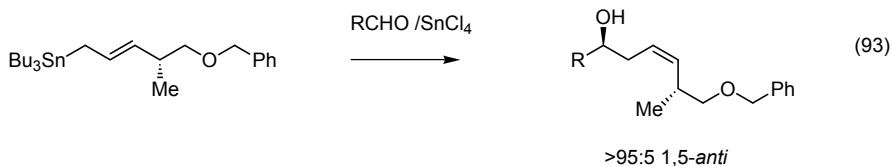
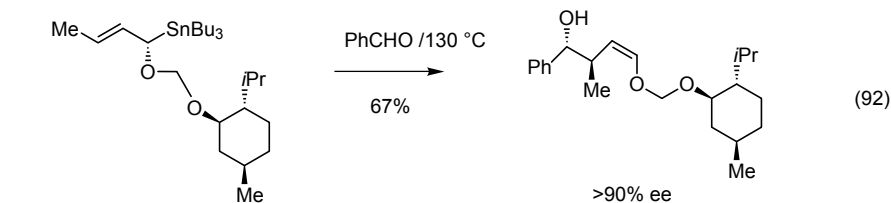
closed transition state
for thermal reaction
[reaction (90)]

Scheme 29

1. substrate-controlled selectivity (chelate-Cram)



2. reagent-controlled selectivity

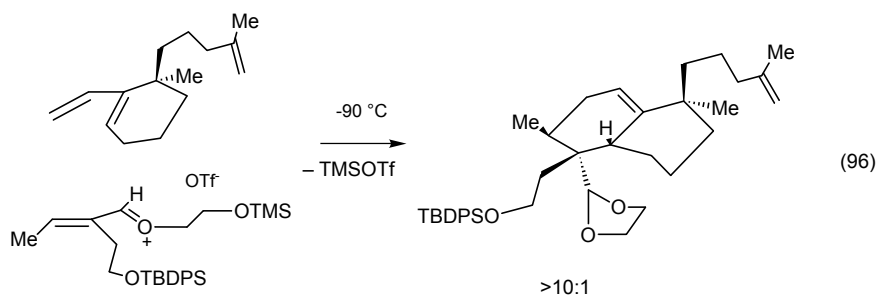
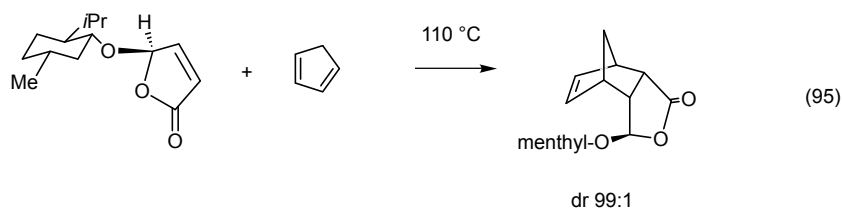
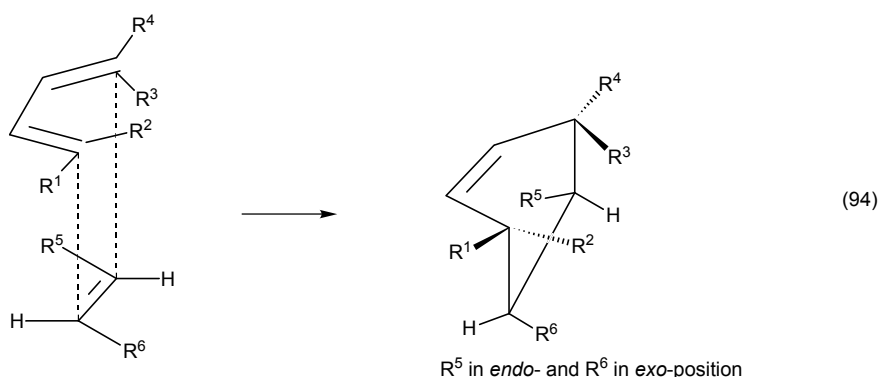
**Scheme 30**

Lewis acid breaks up the closed transition state normally found in thermal reactions. Contrary to the Hiyama-Nozaki reaction the induced stereoselections for allylstannanes+Lewis acids are extremely high, due to chelate-Cram controlled mechanisms [reaction (91), Scheme 30] [76]. Reagent controlled diastereoselectivity may be exerted in terms of 1,3- [reaction (92)] [77] and 1,5-inductions [reaction (93)] [78].

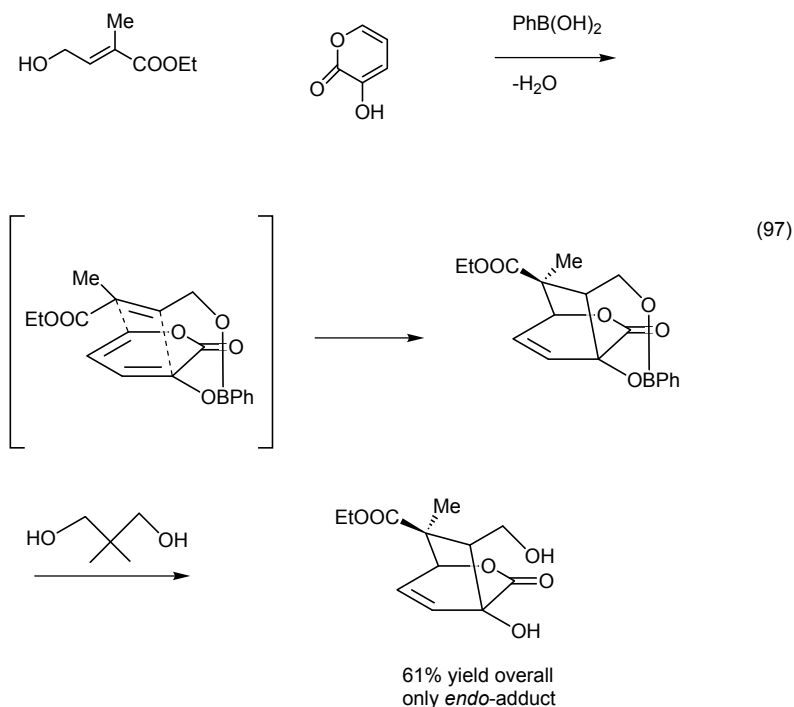
2.3.2***exo-endo-Diastereoselectivity***

This phenomenon is well known in most cycloadditions, i.e., additions in which two components are combined which have two enantiofaces each. Thus altogether four combinations are possible leading to two enantiomeric pairs of *exo-endo*-diastereomers (Scheme 31) [Diels-Alder addition, reaction (94)]. In the arbitrary combination shown R^5 is in the *endo*- and R^6 in the *exo*-position. *Endo*-selectivity in the Diels-Alder reaction (and other cycloadditions) means that the substituent with the higher potential for π - π -interactions with the diene

system adopts the R^5 position. In thermal Diels-Alder additions with acyclic components the *endo*-selectivity is low; it can be increased by Lewis acid catalysis or by using cyclic components such as in reaction (95), Scheme 31 [79]. Reaction (96), Scheme 31 [80] shows how the *endo* activity of an acetal may be increased by temporarily converting it into an oxonium ion. Alternatively, the *endo* selectivity may be increased by using a temporary tether which converts an otherwise acyclic transition state into a cyclic one. Scheme 31 shows how this can be done by connecting two hydroxy groups via a boronic ester which is destroyed after the cycloaddition has taken place [reaction (97)] [81].



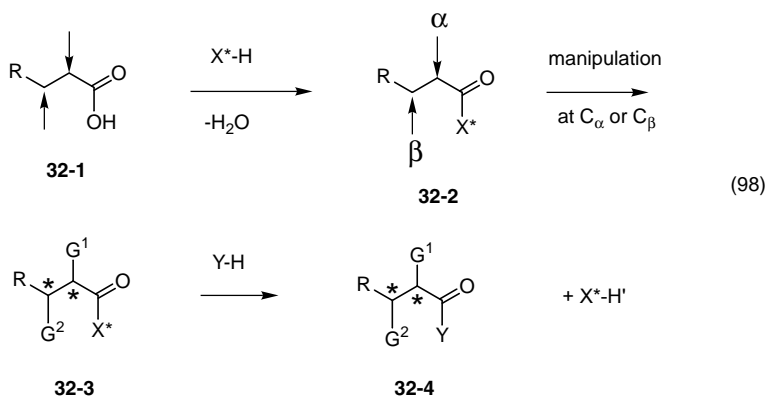
Scheme 31



Scheme 31 (continued)

2.4 Auxiliary Controlled Reactions

These are reactions in which new stereogenic centers are generated by addition to prostereogenic sp^2 carbons. The configuration of these new stereogenic centers is controlled by particular stereogenic units (“chiral auxiliaries”) which are attached covalently in stoichiometric amounts to the substrate and removed afterwards. Scheme 32 [reaction (98)] shows the general procedure for auxiliary based reactions [82]. The substrate **32-1** must have an anchor group (e.g., a carboxylic acid) to which the auxiliary X^*H is attached by a condensation reaction to form compound **32-2** which has prostereogenic reaction sites close to the auxiliary, i.e., normally at C_α or C_β . Next, the desired manipulations at $C_{\alpha/\beta}$ are performed (double bond additions, enolate additions, etc.) and it is hoped that the auxiliary controls these reactions stereochemically so that **32-3** is formed as a single diastereomer. Otherwise, diastereomer separations have to be performed on this stage. After obtaining compound **32-3** stereochemically pure the auxiliary is removed by hydrolysis or similar operations to generate the desired product **32-4** without endangering the newly created stereogenic units. The auxiliary is recovered as X^*H' .



Scheme 32

An ideal auxiliary would be introduced in high yield and be available in large quantities and in high optical purity at a reasonable cost. It should be stable to the desired reaction conditions and provide high diastereomeric excesses. An additional benefit are crystalline intermediates. Basically three types of auxiliaries may be distinguished:

- those which may be recovered after the crucial stereodifferentiating step and re-used immediately ($\text{X}^*\text{-H}'=\text{X}^*\text{-H}$) (“*persistent auxiliaries*”);
- those which are destroyed in course of the workup, but may be restored in their original form by a limited number of operations (“*restorable auxiliaries*”);
- those whose stereogenic centers are destroyed on removal of the auxiliary from the substrate (“*self-immolative auxiliaries*”).

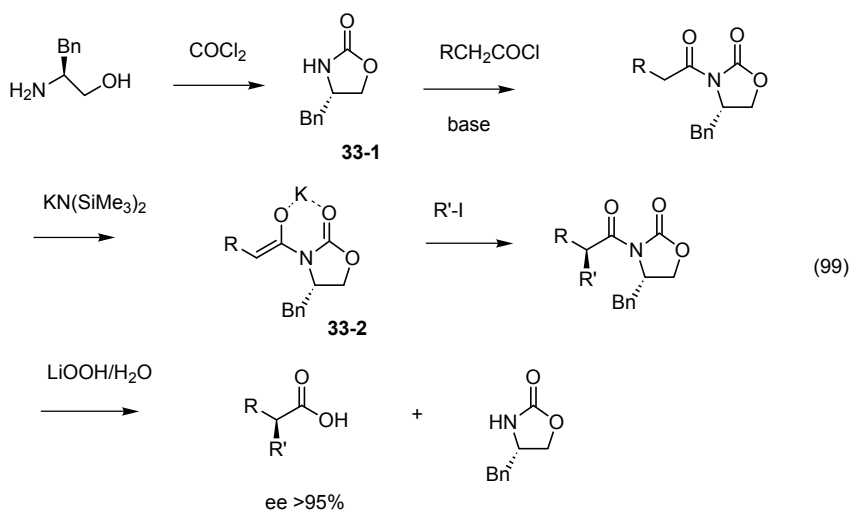
From the practical standpoint the first category is of course the most attractive one, especially if the auxiliary is crystalline and may be easily recovered from the reaction without chromatography. However, also the second category may be acceptable, if the operations required for the recovery of the auxiliary are simple to perform. The last category is of practical use only if the auxiliary is so inexpensive that it can be discarded without hesitation.

In the simplest case the substrate is totally devoid of chiral information so that the chiral induction entirely depends on the auxiliary. In the more complicated case the substrate also contains stereogenic centers which have a stereodirecting influence on the configuration of the newly created stereogenic centers (“*double stereodifferentiation*”). If the substrate and the auxiliary exert comparable stereodirecting effects, the overall selectivity may be increased (“*matched combination*”) or decreased (“*mismatched combination*”) compared to the individual effects. If the auxiliary is available in both enantiomeric forms it is always possible to find the matched situation. If the influence of the auxiliary is much higher than that of the substrate, the reaction is “*auxiliary controlled*”. If on the

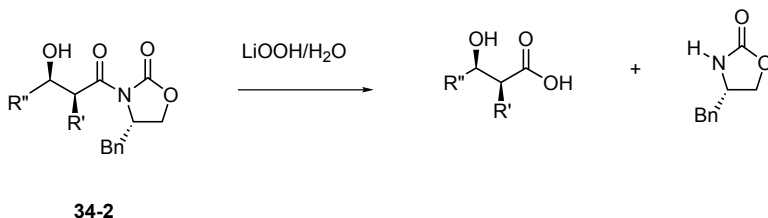
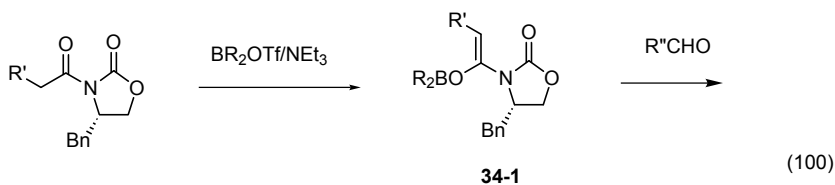
other hand the substrate outweighs the auxiliary the reaction is “*substrate controlled*”. To obtain the utmost stereochemical flexibility of the reaction auxiliary controlled processes are preferred. The aspects of double stereodifferentiation will be dealt with in Sect. 2.6.

Scheme 33 illustrates the use of two standard persistent auxiliaries. The Evans oxazolidinone **33-1** [83] is highly versatile, i.e., suitable for enolate reactions and double bond additions alike. In the enolate alkylation case [reaction (99)] the high diastereoselectivity depends on the formation of a chelate **33-2** which fixes the reaction site in a defined conformation in which one of the diastereofaces is efficiently shielded. The removal of the auxiliary requires the chemoselective cleavage of the exocyclic amide bond which is sometimes difficult to achieve. In boron mediated aldoltype additions [Scheme 34, reaction (100)] no chelate can be formed so that the extremely high diastereoselectivity with which the *syn*-adduct **34-1** is formed must be due to some other effect, presumably allyl 1,3-strain on the stage of the enol borinate **34-1**.

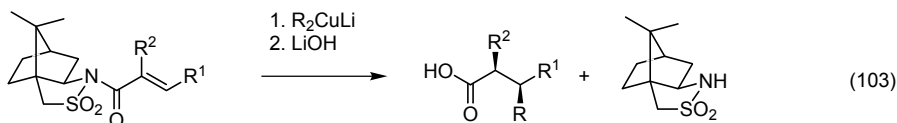
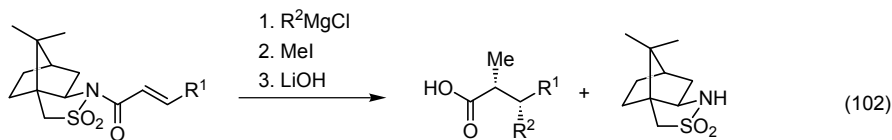
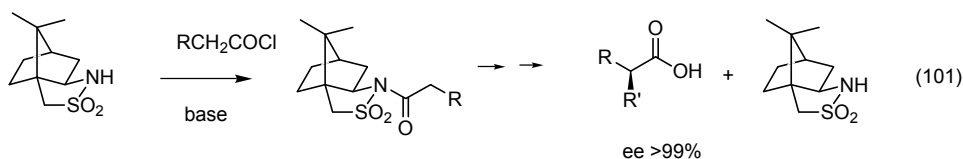
The Oppolzer sultam **35-1** [Scheme 35, reaction (101) [84]] reacts with even higher stereoselectivities and is easier to remove. The main domains of the Oppolzer sultam are conjugate 1,4-additions or simple double bond additions [Scheme 35, reactions (102) and (103)] [85], which show diastereoselectivities of >95% in most cases. Scheme 36 presents examples of persistent, restorable and selfimmolative auxiliaries which are all based on amino acids or amino alcohols. Enders' RAMP-SAMP [86] is attached to ketones or aldehydes in form of a hydrazone **36-1** which is used for highly stereoselective electrophilic α -alkylations. After the reaction the auxiliary is removed via ozonolysis which generates the nitrosamine **36-2** first. In an ensuing step this is reduced to the original auxiliary. In Schöllkopf's bislactim ether alkylations [Scheme 36, reaction (105)]



Scheme 33



Scheme 34

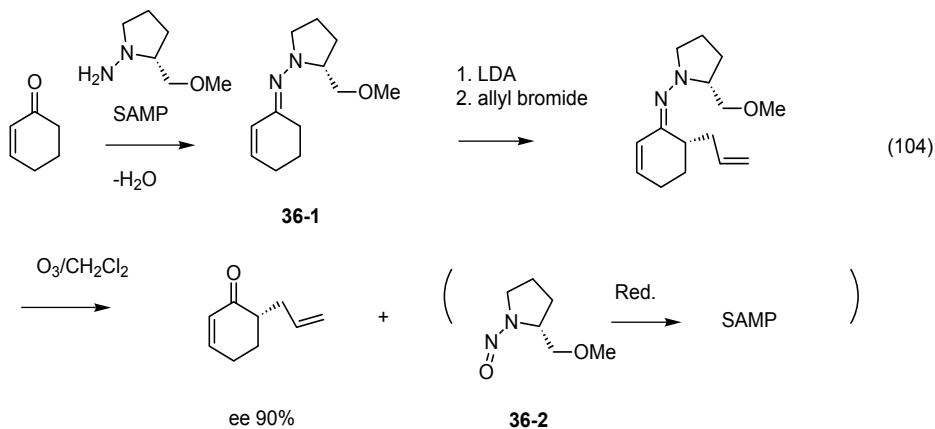


Scheme 35

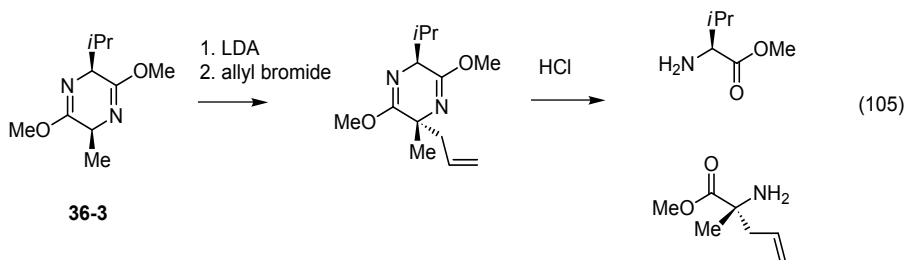
[87] the substrate and the auxiliary amino acid are condensed to form a dimer, the bislactim ether **36-3** which is deprotonated regioselectively at the less hindered position and then alkylated with high stereocontrol. Then the bislactim ether is destroyed and the auxiliary amino acid (normally valine) has to be recycled.

Meyers' bicyclic lactam alkylations [Scheme 36, reaction (106)] [88] use valinol as a persistent auxiliary which is condensed with the keto acid **36-4** to form the bicyclic lactam **36-5** as a rigid template which is deprotonated and alkylated

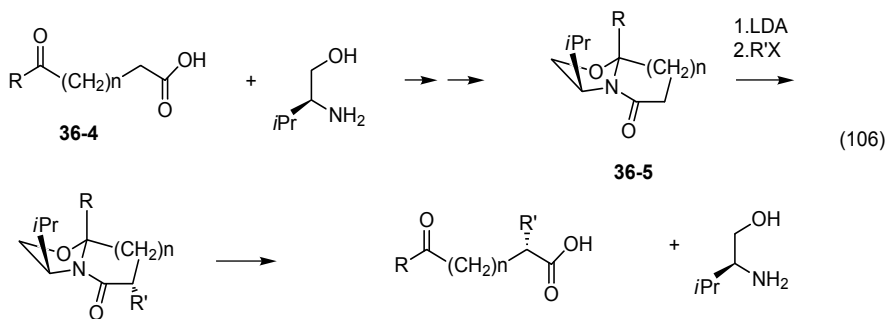
1. Enders' RAMP-SAMP reagents (restorable)



2. Schöllkopf's bislactim ethers (restorable)

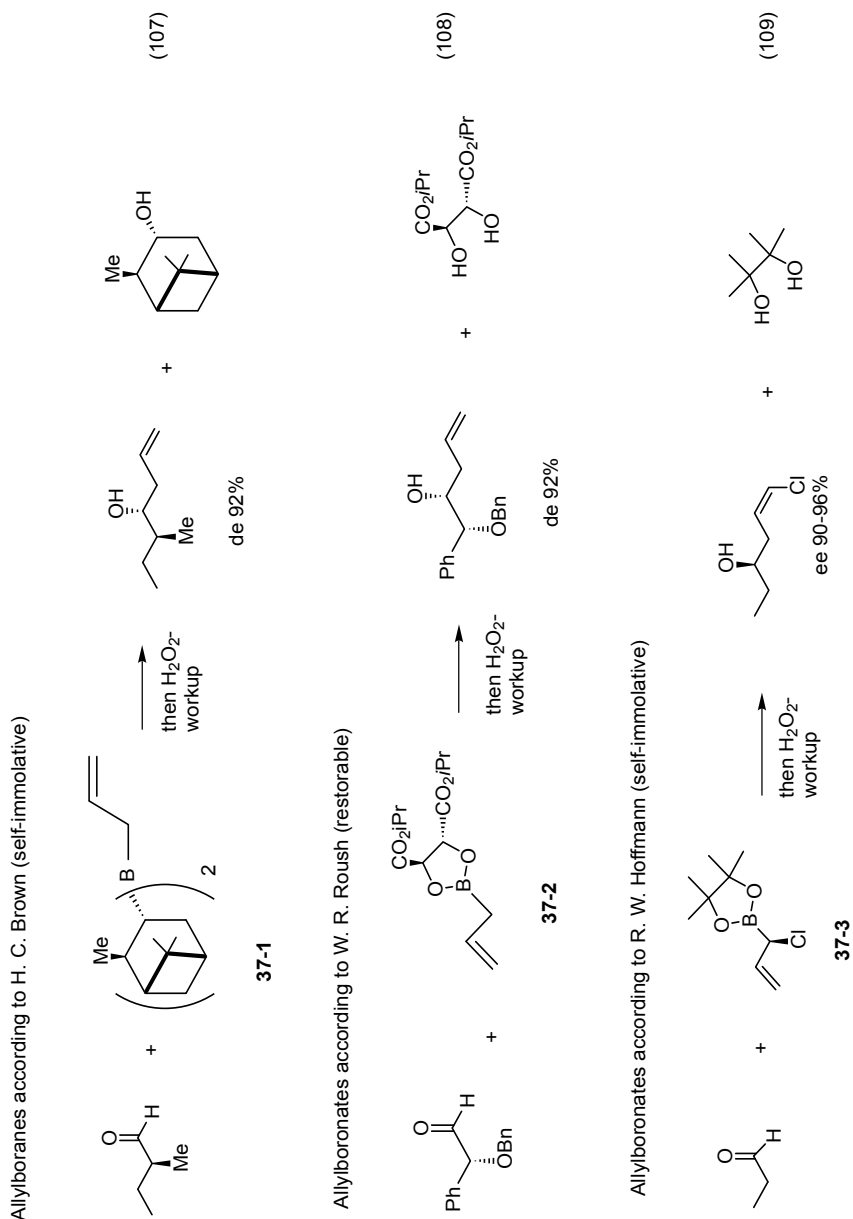


3. Meyers' bicyclic lactams (persistent)



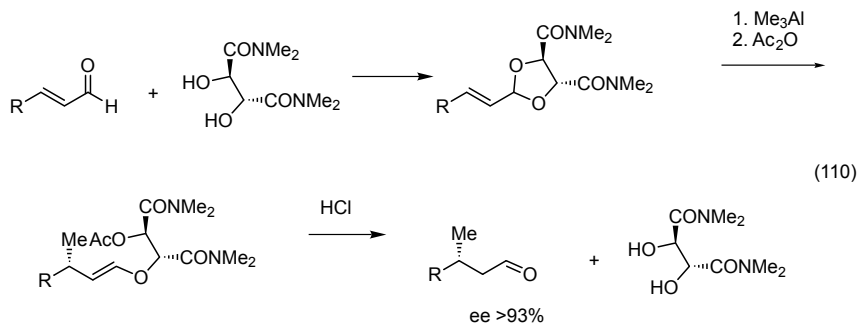
Scheme 36

with high stereocontrol. Valinol is liberated via hydrolysis. A particularly important C/C-connecting reaction is the allylation of carbonyl compounds (Scheme 37) with allylboron derivatives. From the selection given by reactions (107) to (109) in Scheme 37 [89, 90, 91] it follows that only Roush's tartrate based allylborona-

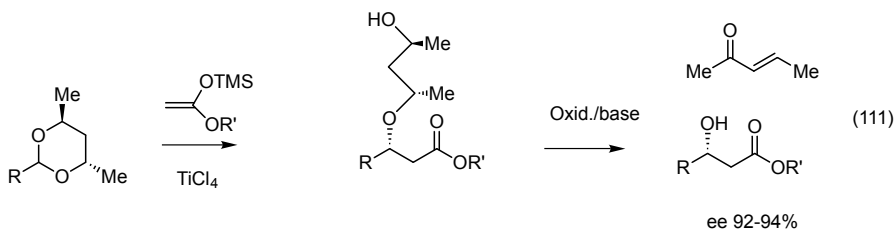


tion uses a restorable auxiliary which has to be transformed back to the allyl-transferring reagent 37-2 in two steps. The other two reagents 37-1 and 37-3 are irretrievably lost by the reaction mechanism, reaction (109), or by the workup, reaction (107). Reactions (107) and (108) also show that these auxiliaries in double stereoselection situations lead to reagent induced stereocontrol, which is also true of 37-3. Chiral acetals (Scheme 38) may be used as restorable and as self-immolative auxiliaries. In both cases [reactions (110) and (111)] [92, 93] the acetal is cleaved during the addition; however, in reaction (110) the diol can be disconnected from the substrate without destroying the stereogenic centers. This is impossible in reaction (111) where the covalent substrate-auxiliary bond can only be disconnected by an E2-type elimination. Hydride transfer reactions (Scheme 39) may be performed for activated ketones such as alkynone 39-1 with alpine borane under high stereocontrol [94]. Mechanistically the reaction is a formal hydroboration of the carbonyl group under regeneration of α -pinene (39-2) which can be transformed into alpine borane with 9-BBN. The NADH analog 39-3 [95] by contrast cannot be restored in optically pure form [reaction (113)]. In Scheme 40 sulfoxides are shown as standard examples for self-immolative chiral auxiliaries. *O*-Menthyl *p*-toluenesulfate is generated as a 1:1-mixture of diastereomers with regard to the sulfur center. By crystallization

Restorable acetal

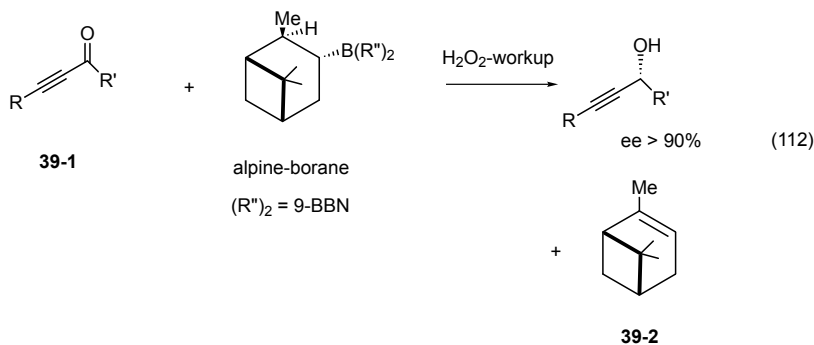


Self-immolative acetal

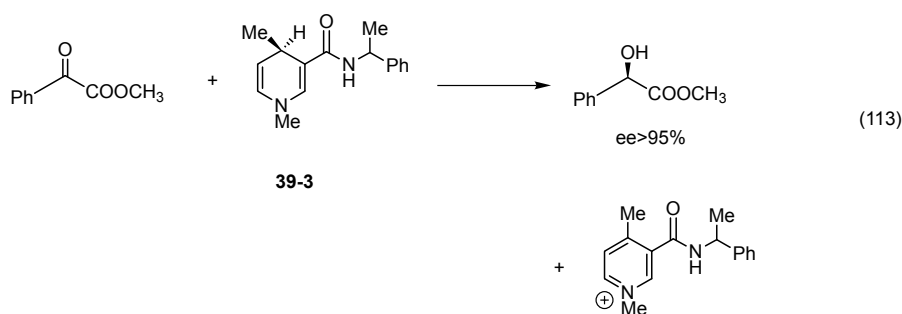


Scheme 38

restorable



self-immolative

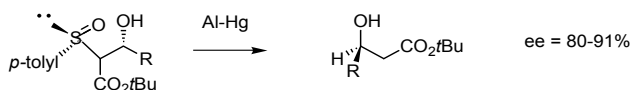
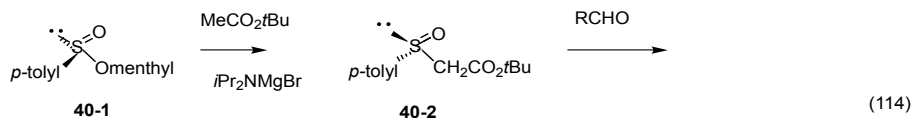


Scheme 39

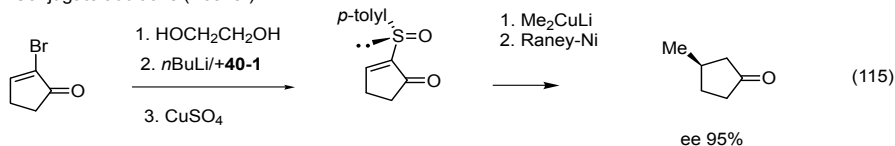
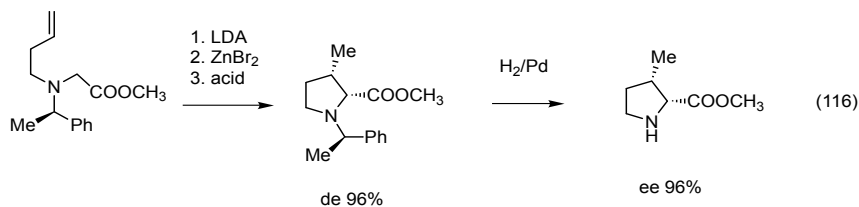
diastereomer **40-1** is isolated in pure form and submitted to an $\text{S}_{\text{N}}2$ -type substitution with *tert*-butyl acetate enolate. Optically pure ester **40-2** is formed which is deprotonated and added to carbonyl compounds with high diastereomeric ratios. After the addition the sulfur/carbon bond is cleaved reductively under destruction of the stereogenic center at sulfur [reaction (114)] [96]. A similar application of **40-1** is shown in reaction (115) [97]. Another example of a self-immolative auxiliary is the use of chiral amino protective groups which show a significant degree of asymmetric induction and are removed hydrogenolytically under loss of their chiral information [reaction (116)] [98].

Sulfoxides

Aldol additions (Solladié)



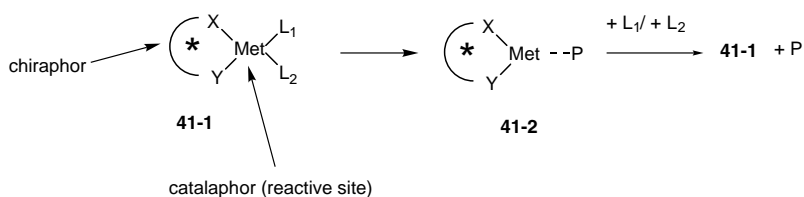
Conjugate additions (Posner)

**Amines****Scheme 40****2.5
Chiral Catalysis**

Using chiral auxiliaries implies that at least one molecule of the auxiliary has to be used for generating one new chiral molecule. Using a chiral catalyst, by contrast, with a turnover number of 1000 means that 1000 new chiral molecules may be generated with the aid of one molecule of the chiral catalyst. Apart from higher chiral economy no covalent attachment is required and the workup is considerably simplified as only trace amounts of the catalyst have to be removed. This insight has greatly stimulated the search for chirally catalyzed reactions

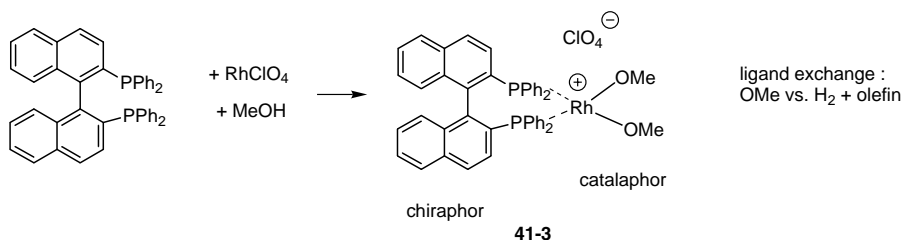
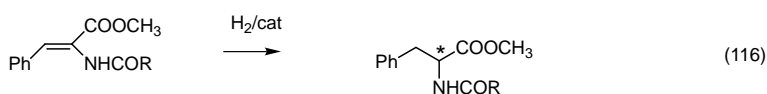
during the past ten years and has led to major breakthroughs in asymmetric synthesis at large [99].

Scheme 41 outlines the essence of chiral catalysis. The chiral catalysts in general work homogeneously which means that they are small molecules, mostly monomeric and contain one (mononuclear) or sometimes two (binuclear) metal atoms in a chelate complex with chiral organic ligands. Typical metals are Pd(0), Pd(II), Rh(I), Rh(II), Cu(II) which are used for essentially non-polar reactions

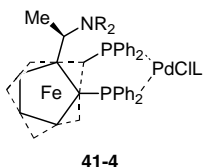
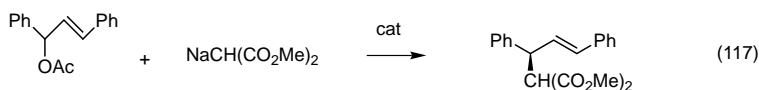


Examples:

1. catalytic hydrogenation of olefins



2. electrophilic allylation of stabilized carbanions



chiraphor : ferrocenyl (axially chiral)

catalaphor :

Pd + 2 PPh₂ ligands:

Pd forms allylic complex with allylic acetate substrate which is electrophilic enough to react with the anion NR₂ binds the anion via Na

Scheme 41

such as catalytic hydrogenation, carbene additions, Heck and Suzuki reactions, etc. In chiral Lewis acidic catalysts Ti(IV), B, Al, or Cr(III) are preferentially used. Characteristic coordination numbers are 4 and 6 with tetrahedral, planar squaric or octahedral complex geometries. The binding forces of the metal Met to the donor atoms X, Y of the ligand are relatively strong and have to be maintained throughout the catalytic cycles. The variable parts of the catalyst (41-1) are the ligands L¹ and L² which are rapidly exchanged (due to the *trans*-effect of X, Y). L¹ is the substrate (e.g., in a catalytic hydrogenation the olefin) and L² the reagent (in this case the H₂ molecule). By the non-covalent attachment to Met

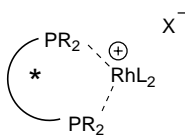
- (1) L¹ and L² are activated to react with one another,
- (2) L¹ and L² are brought into close proximity (entropy effect) and
- (3) L¹ and L² are immersed into a chiral environment, so that one out of several diastereomorphous transition state should be greatly favored.

By this combination of effects the desired reaction is accelerated and proceeds with asymmetric induction. After the reaction the product P in 41-2 must have a much lower binding constant to Met and will therefore be immediately replaced by another L¹, L²-pair to regenerate species 41-1.

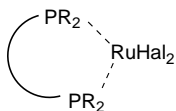
Apparently there are two essential parts to be distinguished in a chiral catalyst: The “*chiraphor*”, i.e., the chiral ligand which bears the chiral information and the “*catalaphor*”, i.e., the metal attenuated by the donors X and Y plus the ligands L¹ and L² to serve as the reactive site. Typically, the catalyst in its storable form just contains the chiraphor part whereas the reactive ligands L¹ and L² are introduced in situ by ligand exchange. In Scheme 41 this is illustrated by the BINAP hydrogenation catalyst 41-3 [reaction (116)], which is assembled in situ from the axially chiral binaphthyldiphosphane (chiraphor) and the rhodium(I) complex (catalaphor). Similarly, the electrophilic allylation [reaction (117)] requires a palladium catalyst 41-4 which is formed from a ferrocenyl ligand and a palladium(II) complex. In Scheme 42 typical catalaphoric subunits are shown for individual catalytic reactions with the chiraphors left unspecified, and Scheme 43 demonstrates that one and the same chiraphoric moiety such as the binaphthyl subunit may be combined with various catalaphors to give catalysts for totally different reaction types [100, 101, 102, 103, 104]. It is also possible to combine two different chiraphoric motifs into hybrid catalysts (Scheme 44): for instance the chiraphor of Carreira's catalyst 44-3 [101] (used in asymmetric Mukaiyama aldolization) is composed of the Aratani saldimine 44-1 [104] and the Noyori binaphthyl 44-2 [99], whereas the Helmchen-Pfaltz-Williams catalyst chiraphor 44-6 (electrophilic allylation) [105] integrates Pfaltz's bisoxazolidone 44-4 and Noyori's BINAP ligand 44-5 [99]. The peculiar aspects of chiral catalysis are covered in the main chapters of this book and need not be enlarged upon in this more general section.

1. catalaphoric subunits :

homogeneous hydrogenation

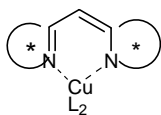


olefins

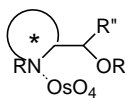


ketones

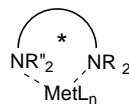
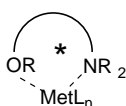
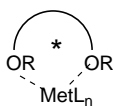
carbene olefin cycloaddition



olefin dihydroxylation

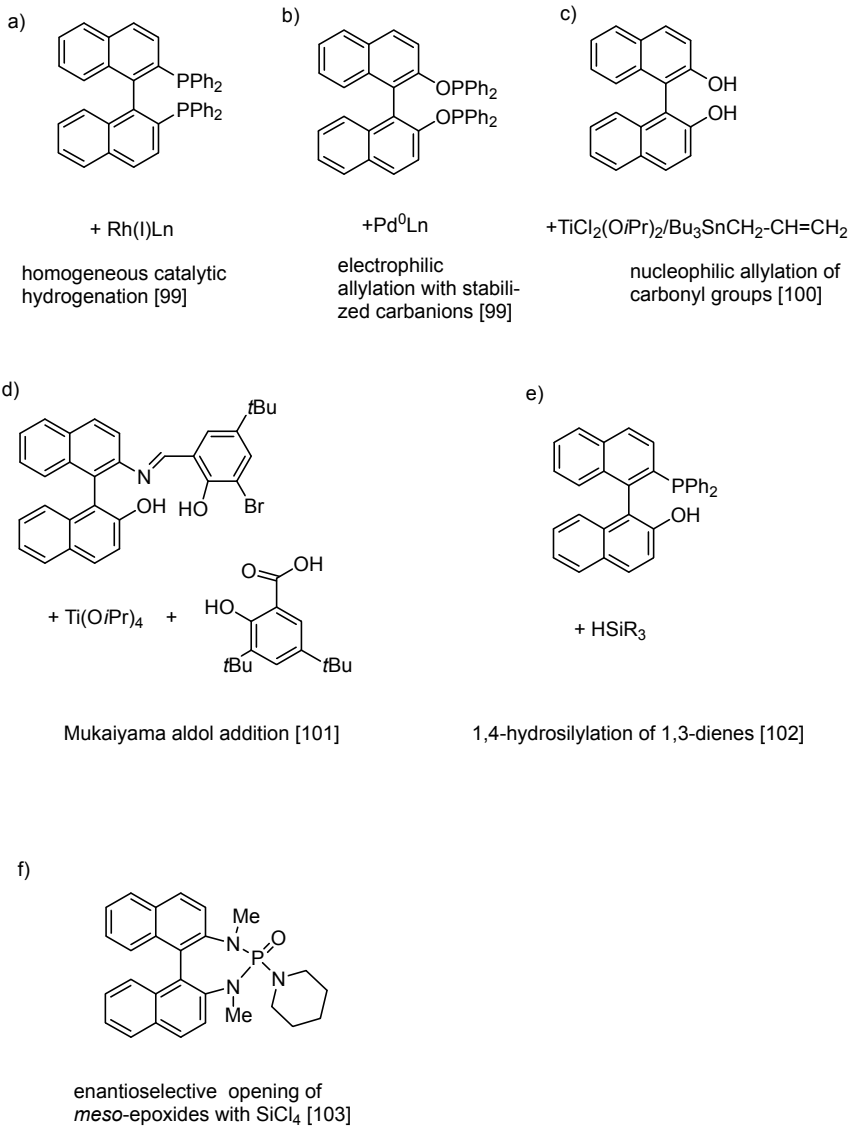


C/C-connections: pericyclic reactions, ene reactions, allylation of carbonyls, Grignard-type additions to carbonyl, aldol-type additions of silyl enol ethers to carbonyl, epoxide opening with cyanide, etc.

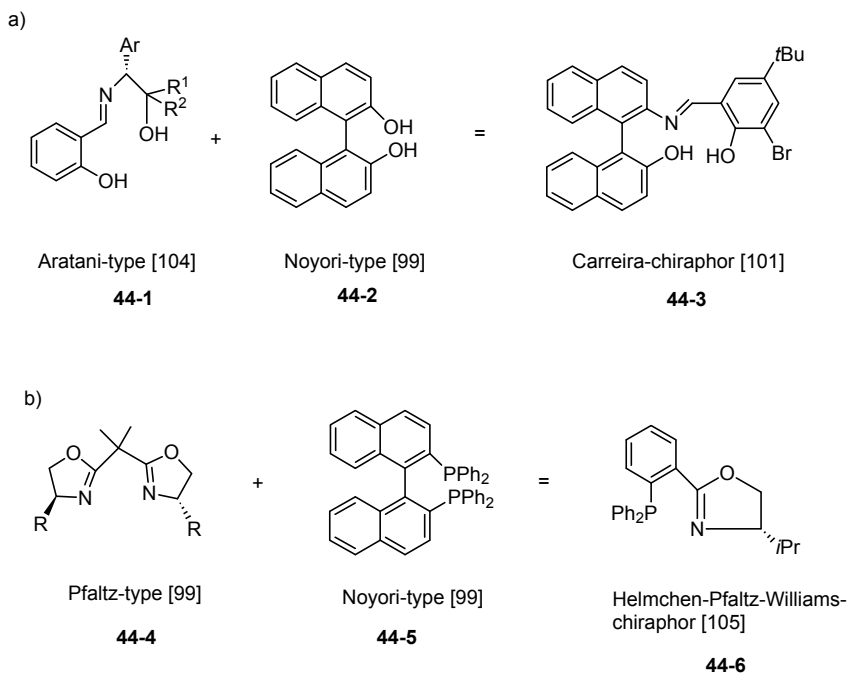


Met = B, Ti, Sn(II), Al, Au(I), Zn, Cr(III), Eu(III)
(Lewis acids forming complexes with the carbonyl)

Scheme 42



Scheme 43



Scheme 44

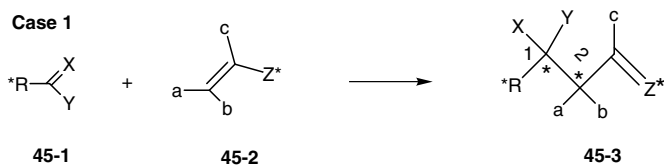
2.6

Double Stereodifferentiation

This is a very common and important phenomenon in asymmetric synthesis. Two cases are known (Scheme 45).

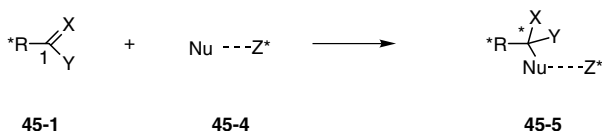
Case 1 has been frequently encountered in aldol type and crotylation reactions of aldehydes.

Thus, the chiral substrate **45-1** typically is an α -chiral aldehyde, whereas the chiral reagent **45-2** is a crotylstannane, -borane, or -boronate or an ester, amide, or ketone enolate with a chiral attachment Z^* . In course of the addition two new stereogenic centers at C-1 and C-2 are formed under the chiral influence of both the substrate (R^*) and the reagent (Z^*). The relative configurations of C-1 vs C-2 are independent of R^* and Z^* and are determined by the existence of an open or a closed transition state which is characteristic of the reaction under consideration. The absolute configurations, however, of C-1/2 are influenced by R^* and Z^* . As the configuration of R^* is unchangeable, the entire stereocontrol depends on Z^* to the effect that, for instance, (R)- Z^* enhances the desired stereoselection (*matched combination*) and (S)- Z^* decreases it (*mismatched combination*). If **45-2** is available in both configurations the matched situation can always be established. If, however, both **45-1** and **45-2** are fragments in the convergent syn-

**chiral substrate****chiral reagent**

prostereogenic carbon in allyl anion type arrangement attached to a chiral ligand, via covalent or noncovalent bond

product with four stereogenic units **two of which** are newly generated. diastereomeric ratio with respect to the newly created stereogenic centers varies with R/S-configuration of Z*

Case 2**chiral substrate****chiral reagent**

nucleophile attached to a chiral ligand, via covalent or noncovalent bond

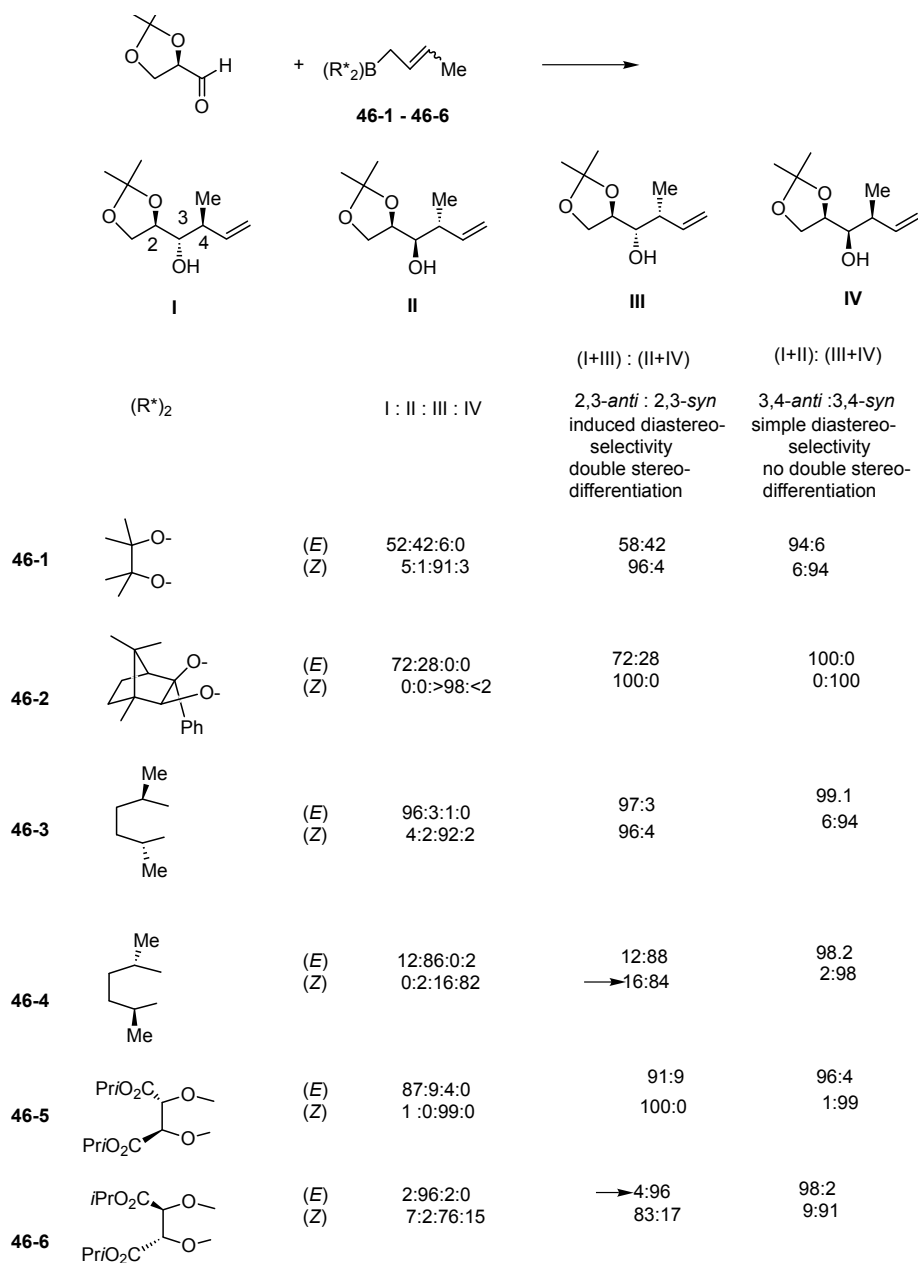
product with two stereogenic units **one of which** has been newly generated. diastereomeric ratio with respect to the newly created stereogenic center varies with R/S-configuration of R*

Scheme 45

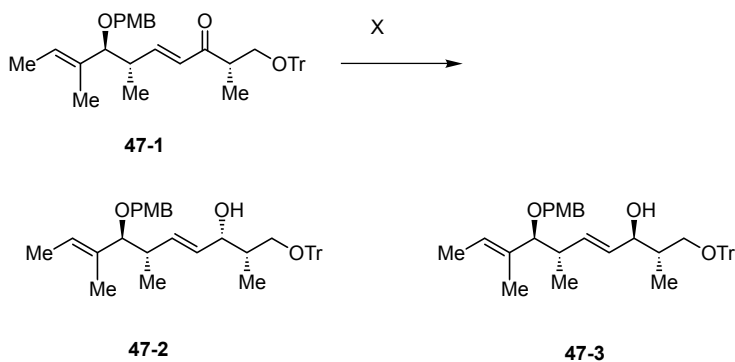
thesis of a larger target molecule, a, b, c may also be chiral and the configurations in both components are normally pre-determined. In this case the stereochemical outcome of the reaction is dubious and may be the undesired one or lead to an unselective reaction.

Case 2 is much simpler and concerns nucleophilic additions to a prostereogenic carbonyl or imine compound **45-1**. In this case the newly created stereogenic center at C-1 is influenced by R* and Z* with respect to matched and mismatched combinations. In principle the influence of R* or Z* may be more dominant. However, from the practical view, asymmetric inductions are easier to plan if the reagent control is much higher than substrate control.

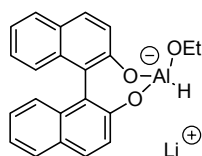
In Scheme 46, case 1 is discussed with respect to the crotylboration of (*R*)-isopropylidene glyceraldehyde. Altogether 4 diastereomers **I** to **IV** may be formed under the influence of the chiral information contained both in the aldehyde and in the crotylboron reagents **46-1** to **46-6** [106, 107, 108, 109]. The simple diastereoselectivity, i.e., the relative configuration with respect to C-3/4 is given by the Zimmerman-Traxler closed transition state and is *anti* for the (*E*)- and *syn* for the (*Z*)-crotyl isomers of **46-1** to **46-6**. It can be seen from Scheme 46 (sixth col-



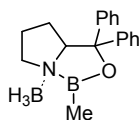
Scheme 46



X	47-2 : 47-3	
DIBAH	1	1
L-selectride	1	1.6
(R)-BINAL-H	1	1.4
(S)-BINAL-H	1	1.2
(S)-CBS	1	26
(R)-CBS	5.5	1



BINAL-H



CBS

Scheme 47

umn of table) that this ratio is not affected by the chiral information of the components. On the other hand, the asymmetric induction liable to double stereodifferentiation is the 2,3-*anti*:2,3-*syn* ratio given by (I+III):(II+IV) (fifth column). Here the reagents do have a very strong influence. The reference for pure substrate control is reagent 46-1 which has no stereogenic unit at all. Here one can see that the addition has a weak 2,3-*anti*-substrate stereocontrol for the (*E*)-crotyl isomer and a very distinct 2,3-*anti* substrate stereocontrol for the (*Z*)-isomer. Reagent 46-2 weakly strengthens this inherent tendency, whereas 46-3 is much more efficient; however, 46-4, which should reverse the effect of 46-3, shows that the reagent influence cannot totally overrule the substrate influence. This is possible for 46-6, but only for the (*E*)-crotyl species, whereas the (*Z*)-isomer is much inferior to 46-4. So in conclusion one can say that the (*E*)-crotylation is a

reagent controlled addition with **46-3** being the best reagent. In contrast, the (*Z*)-crotylation is a *substrate* controlled reaction, **46-4** being the only reagent that can reverse the substrate control from 96:4 to 16:84.

Scheme 47 shows a case 2 example for double stereodifferentiation, the problem being to reduce enone **47-1** preferentially to alcohol **47-2** or **47-3** [110]. The substrate control (DIBAH or L-selectride) is essentially zero, so that the chiral hydride donor must do the job. It can be seen that BINAL-H [111] is ineffective whereas diborane plus the CBS catalyst [112] shows a very pronounced reagent control so that either one of **47-2** and **47-3** may be generated selectively; for the formation of **47-3** the reagent control is much higher than for **47-2**, which is surprising in view of the low substrate control of the process.

3

Practical Applications

In this concluding section the EPC syntheses of six optically active pharmacologically important compounds are discussed with respect to the chiral sources they use. The complexity of the target compounds is gradually increased from a relatively simple molecule (the calcium antagonist diltiazem, two stereogenic centers, Scheme 48) to a highly complex structure (okadaic acid, seventeen stereogenic centers, Scheme 53). In each synthesis the methodology which is used for the introduction of chirality is highlighted and the respective source of chirality is marked with a frame.

3.1

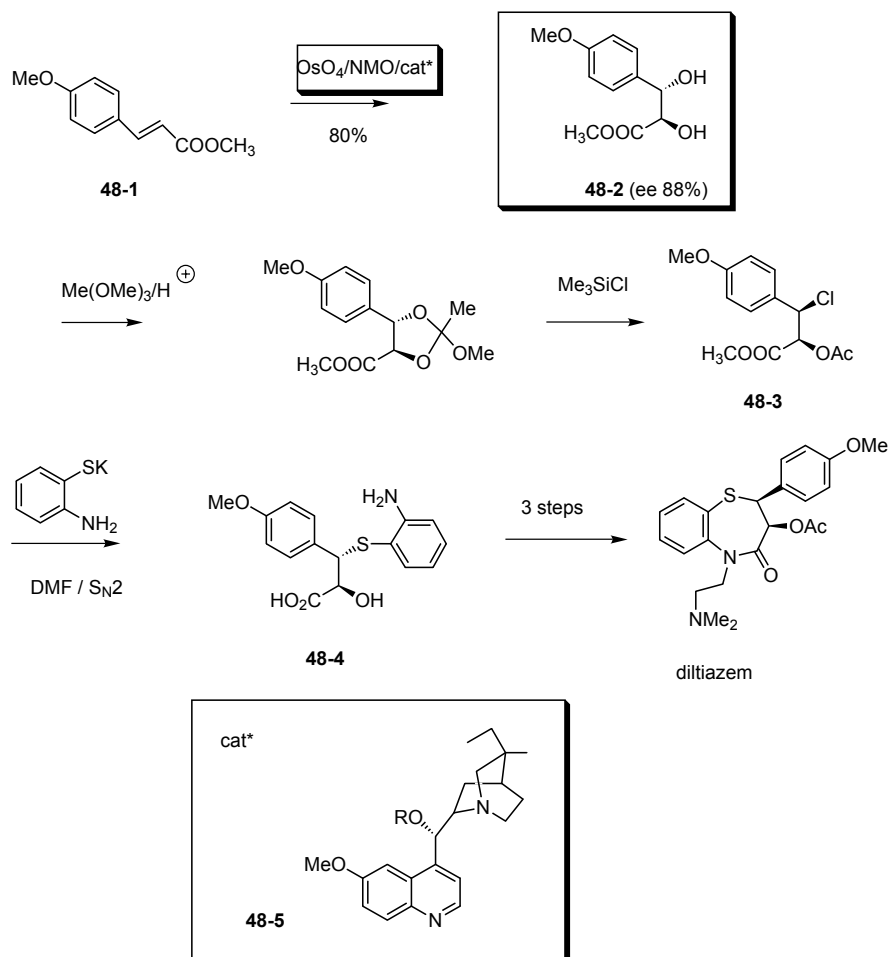
Industrial Synthesis of Diltiazem via Chiral Catalysis (Scheme 48)

Syntheses of relatively simple chiral drugs on an industrial scale are the domain of catalytic or enzymatic methods. In the case of the calcium antagonist diltiazem [113] Sharpless' asymmetric dihydroxylation (AD-reaction) is employed which works particularly efficiently for cinnamic acid derivatives such as **48-1**. In fact diol **48-2** is obtained with good optical enrichment and is then converted into the target compound via 6 routine steps. Alternatively diltiazem is prepared via classical optical resolution or via enzymatic kinetic resolution of suitable intermediates [113].

3.2

Application of a Chiral Auxiliary in the Synthesis of ICI D1542 (Scheme 49)

In suitable cases the application of stoichiometric chiral auxiliaries may be advantageous even on the industrial kilogram-scale. Scheme 49 provides as an example the synthesis of a thromboxane antagonist (ICI D1542) via the Evans aldol strategy [114]. Thus, the chiral auxiliary **49-1** is converted into the amide **49-3** and then submitted to a boron mediated aldol addition leading to **49-4** in diastereomerically pure crystalline form. The auxiliary is removed by reduction and



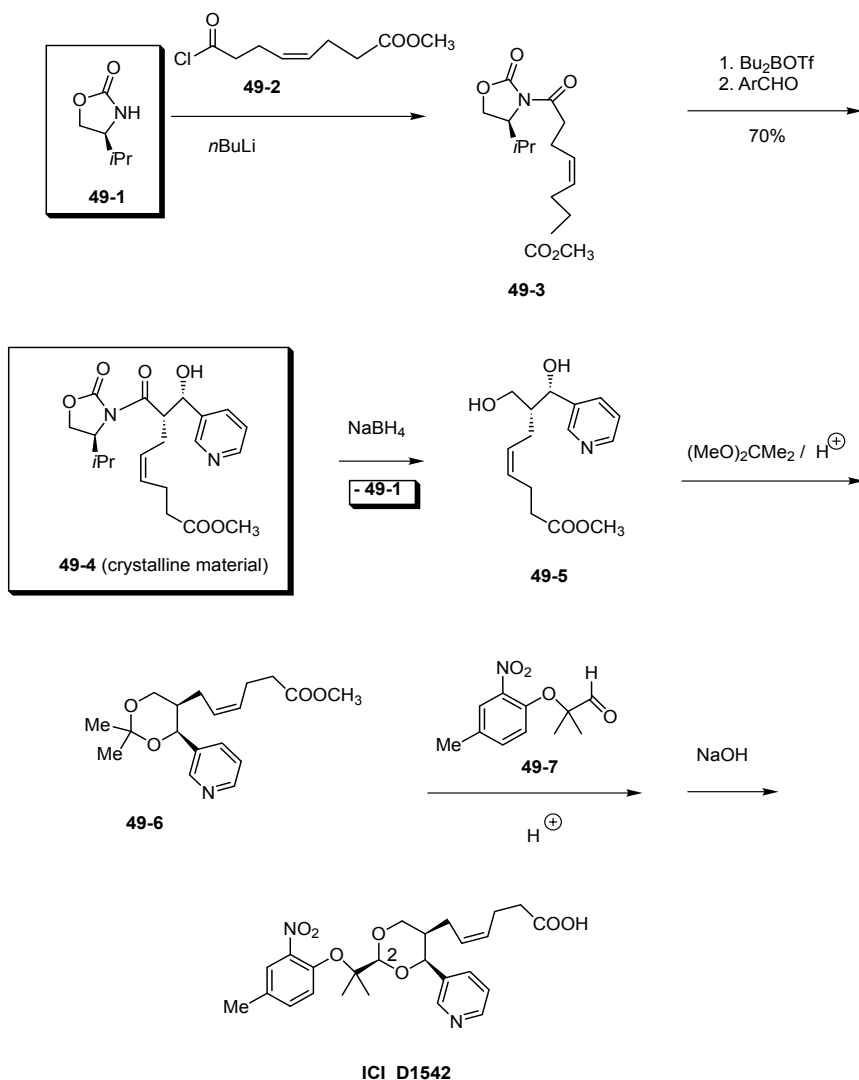
Scheme 48

recycled, and the diol **49-5** is transformed into ICI D 1542 by transketalization with aldehyde **49-7**. The stereogenic center at C-2 is generated stereospecifically via thermodynamic control.

3.3

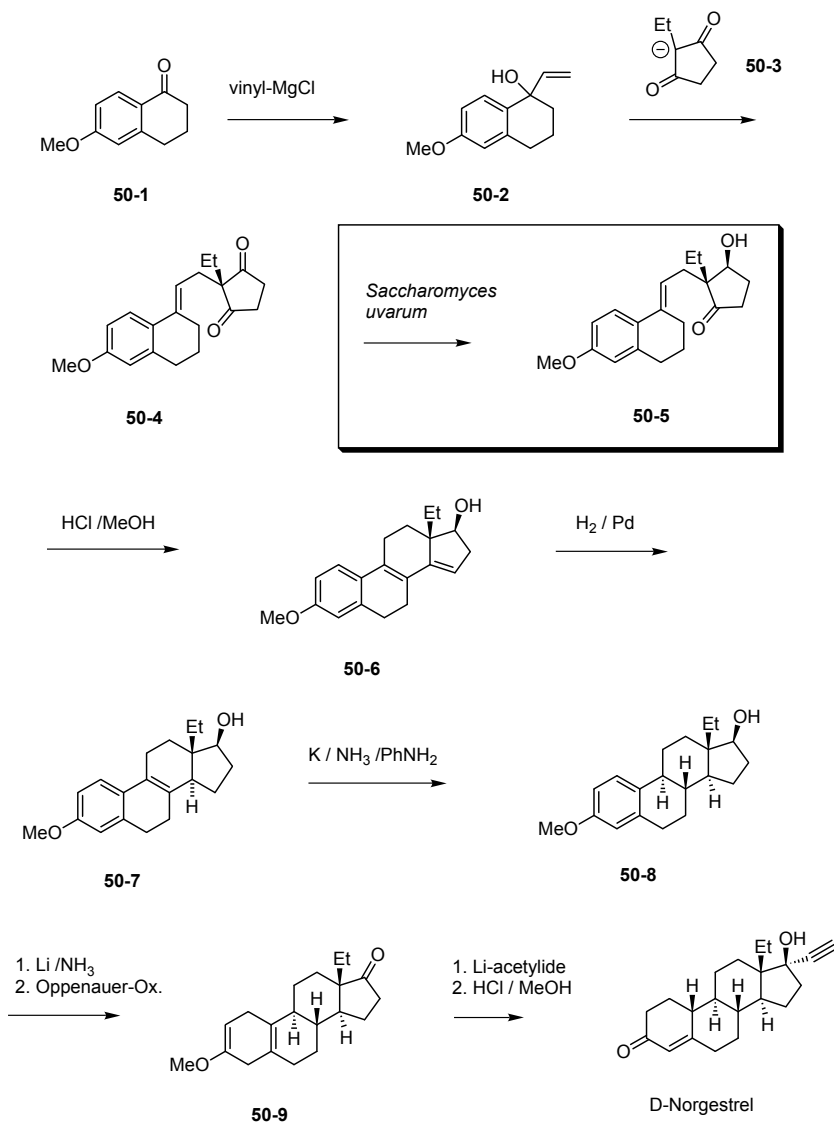
D-Norgestrel via Enzymatic Transformation (Scheme 50)

Most steroids are obtained from natural products via functional group manipulation. D-Norgestrel, a very potent gestagen used in contraceptive drugs, is an exception. Having a 13-ethyl group instead of the natural methyl it cannot be simply derived from a natural steroid and, for this reason has to be prepared by total synthesis (Scheme 50). The strategy is that of a Torgov synthesis modified



Scheme 49

by an enzymatic reduction which introduces two stereogenic centers in one step [115]. In this way intermediate **50-5** is generated stereoselectively and converted under ring closure to the steroid **50-6**. The two stereogenic carbons in **50-6** exert the stereocontrol on the following reactions such as the catalytic hydrogenation to form **50-7** and the Birch type reduction to **50-8**. The last stereocenter at C-17 is introduced by the addition of lithium acetylide diastereoselectively from the less hindered face to furnish D-norgestrel.



Scheme 50

3.4

Dihydrocodeinone via Optical Resolution by Chiral Chromatography (Scheme 51)

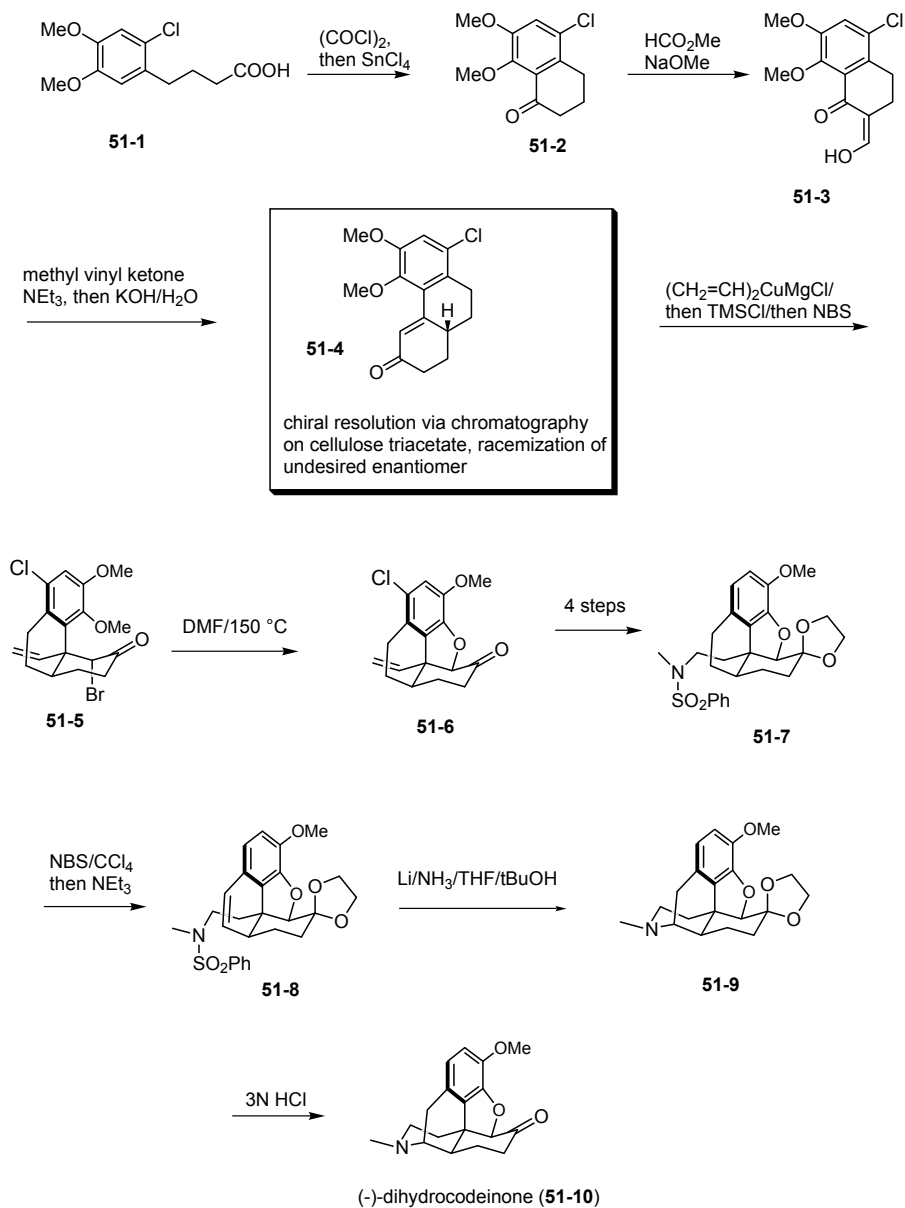
A classical approach to enantiopure compounds is the stoichiometric resolution of the enantiomers by formation of diastereomers with an enantiomerically pure auxiliary. Although several industrial processes are still based on this meth-

od, a more efficient variation is the use of chiral adsorbents so that enantiomeric separation is now possible by simple chromatography. This approach has the immense advantage that no separation and purification of diastereomers and subsequent recycling of the auxiliary is required. A crucial increase in efficiency is achieved by racemization of the undesired enantiomer which is recycled so that in the end the entire racemic material is converted into the desired enantiomer ("chirally economic resolution"). An application of this concept in the synthesis of the morphinane alkaloid dihydrocodeinone is demonstrated in Scheme 51 [116]. The key intermediate **51-4** is prepared from the acid **51-1** by Friedel-Crafts cyclization to **51-2** followed by Robinson annulation to racemic **51-4**. This ketone can be resolved on gram scale into the enantiomers with >99% ee by chromatography on cellulose triacetate. The undesired enantiomer is racemized by treatment with methoxide in methanol. Enantiomerically pure ketone **51-4** is then converted into the bromo ketone **51-5** by cuprate addition and bromination. Heating in DMF closes the dihydrofuran ring to form **51-6**. Elaboration of the vinyl sidechain leads to sulfonamide **51-7** which is then submitted to reductive cyclization. In this way **51-9** is generated which gives the anti-tussive (-)-dihydrocodeinone **51-10** in enantiomerically pure form.

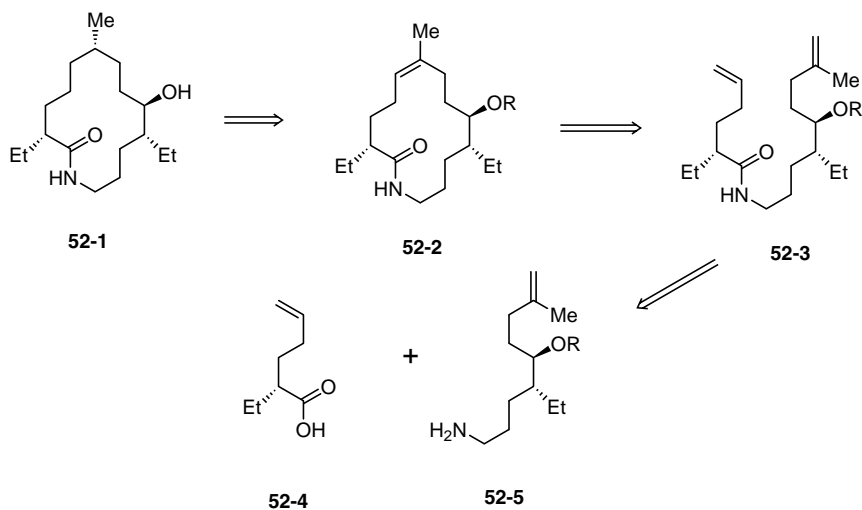
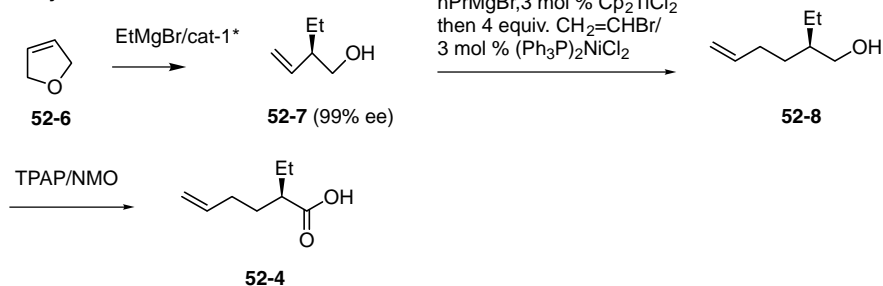
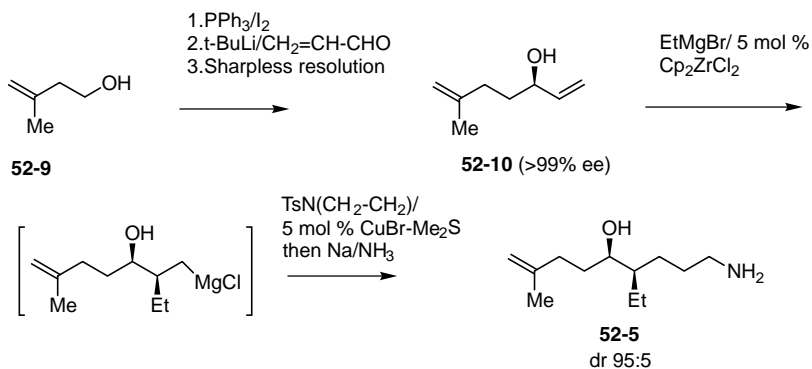
3.5

Fluvirucin B₁ via Chiral Catalysis (Scheme 52)

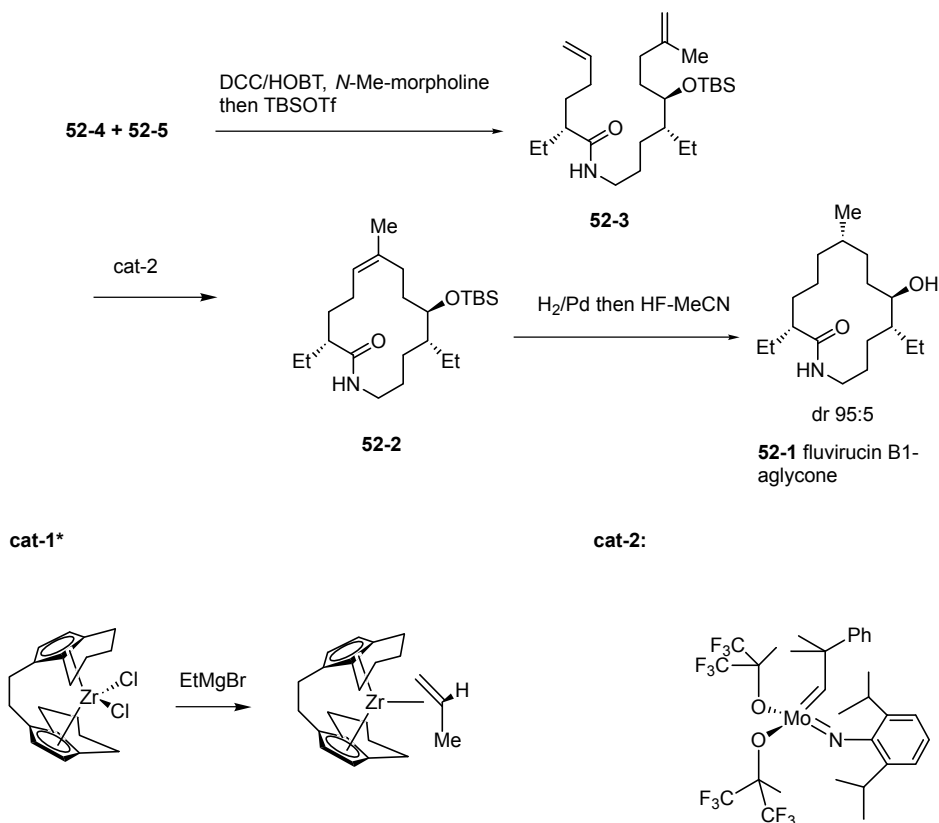
The idea to synthesize a chiral natural product mainly by chiral catalysis was put into practice for the macrolactam fluvirucin B₁ by Hoveyda et al. (Scheme 52) [117]. The basic strategy was that of a convergent synthesis by coupling acid **52-4** and amine **52-5** to amide **52-3** which was to be cyclized to **52-2** via a metathesis reaction. The building blocks **52-4** and **52-5** were synthesized via chiral catalysis. Thus, cat-1* was applied to add ethylmagnesium bromide via carbomagnesiation to dihydrofuran **52-6** to form the alcohol **52-7** enantioselectively. Hydro-magnesiation followed by nickel catalyzed cross coupling of the resulting organo magnesium derivative with vinyl bromide was used for the chain elongation of **52-7** to **52-8** which was oxidized to carboxylic acid **52-4** with ruthenium tetroxide. Compound **52-5** was synthesized via Sharpless resolution of the allyl alcohol **52-10** obtained from **52-9** via organometallic addition to acrolein. Alcohol **52-10** was then submitted to diastereoselective carbomagnesiation and then treated with tosylaziridine to give amine **52-5** after reductive detosylation. Amide formation was achieved under peptide coupling conditions to generate diolefin **52-3** after *O*-silylation. Ring closing metathesis occurs smoothly with catalyst cat-2 to give olefin **52-2** (*Z*)-selectively which was hydrogenated diastereoselectively to the aglycone **52-2**. The synthesis of the glycoside has also been reported [118].



Scheme 51

**Synthesis of 52-4:****Synthesis of 52-5**

Scheme 52

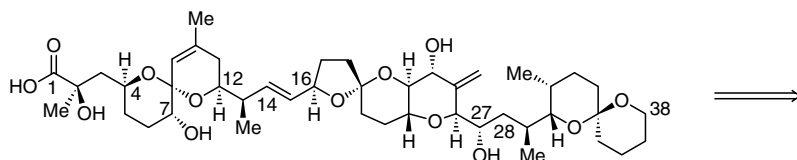


Scheme 52 (continued)

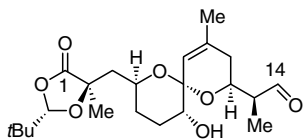
3.6

Convergent Asymmetric Synthesis of a Complex Polyketide: Okadaic Acid (Scheme 53)

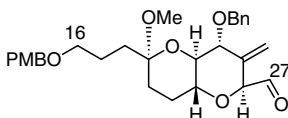
How is the methodology described in this review applied to the EPC-synthesis of a complex natural product? Among the numerous recent examples the synthesis of okadaic acid by Forsyth et al. [119] has been selected because it reflects the state of the art in a very characteristic manner (Scheme 53). It will be noted that the target molecule, an efficient phosphatase inhibitor, has a polypropanoate-polyacetate backbone with three spiro ketals and a dioxane as cyclic subunits. The retrosynthetic analysis reveals a classical convergent approach: the fragments **53-2** to **53-4** are synthesized separately and then assembled by reliable C/C-connecting reactions: for instance C-14 and C-16 are linked together via a Corey-Kwiatkowski-Horner-Emmons-sequence (**53-21**+**53-2**) and C-27 and C-28 are connected by an organolithium aldehyde addition of **53-3** and **53-4**. Addi-



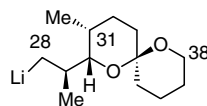
53-1 (Okadaic Acid)
17 stereogenic centers



53-2 6 stereogenic centers

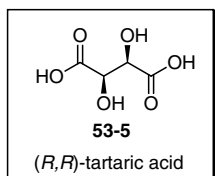


53-3 5 stereogenic centers

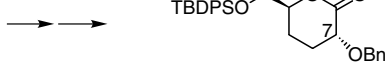
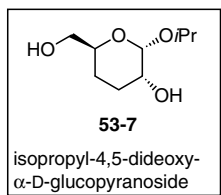


53-4 4 stereogenic centers

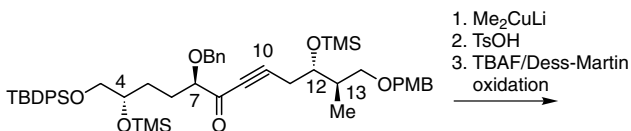
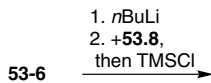
Synthesis of 53-2



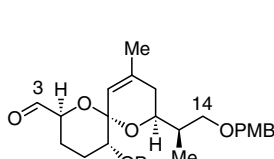
53-6



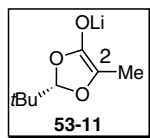
53-8



1. Me_2CuLi
2. TsOH
3. TBAF/Dess-Martin oxidation

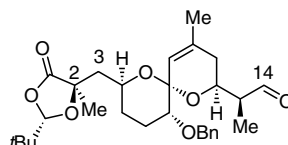


53-10



aldol addition,
followed by deoxy-
genation at C-3

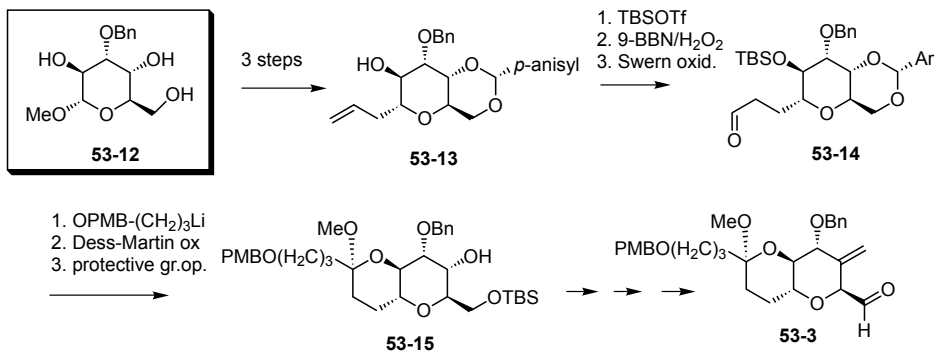
1. DDQ
2. Dess-Martin oxidation



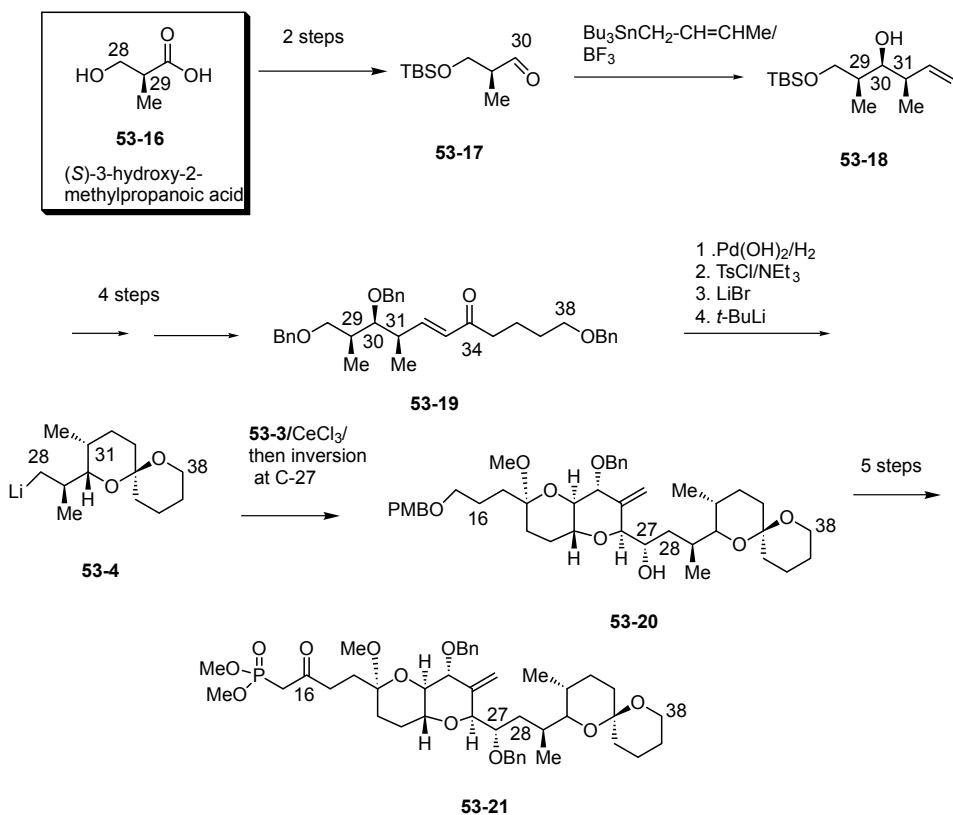
53.2

Scheme 53

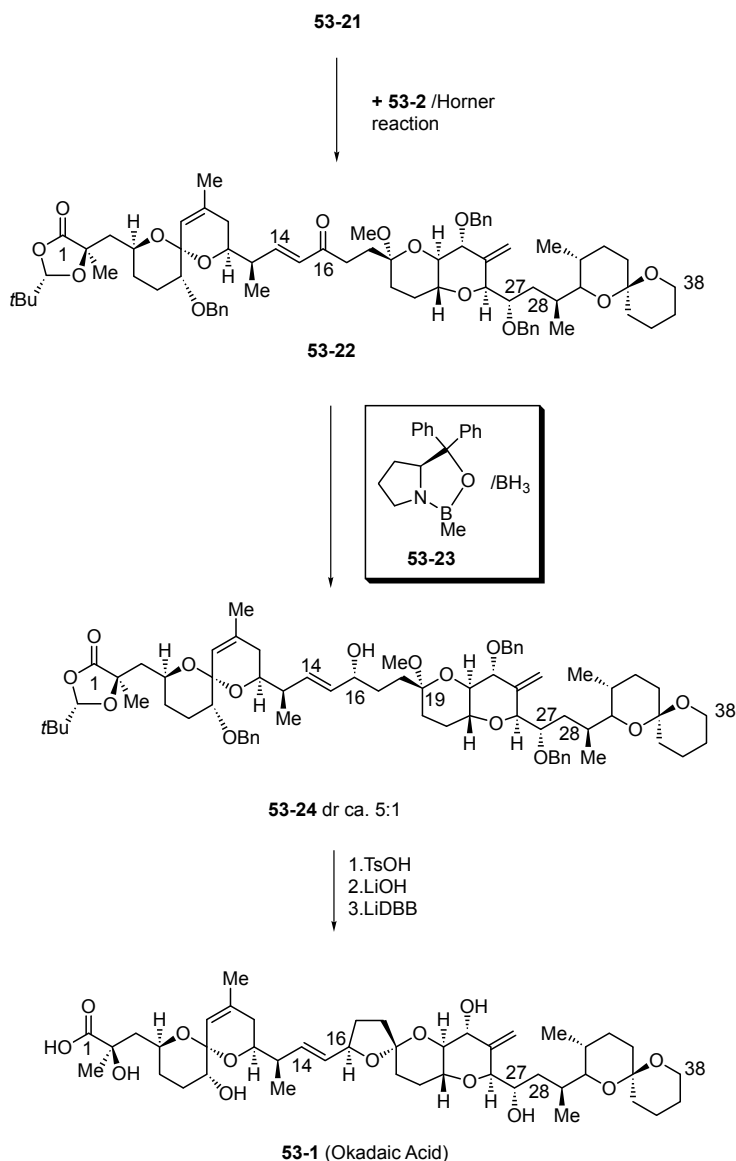
Synthesis of 53-3



Synthesis of 53-4 and Coupling with 53-3



Scheme 53 (continued 1)

**Scheme 53** (continued 2)

tional crucial C/C-connections are the acetylide-lactone addition of **53-6** to **53-8** which leads to **53-9** and the aldol type addition of enolate **53-11** to aldehyde **53-10** generating the C-2/C-3-bond. So, in conclusion, the construction of the carbon skeleton is based on organometallic chemistry which has the advantages of high reactivity, compatibility with various oxygen functions in suitably protected form (ethers and acetals, e.g., in **53-4**, **53-6**, **53-8**, **53-10**, **53-18**, etc.) and high

and predictable stereocontrol (for instance, an aldol type addition is used to establish the configuration at C-2, chelate Cram control secures the configuration at C-27 (after OH-inversion)). In general it can be noted that most stereogenic centers are adapted from the chiral carbon pool: C-12 and C-13 are developed from tartaric acid **53-5** by unambiguous reactions; similarly **53-7** is prepared from a known hexose without stereochemical problems. This guarantees the absolute and relative configuration of **53-9**. The conjugate addition of cuprates to alkynones proceeds *cis*-selectively and the spiroketal center is generated under thermodynamic control with both oxygens in axial positions so that **53-10** results. The aldol addition of **53-10** and **53-11** is controlled by the acetal center in **53-11** which directs the aldehyde *anti* to the *t*-Bu group to establish C-2 in the desired configuration. To this end the superfluous 3-OH is taken into account which has to be removed after the aldol addition by radical deoxygenation. Fragment **53-3** is prepared from the monosaccharide derivative **53-12** with the crucial allylsilane addition in axial direction at the anomeric center at C-22. The stereogenic centers in fragment **53-4** are derived from **53-16** which is converted into the C-30-aldehyde and then submitted to a stereocontrolled Keck-crotylation [120] to form **53-17**. The two new stereogenic centers are created by Felkin-Anh control (C-30) and the open transition state model which is typical for stananes (C-31). Horner reactions such as between **53-21** and **53-2** reliably furnish the (*E*)-enone so that the problem was now to reduce the 16-ketone selectively to the (16*R*)-alcohol. To this end external chirality was applied in form of Corey's CBS-method which uses **53-23** as the chiral catalyst for a carbonyl hydroboration (cf. Scheme 47). The last stereogenic center to be formed is the spiroketal center at C-19 which is achieved via thermodynamic control annulating the spirotetrahydrofuran with the oxygen axial to the oxane ring. Thus, in conclusion, this synthesis is a characteristic combination of chiral carbon pool starting materials (**53-5**, **53-7**, **53-12**, **53-16**) with chiral auxiliaries (**53-11**) and chiral catalysts (**53-23**). In addition to that, a number of stereogenic centers are established by well-established diastereoselective additions (C-22, C-27, C-30, C-31, spiro-ketal centers). It may be said in general that this is the typical strategy currently used in the total synthesis of complex structures [121].

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Chapter 4.1

Non-Linear Effects and Autocatalysis

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Keywords: Asymmetric amplification, Asymmetric catalysis, Asymmetric depletion, Autocatalysis, Chiral auxiliary, Enantiomeric excess, Kinetic models, Non-linear effects, Reservoir effect

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Abbreviations

NLE	non-linear effects
er	enantiomeric ratio
BINOL	1,1'-bi-2-naphthol

1

Introduction

In the last two decades asymmetric catalysis has become an established method for the preparation of compounds of high enantiomeric excess.

In Chapt. 2 of this volume the historical developments of asymmetric catalysis are reviewed. Since one of the main purposes of asymmetric catalysis is to obtain products with the highest possible ee, it appeared obvious to experimentalists to use chiral auxiliaries having the maximum ee possible. In asymmetric catalysis as well as in stoichiometric asymmetric synthesis it has been long considered that the maximum ee of the product (ee_{\max}) may be safely calculated from the observed ee of the product (ee_{prod}) by correcting for the ee of the auxiliary (ee_{aux}) according to Eq. (1).

$$ee_{\text{prod}} = ee_{\max} \times ee_{\text{aux}} \quad (1)$$

For convenience the ees in Eq. (1) and in the following equations are taken with values between 0 and 1. The strict proportionality (*linear correlation*) between ee_{prod} and ee_{aux} depicted in Eq. (1) seems obvious, and can be demonstrated for some simple kinetic systems [1]. It is important to point out that one may speak of linearity only if the enantiomeric purity is described by enantiomeric excess (ee). If the enantiomeric ratio (er) is used instead of the ee then Eq. (1) is replaced by a complicated equation in which er_{prod} is not linear with respect to er_{aux} [2].

2

Early Examples of Departure from Linearity

The study of diastereoselective reactions (chiral substrate, achiral reagent, or catalyst) played an important role in the development of dynamic stereochemistry (e.g., Cram's rule or Prelog's rule). It was pointed out in 1976 by Wynberg and Feringa that asymmetric induction (expressed by the diastereomeric excess or the diastereomer ratio) is dependent not only on the nature of the groups located around the asymmetric centers of the chiral substrate, but also of the enantiomeric excess of the substrate [3]. The authors verified this hypothesis by investigating some diastereoselective reactions performed using a racemic or a fully resolved substrate. For example, the lithium aluminum hydride reduction of racemic or enantiopure camphor gave different isborneol/borneol ratios.

It is interesting to note that Izumi and Tai in 1977 suspected that asymmetric catalysis using more than one chiral ligand could give a deviation from Eq. (1) [4].

Enantioselective reactions (achiral substrate, chiral reagent or catalyst) present a different situation, as a racemic or resolved auxiliary (in the reagent or the catalyst) must necessarily give rise to two different results. The product will be either completely racemic or may have some enantiomeric excess. This is also expressed by Eq. (1) where $ee_{\text{prod}}=0$ when $ee_{\text{aux}}=0$.

In 1986 in collaboration with the group of Prof. C. Agami we questioned the validity of Eq. (1) in asymmetric catalysis [5].

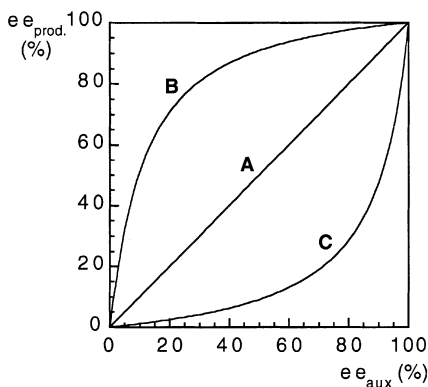
If one plots a graph of ee_{prod} (%) as a function of ee_{aux} one may envisage three basic situations: A, B, or C described in Scheme 1. The straight line A, defined by Eq. (1), is the expected situation (linearity). The concave curve B located above line A represents a situation where values of ee_{prod} are always higher than those predicted by Eq. (1). We called this case a positive non-linear effect, abbreviated as (+)-NLE. The convex curve C indicates experimental values of ee_{prod} less than those expected, termed a negative non-linear effect ((-)-NLE).

By convention we always define ee_{prod} as positive, whatever the absolute configuration and the sign of the specific rotation of the product.

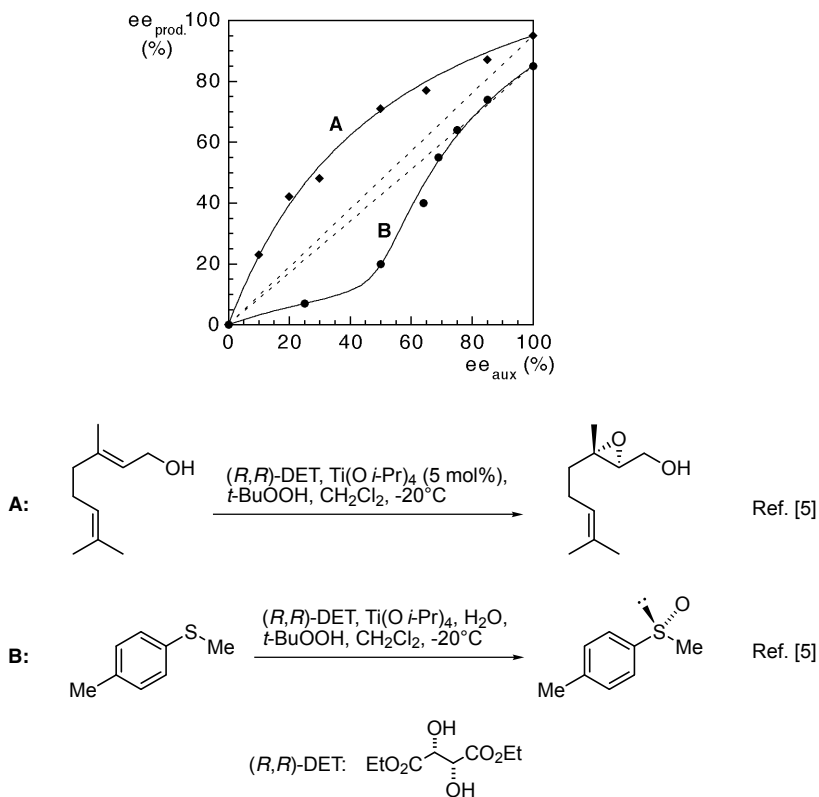
In asymmetric catalysis the amount of the chiral catalyst must be constant throughout the course of the reaction. The structure also remains intact unless the reaction product interacts with the catalyst (c.f. autoinduction phenomenon [6, 7]). In this context we will not consider those reactions with autoinduction.

We discovered examples of non-linear effects in three different reactions:

- (i) Asymmetric epoxidation of allylic alcohols by the Sharpless method.
- (ii) Asymmetric sulfoxidation of methyl *p*-tolyl sulfide by a water-modified Sharpless reagent.
- (iii) Asymmetric aldolization of a triketone catalyzed by proline.



Scheme 1



Scheme 2

The first two reactions (Scheme 2) were stoichiometric with respect to the chiral titanium complex (using *(R,R)*-diethyl tartrate), but they are included in the scope of asymmetric catalysis as the titanium complexes are not consumed.

Since 1986 many examples of NLE have been discovered (for some recent reviews see [8, 9a, 9b, 10]). The asymmetric addition of diethylzinc to benzaldehyde catalyzed by various chiral β -amino alcohols gave rise to the pioneering work in 1988 of Oguni et al. [11] and in 1989 of Noyori et al. [12]. Very strong (+)-NLEs were displayed by these systems (see Sect. 4 below). Oguni proposed the name “asymmetric amplification” as a synonym of (+)-NLE, to term curves such as **B** (Scheme 1). This expression (or its equivalent “chiral amplification”) is now widely used; it is convenient although not strictly defined. In a recent review on asymmetric amplification we discussed this point and also proposed an index of amplification [1]. This index is equal to the enantiomeric ratio of the product divided by the expected enantiomeric ratio calculated for a linear correlation. The ratio $er_{\text{prod}}/er_{\text{calc}}$ is a better index than $ee_{\text{prod}}/ee_{\text{calc}}$ since the latter greatly underestimates the amplification observed with high enantiomeric purities.

3 Some Models for Explaining Non-Linear Effects

Most of the published examples of NLEs deal with organometallic catalysts. These may be abbreviated to ML_n or $(ML)_n$, where M stands for the metal core (surrounded or not by some achiral ligands) and L is a chiral ligand. The n value characterizes the number of chiral ligands in the monomeric or the polymeric molecular species.

In 1994 we developed various kinetic systems able to model NLEs [13]. All these models have in common the formation of additional diastereomeric complexes as soon as the ligand L is not enantiomerically pure. This is the root of the non-linear behavior phenomenon.

Two main classes of processes have to be considered:

- The additional diastereomeric complexes are catalytically active.
- The additional diastereomeric complexes are catalytically inactive.

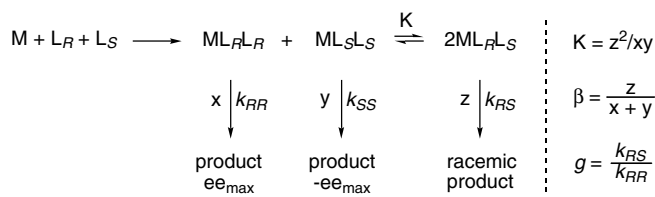
These two cases will be discussed below and sometimes may be interrelated.

3.1 ML_2 Models

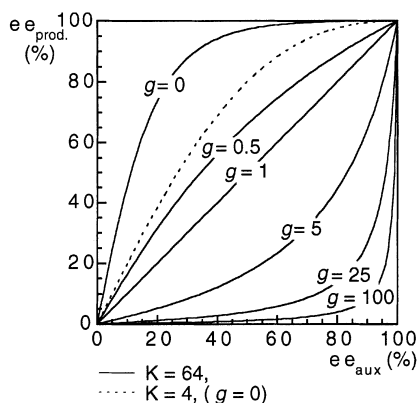
A simple model, based on two chiral ligands L around a metal center is described in Scheme 3. If the chiral ligand is enantiomerically pure the catalyst is either ML_RL_R or ML_SL_S while for partially resolved catalysts an additional catalyst ML_RL_S may be generated. In this last case the product is obtained through three routes, two involving homochiral catalysts and one a heterochiral catalyst (assumed with a *meso*-structure). We were able to calculate the overall ee_{prod} as a function of ee_{aux} [13].

The final relative concentrations of the three catalysts are termed x , y , and z . We also used as an intermediate parameter, the relative amounts of heterochiral versus homochiral catalysts ($\beta = z/(x+y)$). The relative rate constant g and the equilibrium constant K (see Scheme 3 for definitions) are the key parameters for the calculation. An easy kinetic treatment first gave Eq. (2) relating ee_{prod} to the g and β values.

$$ee_{\text{prod.}} = ee_{\text{max}} \times ee_{\text{max}} \times \frac{1+\beta}{1+g\beta} \quad (2)$$



Scheme 3



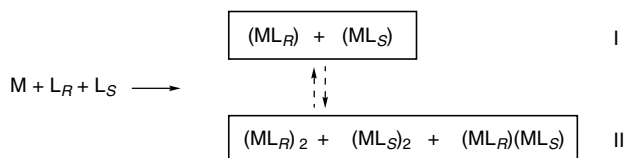
Scheme 4

If $g=1$ (homo and heterochiral complexes have the same reactivity) or if $\beta=0$ (no heterochiral complexes) then Eq. (2) collapses to Eq. (1) and there is a linear correlation between ee_{aux} and ee_{prod} . For all the other values of g and b there is a non-linear correlation. A (+)-NLE is obtained if $g < 1$ and a (-)-NLE is given by $g > 1$. Numerical values of ee_{prod} can be obtained if one knows the value of the equilibrium constant K , as we have found a general relationship between K and β (see [13]). In Scheme 4 are plotted some curves of $ee_{\text{prod}} = f(ee_{\text{aux}})$ as a function of g for $K=64$ (higher amount of *meso*-catalyst). The curve corresponding to $K=4$ (statistical distribution of ligands between the three complexes) is also presented for $g=0$. The maximum asymmetric amplification is observed each time for $g=0$. This is a consequence of sequestration of ligands of racemic composition to a catalytically inactive complex, which consequently enhances the ee of the ligand included in the homochiral catalysts. The (-)-NLE (asymmetric depletion) is linked to a higher reactivity of the *meso* complex than homochiral complexes.

If the three complexes are at a steady state, which does not necessarily involve an equilibrium, K may still be used as a parameter to correlate β with ee_{aux} . K (as defined in Scheme 3) and β are sufficient to obtain the relative amounts x , y , and z of the three competitive catalysts.

Similar calculations have been performed when the catalysts are formed by dimerization of complexes ML_R and ML_S into $(ML_R)_2$, $(ML_S)_2$ and $(ML_R)(ML_S)$ [13].

Blackmond pointed out that since the relative distribution of catalytic complexes can be obtained from the above calculation (e.g., x , y , and z for the ML_2 model) as a function of ee_{aux} , K , and the relative rate constants, it becomes possible to calculate the relative rates (with respect to enantiopure catalyst) [14]. This could provide a useful confirmation of a postulated model.



Scheme 5

3.2

The Reservoir Effect

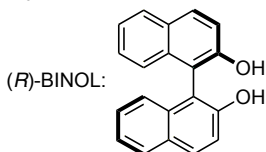
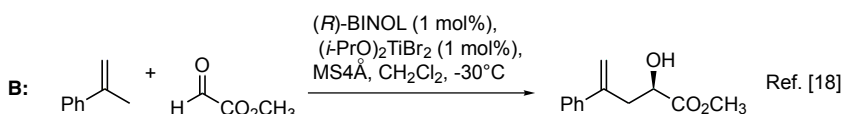
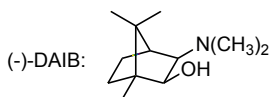
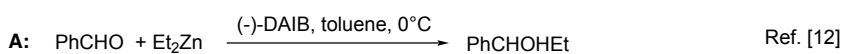
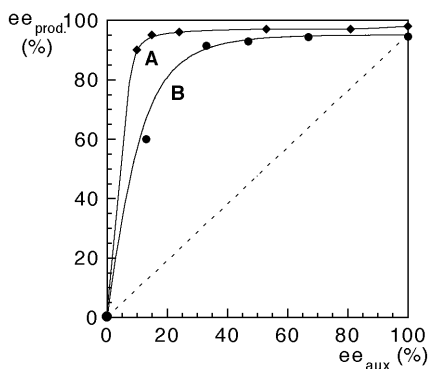
A second and very simple mechanism for the occurrence of NLEs is the “reservoir effect” [13]. This involves the competitive formation of catalytically inactive complexes in addition to the actual catalysts.

A model for the reservoir effect is shown in Scheme 5. A one-ligand system (I) and a two-ligand system (II), formed by dimerization of (I), are in competition with each other. The two systems may or may not be interconnected by an equilibrium. The reservoir could be either II, hence the reaction is catalyzed by species I, or I and the dimeric species II is the catalyst. A modification of the enantiomeric excess (with respect to initial ee_{aux}) of ligands may occur for some distributions of ligands in the various complexes of I and II. For example, let us assume that II is a reservoir storing a large amount of *meso*-dimer. This means that some ligands of racemic composition are sequestered, enhancing the effective ee ($ee_{\text{eff}} > ee_{\text{aux}}$) in the catalytic system I. As a consequence there will be an asymmetric amplification. Calculations are possible to evaluate the influence of the reservoir effect in various situations [13]. There are no strict borders between the kinetic model of Scheme 3 and the reservoir effect in Scheme 5, as already pointed out [13].

4

Reactions Giving Asymmetric Amplification

It was discovered that a (+)-NLE (asymmetric amplification) may occur in various types of catalytic reactions, for a review see [1]. The addition of diorganozincs to aldehydes catalyzed by chiral β -amino alcohols has been studied in depth. After the initial report of Oguni et al. in 1988 [11] it has been mainly Noyori et al. who have investigated this area, giving both spectacular examples of asymmetric amplification [12] and detailed mechanistic studies [12, 13, 14, 15, 16, 17]. Curve A in Scheme 6, represents an example of the asymmetric amplification obtained by Noyori et al. [12], which still remains the highest (+)-NLE known. The authors found that the reaction is first-order with respect to the catalyst and that the asymmetric amplification originates from the accumulation of unreactive *meso*-dimers of the zinc alcoholate of (–)-DAIB. The (+)-NLE may be seen as the consequence of a reservoir, weakly coupled to the catalytic cycle and storing some racemic ligand.



Scheme 6

Some carbonyl ene-reactions catalyzed by chiral titanium complexes were shown by Nakai and Mikami to generate a strong asymmetric amplification, as in curve **B** of Scheme 6 [18].

Many different kinds of catalytic reactions may lead to a (+)-NLE. Owing to lack of space we will just mention the main classes of reactions without details, more details being available in the review article [1].

4.1

Organozinc Additions to Aldehydes

Initially, mainly β -amino alcohols were used as chiral ligands to catalyze the addition of organozincs to aldehydes. In most of the cases investigated a (+)-NLE was observed. Presumably this is a consequence of the greater stability of the dimeric *meso*-zinc alcoholate derived from the β -amino alcohol. In addition to

the examples reported above [11, 12], one must also quote the results obtained by Bolm et al. Using a β -amino alcohol containing a pyridine ring, they obtained one of the highest known asymmetric amplifications [19]. A modest (+)-NLE has been detected by Dosa and Fu in the catalyzed addition of diphenylzinc to 4-bromopropiophenone [20]. γ -Amino thiols are also interesting catalysts, and have been studied by Kellog et al. [21] and van Koten et al. [22]. A γ -amino diselenide catalyst, prepared by Wirth et al. [23] also gave an asymmetric amplification. A β -hydroxysulfoximine as catalyst has provided a significant (+)-NLE in the addition of diethylzinc to benzaldehyde [24].

4.2

Conjugated Addition of Organozincs to Enones

Nickel complexes, prepared by the combination of $\text{Ni}(\text{acac})_2$ with a chiral β -amino alcohol [24, 25] or a β -hydroxysulfoximine [26], catalyze the conjugate addition of diethylzinc to chalcone. Some asymmetric amplifications have been observed.

4.3

Conjugated Addition of Organocuprates to Enones

(+)-NLE have been observed for the 1,4-addition of some organocuprates to cyclic enones when the reaction is performed in the presence of a chiral ligand (diamino alcohol or diamine) [27, 28].

4.4

Allylstannane or Allylsilane Addition to Aldehydes

Various titanium or zirconium complexes have been shown to catalyze the addition of allyl(tri-*n*-butyl)tin [29, 30, 31] or allyltrimethylsilane [32, 33] to aldehydes, giving good enantioselectivities and some asymmetric amplification. In all these examples the chiral auxiliary is derived from (*R*)- or (*S*)-BINOL.

4.5

Glyoxylate Ene Reactions

Titanium complexes involving a chiral auxiliary derived from BINOL, are good catalysts for the glyoxylate ene-reaction (see example in Scheme 6). With these species very high (+)-NLEs have been observed [18, 33, 34, 35].

4.6

Diels-Alder Reactions

Chiral Lewis acids based on titanium [33, 36, 37] or scandium [38] have been used to catalyze the Diels-Alder reactions, and a high asymmetric amplification has been described by Narasaka et al. [36]. This occurs presumably because of

the formation of a dimeric titanium complex of racemic composition which precipitates from the reaction medium. One of the highest (+)-NLE known has been reported by Curran et al. who used a bis-oxazoline/Ni complex as a catalyst [39].

4.7

Oxidation and Reduction

The Sharpless epoxidation of allylic alcohols gives rise to moderate asymmetric amplification [5, 13]. One example is shown in Scheme 2. The epoxidation of chalcone by a hydroperoxide in the presence of a catalyst formed by the combination of (*R*)-BINOL and $Y(Oi-Pr)_3$, displays a similar asymmetric amplification [40]. A weak (+)-NLE was observed [41] for the allylic oxidation of cyclohexenone in the presence of a peroxide and a carboxylic acid, which was catalyzed by a combination of proline, anthraquinone, and $Cu(OAc)_2$. Asymmetric sulfoxidation of methyl *p*-tolyl sulfide by a hydroperoxide in the presence of a titanium/BINOL/water catalyst also gives some asymmetric amplification [42].

4.8

Miscellaneous

In addition to the above reactions, asymmetric amplification has been detected in many different types of reactions, some are listed below. A catalytic 1,3-dipolar addition onto allyl alcohol displays a weak (+)-NLE [43]. Opening of a *meso*-epoxide (epoxycyclohexane) by $TMSN_3$ catalyzed by a salen-Cr complex gave a significant (+)-NLE [44]. The Mukaiyama-aldol condensation of $CH_2=C(OTMS)St-Bu$ onto benzaldehyde has been catalyzed by a BINOL/Ti (*Oi-Pr*)₄ combination, giving a strong asymmetric amplification [45]. The nitro-aldol reaction between nitromethane and (1-naphthyl)OCH₂CHO catalyzed by a chiral lanthanum complex prepared from the dilithium salt of BINOL and $LaCl_3$ gave a weak asymmetric amplification [46]. Faller et al. detected some asymmetric amplification during asymmetric hydrogenation catalyzed by a cationic rhodium complex with chiraphos as the ligand [47]. This was interpreted as the preferential formation of an unreactive *meso*-dimer produced by a double bridging, each chiraphos coordinated to one rhodium which was coordinated to another rhodium by the π -system of a phenyl group.

5

Reactions Giving Asymmetric Depletion

There are very few examples of (–)-NLE, compared to the large number of reported (+)-NLEs.

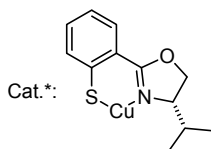
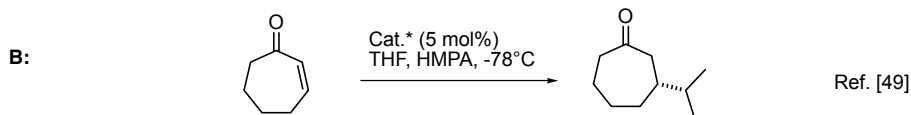
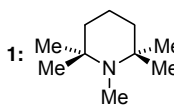
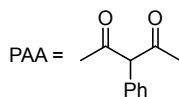
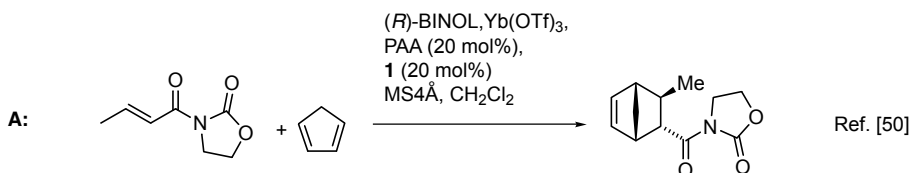
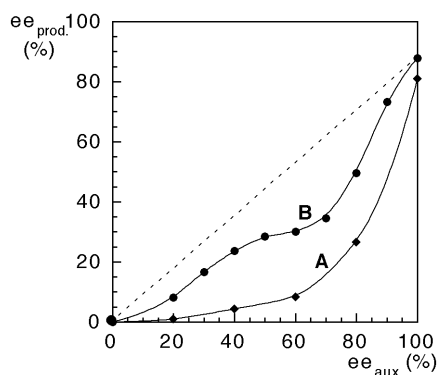
Asymmetric depletion may originate from several mechanisms, for example:

- (i) A kinetic model such as ML_2 , where a reactive *meso*-complex accumulates more racemic product than predicted ($g > 1$, vide supra).
- (ii) A competition between a chiral catalyst with a (+)-NLE behavior and an achiral catalyst: if the asymmetric amplification results from a reservoir ef-

fect, there will be a strong decrease in the catalytic activity with decreasing ee_{aux} , while the good activity of the achiral catalyst will stay constant. The overall effect will be a (-)-NLE.

The asymmetric sulfide oxidation described in Scheme 2 has a (-)-NLE until $ee_{aux}=70\%$ [5]. The (*S*)-proline catalyzed cyclization of a triketone shows a weak asymmetric depletion [5], as does allylic oxidation of cyclohexene in the presence of a catalyst prepared from $Cu(OAc)_2$ and (*S*)-proline [41].

Katsuki et al. studied the Diels-Alder reaction between cyclopentadiene and a crotonamide derivative [48]. Their catalyst was prepared *in situ* from equimolar amounts of $EtAlCl_2$ and a chiral diol. A (-)-NLE was observed in dichlo-



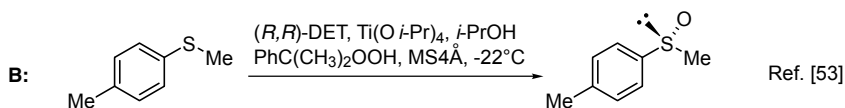
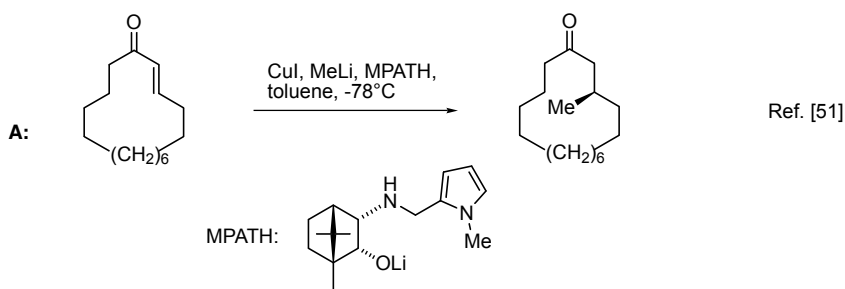
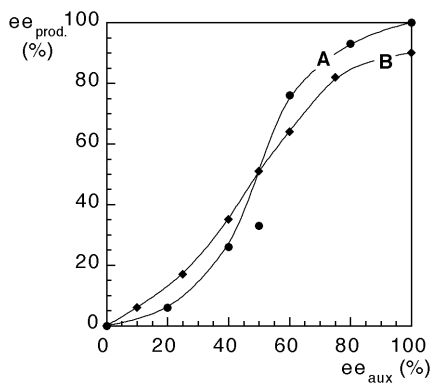
Scheme 7

romethane (presumably because of the formation of oligomeric species), while there is a linear relation in THF (monomeric catalyst).

The largest asymmetric depletion found in the literature is shown in Scheme 7 (Curve A), it was reported by Kobayashi et al. during their studies involving BINOL/lanthanide triflate combinations [49]. It is also interesting to mention the multi-shaped curve B (Scheme 7) observed by Pfaltz and Zhou in the conjugated addition of a Grignard reagent to cycloheptenone, in the presence of a chiral copper catalyst [50].

6 Reactions Giving Simultaneously (+)- and (-)-NLE

In a few cases one may find curves with a concave section followed by a convex portion (or vice-versa), with crossing of the straight line characterizing the absence of NLE. In Scheme 8 (Curve A) a typical example is given, derived from a



Scheme 8

muscone synthesis, by a cuprate addition to a conjugated ketone [51]. Van Koten found a less pronounced phenomenon using a chiral copper aminothiolate as catalyst for addition of MeMgI to benzalacetone [52]. The oxidation of methyl *p*-tolyl sulfide by cumyl hydroperoxide in the presence of a chiral titanium catalyst gave a moderate asymmetric depletion with crossing of the straight line indicating linear behavior (Curve B, Scheme 8) [53].

7

Use of Non-Linear Effects in Mechanistic Studies

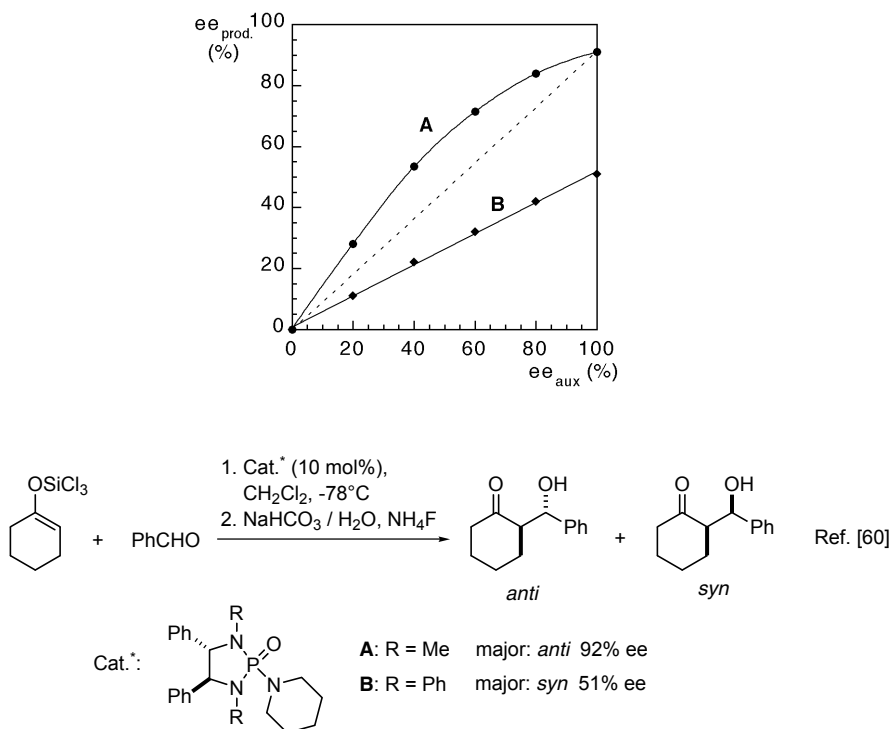
The *presence* of a NLE may afford useful information during the study of an asymmetric catalytic reaction. It is indicative of the formation of diastereomeric species within the catalytic cycle (competing catalysts) or at the periphery of the catalytic cycle (reservoir effects). A frequently encountered situation is the formation of diastereomeric species by aggregation (e.g. dimerization, trimerization, etc.) of a complex.

The *absence* of a NLE has been often taken as a good evidence (not a proof) against aggregation [54, 55, 56, 57, 58].

In many of the examples of Sect. 4 the origin of the asymmetric amplification could be related to the formation of inert or slow-reacting dimeric species (reservoir effect), slowing down the reaction at low ee_{aux} . If the reaction is second-order with respect to the catalyst a deviation from linear behavior may be suspected as two equivalents of catalyst are involved in the turnover-limiting step. Agami et al. have demonstrated that the (*S*)-proline catalyzed intramolecular aldolization of a triketone is second-order with respect to proline [59]. This system displays a moderate (-)-NLE [5]. The opening of an epoxy cyclohexane by TMSN₃ catalyzed by a chiral salen-Cr complex showed a second-order dependency with respect to catalyst [44]. Jacobsen et al. found that there is also an asymmetric amplification. This fits with the proposed interpretation where one salen-CrN₃ species acts as a chiral Lewis acid (activation of the epoxide), while another salen-CrN₃ species behaves as a nucleophile in the turnover-limiting step.

In the cases above (second-order with respect to the catalyst) the *R/R* (*S/S*) or *R/S* combinations are diastereomeric and of different reactivities. This kinetic phenomenon is close to the ML₂ model, as has been noted [13].

Denmark et al. used non-linear effects to identify a higher order molecularity of the catalyst with respect to substrate in one of the pathways for a chiral Lewis base-catalyzed aldol addition reaction [60]. The reaction generates mainly a *syn* or an *anti* aldol, according to the catalysts used (A or B, Scheme 9). It was proposed that the formation of the *anti*-adduct involved two molecules of a chiral phosphoramidate A (the catalyst) bound to a cationic silicon intermediate. In contrast, only one molecule of the more bulky catalyst B can bind to silicon, favoring the formation of the *syn*-adduct. This interpretation is in agreement with the NLE curve observed for catalyst A and the linear behavior observed with catalyst B.



Scheme 9

NLEs can also be useful indicators during the tuning of chiral catalysts by introduction of additives or by some changes of experimental conditions [38, 53].

In asymmetric catalysis the concept of non-linear effects for mixtures of enantiomeric ligands has been extended to the mixtures of diastereomeric ligands [61, 62].

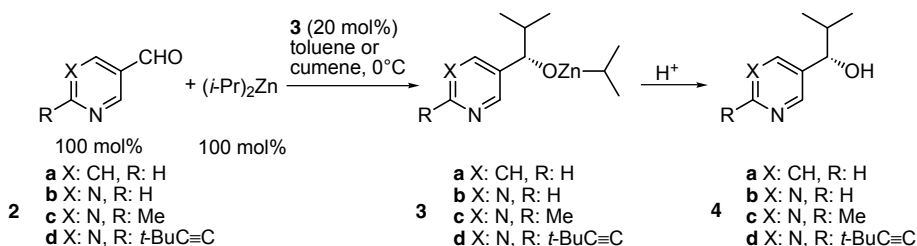
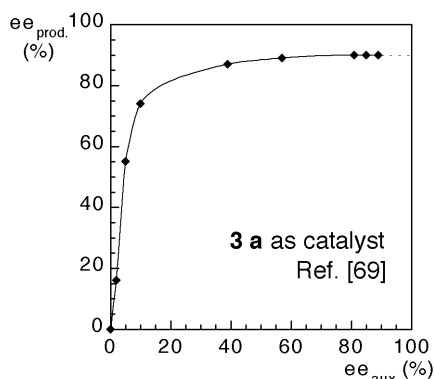
8

Asymmetric Autocatalysis

Autocatalysis is defined as a process where a catalyst catalyzes its own formation. This process has been proposed as one of possibilities for the propagation of optical activity on earth [63]. A problem, not solved by the autocatalysis, is how to amplify a small initial enantiomeric excess to a large value, before using autocatalysis in the propagation step. Frank proposed in 1953 a kinetic model which combines amplification of ee and increase of the amount of product (propagation) [64]. It is based on the reaction: $A+B \rightarrow R+S$, where R and S are enantiomeric products. The reaction towards R is catalyzed by R , while formation of S is catalyzed by S . A second reaction was considered: $R+S \rightarrow P$. This uncatalyzed reaction gives an inert product P which does not participate in the re-

actions. This is an inhibition process, which continuously removes the racemic product. Calculations showed that when the reaction starts with a *R+S* catalyst of very low ee (slightly enriched in *R*), after consumption of a large amount of starting material the product will be exclusively *R*. The inhibition reaction between enantiomeric catalysts is reminiscent of the reservoir effect (Sect. 3.2). Asymmetric autocatalysis alone (even starting with an ee of 99.99%) will necessarily generate a racemic product after a large number of catalytic turnovers [1, 8]. The Frank model overcomes this difficulty by introducing an additional reaction which continuously removes the racemic product.

There are very few examples of autocatalytic asymmetric reactions. The crystallization of achiral compounds (or chiral compounds that easily racemize in solution or in liquid phase), which give spontaneous resolution, is a special class of autocatalytic reaction where the chiral catalyst is the first seed present in the crystallization [65, 66, 67]. Asymmetric autocatalytic reactions in homogeneous conditions were unknown prior to the pioneering work of Soai et al. [9a, 68, 69, 70]. These authors studied the addition of diorganozincs to aromatic aldehydes **2**, as discussed in Sect. 4.1. As chiral catalysts they chose amino alcohols (as zinc alcoholates) which are the products of the reaction. After much investigation [9a, 68, 69, 70] the authors selected to study the addition of diisopropylzinc to pyrimidinecarboxaldehydes **2b,c** (Scheme 10) using zinc alcoholates **3b,c**,



Scheme 10

(0.2 mol equiv.) as the catalyst. Under these conditions, a (*S*)-catalyst **3b** of 5% ee produced the (*S*)-alcohol in 62% yield with 39% ee. Subtracting the initial alcohol used to prepare the catalyst, one calculates that 4.2 times the amount of the starting alcohol were synthesized, with an ee of 55% (amplification index of 7). The curve relating the ee of the newly created product, in each run, as a function of the ee of the initial catalyst is shown in Scheme 10 [69]. This curve is typical of a (+)-NLE. Considerable improvements were recently described by Soai et al., these were obtained by variations in the nature of the R group in **2**. Thus, when R=Me, after several consecutive additions of diisopropylzinc and aldehyde **2c**, in a one-pot process, 3 mg of (*R*)-**3c** with 0.18% ee as the catalyst gave 323 mg of (*R*)-**4c** with 93.1% ee [71]. The best results have been achieved for R=*t*-Bu-C≡C in **2d** and catalyst **3d** [72]. Using the same conditions described above (0.2 mol equiv. of catalyst) catalyst **3d** (>99.5% ee) gave a quantitative yield of the product **4d** with ee>99.5%. This product was used as a catalyst for a new run, and so on. After ten runs the yields and ees of the product remained almost quantitative. This shows an almost perfect automultiplication of the initial chiral catalyst, presumably due to an excellent combination of catalytic activity and high (+)-NLE.

An interesting application of autocatalysis in organozinc chemistry is the detection of very low enantiomeric excesses. It was found by Soai et al. that addition of diisopropylzinc to aldehyde **2c**, in the presence of small amounts of amines or alcohols (<5 mg) with <0.1% ee (acting as ligands of zinc), generates alcohol **4c** with ees in the range of 40 to 85%. This amplification procedure could be used to detect a slight enantiomeric excess in a tiny amount of material, for example from asymmetric destruction of a racemic amino acid by circularly polarized light [73].

9

Conclusion

Non-linear effects were discovered in 1986 [5]. They are now widely recognized in many catalytic reactions, and provide a useful tool for mechanistic investigations. Moreover, they can have some practical applications. For example, in the case of asymmetric amplification it is not necessary to perform a costly complete resolution of a chiral ligand if the reaction involves a strong (+)-NLE. The concept of non-linearity has been extended to mixtures of diastereomeric ligands (*vide supra*). Finally, asymmetric amplification is very useful in reactions which display asymmetric autocatalysis, giving high levels of enantioselectivity after initiation with a catalyst of very low ee.

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Chapter 5.1

Hydrogenation of Functionalized Carbon-Carbon Double Bonds

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Keywords: Rhodium, Ruthenium, Diphosphines, Enamides, Substrate chelation, Pressure and temperature dependence, Dihydrides, Alkyl hydrides, Transient NMR

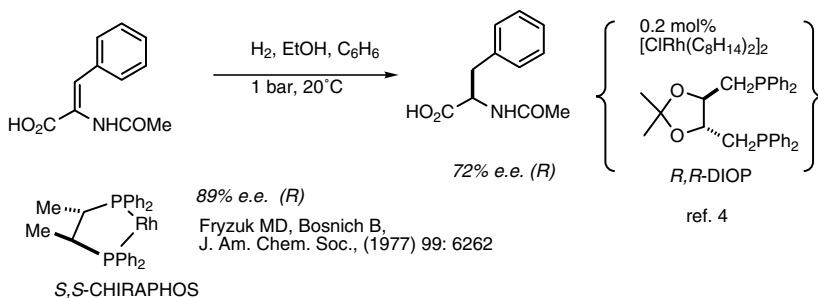
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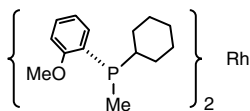
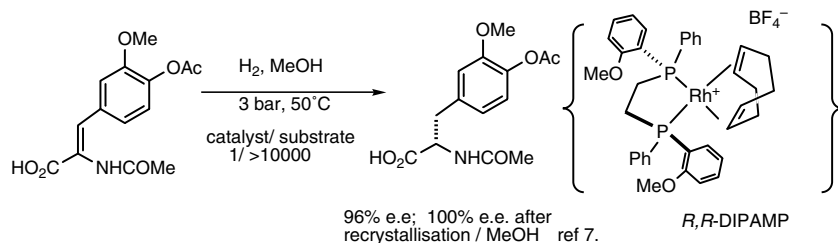
Early Developments

Since the asymmetric hydrogenation of alkenes has the longest history and perhaps the most substantial content of any topic in enantioselective catalysis, it may be appropriate to begin with a brief historical overview. The early success of Wilkinson's catalyst in permitting the controlled reductions of alkenes under mild conditions [1] created a general awareness in the organic chemical community of the possibility for asymmetric synthesis and that was first formally demonstrated through the work of Horner [2] and Knowles [3]. Then as now, the path from concept to practical results was traversed rapidly; two important breakthroughs (Fig. 1) being provided by the respective contributions of Kagan and Dang [4], and the Monsanto group headed by Knowles [5]. Kagan's work dem-

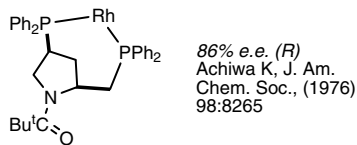
for *Z*-acetamidocinnamic acid



for *Z*-4-acetoxy-3-methoxyacetamidocinnamic acid (*L*-DOPA precursor)



S-CAMP 88% e.e. (R) ref 5



S,S-BPPM

86% e.e. (R)
Achiwa K, J. Am. Chem. Soc., (1976) 98:8265

Fig. 1. Some initial breakthroughs in asymmetric hydrogenation, 1970–1977

onstrated two significant aspects of asymmetric hydrogenation for the first time. The application of chelating diphosphines, for which the first representative was DIOP, proved to be a powerful paradigm not only for hydrogenation but across the field of catalysis. In addition, the perception that amino acids can be synthesized directly from protected dehydroamino acids, themselves easily derived from the oxazolone products of Perkin condensation of aromatic aldehydes and glycine amides, provided a significant impetus; a useful set of targets was shown to be directly accessible by asymmetric catalysis. The Monsanto company, which had initially developed the expertise in phosphorus chirality because of its relevance to agrochemicals, following Mislow's work [6] was then in a position to move to industrial scale production of L-DOPA. Their ligand DIPAMP was a second generation effort, since the first successful ligand for rhodium-catalyzed asymmetric hydrogenation was the chiral monophosphine CAMP. Although that was remarkably successful for its time, the sheer convenience of the corresponding diphosphines, which could be crystallized to enantiomeric purity, rapidly prevailed. The later publication from Knowle's group defined the synthesis of the chelating P-chiral diphosphine DIPAMP and its application to amino acid synthesis, including the famous commercial process for L-DOPA [7].

That set the stage for an intensive worldwide effort in which literally hundreds of new diphosphine ligands were synthesized; almost all based on the Kagan model of backbone chirality in a potentially chelating system. [Backbone chirality was and is a much easier challenge than phosphorus chirality, and the chiral pool possesses many suitable scaffolding components.] Most of these performed reasonably in the defined task of hydrogenating aromatic dehydroamino acids (typically 75–95% ee) but it became obvious that rhodium asymmetric hydrogenation, despite its attractive specificity, is a reaction of limited scope. The reason was better defined when the first NMR characterization of solution intermediates was performed in 1978 [8]; the dehydroamino acid itself forms a chelated complex with rhodium, so that ligand-recognition of the prostereogenic alkene is encouraged because of its high degree of spatial definition on coordination.

The focus changed from rhodium to ruthenium in the mid-1980s (Fig. 2). Initial experiments were carried out by Ikariya's group in Tokyo [9], with additional input from the Takasago Company. Over a remarkably short period of time a number of significant experiments then emanated from Noyori's laboratory [10], such that ruthenium-BINAP hydrogenations became specifically associated with his name. Although the early experiments were concerned with alkene reductions, asymmetric hydrogenation of ketones (discussed in detail in Chapter 6.1) is at least as potent a synthetic method and formed the basis of most of the later work. The differentiation remains in that rhodium asymmetric hydrogenation is a remarkably mild and specific method for dehydroamino acids together with a limited range of closely related alkenes (e.g. itaconates) whilst ruthenium asymmetric hydrogenation has a wider compass. For rhodium, there are many successful ligands and the opportunity for fine tuning in specific cases, whilst BINAP and its close relatives have prevailed in ruthenium asymmetric hydrogenation.

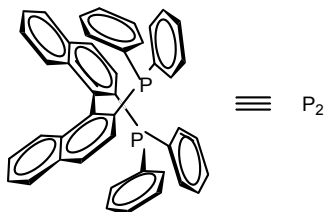
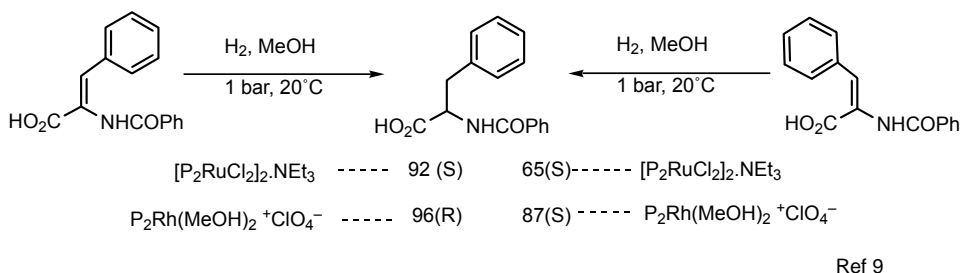


Fig. 2. Early results in ruthenium asymmetric hydrogenation

More recent work has been largely concerned with consolidation, more focused applications in synthesis and the like, with some emphasis on reaction media. For applications in rhodium chemistry there are “third generation” ligands which offer broader substrate applicability and consistently high enantioselectivity. Among these, the Dupont ligands developed by Burk's group (DUPHOS and BPE) are consistently successful. Useful reviews up to 1992 are compiled in ref. [11]. There are also some books on asymmetric catalysis with relevant chapters, the best overview being contained in the published account of Noyori's Baker lectures [12].

The review proper begins with an assessment of the current status of reaction mechanisms and then recent synthetic advances in both rhodium and ruthenium catalytic hydrogenation. In view of the vast literature generated it has been necessary to be selective, particularly in synthesis where advances in ligand design can render even recent work on similar substrates obsolete. Reference to reviews should alleviate the ensuing deficiencies.

2

Mechanistic Studies on Enantioselective Hydrogenation

2.1

Rhodium Catalysts

In order to appreciate the mechanism of rhodium asymmetric hydrogenation, it may be useful first to examine the simpler achiral case of alkene hydrogenation by Wilkinson's catalyst. In early studies [13] assumptions were made about the dihydrogen activation step which proved to be incorrect because of the direct

role required for the P_3 species; the definitive kinetic experiments from Halpern's group [14] clearly demonstrated an inhibition by triphenylphosphine which was consistent only with $ClRh(PPh_3)_2$ being the reactive entity (as, indeed, Wilkinson had originally suggested). This proves to be the true catalytic template and, although trisphosphine complexes are in equilibrium with their bisphosphine counterparts at different points in the cycle, only the former contribute significantly to catalytic turnover [15]. The present understanding of catalytic mechanism is indicated in Fig. 3. The indicated exchange processes can be delineated by ^{31}P -NMR techniques, which also demonstrate the inaccessibility of coordinated alkene complexes in the cycle to direct observation [16].

With the readily accessible points of mechanism in place, remaining unanswered questions can then be analyzed. The fact that all the steps of the catalytic cycle are constructed around the 14-electron template $ClRh(PPh_3)_2$ raises stereochemical points – is that entity the *cis*- or *trans*-diphosphine diastereomer and is its geometry maintained throughout the cycle? In early work a *trans*-bisphosphine arrangement had been assumed, but cases arose where a rigidly *trans*-bisphosphine complex proved to be inactive as a hydrogenation catalyst [17]; in addition, early molecular modeling studies indicated that the *trans*-arrangement provided insufficient space within the coordination sphere for a 1,2-disubstituted alkene in the reactive conformation, for which $Rh-H$ and $C=C$ are parallel [18]. Further progress required additional techniques, which came within the

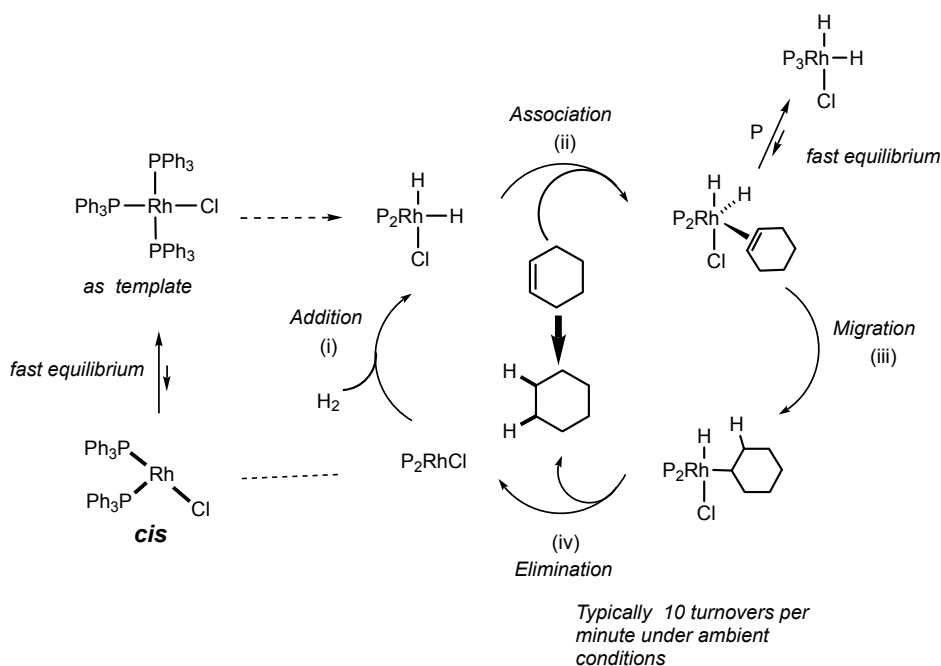


Fig. 3. The catalytic cycle for Wilkinson's catalyst in hydrogenation of simple alkenes

last few years following the adventitious discovery of NMR signal enhancement through catalyzed reaction of the substrate with *para*-hydrogen, (PHIP or PASADENA [19]). This can lead to emission or adsorption enhancement of nuclei in the product associated with the dihydrogen addition process, but more significantly also in reaction transients which would otherwise be invisible to direct observation. The method has been applied in a number of simple cases but, for present purposes, the most significant development has been the characterization of an intermediate, a rhodium alkene dihydride, which is present at too low a concentration to be observed by conventional NMR [20]. Significantly, the observed chemical shifts in the ^1H -NMR spectrum, and their sensitivity to *para*-substituents in styrene when that is the coordinated alkene, are consistent only with the *cis*-geometry shown in Fig. 4, implying that the phosphines are *cis*-disposed in the critical steps of the Wilkinson catalytic cycle. The experiment does not distinguish between two possible diastereomeric structures for the transient intermediate.

The linkage between this work and asymmetric hydrogenation had already been made (inadvertently) before its discovery. Schrock and Osborn had extended Wilkinson's work to include cationic diphosphine complexes, both chelating and non-chelating, and through some careful mechanistic work had established a similar mode of action, particularly for the case of bis-monophosphine rhodium complexes [21]. It later transpired that these cationic species were the basic template in asymmetric hydrogenation (P_2Rh^+ , where P_2 is a chelating diphosphine), replacing $\text{ClRh}(\text{PPh}_3)_2$.

By the late 1970s the structures of the precursor complexes in asymmetric hydrogenation were known in principle. Kagan had speculated on the possible intervention of an enamide complex (alkene and amide carbonyl group bound) [22], while the cationic nature of reaction intermediates for chelate diphosphine catalysts could have been inferred from Osborn's work. A characteristic of the P_2Rh^+ reduction of dehydroamino acids was the extreme rapidity of turnover – at ambient pressure and temperature limited by hydrogen diffusion at the gas-liquid interface under normal experimental conditions and concentrations – and the stability of the catalytic system, which was capable of operating for many thousand turnovers without side-reactions.

The first significant mechanistic experiment was conducted by Halpern, who showed that the *cis*-chelating cationic complexes, isolated as their NBD or COD

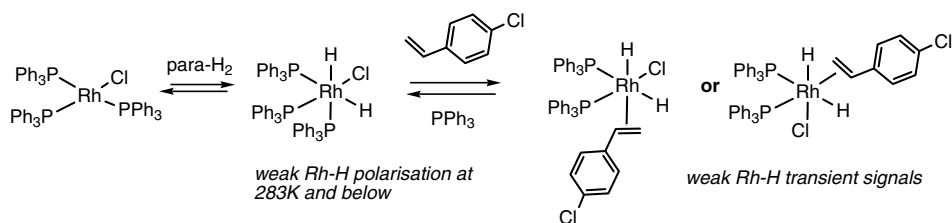
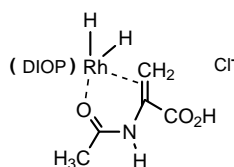


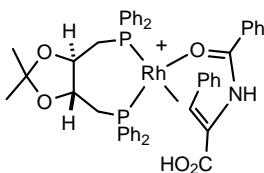
Fig. 4. Transient intermediates revealed by NMR studies on *para*-hydrogen addition

complexes, reacted with dihydrogen to form a solvate $P_2RhS_2^+$ complex, unreactive towards further addition of hydrogen [23]. A reversible, but undetectable, addition of dihydrogen was demonstrated some time later through the equilibration of para-enriched dihydrogen in contact with the methanol solvate [24]. Halpern's observations set the stage for a further critical development; in the presence of *Z*- α -*N*-benzoyldehydrophenylalanine, the solvate (P_2 =DIOP, S_2 =2 MeOH) reacted to form a single complex assigned the enamide structure [25] by ^{31}P -NMR, whilst the *E*-isomer gave a mixture of two complexes. The indication was that the *E*-isomer, which did not hydrogenate enantioselectively with this catalyst, formed a mixture of diastereomeric complexes (Fig. 5). The *Z*-isomer which was efficient in asymmetric hydrogenation, complexed as a single diastereomer. These results were further extended when DIPAMP was the chelating ligand used since addition of *Z*- α -dehydroamino acids or esters revealed both diastereomeric enamide complexes in equilibrium, typically in 10:1 ratio. The structures of these intermediates were further confirmed by X-ray [26] and by ^{13}C - and ^{31}P -NMR spectra of specifically ^{13}C -enriched dehydroamino acids [27].

At this stage mechanistic studies had already progressed beyond what was possible with Wilkinson's catalyst, since alkene complexes are directly observable in simple NMR experiments. This has led to a subclassification of hydrogenation reactions by many authors into the "hydride route" and the "alkene" route. With Wilkinson's catalyst, addition of dihydrogen to rhodium appears to precede the alkene association, whilst for diphosphine chelate complexes in asymmetric hydrogenation the primary addition steps are reversed with alkene association first. This distinction should be treated as a useful guideline rather than an absolute mechanistic distinction, since it informs us more of the catalytic resting state than the turnover-limiting transition state.



Kagan's representation, 1975



Brown and Chaloner, deduced from NMR studies 1978; [the relative configuration of the enamide was initially misassigned].

Fig. 5. Initial experiments in dehydroamino acid and ester complexation

A further step was taken when first Halpern [28] and then Brown [29] were able to identify a further intermediate, the rhodium alkyl hydride formed by addition of dihydrogen to the enamide complex with transfer of a single hydride to the benzylic carbon. For the simple dppe complex studied by Halpern, the interpretation of the experiment was straightforward, but the intermediate derived from DIPAMP by Brown and Chaloner provided a major surprise; only the disfavored minor diastereomer of the enamide complex was reactive towards H_2 . The major/minor equilibrium is so strongly biased towards the former below $-50\text{ }^\circ\text{C}$ that reaction with H_2 is undetected. Only when the solvate complex is allowed to react with the dehydroamino acid derivative under H_2 , well below $-50\text{ }^\circ\text{C}$ (under which conditions up to 35% of the minor diastereomer is initially observed) is the alkyl hydride observed, concomitant with disappearance of that minor diastereomer. This reactive intermediate was characterized by its ^1H -NMR (hydride), the distinctive ^{31}P -NMR and by both heteronuclear coupling and chemical shifts in the ^{13}C -NMR spectra of alkyl hydrides derived from singly and doubly labeled dehydroamino esters.

The configuration of the major diastereomer of the enamide complex was then confirmed by X-ray crystallography in the CHIRAPHOS series [30]. Since the intermediate has the opposite configuration to the reduced product, it was possible to infer that the minor, and in this case unseen diastereomer, provided the reactive catalytic pathway. In the ensuing discussion, this was reinforced by the (incorrect) deduction that the slower turnover rate with CHIRAPHOS was a consequence of the low standing concentration of the minor enamide diastereomer, and by insights into the pressure and temperature dependence of the ee in asymmetric hydrogenation; Halpern deduced that the ee for a minor diastereomer driven cycle would be enhanced by decreasing the pressure and increasing the temperature.

The corresponding iridium enamide complexes and their alkyl hydride counterparts are much more stable, and a full NMR characterization of the alkyl hydride proved possible in the DIPAMP series. Here, as in the corresponding rhodium chemistry, the presumed dihydride precursor proved to be elusive [31]. By employing a different approach to enamide complexes in which an iridium bis-enamide complex was allowed to react with the diphosphine (Fig. 6) both major and minor enamide complexes could be prepared separately; the path to one of them is shown in Fig. 6. The trick was to employ menthyl esters so that stereochemically homogeneous Ir complexes were formed. Some additional structural features of the intermediates were derived from detailed NMR analysis, and especially the role of the OMe group in coordinating to iridium *trans* to the hydride [32].

In terms of coupling these observations of reactive intermediates to a definitive mechanistic framework, the paper of Halpern and Landis plays a central role [33]. Through careful kinetic measurements of hydrogenation as a function of temperature, pressure and catalyst concentration, the soundness of the enamide equilibration/hydrogenation model is established. Rate constants have been derived for the steps defined in Fig. 7 which give self-consistent results for hydro-

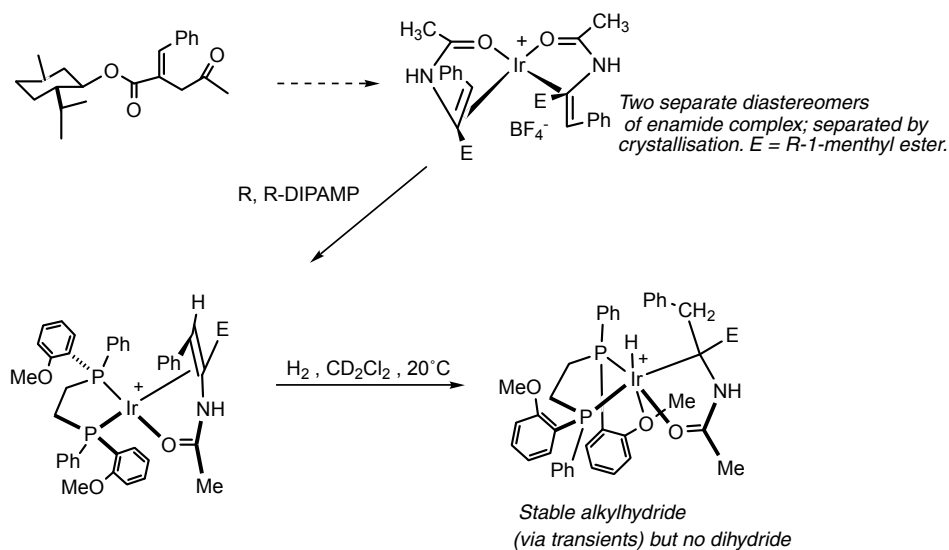


Fig. 6. Iridium analogues of catalytic intermediates in asymmetric hydrogenation

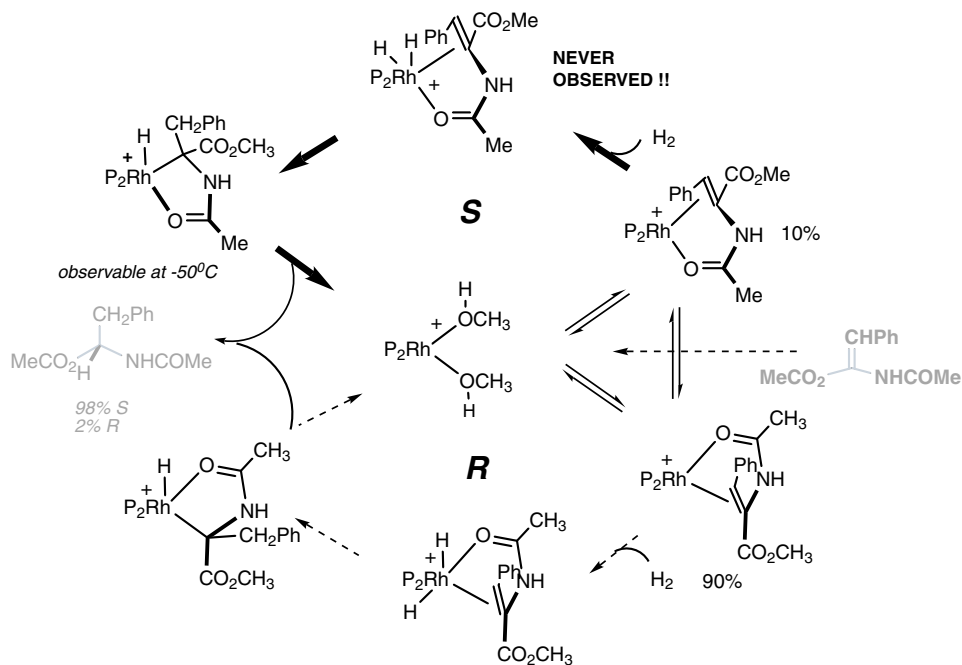


Fig. 7. The full catalytic cycle for asymmetric hydrogenation of enamides with rhodium DI-PAMP complexes

generations conducted under the conventional range of reaction conditions. These results correctly predict that for the DIPAMP ligand involved, the enantiomer excess increases with increasing temperature (as the proportion of the disfavored minor diastereomer increases) whilst decreasing with increasing pressure (as the proportion of hydrogenation occurring through the major diastereomer increases). The turnover-limiting step of catalysis is the addition of dihydrogen to the disfavored enamide complex. At higher pressure, turnover of the minor enamide is subject to saturation whereas the rate of turnover of the major isomer increases linearly with pressure. It transpires that these observations are fairly specific to the DIPAMP-Rh⁺ system, and lie in consequence of the fact that the enamide reactant/solvate equilibrium strongly favors bound reactant. This means that the unproductive major enamide diastereomer resides in a deep energy well and the dissociation may exert an influence on the rate equation. Other ligands reveal much less sensitivity to changes in pressure and temperature.

A refinement of the model resulted from the finding, through NMR spin excitation exchange experiments, that the dominant mechanism for enamide interconversion is intramolecular. This is best explained in terms of alkene dissociation, rotation and return as indicated in Fig. 8 [34a, 34b, 34c, 34d]. In one case, the intramolecular exchange may be observed directly by dynamic NMR when the dehydroamino acid is replaced by the faster exchanging dimethyl itaconate. The results are particularly clear-cut when the unsymmetrical monoanisyl diphosphine OXPAMP is employed. In this case only one of the four possible dihydrides is observed and appears to be the result of internal chelation of the OMe group *trans* to Rh-H. The ease of this intramolecular exchange helps explain some features in the literature on asymmetric hydrogenation; for example, the fact that some examples show enantioselectivities which are extremely sensitive to changes in pressure while others are unaffected [35]. The methoxy-group chelation may only be important after the rate-limiting dihydrogen addition, since DIPAMP (*ortho*-OMeC₆H₄P) is more reactive, but not greatly more enantioselective (97% vs. 90% ee), than its congener with *ortho*-Et [34e].

As recounted, these studies demonstrate that two of the three expected intermediates in asymmetric hydrogenation may be directly observed, but the expected dihydride is too fleeting. There are two further experiments which are pertinent to this issue. A related diphosphine-iridium alkene complex reacts with dihydrogen at low temperatures and a series of alkene dihydrides are observed prior to the formation of the expected alkyl hydride. Based on the ¹H-NMR chemical shifts of the respective Ir-H species, the initial addition (or to be more correct the initially observed species) possesses H *trans* to alkene and H *trans* to phosphine; only at higher temperatures does this rearrange to the expected H *trans* to amide and H *trans* to phosphine structure (Fig. 9a) [36]. A more directly relevant experiment involves para-enriched hydrogen, and in the illustrated case a transient dihydride is observed. A problem is that the spectral characteristics are not entirely in accord with expectations for the proposed structure (the supposed *trans*-P-Rh-H coupling is 4 Hz rather than ca. 120 Hz), but the presence of some transient Rh dihydride is definitive based on the evi-

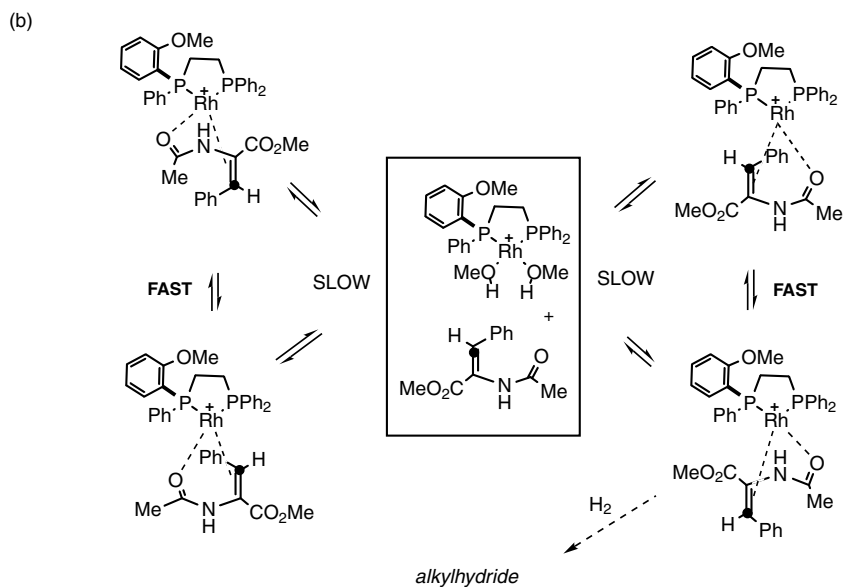
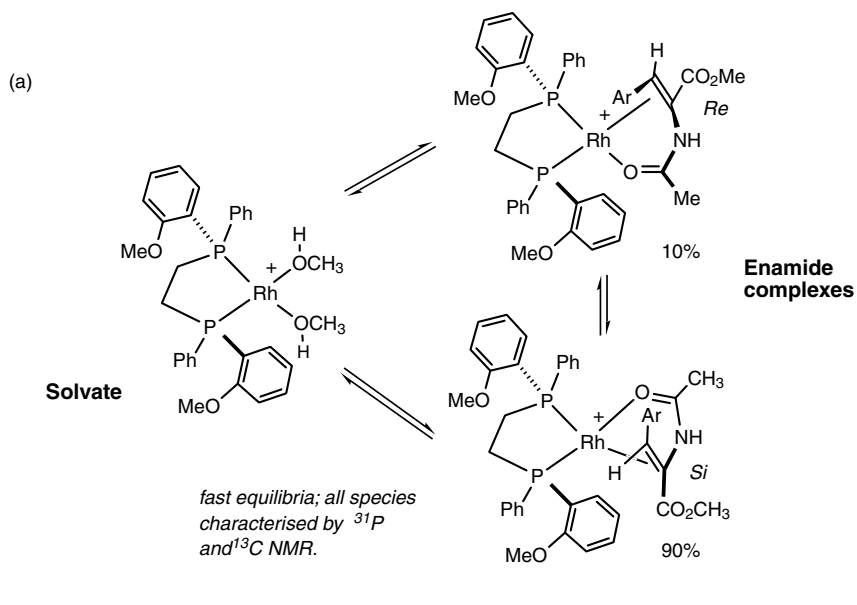


Fig. 8. The intramolecular mechanism for enamide exchange

dence presented. Without ^{13}C labeling of the reactant it would be difficult to prove that it is in the coordination sphere, since it is silent in the enhanced NMR spectrum [37].

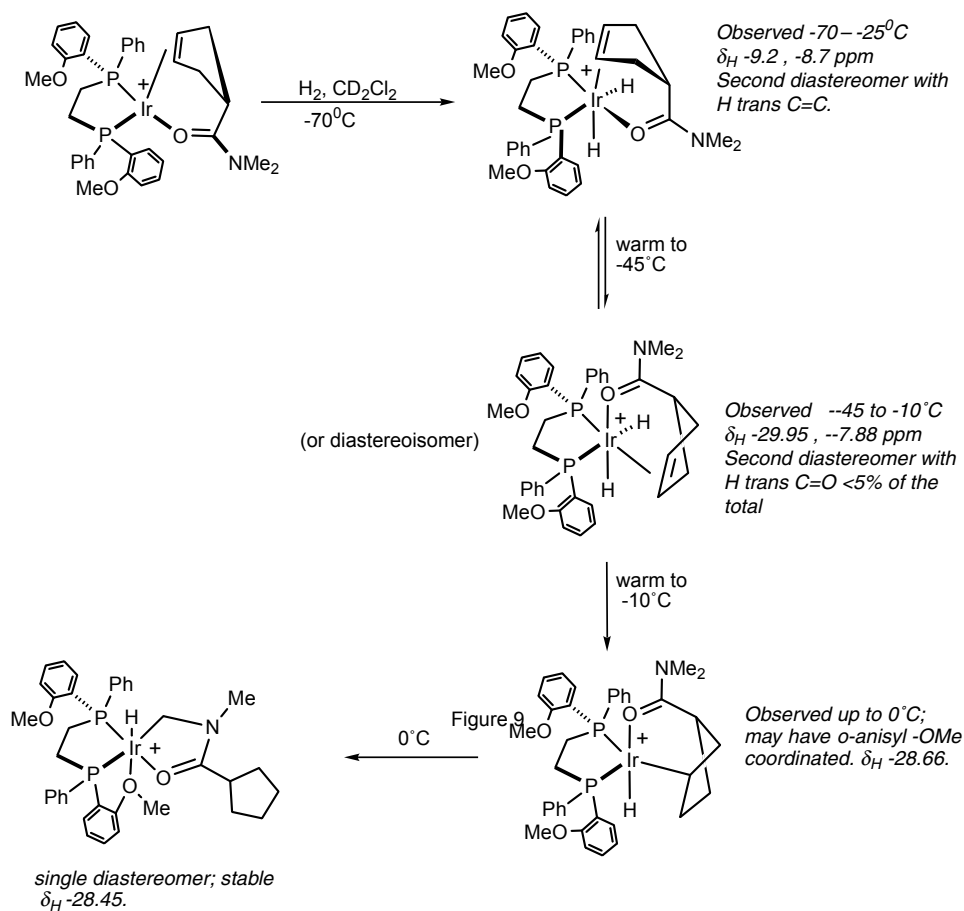


Fig. 9a,b. Observations of dihydrides in iridium diphosphine systems

These experiments represent the limit of direct observation with current techniques and still permit nagging doubts about the generally accepted mechanism on points of detail. Why should the enamide dihydride always be unobservable, despite tests over a wide variety of ligands and reactants? Indirect methods are sparse, one of the most promising being a quantitative analysis of isotope effects. An earlier claim (the reviewer's) [38] of a kinetic isotope effect in the process was not sustained by a rigorous reanalysis [39] although the regioselectivity in H-D addition (D adding to the more substituted carbon with a preference of about 1.2:1) was reaffirmed. An attempt was made to exclude possible pathways on the basis of the observed kinetic and equilibrium isotope effects but without real success; without further structural information on the first formed intermediate dihydride, details of the pathway in the region of the rate-limiting addition of dihydrogen must remain speculative.

2.2

Non-Experimental Approaches

The lack of evidence from physicochemical studies is countered by an ever-increasing body of structural evidence, mainly X-ray data for square-planar chiral rhodium biphosphine complexes. This permits questions about the relationship between the structure of the diphosphine and the efficiency and direction of enantioselection. At a purely empirical level, there are two rules with predictive power, the first being due to the development of early ideas of Bosnich and Fryzuk by Kagan [40], but frequently attributed in later literature to a subsequent paper from the Moscow group [41], and concerned with the configuration of the Rh-diphosphine chelate ring. If this is λ , then the dehydroamino acid is reduced to the *R*-amino acid; if δ then it is reduced to the *S*-amino acid. Kyba examined the crystal structures of a number of dialkene-rhodium diphosphine complexes, and concluded that the twist of the diene with respect to the square plane correlated with the sense of asymmetric hydrogenation [42]. This is demonstrated in Fig. 10, and has been used in the case of DUPHOS ligands to demonstrate that the phospholane and diarylphosphine ligands both conform to this same rule. The X-ray structures cover a wide range of ligand types and indicate that the correlations have considerable generality.

A more detailed approach which has been widely adopted as a basis for the analysis of asymmetric hydrogen is due to Knowles and colleagues at Monsanto [43]. Many of the ligands for asymmetric hydrogenation possess C_2 symmetry. For 5-ring chelates and also for 6- and 7-ring chelates where the backbone is rigid, there is a unique disposition of the *P*-aryl groups [44]. They exist as two C_2 -correlated pairs which are respectively axial and equatorial and imposing a rigid scaffold which limits the free space accessible to the reagent and reactant. This space is subdivided into symmetry-related pairs of quadrants (Fig. 11). Two of the *P*-aryl rings occupy axial positions in the chelate ring and are torsionally constrained to be “edge-on” to the substrate, whereas the other pair are in equatorial positions and constrained to be “face-on”. Closer analysis reveals that it is the face-on equatorial rings that exert the greater steric pressure on vacant coordination sites. For a rigid and spatially demanding ligand like BINAP, the preferential binding of one rather than the other enantioface of a dehydroamino acid is clear; a simple model which is based on a modified Newman projection minimizing steric interactions between the ligand and CO_2R works well [45]. Further enamide X-ray structures have been published, but always of the more stable diastereomer when the ligand is chiral [46]. The energy difference between major and minor enamide diastereomers can be simulated by molecular mechanics with modern parametrization [47].

Considerably less certainty is attached to the rationalization of enantioselectivity in the hydrogenation, which must involve the difference in free energy ΔG^\ddagger between the two diastereomeric transition states of lowest energy. For simplicity, these can be assumed to be of similar structure for routes to the two enantiomers (not necessarily correct!). For cases where substrate binding is strong,

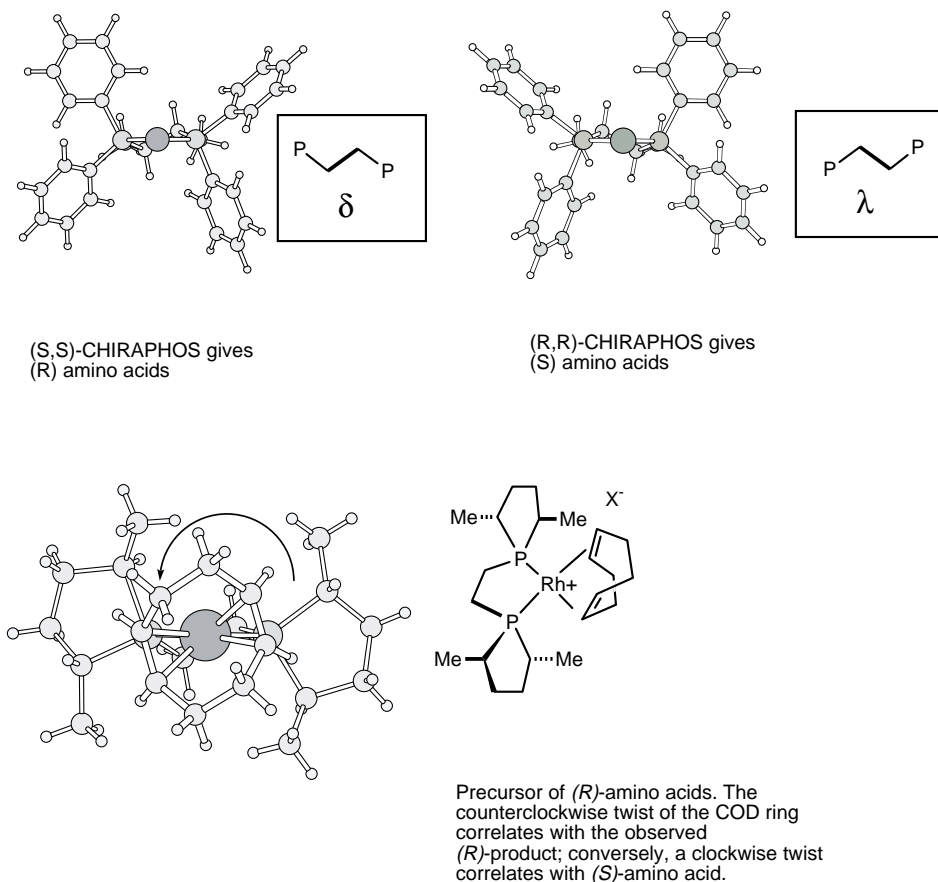
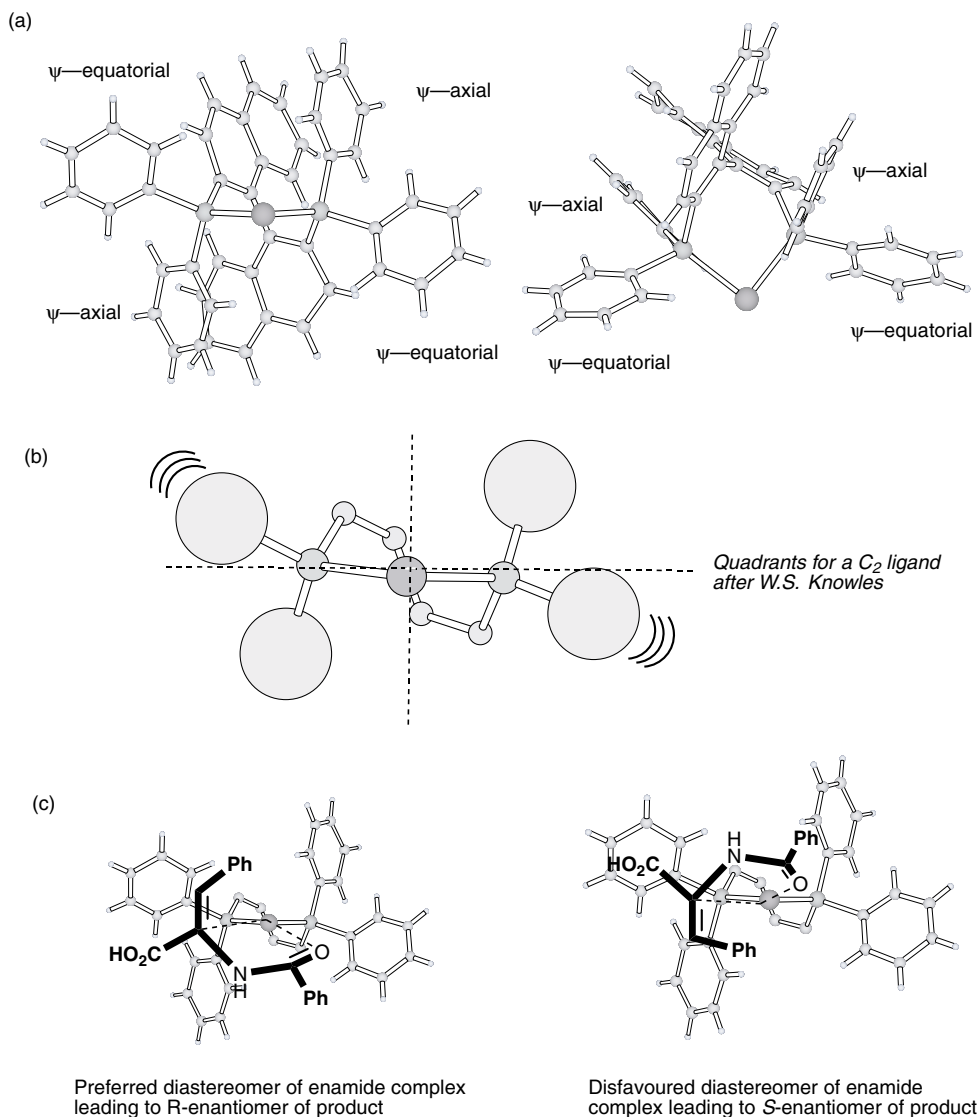


Fig. 10. Empirical correlations between the structures of chiral ligand complexes and the course of asymmetric hydrogenation of dehydroamino acids

and the interconversions of the major and minor diastereomers with one another and with the solvate are fast relative to hydrogen addition, the ground state is the equilibrating enamide manifold. All pathways from that manifold to the H_2 addition TS are kinetically equivalent. That is to say, there is nothing which says whether or not one of the coordinated groups is temporarily dissociated, involving a 14-e complex in the H_2 addition step. A striking fact emerges from Halpern's kinetic analysis of the process. The discrimination in binding constant for the two diastereomeric complexes is about 12:1, but the "on" rate constants are quite similar, favoring the minor diastereomer somewhat. It is the "off" rate constants where most of the variation is evident. Since this process is likely to be driven by alkene decoordination (cf. the NMR-defined intramolecular exchange, which requires it to occur while the amide remains bound) the minor diastereomer has a much more favorable route to a 14-electron intermediate.



Result for R-BINAP Rh : 100% e.e. S-product

Fig. 11. The quadrant approach and rationalization of the relative energies of the two diastereomeric enamide complexes

Particularly since the initial discovery of dihydrogen complexes by Kubas [48], the coordination chemistry of H_2 has revealed rich complexity [49]. There is little information on the precise pathway by which hydrogen adds to coordinative-

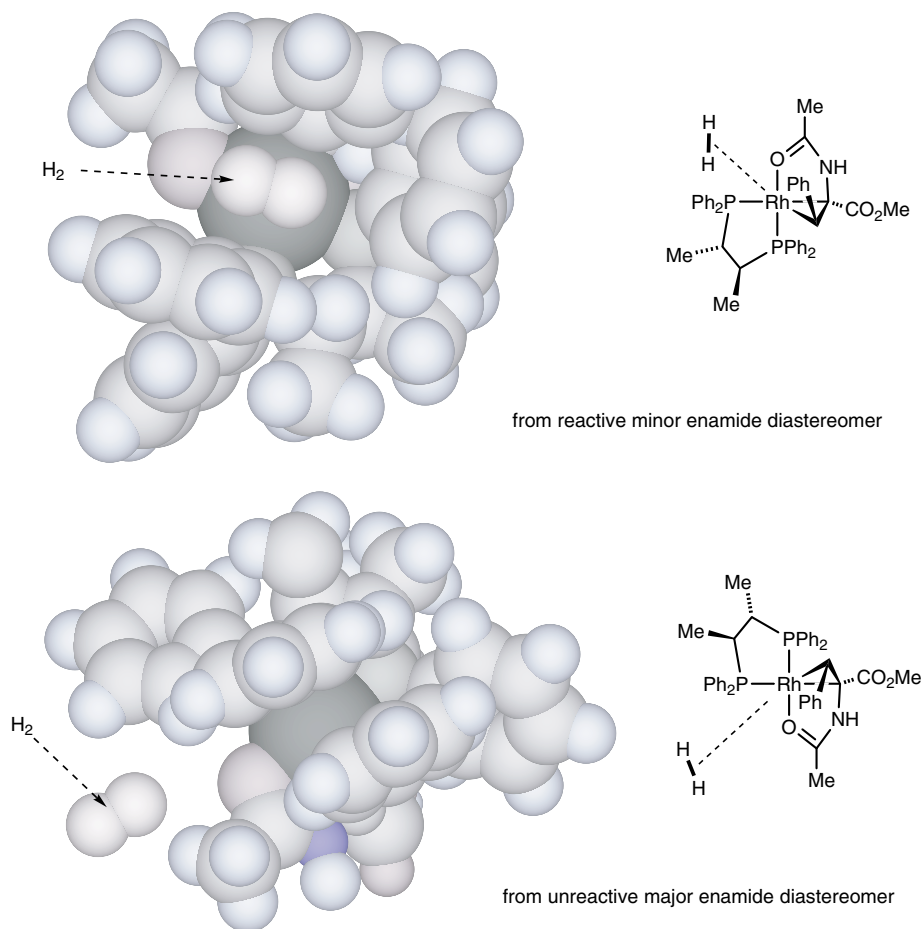


Fig. 12. Possible routes for the dihydrogen addition step starting with the reactive diastereomer of the Me-DUPHOS complex based on X-ray crystal structures of the ligand and (separately) enamide

ly unsaturated transition metal complexes, analysis rather relying on high-level *ab initio* calculations which provide a smooth flow of H-M bond-forming and H-H bond breaking processes coupled to geometrical reorganization [50]. This picture may not be a reflection of the real world. When the RMM of dihydrogen ($=2$) and a typical hydrogenation catalyst (\approx ca. 700) are considered, vibrational excitation of the catalyst is expected to be more productive than excitation of H_2 since the hard H-H stretch at 4000 cm^{-1} is poorly coupled to the softer vibrational modes of the catalytic complex. For these reasons we speculate that the reactive complex is first transformed to a conformationally excited state, with the possibility of ligand (alkene?) dissociation as well, and that dihydrogen reacts with the excited complex with minimal additional input of energy. It seems fairly

certain that there is considerable geometrical distortion in the dihydrogen addition, one clear pointer being the very wide variation in relative reactivity of different diphosphine-rhodium complexes towards H₂ addition and its close correlation with the flexibility of the chelate backbone [51]. Faster hydrogenation rates are associated with flexible chelate ligands with a large bite angle.

Other work has indicated the ease of distortion of supposedly rigid coordination spheres [52] with the ligand metal bonds being much more deformable than the organic components of the complex [53]. Given these potential complexities, and the difficulties in defining the exact TS structure, it is unsurprising that despite several attempts involving either MM or a mixture of MM and quantum approaches [54], real theoretical insights into rhodium asymmetric hydrogenation are still lacking.

A qualitative approach will possibly be more fruitful. Fig. 12 illustrates how the dihydrogen addition step (late with respect to heavy atom locations, early with respect to dihydrogen) might appear for the two diastereomeric pathways of the 16-electron route, with CHIRAPHOS as the ligand. In the alternative 14-electron route, dissociation of the alkene is assumed to occur, followed by irreversible H₂ addition. The process is then consummated by reformation of the alkene-rhodium bond, or by a sigma bond metathesis which bypasses the dihydride state.

There are few reactions which are so transparent, in that true catalytic intermediates before and after the rate-determining state are easily accessible to characterization. The problems which remain in understanding and interpreting rhodium asymmetric hydrogenation arise from a persistent lack of information on the presumed rhodium dihydride; without which the pathway between the enamide complex and the turnover limiting TS for H₂ addition (i.e., the step in which the enantioselectivity of the reaction is set) remains opaque, and hence the overall understanding is elusive.

2.3

Ruthenium Catalysts

Progress in the elucidation of the ruthenium asymmetric hydrogenation pathway is less advanced. With (effectively) a single catalyst and a multitude of reactants a different approach can be taken, since product analysis is more informative here. In general, the catalysts are closely related to BINAP-Ru(OAc)₂ and are advantageously synthesized prior to use; conventionally reactions are conducted at elevated pressure and the stereoselectivity is frequently enhanced at high pressure [55]. It is worthwhile to provide an overview of the scope of these complexes in alkene asymmetric hydrogenation (Fig. 13); individual reductions will be encountered in Section 4. The common feature is that a functional group capable of oxygen lone-pair binding to ruthenium must be in the vicinity of the double bond. As before, the reaction proceeds through a chelate coordinated substrate.

Just as Rh asymmetric hydrogenation is built up on an infrastructure provided by Wilkinson's catalyst, Ru asymmetric hydrogenation has useful precedents.

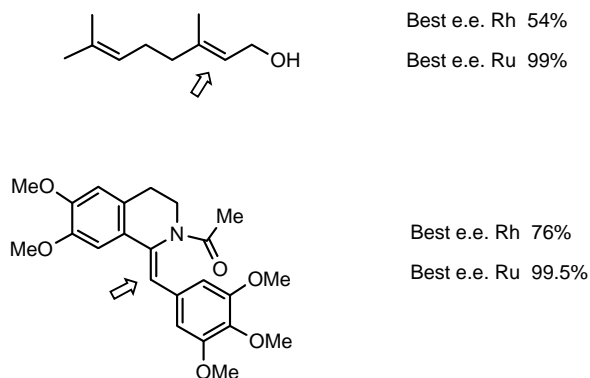


Fig. 13. Examples of asymmetric hydrogenation of functional alkenes with Ru-BINAP complexes, in comparison to Rh catalysis

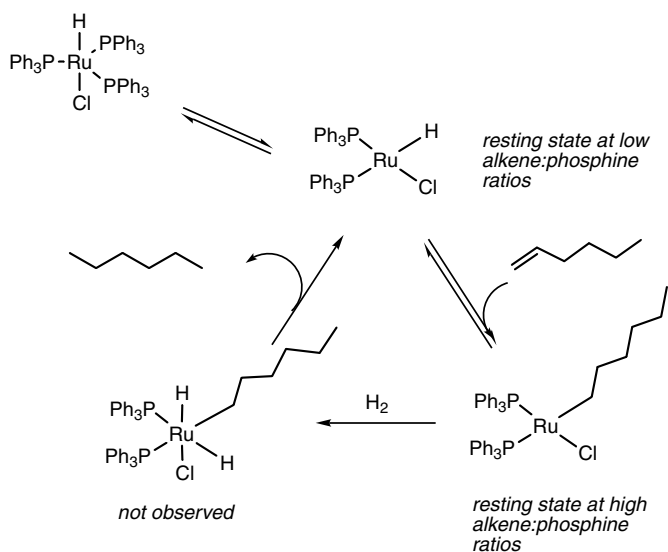


Fig. 14. The mechanism of alkene hydrogenation by $\text{ClRuH}(\text{PPh}_3)_3$ complexes

Interestingly, the mechanism of action of simple ruthenium catalysts is significantly different from that of their rhodium counterparts; experimental evidence points to a $\text{P}_2\text{Ru}(\text{H})\text{Cl}$ template as the 14-electron catalytic template (Fig. 14). This makes a significant difference to the reaction mechanism; alkene coordination is directly followed by hydride transfer to give a ruthenium alkyl species. This then requires a further addition of dihydrogen before a reductive elimination of R-H regenerates the ruthenium monohydride. The specificity of simple $\text{ClRu}(\text{PPh}_3)_n$ -based catalysts is quite different from that of their rhodium coun-

terparts, with much greater sensitivity to steric hindrance in the alkene [56]. In common with the simple rhodium case, there is little in the way of direct observation of true catalytic intermediates.

It is appropriate that the first recorded example of asymmetric hydrogenation by a ruthenium complex involved dehydroamino acids (Fig. 2) [57]. This is perhaps the most obvious experiment to follow up with mechanistic studies, given the weight of precedent in rhodium chemistry. But with one exception, the characterization of reactive intermediates in Ru asymmetric hydrogenation is lacking. When the conventional ruthenium precursors are activated and treated with alkene substrates, the evidence for substrate binding is equivocal, although Bergens was able to characterize several cationic solvate complexes of core structure BINAP-RuH⁺ [58], and demonstrated reaction with a dehydroamino acid to give the complex shown in Fig. 15, which was characterized by X-ray crystallography. This Ru alkyl further reacted with dihydrogen to give the reduction product stoichiometrically in 90% ee at a rate reasonably compatible with its involvement in catalytic turnover. The configuration of this intermediate is consistent with that of the preferred hydrogenation product, and it is known that the overall stereochemical course of *S*-BINAP-Ru reductions of enamides is opposite to that of *S*-BINAP-Rh reductions. This implies that the diastereomer of dehydroamino acid which preferentially binds to the ruthenium catalyst (the major diastereomer) is the one which participates in catalytic turnover, in contrast to the rhodium case [59]. The accessibility of a likely catalytic intermediate has permitted further mechanistic studies [60]. It was shown by deuterium labeling studies that the formation of this intermediate is reversible on the timescale of catalytic turnover. On reaction of the protiated form with D₂, the major product is the *d*₂-iso-

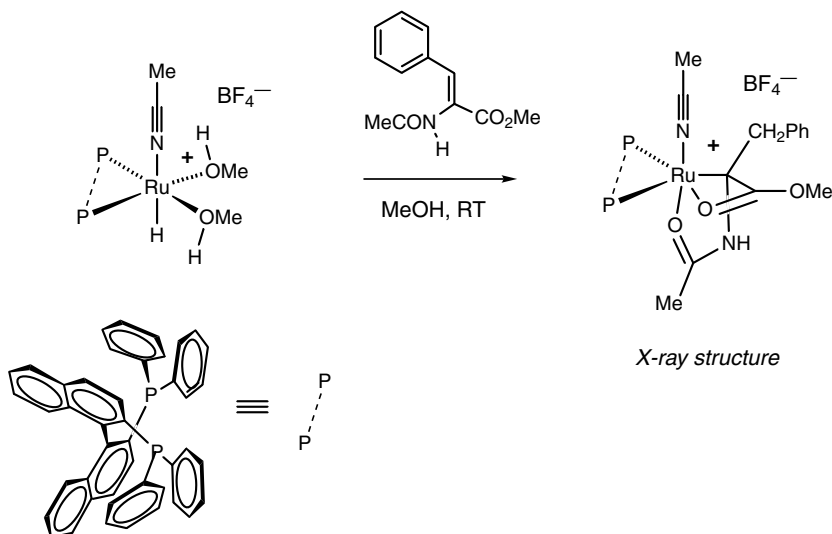


Fig. 15. A reactive intermediate in ruthenium asymmetric hydrogenation

topomer resulting from elimination of Ru-H from the alkyl, Ru-H/Ru-D exchange and then readdition of Ru-D to the coordinated alkene giving the major enantiomer by overall *cis*-addition. About 12% of the overall product is mono-deuterated showing that the competition between reversal of Ru-alkyl formation and D₂ addition favors the former less than tenfold at 4 atm. In acetone, the only products formed under catalytic turnover conditions were *cis*-dideuterated with 92% ee; in MeOH direct solvolysis competes with the Ru-C bond formation but accounts for <4% of the total product. Catalytic hydrogenation of the *E*-diastereomer of alkene occurs with similar ee but by prior *E/Z*-isomerization, reflected in the high level of *d*₃-isotopomer when the reaction was carried out with D₂. Although the correlation was not proved, there is a good correlation in turnover rates in MeOH between the catalytic and stoichiometric regimes.

The implication of these stepwise hydride transfers is that the two atoms introduced come from different molecules of dihydrogen. Deuterium labeling experiments are also revealing in the reduction of unsaturated acids. The kinetics of this reaction have been studied, and under turnover conditions the catalyst exists as a dicarboxylate; the rate law indicating inhibition by excess RCO₂H and first-order dependence on dihydrogen [61]. With D₂ in MeOH the commonest outcome in the reduction of unsaturated acids is a monodeuterated product; this is consistent with reaction proceeding through a chelated alkyl as indicated in Fig. 16 [62]. It is not clear what other ligands are bound to ruthenium at that

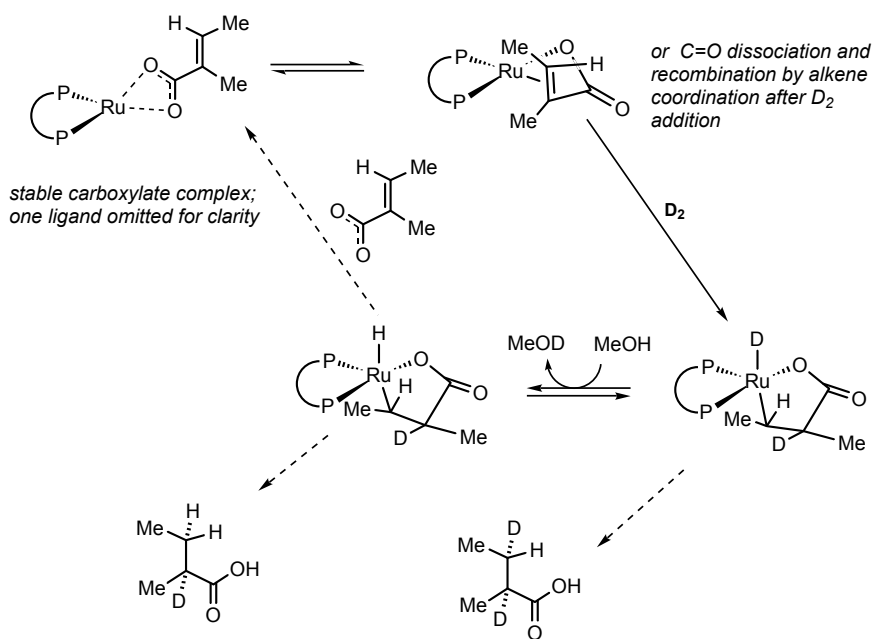


Fig. 16. Mechanism and hydrogen isotope exchange in the Ru-BINAP-catalyzed hydrogenation of unsaturated acids and esters, reflecting the author's views

stage, but the second deuterium has had the opportunity to exchange with MeOH before transfer to carbon, most easily rationalized as a conventional acid-base mechanism. In the hydrogenation of an unsaturated ester with a closely related catalyst the extent of exchange is more evenly distributed between the two sites of addition, so that the interpretation can be quite subtle, depending on the precise structure of the substrate and the reaction conditions. As in the dehydroamino acid case, bound alkenes are not observed and the presumption must be that they are fairly elusive generally in ruthenium chemistry, perhaps consistent with the easy accessibility of ruthenium hydrides under turnover conditions [63].

A further consequence of the easy accessibility of Ru hydrides is the potential competition that they induce between alkene isomerization and hydrogenation. Since the former reaction frequently has a lower kinetic order in $[H_2]$ the best results in hydrogenation (i.e., the highest ees) may be associated with higher pressures. A dramatic example is provided by the hydrogenation of the monoterpene alcohols, geraniol, isogeraniol, and nerol, which exhibit different characteristics. It was originally observed for geraniol that the optimum result of 99% ee was associated with reduction at 100 bar. At low pressures the opposite enantiomer may be produced! This was demonstrated to be due to a competing isomerization to the more reactive isogeraniol; if hydrogenation is slow relative to this interconversion then the reaction takes place essentially exclusively through the disubstituted isomer (Fig. 17). Hence at low pressures the course of reaction can be manipulated through changes in stirring rate, which affects mass transfer of hydrogen, and also by other intrinsic factors. Isomerization is driven by hydroxy coordination to ruthenium, since the enantiomeric course of hydrogenation of nerol is unresponsive to changes in pressure, albeit much slower than geraniol overall. Only geraniol has a C-H bond of the adjacent methyl group *syn*-to hydroxy and hence accessible for reversible transfer to ruthenium [64]. Related homoallylic alcohols reduce quite readily and with high enantioselectivity so that reversible isomerization to the allylic alcohol (which creates a stereogenic center at the migration terminus) is either unimportant or is itself stereospecific [65].

A feature of Ru asymmetric hydrogenation is that, for a given hand of BINAP, a unique correlation between the reactant alkene structure and product configuration is lacking. The empirical working model is summarized in Fig. 18 [66]. It seems to be the case that when the reactant alkene is lightly substituted, the path of Class A holds, but when heavily substituted then the path of Class B holds. The definition of light and heavy substitution centers on the relationship between the binding group and other substituents on the double bond, with *cis*- β being the most demanding and α the least demanding. The models at least seem independent of the binding group so that they reflect common factors in alkene binding to ruthenium during the stereochemically defining steps of hydrogenation.

When the alkene reactant bears a stereogenic center in sufficiently close proximity to the double bond to influence the course of hydrogenation, then the possibility for kinetic resolution arises; one enantiomer will react faster than the other when the catalyst is asymmetric. In rhodium chemistry, the scope is limited but the course is reliably predictable [67]. The allylic alcohol products from

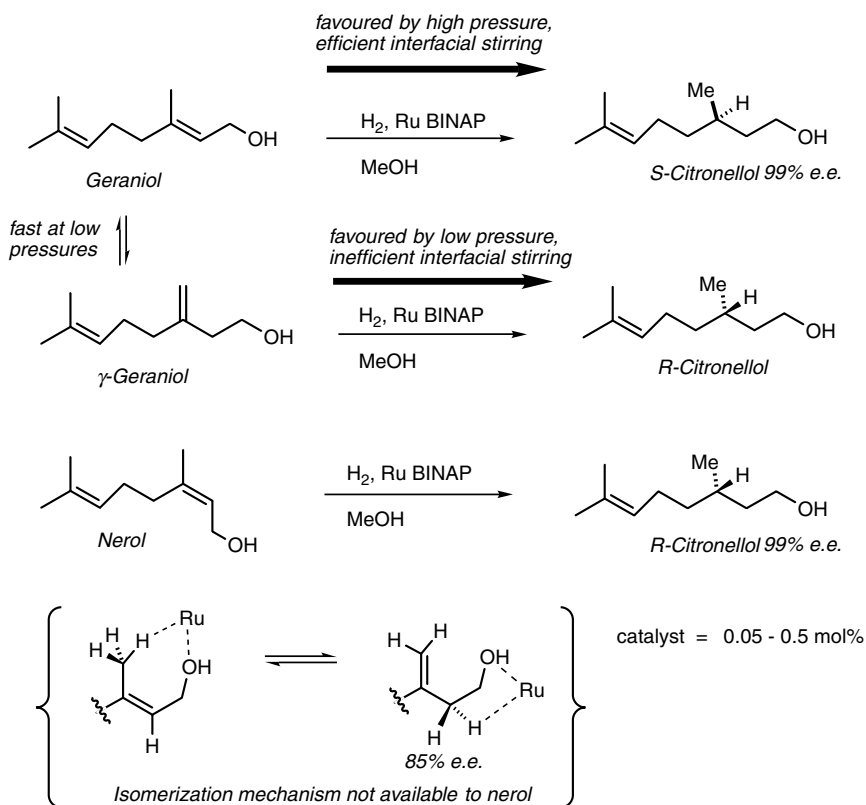
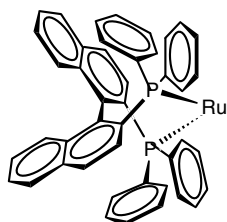


Fig. 17. The competition between hydrogenation and isomerization in the Ru-BINAP-catalyzed reduction of allylic alcohols

the Baylis-Hillman reaction, which bear a structural resemblance to dehydroamino acids, are hydrogenated rapidly under ambient conditions with good stereochemical control by cationic rhodium complexes; the *anti*-diastereomer of reduced product is formed. This indicates that the alkene coordinates preferentially through one of the two diastereotopic faces in order to minimize unfavorable non-bonded interactions in the coordinated alkene, where the hydroxy group is also chelated. When the diphosphine is asymmetric, with DIPAMP as the primary example, then a more than tenfold discrimination in the rate of hydrogenation of the two enantiomers of the alkene ensues. The result of this is that the product is only modestly optically enriched, but the enantiomeric purity of the reactant increases with the extent of reduction, being synthetically useful (>90%) beyond 60% reaction. The same circumstances apply to a range of function-bearing $\alpha\beta$ -unsaturated esters, and one family of $\alpha\beta$ -unsaturated sulfones, as indicated in Fig. 19; both the relative configuration of the product and the absolute configu-



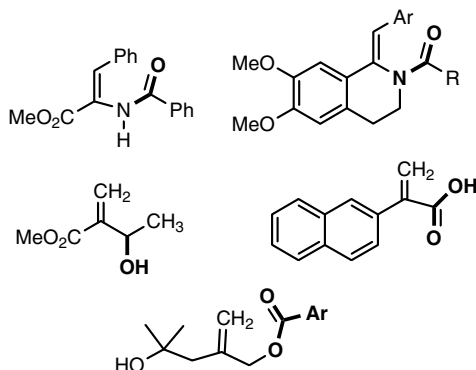
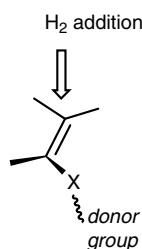
Direction of H_2 addition to alkenes in
(S)-BINAPRu catalytic asymmetric
hydrogenation of alkenes

Examples (donor group highlighted)

Class A

beta-carbon is
unsubstituted or
lightly substituted

e.g Ph cis to donor
group



Class B

beta-carbon is
more heavily
substituted

e.g R trans to
donor group

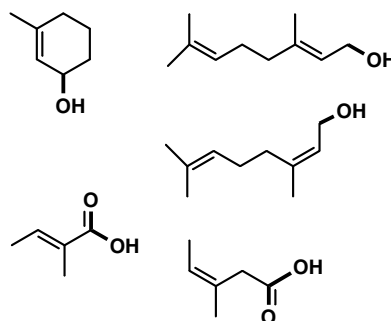
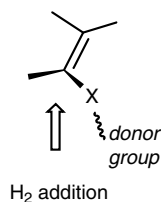


Fig. 18. Models for the stereochemical course of Ru-BINAP hydrogenation of alkenes

ration of the recovered reactant are in accord with prediction [68]. With renewed interest in asymmetric catalysis of Baylis-Hillman reactions [69], the synthetic potential of this overall scheme will merit further appraisal.

Similar kinetic resolution of Baylis-Hillman adducts may be effected by ruthenium BINAP catalysts, with comparable efficiency. But for some cyclic allylic alcohols, the level of discrimination between the enantiomers is so high that preparatively useful routes have been developed to the reactant and both hands of the product in the course of a single set of experiments [70]. In related fashion

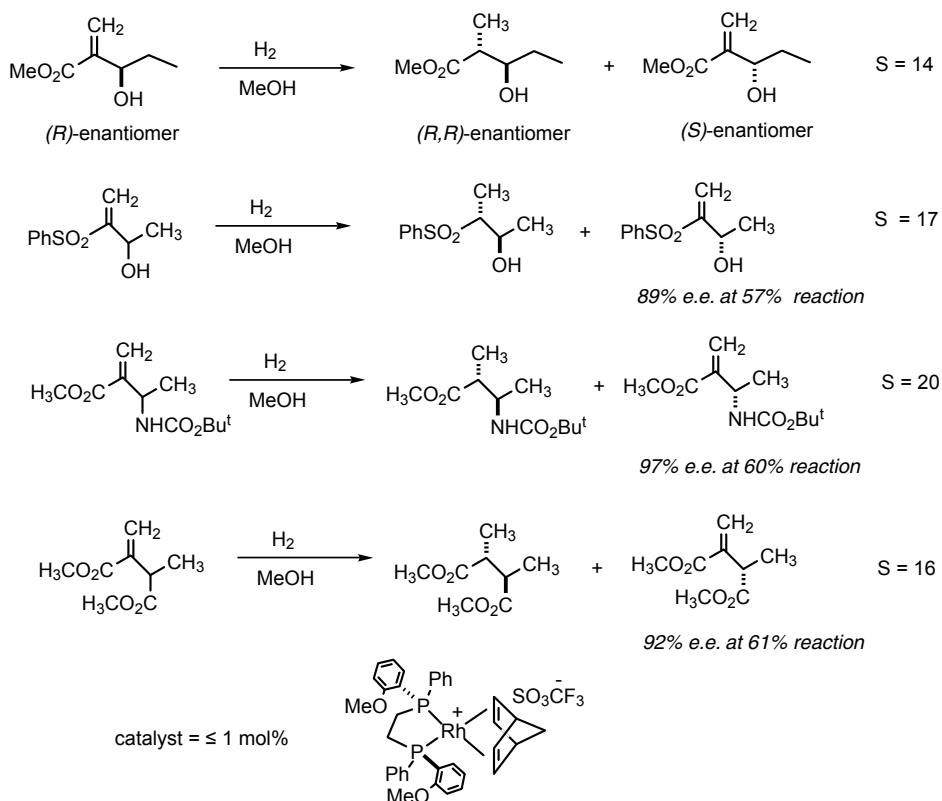


Fig. 19. Kinetic resolution in the Rh-DIPAMP-catalyzed hydrogenation of unsaturated esters and sulfones

the useful prostaglandin intermediate of Fig. 20 may be prepared [71]. Even so, these results are intrinsically less useful than the dynamic kinetic resolutions observed for the hydrogenation of stereochemically labile α -substituted β -ketoesters with catalysts related to Cl_2Ru -BINAP, and discussed elsewhere in this book.

A final example from ruthenium chemistry concerns the hydrogenation of butadiene-2,3-dicarboxylic acid, where it is clear that the second double bond reduction is influenced by the stereochemical course of the first hydrogenation [72]. The half-reduced intermediate is of *S*-configuration; when the racemic monoene is hydrogenated under identical conditions the reaction is neither enantio- nor diastereoselective.

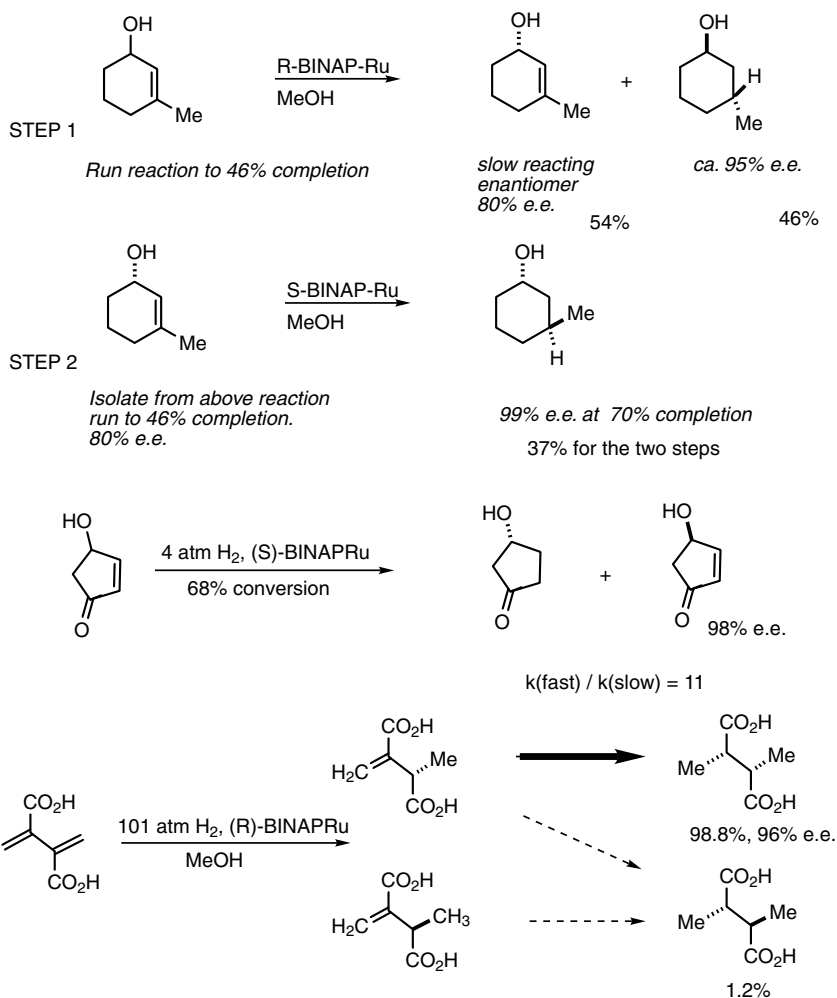


Fig. 20. Substituent direction and kinetic resolutions in ruthenium BINAP hydrogenations

3

Synthetic Studies in Rhodium-Catalyzed Enantioselective Hydrogenation

3.1

Hydrogenation of Dehydroamino Acids; General

The classical application of rhodium asymmetric hydrogenation has been the synthesis of amino-acids from dehydroamino acids, as was seen earlier. The reaction has been applied in more complex cases, for example, the hydrogenation

of dehydrodipeptides and didehydrodipeptides [73]. The early successes indicated by the Monsanto L-DOPA process tended to disguise limitations which were evident even in the initial stages of the work, namely that the successful reactants were limited to *Z*- α -dehydroamino acids and esters which were precursors of aromatic amino-acids. Not only that, the amino group in the reactant was normally protected as a carboxamide, essential to the rate and enantioselectivity, whereas carbamates (Boc, *Z*) tend to be more useful intermediates in the synthesis of complex peptides. Asymmetric hydrogenation of enecarbamates is slower and less efficient with traditional asymmetric catalysts [74]. Early work indicated some success in the hydrogenation of either *E*- or *Z*- β -alkyl- α -acylaminoacrylates when DIPAMP-Rh⁺ was the catalyst, but the reaction was much slower in these cases (particularly for the *E*-isomers) and enantioselectivity was in the range of 65%–96% [75]. A further problem had been the very slow reduction of tetrasubstituted alkenes under the traditional conditions of asymmetric hydrogenation, so that there were no useful examples derived from this class of substrate, with one notable exception [76]. Some typical results are brought together in Fig. 21.

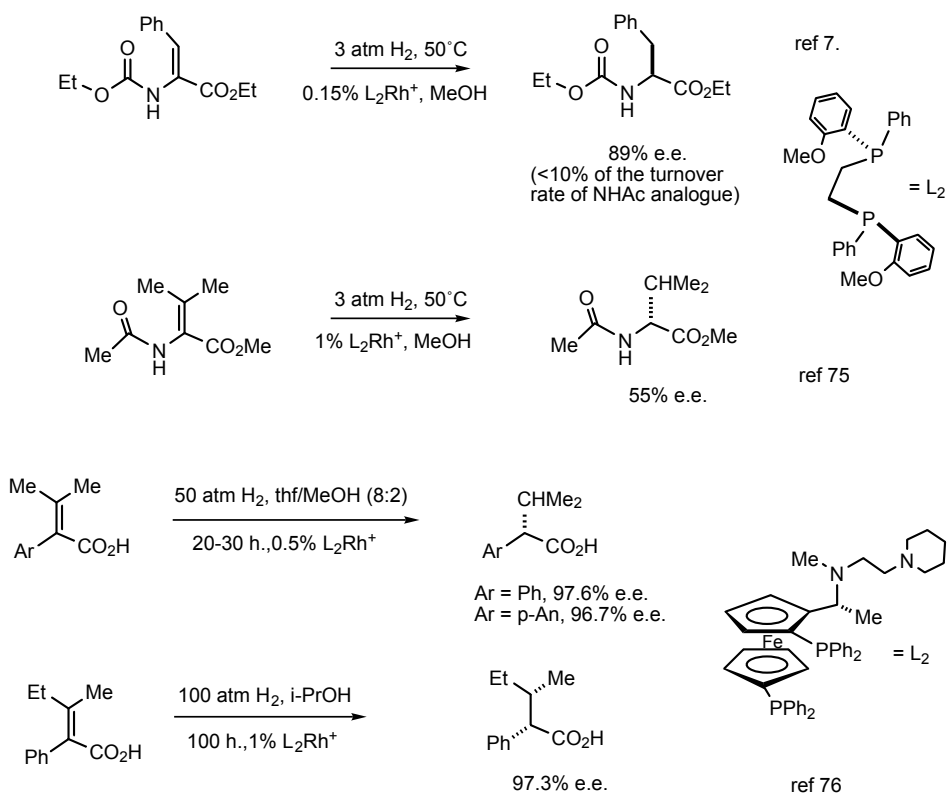
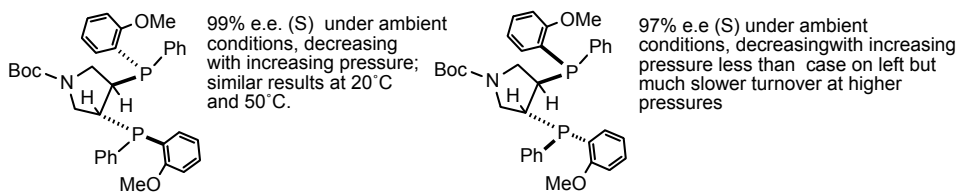


Fig. 21. Some earlier examples of asymmetric hydrogenation in traditionally difficult cases

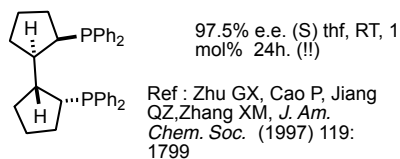
There is thus a lack of broad and general solutions, even in this most favorable case of dehydroamino acid reduction. This has encouraged the synthesis of new ligands intended to alleviate these problems, given the general practical importance of asymmetric hydrogenation. Progress in this domain is still quite empirical and since many of the interesting and novel structures involved will not feature in the detailed discussion, they are gathered together in Fig. 22, which also provides data on prototypical reductions of both natural and non-proteinogenic dehydroamino acids.

Following the early successes of Kagan and Knowles, exceptional reliance was placed on the tetraaryldiphosphine framework as the basis for novel ligand design, it being tacitly assumed that any radical departure would lead to the loss of essential features in the molecular recognition process. Five groups have effectively challenged that premise. The simplest example is due to Imamoto with "conventional" patterns of substitution at phosphorus, who carried out a systematic preparation of one of the simplest conceivable diphosphinoethanes where the phosphorus stereogenic centers both carry a methyl and *tert*-butyl substituent or other bulky group [77]. Only Van der Waals interactions can contribute to the course of asymmetric synthesis in this case and yet the result is effectively complete enantioselectivity. This result is of considerable value in defining the reaction mechanism, since the location of *P*-substituents in the ligand is more clearly defined than in an arylphosphine because of the lack of torsional freedoms (Fig. 23, B), and hence the interaction with the substrate is more readily discerned. A particular point of interest is that the observed course of reaction provides the opposite configuration of the amino acid from the one predicted by the lambda/ delta rule. Discerning the origin of this anomaly will provide important mechanistic clues.

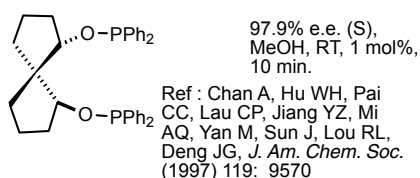
Another successful ligand based on an alkylphosphine is the atropisomerically chiral BICHEP, a variant on BINAP, which is effective for itaconates as well as for dehydroamino acids [78]. The third set of examples in this group was synthesized by Burk and co-workers at Dupont, the (ethano bridged) BPE and (benzo bridged) DUPHOS ligands. The principle of employing a C₂-symmetrical 5-ring heterocycle with equivalent stereogenic centers adjacent to the heteroatom was not new – notably the application of 2,5-dimethylborolidines by Masamune and co-workers – but it was certainly novel when applied to diphosphine ligand design [79]. Ligands based on the biferrocene framework (the TRAP family) [80] possess readily varied alkyl or arylphosphino groups. Finally, the BIPNOR structure is based on a phospholane cycloadduct, which requires resolution and separation of diastereomers after the coupling step [81]. As conventional rhodium catalysts, all of these ligands perform well in the standard protocol of dehydroamino acid reduction, giving enantiomer excesses of >97%. More interest might be derived from their ability, demonstrated for three distinct examples, to reduce β,β -disubstituted dehydroamino acid derivatives with good ee (*vide infra*).



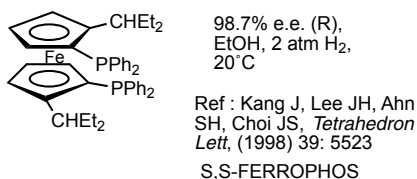
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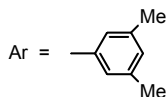
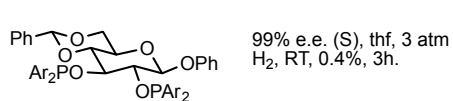
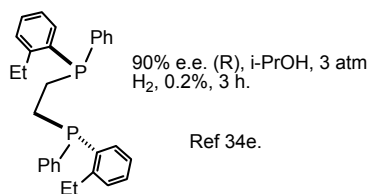
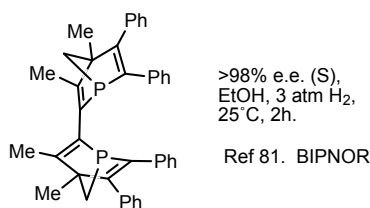
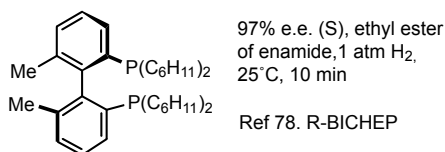
R,R- BICP



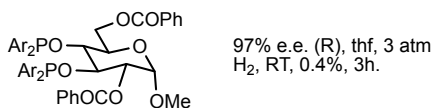
S-SPIROP



S,S-FERROPHOS



RajanBabu TV, Ayers TA, Halliday GA, You KK, Calabrese JC *J. Org Chem.* (1997) 62: 6012



See the extensive earlier work on glucose-derived phosphinites : Selke R, Ohff M, Riepe A, *Tetrahedron* (1996) : 52, 15079 and refs. cited therein.

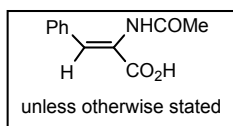


Fig. 22. Some new ligands for rhodium asymmetric hydrogenation (1992 on) of dehydroamino acids

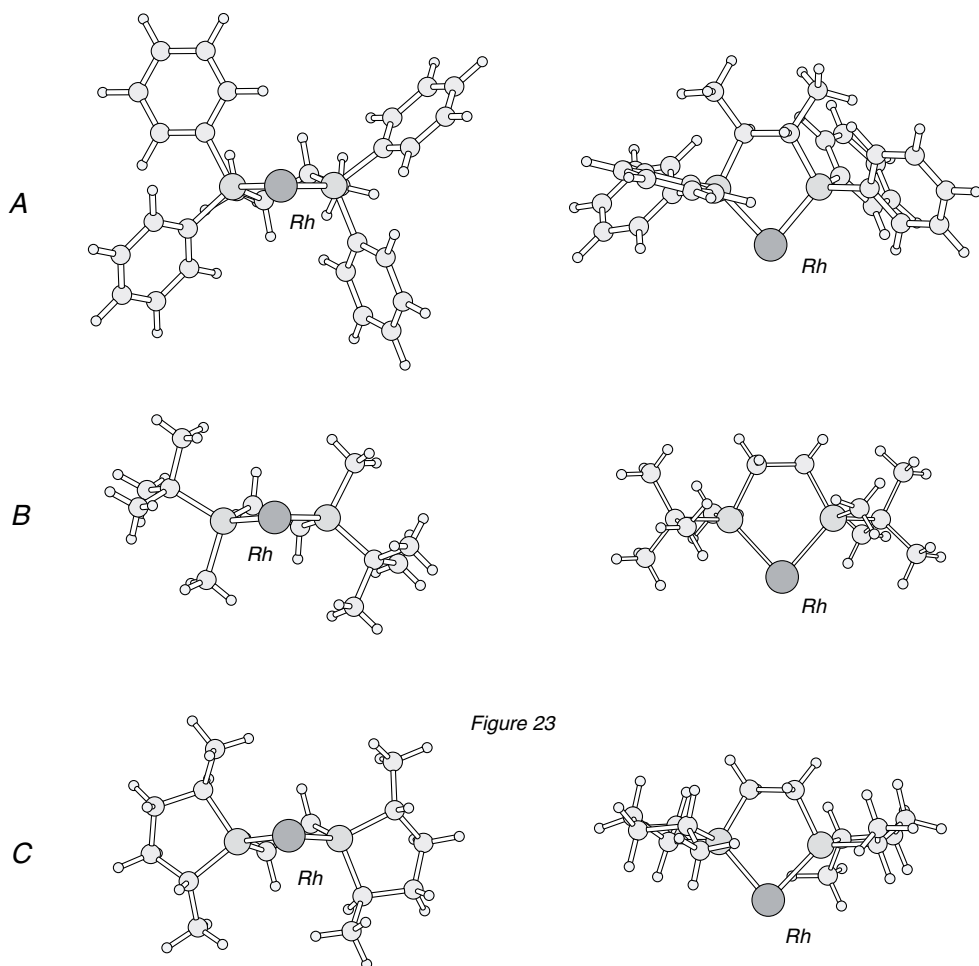


Figure 23

Fig. 23. Comparative structures of alkyl and arylphosphine ligands; (A) (*S,S*)-CHIRAPHOS (B) the (*S,S*)-enantiomer of *t*-BuMeP(CH₂CH₂PMeBu-*t*. and (C) (*R,R*)-BPE shown as Rh complex fragments in elevation and plan view – from X-ray structures

3.2

Specific Examples of Dehydroamino Acid Hydrogenation

There are three identifiable limitations in the Rh complex catalyzed hydrogenation of dehydroamino acids which apply to most of the ligands employed in the older literature. Firstly, the acyl protecting groups are not suitable for further transformations of the protected amino-acid product and need to be further transformed into more generally applicable Boc or Z-protected amines if appli-

cation in peptide coupling is desired. Secondly, the hydrogenation is generally much more efficient for *Z*-monosubstituted amidoacrylates; the *E*-isomers are hydrogenated more slowly and generally with lower enantiomeric efficiency. Finally, the increased steric hindrance and reduced propensity for metal binding means that β,β -disubstituted enamides are difficult to reduce in satisfactory ee.

In a major paper summarizing their earlier results, Burk and co-workers show that the DUPHOS and BPE ligands are capable of high enantiomer excesses, not only in the hydrogenation of conventional *E*- or *Z*-acylamino dehydroamino acids and esters, but also for the less basic and therefore more weakly binding Cbz-carbamate derivatives. An important aspect is that the *E*- and *Z*-stereoisomers give rise to the same product enantiomer in similar enantiomeric excess. In aliphatic cases where the enamide synthesis affords an *E/Z* mixture and the separation is potentially tedious, this means that an unpurified mixture can be used without detriment to the enantiomeric purity of the product [82]. The enantioselectivity of hydrogenation is barely affected by temperature or pressure, and generally MeOH gives superior results with ees of >99% being commonplace. Despite the intense competition, no other ligand family consistently matches this level of efficiency. In some cases the Imamoto system [77] is comparable, although the synthetic route to these ligands (enantioselective deprotonation and homocoupling of RPMe_2BH_3) only readily provides one hand. For both of these catalysts, successful results have been obtained in the hydrogenation of β,β -disubstituted amino acids. Taking first the Burk ligands [83], superior results were obtained with the Me-substituted BPE catalysts (Fig. 24) and a variety of β,β -disubstituted enamides can be hydrogenated in this way in >90% ee. The turnover is much slower than for the monosubstituted enamides; initial pressures of 6 atmospheres plus protracted reaction times and elevated temperatures are the norm. Other new ligands give reasonable results in the hydrogenation of sterically hindered dehydroamino acids. For the Imamoto ligand [77], the enantiomer excess was a little lower, and the experimental conditions comparable. Slightly inferior results were obtained the TRAP ligands with related substrates under similar reaction conditions [80]. A later development of this work has been the hydrogenation of the enol silyl ether or enol ester precursors to both *2S,3S*- and *2S,3R*- β -hydroxy- α -amino acids, with ees for a number of examples in the 89–97% range [84].

The demands of pharmaceutical chemistry continue to throw up challenges for asymmetric hydrogenation, and many of the later innovations come from industrial laboratories. Specific examples are gathered in Fig. 25. In the first case the synthetic dipeptide which mimics the helix-turn-helix motif of DNA-binding proteins can be formed fully and differentially protected through Rh(MeDUPHOS) hydrogenation of the appropriate bis-dehydroamino acid derivative, in 98% diastereomeric purity [85]. The diastereomerically pure acylaminoethanol is produced in a similar level of enantiomeric and diastereomeric purity through a two-stage hydrogenation of the α,β -unsaturated α -acylamino- β' -ketoester. In the first step the alkene double bond is reduced by Rh-BINAP and in the second the ketone carbonyl group is reduced diastereoselectively under catalyst control

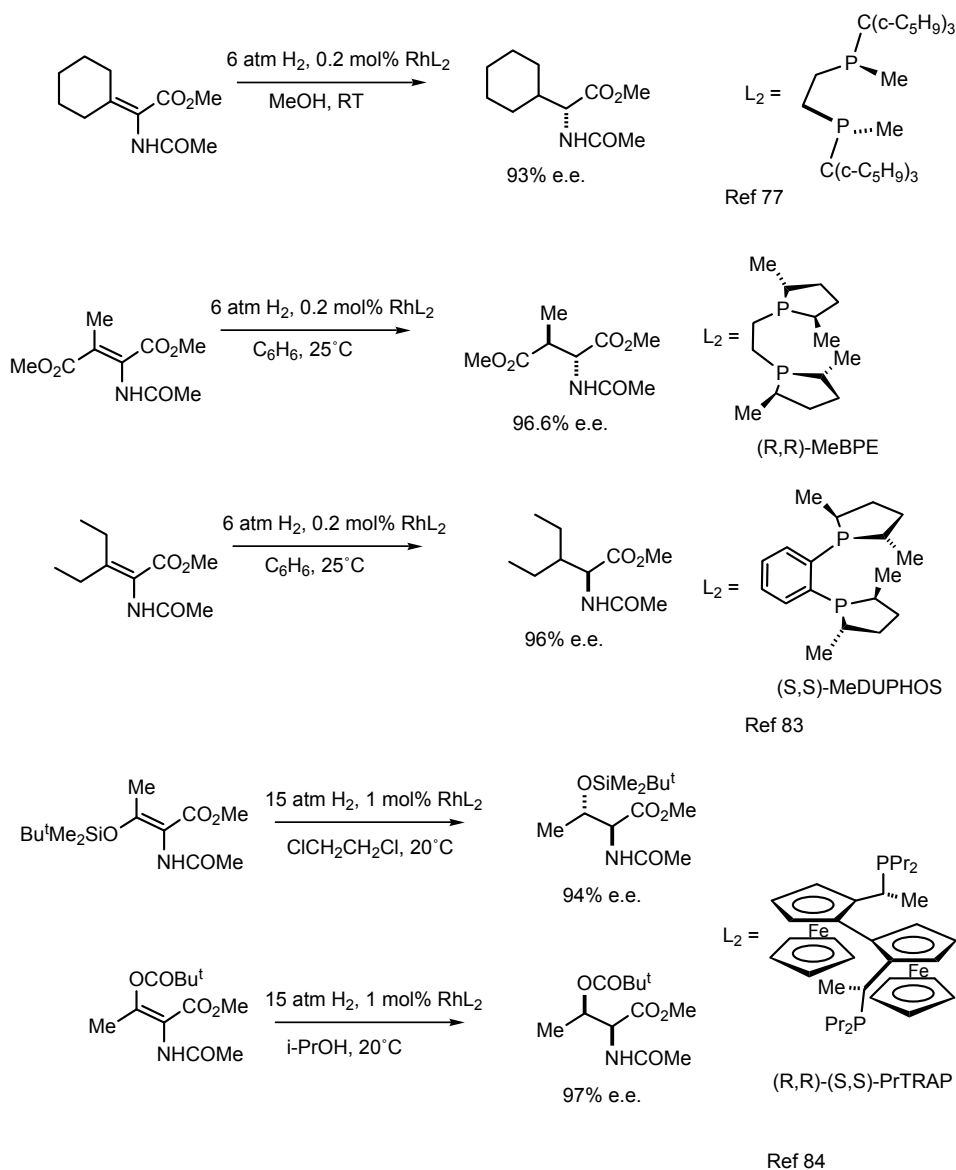


Fig. 24. Asymmetric hydrogenation of tetrasubstituted alkenes with modern catalytic systems

by Ru-BINAP to give the *syn*-product [86]. A further variation on the basic theme concerns the hydrogenation of dehydroamino phosphonates, which are readily prepared from dehydroamino acids by addition of Cl₂ followed by reaction of the dichloride with trialkyl phosphite. With RhBPPM, the hydrogenation step occurs in up to 96% ee [87]. There are few precedents for the asymmetric hydro-

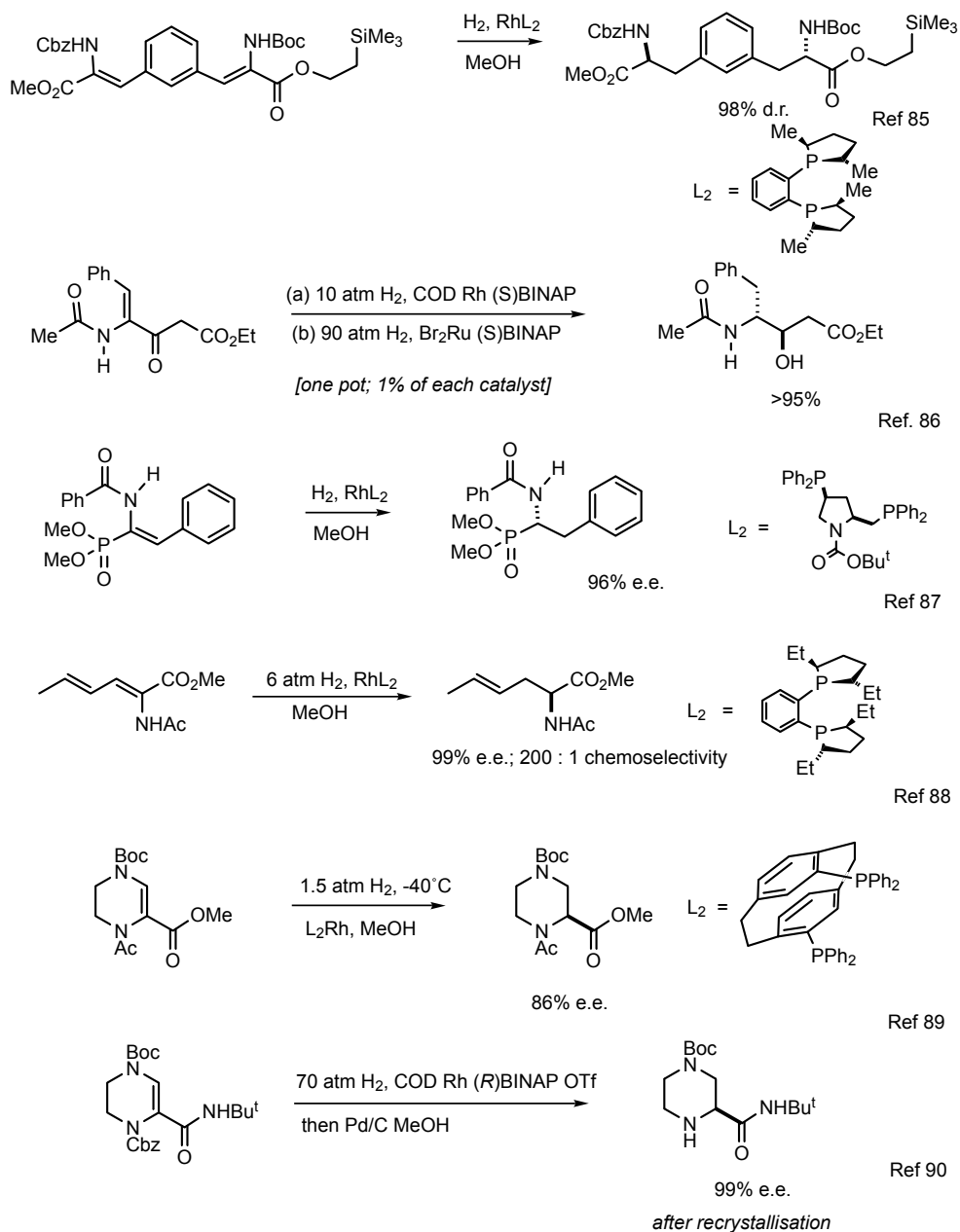


Fig. 25. The Rh-complex-catalyzed asymmetric hydrogenation of reactants related to dehydroamino acids

genation of dienamides, and it has been convincingly shown that the enamide double bond is quite selectively reduced by employing Rh(EtDUPHOS), giving rise to γ,δ -unsaturated amino acids whatever the substitution pattern of the double bond remote from the amino acid terminus [>88].

Endocyclic enamides present a difficult challenge to current methods, and three distinct solutions have emerged for different problems. The Merck ligand PHANEPHOS exploits the planar chirality of [2.2]paracyclophane [89]. Its Rh complex is reactive in asymmetric hydrogenation, giving good enantiomer excesses of amino acids from simple enamides, with the free acids superior to esters, and ees increasing with decreasing temperature ($\ln[R/S]=2440/T-5.88$). Interestingly, the *R*-ligand gives rise to *R*-amino acids except in the case of dehydrovaline which is reduced in 55% ee to the *S*-product. The catalyst seems to be highly reactive and results recorded were obtained by bubbling hydrogen through the solution at $-40\text{ }^\circ\text{C}$. The quoted example involves the hydrogenation of a precursor to Merck's HIV protease inhibitor Crixivan in 86% ee, again at $-40\text{ }^\circ\text{C}$. Rather superior results were obtained working at 70 atm with RhBINAP and a related derivative, this time in 99% ee [90].

A specific driving force for the recent revival of interest in enamide hydrogenation has been the need for a large portfolio of amino acids for combinatorial chemistry. In this field, synthesis of libraries for the assembly of small peptides with maximum variation of the side-chain has been an important goal in this field. The desired amino acids may be prepared by direct asymmetric hydrogenation of the dehydro precursor, or alternatively from bromoaryl dehydro precursors with subsequent elaboration of the C-Br bond by Heck coupling or cross-coupling [91]. Use of this latter approach (Fig. 26) has the advantage that a substantial library can be obtained on the basis of a relatively small number of reductions.

In the hydrogenation of a dehydrodipeptide, an asymmetric catalyst can essentially control the configuration of the second center formed during the reduction

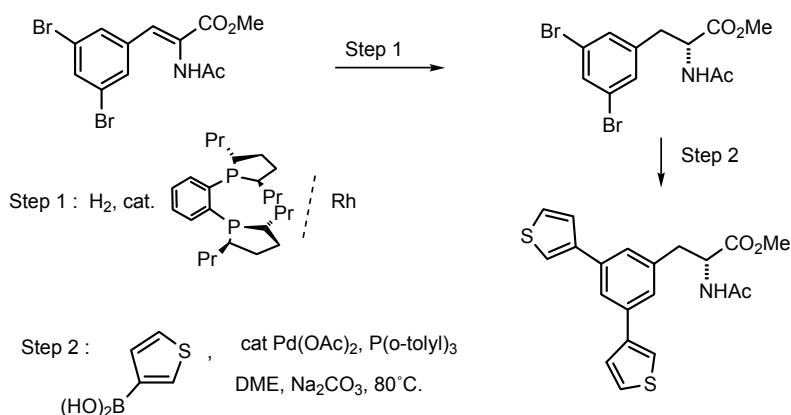


Fig. 26. Asymmetric hydrogenation exemplifying a route to amino-acid diversity

process; the level of substrate control is usually quite small [11]. In one case employing an achiral catalyst, the intracomplex participation of a pendant tertiary amine of the ligand in H-bonding to the terminal CO₂H of the dipeptide can drastically enhance the diastereoselectivity, up to 95% (Fig. 27). In the absence of this functionality the level of stereochemical control is quite low [92]. Dehydrodipeptides can be hydrogenated over heterogeneous catalysts with high diastereoselectivity; the examples provided cover the reduction of prolinyldehydrodipeptides [93] and diketopiperazines, with stereospecific deuteration of prolinyldehydrodipeptides [93] and diketopiperazines, with stereospecific deuteration [94]. A novel method of asymmetric deuteration involves enzymic dehydrogenation of a tryptophan residue, and re-reduction with D₂ and DIPAMP-Rh in >99% de [95].

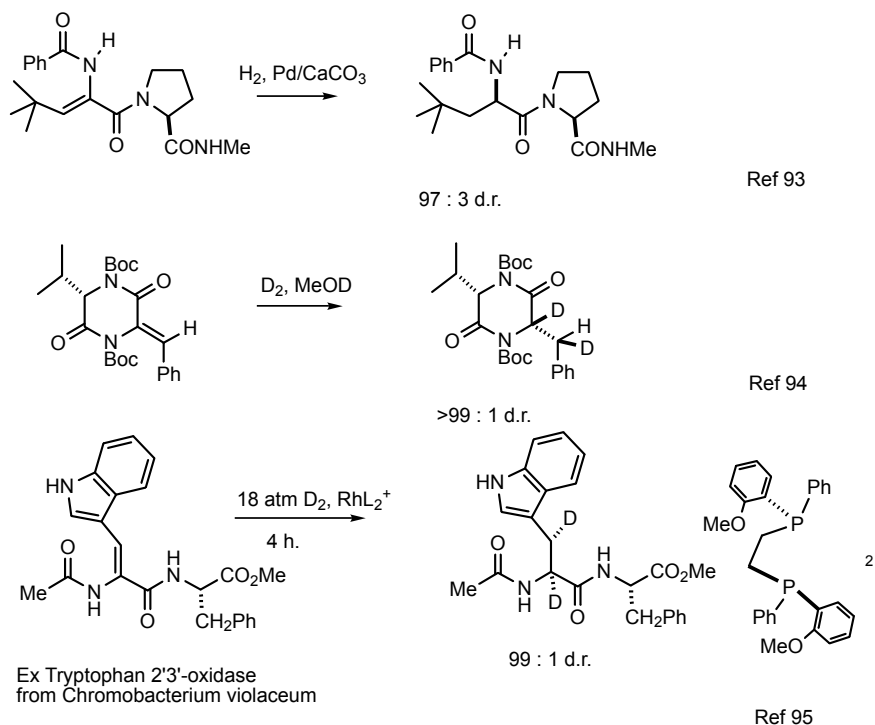


Fig. 27. Asymmetric hydrogenation routes to dipeptides and related compounds

3.3 Unsaturated Carbonyl Compounds

In dehydroamino acid or ester hydrogenation, it is the carbonyl of the amide group which acts as the auxiliary binding site, and the carboxyl group normally plays no direct part up to the rate-limiting transition state. In terms of their gross structural resemblance, the closest set of substrates to dehydroamino acids are alkylidenesuccinic acids and esters, which (in the guise of the parent itaconates) have long been employed as one of the standard tests in the evaluation of new ligands for Rh asymmetric hydrogenation. Data from the older literature may be found in standard works [96]. β -Substitution of the double bond gives rise to the potentially more interesting benzylidenesuccinates, intermediates in the asymmetric synthesis of lignans. Considerable progress has been made in this direction through the work of Achiwa's group, who have systematically varied the aryl residues of direct analogues of established ligands (e.g. BPPM, DIOP) in order to optimize the ee [97]. Increasingly, electron-rich aryl groups lead to increasing enantioselectivity, up to 94% for the transformation shown in Fig. 28. A commercial outlet for this chemistry is found in the synthesis of a renin inhibitor based on benzylidenesuccinic acid. For hydrogenation at the diacid level, the preferred ligand is related to BPPM (but based on the unnatural enantiomer of 4-hydroxyproline), and the reaction conducted in the presence of NEt₃; an ee of 94% is reported under these conditions [98]. The reaction can be carried out on a large scale using an amide which is the direct precursor of the aforementioned renin inhibitor [99]. Here, the optimal ligand is a derivative of Nagel's BDPP, and an ee of 86% was obtained on a 4 M scale, raised to 99% by recrystallization of the crude hydrogenation product. But application of the ubiquitous DUPHOS ligands provides the best general solution to date. The superior ligand in this case is derived from the bis-diethylphospholane, and ees of 97–99% have been obtained for a host of β -substituted esters [100]. The configuration about the double bond is not important; most of the examples were prepared by Stobbe condensation which resulted in a mixture of *E*-isomer with lesser amounts of *Z*-isomer. At a somewhat higher pressure (11.0 vs. 5.5 bar), a tetrasubstituted alkene variant was hydrogenated in 91% ee with the analogous, less sterically demanding Me-BPE ligand. This compares favorably with the 78% ee found for dimethyl β,β -dimethylitaconate employing a Rh complex of the TRAP ligand [101].

Given its therapeutic importance as an anticoagulant, it is surprising that the literature lacks a catalytic asymmetric synthesis of the bioactive *R*-warfarin; it is normally prescribed as the racemate. On attempted hydrogenation of the direct alkene precursor the parent hydroxycoumarin forms an unreactive cyclic hemiketal. Hence the reduction is performed on the sodium salt or on the 4-methoxycoumarin, and with S,S-Rh(EtDUPHOS) occurs in 86–89% ee [102].

An alternative conceptual approach is to build functionality into the ligand to enable direct recognition of the coordinated reactant. The principle has been expounded in a general review [103], and the most successful relevant example to date is due to the group of Yamagishi [104], who have provided powerful evidence

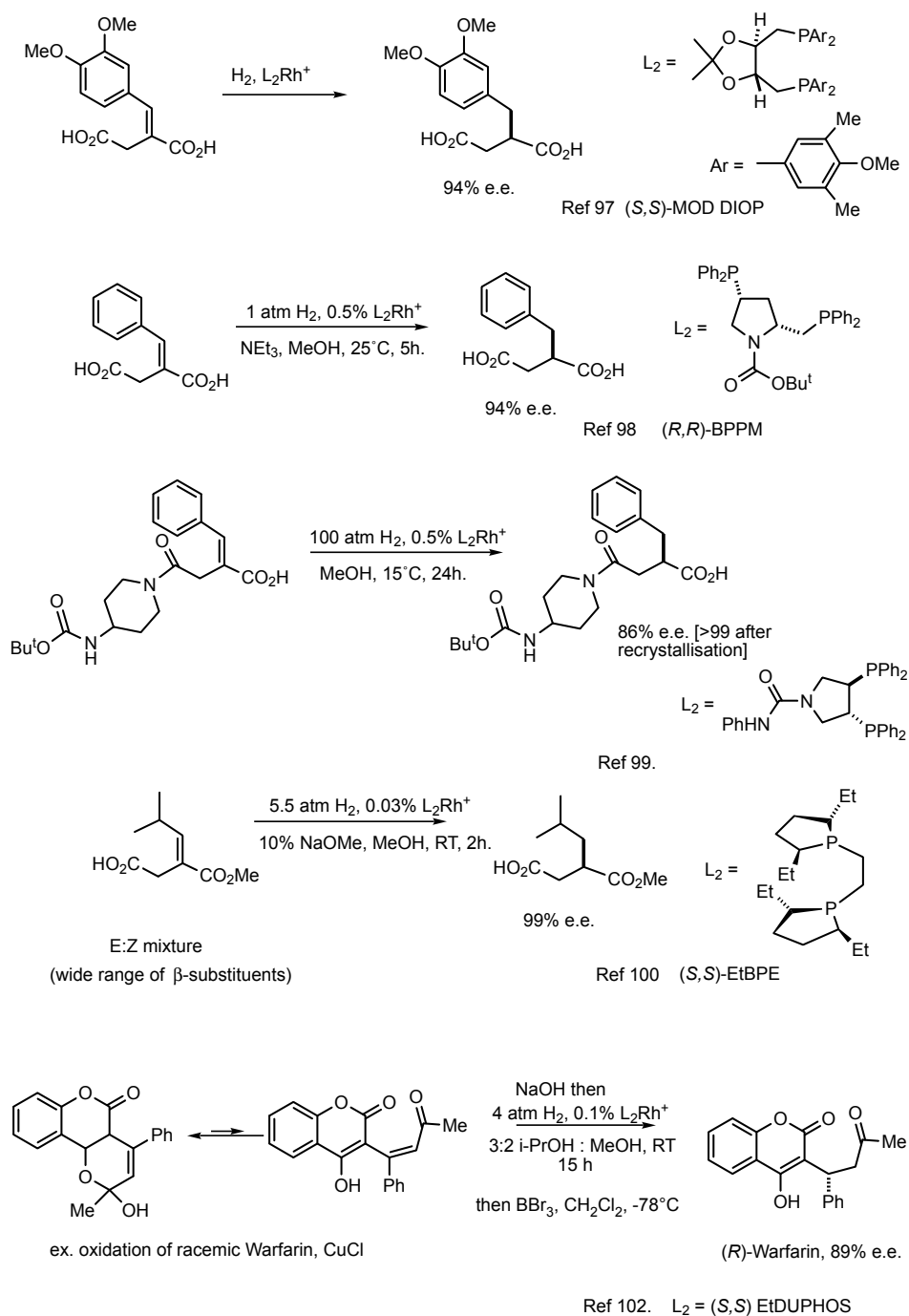
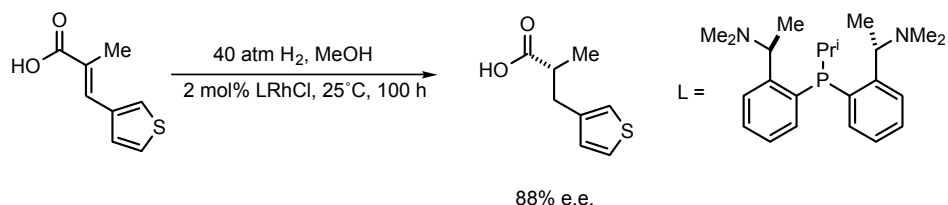


Fig. 28. Asymmetric hydrogenation of unsaturated carbonyl compounds

that the rhodium complex of Fig. 29 is involved in secondary interactions which facilitate the asymmetric hydrogenation of unsaturated carboxylic acids. Although the turnover is slow, comparison with control experiments indicates that the likely intermediate possesses a PN chelate with the unbound nitrogen hydrogen bonded to the coordinated carboxylic acid. A similar principle, developed in more depth in ref. [92], explains the diastereoselectivity observed in hydrogenation of dehydridipeptides when the ligand carries a pendant tertiary amine.



Ref 104, model below

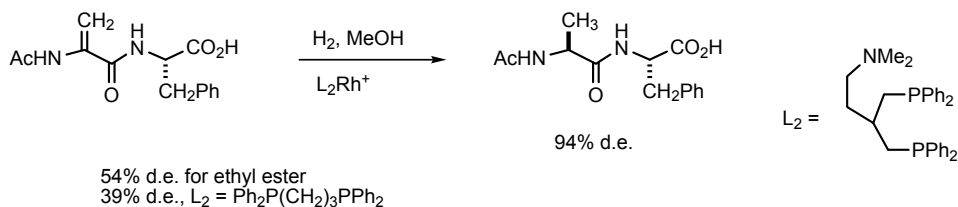
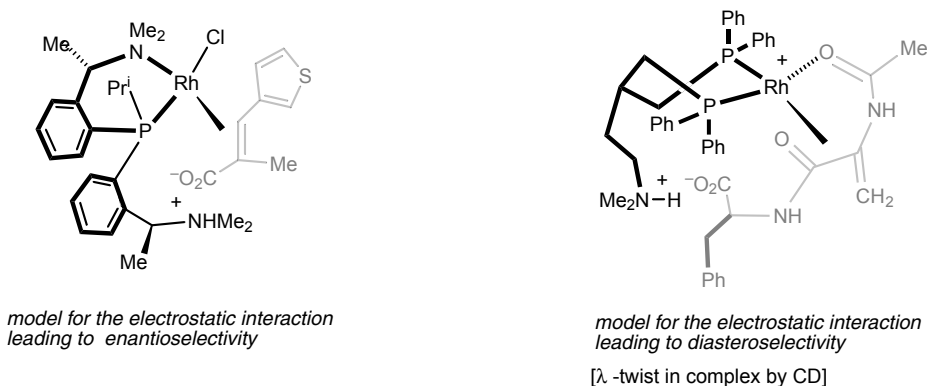


Fig. 29. Remote asymmetric induction in the hydrogenation of unsaturated carboxylic acids

3.4 Enamines, Simple Enamides and Enol Esters

Kagan's demonstration of the asymmetric hydrogenation of simple α -arylenamides was among the earliest results in the field [105]. Little improvement on the ca. 80% ee observed in the original work, which employed Rh DIOP complexes, were reported over the intervening years. With increasing interest in the asymmetric synthesis of amines by reductive methods, reflecting the intrinsic difficulty or lack of generality of other routes, new efforts have been made to develop improved enamide hydrogenations. Much the best and most general method is due to Burk and coworkers where both the DUPHOS and BPE ligands, the phospholanes being substituted with the least sterically demanding Me-groups, are effective [106]. A series of enamides was synthesized from the corresponding ketones and reduced to the corresponding acylamines under optimum conditions in 95–98% ee (Fig. 30). A virtue of the method is that the synthesis produces both double bond diastereomers of the enamide; the *E/Z* mixture can be hydrogenated without purification since both are reduced to a single enantiomer of acylamine. As is discussed in detail elsewhere, asymmetric hydrogenation of endocyclic enamides is best carried out with ruthenium catalysts; but respectable results (70–80% ee) may be obtained by ligand optimization in Rh catalysis.

The successful demonstration of hydrogenation of an enol acetate was demonstrated in Knowle's original paper on DIPAMP, and the range of the reactant was extended subsequently [107]. As in several other cases the superiority of the DUPHOS ligands in this sphere is evident from a full paper, which covers the range of possibilities accessible through simple synthesis [108]. The products are precursors to α -hydroxyacid derivatives, and the method more powerful since the asymmetric hydrogenation of α -ketoacids is difficult to achieve with high enantioselectivity (but see the work of Mortreux, Chapter 6.1). Selected examples of the method are shown in Fig. 31.

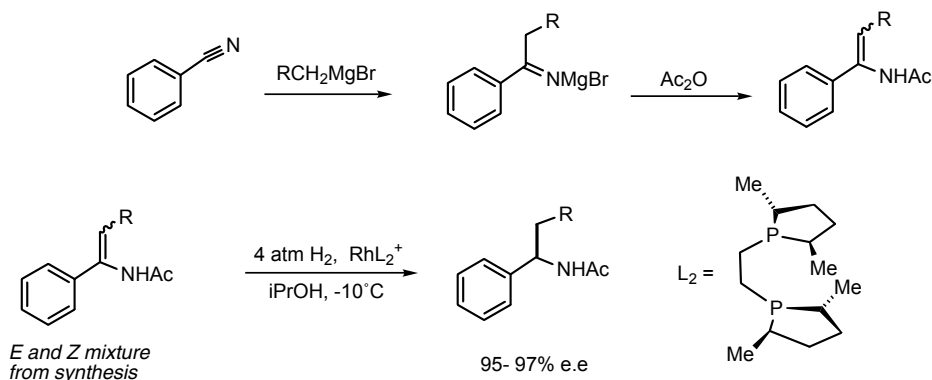


Fig. 30. Asymmetric hydrogenations of simple enamides

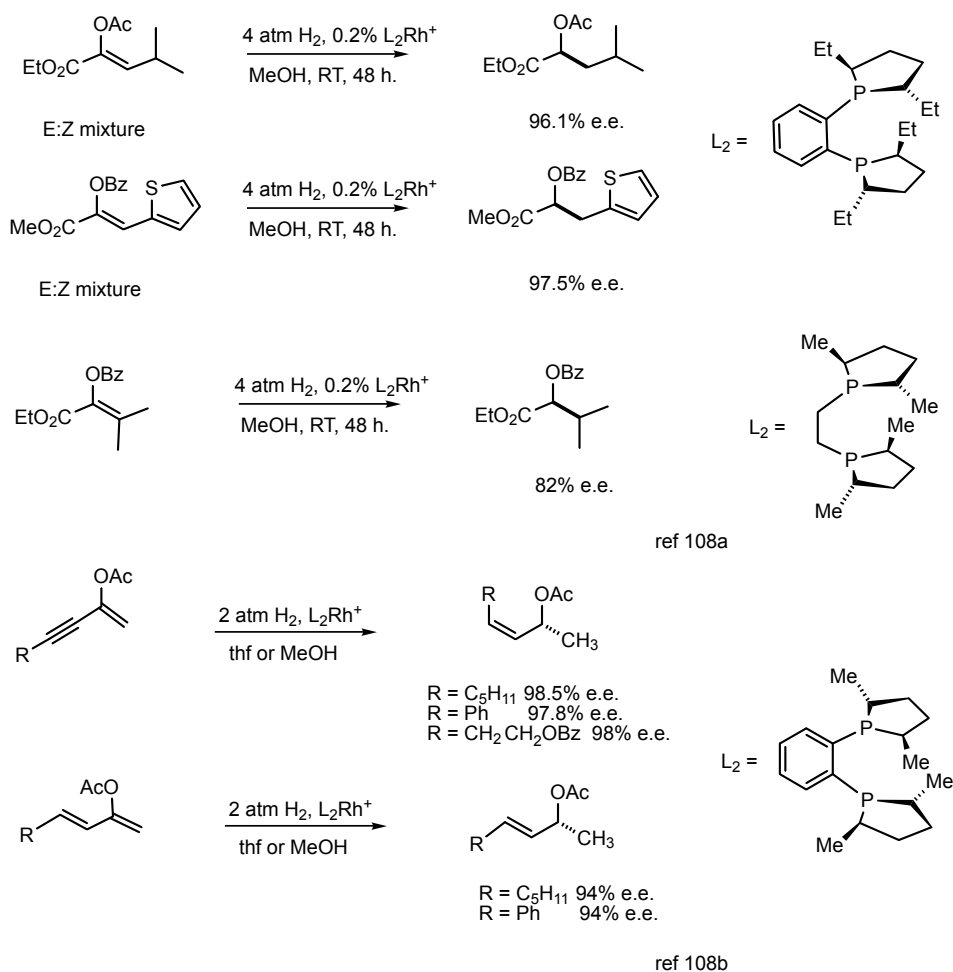


Fig. 31. Asymmetric hydrogenation of enol esters

As a final example not strictly within the bounds of this section, the work of Buchwald's group can be cited [109]. This demonstrates that asymmetric hydrogenations can be achieved with metals other than Rh or Ru (albeit rarely!). In this case, the reduction of simple enamines with high enantioselectivity is demonstrated with titanium catalysts. The genesis of the ligand lies in the cyclopentadienyl complexes developed for stereospecific polymerization, but its application here results in a useful transformation (cyclic enamines provide a difficult problem for the conventional asymmetric hydrogenation catalyst) illustrated in Fig. 32.

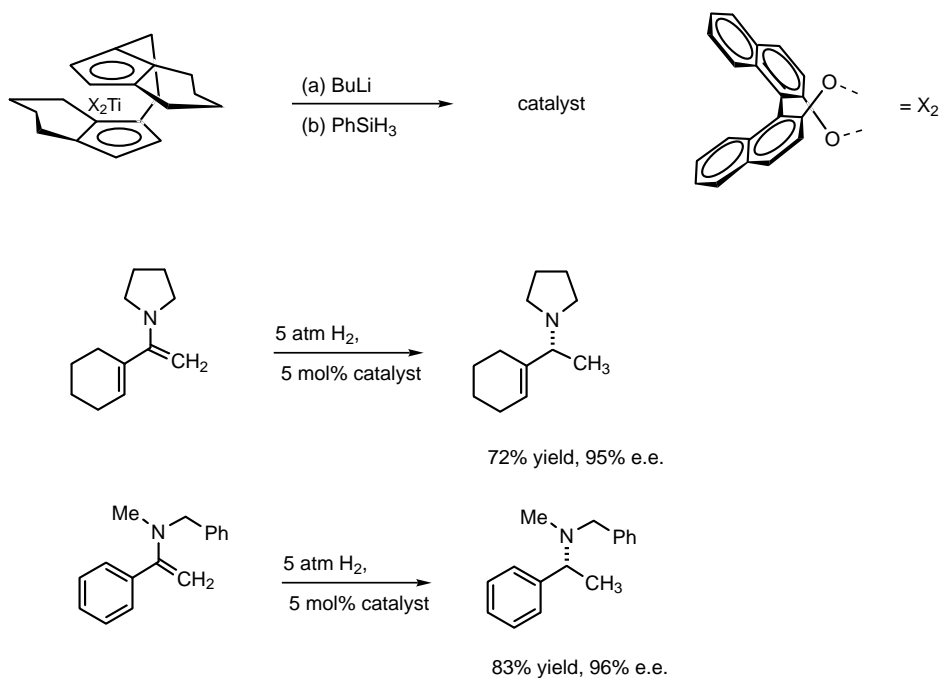


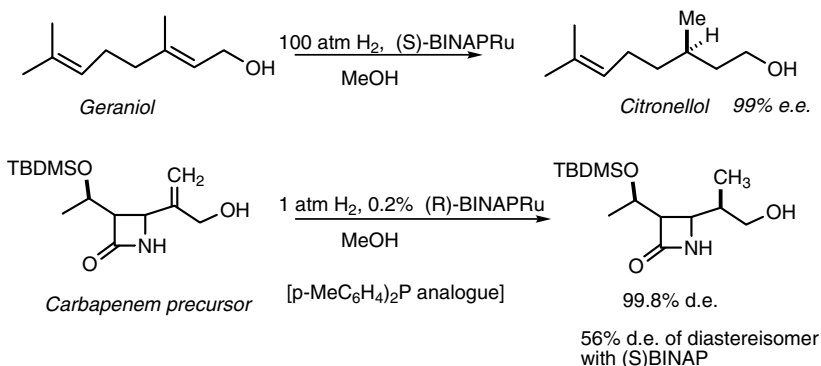
Fig. 32. The titanium-catalyzed asymmetric hydrogenation of enamines

4

Synthetic Studies in Ruthenium-Catalyzed Enantioselective Hydrogenation

The basis of this whole field of endeavor was the discovery of chelating diphosphine-ruthenium(II) complexes reactive as hydrogenation catalysts. Initially, the results were interesting rather than earth-shattering and it was only when the range and specificity of the new catalysts was demonstrated through the output from Noyori's group a decade ago that the exceptional utility was realized [110]. Most of these initial results were directed towards the enantioselective reduction of prochiral alkenes, but the comparable ease and selectivity observed for the asymmetric hydrogenation of prochiral ketones altered the emphasis [111]. Nowadays, the two possibilities of C=O or C=C reduction are both useful or potentially useful across the full scale range of applications in asymmetric synthesis. Naturally, the subject has been well reviewed and Noyori's book [12] provides an account of the first seven years output, the early successes being summarized in the examples of Fig. 33. Although the asymmetric hydrogenation of non-functionalized alkenes will be discussed in detail elsewhere, it is worth noting here that both α -alkylstyrenes [112] and other prostereogenic 1,1-disubstituted alkenes [113] can be hydrogenated in moderately good enantiomer excess employing RuBINAP complexes.

Allylic alcohols



Unsaturated acids

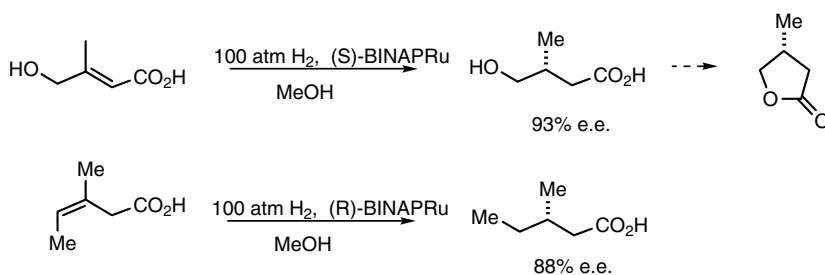


Fig. 33. Examples of ruthenium asymmetric hydrogenations in the initial phase of the work; 1985–1992

In this arena, the dominant ligand has been BINAP, which forms at least the conceptual base for alternative approaches to optimal ligand design including the 6,6'-disubstituted-2,2'-diphosphenobiaryl compounds [114]. Considerable efforts have been made to produce a straightforward route from commercial sources of the metal salts (typically RuCl₂) to catalytically active complexes. For the reduction of ketones the most satisfactory precursors are either *in situ* generated P₂RuCl₂ or P₂RuBr₂, or the related cationic arene complexes P₂Ru(η⁶-ArH)Cl⁺X⁻. There is less consensus about the best precursor for alkene hydrogenations and the Nagoya group have traditionally employed P₂Ru(OAc)₂, the preparation of which is described in Organic Syntheses [115], or the bis-trifluoroacetato variant [116]. The latter has been the subject of a carefully described systematic synthesis suitable for industrial application. A related procedure, which has also been applied to a diverse range of diphosphines, is to allow the hydrate of [COD]₂Ru[O₂CCF₃]₂ to react with the diphosphine in MeOH, when a disolvate complex carrying both the phosphine chelate and η¹-trifluoroacetato ligands can be isolated [117]. Genet has introduced P₂RuR₂ complexes, where R = η³-al-

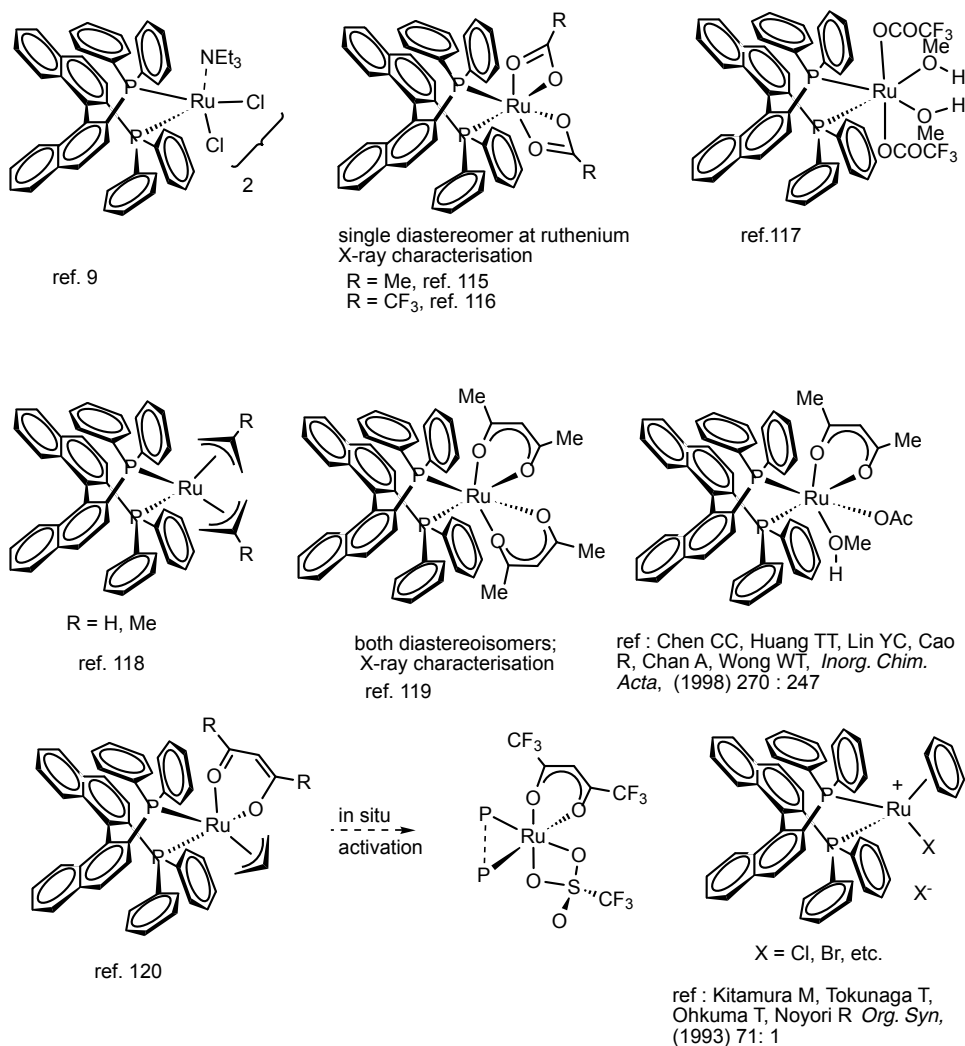


Fig. 34. Preparation of ruthenium-BINAP and related catalysts

lyl or η^3 -methallyl. A variety of diphosphine complexes can be prepared from a single precursor, the bench-stable [COD]RuR₂ species, in this way [118]. Alternatively, acetylacetonates, P₂Ru(acac)₂, can be employed starting from the stable, commercially available Ru(acac)₃ and employing dihydrogen or zinc as an *in situ* reductant [119]. There is a suggestion that one of the acetylacetonate moieties remains coordinated to ruthenium during the catalytic cycle, and that the resulting complex operates with a higher turnover frequency than the corresponding acetate complex. An intriguing feature which arises from this work is

that there are two diastereomers of the BINAPRu(acac)₂ complex and both are formed in the synthesis – one characterized by X-ray analysis. In contrast, the earlier synthesis and crystallographic characterization of the corresponding (OAc)₂ complex revealed only a single diastereomer; the sense of acetate binding at ruthenium is stereospecific. A final option for the preparation of ruthenium catalyst precursors is the stable [COD] or [NBD] ruthenium η^3 -allyl acetoacetates or *F*₆-acetoacetates, from which the diolefin may be displaced by the appropriate diphosphine. These are stable, isolable complexes active in transfer hydrogenation, but need to be activated by treatment with Me₃SiOTf before they become catalytically active [120]. A summary of the main routes to ruthenium catalysts for asymmetric hydrogenation is presented in Fig. 34.

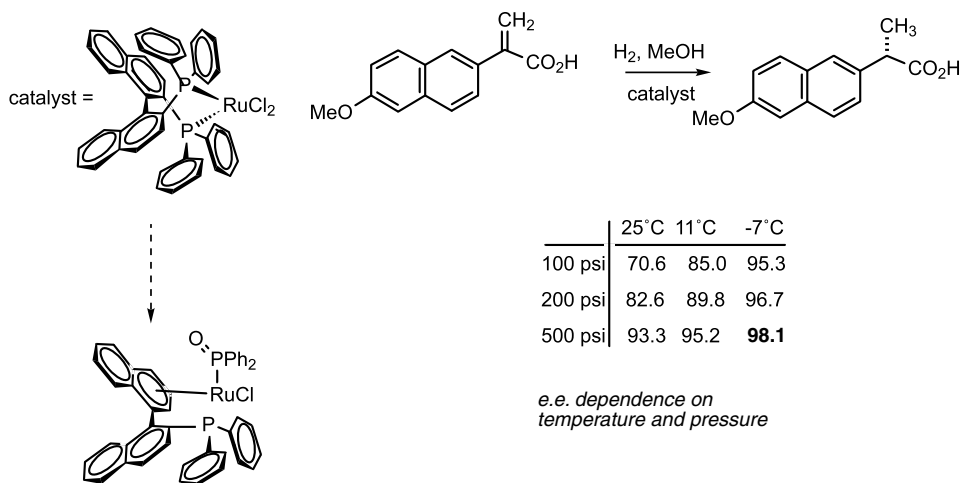
In practice, the rates and enantiomer excesses pertaining to alkene hydrogenations are not strongly dependent on the precursor, and convenience as well as the availability or otherwise of particular Ru complexes will dictate the users' choice. Pre-synthesis of well-defined catalysts is preferable to *in situ* preparation for a novel experiment since it eliminates one additional source of uncertainty and potential failure.

4.1

Unsaturated Carboxylic Acids

One of the driving forces behind ruthenium catalysis is that the high ees coupled with the broad versatility make it a promising reaction for industrial application. Nowhere is this more true than in the reduction of atropic acids, which are direct precursors to α -arylpropionic acids, the major class of non-steroidal anti-inflammatory agents. The *S*-enantiomer has a much higher bioactivity and now that the patents for the main drugs, Naproxen and Ibuprofen, have expired there is a considerable economic stimulus to develop new enantioselective routes. Fig. 35 displays one effort to optimize the synthesis by Monsanto chemists; in the course of this work a catalytically inactive degradation product derived from the BINAP catalyst was isolated [121]. This is somewhat surprising given the generally robust nature of the ruthenium catalysts under high pressure conditions.

As with any synthetic method the testing grounds relate to functional group tolerance and to reactivity. An example of the former is the successful asymmetric hydrogenation of α -fluoro- α,β -unsaturated acids [122]. Both diastereomers of the alkene give rise to the same hand of α -fluoroacid, in contrast to the case of diastereomeric α,β -dialkylated acrylic acids which give opposite enantiomers. An example of the latter is the reduction of an unsaturated carboxylic acid with a tetrasubstituted double bond, optimally in the presence of triethylamine. The product is of pharmaceutical interest in the context of Mibefradil, a calcium antagonist [123]. Success is not guaranteed, however, and in another attempt at synthesis of a pharmaceutical intermediate by asymmetric hydrogenation, the product is formed only in 65% ee, possibly because of the presence of a bulky β -1-naphthyl substituent; the allyl sulfide entity survives the reaction conditions



catalytically inactive complex characterised by X-ray

Fig. 35. The optimization of *S*-Naproxen synthesis using Ru-BINAP asymmetric hydrogenation

[124]. As might be anticipated, vinylphosphonic acids are hydrogenated with reasonable enantiomer excess employing RuBINAP complexes [125] (Fig. 36).

A simple structural modification, namely the reduction of the unsubstituted rings of the BINAP ligand, provides a superior catalyst for the enantioselective hydrogenation of unsaturated acids [126]. The reaction takes place both at lower pressures and with higher enantioselectivities. Hydrogenation of tiglic acid has been the standard protocol for testing new catalysts (the Ru equivalent of MAC reduction) and this new catalytic protocol gives 97% ee under conditions close to ambient. The superior reactivity is still associated with sensitivity to pressure (generally in the direction of increased ee at higher pressures) as observed in the hydrogenation of the direct precursor to Ibuprofen. The catalyst can accommodate β,γ -unsaturated acids as well as tetrasubstituted reactants.

An alternative, and largely untried ligand from Mathey's group, BIPNOR, may provide an interesting alternative to BINAP in the Rh or Ru reduction of unsaturated acids [127].

In asymmetric hydrogenation generally, it is surprising how rarely the “*meso*-trick” has been employed. There is a nice example from Takehashi's work [128] involving a symmetrical divinyl alcohol. In this case both double bonds were reduced, and although the *meso*-diastereomer accounted for 20% of the product, the remaining *R,R*-diacid (isolated as its diester) had 94% ee, giving a simple access to the core portion of an active HIV protease (Fig. 37).

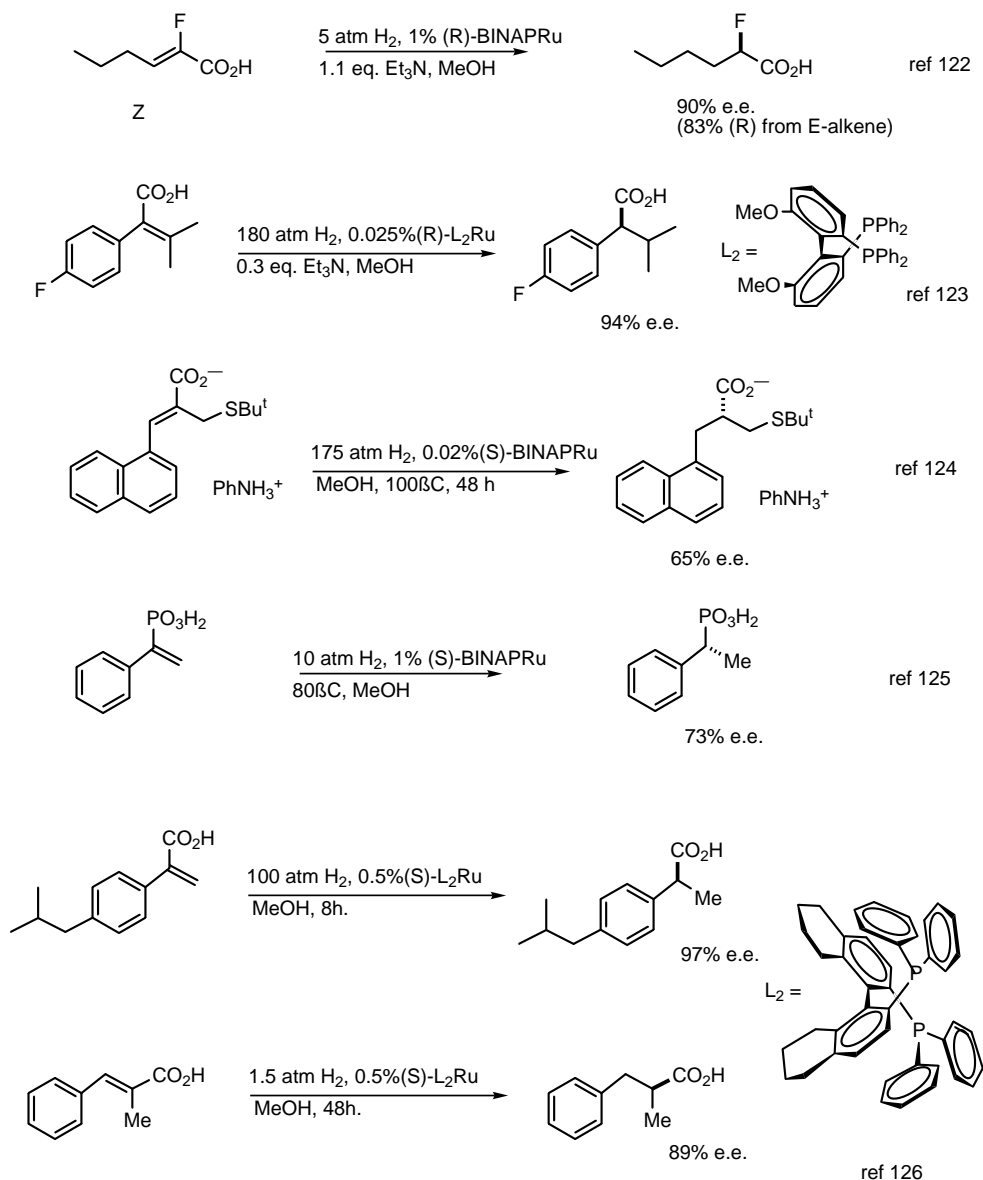


Fig. 36. Ruthenium asymmetric hydrogenation of unsaturated acids

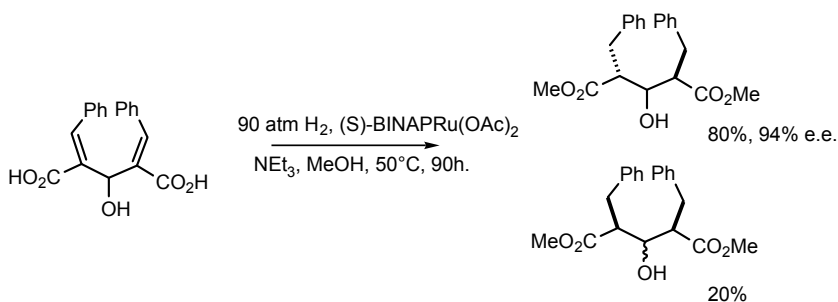


Fig. 37. Double asymmetric hydrogenation of an HIV protease inhibitor precursor

4.2 Enamides

As a general rule, the strongly metal-binding dehydroamino acids and their close relatives are better hydrogenated by asymmetric rhodium rather than ruthenium catalysts. This generality is sometimes overturned by experiment, as in the hydrogenation of a series of methoxycarbonylalkylenamides, which were prepared conventionally from the aldehyde by Horner-Emmons reaction. This synthetic approach gave the *Z*-isomer at -78°C but the thermodynamically preferred *E*-isomer when reaction was carried out at 25°C . Results are shown in Fig. 38, the ee varying somewhat with pressure, albeit not predictably [129]. Of interest is the difference in the characteristics of this catalytic system compared with the typical Rh enamide protocols. In that case the *E*- and *Z*-isomers of trisubstituted dehydroamino acids give the same hand of reduced product (cf. the earlier discussion on the mechanism of ruthenium hydrogenation) whereas they give opposite hands in the present case.

A specific case where BINAPRu complexes give superior results in enamide hydrogenation is that of the alkylidene tetrahydroquinolines shown in Fig. 38, intermediates in the synthesis of morphine relatives [130]. The *N*-formyl derivatives work well in this reaction, although eneformamides were always considered poor substrates in the rhodium-complex-catalyzed hydrogenation of dehydroamino acids. The present chemistry provides a very simple and highly enantioselective route to a range of valuable synthetic intermediates. An endocyclic enamide is hydrogenated slowly but in high ee, giving the antiarrhythmia agent MK-0499 [131a]. For a comparable problem, and again using RuBINAP, the enamide derived from 2,3-benzocapro lactam was hydrogenated in 82% ee [131b].

4.3 Unsaturated Carbonyl Compounds

The conventional model for asymmetric hydrogenation with either Rh or Ru catalysts indicates a vital role for a second functional group (amide, carboxylate)

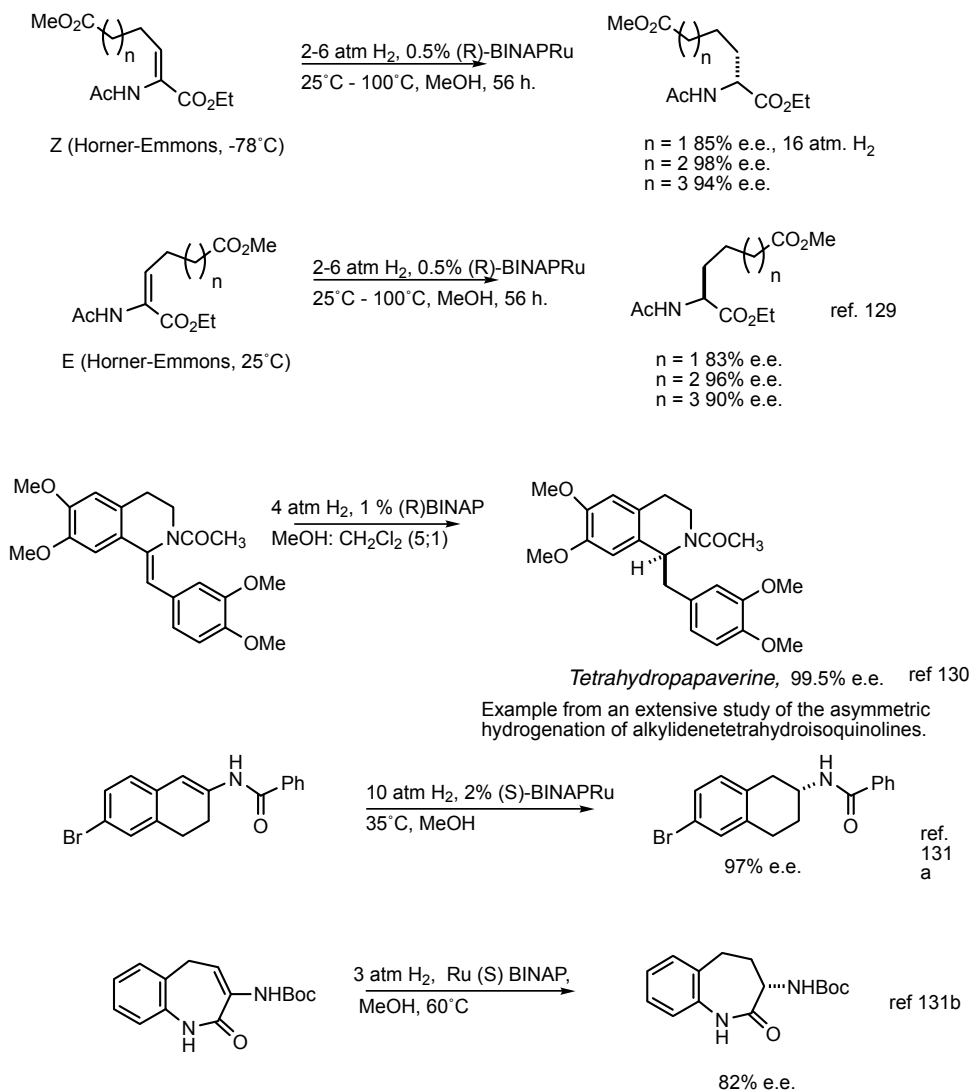


Fig. 38. Asymmetric hydrogenation of enamides by ruthenium complexes

in proximity to the alkene which remains coordinated to the metal throughout the catalytic cycle. Some recent examples in ruthenium chemistry indicate that this factor need not always be a prerequisite for a high enantiomer excess (Fig. 39). Under moderately forcing conditions, and in less polar solvents, *E*-alkylidenecyclopentanones are reduced with high enantioselectivity to the corresponding alkylcyclopentanones, whilst the corresponding *Z*-isomer is poorly reduced with low enantioselectivity. A similar reaction course is observed for α -

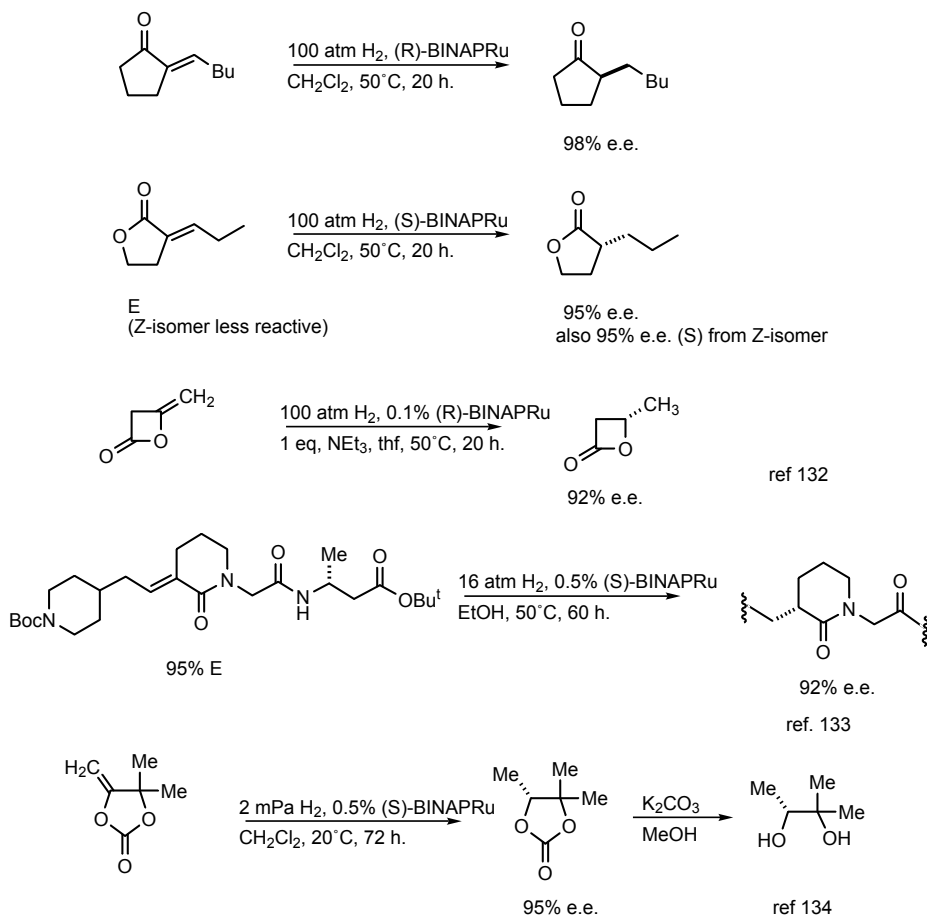


Fig. 39. Ruthenium asymmetric hydrogenation of unsaturated carbonyl compounds

or γ -alkylidenebutyrolactones, and for ketene dimer (in the presence of an equivalent of NEt₃) [132]. In similar vein, a catalytic asymmetric route to a fibrinogen receptor antagonist is provided by hydrogenation of the exocyclic double bond of a late intermediate with the correct lactam side-chain in place [133]. A novel route to secondary, tertiary 1,2-diols in high ee is provided by reduction of a carbonate precursor with RuBINAP. The reactant is itself synthesized by the reaction of a tertiary propargyl alcohol with CO₂ under Ru catalysis [134].

4.4

Unsaturated Alcohols

Since the dramatic initial work of Noyori on the asymmetric hydrogenation of terpenoid allylic alcohols, and the mechanistic refinements discussed earlier

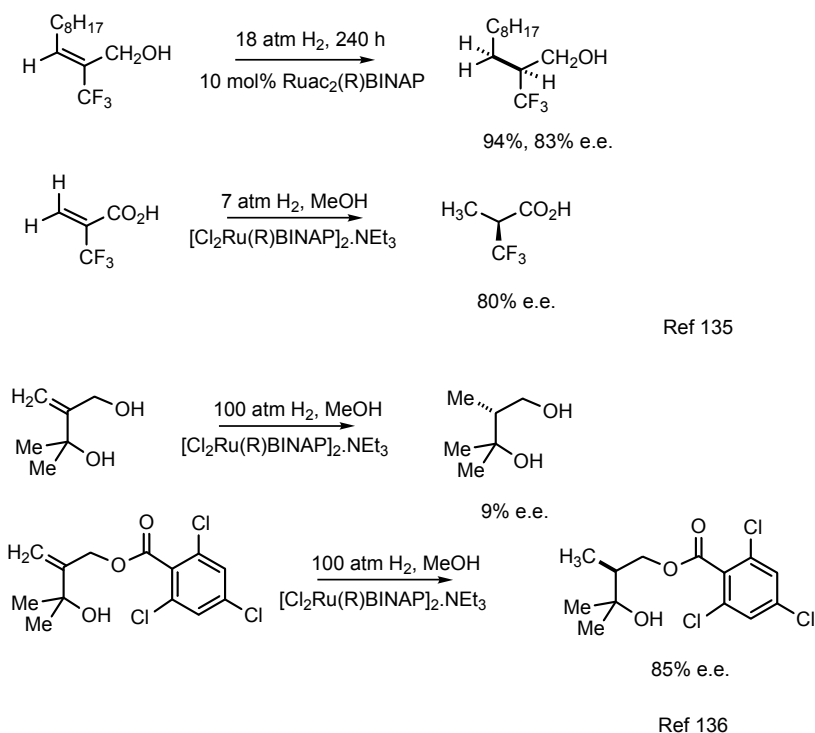


Fig. 40. Recent asymmetric hydrogenation work involving unsaturated alcohols

(ref. [64]), improvements have been steady rather than dramatic. Among the “difficult” allylic alcohols which give respectable results, the readily synthesized 3-alkyl-2-trifluoromethylpropanols offer a precursor to compounds with CF_3 at a stereogenic center [135] Fig. 40). Occasionally, poor results are observed in this area; in such cases the esterification of the allylic alcohol is recommended, leading to superior ee. The direction of H_2 addition in this case is consistent with the ester acting as the secondary coordinating group [136].

4.5

Optimization of Catalyst Structure [137]

The lack of significant variation in the catalysts described in the preceding sections, does not mean that the BINAP structure or very close relatives provides a universal optimum for Ru asymmetric hydrogenation. Workers in Schmid's group at Roche have developed libraries of biaryl ligands which are generally based on simple biphenyls where atropisomerization is blocked by Me- or MeO-substituents at the 6- and 6'-positions. The systematic studies inherent in process development have revealed wide variations in reactivity and enantioselectivity, particularly with regard to variation of the *P*-aryl substituent. In Fig. 41 some

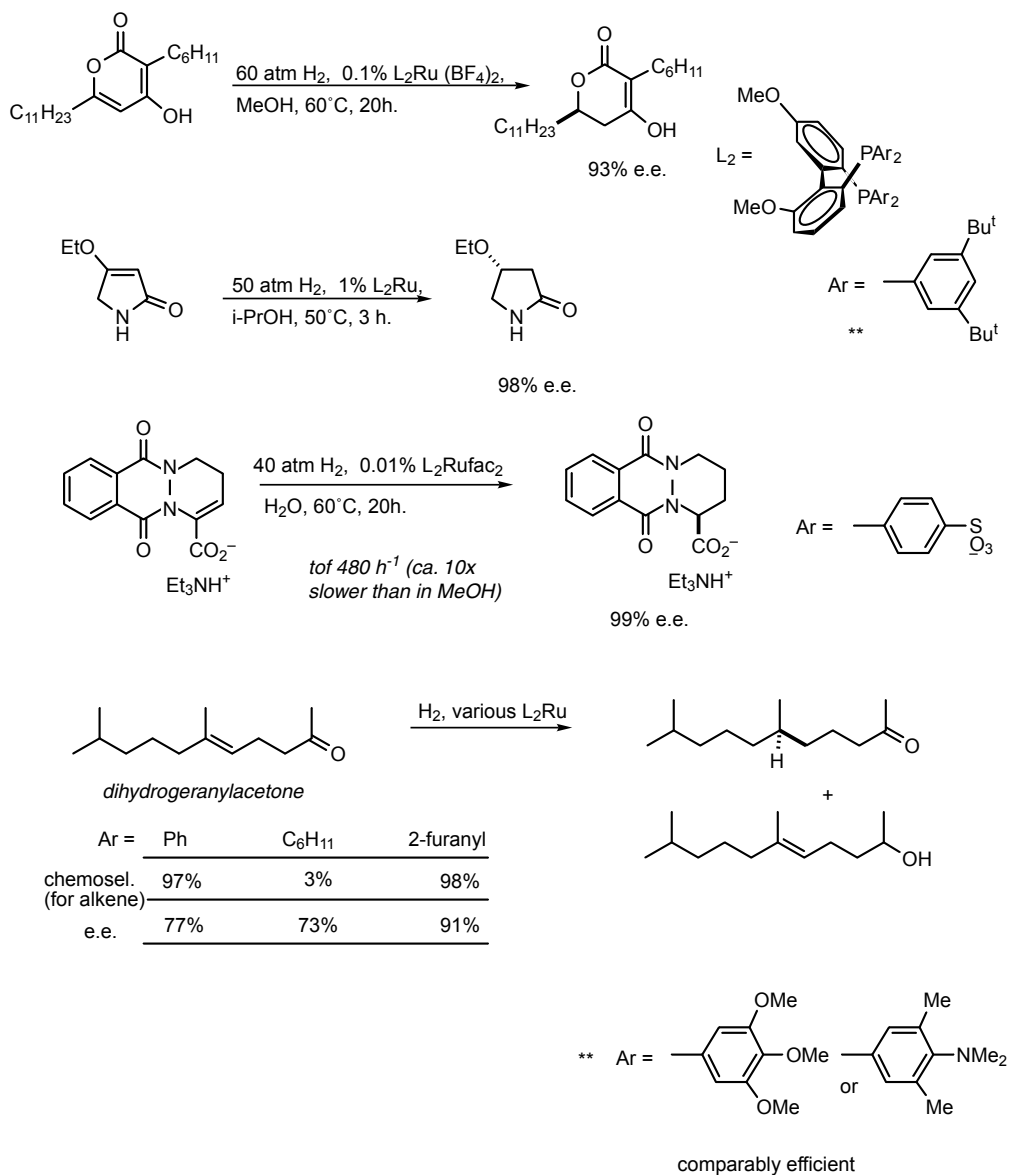


Fig. 41. Systematic variation of biaryl ligands to provide the optimum solution for diverse problems in asymmetric hydrogenation

optimized cases are shown, and it will be seen that significantly different ligand structures pertain for different types of reactant. Taking first dihydrogeranylacetone, where considerations of both chemoselectivity and enantioselectivity apply: the optimum case is for hydrogenation with the difurylphosphine analogue of MeOBIPHEMP, where 91% ee and 98% chemoselectivity is observed. For the dicyclohexylphosphine analogue, the chemoselectivity is 97%. but now towards reduction of the carbonyl group!

A contrast is provided by the hydrogenation of the α -pyrone shown, a precursor in the Roche tetrahydrolipstatin synthesis. Here attempted hydrogenation with BINAP-Ru under standard conditions provides less than 1% reaction. The secret is to employ bulky, electron-rich aryl substituents at phosphorus; several give comparable results but the highest enantioselectivity is provided by the 3,5-di-*tert*-butylphosphine. The same ligand provides high enantioselectivity for the Ru-catalyzed reduction of the enol ether of 3-ketopyrrolidone.

As part of the same program, a *para*-sulfonated aryl residue was prepared for the purpose of optimizing catalysis in aqueous solution. This was applied in the hydrogenation of the diketopyrazine shown in Fig. 41, present as its triethylammonium salt. Reaction occurred about ten times more slowly than appropriate controls performed in MeOH, but still at a practical rate. In contrast to most other examples of water-based asymmetric hydrogenation where the ee is substantially lowered relative to comparable reactions in organic solvents, this occurs in >99% ee. There is a marked counterion effect on the rate (Na⁺ being slower) but not on the enantioselection. Finally in this section, the enantioselective reduction of a non-conjugated unsaturated ketone is very dependent on the substituents at phosphorus in the MeO-BIPHEMP ligand employed, with optimum results obtained for the 2-furyl derivative.

Modification of the BINAP framework provides a viable alternative approach to structural fine tuning. An ingenious synthesis which obviates the need for a resolving agent is to replace 2-naphthol with a derivative of the steroid equilenin (Fig. 42). The ligand is then isolated by a chromatographic separation of diastereomers, since the biaryl coupling reaction produces both the R_{ax} and S_{ax} forms [138]. Since the diphosphine is appreciably more electron-rich than is BINAP, the major ruthenium complex is a more active hydrogenation catalyst than the parent. Increased electron-rich ligation may be the reason for the success of heterocyclic analogues of BINAP in which the binaphthalene is replaced by a bi(benzothiofene) or biindolyl; the resulting Ru complexes are effective both in terms of enantioselectivity and reactivity [139]. Readers of the related Chapter 6.1 on the asymmetric hydrogenation of carbonyl compounds will encounter the Ru complexes of ligands in the DUPHOS family, where the ease of modification of the alkyl substituents of the phospholane enhances the power of the system, since it permits the easy optimization of ee for any substrate [140].

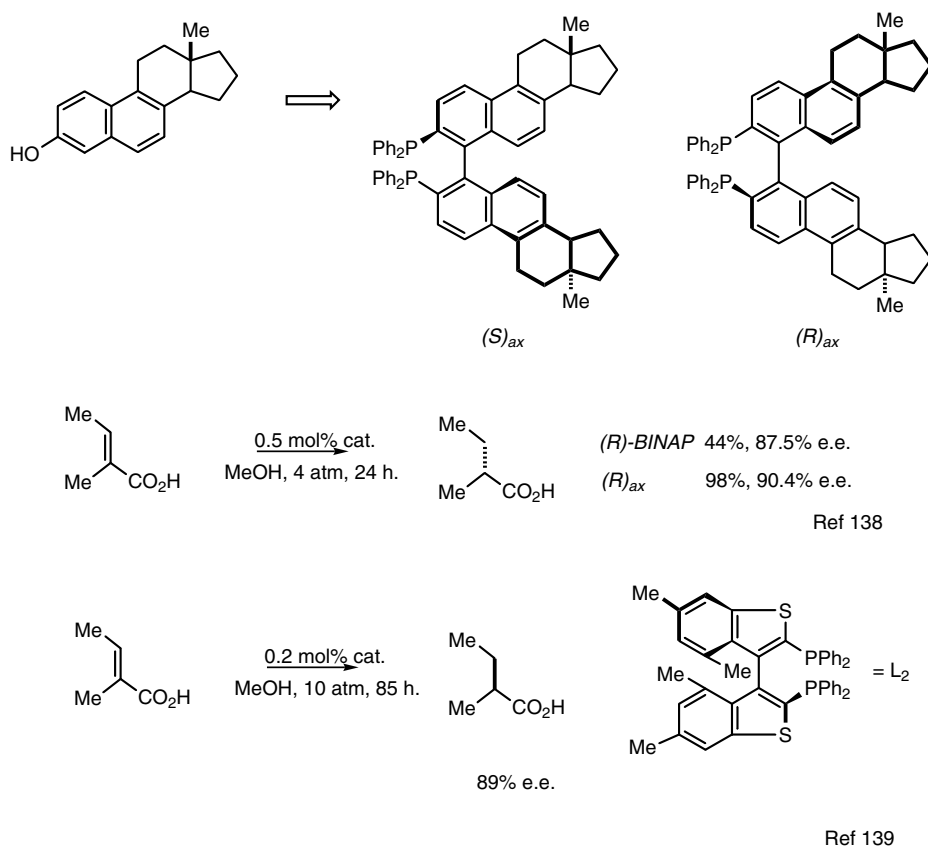


Fig. 42. Some newer ligands for Ru-catalyzed hydrogenation

5

Other Catalyst Systems

5.1

Homogeneous Catalysts

Only a few chiral catalysts based on metals other than rhodium and ruthenium have been reported. The titanocene complexes used by Buchwald et al. [109] for the highly enantioselective hydrogenation of enamines have already been mentioned in Section 3.4 (cf. Fig. 32). Cobalt semicorrin complexes have proven to be efficient catalysts for the enantioselective reduction of α,β -unsaturated carboxylic esters and amides using sodium borohydride as the reducing agent [156, 157]. Other chiral cobalt complexes have also been studied but with less success [11]. Recently, promising results have been obtained with phosphinooxazoline-

iridium complexes [158]. These catalysts gave moderate to excellent ees in the hydrogenation of unfunctionalized aryl-substituted olefins (see Chapter 5.2.6), allylic alcohols (94–96% ee), allylic acetates (91% ee) and ethyl β -methylcinnamate (84% ee).

5.2

Heterogeneous Catalysts

As in the hydrogenation of α - or β -ketoesters, the heterogeneous hydrogenation of polar alkenes at reactive metal surfaces is less developed than its homogeneous counterpart. The payoff for successful developments would be considerable, but there are obvious difficulties associated with the rational design of appropriate catalysts. The “off-the-shelf” character of existing chiral modifiers (e.g. cinchonidine, quinidine) indicates that there is a potential for progress through systematic chemical modification of the addend à la asymmetric dihydroxylation. In a typical result representing the current state of the field, *E*-carboxystilbene is hydrogenated by cinchonidine-modified Pd on titania in DMF/water with up to 72% ee [154], 52% ee in an independent study with Pd on alumina [155]. A competition between reactant, product and modifier for sites on the metal surface is demonstrated by the fact that the ee decreases with time, the more so as the concentration of cinchonidine is lowered.

6

Enantioselective Hydrogenation in Less Commonly Employed Environments

This chapter ends with a brief survey of efforts to extend asymmetric hydrogenation by operating in defined phases, unusual media, at surfaces or on solid supports. In part, this chemistry is driven by the demands for clean technology in fine chemicals manufacturing; the absence of solvent waste is an attractive goal. In addition, commercial considerations dictate that soluble metal catalysts should not contaminate the product. The operational criterion for impurity control is often delectability, and hence improvements in analytical techniques serve to increase the demand for complete catalyst recovery. The rarely realized prospect of a recyclable asymmetric catalyst serves to provide a further stimulus to developments in this area.

For further reading on topics not specifically discussed in this Section, see:

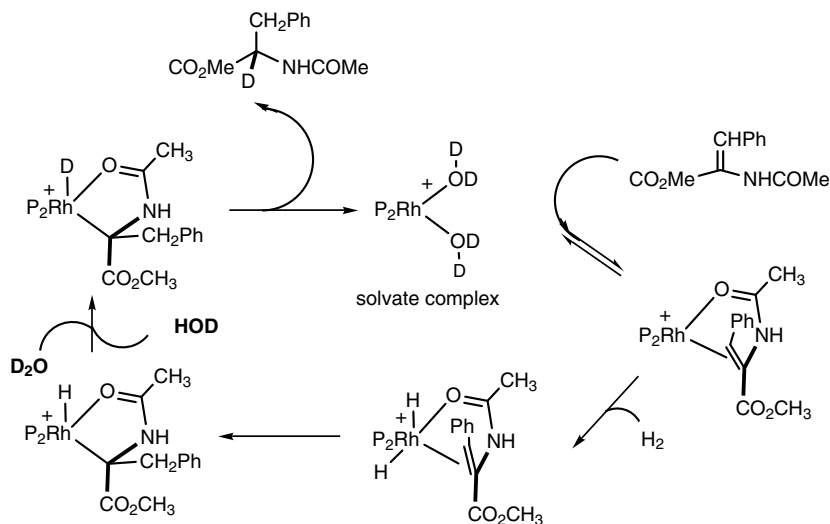
- Asymmetric hydrogenation with polymer-supported catalysts [141];
- Asymmetric hydrogenation in clays [142];
- Asymmetric hydrogenation in zeolites [143].

6.1

Hydrogenation in Water

A full issue of *Journal of Molecular Catalysis A* was devoted to “Catalysis in Water”. This included two general reviews, one devoted to industrial aspects [144,

145]. Changing the reaction medium from an organic solvent to water is not simply a matter of adjusting the solubility of reactant and catalyst; the mechanism may change significantly as well. For example, hydrogen is much less soluble in water than in typical organic solvents. For the catalyst in hydrogenation, the main device for enhancing solubility is sulfonation of one or several of the aryl residues of the phosphine ligand. But the simple analogue of Wilkinson's catalyst operates by a different mechanism. In conventional organic solvents under ambient conditions, the catalyst resting state is ClRhP_3 in equilibrium with ClRhH_2P_3 ; in water, the comparable resting state is HRhP_3 [146]. A more significant role for hydridic states is also emphasized by the reduction of enamides with a water-soluble asymmetric catalyst, as indicated in Fig. 43. The Rh-H intermediate has sufficient lifetime to undergo solvent exchange; up to 80% deuterium incorporation is observed for the product in D_2O [147]. Generally speaking, results with the water-soluble asymmetric catalysts are inferior to the corresponding reactions in organic solvents, at least insofar as ee is concerned. An example involves the conversion of BINAP into a water-soluble ligand by sulfonation; the product analyses reasonably for the tetrasulfonic acid and is suggested to be the product of phenyl ring sulfonation. But it would be truly remarkable if under the forcing reaction conditions there was no sulfonation of the naphthalene rings at C5, 6, and 7. In the hydrogenation of acetamidoacrylic acid, the reduced product was formed in 70% ee, which compared favorably with asymmetric hydrogenation involving the parent ligand in MeOH. The ap-



Rh-H / Rh-D exchange in D_2O is faster than alkylhydride elimination; transfer of the first hydrogen is faster than Rh-H / Rh-D exchange.

Fig. 43. Enantioselective hydrogenation in water

proach illustrates a general problem; in order to make the ligand water-soluble, sulfonation is necessary, but it is an unsatisfactory reaction because of the lack of chemo- and regioselectivity, and the difficulties of characterizing and separating the partially hydrogenated products [148].

An original approach to the problem has been to support the catalyst, in a polar phase, on an accessible surface. The conspicuous success in this area has come from Davis's work [149]; the basic principle is shown in Fig. 44. In this, the Ru-BINAP catalyst is adsorbed in a polar solvent phase on a porous glass bead. The substrate (and product) are in a solvent phase which is immiscible with the adsorbed phase, and in the initially described work the reaction was carried out in water, with concomitant reduction in turnover rate compared to the homogeneous variant. Strikingly better results were obtained when the supported phase was ethylene glycol, and here the efficiency rivaled that of the solution chemistry [150].

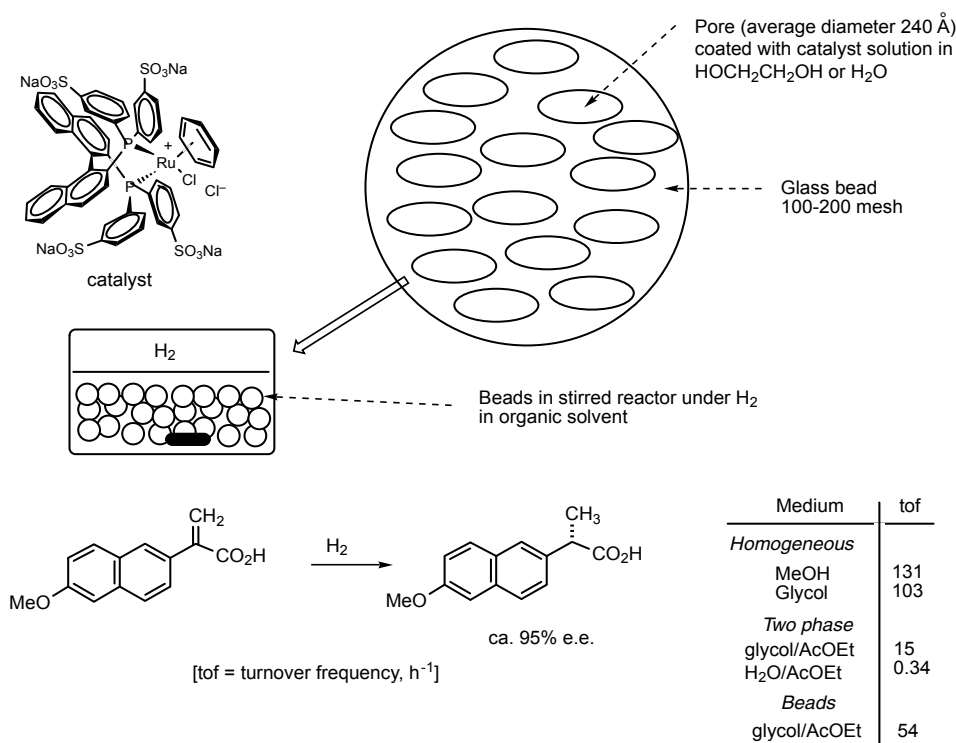


Fig. 44. Porous glass supported two-phase enantioselective hydrogenation

6.2 Hydrogenation in Supercritical Carbon Dioxide

The demonstration that supercritical (sc) CO₂ could be a medium for organic catalysis [151] generated considerable excitement, and turned attention to hydrogenation and particularly asymmetric hydrogenation in this environment. The results with DUPHOS catalysts rival those in conventional media such as MeOH [152]. Because supercritical phases are very non-polar there is a pronounced counter-ion effect; both the triflate and BR₄ (R=3,5-(CF₃)₂C₆H₃) salts of COD·Rh-DUPHOS are soluble in scCO₂, but there are significant differences in the observed ees (Fig. 45). Ruthenium complexes catalyze the asymmetric hydrogenation of α,β-unsaturated carboxylic acids in scCO₂[153].

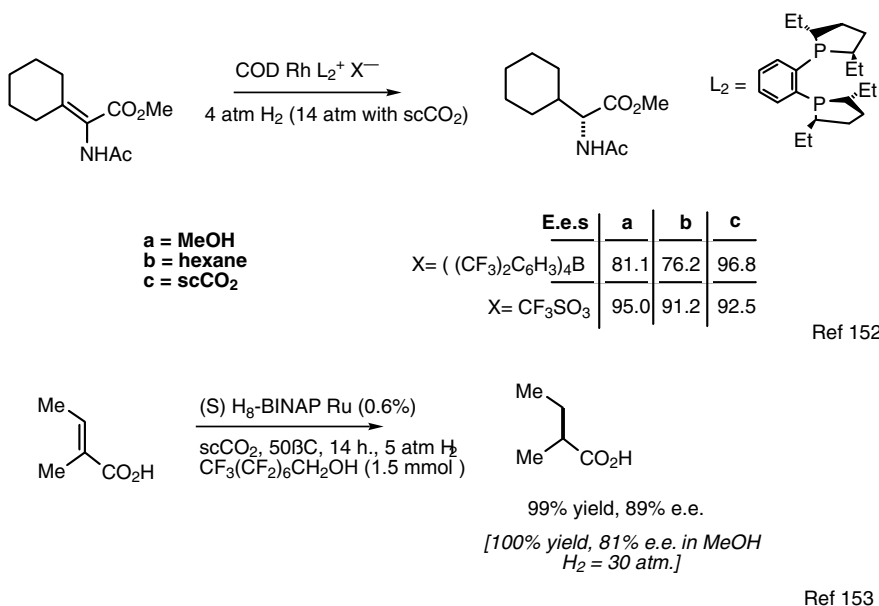


Fig. 45. Asymmetric hydrogenation in supercritical carbon dioxide

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Chapter 5.2

Hydrogenation of Non-Functionalized Carbon-Carbon Double Bonds

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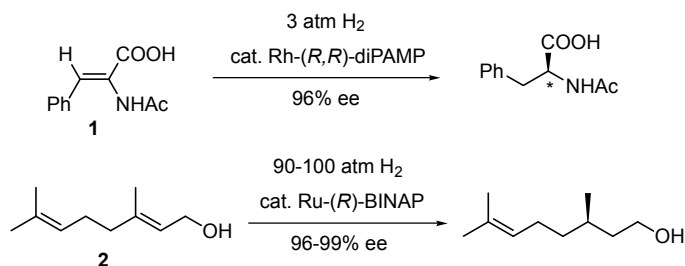
Keywords: Asymmetric hydrogenation, Simple olefins, Unfunctionalized olefins, Chiral metallocenes, Chiral phosphines, Rhodium, Ruthenium, Chiral titanocenes, Chiral zirconocene, Chiral cyclopentadienyllanthanides, Phosphanodihydrooxazole, Iridium, 2-Phenyl-1-butene

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1 Introduction

The highly developed enantioselective hydrogenation of prochiral *functionalized* alkenes using chiral phosphine complexes of ruthenium or rhodium as catalysts has become very common in academic laboratories as well as in industry [1]. As reviewed in the previous chapters, functionalized alkene substrates such as acetamide **1** or allylic alcohol **2** are efficiently hydrogenated in high yields with very high enantioselectivities [2, 3]. The additional coordinating sites in these substrates contribute to more stereoselective reaction pathways.

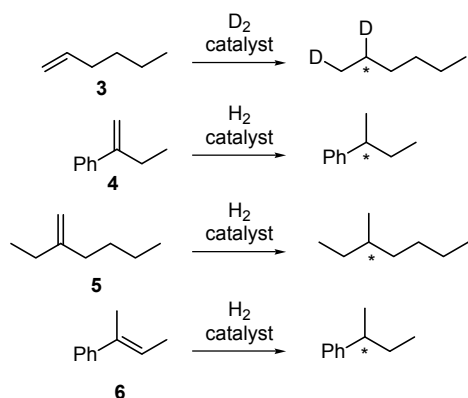
On the other hand, the enantioselective hydrogenation of prochiral *unfunctionalized* substrates has been much less developed and generally furnishes lower enantioselectivities. These *unfunctionalized* substrates often contain a phenyl group in the vicinity of the reactive double bond but do not contain additional coordinating heteroatoms. One can argue that catalysts which can enantioselectively hydrogenate such substrates would be the most general asymmetric hydrogenation catalysts for synthetic applications in different classes of molecules.



The development of highly selective hydrogenation catalysts is impeded in several ways by the very nature of these unfunctionalized substrates. With no precoordination or electronic effects (other than perhaps those involving phenyl groups), the prochiral faces of these substrates must be differentiated through non-bonding, sterically-based interactions as the substrate approaches the active catalytic site and undergoes the stereodifferentiating reaction. Other catalytic reactions, most notably epoxidation [4] and dihydroxylation [5], have recently been shown to overcome the problem of achieving enantioselectivity with these unfunctionalized substrates. But in these reactions, the most selective substrates are often terminal or 1,2-disubstituted alkenes which are functionalized to create new stereocenters and the enantioselectivity can be readily measured by chiral HPLC or chiral GC methods. In order to create new stereocenters in the analogous hydrogenation of, for example, 1-hexene (3), deuterium gas must be used to create a stereocenter. The determination of the enantiomeric purity of the saturated alkane is then a problem in that chiral chromatographic separations do not exist for such substrates. The enantiomeric purity must then be based on the difficult comparison of optical rotations for deuterium labeled compounds with very low specific rotations [6]. The difficulty in determining the stereochemical outcome of the deuteration of terminal alkenes has surely limited the study of this most promising class of substrate. Other types of substrates which have been investigated are unsymmetrically 1,1-disubstituted olefins such as 2-phenyl-1-butene (4) and 2-ethyl-1-hexene (5), and trisubstituted alkenes such as (*E*)-2-phenyl-2-butene (6). Hydrogenation of these substrates creates a new stereocenter without the need for using deuterium gas, but the problem of determining the stereochemical purity of these hydrocarbons remains; without a chromatographic handle these compounds are in most cases not resolved by GC or HPLC methods and the comparison of optical rotations is relied upon [7]. While these analytical difficulties may have slowed the pace of development in this field, some progress has been made and it will be covered in the following sections.

This chapter reviews the development of enantioselective hydrogenation of unfunctionalized alkenes using five types of catalysts:

- chiral phosphines with group 8 metals,
- chiral group 4 reduced metallocene complexes;
- chiral group 4 cationic metallocene complexes;



- chiral cyclopentadienyllanthanide complexes;
- and chiral iridium-phosphanodihydrooxazole complexes.

While the order in which these different systems is discussed roughly follows the historical order of their introduction, each type of complex is undergoing continual development.

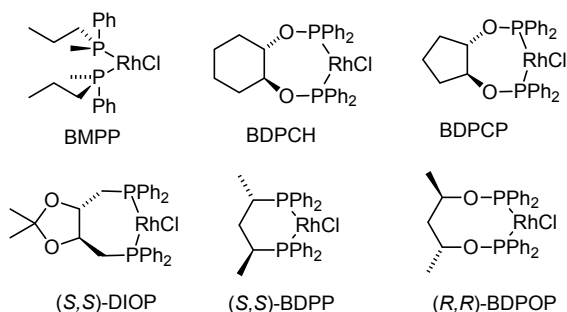
2 Chiral Phosphine/Group 8 Complexes

One of the first examples of the enantioselective hydrogenation of non-functionalized alkenes was the use of a bis(methylphenyl-*n*-propylphosphine) (BMPPP) complex of rhodium to catalyze the reduction of 2-phenyl-1-butene. The enantioselectivity obtained with this non-chelating phosphine was rather low (7% ee, Table 1, entry 1) [8]. As summarized in Table 1 several chiral chelating diphosphine rhodium complexes have subsequently given moderate selectivity in the enantioselective hydrogenation of the benchmark substrate, 2-phenyl-1-butene (entries 2–6) [9, 10, 11]. The best result (65% ee) has been obtained using *trans*-1,2-bis(diphenylphosphinoxy)cyclopentane [9]. Typical conditions for these hy-

Table 1. Enantioselective hydrogenation of 2-phenyl-1-butene

Entry	Catalyst	mol % cat.	% ee	Config.	Reference
1	(<i>S</i>)-BMPP-RhCl	0.5	7	S	[8]
2	(<i>S,S</i>)-DIOP-RhCl	n.a.	25	R	[9]
3	(<i>S,S</i>)-BDPCH-RhCl	n.a.	33	R	[9, 10]
4	(<i>S,S</i>)-BDPCP-RhCl	n.a.	60	R	[9]
5	(<i>S,S</i>)-BDPP-RhCl	1.0	54	S	[11]
6	(<i>R,R</i>)-BDPOP-RhCl	1.0	27	S	[11]

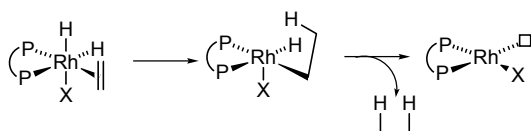
drogenations were 1 atm H₂, 100:1:2 substrate:rhodium:ligand ratio, 30 °C, 20 h [11].



An extensive study utilizing metal complexes of (*R*)-BINAP examined variations of substrate, metal, anionic ligand, hydrogen pressure and solvent [12]. Some of these results for alkenes **4** and **7–11** are presented in Table 2. Both the ruthenium diacetate and rhodium chloride complexes gave low enantioselectivity (9% ee and 29% ee, respectively) in the hydrogenation of 2-phenyl-1-butene under fairly forcing conditions (Rh: substrate:Rh:ligand 120:1:2.2, 30 °C, 25 atm H₂, 70 h; Ru: 250:1:1 substrate:Ru:ligand, 30 °C, 100 atm H₂, 38 h). Increasing the size of the alkyl group in 1-alkyl-1-phenylethylenes from ethyl to isopropyl to *tert*-butyl resulted in a gradual improvement of the enantioselectivity in the case of the ruthenium complex (entries 1–3), while the rhodium complex changed facial preference in going from the ethyl to the isopropyl substituted substrate (entries 7 and 8). Several exocyclic substrates were examined with generally better enantioselectivities being found (entries 4–6 and 10–12). Evidence for competing olefin isomerization followed by hydrogenation was cited as a cause of the

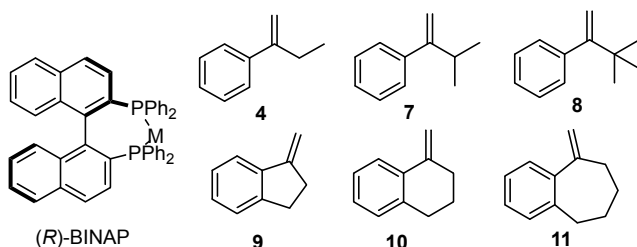
Table 2. Enantioselective hydrogenation using BINAP complexes [12]

Entry	Metal	mol % cat	Substrate	% ee	Config.	Method
1	Ru(II)	0.4	4	9	R	rotation
2	Ru(II)	0.4	7	16	R	rotation
3	Ru(II)	0.4	8	30		GC
4	Ru(II)	0.4	9	78	S	rotation
5	Ru(II)	0.4	10	69	S	GC
6	Ru(II)	0.4	11	23		GC
7	RhCl	0.8	4	29	S	rotation
8	RhCl	0.8	7	35	R	rotation
9	RhCl	0.8	8	40		GC
10	RhI	0.8	9	66	S	rotation
11	RhI	0.8	10	80	S	GC
12	RhI	0.8	11	44		GC



Scheme 1

lower enantioselectivities observed with the ruthenium complex. The rhodium complexes, while less reactive, gave higher selectivities, up to 80% ee in the hydrogenation of 1-methylenetetralin.



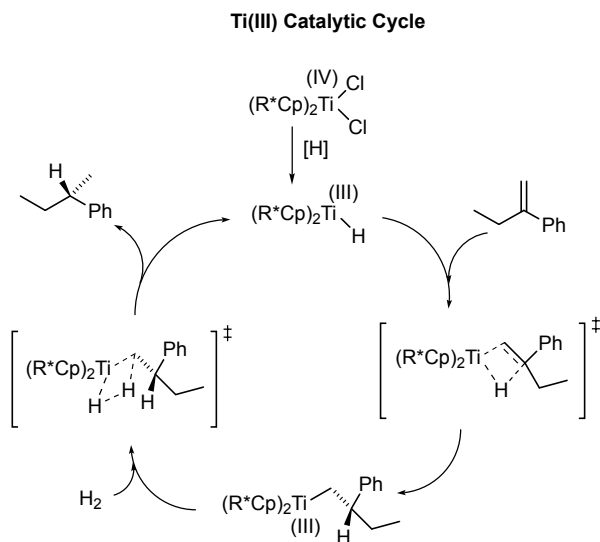
Since some of the hydrogenation products of the exocyclic alkenes could be resolved by GC on chiral columns in less than 40 min, a systematic study of enantioselectivity as a function of reaction conditions was feasible. The selectivities were found to be sensitive to H_2 pressure, anionic ligand, and solvent. For example in the rhodium-catalyzed hydrogenation of 1-methylenetetralin (**10**), changing the anionic ligand from iodide (80% ee) to chloride (36% ee) greatly diminished the enantioselectivity. The postulated mechanism for hydrogenations using these complexes involves the hydrogen transfer shown in Scheme 1 [12].

3

Chiral Group 4 Reduced Metallocene Complexes

The most widely studied approach for the enantioselective hydrogenation of non-functionalized alkenes has been the use of reduced chiral titanocene complexes. The initial promising demonstration utilized bis(menthylcyclopentadienyl)titanium dichloride (**12**) in the presence of Red-Al to catalyze the hydrogenation of 2-phenylbutene in 23% ee (determined by optical rotation) [13, 14, 15]. Two mechanisms have been postulated for hydrogenations involving reduced titanocene catalysts: a Ti(II)/Ti(IV) cycle and the more commonly invoked Ti(III) cycle shown in Scheme 2.

Several additional titanocene catalysts have been examined for the hydrogenation of 2-phenylbutene [16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. The results using titanocene dichlorides **12**–**19** are summarized in Table 3. The enantioselectivity of these hydrogenations has been determined by comparisons of optical rotation with two different literature values (22.7° [28] and 28.4° [7]) for the

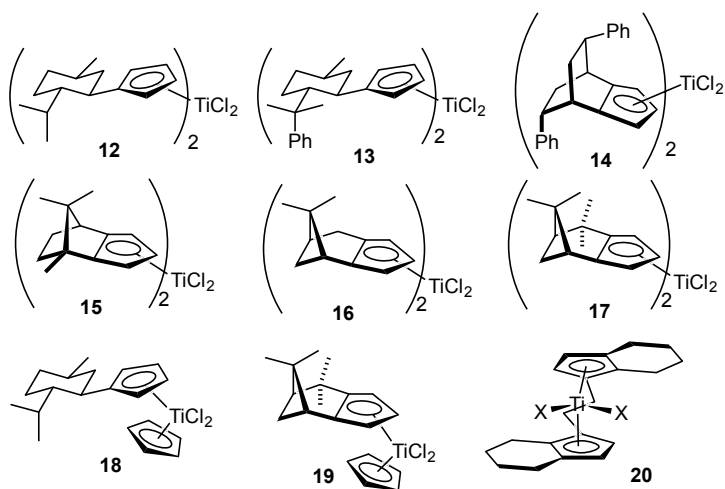
**Scheme 2****Table 3.** Enantioselective hydrogenation of 2-phenylbutene

Entry	Catalyst	mol % cat.	Temp (°C)	% ee	Reference
1	12	1.3	5	23	[15]
2	14	1.0	-75	77 ^a	[16]
3	13	1.0	20	27 ^a	[18]
4	15	1.0	-20	28 ^a	[18, 27]
5	16	1.0	-20	7 ^a	[27]
6	17	1.0	-20	56 ^a	[27]
7	18	1.3	5	18	[15]
8	19	1.0	-20	20 ^a	[27]

^aLiterature values were adjusted using $[\alpha]_D=28.4^\circ$

maximum rotation of independently synthesized, presumably enantiomerically pure 2-phenylbutane. The higher value has recently been confirmed [29], and in order to facilitate comparisons, all of the enantioselectivity data in Table 3 have been calculated using the higher rotation as a common basis. The most selective reduced titanocene catalyst was formed by the reduction of the diphenyl-BCOCp complex **14** and gave an adjusted value of 77% ee for the hydrogenation of 2-phenylbutene at -75 °C (entry 2) [16]. Paquette has published a particularly thorough study of terpene-derived titanocene catalysts [27]. Two general conclusions were drawn in this study. The first is that titanocenes having two substituted cyclopentadienyl ligands are generally more selective than those having

one cyclopentadienyl ligand and one chiral, substituted cyclopentadienyl ligand (compare entries 1 and 7, 6 and 8). The second trend is that increasing substitution on a carbon atom attached to the cyclopentadienyl ligand increases enantioselectivity (compare entries 5 and 6). The highest enantioselectivity (adjusted to 56% ee) using a terpene-derived titanocene was achieved using complex **17** [27]. The corresponding hydrogenation of 2-phenyl-1-butene using reduced zirconocene complexes was very slow (7–32 days) and often gave lower enantioselectivities [27].

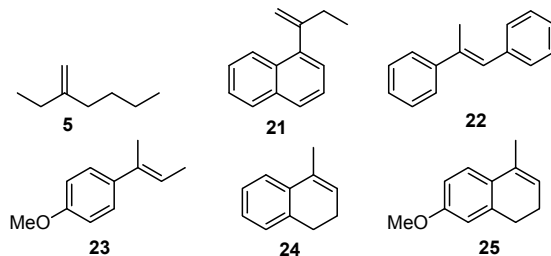


Unbridged bis(cyclopentadienyl)titanium dichlorides have also been used to reduce other 1,1-disubstituted alkenes. The BCOcP complex **14** achieved 41% ee in the hydrogenation of the non-phenyl-substituted 2-ethylhexene (**5**) (Table 4, entry 1) [16]. Paquette has examined several terpene-derived titanocene complexes for the reduction of 2-(1-naphthyl)-1-butene (**21**); the best result (61% ee) was obtained with complex **17** (entry 2) [27]. A number of trisubstituted arylalkenes **22–25** have been hydrogenated under high pressure and often at long reaction times using high catalyst ratios (2000 psi H₂, up to 184 h with 5 mol % catalyst) using a reduced form of Brintzinger's bis(tetrahydroindenyl)titanium

Table 4. Enantioselective hydrogenation of various alkenes

Entry	Catalyst	mol % cat.	Substrate	% ee	Reference
1	14	1.0	5	41	[15]
2	17	1.0	21	61	[27]
3	20	5	22	>99	[30]
4	20	5	23	95	[30]
5	20	5	24	83	[30]
6	20	5	25	93	[30]

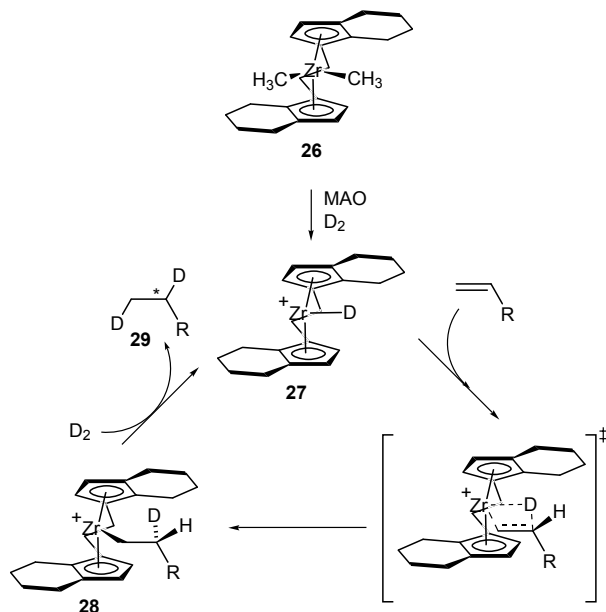
binaphtholate (**20**). In many cases the enantioselectivity was above 90% ee (entries 3–6) [30]. The remote methoxy group in entries 4 and 6 was incorporated to facilitate analytical chromatographic separation of the resultant enantiomers. It is clear that the *ansa*-metallocene **20** is highly selective for this type of hydrogenation, although the usual 5 mol % catalyst loading indicates impractical catalyst activity.



4

Chiral Group 4 Cationic Metallocene Complexes

Cationic zirconocene complexes can catalyze the hydrogenation of alkenes, a property which has been used to terminate olefin polymerization [31]. As shown in Scheme 3, dimethylzirconocene complex **26** can be activated by methylalumox-



Scheme 3

ane (MAO) in the presence of deuterium gas to form the purported cationic complex **27** [32, 33]. Insertion of an alkene into the zirconium-deuterium bond leads to the alkyl complex **28** with the creation of a new stereocenter. Alkyl complex **28** then reacts with D_2 to reform the initial complex **27** with the elimination of the dideuterated product **29**. The facial preference of terminal alkenes in polymerizations catalyzed by **26** is opposite to the facial preference observed in their hydrogenation by **26**. This result has been rationalized by postulating that the approach of the alkene to the active site is thought to occur from the front as shown in Scheme 3, rather than from the side as in polymerizations [33].

The use of the dimethyl derivative **26** was required; the corresponding zirconocene dichloride failed to catalyze the hydrogenation under these conditions. The dimethyl complex **26**, however, is quite active, converting 1750 equivalents of styrene to 1,2-dideuteroethylbenzene within 29 h at room temperature at pressures below 17 atm D_2 in 65% ee [33]. Pentene was deuterated (10 atm D_2) in 23% ee with some oligomer and polymer formation. When the D_2 pressure was lowered, more polymer formed. 2-Phenyl-1-butene was hydrogenated using **26** in 36% ee [33]. Buchwald concomitantly reported similar catalytic hydrogenation results [34].

5

Chiral Cyclopentadienyllanthanide Complexes

Marks has developed a class of remarkably effective catalysts for the enantioselective hydrogenation of 2-phenyl-1-butene [29, 35, 36, 37]. Incorporation of a menthyl chiral auxiliary on the 3-position of an *ansa*-bis(cyclopentadienyl) ligand leads to two diastereomeric complexes of samarium **30** [29]. Similarly, the neomenthyl-substituted complexes **31** can be formed and isolated as pure diastereomers. These complexes are very active catalysts for the hydrogenation of 2-phenyl-1-butene under mild conditions (25 °C, 100–1000:1 substrate:catalyst, 760 mm H_2 , 5 min) [29]. As shown in Table 5, as the lanthanide metal in neomenthyl-substituted complexes **31** becomes smaller, the enantioselectivity decreases from 58% ee (La) to 10% ee (Lu) (entries 1–5). Using a 70:30 mixture of the diastereomers **30a** and **30b** of the menthyl-substituted samarium complex the good enantioselectivity at 25 °C (64% ee) becomes superb at –80 °C (96% ee) (entries 6–10). This same mixture of **30a/30b** catalyzed the deuteration of styrene at 25 °C in 72% ee.

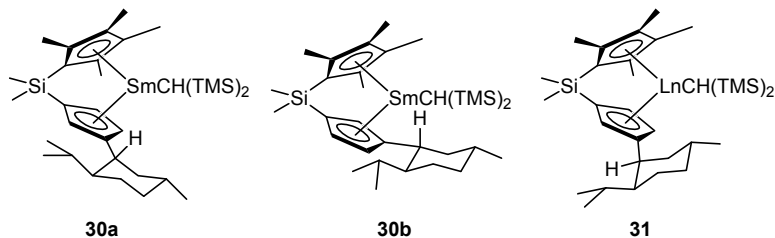


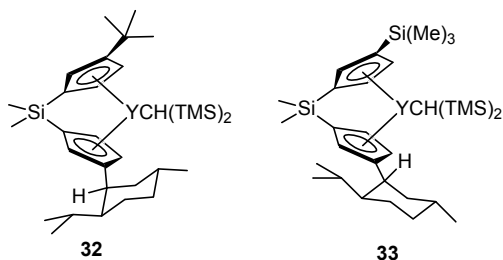
Table 5. Enantioselective hydrogenation of 2-phenyl-1-butene [29]

Entry	Catalyst	mol % cat.	Temp (°C)	% ee
1	31 (Ln=La)	0.6–0.8	25	58
2	31 (Ln=Nb)	0.6–0.8	25	40
3	31 (Ln=Sm)	0.6–0.8	25	19
4	31 (Ln=Y)	0.6–0.8	25	12
5	31 (Ln=Lu)	0.6–0.8	25	10
6	30a/30b (70:30)		25	64
7	30a/30b (70:30)	0.6–0.8	0	71
8	30a/30b (70:30)	0.6–0.8	–30	79
9	30a/30b (70:30)	0.6–0.8	–80	96

Table 6. Enantioselective hydrogenation of various alkenes [36, 37]

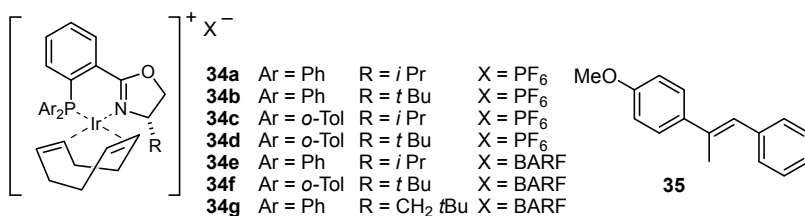
Entry	Catalyst	mol % cat.	Substrate	Temp (°C)	% ee
1	32	0.1–1.0	2-phenyl-1-butene	22	26
2	32	0.1–1.0	styrene	22	3
3	32	0.1–1.0	1-pentene	0	55
4	33	0.1–1.0	2-phenyl-1-butene	22	25
5	33	0.1–1.0	2-ethyl-1-hexene	22	<1
6	33	0.1–1.0	styrene	22	3
7	33	0.1–1.0	1-pentene	0	16

Two other related *ansa*-bis(cyclopentadienyl)lanthanide complexes have been examined for the hydrogenation of various unfunctionalized alkenes [36, 37]. Some of the data is presented in Table 6 using the *tert*-butyl-substituted neomenthyl yttrium complex **32** [36], and the trimethylsilyl-substituted menthyl yttrium complex **33** [37]. Poor to moderate enantioselectivities were observed with these catalysts.



6 Chiral Iridium-Phosphanodihydrooxazole Complexes

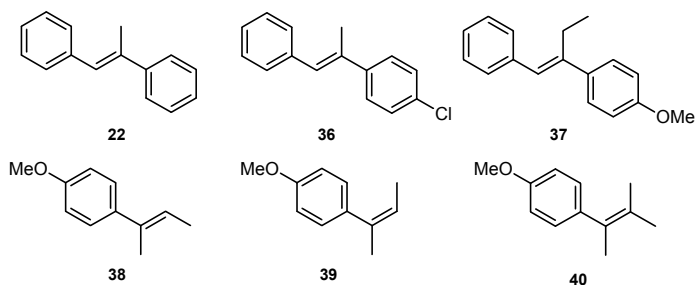
Pfaltz has recently reported a new class of chiral phosphanodihydrooxazole-iridium catalysts **34** for the enantioselective hydrogenation of imines [38]. Based on Crabtree's success using similar achiral catalysts for the hydrogenation of normally unreactive tri- and tetrasubstituted alkenes [39], Pfaltz has now found that chiral phosphanodihydrooxazole-iridium complexes **34a–g** will hydrogenate phenyl-substituted alkenes with high enantioselectivity [40]. As shown in Table 7, the trisubstituted alkene **35** can be hydrogenated under mild conditions (50 bar H₂ at 23 °C) with superior results using complex **34f** (333:1 substrate to catalyst, >99% conversion and 98% ee, entry 6).



These complexes, especially **34f**, have been successfully applied as enantioselective hydrogenation catalysts for a range of other trisubstituted and even tetrasubstituted alkenes, as summarized in Table 8 [40]. Of important practical consideration is that the enantioselectivity for each of the hydrogenation products was determined by chiral HPLC or GC methods. For the trisubstituted alkenes, substrate to catalyst ratios of 1000:1 to 100:1 can be used to give high conversions. With two of the substituents as aryl groups, the enantioselectivities were at least 95% ee (entries 1–3). With only one aryl group on the substrates **38** and **39**, the enantioselectivities were lower (entries 4 and 5). Although the activity was somewhat lower with the tetrasubstituted alkene **40**, the respectable 81% ee indicates that this catalyst system is still the most promising for such hindered substrates.

Table 7. Hydrogenation of **35** using complexes **34a–f** [40]

Entry	Complex	mol % cat.	Conv. [%]	% ee
1	34a	4	78	75
2	34b	4	98	90
3	34c	4	>99	91
4	34d	4	57	97
5	34e	0.3	>99	70
6	34f	0.3	>99	98

**Table 8.** Hydrogenation of tri- and tetrasubstituted alkenes [40]

Entry	Catalyst	mol % cat.	Substrate	% conv.	% ee
1	34f	0.1	22	>99	97
2	34f	0.5	36	98	95
3	34f	0.3	37	97	95
4	34f	0.3	38	>99	61
5	34f	1.0	39	97	42
6	34g	2	40	>99	81

In summary, the hydrogenation of non-functionalized olefins has not consistently reached the high level of enantioselectivities observed with many functionalized substrates. In some cases, however, chiral titanocenes, chiral lanthanide complexes, and now chiral iridium phosphanodihydrooxazole complexes can achieve superior selectivities. With the establishment of a limited number of unfunctionalized alkane products which can be resolved by chiral GC or HPLC methods, the pace of research in this area could be accelerated.

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Chapter 6.1

Hydrogenation of Carbonyl Groups

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Keywords: Asymmetric hydrogenation, Asymmetric transfer hydrogenation, BINAP, Chiral alcohols, Chiral amines, Chiral phosphines, Functionalized ketones, Homogeneous catalysts, Simple ketones

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1

Introduction

Asymmetric hydrogenation and transfer hydrogenation of ketones are ideal means of synthesis of chiral secondary alcohols in view of the operational sim-

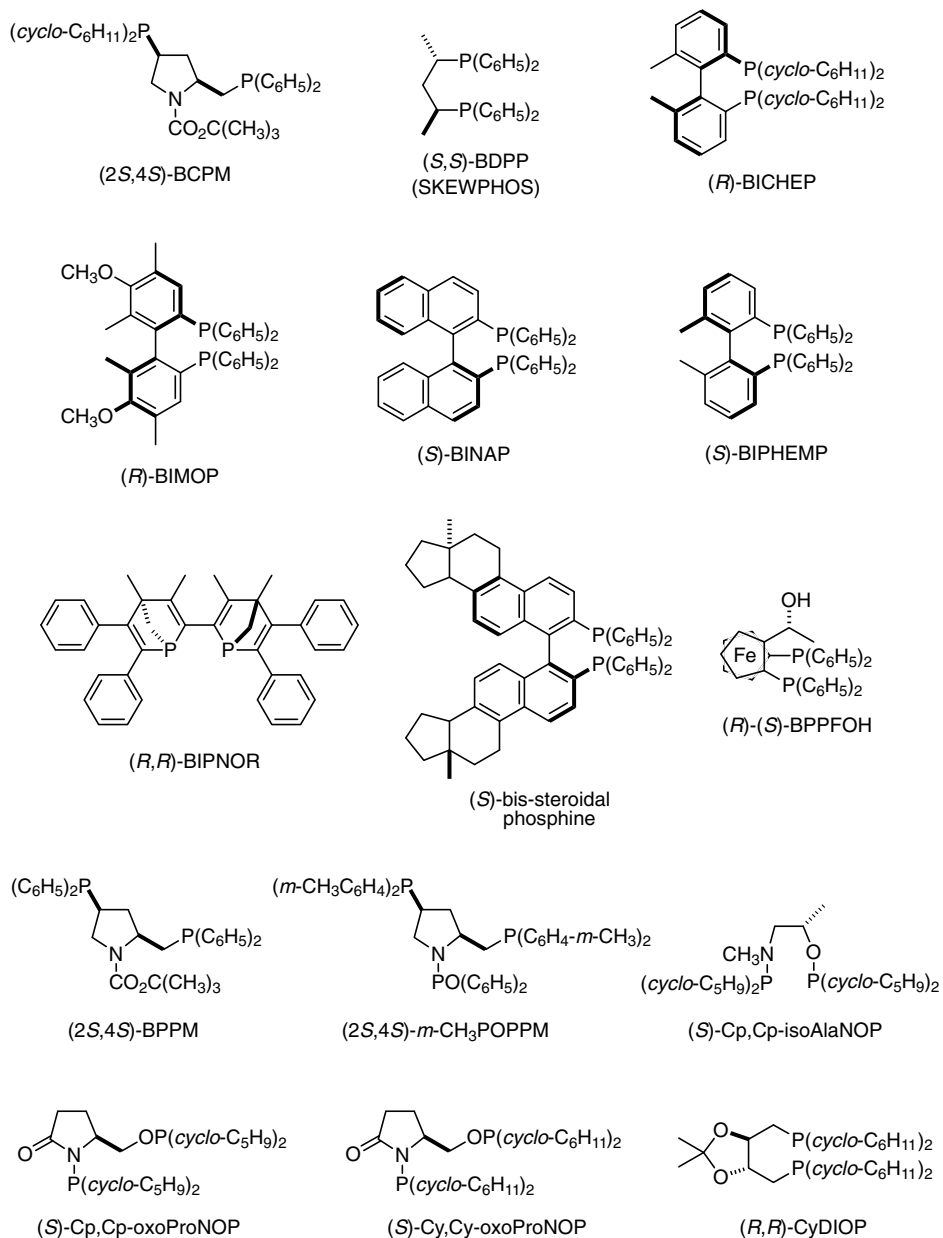


Fig. 1. Diphosphine ligands (in alphabetical order)

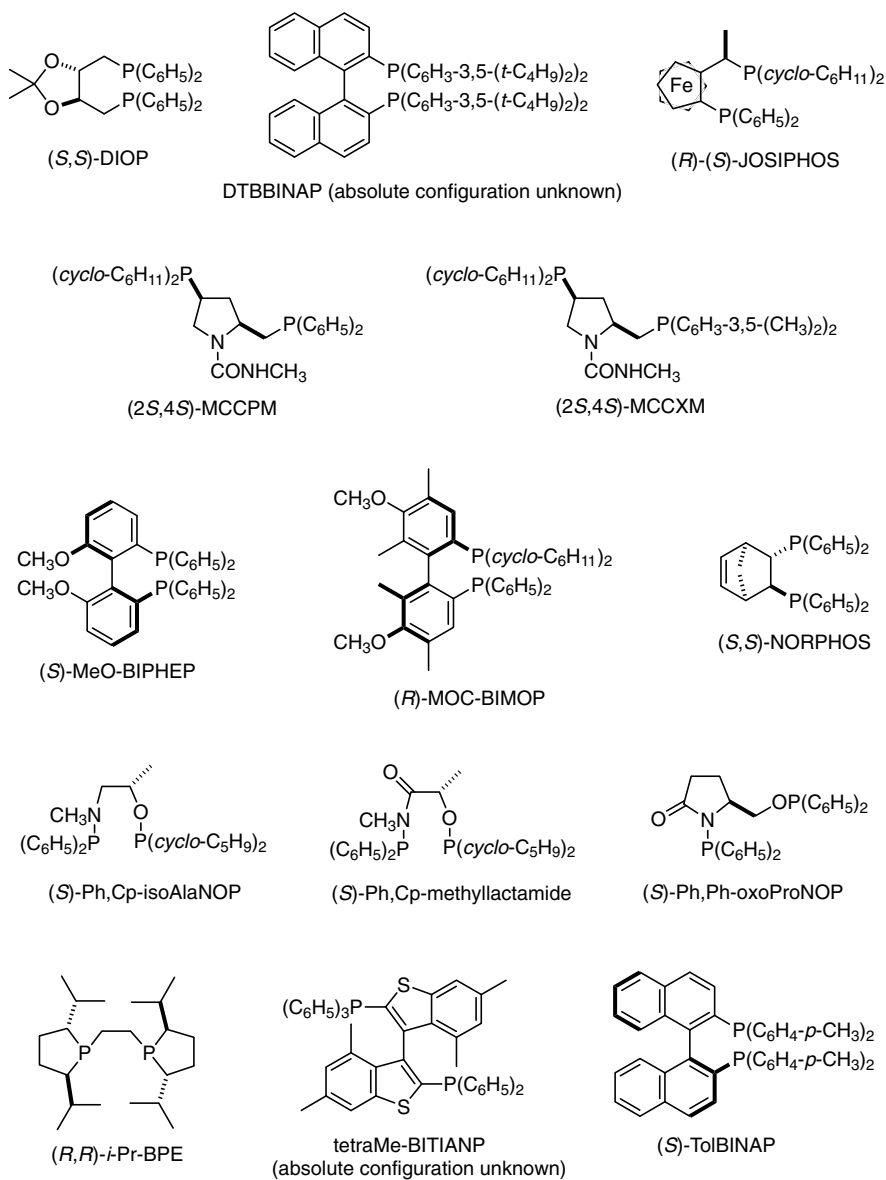


Fig. 1. (continued)

plicity, environmental friendliness, and economics [1, 2]. Chirally modified metal complexes repeatedly activate molecular hydrogen and deliver hydrogen atom(s) to the C=O linkage to give optically active alcohols [1]. Transfer hydrogenation employs stable organic molecules as hydrogen donors in place of hydrogen [2]. Recently, some highly active and enantioselective homogeneous catalysts have been developed for this purpose. General applicability to a wide range of substrates is desirable, particularly in research on biologically active substrates and advanced functional materials. However, none of the existing catalysts can be universal, because there exists a structurally diverse array of ketonic compounds. One has to choose appropriate metallic species and chiral ligands [3] as well as reaction conditions, depending on the substrates. Fig. 1 shows commonly used chiral diphosphines. The nitrogen-based chiral ligands 1 to 25 are classified according to the structural characteristics in Fig. 2, Fig. 3, Fig. 4, Fig. 5, Fig. 6.

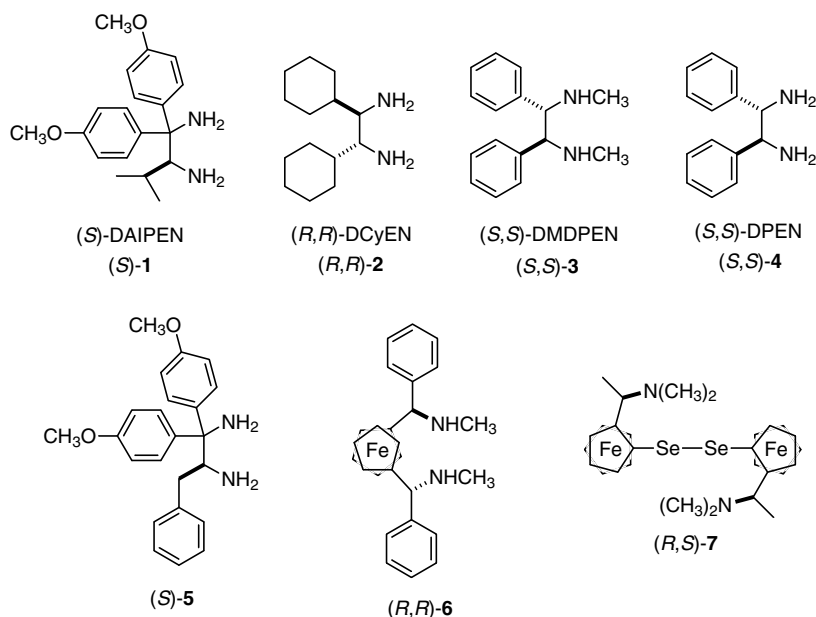


Fig. 2. Diamines

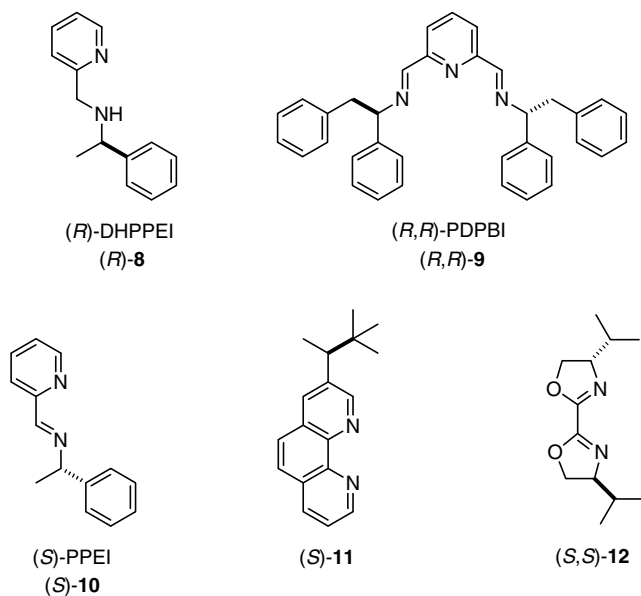


Fig. 3. Pyridines, phenanthrolines, and oxazoles

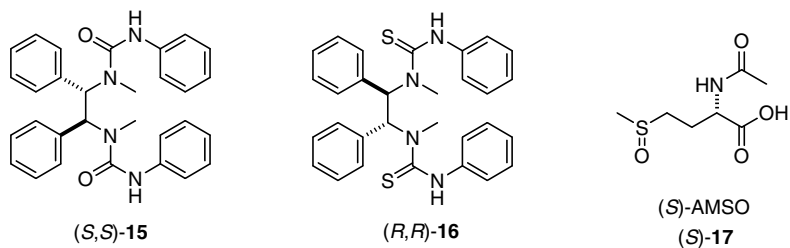
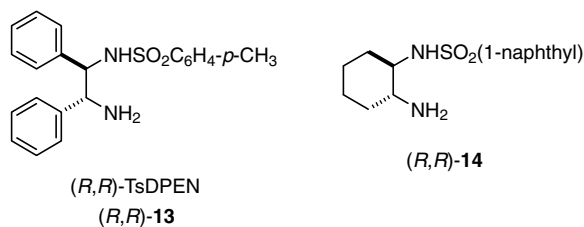


Fig. 4. *N*-Substituted (di)amines

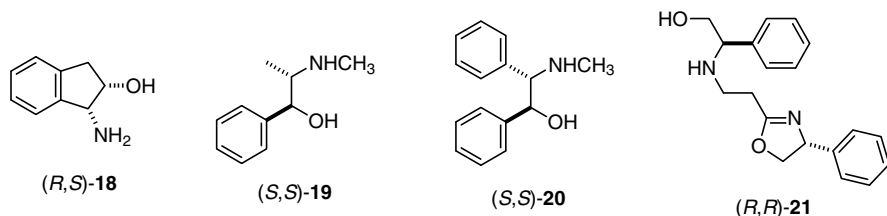


Fig. 5. Amino alcohols

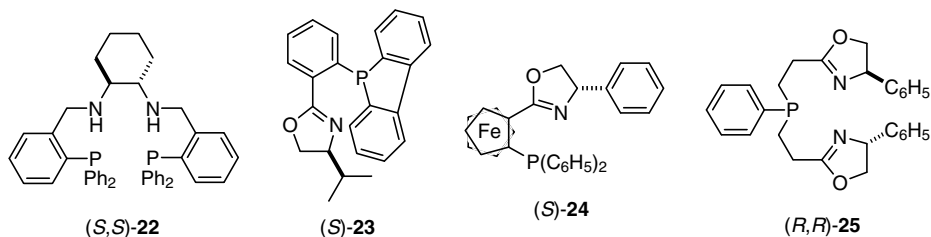


Fig. 6. Amino phosphines

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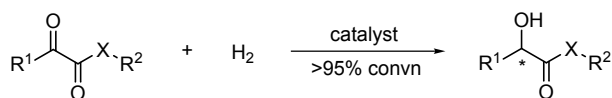
Hydrogenation of Functionalized Ketones

Asymmetric hydrogenation of ketones which have a heteroatom close to the carbonyl group has been extensively studied because of the synthetic significance of the corresponding alcoholic products [1]. The presence of the functionality accelerates and directs asymmetric hydrogenation, probably through interaction with Lewis acidic metals that effectively stabilizes the transition state. In recent years, a high catalytic activity and an excellent level of enantioselectivity have been achieved by means of chiral phosphine-Rh and -Ru complexes.

2.1

Keto Esters

α -Keto Esters and -amides can be transformed to chiral alcohols of high enantiomeric purity, as illustrated in Scheme 1. Hydrogenation of methyl pyruvate catalyzed by an MCCPM-Rh complex gives methyl lactate quantitatively in 87% ee [4]. The enantioface may be differentiated spatially by the chirally arranged diphenylphosphino group on the C2 methylene, while the reactivity would be enhanced by the electron-donating dicyclohexylphosphino group at the C4 position. A Rh complex with Cy,Cy-oxoProNOP shows an excellent enantioselectivity for hydrogenation of ethyl pyruvate and benzoylformamide derivatives [5]. A Ph,Cp-isoAlaNOP-Rh complex effects hydrogenation of α -keto amide



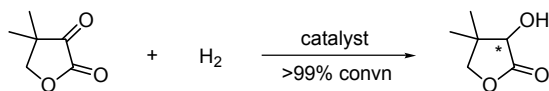
R ¹	X	R ²	Catalyst	Solvent	Pressure [atm]	ee [%]	Confign
CH ₃	O	CH ₃	(2 <i>S</i> ,4 <i>S</i>)-MCCPM-Rh	THF	20	87	R
CH ₃	O	CH ₃	(-)-tetraMe-BITIANP-Ru	CH ₃ OH	97	88	S
CH ₃	O	C ₂ H ₅	(<i>S</i>)-Cy,Cy-oxoProNOP-Rh	toluene	50	95	R
C ₆ H ₅	O	CH ₃	(<i>S</i>)-MeO-BIPHEP-Ru	CH ₃ OH	20	86	S
C ₆ H ₅	O	CH ₃	(<i>R</i>)-BICHEP-Ru	C ₂ H ₅ OH	5	>99	S
C ₆ H ₄ - <i>p</i> -CH ₃	O	CH ₃	(<i>S</i>)-BINAP-Ru	CH ₃ OH	100	93	S
(CH ₂) ₂ C ₆ H ₅	O	C ₂ H ₅	(<i>S,S</i>)-NORPHOS-Rh	CH ₃ OH	99	96	S
C ₆ H ₅	NH	CH ₂ C ₆ H ₅	(<i>S</i>)-Ph,Cp-isoAlaNOP-Rh	toluene	1	88	S
C ₆ H ₅	NH	CH ₂ C ₆ H ₅	(<i>S</i>)-Cy,Cy-oxoProNOP-Rh	toluene	50	95	S
C ₆ H ₅	NH	CH ₂ C ₆ H ₅	(<i>S</i>)-BICHEP-Ru	CH ₃ OH	40	96	R

Scheme 1

derivatives in 88% optical yield [6]. Hydrogenation of ethyl 2-oxo-4-phenylbutanoate catalyzed by a NORPHOS-Rh complex gives an alcohol in 96% ee [7]. Ru complexes with a C₂-chiral diphosphine ligand are also successfully employed. Although hydrogenation of methyl pyruvate with a neutral BINAP-Ru complex proceeds in an optical yield of only 83% [8], the cationic complex with aqueous HBF₄ gives a 93% optical yield for reaction of methyl *p*-methylbenzoylformate [9]. A BICHEP-Ru complex is effective for hydrogenation of methyl benzoylformate and the amide derivative giving the corresponding mandelic products in >99% ee [10]. An electron-rich phosphine function plays key roles for the high enantioselectivity. The MeO-BIPHEP ligand having methoxy groups at the C6 and C6' positions of the biphenyl ring is also effective [11]. A Ru complex of tetraMe-BITIANP containing heteroaromatic rings effects highly enantioselective hydrogenation of methyl pyruvate [12].

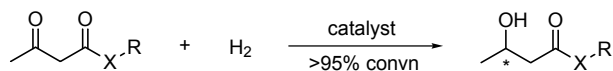
Hydrogenation of ketopantolactone to pantoyl lactone has been frequently used to test the enantioface-differentiating ability of chiral catalysts. As illustrated in Scheme 2, a neutral Rh complex of a pyrrolidine-based diphosphine ligand, BPPM or BCPM, shows a good enantioselectivity [13, 14]. The use of an *m*-CH₃POPPM-Rh complex achieves a 95% optical yield and a turnover frequency (TOF, defined as moles of product per mole of catalyst per hour or second) as high as 50,000 per h with a substrate/catalyst ratio of 150,000 [15, 16]. Rh complexes with a ProNOP or an isoAlaNOP derivative also act as excellent asymmetric catalyst [17]. For example, [Rh(OCOCF₃)(cp,cp-oxopronop)]₂ gives pantoyl lactone in 99% ee. The TOF is up to 3300 per h under 1 atm of hydrogen [17b].

Asymmetric hydrogenation of β-keto esters is most successfully achieved by using BINAP-Ru(II) catalysts [8, 9, 18, 19, 20]. Halogen-containing complexes



Catalyst	Solvent	Pressure [atm]	Temp. [°C]	ee [%]	Confgn
(2 <i>S</i> ,4 <i>S</i>)-BPPM-Rh	benzene	50	30	87	R
(2 <i>S</i> ,4 <i>S</i>)-BCPM-Rh	THF	50	50	92	R
(2 <i>S</i> ,4 <i>S</i>)- <i>m</i> -CH ₃ POPPM-Rh	toluene	12	40	95	R
(<i>S</i>)-Cp,Cp-oxoProNOP-Rh	toluene	1	rt	99	R
(<i>S</i>)-Cp,Cp-isoAlaNOP-Rh	toluene	1	rt	97	S
(<i>S</i>)-Ph,Cp-methylactamide-Rh	toluene	1	rt	87	S

Scheme 2



X	R	Catalyst	Solvent	Pressure [atm]	Temp. [°C]	ee [%]	Confgn
O	CH ₃	RuCl ₂ [(<i>R</i>)-binap]	CH ₃ OH	100	23	>99	R
O	CH ₃	RuCl ₂ [(<i>R</i>)-binap](dmf) _{<i>n</i>}	CH ₃ OH	100	25	99	R
O	CH ₃	[NH ₂ (C ₂ H ₅) ₂][(RuCl-(<i>R</i>)-binap) ₂ (μ-Cl) ₃]	CH ₃ OH	100	25	>99	R
O	CH ₃	[RuI((<i>S</i>)-binap)C ₆ H ₆]I	CH ₃ OH	100	20	99	S
O	CH ₃	Ru(η ³ -CH ₂ C(CH ₃)CH ₂) ₂ -(<i>S</i>)-binap)-HBr	CH ₃ OH	1	rt	97 ^[a]	S
O	CH ₃	(<i>S</i>)-bis-steroidal phosphine-Ru	CH ₃ OH	100	100	99	S
O	CH ₃	(<i>S</i>)-BIPHEMP-Ru	CH ₃ OH	5	50	>99	S
O	CH ₃	(<i>R</i>)-BIMOP-Ru	1:1 CH ₂ Cl ₂ -CH ₃ OH	10	30–40	100	R
O	CH ₃	(<i>R,R</i>)- <i>i</i> -Pr-BPE-Ru	9:1 CH ₃ OH-H ₂ O	4	35	99	S
O	C ₂ H ₅	(+)-tetraMe-BITIANP-Ru	CH ₃ OH	97	70	99	R
O	C ₂ H ₅	(<i>R</i>)-(<i>S</i>)-JOSIPHOS-Rh	CH ₃ OH	20	rt	97	S
N	(CH ₃) ₂	RuBr ₂ [(<i>S</i>)-binap]	C ₂ H ₅ OH	63	27	96	S
S	C ₂ H ₅	RuCl ₂ [(<i>R</i>)-binap]	C ₂ H ₅ OH	95	27	93 ^[b]	R

^[a] 80% yield.

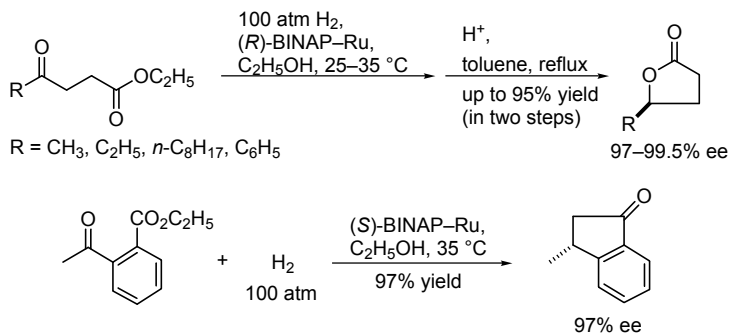
^[b] 42% yield.

Scheme 3

with an empirical formula of $\text{RuX}_2(\text{binap})$ ($X=\text{Cl}, \text{Br}, \text{or I}$; polymeric form) or $\text{RuCl}_2(\text{binap})(\text{dmf})_n$ [21] give nearly perfect enantioselectivity for a wide variety of β -keto esters (Scheme 3). Hydrogenation of methyl 3-oxobutanoate catalyzed by the *R* complexes gives (*R*)-methyl 3-hydroxybutanoate quantitatively in >99% ee [18]. The general sense of enantioselection suggests that the reaction proceeds via a six-membered chelating transition state. The reaction can be conducted with a substrate/Ru ratio of 10,000 in an alcoholic solution. A high enantioselectivity is also achieved for hydrogenation of β -keto amides and thio esters [8]. The remarkable efficiency of the BINAP-Ru complex catalysts prompted the development of many convenient methods for the catalyst preparation [9, 11, 22]. Acidic environments tend to enhance the catalytic activity [22b, f]. Ru complexes with biaryldiphosphines such as BIMOP [23] and BIPHEMP [11] as well as a bis-steroidal phosphine [24] are also effective for asymmetric hydrogenation of β -keto esters. Hydrogenation with a Ru complex of *i*-Pr-BPE, a fully alkylated diphosphine, proceeds under a low pressure of hydrogen [25]. The electron-rich phosphine group is supposed to increase the catalyst's activity. A tetraMe-BITIANP-Ru complex is also suitable for hydrogenation of β -keto esters [12]. A Rh complex of JOSIPHOS, a non- C_2 chiral diphosphine, is effective for asymmetric hydrogenation of ethyl 3-oxobutanoate [26]. Hydrogenation of methyl 3-oxobutanoate catalyzed by a BINAP-Ru complex and *p*-toluenesulfonic acid immobilized in a polydimethylsiloxane membrane matrix gives a chiral alcohol in 92% ee [27]. The reaction rate is comparable with that of the homogeneous system.

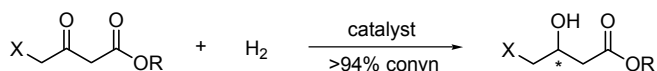
γ -keto esters and *o*-acylbenzoic esters are hydrogenated with a BINAP-Ru complex giving γ -lactones and *o*-phthalides, respectively, with an excellent enantioselectivity (Scheme 4) [28, 29]. Since the sense of enantioselection is the same as that observed with β -keto esters, a seven-membered cyclic transition state should be involved. δ -keto esters are much less reactive than α - and β -keto esters under the standard hydrogenation conditions.

In hydrogenation of ketones which have two functionalities on both sides of the carbonyl group, the enantioselectivity tends to decrease owing to the com-



Scheme 4

petitive interaction of the heteroatoms to the Ru center of the catalyst. The degree and sense of enantioselection are significantly dependent on the bulkiness and electronic properties of coordinating groups. Methyl 5-benzyloxy-3-oxobutanoate is hydrogenated with an (*S*)-BINAP-Ru complex to give an *S* alcohol in 99% ee (Scheme 5) [8]. The degree and sense of enantioselection are the same as those accessible with methyl 3-oxobutanoate. On the other hand, hydrogenation of 4-benzyloxy- and 4-chloro-3-oxobutanoate catalyzed by the (*S*)-BINAP-Ru complex gives hydroxyesters in 78 and 56% ee, respectively, when the reaction is conducted at room temperature. The ee values are dramatically increased to 98 and 97%, respectively, when the temperature is raised to 100 °C [1c, 30]. Hydrogenation of the analogue having a bulky triisopropylsilyloxy group at C4 gives 95% ee even at room temperature [8]. 4-Trimethylammonio-3-oxobutanoic acid chloride is also transformed to the corresponding alcohol with a high enantioselectivity [11]. Although an *i*-Pr-BPE-Ru complex exhibits a moderate enantioselectivity for hydrogenation of methyl 4-chloro-3-oxobutanoate, reaction of its 4-methoxy analogue gives the alcohol in 96% ee [25]. Hydrogenation of ethyl 4-chloro-3-oxobutanoate in the presence of an (*S*)-Ph,Ph-oxoProNOP-Ru complex gives an *S* product with a moderate selectivity [31]. The 4-dimethylamino hydrochloride analogue is hydrogenated with a (2*S*,4*S*)-MCCXM-Rh complex to give an *S* alcohol in 85% ee [32]. Hydrogenation of 4-trimethylammonio-3-oxobutanoic acid chloride affords the hydrochloride of carnitine, which is responsible for transporting long-chain fatty acids through membranes. Hydrogenation products of 4-chloro and 4-dimethylamino derivatives are useful interme-



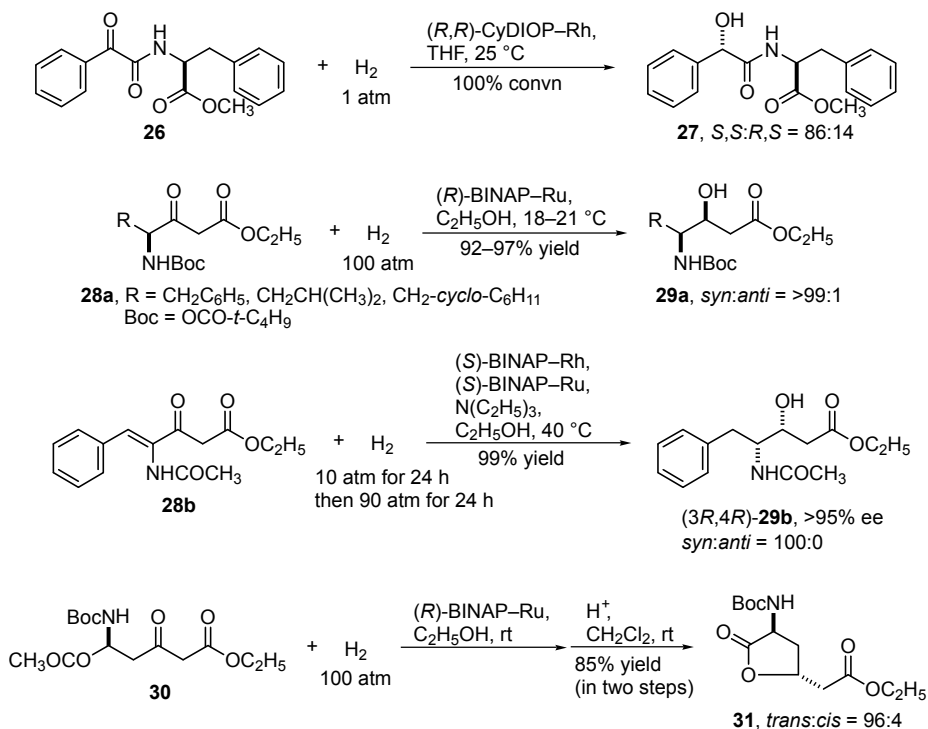
X	R	Catalyst	Pressure [atm]	Temp. [°C]	ee [%]	Confign
CH ₂ OCH ₂ C ₆ H ₅	CH ₃	(<i>S</i>)-BINAP-Ru	50	26	99	<i>S</i>
OCH ₃	CH ₃	(<i>R,R</i>)- <i>i</i> -Pr-BPE-Ru	4	35	96	<i>R</i>
OCH ₂ C ₆ H ₅	C ₂ H ₅	(<i>S</i>)-BINAP-Ru	100	28	78	<i>R</i>
OCH ₂ C ₆ H ₅	C ₂ H ₅	(<i>S</i>)-BINAP-Ru	100	100	98	<i>R</i>
OSi(CH(CH ₃) ₂) ₃	C ₂ H ₅	(<i>S</i>)-BINAP-Ru	100	27	95	<i>R</i>
Cl	CH ₃	(<i>R,R</i>)- <i>i</i> -Pr-BPE-Ru	4	35	76	<i>R</i>
Cl	C ₂ H ₅	(<i>S</i>)-BINAP-Ru	77	24	56	<i>R</i>
Cl	C ₂ H ₅	(<i>S</i>)-BINAP-Ru	100	100	97	<i>R</i>
Cl	C ₂ H ₅	(<i>S</i>)-Ph,Ph-oxoProNOP-Ru	138	20	75	<i>S</i>
NH(CH ₃) ₂ Cl	C ₂ H ₅	(2 <i>S</i> ,4 <i>S</i>)-MCCXM-Rh	20	50	85	<i>S</i>
N(CH ₃) ₃ Cl	H	(<i>R</i>)-BINAP-Ru	100	25	96 ^[a]	<i>S</i>

[a] 75% yield.

Scheme 5

diates for synthesis of carnitine and GABOB which is an antiepileptic and anti-hypotensive drug.

In diastereoselective hydrogenation of a chiral ketone with a chiral catalyst, the degree of stereoselection reflects the enantiodifferentiating ability of the catalyst and the extent of the substrate-based internal asymmetric induction. This phenomenon is popularly called double stereodifferentiation [33]. As illustrated in Scheme 6, hydrogenation of the α -ketoamide **26** derived from an (*S*)-amino ester with an (*R,R*)-CyDIOP-Rh complex gives the (*S,S*)-hydroxyamide **27** and its *R,S* isomer in an 86:14 ratio [34]. On the other hand, when the *S,S* catalyst is employed, the *R,S* alcohol is obtained preferentially. Hydrogenation of a series of the *N*-Boc-protected (*S*)- γ -amino β -keto esters **28a** catalyzed by the (*R*)-BINAP-Ru complex gives predominantly the *syn*-alcohols **29a** [35]. The *S* catalyst under otherwise identical conditions produces the *anti*-isomers selectively. Hydrogenation of γ -acetylamino γ,δ -unsaturated β -keto ester **28b** in the presence of (*S*)-BINAP-Rh and -Ru catalysts affords exclusively (*3R,4R*)-**29b** [36]. First, the C=C linkage of **28b** is selectively reduced by the (*S*)-BINAP-Rh catalyst under low pressure of hydrogen, and then the C=O bond is saturated with the (*S*)-BINAP-Ru catalyst under high pressure conditions. Hydrogenation of the *N*-Boc-protected (*S*)- δ -amino- β -keto ester **30** with an (*R*)-BINAP-Ru complex, followed by cyclization under acidic conditions gives the *trans*-lactone **31** and the *cis*-isomer in a 96:4 ratio [37]. The hydrogenation products **29** and **31** are useful



Scheme 6

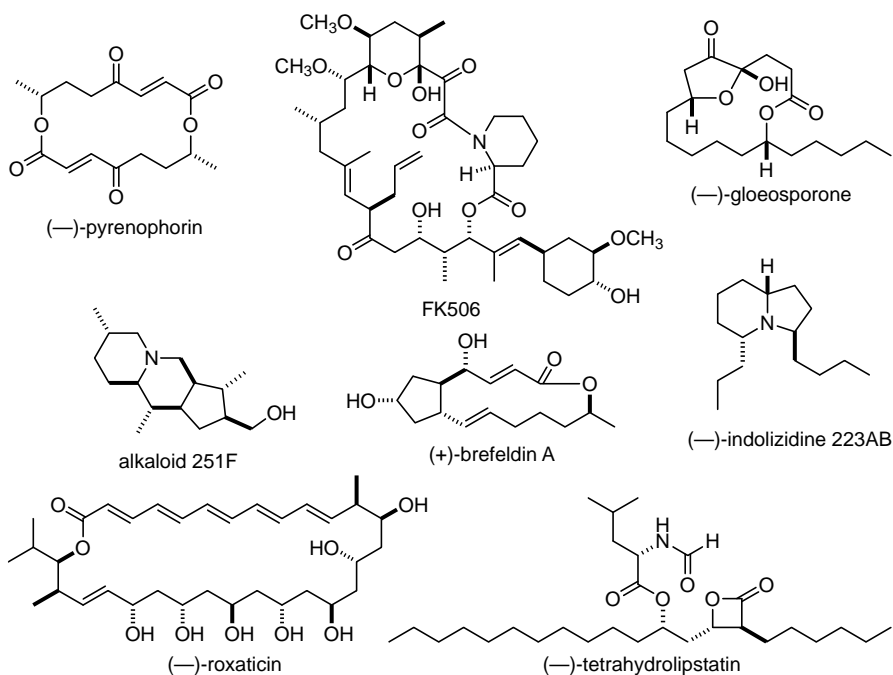


Fig. 7

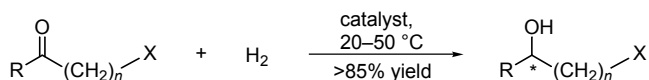
for the synthesis of aspartic proteinase inhibitors and theonellamide F, an anti-fungal agent, respectively.

Recently, homogeneous asymmetric hydrogenation of β - or γ -keto esters was successfully applied to synthesis of a wide variety of natural and unnatural useful compounds. Representative examples are illustrated in Fig. 7 [38].

2.2

Amino-, Hydroxy-, and Phenylthio Ketones

Amino ketones, in either a neutral or hydrochloride form, have frequently been used as substrates of homogeneous asymmetric hydrogenation. As illustrated in Scheme 7, a cationic Rh complex of (*R*)-MOC-BIMOP, an unsymmetrical biaryldiphosphine, effects the hydrogenation of α -aminoacetophenone hydrochloride to give the corresponding (*R*)-amino alcohol in 93% ee [39]. The use of a symmetrical ligand, BIMOP or Cy-BIMOP, gives a moderate or low optical yield. A cationic Rh complex with Cy₂Cy-oxoProNOP shows the same enantioselectivity [40]. The mono-*N*-benzyl analogue is hydrogenated with a (2*S*,4*S*)-MC-CPM-Rh complex to give an *S* alcohol in 93% ee [41]. Epinephrine hydrochloride with 95% ee is conveniently prepared via hydrogenation of the corresponding amino ketone catalyzed by a cationic complex of BPPFOH, a chiral ferrocenyl diphosphine [42]. A high level of enantioselection is achieved in hydrogenation



R	n	X	Catalyst	Pressure [atm]	ee [%]	Confign
C ₆ H ₅	1	NH ₃ Cl	(R)-MOC-BIMOP-Rh	90	93	R
C ₆ H ₅	1	NH ₃ Cl	(S)-Cy,Cy-oxoProNOP-Rh	50	93	S
C ₆ H ₅	1	NH ₂ CH ₂ C ₆ H ₅ Cl	(2S,4S)-MCCPM-Rh	20	93	S
C ₆ H ₃ -3,4-(OH) ₂	1	NH ₂ CH ₃ Cl	(R)-(S)-BPPFOH-Rh	50	95	R
CH ₃	1	N(CH ₃) ₂	(S)-BINAP-Ru	102	99	S
C ₆ H ₅	1	N(CH ₃) ₂	(S)-BINAP-Ru	100	95	S
2-naphthyl	1	N(C ₂ H ₅) ₂	(S,S)-DIOP-Rh	69	95	+
CH ₃	1	NH(CH ₃) ₂ Cl	(S)-Cy,Cy-oxoProNOP-Rh	50	97	S
C ₆ H ₅	1	NH(C ₂ H ₅) ₂ Cl	(2S,4S)-MCCPM-Rh	20	97	S
C ₆ H ₅	2	NH ₂ CH ₃ Cl	(2S,4S)-MCCPM-Rh	30	80	R
C ₆ H ₅	2	NH(CH ₃) ₂ Cl	(S)-Cy,Cy-oxoProNOP-Rh	50	93 ^[a]	R
C ₆ H ₅	2	NH(CH ₃)CH ₂ C ₆ H ₅ Cl	(2S,4S)-MCCPM-Rh	30	91	R
C ₆ H ₅	3	NH(CH ₃) ₂ Cl	(S)-Cy,Cy-oxoProNOP-Rh	50 ^[b]	92	R
C ₆ H ₅	3	NH(CH ₃)CH ₂ C ₆ H ₅ Cl	(2S,4S)-MCCPM-Rh	50	88	R
CH ₃	1	OH	(R)-BINAP-Ru	93	92	R
<i>n</i> -C ₃ H ₇	1	OH	(R)-BINAP-Ru	–	95	R
CH ₃	2	OH	(R)-BINAP-Ru	70	98	R
CH ₃	2	SC ₆ H ₅	(S)-MeO-BIPHEP-Ru	30	98	S
C ₂ H ₅	2	SC ₆ H ₅	(S,S)-BDPP-Ru	30	95	S
CH ₃	3	SC ₆ H ₅	(S)-BINAP-Ru	113 ^[b]	70 ^[c]	S

^[a] Contaminated with 5% of propiophenone.

^[b] At 80 °C.

^[c] 70% yield.

Scheme 7

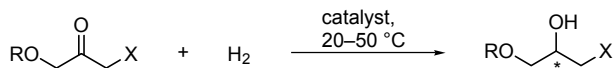
tion of α -dialkylamino ketones using a BINAP-Ru [8, 9] or a DIOP-Rh complex [43]. The dialkylamino group efficiently accelerates the reaction. For example, hydrogenation of α -dimethylaminoacetone is catalyzed by even a normally unreactive BINAP-Ru diacetate complex [8]. A Cy,Cy-oxoProNOP- or MCCPM-Rh complex is suitable for hydrogenation of α -, β -, and γ -amino ketone hydrochlorides to give the corresponding chiral alcohols in up to 97% ee [40, 41, 44]. Hydrogenation of α - and β -hydroxy ketones with an (R)-BINAP-Ru catalyst gives R alcohols in up to 98% ee [8, 45]. The sense of enantioface differentiation is the same as that in hydrogenation of ketoester analogues. β -phenylthio ketones are also enantioselectively hydrogenated with a BINAP-, MeO-BIPHEP-, or BDPP-

Ru complex [46]. The reactivity and selectivity are somewhat decreased when a γ -phenylthio analogue is used as substrate.

Scheme 8 illustrates the enantioselective hydrogenation of bifunctionalized ketones. Hydrogenation of 1-aryloxy-2-oxo-3-propylamine derivatives catalyzed by a (2*S*,4*S*)-MCCPM-Rh complex gives (*S*)-amino alcohols in up to 97% ee [47]. The sense of enantioface selection is opposite that in hydrogenation of α -monoaminoketones (see table of Scheme 7). The BINAP-Ru catalyst is effective for discrimination between a hydroxy group and an alkoxy or aryloxy group, and even between *n*-octadecyl and triphenylmethoxy groups [48].

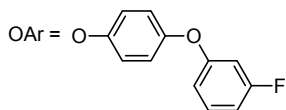
As illustrated in Scheme 9, diastereoselective hydrogenation of (*R*)-amino ketone 32 catalyzed by an (*S*)-(*R*)-BPPFOH-[RhCl(cod)]₂-N(C₂H₅)₃ system in ethyl acetate gives (*R,R*)-amino alcohol 33, an isoproterenol analogue, with >99% purity [49]. On the other hand, the use of [Rh((*S*)-(*R*)-bppfoh)]ClO₄ in methanol gives the *S,R* isomer predominantly. Racemic 1-hydroxy-1-phenyl-2-propanone is kinetically resolved by hydrogenation with an (*R*)-BINAP-Ru complex. The corresponding 1*S*,2*R* diol with 92% optical purity and unreacted *R* substrate in 92% ee are obtained at 50.5% conversion [1c]. The relative reactivity of the enantiomeric substrates, k_S/k_R , is 64:1.

Homogeneous asymmetric hydrogenation of amino- or hydroxy ketones is applied to the synthesis of some biologically active compounds. Examples are given in Fig. 8 [4b, 19g, 47, 48c, 50]. (*R*)-1,2-Propanediol obtained by hydrogenation of 1-hydroxy-2-propanone in the presence of an (*R*)-BINAP-Ru complex is now commercially used for the synthesis of levofloxacin, an antibacterial agent (Dai-ichi Pharmaceutical Co.) [19g].

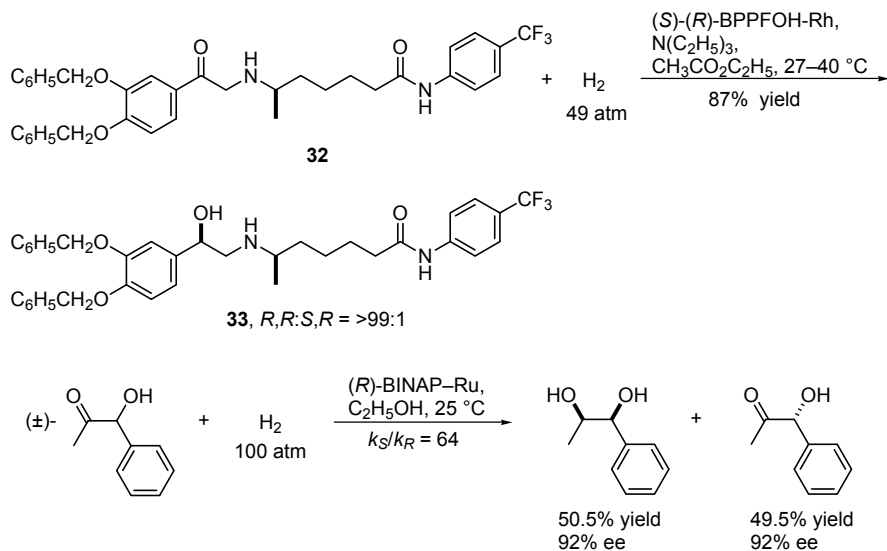


R	X	Catalyst	Pressure [atm]	Yield [%]	ee [%]	Confign
C ₆ H ₅	NH ₂ CH ₂ C ₆ H ₅ Cl	(2 <i>S</i> ,4 <i>S</i>)-MCCPM-Rh	20	100	97	<i>S</i>
Ar ^[a]	OH	(<i>S</i>)-BINAP-Ru	94	86	>95	<i>R</i>
CH ₂ C ₆ H ₅	OH	(<i>S</i>)-BINAP-Ru	97	>98	93	<i>R</i>
<i>n</i> -C ₁₈ H ₃₇	OC(C ₆ H ₅) ₃	(<i>S</i>)-BINAP-Ru	97	>70	>96	<i>R</i>

[a]



Scheme 8



Scheme 9

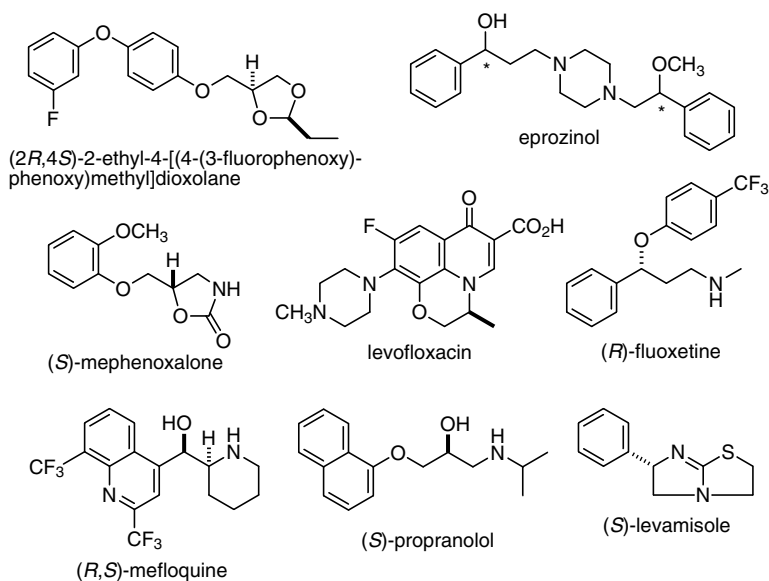


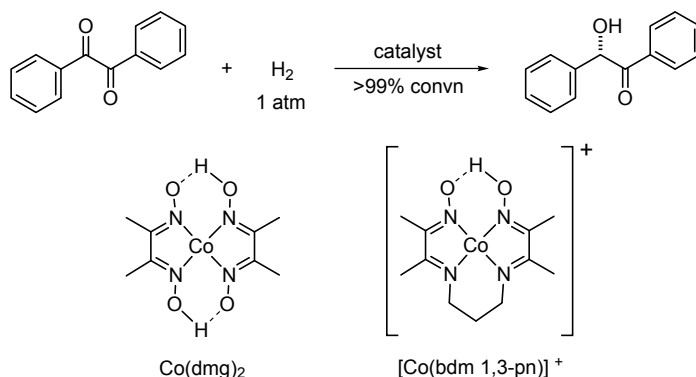
Fig. 8

2.3

Diketones

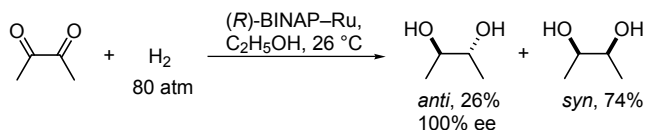
As shown in Scheme 10, homogeneous hydrogenation of benzil with a quinine-benzylamine-Co(dmg)₂ catalyst system gives (*S*)-benzoin in 78% ee [51]. The addition of benzyl amine is crucial for a high reaction rate. Hydrogenation of 1-phenyl-1,2-propanedione catalyzed by this system gives (*S*)-1-hydroxy-1-phenyl-2-propanone with 56% ee in 88% yield, accompanied by 2-hydroxy-1-phenyl-1-propanone in 8% yield [51b]. A catalyst system with the BDM 1,3-pn ligand shows a similar enantioselectivity in hydrogenation of benzil [52]. Double hydrogenation of 2,3-butanedione with an (*R*)-BINAP-Ru complex gives (*R,R*)-2,3-butanediol with 100% ee and the *meso*-diol in a 26:74 ratio (Scheme 11) [8].

Asymmetric hydrogenation of β-diketones catalyzed by a chiral phosphine-Ru complex gives the corresponding chiral diols with an excellent diastereo- and



Catalyst (mol ratio)	Solvent	Temp. [°C]	ee [%]
quinine-quinine·HCl-NH ₂ CH ₂ C ₆ H ₅ -Co(dmg) ₂ (1:1:1:1)	benzene	-10	78
quinine-NH ₂ CH ₂ C ₆ H ₅ -H(BDM 1,3-pn)-CoCl ₂ ·6H ₂ O (4:1:1.2:1)	1:9 (CH ₃) ₂ CHOH-toluene	-8	79

Scheme 10



Scheme 11

enantioselectivity (Scheme 12). Enantiomerically pure (*R,R*)-2,4-pentanediol is obtained via the hydrogenation of 2,4-pentanedione with an (*R*)-BINAP-Ru complex in 99% yield [8]. Hydrogenation of 5-methyl-2,4-hexanedione and 1-phenyl-1,3-butanedione preferentially gives the chiral *anti*-diols [8, 53]. Optically active 2,4-pentanediol is obtainable with a Ru complex of BIPHEMP [54] or BDPP [55]. Methyl 3,5-dioxohexanoate is hydrogenated in the presence of an (*R*)-BINAP-Ru complex to give an 81:19 mixture of *anti*- (3*S*,5*R*, 78% ee) and *syn*-dihydroxy esters [56]. The configuration suggests that the C3 carbonyl group is more reactive than the C5 carbonyl. Optically active 1,3-diphenyl-1,3-propanediol is obtained by BIPHEMP-Ru catalyzed hydrogenation [57]. Hydrogenation of 1,5-dichloro-2,4-pentanedione with the BINAP-Ru complex preferentially gives a chiral diol acting as a versatile chiral building block [58]. 1-Phenyl-1,3-butanedione is hydrogenated selectively to give (*R*)-1-phenyl-3-hydroxybutan-1-one in the presence of $[\text{NH}_2(\text{C}_2\text{H}_5)_2][(\text{RuCl}((\text{R})\text{-binap}))_2(\mu\text{-Cl})_3]$ (Scheme 13) [53]. Hydrogenation of β -diketones catalyzed by a BINAP-Ru com-



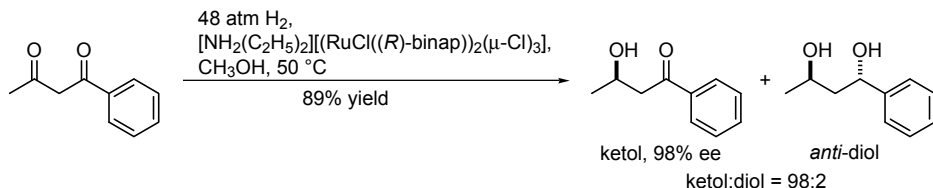
R ¹	R ²	Catalyst	Pressure [atm]	Temp. [°C]	Yield [%]	dr ^[a]	ee [%] ^[b]
CH ₃	CH ₃	(<i>R</i>)-BINAP-Ru	72	30	100	99:1	100
CH ₃	CH ₃	(<i>R</i>)-BIPHEMP-Ru	99	50	100	99:1	>99.9
CH ₃	CH ₃	(<i>R,R</i>)-BDPP-Ru	79	80	100	75:25	97
CH ₃	CH(CH ₃) ₂	(<i>R</i>)-BINAP-Ru	48	50	92	97:3	98
CH ₃	C ₆ H ₅	(<i>R</i>)-BINAP-Ru	83	26	98	94:6	94
CH ₃	CH ₂ CO ₂ CH ₃	(<i>R</i>)-BINAP-Ru	100	50	100 ^[c]	81:19	78
C ₆ H ₅	C ₆ H ₅	(<i>R</i>)-BIPHEMP-Ru	100	40	70	94:6	87
CH ₂ Cl	CH ₂ Cl	(<i>R</i>)-BINAP-Ru	85	102	–	–	92–94

^[a] *Anti:syn* ratio.

^[b] % ee of *anti*-diol.

^[c] A mixture of diol and δ -lactone.

Scheme 12



Scheme 13

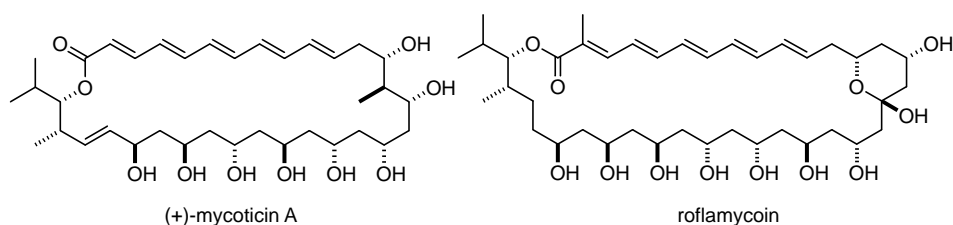
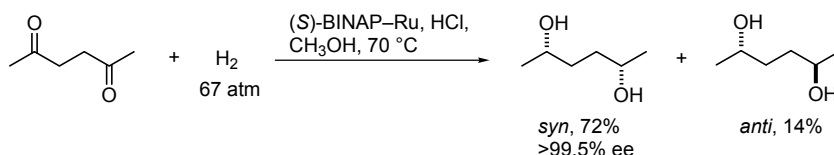


Fig. 9



Scheme 14

plex provides a useful tool for the synthesis of biologically active compounds possessing contiguous polyhydroxy groups (Figure 9) [59]. Hydrogenation of 2,5-hexanedione, a γ -diketone, catalyzed by a BINAP-Ru complex is remarkably accelerated by addition of HCl (substrate:HCl=500:1), resulting in optically pure 2,5-hexanediol in a reasonable yield (Scheme 14) [60].

2.4

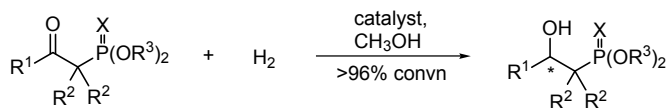
Keto Phosphonates

Scheme 15 illustrates the asymmetric hydrogenation of β -keto phosphonates catalyzed by a BINAP-Ru complex, giving β -hydroxy phosphonates in up to 99% ee [61]. The sense of enantioface differentiation is the same as that of hydrogenation of β -keto carboxylic esters (see table of Scheme 3). The reactivity of the phosphonates is much higher than that of the carboxylic esters so that the hydrogenation proceeds even at 1 to 4 atm of hydrogen and at room temperature. A Ru complex of BDPP also shows high enantioselectivity [46b]. Chiral β -hydroxy phosphonates thus obtained are useful intermediates for the syntheses of phosphonic acid-based antibiotics as well as haptens of catalytic antibodies. Similarly, β -keto thiophosphates are hydrogenated enantioselectively with a MeO-BIPHEP-Ru catalyst [61b].

2.5

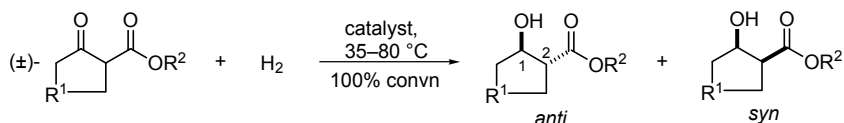
Dynamic Kinetic Resolution

Hydrogenation of racemic α -monosubstituted β -keto esters normally results in four possible stereoisomeric hydroxy esters. Under appropriate conditions, however, a single stereoisomer with two contiguous stereogenic centers can be ob-



R ¹	R ²	R ³	X	Catalyst	Pressure [atm]	Temp. [°C]	ee [%]	Confign
CH ₃	H	CH ₃	O	(<i>R</i>)-BINAP-Ru	4	25	98	R
CH ₃	H	C ₂ H ₅	O	(<i>S</i>)-BINAP-Ru	1	50	99	S
CH ₃	H	C ₂ H ₅	O	(<i>R,R</i>)-BDPP-Ru	30	rt	95	R
CH ₃	CH ₃	CH ₃	O	(<i>R</i>)-BINAP-Ru	4	50	98	R
<i>n</i> -C ₅ H ₁₁	H	CH ₃	O	(<i>S</i>)-BINAP-Ru	100	rt	98	S
CH(CH ₃) ₂	H	CH ₃	O	(<i>S</i>)-BINAP-Ru	4	80	96	S
C ₆ H ₅	H	CH ₃	O	(<i>R</i>)-BINAP-Ru	4	60	95	R
<i>n</i> -C ₅ H ₁₁	H	CH ₃	S	(<i>S</i>)-MeO-BIPHEP-Ru	100	rt	94	S
CH(CH ₃) ₂	H	CH ₃	S	(<i>S</i>)-MeO-BIPHEP-Ru	10	rt	93	S

Scheme 15



R ¹	R ²	Catalyst	Solvent	Pressure [atm]	dr ^[a]	ee [%] ^[b]	Con-fign ^[b]
CH ₂	CH ₃	[RuCl((<i>R</i>)-binap)C ₆ H ₆]Cl	CH ₂ Cl ₂	100	99:1	92	1 <i>R</i> ,2 <i>R</i>
CH ₂	CH ₃	[RuI((<i>S</i>)-binap)-(<i>p</i> -cymene)]I	CH ₂ Cl ₂ ^[c]	97	99:1	95	1 <i>S</i> ,2 <i>S</i>
CH ₂	C ₂ H ₅	Ru(η ³ -CH ₂ C(CH ₃)CH ₂) ₂ -((<i>R</i>)-binap)-HBr	CH ₃ OH	20 ^[d]	97:3	94	1 <i>R</i> ,2 <i>R</i>
CH ₂	CH ₃	(<i>R,R</i>)- <i>i</i> -Pr-BPE-Ru	9:1 CH ₃ OH-H ₂ O	4	96:4	98	1 <i>S</i> ,2 <i>S</i>
CH ₂	CH ₃	(+)-tetraMe-BITIANP-Ru	CH ₃ OH	97	93:7	99	1 <i>R</i> ,2 <i>R</i>
(CH ₂) ₂	C ₂ H ₅	[RuCl((<i>R</i>)-binap)C ₆ H ₆]Cl	CH ₂ Cl ₂	100	95:5	90	1 <i>R</i> ,2 <i>R</i>
(CH ₂) ₂	C ₂ H ₅	Ru(η ³ -CH ₂ C(CH ₃)CH ₂) ₂ -((<i>S</i>)-binap)-HBr	CH ₂ Cl ₂	20	74:26	91	1 <i>S</i> ,2 <i>S</i>
(CH ₂) ₃	CH ₃	[RuCl((<i>R</i>)-binap)C ₆ H ₆]Cl	CH ₂ Cl ₂	100	93:7	93	1 <i>R</i> ,2 <i>R</i>

[a] *Anti:syn* ratio.

[b] Value of *anti*-alcohol.

[c] Containing <1% of water.

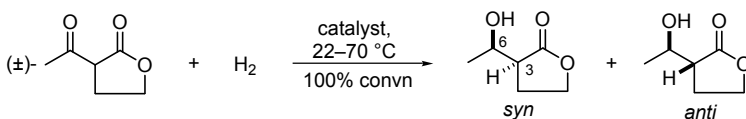
[d] 50% convn.

Scheme 16

tained selectively. Since the configurational lability at the α position causes in situ, rapid equilibration between the enantiomers, one of them can be hydrogenated more facily when it has an *R* (or *S*) configuration. The combined effects of catalyst-based intermolecular chirality transfer and substrate-based intramolecular asymmetric induction [33] are able to kinetically determine the absolute configuration at the α and β positions of product. As shown in Scheme 16, hydrogenation of racemic 2-alkoxycarbonylcycloalkanones in the presence of $[\text{RuCl}((R)\text{-binap})\text{C}_6\text{H}_6]\text{Cl}$ through dynamic kinetic resolution gives 1*R*,2*R* products with consistently high *anti*-selectivity and enantiomeric excess [62]. 2-Methoxycarbonylcyclopentanone in dichloromethane, but not in methanol, is hydrogenated to give an *anti*-hydroxyester in 92% ee and in 99% yield. The degree of stereoselectivity susceptibly reflects the difference in the structure of the ketonic substrate as well as the preparation method of the BINAP-Ru complex and reaction conditions, particularly the nature of solvent [9, 63]. The *anti*-selectivity is decreased to some extent by increasing the ring size, while the enantioselectivity is little affected. The use of a Ru complex of *i*-Pr-BPE [25] or tetraMe-BITIANP [12] also gives the *anti*-product with an excellent stereoselectivity. The kinetic profile of the stereoselective hydrogenation of racemic 2-methoxycarbonylcycloheptanone with an (*R*)-BINAP-Ru complex has been revealed by a computer-aided analysis [64]. Thus hydrogenation of the *R* keto ester in dichloromethane is 9.8 times faster than that of the slow-reacting *S* isomer and the equilibration between the substrate enantiomers occurs 4.4 times faster than hydrogenation of the *S* keto ester. Racemic 3-acetyltetrahydrofuran-2-one is hydrogenated with an (*S*)-BINAP-Ru complex to give the corresponding 3*R*,6*S* compound with an excellent *syn*-selectivity in up to 97% ee (Scheme 17) [9, 62b]. A tetraMe-BITIANP-Ru complex also effects the stereoselective hydrogenation [12].

This stereoselective hydrogenation via dynamic kinetic resolution is applicable to acyclic α -acylamino-, α -amidomethyl-, or α -chloro- β -ketoesters. The α -acylamino and α -amidomethyl substrates are hydrogenated with an (*R*)-BINAP-Ru complex to give 2*S*,3*R* (*syn*) alcohols predominantly in up to 98% ee (Scheme 18) [9, 62a, 65]. With a Ru complex of DTBBINAP, a sterically demanding BINAP analogue, almost perfect diastereo- and enantioselectivity are achieved, although the reaction rate is somewhat lowered [9]. The α -chloro analogue is hydrogenated with a BINAP-Ru($\eta^3\text{-CH}_2\text{C}(\text{CH}_3)\text{CH}_2$)₂(cod) system to give an *anti*-configured chlorohydrin predominantly and in 99% ee [66]. Hydrogenation of α -methyl- β -keto esters in the presence of a BINAP- [62] or *i*-Pr-BPE-Ru complex [25] gives a 32:68 and 58:42 mixture of the corresponding *syn*- and *anti*-alcohols, respectively. The enantioselectivity is uniformly high irrespective of the degree and sense of diastereoselection. In a similar manner, α -acylamino- or α -bromo- β -keto phosphonates are hydrogenated in the presence of a BINAP-Ru complex to give the corresponding *syn*-alcohols selectively in >98% ee (Scheme 19) [61a, 67]. The sense of enantio- and diastereoface differentiation is the same as that of the hydrogenation of α -substituted β -keto carboxylic esters (see table of Scheme 18).

As illustrated in Fig. 10, the stereoselective hydrogenation of configurationally unstable α -monosubstituted β -keto carboxylates and -phosphonates through dy-

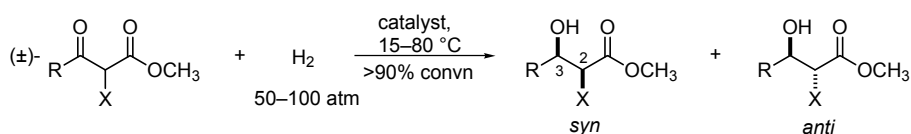


Catalyst	Solvent	Pressure [atm]	dr ^[a]	ee [%] ^[b]	Config ^[b]
[RuCl((<i>R</i>)-binap)C ₆ H ₆]Cl	CH ₃ OH	100	98:2	94	3 <i>S</i> ,6 <i>R</i>
[RuI((<i>S</i>)-binap)(<i>p</i> -cymene)]I	3:1 CH ₃ OH-CH ₂ Cl ₂	97	99:1	97	3 <i>R</i> ,6 <i>S</i>
(+)-tetraMe-BITIANP-Ru	CH ₃ OH	97	96:4	91	3 <i>S</i> ,6 <i>R</i>

^[a] *Syn:anti* ratio.

^[b] Value of *syn*-alcohol.

Scheme 17



R	X	Catalyst	Solvent	dr ^[a]	ee [%] ^[b]	Config ^[b]
CH ₃	NHCOCH ₃	RuBr ₂ [(<i>R</i>)-binap]	CH ₂ Cl ₂	99:1	98	2 <i>S</i> ,3 <i>R</i>
CH ₃	NHCOCH ₃	Ru(η ³ -CH ₂ C(CH ₃)CH ₂) ₂ -((<i>R</i>)-binap)-HCl	CH ₃ OH	76:24	95	2 <i>S</i> ,3 <i>R</i>
CH ₃	NHCOCH(CH ₃) ₂	Ru(η ³ -CH ₂ C(CH ₃)CH ₂) ₂ -((<i>R</i>)-binap)-HBr	CH ₃ OH	77:23	92	2 <i>S</i> ,3 <i>R</i>
Ar ^[c]	NHCOCH ₃	RuBr ₂ [(<i>R</i>)-binap]	CH ₂ Cl ₂	99:1	94	2 <i>S</i> ,3 <i>R</i>
CH ₃	CH ₂ NHCOC ₆ H ₅	[NH ₂ (C ₂ H ₅) ₂][(RuCl((<i>R</i>)-binap)) ₂ (μ-Cl) ₃]	CH ₂ Cl ₂	94:6	98	2 <i>S</i> ,3 <i>R</i>
CH ₃	CH ₂ NHCOC ₆ H ₅	[RuI((<i>S</i>)-binap)(<i>p</i> -cymene)]	CH ₂ Cl ₂ ^[d]	94:6	97	2 <i>R</i> ,3 <i>S</i>
CH ₃	CH ₂ NHCOC ₆ H ₅	(+)-DTBBINAP-Ru	7:1 CH ₂ Cl ₂ -CH ₃ OH	99:1 ^[e]	99	2 <i>S</i> ,3 <i>R</i>
CH ₃	Cl ^[f]	Ru(η ³ -CH ₂ C(CH ₃)CH ₂) ₂ (cod)-(<i>R</i>)-BINAP	CH ₂ Cl ₂	1:99	99 ^[g]	2 <i>R</i> ,3 <i>R</i> ^[g]
CH ₃	CH ₃	(<i>R,R</i>)- <i>i</i> -Pr-BPE-Ru	9:1 CH ₃ OH-H ₂ O ^[h]	58:42	96 ^[g]	2 <i>R</i> ,3 <i>R</i> ^[g]
CH ₃	CH ₃ ^[f]	[RuCl((<i>R</i>)-binap)C ₆ H ₆]Cl	CH ₂ Cl ₂	32:68	94 ^[g]	2 <i>R</i> ,3 <i>R</i> ^[g]

^[a] *Syn:anti* ratio.

^[b] Value of *syn*-alcohol.

^[c] 3,4-Methylenedioxyphenyl.

^[d] Containing 0.5% of water.

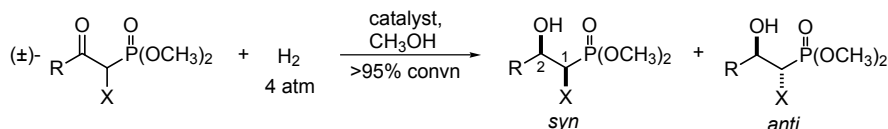
^[e] 55% conversion.

^[f] Ethyl ester.

^[g] Value of *anti*-alcohol.

^[h] 4 atm of H₂.

Scheme 18



R	X	Catalyst	Temp. [°C]	dr ^[a]	ee [%] ^[b]	Config ^[b]
CH ₃	NHCOCH ₃	(<i>R</i>)-BINAP-Ru	25	97:3	>98	1 <i>R</i> ,2 <i>R</i>
C ₆ H ₅	NHCOCH ₃	(<i>R</i>)-BINAP-Ru	45	98:2	95	1 <i>R</i> ,2 <i>R</i>
CH ₃	Br	(<i>S</i>)-BINAP-Ru	25	90:10 ^[c]	98	1 <i>R</i> ,2 <i>S</i>

[a] *Syn:anti* ratio.

[b] Value of *syn*-alcohol.

[c] Contaminated with 15% of debrominated compound.

Scheme 19

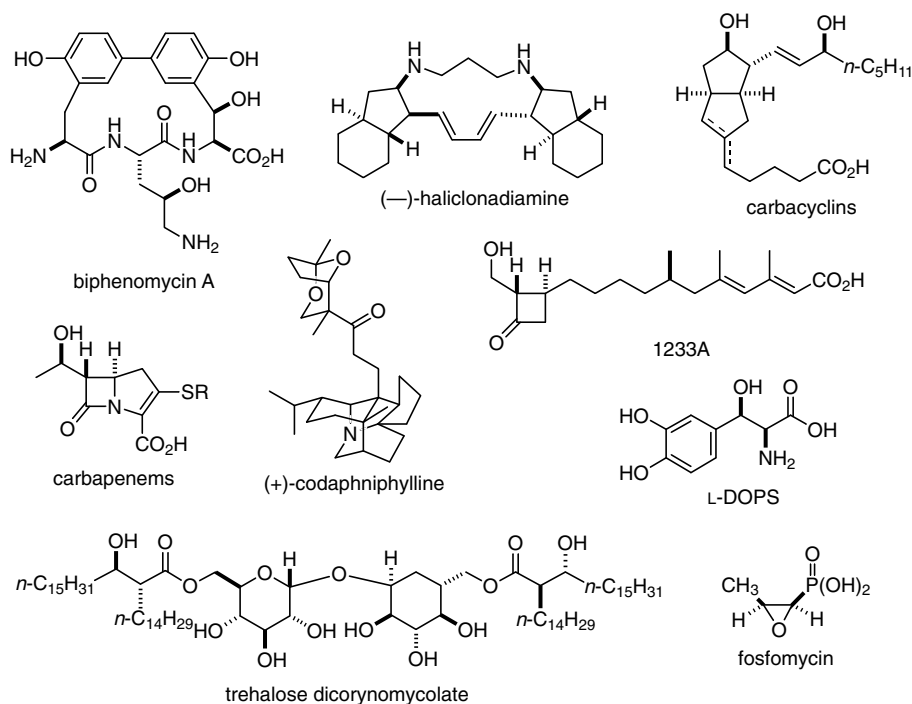


Fig. 10

namic kinetic resolution has been applied to the synthesis of a wide variety of useful bioactive compounds [1c, 19, 61, 62, 68]. The asymmetric synthesis of the 2-acetoxyazetidinone which is a key intermediate for the synthesis of carbapenems is

conducted on a practical scale at Takasago International Corporation using stereoselective hydrogenation of methyl 2-benzamidomethyl-3-oxobutanoate as key step [1c, 19g, 62a, 68b]. Currently this is among the most important asymmetric hydrogenations from an industrial point of view.

3

Hydrogenation of Simple Ketones

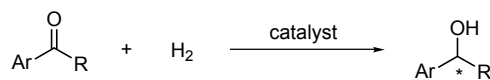
Although neutral or ionic transition metal complexes with bidentate chiral phosphine ligands have successfully been used as catalysts for asymmetric hydrogenation of functionalized olefins and ketones [1], most of them are unable to effect enantioselective hydrogenation of simple ketones [1f]. Only limited chiral Rh, Ir, and Ru complexes have shown high catalytic activity and enantioselectivity in hydrogenation of ketonic substrates having no functionality nearby the carbonyl group. Recently, however, a highly productive method using chiral Ru complexes has been developed.

3.1

Aromatic Ketones

Scheme 20 shows examples of asymmetric hydrogenation of simple aromatic ketones. 1'-Acetonaphthone is hydrogenated with a neutral complex prepared from $[\text{RhCl}(\text{nbd})]_2$ and (S,S)-DIOP in the presence of $\text{N}(\text{C}_2\text{H}_5)_3$ to give the corresponding chiral alcohol in 84% ee [69]. Addition of $\text{N}(\text{C}_2\text{H}_5)_3$ is supposed to promote the production of a reactive Rh hydride species. This is the highest ee value achieved with Rh complexes so far reported. Hydrogenation of acetophenone in the presence of an (S,S)-BDPP-Rh catalyst gave (S)-1-phenylethanol in 82% ee [70].

A breakthrough in this subject is provided by the invention of chiral Ru diphosphine-diamine mixed-ligand complexes. Although a Ru dichloride with phosphine ligands is not very active for hydrogenation of simple ketones, the catalytic activity is enormously enhanced when small amounts of a 1,2-diamine and an alkaline base are added to this complex in 2-propanol [71]. A chiral catalyst system is conveniently prepared in situ by mixing a BINAP- or TolBINAP- RuCl_2 complex, a chiral diamine such as DPEN (4), and an alkaline base [71]. However, use of isolated *trans*- $\text{RuCl}_2(\text{diphosphine})(\text{diamine})$ complexes with a base as cocatalyst can also achieve asymmetric hydrogenation of a wide variety of alkyl aryl ketones under 1 to 10 atm of hydrogen at room temperature with a substrate/catalyst ratio of 10,000 to 100,000, affording the corresponding secondary alcohols in up to 99% ee [72]. Notably, when 45 atm of hydrogen is applied, 601 g of acetophenone can be hydrogenated quantitatively with only 2.2 mg of the Ru complex. The turnover number is 2,400,000, while the TOF at 30% conversion is 228,000 per h or 63 per s. The catalyst system is among the most reactive (pre)catalyst so far reported [73]. In most cases, the combination of (S)-BINAP and an S diamine (or R and R) shows the highest catalytic activity and



catalyst:

[RhCl(nbd)]₂-(*S,S*)-BDPP + N(C₂H₅)₃; (*S,S*)-**34a**

[RhCl(nbd)]₂-(*S,S*)-DIOP + N(C₂H₅)₃; (*S,S*)-**34b**

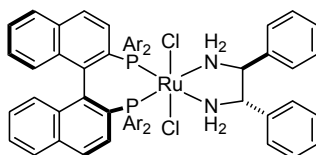
RuCl₂[(*S*)-binap](dmf)_{*n*}-(*S,S*)-**4** + KOH; (*S*),(*S,S*)-**35a**

trans-RuCl₂[(*S*)-tolbinap][(S)-**4**] + KOC(CH₃)₃; (*S*),(*S,S*)-**35b**

trans-RuCl₂[(*S*)-tolbinap][(S)-**1**] + KOC(CH₃)₃; (*S*),(*S*)-**35c**

RuBr₂[(*R,R*)-bipnor]-(*S,S*)-**4** + KOH; (*R,R*),(*S,S*)-**36**

[Ir(cod)((*S*)-binap)]BF₄-P[C₆H₄-*o*-N(CH₃)₂]₂C₆H₅; (*S*)-**37a**



Ar = C₆H₄-*p*-CH₃

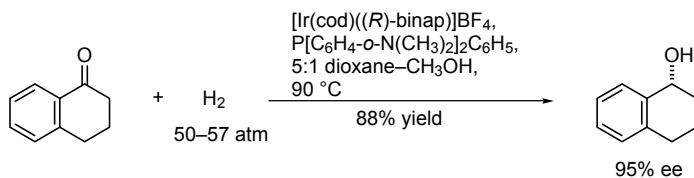
trans-RuCl₂[(*S*)-tolbinap][(S)-**4**]

R	Ar	Catalyst	Solvent	Pressure [atm]	Temp. [°C]	Yield [%]	ee [%]	Confign
CH ₃	C ₆ H ₅	(<i>S,S</i>)- 34a	CH ₃ OH	69	50	72	82	S
CH ₃	C ₆ H ₅	(<i>S</i>),(<i>S,S</i>)- 35b	(CH ₃) ₂ CHOH	45	30	100	80	R
CH ₃	C ₆ H ₅	(<i>S</i>),(<i>S,S</i>)- 35c	(CH ₃) ₂ CHOH	4	26	100	91	R
CH ₃	C ₆ H ₄ - <i>o</i> -CH ₃	(<i>S</i>),(<i>S,S</i>)- 35c	(CH ₃) ₂ CHOH	10	28	94	99	R
CH ₃	C ₆ H ₄ - <i>p</i> - <i>i</i> -C ₄ H ₉	(<i>R</i>),(<i>R,R</i>)- 35b	(CH ₃) ₂ CHOH	10	28	99	96	S
CH ₃	1-naphthyl	(<i>S,S</i>)- 34b	benzene	69	50	100	84	-
CH ₃	1-naphthyl	(<i>S</i>),(<i>S,S</i>)- 35a	(CH ₃) ₂ CHOH	4	25	>99	97	R
CH ₃	2-naphthyl	(<i>R,R</i>),(<i>S,S</i>)- 36	(CH ₃) ₂ CHOH	5	28	65	81	R
C ₂ H ₅	C ₆ H ₄ - <i>p</i> -OCH ₃	(<i>R</i>),(<i>R</i>)- 35c	(CH ₃) ₂ CHOH	10	28	100	95	S
<i>i</i> -C ₃ H ₇	C ₆ H ₅	(<i>S</i>)- 37a	5:1 dioxane-CH ₃ OH	54–61	90	78	84	R

Scheme 20

enantioselectivity. Increases in the bulk of the alkyl group and aromatic ring in the substrates tend to increase the extent of enantioselection. A BIPNOR-Ru(II)-4-KOH system effects hydrogenation of 2'-acetophenone in 81% optical yield [74].

A cationic (*S*)-BINAP-Ir(I) complex combined with an aminophosphine catalyzes hydrogenation of isobutyrophenone affording an *R* alcohol in 84% ee [75]. The degree and sense of enantioface discrimination are highly dependent

**Scheme 21**

on the bulkiness of the alkyl groups. Cyclic aromatic ketones are successfully transformed to the corresponding chiral alcohols by hydrogenation with a BINAP-Ir(I)-aminophosphine system (Scheme 21) [76]. For example, hydrogenation of α -tetralone with the system in a 5:1 dioxane-CH₃OH mixture under 50 to 57 atm of hydrogen at 90 °C gives the chiral alcohol with 95% ee in 88% yield. Under similar conditions, hydrogenation of β -thiacyclopentanone gives the corresponding alcohol in 82% ee. An addition of the aminophosphine auxiliary is crucial to achieve the high catalytic activity and enantioselectivity.

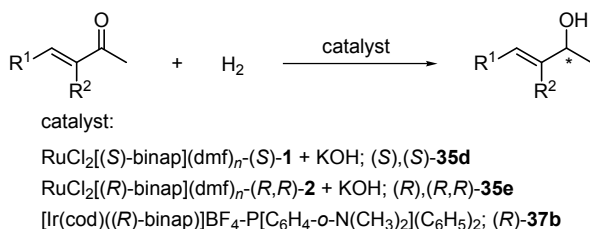
3.2

α,β -Unsaturated Ketones

Asymmetric hydrogenation of α,β -unsaturated ketones is rare. Most existing catalysts, either achiral or chiral, effect preferential saturation of carbon-carbon double bonds over carbonyl groups under a hydrogen atmosphere [77]. This tendency is supposed to arise from the easier interaction of the metal center with an olefinic bond than with a carbonyl moiety.

As illustrated in Scheme 22, however, hydrogenation of β -ionone with an (*R*)-BINAP-Ru(II)-(*R,R*)-DCyEN ((*R,R*)-2)-KOH system under 8 atm of hydrogen at 28 °C quantitatively gives (*S*)- β -ionol in 92% ee [78]. The combined effects of the diamine and inorganic base decelerate the Ru-catalyzed hydrogenation of olefins but accelerate the carbonyl hydrogenation to a large extent. The catalyst system consisting of an (*S*)-BINAP-Ru(II) complex, (*S*)-DAIPEN ((*S*)-1), and KOH ((*S,S*)-35d) promotes hydrogenation of 1-acetylcycloalkenes to give the corresponding allylic alcohols in up to 98% ee [78]. Hydrogenation of benzalacetone with 35d or BINAP-Ir(I)-aminophosphine (37b) [79] gives a chiral unsaturated alcohol with 70 and 65% ee, respectively.

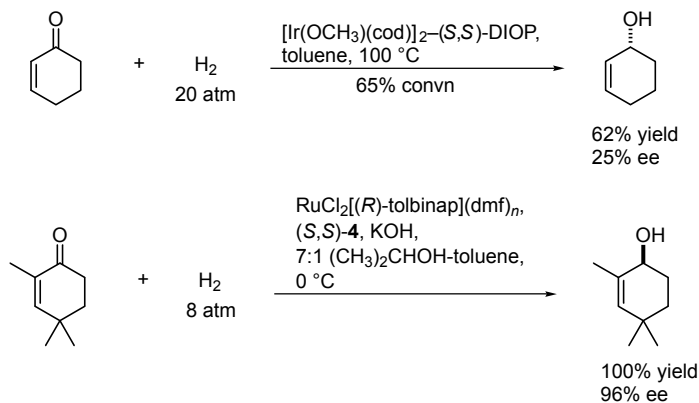
Carbonyl-selective asymmetric hydrogenation of simple 2-cyclohexenone is still difficult. The optical yield obtained with [Ir(OCH₃)(cod)]₂-DIOP is only 25%, while the carbonyl-selectivity is 95% at 65% conversion (Scheme 23) [80]. Hydrogenation of 2,4,4-trimethyl-2-cyclohexenone with a Ru(II)-TolBINAP-4-KOH catalyst system under 8 atm of hydrogen at 0 °C gives 2,4,4-trimethyl-2-cyclohexenol quantitatively in 96% ee [81, 82]. Notably, the combination of (*R*)-TolBINAP and (*S,S*)-4 matched well to give the *S* alcohol with a high ee. The chiral allylic alcohol is the key intermediate in the synthesis of carotenoid-derived odorants and other bioactive compounds [83].



R ¹	R ²	Catalyst	Pressure [atm]	Temp. [°C]	Conv'n [%] ^[a]	ee [%]	Confign
C ₆ H ₅	H	(S),(S)- 35d	8	28	99.8 (99.8)	70	R
C ₆ H ₅	H	(R)- 37b	48	60	72 (97)	65	R
2,6,6-trimethyl-cyclohexenyl	H	(R),(R,R)- 35e	8	28	>99 (>99)	92	S
-(CH ₂) ₃ -		(S),(S)- 35d	4	28	100 (98.7)	91	R
-(CH ₂) ₄ -		(S),(S)- 35d	8	28	99.6 (>99.9)	98	R

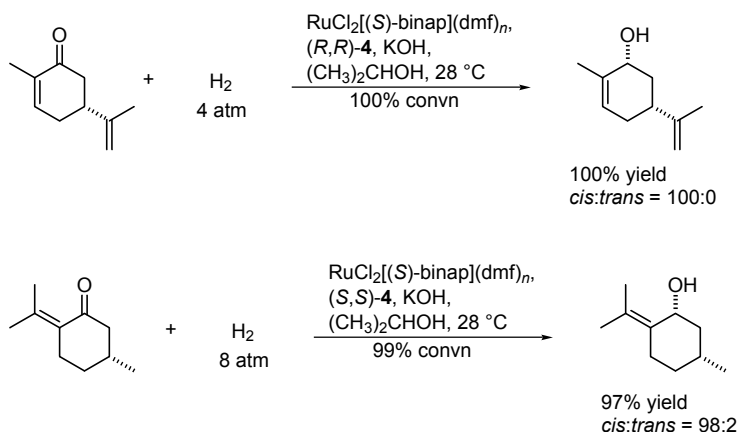
^[a] Content of an allylic alcohol in the whole product is described in parenthesis.

Scheme 22

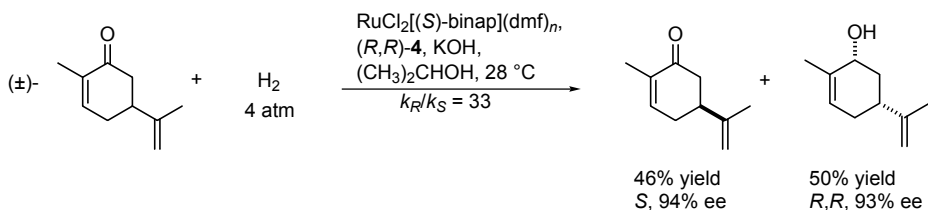


Scheme 23

Hydrogenation of (*R*)-carvone having an isopropenyl group at the C5 stereogenic center has many selectivity problems including 1,2 vs 1,4 selectivity in the conjugated enone moiety, conjugated vs isolated C=C chemoselectivity, and, if the C=O is more reactive, *cis* vs *trans* diastereoselectivity with respect to the C5 substituent. When it is hydrogenated with an (*S*)-BINAP-(*R,R*)-**4** combined system, only (*R,R*)-carveol is produced in 100% yield (Scheme 24) [81]. The reaction occurs with perfect carbonyl-selectivity, leaving both conjugated and non-conjugated C=C bonds intact and with complete 1,5-*cis* stereoselectivity. Reac-



Scheme 24



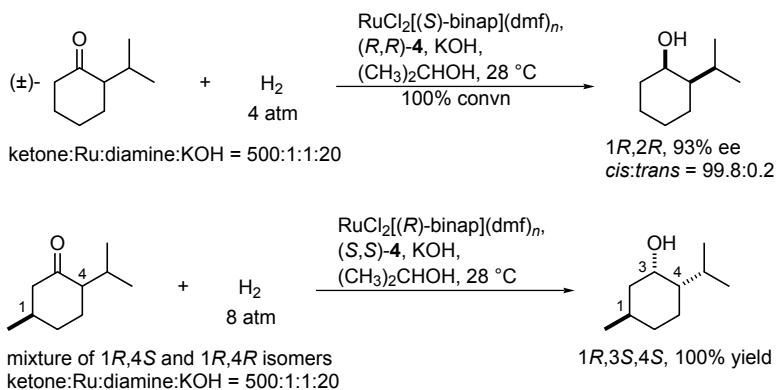
Scheme 25

tion with the enantiomeric (*R*)-BINAP-(*S,S*)-4 catalyst system proceeds rather slowly, affording a 34:66 mixture of the *cis*- and *trans*-isomers in 98% yield. Hydrogenation of (*R*)-pulegone, an *s-cis* chiral enone, with an (*S*)-BINAP-(*S,S*)-4 catalyst system takes place solely at the C=O function to give the *cis*-alcohol and the *trans*-isomer in a 98:2 ratio and in 97% yield [81]. Unlike the reaction of carvone, the combination of an *S* diphosphine and *S,S* diamine displays the highest rate and stereoselectivity. When racemic carvone is hydrogenated with an (*S*)-BINAP-(*R,R*)-4-modified Ru catalyst under the standard conditions, there are obtained unreacted (*S*)-carvone and (1*R*,5*R*)-carveol in high enantiomeric purity (Scheme 25) [81]. The extent of the enantiomer differentiation, k_R/k_S , is calculated to be 33:1.

3.3

Dynamic Kinetic Resolution

As described in section 2.5, chiral ketones having a configurationally labile α stereogenic center can be hydrogenated to a single hydroxy compound among four possible stereoisomers. This methodology utilizing dynamic kinetic resolution is applicable to some α -substituted cycloalkanones. For example, hy-



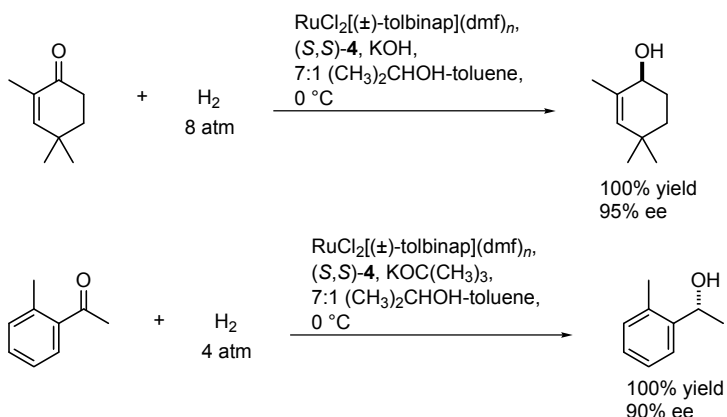
Scheme 26

drogenation of racemic 2-isopropylcyclohexanone catalyzed by a $\text{RuCl}_2[(S)\text{-binap}](\text{dmf})_n\text{-}(R,R)\text{-4}$ combined system in 2-propanol containing an excess amount of KOH gives a 1R,2R alcohol in 93% ee (*cis:trans*=99.8:0.2) (Scheme 26) [84]. The reaction is highly enantio- and diastereoselective. Computer-aided analysis shows that the *R* ketone is hydrogenated 36 times faster than the *S* substrate in the presence of the chiral catalyst and that stereochemical inversion at the α position occurs 47 times faster than hydrogenation of the slow-reacting *S* ketone. In a similar manner, in the presence of an (*R*)-BINAP-(*S,S*)-4 combined system, (–)-menthone possessing a configurationally stable C1 and an unstable C4 chiral center is hydrogenated to give (+)-neomenthol with perfect stereoselectivity [84]. The C1 stereogenic center helps the diastereoface discrimination by a chiral reducing intermediate.

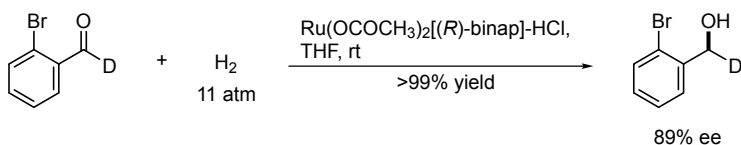
3.4

Asymmetric Activation

The enantiomer-selective activation of racemic metal complexes is a viable methodology for practical asymmetric catalysis whenever optically pure ligands are not easily obtained [85]. In certain cases, one of the catalyst enantiomers can be selectively activated by addition of an appropriate nonracemic auxiliary. For example, racemic $\text{RuCl}_2(\text{tolbinap})(\text{dmf})_n$ is a feeble catalyst for hydrogenation of simple ketones. However, a catalyst system formed from the racemic complex and 1 equiv of (*S,S*)-4 in a 2-propanol-toluene mixture of containing a small amount of KOH effects hydrogenation of 2,4,4-trimethyl-2-cyclohexenone, giving quantitatively an (*S*)-allylic alcohol in 95% ee (Scheme 27) [82]. The ee value is very close to the 96% ee which is attained by using a combination of enantiomerically pure (*R*)-TolBINAP and (*S,S*)-4 (see Scheme 23). The degree and sense of asymmetric induction are highly dependent on the structures of the diphosphine, diamine, and ketone substrate. For example, under the same catalytic conditions, *o*-methylacetophenone gives an *R* alcohol in 90% ee [82]. Separate



Scheme 27



Scheme 28

experiments show that hydrogenation of the substrate with an enantiomerically pure complex consisting of the (*S*)-BINAP-Ru(II) complex and (*S,S*)-4 gives the *R* alcohol in 97.5% ee and that reaction employing (*R,R*)-4 affords the *R* product in only 8% ee [82].

3.5

1-Deuterio Aldehydes

Scheme 28 illustrates the asymmetric hydrogenation of 1-deuterio *o*-bromobenzaldehyde catalyzed by an (*R*)-BINAP-Ru complex and 5 equiv of HCl giving a 1-deuteriobenzyl alcohol in 89% ee [86]. The bromine atom at the *o* position tends to increase the enantioselectivity through its interaction with the metal center of the catalyst. Deuteration of benzaldehyde with this catalyst occurs much more slowly.

4

Transfer Hydrogenation

Transfer hydrogenation of ketones employs stable organic molecules such as 2-propanol [2, 87, 88] and formic acid [89] as hydrogen donors in place of hydrogen gas. This reaction, promoted by a transition metal complex or a main group metal alkoxide, is useful for a small- or medium-scale reduction because

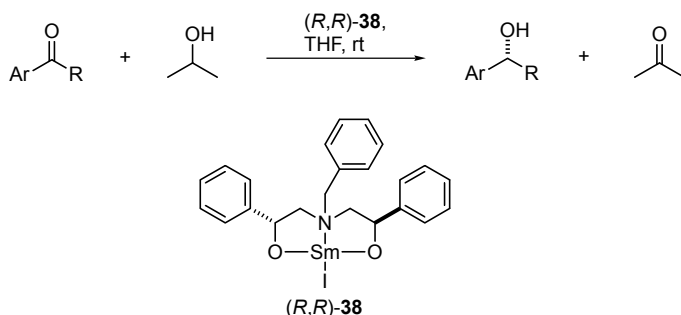
of its operational simplicity. Furthermore, the selectivity including functional group differentiation may be different from those of hydrogenation. Recently, some successful examples of catalytic asymmetric transfer hydrogenation have been reported.

4.1

Meerwein-Ponndorf-Verley Type Reduction

Reduction of ketones using 2-propanol or related alcohols is referred to as Meerwein-Ponndorf-Verley (MPV) reduction [2a, 2d, 87]. Historically, metal alkoxides, typically aluminum 2-propoxide, have been used as stoichiometric promoters for this purpose. The hydrogen migration is conceived to occur through a direct, pericyclic mechanism involving a metal alkoxide and ketonic substrate [90]. Recently, certain lanthanide complexes have proved to act as excellent catalysts [91, 92].

Asymmetric MPV type reduction can be achieved by using a chiral Sm(III) complex **38** (Scheme 29) [93]. Several aryl methyl ketones are reduced in an excellent optical yield, up to 97%. Electronic properties of substrates profoundly affect the reactivity. For example, a *p*-chloro substituent in the benzene ring accelerates the reaction, whereas a *p*-methoxy substituent decelerates the reduction. The presence of an *o*-chloro or *o*-methoxy group effectively enhances the



R	Ar	Conv'n [%]	ee [%]
CH ₃	C ₆ H ₅	83	96
CH ₃	C ₆ H ₄ - <i>o</i> -Cl	100	97
CH ₃	C ₆ H ₄ - <i>o</i> -OCH ₃	100	96
CH ₃	C ₆ H ₄ - <i>p</i> -NO ₂	100	94
CH ₃	C ₆ H ₄ - <i>p</i> -OCH ₃	43	92
CH ₃	1-naphthyl	98	97
C ₂ H ₅	C ₆ H ₄ - <i>o</i> -Cl	95	68

Scheme 29

rate of reduction, perhaps due to the two-point interaction with the central metal. In addition, the degree of enantioselection is highly sensitive to the alkyl group; increasing the size of alkyl group decreases the enantioselectivity. Enantiomeric purity of products is independent of reaction conversion.

4.2

Transition Metal Catalyzed Reduction

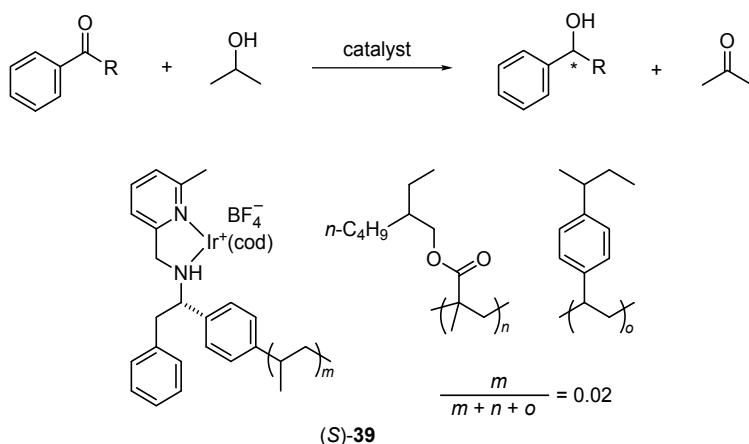
4.2.1

Simple Ketones

Asymmetric transfer hydrogenation of simple ketones has been intensively studied using chiral Rh, Ir, and Ru catalysts [2b, 2c]. Both hydrogenation and transfer hydrogenation are supposed to involve commonly a metal hydride as reducing species [1c, 94, 95]. However, unlike asymmetric hydrogenation where chiral phosphine ligands normally show an excellent performance, transfer hydrogenation uses frequently nitrogen-based chiral ligands [2c], as exemplified in Fig. 2, Fig. 3, Fig. 4, Fig. 5, and Fig. 6. Alkaline bases often act as crucial cocatalysts. In most cases, 2-propanol is used as a hydrogen donor and also as a solvent because of its chemical stability, high solubility of substrates, low toxicity, operational simplicity, and low cost.

Since chiral Ir(I) complexes were found to catalyze asymmetric transfer hydrogenation using 2-propanol, extensive efforts have been devoted to develop an effective asymmetric reduction [2c]. An Ir catalyst prepared in situ from $[\text{IrCl}(\text{cod})]_2$ and a C_2 chiral tetrahydrobis(oxazole) ligand **12** first achieved asymmetric reduction of aromatic ketones in an optimal yield greater than 90% (Scheme 30) [96]. The enantioselectivity is decreased to some extent at higher conversion. Reduction of dialkyl ketones gives racemic alcohols in low yields. A neutral Ir complex having a chiral TsDPEN (**13**) shows a high enantioselectivity for reduction of acetophenone [97]. However, reduction catalyzed by a Rh complex with the same ligand shows lower reactivity and enantioselectivity. The chiral diamine **5** without any substitution on nitrogen atoms also acts as an effective ligand for asymmetric reduction of alkyl aryl ketones in 2-propanol containing KOH [98]. The reactivity and enantioselectivity are sensitive to the steric and electronic properties of the alkyl and aryl groups. Asymmetric reduction of sterically hindered pivalophenone is effected by an $\text{IrI}(\text{cod})[(S)\text{-10}]\text{-NaI-H}_2\text{O}$ system in 2-propanol containing KOH to afford an *S* alcohol selectively [99]. The addition of NaI is supposed to increase the concentration of a neutral species showing a high enantioselectivity. A cationic DHPPEI (**8**)-Ir(I) complex is effective specifically for asymmetric reduction of 1,4-diphenyl-1-butanone [2c]. Significantly, the immobilized system **39** is much more reactive and enantioselective than the homogeneous catalyst in reaction of butyrophenone [2c].

The extent of asymmetric induction with chiral Rh(I) complexes remains unsatisfactory. Enantioselective reduction of acetophenone catalyzed by a Rh complex of the chiral phenanthroline **11** in 2-propanol containing KOH at 60 °C af-

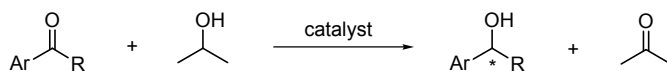


R	Catalyst	Temp. [°C]	Yield [%]	ee [%]	Confign
CH ₃	[IrCl(cod)] ₂ -(R,R)-13+KOC(CH ₃) ₃	rt	87	92	S
C ₂ H ₅	[IrCl(cod)] ₂ -(S)-5+KOH	rt	96	93	R
<i>n</i> -C ₃ H ₇	(S)-39+KOH	60	92	84	S
(CH ₂) ₃ C ₆ H ₅	[Ir(cod)((R)-8)]BF ₄ +KOH	60	–	>90	–
CH(CH ₃) ₂	[IrCl(cod)] ₂ -(S,S)-12+KOH	80	70	91	R
C(CH ₃) ₃	IrI(cod)[(S)-10]-NaI-H ₂ O+KOH	83	91	84	S

Scheme 30

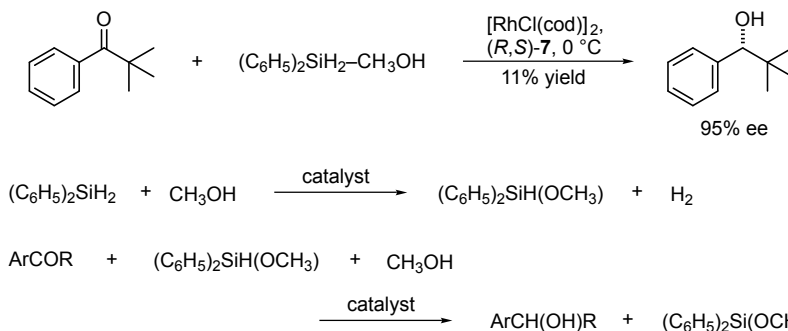
fords an chiral alcohol in 62% ee (Scheme 31) [100]. Such phenanthroline ligands effectively activate Rh(I) complexes, giving a TOF of up to 12,000 per h [2c]. In the presence of the DMDPEN (3)-Rh(I) catalyst, *p*-cyanoacetophenone is reduced to an alcohol in 73% ee [101]. The use of 4 decreases the enantioselectivity. A Rh complex with the chiral diurea 15 shows a moderate to good enantioface selection, up to 80%, for reduction of alkyl aryl ketones [102]. Reduction of *p*-methylacetophenone catalyzed by a Rh complex with AMSO (17) gives an alcohol in 75% ee [103].

As illustrated in Scheme 32, a diphenylsilane-methanol system acts as a hydrogen donor for the reduction of alkyl aryl ketones in the presence of a Rh(I) complex consisting of [RhCl(cod)]₂ and the chiral bis(aminoethylferrocenyl) diselenide 7 [104]. Pivalophenone is thus converted to a chiral alcohol in 95% ee although in a low yield. In the presence of a Rh catalyst, diphenylsilane first reacts with methanol to generate methoxydiphenylsilane and hydrogen, and then a ketone reacts with methoxydiphenylsilane and methanol to afford an alcohol and dimethoxydiphenylsilane.



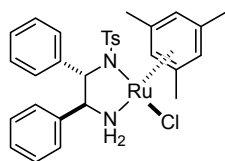
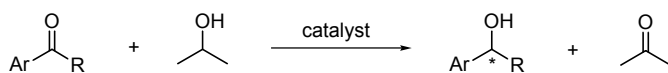
R	Ar	Catalyst	Temp. [°C]	Convsn [%]	ee [%]	Confign
CH ₃	C ₆ H ₅	[RhCl(C ₆ H ₁₀)] ₂ -(S)-11+KOH	60	94	62	S
CH ₃	C ₆ H ₄ - <i>p</i> -CH ₃	[RhCl(C ₆ H ₁₀)] ₂ -(S)-17+KOH	82	31	75	R
CH ₃	C ₆ H ₄ - <i>p</i> -CN	[RhCl(C ₆ H ₁₀)] ₂ -(S,S)-3+KOH	25	100	73	R
C ₂ H ₅	C ₆ H ₅	[RhCl(cod)] ₂ -(S,S)-15+KOC(CH ₃) ₃	60	87	80	R

Scheme 31

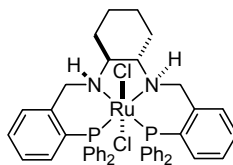


Scheme 32

Pioneering work on Ru-catalyzed transfer hydrogenation has been done with tertiary phosphine-based complexes [95, 105]. However, the enantioselectivity remained moderate [105]. Recently, Ru(II) complexes of type [RuCl₂(arene)]₂ were used as convenient catalyst precursors [106]. Scheme 33 lists some examples of asymmetric transfer hydrogenation of simple aromatic ketones in 2-propanol. The Ru catalysts prepared using [RuCl₂(arene)]₂ and 13 as a chiral auxiliary exhibit an excellent enantioface-discrimination ability [107, 108]. For example, acetophenone is reduced with a Ru complex formulated as (S,S)-40 at room temperature using a 0.1 M solution of 2-propanol containing KOH to give (S)-1-phenylethanol in 95% yield and in 97% ee. In the asymmetric reaction of aromatic ketones, the rate and enantioselectivity are highly sensitive to the steric crowding of the substrates as well as the electronic natures of the substituents in benzene rings. A Ru catalyst with an *N*-arenesulfonylated derivative of chiral cyclohexanediamine 14 shows high enantioselectivity, while a Ru catalyst with a chiral diamine 6 is effective even at -30 °C [109]. Furthermore, a high level of



(S,S)-40



(S,S)-41

R	Ar	Catalyst	Temp. [°C]	Yield [%]	ee [%]	Confign
CH ₃	C ₆ H ₅	(S,S)-40+KOH	rt	95	97	S
CH ₃	C ₆ H ₅	[RuCl ₂ (<i>p</i> -cymene)] ₂ -(R,R)-14+KOH	22	96	92	R
CH ₃	C ₆ H ₅	[RuCl ₂ (<i>p</i> -cymene)] ₂ -(R,S)-18+KOH	rt	70	91	S
CH ₃	C ₆ H ₅	(S,S)-41+KOCH(CH ₃) ₂	45	93	97	R
CH ₃	C ₆ H ₄ - <i>m</i> -Cl	(S,S)-40+KOH	rt	98	98	S
CH ₃	1-naphthyl	[RuCl ₂ (<i>p</i> -cymene)] ₂ -(R,R)-6+KOH	-30	91	90	R
CH ₃	1-naphthyl	[RuCl ₂ (C ₆ (CH ₃) ₆)] ₂ -(S,S)-20+KOH	28	99	93	S
CH ₃	2-naphthyl	(S,S)-40+KOH	rt	93	98	S
C ₂ H ₅	C ₆ H ₅	RuCl ₂ [P(C ₆ H ₅) ₃] ₃ -(S)-24+KOCH(CH ₃) ₂	50	85	96	R
CH(CH ₃) ₂	C ₆ H ₅	[RuCl ₂ (C ₆ H ₆)] ₂ -(R,R)-16+KOC(CH ₃) ₃	82	92	94	S
CH(CH ₃) ₂	C ₆ H ₅	RuCl ₂ [(S)-23][P(C ₆ H ₅) ₃]+NaOH	82	87	92	R
C(CH ₃) ₃	C ₆ H ₅	[RuCl ₂ (C ₆ H ₆)] ₂ -(R,R)-21+NaOCH(CH ₃) ₂	0	96	80	S

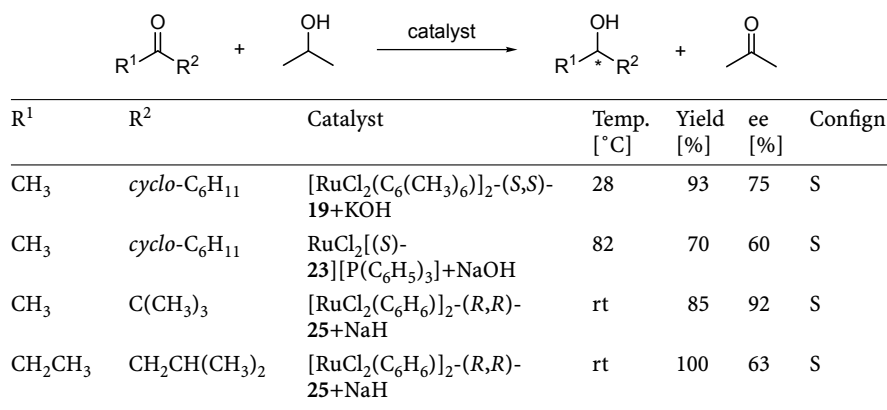
Scheme 33

enantioselectivity is obtained, when an appropriate [RuCl₂(arene)]₂ complex [110] and a chiral β-amino alcohol auxiliary are combined. Ru(II) complexes containing **20** effect asymmetric transfer hydrogenation of aromatic ketones with a higher rate and slightly lower enantioselectivity in comparison to the reaction with **13** [111]. The amino alcohol ligand **18** is also suitable [112]. In these reactions, the presence of an NH₂ or NH terminus in the chiral auxiliaries is crucially important to obtain a high rate and enantioselectivity. The chiral auxiliary **21** is useful for asymmetric reduction of sterically hindered pivalophenone

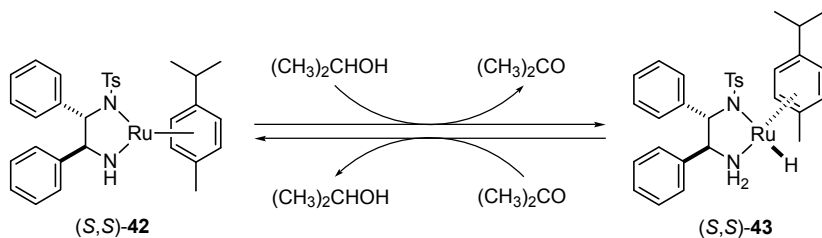
[113]. The chiral bithiourea **16** can also be used for asymmetric reduction of alkyl aryl ketones [114].

High reactivity and enantioselectivity are attainable when a Ru complex with an appropriate chiral aminophosphine ligand is employed as catalyst, whereas simple phosphine-Ru catalysts are not very effective. The use of a $\text{RuCl}_2(\mathbf{23})\text{-}[\text{P}(\text{C}_6\text{H}_5)_3]\text{-NaOH}$ catalyst system in 2-propanol affords an extremely high reaction rate in reaction of acetophenone, the turnover frequency at 82 °C being 42,600 per h [115, 116]. The extent of enantioselection in the reaction of alkyl aryl ketones increases on increasing of bulkiness of the alkyl group in the substrate, as exemplified by reduction of isobutyrophenone in up to 92% optical yield. The aminophosphine ligand **24** also gives 96% optical yield in reduction of propiophenone, where the presence of $\text{P}(\text{C}_6\text{H}_5)_3$ is crucial to obtain a high selectivity [117]. A hexacoordinate Ru complex **41** prepared from *trans*- $\text{RuCl}_2(\text{dmsO})_4$ and the C_2 -symmetrical diphosphine/diamine ligand **22** effects conversion of various acetophenone derivatives to substituted 1-phenylethanols in up to 97% ee [118]. The highest enantioselectivity is obtained when a half equiv of $\text{KOCH}(\text{CH}_3)_2$ with respect to Ru is added. The Ru complex with a structurally similar diphosphine/diimine analogue is much less reactive, indicating that the presence of the NH functions is important for the high reactivity of this system.

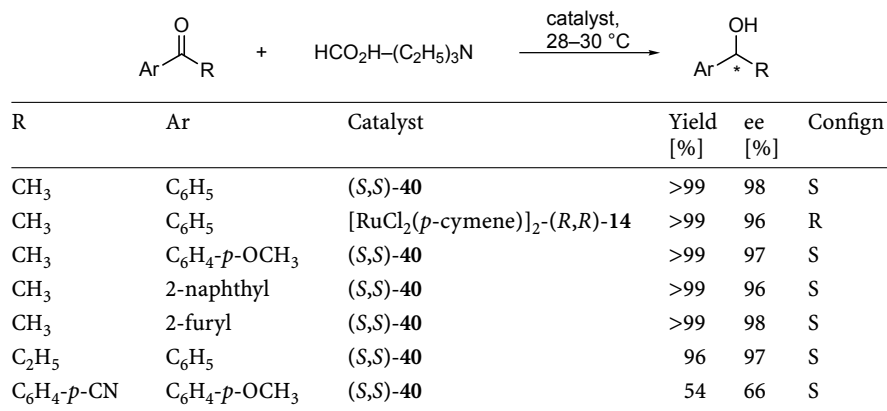
Highly enantioselective reduction of simple aliphatic ketones is difficult to achieve. However, when a Ru catalyst is prepared from $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$, tridentate ligand **25**, and a base, reduction of pinacolone in 2-propanol occurs at room temperature to give a chiral alcohol in 92% ee and 85% yield (Scheme 34) [119]. 5-Methyl-3-hexanone is reduced quantitatively in 63% optical yield. Asymmetric reduction of cyclohexyl methyl ketone with a $[\text{RuCl}_2(\text{C}_6(\text{CH}_3)_6)]_2\text{-}(S,S)\text{-19}$ [111] or $\text{RuCl}_2[(S)\text{-23}][\text{P}(\text{C}_6\text{H}_5)_3]$ [115] system in 2-propanol gives an *S* alcohol in 75 or 60% ee, respectively.



Scheme 34



Scheme 35



Scheme 36

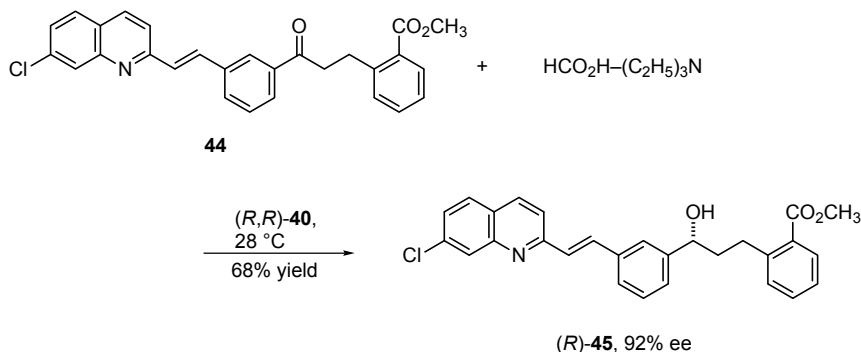
The real catalytic species **42** and key reactive intermediate **43** in asymmetric transfer hydrogenation with a chiral ligand **13**-Ru(II) complex were isolated and characterized (Scheme 35) [120]. Examination of the reactivities of the two complexes as well as the kinetic study fully revealed the reaction mechanism. When the purple complex **42** is treated with 2-propanol at room temperature in the absence of any base, rapid elimination of acetone took place to produce the yellow Ru hydride species **43**. The treatment of this 18-electron species **43** with 10-fold excess of acetone produced instantaneously the 16-electron species **42** and 2-propanol. The purple complex (S,S)-**42** indeed catalyzes the asymmetric reduction of acetophenone in 2-propanol without any base to give (S)-1-phenylethanol in 95% ee. The yellow complex **43** acts in the same manner. Thus a base is required only for the generation of the catalyst **42** from a precursor Ru chloride by elimination of HCl.

2-Propanol is a useful hydrogen donor for catalytic transfer hydrogenation of ketones. However, the unfavorable ketone:alcohol equilibrium ratio often prevents a high conversion [121]. Moreover, the occurrence of its reverse process, due to the 2-propanol/alcoholic product and substrate/acetone structural similarities, frequently deteriorates the enantiomeric purity of the chiral product at the late stage of reaction. Use of the formic acid, another well-behaving and in-

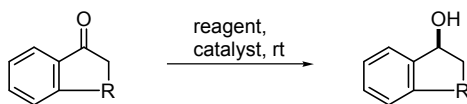
expensive reducing agent, avoids these problems [89]. Because this hydrogen donor, an adduct of H_2 and CO_2 [122], makes the reduction irreversible with truly kinetic enantioselection and, in principle, 100% conversion. In fact, reduction of acetophenone with a 5:2 formic acid- $N(C_2H_5)_3$ azeotropic mixture [123] in the presence of the isolated Ru complex (*S,S*)-**40** at 28 °C gives quantitatively (*S*)-1-phenylethanol in 98% ee (Scheme 36) [108, 124]. Various alkyl aryl ketone can be reduced with a high ee in a 2 to 10 M solution. The presence of $N(C_2H_5)_3$ is necessary to gain a high reactivity. In the presence of (*S,S*)-**40**, 2-acetylfuran is converted to an *S* alcohol without saturating the furan ring. A thiophene ring is not effected either. Reaction of a benzophenone derivative which has a methoxy and cyanide group at the *p*- and *p'*-positions gives the *S* alcohol in 66% ee [124]. A Ru complex generated from $[RuCl_2(p\text{-cymene})_2]$ and (*R,R*)-**14** is also effective for asymmetric reduction using a formic acid- $N(C_2H_5)_3$ mixture [109].

Ketone-selective hydrogenation of a multi-functionalized ketone **44** is achieved by transfer hydrogenation with **40** in a formic acid- $N(C_2H_5)_3$ mixture. In fact, reduction catalyzed by (*R,R*)-**40** gives the desired (*R*)-**45** in 92% ee without affecting the olefinic bond, halogen atom, quinoline ring, and ester group (Scheme 37) [124]. The chiral alcoholic product is an important intermediate in the synthesis of L-699,392 (LTD₄ antagonist) [125].

Notably, the Ru(II) complexes with a chiral ligand **13** achieve highly efficient asymmetric reduction of α -tetralone or α -indanone to give the corresponding chiral cyclic alcohols in up to 99% ee and in 99% yield (Scheme 38) [107, 108, 124]. The low oxidation potential of these substrates prevents the completion of the reaction under equilibrium conditions using 2-propanol as a hydrogen donor [107, 121]. Reduction of α -tetralone with 2-propanol containing a Ru catalyst with a chiral amino alcohol **18** [112] or **19** [111] gives an alcohol in a moderate yield though with an excellent enantioselection. The use of a formic acid- $N(C_2H_5)_3$ system has solved the inherent problem and achieved almost perfect asymmetric synthesis of chiral secondary alcohols [124]. The sense of enantioface discrimination is the same as that in reduction of acyclic aromatic ketones.

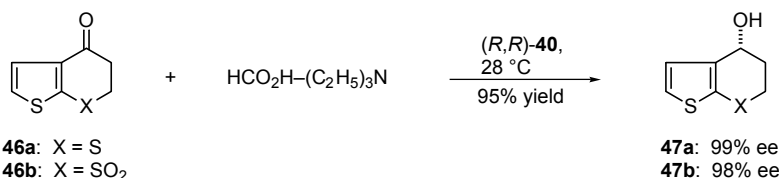


Scheme 37



R	Reagent	Catalyst	Yield [%]	ee [%]
CH ₂	(CH ₃) ₂ CHOH	(S,S)- 40 +KOH	45	91
CH ₂	HCO ₂ H-(C ₂ H ₅) ₃ N	(S,S)- 40	>99	99
(CH ₂) ₂	(CH ₃) ₂ CHOH	(S,S)- 40 +KOH	65	97
(CH ₂) ₂	(CH ₃) ₂ CHOH	[RuCl ₂ (<i>p</i> -cymene)] ₂ -(R,S)- 18 +KOH	40	98
(CH ₂) ₂	(CH ₃) ₂ CHOH	[RuCl ₂ (C ₆ (CH ₃) ₆)] ₂ -(S,S)- 19 +KOH	62	94
(CH ₂) ₂	HCO ₂ H-(C ₂ H ₅) ₃ N	(S,S)- 40	>99	99

Scheme 38



Scheme 39

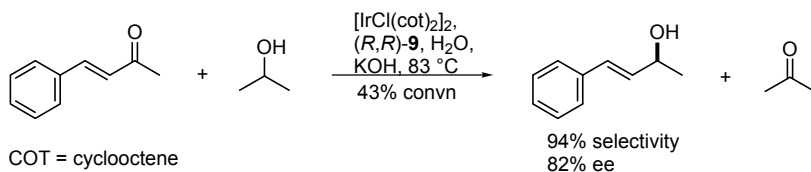
Asymmetric reduction of the sulfur-containing ketones **46a** and **46b** catalyzed by (*R,R*)-**40** leads to *R* alcohols **47a** and **47b** in >98% ee (Scheme 39) [124]. The products are key intermediates for the synthesis of MK-0417 which is a carbonic anhydrase inhibitor [126].

4.2.2

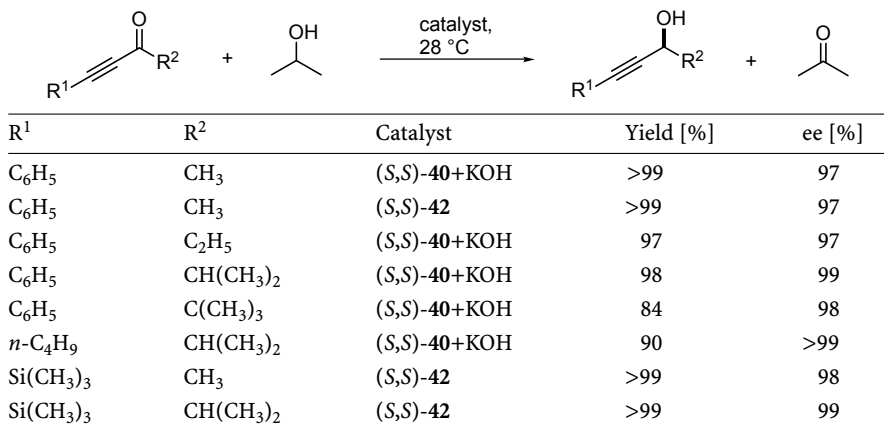
α,β-Olefinic and *α,β*-Acetylenic Ketones

Only a very few examples are known of catalytic systems which exhibit a high carbonyl-selectivity as well as enantioselectivity. Scheme 40 shows the reduction of benzalacetone catalyzed by an (*R,R*)-PDPBI ((*R,R*)-**9**)-Ir(I) complex with 2-propanol containing KOH and H₂O to afford an (*S*)-allylic alcohol with 82% ee at 43% conversion, the chemoselectivity being 94% [127]. The product ee is decreased to 67% at 90% conversion, while the carbonyl-selectivity is unaffected.

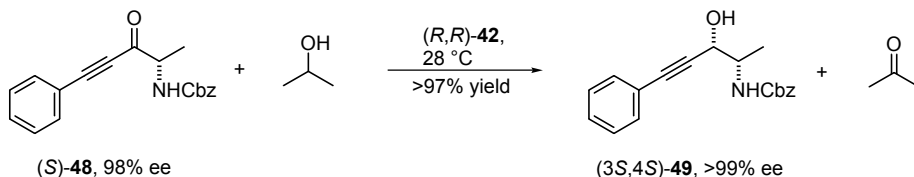
The chiral Ru(II) complex **40** with KOH or isolated catalyst **42** has proved to effect highly enantioselective transfer hydrogenation of various *α,β*-acetylenic ketones in 2-propanol [128]. As illustrated in Scheme 41, a range of propargylic alcohols is formed in an optically active form. The ee values are consistently high regardless of the bulkiness of the alkyl group in the ketonic substrates. 2-Propanol acts as the best hydrogen donor. The ynone/ynol thermodynamic balance



Scheme 40



Scheme 41



Scheme 42

favors the reduced form, so that high conversion, up to 99%, is attainable in such an equilibrium system. The use of a 1:1 mixture of formic acid and N(C₂H₅)₃ diminishes the catalytic activity.

Asymmetric transfer hydrogenation of α,β -acetylenic ketones with a pre-existing stereogenic center affords diastereomeric propargylic alcohols [128]. For example, reduction of a chiral amino ketone (S)-48 with (R,R)-42 in 2-propanol gives (3S,4S)-49 predominantly (Scheme 42), whereas reaction using (S,S)-42 affords the 3R,4S stereoisomer in >97% yield. The sense of diastereoface selection is mostly dependent on the chirality of the Ru catalyst.

4.2.3

Keto Esters

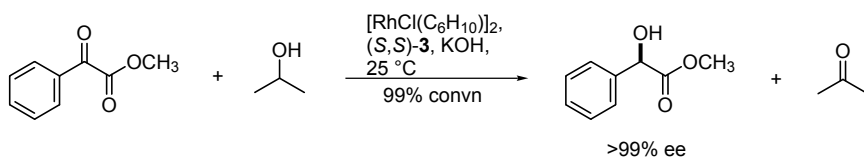
In contrast to asymmetric hydrogenation, examples of stereoselective reduction of functionalized ketones are rare. Scheme 43 illustrates the highly enantioselective reduction of methyl benzoylformate in 2-propanol containing KOH using a catalyst prepared in situ from $[\text{RhCl}(\text{C}_6\text{H}_{10})]_2$ and (*S,S*)-**3** [101]. With the same catalyst, methyl pyruvate is reduced in 5% optical yield.

Several aromatic keto esters are reduced with (*S,S*)-**40** and a formic acid- $\text{N}(\text{C}_2\text{H}_5)_3$ mixture [108, 124]. Scheme 44 shows some examples. The sense of enantioselection is the same as that in reduction of simple aromatic ketones, whereas the extent of enantioselectivity increases in the order of α -, β -, and δ -keto esters.

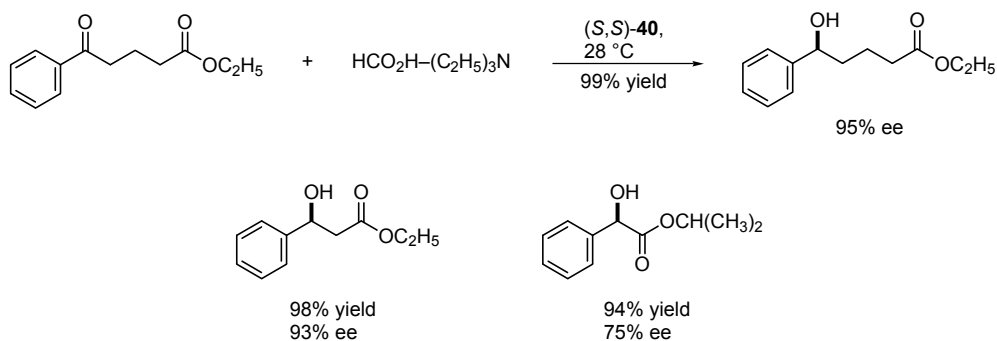
4.3

Kinetic Resolution of Racemic Alcohols

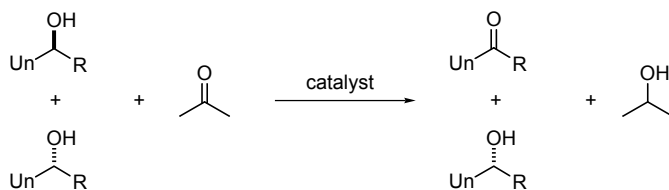
Dehydrogenative oxidation of secondary alcohols in the presence of acetone is the reverse process of transfer hydrogenation of ketones with 2-propanol [87b, 95b]. Kinetic resolution of racemic secondary alcohols is possible using this process with an appropriate chiral catalyst and suitable reaction conditions. As exemplified in Scheme 45, a variety of racemic aromatic or unsaturated alcohols can be effectively resolved in acetone with a diamine-based Ru(II) complex **42** or **50** [129]. Chiral alcohols with an excellent optical purity are recovered at about



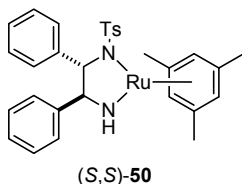
Scheme 43



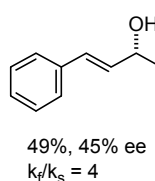
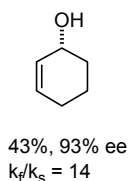
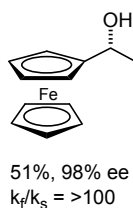
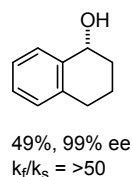
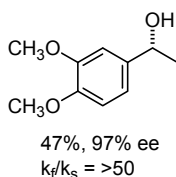
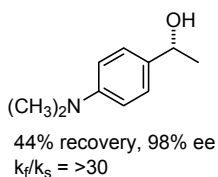
Scheme 44



catalyst = (S,S)-**42** or (S,S)-**50**



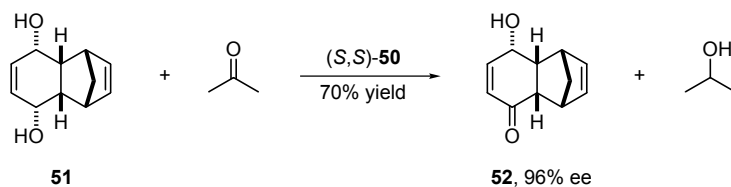
examples:



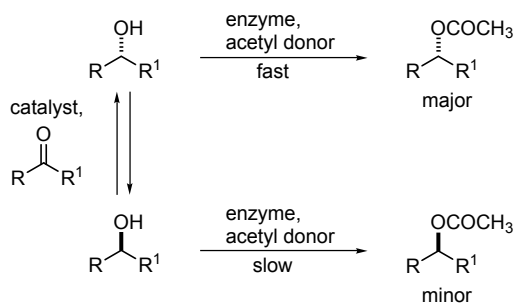
Scheme 45

50% conversion. The efficiency of the resolution, k_f/k_s , is up to $>100:1$. Chiral aromatic alcohols having a high reduction potential [121] are advantageously obtained by this process. These alcohols are difficult to obtain with a high optical purity through transfer hydrogenation of ketones in 2-propanol. Racemic 2-cyclohexanol, a simple cyclic allylic alcohol, is also successfully resolved by this method. The reaction of 4-phenyl-3-buten-2-ol, a flexible allylic alcohol, proceeds with only moderate enantioselectivity, however. Desymmetrization of an unsaturated diol **51** with acetone catalyzed by (S,S)-**50** gives **52** in 96% ee and 70% yield (Scheme 46) [129]. The hydroxy enone is an important building block in the syntheses of various bioactive compounds [130].

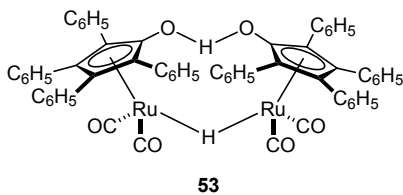
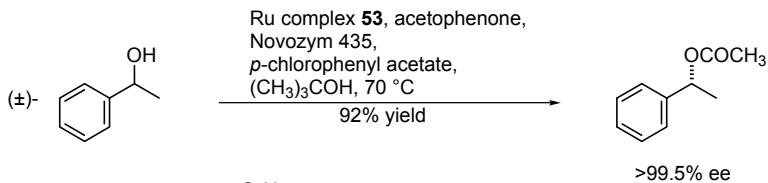
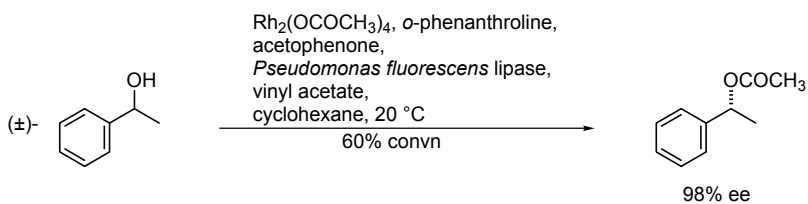
The enantiomer-selective acylation of racemic secondary alcohols using an enzyme is a reliable method for obtaining optically pure compounds in up to



Scheme 46



examples:



Scheme 47

50% yield [131]. The application of the principle of dynamic kinetic resolution (see section 3.3) increases the theoretical yield to 100%. Thus combination of the enzymatic resolution with chemical racemization of alcoholic substrates enables to obtain chiral esters in a high yield (Scheme 47) [132, 133]. Actually, racemic 1-phenylethanol can be converted to its *R* acetate with an excellent ee by the combined use of an achiral Rh or Ru complex, a suitable enzyme, acetophenone, and an acetyl donor. The presence of one equiv of acetophenone is required to achieve a reasonable reaction rate. The Ru complex **53** acts as the best racemization catalyst [133]. *p*-Chlorophenyl acetate is a suitable acetyl donor, because the deacetylated phenolic product does not retard the Ru-mediated racemization.

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Chapter 6.2

Hydrogenation of Imino Groups

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Keywords: Ansa-metallocene titanium complexes: imine hydrogenation, C=N hydrogenation: historical development, C=N reduction: assessment of catalysts, Cyclic imine hydrogenation: effective catalysts, Imine hydrogenation: mechanistic aspects, Ir complexes: imine hydrogenation, Miscellaneous C=N-X reduction: effective catalysts, N-Alkylimine hydrogenation: effective catalysts, N-Arylimine hydrogenation: effective catalysts, Rh Diphosphine complexes: C=N hydrogenation, Ru Complexes: C=N reduction

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1

Introduction and Background

The enantioselective reduction of prochiral C=N double bonds to obtain the corresponding chiral amines still represents a major challenge. Whereas many highly enantioselective chiral catalysts are known for the enantioselective hydrogenation of C=C and C=O bonds, only relatively few effective reduction methods are available for the corresponding C=N functions [1, 2, 3, 4, 5]. Imines and related C=N functions have some chemical peculiarities that make their stereoselective reduction more complex than that of ketones or olefins. Firstly, even though the preparation starting from the corresponding amine derivative and carbonyl compound is relatively simple, complete conversion is not always possible and formation of trimers or oligomers can occur. Then, the resulting C=N compounds are often sensitive to hydrolysis and the presence of enamine as well as *syn/anti* isomers can be a problem as demonstrated for the hydrogenation of imines [6] and of oximes [7]. In addition, many of the homogeneous catalysts can complex with both the starting material and the product imine and as a consequence, catalytic activity is often low.

In this contribution we first give a short description of the historical development of enantioselective C=N hydrogenations. Then, an overview on effective enantioselective catalysts for different types of C=N groups is presented, that is directed to the synthetic chemist involved in synthesis planning. The detailed discussion of the chemistry of selected asymmetric catalysts is meant for the catalyst specialist. Finally, the most useful methods are briefly assessed from a preparative as well as a technical point of view.

2

Historical Development

Chiral amines were always considered important targets for synthetic chemists and attempts to prepare such compounds enantioselectively date back quite early [8]. Table 1 gives selected milestones for the development of enantioselective catalysts for the reduction of C=N functions. At first, only heterogeneous hydrogenation catalysts such as Pt black [9], Pd/C [10], or Raney nickel [11,12] were applied. They were modified with chiral auxiliaries in the hope that some induction, i.e., transfer of chirality from the auxiliary to the reactant might occur. These efforts were undertaken on a purely empirical basis without any understanding of what might influence the desired selectivity. Only very few substrate types were studied and not surprisingly, optical yields were low and could not always be reproduced. The first reports on homogeneous Ru [13] and Rh [14] catalysts appeared in 1975, but useful enantioselectivities were reported by the Marko group only in 1984 [15]. Remarkable progress has been made in the 1990s and now, several very selective catalysts are available for different types of C=N functions. Moreover, the first industrial process was announced in 1996 [20].

Table 1. Selected milestones for the enantioselective hydrogenation of C=N functions

Year	Substrate	Catalyst	Chiral auxiliary ^a	ee (%)	Comment	Ref
1941	oxime	Pt black	menthoxyacetic acid	3	first reported experiment	9
1958	dioxime	Pd	silk fibroin	15	chiral support	10
1975	oxime	Ru complex	diop	15	homogeneous Ru catalyst	13
1975	imine	Rh complex	diop	22	homogeneous Rh catalyst	14
1984	C=N-Alk	Rh complex	bdpp	72	first useful ee	15
1989	C=N-Alk	Rh complex	bdpp _{sulf}	94	first very high ee	16
1990	C=N-Ar	Ir complex	bdpp	84	homogeneous Ir catalyst	17
1992	cyclic imine	Ti complex	ebthi	99	homogeneous Ti catalyst	6
1992	C=N-X	Rh complex	duphos	96	acyl hydrazone	18
1996	C=N-X	Ru complex	N [^] N	97	transfer hydrogenation	19
1996	MEA-imine	Ir complex	xylyphos	80	first industrial application	20

^afor structures of ligands see Fig. 1

3

Synthetically Useful Catalysts for Various C=N Functions

The nature of the substituent directly attached to the N-atom influences the properties (basicity, reduction potential, etc.) of the C=N function more than the nature of the substituents at the carbon atom. For example, it was found that the Ti-ebthi catalyst (Fig. 1) can hydrogenate only *N*-alkylimines but not *N*-arylimines [6]. Oximes and other C=N-X compounds show even a more pronounced variation in their reactivity. The following sections give a short summary of the results obtained for different classes of C=N groups. Only catalysts with synthetically useful selectivities or otherwise of interest were included in Tables 2, 3, 4, 5, and 6 (s/c: substrate/catalyst ratio, tof: turnover frequency at high conversion).

3.1

Enantioselective Reduction of *N*-Arylimines

Most efforts have been concentrated on 2,6-dialkyl-substituted-*N*-arylimines and several of these can be hydrogenated with good ees and modest to very high catalyst activity (Table 2). The reason for this interest is the fact that the corresponding amines with a stereogenic C-atom in an α -position to the nitrogen atom are intermediates for a number of important pesticides and that in many cases one stereoisomer carries most of the biological activity [21]. Because the corresponding ketimines are easily accessible, their enantioselective reduction has been investigated in much detail. In all cases, best results were obtained with Ir-diphosphine catalysts. With the exception of the Ir-bdpp catalyst (Table 2, entry 2.1) [22], the presence of extra iodide ions was usually necessary. For the Ir-ferrocenyldiphosphine catalysts [20], addition of acid led to a dramatic in-

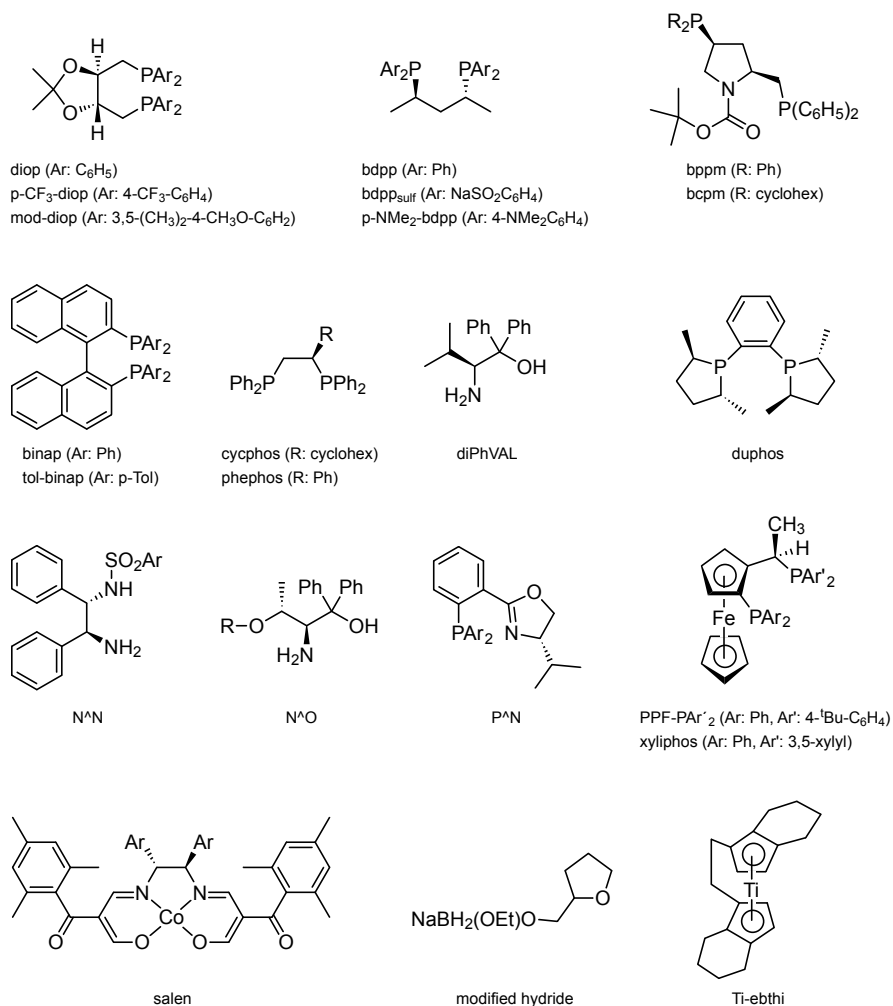


Fig. 1. Structures and abbreviations for chiral ligands

crease in activity and productivity. The reactions usually have to be carried out at relatively high hydrogen pressures. A production process was developed for the hydrogenation of the MEA imine, an intermediate for the Novartis herbicide Dual Magnum (Table 2, entry 2.2) using Ir-xylyphos in the presence of iodide and acid with 80% ee and extremely high s/c ratio and tof values [20].

For the model substrate *N*-phenyl-(1-phenylethylidene)amine, best results were obtained with an Ir phosphanodihydrooxazole catalyst (Table 2, entry 2.5) [23]. The highly enantioselective hydride reduction of the di-imine of entry 2.6 was accomplished with sodium borohydride and sub-stoichiometric amounts of a chiral amino alcohol as catalyst [24].

Table 2. Synthetically useful catalysts for the enantioselective reduction of *N*-arylimines **1** (see Fig. 2): Effective catalysts, reaction conditions, enantioselectivity, activity, and productivity

Entry	R	R'	R''	Catalyst	pH ₂ ^a (bar)	T (°C)	ee (%)	s/c	tof (h ⁻¹)	Ref
2.1		DMA-imine 1a		Ir-bdpp	40	30	90	500	40	22
2.2		MEA-imine 1b		Ir-xyliphos	80	50	80	1,000,000	>200,000	20
2.3		MEA imine 1b		Ir-PPF-PAr' ₂	70	-15	87 ^b	5000	30	39
2.4	Me	CH ₂ OMe	2,5-(Me) ₂ -thioph	Ir-PPF-PAr' ₂	20	5	80 ^{b)}	100	27	39
2.5	Me	Ph	Ph	Ir-P^N	100	5	89	1000	ca. 80	23
2.6	Ph(C=N-Ar)	-(C=N-Ar)Ph		B-N^O	BH ₃	r.t.	99 ^c	200	<1	24

^a or reducing agent^b optimized for selectivity^c of the diamine**Table 3.** Effect of imine structure on catalyst performance for the enantioselective reduction of *N*-arylimines **1** with Ir-diop iodide at 20 bar H₂ and r.t. [17]

Entry	R	R'	R''	ee (%)	tof (h ⁻¹)
3.1	Me	CH ₂ OMe	2-Me-6-Et-Ph	62	200
3.2	Me	CH ₂ OMe	2,6-(Me) ₂ -Ph	68	3.6
3.3	Me	n-Pr	2,6-(Me) ₂ -Ph	52	3.6
3.4	Me	n-Pr	Ph	16	18.5
3.5	Me	CH ₂ OMe	2,5-(Me) ₂ -thioph	58	27
3.6	Me	Ph	Ph	22	5

The only systematic study of the effect of the imine structure on enantioselectivity was reported in connection with the development of the Ir system for the hydrogenation of the MEA imine (see Table 3) [17]. With Ir-diop iodide as catalyst, both the 2,6-alkyl substituents (either Me or Et) of the *N*-phenyl group as well as the methoxy-substituent of R' contribute to the high enantioselectivity. Replacing the methoxy group of the DMA-imine by an ethyl group led to a decrease in ee from 69% to 52%; further replacement of the 2,6-dimethylphenyl group by phenyl gave an ee of 16% (Table 3, entries 3.2, 3.3, and 3.4). It is noteworthy that the 2,6-dimethylphenyl group could be replaced by a 2,5-disubstituted thien-3-yl group without loss in catalyst activity (Table 3, entry 3.5). These results indicate that the presence of an *ortho*-disubstituted ring is the essential requirement for good enantioselectivity. This in contrast to the result obtained for the Ir-phosphanodihydrooxazole system [23].

3.2 Enantioselective Reduction of *N*-Alkylimines

Up to now, most studies with *N*-alkylimines (Fig. 2) were carried out with model compounds, especially with *N*-benzyl-(1-phenylethylidene)amine (and some analogs). One reason for this choice could be the easy preparation of a pure crystalline starting material, another that the primary amines are accessible by hydrogenolysis of the benzyl group. As can be seen in Table 4, Rh-bdpp_{sulf} gave the highest enantioselectivity ever reported for the hydrogenation of an acyclic imine [16]. Rh-cycphos is also able to hydrogenate *N*-alkyl-(1-phenylethylidene) amines with >90% ees, but with rather low catalyst activity [25]. The novel Ir-phosphanodihydrooxazole (Ir-P^{AN}) catalyst (Table 4, entries 4.3 and 4.4) is probably not yet preparatively useful for this transformation (moderate ees, low *s/c* and *tof*) [23]. *N*-Alkylimines of cyclic ketones can be reduced with moderate to good enantioselectivities using a Ru-diamine complex and formate as transfer

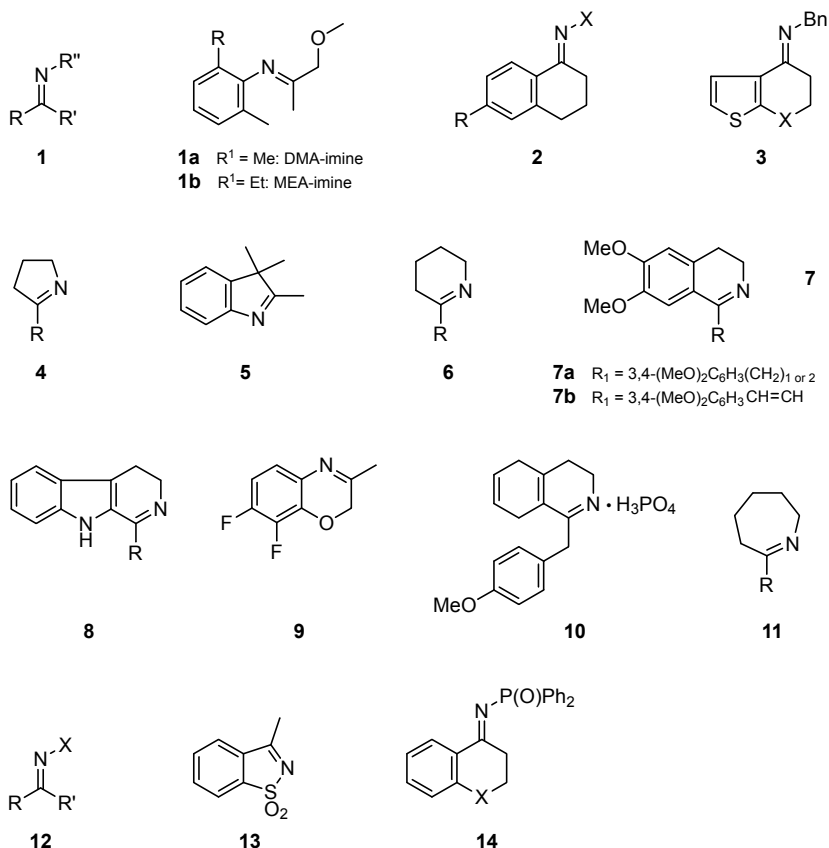


Fig. 2. Structures of substrate molecules

Table 4. Synthetically useful catalysts for the enantioselective reduction of various *N*-alkylimines: Catalyst, reaction conditions, enantioselectivity, activity, and productivity

Entry	C=N	R	R'	R''	Catalyst	pH ₂ ^a (bar)	T (°C)	ee (%)	s/c	tof (h ⁻¹)	Ref
4.1	1	Me	Ph	Bn	Rh-bdpp _{sulf}	70	20	94–96	100	16–85	16
4.2	1	Me	4-(MeO)-Ph	Bn	Rh-cycphos	100	-25	91	100	0.7	25
4.3	1	Me	p-Tol	Bn	Ir-P [^] N	100	r.t.	79	25	2	23
4.4	1	Me	Ph	n-Bu	Ir-P [^] N	100	r.t.	75	25	2	23
4.5	2	H		Bn ^b	Ru-N [^] N	F	28	89	100	15	19
4.6	3				Ru-N [^] N	F	28	85–88	100	7–17	19

^aor reducing agent, F = HCOOH·Et₃N

^bX group

reducing agent (Table 4, entries 4.5 and 4.6) [19]. In general, low s/c ratios have been applied and catalytic activities are very low for all catalysts described in Table 4 except for Rh-bdpp_{sulf} (tof up to 85 h⁻¹).

3.3

Enantioselective Reduction of Cyclic Imines (C=N Group Endocyclic)

Besides the cyclic model compounds **4**, **6**, and **11**, a number of endocyclic imines were investigated because they are intermediates for the synthesis of chiral compounds with biological activity. Indeed, there is a surprisingly high number of substrates that can be hydrogenated with preparatively useful selectivities as depicted in Table 5. Cyclic imines do not have the problem of *syn/anti* isomerism, therefore, in principle higher enantioselectivities can be expected. The most impressive difference in this respect was observed for Ti-ebthi-catalyzed hydrogenations that give ees up to 99% for several cyclic imines whereas non-cyclic imines are reduced with ees <85% [6]. Most hydrogenation reactions have to be carried out at relatively high hydrogen pressures and at low to moderate temperatures.

Much effort was dedicated to the reduction of dihydropapaverin or analogs thereof (**7** in Fig. 2). The resulting chiral amines are intermediates for natural and unnatural opioids. Very good enantioselectivities were reported for Ti-ebthi (Table 5, entry 5.6; see also entries 5.1 and 5.13) but tofs are rather low and the catalyst is quite difficult to handle. The Ru-catalyzed transfer hydrogenation with triethylammonium formate (Table 5, entries 5.7 and 5.8) and Ir-bcpm-catalyzed hydrogenation [26] (Table 5, entry 5.9) are also successful for imines of type **7**, both with moderate tofs. Similarly, the hydrogenation of **8** (Table 5, entry 5.10) leads to alkaloids with biological activity and again Ru-N[^]N is the catalyst of choice [19]. Compound **9** is an intermediate for a new antibacterial agent and can be hydrogenated by Ir-diop to give ees up to 85% (Table 5, entry 5.11) [27]. The formally diastereoselective reduction of folic acid in aqueous phase was accomplished with an Ir-bppm complex adsorbed on silica, whereas in homogeneous

Table 5. Synthetically useful catalysts for the enantioselective reduction of cyclic imines: Effective catalysts, reaction conditions, enantioselectivity, activity, and productivity

Entry	C=N	R	Catalyst	pH ₂ ^a (bar)	T (°C)	ee (%)	s/c	tof (h ⁻¹)	Ref
5.1	4	Alk, Ph	Ti-ebthi	5	45–65	99	100	0.6–2	6
5.2	5		Ir-bcpm	100	–30	91	200	2	30
5.3	5		Ir-Ar ₂ PF-PAr' ₂	70	15	94	250	14	39
5.4	6	Ph	Ti-ebthi	33	65	98	20	0.7	6
5.5	6	Ph	Ir-tol-binap	60	r.t.	91	100	5	29
5.6	7	H	Ti-ebthi	140	65	98	20	0.4	6
5.7	7	Ar	Ru-N [^] N	F	28	84	200	6–25	19
5.8	7a		Ru-N [^] N	F	28	92–95	200	15–30	19
5.9	7b		Ir-bcpm	100	2	86	200	6	26
5.10	8	Me, Ph	Ru-N [^] N	F	28	96–97	1000	35–83	19
5.11	9		Ir-diop	40	0	85	100	–	27
5.12	10		Ir-Ph ₂ PF-P(<i>t</i> -Bu) ₂	70	r.t.	89	1500	75	31
5.13	11	Ph	Ti-ebthi	33	45	98	20	0.7	6
5.14	folic acid		Rh-bppm ^b	50	80	92 ^c	40	<2	28

^aor reducing agent, F = HCOOH·Et₃N^badsorbed on SiO₂^cdiastereomeric excess of tetrahydrofolic acid

solution this complex showed very low selectivity (Table 5, entry 5.14) [28]. Ir-diphosphine catalysts allow the hydrogenation of model compounds **6** (Table 5, entry 5.5) and **5** (Table 5, entries 5.2 and 5.3) as well as of **10**, an intermediate for dextromethorphan (Table 5, entry 5.12) in 89–94% ee with low to good activity and productivity. A technical process has been developed for the latter reaction [31].

3.4

Enantioselective Reduction of Miscellaneous C=N-X Systems

Oximes that are easy to prepare and readily available were among the first C=N derivatives to be tried as starting material for the catalytic preparation of chiral amines. However, with the exception of entry 6.1 in Table 6, all results were disappointing especially for oximes of α -keto acid derivatives leading to α -amino acids [27]. In contrast, quite effective catalysts have been developed that can reduce related C=N-X compounds (suitable are NHCOR, P(O)Ph₂, and Ts) with good to very high ees and in some cases with good catalyst activities as well. A disadvantage of these types of substrate is the fact that the X group has to be split off in order to obtain the corresponding amine, whereas it is usually produced directly when reducing an oxime. Preparatively most useful is probably the hydrogenation of *N*-acyl hydrazones with the Rh-duphos catalyst (Table 6, entries 6.3 and 6.4). This reaction was developed by Burk and Feaster [18] in analogy to

Table 6. Synthetically useful catalysts for the enantioselective reduction of miscellaneous C=N-X systems: Effective catalysts, reaction conditions, enantioselectivity, activity, and productivity

Entry	C=N	R	R'	X	Catalyst	pH ₂ ^{a)} (bar)	T (°C)	ee (%)	s/c	tof (h ⁻¹)	Ref
6.1	12	Me	Ph	OMe	diPhVAL	BH ₃	r.t.	90	4	0.2	32
6.2	12	Me	Ph	P(O)Ph ₂	Co-salen	"H"	0	90	100	34	33
6.3	12	Me	Ar	NHCOPh	Rh-duphos	4	0	88–96	500	14–42	18
6.4	12	Ph	COOMe	NHCOPh	Rh-duphos	4	20	91	500	1000	18
6.5	12	Ph	Et	Ts	Ru-binap	70	40	84	20	<1	33
6.6	2	H		Ts	Ru-binap	70	40	82	20	<1	33
6.7	13				Ru-binap	4	r.t.	99	90	6	34
6.8	2	H, OMe		P(O)Ph ₂	Co-salen	"H"	0	98–99	100	22–25	35
6.9	14				Co-salen	"H"	0	91–94	100	20	35

^aor reducing agent ("H", modified hydride see Fig. 1)

^bX = O, CH₂CH₂ or direct bond

the well known hydrogenation of *N*-acyldehydroamino acid derivatives. The activity of the system is quite high with tofs up to 1000 h⁻¹. Several *N*-sulfonylimines can be hydrogenated with Ru-binap in high to very high optical yields but low activities (Table 6, entries 6.5 to 6.7). Finally, several types of *N*-diphenylphosphinylimines are reduced with a modified borohydride in presence of Co-salen complexes (Table 6, entries 6.2, 6.8, and 6.9). The enantioselectivities are very impressive but activities and s/c ratio are relatively low [35].

4

Discussion of Effective Catalysts

4.1

Homogeneous Metal Catalysts

All effective catalysts for the asymmetric reduction of prochiral C=N groups are based on complexes of rhodium, iridium, ruthenium, and titanium. Whereas in early investigations (before 1984) emphasis was on Rh and Ru catalysts, most recent efforts were devoted to Ir and Ti catalysts. In contrast to the noble metal catalysts which are classical coordination complexes, Buchwald's *ansa*-titanocene catalyst for the enantioselective hydrogenation of ketimines represents a new type of hydrogenation catalyst [6]. In this chapter important results and characteristics of effective enantioselective catalysts and are summarized.

4.1.1

Rhodium-Diphosphine Complexes

Most rhodium catalysts for the enantioselective reduction of the C=N group are prepared in situ from a dimeric Rh-diene complex and a chiral diphosphine. Only few of the tested diphosphine ligands exhibit enantioselectivities >70%: bdpp, cycphos, and phephos for imines and duphos for acylhydrazones. The activity of most Rh-diphosphine complexes for imine hydrogenation is low and therefore most of them are of limited practical use. Although some catalysts work already at ambient reaction conditions, most Rh-diphosphine complexes show low *tofs* even at elevated hydrogen pressures (>60 bar).

Interestingly, it was found that the highest *ees* were obtained with sulfonated diphosphines (bdpp_{sulf}) in an aqueous bi-phasic medium [16]. The degree of sulfonation affected the optical yield. For the hydrogenation of *N*-benzyl-*N*-(1-methylbenzylidene) amine in ethyl acetate-H₂O as solvent, the mono-sulfonated bdpp gave 94% *ee*, compared to 65% *ee* with Rh-bdpp in MeOH. In addition, the activity of the mono-sulfonated catalyst was higher by a factor of 5. A similar increase in enantioselectivity was reported for [Rh(nbd)(bdpp)]ClO₄ as catalyst precursor in presence of reverse AOT micelles (*ee* 92% vs. 80% in neat benzene) [36]. However, it appears that in this case the sulfonate anion, and not the micellar structure, is responsible for the observed increase in optical yields since addition of non-surfactant sulfonate salts also led to higher enantioselectivity. Different catalytic properties are also observed for neutral diphosphine catalysts prepared from [Rh(nbd)Cl]₂ and the corresponding cationic catalysts [Rh(nbd)diphosphine]⁺. It seems that the presence of halide ions affects both the hydrogenation rate as well as the enantioselectivity, albeit differently for different substrates. Whereas the asymmetric hydrogenation of *N*-benzylketimines is affected favorably by the addition of halides [15, 25], the Rh-catalyzed hydrogenation of DMA-imine is inhibited by the presence of iodide [25]. In some cases, the neutral and the cationic catalysts even lead to the opposite product enantiomer [15]. Obviously, the coordination sphere of the rate- and product-determining species is quite different for the two types of Rh complexes.

The reproducibility of rate and enantioselectivity can be a problem as described by the Marko group for the cationic catalyst [Rh(nbd)diphosphine]⁺ and *N*-benzyl-*N*-(1-methylbenzylidene)amine as model substrate [15]. Extensive efforts to find a correlation between purity of imine, water and oxygen content and the catalyst performance were not successful. However, these problems are not uncommon for enantioselective catalytic reactions but were not addressed any more in reports published at a later stage by Marko or other groups.

4.1.2

Iridium Complexes

In the last decade, several types of Ir-based catalysts were developed and applied successfully. The most efficient type, prepared from [Ir(cod)Cl]₂, a chiral di-

phosphine and a halide (iodide), proved to be much more active for the enantioselective hydrogenation of *N*-arylketimines than the rhodium analogs [17]. Despite a significant tendency for deactivation (strongly dependent on temperature, ligand structure, solvent and the basicity of the formed aniline derivative) several Ir catalyst are of practical use for the production of enantiomerically enriched *N*-arylamines. Under optimized reaction conditions, particularly highly pure starting materials, turnover numbers of >1000 can be obtained with a high reaction rate. Additives play a dominant but unpredictable role, acting either as promoters (acid, iodide, amines) or as deactivators (amines, iodide). Enantioselectivities in the range of 80% to >90% were achieved for several types of imines with the newly developed ferrocenyldiphosphines [37] and bdpp; diop also sometimes gives useful results.

For the commercially important MEA hydrogenation the simultaneous presence of acid and iodide promoters was reported to be a critical factor (besides the ligand structure of course) [20]. The dramatic effect was illustrated with a series of screening experiments using a catalyst generated *in-situ* from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and xyliphos. Without or with only one of these additives, the time for complete conversion was in the range of 10–16 h (s/c 800). When both tetrabutylammonium iodide and acetic acid were used, the initial rates increased by a factor of 5 and the time for complete conversion decreased by a factor of 20. The amount of acid necessary for full effect depends on the acid strength. Very strong acids such as H_2SO_4 can be used in extremely small concentrations, as long as the ratio of acid/Ir is >20. Weak acids are effective only at higher concentrations.

Systematic structure-activity relationship studies were carried out with Ir-diphosphine catalysts generated from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and iodide using MEA imine as substrate [20]. Some representative results are summarized in Table 7. Both chelate size and the nature of the substituent at the phosphorus atom affected the catalytic properties of the Ir catalysts. The highest activities as well as good optical yields were obtained with 1,3- and 1,4 diphosphines, in particular with bdpp, diop, and ferrocenyldiphosphines of the type $\text{Ar}_2\text{PF-PAR}'_2$. A comparison of the tof after 4 h and at the end of the reactions shows that Ir-ferrocenyldiphosphines catalysts are more stable than with classical ligands (Table 7, entries 7.1 to 7.6). The ligand bppm gave the best enantioselectivities but showed low activity even at 80 bar (Table 7, entry 7.1). Diop and substituted diop ligands showed similar catalyst performances (Table 7, entries 7.2 to 7.4). However, exchanging the Ph group in bdpp with *p*-(Me)N-Ph led to racemic product (Table 7, entries 7.5 and 7.6). 1,2-Diphosphines such as dipamp, norphos, or chiraphos but also bppfoh were rather unselective (results not shown [20]). Under the test conditions, Ir catalysts containing PPF-PAR'₂ (Table 7, entries 7.8 to 7.14) had quite a high inherent activity and showed little tendency towards deactivation, whereas basic phosphines such as PPF-Pcy₂ (Table 7, entry 7.7) were not very active. Especially PPF-P(3,5-xyl)₂ (xyliphos) turned out to give an exceptionally active catalyst and, even more importantly, it did not deactivate! With this catalysts s/c >10,000 and complete conversion could be achieved. Even from the limited number of examples in Table 7 it is clear that both steric and electronic proper-

Table 7. Hydrogenation of DMA imine with [Ir(cod)Cl]₂-iodide. Effect of diphosphine structure [20]

Entry	ligand	solv.	T °C	pH ₂ bar	tof ₅ ^a [h ⁻¹]	ee [%]
7.1	bppm	B	10	80	6	79
7.2	diop	A	25	25	32 (165)	61
7.3	mod-diop	A	25	25	28 (146)	59
7.4	<i>p</i> -CF ₃ -diop	A	25	25	32 (89)	61
7.5	bdpp	A	-5	25	26 (114)	78
7.6	<i>p</i> -NMe ₂ -bdpp	C	25	25	31	rac
7.7	PPF-Pcy ₂	C	25	50	4	n.d.
7.8	PPF-P(o-MeO-Ph) ₂	C	25	30	132 (190)	7
7.9	PPF-P(m-MeO-Ph) ₂	-	25	25	43 (82)	64
7.10	PPF-P(p-MeO-Ph) ₂	-	25	25	44 (120)	62
7.11	PPF-P(m-tol) ₂	-	25	25	45 (86)	70
7.12	PPF-P(<i>p</i> -CF ₃ -Ph) ₂	C	25	30	133 (170)	56
7.13	PPF-P(3,5-xyl) ₂	C	80	50	331 (950)	75
7.14	PPF-P(3,5-xyl) ₂	-	80	50	807 (1450)	69

Reaction conditions: [Ir(cod)Cl]₂, *n*-Bu₄I, solvent: A: MeOH/tol (1:1); B: *t*-BuOCH₃; C: THF/CH₂Cl₂ (3:1), *s/c*: entries 1–6: 200, entries 7–13: 800, entry 14: 10,000.

^ain parenthesis: tof after 4 h

ties of the Ar' group affect the activity as well as the enantioselectivity of the Ir-PPF-PAr'₂ catalysts.

Strong iodide effects were also observed for the hydrogenation of *N*-benzyl-*N*-(1-methylbenzylidene)amine and of the cyclic imine **5** with [Ir(cod)Cl]₂ and diop and bppm (and analogs thereof) as ligands. In the presence of *n*-Bu₄NI and BiI₃ as promoters and an *s/c* ratio of 200, complete conversion were achieved for both substrates with ees up to 91% for imine **5** [30].

An interesting effect of imide and amine additives was observed for Ir-bcpm and Ir-binap catalysts. The catalyst performance for the hydrogenation of imines **7** was affected by the addition of phthalimide or perfluorophthalimide [26]. The highest enantioselectivity were obtained with the Ir-bcpm catalyst system: 87% ee with F₄-phthalimide and 86% with phthalimide. Primary or secondary amines were found to be useful co-catalysts for the asymmetric hydrogenation of *N*-benzyl-*N*-(1-methylbenzylidene)amine and the cyclic imine **6** (R=Ph) with cationic Ir-binap (or Ir-tol-binap) catalysts [27]. For example, the addition of 5 equiv./Ir-benzylamine increased the ee values from 20% to 70% with *N*-benzyl-*N*-(1-methylbenzylidene)amine and from 40% to 90% with **6** (R=Ph), respectively. Surprisingly, the addition of benzylamine to a neutral in situ Ir/tol-binap complex led to complete catalyst inhibition in the hydrogenation of imine **6** (R=Ph), whereas in absence of this additive complete conversion as achieved with up 89% ee. The role of these co-catalysts is not well understood.

Halogen-free catalysts of the type $[\text{Ir}(\text{diphosphine})(\text{OOCR})_3]$ and $[\text{Ir}(\text{diphosphine})(\text{OOCR})_2\text{H}]$ ($\text{R}=\text{CH}_3, \text{CF}_3$), obtained by treating $[\text{Ir}(\text{diphosphine})\text{HI}]_2$ with $\text{Ag}(\text{OCCF}_3)$ [22], were also active for the hydrogenation of *N*-arylimines but showed a different catalytic profile. For example, with $[\text{Ir}(\text{bdpp})(\text{OCCF}_3)_3]$ as catalyst precursor, DMA imine could be hydrogenated with 90% ee at 0 °C, while the cyclic imine **5** was reduced with only a moderate ee of 35%. It was suggested that the catalysis proceeds in part via initial dissociation of the carboxylate ligand.

Two novel ligand types were recently published that form effective Ir complexes. Osborn and Sablong described a C_2 -symmetric tridentate PNP-ligand that enables the hydrogenation of DMA imine with up to 55% ee [38]. Pfaltz and coworkers [23] reported the development of Ir-phosphanodihydrooxazole (P^\wedgeN) catalysts for the hydrogenation of both *N*-aryl- and *N*-alkylimines. Using cationic Ir complexes of the type $[\text{Ir}(\text{cod})\text{P}^\wedge\text{N}]\text{PF}_6$, *N*-arylimines were hydrogenated with ees up to 89%, *N*-alkylimines with a maximum of 79% ee. In this case, the addition of iodide resulted in a dramatic decrease of the enantioselectivity and a change of the absolute configuration of the major enantiomer.

4.1.3

Ansa-Metallocene-Titanium Complexes

A very different type of catalyst was developed by Buchwald et al. [6]: the chiral Ti complex with Brintzinger's ansa-metallocene ligand (ebthi) is extraordinarily effective for the enantioselective hydrogenation of cyclic imines with high optical yields (>97% ee). Unfortunately, the activity and productivity of this Ti catalyst are relatively low compared to Rh- and Ir-diphosphine catalysts. The stereochemical outcome of the reaction can be predicted by straightforward steric arguments. Acyclic imines are reduced with lower enantioselectivity, probably due to isomerization problems and the presence of *syn/anti* isomers. Studies with multifunctional imines or in presence of other substrates revealed that the scope of the Ti-ebthi catalyst is rather limited. Partial or total catalyst inhibition is observed in presence of most functional groups, except amines, alcohols, acetals, and halides [39].

4.1.4

Ruthenium Complexes

In general, Ru-binap catalysts which show excellent enantioselectivity in the asymmetric reduction of functionalized olefins and ketones are not very suitable for $\text{C}=\text{N}$ hydrogenations. An exception is the hydrogenation of an *N*-sulfonylimine: 99% ee for **13** [34] and 82% and 84% for **2** and **12**, respectively (see Table 6). Other Ru-diphosphine complexes were investigated but proved to be little active and selective [2]. James and coworkers [40] investigated the catalytic activity of several mono and binuclear Ru-containing chiral diphosphines such as $\text{RuCl}_2(\text{diphosphine})(\text{RCN})_2$, $\text{RuCl}_2(\text{diphosphine})(\text{diene})$, $\text{Ru}_2\text{Cl}_4(\text{diphosphine})_2(\text{NEt}_3)$,

or $\text{Ru}_2\text{Cl}_5(\text{diphosphine})_2$ for the enantioselective hydrogenation of imines of type 1. However, all these catalysts showed both low activity and enantioselectivity. The highest optical yield was obtained with $\text{Ru}_2\text{Cl}_5(\text{chiraphos})_2$ (27% ee).

A major breakthrough was achieved with transfer hydrogenation catalysts generated from $[\text{Ru}(\text{Cl}_2(\text{arene}))]$ and a semi-*N*-sulfonated chiral diamine (e.g., *N*-tosyl-1,2-diphenyl-1,2-diaminoethane, $\text{N}^{\wedge}\text{N}$) [19]. With $\text{HCOOH}/\text{NEt}_3$ as donor, enantioselectivities up to 97% were obtained for substrates of types 7 and 8 (s/c: 200–1000; tof: 83 h^{-1}), providing a new general route to alkaloids (Tables 4 and 5). Furthermore, this catalyst exhibited a high chemoselectivity towards the reduction of C=N vs. C=O functions. As a consequence, imines of type 7 can even be reduced in acetone with <5% production of 2-propanol.

4.2

Modified Hydrides and Heterogeneous Catalysts

Hydride reductions of C=N groups are well known in organic chemistry. It was therefore obvious to try to use chiral auxiliaries in order to render the reducing agent enantioselective [41]. The chiral reagent or catalyst is prepared by addition of a chiral diol or amino alcohol and the active species is formed by reaction of OH or NH groups of the chiral auxiliary with the metal hydride. A major drawback of most hydride reduction methods is the fact that stoichiometric or higher amounts of chiral material are needed. At this time only two such catalytic systems are useful for preparative purposes (Table 2, entry 2.6, Table 6, entry 6.1) [24, 32].

The most important heterogeneous systems for the hydrogenation of C=N groups have been reviewed by Blaser and Müller [8]. Neither the use of soluble modifiers nor of chiral supports led to heterogeneous catalysts with useful enantioselectivities. The interaction between adsorbed substrate, the active site and the chiral auxiliary employed until now was probably not sufficient for a good discrimination.

4.3

Mechanistic Aspects

Only a few detailed studies of the reaction mechanism of the homogeneous hydrogenation of imines have been published up to now. A generalization seems to be very difficult for two reasons. First, rather different catalyst types are effective and probably act by different mechanisms. Second, the effect of certain additives (especially iodide and acid/base) is often decisive for ee and rate but a promoter in one case can be a deactivator in another one.

For Rh- and Ir-diphosphine-based catalysts there exist some indications on reactive species and also on hydrogen activation. James and coworkers [2, 25] investigated the Rh-catalyzed DMA-imine hydrogenation and concluded that the imine is η^1 -coordinated via the nitrogen lone pair to the Rh center and not via the π -system of the C=N bond. They also suggested that the hydrogen activation

occurs after the imine is coordinated. Osborn and Chan [42] investigated, isolated, and characterized Ir(III) complexes of the type: $[\text{Ir}(\text{diphosphine})\text{I}_4]^-$, $[\text{Ir}(\text{diphosphine})\text{HI}_2]_2$, and $[\text{Ir}(\text{diphosphine})\text{I}_3]_2$. All three Ir complexes were found to be catalytically active for the hydrogenation of DMA-imine, suggesting the formation of the same active monomeric Ir species as for the in situ formed catalyst by splitting the iodo-bridge.

Based on these results, the catalytic cycle depicted in Fig. 3 can be postulated: Starting species is an Ir(III)-H species that coordinates the imine via the lone pair in a η^1 -manner (as proposed for the Rh-catalyzed reaction). A η^1, η^2 -migration leads to two diastereomeric adducts with a π -coordinated imine that then inserts into the Ir-H bond to give the corresponding Ir-amide complexes. The last step is a simultaneous hydrogenolysis of the Ir-N and the formation of an Ir-H bond, presumably via heterolytic splitting of the dihydrogen bond. In contrast to the Rh-diphosphine catalyzed hydrogenation of C=C bonds that most likely occurs via Rh(I) and Rh(III) species, the cycle in Fig. 3 consists exclusively of Ir(III) species. It is obvious that this basic catalytic cycles neither explains the mode of enantioselection nor the sometimes dramatic effects of additives, e.g., the strong rate enhancement by acids observed for the Ir-xylyphos-catalyzed MEA-imine hydrogenation.

A similar mechanism was proposed for the Ti-catalyzed reactions by Buchwald [6]. The active catalyst, that is produced by reacting ebthi-TiR₂ with *n*-BuLi followed by phenylsilane, was proposed to be the monohydride species ebthi-TiH. Kinetic and deuterium labeling studies are in agreement with the following reaction sequence: ebthi-Ti-H reacts with the imine via 1,2-insertion reaction to form two diastereomeric Ti-amide complexes. Then this intermediate amide complexes reacts via a σ bond metathesis reaction with dihydrogen to regenerate the titanium hydride and to form the two amine enantiomers. The reaction of the titanium amide complex with molecular hydrogen is proposed to be the

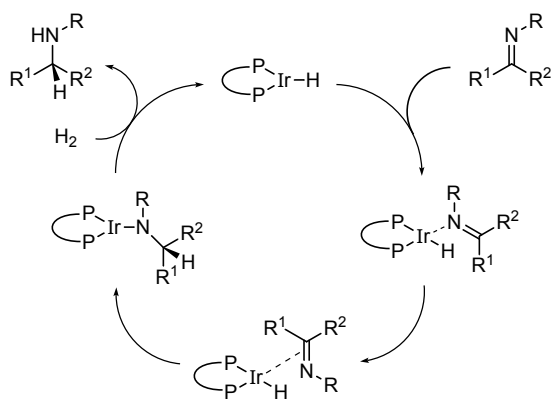


Fig. 3. Schematic catalytic cycle postulated for the Ir-diphosphine catalyzed hydrogenation of *N*-arylimines. Not shown are halide ligands

rate-determining step. The discrimination of the catalyst is due only to the size difference of the imine substituents, thereby explaining the potential detrimental effect of the presence of *syn* and *anti* isomers. The absolute configuration of the major enantiomer can be predicted by simple sterical arguments assuming that the 1,2-insertion is the product determining step.

5

Assessment of Methods

Different criteria are important for assessing the applicability of a catalyst either for preparative purposes or the technical manufacture of chiral fine and specialty chemicals [4, 44]. In both cases, enantioselectivity is of course the decisive prerequisite. For preparative use, easy availability and handling of the catalyst will probably play a major role. For technical applications, catalyst activity (tof), productivity (s/c ratio), availability on a large scale, and of course cost also play an important role. In general, optical yields should be >90%, unless a further enrichment is easy. The minimal activity and productivity required is less predictable. As an example: for an s/c ratio of 1000 and a tof of 10 h⁻¹ the reaction will take 100 h for completion, probably not an acceptable reaction time for a large volume chemical; for preparative use, s/c could be decreased to 100 and the reaction time would be an acceptable 10 h. Table 8 gives a summary on the range of reaction conditions, ees, s/c ratios, and tofs for important chiral catalysts and substrates. An overall assessment for the different systems takes the catalytic properties of a catalyst for a given transformation but also ecological and economical aspects into consideration.

Table 8. Typical ranges of reaction conditions, optical yields, turnover frequencies, and substrate to catalyst ratios for various reactions with preparative potential

Catalyst	Substrate type	pH ₂ (bar)	T (°C)	ee (%)	s/c	tof (h ⁻¹)
Ir diphosphine	N-arylimines	20–80	0–30	80–90	1000–1'000'000	6–>200,000
	cyclic imines	20–40	20–30	85–94	100–1500	2–75
Ir-P^N	imines	100	r.t.	75–89	25–1000	1–>1000
Rh diphosphine	imines	60–100	<0–30	91–96	40–1000	0.1–85
	acyl-hydrazones	4	<0–20	70–96	500–1000	10–1000
Ru diphosphine	C=N-SO ₂ R	4–70	r.t.–40	82–99	20–90	1–6
Ru-N^N	imines	formate	30	85–97	100–1000	6–83
Co-N^N	C=N-P(O)Ph ₂	hydride	0	88–99	100	20–34
Ti-ebthi	cyclic imines	5–33	20–65	98–99	20–100	0.4–2.4

5.1

Catalytic Methods

5.1.1

Enantioselectivity

The results summarized in Table 8 demonstrate that the catalytic reduction of various C=N functions has reached the state of being preparatively useful for a variety of amines. *Catalyst productivity, costs:* Most metal complexes and all ligands are very expensive. If the sometimes rather low s/c ratios used in most studies are not improved, catalyst costs would be medium to high. *Ecological aspects:* Hydrogenation reactions have a very good ecological balance since no stoichiometric by-products are produced. Hydrides and modified formates as reducing agents usually give stoichiometric amounts of by-products that must be disposed of.

5.1.2

Overall Assessment

At the moment, the production process made possible by the extraordinarily active and productive Ir-xyliphos catalyst is the exception, but there are indications that other technical applications might be feasible. For preparative applications in the laboratory some „catalytic know-how“ is required to make these catalysts work. The scope of the various catalyst types is sometimes still rather narrow, but will most likely improve with time. However, in most cases activity and productivity must be improved decisively. As more and more types of ligands are becoming commercially available a broader catalyst screening will become possible. This means that progress regarding both enantioselectivity and activity is quite likely.

5.2

Alternative Reduction Methods

Several *stoichiometric chiral reducing agents* starting from BH_3 , LiAlH_4 or NaBH_4 and relatively cheap amino alcohols or diols have been developed for the reduction of imines and oxime derivatives [3, 43]. Ees are medium to very high. Most effective chiral auxiliaries can be prepared in one or two steps from rather cheap starting materials like amino acids, tartaric acid, or sugars and they can probably be recycled. Because these reagents are used in stoichiometric amounts, the costs for the reduction step will be medium to high anyway. *Overall assessment:* Chiral hydrides are at the moment useful on a laboratory scale but their potential for technical applications is medium to low.

Hydrosilylation seems at the moment not very attractive for C=N functions [3] (also see chap. 6.3). With one exception [45], ees are low to medium and catalyst activity and productivity are low to medium.

Chiral amines can also be produced using *aminotransferases* either by kinetic resolution of the racemic amine or by asymmetric synthesis from the corresponding prochiral ketone. The reaction involves the transfer of an amino group, a proton, and two electrons from a primary amine to a ketone and proceeds via an intermediate imine adduct. A variety of chiral amines can be obtained with high to very high yields. Several transformations have been developed and can be carried out on a 100 kg scale [46].

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Chapter 6.3

Hydrosilylation of Carbonyl and Imino Groups

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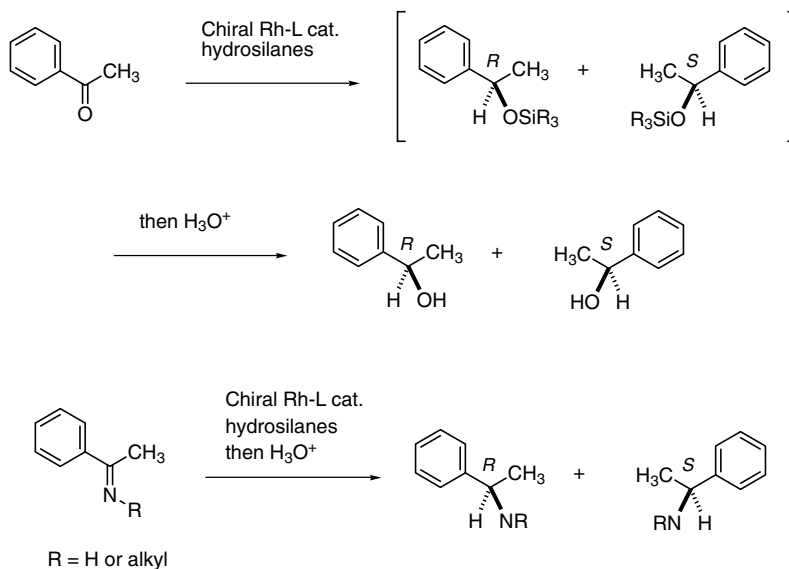
Keywords: Ketones, Secondary alcohols, Imines, Amines, Diphenylsilane, Rhodium catalysts, Titanium catalysts

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1 Introduction

The asymmetric catalytic reduction of ketones ($R_2C=O$) and imines ($R_2C=NR$) with certain organohydrosilanes and transition-metal catalysts is named *hydrosilylation* and has been recognized as a versatile method providing optically active secondary alcohols and primary or secondary amines (Scheme 1) [1]. In this decade, high enantioselectivity over 90% has been realized by several catalytic systems [2, 3]. Therefore the hydrosilylation can achieve a sufficient level to be a preparative method for the asymmetric reduction of double bond substrates. In addition, the manipulative feasibility of the catalytic hydrosilylation has played a major role as a probe reaction of asymmetric catalysis, so that the potential of newly designed chiral ligands and catalysts can be continuously scrutinized.

Historically, since the Wilkinson catalyst [$RhCl(PPh)_3$] proved to be active for hydrosilylation of ketones with hydrosilanes in the early 1970s, the asymmetric version has been examined by using many optically active phosphorus ligands, which were mainly developed for the asymmetric hydrogenation of olefins. Many ketones were catalytically reduced in high yields with moderate enantioselectivities. As representative milestones, the first trial with (+)-DIOP (L1; Fig. 1) and



Scheme 1

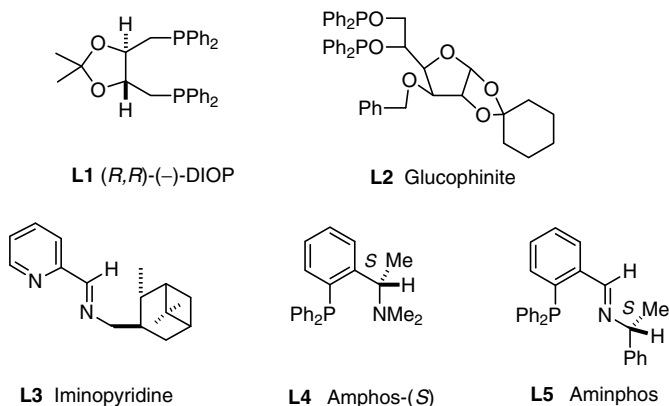
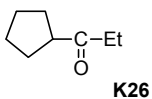
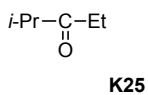
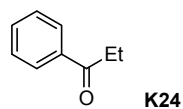
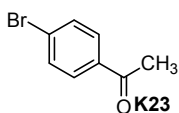
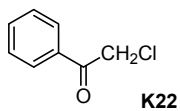
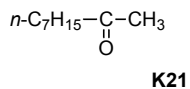
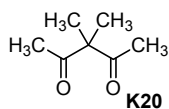
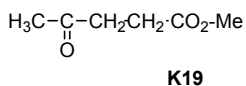
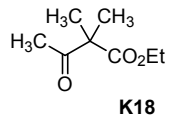
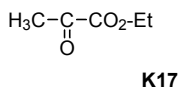
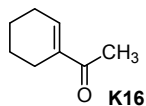
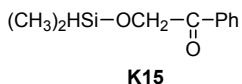
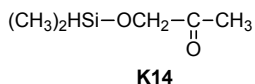
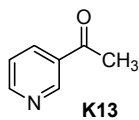
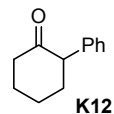
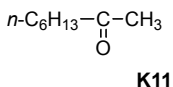
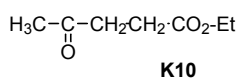
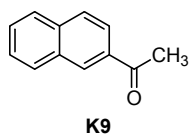
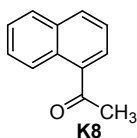
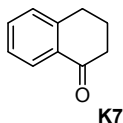
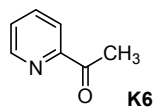
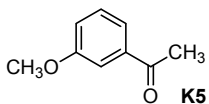
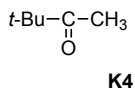
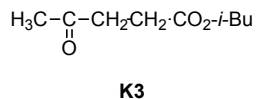
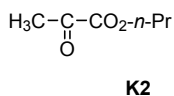
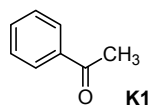


Fig. 1

a rhodium complex (2 mol %) gave 58% ee for the reduction of acetophenone (K1; for abbreviations, see Scheme 2) [4] (Table 1). An improvement with DIOP ligands appeared in the variation of the substrate ketones, such as α -ketoester (*n*-propyl pyruvate, K2) and δ -ketoester (*i*-butyl levulinate, K3), which were transformed in 84–86% ees [5]. In this early work, the use of (1-naphthyl)phenylsilane [(1-Np)PhSiH₂, S2] preferably gave higher % ees than did that of diphenylsilane (Ph₂SiH₂, S1). Glucophinite (L2) slightly increased the % ee to 65% [6].



Scheme 2

Table 1. Asymmetric hydrosilylation of ketones with chiral rhodium catalysts

Ligand	Rh-com- plex ^d	Silane ^b	Ketone ^c	Solvent	L/Rh	Ketone/ Rh	Silane/ Ketone	Temp/Time (°C/h)	Product: secondary alcohol Yield (%)	%ee	abs config	Ref.
L1	(+)-DIOP	S2	K1	benzene	1/1	50/1	2/1	rt/20	100	58	S	4
	(-)-DIOP	S2	K2	benzene	1/1	300/1	1.2/1	0→rt/6	90	85.4	R	5
	(+)-DIOP	S2	K3	benzene	1/1	300/1	1.1/1	0→rt/12	96	84.4	S	5
L2	Glucophimite	S2	K1	benzene	1/1	50/1	1/1	rt/12	65	65	-	6
		S1	K1	benzene	1/1	50/1	1/1	rt/12	65	55	-	6
		S1	K1	no solv.	9/1	100/1	1.1/1	0→25/48	99	78.8	S	7, 8
L4	Amphos-(S)	S1	K1	benzene	1/1	300/1	1.1/1	rt/72	98	72	S	9
L5	Aminphos	S1	K4	THF	2.2/1	500/1	1.1/1	-10/96	93	52.7	S	10
	Pythia	S1	K1	no solv.	8/1	450/1	1.1/1	-20/100	86	87.2	R	12
L7a	Pymox-Et-(S)	S1	K1	no solv.	13/1	140/1	1.1/1	-20/120	99	97.6	R	13
		S1	K5	no solv.	8/1	150/1	1.1/1	-15/192	95	93.3	R	14
		S1	K6	no solv.	8/1	150/1	1.1/1	0→20/18	90	89.6	R	14
		S1	K7	no solv.	8/1	150/1	1.1/1	0→20/18	85	82.6	R	14
		S1	K1	no solv.	5/1	200/1	1/1	0→20/18	60	39.8	S	15
		S1	K1	benzene	5/1	200/1	1/1	0→20/18	60	31.0	S	15
		S1	K1	THF	5/1	200/1	1/1	0→20/18	51	24.0	S	15
		S1	K1	CCl ₄	5/1	200/1	1/1	0→20/18	93	56.6	S	15
		S1	K1	CCl ₄	5/1	200/1	1/1	0→20/18	85	62.2	R	15
		S1	K1	no solv.	5/1	100/1	1.6/1	1.6/1	-5/168	88	60	R
L7b	Pymox- <i>t</i> -Pr-(S)	S1	K1	CCl ₄	5/1	200/1	1/1	0→20/18	90	83.4	R	15
		S1	K1	no solv.	5/1	100/1	1.6/1	-5/24	90	91	R	16
L7c	Pymox- <i>t</i> -Bu-(S)	S1	K1	CCl ₄	5/1	200/1	1/1	0→20/18	90	83.4	R	15
		S1	K1	no solv.	5/1	100/1	1.6/1	-5/24	90	91	R	16

Table 1. Continued




Ligand	Rh-com- plex ^d	Silane ^b	Ketone ^c	Solvent	L/Rh	Ketone/ Rh	Silane/ Ketone	Temp/Time (°C/h)	Product: Yield (%)	secondary alcohol %ee	abs config	Ref.	
L7d Pymox- (CH ₂ OTr)(Ph)	R2	S1	K1	no solv.	4/1	171/1	1.1/1	0/72	96	63.2	R	19	
	R2	S2	K1	no solv.	4/1	171/1	1.1/1	0/72	100	80	R	19	
L7e Pymox- (Bz)(Ph)	R1	S1	K1	CCl ₄	5/1	100/1	1/1	0→rt/18	77	83.1	R	20	
	R1	S1	K1	CCl ₄	5/1	100/1	1/1	0→rt/18	80	89.1	R	16	
L7f Pymox- (<i>i</i> -Pr)(Ph)	R1	S1	K1	no solv.	3/1	100/1	1.6/1	0/28	88	76	S	16	
L8a Pybox- <i>i</i> -Pr- (S,S)	R4a	S1	K1	THF	5/1	100/1	1.6/1	0/2	91	94	S	16	
	R4a	S1	K1 ^d	THF	5/1	100/1	1.6/1	0/3	94	95	S	23	
	R4a	S1	K7	THF	5/1	100/1	1.6/1	0/2	92	99	S	23	
	R4a	S1	K8	THF	5/1	100/1	1.6/1	-5/5	87	94	S	23	
	R4a	S1	K9	THF	5/1	100/1	1.6/1	-5/5	93	93	S	23	
	R4a	S1	K10	THF	7/1	100/1	1.6/1	0/7	91	95	S	23	
	R4a	S1	K11 ^d	THF	5/1	100/1	1.6/1	0/2	85	63	S	23	
	R4a	S1	K12	THF	5/1	100/1	1.6/1	0/4	92	63	S	25	
			K12										
			P1										
			P2										
	L8b Pybox- <i>t</i> -Bu-(S,S)	R4b	S1	K1	THF	5/1	100/1	1.6/1	0/18	92	83	S	23

Table 1. Continued

Ligand	Rh-com- plex ^d	Silane ^b	Ketone ^c	Solvent	L/Rh	Ketone/ Rh	Silane/ Ketone	Temp/Time (°C/h)	Product: secondary alcohol Yield (%)	%ee	abs config	Ref.
L8c Pybox- <i>i</i> -Pr-(4- CO ₂ Me)	R4c	S1	K1	THF	5/1	100/1	1.6/1	-5/4	90	96	S	27
L8d Pybox- <i>i</i> -Pr-(4- OMe)	R4d	S1	K1	THF	5/1	100/1	1.6/1	10/18	86	93	S	26
L8e Pybox- <i>i</i> -Pr-(4- NMe ₂)	R4e	S1	K1	THF	5/1	100/1	1.6/1	20/16	83	90	S	26
L9a Phenanthroline deriv.	R1	S1	K1	toluene	5/1	200/1	1/1	0→rt/18	100	10.8	S	28
L9b Phenanthroline deriv.	R1	S1	K1	toluene	5/1	200/1	1/1	0→rt/18	100	75.6	R	28
L10 Bipyrox- <i>i</i> -Pr- (S,S)	R1/AgBF ₄	S1	K1	THF	4/1	100/1	1.5/1	15/3	67	68	S	29
L11 Bisoxazoline-Bz- (S,S)	R5/AgBF ₄	S1	K1	THF	4/1	100/1	1.5/1	5/2	98	90	S	29
	R1	S1	K1	CCl ₄	10/1	100/1	1.2/1	0	59	84	R	31
L12 Bisoxazoline- (CH ₂) ₂ - <i>i</i> -Pr	R1	S1	K1	CCl ₄	10/1	100/1	1.2/1	rt	-	12	R	31
L13a Bisoxazoline- (S,S)-(R,R)	R1	S1	K1	CCl ₄	8/1	100/1	1.6/1	-5/72	90	64	R	32
L13b Bisoxazoline- (S,S)-(S,S)	R1	S1	K1	CCl ₄	8/1	100/1	1.6/1	-5/72	72	49	R	32
L14 (-)-Sparteine	R6	S1	K1	THF	10/1	1000/1	1.25/1	25	75±5	37±3	S	33
L15a DuPHOS-Et	R1	S1	K13	no solv.	4/1	1000/1	1.1/1	25	65	34	R	33
	R7	-	K14	CH ₂ Cl ₂	1/1	333/1	-	20-25/1	100	78	S	34

Table 1. Continued

Ligand	Rh-com- plex ^d	Silane ^b	Ketone ^c	Solvent	L/Rh	Ketone/ Rh	Silane/ Ketone	Temp/Time (°C/h)	Product: secondary alcohol Yield (%)	%ee	abs config	Ref.
L15b DuPHOS- <i>i</i> -Pr	R8	-	K14	CH ₂ Cl ₂	1/1	333/1	-	20-25/2	100	93	R	34
L16 (S)-(-)-BINAP	R8	-	K15	CH ₂ Cl ₂	1/1	333/1	-	20-25/2	100	67	R	34
	R9	-	K14	CH ₂ Cl ₂	1/1	333/1	-	20-25/0.3	100	20	R	34
	R9	-	K15	CH ₂ Cl ₂	1/1	333/1	-	20-25/0.3	100	45	R	34
L17a (R,R)-(S,S)- TRAP- <i>n</i> -Bu	R10	S1	K1	THF	1.1/1	100/1	1.5/1	-40/11	88	92	S	35
	R10	S1	K16	THF	1.1/1	100/1	1.5/1	-40/12	71	95	S	35
L17b (R,R)-(S,S)- TRAP-Et	R10	S1	K17	THF	1.1/1	100/1	1.5/1	0/4	60	80	S	36
	R10	S1	K18	THF	1.1/1	100/1	1.5/1	-30/11	69	93	S	36
	R10	S1	K20	THF	1.1/1	100/1	2.5/1	-30/58	58(96:4)	99	(2S,4S)	37
L18a (R,R)-TADDOL- Phos.	R1	S1	K1	benzene	10/1	100/1	1.2/1	0-20/10-15	92	62	R	38
:(Ph, Ph-4-Me)	R1	S1	K9	benzene	10/1	100/1	1.2/1	0-20/10-15	60	65	R	38
L18b ":(2-Np, Ph)	R1	S1	K1	benzene	10/1	100/1	1.2/1	0-20/10-15	91	82	R	38
	R1	S1	K9	benzene	10/1	100/1	1.2/1	0-20/10-15	84	84	R	38
L18c ":(2-Np, 2-Np)	R1	S1	K1	benzene	10/1	100/1	1.2/1	0-20/10-15	99	84	R	38
	R1	S1	K9	benzene	10/1	100/1	1.2/1	0-20/10-15	92	87	R	38
L19 (R)-Cystphos	R1	S1	K1	THF	2.2/1	100/1	1.07/1	0/20	99	64	S	39
L20a Ferrocenyl- Phos.-Amine	R11	S1	K1	THF	1.5/1	100/1	1.25/1	20/1	90	87	S	40
L20b	R11	S1	K1	THF	1.5/1	100/1	1.25/1	20/0.2	90	90	S	40

Table 1. Continued

Ligand	Rh-com- plex ^d	Silane ^b	Ketone ^c	Solvent	L/Rh	Ketone/ Rh	Silane/ Ketone	Temp/Time (°C/h)	Product: secondary alcohol Yield (%)	%ee	abs config	Ref.
L20c	R11	S1	K1	THF	1.5/1	100/1	1.25/1	20/0.2	90	90	S	40
L21 (<i>S,S,S</i>)-DIPOF	R1	S1	K1	Et ₂ O	1/1	200/1	1.5/1	25/15–25	100	91	R	41
	R1	S1	K9	Et ₂ O	1/1	200/1	1.5/1	25/15–25	99	88	R	41
	R1	S1	K7	Et ₂ O	1/1	200/1	1.5/1	25/15–25	95	57	R	41
	R1	S1	K21	Et ₂ O	1/1	200/1	1.5/1	25/15–25	92	60	R	41
L22a Phosphinooxa- zoline- <i>i</i> -Pr	R1	S1	K1	THF	10/1	50/1	4/1	-78/-	86	82	R	43
	R1	S2	K1	THF	10/1	50/1	4/1	-78/-	85	86	R	43
	R1	S1	K7	THF	10/1	50/1	4/1	-78/-	70	59	R	43
	R1	S1	K8	THF	10/1	50/1	4/1	-78/-	90	61	R	43
	R1	S1	K1	THF	1.3/1	333/1	1.1/1	0/70	92	82	R	44
	R1	S1	K10	THF	1.3/1	333/1	1.1/1	rt/70	66	52	R	44
L22b Phosphinooxa- zoline- <i>t</i> -Bu	R1	S1	K1	THF	1.3/1	333/1	1.1/1	rt/70	65	40	R	44
L22c Phosphino- oxazoline- <i>i</i> -Pr-[Ph-3,5- (CF ₃) ₂]	R1	S1	K1	THF	1.3/1	333/1	1.1/1	10/70	90	85	R	44
	R1	S2	K1	THF	1.3/1	333/1	1.1/1	-40/70	99	86	R	44
L23 Aminoferrocene- nyl-Se/2	R1	S1	K1	THF	1/1	100/1	1.5/1	0/48	31	85	R	45
	R1	S2	K1	THF	1/1	100/1	1.5/1	0/40	65	82	R	46

Table 1. Continued

Ligand	Rh-com- plex ^a	Silane ^b	Ketone ^c	Solvent	L/Rh	Ketone/ Rh	Silane/ Ketone	Temp/Time (°C/h)	Yield (%)	Product: secondary alcohol abs config	Ref.	
	R1	S1	K22	THF	1/1	100/1	1.5/1	0/120	85	88	R	46

^a Rh-complex, **R1**=[Rh(COD)Cl]₂, **R2**=[Ph(C₂H₄)₂Cl]₂, **R3**=[Rh(COD)(L2)]BF₄, **R4a-e**=RhCl₃(L8a-e)/AgBF₄(2 eq.), **R5**=RhCl₃(L10), **R6**=Rh(COD)BPh₄, **R7**=[Rh(COD)(L15a)]OTf, **R8**=[Rh(COD)(L15b)]OTf, **R9**=[Rh(COD)(L16)]OTf, **R10**=[Rh(COD)₂]BF₄, **R11**=[Rh(NBD)Cl]₂.

^b **S1**=Ph₂SiH₂, **S2**=(1-Naphthyl)PhSiH₂.

^c **K1**=acetophenone, **K2**=*n*-propyl pyruvate (CH₃COCO₂-*n*-Pr), **K3**=*i*-butyl levulinate (CH₃COCH₂CH₂CO₂-*i*-Bu), **K4**=*t*-BuCOCH₃, **K5**=3-MeOPhCOCH₃, **K6**=2-pyridyl methyl ketone, **K7**=1-tetralone, **K8**=1-acetylnaphthalene, **K9**=2-acetylnaphthalene, **K10**=ethyl levulinate, **K11**=2-octanone, **K12**=2-phenylcyclohexanone, **K13**=3-pyridyl methyl ketone, **K14**=Me₂HSiOCH₂COCH₃, **K15**=Me₂HSiOCH₂COPh, **K16**=1-cyclohexenyl methyl ketone, **K17**=ethyl pyruvate, **K18**=2,2-dimethylacetylacetone, **K19**=methyl levulinate, **K20**=3,3-dimethyl-pentane-2,4-dione, **K21**=2-nonanone, **K22**=PhCOCH₂Cl.

^d Ethyl levulinate was initially added.

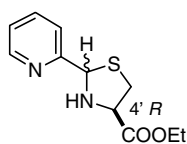
In the early 1980s, nitrogen-based ligands were introduced into this field. Many iminopyridine derivatives prepared by condensation with optically active amines and pyridyl carbonyl compounds were employed for this catalysis [7, 8]. Among them, the iminopyridine (**L3**) attained the highest value of 78.8% ee for acetophenone. Aminophosphine derivatives such as Amphos (**L4**) [9] and Aminphos (**L5**) [10, 11] afforded 50–72% ees. Thus, it was found that the nitrogen atom present in optically active bidentate ligands proved to be superior to the phosphorus atom.

2

Hydrosilylation of C=O and C=N with Chiral Rhodium Catalysts

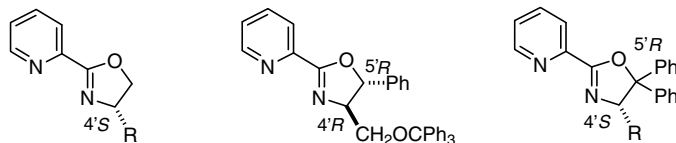
A further breakthrough occurred in the design of nitrogen-based ligands. The chiral pyridine-thiazolidine (Pythia, **L6**, Fig. 2), synthesized by reaction of 2-pyridinecarbaldehyde with L-cysteine ethyl ester, was applied as an additive with $[\text{Rh}(\text{COD})\text{Cl}_2]_2$ (**R1**) (ton = 140–450) at $-20\text{ }^\circ\text{C}$ without solvent [12,13]. Acetophenone (**K1**) was reduced in 87.2–97.6% ees by using an 8–13-fold amount of the ligand **L6** referred to the rhodium atom. Also several aromatic methyl ketones were reduced in an average of 82–93% ee [14]. In this system, diphenylsilane (**S1**) was more effective than 1-naphthylphenylsilane (**S2**). The *R*-absolute configuration of the product secondary alcohols was derived from the *R*-configuration of the 4'-position of the thiazolidine ring. Linear alkyl ketones, such as *n*-butyl methyl ketone, 2-methylpropyl methyl ketone, were also reduced in 52.2% ee and 55.8% ee, respectively [14].

Pyridine-oxazolines (Pymox, **L7**, Fig. 3), first introduced in 1989, were prepared via two routes [15, 16, 17, 18]. The first started from 2-cyanopyridine, which



L6 Pythia

Fig. 2



L7a R = Et Pymox-Et
L7b R = *i*-Pr Pymox-*i*-Pr
L7c R = *t*-Bu Pymox-*t*-Bu

L7d

L7e R = Bz
L7f R = *i*-Pr

Fig. 3

was converted to the imidate by addition of methanol followed by addition of the corresponding optically active amino alcohol [15]. The second route involved amide formation from pyridine-2-carboxylic acid chloride, followed by cyclization with alkali to produce the oxazoline ring [16]. The highest result for asymmetric hydrosilylation was obtained in the case of the *tert*-butyl derivative **L7c** (Pymox-*t*-Bu), 83.4–91% ees [15, 16]. The trityl derivative **L7d** furnished 80% ee for acetophenone with 1-naphthylphenylsilane [19]. In further modifications of the oxazoline ring, two phenyl groups were introduced on the 5'-position of the oxazoline, as in **L7e** and **L7f**, to increase the % ees from ca. 60% up to 83–89% [20]. In the case of Pymox-Rh catalysts, a solvent effect was prominent and the enantioselectivity was increased by use of CCl₄, as compared to benzene or THF [15]. The appropriate excess amount of the ligand proved to be ca. 4–5-fold based on the rhodium atom. In spite of the structural similarity between **L6** and **L7**, the phenomenon that the absolute configuration of the products was reversed from *R* to *S* was entirely different from the case of Pythia **L6**, namely *R* to *R*.

The concept of C₂ symmetry for chiral ligand design has had great success so far in several asymmetric catalyses since DIOP was proposed as the first bidentate phosphine ligand [21, 22]. It is probable that C₂-symmetric ligands can provide homochiral stereotopes to an attacking substrate around an active site of the catalysts. This concept was first applied to a nitrogen-based ligand in a unique tridentate pyridine-bisoxazoline (Pybox) system.

Pybox **L8** (Fig. 4) was synthesized from pyridine-2,6-dicarboxylic acid and optically active amino alcohols via an amido chloride intermediate [16, 23] or via BF₃-catalyzed cyclization of intermediate amino alcohols [24]. The combination of Pybox-*i*-Pr (**L8a**) and [Rh(COD)Cl]₂ (**R1**) exhibited catalytic activity as an *in-situ* catalyst for the reduction of acetophenone (**K1**) to give 76% ee (*S*) [16]. However, the complex RhCl₃(Pybox-*i*-Pr) **R4a** under assistance with AgBF₄ accelerated the reduction in THF to give 94–95% ees [23]. Diphenylsilane (**S1**) was also the best silane in this system. Most aromatic methyl ketones were reduced in 90–99% ees, and reactions of levurinate **K10** and 2-octanone **K11** resulted in 95% ee and in 63% ee, respectively. The Pybox-Rh catalyst **R4a** reduced selectively 2-phenylcyclohexanone **K12** to give the *S*-alcohols for both *trans*- and *cis*-isomers **P1** and **P2** in 96–99% ees [25]. The catalyst **R4a** can differentiate only the enan-

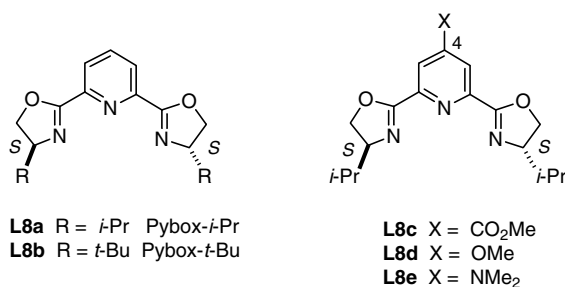


Fig. 4

tioface of ketone and may not be influenced by the neighboring stereo-circumstances.

The *tert*-butyl group on the Pybox skeleton did not give rise to an excellent % ee: 83% with Pybox-*t*-Bu (**L8b**) compared to the cases of Pybox-*i*-Pr and Pymox-*t*-Bu [23].

It was found that the substituents at the 4-position on the pyridine skeleton, as shown in **L8c-e**, affected not only the reaction rate of asymmetric hydrosilylation but also the enantioselectivities [26]. The rhodium complex of **L8c**, having an electron-withdrawing group CO₂Me, catalyzed the reduction of acetophenone with diphenylsilane to give the highest % ee: 96%, at -5 °C for 4 h [27], while the catalysis with **L8e**, having an electron-donating group NMe₂, proceeded at 20 °C for 16 h, and resulted in 90% ee [26]. Thus, the remote substituent effects in asymmetric catalysis were proved to be relevant.

In this catalysis with Pybox-Rh, some very interesting phenomena were observed using 4-*tert*-butylcyclohexanone, which has been known to give mainly the *cis*-cyclohexanol derivative with bulky reducing agents in a kinetically controlled reaction via equatorial attack [25]. However, the catalyst RhCl₃(Pybox-*i*-Pr) **R4a** gave a 67:33 ratio of the *trans*- and *cis*-alcohols, in spite of the fact that the formation of the *cis*-alcohol was expected from bulkiness of the catalyst to proceed in high enantioselectivity.

The bidentate phenanthroline derivative **L9b** (Fig. 5) having a pinane skeleton was found to give a good to excellent % ee: 75.6% for acetophenone, better than the phenanthroline-oxazoline **L9a** as a tridentate ligand [28]. The tetradentate bis(oxazolanyl)-bipyridine Bipymox (**L10**) exhibited 90% ee in its RhCl₃ complex [29]. The absolute configuration, *S*, of the product alcohols was obtained in the same way as in the case of Pybox **L8**.

Simple bis-oxazoline derivatives, derived from oxalic acid or malonic acid, were initially introduced as chiral ligands for asymmetric cyclopropanation and asymmetric allylic substitution [30]. Several bis-oxazolines **L11–13** (Fig. 6) were examined for their efficacy in asymmetric hydrosilylation [31]. Only the benzyl derivative **L11** showed a higher % ee: 84%. It is interesting to note that the absolute configuration of the product alcohol is the same as that with Pymox ligands: *S* to *R*. It was also demonstrated that the backbone skeleton, as shown in **L13a**-(*S,S*)-(*R,R*) and **L13b**-(*S,S*)-(*S,S*), influenced the enantioselectivity: 64% ee (*R*) and 49% ee (*R*), respectively [32].

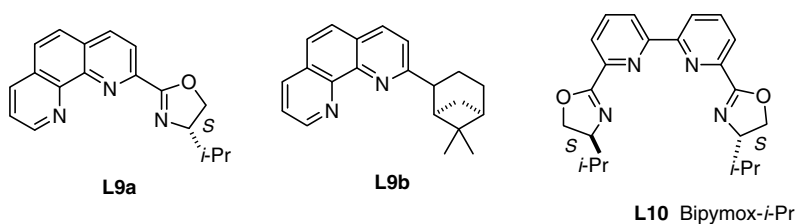


Fig. 5

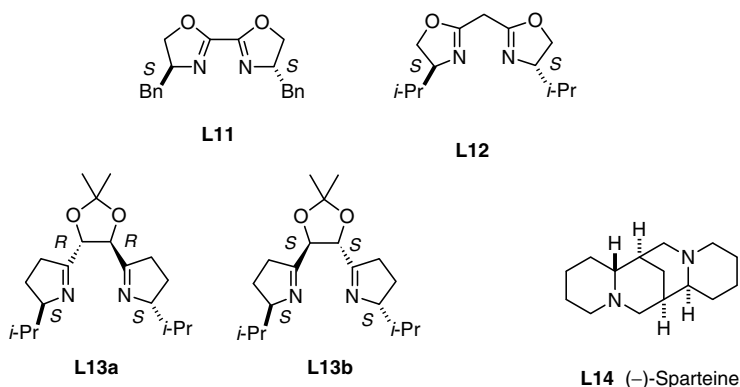


Fig. 6

The above-mentioned success of chiral nitrogen-based ligands during the late 1980s and the early 1990s stimulated further improvements in the design of catalysts. (-)-Sparteine **L14**, which is a popular natural chiral bidentate amine, was examined for the asymmetric hydrosilylation of ketones [33]. Interestingly, an excess of sparteine (4–10-fold based on Rh) was effective to give 65–75% yields of alcohols, but only 34–37% ees for the asymmetric induction.

Newly designed diphosphine ligands were introduced in this field in 1992–1995. The cationic rhodium complexes (**R7** and **R9**) with DuPHOS (**L15a, b**; Fig. 7) were used in a particular case of the intramolecular hydrosilylation of the hydrosilylated hydroxyketones **K14** and **K15**, attaining 93% ee with the isopropyl substituted ligand **L15b** [34]. This method was invoked as an alternative access to chiral 1,2-diols, which are commonly available by asymmetric dihydroxylation of olefins or asymmetric epoxidation of olefins followed by hydroxylation. In this cyclization, under the same conditions, the use of BINAP (**L16**) resulted in 45% ee. It was thought that the congested situation of DuPHOS might be favorable.

In this sense, the idea of a “wide bite-angle” for bidentate phosphines was successfully applied in a new chiral ligand, TRAP (Fig. 8), which is a dimeric compound of ferrocenyl-phosphine, having C_2 symmetry [35, 36, 37]. Of interest in analysis is the TRAP-Rh complex *trans*-[RhCl(CO)(TRAP-*n*-Bu)] consisting of nearly square planar coordination geometry and a P-Rh-P angle of 164.4° . Variation of the substituents on the phosphine of TRAP increased the enantioselectivity to over 90% ee. Using the combination of [Rh(COD)₂]BF₄ (**R10**) with TRAP-*n*-Bu (**L17a**), acetophenone (**K1**) and 1-cyclohexenyl methyl ketone (**K16**) were reduced at -40°C with diphenylsilane to give the *respective* products in 92% ee and 95% ee. Also the keto-esters **K17–19** and the diketone **K20** were reduced with TRAP-Et (**L17b**) in 80–99% ees [36]. This research was thought to be meaningful since TRAP could reach even higher levels of % ee than the chiral diphosphine ligand developed in early years, which could not attain values over 90% ee.

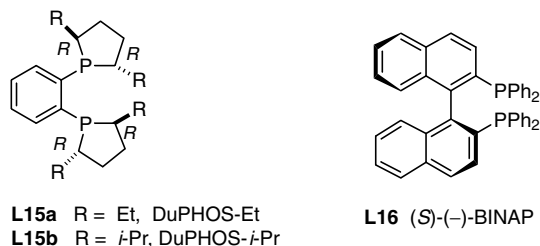


Fig. 7

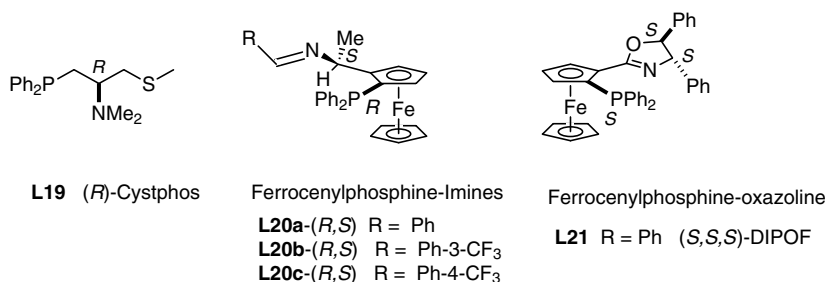
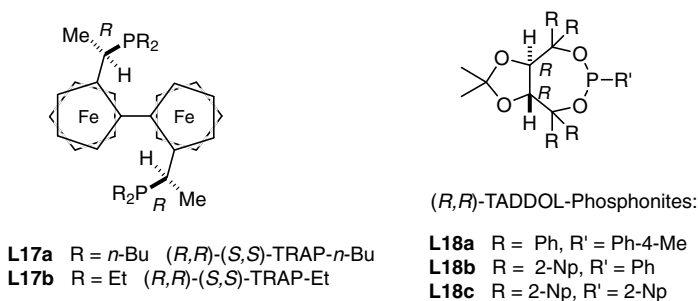


Fig. 8

The monodentate phosphonite ligands **L18a-c** (Fig. 8) modified by TADDOL ligands, which were derived from tartarates, were examined to show relatively high values of % ee: 62–87% ees for acetophenone and 2-naphthyl methyl ketone with diphenylsilane [38]. 2-Naphthyl methyl ketone (**K9**) was reduced in 92% yield with 87% ee (*R*) by using a large excess of **L18c** (10-fold based on Rh) and [Rh(COD)Cl]₂.

Some combined ligands containing both nitrogen and phosphorus atoms have already been examined as described, for example, Amphos or Aminphos, but they afforded only middle ranges of % ee. In the mid-1990s, a new series of the N-P combined ligands was prepared to attain further improvements.

Cystphos (**L19**; Fig. 8) having a methylthio group exhibited 64% ee (*S*) for the reduction of acetophenone as compared to those with Aminphos and Amphos [39]. Thus, the simple chirality possessed in these N-P ligands is effective but affords only middle ranges of % ee. Further improvement was attained by rhodium catalysts with the ferrocenylphosphine imines **L20a-c** and ferrocenylphosphine-oxazoline **L21** (Fig. 8) [40]. The ferrocenylphosphine imine **L20a** reduced acetophenone in 87% ee (*S*). Introduction of a trifluoromethyl group on the phenyl group of the imine slightly improved the % ee to 90%. Similarly, the ferrocenylphosphine-oxazoline DIPOF (**L21**) also attained high catalytic activity, providing 91% ee for acetophenone and 88% ee for 2-naphthyl methyl ketone **K9** [41]. The linear *n*-nonanone **K21** was reduced in 60% ee (*R*).

The phosphinooxazolines **L22** (Fig. 9) were developed in 1993 as powerful ligands for asymmetric allylic substitution reactions in combination of palladium complexes [42]. This N-P type ligand type was also applied to asymmetric hydrosilylation of ketones as an *in situ* catalyst with $[\text{Rh}(\text{COD})\text{Cl}]_2$ [43, 44]. Acetophenone was converted in 82% ee (*R*) with the isopropyl ligand **L22a** and diphenylsilane **S1**. However, 1-tetralone **K7** and 2-naphthyl methyl ketone **K9** gave 59% ee and 61% ee, respectively. The *tert*-butyl substituent on **L22b** decreased the % ee. A bulky substituent on the phosphorus atom, such as the 3,5-(CF_3)₂Ph group in **L22c**, slightly improved the % ee to 85% for acetophenone. In this system, naphthylphenylsilane **S2** gave slightly higher % ees: up to 86%, as shown in the case of DIOP. The significant fact is that the absolute configuration, *S*, of the ligands **L22a-c** produced the *R*-configuration of the product secondary alcohols, similar to the case with Pymox **L7** (pyridine-monooxazoline system). This implies that the structural similarity between the phosphinooxazolines and the pyridine-monooxazolines may give the same absolute configuration, probably via a similar transition state.

The unique chalcogenide-bridged bis-ferrocenylamine **L23** and its derivatives were developed for asymmetric hydrosilylation with diphenylsilane (**S1**) to achieve a higher % ee: 85% for acetophenone and 88% for PhCOCH_2Cl [45, 46]. It was postulated that the ferrocenylamine **L23** binds to the rhodium atom as a new type of tetradentate ligand by an N-Se-Se-N increment.

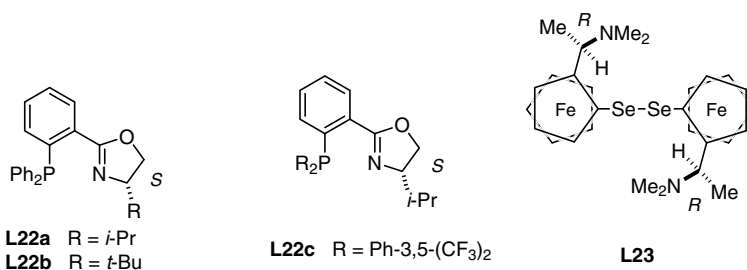


Fig. 9

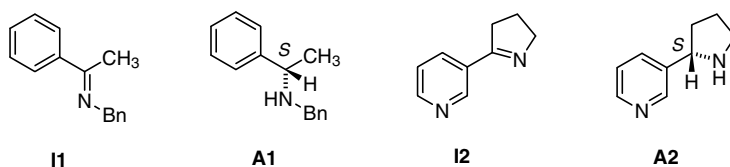


Fig. 10

It was also reported that a chiral heterocyclic carbene rhodium complex catalyzed the reduction of acetophenone with diphenylsilane giving 32% ee and 90% yield [47].

For the asymmetric hydrosilylation of imine derivatives, no improvements have been reported after 1990. Until the late 1980s, for example, the imines were reduced in the middle range of enantioselectivity around 60% ee. The imines **I1** and **I2** (Fig. 10) were converted to the corresponding secondary amines **A1** and **A2** in 65% ee and 66% ee, respectively, with Rh-DIOP catalysts and diphenylsilane [48].

3

Hydrosilylation of C=O and C=N with Chiral Titanium Catalysts

It was originally found in 1988 that a titanium complex $\text{Ti}(\text{Cp})_2\text{Ph}_2$ has a catalytic activity for the hydrosilylation of ketones with hydrosilanes to give secondary alcohols at 90–100 °C [49]. This process was then applied to the reduction of esters under milder conditions with titanocene dichloride [50]. The first attempts at asymmetric hydrosilylation of ketones by titanium-silane catalysts were published in 1994 independently by two groups. Halterman's group reported that the binaphthyl derived catalyst **T1** (Fig. 11) exhibited catalytic activity in THF for the reduction of several aromatic ketones, such as **K1**, **K9**, and **K23**, with triethylsilane at –78 °C to room temperature and resulted in high yields with 14% ee, 40% ee, and 32% ee, respectively [51] (Table 2). Buchwald's group successfully modified the hydrosilylation of ketones in benzene by using the chiral (tetrahydroindenyl)titanium(IV)-binaphthdiolate **T2** (Fig. 11; 4.5 mol % based on ketone) and polymethylhydrosiloxane (5-fold excess based on ketone) giving optically active secondary alcohols in 72–96% yield with 97% ee (*S*) for acetophenone (**K1**), 95% ee (*S*) for 2-naphthyl methyl ketone (**K9**), and 95% ee (*S*) for phenylethyl ketone (**K24**) [52]. However, under the same conditions, ketones with α,β -unsaturation, such as cyclohexyl methyl ketone and 2-phenylethyl methyl ketone, were reduced in lower % ees: 24 and 12%, respectively.

In these catalytic systems, initial treatment of the precatalysts with alkyllithium is mandatory to produce active titanium species via reduction of Ti(IV), which are thought to be a titanium(III) hydride, (modified-Cp)₂Ti(III)H.

The tetrahydroindenyltitanium(IV) chloride **T3** (Fig. 12), assisted by methyl-lithium, also exhibited catalytic activity in the reduction of ketones with diphe-

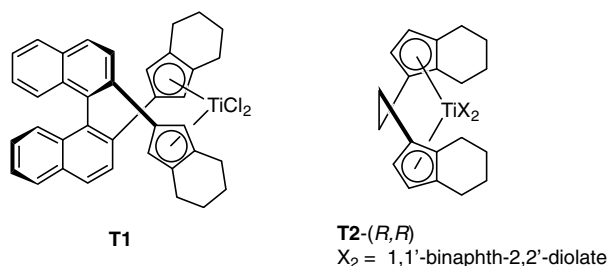


Fig. 11

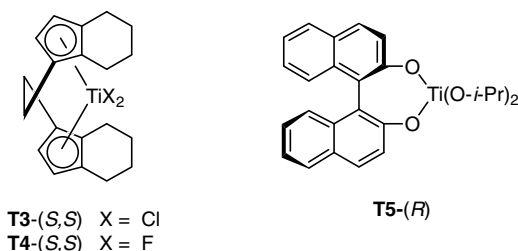


Fig. 12

nylsilane and methylphenylsilane [53]. Although acetophenone was reduced in 90% yield but in a lower % ee, 12%, dialkylketones such as isopropyl ethyl ketone **K25** and cyclopentyl ethyl ketone **K26** were converted into the corresponding alcohols in 65% ee (*R*) and 70% ee (*R*), respectively. In this study, it was initially suggested that the rate-determining step involves either a bimetallic complex or the reaction of two monometallic titanium species.

(*R*)-BINOL-Ti(O-*i*-Pr)₂ **T5** (10 mol %) as a precatalyst was investigated for the asymmetric hydrosilylation in the presence of triethylsilane in ether [54]. At 50 °C, acetophenone was reduced in 54% ee (*R*). In this system, it was found that the enantioselectivity was gradually increased with increasing %-conversion, invoked as an “enantioselective autoinduction”. Therefore, two hypothetical catalytic cycles were postulated.

In the case of the hydrosilylation of C=N bonds, extremely high levels of enantioselectivity were dramatically realized by use of the (tetrahydroindenyl)titanium(IV) fluoride **T4** (Fig. 12) by Buchwald in 1996 [55]. The *in situ* catalyst uniquely derived by mixing the titanocene fluoride **T4** (1.0–0.02 mol %) with phenylsilane PhSiH₃ (1.5 eq referred to ketone) as hydrogen atom donor reduces the imines **I3–I7** (Fig. 13) to the amines **A3–A7** in 80–96% yields (Table 3). An alternative activation method for the titanocene by addition of methanol and pyrrolidine was also described. In this case, the imine from acetophenone and methylamine, **I3**, was converted at room temperature to 35 °C to give the corresponding secondary amine in 94–95% yield with 97–99% ees (*S*). Moreover, alkylimines were also reduced in 92–99% ees.

Table 2. Asymmetric hydroxylation of ketones with chiral titanium catalysts

Catalyst Ti-complex/RLi	Silane	Ketone ^a	Solvent	L/Ti	Ketone/Ti	Silane/Ketone	Temp/Time (°C/h)	Product: secondary alcohol		Ref.
								Yield	%ee	
T1/ <i>n</i> -BuLi	(EtO) ₃ SiH	K1	THF	1/1	200/1	2.5/1	-78-rt/24	100	S	51
	(EtO) ₃ SiH	K9	THF	1/1	200/1	2.5/1	-78-rt/24	90	S	51
	(EtO) ₃ SiH	K23	THF	1/1	200/1	2.5/1	-78-rt/24	100	S	51
T2/ <i>n</i> -BuLi	Me ₃ Si(SiH-MeO) _n SiMe ₃	K1	benzene	1/1	23/1	5/1	rt/22	73	S	52
	Me ₃ Si(SiH-MeO) _n SiMe ₃	K7	benzene	1/1	23/1	5/1	rt/84	92	S	52
	Me ₃ Si(SiH-MeO) _n SiMe ₃	K9	benzene	1/1	23/1	5/1	rt/72	84	S	52
T3/MeLi	Me ₃ Si(SiH-MeO) _n SiMe ₃	K16	benzene	1/1	23/1	5/1	rt/24	72	S	52
	Me ₃ Si(SiH-MeO) _n SiMe ₃	K23	benzene	1/1	23/1	5/1	rt/24	75	S	52
	Me ₃ Si(SiH-MeO) _n SiMe ₃	K24	benzene	1/1	23/1	5/1	rt/24	96	S	52
T5	Ph ₂ SiH ₂	K1	no solv.	1/1	100/1	1/1	rt/300	90	R	53
	PhMeSiH ₂	K25	no solv.	1/1	100/1	1/1	rt/230	91	R	53
	PhMeSiH ₂	K26	THF	1/1	100/1	1/1	rt/600	94	(+)	53
	(EtO) ₃ SiH	K1	Et ₂ O	1/1	10/1	6/1	50/5	98	R	54
	(EtO) ₃ SiH	K8	Et ₂ O	1/1	10/1	6/1	50/5	98	R	54

^a K1=acetophenone, K7=1-tetralone, K8=1-acetylnaphthalene, K9=2-acetylnaphthalene, K16=1-cyclohexenyl methyl ketone, K23=4-BrPhCOCH₃, K24=PhCOEt, K25=*i*-PrCOEt, K26=EtCO-cyclopentyl

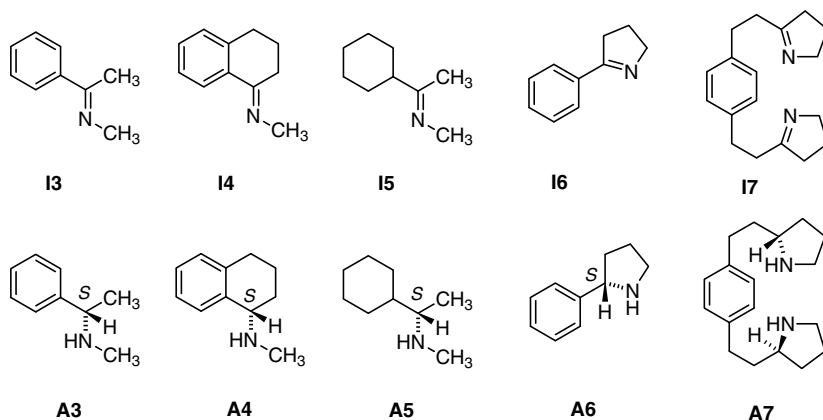


Fig. 13

Table 3. Asymmetric hydrosilylation of imines with the chiral titanium catalyst (*S,S*)-(EBT-HI)TiF₂ (**T4**)

Imine ^a	Imine/Ti	Temp/Time (°C/h)	Product: secondary amine			Ref.	
			Yield (%)	%ee	abs config		
13	100/1	r.t./12	A3	94	97	(-)- <i>S</i>	55
14	100/2.5	r.t./12	A4	80	96	(+)- <i>S</i>	55
15	100/1	r.t./12	A5	88	93	(+)- <i>S</i>	55
16	100/1	r.t./12	A6	97	99	(-)- <i>S</i>	55
17	100/2	r.t./12	A7	64	98	(-)- <i>S</i>	55

^a Imines (**13–17**), **T4** (1–2 mol %), Ph₃SiH (1.5 eq referred to imines), THF

Thus, the chiral titanocene complexes have been developed to exhibit a potentially high activity for the asymmetric hydrosilylation of ketones.

4

Hydrosilylation of C=O and C=N with Miscellaneous Metal Catalysts

The carbon-nitrogen double bonds of nitrones **N1–N3** (Fig. 14) were catalytically reduced with diphenylsilane in the presence of Ru₂Cl₄(Tol-BINAP,**L24**)₂(NEt₃) to give hydroxylamines in high % ees [56]. The hydroxylamine **H1** was obtained in 63% yield with 86% ee (*S*) and the hydroxylamine **H3** was formed in 91% ee. It was also proposed that this process opened a new access to optically active amines from racemic amines, via nitrones and hydroxylamines. The iron complex [(Cp)₂Fe₂(HPMen₂,**L25**)(CO)₂] was reported to be a catalyst in the asymmetric hydrosilylation of ketones under irradiation, where acetophenone was reduced in up to 33% ee [57].

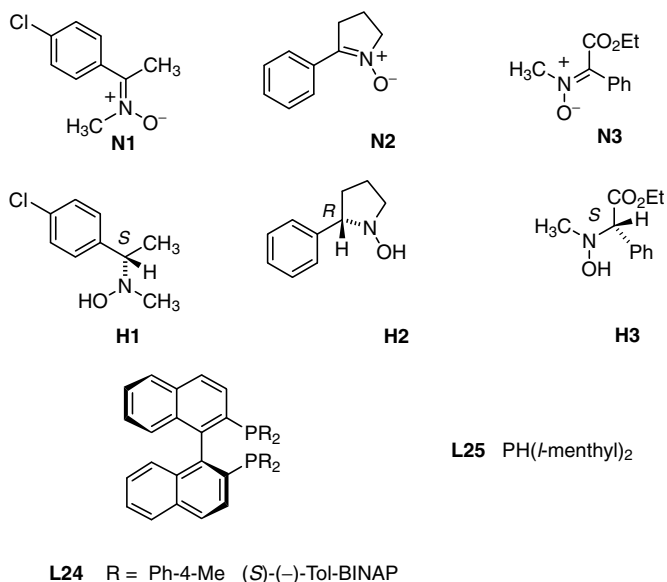


Fig. 14

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Chapter 6.4

Hydroboration of Carbonyl Groups

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Keywords: Hydroboration, Ketone, Reduction, Oxazaborolidine, Oxazaphospholidine, Borane, Borohydride

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1

Introduction

Hydride reduction of carbonyl compounds is one of the most important methods to obtain optically active alcohols. Over the past decade, the asymmetric hydroboration of prochiral ketones has emerged as a useful tool for synthetic chemists. In the early stages of enantioselective reduction of ketones, a number of chiral modified LiAlH_4 reagents has been developed, followed by the preparation of chiral modified borohydrides [1, 2, 3, 4]. A stoichiometric amount of the chiral modifier is required for ketone reduction with these hydride reagents to give the corresponding enantio-enriched secondary alcohols. Borane is another type of hydride reagent. Although complex hydride salts such as LiAlH_4 and NaBH_4 are basic in nature, BH_3 is an acidic reducing agent. The Lewis acidity of borane allows it to be modified by the addition of complexing agents such as enantiopure amines. The first attempt to modify borane by using an enantiopure amine was carried out by Kagan in 1969 [5]. However, these reagents such as amphetamine-borane, *N,N*-dimethylamphetamine-borane, and deoxyephedrine-borane afforded 1-phenylethanol in <5% ee in the reduction of acetophenone. Other attempts using chiral modified amine-borane complexes resulted in only low enantioselectivity in the ketone reduction [6, 7, 8]. Exceptionally high enantioselectivity (82% ee in the reduction of acetophenone) was obtained by using the borane complex of enantiopure β -hydroxysulfoximine [9]. Borane can also be modified by the incorporation of enantiopure alkyl groups through hydroboration. A series of enantiopure mono- and dialkylboranes has been developed by H. C. Brown, and the compounds are very effective for the enantioselective hydroboration of olefins [10]. Optically active borohydrides derived from these alkylboranes are efficient reducing agents for ketone reduction [11, 12, 13]. Enantiopure trialkylboranes are another type of excellent reducing agents, in which the reductions involve an MPV types of process [14]. All these asymmetric reductions proceed stoichiometrically. Since the catalytic activity of oxazaborolidine has been discovered, asymmetric hydroboration of $\text{C}=\text{O}$ is one of the most useful method to obtain optically active alcohols in high enantiomeric purity. Recently, some other catalytic asymmetric reduction systems have been developed for both borohydrides [15] and boranes [16].

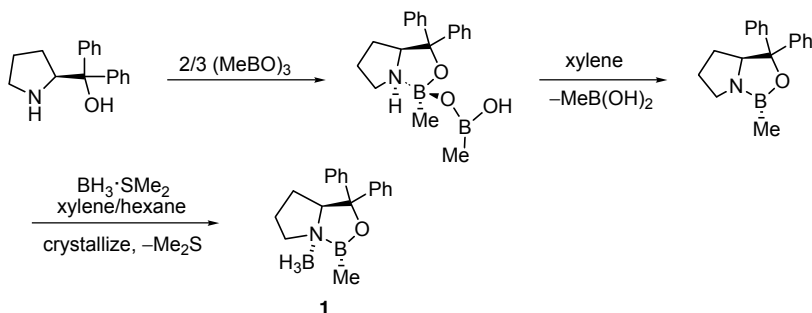
2 Enantioselective Reduction of Ketones with Oxazaborolidine Catalysts

Before the catalytic behavior of 1,3,2-oxazaborolidine was recognized, the enantioselective borane reduction of ketones utilizing stoichiometric amounts of oxazaborolidines prepared *in situ* from borane and β -amino alcohols had been reported in 1981 [17, 18]. Their catalytic properties in the borane reduction of various functional groups were discovered in 1985 [19, 20]. The catalytic behavior of the oxazaborolidine was first found when a simple amino alcohol, 2-aminoethanol, was added to the borane reduction of ketones and aldehydes. The reaction rate of the reduction dramatically increased in the presence of 2-aminoethanol. In the borane reduction of ketones, not only an increase in reaction rate, but also an enantioselective reduction were achieved by using enantiopure amino alcohols instead of 2-aminoethanol. The catalytic behavior of chiral oxazaborolidine was first reported in the reduction of oxime ethers using a catalytic amount of (*S*)-diphenylvalinol [21]. In the presence of the oxazaborolidine catalyst reducing agents other than borane such as AlH_3 and LiAlH_4 can be used. During the last decade, oxazaborolidine chemistry has been widely investigated and become a powerful tool for enantioselective reduction of prochiral ketones, imines, and oximes.

2.1 Catalyst Preparation

The structure of enantiopure 1,3,2-oxazaborolidine was first characterized by Corey [22]. The oxazaborolidine is prepared from an amino alcohol and borane or substituted boronic acids (Scheme 1) [23, 24, 25]. *B*-Methyl derivatives of oxazaborolidine were prepared by the reaction of an amino alcohol with trimethylboroxine [26, 27].

The borane complex **1**, as an important intermediate responsible for the enantioselectivity of ketone reductions, is a remarkably stable solid. An alternative



Scheme 1

method to prepare oxazaborolidines is the reaction of β -amino alcohol with bis(trifluoroethyl)alkylboronates [28].

B-Methoxyoxazaborolidine also performs as an efficient catalyst in the borane reduction of ketones. This catalyst was prepared *in situ* from an amino alcohol and trimethyl borate and used for the reduction [29].

N-Sulfonyloxazaborolidine also acts as catalyst for the borane reduction of ketones [30]. This catalyst may form a borane *O*-adduct which reduces ketones enantioselectively.

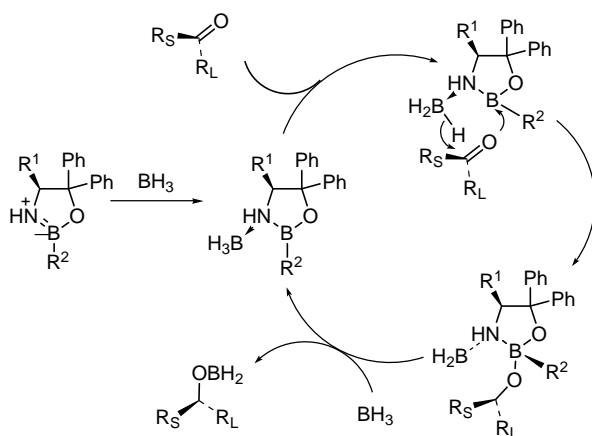
2.2

Mechanism of Catalysis

Borane reduction of carbonyl compounds such as aldehydes, ketones, amides, and carboxylic acids was established in 1960s [10, 31].

In the oxazaborolidine-catalyzed borane reduction, the molecular recognition, two-point binding of borane and the oxygen atom of ketone by the oxazaborolidine, assembles a trimolecular complex which provides the high enantiomeric excess. This reaction may occur by the following sequence: (a) complexation of borane to the nitrogen; (b) coordination of the ketone oxygen to the boron of oxazaborolidine; (c) hydrogen transfer from the coordinated borane to the carbonyl *via* a six-membered cyclic transition state (Scheme 2) [32].

The quantum chemical modeling of such chiral catalysis has been developed by Nevalainen [33]. An investigation into the origin of the enantioselectivity was also carried out using molecular orbital methods [32].



Scheme 2

2.3

Source of Borane Reductant

For the oxazaborolidine-catalyzed reduction of prochiral ketones various borane reductants are employed. Borane-tetrahydrofuran and borane-dimethyl sulfide are the most frequently used reductants. Borane-1,4-thioxane [34], diborane, catecholborane [35, 36, 37, 38], and diethylaniline-borane [39] are also useful borane reductants in this reduction system.

2.4

Reduction of Ketones

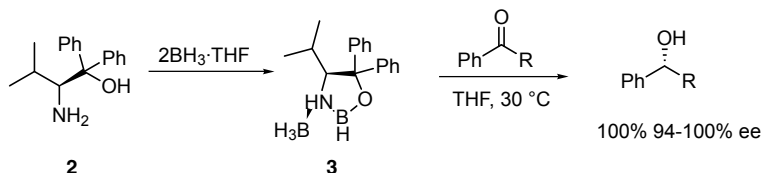
2.4.1

Reduction of Aromatic Ketones

The first successful example of the enantioselective borane reduction of aryl alkyl ketones was performed by using (*S*)-diphenylvalinol **2**. The corresponding alcohols are obtained in up to 100% ee using borane-THF and 0.5 equiv. of **2** in THF at 30 °C (Scheme 3).

The structurally more rigid (*S*)-prolinol-based amino alcohol was introduced early in the study of borane reductions [18]. Sterically more hindered oxazaborolidines **4** (Fig. 1) based on (*S*)-(-)-diphenylhydroxymethylpyrrolidine have been prepared by Corey [23, 25]. These catalysts have been widely used for the borane reduction of various kinds of ketones. After these successful results had appeared for asymmetric ketone reduction, several oxazaborolidines (Fig. 1) were prepared. Many of them were successfully used in the reduction of aromatic ketones. Selected results of enantioselective borane reduction using various oxazaborolidines are shown in Scheme 4. The table to this scheme shows only the data obtained from the reduction of acetophenone as a representative aromatic ketone. In most cases, high enantioselectivity is obtained in the nearly quantitative yield.

Other aromatic ketones are also reduced highly enantioselectively by using oxazaborolidine catalyst. Representative data for the reduction of other aromatic ketones (**53 to 58**) are collected in Fig. 2.



Scheme 3

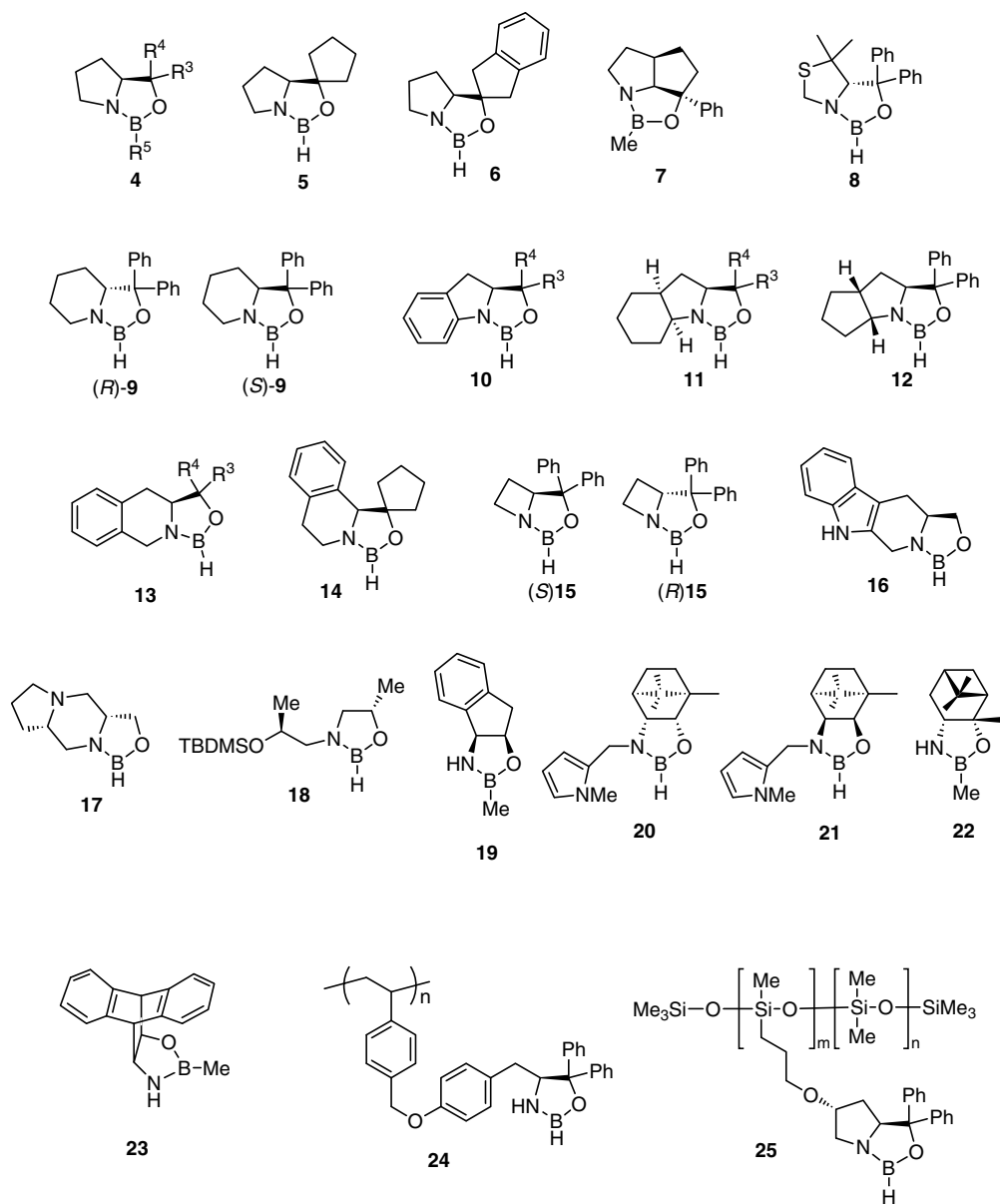
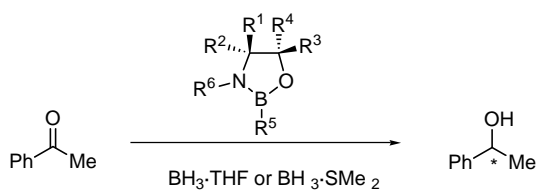


Fig. 1

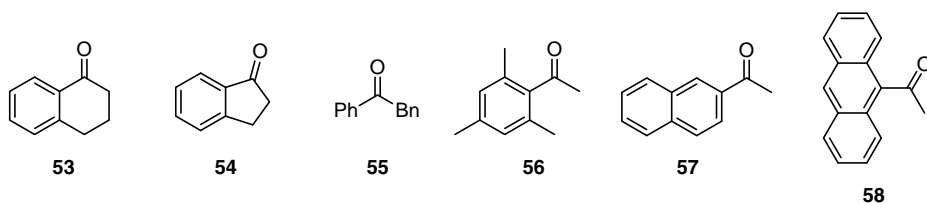


Compound no.	Oxazaborolidine						Yield [%]	ee [%]	Config.	Ref.
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶				
3	<i>i</i> -Pr	H	Ph	Ph	H	H	100	94	<i>R</i>	20
26	<i>i</i> -Pr	H	<i>p</i> -FPh	<i>p</i> -FPh	H	H	100	93	<i>R</i>	40
27	<i>i</i> -Pr	H	<i>p</i> -OMePh	<i>p</i> -OMePh	H	H	76	93	<i>R</i>	40
28	<i>o</i> -ClPhCH ₂	H	Ph	Ph	H	H	85	95	<i>R</i>	41
29	Bn	H	Bu	Bu	H	H	65–93	82	<i>R</i>	42
30	PhCH ₂ CH ₂	H	Bu	Bu	H	H	65–93	72	<i>R</i>	42
31	<i>t</i> -Bu	H	Bu	Bu	H	H	65–93	82	<i>R</i>	42
32	<i>t</i> -Bu	H	H	H	H	H		80	<i>R</i>	43
33	<i>t</i> -Bu	H	Ph	Ph	H	H		89	<i>R</i>	43
34	EtSCH ₂	H	Ph	Ph	H	H	80–95	83	<i>R</i>	44
35	<i>s</i> -Bu	H	Ph	Ph	H	H	100	95	<i>R</i>	20
36	<i>i</i> -Bu	H	Ph	Ph	H	H	100	82	<i>R</i>	20
37	Me	H	Ph	Ph	H	H	100	85	<i>R</i>	20
38	Bn	H	Ph	Ph	H	H	100	87	<i>R</i>	20
39	H	Ph	H	H	H	H		80	<i>R</i>	42
40	H	Ph	Me	Me	H	H	65–93	91	<i>S</i>	42
41	H	Ph	Et	Et	H	H	65–93	92	<i>S</i>	42
42	H	Ph	Pr	Pr	H	H	65–93	91	<i>S</i>	42
43	H	Ph	Bu	Bu	H	H	65–93	90	<i>S</i>	42
44	H	Ph	Allyl	Allyl	H	H	65–93	68	<i>S</i>	42
45	H	Ph	Ph	Ph	Me	H	100	96	<i>R</i>	45
46	H	Me	Ph	H	H	Ms	100	72	<i>R</i>	30
47	Ph	H	Ph	H	H	H	100	>99	<i>R</i>	46
48	Ph	H	Ph	H	Me	H		92	<i>R</i>	47, 48
49	Me	H	Ph	H	H	Me	99–100	83	<i>R</i>	49
50	Me	H	Ph	H	H	Me	95	72	<i>R</i>	50
51	H	Ph	-(CH ₂) ₄ -		H	H	94–99	88	<i>S</i>	51
52	Bn	H	-(CH ₂) ₄ -		H	H	94–99	63	<i>S</i>	51
4a	-	H	Ph	Ph	H	-	100	97	<i>R</i>	22

Scheme 4

Compound no.	Oxazaborolidine						Yield [%]	ee [%]	Config.	Ref.
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶				
4b	-	H	Ph	Ph	Me	-	95	98.8	<i>R</i>	52
4c	-	H	Ph	Ph	Bu	-		92	<i>R</i>	53
4d	-	H	Ph	Ph	Ph	-		72	<i>R</i>	53
4e	-	H	2-Naph	2-Naph	H	-	100	98	<i>R</i>	25
4f	-	H	2-Naph	2-Naph	Me	-	100	98	<i>R</i>	25
5							69	86	<i>R</i>	54
6							86	96	<i>R</i>	55
7							100	98	<i>R</i>	56
8							80–95	87	<i>R</i>	48
<i>(R)</i> -9							85–95	87	<i>S</i>	57
<i>(S)</i> -9							85–95	87	<i>R</i>	58
10a	-	H	H	H	H	-	100	97	<i>R</i>	59
10b	-	H	Ph	Ph	H	-	93	96	<i>R</i>	60
11a	-	H	H	H	H	-	95	90	<i>S</i>	60
11b	-	H	Ph	Ph	H	-	96	49	<i>S</i>	60
12							78	61	<i>S</i>	61
13a	-	H	H	H	H	-	>99	71	<i>R</i>	62
13b	-	H	Ph	Ph	H	-	>99	51	<i>R</i>	62
14							94	88	<i>R</i>	63
<i>(S)</i> -15							100	98	<i>R</i>	43
<i>(R)</i> -15							>90	95	<i>S</i>	64
16							85	88	<i>R</i>	65
17							86	79	<i>S</i>	66
18							98	72	<i>S</i>	67
19							>96	86	<i>R</i>	68
20							68	73	<i>S</i>	69
21							62	73	<i>R</i>	69
22							>90	93	<i>S</i>	57
23								>98	<i>R</i>	70
24							100	76	<i>R</i>	71
25							86	>97	<i>R</i>	72

Scheme 4. Continued



Ketone	Oxazaborolidine	Yield [%]	ee [%]	Config.	Ref.
68	48		94	R	48
68	16	99	96	R	65
69	4b		96	R	90
69	48		90	R	48
70	4b	95	98.6	R	52
71	4c	95	99.7	S	73
72	4b	>90	96	R	74
73	51		>99	S	75

Fig. 2

2.4.1.1

Effect of Temperature on Selectivity

In many stereoselective reactions, the effect of temperature on the selectivity is as expected, with better results being obtained at lower temperature. A lower temperature is often required to increase the selectivity. From the practical point of view, one of the most attractive features of this enantioselective reduction is that excellent enantioselectivity is obtained at a relatively high temperature such as room temperature. In some cases, the selectivity of the oxazaborolidine catalyzed borane reduction increases with increasing temperature until an optimal range is reached (30–50 °C) where the selectivity then begins to decrease [76]. Interpretation of this phenomenon is not so easy. The amount of catalyst dimer that exists in a temperature-dependent equilibrium with the monomeric form, might have an effect on the selectivity.

2.4.1.2

Effect of Additives

In the oxazaborolidine-catalyzed borane reduction of ketones, the effect of additives has been investigated. For example, addition of triethylamine was found to improve the enantioselectivity in the stoichiometric reduction [77]. Some alcohols, e.g., *i*-PrOH, also efficiently enhanced the enantioselectivity of the reduction [78]. When the stoichiometric amount of the oxazaborolidine was used,

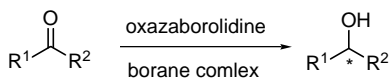
reduction of 4-chromanone was improved from 93% to 98% ee by addition of *i*-PrOH. Even in the catalytic process this additive efficiently enhances the enantioselectivity of various ketone reductions [78].

Some aluminum Lewis acids such as triisobutylaluminum exhibited a rate enhancing effect in the oxazaborolidine-catalyzed borane reduction of ketones [79]. Somewhat higher ees were also obtained in the presence of triisobutylaluminum. However, addition of titanium Lewis acids such as $\text{Ti}(\text{O-}i\text{-Pr})_4$ or TiCl_4 resulted in the complete loss in enantioselectivity.

2.4.2

Reduction of Aliphatic Ketones

Although various kinds of excellent asymmetric reducing agents including chiral modified hydrides have been developed, most of them gave unsatisfactory results in the reduction of dialkyl ketones. Unsaturated groups such as phenol, alkenyl, or alkynyl substituents in the ketone substrate are required to obtain high enantioface differentiation. The oxazaborolidine-catalyzed borane reduction shows high enantioselectivity in the case of the reduction of aliphatic ketones (Scheme 5), which is usually difficult to achieve with other modified hydride reagents. The first example that exceeds 90% ee in the reduction of aliphatic ketone appeared by using **3** [20]. The *B*-methyloxazaborolidine **7** is also an excellent catalyst for the enantioselective reduction of a variety of ketones including aliphatic ones [56]. Catalyst **4b** gave high ees in the reduction of aliphatic ketones [27]. Higher enantioselectivities were achieved in the reduction of aliphatic



R ¹	R ²	Oxazaborolidine	Borane complex	ee[%]	Config.	Ref.
C ₆ H ₁₁	Me	4b	<i>N,N</i> -diethylaniline borane	>99	<i>S</i>	39
C ₆ H ₁₁	Me	7	BH ₃ ·THF	91.8	<i>R</i>	56
<i>i</i> -Pr	Me	4b	<i>N,N</i> -diethylaniline borane	91	<i>S</i>	39
<i>t</i> -Bu	Me	4b	<i>N,N</i> -diethylaniline borane	97.4	<i>R</i>	39
<i>t</i> -Bu	Me	7	BH ₃ ·THF	98.3	<i>R</i>	56
<i>t</i> -Bu	Me	35	BH ₃ ·THF	96	<i>R</i>	20
<i>t</i> -Bu	Me	23	BH ₃ ·SMe ₂	96	<i>S</i>	57
<i>t</i> -Bu	Me	23	BH ₃ ·THF	>99	<i>S</i>	70
Cyclopropyl	<i>i</i> -Pr	4c	Catecholborane	91	<i>R</i>	80

Scheme 5

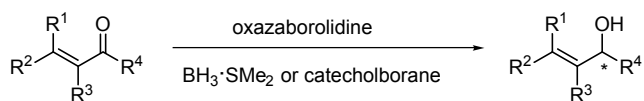
ic ketones using *N,N*-diethylaniline-borane as hydride source in the oxazaborolidine-catalyzed reduction [39]. The highest ee value for the reduction of pinacolone was reported by using **23** [70]. On using this catalyst, other linear aliphatic ketones such as 2-hexanone and 2-pentanone gave moderate levels of enantioselectivity, around 64% ee. There is still room to design more suitable catalysts for the asymmetric reduction of simple dialkyl ketones. Cyclopropyl isopropyl ketone was reduced with catechol-borane in the presence of 0.15 equiv of **4c** to give the alcohol with 91% ee [80]. Other interesting aliphatic ketones are adamantane ketones which are unreactive to chiral reducing agent such as *B*-chlorodiisopinocampheylborane because of their steric hindrance. Various adamantane ketones were found to be reduced efficiently with the oxazaborolidine system [81].

2.4.3

Reduction of α,β -Unsaturated Ketones

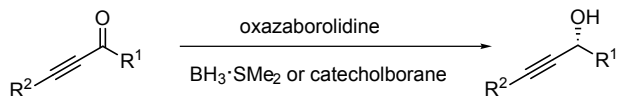
Hydroboration of the C-C unsaturated bond may be a possible side reaction in the reduction of α,β -unsaturated ketones. However, in many cases, some oxazaborolidines successfully catalyze the selective reduction of ketone carbonyls (Scheme 6). The borane reduction of 2-methylnon-1-en-3-one with oxazaborolidine **45** showed a clean conversion to the allylic alcohol (98%, 92% ee *S*) [82]. The same catalyst [83] and **4b** [84] were effective for the reduction of α,β -ynones [83].

The use of catecholborane as reductant can avoid the side reaction caused by BH_3 . The catecholborane procedure functions well at -78°C in toluene. Chiral allylic alcohols were obtained in >95% yield with high ees [35]. Cyclic enones are also reduced enantioselectively to give chiral cyclic allylic alcohols by using catecholborane as reductant [35].



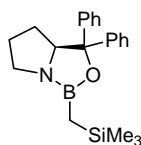
Oxazaborolidine	Reductant	R ¹	R ²	R ³	R ⁴	Yield [%]	% ee	Config.
45	BH_3	H	H	Me	C_6H_{13}	98	92	<i>S</i>
4b	BH_3	H	H	Me	C_6H_{13}	–	92	<i>R</i>
4c	catecholborane	H	Ph	H	Me	>95	92	<i>R</i>
4c	catecholborane	H	<i>p</i> -TsO	H	C_5H_{11}	>95	91	<i>R</i>
4c	catecholborane	2-methyl-2-cyclohexen-1-one				>95	93	<i>R</i>
4c	catecholborane	1-acetyl-1-cyclohexene				>95	81	<i>R</i>

Scheme 6



Oxazaboro- lidine	Reductant	R ¹	R ²	Yield [%]	ee [%]	Config.	Ref.
45	BH ₃ ·Me ₂ S	PhCH ₂ CH ₂	SiMe ₃	92	90	<i>R</i>	83
45	BH ₃ ·Me ₂ S	1-adamantyl	SiMe ₃	80	95	<i>R</i>	83
59	catecholborane	C ₅ H ₁₁	Si ^{<i>i</i>} Pr ₃	98	97	<i>R</i>	85
59	catecholborane	Me	Si ^{<i>i</i>} Pr ₃	100	95	<i>R</i>	85
4b	BH ₃ ·Me ₂ S	cyclohexyl	H	81	98	<i>S</i>	84

Scheme 7



59

Fig. 3

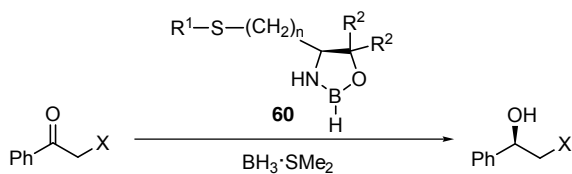
This reduction was applied to the synthesis of some natural products. Catecholborane reduction is also effective for the synthesis of chiral propargylic alcohols (Scheme 7). In this case the catalyst of choice is **59** (Fig. 3) [85].

2.4.4

Reduction of Haloketones

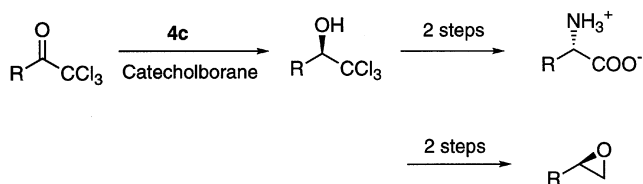
Halo-substituted acetophenones such as *m*-bromo- [74] or *p*-chloroacetophenone [46] were reduced with borane in high enantioselectivity in the presence of oxazaborolidines **4b** and **47**, respectively. Other important halogen-containing ketones are chloromethyl or bromomethyl ketones. Oxazaborolidine reduction of ω -chloro- or ω -bromoacetophenone gives enantio-enriched halohydrins that can be converted into chiral oxiranes [20]. Martens found that the sulfur-containing oxazaborolidine catalysts **60** show high enantioselectivity in this kind of reduction [44, 86, 87]. Enantiopure halohydrins were obtained as shown in Scheme 8.

The catalytic reduction of trifluoromethyl ketones was successfully realized by using catecholborane as reductant. In the case of the reduction of anthryl trifluoromethyl ketone, one recrystallization of the crude (*R*)-alcohol (94% ee) afforded the enantiopure carbinol [35]. Trichloromethyl ketones were also reduced



X	R ¹	n	R ²	Yield [%]	ee [%]
Cl	Me	2	<i>p</i> -MePh	80–95	100
Cl	<i>i</i> -Pr	1	Ph	80–95	100
Br	Me	2	Ph	80–95	100
Br	Me	2	<i>p</i> -MeOPh	80–95	100
Br	<i>i</i> -Pr	1	Ph	80–95	100

Scheme 8



Scheme 9

efficiently with this system to afford enantio-enriched trichloromethylcarbinols, which were converted to α -amino acids [36, 37] and terminal epoxides [88] of high enantiomeric purity (Scheme 9).

Several other α, α, α -trihaloketones can be reduced by this method [38].

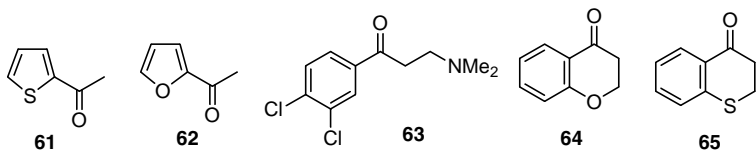
2.4.5

Reduction of Ketones Containing Heteroatoms

Ketones which contain heteroatoms capable of coordinating borane, particularly nitrogen, can be reduced catalytically with oxazaborolidines to afford alcohols with high ees [47]. Oxazaborolidines such as **4a**, **4b**, and **48** were successfully used for the reduction of ketones (**61** to **65**) containing heteroatoms (Fig. 4).

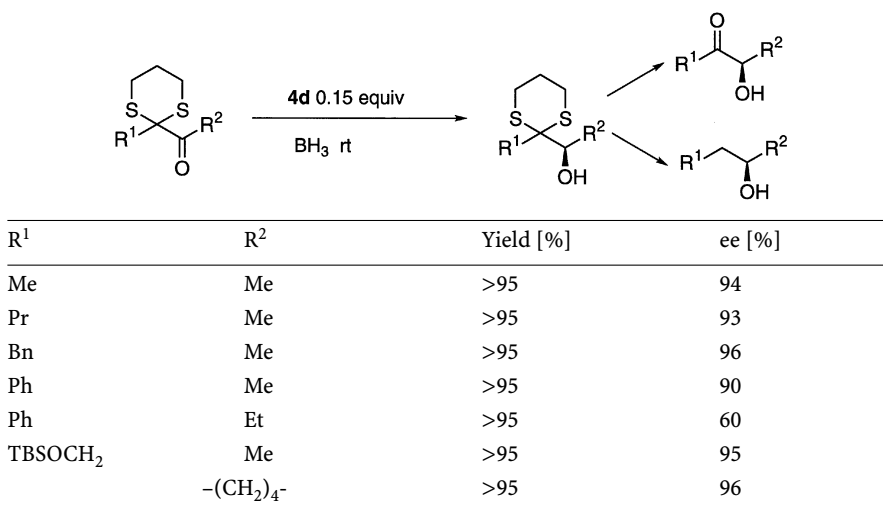
The catecholborane reduction of 2-benzoylpyridine in the presence of **4c** gave only a low ee. However, high enantioselectivity (99%) was achieved in the reduction of the *N*-allylpyridinium ketone derivative [90].

Acyldithianes were reduced asymmetrically to give the enantio-enriched alcohols. As shown in Scheme 10 the obtained alcohols containing a dithiane moiety can be subsequently transformed into useful chiral alcohols in high enantiopurity, compounds that would be inaccessible via direct reduction [91].



Oxazaborolidine	Ketone	Yield [%]	ee [%]	Config.	Ref.
4a	61	75	91	R	89
4a	62	50	93	R	89
4b	63	92	90	R	47
4b	64	92	90	R	47
4b	65	94	92	R	47
(R)-4b	61	91	94	S	47
48	63		94	R	48
48	64		97	R	48

Fig. 4



Scheme 10

2.4.6

Reduction of Diketones

Asymmetric reduction of diketone is one of the easiest ways to obtain chiral diols. Bisoxazaborolidine having two catalytic centers seems to be especially good at catalyzing the enantioselective reduction of prochiral diketones. 1,6-Diphe-

nyl-1,6-hexanedione was reduced by using a bisoxazaborolidine catalyst in 98.4% ee [92].

C_2 -Symmetric chiral 1,4-diols can be prepared by the oxazaborolidine-catalyzed reduction of 2-ene-1,4-diones and 2-yne-1,4-diones [93]. From ferrocenyl diketones, the corresponding C_2 -symmetrical chiral diols were prepared in high ees (>98% ee) [94]. Enantiopure (>99% ee) (*S,S*)-1,2-diarylethanedioles were also synthesized by borane reduction of diaryl 1,2-diones using **4a** [95].

2.4.7

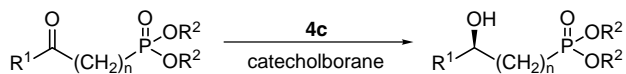
Reduction of α -Ketophosphonates

Because of their biological activity, optically active α -hydroxyphosphonates have received increasing interest. Enantio-enriched dialkyl α -hydroxyphosphonates were obtained by the oxazaborolidine catalyzed reduction of α -ketophosphonates with catecholborane (Scheme 11) [96].

2.4.8

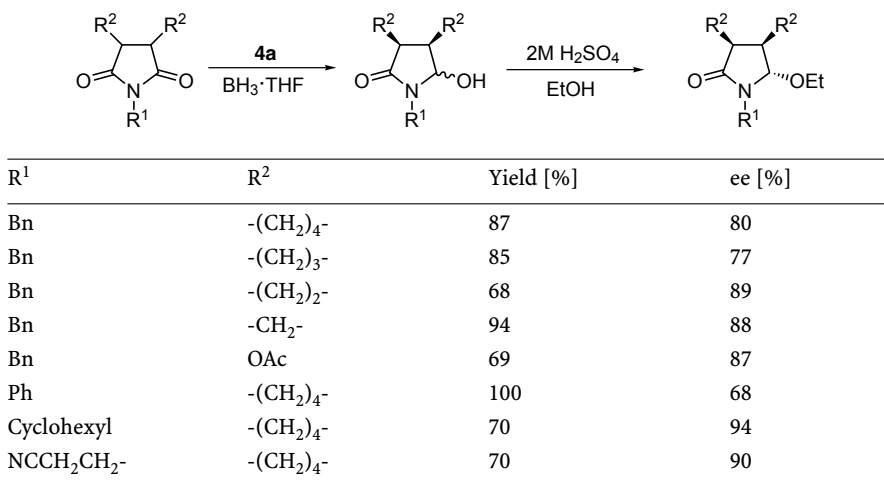
Reduction of Cyclic *meso*-Imides

Treatment of cyclic *meso*-imides with borane in the presence of an oxazaborolidine catalyst led to hydroxylactams which were converted to ethoxylactams in 68–94% ee (Scheme 12). The ethoxylactam was further converted into the benzenesulfonyllactam, which can be crystallized to >99% ee [97].



R ¹	R ²	n	Yield [%]	ee [%]
Ph	<i>i</i> -Pr	0	92	65
<i>o</i> -FPh	<i>i</i> -Pr	0	68	91
<i>o</i> -ClPh	<i>i</i> -Pr	0	96	97
<i>o</i> -BrPh	<i>i</i> -Pr	0	82	95
Me	<i>t</i> -Bu	0	89	81
2,6-FPh	<i>i</i> -Pr	0	96	>99
Ph	<i>i</i> -Pr	1	66	91
Ph	<i>i</i> -Pr	2	58	68

Scheme 11



Scheme 12

2.4.9

Reduction of Acylsilanes

Acylsilanes can be reduced with the borane-oxazaborolidine system to give the corresponding silicon-containing chiral alcohols with good to excellent enantioselectivity [98].

2.4.10

Reduction of Aldehydes

²H-Catecholborane was used as a reductant for aldehydes in the presence of oxazaborolidine catalyst **66** (Fig. 5).

Enantioenriched 1-deuterio primary alcohols were obtained by reduction at -126 °C with high enantioselectivities [25]. Reduction of benzaldehyde gives the 1-deuterio alcohol in 95% ee.

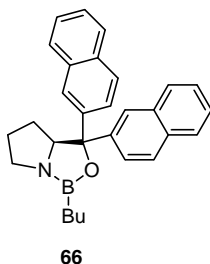


Fig. 5

2.5

Applications to Synthesis

Since oxazaborolidine-catalyzed reductions have proved to be very effective for various kinds of chiral alcohol synthesis, this method has been used as a key step in the synthesis of various natural products. The steroid 20R alcohol was exclusively obtained by borane reduction in the presence of (*S*)-2-amino-2-phenyl-1-ethanol [99]. Catalytic reduction using **4b** has been used in prostaglandin synthesis [100]. The synthesis of the antiarrhythmic drug candidate MK-0499 was achieved by using this method [78]. The enantioselectivities in this reduction were improved by addition of 2-propanol or triethylamine. This catalytic asymmetric reduction has been also utilized for the synthesis of the C3-C9 fragment of octalactin A [82], denopamine, a useful drug for congestive heart failure [101], and enantiomerically pure MK-0417 [53]. The plant growth regulator triapentanol was obtained by reduction of the corresponding (*E*)-enone [102]. The enantioselective synthesis of a potent dopamine D1 antagonist (A77636) was achieved by using the borane reduction as a key reaction [81]. Several other therapeutically important compounds such as ginkgolide B [56] fluoxetine [103], and forskolin [104] have been synthesized in this way.

2.6

Enantioselective Reduction Using Polymer-Supported Catalysts

2.6.1

Insoluble Polymer-Supported Oxazaborolidine Catalysts

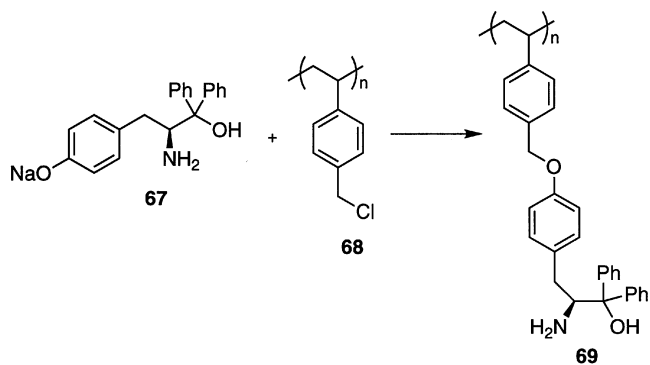
Several enantioselective reductions that use polymer-supported chiral catalysts have been reported. A major advantage of performing enantioselective reactions with polymer-supported catalysts is that their use allows both the recycling of the catalysts and the easy separation of the low molecular weight chiral products. One of the most attractive methods to carry out asymmetric synthesis is the continuous flow system by using an insoluble, polymeric catalyst.

The polymer-supported chiral α -amino alcohol is obtained easily by two methods. One method involves attaching the enantiopure α -amino alcohol to the partially chloromethylated crosslinked polystyrene through a benzyl ether linkage [71, 105] (Scheme 13).

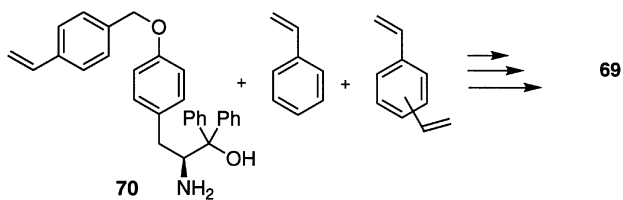
Another route to the chiral polymer is polymerization of chiral monomer with styrene and divinylbenzene as a crosslinking agent (Scheme 14) [106].

For example, borane reduction of butyrophenone using the polymeric catalyst **24** gave the alcohol in quantitative yield with 97% ee [71] (Scheme 15). Since the polymeric catalyst is crosslinked and insoluble in the organic solvent used, this catalyst can be used not only in a batch system, but also in a continuous flow system, in which the ketone is converted into the enantio-enriched alkoxyborane by passing it through a column filled with the polymeric catalyst.

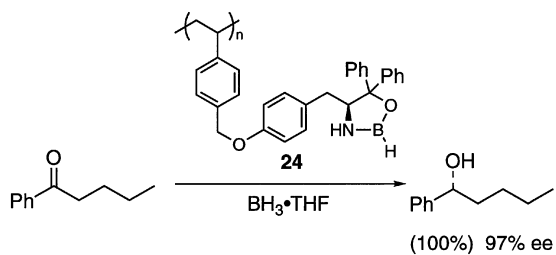
Other polymer-supported oxazaborolidine catalysts (e.g., **71**; Fig. 6) have also been used for the ketone reductions [107, 108].



Scheme 13



Scheme 14



Scheme 15

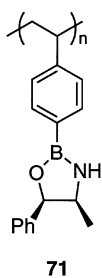


Fig. 6

2.6.2

Homogeneous, Soluble Polymer-Supported Oxazaborolidine Catalysts

Linear polymers carrying chiral oxazaborolidine as a pendant group were prepared from a methylhydrosiloxane-dimethylsiloxane copolymer [72]. Borane reduction using the polymeric oxazaborolidine **25** gave (*R*)-phenylethylalcohol of 97% ee which is as high as in analogous reaction with non-polymeric catalyst. This chiral polymer can be retained by a nanofiltration membrane thus will be suitable for use in a continuously operated membrane reactor.

3

Enantioselective Borane Reduction with Other Lewis Acid Catalysts

3.1

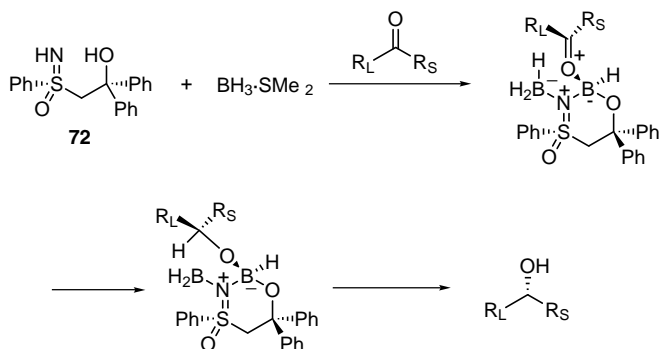
Diazaborolidine-Catalyzed Borane Reduction

Diazaborolidines that are structurally analogous to oxazaborolidine were prepared from a chiral diamine and borane [109]. Their catalytic activity is similar to that of oxazaborolidine. *N*-Sulfonyldiazaborolidine derived from 2-amino-methylpiperidine was used in the reduction of acetophenone (>95% 72% ee) [109].

3.2

β -Hydroxysulfoximine Catalyzed Borane Reduction

Instead of amino alcohols, enantiopure β -hydroxysulfoximines are also efficient chiral auxiliaries for the ketone reduction with borane [110]. Treatment of β -hydroxysulfoximine **72** with borane would form a boron-containing six-membered heterocycle as a catalyst as shown in Scheme 16. The mechanism may be analogous to that for the oxazaborolidine reduction. α -Haloacetophenone and



Scheme 16

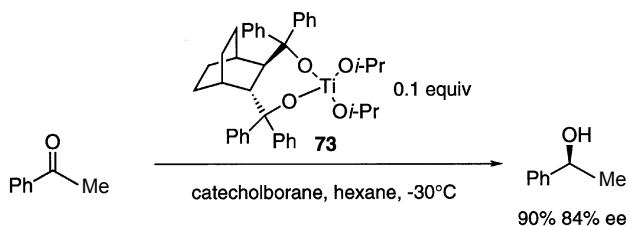
protected α -hydroxyketones gave the corresponding alcohols in up to 84 and 93% ee, respectively [110].

3.3

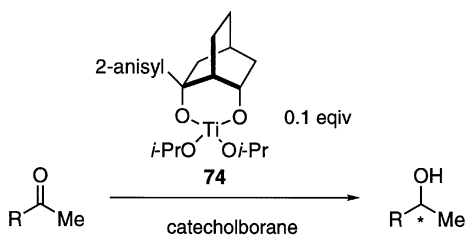
Chirally Modified Titanium(IV) Catalysts

Some chirally modified titanium alkoxides catalyze the reduction of ketones with catecholborane [111, 112]. In the presence of 0.1 equiv of the complex **73**, acetophenone was reduced asymmetrically to give (*S*)-2-phenylethanol with 82% ee (Scheme 17) [112].

More recently, higher ees were reported by using titanium BODOLate **74** [113]. This catalyst gives high ees not only in the reduction of aromatic ketones but also the linear methyl ketones (Scheme 18).



Scheme 17



R	Yield [%]	ee [%]	Config.
Ph	>97	97	<i>R</i>
Hexyl	>98	79	-
Butyl	>98	75	-

Scheme 18

3.4

Chirally Modified Lanthanum Alkoxides

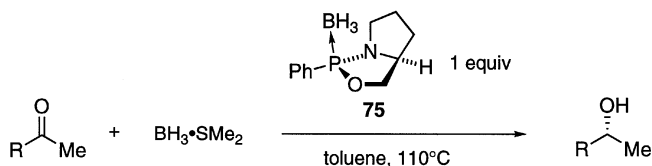
Another chirally modified Lewis acid catalyst used in the borane reduction is the chiral lanthanum alkoxide [114]. The reaction of lanthanum triisopropoxide with enantiopure binaphthol gave a catalyst system for the borane reduction of ketones. Reduction of 6'-methoxy-2'-acetoneaphnone gave the corresponding secondary alcohol in 100% yield with 61.8% ee (S) [114].

4

Oxazaphospholidine-Borane Complex as a Borane Reduction Catalyst

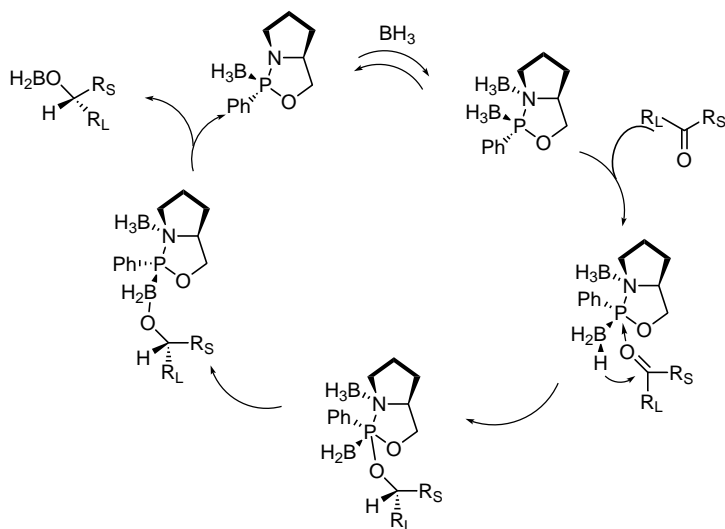
Recently Buono has reported a new class of efficient catalyst systems which contains a chiral oxazaphospholidine-borane complex as a catalyst in the borane reduction of ketones [115, 116]. The oxazaphospholidine-borane complex **75** is easily prepared by action of 1.3 equiv. of $\text{BH}_3 \cdot \text{THF}$ on (2*R*, 5*S*)-2-phenyl-3-oxa-1-azaphosphabicyclo[3.3.0]octane [116]. In the borane reduction in the presence of **75**, the increase of the reaction temperature resulted in higher enantioselectivity (Scheme 19). The use of 0.02 equiv of the catalyst in the reduction of isopropyl methyl ketone afforded the corresponding alcohol with 92% ee at 110 °C. Under stoichiometric conditions, the reduction of acetophenone proceeded with 99% enantioselectivity. A rational mechanism is proposed for the reduction (Scheme 20) [116].

Wills has described new catalysts containing a N-P=O structural unit such as **76** and **77** (Fig. 7) [117, 118, 119]. The highest selectivity (92% ee) using **77** was obtained when 10 mol % of the catalyst was used in the reduction of ω -chloroacetophenone in toluene at 110 °C, whereas the reduction of acetophenone proceeded with 82% ee under the same conditions [120].



R	Equiv of 75	ee [%]	Config.
Ph	1	97	<i>R</i>
Ph	0.02	33	<i>R</i>
$\text{CH}_2\text{CO}_2\text{Et}$	1	79	<i>R</i>
<i>i</i> -Pr	1	75	<i>R</i>

Scheme 19



Scheme 20

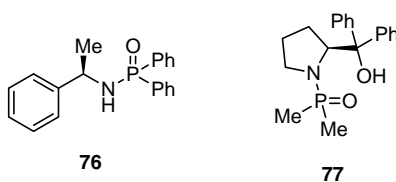


Fig. 7

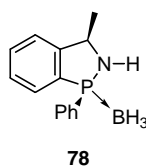
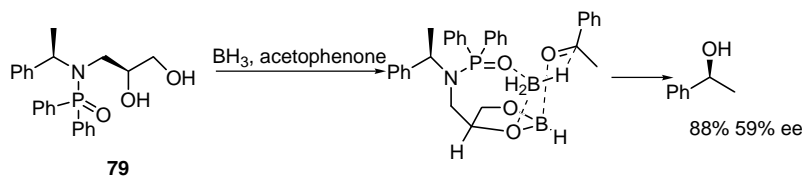


Fig. 8

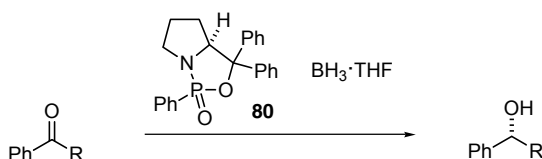
A similar phosphorus catalyst, the dihydrobenzazaphosphole-borane complex **78** (Fig. 8), was prepared and used as catalyst for the borane reduction of acetophenone and gave (*S*)-2-phenylethanol with 23% ee [121].

Using 0.1 equiv of the phosphinamide **79** acetophenone was reduced in 88% yield with 59% ee (Scheme 21) [122].

Martens developed similar catalysts such as **80** which shows high enantioselectivity by using only 1 mol % of the catalyst (Scheme 22) [123].



Scheme 21



R	Cat. 80 [mol %]	ee [%]
Me	10	97
CH ₂ Cl	1	96
CH ₂ Cl	10	>99

Scheme 22

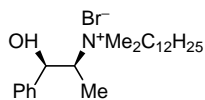
5

Catalytic Reduction Using Borohydride Reagents

Although the catalytic asymmetric borane reductions mentioned above are a powerful tool to obtain highly enantio-enriched alcohols, these require the use of a rather expensive and potentially dangerous borane complex. Sodium borohydride and its solution are safe to handle and inexpensive compared to borane complexes. Thus sodium borohydride is one of the most common industrial reducing agents. However its use in catalytic enantioselective reductions has been limited. One of the most simple asymmetric catalysts is an enantiopure quaternary ammonium salt that acts as phase-transfer catalyst. For instance, in the presence of the chiral salt **81** (Fig. 9), sodium borohydride reduction of acetophenone gave the secondary alcohol in 39% ee [124]. The polymer-supported chiral phase-transfer catalyst **82** (Fig. 10) was developed for the same reduction to give the alcohol in 56% ee [125].

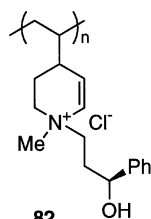
Optically active β -hydroxysulfoximines which catalyze the asymmetric borane reduction of ketones [110], also catalyze the same reaction with sodium borohydride/trimethylsilyl chloride system as reducing agent [126]. Reduction of a protected α -hydroxyacetophenone afforded the alcohol with 90% ee.

Efficient asymmetric borohydride reduction of ketones catalyzed by a chiral aldiminatocobalt(II) complex has recently been developed by Mukaiyama's



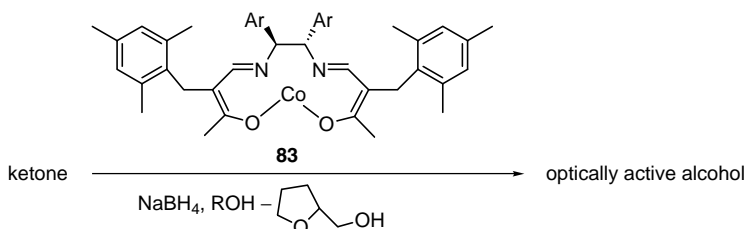
81

Fig. 9



82

Fig. 10



Ketone	ROH	Ar	ee [%]
2,2-dimethyl-1-tetralone	EtOH	Ph	91
tetralone	EtOH	3,5-Me ₂ Ph	90
2,2-dimethyl-4-chromanone	EtOH	3,5-Me ₂ Ph	92
butyrophenone	EtOH	2,4,6-Me ₃ Ph	97
cyclohexyl phenyl ketone	MeOH	2,4,6-Me ₃ Ph	95
isobutyrophenone	MeOH	2,4,6-Me ₃ Ph	95

Scheme 23

group [127, 128, 129, 130]. Although the reduction may be different from hydroboration from the mechanistic point of view, it should be worthy of note as a highly enantioselective catalytic reduction of ketones with borohydride. An amount of 0.1 to 1 mol % of the optically active cobalt(II) complex **83** catalyzes the borohydride reduction of ketone to give the corresponding alcohol in high

chemical and optical yield (Scheme 23). The use of tetrahydrofurfuryl alcohol and ethanol with NaBH_4 significantly improved the enantiofacial selectivity [129].

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Chapter 7

Hydrosilylation of Carbon-Carbon Double Bonds

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Keywords: Hydrosilylation, Olefins, 1,3-Dienes, Platinum catalyst, Nickel catalyst, Rhodium catalyst, Palladium catalyst, Secondary alcohols, Allylsilanes

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1 Introduction

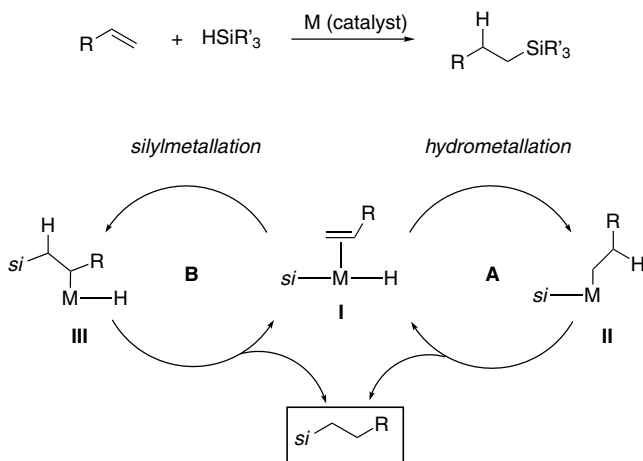
It is well-documented that certain hydrosilanes undergo addition across the carbon-carbon multiple bonds under catalysis by transition metal complexes and the reaction is referred to as the hydrosilylation [1, 2, 3, 4]. Incorporation of chiral ligands into the metal catalyst can, in principle, make the hydrosilylation result in the formation of optically active alkylsilanes. Since an efficient oxidative cleavage of a carbon-silicon bond to furnish a carbon oxygen bond was found by Tamao [5, 6] in 1978, enantioselective hydrosilylation has been recognized to be a variant of the enantioselective hydration of olefins in general. Thus, optically active alkylsilanes are converted to the corresponding optically active alcohols by oxidation, which proceeds with retention of configuration at the stereogenic carbon center to give the alcohols without loss of their enantiomeric purity. The

asymmetric synthesis of optically active alcohols from alkenes has mainly been effected by asymmetric hydroboration with a stoichiometric amount of a chiral hydroborating agent [7]. Use of catalytic systems for asymmetric hydroboration has not always been successful in terms of enantioselectivity or catalytic activity [8]. Asymmetric hydrosilylation has thus become one of the most useful methods for the preparation of optically active alcohols from alkenes [9, 10]. Another important application of catalytic asymmetric hydrosilylation is the 1,4-hydrosilylation of 1,3-dienes which efficiently produces optically active allylic silanes.

2

Mechanism of Hydrosilylation of Olefins Catalyzed by Transition-Metal Complexes

A transition metal complex, ML_n (L =ligand), especially an electron-rich complex of a late transition metal such as Co(I), Rh(I), Ni(0), Pd(0), or Pt(0) as a pre-catalyst, activates both hydrosilanes, $HSiR_3$, and a variety of substrates, typically alkenes. A catalytic cycle is considered to involve further two steps as depicted in Scheme 1. The conventional hydrosilylation of alkenes catalyzed by $H_2PtCl_6 \cdot 6H_2O/iPrOH$ (called the Speier catalyst [11]) is generally assumed to proceed by the Chalk-Harrod mechanism (Scheme 1, cycle A) [12, 13]. Oxidative addition of a hydrosilane gives a hydrido-silyl complex (I) which is coordinated with the substrate alkene (extremely rarely isolated at this stage). The complex I undergoes migratory insertion of the alkene into the M-H bond (*hydrometallation*) to give the alkyl-silyl species (II). Reductive elimination of the alkyl and silyl ligands from II forms the hydrosilylation product. Although the Chalk-Harrod mechanism accounts for an alkene isomerization, an H-D exchange between deuteriosilanes and alkenes, as well as the observed regioselectivity



Scheme 1

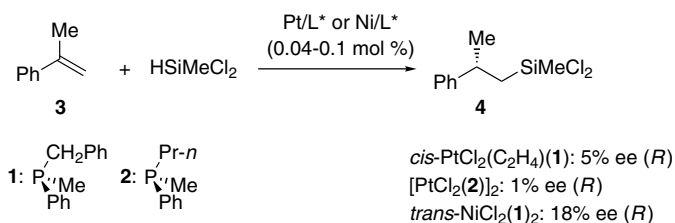
tivity always associated with the catalytic hydrosilylation, an alternative mechanism has been proposed which involves preferentially an alkene insertion into the M-Si bond (*silylmetallation*) by using Rh(I) or Co(III) catalyst precursor to form the β -silylalkyl-hydrido intermediate (III), followed by reductive elimination to complete the hydrosilylation [14, 15, 16] (Scheme 1, cycle B). It is worthy of note that hydrosilanes exhibit a wide spectrum of reactivities in the oxidative addition depending on the substituents on the silicon atom and the nature of the metal catalyst. Thus, Pt complexes tolerate any hydrosilane, such as $\text{HSiCl}_n\text{Me}_{3-n}$ ($n=1\sim 3$), HSi(OR)_3 , or $\text{H}_n\text{SiR}_{4-n}$ ($n=1\sim 3$; R = alkyl or Ph) in the hydrosilylation, while, Pd complexes are applicable mostly to $\text{HSiCl}_n\text{R}_{3-n}$ ($n=2, 3$) and Rh complexes to preferably HSiR_3 [4].

3

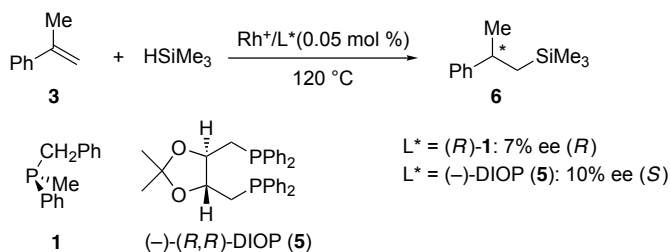
Hydrosilylation of 1,1-Disubstituted and Monosubstituted Olefins

Catalytic asymmetric hydrosilylation has been developed with the help of chiral phosphine ligands. In the initial stage, phosphine ligands with a stereogenic phosphorus atom were used. In the first report, a platinum complex coordinated with (*R*)-benzylmethylphenylphosphine (**1**), *cis*- $\text{PtCl}_2(\text{C}_2\text{H}_4)$ (**1**), was used for the reaction of 2-phenylpropene (**3**) with methylchlorosilane at 40 °C to give (*R*)-1-(methylchlorosilyl)-3-phenylpropane (**4**) with 5% ee [17, 18] (Scheme 2). On use of a platinum catalyst of (*R*)-methylphenylpropylphosphine (**2**) the enantioselectivity was lower (1% ee). Use of the nickel catalyst *trans*- $\text{NiCl}_2(\mathbf{1})_2$ bearing the chiral phosphorus ligand for the hydrosilylation of **3** improved the enantioselectivity, but the enantioselectivity was still not high (18% ee) [19, 20]. Cationic rhodium complexes coordinated with (*R*)-benzylmethylphenylphosphine (**1**) and (-)-DIOP (**5**) as ligand catalyzed the hydrosilylation of 2-phenylpropene (**3**) with trimethylsilane to give 1-(trimethylsilyl)-3-phenylpropane (**6**) in 7% and 10% ee, respectively (Scheme 3) [20].

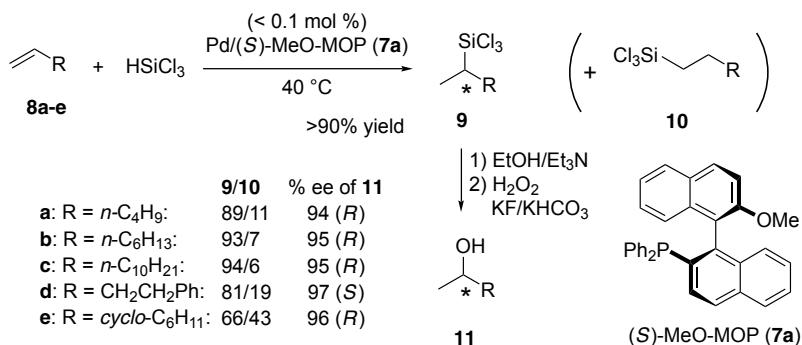
Recently, a palladium complex coordinated with an axially chiral, monodentate phosphine ligand, MeO-MOP (**7a**) or its analogs [21], has been reported to be highly effective for the enantioselective hydrosilylation of alkyl-substituted terminal olefins (Scheme 4) [22, 23]. Simple terminal olefins **8** were transformed efficiently into the corresponding optically active 2-alkanols **11** with enantioselectivities ranging between 94% and 97% ee by the catalytic hydrosilylation-ox-



Scheme 2

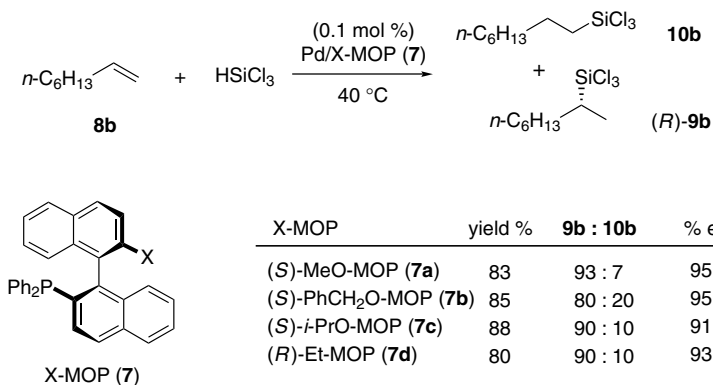


Scheme 3



Scheme 4

idation procedure. For example, the reaction of 1-octene (**8a**) with trichlorosilane in the presence of 0.1 mol % of a palladium catalyst generated from [Pd-Cl(π -C₃H₅)]₂ and (S)-MeO-MOP (**7a**) at 40 °C for 24 h gave 2-octylsilane (**9a**) and 1-octylsilane (**10a**) in a ratio of 93 to 7. The branched isomer was oxidized into (*R*)-2-octanol (**11a**) with 95% ee. It is noteworthy that the reaction of simple terminal alkenes with the MeO-MOP ligand proceeds with high regioselectivity in favor of the branched isomer. No predominant formation of 2-silylalkanes from purely aliphatic 1-alkenes in hydrosilylation reactions has previously been observed with any transition-metal catalysts. Asymmetric hydrosilylation of 4-pentenyl benzoate and 1,5-heptadiene gave the corresponding 2-alkanols with 90% ee and 87% ee, respectively, the ester carbonyl and the internal double bond remaining intact [23]. High selectivity was also observed with the MOP ligands **7b**, **7c**, and **7d**, which have substituents other than methoxy at the 2' position [23] (Scheme 5). Thus, the hydrosilylation of 1-octene (**8b**) with MOP ligands substituted with benzyloxy or isopropoxy gave over 91% enantioselectivity and over 80% regioselectivity, suggesting that the steric bulkiness of the 2'-substituents has little influence on the present asymmetric hydrosilylation. The presence of an alkoxy group at the 2' position of **7** is not essential for high selectivity because replacement of the alkoxy group by an alkyl group did not affect the selectivity.

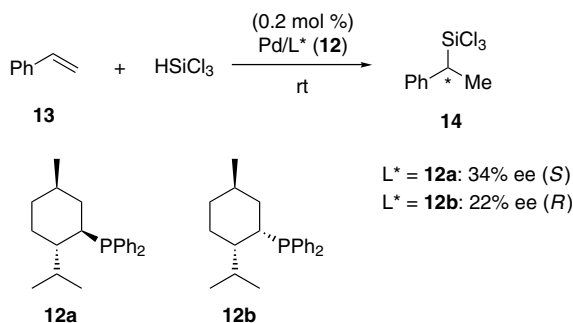


Scheme 5

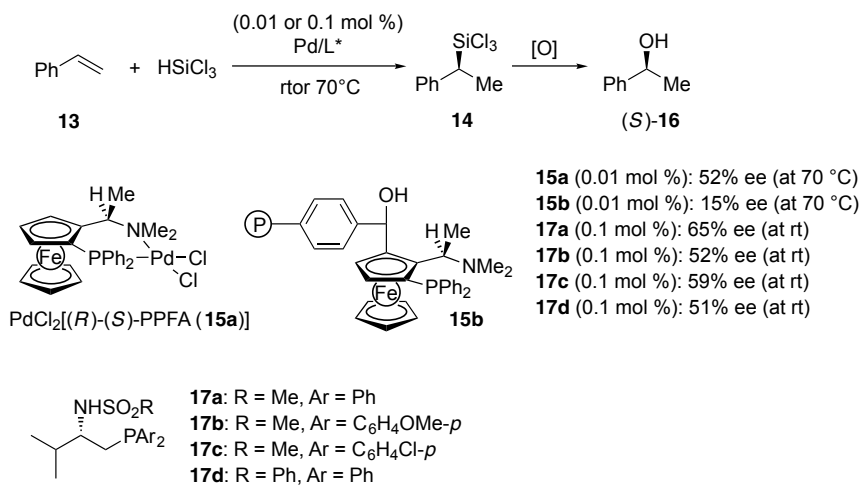
4 Hydrosilylation of Styrenes

Palladium-catalyzed hydrosilylation of styrene derivatives usually proceeds with high regioselectivity to produce benzylic silanes, 1-aryl-1-silylethanes, due to the participation of π -benzylic palladium intermediates [1, 2]. It is known that bisphosphine-palladium complexes are catalytically much less active than monophosphine-palladium complexes and hence asymmetric synthesis has been attempted by use of chiral monodentate phosphine ligands. In the first report, menthyl-diphenylphosphine (**12a**) and neomenthyl-diphenylphosphine (**12b**) [24, 25] were used for the palladium-catalyzed reaction of styrene (**13**) with trichlorosilane. These reactions gave 1-(trichlorosilyl)-1-phenylethane (**14**) in 34% and 22% ee, respectively (Scheme 6). Use of the ferrocenylmonophosphine (*R*)-(*S*)-PPFA (**15a**) [26, 27, 28] for the same reaction improved the enantioselectivity. In this case, the hydrosilylation product was oxidized to (*S*)-1-phenylethanol (**16**) with 52% ee (Scheme 7). The ferrocenylmonophosphine **15b** supported on Merrifield polystyrene has been also used for the hydrosilylation of styrene, although the enantioselectivity was lower (15% ee) [29]. Several chiral (β -*N*-sulfonylaminoalkyl)phosphines **17** were prepared from (*S*)-valinol and used for the asymmetric hydrosilylation of styrene and cyclopentadiene [30]. For styrene, phosphine **17a** which contains a methanesulfonyl group was the most effective giving (*S*)-1-phenylethanol (**16**) with 65% ee. Other amidophosphines **17b–c** are also fairly effective for this asymmetric hydrosilylation (Scheme 7).

The axially chiral, monophosphine ligand, MeO-MOP (**7a**), was not as effective for styrene derivatives as for simple terminal olefins [31]. The palladium-catalyzed hydrosilylation of styrene (**13**) with trichlorosilane in the presence of the (*R*)-MeO-MOP ligand (**7a**) under standard conditions (without solvent) followed by oxidation gave (*R*)-1-phenylethanol (**16**) with only 14% ee (Scheme 8). Use of benzene as solvent for the hydrosilylation reaction improved the enanti-

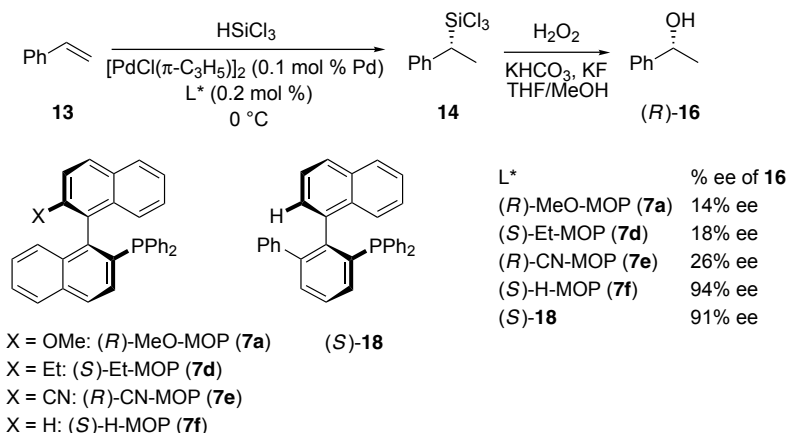


Scheme 6

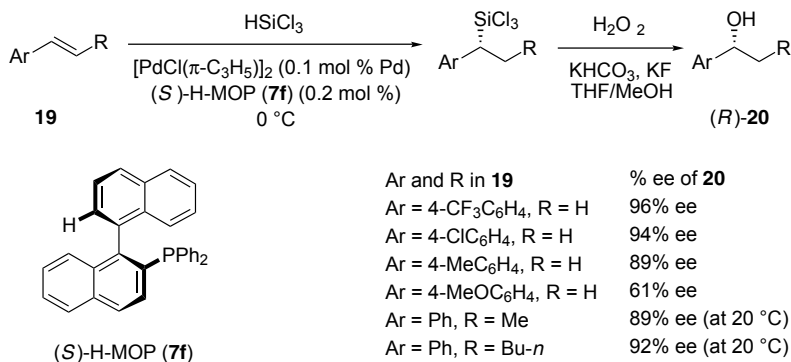


Scheme 7

oselectivity to 71%. For substituted styrenes such as *o*-chlorostyrene or β -methylstyrene, the enantioselectivity was around 80% with the MeO-MOP ligand. The substituents at the 2' position in the MOP ligands strongly affected the enantioselectivity [32]. The ligand H-MOP (**7f**), which has the same 1,1'-binaphthyl skeleton as MeO-MOP but lacks the methoxy group, is particularly effective for the palladium-catalyzed hydrosilylation of styrene giving (*R*)-**16** with 94% ee. On the other hand, the enantiomeric purities of alcohol **16** obtained with Et-MOP (**7d**) and CN-MOP (**7e**) were much lower, 18% ee (*R*) and 26% ee (*R*), respectively. The monophosphine (*S*)-**18** which was prepared through the catalytic asymmetric cross-coupling [33] was as effective as (*S*)-H-MOP (**7f**) for the hydrosilylation of styrene giving (*R*)-**16** with 91% ee. These results suggest that the small size of the hydrogen at the 2' position in H-MOP (**7f**) is important for high enantioselectivity and that the electronic nature of the substituent is not a deci-



Scheme 8



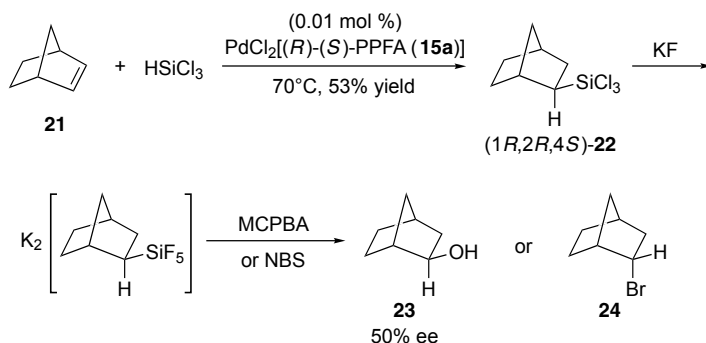
Scheme 9

sive factor in the enantioselection. Asymmetric hydrosilylation of styrenes **19** substituted on the phenyl ring or in the β -position catalyzed by palladium/H-MOP (**7f**) also proceeded with high enantioselectivity giving the corresponding optically active benzylic alcohols **20** in high enantiomeric purity (Scheme 9).

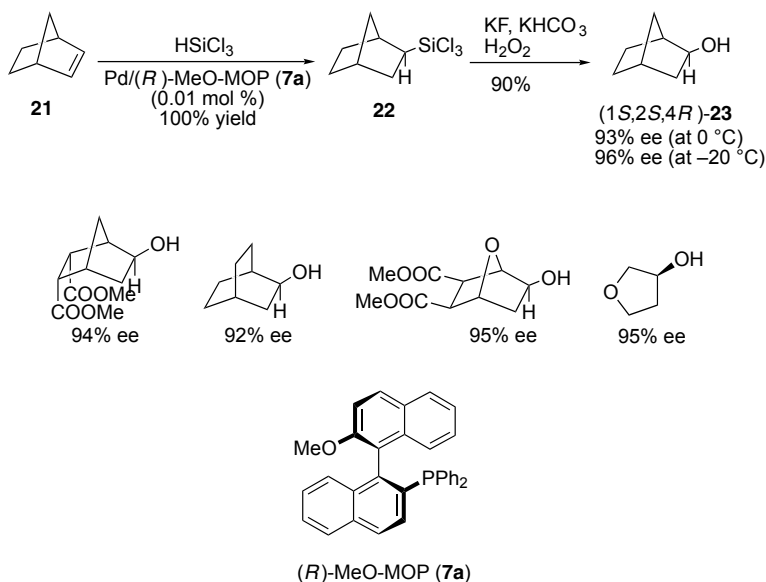
5 Hydrosilylation of Cyclic Olefins

Asymmetric synthesis through a selective monofunctionalization of enantiotopic positions is considered as being one of the most attractive strategies for the one-step construction of multiple chiral carbon centers [34, 35]. Asymmetric hydrosilylation of norbornene (**21**) was first attempted by use of a palladium catalyst coordinated with ferrocenylmonophosphine, *(R)*-*(S)*-PPFA (**15a**) [28]. The

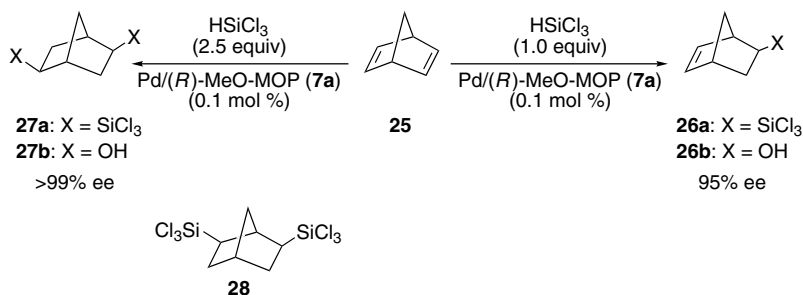
hydrosilylation of **21** with trichlorosilane gave (1*R*,2*R*,4*S*)-*exo*-2-(trichlorosilyl)norbornane (**22**) in about 50% ee (Scheme 10). Treatment of **22** with potassium fluoride followed by oxidation of the resulting pentafluorosilicate with MCPBA or NBS gave *exo*-2-norbornanol (**23**) or *endo*-2-bromonorbornane (**24**), respectively. The palladium-MeO-MOP complex (**7a**) showed much higher enantioselectivity and catalytic activity [36]. The hydrosilylation of norbornene (**21**) with trichlorosilane took place at 0 °C in the presence of 0.01 mol % of the MOP/palladium catalyst to give a quantitative yield of *exo*-2-(trichlorosilyl)norbornane (**22**) as a single product (Scheme 11). Direct oxidation of **22** with hydro-



Scheme 10



Scheme 11



Scheme 12

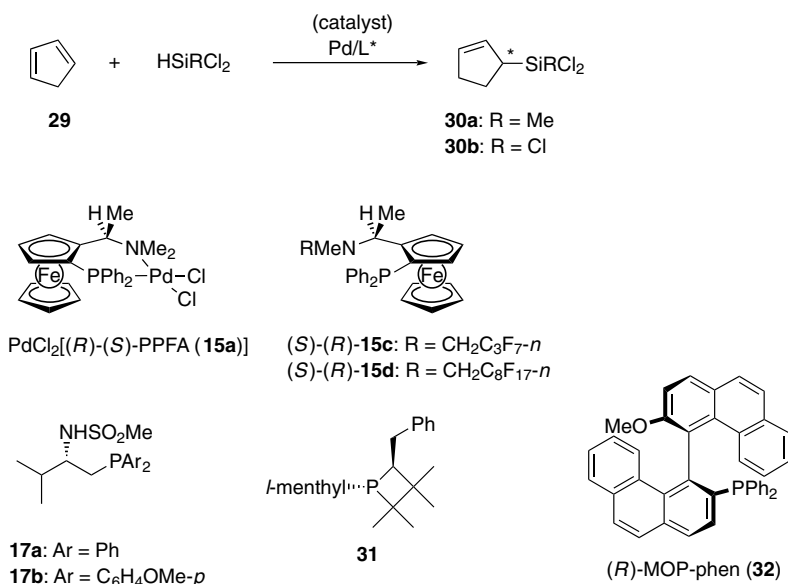
gen peroxide in the presence of a large excess of potassium fluoride and potassium bicarbonate gave (1*S*,2*S*,4*R*)-*exo*-2-norbornanol (**23**) with 93% ee in high yield. Lowering of the temperature to $-20\text{ }^{\circ}\text{C}$ raised the enantiomeric excess to 96% ee. A bicyclo[2.2.2]octene, a diester of norbornenedicarboxylic acid, and 2,5-dihydrofuran derivatives [37] were also successfully subjected to asymmetric hydrosilylation-oxidation under similar reaction conditions to give the corresponding optically active alcohols with enantioselectivities in excess of 92%.

It is remarkable that the monofunctionalization of norbornadiene (**25**) giving *exo*-5-trichlorosilyl-2-norbornene (**26a**) is effected by the palladium-MOP catalyst with high chemo- and enantioselectivity [36] (Scheme 12). Thus, the reaction of **25** with 1.0 equivalent of trichlorosilane and the palladium/MeO-MOP catalyst followed by hydrogen peroxide oxidation gave (1*R*,4*R*,5*S*)-*exo*-5-hydroxy-2-norbornene (**26b**) with 95% ee. The reaction of **25** with 2.5 equivalents of trichlorosilane induced enantioselective hydrosilylation in both double bonds thus giving a 78% yield of chiral disilylnorbornane **27a** and the *meso* isomer **28** in a ratio of 18:1. Oxidation of **27a** gave the diol (1*R*,2*S*,4*R*,5*S*)-**27b** with >99% ee, the high enantiomeric purity being due to the conversion of the minor enantiomer of **26a** to the *meso* product **28**.

6

Hydrosilylation of 1,3-Dienes

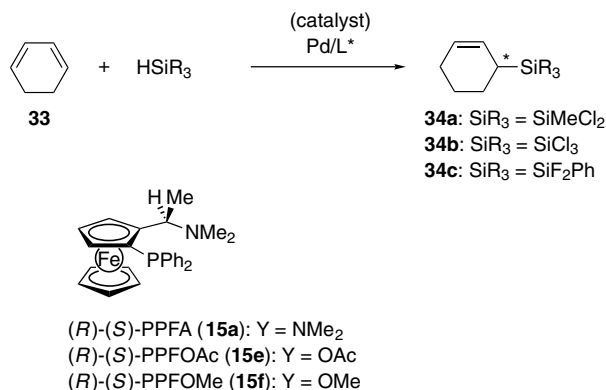
Palladium-catalyzed hydrosilylation of 1,3-dienes is one of the important synthetic methods for allylic silanes, and considerable attention has been directed to the asymmetric synthesis of the latter by catalytic methods [9]. Optically active allylic silanes have been used as chiral allylating reagents in S_{E}' reactions with electrophiles, typically aldehydes [38, 39]. In the presence of Pd catalysts the reaction with hydrosilanes containing electron-withdrawing atoms or substituents on silicon usually proceeds in a 1,4-fashion giving allylic silanes [40, 41]. Asymmetric hydrosilylation of cyclopentadiene (**29**) forming optically active 3-silylcyclopentene (**30**) has been most extensively studied (Scheme 13). In the first report, hydrosilylation of cyclopentadiene (**29**) with methylchlorosilane in the presence of 0.01 mol % of palladium-(*R*)-(S)-PPFA (**15a**) as a catalyst gave



ligand L*	catalyst (mol %)	HSiRCl ₂	temp (°C)	time (h)	yield (%)	% ee of 30	ref
(<i>R</i>)-(<i>S</i>)-PPFA (15a)	0.01	HSiMeCl ₂	30	20	87	25 (<i>S</i>)	42
(<i>S</i>)-(<i>R</i>)- 15c	0.02	HSiCl ₃	25	90	73	57 (<i>R</i>)	43
(<i>S</i>)-(<i>R</i>)- 15c	0.02	HSiCl ₃	0	20	7	60 (<i>R</i>)	43
(<i>S</i>)-(<i>R</i>)- 15d	0.02	HSiCl ₃	25	90	41	55 (<i>R</i>)	43
(<i>S</i>)- 17a	0.1	HSiCl ₃	0	–	82	61 (<i>S</i>)	30
(<i>S</i>)- 17a	0.1	HSiCl ₃	–20	–	35	71 (<i>S</i>)	30
(<i>S</i>)- 17b	0.1	HSiCl ₃	0	–	74	62 (<i>S</i>)	30
31	0.03	HSiCl ₃	70	30	26	44 (<i>S</i>)	44,45
31	0.03	HSiCl ₃	25-30	2	70	54 (<i>S</i>)	44,45
(<i>R</i>)-MOP-phen (32)	0.1	HSiCl ₃	20	120	99	80 (<i>R</i>)	46
(<i>R</i>)-MOP-phen (32)	0.1	HSiCl ₃	40	45	85	72 (<i>R</i>)	46
(<i>R</i>)-MeO-MOP (7a)	0.1	HSiCl ₃	20	14	100	39 (<i>R</i>)	46

Scheme 13

allylsilane (*S*)-**30a** with 24% ee [42]. Use of the ferrocenylphosphines **15c,d** containing perfluoroalkyl groups on the side chain for the reaction of **29** with trichlorosilane increased the enantioselectivity (up to 60% ee) [43]. Some of the (β -*N*-sulfonylaminoalkyl)phosphines (**17**) [30] and phosphetane ligand **31**



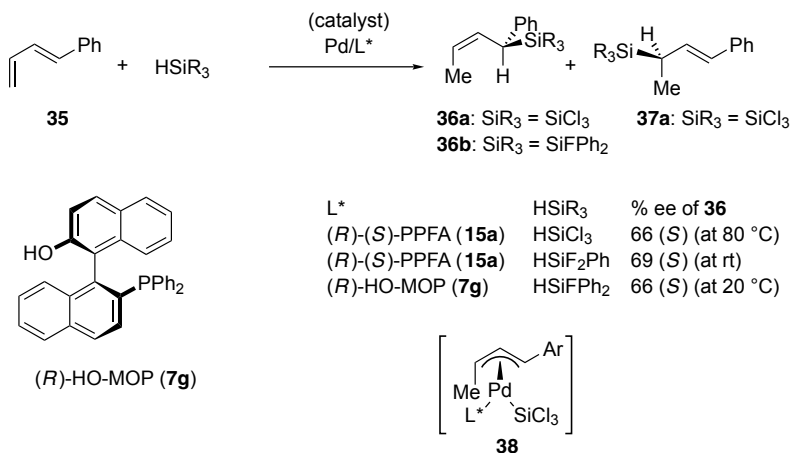
ligand L*	catalyst (mol %)	HSiRCl ₂	temp (°C)	time (h)	yield (%)	% ee of 34	ref
<i>(R)</i> - <i>(S)</i> -PPFA (15a)	0.01	HSiMeCl ₂	30	20	95	2 (<i>S</i>)	42
<i>(R)</i> -MOP-phen (32)	0.1	HSiCl ₃	20	150	99	51 (<i>R</i>)	46
<i>(R)</i> - <i>(S)</i> -PPFOAc (15e)	1	HSiPhF ₂	rt	20	58	77 (<i>S</i>)	47, 48
<i>(R)</i> - <i>(S)</i> -PPFOMe (15f)	1	HSiPhF ₂	rt	20	50	54 (<i>S</i>)	47, 48

Scheme 14

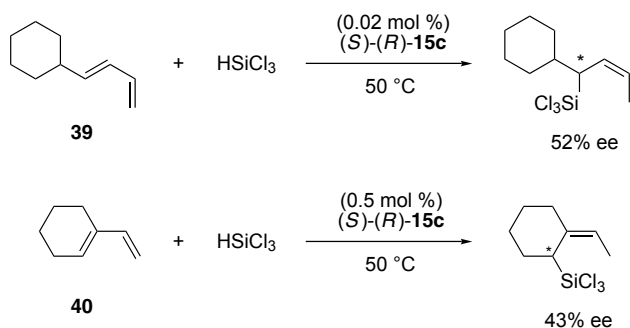
are also useful for the asymmetric hydrosilylation of **29** with trichlorosilane to give **30b** in 71% ee [44, 45]. The highest enantioselectivity so far reported for cyclopentadiene is 80% ee, which was obtained with MOP-phen ligand **32** [46].

For the asymmetric hydrosilylation of 1,3-cyclohexadiene (**33**) (Scheme 14) the enantioselectivity is higher in the reaction with phenyldifluorosilane than that with trichlorosilane or methyldichlorosilane. The reaction of **33** with phenyldifluorosilane in the presence of a palladium catalyst coordinated with ferrocenylphosphine **15e** gave the allylsilane (*S*)-**34c** with 77% ee [47, 48].

Linear 1,3-dienes have been also subjected to the palladium-catalyzed asymmetric hydrosilylation. Reaction of 1-phenyl-1,3-butadiene (**35**) with HSiCl₃ catalyzed by palladium-*(R)*-*(S)*-PPFA (**15a**) gave a mixture of the regioisomeric allylsilanes **36a** and **37a** in a ratio of 94 to 6, the major isomer **36a** and the minor isomer **37a** having 66% ee (*S*) and 30% ee (*R*), respectively (Scheme 15) [49]. The π -allylpalladium intermediate **38** was postulated for this hydrosilylation. Use of phenyldifluorosilane in place of trichlorosilane slightly improved the enantioselectivity [47, 50]. Hydrosilylation of alkyl-substituted 1,3-dienes **39** and **40** in the presence of a ferrocenylmonophosphine-palladium catalyst also proceeded with high regioselectivity to give the corresponding 1,4-addition products with moderate enantioselectivity (Scheme 16) [43, 51].



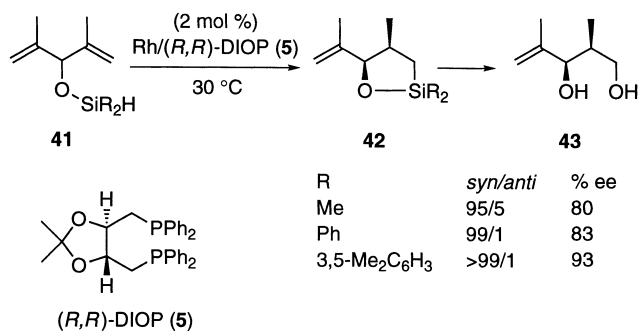
Scheme 15



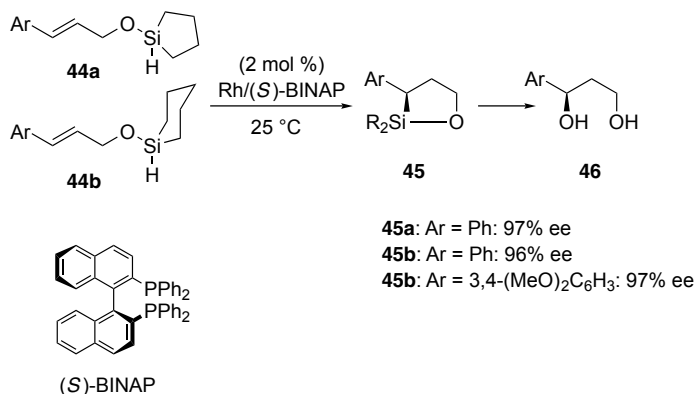
Scheme 16

7 Intramolecular Hydrosilylation

Intramolecular enantioselective hydrosilylation-oxidation of alkenyloxysilanes provides an efficient method for the preparation of optically active polyols from allylic alcohols. Cyclization of silyl ethers **41** of a *meso*-type allylic alcohol in the presence of rhodium-DIOP (**5**) as a catalyst proceeded with high diastereoselectivity and high enantioposition-selectivity. Oxidation of the carbon-silicon bond in the resulting sila-oxa-cyclopentane derivatives **42** gave *syn*-2,4-dimethyl-4-pentene-1,3-diol (**43**) in high enantiomeric excess (Scheme 17) [52]. The enantioselectivity was dependent on the alkyl groups on the silicon, the sterically crowded 3,5-dimethylphenyl group giving the highest selectivity (93% ee).



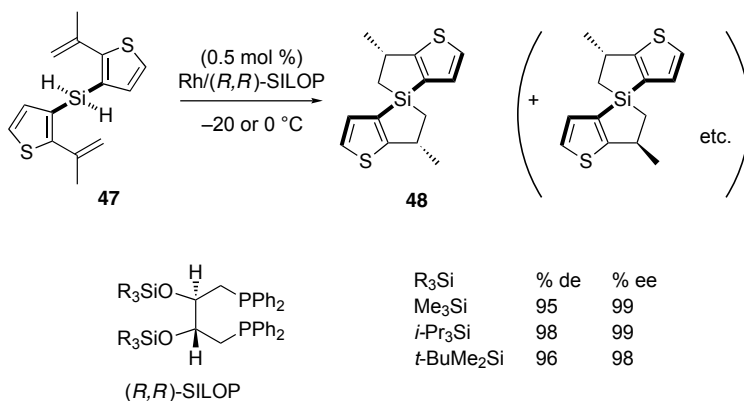
Scheme 17



Scheme 18

Enantioselective cyclization was also successful in the rhodium-catalyzed hydrosilylation of silyl ethers **44** derived from allylic alcohols. High enantioselectivity (up to 97% ee) was observed in the reaction of silyl ethers containing a bulky group on the silicon atom in the presence of a rhodium-BINAP catalyst (Scheme 18) [53]. The cyclization products **45** were readily converted to the 1,3-diols **46** by the oxidation. During studies on this asymmetric hydrosilylation, a silyl-rhodation pathway in the catalytic cycle was demonstrated by a deuterium scrambling method [54].

The axially chiral spiroisilane **48** was efficiently prepared by double intramolecular hydrosilylation of bis(alkenyl)dihydrosilane **47**. By use of the SILOP ligand, a C₂ symmetric spiroisilane which is almost enantiomerically pure was obtained with high diastereoselectivity (Scheme 19) [55]. The SILOP ligand is much more stereoselective for this asymmetric hydrosilylation than DIOP (**5**) that has an analogous structure.



Scheme 19

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Chapter 8

Hydroalumination of Carbon-Carbon Double Bonds

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Keywords: Nickel catalysts, BINAP, Hydrometalation, Reduction, Cyclohexenols, Cycloheptenols, DIBALH, Carbon-metal bond, Organoalane

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1

Introduction

The addition of a metal hydride to an alkene or an alkyne is a useful way of simultaneously introducing stereochemistry and a reactive carbon-metal bond into a molecule. Carbon-metal bonds are among the most versatile reactive species available, due to their reactions with a variety of functional groups and easy transformation into a C-O, C-N, or C-C bond. Transmetalation from one carbon-metal bond (C-M) to a carbon-metal bond which has a different reactivity profile (C-M'), further expands the range of possibilities.

Among the hydrometalations reported to date, hydroboration and hydrosilylation reactions have been the most widely investigated and a wide variety of transformations of carbon-boron and carbon-silicon bonds are known [1, 2, 3, 4, 5, 6, 7, 8, 9]. Hydroalumination is a less often used reaction but the resulting organoalanes are more reactive than either organosilanes or boranes and less reactive than the traditional organometallic reagents derived from lithium or magnesium. Various aluminum hydrides are commercially available or readily prepared by reduction of aluminum halides [10].

Metal catalyzed hydrometalations, specifically hydroboration and hydrosilylation, are particularly attractive due to the potential for enantiocontrol by the use of chiral ligands coordinated to the metal center. While the first metal catalyzed hydroalumination was described more than 40 years ago, the first synthetically useful enantioselective hydroalumination was described in 1995 and the scope and synthetic utility of this reaction are only just emerging.

2

Historical Background

2.1

Nickel Catalyzed Hydroalumination

In 1954, Ziegler and coworkers [11, 12] reported that traces of nickel salts dramatically alter the course of the growth reaction of ethylene with trialkylalanes, the “Aufbau” process. Instead of the low molecular weight polyethylene which was expected, the only product was butene. This observation culminated in Ziegler's discovery of transition metals that were highly effective in polymerizing ethylene, an accomplishment for which he later shared the Nobel Prize. It also opened the door to transition metal catalyzed hydroalumination reactions. In 1968, Eisch and Foxton showed that addition of nickel(II) salts increased the rate of the hydroalumination of alkynes by approximately 100-fold [13]. The active catalyst was believed to be a nickel(0) species.

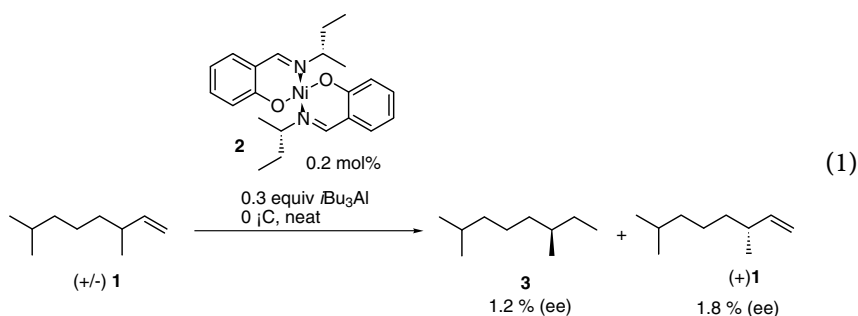
While possible mechanisms for the enantioselective hydroalumination are outlined in a later section, a historical review will put this discussion in perspective. Ziegler proposed that some colloidal nickel species was catalyzing a displacement between an olefin and a trialkylalane [12]. Eisch and Foxton suggested, on the basis of their results with aluminum hydrides and alkynes, that a nickel hydride is formed as an intermediate and proposed a similar mechanism for the Ziegler reaction [13]. Wilke and coworkers suggested that the metal acted as a template to preorganize the olefin and the alkylaluminum leading to a facile exchange reaction in a six-membered cyclic transition state. They provided evidence to support this mechanism by showing that triethylaluminum undergoes rapid and statistical exchange with perdeuterated ethylene in the presence of tris(ethylene)nickel to generate a deuterated triethylaluminum at temperatures as low as $-50\text{ }^{\circ}\text{C}$ [14]. The authors note that no intermediates were observable by NMR spectroscopy. In 1990, Pörschke and coworkers determined the crystal

structure of a cyclododecatrienickel(0)-dimethylaluminum hydride-quinuclidine complex in which the hydride seems to be bridging the nickel and aluminum atoms with a weak nickel-aluminum bond present [15]. The uncertainty over the mechanism of the hydroalumination reaction, which persists to this day [16], significantly complicates a detailed understanding of the enantioselective process.

2.2

Enantioselective Hydroalumination

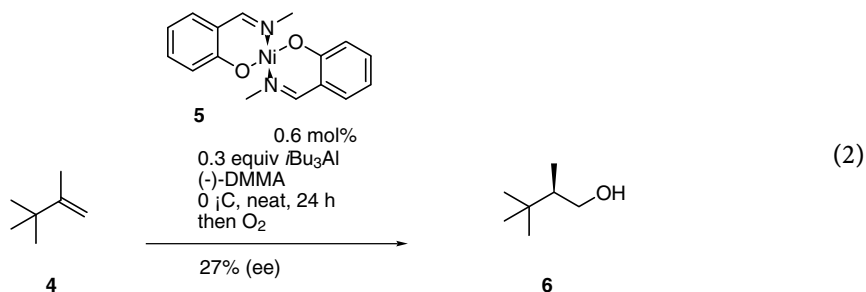
Early attempts at an asymmetric hydroalumination utilized a chiral *sec*-butylsalicylideneimine (*sec*-busal) complexed to Ni(II). Thus, treatment of racemic 3,7-dimethyl-1-octene (**1**) with 0.2 mol % of the complex **2** and 0.3 equivalents of triisobutylaluminum at 0 °C followed by hydrolysis gave the alkane **3** in 1.2% ee as judged by optical rotation, Eq. (1). The unreacted olefin was recovered and found to have an ee of 1.8% on the basis of its optical rotation. The authors conclude that racemic product and starting material would be expected if a naked nickel lacking the ligand or colloidal nickel is involved [17].



Wilke and coworkers showed that trialkylaluminum compounds reduce nickel(II) complexes to nickel(0) and they proposed that complexation of the *sec*-busal to the aluminum, to generate a chiral aluminum species, could also be responsible for the observed effects [12]. Giacomelli and coworkers later reported that the use of a chiral amine, as a Lewis base complex with the trialkylalane, gave products with a small optical rotation in the attempted resolution of some racemic olefins, although as above, the enantioselectivities were extremely low (<1%) [18]. Notably, the authors mention that the use of (-)-(DIOP)NiCl₂ (DIOP=2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bisdiphenylphosphinobutane) as a precatalyst gave products lacking an optical rotation.

An enantioselective hydroalumination of a prochiral olefin was first reported by Giacomelli and coworkers. The authors surveyed a number of chiral amines in the nickel catalyzed hydroalumination of 1,1-disubstituted alkenes. Of the amines examined, *N,N*-dimethylmenthylamine (DMMA) in combination with triisobutylalane and catalytic amounts of Ni(mesal)₂ (mesal = methylsalicylideneimine) (**5**) effected the hydroalumination of 2,3,3-trimethylbutene which, fol-

lowing oxidation, yielded 2,3,3-trimethyl-1-butanol (**6**) in 27% ee, Eq. (2). Again, the authors note the near complete failure of a phosphine-containing ligand, DI-OP, to induce enantioselectivity in this reaction [19].

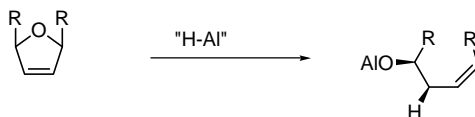


3

Reductive Ring Opening

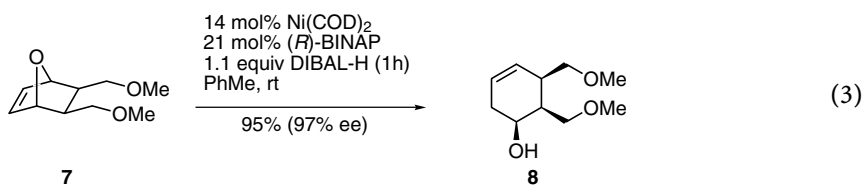
The formal $S_{\text{n}}2'$ addition of aluminum hydride to a cyclic allylic ether results in a reductive ring opening: hydride addition with transposition of the olefin and formation of an aluminum oxygen bond occurs (Scheme 1). The product, on workup, is a homoallylic alcohol and the net result is a reductive cleavage of the carbon-oxygen bond. Reaction with a symmetrical ether containing an olefin would provide an attractive method for the synthesis of homoallylic alcohols. If the reaction was carried out with a chiral reducing agent, homoallylic alcohols in enantiomerically enriched form would be produced.

Lautens and Chiu reported a reductive ring opening of this type in oxabicyclo[n.2.1]alkenes using DIBALH in the presence of bis(cyclooctadiene)nickel [$\text{Ni}(\text{COD})_2$] to give racemic cycloalkenols. Later, phosphine ligands were shown to lead to regioselective reductive opening of unsymmetrical substrates bearing substituents at the bridgehead position. Selectivities up to 380:1 were obtained using bis(diphenylphosphino)butane (dppb) as the ligand. The early attempts to develop an enantioselective process using chiral phosphines such as prophanos, chiraphos, and BINAP were moderately successful and the reductive ring opened products were obtained with ee's of <56%. A important breakthrough came in 1995 when Lautens and Rovis showed that the rate of addition of the reducing agent (DIBALH) had a dramatic effect on the ee in reactions of [2.2.1] substrates catalyzed by $\text{Ni}(\text{COD})_2$ and BINAP (BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl). The following results illustrate this point. Fast addition of DIBALH (<1 s) gave the cyclohexenol in only 56% ee whereas addition over 7 min raised



Scheme 1. Reductive cleavage of dihydrofurans

the ee to 82%. The optimal addition time [using 14 mol % Ni(COD)₂ and 21 mol % BINAP] was found to be 1 h which provided the cyclohexenol in 97% ee, Eq. (3). It was possible to reduce the amount of catalyst to as little as 1–2 mol % (while maintaining a 1.5 to 1.75:1 ratio of ligand:metal) if the time for the addition of DIBALH was increased. For example, ee's in excess of 90% were obtained with 1.5 mol % of nickel and addition of DIBALH over 16 h (cf. Table 3). While an exhaustive survey of ligands has not yet been carried out, BINAP remains the best ligand for this reaction [20].



The reaction conditions were sufficiently mild that a broad range of functional groups and substitution patterns were tolerated including cyclopropyl carbonyl ethers, benzyl (Bn), TIPS (triisopropylsilyl), and TBDPS (*tert*-butyldiphenylsilyl) ethers Eq. (4), Table 1. However, steric congestion close to the reacting olefin resulted in a decrease in enantioselectivity, entry 3, giving the cyclohexenol in 81% yield and 84% ee.

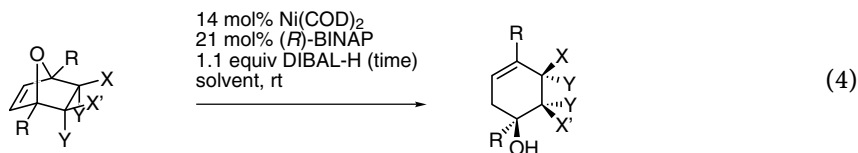


Table 1. Oxabicyclo[2.2.1]heptene ring opening

Entry	R	Y	X	X'	Time (h)	Solvent	Yield (%)	ee (%)
1	H	H	CH ₂ OBn	CH ₂ OBn	6	PhMe	96	97
2	H	CH ₂ OMe		CH ₂	5	THF	88	91
3	Me	H	CH ₂ OMe	CH ₂ OMe	12	PhMe	81	84
4	H	OMe	H	H	2	THF	50	86

Oxabenzonorbornadienes, which contain a strained bicyclic system fused to an aromatic ring, also undergo the enantioselective reductive cleavage reaction. However, milder conditions had to be developed since reactions in toluene typically resulted in the formation of naphthalene and naphthol as byproducts and the ee's of the ring opened product were typically 60%. In the presence of THF, which may reduce the Lewis acidity of DIBALH, the reaction gave the ring opened product in much better yield (88%) and ee (98%). The product of the enantioselective reductive ring opening has been used as a key species in the synthesis of the antidepressant sertraline [21].

A number of oxabenzonorbornadienes were shown to undergo reductive ring openings with ee's between 73 and 93% Eq. (5), Table 2. As was found in the bicyclo [2.2.1] series, steric congestion close to the olefin had the greatest negative effect on the enantioselectivity (entry 4). In contrast, minimal electronic effects were noted and the diminished yield with the electron-rich substrate is probably due to the tendency of the product to dehydrate under the reaction conditions or on workup.

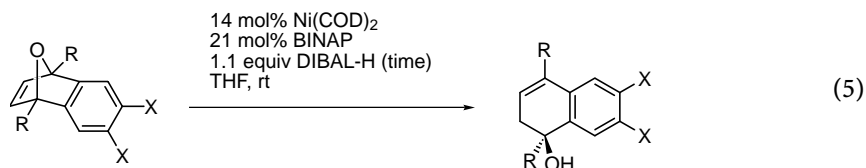
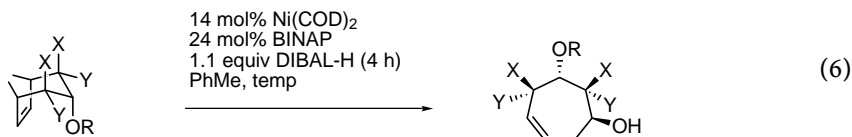


Table 2. Oxabenzonorbornadiene ring opening

Entry	R	X	Time (h)	Yield (%)	ee (%)
1	H	H	1	88	98
2	H	F	3	84	96
3	H	OCH ₂ O	3	58	94
4	Me	H	16	66	73

Oxabicyclo[3.2.1]octenes gave poor results under either of the previously described conditions. In THF or toluene at room temperature, only 20% of the ring opened product was obtained with the balance of the material being the alkane arising from a hydroalumination of the alkene followed by a protonation. Furthermore, the ee of the ring opened product was only 56%. Heating the organoalane produced from the hydroalumination in the presence of a Lewis acid resulted in an increased yield of the ring opened product but with a concomitant loss of enantioselectivity (35 to 45% ee), suggesting that the organoalane is partially racemizing at higher temperatures. However, if the addition of DIBALH is conducted at 60 °C rather than room temperature, the reaction not only proceeds to completion to give exclusively cycloheptenols, but does so with ee's of >90% Eq. (6), Table 3. Various substitution patterns and protecting groups are tolerated. Unprotected alcohols also work well if the alcohol is pretreated with exactly one equivalent of DIBALH to form the aluminum alkoxide which then undergoes ring opening to give the highest enantioselectivity (99.5% ee) and yield (99%) obtained to date (entry 3).

**Table 3.** Ring opening of oxabicyclo[3.2.1]octenes

Entry	X	Y	R	Temp (°C)	Yield (%)	ee (%)
1	H	Me	Me	60	83	97
2	H	H	Me	60	67	95
3	H	H	H	65	99	>99
4	(CH ₂) ₃	H	Me	80	74	97

4

Practical Considerations

4.1

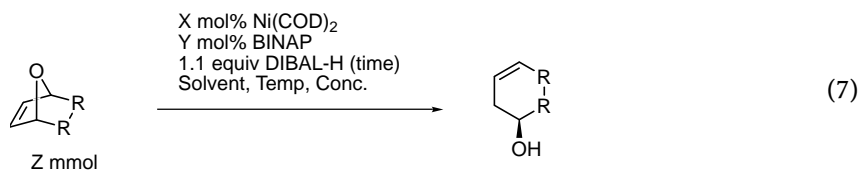
Catalyst Loadings

The early results in the reductive ring opening were obtained using a catalyst loading of 10 to 14 mol % of Ni(COD)₂ and 15 to 21 mol % of the ligand. However, each class of substrates has been shown to undergo the reduction with much lower catalyst loadings if the rate of addition is controlled. For example, a PMB (*para*-methoxybenzyl) ether was subjected to the ring opening reaction in the presence of 1.5 mol % of Ni(COD)₂ and 2.6 mol % of BINAP to give the cyclohexenol in 92% ee and 99% yield Eq. (7), Table 4, entry 1] [22].

Oxabenzonorbornadiene was ring opened on a 7-mmol scale using 1.9 mol % of Ni(COD)₂ and 3.3 mol % of BINAP to give the dihydronaphthalenol isolated in 88% yield and 91% ee [21]. Recrystallization of the alcohol gave material of >98% ee. Reducing the catalyst loading to 1 mol % was possible if the temperature was increased to 40 °C [23].

An oxabicyclo[3.2.1]octene bearing a TIPS ether was reductively cleaved at 65 °C on a 4.5-mmol scale with 4.0 mol % of Ni(COD)₂ and 7.8 mol % of BINAP; the cycloheptenol was obtained in 91% yield and 90% ee [24]. An unprotected alcohol has been ring opened (9.1-mmol scale) using 1 mol % of Ni(COD)₂ and 1.9 mol % of BINAP to give the C₂ symmetrical diol in 83% yield and 98% ee [25]. These reactions have been carried out at 0.2 to 1 M, with similar selectivities.

The catalyst efficiency in these reactions varies from a TON of 20 to 91. It is possible that the catalyst is deactivated by the presence of adventitious oxygen and water, something which is more difficult to avoid at low catalyst loadings and on smaller scales. Examination of the ³¹P-NMR spectrum of the catalyst indicates that the phosphine monoxide and dioxide are formed in the presence of nickel prior to addition of the substrate [23]. Rigorous exclusion of oxygen and water is a necessity for every reaction in this series.

**Table 4.** Larger scale reactions

Entry	R-R	X	Y	Z	Time (h)	Solv.	Temp (°C)	Conc.	Yield (%)	ee (%)
1	CH(CH ₂ OPMB) CH(CH ₂ OPMB)	1.5	2.6	5.9	16	THF	25	0.4	99	92
2	Ph	1.9	3.3	6.9	6	THF	25	0.3	88	91
3	Ph	1	1.8	3.9	5	THF	40	0.5	91	90
4	CH(CH ₃)CH(OTIPS) CH(CH ₃)	4.0	7.8	4.5	24	PhMe	65	0.3	91	90
5	CH ₂ CH(OH)CH ₂	1	1.9	9.1	15	PhMe	65	1.0	83	98

4.2

Catalyst Availability

Both Ni(COD)₂ and BINAP are commercially available. Nickel salts are relatively inexpensive and Ni(COD)₂ is readily available following published procedures [26], and it also is commercially available. All experiments on the reductive opening of oxabicyclic substrates reported to date have used Ni(COD)₂ prepared “in house” and stored in a glove box. BINAP [27] is relatively expensive but about 70% of the ligand can be recovered from the reaction. Phosphine oxides are produced during the course of the reaction and/or during the workup and they must be separated from the non-oxidized ligand. BINAP is air stable and can be stored, transferred and used in the air. Ni(COD)₂ must be stored under an inert atmosphere and although it can be transferred as a solid in the air, it is best stored and transferred in a glove box.

The sensitivity of Ni(COD)₂ to oxygen led to an investigation to determine if nickel(II) complexes were suitable due to their high stability and ease of reduction by organoaluminum compounds. Although the preliminary results were promising, no other source of nickel has been as successful as Ni(COD)₂ itself [23]. Ni[P(OPh)₃]₄, which is significantly more stable to oxygen has also been successfully used in combination with BINAP but the ee's are somewhat lower.

All solvents must be freshly distilled over sodium/benzophenone ketyl or freshly degassed using the freeze/pump/thaw method. Solutions of Ni(COD)₂ are far more sensitive to oxygen than the solid form and were not used in these studies. Ni(COD)₂ and BINAP must be stirred together at a concentration of not less than 0.02 M for a period of about 4 hours which produces a deep burgundy

colored solution. Pink, brown or green colored solutions of the catalyst will lead to low ee's and unreacted starting material.

4.3

Special Considerations

All the reactions described use DIBALH as a solution in hexanes, heptane, or toluene. Slow addition of DIBALH was carried out via a syringe pump using gas-tight syringes. In principle, a good addition funnel might be an adequate substitute, particularly in large-scale reactions if the rate of addition can be carefully and dependably controlled. The reaction was worked up by the addition of Rochelle's salt (potassium sodium tartrate hexahydrate) either as a solution or as a solid. Carbon-aluminum bonds are still present in the reaction so gas evolution and a slight exotherm can be expected.

5

Principal Alternatives

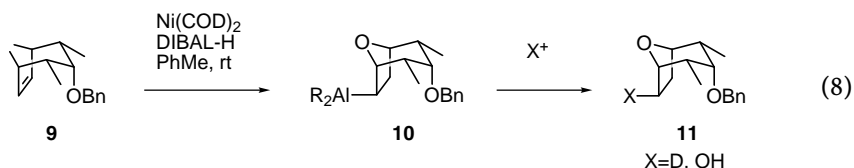
A number of alternatives exist to access enantiomerically enriched cyclohexenols. Most involve either enantioselective Diels-Alder reactions or the conversion of chiral pool compounds [28, 29, 30]. Some catalysts for enantioselective Diels-Alder reaction are somewhat limited in terms of range of dienes and dienophiles which will react. Relatively few studies have used butadiene as the diene component [31, 32, 33]. A relevant case is the catalytic asymmetric Diels-Alder reaction employing 3-borylpropenoic acid oxazolidinones as dienophiles and substituted butadienes in the presence of a catalytic amount of $\text{TiCl}_2(\text{OiPr})_2$ and TADDOL as ligand which works well [34]. Selectivities range from 93 to 98% ee with simple butadienes and subsequent oxidation of the carbon-boron bond affords homoallylic cyclohexenols. Narasaka has also described the use of 3-methylthiofuran as a diene with acrylamide oxazolidinones in the presence of the same catalyst [35]. The cycloaddition generates a oxabicyclo[2.2.1]heptene in 87% ee with moderate *endo:exo* selectivity (85:15). Subsequent Lewis acid-mediated ring opening yields substituted cyclohexenols.

Use of the chiral pool typically requires a series of subsequent transformations to achieve the substitution pattern desired and sometimes may be limited by the availability of only one enantiomer. Microbial oxidations of benzene derivatives have provided an excellent route to cyclohexadienediols in enantiomerically pure form. Although this provides only one enantiomer, synthetic methods have been devised to circumvent this problem [36]. Far fewer methods exist for the enantioselective synthesis of cycloheptenes for which there exists no reaction analogous to the Diels-Alder process [37, 38, 39, 40, 41, 42]. The enantioselective hydroalumination route to dihydronaphthalenols may prove to be particularly important. Only one other method has been reported for the enantioselective synthesis of these compounds; microbial oxidation of dihydronaphthalene by *P. putida* generates the dihydronaphthalenol in >95% ee and 60% yield

but one enantiomer is available which must be separated from other metabolites, including the dihydronaphthalenediol [43, 44].

6 Mechanistic Rationale

The enantioselective reaction was initially thought to proceed via a nickel-catalyzed hydroalumination followed by an elimination of the organoaluminum with cleavage of the oxygen bridge but this proposal seems unlikely in light of recent evidence. In the absence of a phosphine, treatment of an oxabicyclo[3.2.1]octene with nickel and DIBALH led to an organoaluminum species, which was trapped with various electrophiles including D_2O and O_2 Eq. (8).

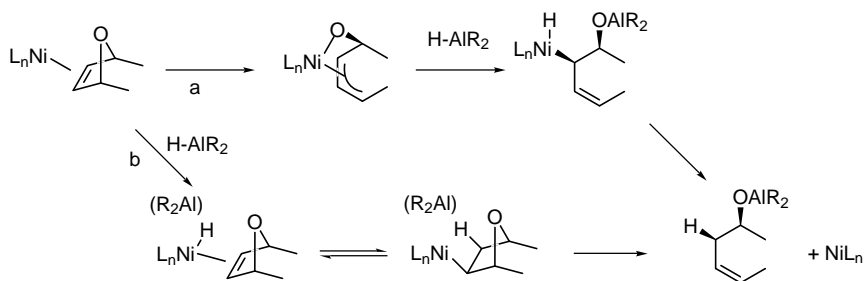


It is difficult to draw detailed conclusions on the location of the aluminum throughout the course of the reaction given the uncertainties associated with the first step of the reaction, namely the interaction between an aluminum hydride and a nickel species.

The phosphine ligand is clearly bound to the nickel as shown by ^{31}P -NMR and by the change in regio- and enantioselectivity as a function of increasing amounts of ligand [23].

Two possible mechanisms are outlined in Scheme 2. Insertion in the allylic C-O bond to form a π -allylic nickel alkoxide would be followed by reduction of the carbon nickel bond (path a). An alternative sequence involves a hydronickeleation of the complexed olefin followed by a β -elimination of the oxygen bridge (path b).

The evidence against path a is that a single regioisomer is observed in all reactions with all class of substrates which might not be expected if a π -allyl nickel



Scheme 2. Possible mechanisms for the reductive ring opening

species were formed. Furthermore, each class of substrates gives the ring opened products with the same sense of addition of the hydride and with similar levels of selectivity. We attribute the need for different conditions (temperature and solvent) for each class of substrate as a result of the difference in strain and inherent reactivity of the bridging oxygen rather than a different mechanism.

A mechanism involving hydronickelation followed by a β -elimination of the oxygen bridge best fits the results obtained to date. For example, when the reaction illustrated in Eq. (8) is carried out in the presence of (*R*)-BINAP, the ee of the alcohol **11**, X=OH, (a side product derived from oxidation of the organoalane **10**) is very different from the ee of the ring opened cyclohexenol. In addition, all attempts to enantioselectively hydroaluminate various norbornene derivatives with this catalyst-ligand combination have produced racemic products. Furthermore, room temperature hydroalumination of a [3.2.1] substrate lacking the bridging oxygen, followed by oxidation of the carbon-aluminum bond, gave a racemic [3.2.1] alcohol.

The evidence accumulated to date suggests that the hydronickelation occurs with little or no selectivity but that the subsequent opening of the diastereomeric nickel species is a highly selective process. It is essential to establish conditions where reversible hydronickelation occurs. The temperature required to create favourable conditions for reversible hydroalumination varies according to the substrate.

7

Conclusions

The enantioselective reductive ring opening reaction of bicyclic ethers is an emerging process whose full scope has not been delineated. Further synthetic and mechanistic studies will be necessary before a detailed understanding of the reaction is available. Nevertheless, the reaction has provided a new route to three synthetically useful classes of molecules which are versatile intermediates in the preparation of biologically active compounds.

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Chapter 9

Hydroboration of Carbon-Carbon Double Bonds

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Keywords: Hydroboration, Olefins, Rhodium catalyst, Palladium catalyst, Secondary alcohols, Allenylboranes

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1

Introduction

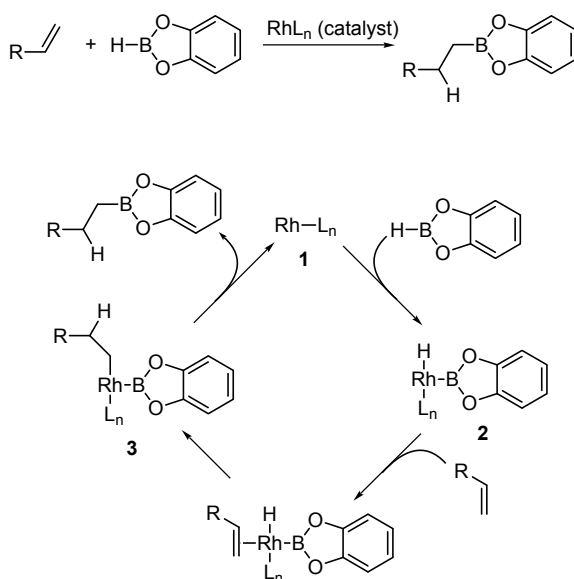
Hydroboration of alkenes and alkynes is one of the most valuable synthetic techniques in organic chemistry because the organoboranes formed are readily converted into various kinds of organic compounds, and the enantioselective version developed by Brown has greatly expanded the scope of the hydroboration [1, 2, 3]. Hydroboration of alkenes with chiral hydroborating agents, such as diisopinocampheylborane is recognized to be a highly efficient reaction for the synthesis of enantiomerically enriched organoboranes [4]. The hydroboration usually does not require any catalyst, but the reaction is slow with the hydroboranes that are substituted with oxygen or nitrogen atoms, and it was reported in 1985 that the hydroboration with catecholborane is catalyzed by a rhodium-phosphine complex [5]. Since this report, increasing attention has been paid to the application of the catalytic hydroboration [6, 7]. The chemoselectivity, regioselectivity, and diastereoselectivity in the hydroboration have been successfully controlled by use of catalysts, the selectivities often being different from those in non-catalyzed hydroboration [6, 7]. The most exciting application of the catalytic hydroboration is the catalytic asymmetric synthesis of chiral organobo-

ranes which is possible by incorporation of chiral ligands on the catalyst. For the catalytic enantioselective hydroboration, rhodium complexes coordinated with enantiomerically pure tertiary phosphine ligands have been mainly used with few exceptions [6, 7].

2

Mechanism of Rhodium-Catalyzed Hydroboration of Olefins

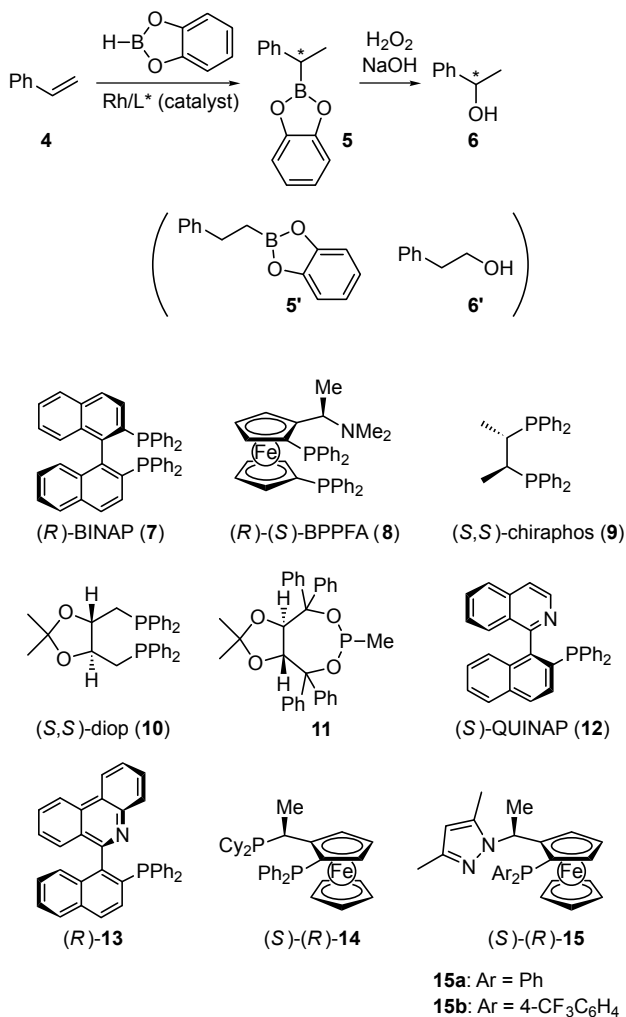
Although the mechanism of rhodium-catalyzed hydroboration has not been well established, the catalytic cycle is accepted to be analogous to that of the catalytic hydrosilylation of olefins [8, 9]. Thus, the catalytic hydroboration involves a hydrido(boryl)rhodium(III) species **2** which is formed by oxidative addition of hydroborane, typically catecholborane, to the rhodium(I) species **1** (Scheme 1). Coordination of an olefin followed by migratory insertion of the olefin into the Rh-H bond gives the alkylboryl species **3**. Reductive elimination of the alkyl and boryl groups from **3** forms the hydroboration product and regenerates the rhodium(I) species **1** to complete the catalytic cycle. The regioselectivity (ratio of linear and branched isomers) is dependent on the catalyst as well as the substituent on the olefin. Alkyl-substituted olefins produce linear isomers preferentially that are achiral while styrene derivatives usually produce branched isomers that are chiral [6, 7]. In the hydroboration of styrene with catecholborane, it has been reported that the ratio of phosphine ligand to rhodium is critical, higher ratios favoring the branched isomer [10, 11, 12].



Scheme 1

3 Hydroboration of Styrene and Its Derivatives

Catalytic asymmetric hydroboration has been most extensively studied with styrene (**4**) as the substrate which produces 1-phenylethanol (**6**) after treatment of the hydroboration product, 1-phenyl-1,3,2-benzodioxaborole (**5**), with alkaline hydrogen peroxide (Scheme 2). The regioselectivity favoring the branched isomer **5** over the linear isomer **5'** is usually high when the reaction is carried out with rhodium complexes coordinated with chelating ligands such as bisphos-



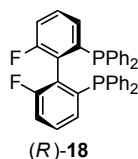
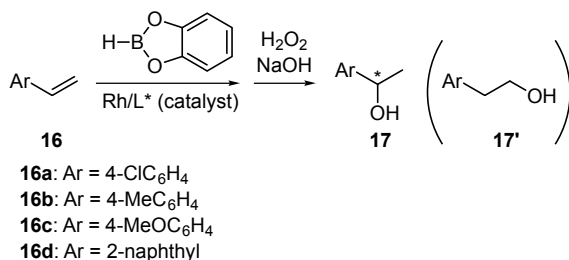
Scheme 2

Table 1. Catalytic asymmetric hydroboration of styrene (**4**) with catecholborane (Scheme 2)

Entry	Catalyst (mol %)	Solvent	Temp [°C]	Time [h]	Yield [%]	ratio 6/6'	% ee (config)	Ref
1	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	DME	-78	6	64	>99/1	96 (<i>R</i>)	13, 14
2	[Rh(cod) ₂]BF ₄ (2)/(<i>R</i>)-BINAP (7) (2)	DME	-78	2	91	>99/1	96 (<i>R</i>)	13, 14
3	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	DME	-50	1	54	>99/1	89 (<i>R</i>)	13, 14
4	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	DME	-30	0.5	57	>99/1	78 (<i>R</i>)	13, 14
5	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	0.5	92	>99/1	57 (<i>R</i>)	13, 14
6	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-(<i>S</i>)-BPPFA (8) (1)	THF	25	0.5	77	95/5	22 (<i>R</i>)	14
7	[Rh(cod) ₂]BF ₄ (1)/(<i>S,S</i>)-chiraphos (9) (1)	THF	25	0.5	98	>99/1	16 (<i>R</i>)	14
8	[Rh(cod) ₂]BF ₄ (1)/(<i>S,S</i>)-DIOP (10) (1)	THF	25	0.5	87	>99/1	4 (<i>R</i>)	14
9	1/2[RhCl(cod)] ₂ (1)/(<i>S,S</i>)-DIOP (10) (1)	THF	25	0.5	64	18/82	3 (<i>R</i>)	14
10	[Rh(cod) ₂]BF ₄ (1)/(<i>R,R</i>)-DIOP (10) (1)	DME	-78				48 (<i>R</i>)	15
11	1/2[RhCl(cod)] ₂ (2)/(<i>S</i>)-BINAP (7) (2)	DME	-78	4 days	63		92 (<i>S</i>)	12
12	1/2[RhCl(cod)] ₂ (2)/(<i>S</i>)-BINAP (7) (2), AlCl ₃	DME	-40	4 days	85		94 (<i>S</i>)	12
13	1/2[RhCl(cod)] ₂ (4)/ 11 (10)	DME	0	2-5	64		26 (<i>R</i>)	16
14	[Rh(cod)((<i>S</i>)-QUINAP (12))] OTf (1)	THF	20		72	96/4	91 (<i>R</i>)	17,18
15	[Rh(cod)((<i>R</i>)- 13)]OTf (1)	THF	20				67 (<i>R</i>)	18
16	[Rh(nbd) ₂]BF ₄ (2)/(<i>S</i>)-(<i>R</i>)- 14 (2)	DME	-78	10	65	>99/1	92 (<i>R</i>)	19
17	[Rh(cod) ₂]BF ₄ (1)/(<i>S</i>)-(<i>R</i>)- 15a (1)	THF	20		91	66/34	95 (<i>R</i>)	20
18	[Rh(cod) ₂]BF ₄ (1)/(<i>S</i>)-(<i>R</i>)- 15b (1)	THF	20		68	60/40	98 (<i>R</i>)	20

phines [13, 14]. It has been suggested that this selectivity is attributable to a cationic π -benzylrhodium intermediate [13]. In a typical example, the reaction of styrene (**4**) with catecholborane proceeded with high regioselectivity in the presence of rhodium catalyst generated from $[\text{Rh}(\text{cod})_2]\text{BF}_4$ and (*R*)-BINAP (**7**) in DME at $-78\text{ }^\circ\text{C}$ to give high yield of (*R*)-1-phenylethanol (**6**) of up to 96% ee (entries 1 and 2, in Table 1). DME is the solvent of choice for the reaction at this low temperature because catecholborane is not soluble in other solvents such as THF. The enantioselectivity is strongly dependent on the reaction temperature, at the lower temperature the higher selectivity being observed. The reaction at $25\text{ }^\circ\text{C}$, $-30\text{ }^\circ\text{C}$, and $-50\text{ }^\circ\text{C}$ gave (*R*)-**6** of 57%, 78%, and 89% ee, respectively (Table 1, entries 3–5). Some other chiral bisphosphine ligands, BPPFA (**8**) [14], chiraphos (**9**) [14], and DIOP (**10**) [14, 15], and the cyclic phosphinite **11** [16] are much less effective than BINAP (**7**) in this case (Table 1, entries 6–13). Axially chiral isoquinoline derivatives **12** and **13** [17, 18] which can coordinate to rhodium with the diphenylphosphino group and the sp^2 nitrogen atom, are effective ligands giving **6** of 91% ee at the reaction temperature of $20\text{ }^\circ\text{C}$ (Table 1, entries 14 and 15). The ferrocenylbisphosphine ligand **14** induces similar ee's as BINAP (92% ee [19]; Table 1, entry 16). The regioselectivity favoring the branched isomer **5** is also high with ligand **14**. Several pyrazole-containing ferrocenylphosphines **15** have been prepared and tested in this reaction [20, 21]. The enantioselectivity is high at $20\text{ }^\circ\text{C}$ although the regioselectivity is low (Table 1, entries 17 and 18).

Styrenes containing electron-withdrawing or electron-releasing groups on the phenyl ring **16** also react smoothly with catecholborane in the presence of rhodium catalyst coordinated with BINAP (**7**) or QUINAP (**12**) giving high yields of 1-arylethanol **17** in high enantiomeric purity [12, 13, 14, 17, 18, 22] (Scheme 3). The enantioselectivities for the reaction of 4-chloro- (**16a**), 4-methyl- (**16b**), and 4-methoxystyrene (**16c**) are 91% ee, 96% ee, and 94% ee, respectively (entries 1, 5 and 8 in Table 2). The regioselectivity favoring the chiral benzylic alcohol **17** is



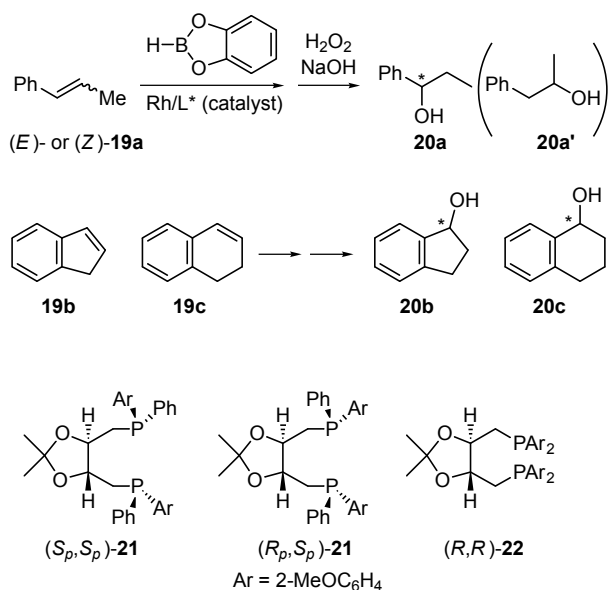
Scheme 3

Table 2. Catalytic asymmetric hydroboration of styrene derivatives (**16**) with catecholborane (Scheme 3)

Entry	Olefin	Catalyst [mol %]	Solvent	Temp [°C]	Time [h]	Yield [%]	Ratio 17/17'	% ee (config)	Ref
1	16a	[Rh(cod) ₂]BF ₄ (2)/(R)-BINAP (7) (2)	DME	-78	6	98	>99/1	91 (R)	13, 14
2	16b	[Rh(cod) ₂]BF ₄ (2)/(R)-BINAP (7) (2)	DME	-78	2	77	>99/1	94 (R)	13, 14
3	16c	[Rh(cod) ₂]BF ₄ (2)/(R)-BINAP (7) (2)	THF/ DME	-78	6	54	>99/1	89 (R)	13, 14
4	16a	1/2[RhCl(cod)] ₂ (2)/(S)-BINAP (7) (2)	DME	-78	3 days	95		91 (S)	12
5	16b	1/2[RhCl(cod)] ₂ (2)/(S)-BINAP (7) (2)	DME	-78	3 days	95		96 (S)	12
6	16c	Rh(acac) (cod) (2)/(R) - 18 (2)	THF	0	1.5	90	78/22	78 (R)	22
7	16a	[Rh(cod) (S)-QUINAP (12)]OTf (1)	THF	20		56	96/4	78 (S)	17
8	16c	[Rh(cod) (S)-QUINAP (12)] OTf (1)	THF	20		57	95/5	94 (S)	17
9	16d	[Rh(cod)((S)- QUINAP (12)]OTf (1)	THF	20	2	64		89 (S)	18

usually very high irrespective of the electronic nature of the substituents on the phenyl ring.

Since β -methylstyrene (**19a**) is less reactive than unsubstituted styrene, the reaction is usually carried out at -5 °C or higher temperature (Scheme 4). In the catalytic hydroboration of **19a** the boryl group is introduced in the benzylic position to give 1-phenylpropanol (**20a**) with high regioselectivities [14, 18, 23] (entries 1–8 in Table 3). The highest enantioselectivity (95% ee) was reported with the rhodium catalyst coordinated with the isoquinoline ligand QUINAP (**12**) (Table 3, entry 4). Indene (**19b**) has been also examined as a substrate with several chiral ligands [14, 15, 17, 18, 19, 23, 24] (Table 3, entries 9–15). Here again QUINAP (**12**) is a more effective ligand than BINAP (**7**) giving 1-indanol (**20b**) of 91% ee (Table 3, entry 10). DIOP (**10**) and its analogues **21** and **22**, which are modified on the diphenylphosphino group, afford moderate ee's between 50 and 80% in this reaction (Table 3, entries 13–18).



Scheme 4

Table 3. Catalytic asymmetric hydroboration of β -methylstyrene (**19a**), indene (**19b**), and 1,2-dihydronaphthalene (**19c**) with catecholborane (Scheme 4)

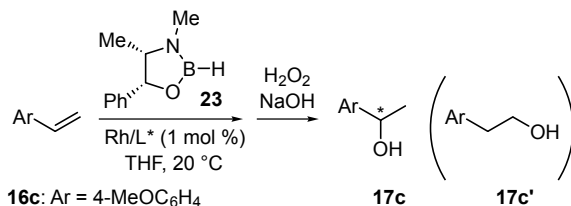
Entry	Olefin	Catalyst (mol %)	Solvent	Temp [°C]	Time [h]	Yield [%]	Ratio 20/20' (config)	% ee	Ref
1	(<i>E</i>)- 19a	$[\text{Rh}(\text{cod})_2]\text{BF}_4$ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	34	65	>99/1	42 (<i>S</i>)	14
2	(<i>Z</i>)- 19a	$[\text{Rh}(\text{cod})_2]\text{BF}_4$ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	48	65	>99/1	18 (<i>S</i>)	14
3	(<i>E</i>)- 19a	$[\text{Rh}(\text{cod})((\text{S})\text{-QUINAP (12))}] \text{OTf}$ (1)	THF	20	2	64		95 (<i>S</i>)	18
4	(<i>E</i>)- 19a	$[\text{Rh}(\text{cod})((\text{R})\text{-13})] \text{OTf}$ (1)	THF	20	2	60		91 (<i>R</i>)	18
5	(<i>Z</i>)- 19a	$[\text{Rh}(\text{cod})((\text{S})\text{-QUINAP (12))}] \text{OTf}$ (1)	THF	20	2	60		93 (<i>S</i>)	18
6	(<i>E</i>)- 19a	$1/2[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (1)/(<i>S,S</i>)-DIOP (10) (1)	PhMe	-5	3 days	79		41 (<i>S</i>)	23
7	(<i>Z</i>)- 19a	$1/2[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (1)/(<i>S,S</i>)-DIOP (10) (1)	PhMe	-5	3 days	86		47 (<i>S</i>)	23
8	(<i>E</i>)- 19a	$1/2[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (1)/(<i>R</i>)-BINAP (7) (1)	PhMe	-5	3 days	42		36 (<i>S</i>)	23
9	19b	$[\text{Rh}(\text{cod})_2]\text{BF}_4$ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	3	65	93/7	13 (<i>S</i>)	14

Table 3 (continued)

Entry	Olefin	Catalyst (mol %)	Solvent	Temp [°C]	Time [h]	Yield [%]	Ratio 20/20'	% ee (config)	Ref
10	19b	[Rh(cod)((<i>S</i>)-QUINAP (12))]OTf (1)	THF	20	2	58	>99/1	91 (<i>S</i>)	17, 18
11	19b	[Rh(cod)((<i>R</i>)-13)]OTf (1)	THF	20	2	59		64 (<i>R</i>)	18
12	19b	[Rh(nbd) ₂]BF ₄ (1)/(<i>S</i>)-(<i>R</i>)- 14 (1)	DME	25		70	93/7	42 (<i>R</i>)	19
13	19b	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>S,S</i>)-DIOP (10) (1)	PhMe	-5	3 days	93		58 (<i>R</i>)	23
14	19b	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>S,S</i>)-DIOP (10) (1)	PhMe	-30	5 days	91		74 (<i>R</i>)	23
15	19b	1/2[RhCl(cod)] ₂ (1)/(<i>R,R</i>)-DIOP (10) (1)	THF	-25				74 (<i>S</i>)	15
16	19b	1/2[RhCl(cod)] ₂ (1)/(<i>S_pS_p</i>)- 21 (1)	THF	-25				49 (<i>S</i>)	15
17	19b	1/2[RhCl(cod)] ₂ (1)/(<i>R_pS_p</i>)- 21 (1)	THF	-25				77 (<i>S</i>)	15
18	19b	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)- 22 (2)	PhMe	-25				59 (<i>S</i>)	24
19	19c	[Rh(cod)((<i>S</i>)-QUINAP (12))]Otf (1)	THF	20	2	68		37 (<i>S</i>)	17, 18
20	19c	[Rh(cod)((<i>R</i>)-13)]OTf (1)	THF	20	2	69		84 (<i>R</i>)	18
21	19c	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>S,S</i>)-DIOP (10) (1)	PhMe	-5	3 days	58		14 (<i>R</i>)	23

An enantiomerically pure chiral hydroborating agent, **23**, which is derived from ephedrine, has been used for the rhodium-catalyzed enantioselective hydroboration of 4-methoxystyrene (**16c**) (Scheme 5) [25]. Double stereodifferentiation was observed in the reaction catalyzed by rhodium complexes coordinated with (*R*)-BINAP and (*S*)-BINAP. The reaction of **16c** with **23** in the presence of (*R*)-BINAP-Rh gave the alcohol (*S*)-**17c** of 86% ee, while the reaction in the presence of (*S*)-BINAP-Rh gave (*S*)-**17c** of 8% ee. Thus, the combination of **23** with (*R*)-BINAP is a matching pair. The hydroborane **23** gave the non-racemic product **17c** (17% ee) in the reaction catalyzed by an achiral rhodium catalyst bearing triphenylphosphine as a ligand.

Styrylboronic ester **24** was subjected to the catalytic hydroboration with catecholborane in the presence of rhodium complexes coordinated with chiral bisphosphine ligands. Oxidation of the resulting 1,2-diboryl product **25** gave optically active 1-phenyl-1,2-ethanediol (**26**) (Scheme 6) [26]. The reaction with BINAP (**7**) at -60 °C gave (*S*)-diol **26** of over 70% ee.



L*: yield and % ee of **17c**

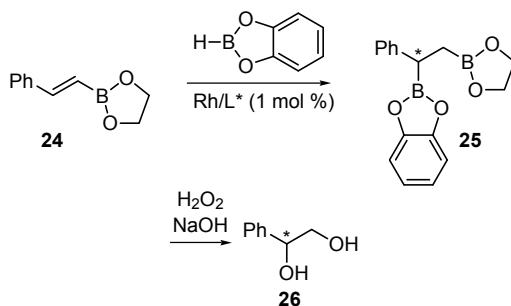
PPh₃: 36% yield, 17% ee (*S*)

dppb: 95% yield, 5% ee (*S*)

(*R*)-BINAP (**7**): 32% yield, 86% ee (*S*)

(*S*)-BINAP (**7**): 25% yield, 8% ee (*S*)

Scheme 5



catalyst: temp, yield, and % ee of **26**

[Rh(cod)₂]BF₄/(*S,S*)-chiraphos (**9**): -20 °C, 13% yield, 73% ee (*R*)

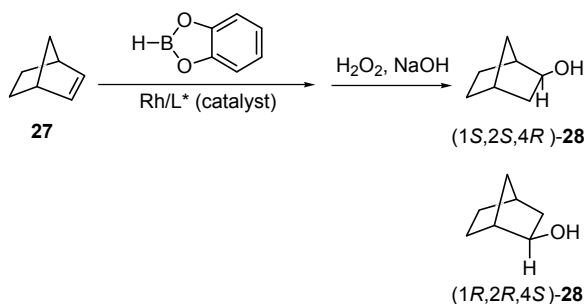
[Rh(cod)₂]BF₄/(*R*)-BINAP (**7**): -60 °C, 49% yield, 72% ee (*S*)

[RhCl(cod)]₂/(*R*)-BINAP (**7**): -60 °C, <9% yield, 79% ee (*S*)

Scheme 6

4 Hydroboration of Other Olefins

Asymmetric hydroboration of norbornene (**27**) is a synthetically useful transformation forming optically active norbornanol (**28**) which is an important chiral synthon. The catalytic enantioselective hydroboration with catecholborane was examined using rhodium complexes coordinated with several chiral phosphine ligands (Scheme 7 and Table 4) [14, 15, 17, 23, 24, 27]. For this reaction, DIOP (**10**) and its derivatives **21** and **22**, which are modified on the diphenylphosphino group, are more enantioselective ligands than BINAP (**7**) or chiraphos (**9**). The highest enantioselectivity was observed in the reaction at -25 °C



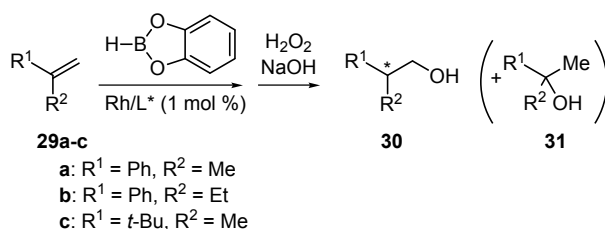
Scheme 7

Table 4. Catalytic asymmetric hydroboration of norbornene (**27**) with catecholborane forming *exo*-norbornanol (**28**) (Scheme 7)

Entry	Catalyst (mol %)	Solvent	Temp [°C]	Time [h]	Yield [%]	% ee (config)	Ref
1	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)-DIOF (10) (2)	THF	-25			60 (<i>1R</i>)	15, 24, 27
2	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)-DIOF (10) (2)	THF	-5			49 (<i>1R</i>)	24, 27
3	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>S,S</i>)-DIOF (10) (1)	PhMe	-5	3 days	81	59 (<i>1S</i>)	23
4	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>S,S</i>)-chiraphos (9) (1)	PhMe	-5	3 days	76	10 (<i>1S</i>)	23
5	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	1	61	15 (<i>1S</i>)	14
6	1/2[RhCl(cod)] ₂ (1)/(<i>R</i>)-BINAP (7) (1)	THF	-25			65 (<i>1R</i>)	24, 27
7	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)- 22 (2)	THF	-25			82 (<i>1R</i>)	24
8	1/2[RhCl(cod)] ₂ (1)/(<i>S_pS_p</i>)- 21 (1)	THF	-25			84 (<i>1R</i>)	15
9	1/2[RhCl(cod)] ₂ (1)/(<i>R_pS_p</i>)- 21 (1)	THF	-25			80 (<i>1R</i>)	15
10	[Rh(cod)((<i>S</i>)-QUINAP (12))]OTf (1)	THF	20			52 (<i>1S</i>)	17

catalyzed by the rhodium complex generated in situ from [RhCl(cod)]₂ and (*S_pS_p*)-**21**, which gave (*1R,2R,4S*)-**28** of 84% ee [15]. Attempts to use cationic rhodium catalysts or catecholboranes containing alkyl substituents on the catechol moiety did not improve the enantioselectivity [24].

The reaction of 1,1-disubstituted olefins **29** [14, 23, 24, 27] usually requires higher reaction temperature than that of styrene or norbornene, and the enan-



Scheme 8

Table 5. Catalytic asymmetric hydroboration of 1,1-disubstituted olefins (**29**) with catecholborane (Scheme 8)

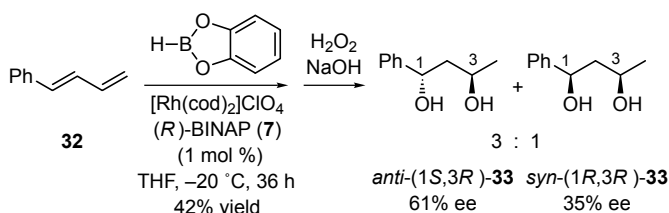
Entry	Olefin	Catalyst (mol %)	Solvent	Temp [°C]	Time [h]	Yield [%]	Ratio of 30/31	% ee (config) of 30	Ref
1	29a	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	3.5	27	61/39	19 (<i>S</i>)	14
2	29a	1/2[RhCl(cod)] ₂ (2)/(<i>R</i>)-BINAP (7) (2)	THF	-5			85/15	25 (<i>S</i>)	24
3	29a	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>R</i>)-BINAP (7) (1)	PhMe	-5	3 days	73		38 (<i>S</i>)	23
4	29a	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)-DIOP (10) (2)	THF	-5			90/10	27 (<i>R</i>)	24, 27
5	29a	1/2[RhCl(C ₂ H ₄) ₂] ₂ (1)/(<i>S,S</i>)-DIOP (10) (1)	PhMe	-5	3 days	27		38 (<i>S</i>)	23
6	29a	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)- 22 (2)	THF	25				15 (<i>R</i>)	24
7	29b	[Rh(cod) ₂]BF ₄ (1)/(<i>R</i>)-BINAP (7) (1)	THF	25	41	50	>99/1	47 (<i>S</i>)	14
8	29c	1/2[RhCl(cod)] ₂ (2)/(<i>R,R</i>)-DIOP (10) (2)	THF	-5				69 (<i>R</i>)	24, 27

tioselectivity is generally lower. The reaction of 2-phenylpropene (**29a**) with catecholborane followed by oxidation produces a mixture of regioisomers consisting of 2-phenyl-1-propanol (**30a**) as the main product and 2-phenyl-2-propanol (**31a**) (Scheme 8 and Table 5). The highest enantioselectivity is 38% ee which has been reported in the reaction with BINAP or DIOP (Table 5, entries 3 and 5). The enantioselectivity is higher in the reaction of 2-phenyl-1-butene (**29b**) and 2,3,3-trimethyl-1-butene (**29c**), which gave the corresponding chiral alcohols of 47% ee and 69% ee, respectively (Table 5, entries 7 and 8).

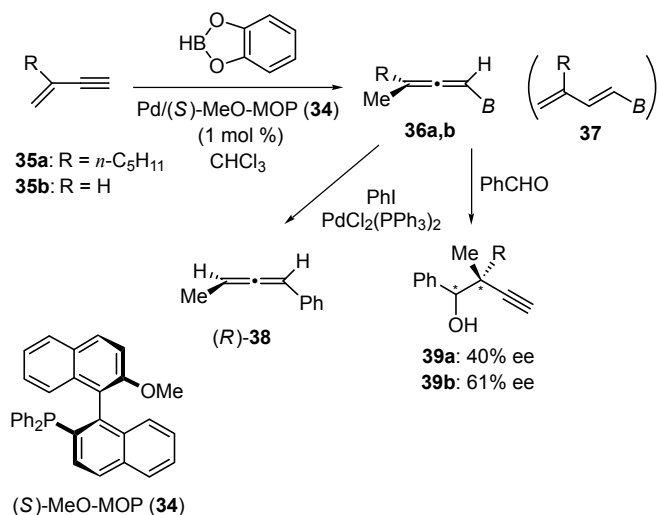
5 Hydroboration of 1,3-Dienes and 1,3-Enynes

An interesting regioselectivity has been reported in the rhodium-catalyzed hydroboration of 1-phenyl-1,3-butadiene (**32**) with excess catecholborane (Scheme 9) [28]. Double hydroboration takes place to give, after oxidation, 1-phenyl-1,3-butanediol (**33**) with high regioselectivity. The *anti*/*syn* ratio is dependent on the phosphine ligand, 10/1 with triphenylphosphine and 3/1 with BINAP (**7**). The ee's of the *anti*- and *syn*-isomers were found to be 61% and 35%, respectively, their absolute configurations being same at C(3) and opposite at C(1).

Phosphine-palladium complexes are known to catalyze the addition of catecholborane to 1,3-enynes [29,30]. The addition mode is determined by the phosphine ligand, 1,2-addition to the triple bond of 2-substituted-1-buten-3-yne ($\text{CH}_2=\text{CR}-\text{C}\equiv\text{CH}$) forming 1,3-dienylboranes ($\text{CH}_2=\text{CR}-\text{CH}=\text{CH}(\text{BO}_2\text{C}_6\text{H}_4)$) taking place with chelating bisphosphine ligands while 1,4-addition forming allenylboranes ($\text{CH}_3(\text{R})\text{C}=\text{C}=\text{CH}(\text{BO}_2\text{C}_6\text{H}_4)$) takes place with monophosphine ligands. The palladium-catalyzed hydroboration of 1,3-enynes has been carried out enantioselectively using the chiral monophosphine ligand (*S*)-MeO-MOP (**34**) [31]. Thus, the reaction of 2-pentyl-1-buten-3-yne (**35a**) with catecholborane at -30°C in the presence of 1 mol % of a palladium catalyst generated from $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and (*S*)-MeO-MOP (Pd/P=1/1) gave allenylborane **36a** together with a small amount of 1,3-dienylborane **37a** (Scheme 10). The allenylborane **36a** had an ee of 40% which was determined after the transformation to the homopropargyl alcohol **39a**. The enantioselectivity is higher in the reaction of 1-buten-3-yne (**35b**) which gave allenylborane (*R*)-**36b** of 61% ee. The absolute configuration was assigned by correlation with allene (*R*)-**38**.



Scheme 9



Scheme 10

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Chapter 10

Hydrocyanation of Carbon-Carbon Double Bonds

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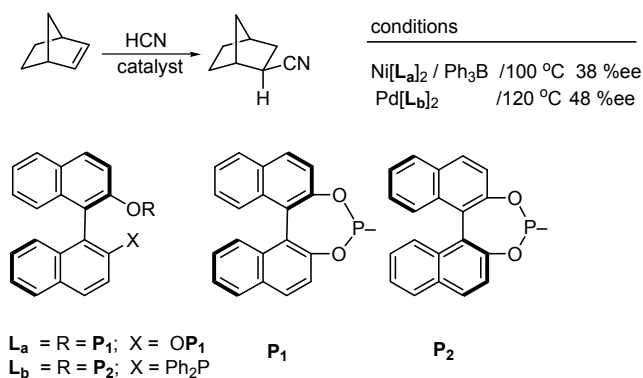
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Keywords: Asymmetric hydrocyanation, Hydrogen cyanide, Vinylarenes, 2-Arylpropanoic acids, Naproxen, Arylphosphinites, Carbohydrate ligands, Electronic effects, Electronic asymmetry

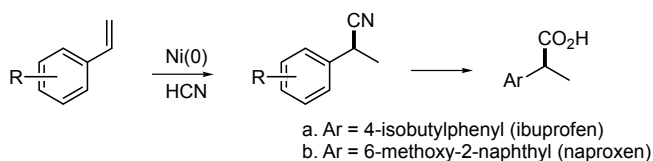
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1 Introduction

Hydrocyanation of alkenes and alkynes offers a direct and economical way to produce organonitriles which can be transformed into a variety of other val-



Scheme 1



Scheme 2

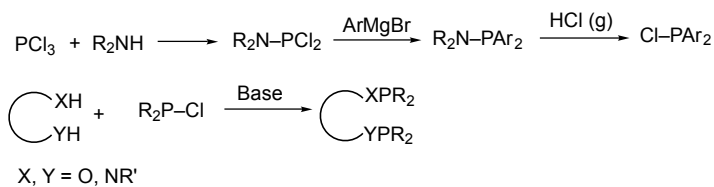
uable intermediates such as amines, aldehydes, acids, and esters [1]. In one of the most profitable applications of homogeneous catalysis, DuPont produces over a billion pounds of adiponitrile each year by the hydrocyanation of butadiene. Yet there had been only very limited research activity directed towards finding an asymmetric variation of this reaction until 1992. Most of the early studies in this area focused on the HCN additions to norbornene and its derivatives (Scheme 1) [2]. Although these reactions gave exclusively the *exo*-isomer, the highest enantiomeric excess (ee) reported to date for this class of substrates is only 48%, using a BINAPHOS(L_b)-Pd complex at 120 °C [2e].

An important class of compounds that can be prepared by this route is the 2-arylpropionitriles, precursors for the widely used anti-inflammatory 2-arylpropanoic acids [3]. Of these, only naproxen [(*S*)-2-(6-methoxynaphthyl)propanoic acid] is sold as an optically pure drug. Nugent and McKinney first reported efficient syntheses of racemic ibuprofen and naproxen via the $\text{Ni}[\text{P}(\text{O}-p\text{-tolyl})_3]_4$ -catalyzed hydrocyanation of the corresponding vinylarene precursors (Scheme 2) [4].

2

The Asymmetric Hydrocyanation of Vinylarenes. 1,2-Phosphetes as Ligands

In the earliest attempt at the asymmetric hydrocyanation of styrene, Gosser obtained 10% ee in the Ni-DIOP-catalyzed reaction [5]. Our initial studies were

**Scheme 3**

carried out with vicinal diaryl phosphinites and aminophosphine-phosphinites of commercially available diols and amino alcohols (Scheme 3). Hydrocyanation of vinylnaphthalene (VN) and 6-methoxy-2-vinylnaphthalene (MVN) using dimethyl tartrate, binaphthol, propranolol, pseudoephedrine, prolinol, pinenediol, and various steroidal diols as ligand precursors gave only disappointing selectivities [6]. However, these studies established that the 1,2-*bis*-diaryl phosphinites are excellent ligands for the Ni(0)-catalyzed hydrocyanation of vinylarenes.

3

Experimental and Analytical Protocols [7]

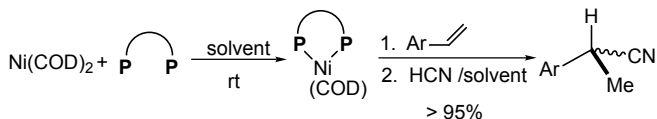
The scouting reactions were carried out by dropwise addition of a hydrocarbon solution of HCN to a solution of the vinylarene in a hydrocarbon solvent and, typically 1–5 mol % of the Ni-catalyst. The Ni-catalyst was prepared *in situ* by stirring a solution of the 1,2-*bis*-diaryl phosphinite with 1 equiv of Ni(COD)₂ (COD=1,5-cyclooctadiene) for several minutes at ambient temperature under a nitrogen atmosphere (Scheme 4). The reaction gave almost exclusively the corresponding 2-arypropionitrile in varying chemical and optical yields depending on the phosphinite and the reaction conditions. The enantioselectivity was determined by HPLC analysis of the product nitrile using a Diacel Chiracel OJ column.

Strong solvent effects were observed in the asymmetric hydrocyanation of MVN, with the highest ees seen in non-polar solvents. For example, ees of 27, 65, 78, and 85% were obtained in acetonitrile, THF, benzene, and hexane, respectively, in the (1a)-catalyzed hydrocyanation of MVN at room temperature. Hexafluorobenzene gave results comparable to those obtained in hexane. Modest increases in enantioselectivity have been observed by lowering the temperature to 0–10 °C.

4

Asymmetric Hydrocyanation with Carbohydrate-Derived Phosphorus Ligands

The highest enantioselectivities have been obtained for the asymmetric hydrocyanation of vinylarenes using carbohydrate-derived phosphinite-Ni catalysts. In the initial ligand scouting, carbohydrates appeared to show the most promise,



Scheme 4

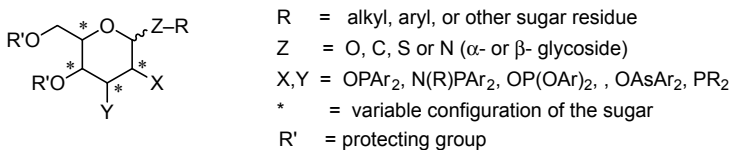


Fig. 1. Tunable sites on a sugar-derived ligand

since they provided structurally diverse and easily tunable frameworks (Fig. 1) for the construction of chiral phosphinite ligands.

4.1

Effect of the Sugar Backbone and the Site of Phosphorus Attachment

Our modular approach to ligand design was considerably facilitated by the extensive literature on carbohydrate and phosphorus synthetic methodologies. Thus, over 100 1,2- and 1,3-diarylphosphinite ligands were synthesized from various sugars including, glucose, galactose, fructose, 2-acetamidoglucose, lactose and trehalose [7, 8]. Four of these scaffoldings along with the substituents on the *P*-aryl groups that were examined are shown in Fig. 2. The results of hydrocyanation of vinyl naphthalenes using these ligands are shown in Table 1. Inspection of these results suggest that the local chirality defined by the phosphenoxy-bearing carbons controls the absolute configuration of the major product. Thus, ligands of the type 2,3-bis-*O*-disubstituted *D*-gluco-diarylphosphinite (1) gave the (*S*)-nitrile as the major product, while the corresponding 3,4-bis-*O*-diarylphosphinite (2) gave the (*R*)-nitrile (entries 1 and 2). In a related observation, 3,4-disubstituted methyl α -*D*-fructofuranoside 3,4-bis-*O*-diarylphosphinite (3) also was found to give the *R*-nitrile. These and other initial results suggested that the phenyl 4,6-*O*-benzylidene- β -*D*-glucopyranoside (1) was the best and most accessible sugar backbone, and this system was chosen for detailed study of hydrocyanation of 6-methoxy-2-vinylnaphthalene.

4.2

Steric and Electronic Effects of Phosphorus Substituents

While the steric and electronic effects of the aglycone (*Z*-*R* in Fig. 1) showed a modest, yet discernible, improvement on the selectivity of the reaction, substituents on the ligating phosphorus had the most pronounced effect [6, 7]. Hydro-

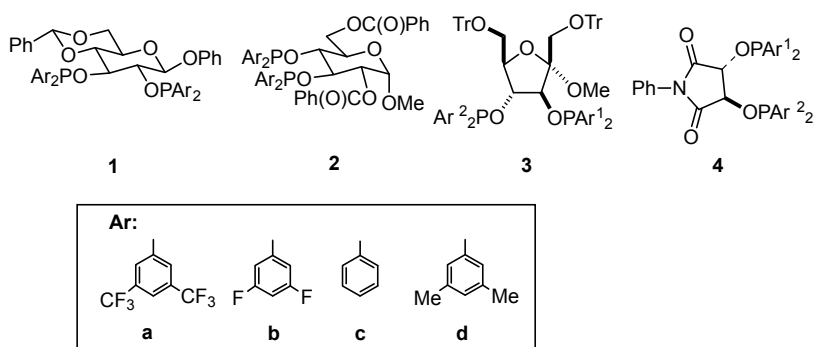


Fig. 2. Prototypical phosphinites used as ligands in asymmetric hydrocyanation

Table 1. Hydrocyanation of 2-methoxy-6-vinylnaphthalene: effect of sugar backbone

Entry	Ligand	Phosphinite	% ee
1	1	Ph ₂ P	40 (<i>S</i>)
2	2	Ph ₂ P	20 (<i>R</i>)
3	3	Ph ₂ P	30 (<i>R</i>)
4	4	Ph ₂ P	43 (<i>R</i>)

Table 2. The electronic effect on asymmetric hydrocyanation of vinylarenes

Substrate	Ligand (% ee) ^a			
	1a	1b	1c	1d
2-methoxy-6-vinylnaphthalene	85–91	78 ^b	35 ^c	16 ^c
2-vinylnaphthalene	77	75	46 ^c	25 ^c
1-vinylnaphthalene	68	–	63	–
acenaphthene	59	–	0	–
3-fluoro-4-phenylstyrene	55	–	10 ^c	–
4-isobutylstyrene ^d	56	38	6	–
4-trifluoromethylstyrene ^d	14	9	1	–

^a0.10–0.20 M alkene, 1.0–5.0 mol% Ni(COD)₂/L in hexane. ^bToluene. ^cBenzene. ^d0.65 mmol alkene, 0.020 mmol Ni(COD)₂, 0.020 mmol ligand, 0.65 mmol HCN in 5 mL hexane, 24 h

cyantion of a number of vinylarenes using *o*-, *m*-, and *p*-substituted gluco-dia-rylphosphinite ligands (1a–d) led to the unexpected discovery that the electronic characteristics of the phosphorus-aryl substituents had a much greater impact on the enantioselectivity than the inherent size of the group [6]. This electronic effect can be seen clearly from the result obtained using *m*-disubstituted ligands (1a–d, Fig. 2), as shown in Table 2. The ees increased dramatically (from 16% to >85% for MVN) as the electron-withdrawing power of the *P*-aryl substituent increased (for 1a–d, $\sigma_m = -0.07, 0, 0.34, 0.43$, respectively).

The asymmetric hydrocyanation of a series of *p*-substituted styrene derivatives showed that indeed the electron-deficient catalyst gave the highest ees in every case (e.g. for 4-methylstyrene: **1a** – 70%; **1b** – 47%; **1c** – 1%). Yet the electronic nature of the substrate also seems to play an important role. For example, the following % ees were observed using **1a** for a series of substituted styrenes: 4-Me – 70; 4-Ph – 68; 4-phenoxy – 60; 4-*iso*-Bu – 56; 4-MeO – 52; 4-Cl – 40; 4-F – 28; 4-CF₃ – 14.

5

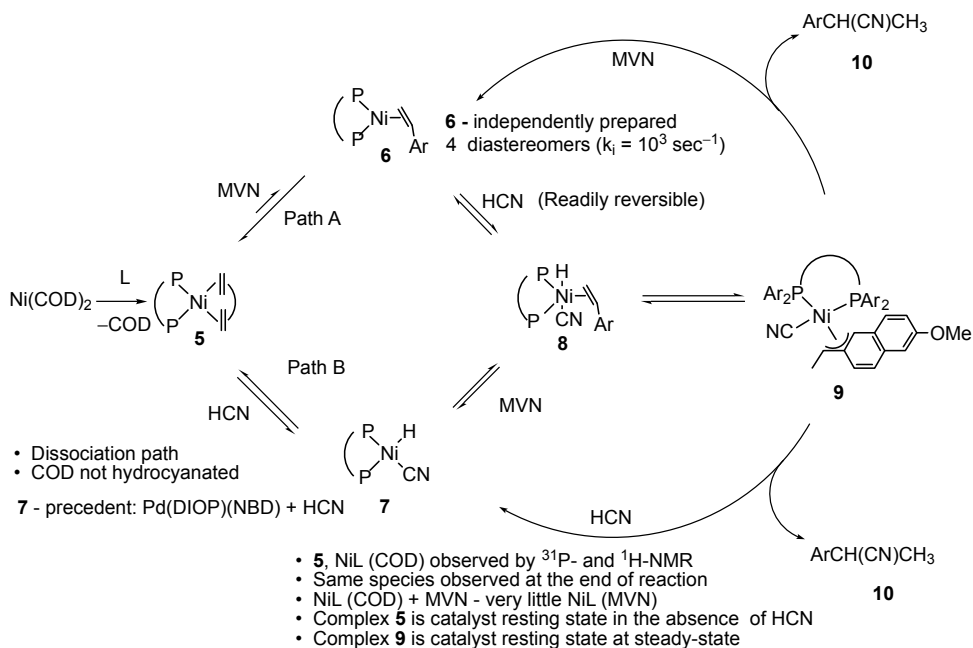
Reaction Mechanism [7]

5.1

The Catalytic Cycle

Based on the extensive studies reported for the triaryl phosphite-nickel complex catalyzed hydrocyanation of alkenes [1] and our own findings, we propose a general catalytic cycle shown in Scheme 5 for the Ni(COD)₂/L/MVN system. This simplified catalytic cycle is meant to encompass the various diastereomeric pathways generated by the ligand C₁ symmetry.

All available data implies that the catalyst comprises a single chelating ligand and one vinylarene. We synthesized a series of Ni-(**1a**)-alkene complexes (alkene = COD, *trans*-stilbene, diphenylacetylene, MVN), all of which function as cata-



Scheme 5

lysts for the asymmetric hydrocyanation of MVN. The enantioselectivities depend only on the ligand used. Bis-chelate complexes Ni-[**1a**]₂, Ni-[**1c**]₂, and a carbonyl complex [1a]-Ni(CO)₂ were either catalytically inactive or much less active. The bis-CO complex can be heated with MVN in toluene to produce Ni-[1a]-(MVN) which is catalytically competent and gives the same ee as the Ni-[1a]-(COD) complex **5**.

The complex Ni-[1a]-(MVN), **6**, which is proposed as a catalyst loop species, exists in solution as a mixture of rapidly equilibrating diastereomers and was characterized by variable temperature ³¹P-NMR spectroscopy.

The ee is independent of conversion, catalyst loading, and addition of other substrates, Lewis bases such as THF, 2-Me-THF, or enriched nitriles. It can be concluded that auxiliary ligands do not coordinate to NiL during any of the enantioselective steps.

The entrance into the catalytic cycle from complex **5** may occur via a small equilibrium concentration of Ni-(1a)-(MVN) complex **6** (path A, Scheme 5) and/or via oxidative addition of HCN to generate the species Ni-[1a]-HCN, **7** (path B). In either event, formation of the hydridoalkene complex Ni-[1]-(MVN)(H)(CN), **8**, occurs and is followed by an insertion reaction to produce the (η³-benzyl)nickel cyanide intermediate **9**. Although this allyl-type species has not been directly detected, the exclusive formation of the branched nitrile supports its intermediacy. Analogous intermediates have been postulated in the hydrocyanation of 1,3-butadiene with Ni[P(O-*o*-tolyl)₃]₃ or Ni[P(OEt)₃]₄ and in the hydrocyanation of styrene with Ni[P(O-*p*-tolyl)₃]₄. Examples of other nickel-benzyl complexes exhibiting similar allylic interactions in the solution and solid state are also known.

The only completely irreversible step is the final reductive elimination of the product 2-arylpropionitrile (**10**) from **9**. Optically pure 2-arylpropionitrile subjected to the reaction conditions does not undergo epimerization.

5.2 Kinetic Studies

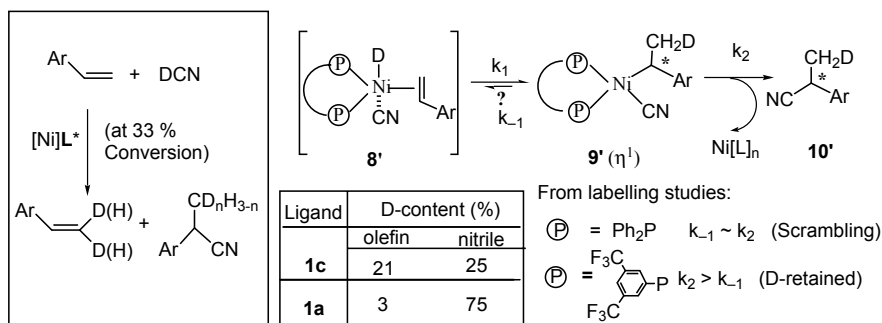
In a kinetic study, the reaction was found to be first order in MVN and HCN over concentration ranges below 0.04 M in each reagent. This saturation kinetics implies that the catalyst resting state shifts from Ni-[1a]-(COD), **5** (Scheme 5), to either **8** or **9**. Based on the known stability of the 18-electron allylic hydrocyanation intermediates (vide supra) and the exclusive regioselectivity of this reaction, we believe that complex **9** is the catalyst resting state under most hydrocyanation conditions. Under these saturation conditions, a maximum activity of 2000 turnovers/h (turnover=mol of nitrile/mol of nickel) was observed for the ligand **1a**. One of the minor complications of the reaction is the catalyst deactivation which removes Ni(0) from the system by an oxidative addition of HCN to form Ni(CN)₂. A practical consequence of this side reaction is that the catalyst life time is reduced to 700–800 turnovers, unless a fresh supply of Ni(COD)₂ is introduced into the medium.

5.3 Origin of Enantioselectivity

If the path A in Scheme 5 represents the significant kinetic route, then the earliest point in the mechanism where chiral recognition of MVN can occur is in the formation of the Ni-[1a]-MVN complex **6**. The ^{31}P -NMR spectrum of Ni-[1a]-MVN shows the presence of four diastereomers which result from the coordination of opposite faces of MVN to the C_1 symmetric Ni-[1a] group. Even though this ligand system gives very high enantioselectivity (92:8, for the two enantiomers corresponding to HCN addition to the *si* vs *re* faces of MVN) for the hydrocyanation of MVN, the equilibrium of diastereomers found in the ^{31}P -NMR shows that there is no large ground state differentiation between the two enantiofaces of MVN. These diastereomers will be equilibrated if the oxidative addition of HCN to **5** is much slower than the interconversion of the diastereomers. Although the rate of HCN addition to **5** has not been measured, the insensitivity of enantioselectivity to HCN concentration suggests that the diastereomers are under equilibrium control.

If path B in Scheme 5 predominates, the initial chiral recognition will occur in the formation of **8**. The rate of interconversion between the diastereomers of **8** is unknown; however, deuterium-labeling studies (vide infra) show that the formation of **8** could be readily reversible, at least with **1c** and **1d** as ligands.

Information about the relative rates of formation and disappearance of the undetected intermediate(s) NiL(MVN)(H)(CN) (**8**) and (**9**) were obtained by hydrocyanating 6-methoxy-2-vinylnaphthalene with DCN using catalysts prepared from Ni(COD) $_2$ and ligands **1a–d** (see Fig. 2). The reaction was stopped at ~33% completion and the unreacted starting material and products were isolated and the deuterium contents in both were determined by ^2H -, ^1H -, and $^{13}\text{C}\{^1\text{H}\}$ -NMR spectroscopy (Scheme 6). Only trace of deuterium incorporation into the recovered starting material is observed in the case of the electron-withdrawing phosphinite **1a**, which gave the highest ee. However, significant amount of deuterium incorporation was observed in the unreacted olefin when the more



Scheme 6

electron-rich phosphinite (**1c**) was used. The extent of scrambling correlates with the electron-withdrawing character of the phosphorus aryl substituent, increasing in the order **1a**<**1b**<<**1c**~**1d**. An explanation consistent with this observation starts from the assumption that the formation of the Ni[1](MVN)(H)(CN) complex is reversible. The labeling results are best explained if one assumes that in the case of the electron-withdrawing ligands **1a** or **1b** the enantioselective step, i.e., the first irreversible step involving the chiral catalyst, is the insertion of the olefin into the Ni-D bond. With the electron-deficient ligands, this step is followed by a fast reductive elimination of the product from the benzyl complex **9'** to give the product nitrile. In the case of the more electron-rich phosphinites, the reductive elimination is slow and the β -hydride elimination (**9'**→**8'**) effectively competes with the C-C bond formation (**9'**→**10'**). In this process either the D or the H from the methyl group can be removed as the Ni-hydride. Such a mechanistic scheme would provide a route for the extensive D-scrambling observed in these electron-rich systems, if one assumes that the vinylarene is readily liberated from **8'**.

6

Electronic Effects and Enantioselectivity [9]

The origin of the relation between higher enantioselectivities and electron-withdrawing aryl substituents must remain speculative because the rates of many of the fundamental steps and the precise structures of the intermediates are still largely unknown. The experimental evidence for the NiL system clearly shows that the enantioselectivity is not controlled by *direct* steric interactions between the *meta*- and *para*-P-aryl substituent and the alkene. Although such steric factors are the determinants of the sense of chiral induction, our data show that there is also a strong electronic component present in the NiL catalyst system that can be used to enhance the inherent preference for *S*- vs *R*-nitriles. We suggest that the barrier for the alkene insertion and/or reductive elimination of the final product is disproportionately lower for the *S*-pathways as the electron density at nickel is reduced, and that this is the origin of the electronic effect.

6.1

Effect of Electronic Asymmetry: Fine Tuning of a Ligand [10]

In the preliminary screening of various carbohydrate frame works we discovered that 3,4-bis-diarylphosphinites from methyl α - and β -D-fructofuranosides gave the *R*-nitrile upon Ni(0)-catalyzed hydrocyanation of MVN (Table 1, entry 3). We reasoned that the methyl α -fructofuranoside is an especially attractive scaffolding for further fine-tuning of the ligand by virtue of the fact that the two hydroxy groups (C3 and C4) are placed in completely different steric environments. Accordingly, we prepared a series of electronically 'symmetrical' and 'unsymmetrical' bis(diaryl)phosphinite ligands from this sugar as shown (Fig. 3). Several of these ligands have the unique feature that the steric effects

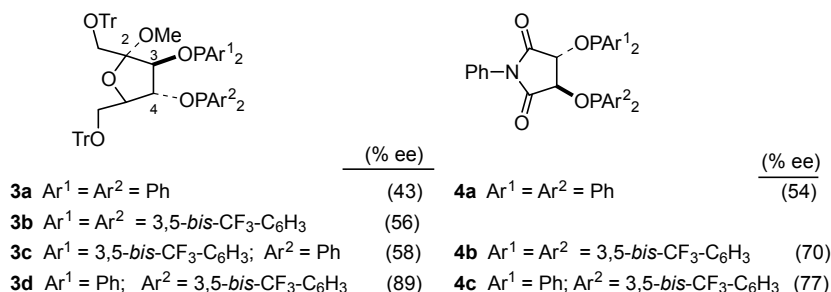


Fig. 3. Enantioselectivity for electronically unsymmetrical ligands

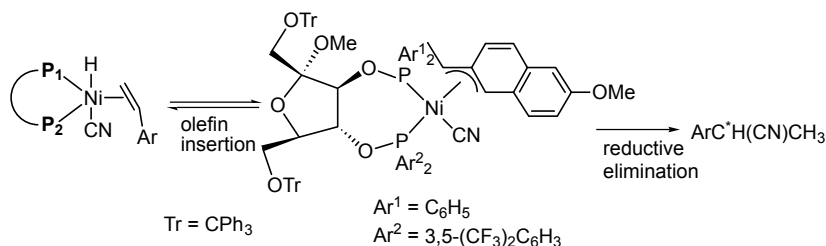


Fig. 4. Benzyl intermediates with an electronically unsymmetrical ligand

around the two chelating phosphorus atoms are largely kept constant, while the relative electron densities on these atoms can be systematically varied [10]. Results of hydrocyanation of MVN are also shown in Fig. 3.

As anticipated from our previous work, electron-donating substituents on the phosphorus aryl groups give the lowest ees. Electron-deficient phosphinites increase the selectivity to some extent. But the highest ee was obtained with C4 carrying the electron-deficient phosphinite and C3 the electron-rich one. Electron-rich phosphorus on C4 and electron-deficient P on C4 gave only marginal ee. Several other examples [10] of electronically unsymmetrical phosphinites in the fructose series corroborate this general trend. A similar observation was also made using (3*S*,4*S*)-tartranil phosphinites (Fig. 3); the highest ee, 77% (*S*), was obtained with a mixed phenyl/3,5-bis(trifluoromethyl)phenyl derivative (**4c**) whereas the C₂-symmetric phenyl and 3,5-bis(trifluoromethyl)phenyl derivatives **4a** and **4b** gave 54 and 70% ee, respectively.

As we have argued before, if the primary effect of electron-withdrawing phosphorus aryl substituents is to accelerate the final reductive elimination, then the enhancement of enantioselectivity may result because one of the diastereomers of the benzylic complex (Fig. 4) may be disproportionately affected. The precise factors favoring a particular diastereomer (its formation or its decomposition) are presently unclear, but the results with the α -methyl fructofuranoside ligand frame strongly suggest the importance of a *stereo-electronic* component. For example, the effect of electronic asymmetry may reflect the importance of a *trans*

relationship between the η^3 -aryl fragment and the phosphorus bearing the electron-withdrawing aryl groups (Fig. 4).

7

Asymmetric Hydrocyanation of Vinylarenes: Some Practical Considerations

The nickel catalyst derived from **1a** (Fig. 2) can be used for hydrocyanation of 2-methoxy-6-vinylnaphthalene and other vinylarenes giving nearly quantitative conversions to the corresponding nitriles. In all of the reactions we have attempted, including those of the naproxen, ibuprofen, and ketoprofen precursors, no polymerization of the olefins or formation of the linear nitriles was observed. The latter is a major limitation of the analogous Rh-catalyzed hydroformylation route to profen drugs [11]. Enantioselectivity remains modest for all vinylarenes other than MVN, and further optimization will be needed for these substrates. For MVN, both nitrile isomers have been produced in over 90% ee. The enriched nitriles can be recrystallized to provide optically pure (>99.5%) naproxen nitrile which can be converted into (*S*)-naproxen in a two step process which involves treatment with diisobutylaluminum hydride followed by oxidation of the intermediate imine with NaClO_2 . Improvements in the yield of this recrystallization and a more cost-effective acid hydrolysis would be highly desirable for the manufacture of the drug. Such a hydrolysis reaction has some precedent in the area of cyanohydrin and aminonitrile hydrolysis [12]. For example, 4-methoxymandelonitrile can be hydrolyzed to the corresponding acid without racemization. Another important consideration is the catalyst turnover. Life time of the Ni-(**1a**)-(COD) is limited to 700–800 turnovers in the asymmetric hydrocyanation of MVN due to oxidative addition of HCN to Ni(0) giving catalytically incompetent $\text{Ni}(\text{CN})_2$ with dissociation of the ligand. However, we have been able to obtain up to 4400–5000 turnovers in the more expensive ligand by periodically feeding more $\text{Ni}(\text{COD})_2$ to the reaction mixture. Other important technical and economical issues related to large scale production are the availability and cost of MVN, $\text{Ni}(\text{COD})_2$, and $[3,5\text{-bis-CF}_3\text{-C}_6\text{H}_3]_2\text{PCL}$. However, it should be emphasized that preliminary cost estimates suggest that none of these are insurmountable, considering ambient reaction conditions, the high catalyst turnover frequency and the exquisite selectivity of the reaction. The cost of the ligand precursor (*D*-glucose), and the ease of post-reaction recovery of the products should also make this a very attractive route for the production of *S*-naproxen.

8

Asymmetric Hydrocyanation: Future Prospects

Hydrocyanation of other functional groups such as aldehydes and imines have also been carried out. An industrial process for the synthesis of the pyrethroid insecticide ASANA depends on a cyclic dipeptide-mediated addition of HCN to

m-phenoxybenzaldehyde, a reaction pioneered by Inoue [12, 13]. Asymmetric Strecker reaction for the synthesis of amino acids is yet another application of related chemistry [14].

In the metal catalyzed hydrocyanation area, the stage is set for major improvements in enantioselectivity for simple styrene derivatives. Asymmetric hydrocyanation of dienes and functionalized olefins is another exciting area ripe for further explorations.

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Chapter 11

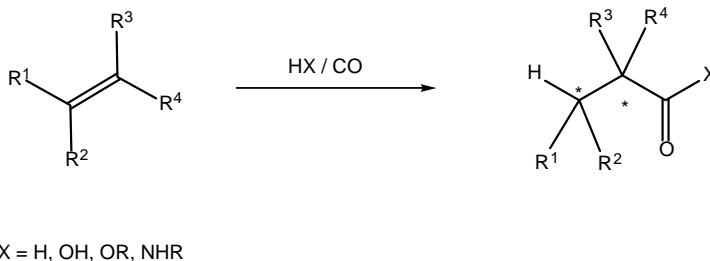
Hydrocarbonylation of Carbon-Carbon Double Bonds

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Keywords: Olefins, Carbonylation, Hydroformylation, Hydrocarboxylation

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Scheme 1. A general scheme for asymmetric hydrocarbonylation

1 Introduction

Hydrocarbonylation is now one of the most important industrial processes using homogeneous transition metal catalysts. The reaction introduces a new C-C bond as well as a functional group into a substrate. Recently, asymmetric hydrocarbonylation of olefins, which is possible only with a man-made catalyst, is attracting much attention because the products, optically active aldehydes, carboxylic acids, and their derivatives, are very important as precursors for a variety of fine chemicals. Among them, the asymmetric hydroformylation reaction has been most extensively examined. In the last decade, this area has made remarkable progress in improving catalytic activity and selectivities, i.e., chemo- (hydroformylation vs hydrogenation), regio- (mainly *iso* vs *normal*), and enantioselectivity. This chapter mostly focuses on the recent advances in the area of asymmetric hydroformylation (Scheme 1). Related asymmetric hydrocarbonylation reactions are also mentioned.

2 Hydroformylation

2.1 Overview

Since its discovery by Roelen in 1938 [1], the hydroformylation process was exclusively based on cobalt as catalyst metal, until the development of rhodium-phosphine complexes in the late 1960s [2]. Industrial efforts have been focused on the preparation of *normal*-aldehydes (linear aldehydes) from 1-alkenes. In contrast, asymmetric hydroformylation, which requires *iso*-aldehydes (branched aldehydes) to be formed from 1-alkenes, was first examined in the early 1970s by four groups independently, using Rh(I) complexes of chiral phosphines as catalysts [3, 4, 5, 6]. Since then, a number of chiral ligands have been developed for

asymmetric hydroformylation and used in combination with transition metal ions, especially Pt(II) and Rh(I). Some of the representative chiral catalysts discussed in this chapter are shown in Fig. 1 along with their abbreviations. A general scheme is shown in Scheme 2. Asymmetric hydroformylation of 1-alkenes has been the most extensively studied reaction.

Although the “first generation” catalysts were Rh(I) complexes of chiral ligands, Pt(II) was considered to be the superior metal in asymmetric hydroformylation until the early 1990s. Using a chiral bisphosphine-PtCl₂ complex as a cata-

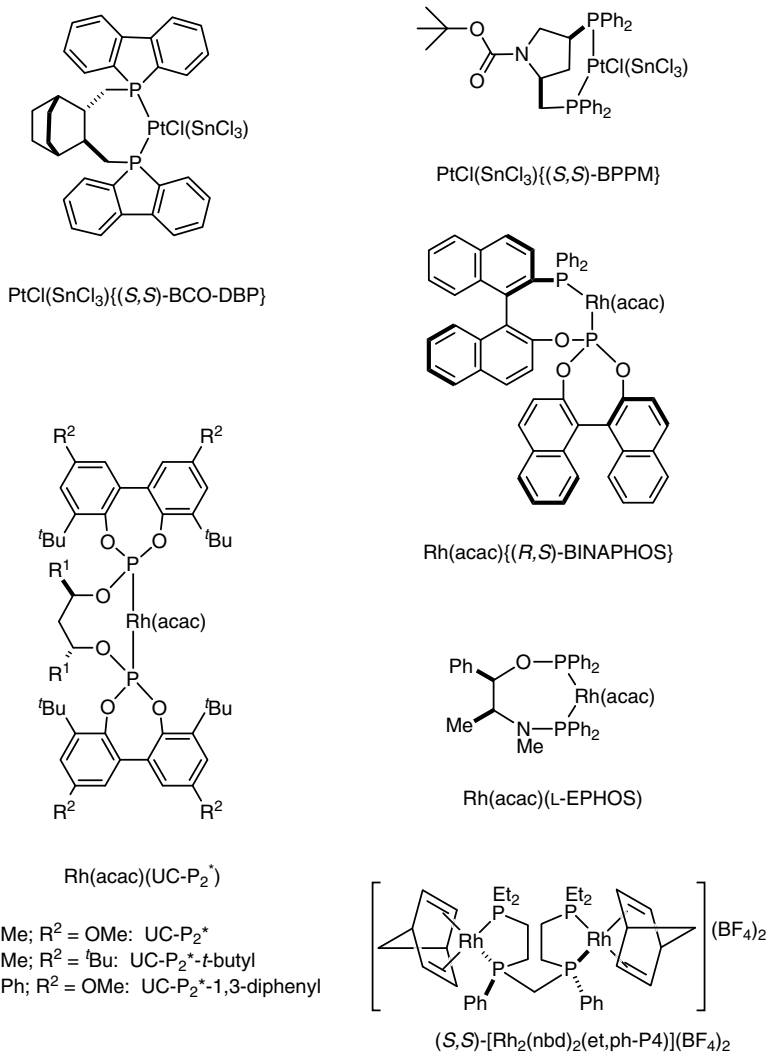
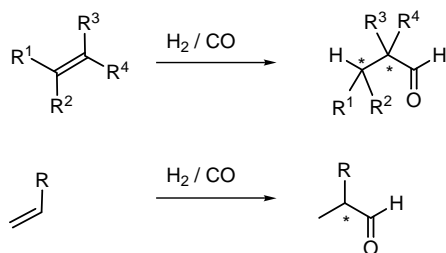


Fig. 1. Examples of chiral catalysts used in asymmetric hydroformylation



Scheme 2. General schemes for asymmetric hydroformylation

lyst, higher activity and improved *iso/normal*-selectivity were achieved by addition of a Lewis acid such as SnCl_2 , which provides a new species, $\text{PtCl}(\text{SnCl}_3)$ (bisphosphine) [7]. This “second generation” catalyst reached the highest level of % ee (up to 96% ee) in the asymmetric hydroformylation of styrene in 1991, as was reported by Stille [8] and by Consiglio [9]. They utilized PtCl_2 complexes of the chiral bisphosphine ligands, BPPM and BCO-DBP, respectively, in combination with SnCl_2 . Unfortunately, however, the catalysts suffer from low *iso*-selectivity, competitive hydrogenation, or low catalytic activity. In addition, application of these catalysts to the asymmetric hydroformylation of other olefins, such as heteroatom-substituted or aliphatic alkenes, resulted in low enantioselectivities. Nevertheless, the results were remarkable at that time and the achievements have been summarized in an excellent review article [10]. Continuous developments in this area are still being made, as can be seen from recent publications [11, 12, 13].

Under these circumstances, the “third generation” catalysts, Rh(I)-chiral bisphosphites and Rh(I)-chiral phosphine-phosphites, have been developed in 1992–1993. Apart from the asymmetric aspect, it was reported in the 1980s that rhodium(I) complexes of phosphites, especially those bearing bulky substituents, showed high activities in the hydroformylation of 1-alkene to give *normal*-aldehydes [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. This “phosphite revolution” in achiral aldehyde synthesis led to remarkable advances in the asymmetric hydroformylation area. Thus, the “third generation” catalysts, Rh(I) complexes of chiral phosphites or related ligands, have been developed. Chiral variants of bidentate phosphites first appeared in the patent literature in 1992. Babin and Whiteker reported the hydroformylation of styrene in up to 90% ee using chiral bisphosphites UC- P_2^* and derivatives as ligands although the ees observed for other substrates, such as 1-hexene and vinyl acetate, were not satisfactory (50 and 20%, respectively) [27]. Since then, intensive efforts have been devoted by van Leeuwen and others to the development of more efficient catalysts based on chiral phosphites and phosphinites [28, 29, 30, 31, 32].

At this stage, Rh(I) catalysts became the most promising candidates for the asymmetric hydroformylation in comparison with Pt(II) catalysts. In 1992, the authors reported the use of a chiral bisphosphite derived from binaphthol for the

asymmetric hydroformylation of vinyl acetate [31]. Although the enantioselectivity stagnated around 50% ee, an interesting difference was observed between the reaction with the bisphosphite and that with the bisphosphines. With bisphosphine ligands, at least 3 to 6 equivalents (based on Rh) of the ligand were required to achieve the highest % ee obtainable with the ligand, because dissociation of the chiral phosphine produces “unmodified Rh species” which are active for hydroformylation to produce racemic aldehydes. On the other hand, with the bisphosphite in the above mentioned study, 1.1 equivalents were sufficient to give the product in 45% ee, the highest level of enantioselectivity achieved with this ligand [31]. This observation prompted the authors to synthesize chiral phosphine-phosphite ligands, (*R**,*S**)- and (*R**,*R**)-BINAPHOSes, which were expected to combine the high enantioselection obtained with bisphosphines, e.g., BINAP in asymmetric hydrogenation, with the apparently efficient coordination of the phosphite moiety [33]. Thus, somewhat unexpectedly, a Rh(I) complex of one of the two diastereomers, (*R**,*S**)-BINAPHOS, provided much higher enantioselectivity than bisphosphine- or bisphosphite-complexes, mostly above 90% ee, for a wide variety of substrates. Practical examples will be described in the latter part of this chapter. In most cases, 2.0–2.5 equivalents were sufficient to achieve the highest enantioselectivities. Another characteristic feature of the phosphine-phosphite ligand is its unsymmetrical structure. Since the invention of DIPAMP, DIOP, and BINAP as excellent ligands for asymmetric hydrogenation, ligand design had been shackled to the principle of C_2 symmetry [34]. Rather surprisingly, a chiral phosphine-phosphite ligand (*R,S*)-BINAPHOS, an unsymmetrical bidentate ligand, achieved the highest level of ees as well as satisfactory regioselectivity and catalytic activity for a wide variety of olefins. The results are promising and encouraged by the success of (*R,S*)-BINAPHOS, other unsymmetrical ligands were prepared and applied to asymmetric hydroformylation [35, 36, 37, 38].

A recent example of another class of interesting catalyst was reported by Stanley, namely a bimetallic Rh complex provided by a tetrakisphosphine ligand. Up to 85% ee has been achieved in the hydroformylation of vinyl carboxylates, although the applicable substrates are still limited [39]. As a bimetallic system, the chiral dithiolate-bridged dinuclear Rh complex has been described with results of up to 10% ee for styrene [40]. Addition of chiral bisphosphine to the dithiolate-Rh system improved the ee up to 55% [41], but in this case, the dissociation of the two Rh centers into monometallic species has been claimed recently [42]. In this article, emphasis is placed on the third generation Rh(I) catalyst and the earlier generations are mentioned only briefly. Excellent review articles are available on the latter topics [10, 36, 43, 44, 45, 46, 47, 48].

2.2

Mechanism of Catalysis

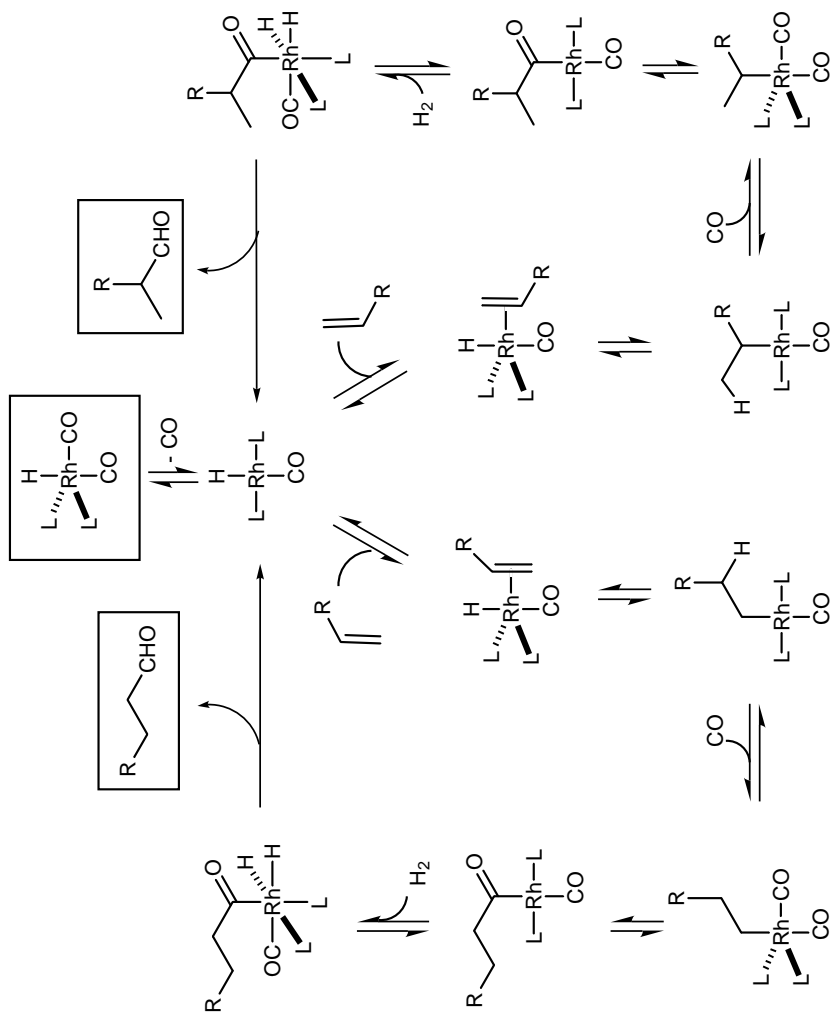
2.2.1

Mechanism of Hydroformylation Catalyzed by Rh(I)-Phosphine Complexes

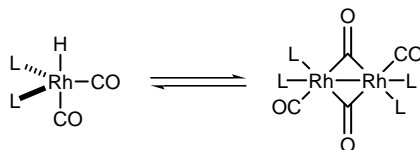
The dissociative mechanism, first proposed by Wilkinson, is now most generally accepted for bidentate phosphine-Rh(I) catalyzed hydroformylation [49]. For monodentate phosphine complexes, the associative mechanism is often applied [49]. In spite of intensive studies from theoretical viewpoints [50, 51], difficulties arise in attempts to establish a “general theory” because the mechanism, especially the relative reaction rate of each step, varies depending on the reaction conditions, such as employed ligands, H₂ and CO pressures, solvents, and temperatures [17, 52, 53, 54]. The discussions in this chapter mainly rely on Wilkinson's dissociative mechanism shown in Scheme 3. The left and right cycles produce *normal*- and *iso*-aldehydes, respectively.

Regardless of the anionic ligand attached to Rh in a catalyst precursor, the rhodium hydride complex RhH(CO)₂(phosphine)₂ is produced as a key intermediate in the catalytic cycle. Dissociation of CO from the complex gives the unsaturated species RhH(CO)(phosphine)₂, which accepts the coordination of an olefin. Olefin insertion into the Rh-H bond generates the alkylrhodium complex Rh(alkyl)(CO)(phosphine)₂. Coordination of one more CO molecules is followed by migratory insertion of the alkyl group to one of the coordinated CO fragments. Oxidative addition of H₂ and reductive elimination of the product aldehyde completes the catalytic cycle. In some reports, a bimetallic process, RC(=O)MLn + LmMH → RC(=O)H + LmM-MLn, is suggested in which the cycle avoids the oxidative addition of H₂ to the acylrhodium complex [17, 55, 56, 57].

A higher H₂ pressure often accelerates the reaction in Rh-phosphine catalyzed systems [58]. On the basis of these data, the oxidative addition of H₂ was suggested to be the rate-determining step by Wilkinson. Recently, a more pertinent interpretation of these data has been reported [42, 59]. A rhodium phosphine complex, RhH(CO)₂(phosphine)₂, often forms a dimeric species under the H₂/CO atmosphere (Scheme 4) [60]. The active species is the monometallic one and the process of dissociation of the dimer by hydrogenolysis influences the reaction rate, especially at a high concentration of Rh and low pressure of H₂. Similarly, a higher CO pressure often results in a depressed reaction rate. This should be attributed to the fact that the dissociation of CO from RhH(CO)₂(phosphine)₂ is required to continue the cycle. Considering these facts, steps independent from the pressures of H₂ or CO, e.g., the olefin coordination/insertion to Rh-H complex can be the rate-determining step.



Scheme 3. Wilkinson's dissociative mechanism for hydroformylation of olefins catalyzed by a phosphine-Rh(I) complex



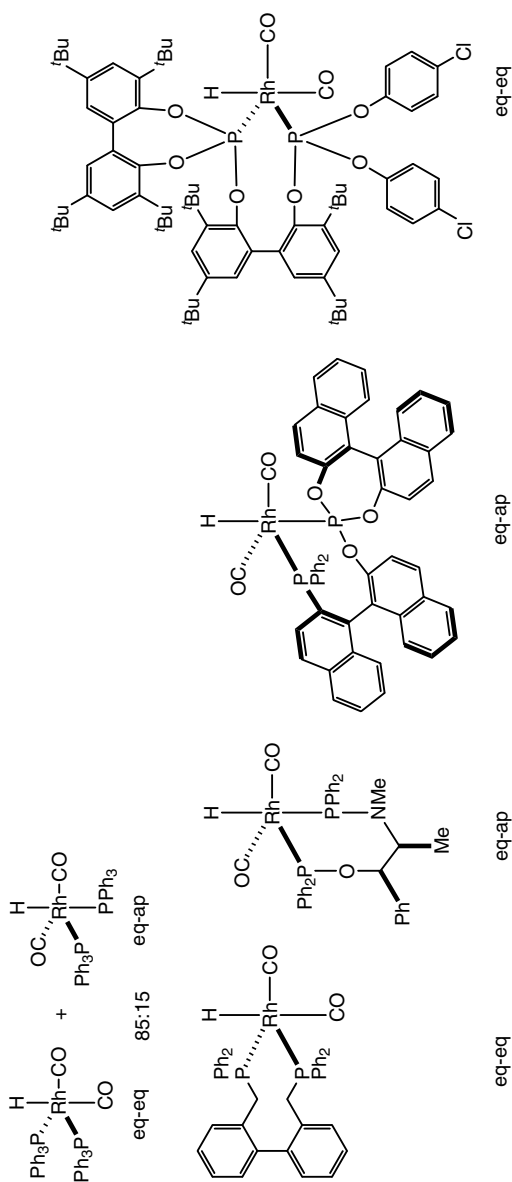
Scheme 4. A suggested dimer formation which causes loss of catalytic activity

2.2.2

Structure of $\text{RhH}(\text{CO})_2\text{L}_2$

It is considered essential to form a single catalytically active species in order to achieve high selectivity, because multiple species would give different products via different reaction pathways. With monodentate phosphines, Brown and Kent have reported that $\text{RhH}(\text{CO})_2(\text{PPh}_3)_2$ exists as an 85:15 mixture of two isomers at -55°C in which the two phosphines are placed on equatorial-equatorial and equatorial-apical positions, respectively (Structure 1) [61]. At higher temperatures, these two isomers are present in a rapid equilibrium. The work by the Eastman Kodak group [62] and by Casey [63, 64, 65] is noteworthy from the viewpoint of controlling the distribution of these two species. They investigated a bidentate ligand which binds to Rh(I) in an equatorial-equatorial fashion and was suitable to give higher regioselectivity to *normal*-aldehydes from aliphatic 1-alkenes [63, 64]. The concept of the natural bite angle affected the ligand design work of other researchers [65].

On the basis of these studies, the structure of $\text{RhH}(\text{CO})_2\text{L}_2$ became a topic of interest. Mortreux and Petit first investigated the structure of a Rh(I) complex bearing an unsymmetrical bidentate ligand [66]. Using a chiral aminophosphine-phosphinite, they prepared a $\text{RhH}(\text{CO})_2(\text{ligand})$ complex and determined its structure to be a trigonal bipyramidal in which the aminophosphine and the hydride occupy the two apical positions. Similarly, Takaya and Nozaki found that $\text{RhH}(\text{CO})_2[(R,S)\text{-BINAPHOS}]$ exists as a single species in which the phosphine occupies an equatorial position and the phosphite an apical one, being *trans* to the hydride. This particular complex $\text{RhH}(\text{CO})_2[(R,S)\text{-BINAPHOS}]$ is indeed active for the asymmetric hydroformylation, demonstrating that it is most likely an intermediate involved in the catalytic cycle. A proposal that the existence of a single species is essential to achieve high ee has been established [67, 68]. The principle of a unique coordination mode of $\text{RhH}(\text{CO})_2\text{L}_2$ was also applied to the Rh-chiral phosphite system. Van Leeuwen and his coworkers reported an X-ray structure of $\text{RhH}(\text{CO})_2\text{L}_2$ in which L is a bulky bisphosphite [22, 69]. Two phosphorus atoms occupy the equatorial positions of the central Rh atom, and the hydride and one of the two carbonyls are at the apical positions. Systematic studies were carried out by the same research group on the relation between the structure of the chiral bisphosphite ligands and the enantioselectivities obtained with Rh(I) complexes of these ligands in the asymmetric hydroformylation of styrene [28, 29, 30]. It is concluded that the highest enantioselectivities are obtained when the ligand exclusively coordinates in an equatorial-equatorial fashion. The coexistence of an equatorial-apical isomer reduces the ees. It should be noted that the reaction step responsible for the enantioselection of the product aldehyde is not directly related to the structure of $\text{RhH}(\text{CO})_2\text{L}_2$ (*vide infra*). Nevertheless, it is interesting to find that the ligands which form rigid $\text{RhH}(\text{CO})_2\text{L}_2$ complexes seem to give high enantioselectivities in asymmetric hydroformylation.

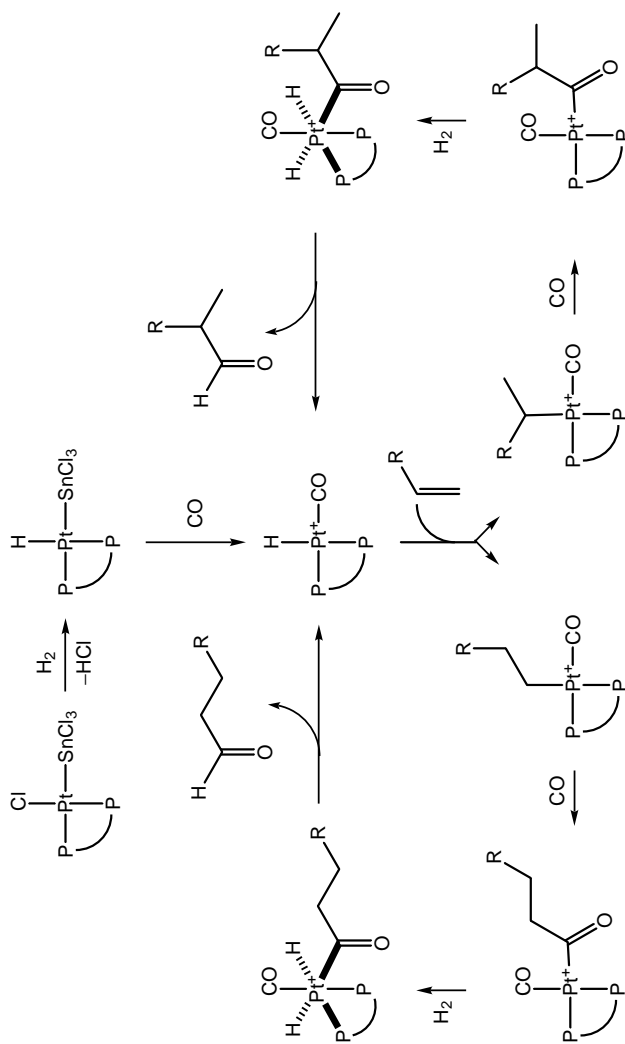


Structure 1. Structures of $\text{RhH}(\text{CO})_2(\text{L})$

2.2.3

Mechanism of Hydroformylation Catalyzed by Pt(II)-Ligand Complexes

Hydroformylation with platinum complexes proceeds as described in Scheme 5 when a Lewis acid, e.g., SnCl_2 , is added. The Lewis acid removes the chloride from the platinum center to afford a vacant coordination site to which the olefins can coordinate. Asymmetric induction occurs during the formation of alkyl intermediates via olefin insertion into the Pt-H bond [8]. Most importantly, the regio- and enantioselectivities are strongly influenced by the reaction temperature in the Pt(II)-catalyzed asymmetric hydroformylations [10, 70, 71, 72, 73]. Re-



Scheme 5. A proposed mechanism for the Pt-catalyzed hydroformylation of olefins

cently, the use of a Pt-bisphosphite catalyst was also reported to give high % ees [74].

2.3

Basis for Stereinduction

If one wants to discuss the enantioselectivity of the reactions, it is essential to know which step is irreversible or rate determining in the catalytic cycle. In the case of hydroformylation, each step seems to vary its rate depending on the reaction conditions as was mentioned before. The basis for stereinduction should thus only be discussed with careful consideration of these points.

2.3.1

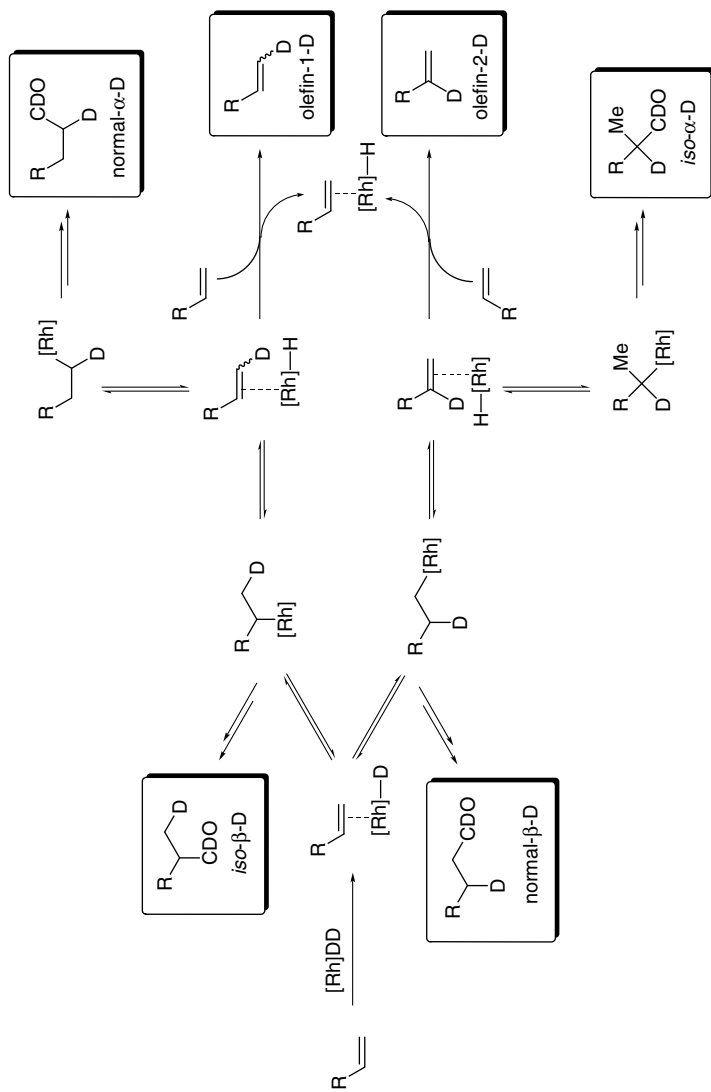
Deuterioformylation

Deuterioformylation is one of the best methods to disclose the reversibility of olefin insertion (Scheme 6) [75]. If it is reversible, the recovered olefin may contain deuterium on an sp^2 carbon and the product aldehydes may have deuterium at both α - and β -positions of the formyl group. If not, the olefin should contain no deuterium and the β -position of the formyl group must contain one deuterium. In the latter case, asymmetric induction takes place either when the olefin coordinates to the Rh center or at the transition state of olefin insertion into the Rh-H bond. In the former case, on the other hand, the catalytic cycle would behave in a Curtin-Hammett manner in which two or more diastereomeric intermediates are in rapid equilibrium and the major enantiomer would be produced from the more reactive intermediate. Generally, the reversibility of the olefin insertion varies depending on the substrates and the reaction conditions [54]. For example, in the asymmetric hydroformylation with Rh(I)-(R,S)-BINAPHOS, it is irreversible for 1-hexene at the H_2 -CO total pressure of 1–100 atm but is partially reversible for styrene at a total pressure of 1 atm [76]. The spin-labeling method was successfully utilized by Gladfelter and coworkers in order to prove the reversibility of olefin insertion into Rh(I)-H in an achiral bidentate phosphite complex. In this study, they reported that the olefin insertion to Rh-H is highly reversible with their bisphosphites [55].

2.3.2

Proposed Models for the Enantiofacial Selection

In the case that the olefin insertion into a Rh-H bond is irreversible, the enantioface of a prochiral olefin is discriminated during this step. Thus, the structure of the Rh complex at the transition state becomes important. Here, we introduce an example of a theoretical approach most recently reported by Herrmann and his coworkers [77, 78]. The two structures shown in Fig. 2 as TS I and TS II illustrate the possible transition states of olefin insertion into $RhH(CO)\{(R,S)\text{-BINAPHOS}\}$. Density functional theory calculations on model rhodium complexes bearing



Scheme 6. Deuterioformylation reveals the reversibility of the olefin insertion

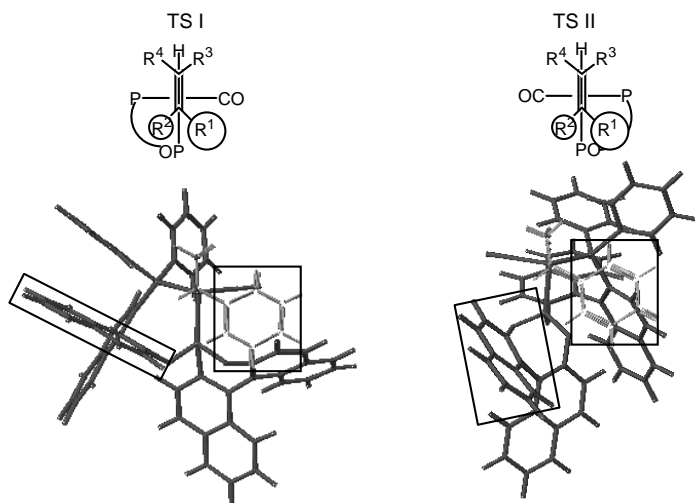


Fig. 2. Upper: Two possible transition states, namely TS I (left) and TS II (right) for an olefin ($R^1R^2C=CR^3R^4$) insertion into the Rh-H bond of $RhH(CO)[(R,S)\text{-BINAPHOS}]$. Lower: Transition states TS I (left) and TS II (right) for styrene (gray lines) insertion into the Rh-H bond of $RhH(CO)[(R,S)\text{-BINAPHOS}]$ (black lines). *Re*-face bindings to Rh are calculated to show lower energy levels than *si*-face bindings in both TS I (by 7.1 kcal/mol) and in TS II (by 1.8 kcal/mol). In both structures, the facial selection seems to arise from the steric repulsion between the phenyl group of styrene and one of the naphthyls of $(R,S)\text{-BINAPHOS}$ (marked with rectangles)

PH_3 ligands were followed by force field calculations on the “real” system. In this manner, it was concluded that both transition states TS I and TS II show lower energies for *re*-face than *si*-face styrene insertion. An interesting issue of this work is that the $RhH(CO)\{(R,R)\text{-BINAPHOS}\}$ would result in *si*-face selection by TS I and *re*-face selection by TS II. This matches the experimental results that the $Rh\text{-}(R,R)\text{-BINAPHOS}$ complex gives aldehydes in much lower ees than the $Rh\text{-}(R,S)\text{-BINAPHOS}$ complex. Similarly, the enantioselectivity observed for (*Z*)-2-butene was nicely explained with the same model.

2.4

Scope and Limitations

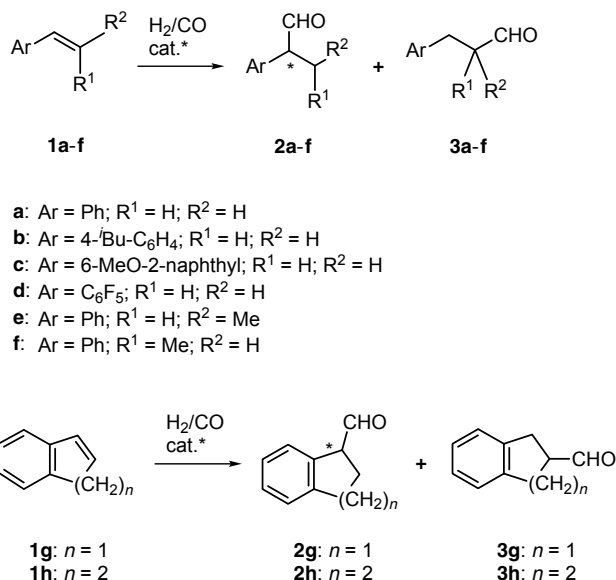
Representative examples of asymmetric hydroformylation are summarized in this section.

2.4.1

Asymmetric Hydroformylation of Arylalkenes

Styrene and its derivatives have been most intensively studied as substrates for asymmetric hydroformylation because of their high reactivity and high selectiv-

ity for *iso*-aldehydes. Furthermore, the *oxo*-aldehydes derived from these olefins can be converted to various pharmaceuticals such as non-steroidal anti-inflammatory drugs (NSAID) [44, 79]. Some of the representative results obtained for the asymmetric hydroformylation of styrene (**1a**) are summarized in Scheme 7 and Table 1. Chiral bisphosphine complexes of Pt(II) are used in the presence of 2–3 equivalents of SnCl₂. With PtCl₂-SnCl₂-(*R,R*)-BCO-DBP, the regioselectivity *iso/normal*=80/20 and the enantioselectivity of 85% ee (*S*) for *iso*-aldehyde were achieved, but the chemoselectivity to aldehydes was rather low (67%) and hydrogenated compounds were obtained as byproducts (run 1) [9]. Asymmetric hydroformylation with PtCl₂-SnCl₂-(*S,S*)-BPPM produces the corresponding aldehydes with lower regioselectivity, *iso/normal*=31/69 (run 2) [8]. Racemization of the product aldehyde was observed due to an epimerization of the chiral center under the acidic conditions. In order to avoid this epimerization, Stille used CH(OEt)₃ as solvent so that the product aldehyde could be trapped as the corresponding diethyl acetal (run 3). The reproducibility of the CH(OEt)₃ effect is argued by Consiglio in his review article [43], although the editor of his article, Ojima, comments that the reported results were confirmed. In any case, this method may not be recommended from a practical viewpoint because the reaction proceeds extremely slowly in CH(OEt)₃. The (*S,S*)-BPPM catalyst was successfully applied to the asymmetric hydroformylation of 2-vinyl-6-methoxynaphthalene, giving *iso/normal*=41/59, >96% ee [80]. Noteworthy for the Pt system is the temperature dependency of the regio- and enantioselectivities [10]. This



Scheme 7. Arylalkenes

Table 1. Hydroformylation of styrene (**1a**) and its derivatives (**1b–h**) catalyzed by chiral Pt(II) or Rh(I) complexes

run	substrate	catalyst	CO/H ₂ atm/atm	temp °C	conv % (time, h)	TOF ^a ×10 ⁻³	iso/nor- mal/2/3	% ee of 2 (config.)	Refer- ence
1	styrene (1a)	PtCl(SnCl ₃){(R,R)-BCO-DBP}	70/140	60	95 (2.3) ^b	41	80/20	85 (S)	9
2		PtCl(SnCl ₃){(S,S)-BPPM}	80/80	60	40 (4)	4.0	31/69	70 (S)	8
3		PtCl(SnCl ₃){(S,S)-BPPM} ^c	80/80	60	100 (150)	0.27	33/67	>96 (S)	8
4		Rh(acac){(R,R)-UC-P ₂ [*] }	19/19	25	nr ^d	e	98/2	90 (S)	27
5		Rh(acac){(R,S)-BINAPHOS}	50/50	60	>99 (40)	>47	88/12	94 (R)	67
6		Rh(acac){(R,S)-BINAPHOS}	5/5	40	52 (5)	100	90/10	94 (R)	76
7		Rh(acac){(S,R)-BIPHEMPOS}	50/50	60	>99 (42)	>2.4	90/10	94 (S)	81
8	4 ⁻ Bn-styrene (1b)	Rh(acac){(R,R)-UC-P ₂ [*] }	15/5	nr ^d	nr ^d	f	99/1	82 (S)	27
9		Rh(acac){(S,R)-BINAPHOS}	50/50	60	>99 (66)	1.5	88/12	92 (S)	67
10	2-(6-MeOC ₁₀ H ₆)CH=CH ₂ (1c)	Rh(acac){(R,R)-UC-P ₂ [*] }	15/3	nr ^d	nr ^d	g	99/1	85 (R)	27
11	C ₆ F ₅ CH=CH ₂ (1d)	Rh(acac){(R,S)-BINAPHOS}	50/50	30	85 (44)	1.9	97/3	96 (R)	67
12	(E)-PhCH=CHMe (1e)	Rh(acac){(R,S)-BINAPHOS}	50/50	80	48 (61)	0.79	98/2	80 (R)	67
13	1e +(Z)-PhCH=CHMe (1f) (1:1)	Rh(acac){(R,S)-BINAPHOS}	50/50	80	53 (38)	1.4	78/22	79 (R)	67
14	indene (1g)	Rh(acac){(S,R)-BIPHEMPOS}	50/50	60	62 (20)	0.78	92/8	88 (+)	81
15	dihydronaphthalene (1h)	Rh(acac){(R,S)-BINAPHOS}	50/50	60	79 (20)	12	96/4	96 (-)	82

^a TOF: (mol of product)·(mol of metal)⁻¹·h⁻¹.^b Selectivity to aldehyde was 67%. Hydrogenated compound was obtained as a by product.^c Triethyl orthoformate is used as a solvent. Product aldehydes are obtained as diethylacetals.^d Not reported.^e 0.11 g·mol⁻¹·h⁻¹ at [Rh]=250 ppm.^f 0.1 g·mol⁻¹·h⁻¹ at [Rh]=250 ppm.^g 0.1 g·mol⁻¹·h⁻¹ at [Rh]=250 ppm.

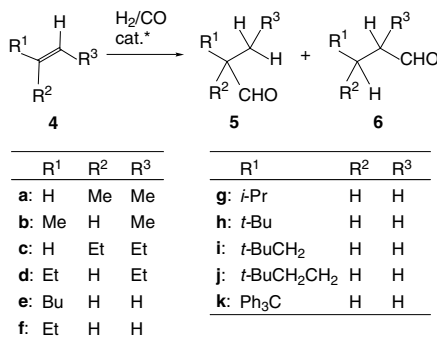
may also be attributed to the racemization of the product *iso*-aldehyde which is caused by the acidity of the catalyst.

When Rh(I) complexes of chiral ligands are employed, excess amounts of free ligands are often added to the Rh(I) complexes, in order to prevent the reaction being catalyzed by unmodified rhodium species. The chiral bisphosphite UC-P2* was successfully applied to the Rh(I)-catalyzed asymmetric hydroformylation (*iso/normal*=98/2, 90% ee) (run 4) [27]. The phosphine-phosphite ligands, (*R,S*)-BINAPHOS and (*S,R*)-BIPHEMPOS gave even higher enantioselectivities (*iso/normal*=88/12, 94% ee, run 5 and 90/10, 94% ee, run 7, respectively) [67, 68, 81]. A turnover frequency of 100 (mol of aldehydes)×(mol of Rh)⁻¹(h)⁻¹ was achieved at 40 °C under a total pressure of 10 atm (H₂/CO=1/1) (run 6) [76]. Similarly, (*S*)-2-(4-isobutylphenyl)propanal (**2b**) was derived from *para*-isobutylstyrene (**1b**) in 92% ee, which is the precursor of the anti-inflammatory (*S*)-ibuprofen (run 9). The asymmetric hydroformylation is applicable to internal alkenes, having a single aromatic substituent (runs 12 and 13). The major product is known as an intermediate for the synthesis of the spasmolytic butetamate [44]. The cyclic olefins indene (**1g**) and 1,2-dihydronaphthalene (**1h**) gave 1-formylindane and 1-formyl-1,2,3,4-tetrahydronaphthalene with high regio- and enantioselectivities. The former product can be converted to the corresponding amines with hypotensive activity in a single step by reductive amination with a Ni or Pt catalyst, and the latter is a synthetic intermediate for the synthesis of a vasoconstrictor tetrahydrozoline [44].

2.4.2

Asymmetric Hydroformylation of Aliphatic Alkenes

Symmetrical *cis*-olefins, such as (*Z*)-2-butene and (*Z*)-3-hexene, do not have an enantioface to be distinguished. Therefore, the % ees arise from the regioselection by the catalyst, that is, which *sp*²-carbon should be selected when the olefin is coordinated to the metal center. (*Z*)-2-butene with Rh(*acac*)[(*R,S*)-BINAPHOS] gave (*S*)-2-methylbutanal as a single product with 82% ee (Scheme 8 and Table 2,

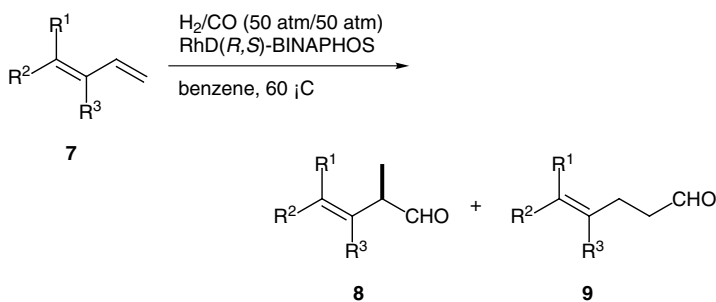


Scheme 8. Aliphatic alkenes

Table 2. Asymmetric hydroformylation of aliphatic ethenes 4a–k

run	substrate	catalyst	temp	CO/H ₂	conv % (time, h)	TOF ^a ×10 ⁻³	iso/normal 5/6	% ee of 5 (config)	Reference
1	(Z)-2-butene (4a)	Rh(acac){(R,S)-BINAPHOS}	30	50/50	nr ^b (44)	10	-	82 (S)	67,82
2		PtCl(SnCl ₃){(R,R)-BCO-DBP}	80	70/150	67 (21)	31	- ^{de}	30 (R)	9
3	(E)-2-butene (4b)	Rh(acac){(R,S)-BINAPHOS}	60	50/50	nr ^b (45)	0.5	-	48 (S)	67,82
4		PtCl(SnCl ₃){(R,R)-BCO-DBP}	80	70/150	65 (30)	21	- ^{de}	29 (R)	9
5	(Z)-3-hexene (4c)	Rh(acac){(R,S)-BINAPHOS}	30	50/50	32 (42)	0.77	-	79 (S)	67
6	(E)-3-hexene (4d)	Rh(acac){(S,R)-BINAPHOS}	30	50/50	17 (42)	0.41	-	69 (R)	67
7	1-butene (4f)	Rh(acac){(R,S)-BINAPHOS}	30	35/35	nr ^b	23	21/79	83 (R)	67
8		PtCl(SnCl ₃){(R,R)-BCO-DBP}	80	70/150	34(4)	73	14/86	67 (S)	9
9	1-hexene (4e)	Rh(acac){(R,S)-BINAPHOS}	30	50/50	24	5.4	24/76	82 (R)	67
10		Rh(acac){(R,R)-UC-P ₂ ^f }	nr	22/22	nr ^b	c	67/33	20 (S)	27
11	3-methyl-1-butene (4g)	Rh(acac){(R,S)-BINAPHOS}	30	50/50	48	18.7	8/92	83 (R)	83
12	3,3-dimethyl-1-butene (4h)	Rh(acac){(R,S)-BINAPHOS}	50	50/50	49	1.4	0/100	-	83
13	4,4-dimethyl-1-pentene (4i)	Rh(acac){(R,S)-BINAPHOS}	50	50/50	87	1.1	43/57	92 (-)	83
14	5,5-dimethyl-1-hexene (4j)	Rh(acac){(R,S)-BINAPHOS}	50	50/50	68	1.3	26/74	77 (-)	83
15	3,3,3-triphenyl-1-propene (4k)	Rh(acac){(R,S)-BINAPHOS}	50	50/50	20	>5.0	60/40	>99 (+)	83

^a TOF: (mol of product)·(mol of metal)⁻¹·h⁻¹.^b Not reported.^c 0.15 g·mol⁻¹·h⁻¹ at [Rh]=250 ppm.^d 1-pentanal was obtained as a by-product.^e 2-methylbutanal/1-pentanal=87/13.



	R ¹	R ²	R ³	8	9
a:	H	-(CH ₂) ₄ -		82%, 96% <i>ee</i> (<i>R</i>)	12%
b:	Me	Me	H	72%, 80% <i>ee</i> (<i>R</i>)	20%
c:	H	Ph	H	81%, 90% <i>ee</i> (<i>R</i>)	4%

Scheme 9. Dienes

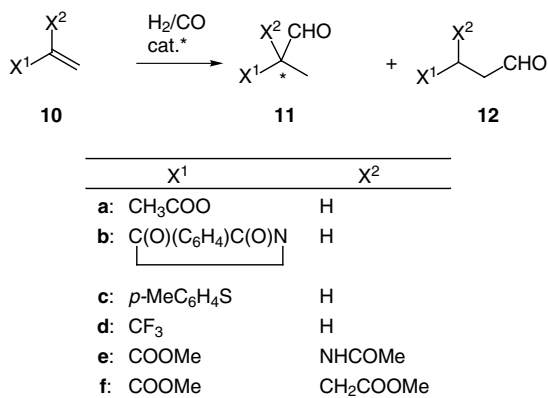
run 1) [67, 68, 82]. The absence of pentanal clearly excludes the possibility of isomerization of 2-butene to 1-butene under the reaction conditions. This fact is crucial for the high enantioselectivity, because 1-butene and 2-butene are converted into 2-methylpropanal of opposite absolute configurations by the same catalyst (runs 1 and 7). In contrast, the *normal*-aldehyde was obtained with a Pt complex (runs 2 and 4). Compared to the (*Z*)-isomer, hydroformylation of (*E*)-2-butene occurred more slowly and resulted in lower *ees* (run 3). Similar tendencies were observed with 3-hexenes (runs 5 and 6). Asymmetric hydroformylation of terminal aliphatic ethenes has not been satisfactory from the preparative point of view because of the low regioselectivity for the *iso*-aldehydes, although the enantiomeric excess of the *iso*-aldehyde reached over 80% (runs 7, 9, 11–15). Apparently, the larger substituents on the allylic carbon raised the *iso*-selectivity to some extent (e.g., runs 13 and 15) [83].

While hydroformylation of 1,3-butadiene has been intensively studied for the purpose of obtaining adipic acid [84, 85], asymmetric hydroformylation of conjugated dienes has remained almost unexplored. A highly selective asymmetric hydroformylation of 1,3-dienes was reported using Rh(acac)[(*R,S*)-BINAPHOS] as catalyst to give optically active β,γ -unsaturated aldehydes (Scheme 9) [86, 87].

2.4.3

Asymmetric Hydroformylation of Alkenes Bearing Functional Groups

Hydroformylation of functionalized ethenes has been recognized to be more difficult than that of arylenes, because of the low reactivity of the substrates and possible undesired side reactions. Hydroformylation with representative chiral catalysts are summarized in Scheme 10 and Table 3. Obviously, Rh(I) catalysts



Scheme 10. Functionalized alkenes

are much more advantageous for this family of substrates, especially in the view of regioselectivity (runs 1–4 and 5–6). With (*R,S*)-BINAPHOS-Rh(I), vinyl acetate (**10a**) was converted into (*S*)-2-acetoxypropanal (86% yield, 92% ee) along with 3-acetoxypropanal (14% yield) (run 1). This enantioselectivity obtained with (*R,S*)-BINAPHOS is even remarkable compared to the values with other Rh-catalysts. It is noteworthy that the combined yield of the aldehydes was quantitative from vinyl acetate and no byproduct was observed. Chiral 3-carboxypropanals can be readily converted to lactic acid derivatives [44], attracting interest as a monomer of biodegradable or bioabsorbable polymers. Derivatives of threonine, a natural amino acid, can also be synthesized from these aldehydes. For the asymmetric hydroformylation of vinyl acetate, an interesting bimetallic catalyst Rh₂(allyl)₂(*et,ph*-P4)/HBF₄ has recently been reported (run 3) [39]. Although the use of this catalyst has yet been limited to vinyl carboxylates, application of the concept of bimetallic systems seems to be promising.

Hydroformylation of *N*-vinylphthalimide (**10b**) gives *N*-(1-formylethyl)-phthalimide which is a precursor of alanine, one of the essential amino acids. Vinyl sulfide (**10c**) are also converted into the corresponding aldehydes with high regio- and enantioselectivities in spite of the fact that sulfides often behave as a catalyst poison [88]. Since the introduction of fluorine-containing substituents into biologically active agents often induces unique physiological activities, synthesis of organofluorine compounds has attracted much attention recently. Hydroformylation of the fluorinated ethene **10d**, for example, is a convenient way to synthesize such compounds [89,90]. The dehydroamino acid **10e** was converted into the corresponding aldehyde with 100% selectivity and 59% ee using RhH(CO)(PPh₃)₃-(*R,R*)-DIOP [91, 92]. With the same catalyst, itaconic acid dimethyl ester (**10f**) yielded the product with *i/n*=95/5 and the ee of the major one was 9% [93]. With PtCl₂{(*R,R*)-DIOP}-SnCl₂, the opposite regio isomer was produced with higher enantioselectivity (82% ee), but the chemoselectivity to aldehyde was limited to only 35% (run 11).

Table 3. Hydroformylation of Heteroatom-Substituted Ethenes (**10a-f**)

run	substrate	catalyst	temp, °C	CO/H ₂ , atm/atm	conv., % (time, h)	TOF, a h ⁻¹	11/12	% ee of 11 (config)	Refer- ence
1	vinyl acetate (10a)	Rh(acac){(<i>R,S</i>)-BINAPHOS}	60	50/50	>99 (36)	11	86/14	92 (S)	67
2		Rh(acac){(<i>R,R</i>)-UC-P ₂ [*] }	50	5/5	nr ^b	c	100/0	50 (S)	27
3		Rh ₂ (nbd) ₂ {(<i>S,S</i>)-et,ph-P4}	90	3/3	nr ^b	125	80/20	85 (nr ^b)	39
4		PtCl(SnCl ₃){(<i>S,S</i>)-BPPM}	60	90/90	70 (40)	7.6	30/70	80 (S)	8
5	vinyl phthalimide (10b)	Rh(acac){(<i>S,R</i>)-BINAPHOS}	60	50/50	98 (90)	3.3	89/11	85 (R)	67
6		PtCl(SnCl ₃){(<i>S,S</i>)-BPPM}	60	90/90	52 (46)	4.2	33/67	73 (R)	8
8	<i>p</i> -tolyl vinyl sulfide (10c)	Rh(acac){(<i>R,S</i>)-BINAPHOS}	40	50/50	96 (20)	4.8	96/4	74 (S)	67,88
9	3,3,3-trifluoro-1-propene (10d)	Rh(acac){(<i>R,S</i>)-BINAPHOS}	40	50/50	– (46)	8.3	95/5	93 (S)	67
10	methyl <i>N</i> -acetamidoacrylate (10e)	RhH(CO)(PPh ₃) ₃ / <i>(R,R)</i> -DIOP	80	8/82	100 (70)	1.4	100/0	59 (R)	91,92
11	dimethyl itaconate (10f)	PtCl(SnCl ₃){(<i>R,R</i>)-DIOP}	100	40/40	80 (45)	3.6	0/100 ^d	82 (R) ^e	93

^a TOF: (mol of product)·(mol of metal)⁻¹·h⁻¹.

^b Not reported.

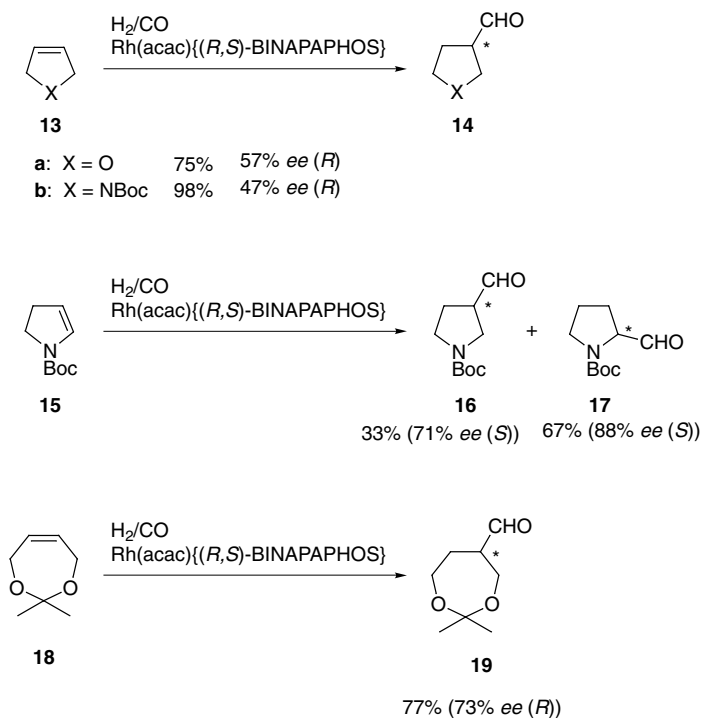
^c 0.12 g·mol⁻¹·h⁻¹ at [Rh]=250 ppm.

^d The selectivity to aldehyde was 35% and hydrogenated product was given in 65% selectivity, 53% ee (*R*).

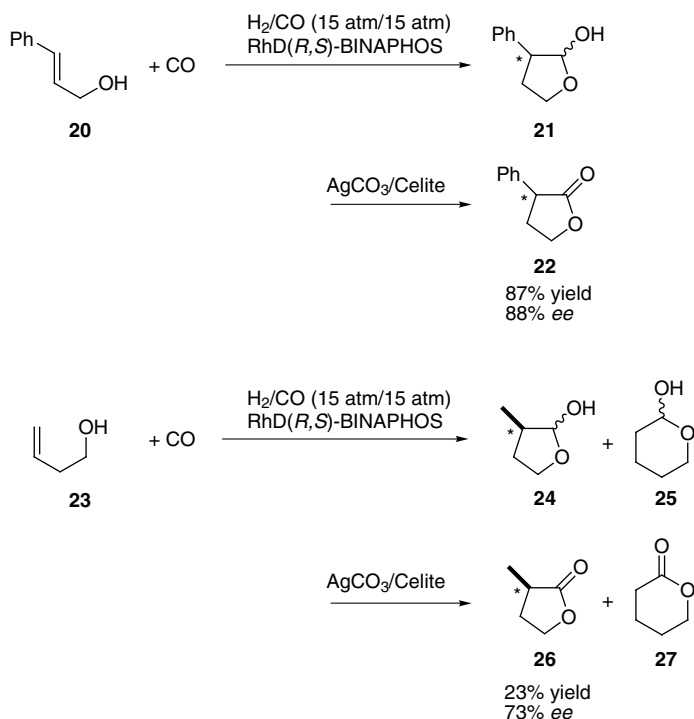
^e Aldehyde 11f was not produced and the % ee of 12f is described.

Some heterocyclic systems such as tetrahydrofuran, tetrahydropyran, thiophene, and pyrrolidine are found in a wide range of biologically active compounds. Hydroformylation of these heterocyclic olefins provides a potential synthetic route for the synthesis of these targets (Scheme 11) [93, 94]. Asymmetric hydroformylation of α -methylene- γ -butyrolactone using the cationic Rh(I)-(R)-BINAP complex as a catalyst is also reported to give an aldehydic lactone containing a quaternary chiral center in up to 37% ee [95].

When allylic and homoallylic alcohols are subjected to hydroformylation, the product was obtained as a lactol, e.g., 3-phenyl-2-hydroxytetrahydrofuran (Scheme 12) [96]. Due to the relative configuration between the C-2 and C-3 carbons, it was formed as a 1:1 diastereomeric mixture. The enantiomeric excesses were determined by oxidizing the lactols into the corresponding lactones.



Scheme 11. Heterocyclic olefins

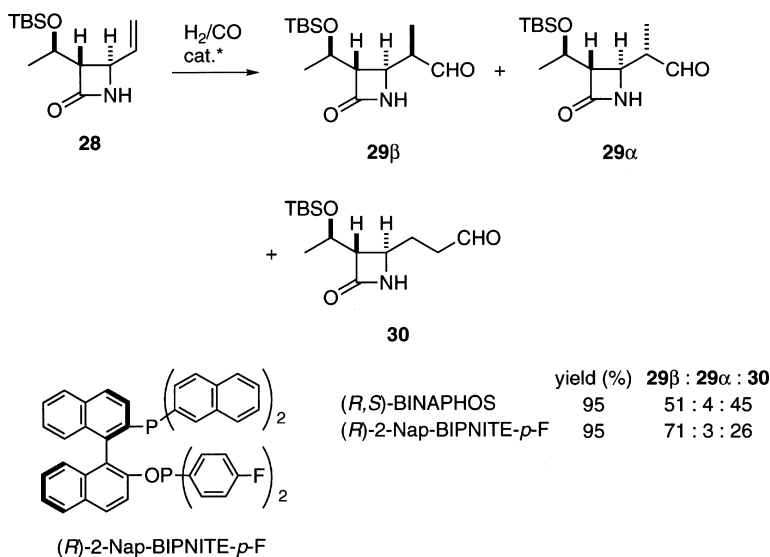
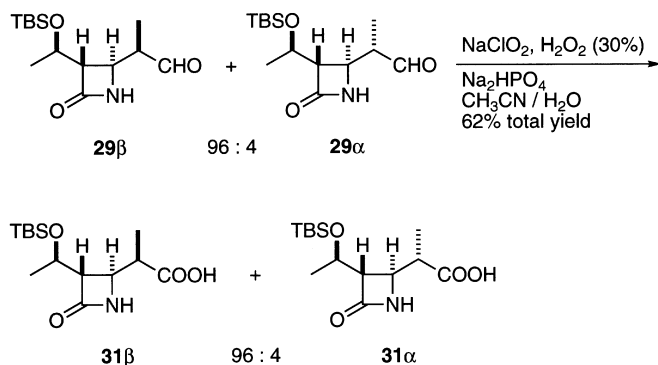


Scheme 12. Allylic alcohols

2.4.4

Diastereoselective Hydroformylation in Fine Chemical Synthesis

One of the goals of homogeneous asymmetric catalysis may be its application to the production of fine chemicals, such as pharmaceuticals, agrochemicals, flavors, and fragrances [97]. When hydroformylation is applied for such a purpose, the substrate olefins often possess one or more chiral centers. An example of diastereoselective hydroformylation is cited below briefly [98]. Hydroformylation of (3*S*,4*R*)-3-[(*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-vinyl- β -lactam (**28**) with Rh(I)-(R,S)-BINAPHOS afforded the desired product **29 β** , its epimer **29 α** , and the linear isomer **30** in a ratio of 51:4:45 (Scheme 13). In addition to the phosphine-phosphite ligand (R,S)-BINAPHOS, another class of chiral ligands, phosphine-phosphinites, was also effective [99]. The aldehydes **29** and **30** can be oxidized to the corresponding carboxylic acids without any epimerization (Scheme 14). The stereoselective synthesis of 1 β -methylcarbapenem is of much interest due to its high potential as an antibacterial antibiotic, and **29 β** is an attractive intermediate for this family of compounds. The commercial application of this method is currently under investigation at Takasago Co. [100].

Scheme 13. β -Lactam HF

Scheme 14. Oxidation

2.5

Practical Aspects

2.5.1

Catalyst Availability, Preparation, and Handling

Catalyst precursors, for example PtCl_2 and $\text{Rh}(\text{CO})_2(\text{acac})$, are both commercially available, e.g., from Strem Chemicals Inc. (\$52/g and \$120/g, respectively, in the catalog of 1992). Most of the ligands are synthesized from commercially

available optically active reagents. For example, (*R,S*)-BINAPHOS is prepared from (*R*)- and (*S*)-1,1'-binaphthalene-2,2'-diol [67, 68]. Bisphosphites UC-P₂* have their chiral origin in 1,3-diols, e.g., 2,4-pentanediol [27]. Sugar is also used as a chiral source of chiral bisphosphites [32]. Chiral amino alcohols are used for the synthesis of BPPM [8] and EPHOS [66]. Meanwhile, BCO-DBP is derived from bicyclo[2.2.2]oct-5-ene-2,3-*trans*-dicarboxylic acid whose racemic mixture was resolved with chiral amines [9]. Resolution by chiral HPLC is applied to obtain optically pure et, ph-P4 [39].

Generally, simple mixing of the ligands with the metal salts produces the catalyst precursors. Then, substrate olefin, H₂, and CO are charged to the mixture of the metal salts and chiral ligands without any particular pretreatment. For the chiral phosphite-Rh(I) systems, however, an incubation time at heated temperature is required to start the reaction from Rh(acac)(CO)₂ if the reaction temperature is below 80 °C. Addition of SnCl₂ is often required to achieve satisfactory catalytic activity in Pt-catalyzed reactions. In Rh-catalyzed reactions, it is essential to add excess ligand for Rh (usually 2–4 equivalents of phosphine-phosphite or >4 equivalents of bisphosphine), because unmodified Rh species often possess higher catalytic activity than the modified ones.

The metal salts such as PtCl₂ and Rh(CO)₂(acac) are air-stable and can be kept under air. The corresponding chiral complexes with ligands, L*₂PtCl₂ and L*₂Rh(acac), are also air-stable unless the ligand reacts with water or oxygen. On the other hand, however, the complexes become extremely oxygen sensitive once they are treated with H₂/CO. For these complexes, the loss of CO also causes the decomposition of the active species. Thus, recycling the catalyst requires strictly inert conditions, preferable under CO.

2.5.2

Conditions, Equipment, and Scale

For a high-pressure experiment, the use of a stainless-steel autoclave is required. Glass pressure bottles may be used for lower pressure conditions. Since the active species are very air-sensitive (*vide supra*), manipulations under inert gas atmosphere are essential. Stirring speed often influences the turnover number and sometimes the selectivities, due to the liquid-gas two-phase nature of the reaction. For a laboratory experiment, a 50-mL microautoclave is suitable to transform ca. 10 g of styrene into the corresponding chiral aldehyde using (*R,S*)-BINAPHOS-Rh(I) catalyst under 100 atm of syngas. Although above 4,500,000 tons/year of butanal are produced by hydroformylation of propene (estimated in 1993) [101], no industrial process has yet been established for asymmetric hydroformylation.

2.5.3

Catalyst Efficiency, Loading, and Recovery

Turnover numbers (TON) up to 2,000 in 24 h have been achieved using the (*R,S*)-BINAPHOS-Rh(I) catalyst for styrene and vinyl acetate. In most cases reported herein, a substrate/catalyst ratio of 100–1000 is employed. Although phosphite ligands are known to decompose by reaction with product aldehydes, this decomposition seems to be much slower compared to the hydroformylation reaction.

Aiming at the recovery of the catalyst, Stille established the polystyrene-supported catalyst for asymmetric hydroformylation [80]. A significant loss of catalytic activity was observed due to the polymer-support but the enantioselectivity of the homogeneous conditions was maintained. The catalyst was reused with slight loss of activity and selectivity. While still employed less than 10% of divinylbenzene to prepare cross-linked polystyrene, Rh complexes of (*R,S*)-BINAPHOS which were copolymerized with divinylbenzene/styrene=55/45 realized the same level of regio- and enantioselectivities as the homogeneous analog [102]. The recovery of the catalyst was possible and the reused catalyst showed equal level of selectivity. As a reaction medium for “homogeneous” asymmetric hydroformylation, supercritical CO₂ has been examined but the *ee*s are lower in comparison to its homogeneous counterpart [103]. Very recently, applications of a biphasic system to asymmetric hydroformylation have been reported [104].

2.5.4

Safety Considerations

Carbon monoxide is highly toxic and both H₂ and CO are flammable. All manipulations concerning to these gases should be carried out in a hood. For CO, one needs a detection system.

3

Hydrocarboxylation and Related Reactions

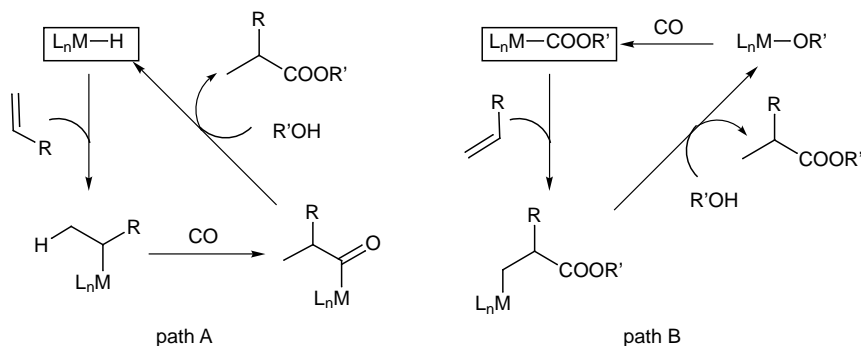
Carboxylic acids and their derivatives, esters, amides, anhydrides, and acyl halides, are formally synthesized from olefins, carbon monoxide, and compounds represented with HX where X- equals OR-, NR₂-, etc (see Scheme 1). Considering that the chiral aldehydes obtained by asymmetric hydroformylation of vinylarenes are often oxidized in order to exhibit biological activities, asymmetric hydrocarboxylation and its related reactions naturally attract much attention. Unfortunately, however, as yet only less successful work has been reported on this subject than on hydroformylation. Palladium(II) is most commonly used for this purpose. Asymmetric hydrocarboxylation of olefins was first reported in 1973 by Pino using PdCl₂ and (-)-DIOP [105]. Chiusoli reached 52% *ee* in the

asymmetric hydrocarboxymethoxylation of styrene using neomentyldiphenylphosphine (NMDPP) as a chiral ligand [106]. In 1990, Alper reported the synthesis of acids in high enantioselectivity (91% ee) using BNPPA for the Pd(II)-catalyzed hydrocarboxylation of 2-vinyl-6-methoxynaphthalene [107], but it should be noted that the chemistry of this reagent has not been elaborated since the original report. Several attempts followed using Pd(II) catalysts in combination with chiral phosphines [108, 109]. Cyclohydrocarbonylation is a topic of recent interest and a few examples are covered in this article [110, 111, 112].

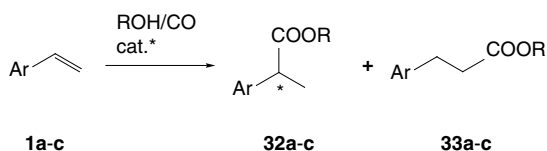
As a mechanism for the hydrocarboxylation, two possibilities are suggested [113, 114, 115]. One is similar to that of hydroformylation in which the cycle starts with a hydridometal complex (Scheme 15, path A) [113]. In this path, olefin insertion takes place into an M-H bond and then migratory insertion of CO into an alkyl-metal bond gives an acylmetal complex. Alcoholysis of the acylmetal species reproduces the metal hydride and yields the ester. Another mechanism in which the active species is a carbalkoxymetal complex has been proposed (path B) [114]. Here, olefin insertion into a metal-carbon bond of the alkoxycarbonylmetal species is followed by alcoholysis to give the product ester and the alkoxymetal complex. Insertion of CO into the alkoxymetal species reproduces the carbalkoxymetal complex. No details have yet been disclosed and the mechanism may vary depending on the metals and the reaction conditions, especially the existence of acids or bases.

In spite of intensive efforts by numerous research groups, practically efficient methods for the asymmetric hydrocarboxylation have not yet been reported. Styrene and other vinylaromatics are most widely examined and the data for representative examples are summarized in Scheme 16 and Table 4 (see Structure 2 for catalysts). The products are of much interest as synthetical intermediates for bioactive compounds. Although some of the reports reach high ees, the studies are still on their way to be completed.

Asymmetric hydrocarboxylation of α -methylstyrene was also examined, leading to 3-phenylbutanal, the *normal*-product. The highest enantiomeric excess is

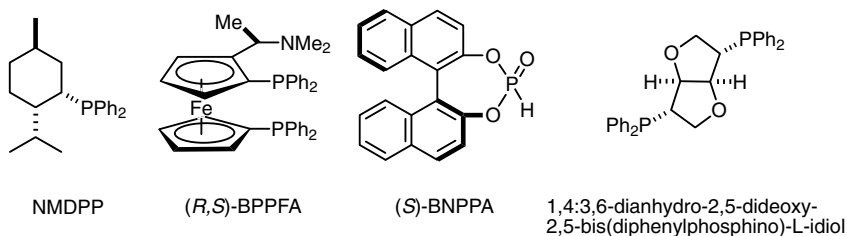


Scheme 15. Two proposed paths for the hydrocarboxylation of olefins

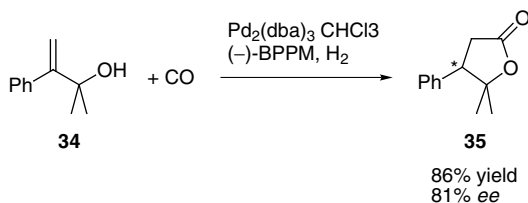


- a:** Ar = Ph
b: Ar = 4-*t*-Bu-C₆H₄
c: Ar = 6-MeO-2-naphthyl

Scheme 16. Asymmetric hydrocarboxylation of ArCH=CH₂



Structure 2. Examples of chiral ligands used in Pd-catalyzed asymmetric hydrocarboxylations



Scheme 17. Cyclocarbonylation

below 60% for this substrate [116, 117, 118, 119]. When an allylic alcohol is treated with a chiral Pd complex under CO, cyclohydrocarbonylation occurs to give the corresponding γ -butyrolactone in an asymmetric manner (Scheme 17) [111, 112].

Table 4. Hydrocarboxylation of styrene (**1a**) and its derivatives (**1b–c**) catalyzed by chiral Pd(II) complexes

run	substrate	ROH	catalyst	CO atm	temp, °C	yield, % (time, h)	iso/normal 32/33	% ee of 32 (config.)	Reference
1	styrene (1a)	MeOH	Pd-dba/NMDPP	1	50	94 (4)	94/6	52 (nr ^c)	106
2		MeOH	Pd(OAc) ₂ /(S)-(R)-BPPFA/TsOH	20	rt	17 (20)	44/56	86 (S)	108
3		MeOH	PdCl ₂ /CuCl ₂ /L ^{*a}	50	80	97 (24)	96/4	99 (S) ^b	109
4	4- ⁱ Bu-styrene (1b)	H ₂ O	(S)-BNPPA/PdCl ₂ /HCl/H ₂ O/CuCl ₂ /O ₂	<1	rt	89 (18)	100/0	83 (S) ^b	107
5	2-(6-MeOC ₁₀ H ₆)CH=CH ₂ (1c)	H ₂ O	(S)-BNPPA/PdCl ₂ /HCl/H ₂ O/CuCl ₂ /O ₂	<1	rt	71 (18)	100/0	85 (S) ^b	107
6		MeOH	Pd-dba/NMDPP	1	50	94 (4)	94/6	42 (nr ^c)	106

^a L^{*}=1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-L-idiol.

^b Optical purity.

^c Not reported

4

Conclusion and Outlook

The historic discovery of Rh complexes of chiral bisphosphites and phosphine-phosphites dramatically raised the enantioselectivities of asymmetric hydrocarbonylation from ~50% ee to almost quantitative values in the first half of the 1990s. The successes with Rh catalysts seemed to replace the earlier used Pt catalysts which often suffered from extensive side reactions such as hydrogenation and isomerization, and low selectivity to *iso*-aldehydes. At this stage, asymmetric hydroformylation has reached the level of enantioselectivity of asymmetric hydrogenation, the most studied asymmetric reaction.

Although the ligands used so far are expensive, improvement of the catalytic activity may make possible the industrial use of the reaction. Thus, further development of ligands and reaction conditions are required, especially for commercial purposes. Both from economical and environmental viewpoints, recycling of the catalysts will be more stressed in the future studies.

Stereoselective hydroformylation will also be more and more applied to the total synthesis of complex high molecular weight compounds, e.g., natural products. In this respect, diastereoselectivity will be further investigated because substrate olefins for such a purpose often possess one or more chiral centers. Hydroformylation with a chiral catalyst should be widely employed for this purpose because the diastereoselectivity can be improved by a matched combination of a chiral ligand and a chiral substrate.

In spite of its potential applicability in fine chemical synthesis, asymmetric hydrocarboxylation seems to be waiting for a conceptual improvement to meet practical interests.

Acknowledgments: The author is grateful for the helpful suggestions and comments by the following people. Prof. P. W. N. M. van Leeuwen (Universiteit van Amsterdam, The Netherlands), Prof. W. A. Herrmann and D. Gleich (Technische Universität München, Germany), Profs. A. Mortreux and F. Agbossou (Ecole Nationale Supérieure de Chimie de Lille, France), Prof. I. Ojima (State University of New York at Stony Brook, USA), Prof. C. Claver (Universitat Rovira I Virgili, Pça. Imperial Tàrraco, Spain), and Dr. T. Horiuchi (Ono Pharmaceutical Co. Ltd., Japan). She also thanks Prof. W.A. Herrmann and D. Gleich for kindly sending information about Fig. 2.

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Chapter 12

Hydrovinylation of Carbon-Carbon Double Bonds

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Keywords: Asymmetric hydrovinylation, Ethylene, Vinylarene, Diene, Norbornene, 2-Arylpropanoic acid, Nickel, Palladium, π -Allylnickel bromide, Phospholane, Ligand tuning, Hemilabile ligand, Catalyzed cyclization, 1,6-Diene

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List of Abbreviations

MOP-OMe 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl
MVN 6-methoxy-2-vinylnaphthalene
TFPB tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion

1 Introduction

One of the major challenges facing organic synthesis is the enantioselective incorporation of feedstock materials such as CO, HCN, and ethylene into prochiral molecules. Such reactions would have potential applications in large-scale syn-

thesis of valuable pharmaceutical and agricultural intermediates [1]. In addition, they would enrich our repertoire of environmentally benign chemical processes. In this context, an important reaction that has not received much attention is the Ni-catalyzed codimerization of simple olefins, of which the hydrovinylation reaction (addition of ethylene to other olefins) is a prototypical example. The mechanistically related propene dimerization [2] and ethylene oligomerization [3] reactions proceed with astonishingly high turnover frequencies for the nickel catalysts.

2

Hydrovinylation of Vinyl Arenes: Reaction Protocols

Hydrovinylation reactions of vinylarenes, Eq. (1), have been investigated most extensively because of the importance of 3-aryl-1-butenes as potential intermediates for widely used anti-inflammatory 2-arylpropanoic acids [4]. Since the first report of a high pressure (1000 atm) ethylene/styrene codimerization in the presence of RhCl_3 [5] various metals such as Ru [6], Co [7], Pd [8], and Ni [9, 10, 11, 12] have been used, even though Pd and Ni appear to be the most active metals. In most of the early studies, styrene served as a prototypical test case, and almost invariably, the reaction was complicated by isomerization of the initially formed 3-aryl-1-butene (**1**) to a mixture of the *Z*- and *E*-2-aryl-2-butenes (**2**) and oligomerization of the starting olefins. The best results obtained to date are compiled in Table 1.

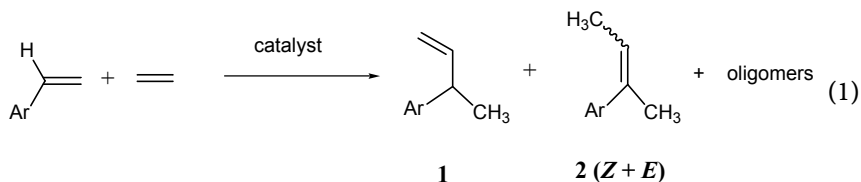
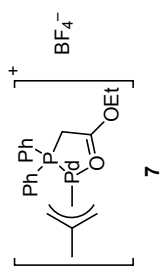


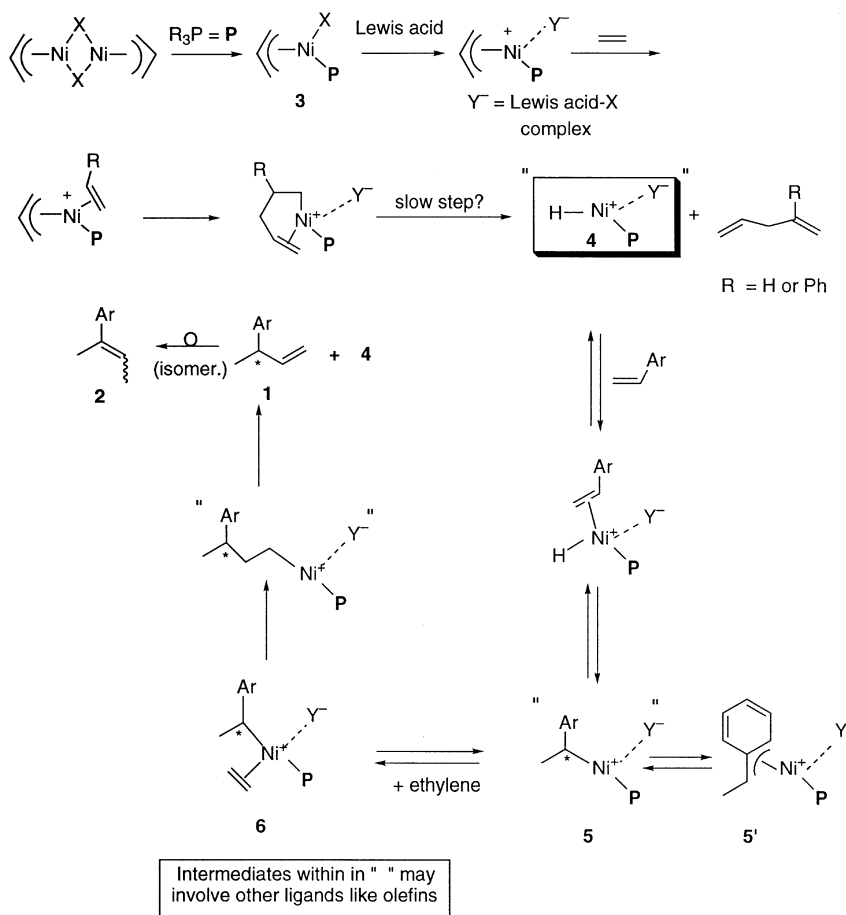
Table 1. Hydrovinylation of vinylarenes: best practices



Entry	Catalyst precursor	Reaction conditions	Yield %	Selectivity for 3-Ph-1-butene (1)	Remarks	Ref.
1.	$(\text{Ph}_3\text{P})_2\text{Ni}(\text{mesityl})\text{Br}$	Styrene/Ni=17 $\text{BF}_3 \cdot \text{OEt}_2$, 0 °C, 15 min, <1 atm C_2H_4 , CH_2Cl_2	67	91%	- 9% isomers and styrene dimer	9a
2.	$[(\text{PhCH}_2)_3\text{P}]_2\text{Ni}^+(\text{mesityl})$ $(\text{CH}_3\text{CN})\text{BF}_4^-$	Styrene/Ni=500–1000 25 °C, 1 h, 15 atm C_2H_4 , THF	96	97%	- poor yield with α -Me-styrene - tolerant to Cl, OMe groups - exotherm at the end of reaction.	9b
3.	$[\text{Ni}(\text{CH}_3\text{CN})_6][\text{BF}_4]_2$, Ph_3P , EtAlCl_2	Styrene/Ni=400 25 °C, 30 min, 10 atm C_2H_4 , CH_2Cl_2	90	90%	- not tolerant to Lewis basic groups (Cl, OMe) on arene	10
4.	$(\eta^3\text{-C}_4\text{H}_7)\text{Pd}^+\text{-7)}\text{BF}_4^-$	(a) Styrene/Pd=400 25 °C, 30 atm C_2H_4 , CH_2Cl_2 , 1 h (b) same, 3 h	41 100	92 9	8% isom. 91% isom.	8d
5.	$[(\text{allyl})\text{Ni-Br}]_2/\text{Ph}_3\text{P}/$ AgOTf	Styrene/Ni=286 CH_2Cl_2 , -56 °C, 2 h	99+	99+	- excellent yields (>95% in many cases, see Table 2) - tolerant to halogen, alkoxy, $\text{N}(\text{Ts})_2$, $\text{OC}(\text{O})\text{R}$, CO_2R - works with propene (-15 °C) and other vinylarenes - amenable to asymmetric catalysis	12

3 Mechanism of Catalysis and a New Protocol

The mechanism of the reaction may involve a cationic nickel hydride associated with a weakly coordinated counterion (4, Scheme 1) as the true catalyst. This species is formed by the Lewis acid-assisted dissociation of the Ni-X bond from the 16-electron phosphine complex 3, coordination of ethylene (or styrene), coupling of the allyl and vinyl moieties, and subsequent β -hydride elimination [11a]. Insertion of the vinylarene into the Ni-H bond gives a benzylic complex 5, which can be stabilized as an η^3 -intermediate 5'. The coordinately unsaturated 5 can react with ethylene (and possibly *not another vinylarene*, if the phosphine is sufficiently bulky) to give 6, which can undergo an insertion followed by β -hydride



Scheme 1. Mechanism of hydrovinylation reaction

elimination, completing the catalytic cycle. Some of the limitations encountered in the previous attempts could be traced to two factors:

- (a) the poor reactivity of the substrates carrying a heteroatom could result from the reaction of the Lewis acid (for example, Et_2AlCl) with these Lewis basic centers;
- (b) the isomerization of the initially formed 3-aryl-1-butene (**1**) to 2-aryl-2-butene(s) could be mediated by a very reactive nickel (or palladium) hydride.

The isomerization reaction appears to be a major drawback, especially of the Pd-mediated reaction [8].

The scope and selectivity of hydrovinylation could be significantly increased by eliminating the troublesome Lewis acid, and using in its place, a silver salt with a weakly coordinating counter anion such as OTf [Eq. (2) and Table 1, entry 5] [13] or by using a non-coordinating counteranion such tetraarylborate (Ar_4B^-) [14] in conjunction with a hemilabile group [15] on the phosphine [vide infra Eq. (9)]. Furthermore, it is possible to prevent the isomerization of the initially formed terminal olefin (e.g., 1- \rightarrow 2) by manipulation of the phosphine ligand, **P**, and the reaction conditions. The new protocol, Eq. (2), gave *unprecedented* chemical yield and selectivity in the hydrovinylation of a series of vinylarenes (Table 2) [12]. 4-Isobutylstyrene, 3-fluoro-4-phenylstyrene, and 2-methoxy-6-vinylnaphthalene, all potential precursors for anti-inflammatory agents, gave excellent yields of the expected hydrovinylation products.

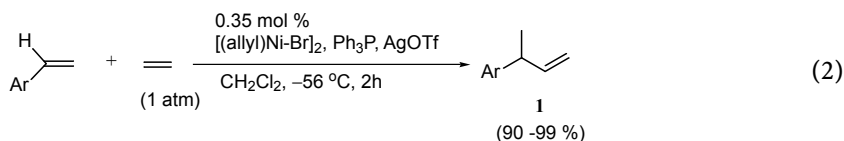


Table 2. Hydrovinylation of vinylarenes [12]

Entry	Substrate	% Yield ^[a]	Conditions ^[b]
1.	Styrene	>95 (99 ⁺)	(i)
2.	3-methylstyrene	>95 (98)	(i)
3.	4-methoxystyrene	>95 (98)	(i)
4.	4-bromostyrene	>95 (98)	(i)
5.	2-vinylnaphthalene	(99 ⁺)	(i)
6.	6-MeO-2-vinyl-naphthalene	(90) (97)	(i), 0.5 mol% cat. (ii)
7.	4- <i>i</i> -Bu-styrene	>90 (99 ⁺) >97 (99 ⁺)	(i), 1.4 mol% cat. (iii)
8.	3-F-4-Ph-styrene	(88)	(i)

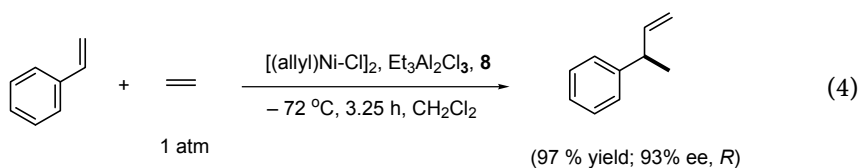
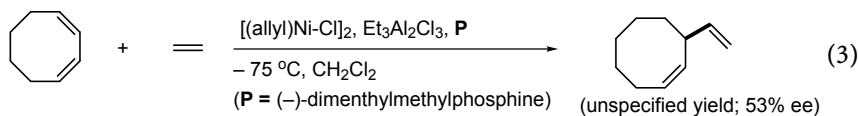
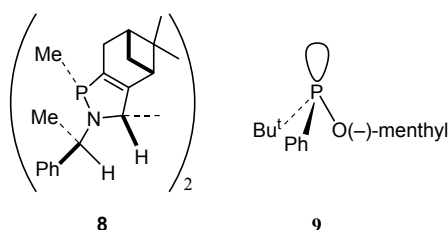
^[a]In brackets are the yields estimated by gas chromatography

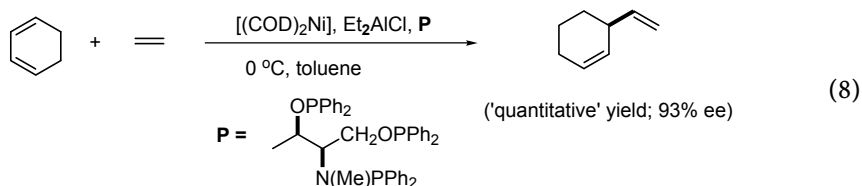
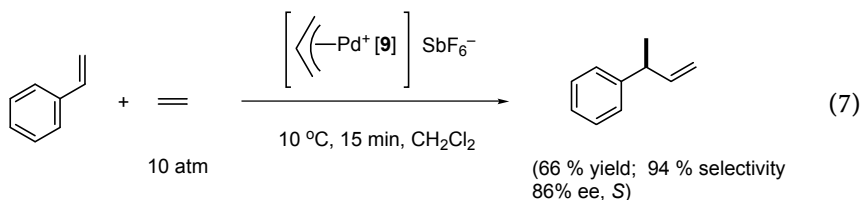
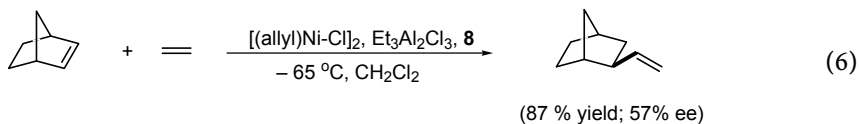
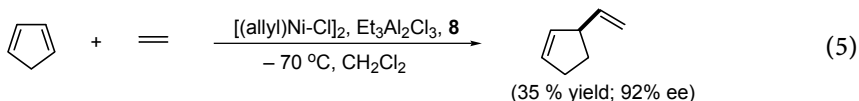
^[b](i) $[(\text{allyl})\text{NiBr}]_2$, (0.35 mol %)/ $\text{Ph}_3\text{P}/\text{AgOTf}/\text{CH}_2\text{Cl}_2/-55^\circ\text{C}/2\text{h}$; (ii) $[(\text{allyl})\text{NiBr}]_2$, (0.70 mol %)/(*R*)-MOP (**10a**)/ $\text{Ar}'_4\text{B}^-\text{Na}^+/\text{CH}_2\text{Cl}_2/-56^\circ\text{C}/2\text{h}$; (iii) $[(\text{allyl})\text{NiBr}]_2$, (0.70 mol %)/(*R*)-MOP-OBn (**10b**)/ $\text{Ar}'_4\text{B}^-\text{Na}^+/\text{CH}_2\text{Cl}_2/-56^\circ\text{C}/2\text{h}$

4 Asymmetric Synthesis

4.1 Asymmetric Catalysis of Hydrovinylation Reactions

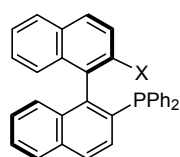
Heterodimerization reaction of 1,3-cyclooctadiene, Eq. (3), with ethylene was one of the first examples of an asymmetric carbon-carbon bond-forming reaction ever reported, even though the selectivity was unacceptably low [16]. Under similar conditions, norbornadiene gave up to 49% yield (77.5% ee) of (+)-vinyl-norbornene. These reactions appear to be plagued by isomerization and other side reactions. The reaction conditions for this and many other hydrovinylations have been reported only in reviews and patents and the details of selectivity and full characterization of the products are often difficult to find. The best procedures for asymmetric hydrovinylations of vinylarenes, Eq. (4) [11b], cyclopentadiene, Eq. (5) [11b], and norbornene, Eq. (6) [11b] use an azaphospholene ligand (structure **8**) with $[(\text{allyl})\text{NiCl}]_2$ and $\text{Et}_3\text{Al}_2\text{Cl}_3$ or Et_2AlCl . An extensive review of this work done by the Wilke group has recently appeared [11d]. Unfortunately, the azaphospholene **8** is a very special ligand and, attempts to modify its structure have not been successful [11e]. A (-) menthol-derived *P*-chiral phosphinite (structure **9**) [8e] could represent an important class of ligands for Pd-catalyzed hydrovinylation of vinylarenes if the selectivity and yield can be improved, Eq. (7). The only other substrate where moderate enantioselectivity for the hydrovinylation reaction has been achieved is 1,3-cyclohexadiene, Eq. (8) [17].



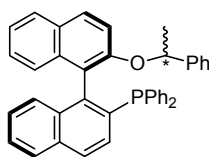


It was known for sometime that chelating phosphines [18], inhibited the hydrovinylation reaction, whereas a properly chosen monophosphine that also carries a hemilabile group [15] might have an advantage, since such a group can stabilize the putative cationic intermediates by internal coordination. In addition, this coordination might lead to better diastereoselective discrimination in the key Ni-H addition to the prochiral faces of the olefin during the early stages of the reaction (Scheme 1). Accordingly, we found that Hayashi's 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl (MOP, **10a**) [19], which carries a hemilabile methoxy group, is an excellent ligand for hydrovinylation, especially in the presence of a non-coordinating counter anion such as the tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion (TFPB)[14, 20]. Curiously, the triflate anion was ineffective in this reaction. 2-Methoxy-6-vinylnaphthalene (MVN) and 4-isobutylstyrene gave nearly quantitative yields of the products in 62% and 40% ee (*S*-isomers), respectively, Eq. (9) [12]. In addition, we also discovered that a minor modification in the ligand structure (**10b**), with the use of $-\text{OCH}_2\text{Ph}$ instead of $-\text{OMe}$, improved the ee for MVN to 80% when the reaction was carried out at

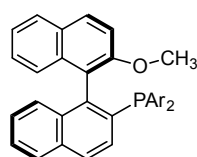
-70 °C. These weakly coordinating oxygens of the ligand appear to be crucial for the success of the reaction since yield and enantioselectivity for the ligand with ethyl group (**10c**) in place of the methoxy group are only 13% and 3% ee, respectively. Further support for the hemilabile coordination comes from the different reactivities of the two diastereomers of ligands **11a** and **11b**. The former gave a nearly quantitative yield (>99%) of the product in 71% ee, whereas the latter gave 79% yield and 65% ee under otherwise identical conditions. Substitution at the 2'-position with coordinating groups such as acetoxy (**10d**) and diphenylphosphine oxide (**10e**) totally inhibits the reaction at low temperature. Finally, the electronic effect of the ligand on the hydrovinylation selectivity was examined with the ligands **10a**, **12a**, and **13a**. Ligand electronic effects appear to have no effect on this reaction [21]; in each case the chemical yield and ee were almost identical (94±2% and 63±1%, respectively).



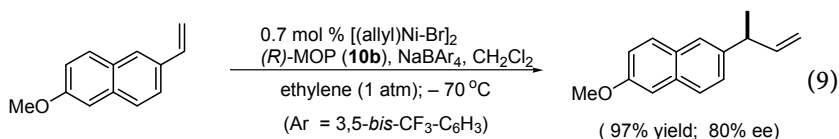
- 10a** X = OCH₃
10b X = OCH₂Ph
10c X = CH₂CH₃
10d X = OC(O)CH₃
10e X = P(O)Ph₂



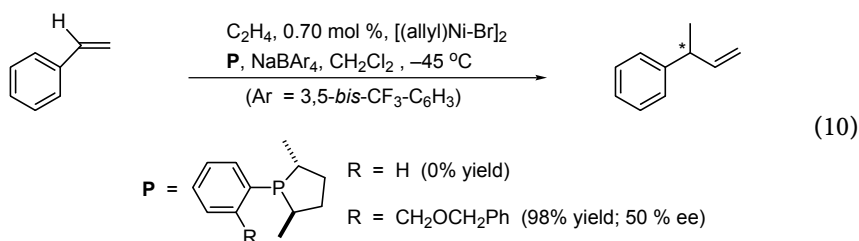
- 11a** * = (R)
11b * = (S)



- 10a** Ar = Ph
12a Ar = 3,5-(Me)₂-C₆H₃
13a Ar = 3,5-(CF₃)₂-C₆H₃



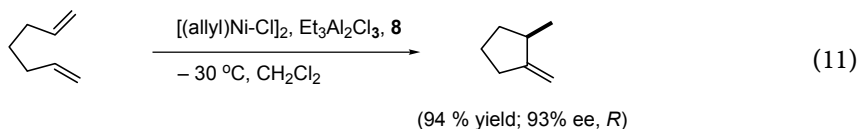
Since the original discovery of the importance of the hemilabile ligand for high enantioselectivity, we have recognized that such effects are equally important in a number of other monophosphines that promote the hydrovinylation reaction [22]. One example is shown in Eq. (10).



4.2

Asymmetric Catalysis of Related Reactions

The cyclization of 1,6-heptadiene to give 1-methylene-2-methylcyclopentane, shown in Eq. (11), has been claimed to proceed in 94% yield and 93% ee in the presence of $[(\text{allyl})\text{NiCl}]_2$, $\text{Et}_3\text{Al}_2\text{Cl}_3$, and **8** in dichloromethane at $-30\text{ }^\circ\text{C}$ [11b]. Thus far only a modest enantioselectivity has been achieved for a mechanistically related enyne cyclization [23].



5

Practical Aspects

The hydrovinylation of styrene has been carried out at $-60\text{ }^\circ\text{C}$ on an 8.26 kg (79.6 mol) scale by the Wilke group using the azaphospholene ligand **8**. The yield (41%) and enantioselectivity (87.4% ee) are lower than what is observed for small-scale reactions, and further developmental efforts are needed before the reaction can be practiced on an industrial scale. The low temperature and the esoteric nature of the ligand may also limit further applications of this chemistry. Discovery of new protocols which yield nearly quantitative yields [12] on a laboratory scale, the use of other metals (especially palladium), and a new generation of ligands that are under investigation in several laboratories may ultimately overcome the current problems.

6

Scope and Limitations

As outlined earlier, the reaction is currently limited to heterodimerization of ethylene with vinylarenes, cyclic dienes, or strained olefins such as norbornene. Among other α -olefins, propene (yields $>90\%$) alone has been shown to participate in the reaction under conditions described in Eq. (2) [24]. Methyl substitution at the α - or β -carbons of the styrene also leads to poor yields (21 and 49%, respectively) under these conditions. No enantioselective reactions of these substrates have been carried out. Preliminary experiments indicate that vinylarenes with strongly electron-withdrawing groups on the aromatic nucleus [for example, 3,5-bis(trifluoromethyl)styrene or 2-vinylpyridine] are poor substrates for this reaction [22].

Related intramolecular dimerization reactions have been carried out [25, 26], even though, except for one isolated example, Eq. (11) in the patent literature [11b], no useful enantioselective version has been documented.

7

Principal Alternatives

While it is difficult to envisage a conceptually simpler alternative route to the hydrovinylation products, the oxidative cleavage products which are the principal intended targets of this chemistry can also be prepared via hydroformylation [1a] and hydrocyanation of the corresponding olefin [1b]. For hydroformylation, regioselectivity (branched to linear ratio of the aldehyde products) still remains a major problem, whereas practical levels of enantioselectivity (>90% ee) for the hydrocyanation reaction has been demonstrated only for 6-methoxy-2-vinylnaphthalene.

8

Conclusion and Future Prospects

The heterodimerization of olefins appears to have great potential as a carbon-carbon bond forming reaction when the two olefins involved have different reactivities. With ethylene as one of the reactants, this difference could have its origin in electronic (e.g., vinylarenes, dienes) or strain (e.g., bicyclo[2.2.1]heptenes) factors. Anecdotal evidence seems to suggest that very high turnover numbers can be realized for the reaction, and the reaction conditions are tolerant to a wide spectrum of common organic functional groups. Excellent control of selectivity based on the properties of the ligand has been demonstrated. The results from recent discoveries could be further exploited using a number of widely different 'tunable' ligands that have been shown viable for this demanding reaction. With the increased efforts in a number of laboratories, an expansion of the scope of the asymmetric hydrovinylation reaction can be expected in the near future.

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Chapter 13

Carbometalation of Carbon-Carbon Double Bonds

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Keywords: Zirconium, Nickel, Enantioselective, Kinetic Resolution, Alkylation

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1 Introduction

The development of catalytic C-C bond forming reactions that proceed under mild conditions in an enantioselective fashion (>95% enantiomeric excess) stands as an important and challenging task in chemical synthesis [1]. Whereas reactions that involve the addition of alkylmetal reagents to C=O bonds are common, addition of alkylmetal species to alkenes, both easily available reagents, does not occur readily under most circumstances. Thus, an appropriate catalyst that efficiently promotes olefin alkylation may bring to the fore a process that would be of great synthetic utility. In addition to the significance of C-C bonds and addressing the need for efficient and selective methods to synthesize them,

this class of reactions is important, since the product of the asymmetric addition of an alkylmetal to an olefin is a new *chiral* alkylmetal, which can be further functionalized to make available a range of non-racemic compounds.

This article presents a review of recent advances in the catalytic addition of alkylmetal reagents to olefins, excluding reactions that involve unsaturated carbonyl compounds as substrates (conjugate addition) [2]. As described below, these reactions provide efficient and selective routes to the synthesis of a wide variety of chiral, non-racemic organic molecules that can be used in the fabrication of a number of highly functionalized molecules.

2

Zirconocene-Catalyzed Enantioselective Alkylation Reactions

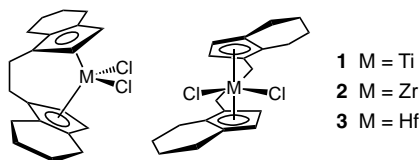
2.1

Catalytic Enantioselective Alkylation of Olefins with Alkylmagnesium Halides

Chiral C_2 -symmetric *ansa*-metallocenes, also referred to as bridged metallocenes, have found extensive use as catalysts that effect C-C bond-forming processes in an enantioselective manner [3]. In general, bridged ethylene(bis-tetrahydroindenyl)-metallocene dichlorides (1–3, Scheme 1) put forth attractive options for the design of asymmetric reactions because of their geometrically-constrained structure and relative ease of preparation.


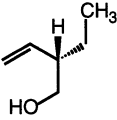
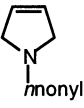
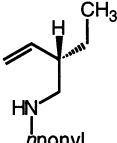

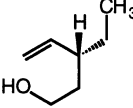

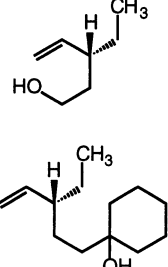
Work in our laboratories in connection with the zirconocene-catalyzed addition of Grignard reagents to alkenes (carbomagnesation) as a method for selective C-C bond formation has resulted in the development of catalytic transformations that are carried out at ambient temperature to afford synthetically useful products with excellent enantiomeric purity. As illustrated in Table 1, in the presence of 2.5–10 mol % non-racemic (EBTHI)ZrCl₂ [or (EBTHI)Zr-binol] and EtMgCl as the alkylating agent, five-, six-, and seven-membered unsaturated heterocyclic systems undergo facile asymmetric ethylmagnesation [4].

The rate of catalytic ethylmagnesation in the terminal alkenes of the reaction products is sufficiently slower, so that unsaturated alcohols and amines can be isolated in high yield (the second alkylation is not generally diastereoselective). Zr-catalyzed asymmetric olefin alkylation thus affords non-racemic reaction products that bear an alkene and a carbinol unit, functional groups that are readily amenable to a wide range of subsequent derivatization procedures.

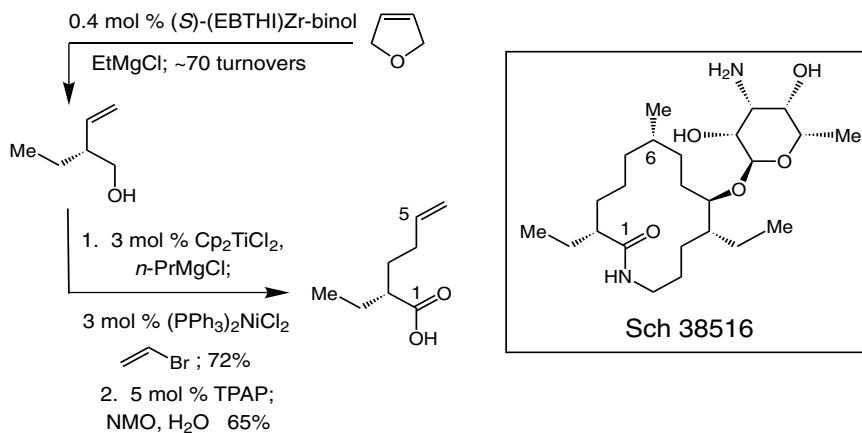


Scheme 1. Group IV ethylene-bridged bis(tetrahydroindenyl) systems represent well-defined complexes that may be used in asymmetric synthesis

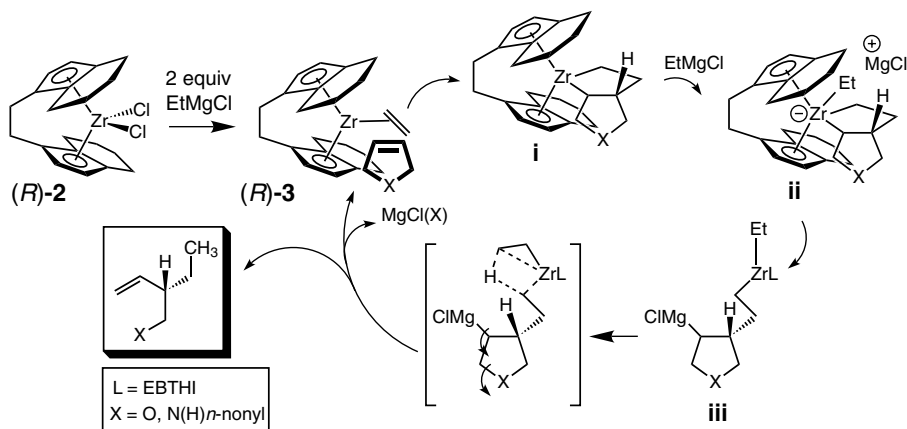
Table 1. (EBTHI)Zr-catalyzed enantioselective ethylmagnesation of unsaturated heterocycles^[a]

entry	Substrate	Product	ee (%)	Yield (%)
1			>97	65
2			>95	75
3			95	73
4			92	75

^[a]Reaction conditions: 10 mol % (*R*)-2, 5.0 equiv. EtMgCl, THF, 22 °C for 6–12 h. Entry 1 with 2.5 mol % (*R*)-2

**Scheme 2.** Demonstration of the utility of (EBTHI)Zr-catalyzed ethylmagnesation in the enantioselective synthesis of the macrocyclic aglycone Sch 38516

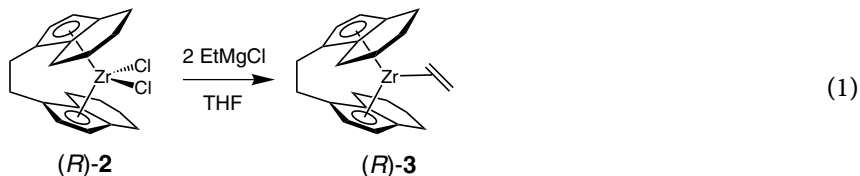
We have utilized the stereoselective ethylmagnesation shown in entry 1 of Table 1 as a key step in the first enantioselective total synthesis of the antifungal agent Sch 38516 [5]. As illustrated in Scheme 2, further functionalization of the



Scheme 3. Catalytic cycle proposed for the (EBTHI)Zr-catalyzed ethylmagnesiation of unsaturated heterocycles

Zr-catalyzed ethylmagnesiation product through three subsequent catalytic procedures (Ti-catalyzed hydromagnesiation, Ni-catalyzed cross-coupling, and Ru-catalyzed oxidation) delivers the requisite carboxylic acid synthon in >99% ee. This synthesis route underlines the utility of the Zr-catalyzed carbomagnesiation protocol: the reaction product carries an alkene and an alcohol function and can thus be readily functionalized to a variety of other non-racemic intermediates.

The catalytic cycle that we have proposed to account for the enantioselective ethylmagnesiations is illustrated in Scheme 3. Asymmetric carbomagnesiation is initiated by the chiral zirconocene-ethylene complex (R)-3, formed upon reaction of dichloride (R)-2 with EtMgCl [Eq (1); the dichloride salt or the binol complex may be used with equal efficiency] [6]. Coupling of the alkene substrate with (R)-3 leads to the formation of the metallacyclopentane intermediate i. In the proposed catalytic cycle, reaction of i with EtMgCl affords zirconate ii, which undergoes Zr-Mg ligand exchange to yield iii. Subsequent β -hydride abstraction, accompanied by intramolecular magnesium-alkoxide elimination, leads to the release of the carbomagnesiation product and regeneration of 3 [7].



An important aspect in the carbomagnesiation of six-membered and larger heterocyclic rings is the exclusive intermediacy of metallacyclopentanes where the C-Zr bond is formed α to the heterocycle C-X bond. Whether the regioselectivity in the zirconacycle formation is kinetically nonselective and rapidly reversible, where it is only one regioisomer that is active in the catalytic cycle, or

whether formation of the metallacycle is kinetically selective (stabilization of electron density upon formation of the C-Zr bond by the adjacent C-X bond) [8], has not been rigorously determined. However, as will be discussed below, the regioselectivity with which the intermediate zirconacyclopentane is formed is critical in the (EBTHI)Zr-catalyzed kinetic resolution of heterocyclic alkenes.

Why does the (EBTHI)Zr system induce such high levels of enantioselectivity in the C-C bond formation process? It is plausible that the observed levels of enantioselection arise from minimization of unfavorable steric and torsional interactions in the complex that is formed between **3** and the heterocycle substrates (Scheme 3). The alternative mode of addition, illustrated in Fig. 1, would lead to costly steric repulsions between the olefin substituents and the cyclohexyl group of the chiral ligand [6]. Thus, reactions of simple terminal olefins under identical conditions results in little or no enantioselectivity. This is presumably because in the absence of the alkenyl substituent (of the carbon that bonds with Zr in **i**) the aforementioned steric interactions are ameliorated and the olefin substrate reacts indiscriminately through the two modes of substrate-catalyst binding represented in Fig. 1.

These alkylation processes become particularly attractive when used in conjunction with the powerful catalytic ring-closing metathesis protocols. The requisite starting materials can be readily prepared in high yield and catalytically [9]. The examples shown in Scheme 4 demonstrate that synthesis of the heterocyclic alkene and subsequent alkylation can be carried out in a single vessel to afford unsaturated alcohols and amides in good yield >99% ee (judged by GLC analysis) [10].

Catalytic alkylations where higher alkyls of magnesium are used (Table 2) proceed less efficiently (35–40% yield of isolated product) but with similarly high levels of enantioselection (>90% ee). A number of issues in connection to the data illustrated in Table 2 merit comment.

(1) With 2,5-dihydrofuran as substrate, at 22 °C a mixture of branched (**4** or **6**) and *n*-alkyl products (**5** or **7**) are obtained. When the reaction mixture is heated to 70 °C, the branched adducts **4** and **6** become the major product isomers. In contrast, with the six-membered heterocycle, reactions at 22 °C are selective (entries 3 and 6, Table 2).

(2) With *n*-BuMgCl as the alkylating agent, high levels of diastereoselection are observed as well (entry 6).

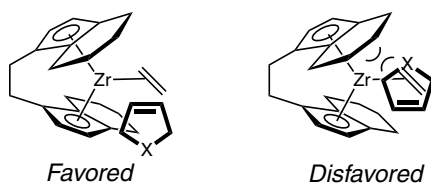
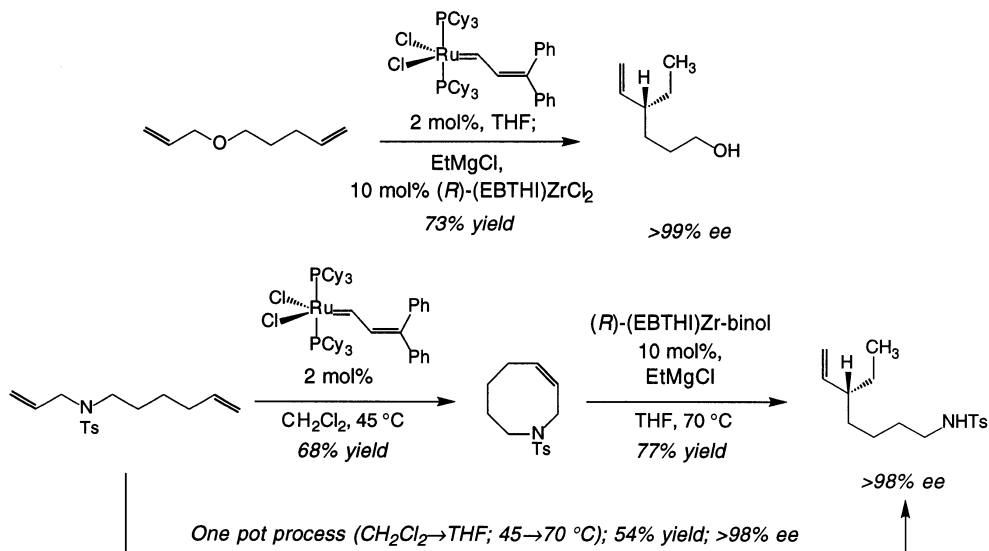


Fig. 1. Substrate-catalyst (**3**) interactions favor a specific mode of alkene insertion into the zirconocene complex


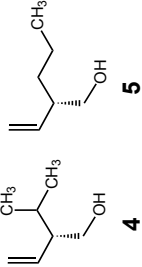


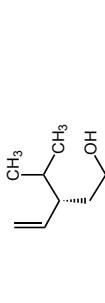

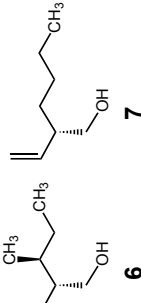


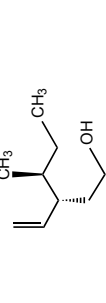


Scheme 4. Ru-catalyzed ring-closing metathesis processes, in conjunction with Zr-catalyzed enantioselective alkylation reactions provide a convenient protocol for efficient synthesis of optically pure materials

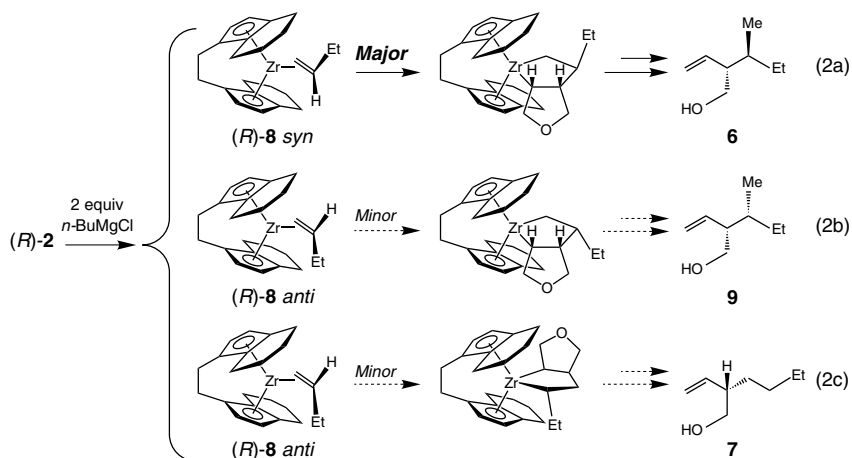
The aforementioned observations carry significant mechanistic implications. As illustrated in Eqs. (2a–c), in the chemistry of zirconocene-alkene complexes that are derived from the longer chain alkylmagnesium halides several additional selectivity issues present themselves.

- (1) The derived transition metal-alkene complex can exist in two diastereomeric forms, exemplified in Eqs. (2a, b) with (*R*)-**8** *anti* and *syn*; reaction through these stereoisomeric complexes can lead to the formation of different product diastereomers [compare Eqs. (2a) and (2b), or Eqs. (2b) and (2c)]. The data in Table 2 indicate that the mode of addition shown in Eq (2a) is preferred.
- (2) As illustrated in Eqs. (2b) and (2c), the carbomagnesation process can afford either the *n*-alkyl or the branched product. Alkene substrate insertion from the more substituted front of the zirconocene-alkene system affords the branched isomer [Eq. (2b)], whereas reaction from the less substituted end of the (EBTHI)Zr-olefin system leads to the formation of the straight chain product [Eq. (2c)]. The results shown in Table 2 indicate that, depending on the reaction conditions, products derived from the two isomeric metallacyclopentane formation can be competitive.

Table 2. (EBTHI)Zr-catalyzed enantioselective carbomagnesation of unsaturated heterocycles with longer chain alkylmagnesium chlorides^[a]

Entry	Substrate	Major product(s)	Tem- perature (°C)	RMgCl	Regio selectivity	ee,%	Diastereoselectivity
1			22	<i>n</i> -PrMgCl	2 : 1	99 (4), 99 (5)	--
2			70	<i>n</i> -PrMgCl	20 : 1	94 (4)	--
3			22	<i>n</i> -PrMgCl	>25 : 1	98	--
4			22	<i>n</i> -BuMgCl	2 : 1	>99 (6), >99 (7)	15 : 1
5			70	<i>n</i> -BuMgCl	15 : 1	90 (6)	13 : 1
6			22	<i>n</i> -BuMgCl	>25 : 1	>95	>25 : 1

^[a]Reaction conditions: 5 equiv alkylMgCl, 10 mol % (*R*)-**2**, 16 h; all yields: 35–40% after silica gel chromatography



Detailed studies from these laboratories shed light on the mechanistic intricacies of asymmetric catalytic carbomagnesations, allowing for an understanding of the above trends in regio- and stereoselectivity [6]. Importantly, our mechanistic studies indicate that there is no preference for the formation of either the *anti* or the *syn* (EBTHI)Zr-olefin isomers (e.g., **8 anti** vs **8 syn**); it is only that one metallocene-alkene diastereomer (*syn*) is more reactive. Our mechanistic studies also indicate that zirconacyclopentane intermediates (**i** in Scheme 3) do not spontaneously eliminate to the derived zirconocene-alkoxide; Zr-Mg ligand exchange is likely a prerequisite for the alkoxide elimination and formation of the terminal alkene.

2.2

Zr-Catalyzed Kinetic Resolution of Unsaturated Heterocycles

The high levels of enantioselectivity obtained in the asymmetric catalytic carbomagnesation reactions (Tables 1 and 2) imply an organized (EBTHI)Zr-alkene complex interaction with the heterocyclic alkene substrates. It therefore follows that if chiral unsaturated pyrans or furans are employed, the resident center of asymmetry may induce differential rates of reaction, such that after ~50% conversion one enantiomer of the chiral alkene can be recovered in high enantiomeric purity. As an example, molecular models indicate that with a 2-substituted pyran, as shown in Fig. 2, mode of addition labeled as I should be significantly favored over II or III, where unfavorable steric interactions between the (EBTHI)Zr-complex and the olefinic substrate should lead to significant catalyst-substrate complex destabilization.

As the data in Table 3 indicate, in the presence of catalytic amounts of non-racemic (EBTHI)ZrCl₂, a variety of unsaturated pyrans can be resolved effectively to deliver these synthetically useful heterocycles in excellent enantiomeric puri-

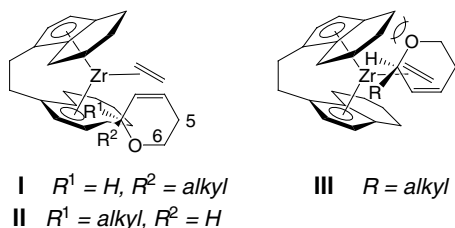


Fig. 2. Preferential association of one pyran enantiomer with (R)-(EBTHI)Zr-ethylene complex

Table 3. (EBTHI)Zr-catalyzed kinetic resolution of unsaturated pyrans^[a]

Entry	Substrate	Conversion (%)	Mol. % cat.	Unreacted substrate config., ee(%)	
1		60	10	R, 96	
2		60	10	S, 41	
3		a R = MgCl	56	10	R, >99
		b R = TBS	60	10	R, >99
4		58	20	R, 99	
5		a R = MgCl	63	10	R, >99
		b R = TBS	61	10	R, 94

^[a]Reaction conditions: indicated mol % (R)-2, 5.0 equiv of EtMgCl, 70 °C, THF. Mass recovery in all reactions >85%

ty [11]. A number of important issues in connection to the catalytic kinetic resolution of pyrans are noteworthy.

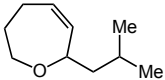
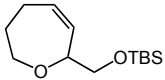
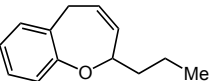
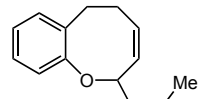
- (1) Reactions performed at elevated temperatures (70 °C) afford recovered starting materials with significantly higher levels of enantiomeric purity, compared to processes carried out at 22 °C. For example, the 2-substituted pyran shown in entry 1 of Table 3, when subjected to the same reaction conditions but at room temperature, is recovered after 60% conversion in 88% ee (vs 96% ee at 70 °C).
- (2) Consistent with the models illustrated in Fig. 2, 6-substituted pyrans (Table 3, entry 2) are not resolved effectively (C6 substituent should not strongly in-

- teract with the catalyst structure; see Fig. 2); however, with a C2 substituent also present, resolution proceeds with excellent efficiency (entry 3).
- (3) Pyrans that bear a C5 group are resolved with high selectivity as well (entry 4). In this class of substrates, one enantiomer reacts more slowly, presumably because its association with the zirconocene-alkene complex leads to sterically unfavorable interactions between the C5 alkyl unit and the coordinated ethylene ligand.

As the representative data in Table 4 indicate, the Zr-catalyzed resolution technology may be applied to medium ring heterocycles as well; in certain instances (e.g., entries 1 and 2) the recovered starting material can be obtained with outstanding enantiomeric purity. Comparison of the data shown in entries 1 and 3 of Table 4 indicates that the presence of an aromatic substituent can have an adverse influence on the outcome of the catalytic resolution. That the eight-membered ring substrate in Table 4 (entry 4) is resolved more efficiently may imply that the origin of the adverse influence is more due to conformational preferences of the heterocycle than the attendant electronic factors (α phenoxy group is a better leaving group than an alkoxy unit).

Availability of oxepins that carry a side chain containing a Lewis basic oxygen atom (entry 2, Table 4) has further important implications in enantioselective synthesis: The derived alcohol, benzyl ether or MEM-ethers, where resident Lewis basic heteroatoms are less sterically hindered, undergo diastereoselective uncatalyzed alkylation reactions readily when treated to a variety of Grignard

Table 4. Zirconocene-catalyzed kinetic resolution of 2-substituted medium ring heterocycles^[a]

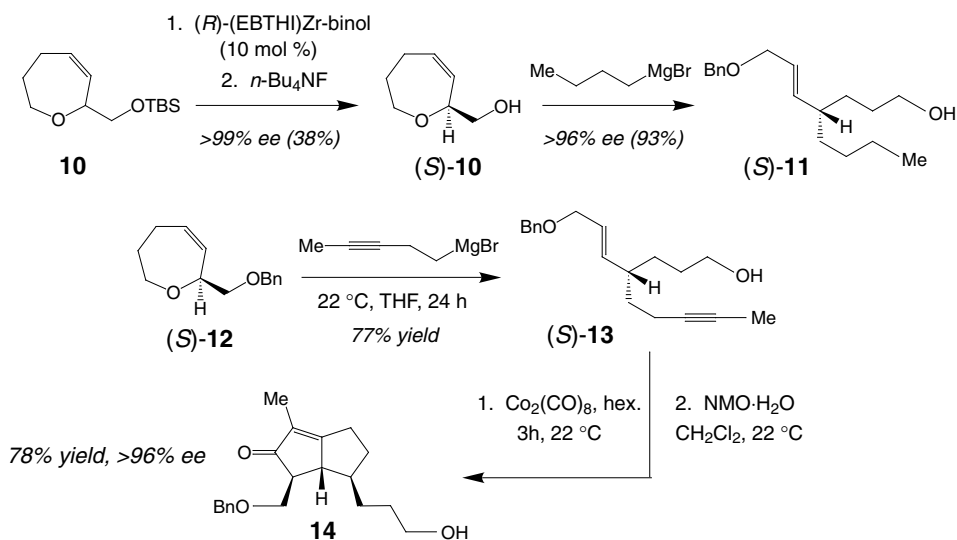
Entry	Substrate	Conversion (%)	time	Unreacted substrate config., ee(%)
1		58	30 min	<i>R</i> , >99
2		63	100 min	<i>R</i> , 96
3		60	8 hr	<i>R</i> , 60
4		63	11 hr	<i>R</i> , 79

^[a]Reaction conditions: indicated mol % (*R*)-2, 5.0 equiv of EtMgCl, 70 °C, THF. Mass recovery in all reactions >85%

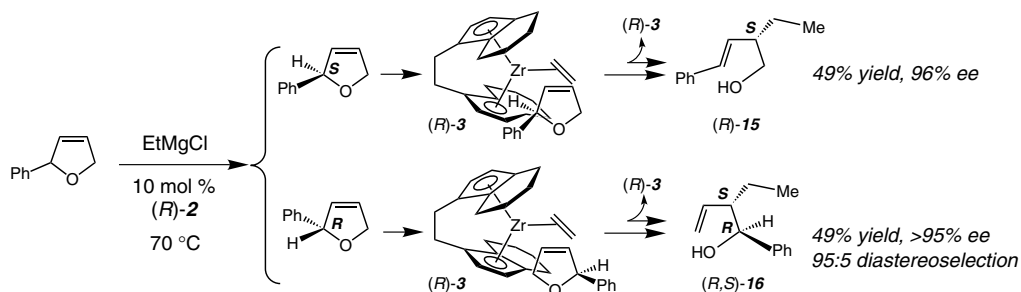
reagents [12]. The examples shown in Scheme 5 serve to demonstrate the excellent synthetic potential of these stereoselective alkylation technologies.

Thus, resolution of the TBS-protected oxepin **10**, conversion to the derived alcohol and diastereoselective alkylation with *n*BuMgBr affords **11** with >96% ee in 93% yield. As shown in Scheme 5, alkylation of (*S*)-**12** with an alkyne-bearing Grignard agent (\rightarrow (*S*)-**13**), allows for a subsequent Pauson-Khand cyclization reaction to provide the corresponding bicyclic compound **14** in the optically pure form. In connection with the facility of these olefin alkylations, it is important to note that the asymmetric Zr-catalyzed alkylations with longer chain alkylmagnesium halides (see Table 2) are more sluggish than those involving EtMgCl. Furthermore, when catalytic alkylation does occur, the corresponding branched products are obtained; that is, with *n*-PrMgCl and *n*-BuMgCl, *i*-Pr and *sec*-Bu addition products are formed, respectively [10]. The uncatalyzed alkylation reaction described here thus complements the enantioselective Zr-catalyzed protocol.

Zirconocene-catalyzed kinetic resolution of dihydrofurans is also possible, as illustrated in Scheme 6 [13]. Unlike their six-membered ring counterparts, both of the heterocycle enantiomers react readily, but through distinctly different reaction pathways, to afford – in high diastereomeric and enantiomeric purity – constitutional isomers that are readily separable. A plausible reason for the difference in the reactivity pattern of pyrans and furans is that, in the latter group of compounds, both olefinic carbons are adjacent to a C-O bond: C-Zr bond formation can take place at either end of the C-C π -system. The furan substrate and



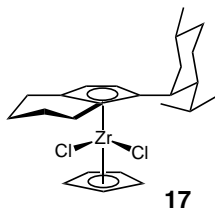
Scheme 5. Chiral medium-ring heterocycles that have been resolved by the Zr-catalyzed kinetic resolution are subject to highly diastereoselective alkylations that afford synthetically useful materials in the optically pure form



Scheme 6. (EBTHI)Zr-catalyzed kinetic resolution of dihydrofurans

the (EBTHI)Zr-alkene complex (R)-**3** interact so that unfavorable steric interactions are avoided, leading to the formation of readily separable non-racemic products in the manner illustrated in Scheme 6.

Subsequent to our studies, Whitby and coworkers reported that the enantioselective alkylations of the type illustrated in Scheme 6 can also be carried out with the non-bridged chiral zirconocene **17** [14]. Enantioselectivities are, however, notably lower when alkylations are carried out in the presence of **17**. As an example, the new chiral metallocene affords **15** and **16** (Scheme 6) in 82% and 78% ee, respectively.

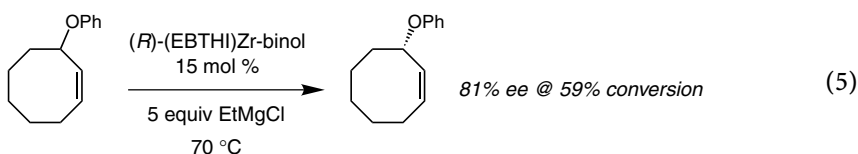
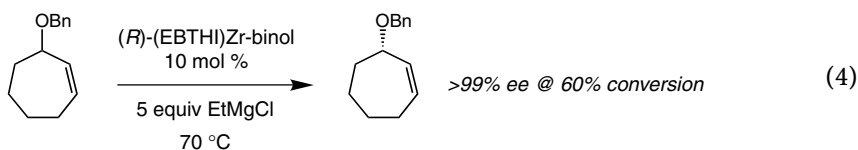
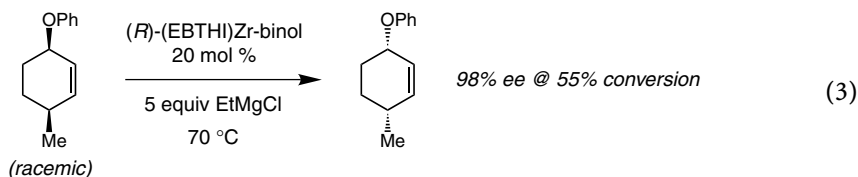


2.3

Zr-Catalyzed Kinetic Resolution of Cyclic Allylic Ethers

As depicted in Eqs (3)–(5), kinetic resolution of a variety of cyclic allylic ethers is effected by asymmetric Zr-catalyzed carbomagnesation. Importantly, in addition to six-membered ethers, seven- and eight-membered ring systems can be readily resolved by the Zr-catalyzed protocol. It is worthy of note that the powerful Ti-catalyzed asymmetric epoxidation procedure of Sharpless [15] is often used in the preparation of optically pure acyclic allylic alcohols through the catalytic kinetic resolution of easily accessible racemic mixtures [16]. When the catalytic epoxidation is applied to cyclic allylic substrates, reaction rates are retarded and lower levels of enantioselectivity are observed. Ru-catalyzed asymmetric hydrogenation has been employed by Noyori to effect resolution of five-

and six-membered allylic carbinols [17]; in this instance, as with the Ti-catalyzed procedure, the presence of an unprotected hydroxyl function is required.



Modes of addition shown in Fig. 3 are similar to those shown in Fig. 2 and are consistent with existing mechanistic work [5, 6]; they accurately predict the identity of the slower reacting enantiomer. It must be noted, however, that variations in the observed *levels* of selectivity as a function of the steric and electronic natures of substituents and the ring size cannot be predicted based on these models alone; more subtle factors are clearly at work. In spite of such mechanistic questions, the metal-catalyzed resolution protocol provides an attractive option in asymmetric synthesis. This is because, although the maximum possible yield is $\sim 40\%$, it requires easily accessible racemic starting materials and conversion levels can be manipulated so that truly pure samples of substrate enantiomers are obtained.

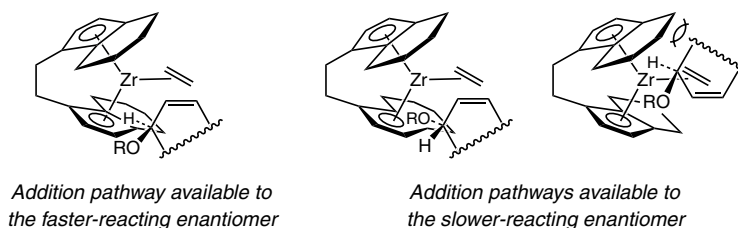
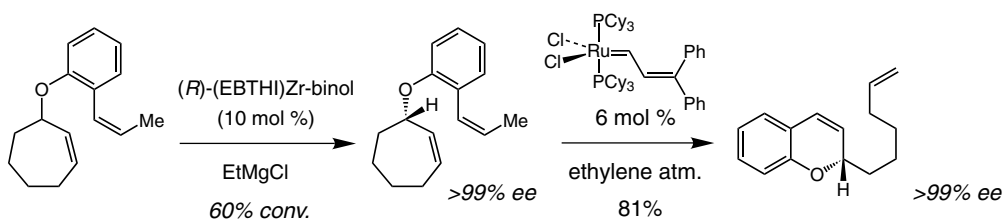


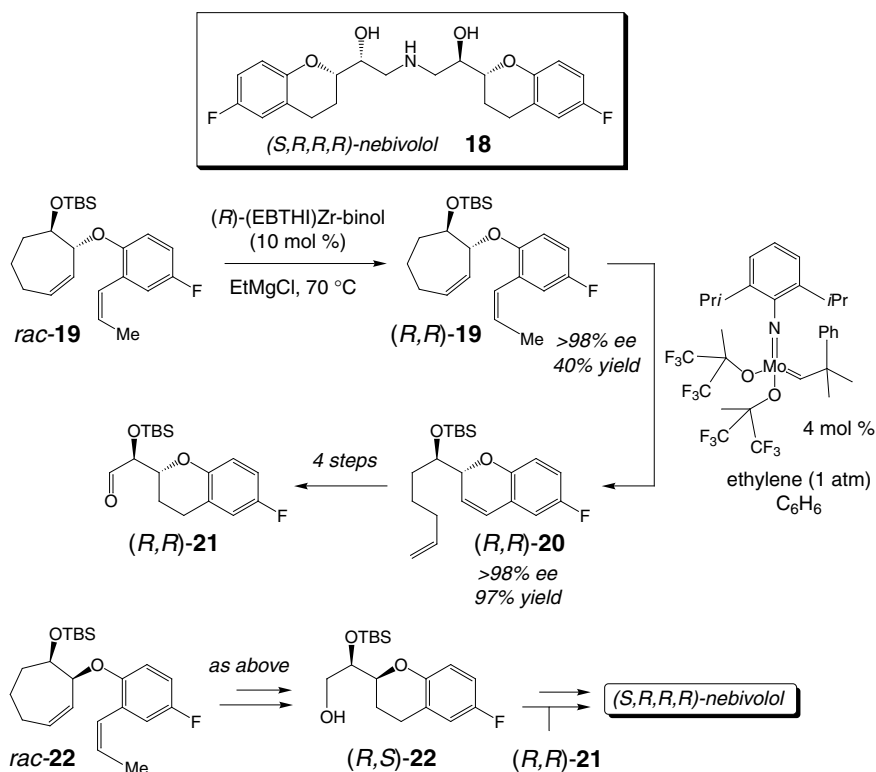
Fig. 3. Various modes of addition of cyclic allylic ethers to (EBTHI)Zr-alkene complex

The synthetic versatility and significance of the Zr-catalyzed kinetic resolution of cyclic allylic ethers is readily demonstrated in the example provided in Scheme 7. Optically pure starting allylic ether, obtained by the above-mentioned catalytic kinetic resolution, undergoes a facile Ru-catalyzed rearrangement to afford chromene in $>99\%$ ee [18]. Unlike unsaturated pyrans discussed above, chiral 2-substituted chromenes are not readily resolved by the Zr-catalyzed protocol. Optically pure styrenyl ethers, such as that shown in Scheme 7, are readily obtained by the Zr-catalyzed kinetic resolution, allowing for the efficient and enantioselective preparation of these important chromene heterocycles by a sequential catalytic protocol.

To examine and challenge the utility of the two-step catalytic resolution-chromene synthesis process in synthesis [19], we undertook a convergent and enantioselective total synthesis of the potent antihypertensive agent (*S,R,R,R*)-neбиволол (**18**) [20]. As illustrated in Scheme 8, the two key fragments (*R,R*)-**21** and (*R,S*)-**22**, which were subsequently joined to afford the target molecule, were prepared in the optically pure form by the catalytic resolution technology discussed above. Importantly, efficient and selective methods were established for the modification of the chromene alkenyl side chain. These studies allowed us to enhance the utility of the initial methodological investigations: they demonstrate that, although the carbocyclic system may be used as the framework for the Zr- and the Mo-catalyzed reactions, the resulting 2-substituted chromene can be functionalized in a variety of manners to afford a multitude of chiral non-racemic heterocycles [21]. Another interesting feature of this total synthesis is that, whereas the preparation of (*R,R*)-**19** requires the use of the (*R*)-Zr(EBTHI) catalyst, synthesis of (*R,S*)-**22** is carried out by catalytic kinetic resolution with (*S*)-Zr(EBTHI) complex. Thus, the recently developed procedure of Buchwald [22] is used to resolve *rac*-(EBTHI)Zr to obtain (*R*)-Zr(EBTHI)-binol and (*S*)-Zr(EBTHI)-biphen to accomplish this total synthesis in an efficient manner.



Scheme 7. Tandem Zr-catalyzed kinetic resolution and Ru-catalyzed rearrangement affords chiral chromenes in high enantiomeric purity



Scheme 8. The tandem Zr-catalyzed kinetic resolution, Mo-catalyzed conversion of styrenyl ethers to chromenes is used in the first convergent and enantioselective total synthesis of the antihypertensive agent (S,R,R,R)-neбиволol

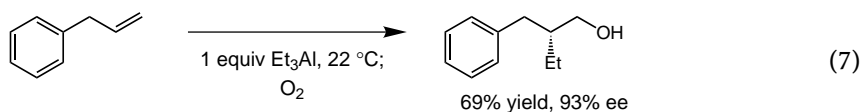
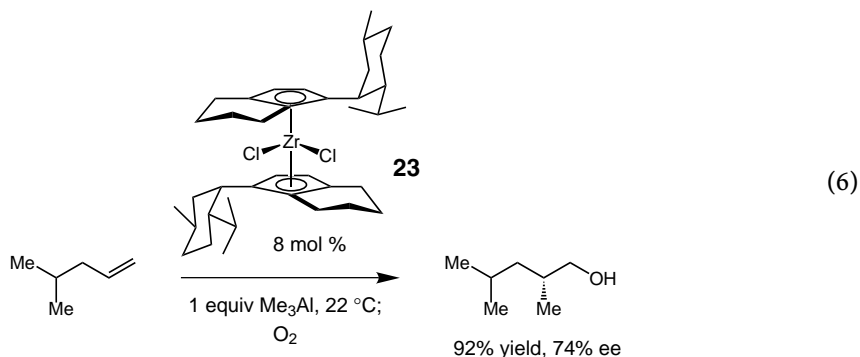
2.4

Catalytic Enantioselective Alkylation of Olefins with Alkylaluminums

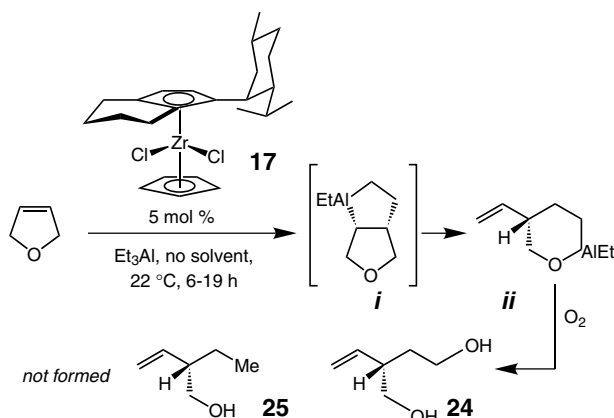
The zirconocene-catalyzed enantioselective carbomagnesation accomplishes the addition of an alkylmagnesium halide to an alkene, where the resulting carbometallation product is suitable for a variety of additional functionalization reactions (see Scheme 2). Excellent enantioselectivity is obtained in reactions with Et-, *n*-Pr- and *n*-BuMgCl, and the catalytic resolution processes allow for preparation of a variety of non-racemic heterocycles. Nonetheless, the development of reaction processes where a larger variety of olefinic substrates and alkylmetals (e.g., methyl-, vinyl-, phenylmagnesium halides, etc.) can be added to unfunctionalized alkenes efficiently and enantioselectively stands as a challenging goal in enantioselective reaction design.

As illustrated below [Eqs. (6) and (7)], recent reports by Negishi and coworkers, where Erker's non-bridged chiral zirconocene **23** [23] is used as catalyst, is

an important and impressive step towards this end [24]. An impressive range of alkylaluminum reagents can be added with high efficiency and excellent enantioselectivity (>90% ee). A remarkable aspect of this work is that through a change in reaction medium (1,1,1-trichloroethane is used as solvent), catalytic alkylations proceed through carbometallation of the alkene (direct addition of cationic alkylzirconium to the olefin, followed by Zr-Al ligand exchange), rather than involving the formation of a metallacyclopentane; under conditions that zirconocyclopentanes serve as intermediates, selectivities are notably lower. Another notable aspect of the Negishi work is that the use of Erker system appears to be imperative: with the aforementioned (EBTHI)Zr as catalyst, alkylations are not as efficient or stereoselective.



In 1997, Whitby reported that treatment of 2,5-dihydrofuran with Et_3Al in the presence of 5 mol % **17** leads to the enantioselective formation of **24**, rather than the product obtained from catalytic carbomagnesations (**25**) [25]. This outcome can be rationalized based on Dzhemilev's pioneering report that with Et_3Al , in contrast to EtMgCl (see Scheme 3), the intermediate aluminacyclopentane (*i*) is converted to the corresponding aluminaoxacyclopentane *ii* (Scheme 9). To ensure the predominant formation of **24**, however, catalytic alkylations must be carried out in absence of any solvent.



Scheme 9. Zr-catalyzed enantioselective alkylation with neat Et_3Al can lead to an alternate reactivity pattern (formation of **27** rather than **25**)

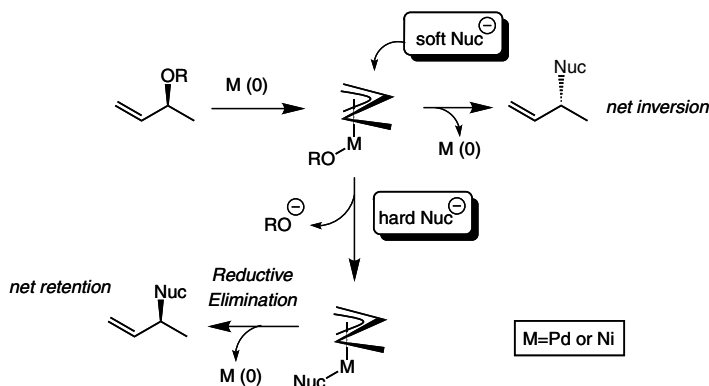
3

Ni-Catalyzed Enantioselective Alkylation Reactions

In the Zr-catalyzed enantioselective alkylation reactions discussed above, we discussed transformations that involve the addition of alkylmagnesium halides and alkylaluminum reagents to olefins. With the exception of studies carried out by Negishi and coworkers, all other processes involve the reaction of a C-C π system that is adjacent to a C-O bond. Also with the exception of the Negishi study [Eqs. (6) and (7)], where direct olefin carbometallation occurs, all enantioselective alkylations involve the intermediacy of a metallacyclopentane (cf. Scheme 3). In this segment of our discussion, we will examine the Ni-catalyzed addition of hard nucleophiles (e.g., alkylmagnesium halides) to olefins that bear a neighboring C-O unit. These reactions transpire by neither of the above two mechanistic manifolds (metallacyclopentane intermediacy or direct carbometallation). Rather, these processes take place via a Ni- π -allyl complex.

Allylic ethers and alcohols have long been known to react with Grignard reagents in the presence of an appropriate Ni-based complex containing phosphine ligands [26]. These reactions are related to the well-studied Pd-catalyzed allylic substitution reactions that utilize soft nucleophiles [27], and a number of important mechanistic studies on the stereochemical outcome of this class of transformations have been carried out [28].

In general, the catalytic cycle for the transition-metal catalyzed allylic substitution reactions involves initial attack of the metal at the double bond followed by oxidative insertion into the antiperiplanar C-O bond to afford the π -allyl system. At this point, depending on whether soft or hard nucleophiles are used, however, the alkylation reaction proceeds through distinctly different pathways (Scheme 10). With soft nucleophiles, where Pd is often the metal center of choice,



Scheme 10. Depending on the nature of the incoming nucleophile, the addition to the metal- π -allyl complex may proceed with retention or inversion of stereochemistry

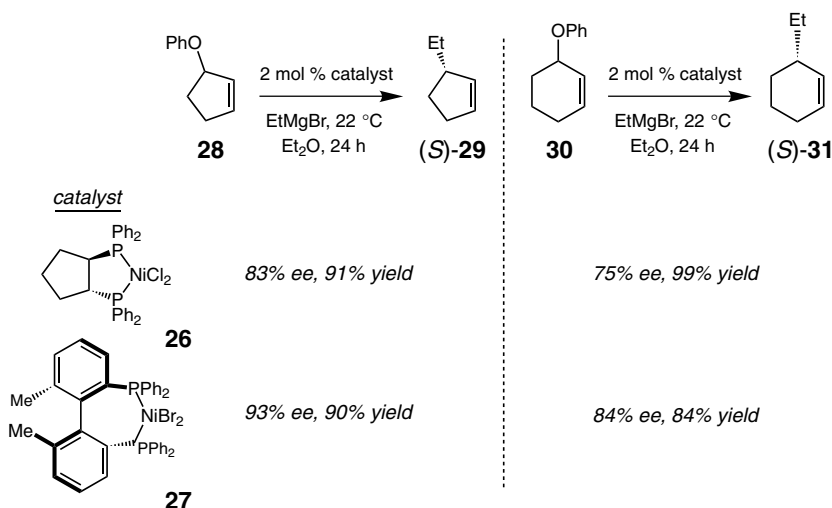
reactions proceed by the backside addition of the nucleophile to the π -allyl system, to afford the new C-C bond with net inversion of stereochemistry. However, with hard nucleophiles, where Ni can serve as an effective transition metal template, the reaction usually involves the initial addition of the alkylmetal to the transition metal center, followed by a reductive elimination to lead to the generation of the C-C bond. Such reactions, as a result, take place with net retention of stereochemistry.

From a reaction design point of view, the latter class of reactions present a more attractive strategy for the transfer of chirality from chiral ligands on the metal to the C-C bond forming event. Indeed, a number of research teams have developed ingenious ligands that overcome the geometric distance that exist in the anti addition of soft nucleophiles to metal- π -allyl systems – a factor that is expected to diminish the asymmetric induction that may be caused by the metal's chiral ligands [29]. With the reaction of hard nucleophiles, since the alkyl group adds from the same environment inhabited by the metal's chiral ligands, the influence of such ligands in transferring their chirality should be more pronounced.

3.1

Asymmetric Ni-Catalyzed Addition of Grignard Reagents to Allylic Ethers

As illustrated in Scheme 11, Consiglio and coworkers have shown that in the presence of an appropriate chiral Ni catalyst, the addition of EtMgBr to cyclic allylic phenyl ethers occurs with high enantioselection and excellent yield (>90%) [30]. Thus, in the presence of 2 mol % Ni dibromide or dichloride complexes of (+)-(R,R)-cyclopentane-1,2-diylbis(diphenylphosphine) (**26**), reaction of cyclopentenyl ether **28** with EtMgBr results in the formation of 1-ethylcyclopentene (*S*)-**29** in 91% yield and with 83% ee. Higher levels of enantiocontrol are observed when (*R*)-6,6'-dimethylbiphenyl-2,2'-diylbis(diphenylphosphine) (bi-



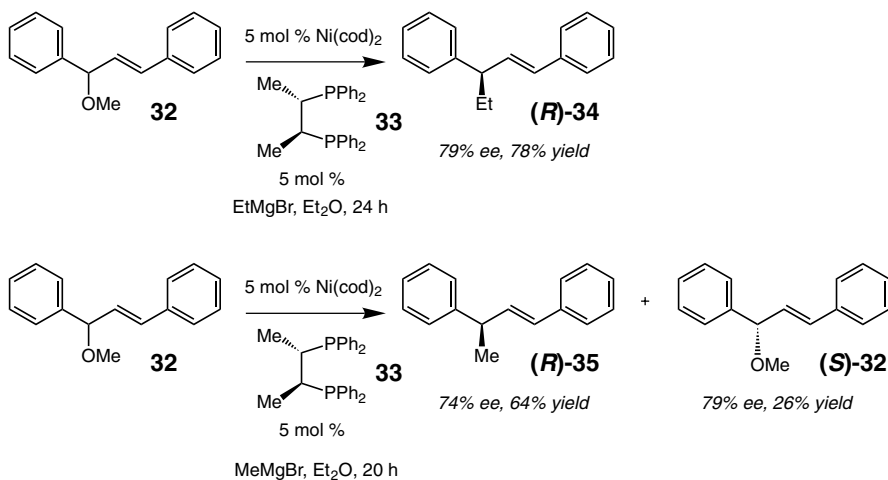
Scheme 11. Ni-catalyzed allylic substitution reactions with EtMgBr

phemp, 27) is used as the chiral ligand: (*S*)-**29** is obtained in 93% ee and 90% yield. Variation of catalyst structures demonstrated that the enantioselectivity is dependent on steric rather than electronic factors; in contrast, the nature of the leaving group, solvent or of the halide of the Grignard reagent proved not to affect to outcomes of catalytic alkylations.

Catalytic allylic substitutions with cyclohexenyl substrate **30** proceeds following similar overall trends but with generally lower levels of enantioselection (Scheme 11). Consiglio has suggested that this difference in enantiofacial selectivity may be attributed to the more rigid allyl moiety in the five-membered ring starting material **28**. The present catalytic enantioselective C-C bond forming reaction is only appreciably enantioselective when EtMgBr is used (e.g., 12% ee with MeMgBr and 71% ee with *n*-PrMgBr). Nonetheless this study represents a critical first step towards the development of this class of catalytic asymmetric reactions and does allow ready access to various optically enriched cyclic hydrocarbons.

More recently, RajanBabu has reported that in the presence of appropriate chiral Ni-based catalysts, enantioselective addition of Grignard reagents to acyclic allylic ethers may be effected (Scheme 12) [31]. Within this context, a systematic study of the effect of reaction solvent, leaving groups, chiral ligands and nucleophiles was undertaken. As shown in Scheme 12, treatment of allylic ether **32** with EtMgBr in the presence of 5 mol % of (*S,S*)-chiraphos-Ni complex [formed upon treatment of Ni(cod)₂ with (*S,S*)-chiraphos **33**] results in the formation of (*R*)-**34** in 79% ee and 78% yield.

A significant corollary to the RajanBabu study is that the Ni-catalyzed allylic substitution may be used in the catalytic kinetic resolution of related chiral allylic ethers. That is, under the same reaction conditions as described above, the



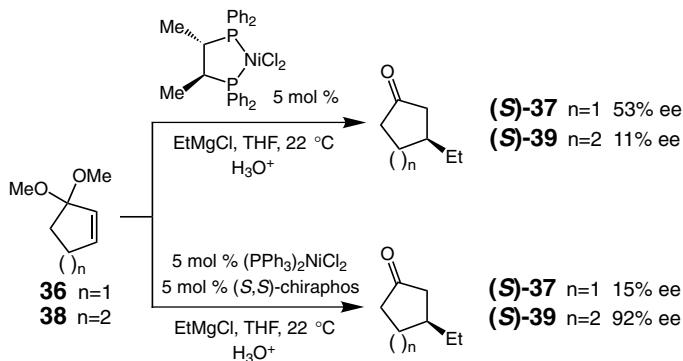
Scheme 12. Ni-catalyzed addition of alkylmagnesium halides to acyclic allylic ethers can effect both catalytic enantioselective alkylation and kinetic resolution

allylic ether substrate is recovered in 79% ee (26% yield); furthermore, the alkylation product is isolated in 74% ee and 64% yield. These data in relation to Ni-catalyzed kinetic resolution of acyclic allylic ethers are particularly noteworthy in light of the fact that Consiglio had originally reported that in the catalytic alkylation of racemic 1-phenoxy-cycloalkenes, there is little or no rate difference between the transformations of the two substrate enantiomers [32]. Since a Ni- π -allyl intermediate is likely formed in these reactions, such kinetic resolution data suggest that, at least in certain systems, the ionization step be enantioselective and could be exploited for control of stereoselectivity.

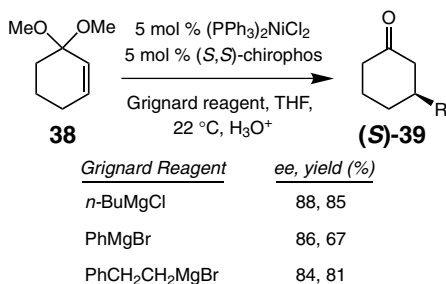
3.2

Asymmetric Ni-Catalyzed Addition of Grignard Reagents to Allylic Acetals

Research in our laboratories has been directed towards the development of Ni-catalyzed and enantioselective addition of Grignard reagents to allylic acetals. In the presence of appropriate Ni complexes [e.g., (dppe)NiCl₂], these reactions proceed with excellent regioselectivity. As illustrated in Scheme 13, we recently established that when cyclopentenyl acetal **36** is treated with EtMgCl in the presence of (*S,S*)-chiraphosNiCl₂, (*S*)-**37** is obtained in 53% ee and 85% yield [33]. When the chiral catalyst is prepared *in situ*, by premixing of (PPh₃)₂NiCl₂ and (*S,S*)-chiraphos, enantioselectivity drops to 15%, as there is ~25% background reaction in the presence (PPh₃)₂NiCl₂. When cyclohexenyl acetal **38** is treated with (*S,S*)-chiraphosNiCl₂, **39** is obtained in only 11% ee and 80% yield. Remarkably, when the *in situ* method is utilized, (*S*)-**39** is formed in 92% ee (90% yield). Control experiments clearly indicate that it is the excess PPh₃ present in the *in situ* method is responsible for the dramatic improvement in enantioselectivity.



Scheme 13. Ni-catalyzed addition of alkylmagnesium halides to unsaturated cyclohexenyl acetals is significantly more enantioselective in the presence of excess PPh_3



Scheme 14. Ni-catalyzed addition of alkylmagnesium halides to unsaturated cyclohexenyl acetals

tion. That there is no diminution of selectivity with the *in situ* method is consistent with the fact that six-membered ring acetals are inert towards alkylmagnesium halides in the presence of $(\text{PPh}_3)_2\text{NiCl}_2$. The notable enhancement in selectivity is intriguing and unexpected however.

A better understanding of the above mechanistic dilemma will require future detailed mechanistic studies. Nonetheless, as shown in Scheme 14, a variety of Grignard reagents can be used in these Ni-catalyzed enantioselective alkylations to afford a range of non-racemic materials in excellent yield.

4

Summary and Outlook

The chemistry described in this article demonstrates that chiral metallocene and Ni-phosphine complexes can be used to effect an important reaction that is largely unprecedented in classical organic chemistry: addition of alkylmagnesi-

um halides to unactivated olefins. Although EBTHI metallocenes have proven to be effective at promoting the above enantioselective transformations, the equipment required to prepare such catalysts (glovebox and high pressure hydrogenation apparatus), as well as costs associated with the required metallocene resolution (non-racemic binaphthol=\$45/1 g) suggests that more attractive catalyst alternatives may be desired. Promising advances toward more facile syntheses of inexpensive and chiral (EBTHI)MX₂ equivalents may eventually provide more practical alternatives to this powerful class of transition metal catalysts. As discussed above, recent advances in the use of non-bridged metallocenes, where a resolution step is obviated, may also provide attractive and effective solutions to this problem.

Although the chemistry reviewed in this article demonstrates a variety of formerly-inaccessible protocols which are now available that afford C-C bonds in an enantioselective manner, we are a long way away from having reached a point where sufficiently diverse protocols are available that will allow us to catalytically and enantioselectively alkylate a considerable range of alkene substrates with almost any alkylmetal system. To reach this goal, metals other than Zr, Ni, Mg and Al may have to be brought into the fold. There is thus little doubt that future exciting discoveries in the area of design and development of useful asymmetric catalytic C-C bond forming transformations are in the making.

Acknowledgements: The National Institutes of Health (GM-47480) and the National Science Foundation (CHE-9257580 and CHE-9632278) provide generous support of our programs. Additional support from Pfizer, Johnson & Johnson, Eli Lilly, Zeneca, Glaxo, Monsanto, Sloan and Dreyfus Foundations and the Spanish Ministry of Education are acknowledged. We are most grateful to our co-workers and colleagues Zhongmin Xu, James P. Morken, Ahmad F. Hourri, Mary T. Didiuk, Michael S. Visser, Joseph P. A. Harrity, Charles W. Johannes, Jeffrey A. Adams, Daniel C. La, Enrique-Bengoa Gomez, Gabriel A. Weatherhead, Courtney Luchaco, Nina R. Horan, Derek A. Cogan and John D. Gleason for their important contributions to various aspects of the projects described herein.

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Chapter 14

Heck Reaction

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Keywords: Carbopalladation, Asymmetric Heck reaction, Vinylation, Arylation

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1**Introduction**

The palladium mediated coupling of aryl or vinyl iodides, bromides, or triflates with alkenes in the presence of base, in other words, the Pd-catalyzed arylation or vinylation of alkenes, is generally referred to as the Heck reaction. It has been known to synthetic chemists since the late 1960s [1, 2, 3]. As a great advantage the Heck reaction is not limited to activated alkenes. The substrate can be a simple olefin (with ethylene being the most reactive one), or it can contain a variety of functional groups, such as ester, ether, carboxyl, phenolic, or cyano groups. In spite of it displaying many of the benefits usually associated with Pd-mediated reactions [4] (in particular, ease of scale-up and tolerance of water and/or other functional groups), interest in the reaction has been sporadic, largely due to problems of regiocontrol in the case of unsymmetrical alkene substrates and to an incomplete understanding of the reaction mechanism. In recent years, however, the attention paid to the reaction has increased dramatically [5], and perhaps the most significant development to date has been the advent of an enantioselective variant [6, 7].

Given the many reports of chiral phosphine ligands dating from the early 1970s [8], it is perhaps somewhat surprising that the phosphine-mediated Heck reaction was not subjected to asymmetrization attempts until the late 1980s, although in fairness it can be pointed out that the reaction has not usually been used to generate stereogenic centers [9], and that for many years chelating diphosphines in general were thought to be unsuitable catalysts [10]. Reports of successful examples of the asymmetric Heck reaction (hereafter abbreviated AHR) were, however, published in 1989 and the reaction has since been successfully developed to the point where both tertiary and quaternary centers can be generated with *ee*'s $\geq 80\%$. The bulk of the reported examples involve intramolecular reactions (i.e., ring closures) [11], which have the advantage of allowing relatively easy control of alkene regiochemistry and geometry in the product and of tolerating less reactive alkene substrates. In contrast, successful intermolecular reactions have until very recently been limited to quite reactive substrates, principally O- and N-heterocycles, and to the formation of tertiary centers on ring carbon atoms, which again simplifies the question of alkene regiochemistry.

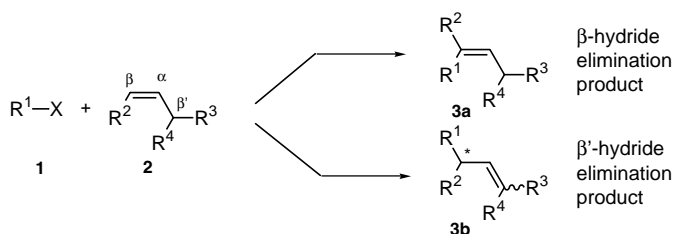
The present paper gives a survey of the relevant literature up to the end of 1997, beginning with a discussion of the mechanistic aspects relevant for stereoselection in the AHR and concluding with an assessment of likely future developments. The classification of the sections proceeds according to the various types of underlying carbon skeletons or natural product fragments of the resulting compounds. Diastereoselective variations [5] which have been frequently utilized for the construction of natural products are generally not included. At present, no enzymatic methods for the arylation or vinylation of alkenes in the laboratory are known.

2 Mechanism

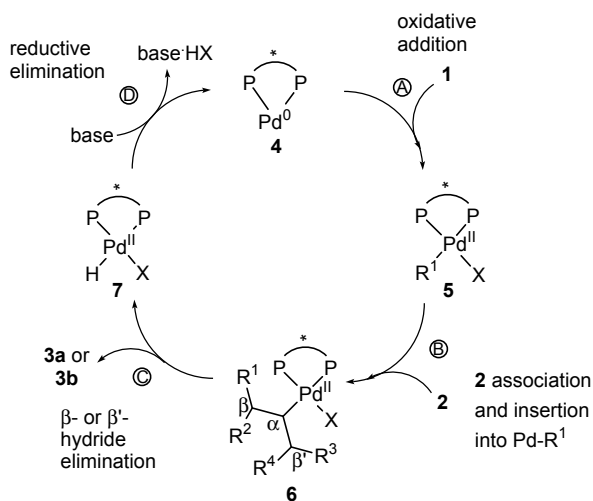
Comprehensive overviews of the current state of mechanistic theory regarding the Heck reaction have been provided in two recent review articles [5, 12]. In the following the discussion will be a selective one, focusing primarily on the factors which impart the regio- and enantiocontrol necessary for a successful AHR [13, 14].

2.1 Factors Governing Regioselectivity

The mechanism of the Heck reaction (Scheme 1a) with bidentate phosphine ligands is generally thought to follow the four-step catalytic cycle shown in Scheme 1b, with the individual steps being: A) oxidative addition of **1** to the Pd⁰



Scheme 1a. Heck reaction with disubstituted alkenes bearing β- and β'-hydrogens



Scheme 1b. Catalytic cycle for the Heck reaction

species **4**, bearing a bidentate phosphine ligand, to give the Pd^{II} species **5**, B) coordination and then *syn*-insertion of the alkene substrate **2** into the Pd-R¹ bond of **5** to give **6**, C) β- or β'-hydride elimination from **6** to give either **3a** or **3b**, and finally D) regeneration of **4** by reductive elimination of HX from **7**.

The three major factors governing regioselectivity are:

- i) The regioselectivity of the insertion into Pd-R¹ is heavily dependent upon the nature of the steric and electronic environment provided by R², R³, and R⁴ for unsymmetrical alkenes. This lack of selectivity, which has tended to limit the scope of the reaction somewhat, can be overcome by selecting appropriate chiral ligands and reaction conditions.
- ii) The problem of competing β- and β'-hydride elimination from **6** further complicates the regioselectivity issue, to the extent that the majority of reported Heck reactions simply avoid the problem by using simple acrylate ester substrates (R²=CO₂R, monosubstituted alkene), which through their highly unsymmetrical steric and electronic environments also avoid any problems with regioselectivity in step B. While this constitutes a mild and quite powerful method for the synthesis of aryl acrylates, by eliminating the possibility of β'-hydride elimination an opportunity to form a tertiary chiral center is lost.
- iii) Even if the regioselectivity of step C can be controlled a further problem lies in its reversibility, which can result in re-insertion of the **3b** alkene into the Pd-H bond in **7** either to regenerate **6** or to form a regioisomer of it with the Pd atom attached to the same carbon atom as R³ and R⁴. If either of these substituents contains a suitably positioned hydrogen atom then the possibility exists of isomerization of the α, β'-alkene into a β', γ'-position, a problem which is especially prone to occur for endocyclic alkene products (see Sect. 4.2).

Fortunately methods have been developed to suppress this, involving the addition of thallium [15] or silver [16, 17] salts to the reaction mixture. The latter are usually preferred owing to their lower toxicity and fortuitous double role as enhancers of enantioselectivity (*vide infra*).

A preference for **3b** rather than **3a** formation is essential for the AHR to occur, and thus an examination of the factors controlling the competing elimination processes in step C and the consequent prerequisites for ensuring the predominance of the desired pathway is clearly appropriate. As both insertion into **5** and elimination from **6** are *syn*- processes, rotation about the alkene σ-bond is required before β-hydride elimination can occur. This might be expected to make β'-hydride elimination the kinetically more favorable pathway. More significantly, for endocyclic alkenes the necessary σ-bond rotation is not feasible for steric reasons, making β'-hydride elimination the only possible course. It is primarily for this reason that all the AHRs forming tertiary centers which have been reported (with the exception of Tietze et al.'s allylsilane work, see Sect. 4.1.5) involve endocyclic alkene substrates. Other methods to direct the selectivity of step C involve choosing suitable Rⁿ groups to influence the relative thermodynamic stabilities of the possible products, the most common tactic being to

make R^3 or $R^4=OH$ or OR , resulting in the formation of an enol (which subsequently tautomerizes to the aldehyde or ketone) or enol ether. A similar strategy commonly employed in AHRs is to choose $R^3/R^4=alkenyl$, resulting in the formation of a conjugated diene product. Either approach may be used in addition to the choice of a cyclic substrate as a way of providing an extra driving force to the reaction, and this indeed occurs in many of the published AHR examples.

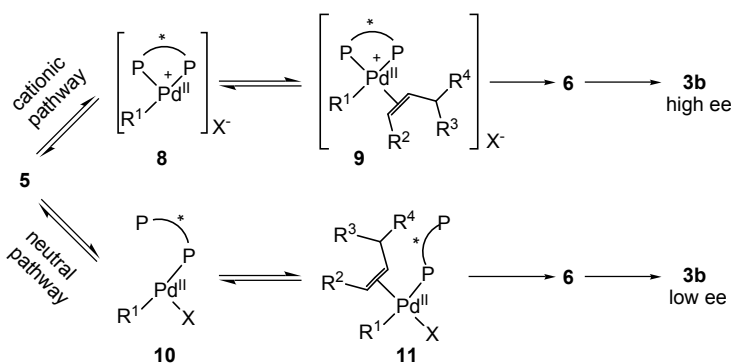
2.2

Factors Governing Enantioselectivity

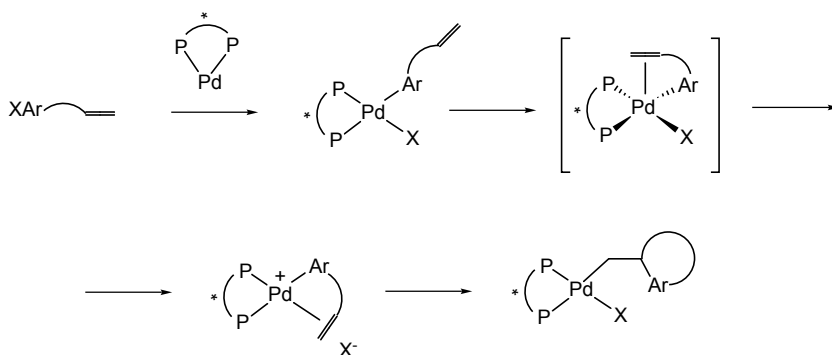
The key step in the catalytic cycle with regard to enantioselectivity is clearly B), association of the alkene **2** and insertion of it into the $Pd-R^1$ bond. As with the Heck reaction itself, the mechanism for this process remains a matter for conjecture, with the overall rationale currently in favor having been proposed in 1991 by Ozawa and Hayashi [18] and independently by Cabri [19] (although the cationic pathway via **8** and **9** had been proposed as early as 1990 [20]). Its development and subsequent evolution has recently been reviewed by the latter author [12].

Two possible routes are proposed (Scheme 2a), the former (“cationic”) pathway beginning with the dissociation of X from **5** to generate the tri-coordinate $14 e^-$ cationic complex **8** with the accompanying counterion X^- . Complexation of **2** into the vacant site then gives the $16 e^-$ species **9**, and insertion of **2** into the $Pd-R^1$ bond followed by reformation of the $Pd-X$ bond gives **6** as desired, with the chiral bidentate ligand having remained fully chelated throughout and so having maximized the asymmetric induction. The alternative (“neutral”) pathway starts with dissociation of one arm of the bidentate ligand resulting in the neutral species **10**; association and complexation into the vacant site of **2** gives the neutral species **11**, which by alkene insertion into $Pd-R^1$ and re-complexation of the previously displaced phosphine moiety also gives **6**.

The nature of X in **1** (and thus the strength of the $Pd-X$ bond in **5**) is clearly an important factor; unless the reaction conditions are modified aryl and vinyl tri-



Scheme 2a. Cationic and neutral pathways for the AHR mechanism



Scheme 2b. Proposed neutral pathway for an intramolecular AHR including the formation of a cationic four-coordinate intermediate

flates are generally assumed to follow the cationic pathway (the Pd-OTf bond being weak [21]) with either route being available to reactions using aryl/vinyl halides. In practice it has proven possible to influence which pathway will be followed in a given Heck process, either by adding silver salts to the reaction of an aryl/vinyl halide (the halophilic Ag^+ salt sequestering the halide from **5** and replacing it with its own anionic component [6]), or by adding excesses of halide anions to reactions using triflates (resulting in nucleophilic displacement of the triflate anion from **5** [22]). The nature of the alkene substrate is also important, with electron-rich olefins favoring the cationic pathway (and so being the most suitable for the AHR) while the neutral pathway makes for faster reaction with electron-poor substrates [19].

The partial dissociation of the chiral ligand during the neutral process would seem to make it less well suited to asymmetric induction, however, and the evidence of most of the AHRs reported so far seems to indicate that conditions which favor the cationic route also give the best enantiomeric excesses. However, a significant exception to this rule has been found (see also Sect. 5.1): Overman et al. observed that for a special aryl *triflate* [(*Z*)-butenamide triflate] the addition of halide salts to the reaction mixture resulted in a dramatic increase in enantiomeric excess of the intramolecular Heck reaction product [23]. If on the other hand the corresponding aryl *iodide* was used as starting material high ee's could be obtained without further additives. Overman concluded that in the case of this substrate the neutral pathway must be the more enantioselective one. Furthermore, it was shown that when the bidentate diphosphine ligand (*R*)-BINAP was substituted by potentially monodentate analogues of (*R*)-BINAP, only low enantioselections were obtained for this example. This can be seen as evidence that both phosphines of the diphosphine ligand remain coordinated to the Pd center during the enantioselective step. To account for these findings mechanistically a “refined” neutral pathway for the AHR involving a pentacoordinate intermediate without partial dissociation of the diphosphine was suggested (Scheme 2b).

It is clear that considerations on the geometry of the palladium center during the catalytic cycle are fundamental for further developments of more detailed descriptions of the stereoselection. Explicit three-dimensional rationalizations on how the chirality is transferred from the ligand to the substrate are not available for the AHR at present or are just beginning to emerge (see Sect. 4.1.4).

3 Practical Aspects

The AHR is carried out under similar or identical reaction conditions generally associated with racemic versions of the Heck reaction using standard laboratory glassware. The solvents which have been used include benzene, dichloroethane, diglyme, dimethylacetamide, DMSO, THF, or even mixtures containing water and the reaction usually requires elevated temperatures (reflux, about 60 to 100 °C) to proceed with reasonable speed. Generally, degassed solvents and an inert atmosphere (nitrogen or argon) are necessary to avoid decomposition of the Pd-intermediates, oxidation of the phosphine ligand, and the formation of other side products. The bases which have been applied are numerous and range from K_2CO_3 to proton sponge. The catalyst is conveniently prepared in situ. Examples for palladium sources are $Pd(OAc)_2$ or $Pd_2dba_3 \cdot CHCl_3$ (dba=dibenzylideneacetone) among others, with usually at least about 3 to 10 mol % catalyst being required for reasonable yields and reaction rates. It should be noted that the catalyst stability and turnover numbers are relatively low compared to other catalytic processes and recovery of the catalyst is usually not practical. However, as AHRs can be employed for the construction of valuable natural products a somewhat higher catalyst cost can be tolerated.

Explicit laboratory procedures can be found in the references.

4 Formation of Tertiary Centers

4.1 Intramolecular

4.1.1 *Decalins*

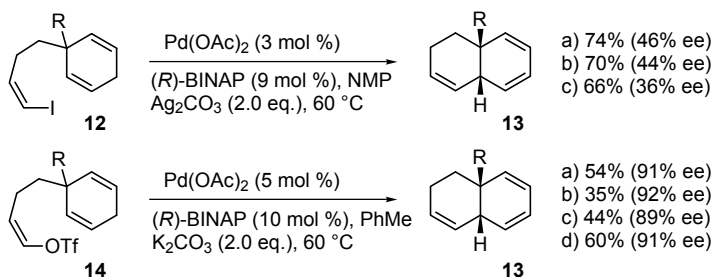
The first example of the AHR was reported in 1989, and involved the conversion of the prochiral vinyl iodides **12a-c** into the chiral decalin systems **13a-c**, as shown in Scheme 3 [24]. The reaction conditions (dipolar aprotic solvent and presence of silver salts), while similar to those of a previously reported non-enantioselective method [16], differ crucially in respect of the choice of chiral ligand and of solvent – very low or negligible ee's were obtained using THF, MeCN, or DMSO, with the preferred solvent being *N*-methyl-2-pyrrolidinone (NMP). Similarly, the widely used chiral phosphine ligands BPPM [1-*tert*-butoxycarbonyl-4-diphe-

nylphosphino-2-(diphenylphosphinomethyl)azolidine] and BPPFA {*N,N*-dimethyl-1-[1',2-bis(diphenylphosphino)ferrocenyl]ethylamine} failed to give significant asymmetric induction, with (*R*)-BINAP proving to be the ligand of choice, a pattern which has been repeated in most (though not all, see Sect. 4.1.3) of the reported examples of the AHR. By using a prochiral substrate two stereocenters can be set in one step, a tactic which is used repeatedly in the tertiary centre-generating AHRs reported by the Shibasaki group.

The modest ee's reported (33 to 46% ee) for the conversion of **12** to **13** (Scheme 3) were greatly improved as a result of a study of the effects on the reaction of varying the anionic component of both the Pd source and, more particularly, the silver salt [20]. It was found that the use of a Pd⁰ catalyst complex pre-formed in situ from Cl₂Pd(*R*)-BINAP [25], (*R*)-BINAP, and cyclohexene, gave greatly improved ee's relative to the 1:3 Pd(OAc)₂/*(R)*-BINAP pre-reduced catalyst used in the original work; in contrast, the use of AgOAc as the Ag⁺ source reduced the ee to almost zero, clearly indicating the undesirability of the nucleophilic acetate counterion, which perhaps forms a Pd-OAc bond to replace the dissociated Pd-I bond and so inhibits the cationic pathway. The best Ag⁺ source in terms of ee was found to be Ag₃PO₄ (most likely due to the very low nucleophilicity of the Ag₂PO₄⁻ anion), with the sparingly soluble CaCO₃ being added as the basic component. Under these conditions **13b** was obtained in 80% ee and 67% yield.

The very recent introduction of the new ligand 2,2'-bis(diphenylarsino)-1,1'-binaphthyl (BINAs) [26], the diarsine equivalent of BINAP, helped to considerably increase the yield for the conversion of **12b** to **13b**. After optimization the product **13b** could be prepared in 90% chemical yield and with 82% ee [26].

The use of the vinyl triflates **14a-d** in place of iodides **12a-c** gave still better results (Scheme 3) [27] as well as allowing the omission of expensive silver salts and the use of hydrocarbon solvents (PhMe or PhH) in which the deleterious effects of Pd(OAc)₂ on ee seen in NMP are not repeated. Thus products **13a-d** were obtained in 35 to 60% yields and uniformly excellent (89 to 92%) ee's under the conditions indicated.



R groups : a) R=CO₂Me, b) R=CH₂OTBS, c) R=CH₂OAc, d) R=CH₂OPv

Scheme 3

The scope of the reaction was extended somewhat by the use of the trisubstituted vinyl iodide **15**, which gave the decalin systems **16a** and **16b** in yields of 63% (83% ee) and 67% (87% ee), respectively (Scheme 4) [27]. The deleterious effect of the acetate counterion on ee and superiority of the $\text{Ag}_3\text{PO}_4/\text{CaCO}_3$ additive combination seen for the AHR converting **12** to **13** are reproduced here. Interestingly, **16a** was accompanied by a minor amount (35%) of the desilylated alcohol **16c**, which displayed a higher enantiomeric excess (92%) – control experiments indicated that desilylation was occurring via transmetalation to Pd after completion of the ring closure. No such free hydroxy formation was seen in the case of acetate **15b**.

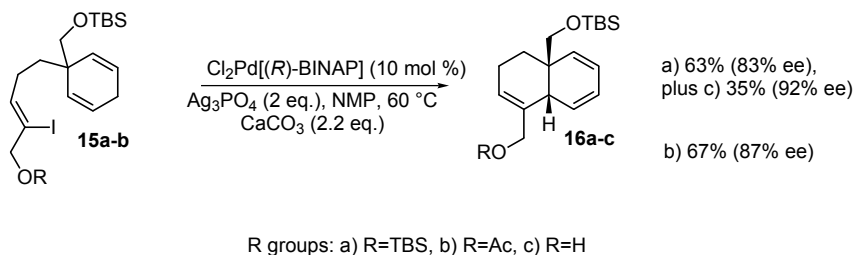
A more significant extension in scope was the synthesis of a range of bicyclic enones and dienones, including a key intermediate **20** in Danishefsky's synthesis [28] of vernolepin **21**. The AHR involved was initially the conversion of divinyl alcohol **17** to the chiral decalin system **19**, via the intermediate **18** (Scheme 5) [29]. The best solvent for this was found to be 1,2-dichloroethane (DCE), with the addition of *t*-BuOH having a beneficial effect on reaction rate and chemical yield without reducing the enantiomeric excess [30]. Compound **19** was converted to **20** via a 9-step process; an alternative approach was also found which started from the more readily available **13a** [31]. Application of the DCE/tertiary alcohol solvent system for the conversion of **14a** to **13a** gave an improved yield compared to that previously reported; a study of the various tertiary alcohols revealed pinacol to be the most efficacious, giving **13a** in 78% yield with 95% ee. The authors successfully synthesized (+)-**21**, thereby enabling assignment of its absolute configuration.

4.1.2

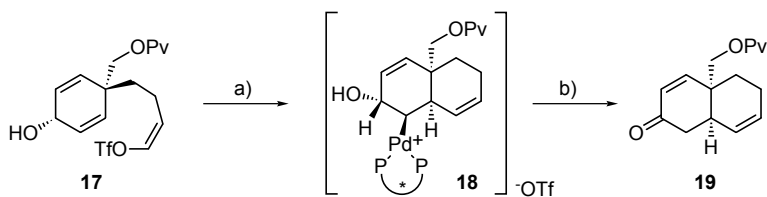
Hydrindans

The general method described in Sect. 4.1.1 for decalin synthesis has also been applied to the synthesis of 6,5-ring systems through the formation of hydrindans (Scheme 6) [32].

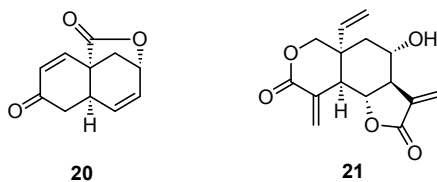
Both iodides **22a-e** and triflate **24** can be converted to the corresponding *cis*-hydrindans by similar methods to those used for decalins; once again Ag_3PO_4 was found to be the most effective silver salt in the conversion of the former. Small



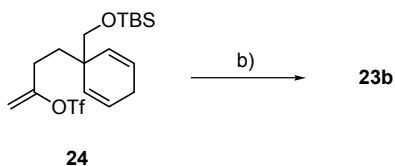
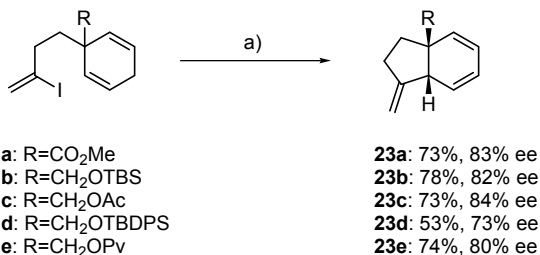
Scheme 4



a) $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (9 mol % Pd), (*R*)-BINAP (11.3 mol %), K_2CO_3 (2 eq.), *t*-BuOH (11 eq.), $\text{ClCH}_2\text{CH}_2\text{Cl}$, 60 °C, 3 days. b) β -hydride elimination, then tautomerization, 76%, 86% ee.

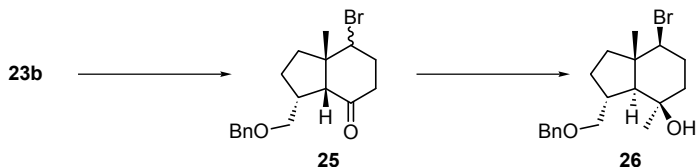


Scheme 5. Synthesis of a key intermediate for vernolepin



a) $\text{PdCl}_2[(R)\text{-BINAP}]$ (10 mol %), Ag_3PO_4 (2.0 eq.), CaCO_3 (2.2 eq.), NMP, 60 °C.
b) $\text{Pd}(\text{OAc})_2$ (5 mol%), (*R*)-BINAP (10 mol %), K_2CO_3 (2.0 eq.), PhH, 60 °C, 64 h, 63% (73% ee).

Scheme 6



Scheme 7

increases ($\leq 5\%$) in ee could be obtained for 22a-c by pre-reducing the palladium catalyst in situ. The triflate 24 gave 23b in slightly lower ee than seen for the corresponding conversion of 22b, with potassium carbonate being found to be the most effective base.

The hydrindan 23b was later converted by the same group into 26 (Scheme 7) [33], which is a key intermediate in the syntheses of (-)-oppositol and (-)-pre-pinnaterpene [34]. The conversion involved oxidation of the diene moiety with singlet oxygen, and is notable for the clean epimerization of the ring junction to give the *trans*-configuration (25 to 26), which demonstrates that both *cis*- and *trans*-junctions can be obtained from the AHR products.

4.1.3

Indolizidines

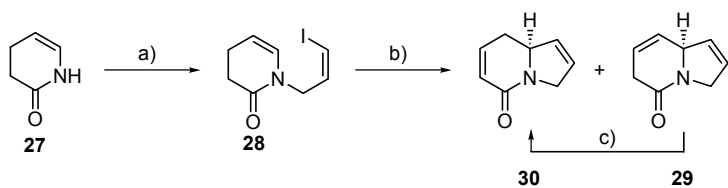
The 6,5-bicyclic synthesis outlined above has been extended to indolizidines, formed by AHR of a suitable prochiral alkenyl iodide such as 28, which can be easily prepared by allylation of the lactam 27. In contrast to purely carbogenic systems, however, the most effective ligand proves to be BPPFOH ((*R*)- α -[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol) 31 [35] which gives results clearly superior to those obtained with BINAP (Scheme 8) [36, 37].

The use of an Ag-exchanged zeolite also appears to give somewhat better results than the more usual Ag_3PO_4 silver source. The desired indolizidine 30 is obtained as a mixture (94% yield, 86% ee) with the isomer 29; however, treatment of the mixture with catalytic Pd/C in MeOH at room temperature gives clean isomerization to 30 in essentially quantitative yield. Compound 30 has been converted to the natural products lentiginosine 32, 1,2-diepileptiginosine, and gephyrotoxin 209D 33 [38].

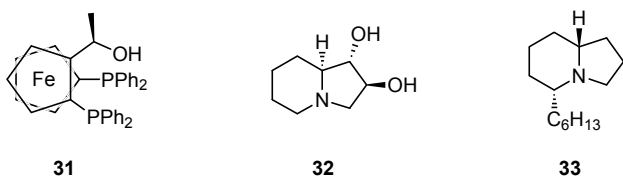
4.1.4

Diquinanes

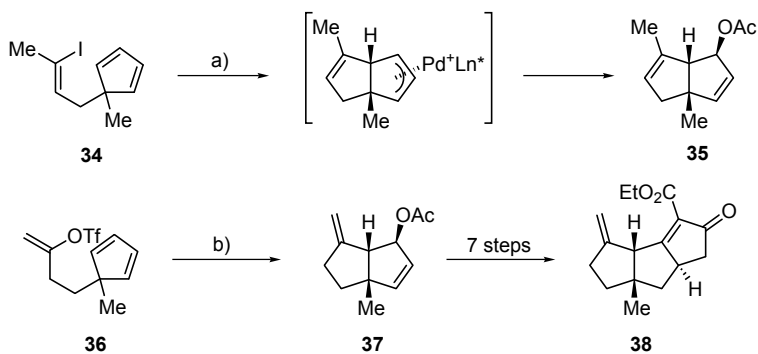
The successful execution of AHRs for the formation of 6,6- and 6,5-ring systems from prochiral substrates clearly suggested an extension of the method to the formation of 5,5-systems, which form the backbone of a large number of natural products. The use of prochiral cyclopentadienyl systems, however, involves the



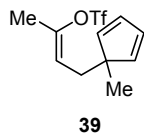
a) NaH, DMF, then (Z)-CHI=CH-CH₂I, 68%. b) Pd₂dba₃·CHCl₃ (4 mol % Pd), (R)-(-)-BPPFOH (9.6 mol %), Ag-exchanged zeolite (corresponds to ca. 6 eq. Ag), CaCO₃, DMSO-DMF, 0 °C, 94% (86% ee). c) Pd/C, MeOH, 23 °C, quantitative.



Scheme 8



a) [Pd(allyl)Cl]₂, (R,R)-CHIRAPHOS, Bu₄NOAc, PhMe, 60 °C, 6 days, 61% (20% ee).
 b) Pd(OAc)₂, (S)-BINAP, Bu₄NOAc, DMSO, 25 °C, 2.5 h, 89% (80% ee).



Scheme 9

generation of a π -allylpalladium species, which must then be trapped out with a suitable nucleophile [39]. The greater reactivity of the 1,3-diene substrate towards the silver salts used in the reactions and the propensity for undesirable side-reactions such as Diels-Alder cycloadditions must also be kept in mind. The former problem, in fact, figures prominently in the first example to be published of AHR-based diquinane synthesis (Scheme 9) [40, 41].

Although cyclization of iodide **34** could be carried out to give the bicyclo[3.3.0]octane **35** in reasonable yield, the observed ee's were low [ca. 20%; a slightly higher ee was obtained with (*S*)-BINAP, but at the cost of greatly reduced yield]. The authors attribute this failing mainly to a clearly observed instability of **34** in the presence of silver salts, necessitating their omission from the reaction medium and so forfeiting the beneficial effects noted in earlier work [20]. The presence of tetrabutylammonium acetate, a source of nucleophilic acetate appears to be essential, as the reaction does not proceed in its absence; this was in fact the first example of an AHR followed by anion capture. The problem of low ee was circumvented by employing the triflate **36** (chosen instead of the more obvious analog **39** on the grounds of ease of synthesis), which gave the diquinane **37** with 80% ee and in 89% yield. The authors converted this to the triquinane **38**, an intermediate in a previously described synthesis of $\Delta^{9(12)}$ -capnellene-3 β , 8 β , 10 α -triol [42], and later developed the first *catalytic* asymmetric synthesis of $\Delta^{9(12)}$ -capnellene **41** itself by trapping the π -allyl-Pd intermediate with a suitable β -dicarbonyl carbanion (Scheme 10) [43].

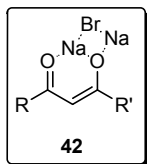
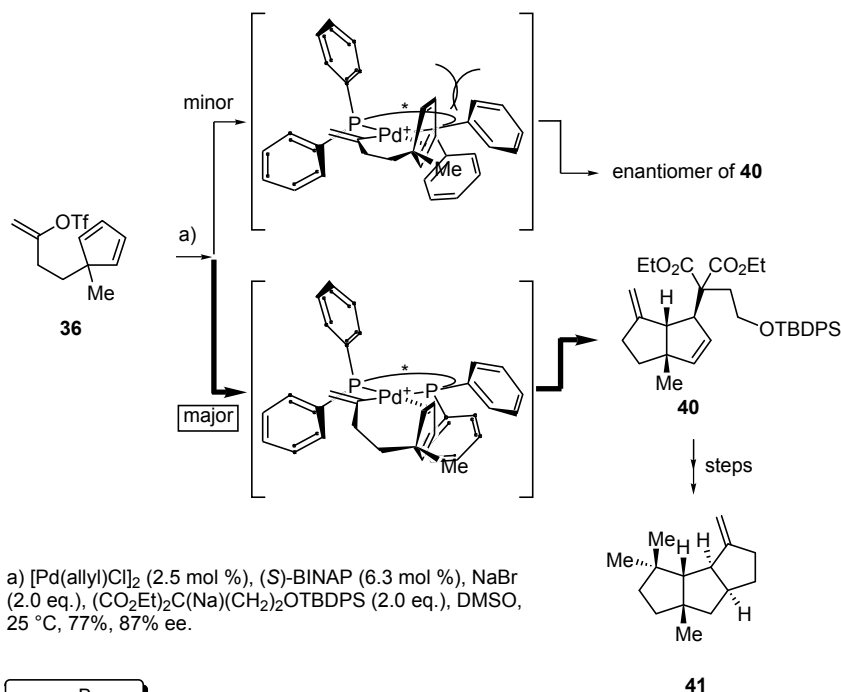
In this case BINAP was found to be the most effective ligand, and the addition of sodium bromide also significantly improved the ee's in all cases studied. The latter effect is attributed to a suppression (due to formation of a stabilizing complex of type **42** with the sodium enolate) of small amounts of anion exchange which may be taking place between free malonate anions and the triflate anion in the cationic intermediate of type **9**.

4.1.5

Allylsilanes

All of the examples discussed so far have relied on the use of an endocyclic alkene substrate to resolve the β - vs. β' -hydride elimination regiocontrol problem discussed in Sect. 2.1. A more general approach to the problem has been described by Tietze et al. and involves the use of allylsilanes as the alkene component (Scheme 11) [44].

By careful choice of reaction conditions either a vinyl- or a trimethylsilylvinyl-substituted carbocyclic species can be produced in the non-enantioselective reaction. Under conditions suitable for the AHR, however, the former product predominates (e.g., reaction of **43** to **44**). Yields and enantiomeric excesses appear to be good, and the method has been successfully applied to the synthesis of the norsesquiterpene 7-demethyl-2-methoxycalamene **47**, via the key cyclization of **45** to **46** [45, 46].



Scheme 10

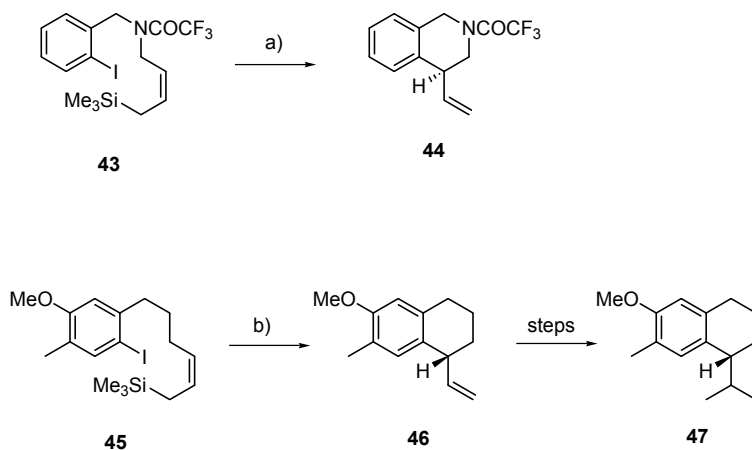
4.2

Intermolecular

4.2.1

Dihydrofurans and Cyclic Enol Ethers

The first example of the intermolecular AHR was reported by Hayashi et al. and involved the asymmetric arylation of 2,3-dihydrofurans using aryl triflates [18]. Although little or no enantiomeric excess was obtained when aryl iodide/silver salt combinations were used, the use of triflates along with the familiar Pd(OAc)₂/BINAP catalyst system resulted in the formation of the 2-aryl-2,3-dihydrofuran product **54**, together with minor amounts of the 2,5-dihydrofuran isomer **55**. The rationale proposed by the authors for this outcome is shown in Scheme 12; it is hypothesized that addition of the catalytic complex to either face of the sub-



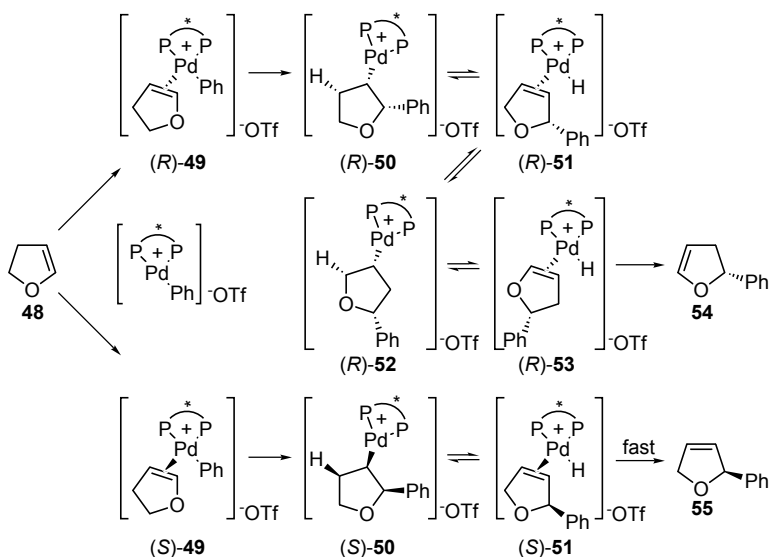
a) $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ (2.5 mol %), (*S*)-BINAP (7.0 mol %), Ag_3PO_4 (1 eq.), DMF, 75°C , 48 h, 63% (72% ee); b) $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ (2.5 mol %), (*R*)-BINAP (7.0 mol %), Ag_3PO_4 (1.1 eq.), DMF, 80°C , 48 h, 91% (92% ee).

Scheme 11

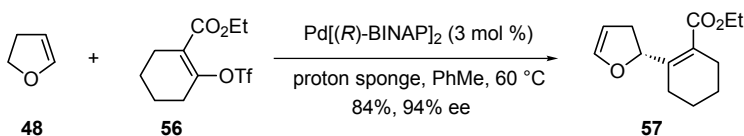
strate can take place, ultimately producing the complexes (*R*)-**51** and (*S*)-**51**, but that in the case of the latter unfavorable steric factors cause an immediate dissociation of the Pd species, producing the minor product **55**.

In contrast (*R*)-**51** is able to undergo a reinsertion of the alkene into the Pd-H bond followed by a second β -hydride elimination to produce the product **54**. The overall effect is a kinetic resolution of (*R*) and (*S*)-**51**, effectively enhancing the facial selectivity shown in the initial transformation of **48** to **49** by selectively removing the **51** enantiomer produced by complexation to the undesired face of **48**. As might be expected from the above argument, reaction conditions which give proportionally larger amounts of **55** also appear to give the best ee's for the major product **54**; thus, when proton sponge is used as the base the product **54** is obtained with >96% ee, at the cost of a 71:29 ratio of **54**:**55**, whereas in contrast using Na_2CO_3 gives a lower ee (75%) but much better regioselectivity (97:3) [47, 48]. The authors note that the presence of the nucleophilic acetate anion in the reaction medium assists the dissociation of (*S*)-**51** [and presumably (*R*)-**51** as well], making possible the formation of **55** [49]. Even more impressive results have been obtained using vinyl triflates. For example, the AHR between **48** and triflate **56** gives the expected major product **57** with 94% ee, without formation of the undesired regioisomer (Scheme 13) [50].

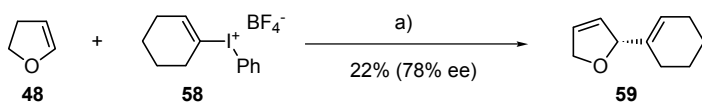
An interesting corollary to this work has been reported by Reiser et al. who found that at high pressure the ee of the major product in the conversion of **48** to **54**/**55** is dramatically increased, suggesting that such conditions enhance the kinetic resolution process [51]. Shibasaki et al. have shown that the reaction can be carried out us-



Scheme 12. Mechanism for intermolecular AHRs with dihydrofurans



Scheme 13



Scheme 14

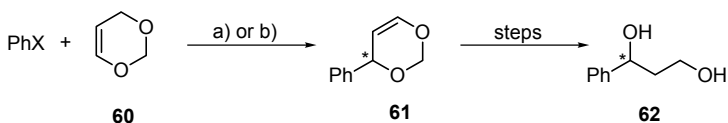
ing alkenyliodonium salts instead of vinyl triflates (transformation of 58 to 59, Scheme 14), although yields are lower due to the highly reactive nature of the salts, which leads to competition from uncatalyzed and/or non-phosphine mediated processes [52]. Interestingly, only the 2-vinyl-2,5-dihydrofuran product is obtained, suggesting that dissociation from the Pd complex formed after the first β -hydride elimination is more rapid than when using triflates.

Finally, the asymmetric arylation of **60** has also been reported, although the yields and ee's are more modest (Scheme 15) [53]. Hydrolysis of the product **61** conveniently gives the 1,3-diol **62**, an intermediate in the Sharpless synthesis of fluoxetine [54].

4.2.2 Dihydropyrroles

The methods described for arylation of dihydrofurans (see above) have also been applied to 2,3-dihydropyrroles such as **63** [55], with similar patterns of regio- and enantioselectivity being observed. Thus little or no ee was obtained when using aryl iodides, but aryl triflates gave mixtures of 2-aryl-2,3-dihydropyrroles **64** and 2-aryl-2,5-dihydropyrroles **65**, with the former predominating and the kinetic resolution process again being in effect, as evidenced by another inverse relationship between the ee of **64** and the **64:65** ratio (Scheme 16). The reaction was also successfully extended to vinyl triflates, which gave even better ee's than obtained for the dihydrofurans [50].

An example of a reaction with 2,5-dihydropyrroles has also been recently disclosed [56]. Arylation of **66** using 1-naphthyl triflate and an (*R*)-BINAP/ Pd(OAc)₂/*i*-Pr₂NEt system in DMF gave the 3-arylation product **67** (Scheme 17) with moderate yield and ee. It was found that the addition of excess acetate served to suppress formation of the undesired 2-arylation product (which was formed after initial isomerization of the double bond in **66**), and this was conveniently achieved by adding TIOAc, with the thallium cation acting as a co-catalyst. Unfortunately, attempts to carry out this reaction with other aryl triflates or with aryl iodides were unsuccessful.

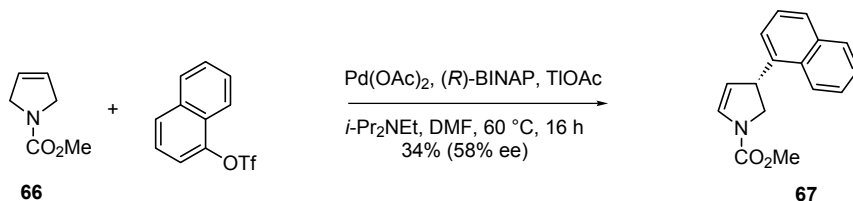


a) for X=I: Pd(OAc)₂, (*R*)-BINAP, Ag₂CO₃, DMF, 60 °C, 48 h, 62%, 43% ee;
b) for X=OTf: Pd(OAc)₂, (*R*)-BINAP, *i*-Pr₂NEt, DMF, 60 °C, 48 h, 37%, ~35% ee.

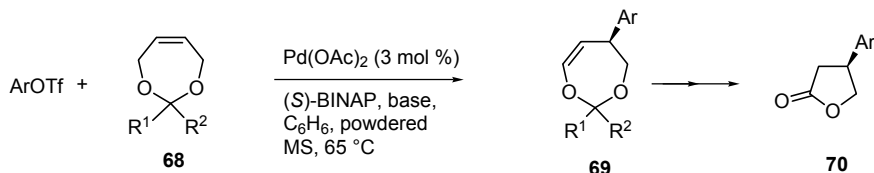
Scheme 15



Scheme 16



Scheme 17



Scheme 18

4.2.3

Dihydrodioxepins

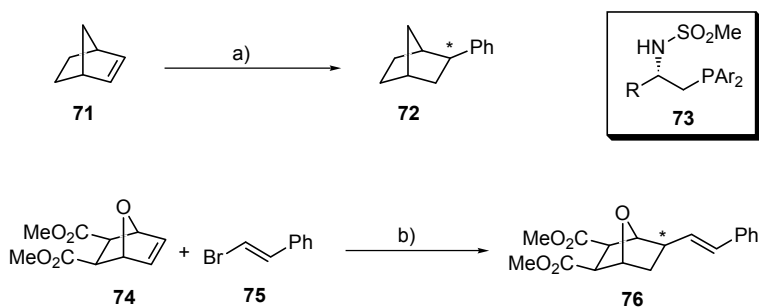
Arylation of the 4,7-dihydro-1,3-dioxepin system **68** (easily derived from *cis*-2-butene-1,4-diol), once again using the triflate, was reported by Shibasaki et al. in 1994 [57]. The reaction is significant in that the resulting enol ethers are easily converted (by hydrolysis and then oxidation of the intermediate lactol) to chiral β -aryl- γ -butyrolactones **70**, which are themselves useful synthetic intermediates (Scheme 18) [58]. Also noteworthy is the important role played by added molecular sieves (MS), which enhance both chemical yield *and* ee. This was the first time that such an effect had been noted for the AHR.

A combination of 3 Å MS and potassium carbonate base was found to be the most effective, with the best auxiliary system ($R^1=R^2=H$) giving **69** with a satisfactory 72% ee and in 84% yield. Gratifyingly, these figures showed only minor perturbations when the Ar ring substituents were varied. Significantly improved ee's have recently been reported for this process using a new ligand system (see Sect. 6) [59].

4.2.4

Hydroarylations of [2.2.1]Bicyclic Compounds

Asymmetric hydroarylation/hydrovinylation, although not strictly a Heck reaction as the β -hydride elimination step is replaced by reductive elimination, nevertheless shares a common mechanistic pathway with regard to the enantioselective step and so will be discussed briefly. In 1991 Brunner et al. first reported hydrophenylations of norbornene and norbornadiene using aryl iodides, al-



a) Ph-OTf, Pd(OAc)₂, **73** (R=CHMe₂, Ar=Ph), *i*-Pr₂NEt, HCO₂H, DMSO, 65 °C, 20 h, 81%, 74% ee.

b) Pd{(R)-BINAP}₂ (1 mol %), HCO₂H, Et₃N, Cl(CH₂)₂Cl, 40 °C, 63%, >96% ee.

Scheme 19

though the ee's obtained were low (<40%). The preferred ligand was (-)-Norphos; BINAP does not appear to have been tested [60]. The system has since been revisited by Achiwa et al. as a means of testing novel phosphine ligands of the general structure **73** [61, 62]. Using these the conversion of **71** to **72** could be carried out in 81% yield and 74% ee (Scheme 19).

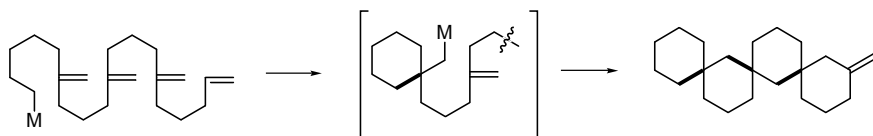
Hayashi et al. have carried out AHRs using vinyl iodides and triflates both on norbornene and on hetero-analogues such as **74**: excellent ee's and satisfactory yields were obtained [63]. Hydrophenylation of a similar system has been reported by Fiaud [64].

5 Formation of Quaternary Centers

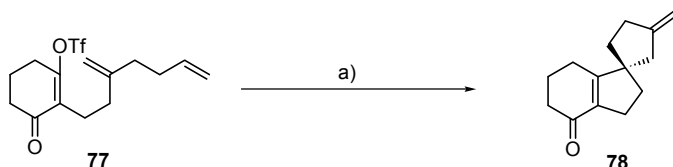
5.1 Spirocyclizations and Alkaloid Synthesis

The enantioselective formation of quaternary carbon centers remains a significant challenge to the synthetic chemist [65]. To use the AHR in this role has the obvious attraction of removing the problem of competing pathways in step C (see Scheme 1b), as no β-hydrogen is present to compete with the desired β'-hydride elimination step – the need to use endocyclic alkene substrates is thus removed.

The first successful case was reported by Overman et al. in 1989 [66], a pioneering strategy, which opened the way for the development of AHRs leading to quaternary centers. Furthermore it was outlined that polycyclizations are well within the scope of the Heck reaction. According to Scheme 20 it can be expected that contrary to the case of polycyclizations of carbocations and free radicals, cy-



Scheme 20. Polyene cyclization mediated by transition metals with formation of quaternary carbon centers



a) 10 mol % Pd(OAc)₂, 10 mol % (*S,S*)-DIOP,
Et₃N, benzene, 25 °C, 1h, 90%, 45% ee.

Scheme 21

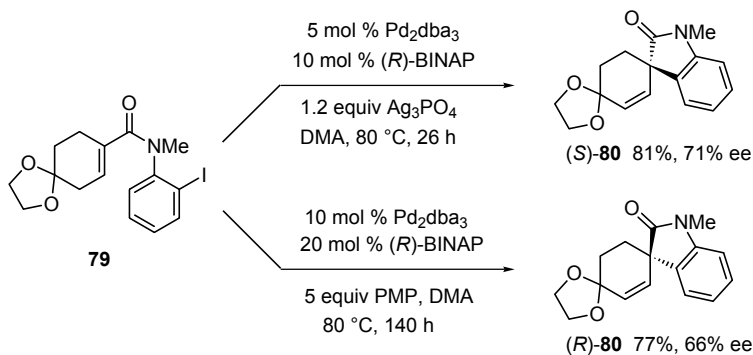
cyclizations resulting from sequential intramolecular insertions of palladium metal alkyls will be most effective when the transition metal propagates at the least substituted termini of the participating alkene units.

As with the work creating tertiary centers reported by Shibasaki et. al., which was described in Sect. 4, the enantiomeric excesses of the cyclizations obtained at the outset were modest, with the spirocyclic system **78** being obtained in good yield and moderate ee when (*S,S*)-DIOP was substituted for triphenylphosphine (Scheme 21).

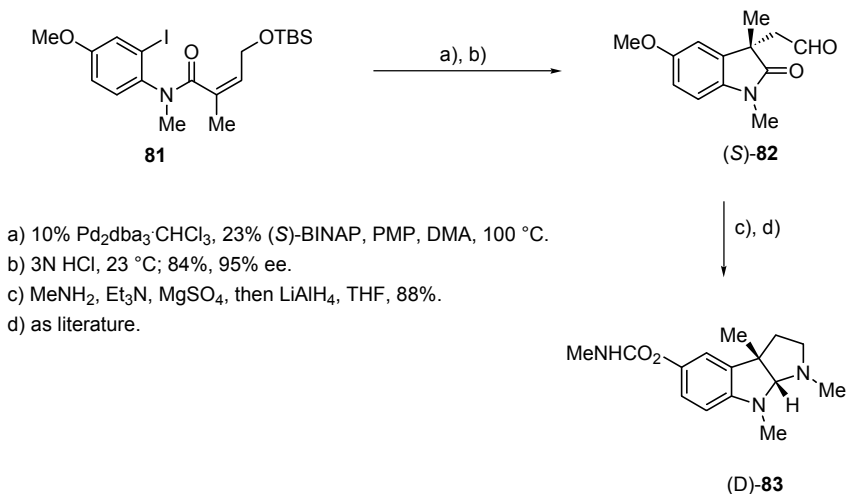
Although this work clearly demonstrated the viability of such a process, the full potential of the approach did not become fully apparent until the publication of a remarkable study concerning the synthesis of spiroxindoles (Scheme 22) [67].

Carrying out the AH cyclization of iodoanilide **79** in a dipolar aprotic solvent (in this case dimethylacetamide, DMA) in the presence of Ag₃PO₄ gave (*S*)-**80** in 81% yield and with 71% ee, results very similar to those achieved by other workers for tertiary centers under such conditions. However, by carrying out the reaction in the absence of Ag salts and using 1,2,2,6,6-pentamethylpiperidine (PMP) as the base, the opposite (*R*)-**80** enantiomer was obtained *using the same enantiomer* of BINAP.

Similar studies of the cyclization of alkene **81** revealed that when (*E*)-**81** is used the effect is reproduced, although the ee's of the enantiomer obtained when using PMP are low (30 to 40%). In contrast, when (*Z*)-**81** is used in conjunction with (*R*)-BINAP *both* sets of conditions give the expected (*R*)-enantiomer of **82** with good yields and excellent (>90%) ee's [68]. These results appear to suggest that the observed "geometry effect" (identical to that observed by Shibasaki et al.



Scheme 22



Scheme 23

for carbocycle formation, *vide infra*) is rather more powerful than the “base/additive effect” in determining the sense of chiral induction. The use of (*S*)-BINAP under otherwise identical conditions of course gives (*S*)-**82**, which can be converted to the natural product physostigmine **83** via methylimine formation and reductive cyclization (Scheme 23), followed by anisole demethylation and reaction of the resulting phenol with methyl isocyanate [69].

These surprising results proved to be a powerful spur to mechanistic investigation of the AHR, as they effectively rebutted the prevailing view that the cationic pathway is the only mechanism capable of producing high ee's, by demonstrating that the alternative neutral pathway is also apt to do so with certain substrates. The “base/additive effect” has, however, yet to be reported for substrates

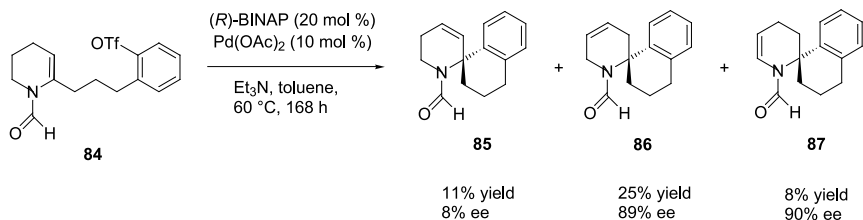
other than acrylamides, a substrate-specificity which must be taken into account before broader conclusions can be drawn regarding the AHR mechanism, especially the means by which the enantioselectivity reversal occurs.

5.2

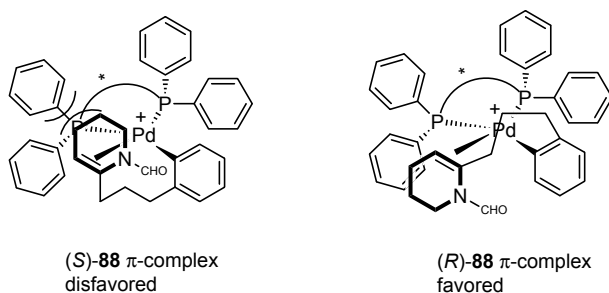
Tetrahydropyridines

Interesting attempts to asymmetrically cyclize an intramolecular Heck reaction with 1,2,3,4-tetrahydropyridines also giving access to spirocyclic systems have not been successful at the beginning [70]. However, by using *N*-formyl-1,2,3,4-tetrahydropyridines, Ripa and Hallberg succeeded in preparing various spirocyclic derivatives of tetrahydropyridines in moderate yields (Scheme 24) [71]. The asymmetric cyclization of **84** using (*R*)-BINAP as chiral ligand resulted in the formation of three isomers **85**, **86**, and **87** with a rather long reaction time being required. Good ee's have been obtained for the products **86** and **87** (89% and 90%).

The migration of the double bond could not be controlled effectively by varying the reaction conditions. Interestingly, the introduction of the chiral (phosphinoaryl)oxazoline (first reported by Pfaltz; see Sect. 6) as a ligand helped to suppress the formation of the double bond isomer **87**. At the same time the regioselectivity could be considerably changed in favor of the formation of **85** to yield a 6:1 mixture of (*R*)-**85** (87% ee) and (*R*)-**86** (>99% ee) after 48 h at 110 °C,



Scheme 24



Scheme 25. Diastereomeric π -complexes during the AHR of **84** in the presence of (*R*)-BINAP

using $(i\text{-Pr})_2\text{NEt}$ as base [71]. A rationalization for the observed excellent enantioselectivities in the case of (R) -BINAP is shown in Scheme 25. It was suggested that one of the diastereomeric π -complexes [(S) -88], formed after oxidative addition of the triflate could be sterically more crowded. A similar argumentation, based on steric arguments, was used to explain the subsequent migration of the double bond and the considerably differing ee's of the double bond isomers.

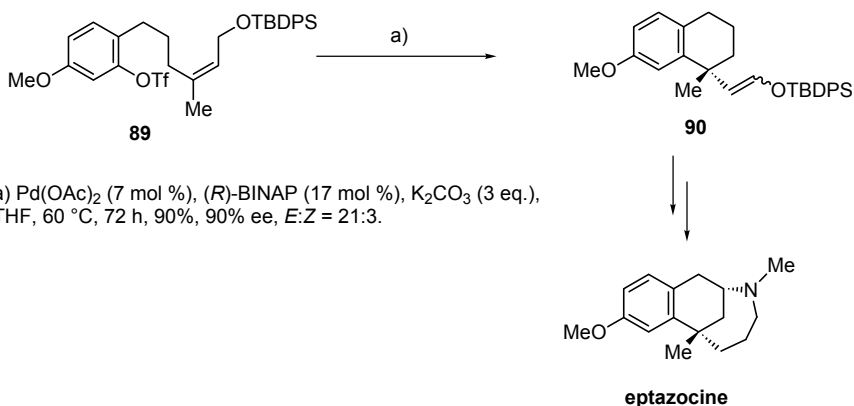
If the corresponding iodide was used instead of the triflate **84** only low to moderate ee's have been observed. Furthermore, it seems that the role of the N -formyl moiety could be important for chiral induction and this could provide further information about the mechanism.

5.3

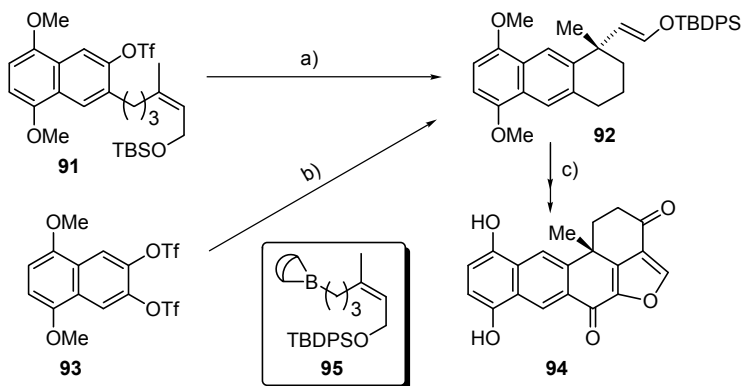
Eptazocine and Halenaquinol

The synthesis of benzylic quaternary centres by AHR has also been reported by Shibasaki et al. in connection with syntheses of $(-)$ -eptazocine [72] and of halenaquinone and halenaquinol **94** [73]. As in Sect. 5.1 the key steps in both syntheses involve the formation of a quaternary carbon center by asymmetric Heck arylation of a trisubstituted alkene, with BINAP being the preferred ligand. The "geometry effect" seen by Overman for spiroxindoles (vide supra) is clearly present, with the Z -alkene giving much better enantioselectivity and, in the case of model studies of the step **89** to **90** in the eptazocine synthesis, the opposite enantiomer to that obtained when using the E -alkene. The conversion of **89** to **90** (Scheme 26) was achieved with excellent yield and ee; desilylation gave the corresponding aldehyde [74], which was converted to $(-)$ -eptazocine via a 5-step sequence.

The synthesis of halenaquinol **94** (and its oxidation product halenaquinone) initially featured the conversion of **91** to **92** as a key step (Scheme 27), which gave the desired product in 78% yield and 87% ee under very similar conditions used



Scheme 26



- a) Pd(OAc)₂ (10 mol %), (S)-BINAP (20 mol %), K₂CO₃, THF, 60°C, 78% (87% ee).
 b) **95** (1.1 eq.), Pd(OAc)₂ (20 mol %), (S)-BINAP (40 mol %), K₂CO₃, THF, 20% (85% ee). c) 12 steps, 12% overall.

Scheme 27

for the conversion of **89** to **90**. However, in line with the current trend towards sequential or “one-pot” transformations [75, 76] (vide infra), the authors were able to combine the AHR step with a Suzuki-type coupling of the trialkylborane **95** (itself pre-generated in situ by hydroboration) with the C₂-symmetric ditriflate **93** and so obtain **92** rather more directly. While the chemical yield of this sequence is still low (20%) and the catalyst loading rather high (20 mol%) the ee is excellent (85%), suggesting that further development of the method should be feasible.

5.4

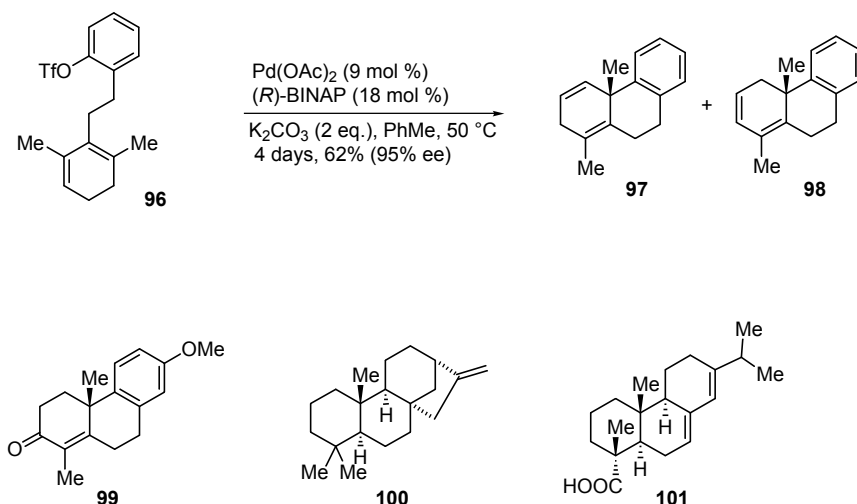
Sesquiterpenes

One further example of quaternary center formation by AHR has been reported, this being the conversion of the aryl triflate **96** to a 3:1 mixture of the tricyclic compound **97** and its isomer **98**, both of which can be converted to the enone **99**, a key intermediate in the syntheses of kaurene **100** and abietic acid **101** (Scheme 28) [77, 78]. Compound **97** can also be quantitatively isomerized to **98**. The essentially complete selectivity towards 6-*exo* cyclization is noteworthy. The authors rationalize this on the basis of unfavorable steric interactions in the alternative intermediates.

6 Future Directions

6.1 Ligands

The great majority of AHRs reported so far have utilized the BINAP ligand system, which has proven to be the most effective in most of the cases in which the performances of different ligands has been assessed. The significant number of exceptions to this rule, however, suggest that experimentation with alternatives may prove worthwhile. The most dramatic development of late has definitely been the introduction by Pfaltz et al. of the oxazoline-based ligands **102** [79], which give distinctly improved ee's with several previously reported AHRs [59]. For example, the Hayashi-type AHR of dihydrofuran **48** with cyclohexenyl triflate catalyzed by Pd(dba)₂ and **102** (R=*tert*-butyl) with *i*-Pr₂NEt as the base gives the 2-alkenyl-2,5-dihydrofuran product **59** in 92% yield and with >99% ee, a major improvement on the ee's obtained with BINAP [80]. Similar to the vinylation of **48** using iodonium salt **58**, no trace of the isomeric 2-alkenyl-2,3-dihydrofuran product is formed, indicating that rapid dissociation of the catalyst from the initial product of β'-hydride elimination occurs. Remarkably, the resistance of the first-formed product alkene to isomerization by this catalyst is so pronounced as to allow the arylation and/or alkenylation of cyclopentene, giving regiodefined products such as **103** with high yields, excellent ee's, and only small amounts (<5%) of the unwanted regioisomers such as **104** (Scheme 29). This catalyst system is also interesting in terms of reaction rates and decreased catalyst loading, indicating higher catalyst turnover compared to BINAP (see Sect. 6.2).



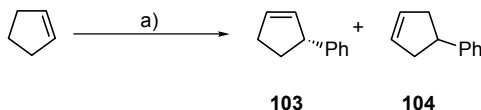
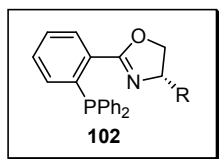
Scheme 28

An example for an alkenylation reaction utilizing **102** [$R=C(CH_3)_3$] is given in Scheme 30. Again, excellent selectivity towards the less isomerized product **105** as well as high ee's have been observed [59].

The conversions outlined in Scheme 29 and Scheme 30 are also noteworthy in so far as they constitute examples of intermolecular AHRs of very simple starting materials with no other functionality or heteroatom present than is required for the Heck reaction to proceed. Simple hydrocarbon skeletons are the resulting products.

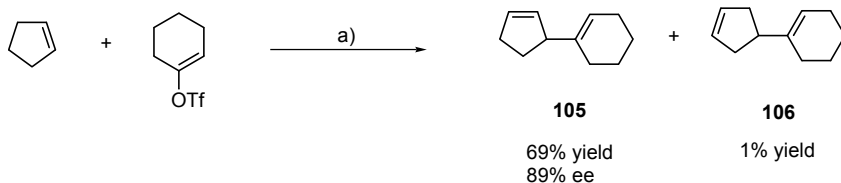
Two further examples for arylation reactions catalyzed by phosphanyldihydrooxazole-palladium complexes are shown in Scheme 31 with the formation of **107** and **108** in high yields and excellent ee's [81].

The application of ligand **102** has successfully been extended to derivatizations of nitrogen containing substrates. Arylation of the 2,3-dihydropyrrole **63** with phenyl triflate catalyzed by the **102**-palladium complex [$R=C(CH_3)_3$] produced the single isomer **65** with 88% yield and in 85% ee [81].



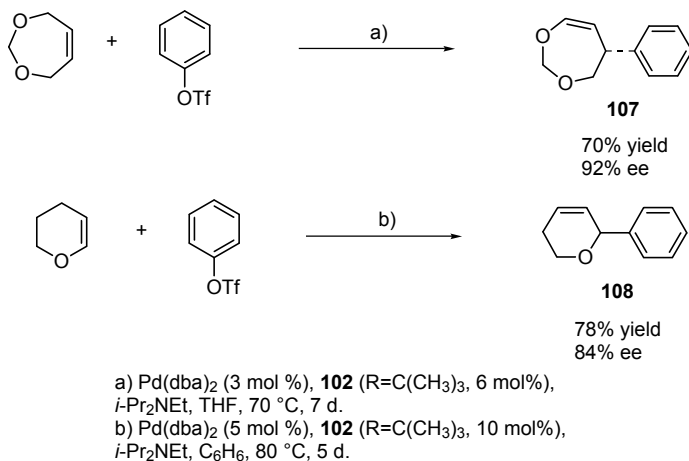
a) PhOTf, Pd(dba)₂ (3 mol %), **102** ($R=C(CH_3)_3$, 6 mol %), *i*-Pr₂NEt, THF, 70 °C, 5 days, 80%, 86% ee, 103:104 99:1.

Scheme 29

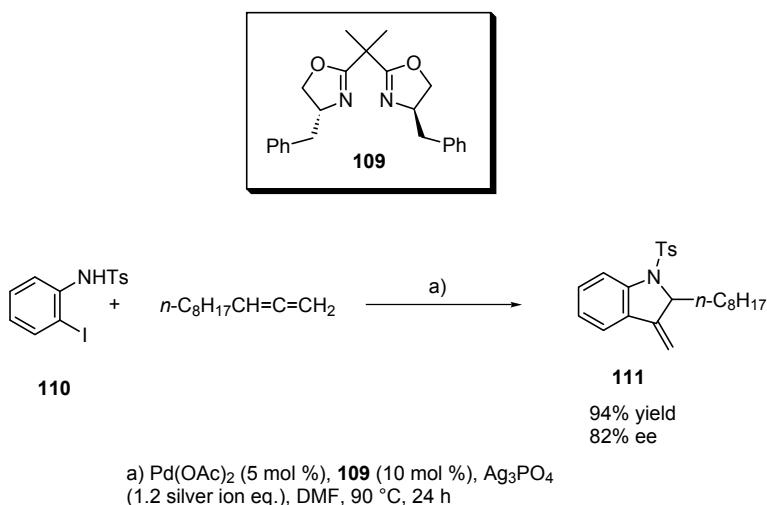


a) Pd(dba)₂ (3 mol %), **102** ($R=C(CH_3)_3$, 6 mol %), *i*-Pr₂NEt, C₆H₆, 40 °C, 4 - 5 d.

Scheme 30



Scheme 31



Scheme 32

Interestingly, phosphinoxazolines **102** with smaller R groups than $\text{R}=\text{C}(\text{CH}_3)_3$ have been found to produce less reactive catalysts. This finding was very unusual since with $\text{C}(\text{CH}_3)_3$ being a very bulky group the steric hindrance near the metal center could actually be expected to slow down a metal-catalyzed process.

The use of a chiral bisoxazoline ligand **109** for the enantioselective palladium-catalyzed annulation of allenes has been reported by Larock and Zenner (an example is given in Scheme 32) [82]. Even though the alkene insertion step here is followed by an intramolecular nucleophilic attack of the amine functionality

(which could be described as an “intramolecular anion capture process”) and the reaction is not strictly an AHR, the high yields and ee's obtained for various substrates are remarkable.

Summarizing the results obtained with BINAP, with the new diarsine ligand mentioned in Sect. 4.1.1, and with bisoxazoline **109**, it seems evident that various donor atoms (N, P, As) can be contained in ligands which provide the best solution to a given AHR problem. Accordingly, very recently 2-diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl (BINAPAs) has been synthesized and successfully applied in AHRs of a system similar to **91** with superior reactivity compared to BINAP [83].

Remarkable *diastereoselectivities* have also been observed for AHR with the chiral auxiliaries RAMP or SAMP present in the substrate using triphenylphosphine as a ligand [84]. Even a “ligandless” version of a palladium(0) catalyst has been described for an intramolecular Heck reaction with very good diastereoselectivity of the resulting spirocyclic oxindole. This catalyst could still be tailored by adding Ag_3PO_4 , resulting in the formation of the opposite diastereomer [85].

6.2

Methodological Developments

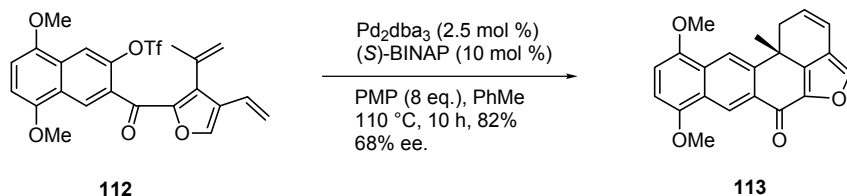
The increase of the catalyst turnover numbers is indeed one other major area where further improvements could be expected. Such improvements have recently been achieved for the standard Heck reaction by the use of high pressure conditions [86], the use of preformed palladacycles as catalysts [87], or by using a macrocyclic tetraphole as ligand [88]. Dendritic diphosphine-palladium complexes as catalysts for Heck reactions have also been reported to possess superior stability compared to the monomeric parent compounds [89]. Transferring such innovations to the AHR remains an important goal.

The current surge of interest in combinatorial chemistry [90, 91] may also prove to be highly significant to the development of new ligands, as both Heck reactions on solid support [92] and the generation and screening of chiral phosphine ligand libraries [93] have recently been demonstrated, potentially opening the way to combinatorial screening of AHR catalyst systems.

The move away from bulky BINAP ligands which Pfaltz's work may foreshadow would certainly simplify library construction. The ready availability of chiral oxazolines from peptide residues may also be helpful in this respect [94, 95, 96].

Microwave-promoted Heck reactions are another recent development. It was shown that Heck reactions of common substrates like *p*-iodoanisole and methyl acrylate, which under standard conditions need several hours for reasonable conversions, can be carried out in just a few minutes if DMF is used as a solvent and microwave irradiation is applied [97].

Finally, a very recent synthesis of the halenaquinol-related natural product (+)-xestoquinone by Key and co-workers [98] has provided confirmation of the suitability of the AHR for inclusion in Pd-mediated “cascade” polyene reactions [99]. The one-pot transformation of triflate **112** into the pentacyclic product **113**



Scheme 33

(Scheme 33) is achieved using conditions typical for the AHR, and gives (+)-113 with a respectable 68% ee. Interestingly, the iodide analogue of 112 gives little or no asymmetric induction, even in the presence of silver salts.

7

Summary and Conclusions

From its modest beginnings in the late 1980s the AHR (asymmetric Heck reaction) has developed into a powerful method for the synthesis of both tertiary and quaternary chiral carbon centers, with enantiomeric excesses typically in excess of 80% and in some cases much higher. A variety of carbocyclic and heterocyclic systems can be constructed or modified including spirocyclic systems. Although problems of regioselectivity with respect to the product alkene continue to limit the scope of the reaction somewhat there are indications that these may be surmountable, and that a new generation of ligands, which dissociate more rapidly from the products, may improve both enantio- and regiocontrol. It is to be hoped that the efficiency of the catalysts can be increased and that the search for improved ligand systems will be greatly assisted by combinatorial screening methods, to which the mild and functionality-tolerant AHR may prove to be well suited. Certainly the reaction has proven to be useful in one-pot multi-step processes [100]. Since the Heck reaction, as a transition metal-catalyzed process, could be an attractive method in terms of “atom economy” [101] it remains to be seen if industrial applications will follow.

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Chapter 15

Pauson-Khand Type Reactions

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Keywords: Pauson-Khand, Cyclopentenone, Enyne, Titanocene, Ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl (EBTHI) ligand, Chiral enyne, Chiral auxiliary

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1 Introduction

The introduction of transition metal catalysts has led to a revolution in the field of organic synthesis. Some of the most powerful applications have involved transition metal-promoted cycloadditions [1, 2, 3]. These methodologies have provided for the rapid construction of complex carbo- and heterocyclic structures

from simple, readily available starting materials. These processes also represent excellent examples of atom economy in synthesis [4]. Many of these reactions, such as the [2+2+2] cyclotrimerization of alkynes [5], the [4+2] addition of dienes and alkynes [6], and the [4+4] addition of dienes [7] and enyne cycloisomerizations [8], have seen elegant application in the total synthesis of complex molecules (Fig. 1).

To date, the most commonly used transition metal-promoted cycloaddition in organic synthesis is the Pauson-Khand reaction. First reported by Pauson and Khand in 1973 [9], this transformation is the cobalt-mediated [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide to form a cyclopentenone, Eq. (1). Although mechanistic understanding is limited, the accepted mechanism for the transformation is depicted in Fig. 2. Loss of two equivalents of CO followed by complexation of an alkyne produces **1**. Subsequent loss of CO from

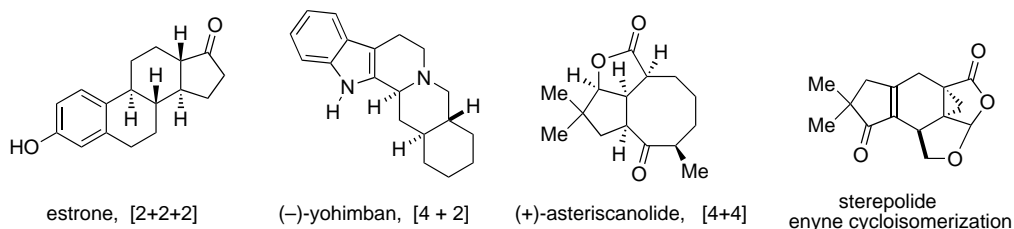


Fig. 1. Total synthesis applications of transition metal-promoted cycloadditions

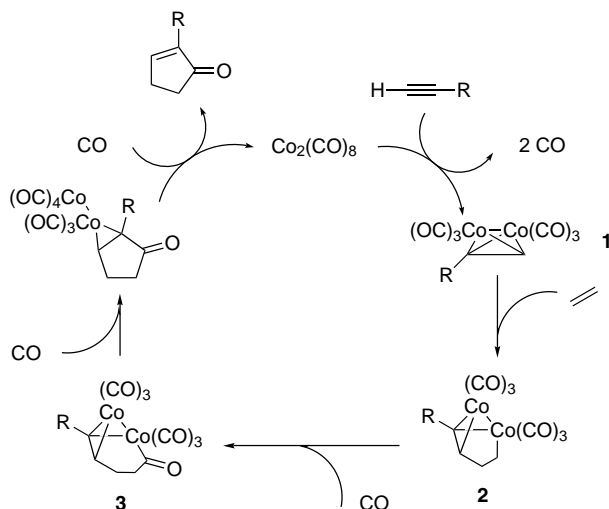
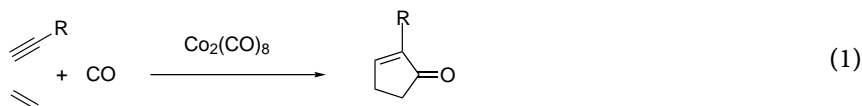


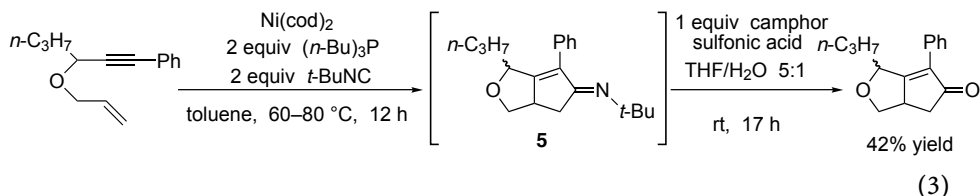
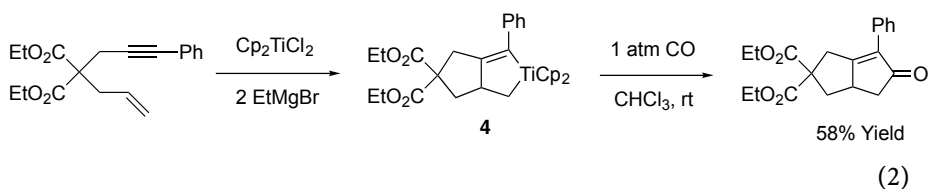
Fig. 2. Proposed mechanism for the Pauson-Khand reaction

1 and alkene insertion yields cobaltacycle 2. Alkyl migration provides acyl complex 3, which upon reductive elimination liberates the cyclopentenone product.

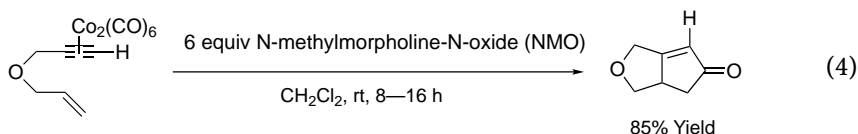


Apart from studies by Pauson and coworkers, this reaction was not widely investigated until the seminal report by Schore in 1981 which detailed the first intramolecular example of a Pauson-Khand reaction [10]. Following this report, activity in this area flourished, and the frequent application of this methodology in the total synthesis of natural and unnatural products demonstrated the versatility of this reaction. A detailed discussion of these efforts is beyond the scope of this article, but a number of excellent reviews on the subject have been published [11].

In the strictest sense the Pauson-Khand reaction refers only to the cobalt-mediated cycloaddition shown in Eq. (1). However, a multitude of transition metals are capable of promoting Pauson-Khand type cyclizations involving the same net transformation: production of a cyclopentenone from an alkyne, alkene, and CO. This includes a variety of transition metal carbonyl complexes: $\text{Fe}(\text{CO})_4(\text{acetone})$ [12, 13], $\text{W}(\text{CO})_5(\text{THF})$ [14], $\text{Cr}(\text{CO})_5\text{F}^-$ [15], $\text{Cp}_2\text{Mo}_2(\text{CO})_4$ [16], and $\text{Mo}(\text{CO})_6$ [17]. This transformation can also be achieved by treating preformed metallacyclopentenes such as 4, derived from Cp_2TiCl_2 [18] or Cp_2ZrCl_2 [19], with carbon monoxide, Eq. (2). Finally, related protocols using isonitriles in place of carbon monoxide, e.g., $\text{Ni}(\text{cod})_2/\text{RNC}$ and “ Cp_2Ti ”/RNC [20, 18], produce iminocyclopentenes such as 5, which can be hydrolyzed to the corresponding cyclopentenones, Eq. (3). In order to avoid confusion, the term Pauson-Khand will be applied only to reactions involving cobalt, while Pauson-Khand type will be used to describe all transition metal-promoted cyclopentenone syntheses.



Although it has seen wide application in total synthesis, the original protocol for the Pauson-Khand cyclization suffered from several drawbacks. Generally, reactions required high temperatures, extended reaction times, and produced the cyclopentenones in low to moderate yields. A variety of modifications of this procedure have been reported that allow the use of milder reaction conditions while realizing enhanced yields [11]. In 1990, Schreiber and coworkers introduced the use of tertiary amine oxides as efficient promoters of the intramolecular Pauson-Khand reaction, Eq. (4) [21]. The *N*-oxide presumably oxidized CO ligands to CO₂, thereby opening coordination sites on the cobalt cluster and facilitating cyclization. Because this protocol could be carried out at or below room temperature and allowed for the production of cyclopentenones in good to excellent yields, it became the methodology of choice in most circumstances.



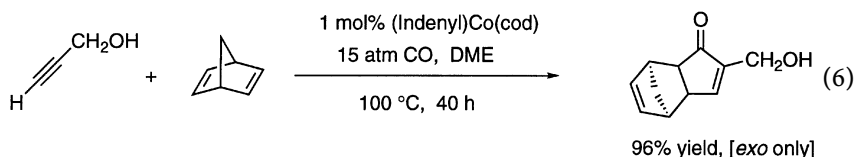
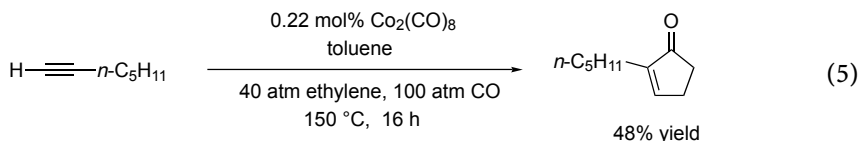
There has been significant interest in the development of a catalytic asymmetric Pauson-Khand type reaction because of its vast potential in organic synthesis. A boom in research activity in this field has focused in two areas – the development of catalytic Pauson-Khand type cyclizations and of stoichiometric syntheses of optically active cyclopentenones via the Pauson-Khand reaction, including a recent report of the first intramolecular catalytic asymmetric Pauson-Khand type cyclization. In this review, the existing catalytic systems will be briefly surveyed followed by a detailed analysis of the asymmetric variant. The stoichiometric syntheses of optically active cyclopentenones will also be discussed.

2 Catalytic Pauson-Khand Type Reaction

2.1 Intermolecular

The first report of a catalytic intermolecular cyclization was made by Pauson and Khand in 1974 [22], but the scope was limited to gaseous acetylene as the alkyne partner, strained olefins such as norbornene and norbornadiene as the alkene component, and TON's (turnover numbers) were modest (8–11). Several subsequent reports detailed the production of cyclopentenones from a substoichiometric amount of Co₂(CO)₈, but none were as efficient as Pauson's initial work [23, 24]. Using ethylene as the alkene component, Rautenstrauch demonstrated the first efficient catalytic Pauson-Khand cyclization with a TON of 220, Eq. (5) [25]. A more general catalyst system employing (indenyl)Co(cod) was recently reported by Chung and Jeong, Eq. (6) [26]. The reaction was quite effec-

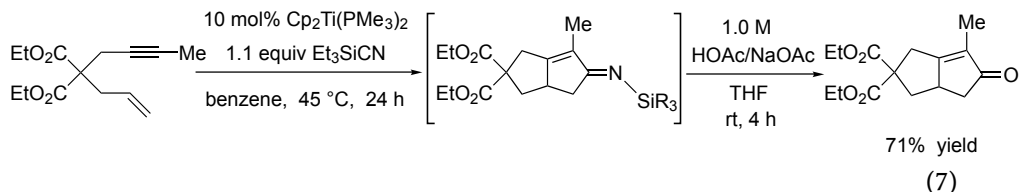
tive for the coupling of norbornene and norbornadiene with terminal alkynes, though less so with internal alkynes. An improved catalyst, derived from $\text{Co}(\text{acac})_2$ and NaBH_4 , was subsequently shown to display greater functional group tolerance, particularly to esters and halides [27]. It should be noted that these later two systems were also capable of effecting the catalytic intramolecular cyclization (vide infra).



2.2 Intramolecular

2.2.1 Trialkylsilyl Cyanide

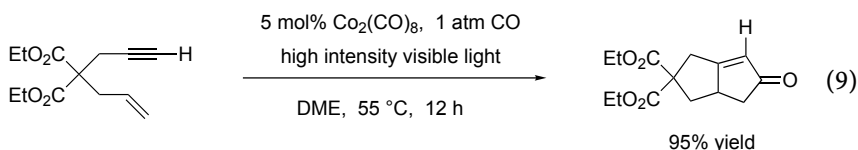
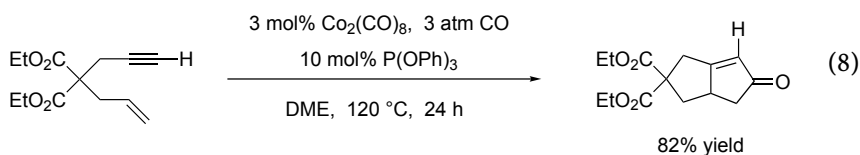
The first report of a catalytic intramolecular Pauson-Khand type cyclization involved a related isocyanide insertion reaction (vide supra). Treatment of a stoichiometric amount of titanacyclopentenes such as **4** with 2,6-xylyl isocyanide was found to produce iminocyclopentenes like **5** [18] [see Eqs.(2) and (3)]. Attempts to perform a catalytic cyclization were unsuccessful due to catalyst deactivation in the presence of a slight excess of alkyl or aryl isocyanide. Instead trialkylsilyl cyanides, which exist in highly unfavorable equilibria with the corresponding isocyanide isomers (>99:1), were utilized to control the concentration of isocyanide in solution. This approach led to the catalytic formation of iminocyclopentenes, which were hydrolyzed to the corresponding cyclopentenones in moderate to good yields [43–80%, Eq. (7)] [28, 29]. Subsequently, it was demonstrated that the silyl cyanide approach could be utilized to effect a nickel-catalyzed iminocyclopentene synthesis [30]. This system represented an improvement over the titanium-based methodology both in terms of functional group tolerance (aliphatic ketones and nitriles were compatible) and scope of olefin substitution (substrates containing 1,2-disubstituted olefins could be cyclized).



2.2.2

Cobalt-Based Reactions

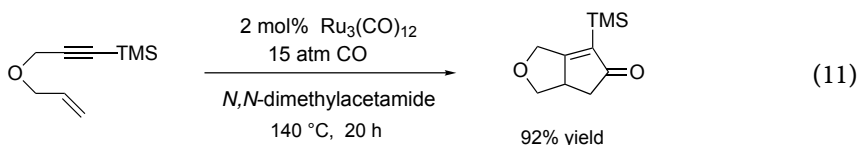
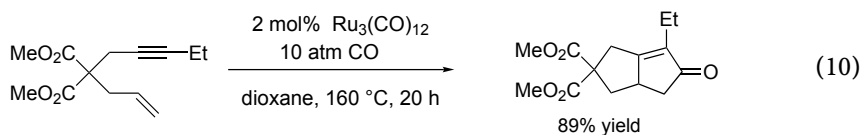
In 1994, Jeong and coworkers reported a catalytic intramolecular Pauson-Khand reaction, Eq. (8) [31]. The key to their approach was the use of $\text{P}(\text{OPh})_3$ as an additional ligand. The phosphite reportedly helped stabilize low-valent cobalt intermediates and prevented the formation of catalytically inactive cobalt clusters. In general, yields were better for this protocol relative to the isocyanide methods mentioned above because the yield-limiting imine hydrolysis was circumvented. A general characteristic of the intramolecular Pauson-Khand reaction has been that enynes containing terminal alkynes could be transformed more efficiently than enynes with substituted alkynes; the opposite trend was observed for both of the isocyanide processes. A different approach to catalysis was also reported by Livinghouse, Eq. (9) [32]. High-intensity visible light was utilized to induce CO dissociation and to thereby promote cyclization. This method had the advantage of employing mild reaction conditions (1 atm CO, 55 °C for 12 h). Very recently, Jeong has demonstrated the feasibility of performing the catalytic Pauson-Khand (both intra- and intermolecularly) in supercritical CO_2 [33].



2.2.3

Other Transition Metal Carbonyl Complexes

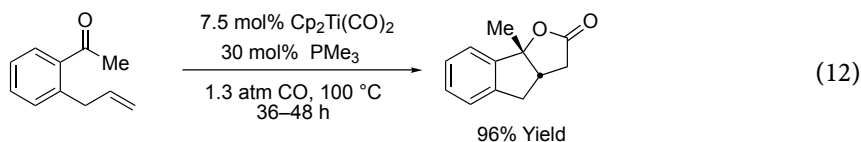
Another important development in the area of catalytic Pauson-Khand type cyclizations has been the discovery of other transition metal carbonyl complexes which are capable of effecting the catalytic synthesis of cyclopentenones. Two recent reports from Murai and Mitsudo detailed a $\text{Ru}_3(\text{CO})_{12}$ -catalyzed enyne cyclocarbonylation, Eqs. (10) and (11) [34, 35]. While this protocol allowed for the cyclization of a variety of 1,6-enynes, the cyclizations of terminal alkynes as well as 1,7-enynes were problematic. The feasibility of using $\text{Cp}_2\text{Ti}(\text{CO})_2$ as a catalyst for the intramolecular Pauson-Khand type cyclization of a variety of 1,6- and 1,7-enynes (vide infra) has also been demonstrated [36]. Based on the wide array of transition metals that are capable of effecting stoichiometric Pauson-Khand type cyclizations (vide supra), the development of more catalytic systems is to be expected; this should greatly facilitate the search for catalytic asymmetric variants.

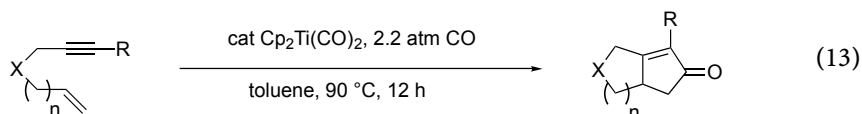


3

Titanocene-Catalyzed Pauson-Khand Type Reaction

In the course of studying the stoichiometric, carbonylative synthesis of γ -butyrolactones from enones and a titanocene complex [37], it was observed that certain aryl enones could be cyclocarbonylated in a catalytic manner, Eq. (12) [38]. This success in effecting a titanocene-catalyzed cyclocarbonylation led to an examination of the analogous reaction with enyne substrates. Indeed, it was found that under similar conditions, a titanocene-catalyzed Pauson-Khand type cyclization was possible, Eq. (13) [36].





As can be seen in Table 1, an array of enynes could be successfully cyclocarbonylated using this methodology. Functional groups such as ethers, amines and esters were compatible with the reaction conditions (entries 1–3), as has been previously demonstrated in the related titanocene-catalyzed iminocyclopentene synthesis (*vide supra*). This catalyst system also allowed for the utilization of substrates containing a variety of functional groups which were generally incompatible with other low-valent Group 4 metallocenes, such as terminal alkynes (entry 9), aliphatic nitriles and ketones (entries 4 and 5), and aromatic halides, nitriles and esters (entries 6–8). Aromatic ketones and nitro groups, free amines and alcohols, methyl amides, and ketones and esters directly attached to the alkyne (Fig. 3, 6–12) were not tolerated.

Table 1. Cyclopentenones from enynes with monosubstituted alkenes

	R	X	n	Catalyst (%)	Yield (%)
1	Ph	O	1	5	92
2	Me	NPh	1	10	88
3–5	Ph	$\begin{matrix} E > \\ E > \end{matrix}$ $\begin{matrix} E > \\ NC > \end{matrix}$ $\begin{matrix} E > \\ Me(O)C > \end{matrix}$	1	5, 7.5, 7.5	95, 75, 93
6–8	p-BrPh, p-CNPh, p-Eph	$\begin{matrix} E > \\ E > \end{matrix}$	1	5, 7.5, 5	91, 72, 86
9	H	$\begin{matrix} E' > \\ E' > \end{matrix}$	1	20	85
10	Me	$\begin{matrix} E' > \\ E' > \end{matrix}$	2	10	88

E = CO₂Et, E' = CO₂t-Bu

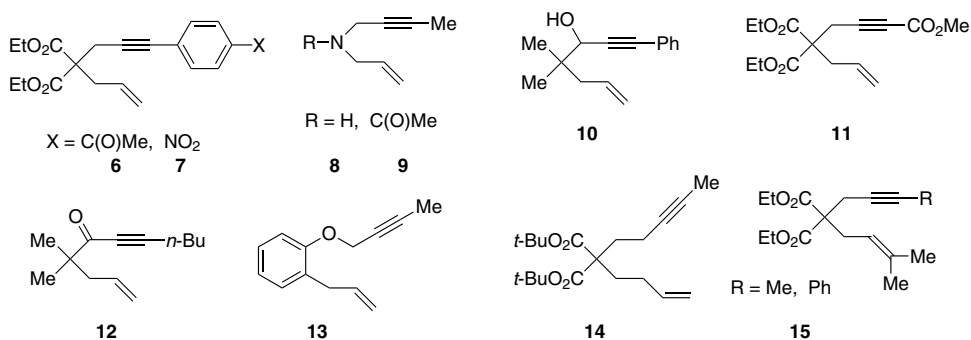


Fig. 3. Substrates which cannot be cyclized with the Cp₂Ti(CO)₂ catalyst

The titanocene-catalyzed Pauson-Khand type cyclization was also applicable to enynes of different length and those containing substituted olefins. Unlike the $\text{Ru}_3(\text{CO})_{12}$ -catalyzed protocols, 1,7-enynes could be cyclized in excellent yield (Table 1, entry 10); one such example for a cobalt-catalyzed reaction has been reported [32]. All attempts to cyclize 1,8-enynes have been unsuccessful (Fig. 3, 13 and 14). The titanocene system also accommodated olefin substitution on 1,6-enynes, Eq. (14), and Table 2. Both 6,6-disubstituted and cyclic 6,7-disubstituted olefin substrates [see labelling scheme in Eq. (16)] were converted to cyclopentenones in excellent yields (Table 2, entries 1–3). Reactions of substrates containing acyclic 6,7-disubstituted olefins were more problematic, requiring higher amounts of catalyst and producing only moderate yields of the corresponding cyclopentenones (Table 2, entries 4 and 5). The cyclization of enynes which contain both a substituted alkyne and olefin has not been demonstrated with any of the cobalt-based catalytic Pauson-Khand cyclizations, although $\text{Ru}_3(\text{CO})_{12}$ is capable of effecting such transformations [35]. The extension of the $\text{Cp}_2\text{Ti}(\text{CO})_2$ system to the cyclization of substrates containing trisubstituted olefins has been unsuccessful (Fig. 3, 15).

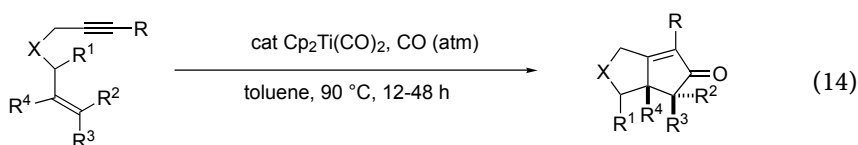


Table 2. Cyclopentenones from enynes with disubstituted alkenes

	R	X	R ¹	R ²	R ³	R ⁴	Catalyst (%)	Pressure	Yield (%)	dr
1	Me	<i>E'</i> <i>E'</i> >	H	H	H	Me	5	2.2	94	
2–3	Me, Ph	<i>E</i> <i>E</i> >	-(CH ₂) ₃ -	H	H	H	10, 10	1.3	86, 91	
4	Ph	<i>E</i> <i>E</i> >	H	Me	H	H	20	2.2	57	4.2:1 exo Me
5	Ph	<i>E</i> <i>E</i> >	H	H	Me	H	20	2.2	79	1.9:1 endo Me

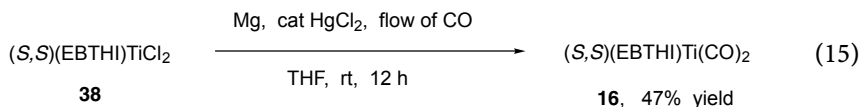
E=CO₂Et, E'=CO₂*t*-Bu

4 Catalytic Asymmetric Pauson-Khand Type Reaction

The availability of a chiral version of $\text{Cp}_2\text{Ti}(\text{CO})_2$ was instrumental in the development of the first catalytic asymmetric Pauson-Khand type reaction [39]. This work utilized a catalyst containing the ethylene-1,2-bis(η^5 -4,5,6,7-tetrahydro-1-indenyl) (EBTHI) ligand (Fig. 4, **16**) first introduced into Group 4 chemistry by Brintzinger [40]. Complexes containing this ligand have proven extremely effective in a number of applications in asymmetric catalysis [41].

4.1 Catalyst Choice and Procedure

The requisite asymmetric catalyst (*S,S*)(EBTHI) $\text{Ti}(\text{CO})_2$ (**16**) was most conveniently prepared *in situ* from (*S,S*)(EBTHI) $\text{Ti}(\text{Me})_2$ under a CO atmosphere [42]. The dicarbonyl complex could be isolated by a reductive carbonylation of (*S,S*)(EBTHI) TiCl_2 , Eq. (15) [43]. Since no significant advantage to the use of isolated (*S,S*)(EBTHI) $\text{Ti}(\text{CO})_2$ was found, (*S,S*)(EBTHI) $\text{Ti}(\text{Me})_2$ was used as a precatalyst due to its ease of preparation and greater stability.



The conditions for the asymmetric reaction are almost identical to those developed for the titanocene-catalyzed version of the process, Eq. (16). In an argon-filled glovebox, a dry resealable Schlenk flask is charged with (*S,S*)-(EBTHI) $\text{Ti}(\text{Me})_2$ (0.025 mmol, 8 mg), toluene (3 mL) and the substrate (0.50 mmol). The Schlenk flask is removed from the glovebox, evacuated and backfilled with 14 psig CO. [**Caution:** Appropriate precautions should be taken when performing reactions under elevated pressure, particularly with regards to the toxicity of CO.] After heating to 90 °C for 12–48 h, the reaction mixture is cooled to room temperature, and the CO is cautiously released in the hood. The crude reaction mixture is filtered through a plug of silica gel with the aid of diethyl ether and is purified by flash chromatography. [**Note:** Most substrates are passed through a plug of alumina in the glovebox prior to reaction to remove adventitious moisture.

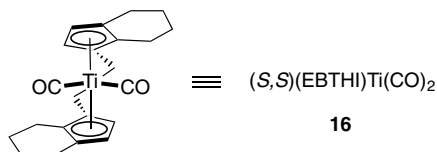


Fig. 4. Asymmetric catalyst for the Pauson-Khand type cyclization

4.2 Mechanism and Absolute Configuration

The mechanism of this transformation is unclear at the present time, but two possibilities are pictured below. In the first (Fig. 5), loss of a CO ligand and binding of the acetylene initially provides the η^2 -alkyne complex **17**. Subsequent loss of a second equivalent of CO allows for coordination of the alkene to give **17a**. Insertion of the olefin into the titanium-carbon bond of the alkyne complex produces metallacyclopentene **18**. The insertion of CO generates acyl complex **19** which, upon reductive elimination, yields the observed cyclopentenone product. A second plausible mechanism (Fig. 6) involves initial formation of metal-

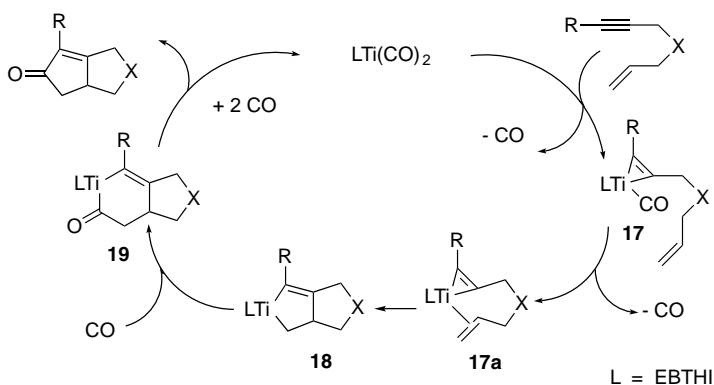


Fig. 5. First proposed mechanism for the asymmetric Pauson-Khand type reaction

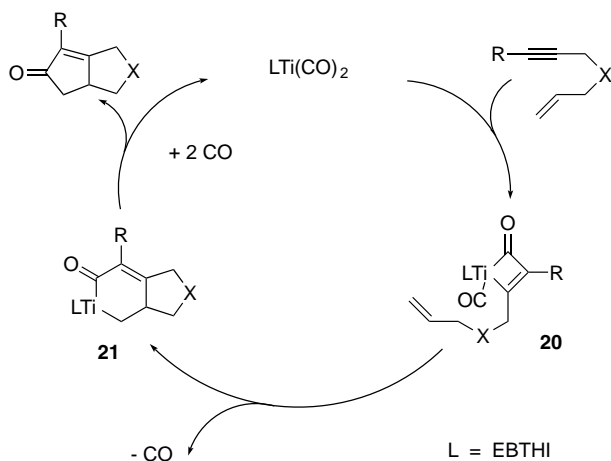


Fig. 6. Second proposed mechanism for the asymmetric Pauson-Khand type reaction

lacyclobutenone **20** followed by insertion of the pendant olefin to provide acyl complex **21**; reductive elimination provides the cyclopentenone product. The absolute configuration of the cyclopentenone products has been assigned based upon an X-ray crystal structure of the (*S*)-camphorsulfonate salt of the enone from Table 3, entry 6 [44].

4.3

Scope and Limitations

A variety of 1,6-enynes could be cyclized with excellent enantioselectivity using **16**. While the functional group tolerance of this reaction has not yet been explored extensively, a high degree of correlation with the titanocene-catalyzed reaction, where a wide range of functional groups have proven to be compatible (Table 1), should be expected. With regards to alkyne substituents R in Eq. (16), 1,6-enynes containing R=phenyl, *n*-alkyl, and methyl (Table 3, entries 3–5) were efficiently converted to cyclopentenone products of high ee. With larger R groups, such as *i*-Pr, *c*-pentyl, and HSi(Me)₂ (Fig. 8, **26–28**) no cyclization was observed, presumably due to unfavorable steric interactions between R and the EBTHI ligand. With a 1,6-enyne containing a terminal alkyne (R=H, Table 3, entry 8), greatly diminished ees were observed for the corresponding cyclopentenone, indicating that an interaction between the alkyne substituent and the ligand may have contributed to the enantioselectivity of these cyclizations.

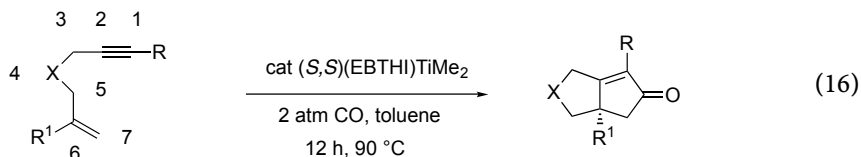


Table 3. Catalytic asymmetric Pauson-Khand type cyclization

	R	X	R ¹	Catalyst (%)	Yield (%)	ee
1–2	Ph	O, CH ₂	H	20, 20	85, 70	96, 87
3–5	Ph, <i>n</i> -Pr, Me	$\begin{matrix} E \\ E' > \end{matrix}$	H	7.5, 5, 5	92, 94, 90	94, 89, 87
6	Me	NBn	H	15	82	92
7	Me	$\begin{matrix} E' \\ E' > \end{matrix}$	Me	20	90	72
8	H	$\begin{matrix} E' \\ E' > \end{matrix}$	H	20	87	50
9	Me	CH ₂ C(E) ₂	H	20	77	47

E=CO₂Et, E'=CO₂*t*-Bu

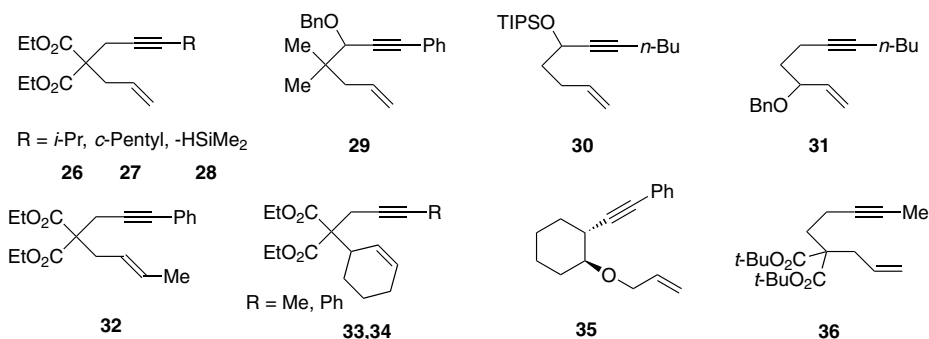


Fig. 7. Substrates which cannot be cyclized with the $(\text{EBTHI})\text{Ti}(\text{CO})_2$ catalyst

Significant differences have also been observed for the cyclization of 1,6-enynes substituted in the 3, 4, or 5 position, Eq. (16). A variety of different 4-substituted enynes (Table 3, entries 1, 2, 3, and 6) have been converted to cyclopentenones with high levels of enantioselectivity. However, attempts to cyclize enynes substituted at the 3- (Fig. 7, **29** and **30**) or 5- (Fig. 7, **31**) position have failed. As with the bulky R groups, these failures likely arose from unfavorable steric interactions between these proximal substituents and the EBTHI ligand.

The cyclization of 1,6-enynes containing substituted olefins has met with limited success. An enyne with a 6,6-disubstituted olefin could be converted to the corresponding cyclopentenone using **16** (Table 3, entry 7), but with decreased levels of enantioselectivity in comparison to simple 1,6-enynes. As with alkyne substitution, the interaction of the olefin substituent at this position appeared important to enantioselectivity. Due to the steric bulk of the EBTHI ligand, enynes containing 6,7-disubstituted olefins could not be cyclized (Fig. 7, **32–34**).

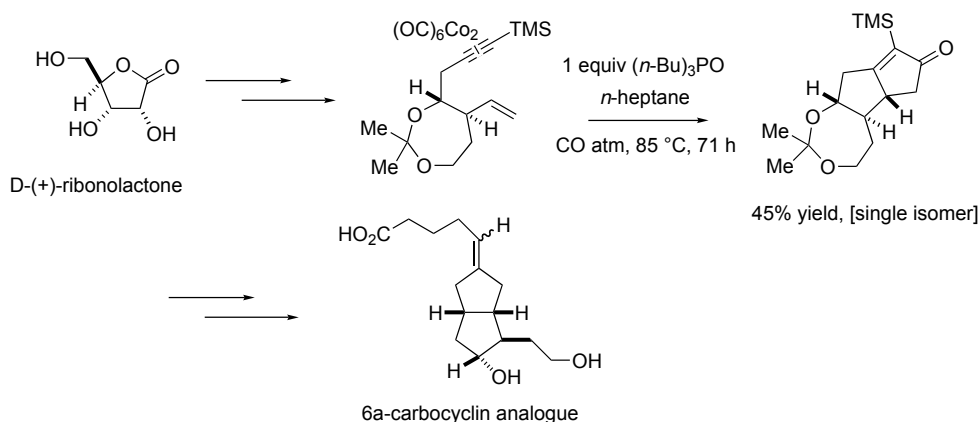
Finally, attempts have been made to cyclize 1,7-enynes. These substrates were either converted to cyclopentenones with low enantioselectivity (Table 3, entry 9) or could not be cyclized at all with **16** (Fig. 7, **35** and **36**). The failure to cyclize certain 1,7-enynes emphasized the problems inherent in utilizing a bulky ligand such as EBTHI.

5 Stoichiometric Pauson-Khand-Based Syntheses of Optically Active Cyclopentenones

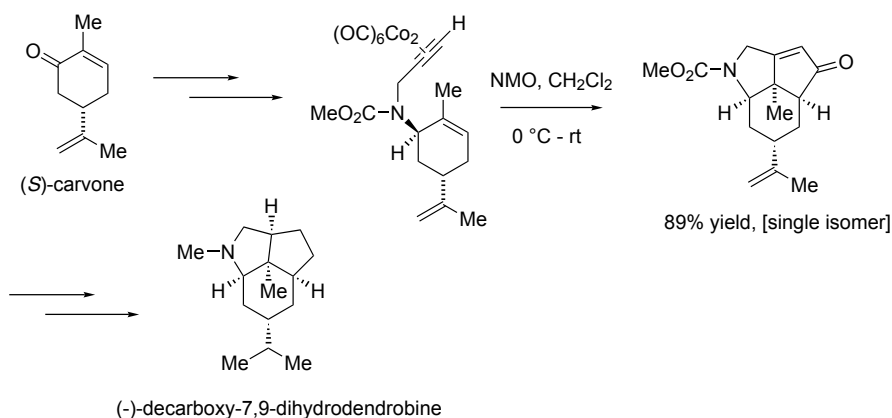
5.1 Diastereoselective Cyclization of Optically Active Enynes

The diastereocontrolled cyclization of chiral enynes has been extensively studied [11], and its application with optically active enynes represents a major focus in the efforts to synthesize optically active cyclopentenones via the Pauson-Khand reaction. For the purposes of this review, the discussion of this subject

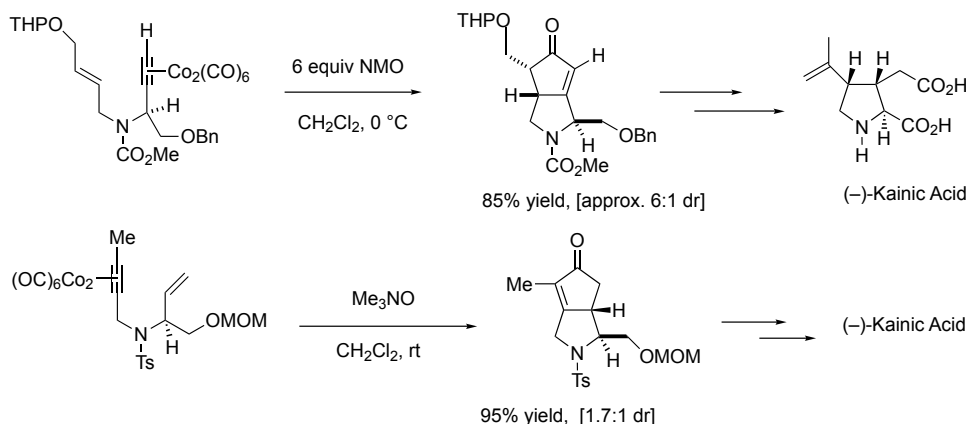
will be limited to applications in total synthesis. One of the earliest examples involved Magnus' synthesis of a carbocyclin analogue starting from D-(+)-ribonolactone via a completely diastereoselective cyclization (Scheme 1) [45]. A related approach to a diastereomeric carbocyclin analogue was also reported by Mulzer [46]. Takano has demonstrated the feasibility of utilizing the Pauson-Khand cyclization for the total synthesis of (-)-dendrobine through a synthesis of decarboxy-7,9-dihydrodendrobine starting from (S)-carvone (Scheme 2) [47]. Two groups have described conceptually different syntheses of (-)- α -kainic acid (Scheme 3) which rely on a Pauson-Khand cyclization [48, 49]. You has since improved the diastereoselectivity of the Pauson-Khand reaction in his sequence by employing a modified cyclic enyne [50]. A particularly elegant application of the



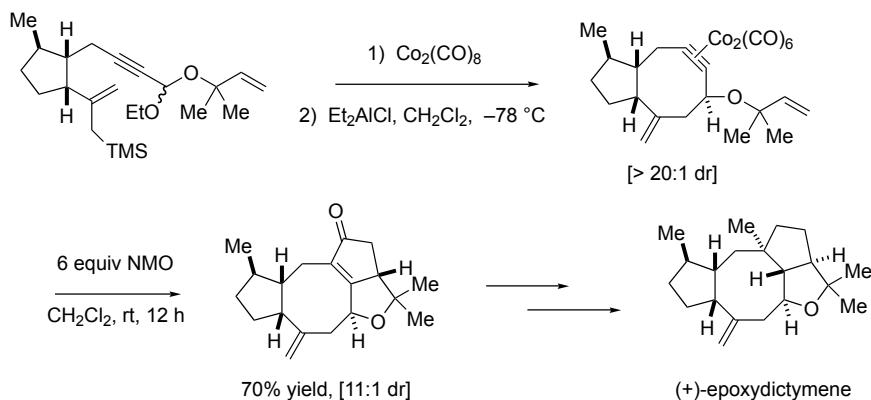
Scheme 1. Synthesis of a carbocyclin analogue



Scheme 2. Synthesis of (-)-decarboxy-7,9-dihydrodendrobine



Scheme 3. Two syntheses of (-)-kainic Acid



Scheme 4. Synthesis of (+)-epoxydictymene

Pauson-Khand reaction was described in Schreiber's synthesis of (+)-epoxydictymene (Scheme 4) [51, 52]. The $\text{Co}_2(\text{CO})_6$ -alkyne complex first participated in a Nicholas reaction to form an eight-member ring. Subsequent Pauson-Khand cyclization provided the final 5,5-ring system.

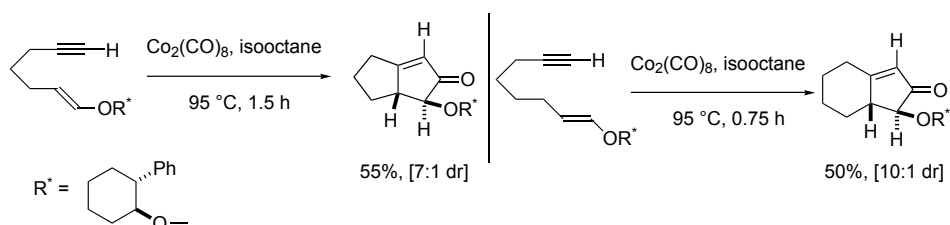
5.2

Chiral Auxiliaries

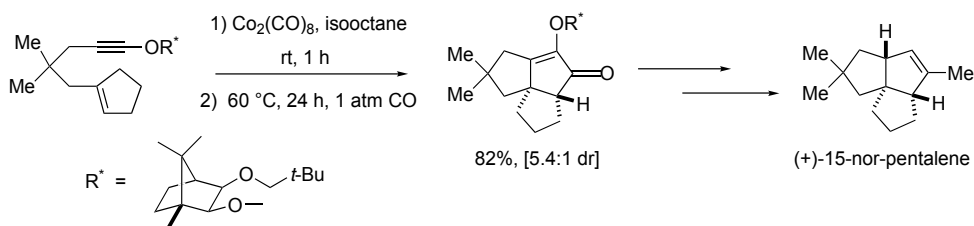
Another approach to the stoichiometric enantioselective Pauson-Khand reaction involves the use of chiral auxiliaries. Extensive investigations on this subject have been carried out by Pericàs, Moyano, Greene, and coworkers. Initial reports detailed the use of *trans*-2-phenylcyclohexanol as a chiral auxiliary for the

intramolecular Pauson-Khand reaction [53]. When attached to the alkene terminus of an enyne, both 1,6- and 1,7-enynes were found to cyclize with high levels (7:1 and 10:1, respectively) of diastereoselectivity (Scheme 5); this methodology was exploited in a formal total synthesis of (+)-hirsutene. Substrates containing *trans*-2-phenylcyclohexanol attached to the alkyne portion of a 1,6-enyne were cyclized with lower diastereoselectivity (3:1); however, a camphor-derived chiral auxiliary (R^* in Scheme 6) proved more selective (~9:1) in these cases [54]. The chiral auxiliary approach has also been utilized in the synthesis of angular triquinane ring systems [55], including a recent total synthesis of (+)-15-nor-pentalene (Scheme 6) [56].

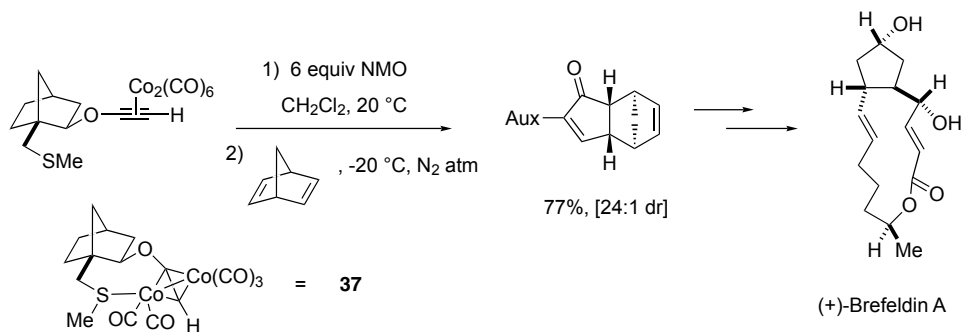
Substantial progress has also been made in the chiral auxiliary-based approach to an enantioselective intermolecular Pauson-Khand reaction. Initial studies utilizing alkynes substituted with *trans*-2-phenylcyclohexanol produced cyclopentenones with low drs, however, the diastereomers were easily separable [57]. The use of 10-(methylthio)isoborneol as a chiral auxiliary led to more diastereoselective cyclizations [$>9:1$ for three different olefins (Scheme 7)] [58]. The thiomethyl moiety was crucial for the high levels of selectivity, and an intermediate like **37** has been proposed to account for this fact. Both of these approaches have been utilized in formal total syntheses of (+)-brefeldin A [59]. Recent reports involving alkynes substituted with ester, thio- and dithioether chiral auxiliaries have expanded the scope of viable alkyne substrates, although the resulting cyclopentenones are obtained with low levels of diastereoselectivity [60, 61, 62]. The highest levels of selectivity have been reported using Oppolzer's



Scheme 5. *trans*-2-Phenylcyclohexanol as a chiral auxiliary for the intramolecular Pauson-Khand reaction

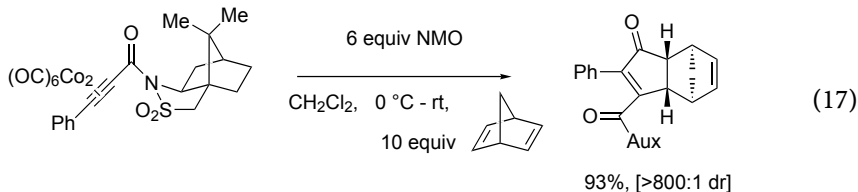


Scheme 6. A camphor-derived chiral auxiliary for the intramolecular Pauson-Khand reaction



Scheme 7. 10-(Methylthio)isoborneol as a chiral auxiliary for the intermolecular Pauson-Khand reaction

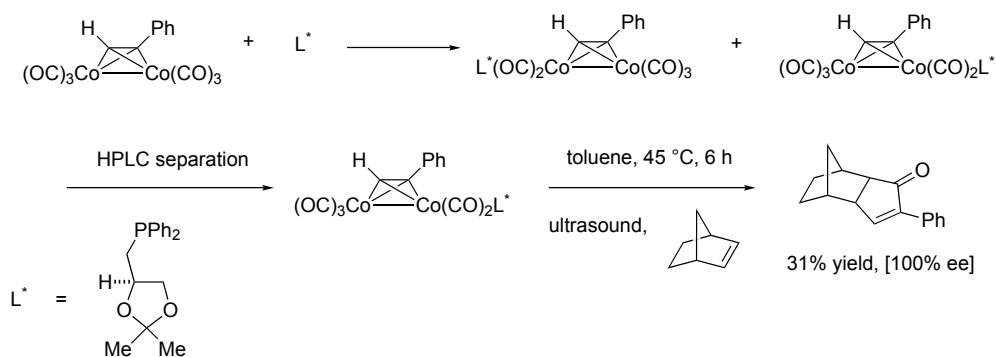
2,10-camphorsultam auxiliary (>800:1), Eq. (17) [63]. Despite the progress in this field, a general approach to the asymmetric intermolecular Pauson-Khand reaction which accommodates a wide array of alkynes and unstrained alkenes remains an elusive goal. Additionally, no attempts to utilize the catalytic Pauson-Khand type cyclizations with chiral auxiliaries have been reported.



5.3 Chiral Ligands and Amine Oxides

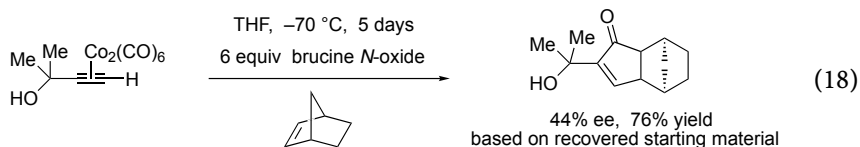
The use of chiral ligands has also been explored as a method of asymmetric induction in the Pauson-Khand reaction. To date, all of these reports have involved the addition of (*R*)-(+)-Glyphos to a preformed Co-alkyne complex and subsequent separation of the resulting diastereomers by HPLC. Under reaction conditions which prevented isomerization of the alkyne complex, the subsequent Pauson-Khand reaction proceeded with high levels of diastereoselectivity (Scheme 8) [64]. Kerr demonstrated that the use of amine oxide promoters in this process led to significantly improved yields [65]. A related approach involving an achiral ligand and a chiral alkyne has been reported by Chung and coworkers [66]. The use of a chiral ligand in the Pauson-Khand reaction, where separation of diastereomeric complexes would be unnecessary, has yet to be demonstrated.

A final conceptually unique approach to the asymmetric Pauson-Khand type cyclization involved the use of chiral amine oxide promoters. Kerr has reported



Scheme 8. Diastereoselective Pauson-Khand reaction via diastereomerically pure alkyne complex

an example of the intermolecular Pauson-Khand reaction where addition of six equivalents of brucine *N*-oxide provided modest levels of enantioselectivity, Eq. (18) [67].



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Chapter 16.1

Cyclopropanation and C-H Insertion with Cu

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Keywords: Copper catalysts, Metal carbenes, Diazo compounds, Cyclopropanes, C-H insertion, Ylides

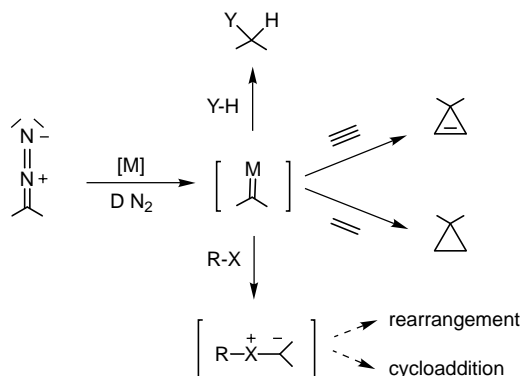
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1 Introduction

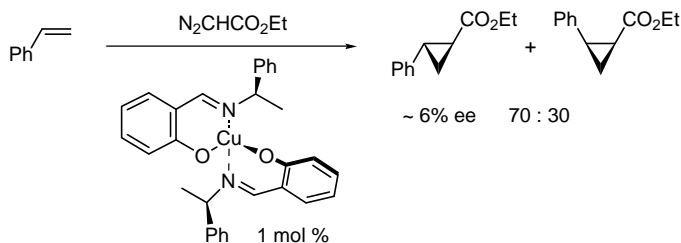
Cyclopropanes play an important role as starting materials and intermediates in organic synthesis because, due to the ring strain, they can be converted to a variety of useful products by cleavage of the three-membered ring [1, 2]. There are also numerous natural and synthetic cyclopropanes displaying interesting physiological activities [3, 4]. Therefore, great efforts have been made to develop efficient diastereo- and enantioselective methods for the construction of cyclopropane rings [2, 5]. A particularly versatile method is the metal-catalyzed cyclo-

propanation of olefins with diazo compounds and, during the last two decades, various efficient homogeneous metal catalysts have been found which have considerably broadened the scope of this reaction [6, 7, 8, 9, 10]. In addition, the same type of catalysts can also be used to carry out other synthetically useful transformations of diazo compounds such as cyclopropanation, insertion into C-H and other X-H bonds, or ylide formation followed by rearrangement or cycloaddition reactions (Scheme 1) [9, 10]. There is ample, albeit indirect, evidence that these reactions proceed via metal carbenes as short-lived intermediates [6, 7, 11] and, consistent with such a mechanism, the reaction course strongly depends on the nature of the metal and the catalyst structure. By proper choice of a specific metal-ligand combination, it is often possible to discriminate between two competing pathways (e.g., cyclopropanation and C-H insertion) or to control the stereoselectivity of the reaction [12, 13]. Moreover, if a chiral ligand is used, optically active products can be obtained.

In 1966 Nozaki et al. [14] reported the first examples of enantioselective metal-catalyzed cyclopropanation reactions of diazo compounds. Although the enantiomeric excesses induced by chiral copper-salicylaldimine complexes were low (Scheme 2), this work proved to be seminal as it demonstrated the principle



Scheme 1



Scheme 2

that a homogeneous metal-catalyzed process can be rendered enantioselective by attaching a chiral ligand to the metal center. In addition, the results served as a starting point for Aratani and his research group at Sumitomo Co. who, by systematic variation and optimization of the salicylaldimine structure, developed the first practically useful catalyst for enantioselective cyclopropanation (see Section 4.1) [15, 16, 17, 18]. Subsequently, various other highly enantioselective copper catalysts have been found which are described in this chapter. A further significant breakthrough was made by Doyle [13] who discovered a new type of catalyst for cyclopropanation and C-H insertion, chiral dinuclear rhodium(II) complexes. These remarkably efficient and highly enantioselective catalysts are discussed in chap. 16.2.

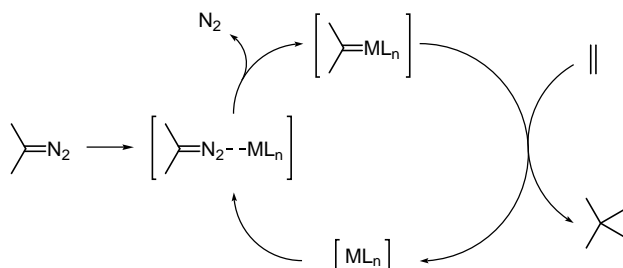
Besides Cu and Rh, various other metals are known to catalyze the decomposition of diazo compounds [6, 7, 8, 9, 10]. Palladium complexes, e.g., are efficient catalysts for the cyclopropanation of electron-deficient C-C double bonds with diazoalkanes [19, 20, 21], in contrast to Cu and Rh catalysts which are better suited for reactions with electron-rich olefins. Unfortunately, attempts to develop chiral Pd catalysts for enantioselective cyclopropanation have not been successful so far [22]. More promising results have been obtained with cobalt and ruthenium complexes. These and other chiral metal catalysts, that have been studied besides Cu and Rh complexes, are discussed in chap. 16.3. The same chapter also covers a new direction of research that has recently been taken with the development of catalytic enantioselective Simmons-Smith reactions.

The same chiral catalysts developed for enantioselective cyclopropanation and C-H insertion have also been used for enantioselective transformations of diazo compounds via ylides (cf. Scheme 1 and Section 6). Although this area is still in its infancy, recent results suggest that it will see significant progress in near future. An up-to-date summary including rhodium catalysts can be found in a recent review [13], while in this chapter only a few examples are given that illustrate the use of chiral copper catalysts to induce enantioselective reactions involving [1,2]- or [2,3]-sigmatropic rearrangements of ylides.

The extensive literature on enantioselective cyclopropanation and other reactions of diazo compounds with chiral catalysts has been summarized in numerous reviews and books [9, 10, 23, 24, 25, 26, 27]. Excellent recent surveys are available that illustrate the current state of the art in the field. Here, only a selection is presented with the focus on the most general and practically useful catalysts and some recent promising developments that have the potential to lead to new methodological advances.

2 Mechanistic Aspects

The mechanism of transition metal-catalyzed nitrogen extrusion from diazo compounds is not known in detail, but there is general agreement that metal-carbene complexes are formed in this process (Scheme 3) [6, 7, 11, 28, 29, 30, 31, 32]. Attempts to detect these elusive species in catalytic reactions have not been



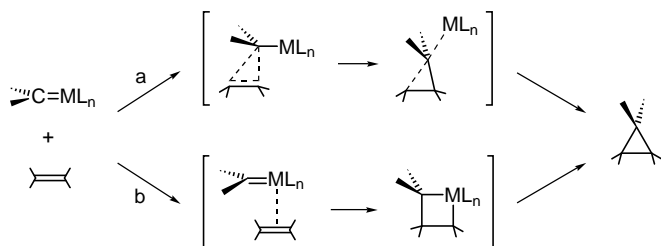
Scheme 3

successful so far. Evidence for their existence comes from reactivity-selectivity correlations between stoichiometric cyclopropanation reactions of well-characterized metal-carbene complexes and catalytic reactions postulated to proceed through structurally similar intermediates. More recently, ruthenium and osmium carbene complexes have been isolated from stoichiometric reactions with diazoacetates and demonstrated to be active catalysts for cyclopropanation and olefin formation [30, 31, 32]. For the copper catalysts discussed in this chapter, it is assumed that they react by an analogous mechanism via short-lived copper-carbene intermediates.

Mechanistic studies of rhodium porphyrins as cyclopropanation catalysts have resulted in the spectroscopic identification of several potential intermediates in the reaction of ethyl diazoacetate with olefins, including a diazonium(ethoxycarbonyl)methyl-rhodium complex formed by electrophilic addition of the rhodium center to the α -C atom of ethyl diazoacetate [29]. It is not known if analogous intermediates are also formed in analogous reactions of copper catalysts. However, the initial part of the catalytic cycle leading to the metal carbene intermediate is not of primary concern for the enantioselective reactions described herein. It is the second part, the reaction of the metal-carbene complex with the substrate, that is the enantioselective step.

The metal-carbene complexes postulated as intermediates in transition metal-catalyzed reactions of diazo compounds are electrophilic species (especially if they are derived from α -diazocarbonyl compounds). Accordingly, electron-rich olefins are the most suitable substrates for copper-catalyzed cyclopropanations, whereas electron-poor substrates such as α,β -unsaturated carbonyl compounds in general are not sufficiently reactive.

The cyclopropanation is initiated by the interaction of the electrophilic metal-carbene species with the π -system of the olefin (Scheme 4). Two different mechanisms have been proposed for the formation of the cyclopropane ring: a concerted pathway (a) or a two-step process via a metallacyclobutane (b). The first pathway (a) resembles the mode of addition of free carbenes to (C=C) double bonds [33] and has been proposed for reactions of metal carbenoids by various authors [7, 11]. The principal bonding interaction in this case initially develops between the electrophilic carbenoid C-atom and the π -system of the C-C double



Scheme 4

bond. The second pathway (b) begins with coordination of the olefin to the metal center leading to a metallacyclobutane as the central intermediate which then undergoes reductive elimination. The formation of metallacyclobutanes from metal carbenes and the reductive elimination to cyclopropanes are well-known steps in organometallic chemistry. Both pathways are compatible with the literature data, although for many of the copper catalysts discussed in this chapter, which bear sterically demanding chiral ligands, a metallacyclobutane intermediate seems less attractive for steric reasons.

The oxidation state of the copper center in the active catalyst has been the subject of considerable controversy [7, 11, 34, 35]. In many cases, it has been observed that under the reaction conditions, Cu(II) complexes are reduced to Cu(I) complexes by the diazo compound. This led to the general conclusion that the active catalyst is a Cu(I) species, irrespective of the initial oxidation state of the copper complex used as precatalyst. Although this point has not been conclusively settled for all Cu(I) and Cu(II) complexes used as catalysts, for many of the reactions described in this chapter, there is ample evidence for a Cu(I) species as the active catalyst (see, e.g., [18, 36, 37]).

Bis(semicorrinato)copper(II) complexes (see Sect. 4.1), e.g., exhibit no apparent reactivity towards α -diazocarbonyl compounds at ambient temperature [36]. However, when they are treated with ethyl diazoacetate at 60–80 °C for a few minutes, their characteristic violet color disappears with concomitant evolution of nitrogen. The resulting yellowish-brown solution remains catalytically active upon cooling to room temperature under nitrogen. Treatment with 1–2 molar equivalents of phenylhydrazine at room temperature also produces an active catalyst. When a solution of the activated copper complex is flushed with oxygen, the catalytic activity is lost and the original violet bis(semicorrinato)copper(II) complex can be recovered in high yield. Analogous observations have been reported by Aratani [18] for salicylaldehyde-Cu(II) complexes. When Cu(I) complexes are used as catalyst precursors, activation is usually not necessary and the reaction starts immediately upon addition of the diazo compound [36, 37].

3

Practical Aspects

The most versatile carbene precursors are α -diazocarbonyl compounds such as diazoacetic acid esters because they are readily prepared, easy to handle and much more stable than ordinary diazoalkanes [10, 38]. Nevertheless, one should always be aware of the potential hazards of diazo compounds in general [39], but if the necessary precautions are taken, they can be safely handled even on an industrial scale [18]. The most frequently used reagent is commercially available ethyl diazoacetate. Besides α -diazocarbonyl reagents, diazomethane [40, 41] and a γ -diazocrylate derivative [42] have been used in enantioselective Cu-catalyzed cyclopropanations but the scope of these reactions has not been studied systematically. It has been shown in certain cases that diazo compounds can be replaced by other carbene precursors such as iodonium ylides, sulfonium ylides, or lithiated sulfones [8, 43], but successful applications of these reagents in enantioselective Cu-catalyzed reactions have not been reported yet.

A side reaction encountered in most metal-catalyzed processes of diazo compounds is the coupling of two diazo compounds to give an alkene. In cyclopropanations with ethyl diazoacetate, e.g., mixtures of diethyl fumarate and maleate are always formed to some extent. Obviously, the diazo compound and the olefin compete in the reaction with the metal-carbene intermediate. In order to suppress this undesired side reaction, the concentration of the diazo compound has to be kept low by slow addition, preferably by means of a syringe pump.

As mentioned in Sect. 2, both Cu(II) or Cu(I) complexes can be used as pre-catalysts. Copper(II) complexes have the advantage that they are air-stable and that they can often be obtained in pure form by recrystallization. However, they have to be reduced to the copper(I) oxidation state before the reaction. This is achieved either by heating the reaction mixture for a short time to 60–90 °C in the presence of the diazo compound and then cooling down to the reaction temperature under nitrogen or argon, or by addition of a reducing agent such as phenylhydrazine at ambient temperature. The latter method is often preferred because it avoids heat treatment, allowing for a more controlled activation. In some cases, somewhat higher yields have been recorded using phenylhydrazine rather than thermal activation [44]. If the catalyst is prepared from a Cu(I) salt and the chiral ligand, no activation is necessary. Because of the air-sensitivity of Cu(I) compounds, all manipulations have to be carried out in an inert atmosphere. Often the active catalyst is prepared in situ in the reaction solvent from Cu(I) triflate or another suitable Cu(I) salt and a slight excess of the chiral ligand. After filtration, in order to remove possible traces of insoluble Cu salts which do not contain the chiral ligand, the olefin is added to the catalyst solution and the reaction started by slow addition of the diazo compound. The in situ method is particularly convenient for the preparation of catalysts with neutral chiral ligands [37]. Copper(I) catalysts with anionic chiral ligands have been prepared in situ from *t*-BuOCu(I) and the protonated ligand L-H [36, 40]. Cu(I) *tert*-butoxide is a very reactive metalating agent which readily dissolves in apo-

lar solvents. It can be obtained in high purity by sublimation but its high sensitivity to oxygen is a disadvantage.

Typically, 1–2 mol % of catalyst is used but in some cases, the catalyst loadings can be reduced to 0.1 mol % without loss of yield or ee [37]. At Sumitomo Co. a technical process for the enantioselective cyclopropanation of 2-methylpropene has been developed [18] but details about the scale, catalyst loading, or turnover frequency are not available. The reactions are usually carried out in chlorinated solvents such as dichloromethane, chloroform, or 1,2-dichloroethane. Sometimes, the ee's differ significantly in these solvents but no general rules for the best choice of solvent can be given [45, 46]. Coordinating solvents such as ethers or acetonitrile decrease the reactivity of the catalyst and, in general, should be avoided (for an exception, see Scheme 16 in Sect. 5). Normally reactions are run at room temperature, but for less reactive olefins or diazo compounds (e.g., diazomalonates), higher temperatures may be necessary [46, 47, 48].

4

Cyclopropanation

4.1

Intermolecular Reactions

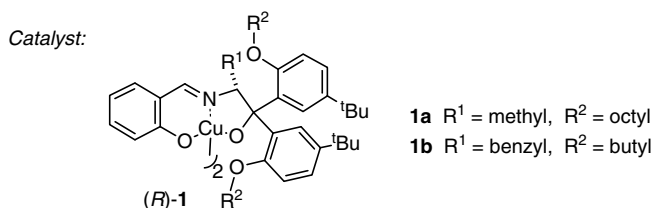
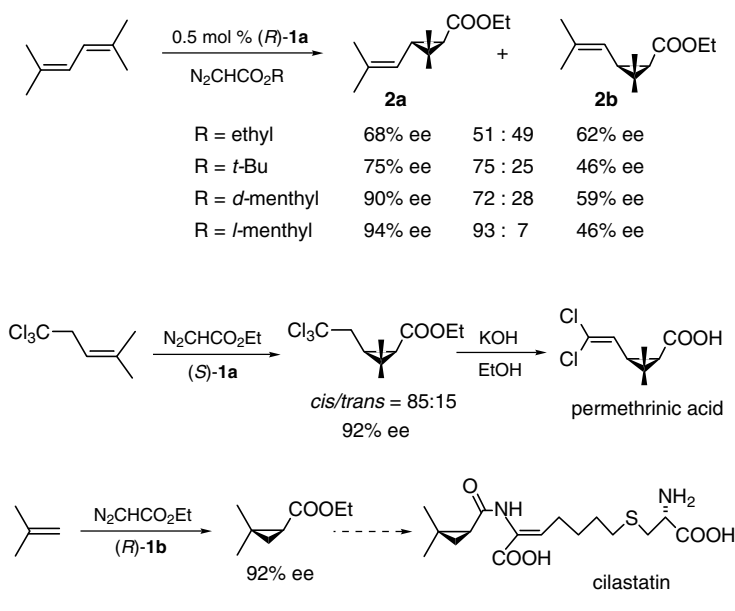
4.1.1

Cu-Salicylaldimine Catalysts

Inspired by the work of Nozaki and coworkers (Scheme 2) [14], a number of research groups initiated a search for more efficient catalysts for enantioselective cyclopropanation. The most spectacular advances were made by Aratani and coworkers whose aim was to develop a catalyst for the industrial production of pyrethroids [15, 16, 17, 18, 49]. After extensive evaluation of many different salicylaldimine ligands, they eventually found a practically useful catalyst which gave moderate to high enantioselectivities in the cyclopropanation of various olefins with alkyl diazoacetates (Scheme 5 and Table 1).

In this way, esters of chrysanthemic acid (**2**) [15, 16, 18] and permethrinic acid [17, 18], which are important precursors for the synthesis of pyrethroid insecticides, can be prepared in >90% ee. Although enantioselective cyclopropanation cannot compete with conventional industrial syntheses of optically active pyrethroids, a technical process for the cyclopropanation of 2-methylpropene was successfully implemented at Sumitomo [18]. The product, ethyl (+)-2,2-dimethylcyclopropanecarboxylate, serves as a starting material for the production of cilastatin, a dehydropeptidase inhibitor used as a drug to suppress the degradation of the β -lactam antibiotic iminipenem.

Other mono and disubstituted olefins that were studied gave ees in the range of 70–90% ee (Table 1) [17]. In general, the thermodynamically more stable *trans*-isomer is the major product. The cyclopropanation of 1,1,1-trichloro-4-methyl-


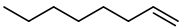

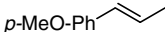




Scheme 5

3-pentene (Scheme 5) that affords mainly the less stable *cis*-isomer, is a notable exception (cf. also [50]).

The copper(II) complexes **1** have to be activated by heat treatment in the presence of the diazo compound or with a substituted hydrazine [18]. The enantioselectivity of the catalyst strongly depends on the particular structure of the substituents at the periphery of the five-membered chelate ring. With a secondary alkyl group instead of a methyl or benzyl group at the stereogenic center (R¹), or with less bulky substituents at the two aryl groups, the ees are substantially lower. Variation of ester group of the diazo compound also has an effect on the stereoselectivity (Scheme 5). In the cyclopropanation of 2,5-dimethyl-2,4-hexadiene, the ee of the *trans*-product and the *trans/cis*-selectivity increase with bulkier ester groups, a phenomenon that is also observed with other types of copper catalysts. In menthyl diazoacetate, both the steric bulk and the chirality of the ester group play a role. Although the stereoselectivity is largely controlled by the chiral catalyst, there are distinct differences in the ees and *cis/trans* ratios be-

Table 1. Cyclopropanation of various olefins with catalyst **1**

Olefin	<i>trans/cis</i>	% ee (<i>trans</i>)	% ee (<i>cis</i>)
	82 : 18	81	78
	78 : 22	84	64
	—	84	—
	88 : 12	89	60
	—	75	—
	60 : 40	68	86

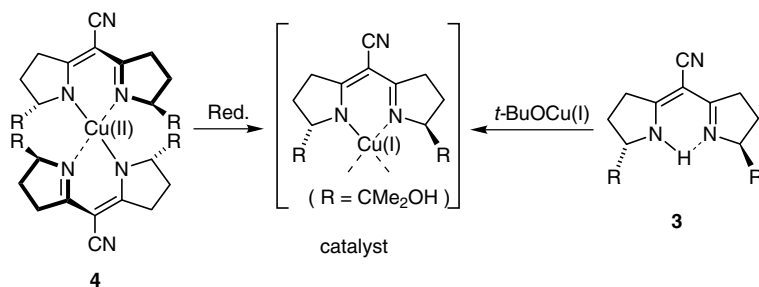
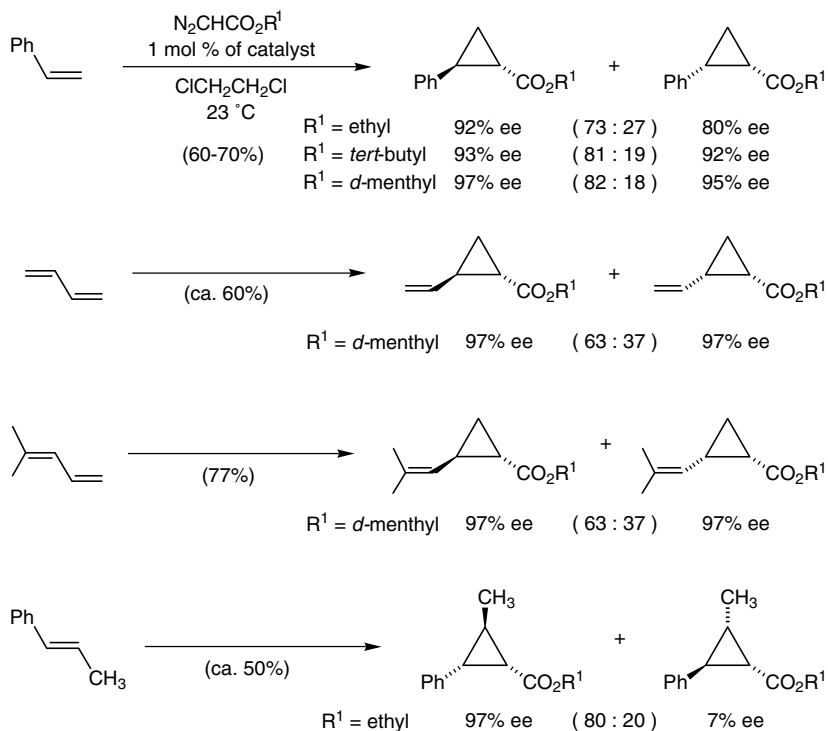
tween the matched (*R*-catalyst and *l*-menthyl) and the mismatched case. Originally, *d*- or *l*-menthyl esters were used quite frequently, because the ratio of the diastereomeric products corresponding to the two enantiomers obtained from achiral diazoacetates, could be readily determined by GC. However, with the advent of efficient chiral GC and HPLC columns, this aspect became less important.

4.1.2

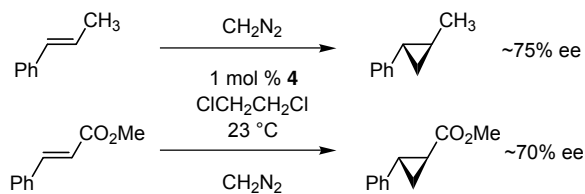
Cu-Semicorrin and -Bisoxazoline Catalysts

A new class of ligands, C_2 -symmetrical semicorrins, was introduced in 1986 [36, 40, 51, 52, 53]. Of the various derivatives that were tested in copper-catalyzed cyclopropanations, the semicorrin **3** ($R=CMe_2OH$) bearing two bulky substituents at the stereogenic centers was found to be the most effective ligand. Using the stable crystalline Cu(II) complex **4** as a catalyst precursor, ees of >90% could be achieved in the cyclopropanation of terminal [36, 51, 53] and 1,2-disubstituted olefins [48b] (Scheme 6) which exceeded the enantioselectivities of salicylaldimine-derived catalysts **1**. With trisubstituted olefins, on the other hand, Aratani's catalysts are more effective. There is ample evidence that the active catalyst is a mono(semicorrinato)copper(I) complex which is generated from complex **4** either by heating in the presence of the diazo compound or by treatment with phenylhydrazine at ambient temperature [36, 40]. Alternatively, the catalyst may be generated in situ from the free ligand **3** and copper(I) *tert*-butoxide, although this method is less convenient because of the air-sensitivity of Cu(*Ot*-Bu).

Cyclopropanation with diazomethane was also briefly investigated but the reaction has not been developed into a practical method as yet (Scheme 7) [40, 41].



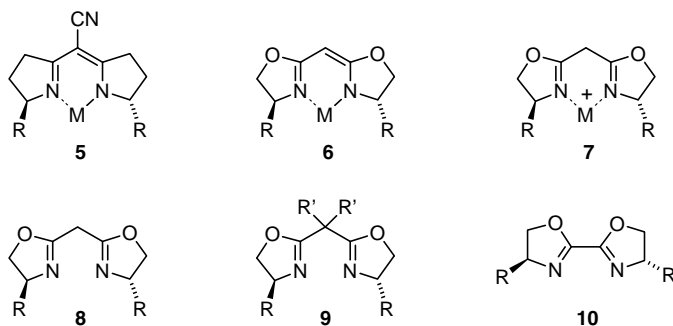
Scheme 6



Scheme 7

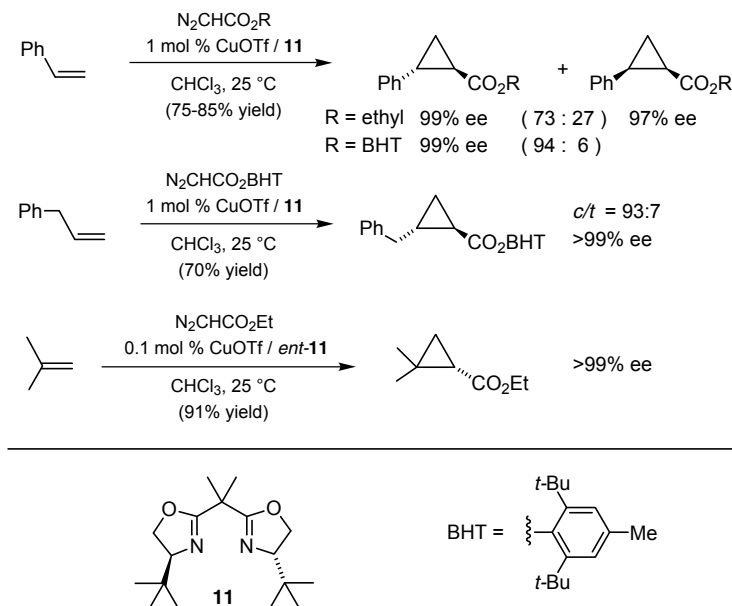
Diazomethane was slowly introduced into the reaction mixture as a gas by conducting a stream of argon through a reservoir containing a solution of diazomethane in triethyleneglycol dimethyl ether and from there through a teflon tubing into a solution of the olefin and the catalyst in 1,2-dichloroethane. Using catalyst **4** and (*E*)-1-phenylpropene or methyl cinnamate as substrates, enantioselectivities of 70–75% ee were obtained but the conversion was low (98% yield based on 47% conversion, 77% yield/33% conversion, respectively).

The development of bisoxazoline ligands **8** and **9**, which are patterned on the semicorrins **5**, led to even more selective catalysts that considerably enhanced the scope of enantioselective cyclopropanation [37, 53, 54, 55, 56, 57, 58]. The bisoxazolines **8** can coordinate as anionic ligands, affording complexes of the type ML (**6**) or ML₂ analogous to the semicorrins **5**, or as neutral ligands forming cationic copper complexes of type **7**. Neutral Cu(I)-bisoxazoline complexes of type **6** gave similar results in the cyclopropanation of terminal olefins as their semicorrin counterparts [55, 57]. Evans et al. [37] observed that bisoxazolines **9** bearing geminal substituents at the methylene bridge, which prevent deprotonation at this position, are more effective ligands than their unsubstituted analogues **8**. The bisoxazolines **10**, which form five-membered chelate rings, induced only very low ees in the cyclopropanation of styrene.



The cationic Cu(I) complex, which is readily prepared from the bis(*tert*-butyloxazoline) **11** and copper(I) triflate, is the most efficient catalyst available today for the cyclopropanation of mono- and disubstituted terminal olefins with diazoacetates (Scheme 8) [37, 58]. In the reaction of ethyl diazoacetate with 2-methylpropene, >99% ee and high yields can be obtained with this catalyst using substrate/catalyst ratios as high as 1000:1. Monosubstituted olefins also react with very high enantioselectivities. The *trans/cis* ratio increases with the steric bulk of the ester group of the diazo compound. With the BHT ester, the more stable *trans*-isomer is formed with selectivities of >10:1. Steric hindrance prevents ester hydrolysis but the BHT group can be removed by reduction with LiAlH₄. Because the *cis* product reacts more slowly, the *trans* isomer is enriched during the reduction.

With all Cu catalysts, the *trans/cis* selectivities in the cyclopropanation of monosubstituted olefins are only moderate. They depend mainly on the struc-

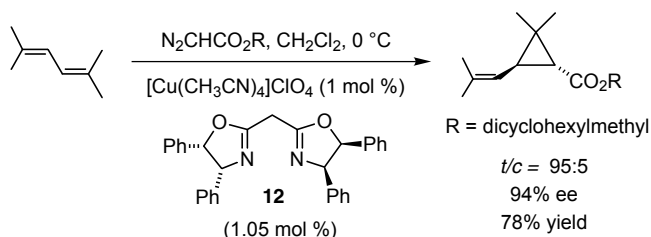


Scheme 8

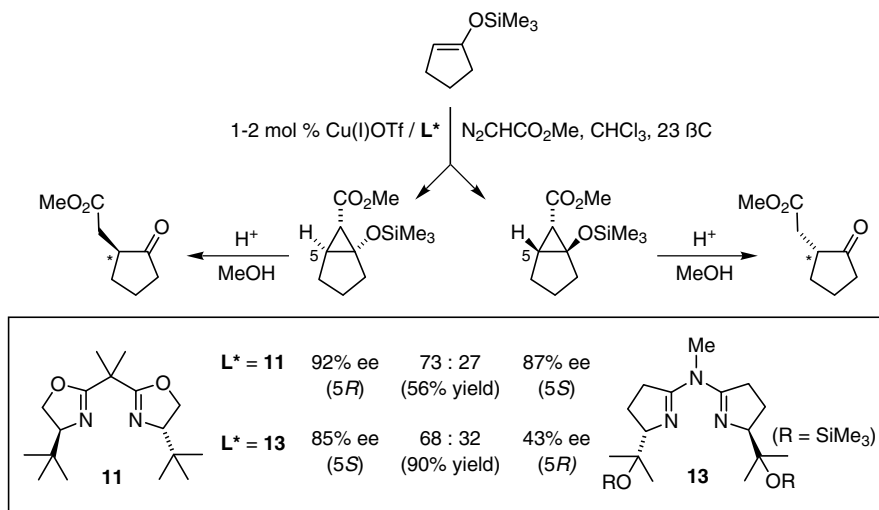
ture of the diazo ester rather than the chiral ligand. With 1,2-disubstituted or certain trisubstituted olefins, on the other hand, the chiral ligand also influences the *trans/cis* ratio. A mechanistic model rationalizing the diastereo- and enantioselectivities of semicorrin- and bisoxazoline-copper catalysts is discussed in Sect. 7. While diastereocontrol in the Cu-catalyzed cyclopropanation of many olefins is still an unsolved problem, recently, ruthenium catalysts have been reported that produce higher *trans/cis* ratios in reactions of monosubstituted olefins (see Chap. 16.3).

Although many different bisoxazolines and other semicorrin-type ligands have been prepared [53, 54], the bis(*tert*-butyl)oxazoline **11** is still the most versatile ligand for cyclopropanation. However, there are certain applications which give better results with other ligands. For the cyclopropanation of trisubstituted and 1,2-disubstituted (*Z*)-olefins, Lowenthal and Masamune found the bisoxazoline **12** to be superior to the bis(*tert*-butyloxazoline) **11** [56]. This is illustrated by the reaction of 2,5-dimethyl-2,4-hexadiene leading to chrysanthemates (Scheme 9). Again, the best diastereo- and enantioselectivities were obtained with bulky diazoacetates. Both the *trans/cis* ratios and ees were similar to those reported for Aratani's catalyst (Scheme 5).

Silyloxycyclopropanes, which are readily available by cyclopropanation of silyl enol ethers, are versatile intermediates in organic synthesis. Reißig, who has developed this chemistry, has studied enantioselective cyclopropanations of silyl enol ethers systematically [59]. The products which can be obtained from silyloxycyclopentene and diazoacetates in optically active form can be converted



Scheme 9



Scheme 10

to γ -ketocarboxylates by ring cleavage under mild conditions (Scheme 10). Recently, the enantioselectivities in this transformation have been improved using the bisoxazoline **11** and the azasemicorin **13** [44] as ligands (Scheme 10) [45]. The bisoxazoline **11** affords the best ees, however, the yields are only moderate, probably because the Lewis acidity of the cationic copper catalyst promotes cleavage of the silyloxy group. Significantly higher yields are obtained with the azasemicorin **13** but the ees are somewhat lower. Because the *cis*- and the *trans*-products produce ring-opening products of opposite configuration, it is necessary to separate the two isomers completely before cleaving the cyclopropane ring. However, chromatographic separation is sometimes difficult because of the instability of the silyloxycyclopropane unit. Some of the problems caused by the acid lability of the silyl ethers could be relieved by adding small amounts of 2,2,6,6-tetramethylpiperidine to the reaction mixture or by using the more stable

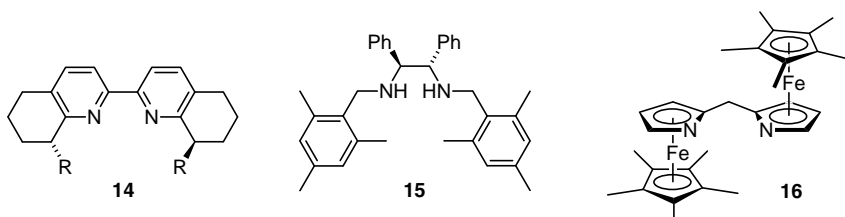
triisopropylsilyl ethers although at the expense of slightly lower ees. The triisopropylsilyl ether derived from cyclohexanone afforded the *trans*-product in 86% ee (*trans*/*cis* 69:31) with ligand **13**. Interestingly, the best ees in all these reactions were obtained with methyl diazoacetate rather than more bulky esters. An intramolecular cyclopropanation of a silyl enol ether is shown in Sect. 4.2.

Although diazomalones or other diazo compounds derived from 1,3-dicarbonyl compounds are easy to prepare and give access to synthetically useful products, no suitable catalysts have been reported for enantioselective cyclopropanations with these reagents. The stability of diazomalones requires elevated reaction temperatures and in general the yields and ees are low. With a catalyst prepared from CuOTf and ligand **13**, ees in the range of 30–65% and 20–45% yield were obtained in the cyclopropanation of styrene with methyl or ethyl diazomalone at 70 °C [46] (see also Sect. 4.2 and, for the use of diazodimedone, the next subsection).

4.1.3

Other Catalysts

Many other chiral copper catalysts have been reported, most of them being derived from C_2 -symmetrical bidentate nitrogen ligands [13, 27]. Some ligands such as the bipyridine derivatives **14** [60, 61, 62], the diamine **15** [63] and the bis(azaferrocene) **16** [64] are capable to induce high ees, but none of them can compete so far with chiral bisoxazolines in terms of high selectivity combined with effectiveness, general applicability and ease of preparation.



A chiral copper catalyst derived from 3-(trifluoroacetyl)camphor was reported to induce up to 100% ee in the cyclopropanation of styrene with diazodimedone [65] but no further studies of this reaction have been published since. Recently, the same catalyst was used for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene [66] and up to 87% ee was reported for the *trans*-product derived from menthyl diazoacetate.

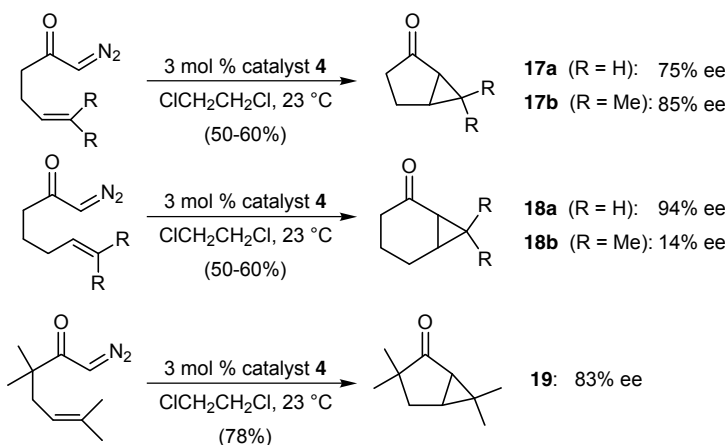
4.2

Intramolecular Reactions

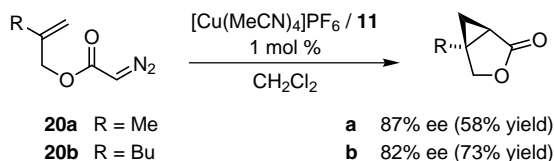
Since 1961, when Stork and Ficini [67] reported the first example of an intramolecular cyclopropanation starting from an alkenyl-diazocarbonyl compound,

cyclizations of this type have been widely used in organic synthesis [68]. Therefore, numerous studies of intramolecular cyclopropanations with chiral catalysts have been carried out and many useful enantioselective transformations have been reported [13]. Depending on the particular class of substrate, either dinuclear rhodium(I) (Chap. 16.2) or copper complexes with semicorrin or bisoxazoline ligands have given the best results. These two classes of catalysts exhibit remarkably different properties and their scope is largely complementary.

The semicorrin catalyst **4** (cf. Scheme 6) has been employed in cyclization reactions of alkenyl diazoketones (Scheme 11) [48]. The enantioselectivities were strongly dependent on the substitution pattern of the C-C double bond and varied between 94% ee for **18a** and 14% ee for the corresponding dimethyl-substituted analog **18b**. Similar ees were obtained with the bisoxazoline **11** and azasemicorrins such as **13** (structures: see Scheme 10). Interestingly, analogous cyclizations of allyl and homoallyl diazoacetates gave disappointingly low ees with these catalysts. The only esters that were reported to give reasonably high ees, are the 2-methyl- and 2-butylallyl diazoacetates **20a** and **20b** (Scheme 12) [69]. For this class of substrate, Doyle's dinuclear rhodium complexes are more efficient catalysts (see Chap. 16.2) whereas rhodium catalysts, on the other hand, are less suited for cyclizations of alkenyl diazoketones.



Scheme 11



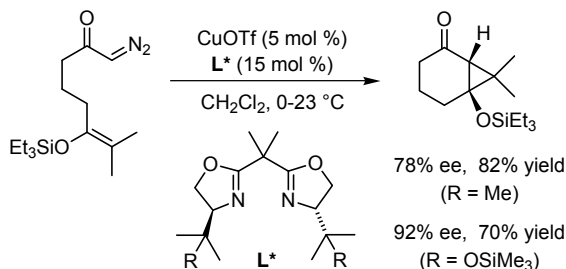
Scheme 12

Related cyclization reactions of α,α' -dicarbonyldiazo compounds derived from unsaturated β -keto esters [48] and allyl alkyl malonates [47] have been studied but only modest enantioselectivities of up to 30–40% ee have been achieved.

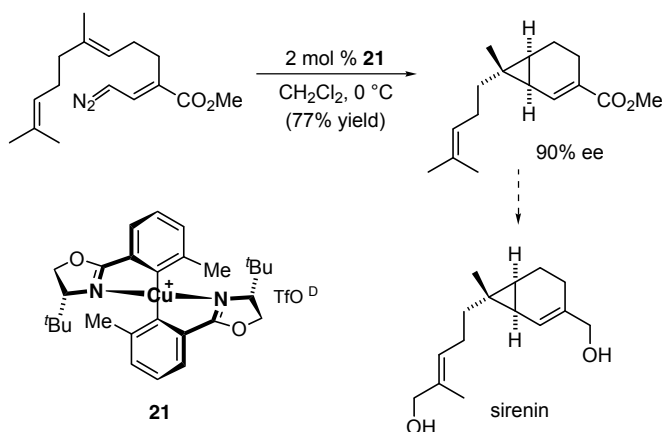
Recently, Shibasaki et al. [70] reported an example of a highly selective intramolecular cyclopropanation reaction of a silyl enol ether (Scheme 13). The most effective ligand in this case was a bisoxazoline with two sterically demanding $(\text{Me}_3\text{SiO})\text{Me}_2\text{C}$ groups at the stereogenic centers.

Corey et al. [42] have developed an interesting new bisoxazoline ligand with a biphenyl backbone [71] which was successfully applied in the key-step of the synthesis of the chemotactic factor sirenin (Scheme 14). The crystalline copper complex **21** emerged as the most effective catalyst for this reaction after extensive screening of a series of chiral Cu and Rh complexes. Other reactions with catalyst **21** have not been reported.

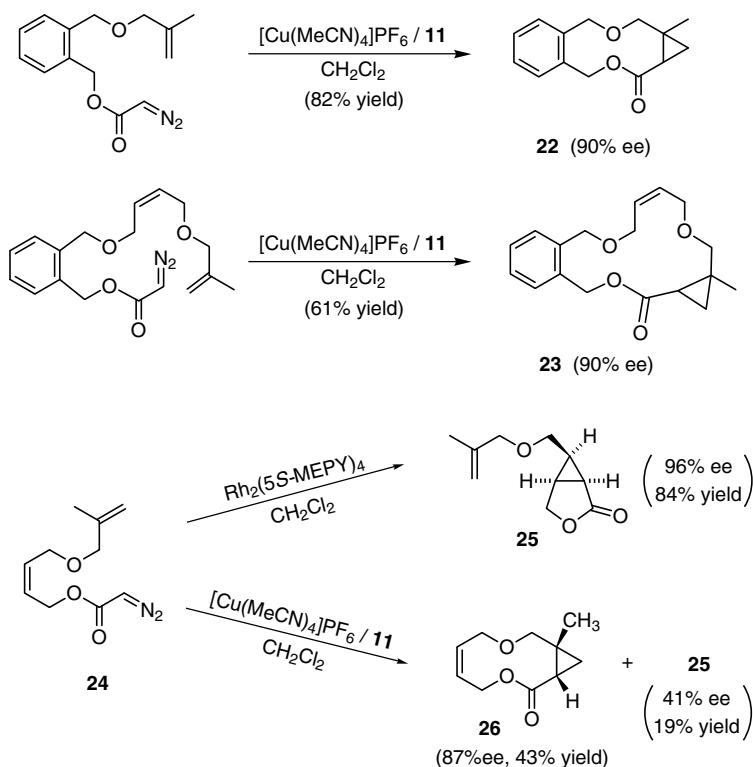
Copper-bisoxazoline complexes have emerged as remarkably effective catalysts for the synthesis of macrocycles from ω -alkenyl diazoacetates (Scheme 15) [13, 27, 73, 74]. The 10- and 15-membered ring lactones **22** and **23**, e.g., can be



Scheme 13



Scheme 14



Scheme 15

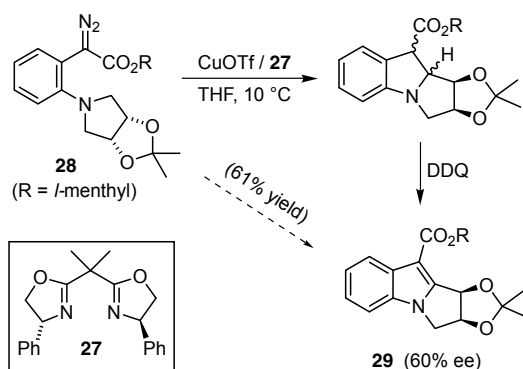
prepared in high enantiomeric purity with high efficiency. The 15-membered ring lactone **23** is formed with high preference over the 10-membered ring lactone. Chiral dirhodium catalysts proved to be less suited for macrocyclization reactions of this type. The unique preference of copper-bisoxazoline catalysts to promote the formation of large rings is demonstrated by the reaction of substrate **24** which can either cyclize to the five-membered lactone **25** or to the macrocycle **26**. The copper-catalyzed reaction produces preferentially the 10-membered lactone **26** (26:25=69:31) whereas the rhodium-catalyzed process leads exclusively to **25**.

5 C-H Insertion

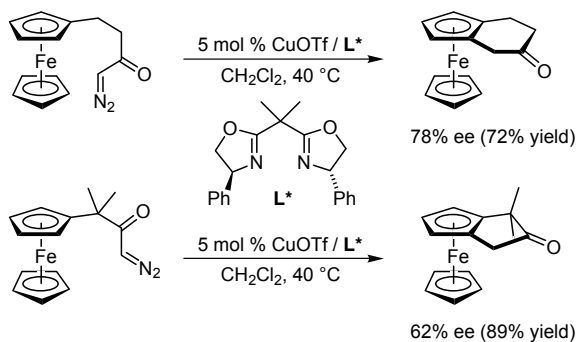
Enantioselective C-H insertion is clearly the domain of chiral dinuclear rhodium catalysts (see Chap. 16.2). Only very few examples of enantioselective copper-catalyzed reactions of this type have been reported. As a possible approach to the mitomycine ring system, Sulikowski has studied the cyclization of diazo esters **28** quite extensively using various chiral transition metal catalysts

(Scheme 16) [75, 76, 77]. In collaboration with Burgess, 96 metal-ligand-solvent combinations were examined using a microtiter plate [78]. The stereodirecting effect of the *l*-menthyl ester group, which was introduced to facilitate chromatographic analysis of the products, was found to be negligible. Therefore, the diastereoselectivities in this reaction closely correspond to the enantioselectivities of the various catalysts. Among seven different metal salts, copper and silver complexes with the bisoxazoline ligand **27** were found to be the most effective catalysts. The four diastereomeric pairs of enantiomers were directly oxidized to the product **29** with DDQ. Using the copper complex of ligand **27**, the final product **29** was obtained in 61% overall yield with an ee (or, more correctly de) of 60%. The corresponding silver complex afforded 75% yield and 56% ee (THF, 25 °C). Interestingly, THF was found to be a better solvent in this case than CHCl₃.

Siegel and Schmalz [79] reported a new approach to optically active ferrocenes with planar chirality, based on a Cu-catalyzed C-H insertion (Scheme 17). Both a five- and a six-membered ring could be formed in this way. Using a copper-bisoxazoline catalyst, good yields and ees in the range of 60–80% could be obtained, whereas chiral dirhodium catalysts proved to be ineffective in this case.



Scheme 16



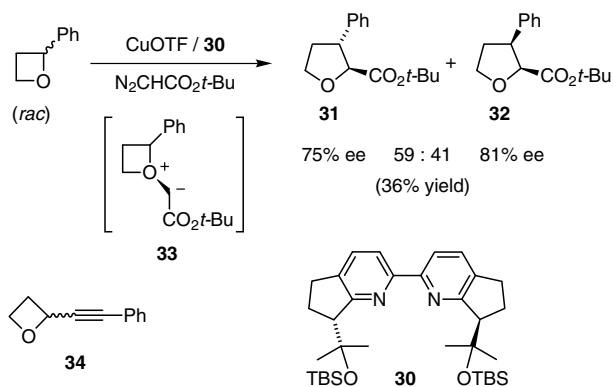
Scheme 17

6 Reactions via Ylides

Carbenes are known to add to heteroatoms with lone pairs, such as N, O, S, or I, to form ylides (cf. Scheme 1). These reactive intermediates can rearrange to stable products or, as in the case of carbonyl or azomethine ylides, undergo cycloaddition reactions [6, 9, 10]. If the ylide is generated from a chiral non-racemic metal carbene, optically active products may be formed supposing that the chiral metal complex remains associated with the ylide or that a chiral free ylide is formed that does not racemize before it is converted to the final product. Although the first example of a catalytic enantioselective transformation via an oxygen ylide has been reported by Nozaki et al. [14] more than 30 years ago, promising enantioselectivities have been observed only very recently [13].

Using their newly developed chiral bipyridine ligand **30**, Katsuki and coworkers [61, 62] were able to substantially improve the enantioselectivities originally reported by Nozaki et al. [14] for the transformation shown in Scheme 18. Using *tert*-butyl diazoacetate and 1 mol % of the Cu(I) catalyst derived from ligand **30**, racemic 2-phenyloxetane was converted to a mixture of two optically active diastereomers **31** and **32** with 75 and 81% ee, both having the same absolute configuration at the carboxy-bearing carbon atom. This shows that the stereoselectivity is mainly controlled by the chiral catalyst and not by the chirality of the phenyloxetane. The configuration at the phenyl-bearing carbon atom of **31** and **32**, obtained from optically active 2-phenyloxetane, implies that the [1,2]-rearrangement of the postulated ylide intermediate **33** occurs with retention of configuration at the migrating center. In the same way, racemic oxetane **34** was converted to a 1:1 mixture of the corresponding *cis*- and *trans* tetrahydrofuran derivatives in 88% yield with ees of 71 and 75% [80].

Doyle and coworkers have recently reported a remarkable example of an enantioselective cyclization to a large ring lactone via an oxygen ylide and subsequent

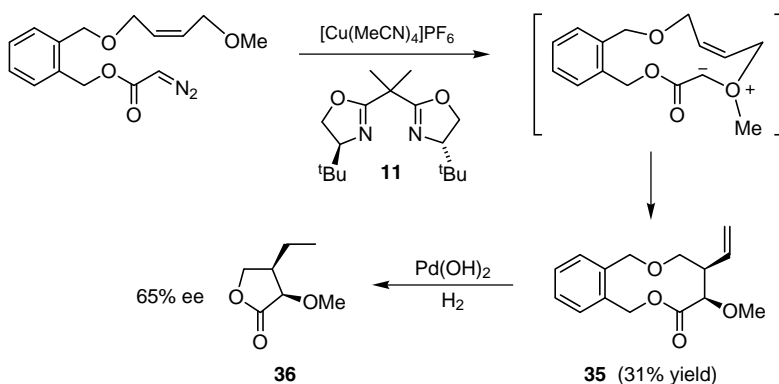


Scheme 18

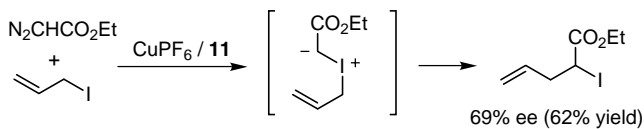
[2,3]-sigmatropic rearrangement (Scheme 19) [13]. The ylide-derived product **35** was isolated in 31% yield while only 4% of the product resulting from intramolecular cyclopropanation were found. The relative configuration and the ee of the main product **35** were determined by conversion to the five-membered lactone **36**.

As shown by Uemura and coworkers, related enantioselective intermolecular reactions via sulfur and selenium ylides are also possible. The products resulting from a [2,3]-sigmatropic rearrangement of the ylides were obtained in 14–41% ee using copper-bisoxazoline or dinuclear rhodium catalysts [81]. An intriguing transformation of allyl iodide to optically active ethyl 2-iodopent-4-enoate has been realized by Doyle and coworkers (Scheme 20) [13]. The substantial ee of 69% implies that the chiral metal catalyst remains bound to the iodonium ylide during the [2,3]-sigmatropic rearrangement, because the free ylide would be achiral and afford racemic product.

The examples shown in this section clearly indicate the potential of catalytic processes via ylides for enantioselective transformations. Although at present, the efficiencies and enantioselectivities are still moderate, this exciting new area of research will certainly develop further in the coming years.



Scheme 19



Scheme 20

7

Mechanistic Rationale for the Stereoselectivity of Cyclopropanations

As pointed out in Sect. 2, there is general agreement that copper-catalyzed cyclopropanation reactions of diazo compounds involve metal-carbene complexes as intermediates. If this assumption is correct then the enantioselection must occur in the reaction of the metal-carbene with the olefin. Although the structures of the chiral copper catalysts that have been used so far vary considerably, the selectivities displayed by these catalysts have two important stereochemical features in common. Firstly, in the cyclopropanation of terminal olefins with alkyl diazoacetates, the absolute configuration of the *cis*- and the *trans*-product at the asymmetric carbon atom derived from the diazo compound is the same. Secondly, although the chiral ligand efficiently controls the enantioselectivity of the reaction, its influence on the *cis/trans*-selectivity in the cyclopropanation of styrene and other terminal olefins is negligible. In the cyclopropanation of styrene with ethyl diazoacetate, e.g., the ratio of the *trans*- and the *cis*-product ranges between 70:30 and 75:25 with all catalysts. The *cis/trans*-selectivity in the cyclopropanation of terminal olefins appears to be determined almost exclusively by the alkoxy group of the diazo ester and the substituents at the olefinic double bond, irrespective of the particular structure of the catalyst.

The stereoselectivity can be explained by the occurrence of a metal-carbene intermediate in which one of the two enantiotopic faces of the trigonal carbene C-atom is shielded by the chiral ligand such that the olefin preferentially approaches from the less hindered side (Fig. 1). Consequently, the *cis*- and the *trans*-product have the same absolute configuration at the carboxyl-bearing carbon atom.

Aratani has rationalized the stereoselectivity of his catalysts by a model based on a metallacyclobutene intermediate (cf. Scheme 4, reaction b) [18]. For semicorrin and related ligands, formation of a metallacyclobutane seems less attractive because of steric hindrance, and a different pathway, analogous to reaction a in Scheme 4, has been proposed [36, 40, 53b]. Fig. 2 shows the postulated ster-

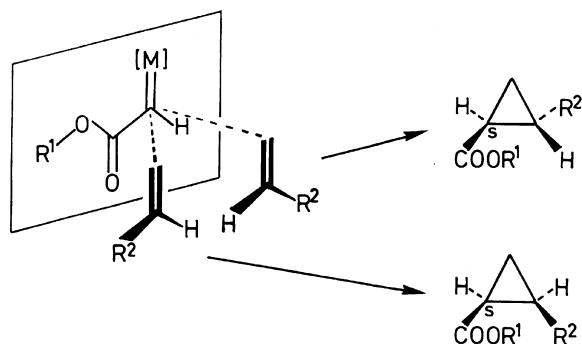


Fig. 1

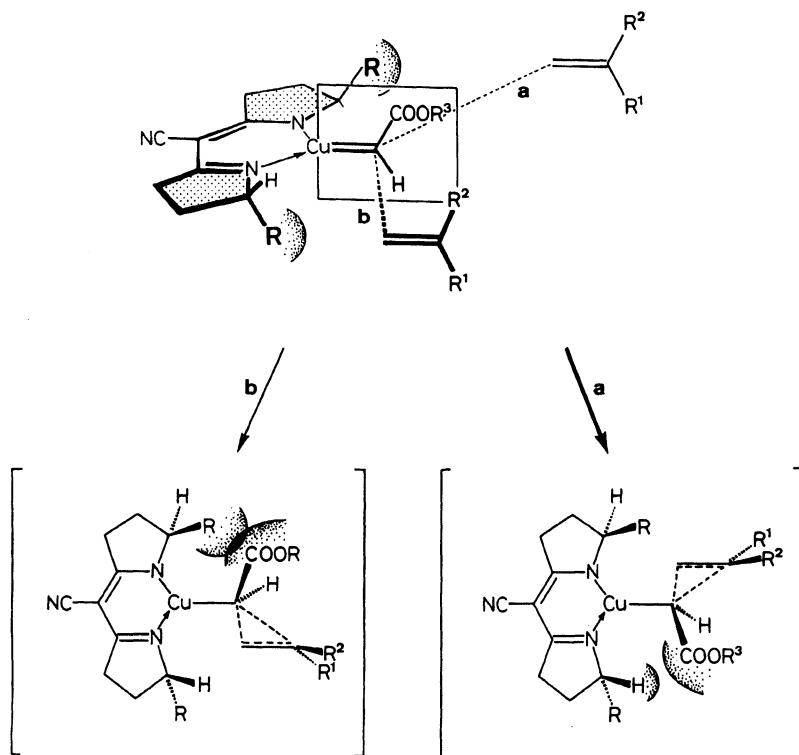


Fig.2

eochemical course of the enantioselectivity-determining step in the cyclopropanation of terminal olefins. The plane defined by the trigonal carbene atom is assumed to be perpendicular to the ligand plane. This geometry is expected to be favored over a planar geometry for steric and, possibly, also electronic reasons. The olefin approaches the metal-carbene either from the front- or the back-side along pathway **b** or **a**. The principal bonding interaction initially develops between the electrophilic carbenoid C-atom and the terminal olefinic C-atom which is sterically more accessible and more nucleophilic than the substituted end of the (C=C) double bond. As a result of this interaction, the two trigonal centers become pyramidal. Depending on the direction of attack, the alkoxy carbonyl group at the carbenoid center either moves forward or backward relative to the plane bisecting the semicorrin ligand (pathways **a** and **b**). In the latter case (**b**), a repulsive steric interaction builds up between the ester group and the adjacent substituent at the stereogenic center of the semicorrin. Accordingly, pathway **a** which either leads to the *cis*-(1*S*)- or to the *trans*-(1*S*)-cyclopropane-carboxylate, is expected to be favored over pathway **b**, consistent with the experimental data.

In this model, the ee crucially depends on the interaction between the ester group and the adjacent R substituent of the chiral ligand, in line with the obser-

vation that bulkier esters lead to higher ees. The model also accounts for the fact that the *cis/trans*-selectivity of the catalyst almost exclusively depends on the structure of the olefin and the diazo compound, whereas the effect of the chiral ligand is negligible. In a transition structure of the type depicted in Fig. 2, the substituents at the olefinic double bond are too remote to experience any significant influence from the chiral ligand. Therefore, the *cis/trans*-selectivity is expected to be determined mainly by the interactions between the olefinic substituents and the ester group of the carbenoid moiety.

The model also explains the enantioselectivity in the cyclopropanation of (*E*)-1-phenylpropene with diazomethane (Scheme 7). Again it is assumed that the more nucleophilic π -center is attacked by the carbenoid (Fig. 3). In this case, the two faces of the trigonal carbene unit are homotopic and, accordingly, the front- and back-side approaches are stereochemically indistinguishable. Therefore, the observed enantioselectivity must originate from the interaction between the olefin and the chiral ligand. Fig. 3 shows the pathway leading to the major enantiomer which is favored because the olefinic methyl group points away from the adjacent R substituent of the semicorrin. The alternative pathway leading to the opposite enantiomer is destabilized because it results in a repulsive steric interaction between the methyl group and the R substituent.

Analysis of the reaction of diazoacetate with (*E*)-1-phenylpropene [48b] (Scheme 6) is more complex because both the interaction between the ester group and the chiral ligand as well as the interaction between the olefin and the chiral ligand are important. This is illustrated in Fig. 4 which also lists the relative ratios of the four possible stereoisomeric products. Pathway **a** is expected to be clearly favored because it avoids any steric repulsion between the chiral ligand and the olefinic methyl or the ester group. Pathway **a'** leading to the enantiomer of **37** is strongly destabilized as it suffers from two repulsive steric interactions (methyl- R^1 , ester- R^1). This explains, why the *cis*-product **37** is formed with high ee. Pathways **b** and **b'** are less favorable than **a** because both involve one repulsive interaction (**b**: methyl- R^1 , **b'**: ester- R^1). Consistent with this analysis, the *cis*-product **37** is the major product and the two enantiomeric *trans*-isomers **38** and *ent*-**38** are obtained in an almost 1:1 ratio. Ito and Katsuki [60] tested chiral bipyridine ligands of type **14** in this reaction and reported similar results which they could also rationalize using this model.

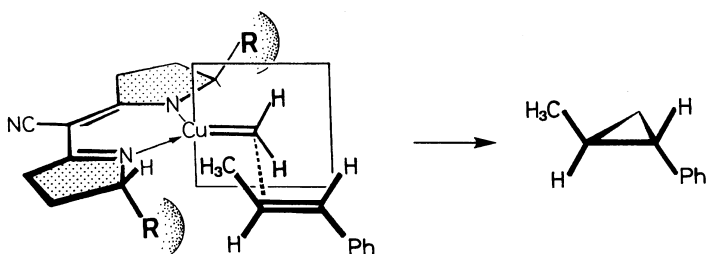


Fig. 3

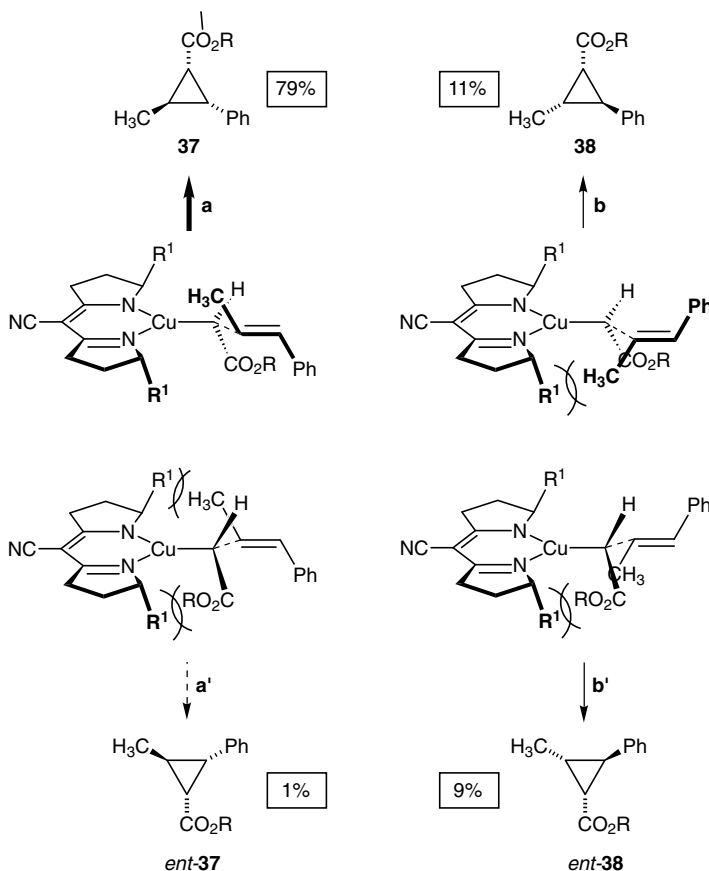


Fig. 4

It should be pointed out that there is no direct experimental evidence supporting the proposed structures of the metal-carbene intermediates and the transition structures. Nevertheless, as shown in this section, the proposed model rationalizes the observed stereoselectivities in a number of cases and, thus, should prove useful for the design of new chiral ligands.

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Chapter 16.2

Cyclopropanation and C-H Insertion with Rh

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Keywords: Rhodium, Carbon-Hydrogen Insertion, Cyclopropanation, Chiral, Asymmetric, Enantioselective, Intermolecular, Intramolecular, Diazocarbonyl Compounds

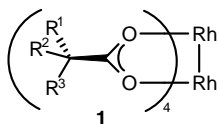
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1 Introduction

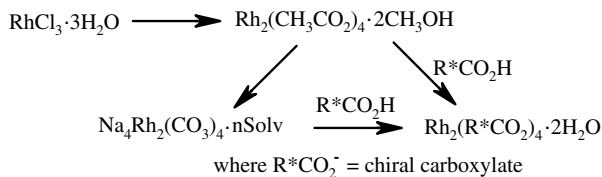
Cyclopropanation and C-H insertion are but two of a broad spectrum of reactions of diazo compounds that are catalyzed efficiently by rhodium (II) carboxylates and rhodium(II) carboxamides. In this regard, α -diazocarbonyl derivatives are the most significant within the general classification of diazo compounds. Prior to the introduction of chiral rhodium catalysts, their achiral counterparts were already well established as catalysts of choice for several diazocarbonyl transformations, including cyclopropanation and C-H insertion. The pioneering work of Teyssie and co-workers [1] had identified rhodium (II) acetate and rhodium (II) trifluoroacetate as among the most effective catalysts, often achieving exceptionally high turnover numbers. These molecules of D_{4h} symmetry, having four bridging carboxylate ligands and one vacant co-ordination site per metal atom [2, 3, 4], display an octahedral geometry with each electron deficient rhodium atom surrounded by an electron-rich wall of oxygen atoms.

Numerous subsequent studies showed that a high degree of control of both reactivity and selectivity could be achieved by varying the nature of the carboxylate or carboxamide ligands on the metal core. This approach to the control of selectivity has proved to be a very effective guide to catalyst development.

In 1990, Brunner [5], McKervey [6], and Ikegami [7] and their respective co-workers independently introduced chiral rhodium(II) carboxylates for asymmetric diazocarbonyl transformations. At that time the only chiral rhodium(II) carboxylates known were those derived from (*R*) and (*S*)-mandelic acid which had been prepared by Cotton and co-workers [8] for structural and chiroptical studies. Enantiopure carboxylates (**1**) on a dirhodium core (substituents varied from H, Me, and Ph to OH, NHAc, and CF₃) were assessed by Brunner [5] for enantioselective cyclopropanation of alkenes with ethyl diazoacetate. McKervey [6] and Ikegami [7] took advantage of the natural chirality of amino acids to prepare rhodium carboxylates of L-proline and L-phenylalanine, having first suitably protected the amino function.



There are two general routes to new chiral rhodium(II) carboxylates, both involving the rhodium(II) acetate dimer. McKervey and Roos [9] converted the acetate into the carbonate which was then reacted with the enantiopure carboxylic acid, whereas Ikegami went directly from the acetate to the carboxylates (Scheme 1). Later studies showed that the presence of the amino group in the amino acid offered a further means of modulating enantioselectivity, in that in many cases the catalyst's performance was found to be dependent on the nature of the protecting group on the nitrogen. Originally, McKervey and co-workers used *N*-benzenesulfonyl as the protecting group. Later Davies [10] introduced *N*-*p*-*tert*-butylbenzenesulfonyl and *N*-*p*-dodecylbenzenesulfonyl protection and found enhanced performance and better catalyst solubility in non-polar solvents. The pool of available rhodium(II) carboxylates with monochiral ligands has enlarged considerably since 1990. A selection of catalysts are collected in Fig. 1 and Fig 2. The X-ray crystal structures of the Rh₂(*S*-mandelate)₄ (**2**) [8] and



Scheme 1

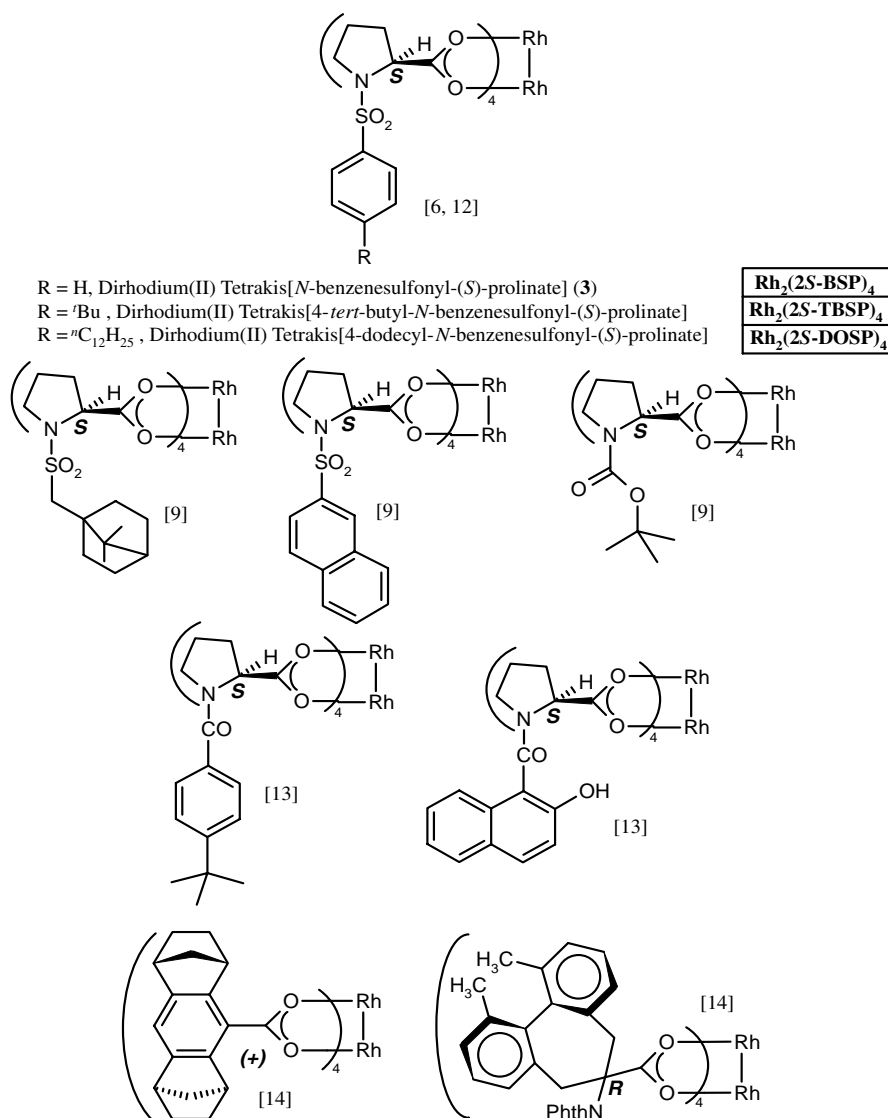


Fig. 1

Rh₂(*N*-benzenesulfonyl-(*S*)-prolinate)₄ (**3**) [11] are displayed in Fig. 3. In the former, two ethanol molecules occupy the vacant coordinate sites on each rhodium atom, whereas in the latter these sites are occupied by methanol molecules.

In 1993 Doyle and co-workers [18], in a very significant development in asymmetric synthesis employing diazocarbonyl chemistry, introduced chiral rhodium(II) carboxamidate as catalysts. The most effective of these catalysts were

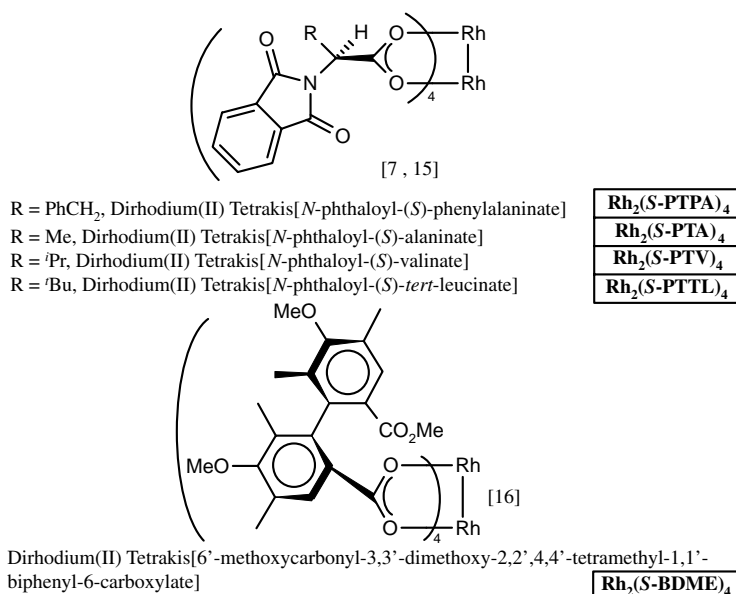


Fig. 2

those with ligands based on enantiopure 2-oxopyrrolidine, 2-oxazolidinone, *N*-acylimidazolidin-2-one and 2-azetidinone (Fig. 4), each with an attachment R on the ring in the form of a carboxylate ester. For many of the catalysts illustrated in Fig. 4, both enantiomeric forms are available. The (*R*) and (*S*) forms of Rh₂(MEPY)₄, Rh₂(MEOX)₄ and Rh₂(MPPIM)₄ have been commercialized and are available from Aldrich and (in Europe) Acros. The X-ray crystal structures of Rh₂(5*R*-MEPY)₄ (4) [18] and Rh₂(4*S*-MPPIM)₄ (5) [19], as bis-acetonitrile complexes (Fig. 5), reveal that they possess the (*cis*-2,2) geometry of Fig. 6, with two oxygen atoms and two nitrogen atoms bound to each rhodium with the two nitrogens adjacent to each other. These catalysts have much more rigid structures than their carboxylate counterparts and the rhodium atoms are closer to the chiral elements of the ligands. Although most of these dirhodium (II) compounds are soluble in dichloromethane, increasing the lipophilicity is easily achieved by increasing the hydrocarbon content of the alkyl group in the ester R, as for example in Rh₂(5*S*-ODPY)₄. The characteristic geometry of each structure is shown in Fig. 7 with the group R projecting nearly perpendicular from the plane of the ligand. For R=CO₂Me, the arrangement in Fig. 7 represents the (*R*) configuration. The representations in Fig. 7 reveal a rhodium face with four quadrants, designated clockwise by the (*N*, *N*), (*N*, *O*), (*O*, *O*), and (*O*, *N*) ligated atoms.

Dirhodium (II) phosphates and rhodium (III) porphyrins, examples of which are shown in Fig. 8, have also been used for asymmetric induction in diazo decomposition.

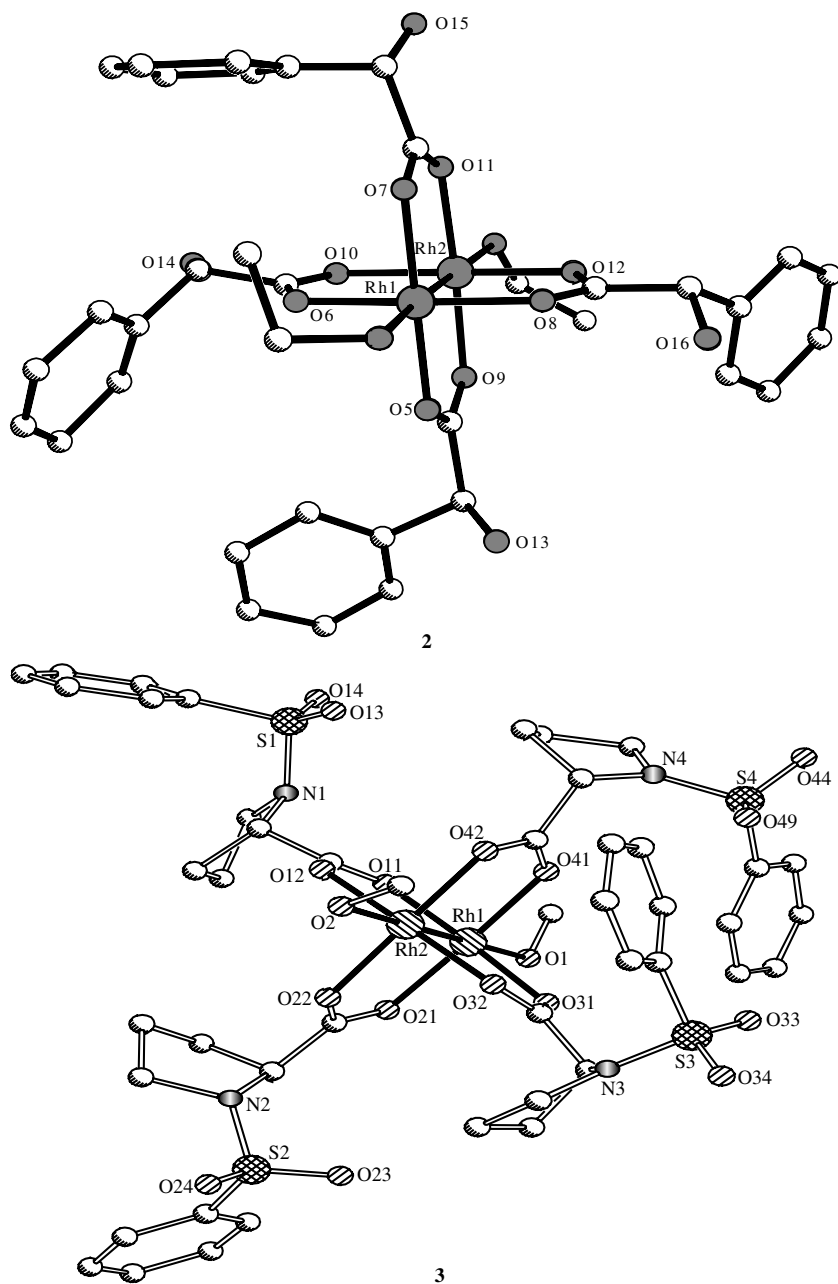
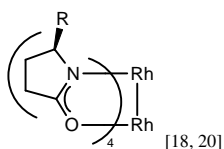
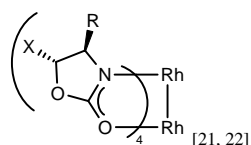
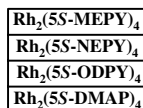


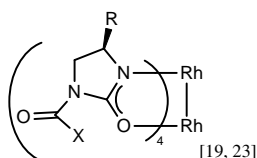
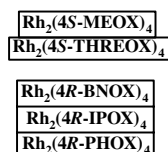
Fig. 3. The X-ray crystal structures of $\text{Rh}_2(\text{S-Mandelate})_4(\text{EtOH})_2$ (2) and $\text{Rh}_2(\text{N-benzenesulfonyl-(S)-proline})_4(\text{MeOH})_2$ (3)



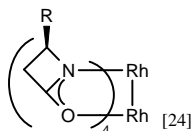
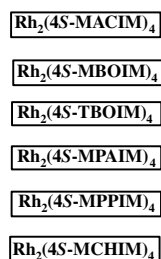
- R = COOMe, Dirhodium(II) Tetrakis[methyl-2-oxopyrrolidine-5(*S*)-carboxylate]
 R = COOCH₂Me₃, Dirhodium(II) Tetrakis[neopentyl-2-oxopyrrolidine-5(*S*)-carboxylate]
 R = COO(CH₂)₁₇CH₃, Dirhodium(II) Tetrakis[octadecyl-2-oxopyrrolidine-5(*S*)-carboxylate]
 R = CONMe₂, Dirhodium(II) Tetrakis[*N,N*-dimethyl-2-pyrrolidone-5(*S*)-carboxamide]



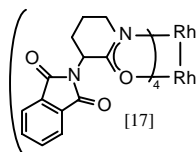
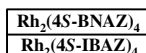
- R = COOMe, X = H: Dirhodium(II) Tetrakis[methyl-2-oxooxazolidine-4(*S*)-carboxylate]
 R = COOMe, X = CH₃: Dirhodium(II) Tetrakis[methyl-5(*R*)-methyl-2-oxooxazolidine-4(*S*)-carboxylate]
 R = CH₂Ph, X = H: Dirhodium(II) Tetrakis[benzyl-2-oxooxazolidine-4(*R*)-carboxylate]
 R = ⁱPr, X = H: Dirhodium(II) Tetrakis[isopropyl-2-oxooxazolidine-4(*R*)-carboxylate]
 R = Ph, X = H: Dirhodium(II) Tetrakis[phenyl-2-oxooxazolidine-4(*R*)-carboxylate]



- R = COOMe, X = CH₃: Dirhodium(II) Tetrakis[methyl-1-acetylimidazolidin-2-one-4(*S*)-carboxylate]
 R = COOMe, X = Ph: Dirhodium(II) Tetrakis[methyl-1-benzoyl-2-oxoimidazolidine-4(*S*)-carboxylate]
 R = COOMe, X = 4-*t*Bu-Ph: Dirhodium(II) Tetrakis[methyl-1-(4-*tert*-butylbenzoyl)-2-oxoimidazolidine-4(*S*)-carboxylate]
 R = COOMe, X = PhCH₂: Dirhodium(II) Tetrakis[methyl-1-phenylacetylimidazolidin-2-one-4(*S*)-carboxylate]
 R = COOMe, X = PhCH₂CH₂: Dirhodium(II) Tetrakis[methyl-1-(3-phenyl propanoyl)-imidazolidin-2-one-4(*S*)-carboxylate]
 R = COOMe, X = *c*-C₆H₁₁CH₂: Dirhodium(II) Tetrakis[methyl-1-(cyclohexylacetyl)-imidazolidin-2-one-4(*S*)-carboxylate]



- R = COOCH₂Ph: Dirhodium(II) Tetrakis[benzyl-2-oxaazetidone-4(*S*)-carboxylate]
 R = COOCH₂CHMe₂: Dirhodium(II) Tetrakis[isobutyl-2-oxaazetidone-4(*S*)-carboxylate]



- Dirhodium(II) Tetrakis[3(*S*)-*N*-phthalimido-2-piperidonate]



Fig. 4

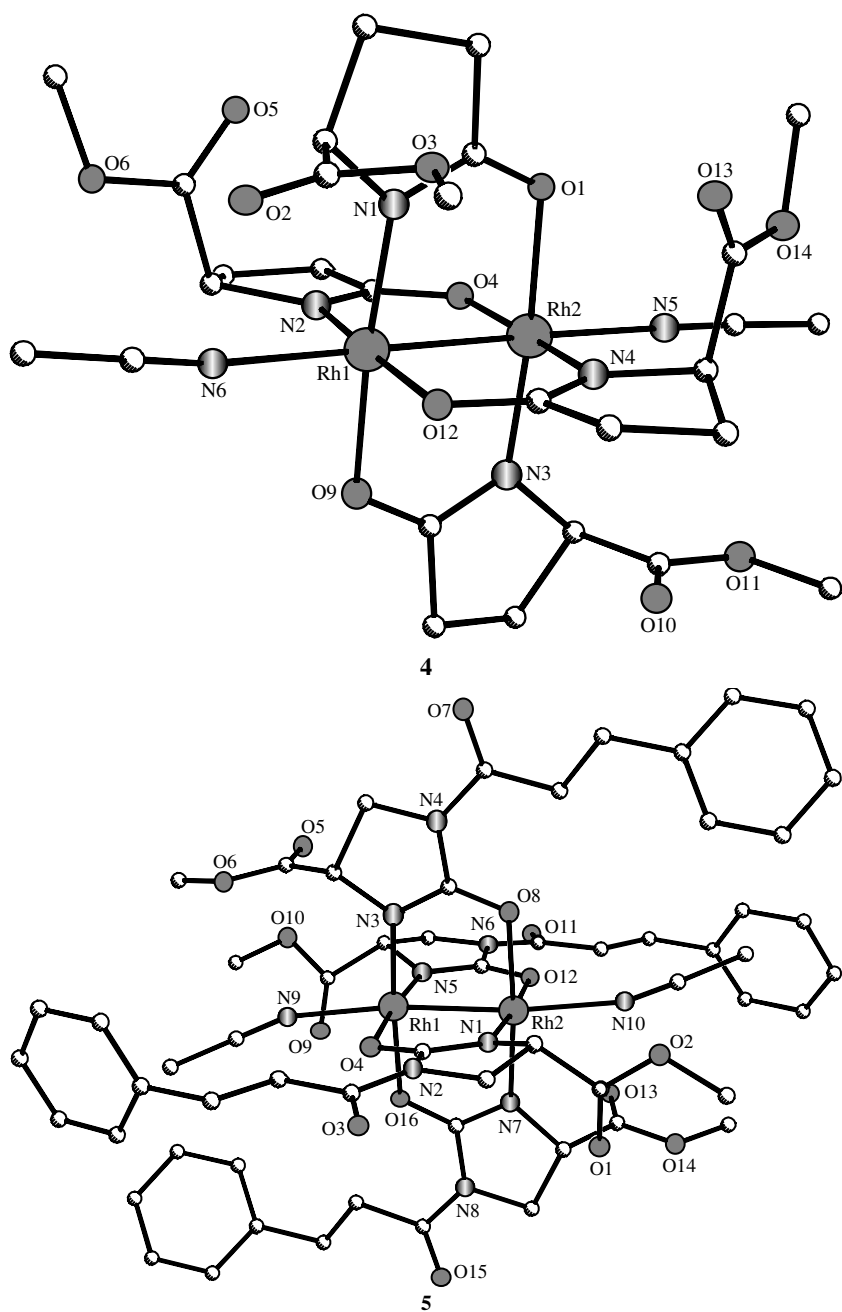


Fig. 5. The X-ray crystal structures of $\text{Rh}_2(5R\text{-MEPY})_4(\text{CH}_3\text{CN})_2$ (4) and $\text{Rh}_2(4S\text{-MPPIM})_4(\text{CH}_3\text{CN})_2$ (5)

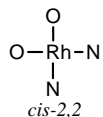


Fig. 6

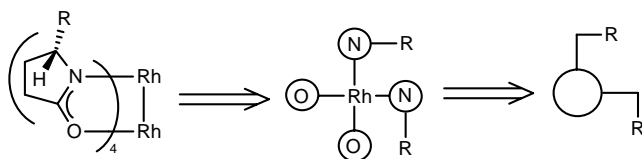
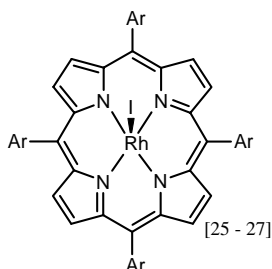
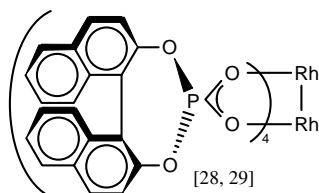
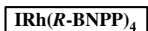


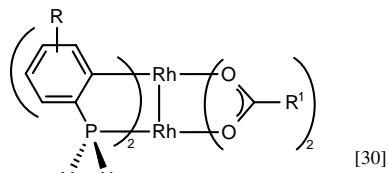
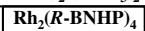
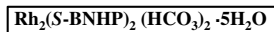
Fig. 7



Iodorhodium(III) mesotetraarylporphyrins, Ar = phenyl, mesityl
Iodo(5a, 10b, 15a, 20b,-tetrakis[(R)-1,1'-binaphth-2-yl]-porphyrinato)
rhodium(III)



Dirhodium Bis[(S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate]
Dirhodium Tetrakis[(R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate]

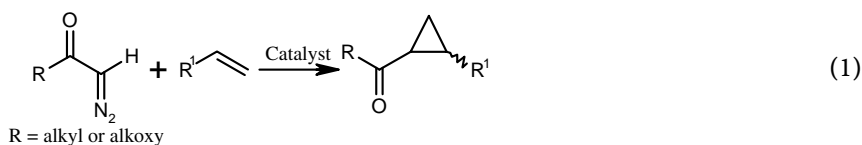


X = C₆H₅, Y = CH₃, R = H, R' = CH₃
X = Y = *p*-CF₃C₆H₄, R = *p*-CF₃, R' = CH₃
X = Y = C₆H₅, R = H, R' = CF₃

Fig. 8

2 Catalytic Cyclopropanation

Diazo compounds, most commonly diazoesters or diazoketones, are the reagents of choice for metal-catalyzed cyclopropanation of alkenes (Eq. 1) [31]. Of the two, diazoesters, and particularly ethyl diazoacetate (EDA), are the more frequently used in synthesis.

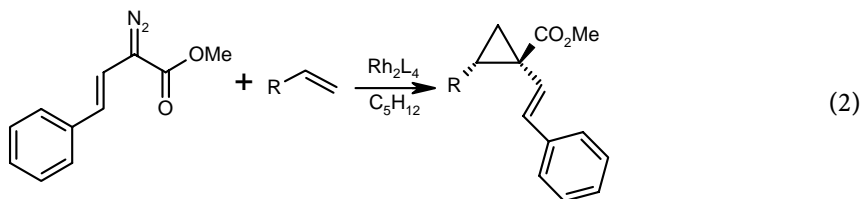


By 1990, when the possibility of achieving enantioselectivity through the use of chiral rhodium catalysts was first addressed, a considerable body of facts had already been accumulated on aspects of diastereoselectivity. For an account of the development of chiral copper catalysts, which predated their rhodium counterparts, see Chapter 16.1. By 1986 Doyle [31] had concluded that intermolecular cyclopropanation was remarkably insensitive to structural effects in the alkene. This insensitivity was ascribed to the inherently high electrophilicity of the intermediate metal carbene which commences bond formation with the olefinic bond at distances sufficiently remote from the carbene center to allow only limited interaction with the substituents on the double bond. At first glance, this insensitivity might militate against the realization of high levels of enantioselectivity. However, there were other more favorable indications. In particular in the diazoester series (N_2CHCO_2R) the substituent R, if sufficiently large, can have a profound effect on diastereoselectivity. Of even greater significance was the fact that the nature of the ligands on the dirhodium core can have a major influence on diastereoselectivity. In fact, this latter feature became the key to the development of effective chiral rhodium catalysts for enantioselective cyclopropanation. In a more general way ligand switching has become a powerful tool in the chemoselectivity of many other transformations of diazocarbonyl compounds [31].

2.1 Intermolecular Cyclopropanation

The first example of the use of a chiral catalyst for asymmetric cyclopropanation was published by Nozaki and co-workers in 1966 [32]. Although these early studies were characterized by low levels of enantiocontrol, they were the forerunner to recent discoveries which have established catalytic asymmetric cyclopropanation as a reliable method for producing a range of substituted cyclopropanes in high enantiomeric purity. The application of chiral copper catalysts is discussed in Chapter 16.1; the emphasis here is on rhodium (II) catalysts.

Of the various rhodium(II) carboxylates $[\text{Rh}_2(\text{OCOR}^*)_4]$, $\text{R}^* = \text{chiral residue}$ currently available, those based on *N*-substituted L-proline (Fig. 1) are among the most efficient in enantioselective cyclopropanation. Introduced by McKervey and co-workers [6, 9] for intramolecular diazo carbonyl reactions, the *N*-benzenesulfonyl proline, $\text{Rh}_2(2\text{S-TBSP})_4$ (3), has been recently developed by Davies et al. [10, 12] to the point where the *N*-*tert*-butylbenzenesulfonyl and *N*-dodecylbenzenesulfonyl derivatives, $\text{Rh}_2(2\text{S-TBSP})_4$ and $\text{Rh}_2(2\text{S-DOSP})_4$ (Fig. 1), are now among the most efficient in intermolecular cyclopropanation of terminal alkenes with vinyl diazoesters of the type in Eq. (2). A selection of the results obtained are summarized in Eq. (2). Enantiomeric excesses of 59% ($\text{EtOCH}=\text{CH}_2$) and higher, but mostly greater than 90%, were observed with monosubstituted alkenes at room temperature.



L	R	yield [%]	Temp. [°C]	% ee, (Config.)
2S-TBSP	C_6H_5	79	25	90 (1 <i>S</i> ,2 <i>S</i>)
2S-DOSP	C_6H_5	68	-78	98 (1 <i>S</i> ,2 <i>S</i>)
2S-TBSP	<i>p</i> -Cl C_6H_4	91	25	89 (1 <i>S</i> ,2 <i>S</i>)
2S-DOSP	<i>p</i> -Cl C_6H_4	70	-78	>97 (1 <i>S</i> ,2 <i>S</i>)
2S-TBSP	<i>p</i> -MeOC C_6H_4	87	25	83 (1 <i>S</i> ,2 <i>S</i>)
2S-DOSP	<i>p</i> -MeOC C_6H_4	41	-78	90 (1 <i>S</i> ,2 <i>S</i>)
2S-TBSP	AcO	40	25	76
2S-DOSP	AcO	26	-78	95
2S-TBSP	EtO	83	25	59
2S-DOSP	EtO	65	-78	93
2S-TBSP	^{<i>n</i>} Bu	63	25	>90
2S-TBSP	Et	65	25	>95
2S-TBSP	^{<i>i</i>} Pr	58	25	95

Diastereoselectivity in all cases was excellent, with the *trans*-isomer favored over the *cis*-isomer by ratios of ca. 40:1 to 70:1. Interestingly, the preferred alkyl group in the ester was methyl; larger groups decreased enantiocontrol. Higher enantioselectivities were found for reactions performed in pentane rather than dichloromethane and reactions of monosubstituted alkenes in pentane at -78 °C using the more soluble catalyst, $\text{Rh}_2(2\text{S-DOSP})_4$, uniformly gave enantiomer excesses of >90%, 93% in the case of the highly reactive ethyl vinyl ether. The two styrene-vinyl diazoester adducts, (6) and (7) in Fig. 9, obtained through the use

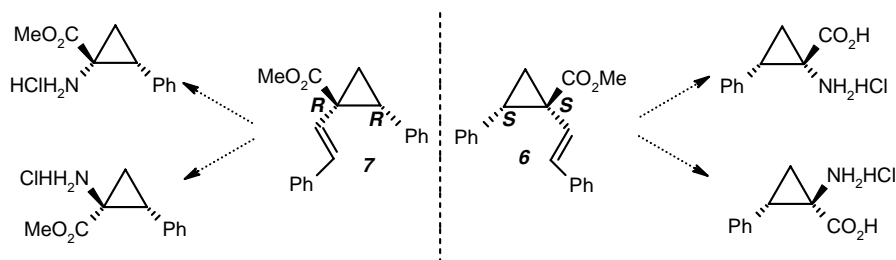
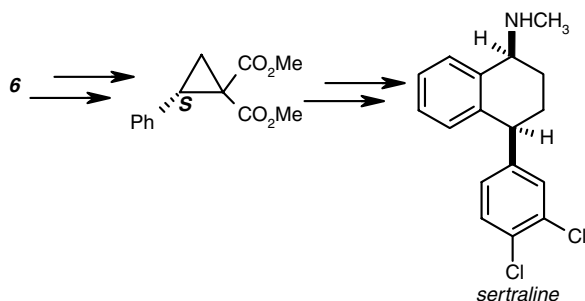
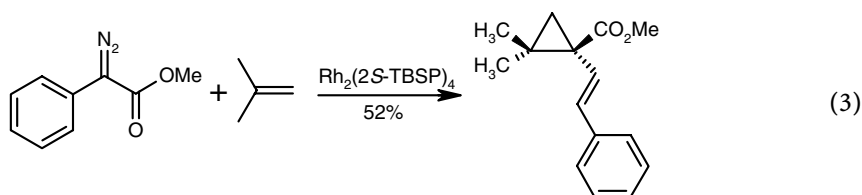


Fig.9



Scheme 2

of $\text{Rh}_2(2\text{S-DOSP})_4$ and its enantiomer were subsequently used by Davies to synthesize all four stereoisomers of 2-phenylcyclopropane-1-amino acid. The 1*S*, 2*S*-isomer (6) was also used by Corey and Grant in their enantioselective synthesis of the antidepressant sertraline (Scheme 2) [33]. Excellent stereocontrol accompanies the cyclopropanation of 1,1-disubstituted alkenes, with vinyl diazoesters, e.g., 2-methylpropene, Eq. (3), yielded a product with 95% ee. With *trans*-disubstituted alkenes, cyclopropanation was not observed.



Davies has provided a detailed analysis of how the arrangement of four proline ligands around a dirhodium core can lead to a metal carbene intermediate that reacts further with such high stereocontrol [12]. The two most striking features of the vinyl diazoester cyclopropanations are the excellent diastereoselectivity and the total lack of reactivity of *trans*-disubstituted alkenes. The former is accounted for by the structure of the vinyl diazoester which suggests that high

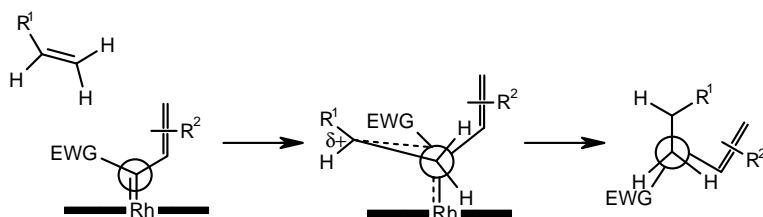


Fig. 10

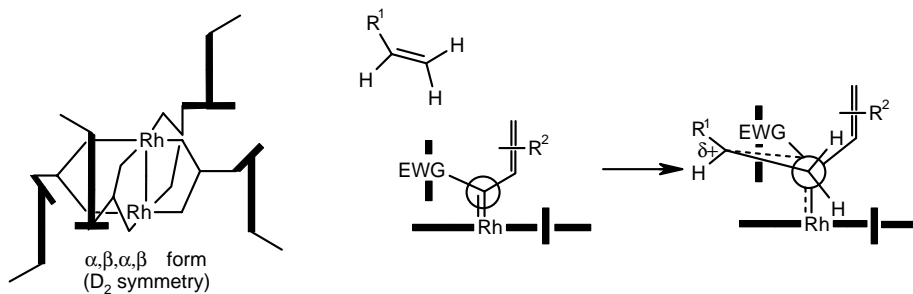
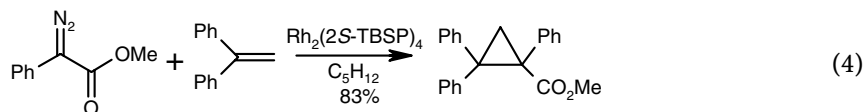


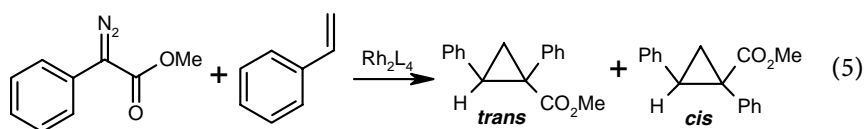
Fig. 11

diastereoselectivity requires a metal carbene with both an electron withdrawing group (such as an ester) and an electron donating group (such as an alkenyl or phenyl). A mechanism consistent with these features is shown in Fig. 10. The alkene approaches the metal vinylcarbene side-on in a non-synchronous way from the side of the electron-withdrawing group with its bulky functionality pointing away from the surface of the metal. Such an arrangement would explain the lack of reactivity of a *trans*-alkene whose substituent would point directly towards the dirhodium core. The catalysis step is postulated as occurring through the D_2 symmetric conformation of the complex represented in Fig. 11, where the bold lines represent the steric influence of the *N*-arenesulfonyl group. In support of the proposed requirement for the metal carbene to have both electron-withdrawing and electron-donating substituents is the behavior of phenyldiazoacetate and 1,1-diphenylethylene where application of the prolinatc catalyst (Fig. 1) in pentane produces the cyclopropane in Eq. (4) with an ee of 97% [34(a)]. The solvent's contribution to enhancement of stereocontrol is believed to be solvent-



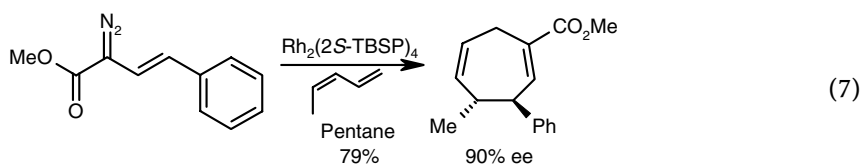
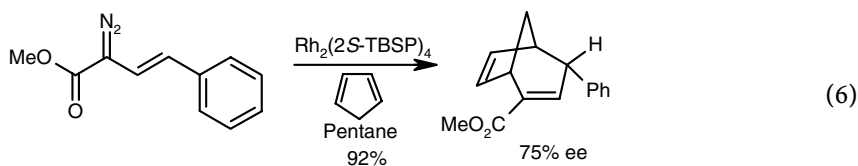
induced favorable orientation of the prolinatc ligands. With a selection of mono- and disubstituted alkenes [34 (a) and 34 (b)], methyl phenyldiazoacetate formed

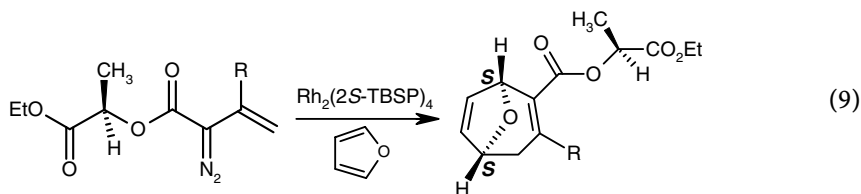
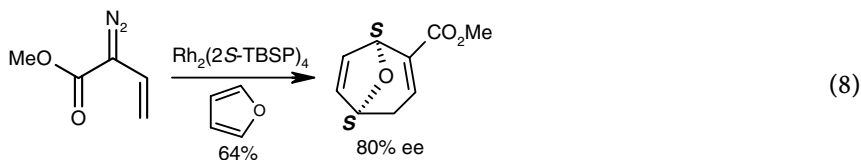
cyclopropanes with high diastereocontrol and enantiomeric excesses ranging from 60 to 85%; vinyl or phenyl substituents on the diazoacetate are essential to high enantiocontrol, Eq. (5).



L	Solvent	Yield [%]	<i>trans</i> : <i>cis</i>	<i>trans</i> , % ee
4S-TBOIM	CH ₂ Cl ₂	63	95:5	77
4S-TBOIM	Pentane	69	94:6	75
2S-BSP	CH ₂ Cl ₂	45	97:3	60
2S-TBSP	CH ₂ Cl ₂	77	97:3	61
2S-TBSP	Pentane	73	96:4	85

Davies and co-workers [12, 35] have exploited one particular aspect of the asymmetric cyclopropanation of alkenes with vinyl diazoacetates, namely, application to substrates suitable for subsequent Cope rearrangement. Cyclopropanation of dienes with predominant *cis*-1,2-divinyl diastereoselection makes possible subsequent facile [3,3]-sigmatropic rearrangement with entry to 1,4-cycloheptadienes or bicyclic dienes. Two such examples employing cyclopentadiene and penta-1,3-diene as substrates and the rhodium(II) prolininate catalyst, Rh₂(2S-TBSP)₄ in Fig. 1, are shown in Eq. (6) and Eq. (7), respectively; *cis*-1,2-divinylcyclopropanes are presumed to be intermediates in these annulation reactions. In contrast, ethyl diazoacetate and styrene with the prolininate catalyst (Fig. 1) under otherwise identical conditions yield products with low diastereoselectivity (*trans*:*cis* ratio, 1.2:1) and low enantioselectivity (*trans*, 6%; *cis*, 30% ee). However, the stereocontrol achievable with ethyl diazoacetate is catalyst dependent. A later paper by Davies and co-workers [36] displayed the decomposition of vinyl diazomethanes in the presence of furans to give oxabicyclic products using Rh₂(2S-TBSP)₄ as catalyst, Eq. (8) and Eq. (9).





R	Yield [%]	% de
H	51	68
OTBDMS	97	80

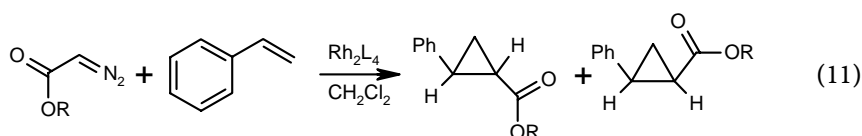
Ishitani and Achiwa [16] have recently prepared an axially disymmetric rhodium (II) biphenylcarboxylate catalyst, $\text{Rh}_2(\text{S-BDME})_4$ of Fig. 2, and found that although the *trans:cis* diastereoselectivity in its catalysis of the styrene-EDA reaction was poor, the enantiocontrol was better than that observed with the proline catalyst. The biphenyl based catalyst yielded an 87% ee for the cyclopropanation of 2-naphthylethene and *tert*-butyl diazoacetate, though again the diastereoselectivity was very low. Use of an additional chiral auxiliary in the diazoester as in the *d*-menthyl derivative in Eq. (10) furnished a mixture of cyclopropanes, the *cis*-isomer of which was found to have an ee of 99%.



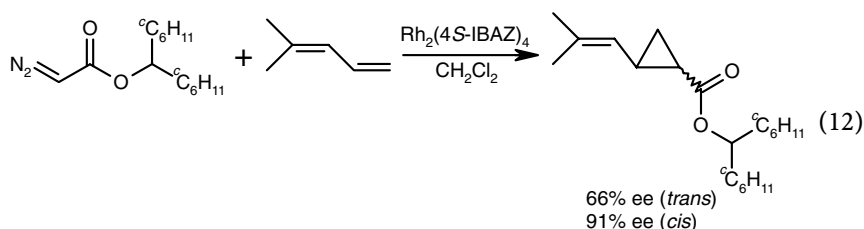
L	R	R1	Yield [%]	<i>cis:trans</i>	<i>cis</i> , % ee	<i>trans</i> , % ee
S-BDME	Ph	Et	96	69:31	53	57
S-MEPY	Ph	Et	trace	-	-	-
S-BDME	naphth-2-yl	<i>t</i> Bu	59	52:48	87	35
S-MEPY	naphth-2-yl	<i>t</i> Bu	8	48:52	81	84
S-BDME	Ph	<i>d</i> -menthyl	100	63:37	99	45
S-MEPY	Ph	<i>d</i> -menthyl	64	43:57	91	24

Doyle's catalysts have also been applied to asymmetric intermolecular cyclopropanation, mainly in the styrene-diazoester reaction. Diazoesters include EDA, dicyclohexylmethyl diazoacetate, and *d*-menthyl diazoacetate. In general the effectiveness of Doyle's rhodium (II) carboxamidates in enantiocontrol is lower

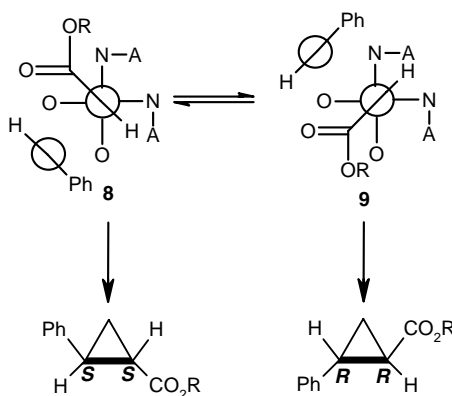
than that of the chiral salicylaldimine, semicorrin, or bis(oxazoline) ligated copper catalysts for the same alkene-diazoester combinations (see Chapter 16.1). Oxazolidinone ligands with a carboxylate substituent adjacent to the nitrogen atom, i.e., as in $\text{Rh}_2(4S\text{-MEOX})_4$ of Fig. 4, exert greater enantiocontrol than do benzyl or isopropyl substituents ($\text{Rh}_2(4R\text{-BNOX})_4$ and $\text{Rh}_2(4R\text{-IPOX})_4$, respectively). However, the catalyst with a phenyl substituent, $\text{Rh}_2(4S\text{-PHOX})_4$, nearly matches the $\text{Rh}_2(4S\text{-MEOX})_4$ catalyst in enantiocontrol of the styrene-diazoester reaction and, furthermore, provides a high preference for the *cis* isomer of the product. $\text{Rh}_2(4S\text{-IBAZ})_4$, the oxoazetidone-based catalyst, also shows a preference for *cis*-cyclopropane product and, for the case of dicyclohexyl diazoacetate and styrene, excellent enantiocontrol (95% ee). A summary of these cyclopropanation results is shown in Eq. (11) [22, 23, 37]. Similar results are observed with the cyclopropanation of 4-methyl-1,3-pentadiene with styrene catalysed by $\text{Rh}_2(4S\text{-IBAZ})_4$ [24] in Eq. (12) (where *trans/cis*=46:54).



R	L	Yield [%] (<i>trans</i>)	Yield [%] (<i>cis</i>)
<i>d</i> -menthyl	5S-MEPY	57 (31% de)	43 (88% de)
Et	5S-MEPY	56 (58% ee)	44 (33% ee)
<i>l</i> -menthyl	4S-PHOX	27 (40% de)	73 (72% de)
Et	4S-PHOX	34 (24% ee)	66 (57% ee)
<i>d</i> -menthyl	4S-BNOX	67 (34% de)	33 (63% de)
Et	4S-BNOX	46 (8% ee)	54 (13% ee)
(^c C ₆ H ₁₁) ₂ CH	4S-IBAZ	34 (77% ee)	66 (95% ee)
Et	4S-IBAZ	36 (47% ee)	64 (73% ee)
Et	4S-MACIM	43 (30% ee)	57 (37% ee)

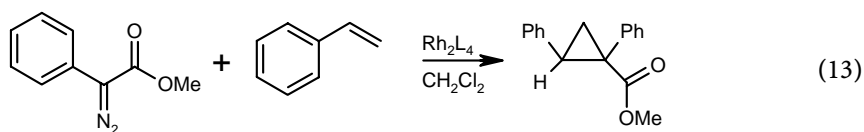


Molecular modeling has been used to evaluate the minimum energy conformations for the metal carbene in these reactions [18]. There are two limiting conformations shown in Scheme 3, where A represents the substituent on the ligand residues attached through nitrogen: one (8) whose attachment is in the (*O,O*)-



Scheme 3

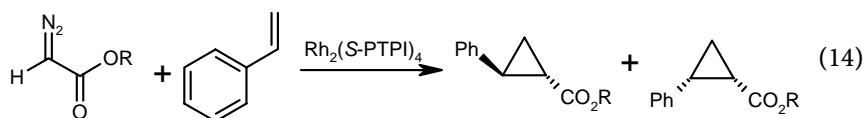
quadrant, and the other (9) whose attachment is in the (*O*, *N*)-quadrant. For $\text{Rh}_2(5R\text{-MEPY})_4$ conformation (9) ($A=\text{CO}_2\text{Me}$) is favored over (8) by about 3 kcal·mol⁻¹, whereas for $\text{Rh}_2(4S\text{-BNOX})_4$ ($A=\text{CH}_2\text{Ph}$), the energy difference is negligible. However, the results of modeling a transition state in which styrene is the olefinic partner revealed that attack on the less conformationally stable metal carbene (8) was preferred over (9), which is consistent with experiment. Enantiocontrol is thus not direct interaction of the ligand's chiral attachment with the alkene substituent; rather it derives from the influence of the substituent *A* on the conformational populations of the metal carbene in the transition state for addition. The rhodium(II) carboxamidates are also effective in the cyclopropanation of styrene with methyl phenyldiazoacetate, Eq. (13). The *cis*-isomer is the dominant cyclopropane product (> 95%), but enantiocontrol is limited [28].



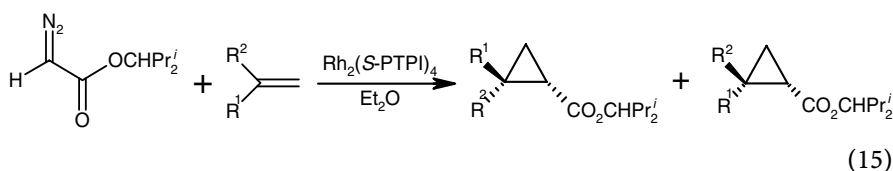
L	% ee
5S-MEPY	49
4S-MEOX	41
4S-MBOIM	46
4S-TBOIM	78

Other studies on intermolecular cyclopropanation reactions include that of Hashimoto and co-workers [17] which reveals further significant solvent effects. The chiral catalyst employed was the dirhodium (II) tetrakis[3(*S*)-*N*-phthaloyl-

2-piperidinoate], $\text{Rh}_2(\text{S-PTPI})_4$ of Fig. 2. The reaction of 2,4-dimethyl-3-pentyl diazoacetate with styrene, Eq. (14), was studied in dichloromethane, dichloroethane, chloroform, diethyl ether, tetrahydrofuran, benzene, and dimethylformamide. Enantiocontrol was highest in diethyl ether with 98% ee in the *trans*-cyclopropane and 96% ee in the *cis*-cyclopropane, the *trans* product being the major diastereoisomer. Tetrahydrofuran was much less discriminating than diethyl ether; of the halogenated solvents, chloroform was the least effective. Also highlighted in the paper is enantioselective cyclopropanation of 1,1-disubstituted terminal alkenes using $\text{Rh}_2(\text{S-PTPI})_4$ as catalyst, Eq. (15). Although the *trans*-cyclopropane product predominates over the *cis*-cyclopropane, both have significantly high ee values.



R	Solvent	<i>trans</i> :yield [%]	<i>trans</i> :%ee	<i>cis</i> :yield [%]	<i>cis</i> :%ee
CHPr _i ₂	CH ₂ Cl ₂	54	49	19	63
CHPr _i ₂	CHCl ₃	47	7	28	22
CHPr _i ₂	C ₆ H ₆	29	79	15	76
CHPr _i ₂	Et ₂ O	54	98	19	96
Et	Et ₂ O	36	51	27	49
CH(^c C ₆ H ₁₁) ₂	Et ₂ O	45	90	19	90
CHPr _i ₂	THF	30	79	12	82
CHPr _i ₂	DMF	47	79	19	81



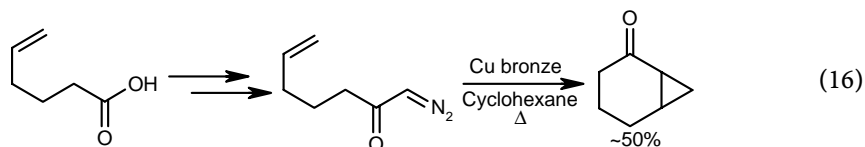
R ¹	R ²	<i>trans</i> : yield [%]	<i>trans</i> : % ee	<i>cis</i> : yield [%]	<i>cis</i> : % ee
<i>p</i> -MeOC ₆ H ₄	H	40	95	21	97
<i>p</i> -ClC ₆ H ₄	H	30	98	28	98
(<i>E</i>)-PhCH=CH	H	26	96	29	98
<i>n</i> -C ₆ H ₁₃	H	37	89	15	82
Ph	Ph	77	95	-	-
Ph	Me	43	94	37	95
Me	Me	34	95	-	-

Among other examples of catalysed asymmetric cyclopropanation using rhodium (II) complexes are those involving Kodadek's "chiral wall" and "chiral fortress" porphyrins [26, 27], e.g., $\text{IRh}(\text{R-BNPP})_4$ in Fig. 8. These unique designs provide high turnover numbers ($>1,800$) and relatively high diastereoselectivities ($\geq 70:30$, *cis:trans*), but enantiocontrol in cyclopropanation with EDA was at best moderate ($\leq 60\%$ ee). The $\text{Rh}_2(4\text{S-IBAZ})_4$ catalyst (Fig. 4) exerts comparable diastereoselection and significantly better enantioselectivity.

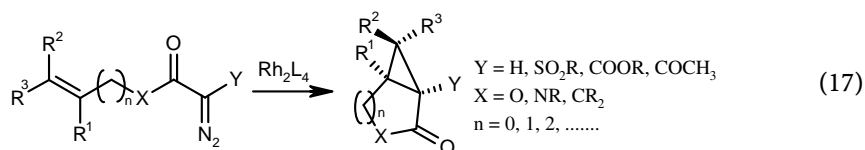
2.2

Intramolecular Cyclopropanation

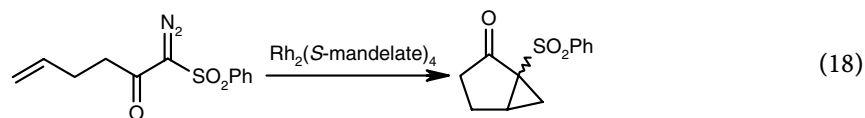
The potential of intramolecular cyclopropanation for the construction of fused-ring carbocycles was first reported in 1961 by Stork and Ficini [38] who showed that copper-catalyzed cyclization of a simple diazoketone derived from 5-hexenoic acid produced a bicyclo[4.1.0]heptane derivative, Eq. (16).



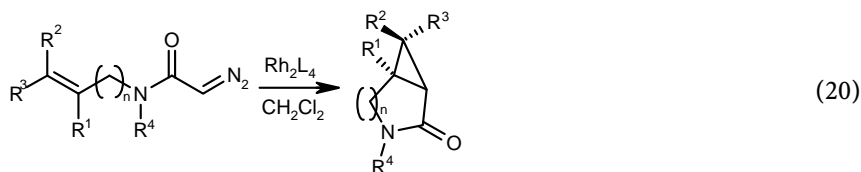
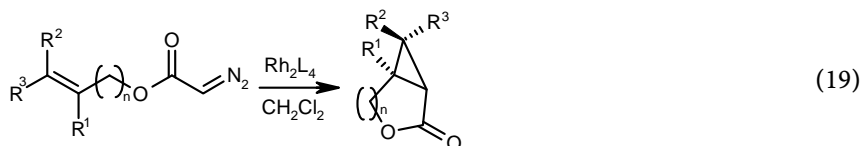
In the ensuing years there have been numerous demonstrations of the power of this process in the synthesis of natural products and theoretically significant unnatural products. Intramolecular cyclopropanation is applicable not just to diazoketones, but to diazoamides and vinyl diazo compounds. Unlike its intermolecular counterpart, the very nature of the cyclization process allows for far greater regiocontrol and stereocontrol. There appears to be a preference for five-membered ring formation, Eq. (17) [39], though ring sizes up to 20 atoms have been realized and the product is a single diastereoisomer.



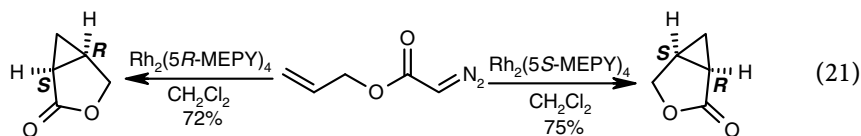
Early efforts in enantioselective intramolecular cyclopropanation using chiral rhodium catalysts focused on the use of carboxylates as ligands and although these catalysts were highly efficient kinetically in diazo decomposition, the enantiomeric excesses in the products were very limited. For example, $\text{Rh}_2(\text{S-mandelate})_4$, (2) in Fig. 3, achieved an ee of 12% in the cyclization in Eq. (18) [40].



The most significant breakthrough in this area was Doyle's introduction of chiral rhodium (II) carboxamidates (Fig. 4). These catalysts show an exceptional ability to direct highly enantioselective intramolecular cyclopropanation of allylic and homoallylic diazoesters, Eq. (19), and diazoamides, Eq. (20).



Allyl diazoacetate, the simplest substrate, with $\text{Rh}_2(5S\text{-MEPY})_4$ and $\text{Rh}_2(5R\text{-MEPY})_4$ in amounts as low as 0.1 mol % furnished the enantiomeric 3-oxabicyclo[3.1.0]hexan-2-ones (72% and 75% yields in 95% ee, Eq. (21)).



It is equally significant that these high levels of enantiocontrol are consistently attainable with an entire range of *cis*-disubstituted allyl diazoacetates and with trisubstituted analogues, a selection of which is summarized in Table 1 and Eq. (19). The trisubstituted systems include those prepared from nerol (93% ee), Eq. (22) and geraniol (95% ee), Eq. (23).

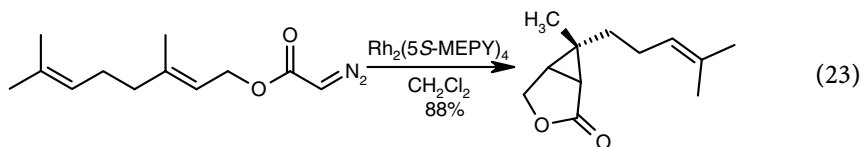
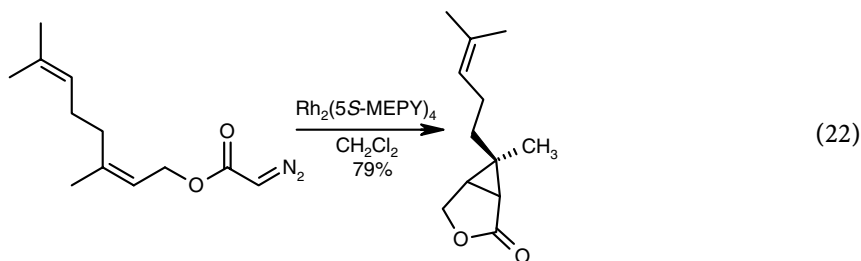
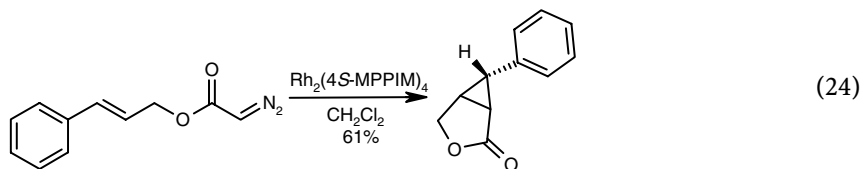


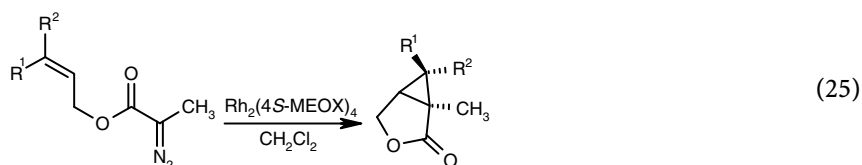
Table 1. Enantioselective intramolecular cyclopropanation of allylic diazoacetates ($n=1$) catalyzed by $\text{Rh}_2(5\text{S-MEPY})_4$, Eq. (19)

R^1	R^2	R^3	Yield [%]	% ee	Config.
H	Ph	H	70	≥ 94	1 <i>R</i> ,5 <i>S</i>
H	CH_3CH_2	H	88	≥ 94	1 <i>R</i> ,5 <i>S</i>
H	PhCH_2	H	80	≥ 94	1 <i>R</i> ,5 <i>S</i>
H	$(\text{CH}_3)_2\text{CHCH}_2$	H	73	≥ 94	1 <i>R</i> ,5 <i>S</i>
H	$(\text{CH}_3)_2\text{CH}$	H	85	≥ 94	1 <i>R</i> ,5 <i>S</i>
H	$(^i\text{Bu})_3\text{Sn}$	H	79	≥ 94	1 <i>R</i> ,5 <i>S</i>
H	I	H	78	≥ 94	1 <i>R</i> ,5 <i>S</i>

With *trans*-disubstituted allylic systems, the $\text{Rh}_2(\text{MEPY})_4$ catalysts exhibit lower levels of stereocontrol. However, here again ligand switching corrects the efficiency since the steric bias imposed through the application of the *N*-acylimidazolidinone-ligated catalysts raises enantioselectivity with *trans* systems to levels $\geq 95\%$ ee. For example, the cinnamyl alcohol-derived diazoester in Eq. (24), with $\text{Rh}_2(4\text{S-MPPIM})_4$ as catalyst, furnishes the bicyclic product with an ee of 96%.

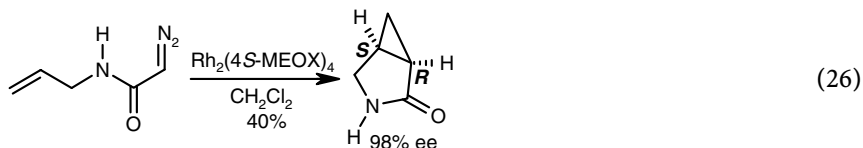


Similarly, significant improvements with methallyl and (*n*-butyl)allyl diazoacetates can be achieved by switching catalysts from $\text{Rh}_2(\text{MEPY})_4$ to $\text{Rh}_2(\text{MP-PIM})_4$. Allyl diazoesters other than diazoacetates have not yet been examined in detail. Encouragingly, Doyle's group [41] have found that high levels of enantiocontrol in intramolecular cyclopropanation can be realized with allyl diazopropionates and the $\text{Rh}_2(4\text{S-MEOX})_4$ catalyst, Eq. (25).

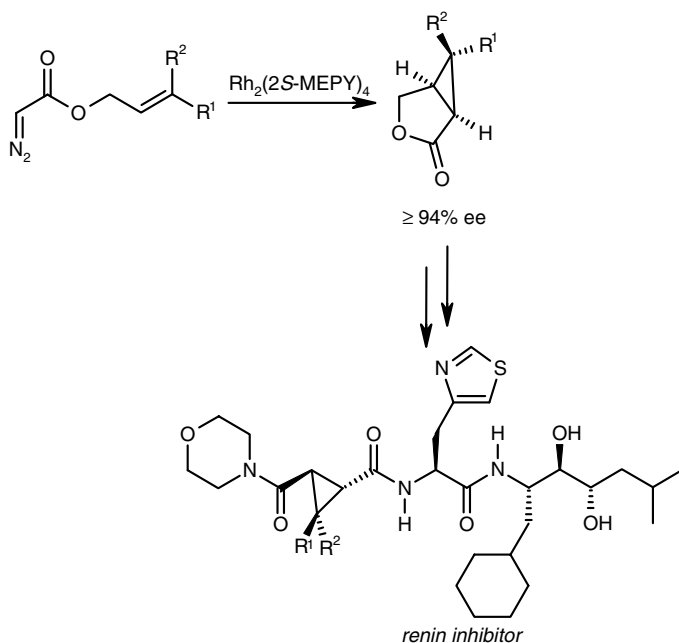


R^1	R^2	Yield [%]	% ee
Me	Me	81	71
^iPr	H	62	85
Ph	H	65	78
H	<i>n</i> Pr	46	52
H	Ph	70	43

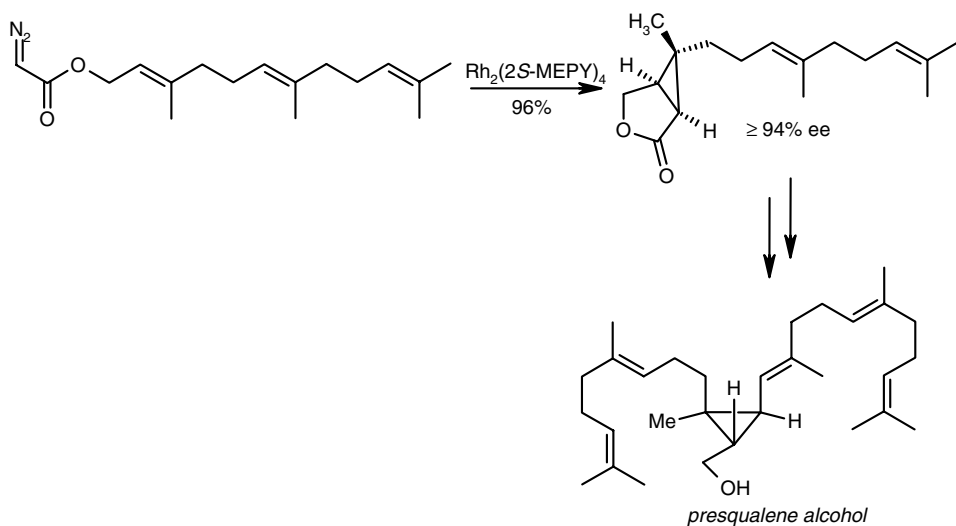
The consistency of the high levels of enantiocontrol accessible in these diazoester cyclizations is underpinned by their growing applications in enantioselective synthesis of bioactive molecules containing cyclopropane units. Notable examples include the preparation of multifunctional cyclopropanes as peptide isosteres for renin inhibitors (Scheme 4) [42]; presqualene alcohol from farnesyl diazoacetate (Scheme 5) [43]; the GABA analogue 3-azabicyclo[3.1.0]hexan-2-one from *N*-allyldiazoacetamide, Eq. (26) [23]; and precursors of (1*R*,3*S*)-*cis*-chrysanthemic acid and the pheromone, *R*-(-)-dictyopterene C (Scheme 6) [44, 45].



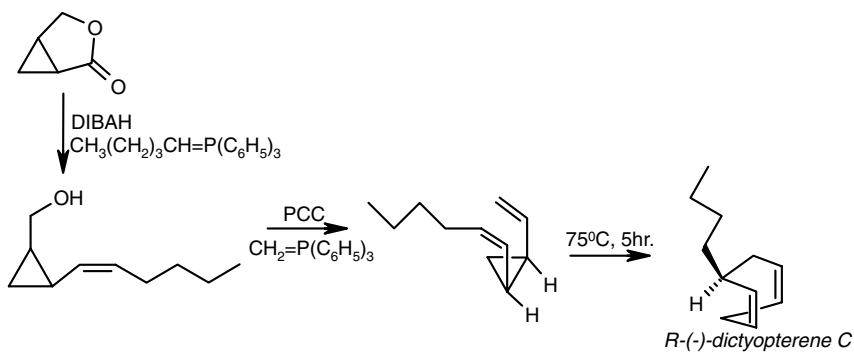
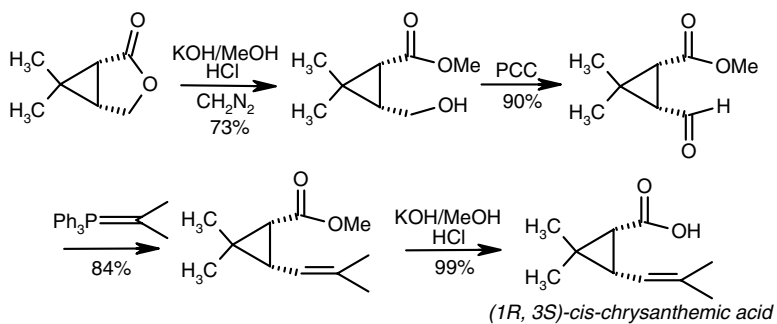
Homoallylic diazoacetates also undergo intramolecular cyclopropanation, Table 2 and Eq. (19), and although enantiocontrol has been achieved through the use of chiral rhodium(II) catalysts, the ee levels are generally lower than those observed with allylic diazoacetates [23, 46]. The substitution pattern of the double bond in these systems did not greatly influence the % ee values, nor was β -hydride elimination a significant competing side reaction (20% in most cases). Of three catalysts screened, $\text{Rh}_2(5S\text{-MEPY})_4$ was the most promising (Fig. 4).



Scheme 4



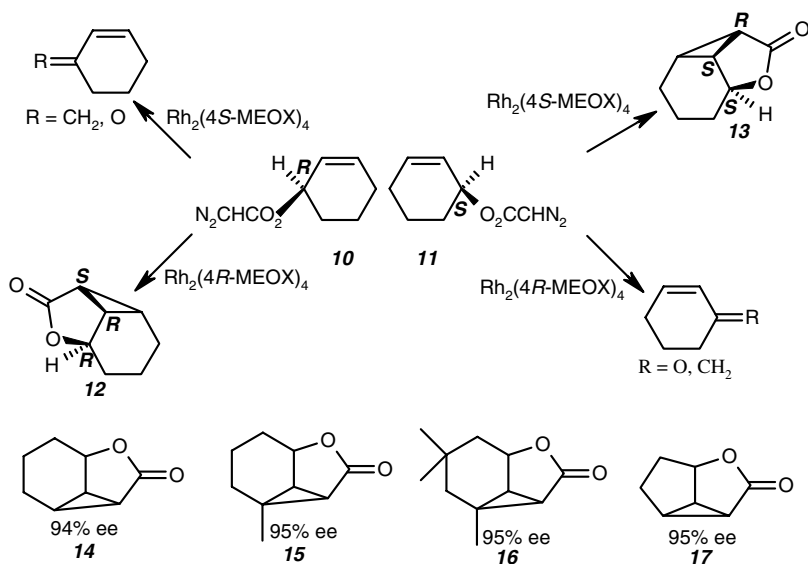
Scheme 5



Scheme 6

Table 2. Enantioselective intramolecular cyclopropanation of homoallylic diazoacetates ($n=2$) catalyzed by $\text{Rh}_2(5S\text{-MEPY})_4$, Eq. (19)

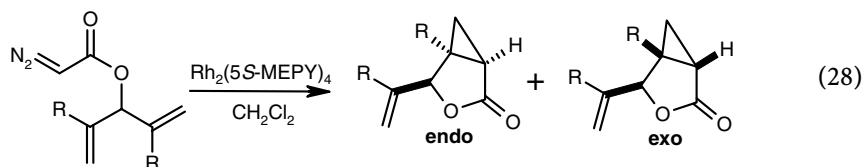
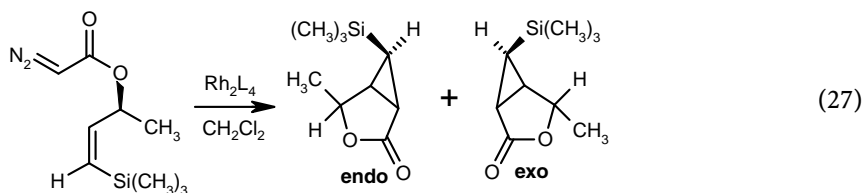
R^1	R^2	R^3	Yield [%]	% ee	Config.
H	H	H	80	71	1 <i>R</i> ,6 <i>S</i>
H	CH_3	CH_3	74	77	1 <i>S</i> ,6 <i>R</i>
H	Ph	H	73	88	1 <i>S</i> ,6 <i>R</i>
H	CH_3CH_2	H	80	90	1 <i>S</i> ,6 <i>R</i>
H	<i>c</i> - $\text{C}_6\text{H}_{11}\text{CH}_2$	H	77	80	1 <i>S</i> ,6 <i>R</i>
H	PhCH_2	H	68	80	1 <i>S</i> ,6 <i>R</i>
H	Me_3Si	H	65	86	1 <i>S</i> ,6 <i>R</i>
H	H	Ph	55	73	1 <i>S</i> ,6 <i>R</i>
H	H	CH_3CH_2	65	82	1 <i>S</i> ,6 <i>R</i>
CH_3	H	H	76	83	1 <i>R</i> ,6 <i>S</i>

**Scheme 7**

In a useful extension of this methodology for enantioselection in intramolecular cyclopropanation, Doyle's group have used chiral rhodium (II) carboxamidates to effect enantiomer differentiation in reactions of racemic secondary allylic diazoacetates [47]. The catalyst-enantiomer matching approach has also been applied very successfully to intramolecular C-H insertion reactions (*vide infra*). The (*R*)- and (*S*)-enantiomers, (**10**) and (**11**), respectively, of cyclohex-2-en-1-yl diazoacetate are displayed in Scheme 7. On exposure to $\text{Rh}_2(4R\text{-MEOX})_4$ the (*R*)-enantiomer (**10**) undergoes cyclopropanation to form tricyclic ketone

(12) whereas the enantiomeric catalyst $\text{Rh}_2(4S\text{-MEOX})_4$ eschews cyclopropanation in favor of methylenecyclohexene and cyclohexenone, the products of elimination processes. With $\text{Rh}_2(4R\text{-MEOX})_4$ the (*S*)-enantiomer (11) undergoes the elimination process whereas $\text{Rh}_2(4S\text{-MEOX})_4$ promotes cyclopropanation (13) [48]. This methodology has made available several of the tricyclic lactones (14–17) in Scheme 7 with ee of 94% or better. With acyclic racemic secondary allylic diazoacetates, enantiomer differentiation has also been demonstrated.

The work of Martin and co-workers [49] has shown that excellent diastereocontrol can be achieved in cyclopropanation of single enantiomers of chiral secondary diazoesters by catalyst matching. Thus, while $\text{Rh}_2(5R\text{-MEPY})_4$ and the (*S*)-diazoester in Eq. (27) react to afford a 37:63, *endo:exo* mixture of diastereoisomeric cyclopropanes, the 5*S*-MEPY catalyst affords a >95:<5 ratio of the same products. A final illustrative example of the versatility of this methodology is shown in Eq. (28). Here diazoacetates of prochiral divinyl carbinols undergo intramolecular cyclopropanation catalysed by $\text{Rh}_2(5S\text{-MEPY})_4$ with exceptional enantiocontrol [49].



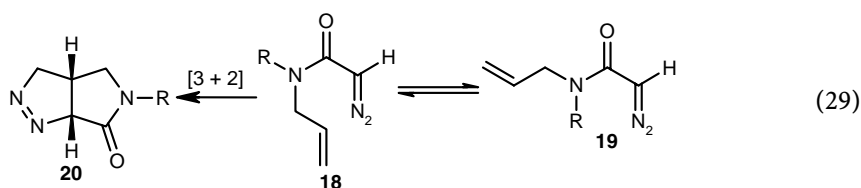
R	Yield [%]	<i>endo</i> : % yield (% ee)	<i>exo</i> : % yield (% ee)
H	75	>95 (≥94)	<5
CH ₃	73	45 (92)	55 (91)

Enantiocontrol in intramolecular cyclopropanation reactions of diazoacetamides has been developed to levels comparable with those now accessible with diazoesters. Several substituent variations in Eq. (20) are summarized in Table 3, which reveals examples where ee's exceed 90%. In general diazoamides have a conformational feature which differs from their diazoester counterparts, namely, the relatively slow syn-anti isomerization by rotation about the N-CO bond. If the interconversion of (18) and (19) or their respective metal carbenes is slow relative to the reaction timescale [50], only isomer (18) can lead to intramolecular cyclopropanation. However, an alternative process to which (18) is prone un-

Table 3. Enantioselective intramolecular cyclopropanation of allylic and homoallylic diazoacetamides, Eq. (20)

L	n	R ¹	R ²	R ³	R ⁴	Yield [%]	% ee	Config.
4S-MEOX	1	H	H	H	H	40	98	1R,5S
5S-MEPY	1	H	H	H	CH ₃	62	93	1R,5S
4S-MEOX	1	H	CH ₃	CH ₃	CH ₃	91	94	1S,5R
4S-MPPIM	1	H	CH ₃	CH ₃	CH ₃	88	94	1S,5R
4S-MPPIM	1	H	ⁿ Pr	H	CH ₃	88	95	1R,5S
4S-MPPIM	1	H	H	ⁿ Pr	CH ₃	93	92	1R,5S
4S-MPPIM	1	H	CH ₃	Me ₂ C=CH(CH ₂) ₂	CH ₃	95	93	1S,5R
5S-MEPY	2	H	Et	H	^t Bu	94	90	1S,6R

der catalytic conditions is intramolecular [3+2] dipolar cycloaddition, Eq. (29), to affords (20).



3

Carbon-Hydrogen Insertion Reactions

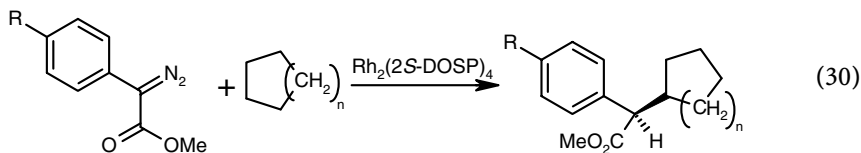
The potential benefits to organic synthesis of efficient insertion reactions of metal carbenes into unactivated carbon-hydrogen bonds have long been recognized. The major obstacles to the exploitation of C-H insertion reactions have been poor control of chemoselectivity and regioselectivity, especially in conformationally mobile systems. Catalytic decomposition of diazocarbonyl precursors is the method of choice for generating metal carbenes and since the introduction of rhodium (II) catalysts, significant progress has been made in applications of C-H insertion, including the enantioselective version, in the formation of carbon-carbon bonds. Chiral rhodium (II) carboxylates and carboxamides are among the most effective catalysts in promoting high levels of enantiocontrol.

3.1

Intermolecular C-H Insertion

There are few significant examples of rhodium(II) catalyzed asymmetric intermolecular C-H insertion reactions. In the most recent, and noteworthy, example Davies and Hansen [51] used reactions of the type shown in Eq. (30) to demon-

strate that aryl diazoacetates react with cycloalkanes (cyclopropane, cyclohexane, cycloheptane) in the presence of $\text{Rh}_2(2S\text{-DOSP})_4$ to form cycloalkyl adducts in good to excellent yield with enantiomeric excesses of 60–93%. The cycloalkane functions as both reactant and solvent, and although reaction does occur at room temperature, chemical yields were best at the reflux temperature of the cycloalkane. The results obtained with methyl phenyldiazoacetate ($R=\text{H}$) and its *p*-chloro- and *p*-methoxy derivatives ($R=\text{Cl}$, OMe) are summarized in Eq. (30). The highest enantioselectivity (93%) was observed for the insertion of *p*-chlorophenyldiazoacetate into cyclohexane at 25 °C.



R	n	Temp. [°C]	Yield [%]	% ee
OMe	1	50	55	83
H	1	50	84	87
Cl	1	50	78	89
OMe	2	81	85	67
H	2	81	83	81
H	2	50	69	88
Cl	2	81	91	86
Cl	2	25	53	93
OMe	3	118	78	60
H	3	118	84	70
Cl	3	118	96	81

The absolute configuration of the cyclopentyl phenylacetate ($R=\text{H}$) produced by the *S*-isomer of the catalyst, was established as *R*; by analogy, the other C-H insertion products were presumed to be *R*. A transition state model similar to that proposed for asymmetric cyclopropanation with the same catalyst was used to interpret the asymmetric induction observed in C-H insertion. The rhodium carbene complex is represented as in Fig. 12 with the catalyst presumed to be-

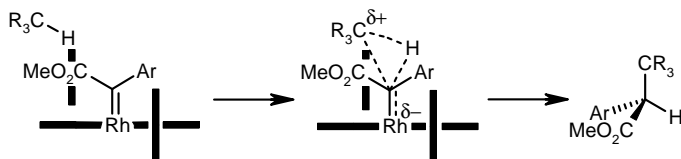
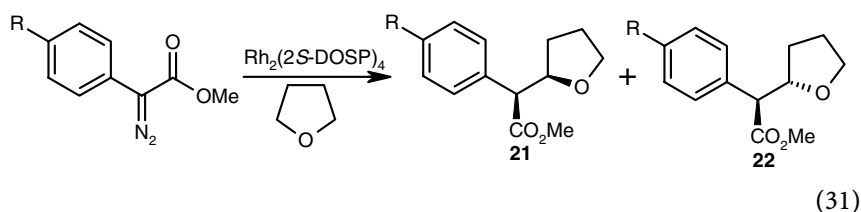


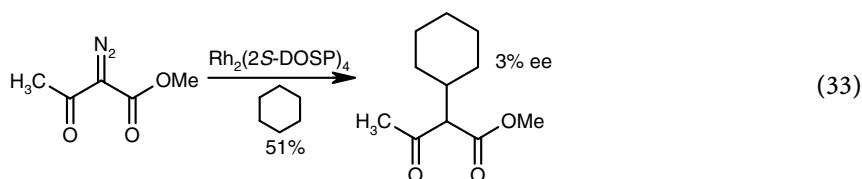
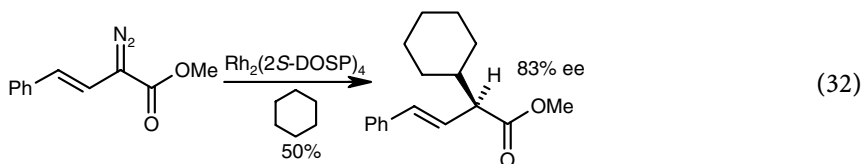
Fig. 12

have as if it possesses D_2 symmetry. Positive charge builds up in the transition state as the cycloalkane commences bonding over the side of the ester group of the metal carbene. Rotation of the cycloalkyl group away from the catalyst completes the reaction leading to the observed *R* configuration of the product.

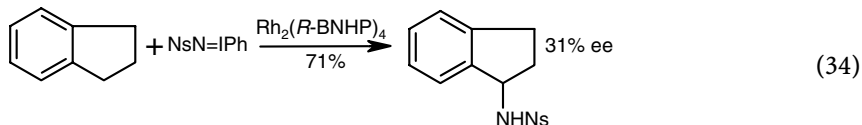
Significant levels of enantiocontrol were also observed in the $Rh_2(2S-DOSP)_4$ catalyzed reaction of aryl diazoacetates with tetrahydrofuran where C-H insertion occurred exclusively at the 2-position, Eq. (31) [51]. Two diastereoisomeric products, (21) and (22), are formed, with a preference for isomer (21) and comparable levels of enantioselectivity in each ((21): 52–76% ee; (22): 51–71% ee). It is premature to assess the general efficacy of catalyzed asymmetric intermolecular C-H insertion. Preliminary studies by Davies and Hansen [51] suggest that enantiocontrol may be very substrate dependent. For example, the vinyl diazo-carbonyl precursor in Eq. (32) and cyclohexane with $Rh_2(2S-DOSP)_4$ as catalyst react with an enantioselectivity (83% ee) comparable to that obtained with aryl diazoacetates, whereas diazoacetoacetates when treated similarly, show very minor levels of enantiocontrol (3% ee) in Eq. (33).



R	Temp. [°C]	Yield [%]	21:22	21: % ee	22: % ee
OMe	65	63	2.5	68	66
H	65	82	2.3	60	61
Cl	65	48	1.7	52	51
Cl	25	57	1.9	76	71
NO ₂	65	50	1.8	69	58



Müller and co-workers [52] have studied the intermolecular rhodium (II) catalyzed C-H insertion of a nitrene derived from [*N*-(*p*-nitrobenzenesulfonyl)imino]phenyliodinane into cycloalkanes, cycloalkenes, and cyclic ethers. In one example involving indane as the substrate with Pirrung's chiral phosphate catalyst, the product showed an enantioenrichment of 31% ee, Eq. (34).



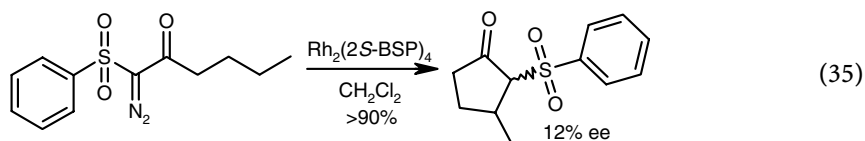
3.2

Intramolecular C-H Insertion

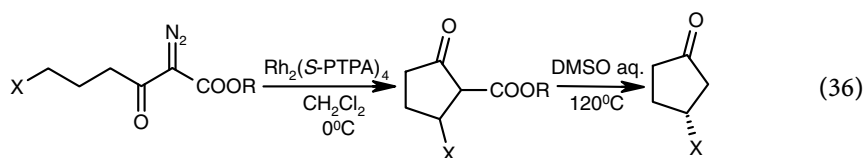
Major advances have been made in enantioselective intramolecular C-H insertion in a relatively short space of time. Because of the superiority of rhodium catalysts over copper catalysts for C-H insertion, the focus has been very much on development of chiral versions of the former. Both the structure of the diazo precursors and the ligands on the catalyst can have a profound influence on diastereoselectivity and enantioselectivity, two important determinants on the efficacy of C-H insertion in stereoselective synthesis. Chemoselectivity is another control feature on which catalyst design can have a major influence.

The most commonly used chiral catalysts are the amino acid based rhodium (II) carboxylates of Hashimoto and Ikegami, and McKerverve, and the chiral rhodium (II) carboxamidates of Doyle. The amino acid based catalysts exhibit their highest levels of stereocontrol with non-terminal diazoketones of structure $\text{RCOCHN}_2\text{R}_1$ where $\text{R}_1 \neq \text{H}$, while the rhodium (II) carboxamidates display high enantiocontrol with diazoacetates.

Applications of the chiral rhodium (II) carboxylates to the cyclization of α -diazo- β -ketosulfones, Eq. (35), have shown that while they are catalytically active at or below room temperature, they provide only low enantiomeric excesses [6].

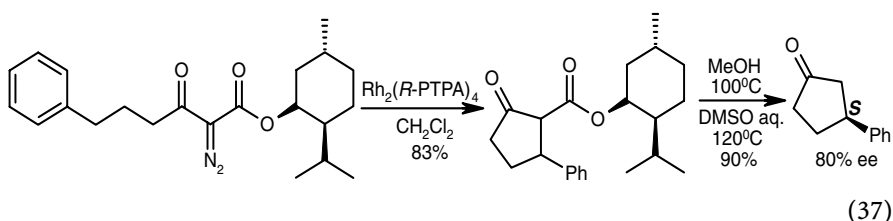


Ikegami's study of asymmetric C-H insertion reactions with α -diazo- β -ketesters is summarized in Eq. (36).

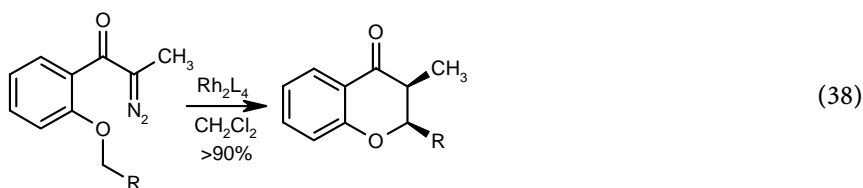


R	X	Yield [%]	% ee
Me	Me	76	24
C ⁱ Pr ₂ Me	Me	63	32
Me	Ph	96	46
C ⁱ Pr ₂ Me	Ph	81	76
CH ⁱ Pr ₂	4-TfOC ₆ H ₄	84	80

With the rhodium(II)-*N*-phthalimido phenylalaninate catalyst (Fig. 2), cyclopentanone derivatives could be obtained in 43–96% yield, but with modest ee levels in most cases [7]. Use of alanine, phenylglycine, or alkoxyferrocenecarboxylic acids as chiral ligands on rhodium (II) did not improve enantioselectivity. However, substrate modification did offer some increase in enantiocontrol, e.g., by increasing the steric bulk of the ester alkyl group from methyl to diisopropylmethylcarbonyl, Eq. (36) [53]. Additional reconstruction involved substituted phenyl or vinyl groups at the insertion site [54]. Furthermore, with esters of chiral alcohols including (+)-neomenthol, double diastereoselection occurred and the product was obtained with 80% ee, Eq. (37) [55].

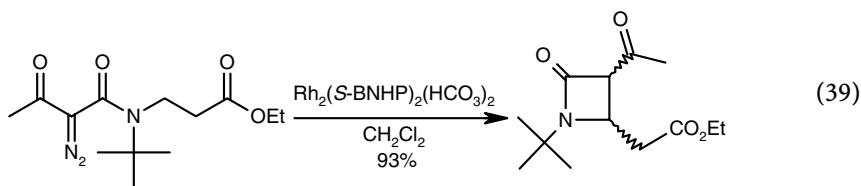


With some conformationally less mobile substrates such as those in Eq. (38), ee values up to 82% and high diastereoselectivity, characterize the use of the *N*-protected amino acid-ligated rhodium(II) catalysts for chromanone formation [56, 57].

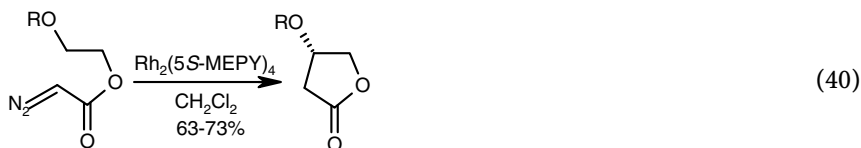


L	R	<i>cis:trans</i>	% ee
2S-BSP	CH ₃	75:25	82
2S-BSP	Ph	89:11	62
2S-BSP	CHCH ₂	93:7	79
(S-BNHP) ₂ (HCO ₃) ₂	CHCH ₂	94:6	33

The *N*-benzenesulfonylprolinolate catalyst, (3) of Fig. 1, provided the highest levels of stereocontrol. The binaphthyl hydrogen phosphate rhodium (II) catalyst also promoted chromanone formation and while the *cis*-diastereoselectivity was excellent (94%), the enantiocontrol was modest (33% ee); application of this catalyst to the β -lactam-forming C-H insertion reaction in Eq. (39) revealed high chemoselectivity (93% yield of *trans*), but low enantioselectivity (26% ee) [28].

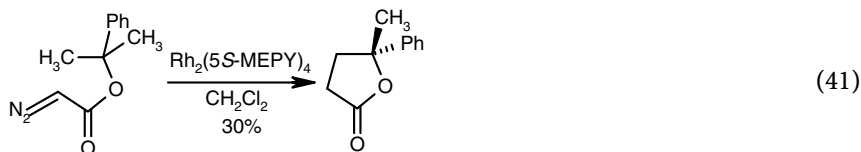


Doyle's chiral rhodium (II) carboxamidates have proved to be exceptionally successful for asymmetric C-H insertion reactions of diazoacetates and some diazoacetamides leading to lactones and lactams, respectively. With 2-alkoxyethyl diazoacetates and the $\text{Rh}_2(5S\text{- and }5R\text{-MEPY})_4$ catalysts, for example, highly enantioselective intramolecular C-H insertion reactions occur, the 5*S*-catalyst, Eq. (40), and 5*R*-catalyst furnishing the *S*- and *R*-lactone, respectively [58]. A polymer-bound version of $\text{Rh}_2(5S\text{-MEPY})_4$ has also been applied to the cyclization in Eq. (40) to yield the lactone with 69% ee (*R*=Me); the catalyst could be recovered by filtration and reused several times, but with decreasing enantioselectivity [59].

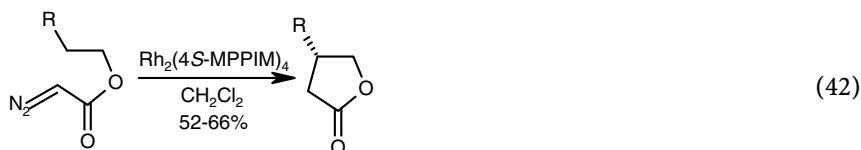


R	% ee
Me	91
Et	89
Bn	87

Comparable levels of stereocontrol were observed in the $\text{Rh}_2(\text{MEPY})_4$ -catalyzed lactonization in Eq. (41) (76% ee); competition from intramolecular aromatic cycloaddition reduced somewhat the chemoselectivity of the reaction [58].



Diazoacetates derived from simple primary alcohols also undergo γ -lactone formation in moderate to good yield. Through the use of $\text{Rh}_2(4S\text{-MPPIM})_4$ as catalyst, Eq. (42), excellent stereocontrol is attainable (up to 96% ee) [60, 61].



R	% ee
Et	96
<i>i</i> Bu	95
PhCH ₂	89
<i>m</i> -MeOC ₆ H ₄ CH ₂	92
3,4-(MeO) ₂ C ₆ H ₃ CH ₂	94

There is also excellent regiocontrol, the alternative C-H insertion reaction leading to β -lactone formation amounting to less than 5%. A good test of the reliability of the stereocontrol in such C-H insertion reactions is provided by very successful applications to the asymmetric synthesis of a series of naturally occurring lignans (Fig. 13), among which are (-)-enterolactone (**23**) (93% ee), (+)-arctigenin (**24**) (93% ee), and (+)-isodeoxypodophyllotoxin (**25**) (>99% ee) in high enantiomeric purity from simple cinnamic acid precursors [61]. An outline of the synthesis of (+)-arctigenin is shown in Scheme 8.

There is now general agreement that catalyzed C-H insertion with diazo compounds occurs through an electrophilic metal carbene intermediate. According to Doyle's analysis of the mechanism, reaction is initiated by overlap of the metal carbene's carbon p-orbital with the σ -orbital of the reacting C-H bond. The formation of the new C-C and C-H bonds occurs simultaneously with dissociation of the rhodium(II) species (Scheme 9). As the hydrogen atom migrates to the carbenic center, the substituents attached to the carbon atom undergoing inser-

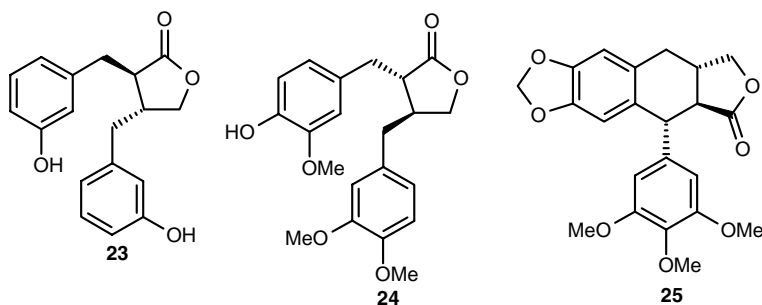
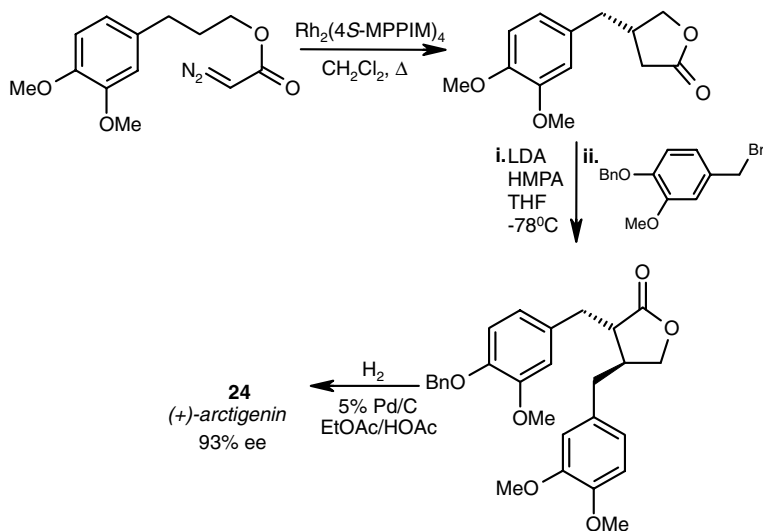
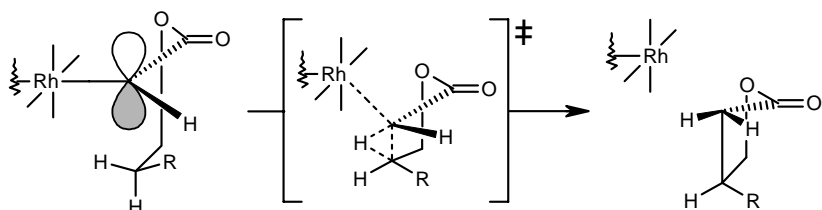


Fig. 13



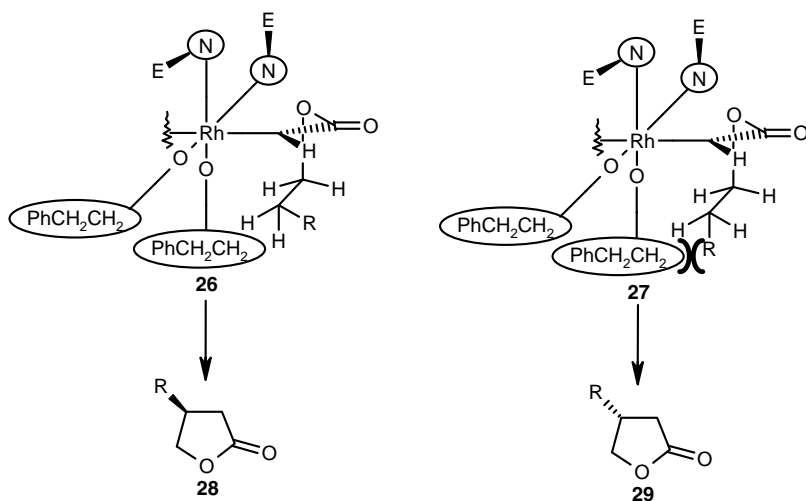
Scheme 8



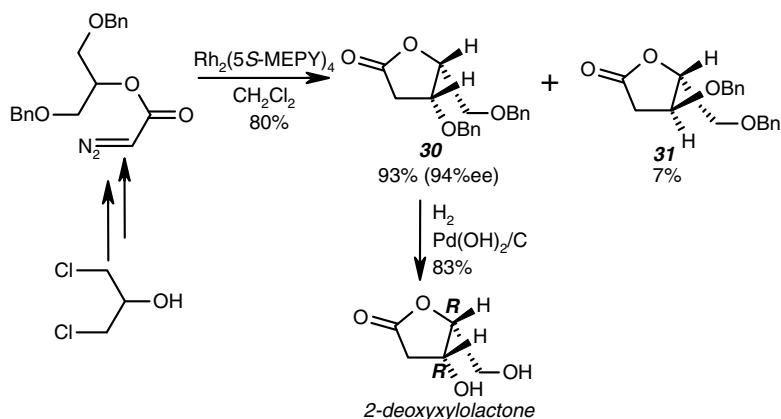
Scheme 9

tion rotate towards the resting positions that approximate to their locations in the reaction product. By applying this mechanistic analysis to asymmetric C-H insertion with a chiral catalyst, it is possible to predict the absolute configuration of the products formed in the $\text{Rh}_2(\text{MPPIM})_4$ catalyzed reactions using the model in Scheme 10. The metal carbene is depicted by conformations (26) and (27), each positioned to undergo C-H insertion to form the enantiomeric lactones (28) and (29), respectively. The high preference for (28), even when R is as small as ethyl (96% ee), can be attributed to the steric repulsion between the *N*-3-phenylpropanoyl residue of the imidazolidinone ligand and the *anti* R group in (27). The *syn* conformation (26) places the R group away from the ligand residue, thus providing a lower-energy transition state for C-H insertion.

Doyle's catalysts and methodology have been extended to C-H insertion reactions of diazoacetates derived from secondary acyclic and cyclic alcohols where diastereoselectivity becomes an integral component of the overall stereocontrol objective. Two outstanding examples in the acyclic series are shown in Scheme 11

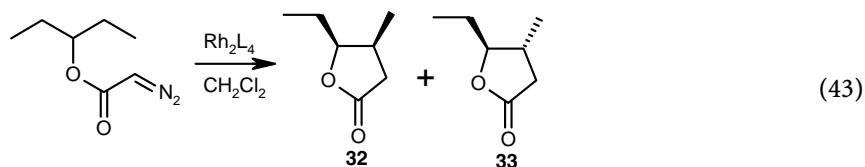


Scheme 10



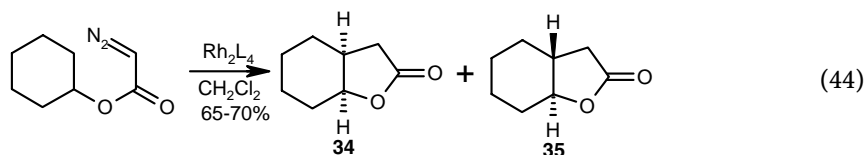
Scheme 11

and Eq. (43). In the former Rh₂(5*R*-MEPY)₄ was used to catalyze highly diastereoselective and enantioselective C-H insertion reactions of simple glycerol-derived diazoacetate to form 2-deoxyxylolactone derivatives (**30**) and (**31**); as little as 0.1 mol % of catalyst was required to effect complete reaction (1,000 turnovers). The efficacy of these cyclizations is enhanced by ether oxygen atom activation of adjacent C-H bonds [40]. In the related example in Eq. (43), where ether oxygen atom activation is absent, enantioselectivity remains high with Rh₂(MEPY)₄ catalysis, but diastereocontrol is diminished. However, both Rh₂(4*S*-MPPIM)₄ and Rh₂(4*S*-MCHIM)₄ restore complete stereocontrol, the latter furnishing the *cis*-lactone in 88% yield and with a de of 98% and an ee of 99% [62].



L	% yield	32:33	32: % ee	33: % ee
4S-MCHIM	88	98:2	99	-
4S-MPPIM	81	97:3	99	-
4S-MACIM	81	94:6	86	36
5S-MEPY	70	78:22	98	71
4S-MEOX	75	69:31	98	92

Equally successful stereocontrol has been achieved with secondary cycloalkyl diazoacetates where diastereoselectivity is associated with the formation of *cis*- and *trans*-fused bicyclic lactones. With cyclohexyl diazoacetate, Eq. (44) and $\text{Rh}_2(\text{OAc})_4$ racemic lactones with only a small preference for the *trans*-isomer are formed (60:40). Use of chiral $\text{Rh}_2(5\text{S-MEPY})_4$ led to diastereocontrol of only 3:1, but enantiocontrol was nearly complete (97% ee) in the *cis*-lactone. However, both high enantiocontrol and nearly full diastereocontrol were realized with $\text{Rh}_2(4\text{S-MACIM})_4$. $\text{Rh}_2(4\text{S-MEOX})_4$, the oxazolinidinone analog of $\text{Rh}_2(5\text{S-MEPY})_4$, catalyzed high enantiocontrol, but little diastereocontrol [63]. Similarly high enantio- and diastereoselectivities have been observed with cyclopentyl, cycloheptyl, and cyclooctyl diazoacetates, with *cis*- or *trans*-4-methylcyclohexyl diazoacetate (where preferential insertion into equatorial bonds leads to lactones (36) and (37) in Fig. 14) has been demonstrated [63, 64] and with 2-adamantyl diazoacetate (Fig. 14, (38)) [21]. With these substrates $\text{Rh}_2(\text{MEOX})_4$ catalysts achieved the highest levels of enantiocontrol.



L	34:35	34: % ee	35: % ee
OAc	40:60	-	-
4S-MEOX	55:45	96	95
5S-MEPY	75:25	97	91
5S-MACIM	99:1	97	65

Enantiocontrol in C-H insertion with tertiary alkyl diazoacetates is also attainable using chiral rhodium(II) carboxamidates [65]. Although only a limited

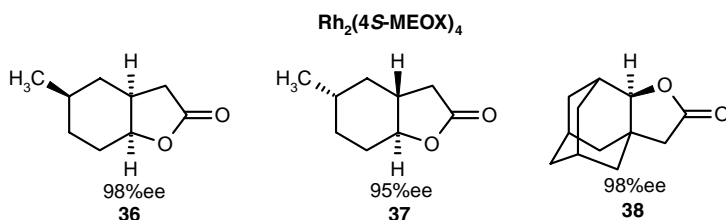
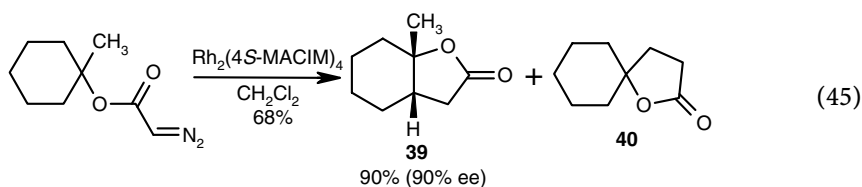
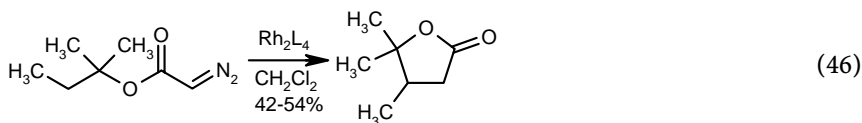


Fig. 14

number of examples are yet available, $\text{Rh}_2(4S\text{-MACIM})_4$ appears to be the catalyst of choice for producing high ee levels as, for example, that in Eq. (45).



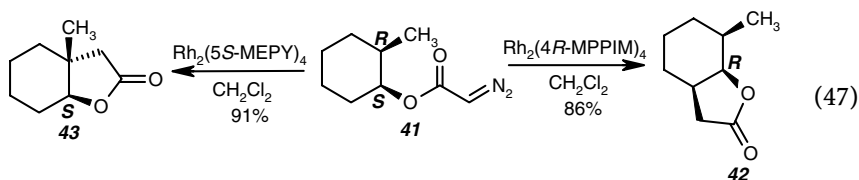
Regioselectivity can be an issue even when competition in C-H insertion is with electronically unfavorable primary C-H bonds, although electronic preferences can be outweighed by conformational restrictions. In the example in Eq. (45) the minor (10%) product (**40**) is that of primary C-H insertion. Interestingly, even when only one C-H insertion product is formed, catalysts with ligands of identical configuration, but otherwise of different constitution can give products whose absolute configurations are opposite. Such is the case illustrated in Eq. (46) where the *S*-MEOX and *S*-MACIM ligands produce the (-)- and (+)-enantiomers of the same product.



L	% ee
4 <i>S</i> -MEOX	21 (-)
4 <i>S</i> -MACIM	62 (+)

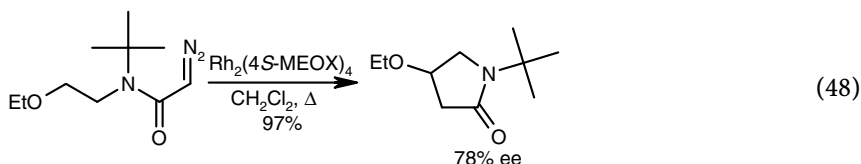
The idea of matching individual diazoacetate enantiomers with a particular chiral dirhodium (II) has been very successfully exploited by Doyle's group to optimize diastereocontrol and regiocontrol in product formation. The behavior of the individual enantiomers of *cis*-2-methylcyclohexyl diazoacetate, Eq. (47) provides an illustrative example of the power of this approach in regioselective synthesis. Whereas the (1*S*,1*R*)-enantiomer of (**41**) forms the all *cis*-bicyclic lac-

tone (**42**) when treated with $\text{Rh}_2(4R\text{-MPPIM})_4$, the same precursor on exposure to $\text{Rh}_2(5S\text{-MEPY})_4$ furnishes the regioisomeric bicyclic lactone (**43**), both reactions occurring with excellent yields. Repetition of these reactions with the (1*R*,2*S*)-enantiomer of the diazoacetate (**41**) confirmed the mirror image relationships [66].

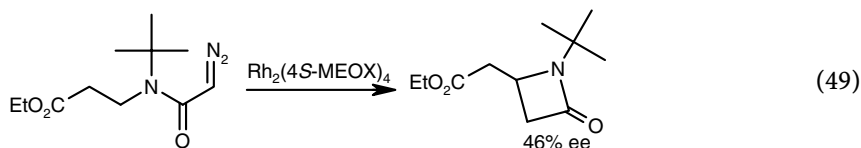


Examples of enantioselective intramolecular C-H insertion reactions of diazoacetamides are known and though less extensive than those with diazoester substrates, there already are indications that excellent levels of stereocontrol are attainable. It is very likely that catalyst development will extend further the scope of this approach to the enantioselective synthesis of *N*-heterocycles.

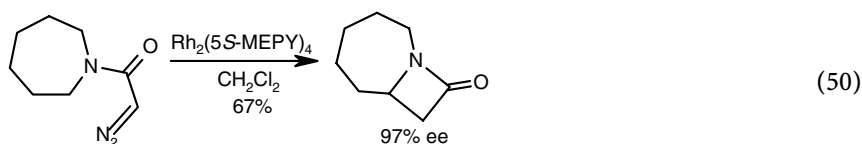
$\text{Rh}_2(5S\text{-MEPY})_4$ and $\text{Rh}_2(4S\text{-MEOX})_4$ both catalyze the cyclization of *N*-alkyl-*N*-(*tert*-butyl)diazoacetamides to lactams [67(a), 67(b)]. Substituents at the 2-position of the *N*-alkyl group influence regioselectivity to the extent that when the substituent is an alkoxy group, as in Eq. (48), only the γ -lactam is produced.



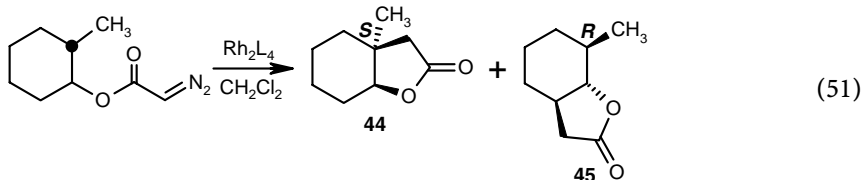
Of the two catalysts investigated, $\text{Rh}_2(4S\text{-MEOX})_4$ gave significantly higher enantioselectivity (up to 78% ee) than $\text{Rh}_2(5S\text{-MEPY})_4$. When the *N*-alkyl group at the 2-position is a carboxylate group as in Eq. (49), β -lactam formation occurs in moderate ee (46%), but here there is competition from an alternative C-H insertion into the *tert*-butyl substituent.



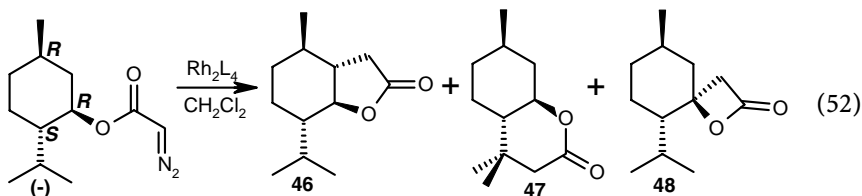
However, when the *N*-alkyl substituents are tied back in a cyclic structure, as in the example in Eq. (50), γ -lactam formation is rendered more unfavourable geometrically and β -lactam formation becomes the sole reaction pathway with nearly complete enantiocontrol (97% ee) [68].



Similar examples of product control induced by chiral catalysts have been found with *trans*-2-methylcyclohexyl diazoacetate, Eq. (51), (+)- and (-)-menthyl diazoacetate, Eq. (52), (+)-neomenthyl diazoacetate, Eq. (53), and (+)- and (-)-2-octyl diazoacetate, Eq. (54). The very high levels of diastereoselectivity exhibited by the cyclohexyl diazoacetate cyclisations is due to the preference for C-H insertion to occur at equatorial C-H bonds [66].

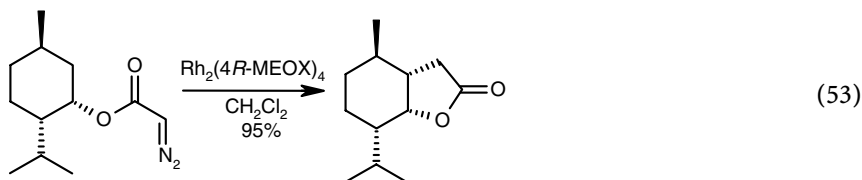


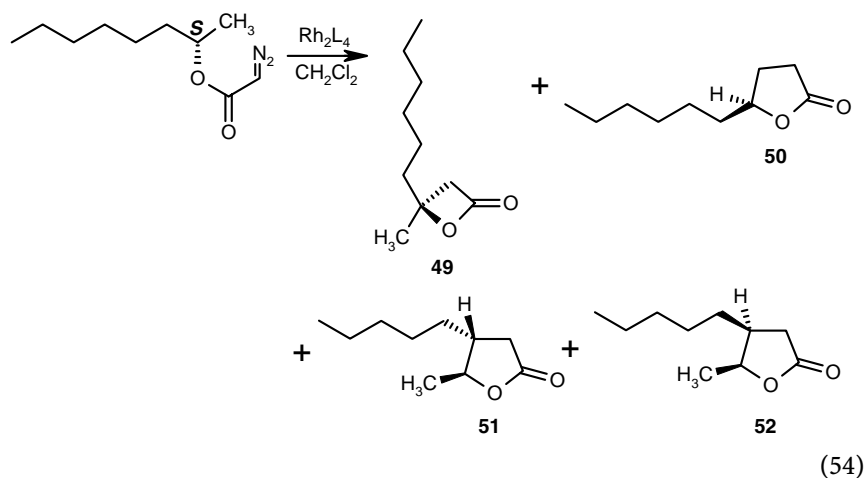
L	44: yield [%] (% ee)	45: yield [%] (% ee)
5S-MEPY	49 (80)	40 (93)
4S-MEOX	39 (96)	50 (95)
4S-MACIM	18 (87)	19 (49)



L	46: yield [%]	47: yield [%]	48: yield [%]
5S-MEPY	73 (44)	27 (56)	–
5R-MEPY	42 (75)	58 (25)	–
4S-MEOX	>99 (29)	<1 (53)	– (18)
4R-MEOX	28 (>99)	50 (<1)	22 (–)

Yields in parentheses refer to the diazo decomposition of (+)-menthyl diazoacetate.





Diazo	L	49: yield [%]	50: yield [%]	51: yield [%]	52: yield [%]
S	5R-MEPY	65	14	14	7
S	4R-MEOX	85	9	4	2
R	5S-MEPY	66	14	14	6
R	4S-MEOX	83	10	4	3

Analysis of catalyst structure and shape provides an understanding of the way in which the ligands on the dirhodium core influence stereoselectivity. The chiral $\text{Rh}_2(\text{MEPY})_4$ and $\text{Rh}_2(\text{MEOX})_4$ catalysts have two closed, i.e., occupied, quadrants and two open quadrants on the dirhodium face as shown in (53), Fig. 15 where $\text{E}=\text{CO}_2\text{Me}$. In forming the metal-carbon bond the bound carbene adopts a position in which steric interference with the ligand's ester attachment is minimized, as in (54) of Fig. 15. $\text{Rh}_2(\text{MEOX})_4$ offers a more open framework for C-H insertion than does $\text{Rh}_2(\text{MEPY})_4$ and diastereocontrol is often greater with the latter, although the reverse is true for regioselectivity. The chiral *N*-acylimidazolidinone catalysts, e.g., $\text{Rh}_2(4\text{S-MACIM})_4$ in Fig. 4, display a selectivity which differs considerably from that of either $\text{Rh}_2(\text{MEPY})_4$ or $\text{Rh}_2(\text{MEOX})_4$. In (53) the open quadrants are restricted, cf. (55) in Fig. 16, and the metal carbene (56) is subject to steric repulsion from both the ligand's ester ($\text{E}=\text{O}_2\text{Me}$) and acyl ($\text{Ac}=\text{NCOR}$) groups [19]. The influence of chiral catalysts on diastereoselection in C-H insertion of cycloalkyl diazoacetates is understandable in terms of the preferred conformations of the putative metal carbene intermediates. The equatorial-axial conformational equilibrium of the cyclohexyl ring provides access of the metal carbene to equatorial C-H bonds, insertion into which yields the *trans*-fused lactone (59) or the *cis*-fused lactone (60) in Scheme 12.

Insertion into axial C-H bonds by the metal carbene is prevented by crowding of the cyclohexane ring into the face of the catalyst. In the absence of significant steric influences from the catalyst face adjacent to the cyclohexyl group, both di-

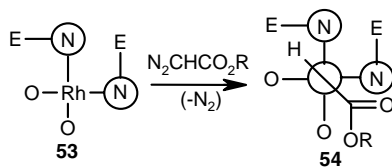


Fig. 15

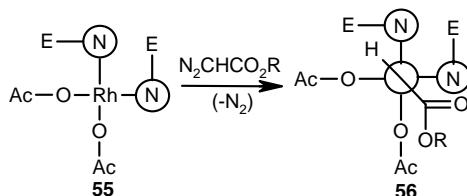
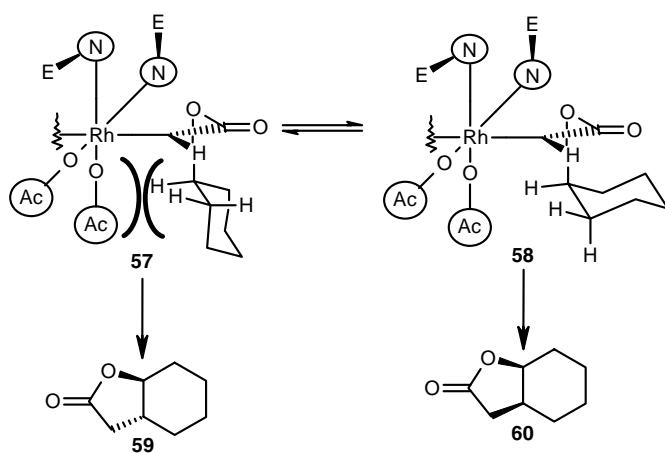


Fig. 16

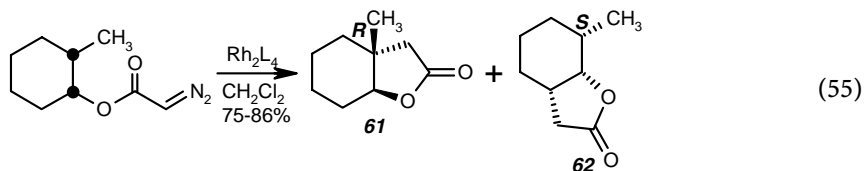


Scheme 12

astereoisomers are formed. However, by placing substituents in those quadrants of the catalyst face that destabilize (**57**) relative to (**58**), i.e., as in $\text{Rh}_2(4S\text{-MACIM})_4$ and $\text{Rh}_2(4S\text{-MPPIM})_4$ the *cis*-lactone (**60**) becomes the preferred diastereoisomer.

A final example of the use of chiral rhodium (II) catalysts in stereoselective synthesis concerns enantiomer differentiation in reactions of racemic mixtures of diazoacetates. This is made possible by the high levels of diastereoselectivity

and regioselectivity that characterize the decomposition of the individual enantiomers of diazoacetates. For example, the racemic 2-methylcyclohexyl diazoacetate in Eq. (55) on exposure to $\text{Rh}_2(5\text{S-MEPY})_4$ furnishes about equal amounts of two regioisomeric lactones (**61**) and (**62**), each with high levels (>90% ee) of enantiocontrol [66, 69]. With the $\text{Rh}_2(4\text{S-MEOX})_4$ catalyst enantiocontrol in the formation of both lactones is essentially complete.



L	61 : yield [%] (% ee)	62 : yield [%] (% ee)
5S-MEPY	45 (91)	49 (98)
4S-MEOX	40 (99)	47 (99)
4S-MACIM	11 (87)	66 (77)

Enantiomer differentiation has also been demonstrated in the cyclization of the racemic *trans*-counterpart of 2-methylcyclohexyl diazoacetate and (\pm)-2-octyl diazoacetate.

4

Conclusions

The development of chiral rhodium (II) catalysts has resulted in major advances in asymmetric cyclopropanation and C-H insertion. High levels of chemoselectivity and regiocontrol are easily accessible. Furthermore, control of diastereoselectivity and enantioselectivity are now standard features of both processes. Catalyst design has provided the key to success in these important applications of diazocarbonyl compounds.

Acknowledgements: We thank Professor Mike P. Doyle and Dr. Tao Ye for their invaluable assistance and advice in preparing this chapter.

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Chapter 16.3

Cyclopropanation and C-H Insertion with Metals Other Than Cu and Rh

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Keywords: Cyclopropanation, Simmons-Smith, C-H insertion, Diazo compounds, Carbenes

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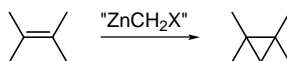
List of Abbreviations

AL	Lewis acid
<i>i</i> -Bu	<i>iso</i> -butyl
cat	catalyzed
cyc	cyclohexyl
cdq	camphorquinone- α -dioximato
ment	menthyl
naph	naphthyl
pybox	bis(oxazolinyl)pyridine
uncat	uncatalyzed
rt	room temperature

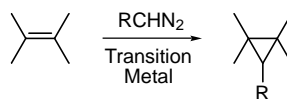
1 Cyclopropanation

In recent years, considerable efforts have been directed towards the development of new methods for the enantioselective synthesis of cyclopropanes [1, 2, 3]. The usefulness of this transformation first became apparent when it was discovered that some chiral cyclopropane-containing pyrethroids were highly effective insecticides. More importantly, the biological activity of these compounds was directly related to the cyclopropane stereochemistry [4]. One of the most ef-

Simmons-Smith



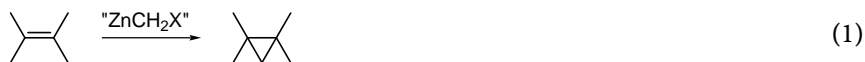
Diazo decomposition

**Scheme 1**

fective strategies available to generate a three-membered ring involves the concerted addition of a methylene group to an olefin. The Simmons-Smith cyclopropanation (and related reactions), and the cyclopropanation reaction of olefins using the transition metal-catalyzed decomposition of diazo compounds have received considerable attention in the last few decades (Scheme 1). This chapter will describe the catalytic enantioselective versions of these reactions in which metals other than copper and rhodium are involved.

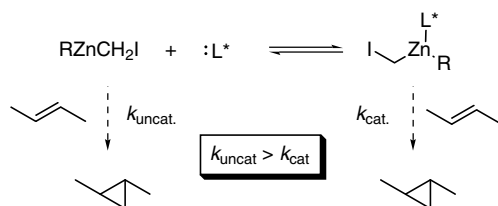
1.1**Simmons-Smith Reaction**

Simmons and Smith discovered that the oxidative insertion of zinc into diiodomethane produces a reagent (IZnCH_2I) that is capable of converting a variety of alkenes into their corresponding cyclopropane derivatives [5]. This method has become one of the most widely used to make three-membered rings [6]. The efficiency of this transformation has stimulated the search for several alternative methods to prepare related ZnCH_2X species that are also very effective cyclopropanating reagents with unique properties and reactivities. Eq. (1) gives an overview of the different methods available to prepare the zinc carbenoid reagents.



Method	Reactants	Reagent
oxidative addition	Zn/activator, CH_2I_2	IZnCH_2I
metal-halogen exchange	$\text{EtZnI}:\text{CH}_2\text{I}_2$ (1:1)	IZnCH_2I
	$\text{Et}_2\text{Zn}:\text{CH}_2\text{I}_2$ (1:1)	EtZnCH_2I
	$\text{Et}_2\text{Zn}:\text{XCH}_2\text{I}$ (1:2)	$\text{Zn}(\text{CH}_2\text{X})_2$
nucleophilic displacement	$\text{ZnX}_2:\text{CH}_2\text{N}_2$ (1:1)	XZnCH_2X
	$\text{ZnX}_2:\text{CH}_2\text{N}_2$ (1:2)	$\text{Zn}(\text{CH}_2\text{X})_2$

Cyclopropanation reactions using these reagents are characteristically stereospecific, applicable to a variety of olefins, and compatible with several func-

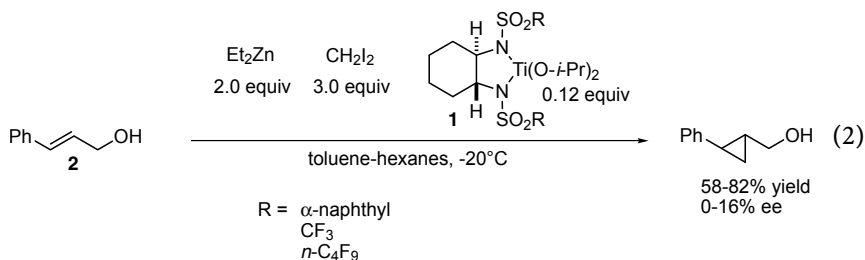


Scheme 2

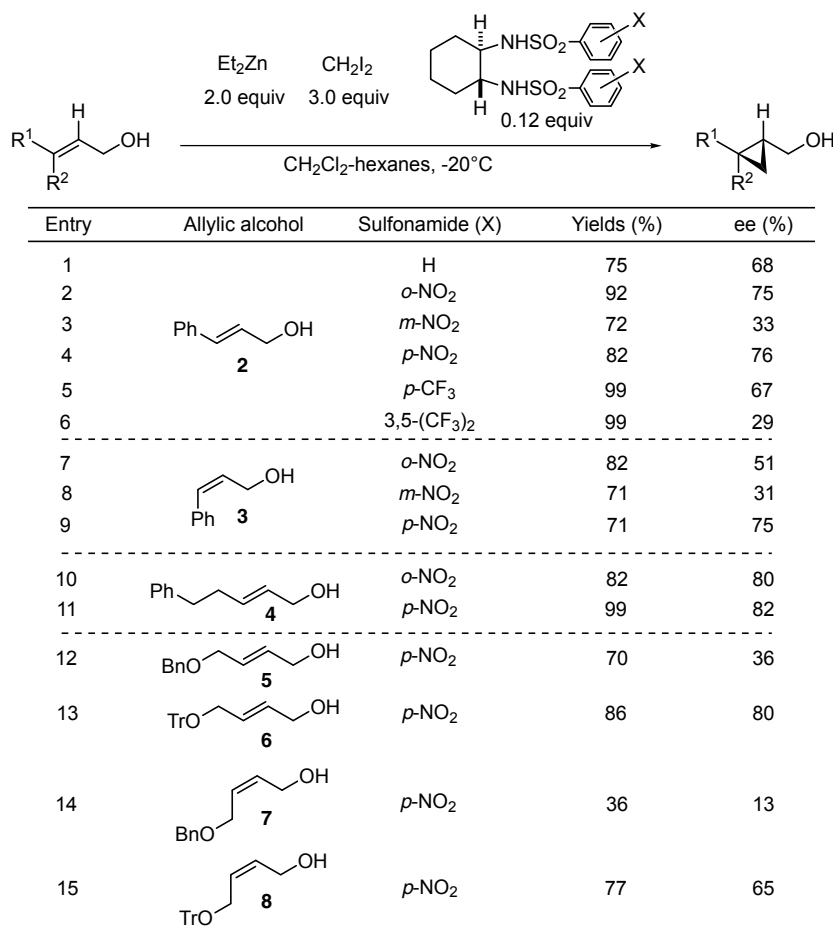
tional groups. It was also observed that proximal basic groups could “direct” the delivery of the methylene group by complexing the zinc carbenoid reagent. The first attempts to control the enantioselectivity by the addition of a chiral ligand in Simmons-Smith cyclopropanation reaction were reported by Furukawa [7] and Inouye [8, 9]. They showed that addition of stoichiometric amounts of L-leucine and (–)-menthol, respectively, did not lead to any stereochemical induction.

One of the challenging issue in this reaction is to find a way to accelerate the cyclopropanation reaction upon addition of a chiral additive (Scheme 2). It is now well established that uncomplexed zinc carbenoid reagents are in rapid equilibrium with their complexed forms in the presence of basic ligands. Since these reagents are electrophilic species, the chiral, complexed reagent is usually a less reactive cyclopropanating reagent than the achiral, uncomplexed zinc carbenoid. For this reason, most of the successful chiral ligands that have been developed for the catalytic enantioselective addition of dialkylzinc to aldehydes are ineffective at inducing any selectivity in the Simmons-Smith cyclopropanation reaction.

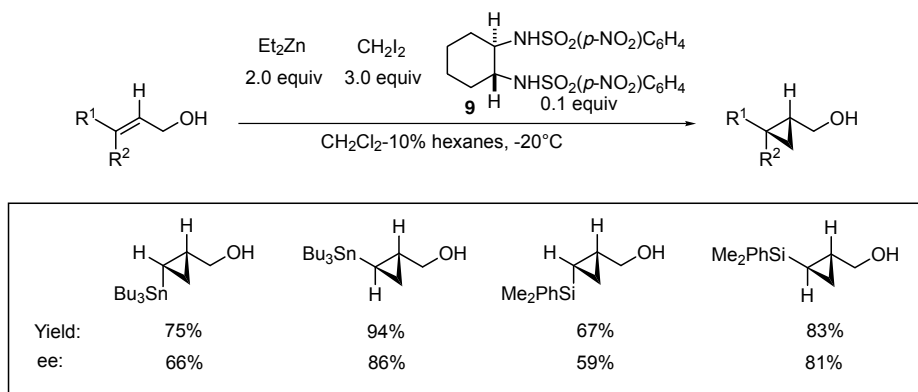
Kobayashi and coworkers made a major breakthrough in this area by showing that the Simmons-Smith cyclopropanation reaction could be significantly accelerated by a chiral catalyst [10, 11, 12]. They found that unprecedentedly good enantioselectivities and rate enhancements were observed if a C_2 -symmetric chiral disulfonamide ligand was added in catalytic amounts to the zinc-mediated cyclopropanation of allylic alcohols. Their initial studies involved the Lewis acid-catalyzed Simmons-Smith reaction of the cinnamyl alcohol **2** in the presence of the disulfonamide-modified titanium catalyst **1** which proceeded smoothly to afford the corresponding cyclopropane in good yield, but with low enantioselectivity (Eq. (2)). However, they made the key observation that the cyclopropanation reaction was slightly accelerated in the presence of a titanium catalyst.



They later found that the disulfonamide-modified zinc complexes were much more effective catalysts. The reaction of several allylic alcohols with diethylzinc and methylene iodide in the presence of differently substituted arylsulfonamides derived ligands was examined in detail (Scheme 3). Although the *p*-trifluoromethylbenzenesulfonamide catalyst (entry 5) facilitated the cyclopropanation of cinnamyl alcohol (**2**), the enantioselectivity observed was slightly lower than that observed with the *o*-nitro- or the *p*-nitrobenzenesulfonamide ligand (entries 2 and 4). Substitution at the *meta*-position resulted in a significant decrease of the enantioselectivity, probably due to steric reasons (entries 3 and 6). The cyclopropanation of (*Z*)-cinnamyl alcohol (**3**) and (*E*)-5-phenyl-2-penten-1-ol (**4**) was also performed and enantioselectivities of 75% and 82% were observed with the *p*-nitrobenzenesulfonamide ligand (entries 9 and 11). Trityl ethers **6** and **8** gave good enantioselectivities, however, poor enantioselectivities



Scheme 3

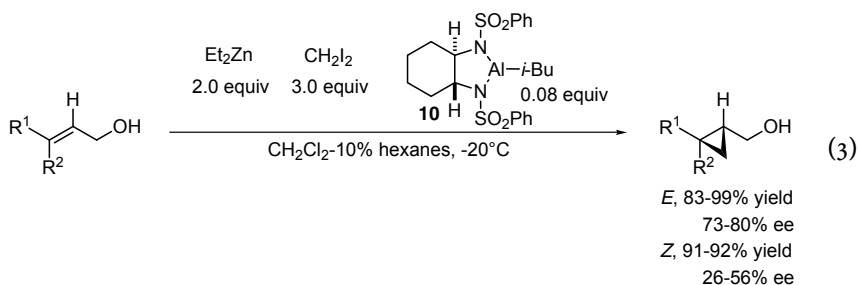


Scheme 4

were observed in the case of benzyl ethers **5** and **7**. Apparently, a competitive, non-enantioselective ether-directed cyclopropanation has been postulated to have occurred in the case of benzyl ethers **5** and **7** in order to explain the lower enantioselectivities observed.

The effect of solvent was also studied and complexing solvents such as THF or Et₂O inhibited the cyclopropanation reaction. Furthermore, the presence of an unprotected allylic alcohol was found to be essential, since the methyl or benzyl ether derived from cinnamyl alcohol afforded almost racemic cyclopropanes. This method has also been extended to the enantioselective cyclopropanation of vinylsilanes and -stannanes (Scheme 4) [13]. The corresponding optically active silyl- and stannyl-substituted cyclopropylmethanols were obtained in the presence of the chiral *N,N'*-bis(*p*-nitrobenzenesulfonyl)-1,2-cyclohexanediamine **9**.

Equally high enantioselectivities were observed if the zinc-derived Lewis acid was replaced by the analogous aluminum catalyst **10**, prepared from (1*R*,2*R*)-*N,N'*-bis(benzenesulfonyl)-1,2-cyclohexanediamine and *i*-Bu₂AlH (Eq. (3)) [14].



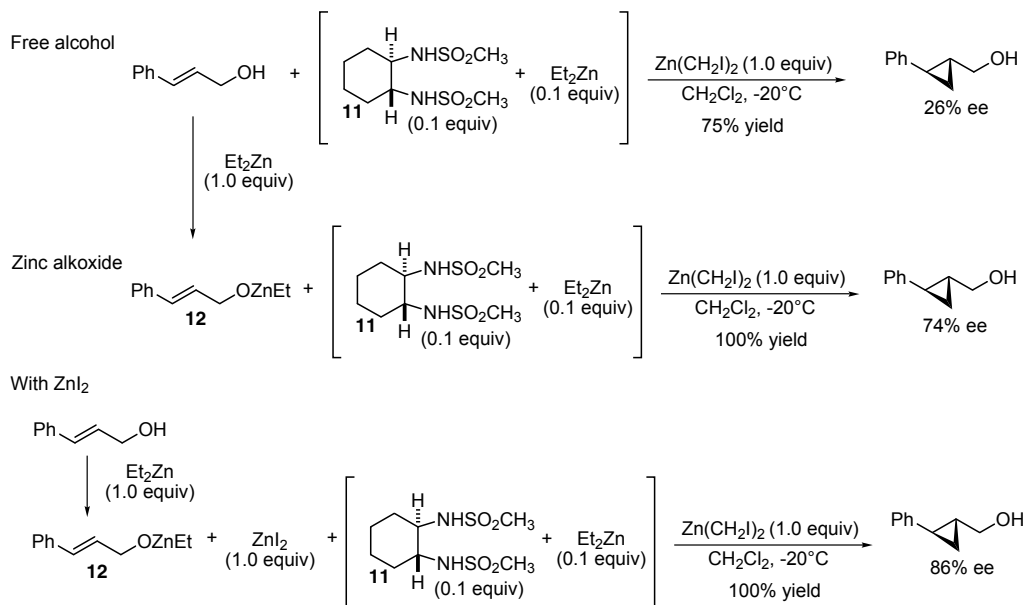
The different parameters involved in the enantioselective cyclopropanation of allylic alcohols using disulfonamide-derived ligands were also extensively studied by Denmark. He has shown that the rate and selectivity of the cyclopropanation reaction of cinnamyl alcohol using bis(iodomethyl)zinc and the

bis(sulfonamide) **11** were greatly dependent on the order of addition of the reagents and on the nature of the reagents (Scheme 5) [15]. The independent preformation of the ethylzinc alkoxide **12** and of bis(iodomethyl)zinc was found to be crucial. He later discovered that the addition of a stoichiometric amount of ZnI_2 (best results were obtained if it was formed in situ from Et_2Zn and I_2) slightly improved the enantioselectivities. Intrigued by the effect of the zinc iodide on both the rate and the enantiomeric excesses, Denmark has performed reaction studies and spectroscopic investigations [16]. These studies have shown that this remarkable influence is probably the result of reagent modification via a Schlenk equilibrium that produces the more reactive and selective (iodomethyl)zinc iodide [17].

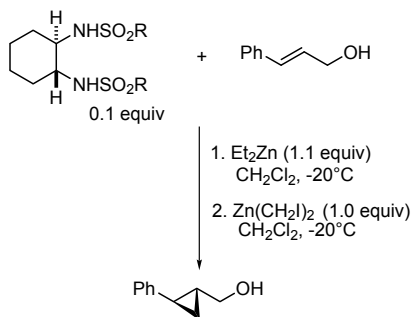
An extensive structure-selectivity study was then undertaken by this group. They found a marked sensitivity to the spatial relationship of the amine groups, also the enantioselectivities were modestly dependent on the nature of the sulfonamide residue (Scheme 6) [18]. It turned out that the dimethylsulfonamide ligand, derived from *trans*-cyclohexanediamine, led to cyclopropane formation with higher enantioselectivities.

Denmark has also shown that the uncatalyzed ethylidenation of cinnamyl alcohol using bis(1-iodoethyl)zinc produced the cyclopropanes **13** and **14** in a 71:29 ratio (Scheme 7) [19]. This ratio decreased to 65:35 (**13**:**14**) in the presence of the disulfonamide **11**. Both compounds had modest enantiomeric excesses.

Furthermore, Denmark has carried out the catalytic and enantioselective cyclopropanation of a broad range of allylic alcohols and one homoallylic alcohol

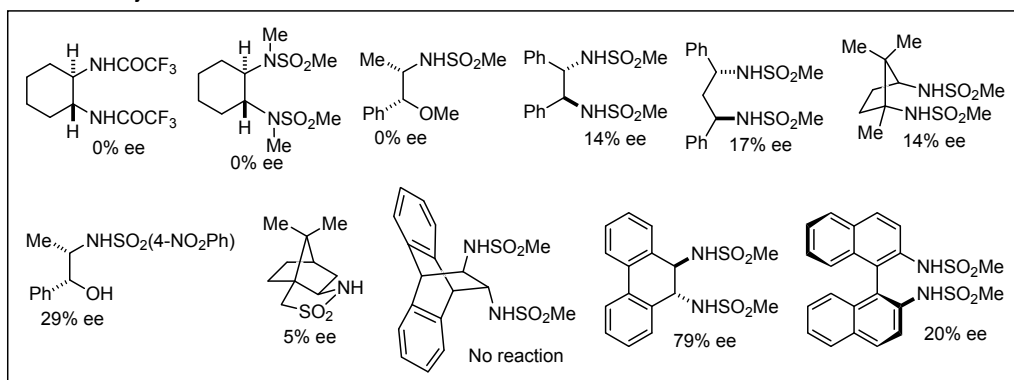


Scheme 5

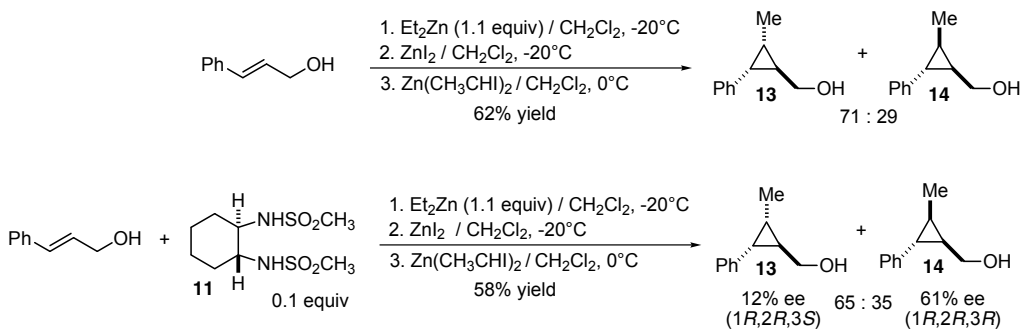


Chiral diamine (R)	ee (%)
Me	80
Et	67
<i>i</i> -Pr	49
CF ₃	15 (opposite enantiomer)
Ph	76
2,4,6-Me ₃ Ph	32
1-naphtyl	48
4-NO ₂ Ph	76
2-NO ₂ -4-CF ₃ Ph	63
4-CH ₃ OPh	74
C ₆ F ₅	29

Other Catalysts:



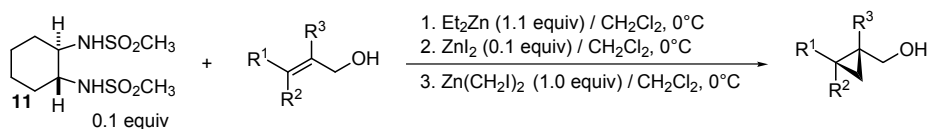
Scheme 6



Scheme 7

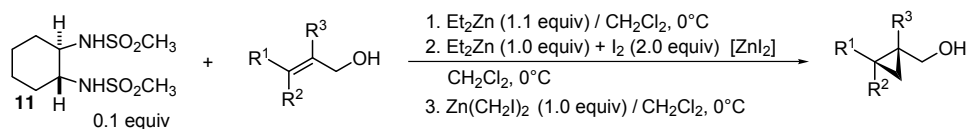
under optimized conditions using 10 mol % of the *N,N*-bis(methanesulfonyl) derivative of (*R,R*)-1,2-diaminocyclohexane (**11**) [20]. The stereoselectivity of the cyclopropanation was found to be independent of olefin geometry and it worked well for substrates bearing both aliphatic and aromatic substituents at

either or both 3-positions of the allylic alcohol (Scheme 8). However, a methyl substituent at the 2-position of the allylic alcohol was not well tolerated and it led to low reaction rates and poor enantioselectivities. The poor results with a homoallylic alcohol (88% yield, 5% ee, not shown in Scheme 8), clearly illustrated the critical importance of the proximity of the hydroxymethyl group to the double bond.



Yield: 91%	89%	91%	98%	90%
ee: 80%	81%	73%	66%	5%
Yield: 81%	93%	88%	94%	97%
ee: 81%	72%	81%	79%	10%
Yield: 98%	90%	85%	85%	
ee: 26%	50%	43%	16%	

In situ generation of ZnI_2



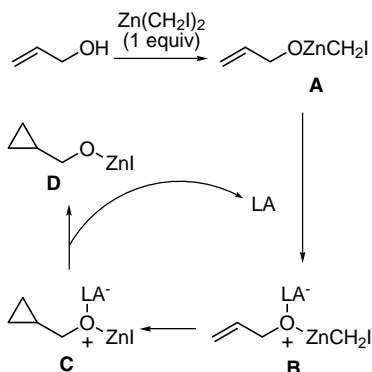
Yield: 92%	88%	92%	89%	91%
ee: 89%	89%	89%	82%	3%

Scheme 8

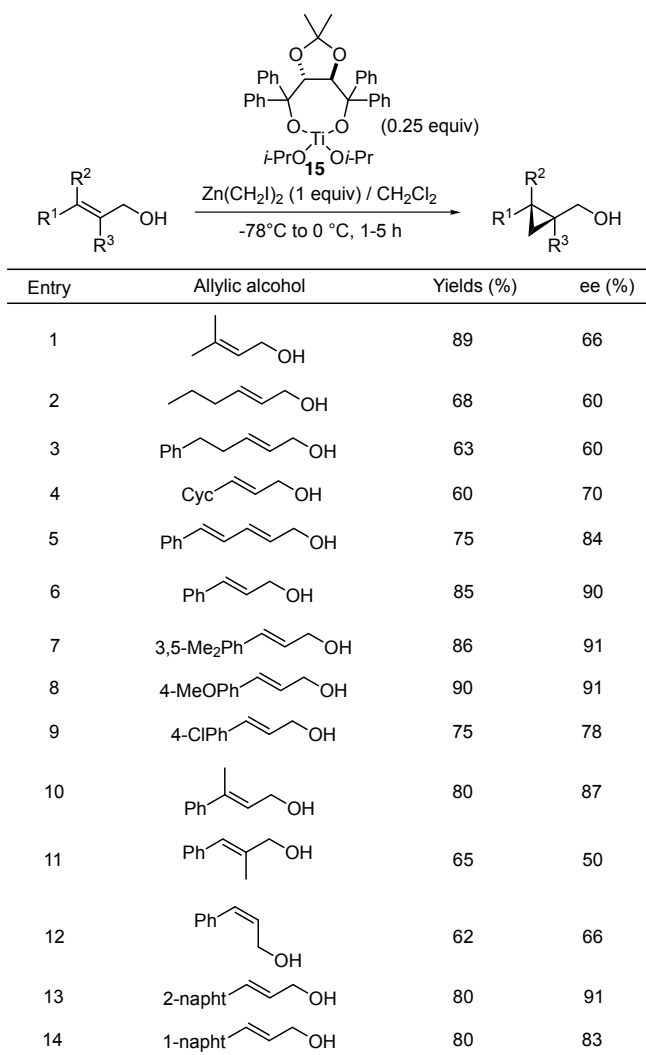
Charette and Brochu have reported an alternative protocol for the Lewis acid-catalyzed cyclopropanation reaction of allylic alcohols, in which the uncatalyzed process is minimized [21]. The addition of $\text{Zn}(\text{CH}_2\text{I})_2$ (1 equiv) to an allylic alcohol (1 equiv) produced the iodomethylzinc alkoxide (Scheme 9). Methylene transfer from these less reactive species is triggered by the addition of a Lewis acid in catalytic amounts. Several achiral Lewis acids such as TiCl_4 , SnCl_4 , and BBr_3 were effective in inducing the cyclopropanation.

Conversely, the use of the titanium-derived chiral Lewis acid **15** produced the corresponding cyclopropane derived from aryl-substituted allylic alcohols in up to 90% ee (Scheme 10). This substoichiometric system is particularly effective with aryl-substituted allylic alcohols. However, the cyclopropanation of alkyl-substituted allylic alcohols led to lower enantiomeric excesses.

It is apparent that significant progress has been made towards the development of an efficient catalytic, asymmetric cyclopropanation using zinc-derived reagents but there is still room for much further improvement. More specifically, the design of better catalysts to increase the scope of the reaction and to improve the enantioselectivities is one of the top research priorities in this area. Furthermore, the simplification of reaction protocol would greatly contribute to make this approach attractive to synthetic chemists and competitive with the other asymmetric, catalytic cyclopropanation reactions.



Scheme 9



Scheme 10

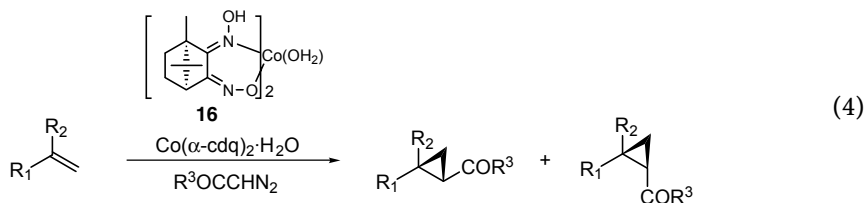
1.2

Metal-Catalyzed Decomposition of Diazo Compounds

Another efficient method to obtain metal carbenoid species is by treating diazo compounds with catalytic amounts of transition metals (see preceding two papers) [22, 23, 24]. Although α -diazo carbonyl compounds [23] are very useful precursors for this transformation, alkyl- or aryl-substituted diazo compounds can be also used [24, 25]. The most effective catalysts for this reaction are rhodium and copper based, but several other transition metals, possessing a vacant

coordination site, have also been tested. For example, complexes derived from Ru, Pd, Ni, Mo, Co, Re and W have been reported to be efficient catalysts for the cyclopropanation reaction of olefins using diazo compounds [26, 27]. Recently, Hossain and coworkers have reported the first example of an iron Lewis acid-catalyzed decomposition of ethyl diazoacetate and phenyldiazomethane to provide cyclopropanes with a predominant *cis* selectivity [28, 29]. Iron(II) porphyrin complexes were later found to be active catalysts for the cyclopropanation of alkenes using ethyl diazoacetate [30]. However, in this case, the *trans* cyclopropyl ester product was mainly observed. Some osmium and platinum complexes have also been reported to be useful in the cyclopropanation of styrene and related olefins with diazoesters, producing the *trans* isomer preferentially [31, 32, 33]. Asymmetric versions of these reactions have not appeared yet. Chiral cobalt and ruthenium complexes were reported to provide enantiomerically enriched cyclopropanes. Finally, many attempts to develop good chiral ligands derived from palladium catalysts have also been described, but with very little success. These chiral systems will be described in the next pages.

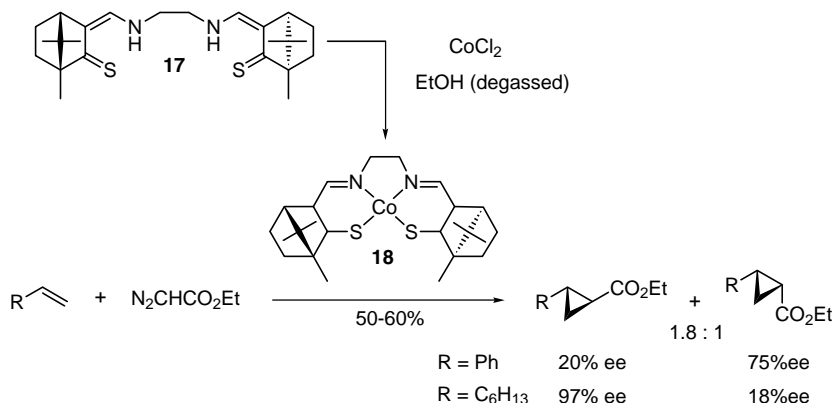
As early as in 1974, Nakamura, Otsuka and coworkers reported the enantioselective cyclopropanation of styrene with ethyl diazoacetate catalyzed by the bis[(1)-camphorquinone- α -dioximate]cobalt(II) **16** that gave the 2-phenylcyclopropane carboxylate in 75% ee for the *E* isomer and 67% ee for the *Z* isomer (Eq. (4)) [34, 35, 36, 37]. The catalyst proved to be useful for a wide range of conjugated dienes, 1,1-disubstituted olefins, as well as α,β -unsaturated esters and nitriles. The reaction occurred selectively at a terminal double bond conjugated with a vinyl, aryl or alkoxy carbonyl group. The reactions for which the enantioselectivities have been determined are shown below. Although the enantioselectivities were relatively high, the diastereoselectivities were low. As expected, the bulkier neo-pentyl diazoacetate increased the diastereocontrol up to 70:30 and the enantiocontrol up to 88 and 81% for the *E* and *Z* isomers, respectively.



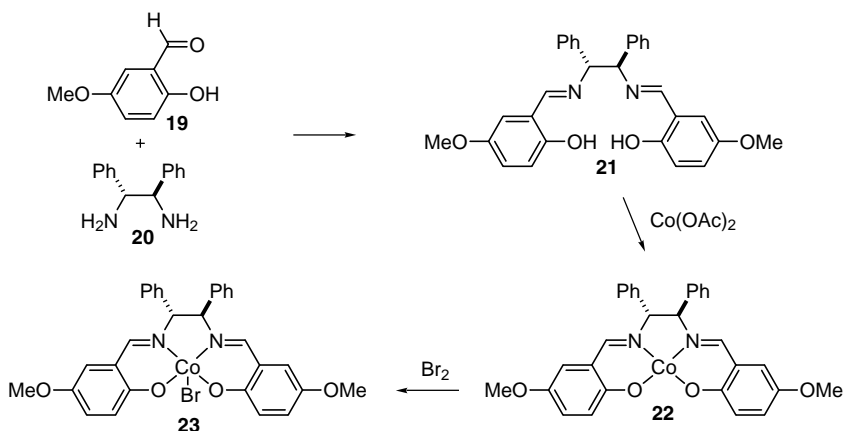
R ¹	R ²	Reagent	Yield (%)	dr (%) (<i>trans</i> : <i>cis</i>)	ee (%) (<i>trans</i>)	ee (%) (<i>cis</i>)
Ph	H	EtO ₂ CCHN ₂	92	46:54	75	67
Ph	H	neo-pentyl-COCHN ₂	87	70:30	88	81
Ph	H	PhCOCHN ₂	44	–	20	–
Ph	CO ₂ Me	EtO ₂ CCHN ₂	92	–	71	37
Ph	Ph	EtO ₂ CCHN ₂	95	–	70	–

Moderate yields and low ee's were observed with an α -diazo ketone and nitrile. These authors also investigated the use of a series of metal(II) complexes, including Co, Pd, and Ni, with chiral ligands derived from optically active amines, β -diketones or 1,2-dioximes. The enantioselectivities observed with these complexes for the cyclopropanation of styrene with ethyl diazoacetate were less than 15% (mostly in a range of 0–6%).

Recently, another cobalt(II)/camphor-derived complex was developed for performing the asymmetric cyclopropanation of olefins [38]. The complex **18** was prepared by reacting the ligand **17**, synthesized by condensation of (1*R*)-3-hydroxymethylbornane-2-thione and the corresponding diamine, with cobalt(II) dichloride hexahydrate in degassed ethanol (Scheme 11). The cyclopropane derivatives were obtained in 50–60% yield using 3 mol % of the catalyst **18** and ethyl diazoacetate in styrene or 1-octene as solvent. The diastereomeric ratios were low for both styrene and 1-octene.



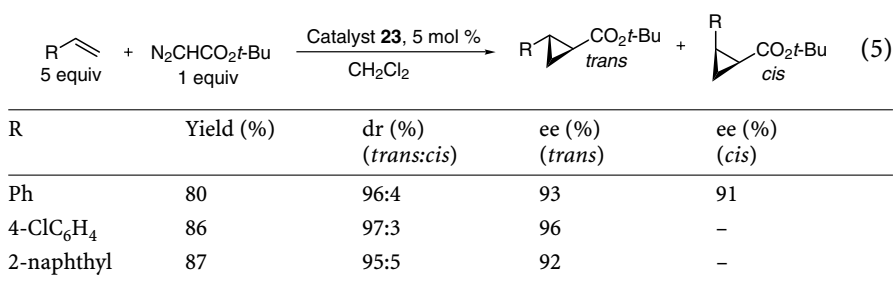
Scheme 11



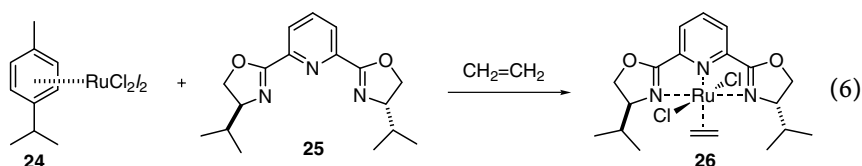
Scheme 12

More recently, Katsuki and coworkers have shown that (salen)Co(III) bromide **23** is an efficient catalyst for the asymmetric cyclopropanation of styrene derivatives [39, 40, 41]. The Co(III)-salen complex **23** was obtained from the oxidation of the corresponding Co(II)-salen complex **22** by bromine (Scheme 12). The Co(II)-salen complex **22** was synthesized from Co(OAc)₂ and the corresponding salen ligand **21** which, in turn, was prepared from (1*R*,2*R*)-1,2-diphenylethylenediamine (**20**) and the corresponding substituted salicylaldehyde **19**.

The cyclopropanation of styrene with *t*-butyl diazoacetate in the presence of 5 mol % of (salen)Co(III) bromide **23** produced the corresponding *trans*-cyclopropane-carboxylate, with high diastereomeric ratio and enantiomeric excess (Eq. (5)). The asymmetric cyclopropanations of other styrene derivatives also showed high enantioselectivities as well as high *trans*:*cis* selectivities. However, the reaction of disubstituted olefins, such as indene, was sluggish. The use of Co(III) instead of Co(II) seemed to be critical, since Nakamura reported that much lower enantioselectivities were observed with optically active (salen)cobalt(II) complexes.

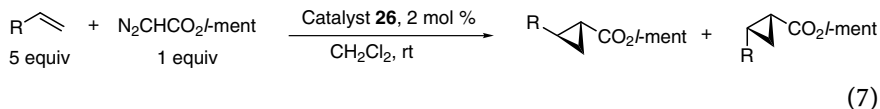


Nishiyama and coworkers reported that chiral ruthenium(II) bis(oxazolinyl)pyridine complexes were efficient catalysts for the asymmetric cyclopropanation reaction of terminal olefins [42, 43]. The *trans*-RuCl₂(pybox-*i*-Pr)(ethylene) complex **26** was produced from a mixture of optically active bis(2-oxazolin-2-yl)pyridine, (pybox-*i*-Pr) **25**, and [RuCl₂(*p*-cymene)]₂ **24** in an atmosphere of ethylene and proved to be a powerful catalyst for asymmetric cyclopropanation reactions, Eq. (6).



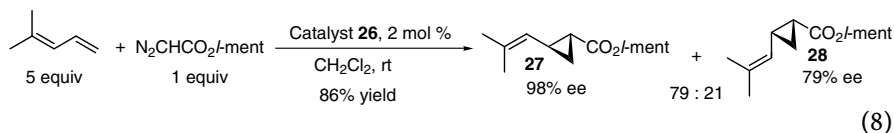
The best results for the cyclopropanation of styrene were observed with *l*-menthyl diazoacetate and 2 mol % of catalyst **26**. Under these conditions, the corresponding *trans*-phenylcyclopropane-1-carboxylate was isolated in 84% yield with excellent diastereoselectivity and enantioselectivity, Eq. (7). The *trans*-se-

lectivities in this case were significantly higher than with chiral copper complexes. Similar selectivities were observed using only 1 mol % of the catalyst. Styrene derivatives also gave very good results. Excellent diastereomeric ratios and enantioselectivities were found with aliphatic terminal olefins, but the yields were lower.

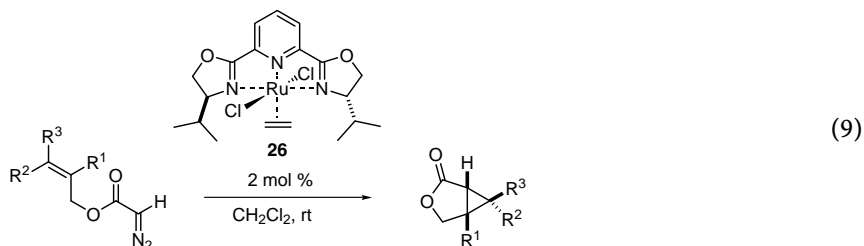


R	Yield (%)	dr (%) (<i>trans</i> : <i>cis</i>)	ee (%) (<i>trans</i>)	ee (%) (<i>cis</i>)
Ph	84	98:2	96	84
4-ClC ₆ H ₄	84	96:4	95	83
4-MeOPh	96	95:5	97	–
PhCH ₂	45	93:7	97	–
<i>n</i> -C ₃ H ₁₁	54	92:8	98	94

Conjugated dienes can be regioselectively cyclopropanated at the terminal double bond with excellent chemoselectivity to produce the corresponding vinylcyclopropanes **27** and **28** in 86% yield and with a moderate diastereomeric ratio, Eq. (8). The enantioselectivity for the *trans* isomer **27** was excellent. On the other hand, β -methylstyrene, 2,5-dimethyl-2,4-hexadiene, cyclopentene, and indene could not be cyclopropanated under the same reaction conditions.

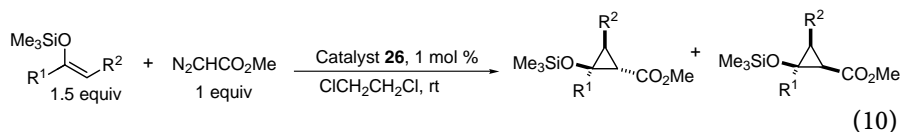


In spite of the low reactivity of 1,2-disubstituted and trisubstituted olefins in the intermolecular cyclopropanation, some allyl diazoacetates were easily cyclopropanated to give the corresponding 3-oxabicyclo[3.1.0]hexan-2-one derivatives [44]. The *trans* isomers gave good results (from 76 to 86% ee), but low enantioselectivities were observed for the *cis* derivatives, Eq. (9). The diazo substrates containing a 2-alkyl substituent did not undergo intramolecular cyclopropanation under a variety of reaction conditions. In these cases, carbene dimers were the only isolated products.



R ¹	R ²	R ³	Yield (%)	ee (%)
H	H	Ph	93	86
H	Ph	H	79	24
H	Me	Me	91	76
H	H	<i>n</i> -Pr	68	78
H	<i>n</i> -Pr	H	54	21
Me	H	H	0	–
Bu	H	H	0	–

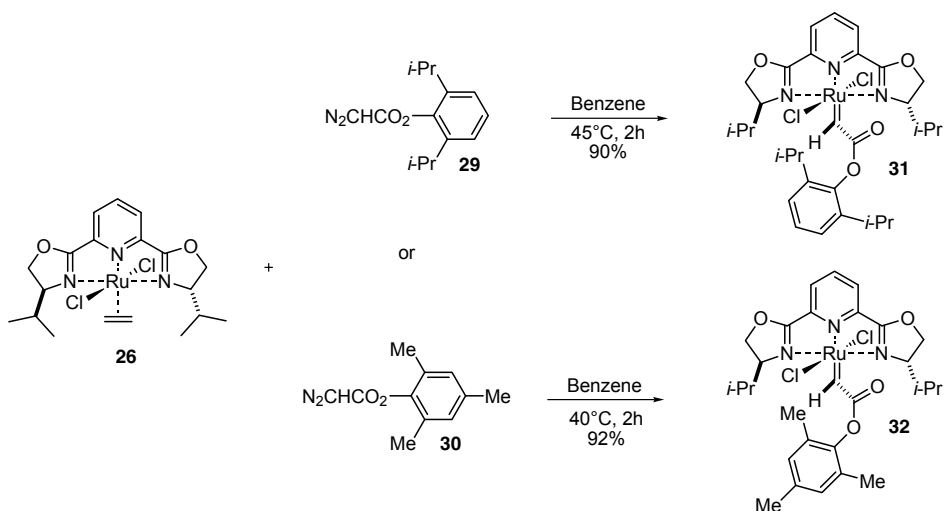
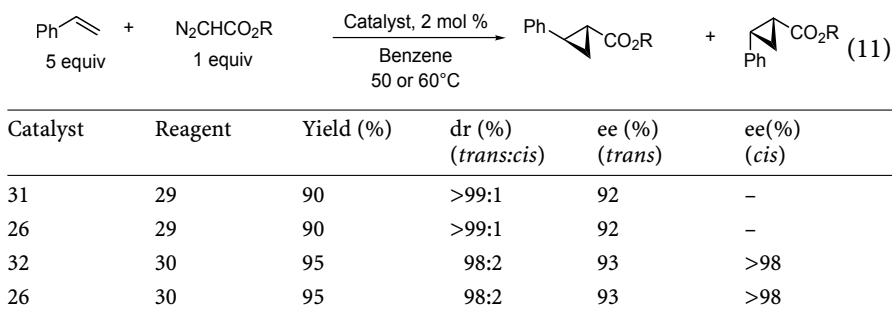
Very recently, Reissig has examined catalyst **26** with regard to the synthesis of non-racemic 2-siloxycyclopropanecarboxylate derivatives [45]. Catalyst **26** was active for the cyclopropanation of terminal enol ethers, but no cyclopropanated product was observed with internal enol ethers. The corresponding *trans* cyclopropane compound was isolated from the unsubstituted enol ether with moderate diastereoselectivity and moderate to low enantioselectivities, Eq. (10). Conversely, the corresponding *cis*-cyclopropane was preferentially formed from 1-substituted enol ethers with moderate diastereomeric ratios and enantioselectivities.



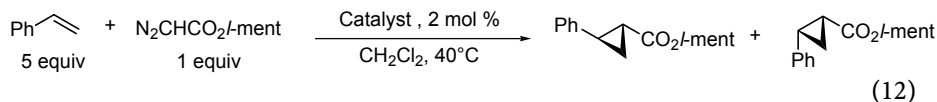
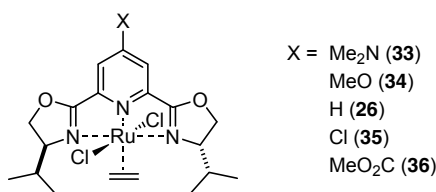
R ¹	R ²	Yield (%)	dr (%) (<i>trans</i> : <i>cis</i>)	ee (%) (<i>trans</i>)	ee (%) (<i>cis</i>)
H	H	44	72:28	41	13
Ph	H	75	36:64	53	43
H	Me	0			
Ph	Me	0			

Conversely, Nishiyama and coworkers have shown that the reactions of [RuCl₂(pybox)-(C₂H₄)] **26** with 2,6-di-*tert*-butyltolyl diazoacetate, 2,6-diisopropylphenyl diazoacetate (**29**), or 2,4,6-trimethylphenyl diazoacetate (**30**) gave the corresponding stable carbene complexes (**31** and **32**) in high yields (Scheme 13) [46].

These carbene complexes exhibited catalytic activity in the asymmetric cyclopropanation of styrene with the corresponding bulky aromatic diazoacetate. Very high diastereomeric ratios and enantioselectivities were observed with catalysts **31** and **32** as well as with the ethylene complex **26**, the reactions thereby producing the corresponding *trans*-phenylcyclopropanecarboxylate, Eq. (11).

**Scheme 13**

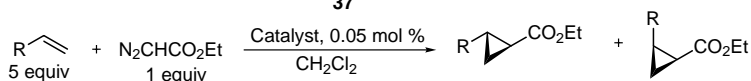
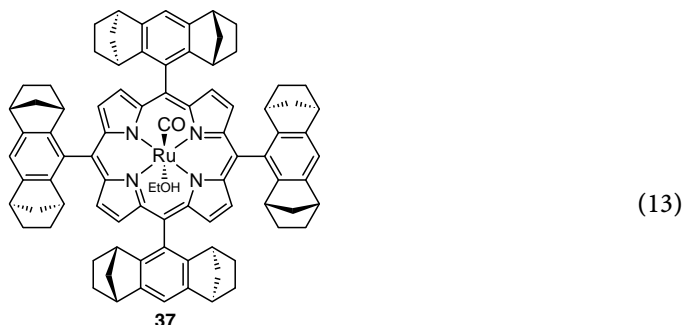
Nishiyama's group have also studied some structural modifications of the [RuCl₂(pybox)-(C₂H₄)] complex and electronic control by remote substituents far from the catalytically active center was observed [47]. It was found that electron-withdrawing groups increased the catalytic activity, but electron-donating groups decreased it. The enantiomeric ratios of cyclopropanes with the electron-withdrawing groups, X = Cl and CO₂Me (**35** and **36**), are higher than those observed with the electron-donating groups, X = OMe and NMe₂ (**33** and **34**), Eq. (12). However, the *trans*:*cis* ratios of the products were not affected by the nature of the aryl substituent. The intramolecular cyclopropanation with these catalysts also gave rise to similar trends.



Catalyst	Yield (%)	dr (%) (<i>trans:cis</i>)	ee (%) (<i>trans</i>)	ee (%) (<i>cis</i>)
33	79	94:6	84	38
34	89	96:4	90	67
26	93	97:3	93	79
35	93	97:3	94	83
36	95	96:4	97	85

Finally, Nishiyama and coworkers have reported that other chiral Ru(II) complexes gave lower selectivities than those observed with the [RuCl₂(pybox)-(C₂H₄)] complex **26** [48, 49].

Another very good chiral Ru(II) catalyst for the asymmetric cyclopropanation of styrene with ethyl diazoacetate was recently reported [50, 51]. The chiral ruthenium-porphyrin **37** was found to provide optically active phenylcyclopropane derivatives with a very high catalyst turnover number. A 96:4 *trans:cis* ratio of products was obtained with styrene and in the presence of only 0.05 mol % of the catalyst **37**. The ee of the *trans* isomer was 91%, Eq. (13). Similar results with high *trans:cis* selectivities and high enantioselectivities for the *trans* product have also been found with other substituted styrenes.



R	Yield (%)	dr (%) (<i>trans:cis</i>)	ee (%) (<i>trans</i>)	ee (%) (<i>cis</i>)
Ph	63	96:4	91	4
4-ClC ₆ H ₄	66	96:4	90	4
4-MeC ₆ H ₄	78	95:5	81	9
4-MeOC ₆ H ₄	61	94:6	85	8
α -methylstyrene	69	75:25	87	35

Very recently, Simmonneaux has reported that a chiral ruthenium-porphyrin complex is an active catalyst for cyclopropanation of styrene, but the corresponding cyclopropanes were produced with low to moderate enantiomeric excesses [52].

In 1978, Nakamura and coworkers studied the decomposition of the carbenoid prepared from ethyl diazoacetate and various palladium complexes [53]. They have found that the use of several chiral ligands did not induce any appreciable enantioselectivity when the cyclopropanation was carried out with ethyl diazoacetate and styrene. From these observations, it was postulated that the chiral ligand did not seem to be tightly bound to the active catalytic species.

Almost 20 years later, Cativiela investigated a series of chiral amino acidato Pd(II) complexes for cyclopropanation of styrene with diazoacetates (Fig. 1) [54]. In general, these catalytic systems provided good conversions (40–60% with 2 equiv of styrene) to afford the corresponding cyclopropyl derivatives, but with a low *trans* selectivity (\sim 2:1) and enantioselectivity (3–8% ee). The diastereoselectivities were slightly improved (2:1, *trans:cis*, 20% ee), with the use of chiral catalysts and chiral diazoacetate derivatives.

Recently, Denmark and coworkers have confirmed that asymmetric cyclopropanation with chiral palladium complexes was not efficient [55]. They reported a systematic study toward the development of an enantioselective diazomethane-based cyclopropanation reagent derived from bis(oxazoline)palladium(II) complexes. In addition to the novel carbon-bound complexes, several simple palladium chelates were synthesized and evaluated in the cyclopropanation of various electron-deficient olefins (Fig. 2). Although all catalysts were effective at inducing the cyclopropanation, the products obtained were racemic in all the

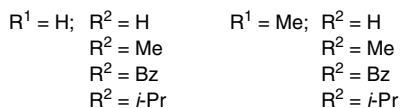
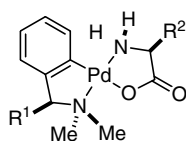


Fig. 1

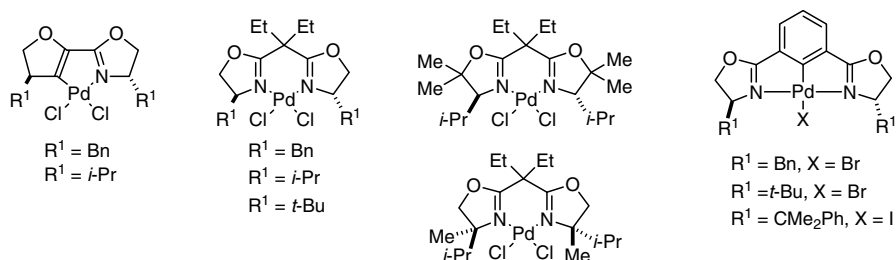


Fig. 2

cases. As postulated by Nakamura, these results were rationalized by invoking either partial or complete bis(oxazoline) decomplexation during the course of the reaction.

In conclusion, the ruthenium complexes are the best chiral catalysts developed so far with metals other than Cu and Rh. Excellent diastereo- and enantioselectivities were observed with some specific systems, but the scope of the intermolecular reaction is somewhat limited.

2

C-H Insertion

Metal carbenoids are not only involved in cyclopropanation reactions, but these species also give rise to insertion into C-H bonds [23] (see Chapters 26.1 and 26.2). Although the first catalysts were copper-based, the insertion of metal-associated carbenes into carbon-hydrogen bonds has undergone a renaissance with the advent of rhodium(II) carboxylate catalysts [56]. Metal-catalyzed enantioselective C-H insertions of carbenes have not been studied in great detail. Most of the efficient enantioselective versions of this reaction involve chiral rhodium complexes and until recently, the use of chiral catalysts derived from metals other than copper and rhodium for the asymmetric C-H insertion of metal-associated carbenes are still unexplored.

In 1996, Burgess and coworkers investigated different chiral catalysts, involving several transition metals, for the conversion of diazo compound **38** into **39** (Scheme 14) [57]. Their strategy relied on examining 96 potential systems using a microtitre plate format. They have tested five different ligands, three different bis(oxazolidine) ligands (**41–43**), a salen-type ligand (**45**) and sparteine (**44**), in combination with different metal salts and four different solvents. The complexes that were tested (other than copper and rhodium) were derived from silver(I), scandium(III), gold(I), lanthanum(III), and ytterbium(III). Scheme 14 shows the data that were obtained from the high throughput screen.

This procedure can only be used to generate leads for further investigations and the most encouraging complexes have been further optimized in the classical way. However, low to moderate yield and selectivities were usually observed.

Ligand	Metal salt	THF	Diastereomeric ratio (yield(%))			
			MeCN	CHCl ₃	MePh	
 41	AgSbF ₆	1.5 : 1 (45)	1.1 : 1 (54)	2.3 : 1 (6.7)	1.9 : 1 (25)	
	Sc(OTf) ₃	---	---	---	1.6 : 1 (36)	
	La(OTf) ₃	1.5 : 1 (12)	1.1 : 1 (0.3)	1 : 1.2 (27)	1 : 1.3 (19)	
	Yb(OTf) ₃	1.3 : 1 (0.7)	---	---	1 : 1.4 (0.4)	
 42	AgSbF ₆	2.7 : 1 (44)	1.2 : 1 (36)	1 : 1.1 (1.9)	1.1 : 1 (32)	
	Sc(OTf) ₃	1.1 : 1 (9.9)	---	1 : 1.2 (3.2)	1.6 : 1 (45)	
 43	AgSbF ₆	2.0 : 1 (10)	1.4 : 1 (8.0)	1 : 1.4 (7.9)	1 : 1.4 (36)	
	Sc(OTf) ₃	---	---	---	1 : 1.5 (43)	
 44	AgSbF ₆	1.7 : 1 (0.5)	1.7 : 1 (8.1)	1 : 1.2 (39)	1 : 1.4 (37)	
	Sc(OTf) ₃	3.4 : 1 (0.9)	1.3 : 1 (0.1)	1 : 1.3 (2.3)	1 : 1.1 (34)	
 45	AgSbF ₆	1.8 : 1 (15)	1.3 : 1 (3.4)	1.2 : 1 (0.5)	1.4 : 1 (14)	
	Sc(OTf) ₃	1 : 1.5 (0.2)	1.7 : 1 (0.1)	1.3 : 1 (0.1)	---	
	AuCl(SMe ₂)	1.0 : 1 (5.8)	1 : 1.1 (1.8)	1 : 1.3 (22)	1 : 1.4 (14)	

Scheme 14

The best result was obtained with bis(oxazolidine) ligand **42** and AgSbF₆ in THF, which provided the product **40** in a 3.5:1 diastereomeric ratio and 75% yield.

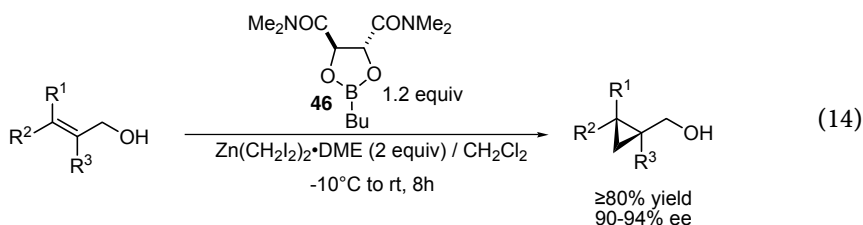
In conclusion, a general and efficient methodology has not yet been developed with chiral metal complexes involving metals other than copper and rhodium, for the asymmetric C-H insertion of carbenoids.

3 Principal Alternatives

Optically active cyclopropanes may be obtained from the enzymatic or microbial resolution of some three-membered ring [1].

A number of chiral auxiliary-based approaches for the Simmons-Smith cyclopropanation have been reported and many of them offer the advantage of producing enantiomerically pure cyclopropyl derivatives after the cleavage of the

auxiliary. Chiral allylic ethers, acetals, α,β -unsaturated acylmetals, enamines, and enol ethers have been successfully converted into chiral non-racemic cyclopropanes [6]. Most of these chiral auxiliaries are based on the ability of proximal basic groups to direct the methylene transfer, from the zinc reagent to a nearby olefin. Several stoichiometric chiral additives for the enantioselective cyclopropanation of allylic alcohols have been reported. The most efficient chiral ligand is the dioxaborolane **46**, prepared from the commercially available *N,N,N',N'*-tetramethyltartaric acid diamide and butylboronic acid [58, 59]. The corresponding substituted cyclopropylmethanols of a variety of allylic alcohols are produced with excellent enantioselectivities (90–93% ee) when a mixture of the alcohol and ligand **46** is added to the preformed halomethylzinc reagent, Eq. (14). This methodology is one of the most practical to date for the preparation of enantiomerically enriched substituted cyclopropylmethanols.



For example, it has been used to elaborate the chiral cyclopropanes subunits of Curacin A [60], and of the structurally fascinating FR-900848 [61] and U-106305 [62]. The chiral dioxaborolane-derived ligand was also effective to synthesize 1,2,3-substituted cyclopropanes [63]. Excellent to outstanding diastereoselectivities and enantioselectivities were observed when a variety of allylic alcohols were treated with the reagent formed by mixing 1,1-diodoethane and diethylzinc. It was also shown that functionalized 1,1-diodoalkanes could also be used in this reaction.

The intramolecular C-H insertion of chiral diazo compounds has been catalyzed by several metal salts derived from Ag(I), Ni(II), Pd(II), and Co(III) [64, 65]. The use of some stoichiometric chiral Fischer carbene complexes has also been reported to give the corresponding cyclic products with good selectivities [66, 67].

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Chapter 17

Aziridination

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Keywords: Aziridine, Diimine ligands, Bisoxazoline, Copper

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1

Introduction

Compared to the enormous level of progress that has been made in the design and study of chiral epoxidation catalysts (Chaps. 19.1–19.3), it must be said that the field of asymmetric aziridination catalysis has remained relatively undeveloped. This can in no way be attributed to a lower level of interest in aziridines as chiral building blocks for synthesis. Indeed, the reactivity [1] and synthesis [2] of these targets have long been a subject of interest to synthetic chemists since, in many ways, aziridines rival epoxides in their versatility as electrophilic reagents. The reason for the relative lack of progress lies clearly in the fact that the discovery of useful methods for asymmetric aziridination has proven to be exceedingly difficult. Whereas there are a large number of biological and industrial epoxidation systems that served as a foundation for research in asymmetric epoxidation catalysis, no such guidance has been available to help influence the design of aziridination catalysts. In fact, it was only very recently that a synthetically useful catalytic system for the direct synthesis of *racemic* epoxides was devised [3].

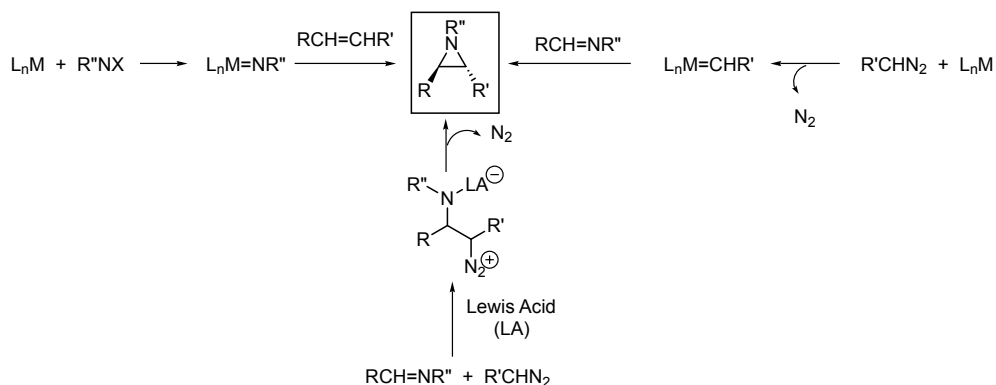


Fig. 1

Three fundamentally different approaches to the design of asymmetric catalysts for aziridination have been taken (Fig. 1). Transfer of a nitrene group to an olefin – the formal analog of oxo-transfer to generate epoxides – has received the greater share of the attention thus far. More recently, enantioselective reactions between diazo esters and imines mediated either by carbene transfer catalysts or Lewis acid catalysts have been demonstrated. While as yet no widely effective or general method has emerged, the foundation certainly has been laid for a breakthrough in this field. This chapter will provide an overview of progress made to date with all three strategies.

2 Aziridination via Imido Transfer Catalysis

Based on a most simple analysis, one might approach the design of a metal-imido transfer catalyst by considering the corresponding reactivity of metal-carbenoid complexes or metal-oxo complexes (Fig. 2). It is interesting, in fact, that all of the imido transfer catalysts identified thus far fall into the general category of olefin epoxidation or cyclopropanation catalysts.

2.1 Oxo-Transfer Type Catalysts

In 1983, Groves demonstrated the stoichiometric aziridination of alkenes from a manganese-imido complex generated *in situ* from an isolable (porphyrin)manganese-nitrido intermediate (Scheme 1) [4]. This reactivity has recently been exploited with success by DuBois, Carreira and coworkers in the context of (salen)manganese-derived systems for the amination of enol ether derivatives (Scheme 2) [5, 6, 7, 8]. Although not isolated, aziridine intermediates are probably involved in these reactions.

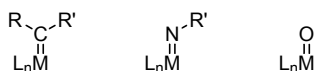
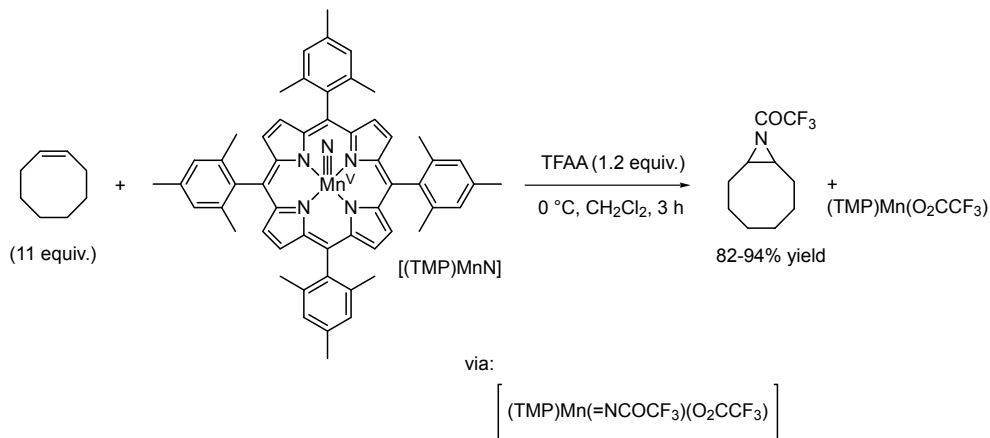
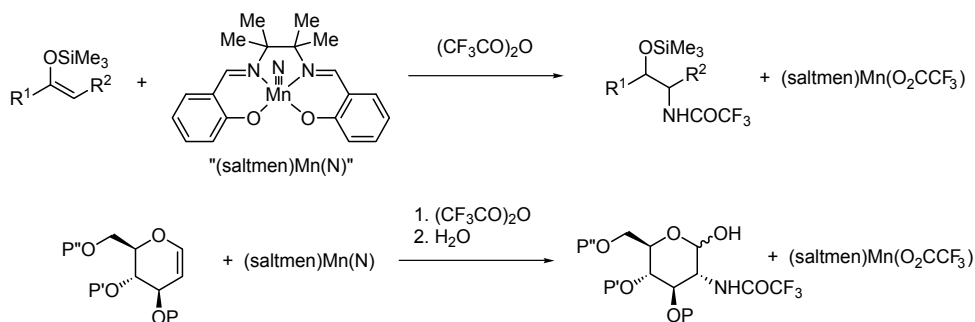


Fig. 2



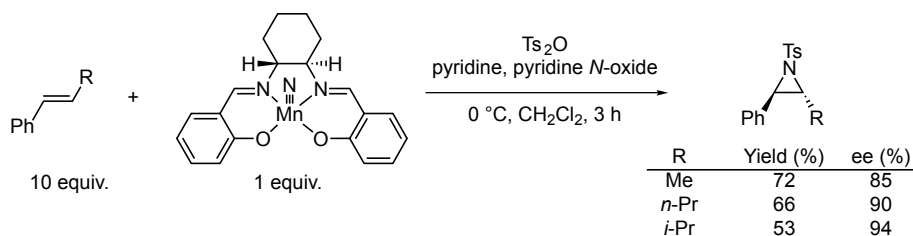
Scheme 1



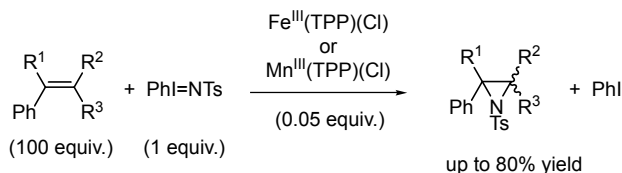
Scheme 2

Chiral analogs of the Carreira systems were studied by Komatsu, who reported that good levels of enantioselection could be obtained in the aziridination of certain *trans*-olefins with a 1,2-diaminocyclohexane-derived (salen)Mn-nitrido complex (Scheme 3) [9].

All of the examples described above involve stoichiometric imido transfer to the alkene substrate. A crucial advance in the area of catalytic oxidation was made by Mansuy, who disclosed the first example of catalytic aziridination of alkenes in 1984 [10]. Both iron- and manganese-based porphyrin complexes were found



Scheme 3



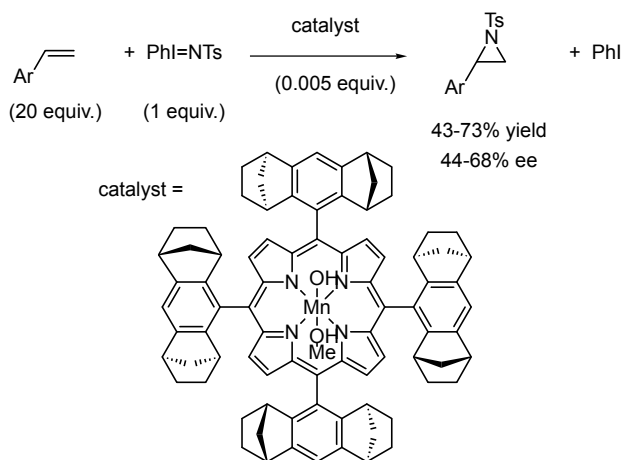
TPP = tetraphenylporphyrin

Scheme 4

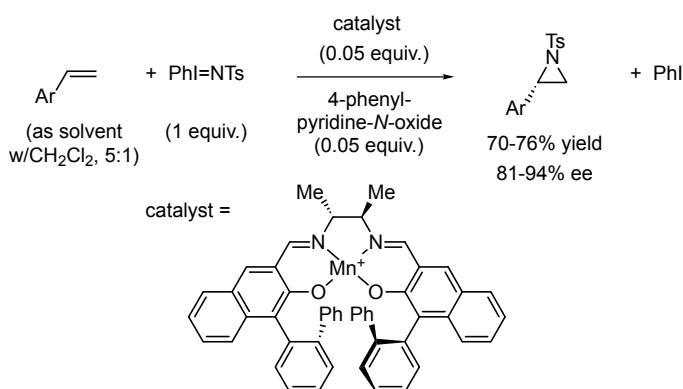
to catalyze nitrido transfer from *N*-*p*-(tosylsulfonyl)imino]phenyliodinane (PhI=NTs) with moderate efficiency (Scheme 4). While PhI=NTs is hardly an ideal reagent for aziridination given its expense, insolubility, and the fact that it generates a relatively heavy stoichiometric by-product (PhI), it has proven to be uniquely effective for catalytic imido transfer reactions [11]. To date, use of the far more practically attractive reagent Chloramine T (NaClNTs) has not been reduced to practice with metal catalysts. The identification of synthetically useful nitrene sources for catalytic asymmetric aziridination remains a central problem in this field.

Although a large number of chiral porphyrin catalysts has been developed for study in asymmetric epoxidation chemistry [12], to date only one example has been applied to aziridination. In that instance, Lai and coworkers reported the use of the Halterman porphyrin catalyst in the aziridination of styrene derivatives with moderate enantioselectivity (Scheme 5) [13].

The more thoroughly developed salen-based catalysts have also been studied in the context of aziridination, albeit with limited success. While Burrows observed no measurable enantioselection in the aziridination of styrene derivatives using simple chiral (salen)Mn catalysts derived from 1,2-phenylethylenediamine [14], Katsuki encountered some success (up to 28% ee in the aziridination of styrene) with more complex derivatives of the same diamine [15]. Substantially improved enantioselectivities were observed with a less hindered diamine backbone associated with highly optimized chiral salicylide elements. Thus, up to 94% ee has been obtained in the aziridination of styrene with a 2,3-diaminobutane-derived catalyst (Scheme 6) [16]. Incorporation of catalytic levels of a py-



Scheme 5



Scheme 6

ridine *N*-oxide derivative proved critical for the attainment of high enantioselectivity. Although very little is known with regard to the scope of this system, the preliminary report [16] indicates that it may be quite limited. Nonetheless, it is apparent that (salen)Mn-based catalyst systems are quite promising and merit further investigation for asymmetric aziridination.

2.2

Cyclopropanation Type Catalysts

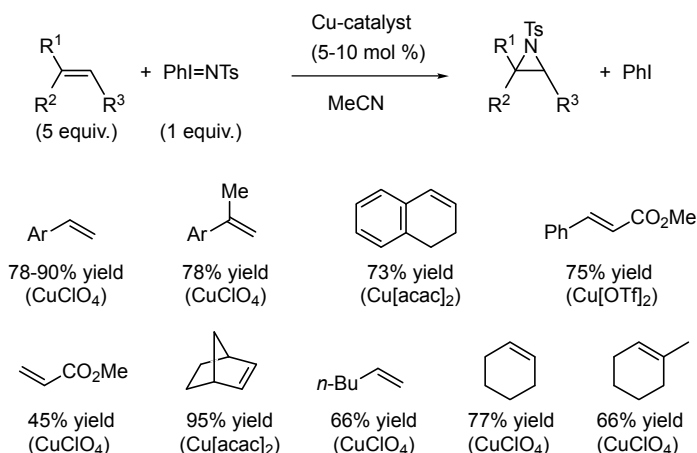
A crucial discovery in aziridination catalysis was made by Evans in the early 1990s, when he demonstrated that low-valent metal ions typically used for cyclopropanation were competent catalysts for the aziridination of alkenes with PhI=

NTs [17, 18]. Simple copper(I) and copper(II) salts were found to be effective catalysts for the preparation of a wide range of racemic aziridines (Scheme 7). More recently, rhodium-based catalysts have been applied with success to the reaction of $\text{PhI}=\text{NNs}$ with alkenes [19]. Along with Sharpless's recently-disclosed bromonium ion-catalyzed reaction [3], the copper-catalyzed aziridination of olefins with $\text{PhI}=\text{NTs}$ is probably the most general catalytic method devised thus far for the direct synthesis of racemic aziridines from alkenes.

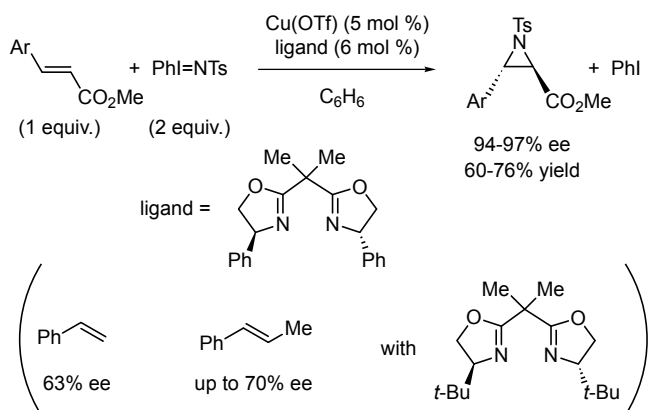
Given the significant existing knowledge-base in asymmetric catalytic cyclopropanation (Chap. 16), the discovery that metal ions useful for catalysis of carbene transfer to alkenes were also effective for nitrene transfer to the same substrates opened a clear new direction for research in asymmetric aziridination. Brief mention of the asymmetric catalysis of the aziridination of styrene was made in two early reports on (bisoxazoline)copper-catalyzed asymmetric cyclopropanations [20, 21], and subsequently new methods for copper-catalyzed asymmetric aziridination were revealed in two independent studies published simultaneously by Jacobsen and Evans [22, 23].

The Evans system employs chiral bisoxazoline ligands with copper(I) triflate. Exceptionally high levels of enantioselection were observed in the aziridination of cinnamate ester derivatives (Scheme 8), but thus far no other substrate classes have been demonstrated to undergo aziridination with synthetically-useful levels of stereoinduction.

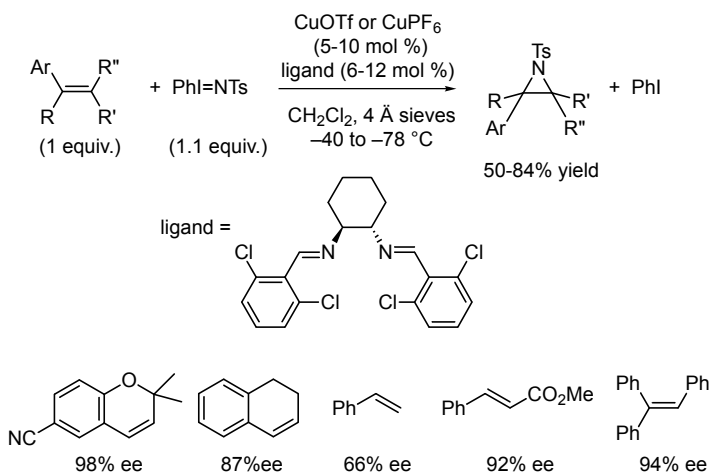
The Jacobsen system employs 1,2-diimine derivatives – a previously undeveloped class of chiral ligands – with copper(I) salts. The optimal diamine precursor was found to be 1,2-diaminocyclohexane, and among the large number of benzaldehyde derivatives examined, [24] ligands prepared from 2,6-dichlorobenzaldehyde proved most enantioselective in promoting catalysis of the aziridination reaction by Cu(I) salts. Although again the scope of the reaction was found



Scheme 7



Scheme 8



Scheme 9

to be limited, high levels of enantioselection were observed for alkenes with a variety of substitution patterns (Scheme 9) [22, 25]. The presence of at least one aromatic group in conjugation to the alkene is a strict requirement for high enantioselection, a phenomenon that may be tied to the observation of attractive aromatic-aromatic interactions between the ligand and substrate in both solution and the solid state [26].

At least two reasonable mechanisms for copper-catalyzed aziridination using PhI=NTs can be postulated (Fig. 3). In one, copper is a redox catalyst and aziridination proceeds through a discrete, high-valent copper-imido intermediate (mechanism a). Alternatively, the copper catalyst may serve only as a Lewis acid

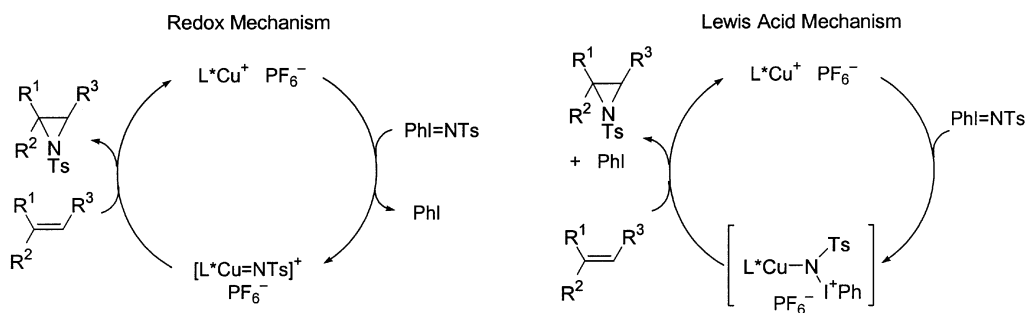
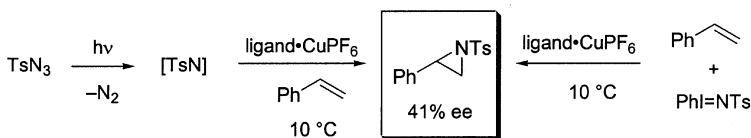


Fig. 3



Scheme 10

for activation of the hypervalent iodine reagent. Mechanistic analysis of the (diimine)Cu-catalyzed aziridination reaction provided support for the former, redox mechanism [24]. Thus, aziridination of styrene employing either PhI=NTs or photogenerated nitrene [NTs] occurred with the same level of enantioselection with a given chiral ligand, thereby precluding the presence of the aryl iodide component of PhI=NTs in the ee-determining transition state assembly (Scheme 10). Also, differently substituted ArI=NTs derivatives all afforded the same ees with a representative sampling of substrates. A surprisingly close correlation was observed between ees obtained in cyclopropanation and aziridination reactions of 1,2-dihydronaphthalene with a range of different chiral diimine ligands, raising the interesting possibility that these two different reactions might in fact proceed through similar transition structure assemblies [24].

3

Aziridination via Carbene Transfer Catalysis

The catalytic transfer of carbenes to imines (Fig. 4) represents a method for the preparation of aziridines complementary to the imido transfer strategies summarized above. The synthetic accessibility of imines and diazocarbonyl compounds, combined with the relative cleanliness of diazo chemistry and the inherent convergence associated with the coupling of two potentially complex reaction partners offer considerable incentive for developing this approach.

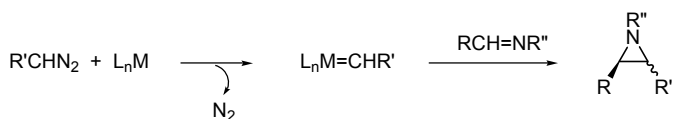
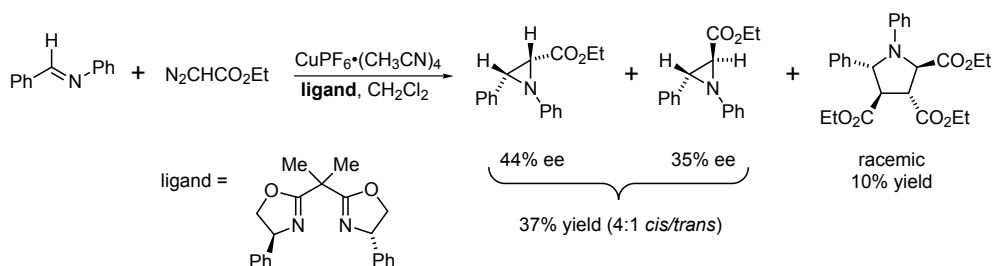


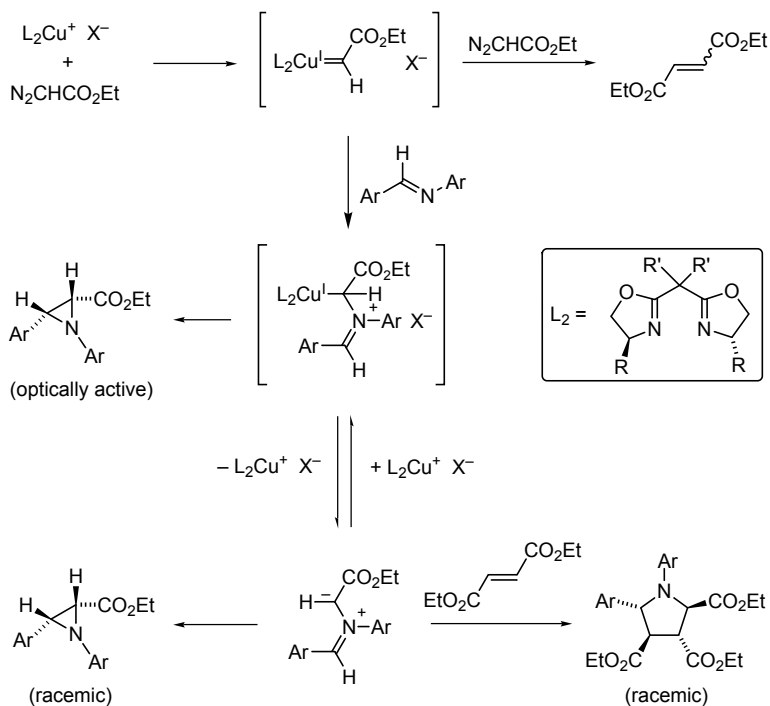
Fig. 4



Scheme 11

However, at this stage relatively little progress has been made in research on asymmetric catalytic carbene transfer to imines. In 1995, Jacobsen and Jorgensen reported independently that reaction of ethyl diazoacetate with selected imines can be catalyzed by copper salts [27, 28]. In the former case [27], moderate levels of enantioselection were found to be imparted by bisoxazoline ligands associated with the copper catalyst (Scheme 11). The observation of racemic pyrrolidine byproducts in the reaction was taken to support a mechanism of catalysis involving initial formation of a copper-bound azomethine ylide intermediate (Scheme 12). Collapse of this intermediate to the optically active aziridine apparently competes with dissociation of the copper to a free azomethine ylide. The latter can react with fumarate formed by diazoester decomposition in a dipolar cycloaddition to afford racemic pyrrolidine.

A different and very appealing strategy for enantioselective carbene transfer to imines has been devised by Aggarwal in an extension of his aldehyde epoxidation methodology (Chap. 18.3) [29]. In this approach, carbene transfer is mediated by a chiral sulfide, with the ee-determining step in the aziridination being reaction of an intermediate sulfur ylide with the imine (Fig. 5). Excellent enantioselectivities and moderate diastereoselectivity were obtained in the reaction of phenyldiazomethane with benzaldehyde imine derivatives (Scheme 13). Although the scope of this method is limited at this stage to the preparation of stilbene imine derivatives, the levels of asymmetric induction for aziridination are certainly among the highest reported to date for any catalytic method.



Scheme 12

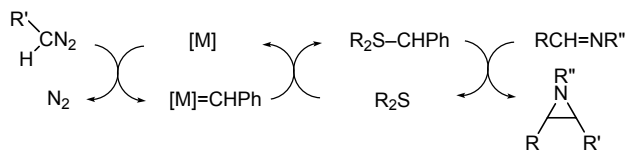
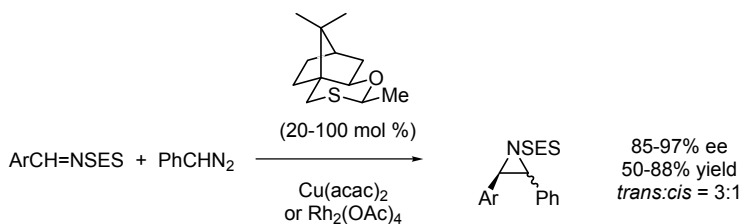


Fig. 5



SES = β -(trimethylsilyl)ethanesulfonyl

Scheme 13

4 Aziridination by Lewis Acid Catalysis

A new pathway for catalytic aziridination was uncovered recently by Brookhart and Templeton [30]. Standard Lewis acids such as BF_3 , AlCl_3 , and TiCl_4 were found to promote the reaction of ethyl diazoacetate with imines to generate the corresponding aziridines in good yield. A simple mechanism involving imine activation and alkylation by the diazo compound was advanced to account for this result (Fig. 6).

A screen of chiral Lewis acids was carried out by Jorgensen, but this effort failed to reveal any effective enantioselective catalysts [31]. However, very recently Wulff disclosed an extremely exciting result in the VAPOL- BH_3 catalyzed reaction between ethyl diazoacetate and imines (Scheme 14) [32]. Although the details had not been published at the time this chapter was written, it seems likely that this method will constitute an important breakthrough and establish a new direction for future research in the field of asymmetric aziridination catalysis.

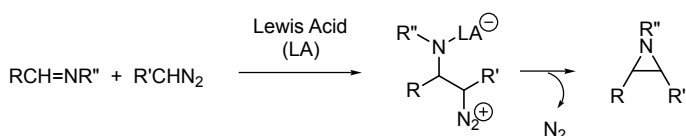
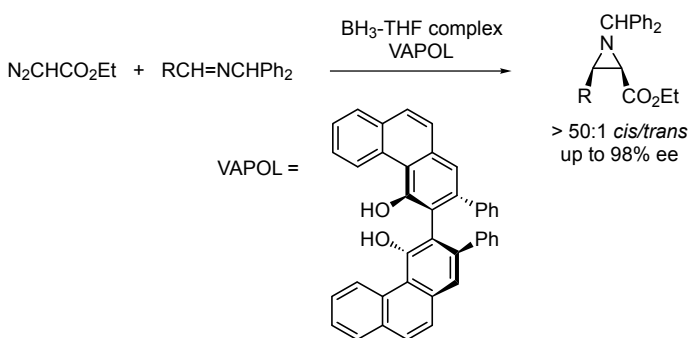


Fig. 6



Scheme 14

5

Conclusion

Three different strategies for solving the asymmetric aziridination problem have been advanced. Although at this stage none of the three has been refined into a widely useful synthetic method, the foundation is certainly laid for continued progress. Future research will need to focus not only on the development of more enantioselective and broadly effective catalyst systems, but also on the identification of practical reagents for the assembly of the aziridines.

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Chapter 18.1

Epoxidation of Allylic Alcohols

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Keywords: Epoxidation, Epoxy alcohol, Allylic alcohol, Titanium-mediated epoxidation, Titanium tartrate complex, Kinetic resolution, Ligand acceleration

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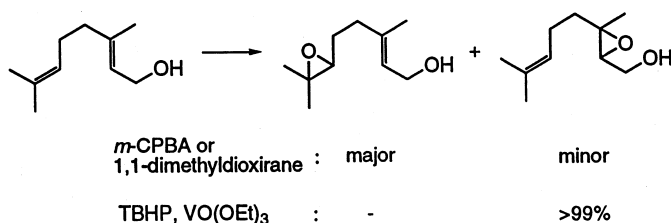
1 Introduction

Various nucleophiles react with epoxides stereospecifically to give 1,2-difunctionalized products, establishing the stereochemistry of two vicinal carbons; accordingly, optically active epoxides serve as useful synthetic intermediates for the construction of wide range of enantiopure compounds. Thus, the synthesis of optically active epoxides is the very important objective in organic synthesis [1, 2, 3, 4, 5, 6, 7]. Although there are many methods for this purpose available today, epoxidation of olefins is the most important one from the synthetic point

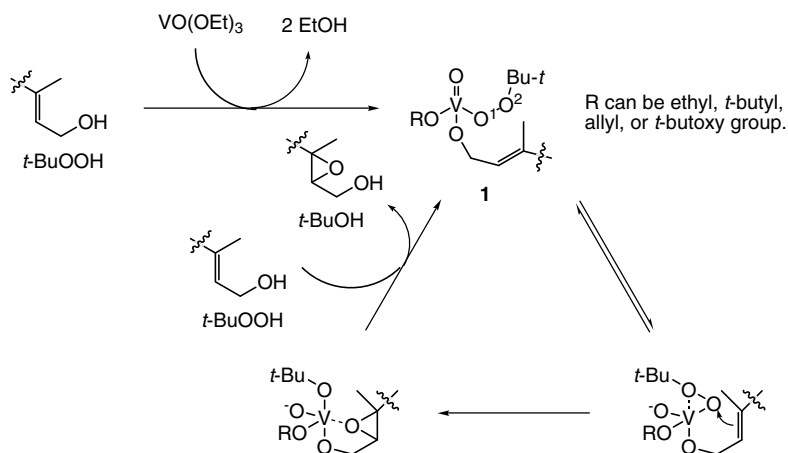
of view. In particular, metal-catalyzed epoxidation of allylic alcohols is of high synthetic value for the following reasons: (i) easy availability of allylic alcohols in a stereocontrolled fashion; for example, *E*- and *Z*-allylic alcohols can be prepared stereoselectively from aldehydes by using the Wittig reaction as a key step; (ii) mild reaction conditions: many functional groups tolerate the reaction conditions required for the metal-catalyzed epoxidation; (iii) formation of a three consecutively oxygenated carbon structure: these oxygen functionalities (epoxide and hydroxy groups) can be readily substituted with nucleophiles in regio- and stereo-selective manners, thus making epoxy alcohols remarkably versatile synthetic intermediates.

The isolated double bond is more reactive toward electrophiles than the double bond having a hydroxy group at the allylic carbon because the interaction between the π -orbital of the double bond and the σ^* -orbital of the C-O bond lowers the level of HOMO of the allylic alcohol. Therefore, for example, epoxidation of geraniol with peracids or dioxiranes occurs at the isolated double bond preferentially. However, treatment of geraniol with *tert*-butyl hydroperoxide (TBHP) in the presence of a metal catalyst such as VO(OR)₃ gives 2,3-epoxygeraniol exclusively, despite low reactivity of the C2-double bond (Scheme 1) [8,9]. Reversal of regioselectivity is explained as follows (Scheme 2) [10]. Exchange of the ligand of metal alkoxides with alcohol generally occurs smoothly and, in the vanadium-catalyzed epoxidation of allylic alcohols, alkoxide exchange gives an intermediate vanadium species **1** loaded with allyl alcohol and TBHP (remember that TBHP is a kind of alcohol). Coordination of the distal oxygen (O²) in **1** to vanadium ion activates peroxide and promotes intramolecular epoxidation, wherein the attack of the C2-double bond on the peroxide is entropically more favored than that of the C6-double bond. Finally, exchange of the resulting epoxy alkoxide and *tert*-butyl alkoxide with allylic alcohol and TBHP completes catalytic cycle, giving a 2,3-epoxy alcohol as the product. In this cycle, the alkoxide ligand (RO) does not participate in the oxygen atom transfer reaction at all, though it is located close to the reaction site during the reaction. Therefore, the oxygen atom transfer reaction is expected to proceed in an asymmetric atmosphere, if this bystander ligand is replaced by an optically active ligand.

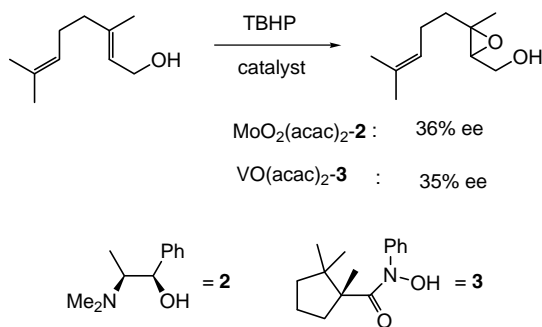
Along this line, two pioneering studies on asymmetric epoxidation (AE is used in this chapter for short) of allylic alcohols have been reported by Yamada [11] and Sharpless [12], independently (Scheme 3). Although the enantioselectivity



Scheme 1



Scheme 2



Scheme 3

tivity in these reactions was modest, these examples demonstrated that metal-mediated AE was a promising approach to the synthesis of optically active epoxy alcohols.

The epoxidation using optically active hydroperoxide both as chiral source and oxidant has also been studied as an alternative approach to metal-mediated AE of allylic alcohols, but there is still much room for improvement in this approach [13].

2 Asymmetric Epoxidation of Allylic Alcohols

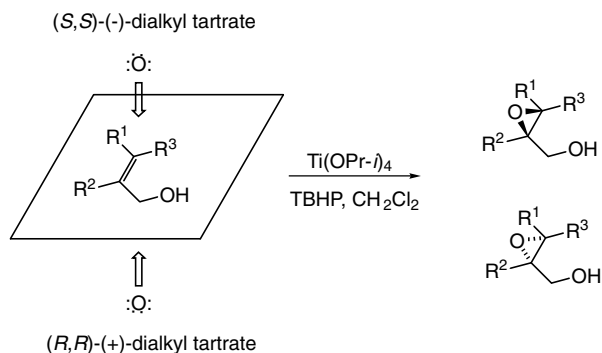
In 1980, a highly enantioselective epoxidation of allylic alcohols was first reported by Katsuki and Sharpless [14]. This successful result was obtained by the use of a titanium-tartrate complex as the catalyst which has led by the following con-

siderations and serendipitous discoveries [15, 16, 17]: (i) A metal alkoxide having more than two alkoxy ligands can be a catalyst for the AE of allylic alcohols (Scheme 2). In particular, the use of metal tetra- or pentaalkoxides such as $\text{Ti}(\text{OR})_4$ or $\text{Ta}(\text{OR})_5$ was considered to be advantageous because they allow the use of an optically active diol or triol which can form stable chelate complexes with these metal alkoxides, as a chiral ligand. Such stable chelate formation was expected to suppress the *in situ* formation of the undesired metal species which might catalyze non- or low enantioselective epoxidation process. (ii) The titanium complex bearing a multidentate ligand such as pyridine-2,6-dicarboxylic acid or dialkyl tartrate was found to show higher catalytic activity than the parent titanium tetraalkoxide in the preliminary experiment. This is the first example for the enhancement of the catalytic activity of a metal complex by ligand exchange. This phenomenon is now called as ligand acceleration [15]. This ligand acceleration promoted the otherwise disregarded titanium complex to an excellent catalyst for AE. Ligand acceleration was not observed in the epoxidations using hafnium, vanadium, niobium, or tantalum complexes as a catalyst.

2.1

General Aspects of Titanium-Catalyzed Asymmetric Epoxidation of Primary Allylic Alcohols

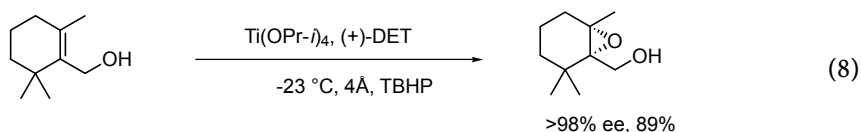
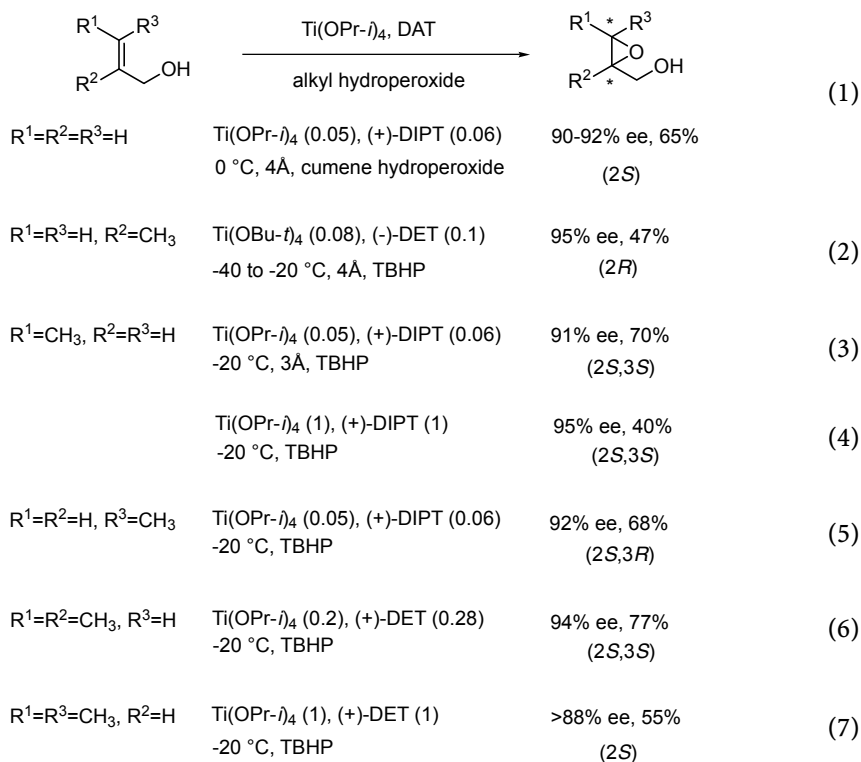
Epoxidation of primary allylic alcohols using a titanium tetrakisopropoxide, dialkyl tartrate (DAT), and TBHP system generally proceeds with high enantioselectivity, greater than 90% ee except for some substrates (*vide infra*) and the sense of enantioface selection is determined by the chirality of the DAT used (Scheme 4). When an allylic alcohol is described with the hydroxymethyl group at the bottom right, oxygen atom transfer occurs from the bottom side in the reaction using (*R,R*)-(+)-DAT and from the top side in the reaction using (*S,S*)-(-)-DAT. There is no exception in the reactions of achiral allylic alcohols to this empirical rule on stereochemistry [3, 4, 6]. However, epoxidation of some chiral allylic alcohols shows unusual face selectivity, as discussed later.



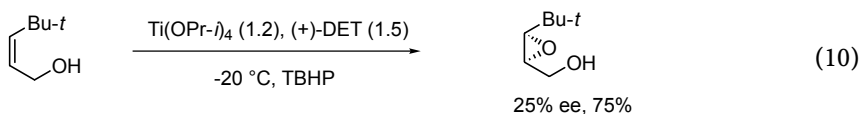
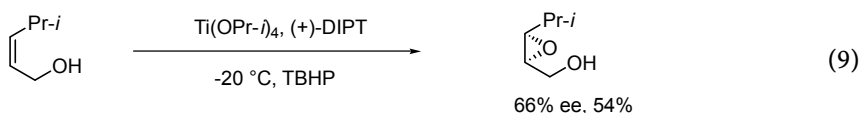
Scheme 4

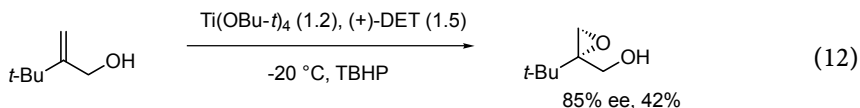
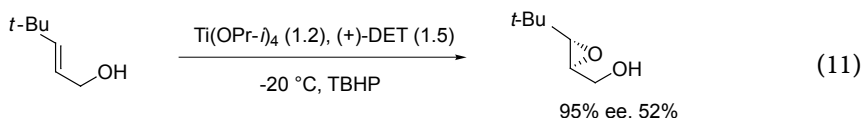
Titanium-catalyzed epoxidation can be performed in a catalytic manner like other metal-catalyzed epoxidation, but the first reported titanium-tartrate mediated epoxidation was a stoichiometric reaction because of the high sensitivity of the titanium-tartrate complex to water. Thus, catalytic AE was first realized when the reaction was performed in the presence of 3 Å or 4 Å molecular sieves [18]. Catalytic AE has the following advantages over the stoichiometric reaction: (i) The work-up procedure is easier, especially when the resulting epoxy alcohols are highly water soluble. (ii) Higher substrate concentrations are possible. (iii) Products can be derivatized *in situ* as needed. (iv) Many Lewis acid-sensitive epoxy alcohols tolerate the catalytic conditions. (v) The catalytic reaction is more economic: use of smaller amounts of reagents and solvent. In spite of these limitations, the stoichiometric reaction is still used in many organic syntheses probably because all the reagents required for the reaction are cheap and stoichiometric reactions show 1–5% better enantioselectivity than catalytic reactions in most cases. It should be noted that use of 10–20% excess of tartrate to titanium alkoxide has been recommended for this epoxidation to run successfully in either catalytic or stoichiometric conditions.

The following examples are representative of AE of achiral allylic alcohols (Eqs. 1 to 8). Regardless of substitution pattern of the olefinic parts, a high enantioselectivity of >90% ee is realized, except for the epoxidation of allylic alcohols bearing a *Z*-substituent (R^3) (see below). Diisopropyl tartrate (DIPT), diethyl tartrate (DET), and dimethyl tartrate (DMT) can be used equally as a chiral source. This description is, however, limited to AE of primary allylic alcohols and use of tartaric acid esters having a bulky ester alkyl group such as dicyclohexyl tartrate (DCHT) or DIPT is recommended for epoxidation of secondary allylic alcohols (see the next section) [3, 4, 6, 18, 19]. Although catalytic epoxidation is always preferable, the epoxidation of allyl alcohol or 2-substituted allyl alcohol is, in particular, recommended to be carried out in a catalytic manner, because the titanium-DAT complex possesses Lewis acidity and the resulting terminal epoxide is sensitive to nucleophilic epoxide opening in the presence of Lewis acid catalyst (Eqs. 1 and 2) [18]. Use of $Ti(OBu-t)_4$ instead of $Ti(OPr-i)_4$ reduces the side reaction of nucleophilic epoxide opening and increases the yield of the epoxide (Eq. 2) [20]. Use of $Ti(OBu-t)_4$ is, however, recommended only for the epoxidation of primary allylic alcohols [21]. As a terminal oxidant, TBHP is the most widely employed since its use generally shows acceptable enantioselectivity, its anhydrous decane solution is commercially available, and furthermore it leaves volatile *tert*-butyl alcohol that can be readily removed under reduced pressure, after oxygen atom transfer. Cumene hydroperoxide and trityl hydroperoxide can also be used as an oxidant and, for some examples, they show better enantioselectivity than TBHP.

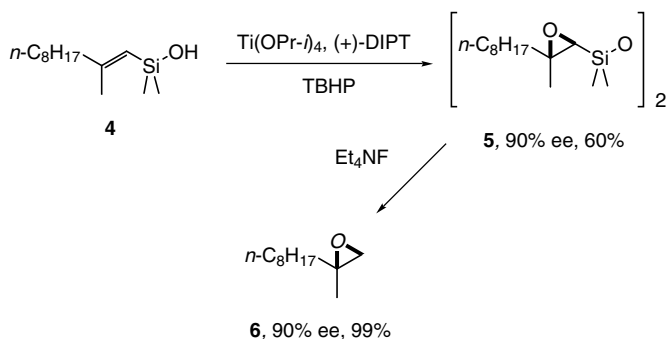


The presence of a bulky *Z*-substituent (R^3), especially the substituent branched at the allylic carbon, depresses or vitiates the enantioselectivity of the reaction (Eqs. 9 and 10) [27, 28]. In contrast, epoxidation of the substrates bearing a bulky *E*-substituent shows standard enantioselectivity (Eq. 11) [28]. On the other hand, a bulky C2-substituent only affects the enantioselectivity to some extent (Eq. 12) [28].





The substrate of the present reaction is not limited to allylic alcohols. Alkenyldimethylsilanols, which are structurally similar to allylic alcohols, are amenable to epoxidation. For example, epoxidation of silanol **4** using (+)-DIPT as the chiral source provides the (2*S*,3*S*)-epoxydisiloxane **5** in 90% ee, the configuration of which is consistent with the empirical rule (Scheme 4) [29]. Protodesilylation of **5** with fluoride ion provides the terminal epoxide **6**. This procedure is a useful method for the synthesis of simple terminal epoxides.



2.2

Mechanism of Asymmetric Induction by the Titanium Tartrate Complex

The titanium-tartrate complex was proven to have a dimeric structure by X-ray analysis [30, 31]. The complex has been considered to maintain the dimeric structure also in solution. Based on the X-ray structure, Sharpless has proposed the transition state model **7** for the present epoxidation (Fig. 1). The coordination of the distal oxygen (O^2) in the loaded TBHP activates the peroxy bond and facilitates the nucleophilic attack of the double bond as discussed in the beginning of this chapter. Both stereochemistry and substrate reactivity in this reaction can be reasonably explained with the model **7** [3, 4, 6, 30, 31]. The loaded substrate takes a conformation having a small dihedral angle (O-C-C=C , *ca.* 30°) to deliver its olefinic moiety in an appropriate space for the epoxidation. The *E*-substituent

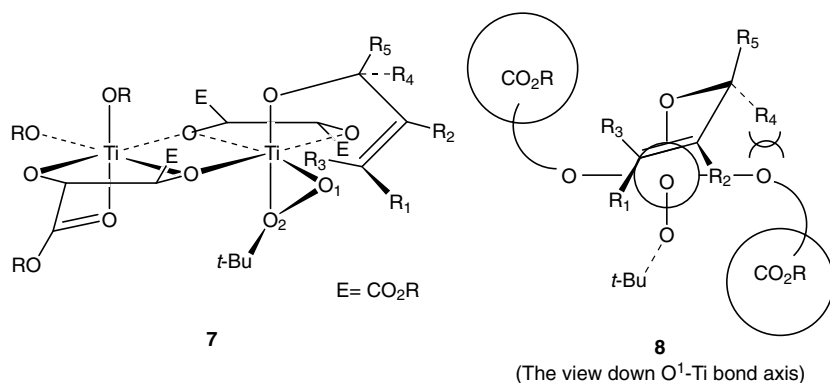


Fig. 1

(R¹) protrudes into an open quadrant and, therefore, *trans*-allylic alcohols always show standard enantioselectivity, irrespective of the bulkiness of the *E*-substituent. On the other hand, the C2-substituent (R²) exists in the vicinity of the tartrate ligand and the bulky substituent affects the conformation, causing depression of enantioselectivity to some extent. The *Z*-substituent (R³) is directed toward the ligand. Thus, the presence of a bulky *Z*-substituent makes it difficult for the substrate to take the desired conformation, decreasing enantioselectivity to a considerable extent. The loaded substrate suffers from steric hindrance when R⁴≠H (see 8) and epoxidation of such a substrate is strongly retarded. This explains the kinetic resolution of racemic secondary allylic alcohols (see section 3). The enantiomer (R⁴≠H, R⁵=H) reacts much slower than the other enantiomer (R⁵≠H, R⁴=H). The poor reactivity of tertiary allylic alcohols can also be explained for the same reason.

The olefin attacks the activated peroxide nucleophilically in this reaction (*vide supra*) and substrate reactivity increases as the olefinic electron density increases [32]. For example, epoxidation of *p*-methoxycinnamyl alcohol is ten times faster than that of *p*-nitrocinnamyl alcohol.

2.3

Scope of the Titanium-Catalyzed Asymmetric Epoxidation

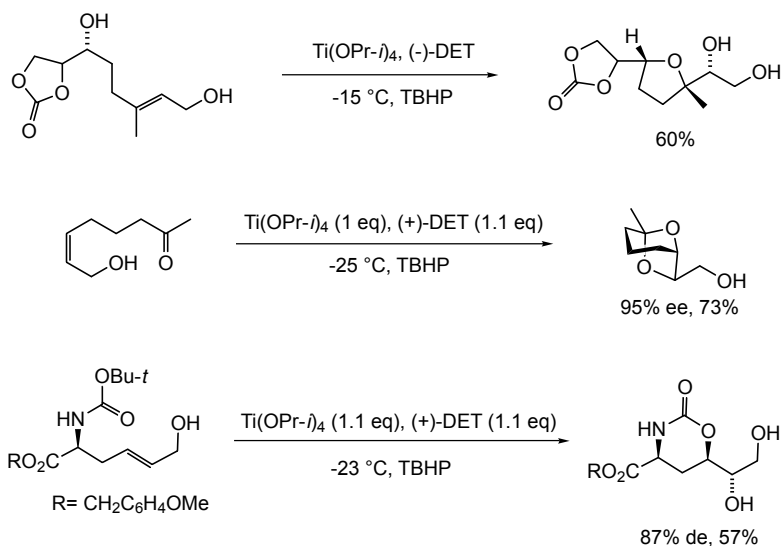
As described above, the major advantage of the present epoxidation is that allylic alcohols of any substitution pattern can be used as the substrates, although some *cis*-allylic alcohols show sub-standard enantioselectivity (*vide infra*) [3, 4, 6]. Another advantage is that many functional groups tolerate the reaction conditions. Epoxidation of substrates bearing the functional groups listed in Table 1 occurs normally and shows standard enantioselectivity [3, 4, 6]. Among these functional groups, however, nucleophilic ones such as hydroxy [33], carbonyl [34], and carbamate groups [35] often react *in situ* with the produced epoxides intramolecularly to give the cyclized products (Scheme 5).

Table 1. List of functional groups tolerable to the titanium-mediated epoxidation^{a,b}

- 1) -OH^{*,**}
- 2) -OR (R=alkyl, benzyl, and aryl)
- 3) -OCH₂OR, -OCR₂OR [This group includes acetal protecting groups such as methoxymethyl (MOM),^{*} methoxyethoxymethoxy (MEM), tetrahydropyranyl (THP) and acetonide]
- 4) OSiRR'R''
- 5) -OC(=O)R, -OC(=O)OR, -OC(=O)NRR'^{*,**}
- 6) -OSO₂R
- 7) -NRC(=O)R'^{*,**} -NHSO₂R, -NO₂, -N₃
- 8) -P(=O)R₂^{*}
- 9) -CH(OR)₂, -CR(OR')₂
- 10) -C(=O)R,^{**} -CO₂R, -CONRR', -C(=NR)OR'
- 11) -CN
- 12) -CR=CR'R'' (isolated olefins. see sect. 2.5), -CH=CHCH₂SiR₃, -CH=CRSiR₃
- 13) -C≡CR, -C≡CSiR₃

^a Enantioselectivity may suffer, in case that the substrate carries the asterisked functional group near to the allylic alcohol, see text.

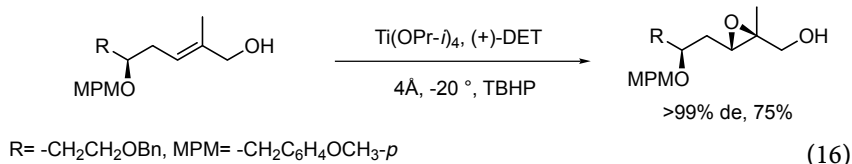
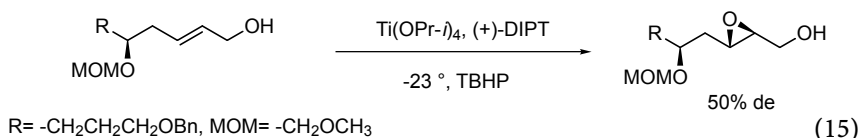
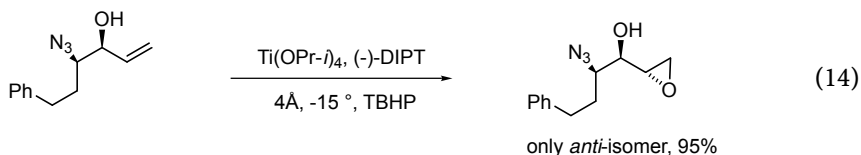
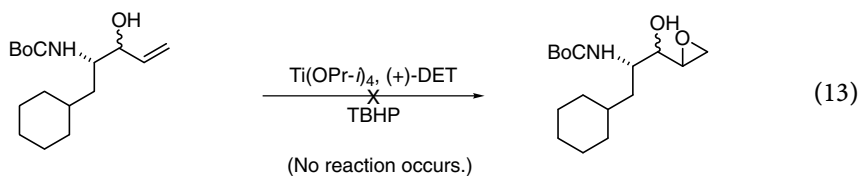
^b The doubly asterisked functional group may undergo *in situ* intramolecular cyclization, when it locates near the generated epoxide, see text.



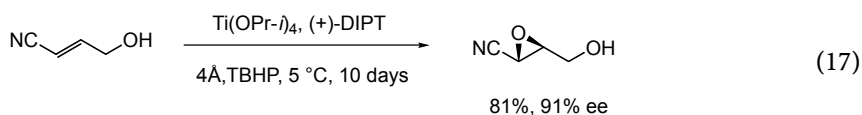
Scheme 5

Despite the above description, some substrates bearing a coordinating functional group near to the allylic hydroxy group show unusual behavior (sub-standard enantioselectivity and/or slow reaction). For example, the allylic alco-

hol bearing a vicinal carbamate group does not undergo the desired epoxidation (Eq. 13) [36]. This is probably because the coordination of the neighboring group to titanium ion prevents the allylic alcohol loaded on the catalyst from taking the conformation desired for AE. The modest enantioselectivity reported in Eq. 15 is also attributed to the same reason [37]. For some cases, these problems can be avoided by the substitution of the polar group with a synthetically equivalent but less polar group (Eq. 14) [38] or by the appropriate choice of the protecting group (Eq. 16) [39].

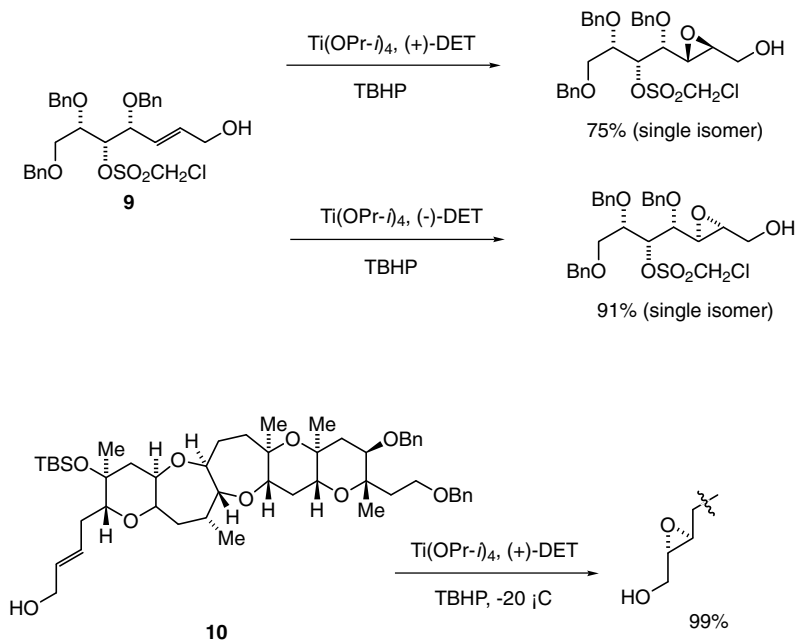


As described in the sect. 2.2, olefins serve as nucleophiles in titanium-mediated epoxidation. Therefore, the reactivity of the substrate bearing an electron-withdrawing group is low and the epoxidation of this class of substrates requires a long reaction time or an elevated reaction temperature (5 °C to rt), although standard enantioselectivity is observed (Eq. 17) [40, 41]. The reaction at higher temperature may cause the undesired epoxide ring opening which can be overcome to a considerable extent by using Ti(OBu-*t*)₄ instead of Ti(OPr-*i*)₄.



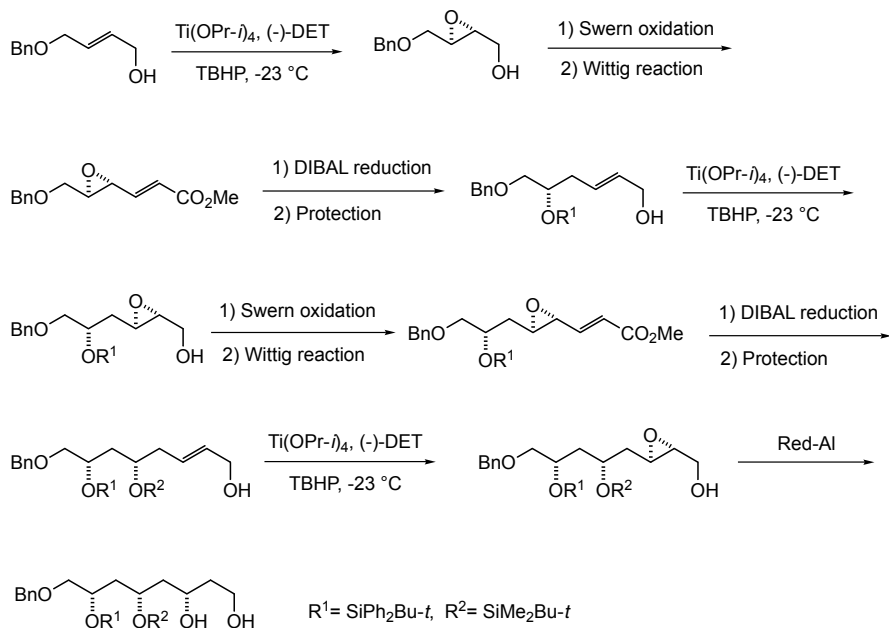
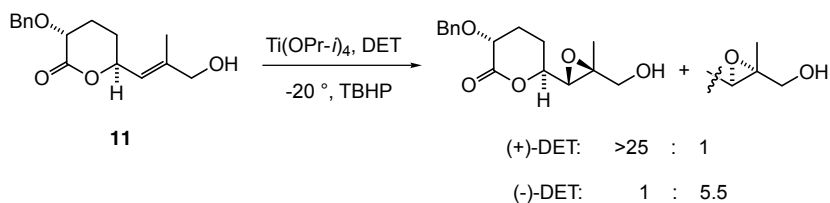
When the allylic alcohol has a chiral substituent, diastereofacial control by the chiral center (substrate control) competes with facial control by the titanium-tartrate complex. When the senses of two facial controls match, high enantioselectivity can be expected but, when mismatched, enantioselectivity suffers. The strength of substrate control depends strongly upon the location of chiral center in the substrate.

As discussed in the preceding section, the *E*-substituent protrudes into the open quadrant (Fig. 1) and chiral *E*-substituents have little effect on the stereoselectivity of the epoxidation. Thus, most *E*-allylic alcohols show standard facial selectivity. Even a densely functionalized substrate such as **9** [42] and **10** [43] can be epoxidized with high enantioselectivity.



Reiterative use of AE of *E*-allylic alcohols provides efficient approaches toward the stereoselective construction of the compounds such as polyols and polypropionate segments bearing consecutive asymmetric centers. For example, the 1,3,5,7-polyol chain of amphotericin B has been synthesized by using AE three times as key steps (Scheme 6) [44, 45].

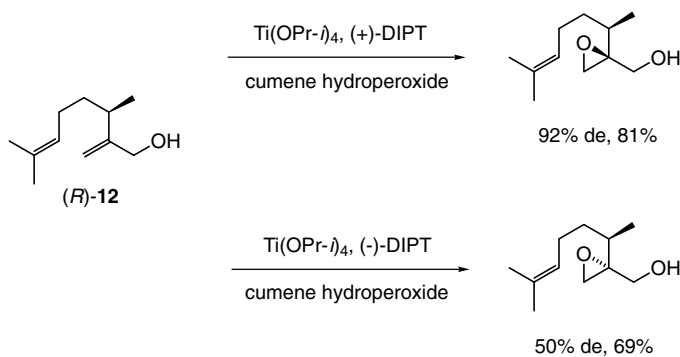
However, care must be taken when a polar group exists in the *E*-substituent or when the conformation of the chiral *E*-substituent is fixed for some reason. The conformation of the *E*-substituent in **11** is regulated by allylic strain and it exerts strong diastereofacial control [46]. Accordingly, the stereoselectivity of the epoxidation strongly depends on the enantiomer of the tartrate used. Asymmetric induction by (+)-DET matches the substrate control.

**Scheme 6****Scheme 7**

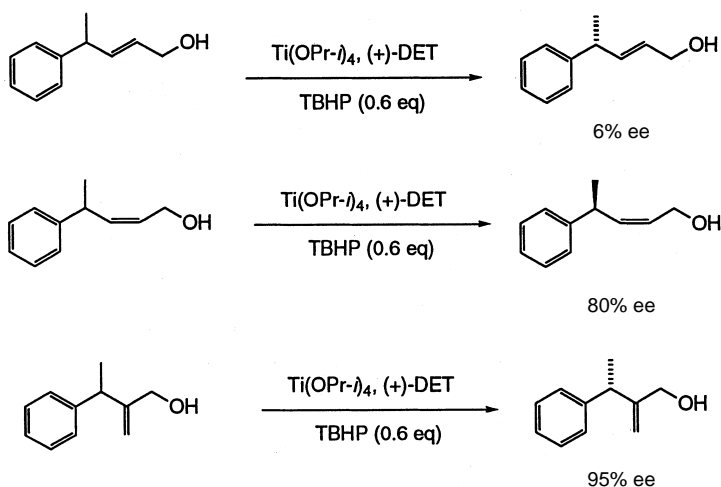
Chiral *Z*-substituents strongly influence the stereoselectivity and reaction rate because they exist near to the titanium ion and lack conformational freedom due to the allylic strain caused by the small O-C-C=C dihedral angle (Fig. 1).

Therefore, many *Z*-chiral substrates show substandard face selectivity and low reactivity, especially when the *Z*-substrate is bulky and/or functionalized (Scheme 7) [47]. Epoxydations of some chiral *Z*-substrates do not follow the empirical rules on stereochemistry.

The chiral C2-substituent also affects enantioselectivity to some extent. For example, epoxydation of (*R*)-**12** using (+)-DIPT as a chiral source afforded a (2*S*)-epoxide of 92% de, while epoxydation using (–)-DIPT afforded a (2*R*)-epoxide of 50% de [48].



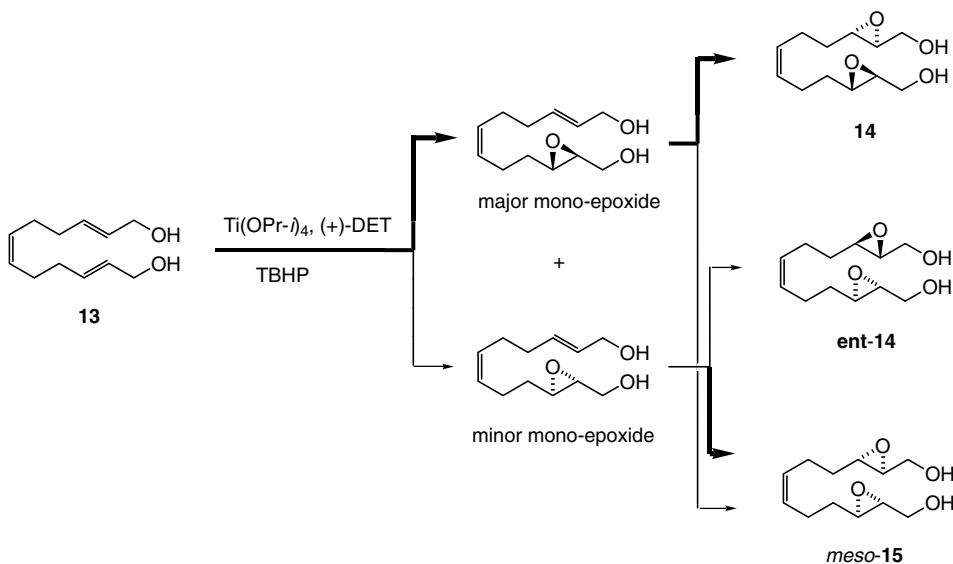
A similar chiral substituent effect is also observed in kinetic resolution of racemic primary allylic alcohols (Scheme 8). For example, both the enantiomers of racemic *E*-allylic alcohol are epoxydized at almost the same rate, while efficient kinetic resolution occurs in the epoxydation of racemic *Z*- and 2-substituted allylic alcohols [49].



Scheme 8

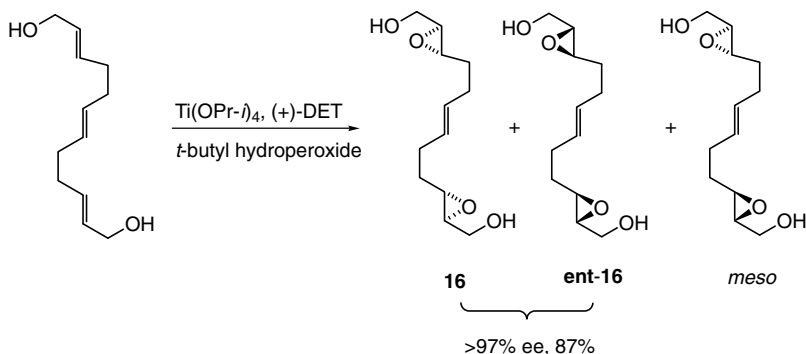
2.4 Asymmetric Epoxidation of Bisallylic Alcohols

AE of bisallylic alcohols possessing C_s - or C_2 -symmetry gives the corresponding diepoxy compounds of extremely high enantiopurity. In the epoxidation of C_s -bisallylic alcohols, the minor enantiomer of an intermediate monoepoxide gives the *meso*-diepoxide exclusively in the second epoxidation and the formation of the minor enantiomer of the chiral diepoxide is very small, while the major enantiomer of the mono-epoxide gives the major enantiomer of the chiral diepoxide preferentially. Thus the enantiomeric excess of the chiral diepoxide becomes extremely high (Scheme 9). For example, if the epoxidation proceeds with the usual face selectivity (95% ee), the diepoxy product of bisallylic alcohol **13** should be a mixture of **14**, *ent*-**14**, and *meso*-**15** in the ratio of 361:1:38. The ratio of **14** (**14** + *ent*-**14**) and *meso*-**15** is actually 9:1, although the enantiopurity of **14** has not been determined [50, 51, 52].

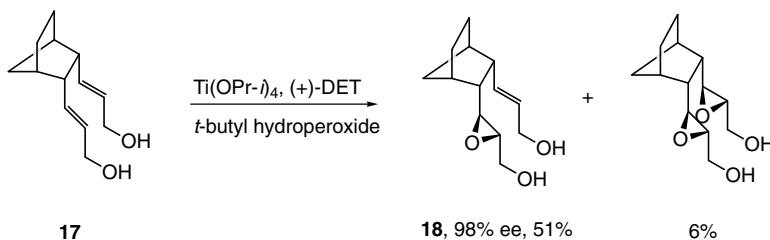


Scheme 9

Epoxidation of the C₂-bis allylic alcohol also provides the diepoxide **16** in high enantiomeric excess (>97% ee [53].)



AE of the *meso*-bisallylic alcohol **17** has also been examined [54]. In this class of substrate, the first epoxidation occurs smoothly in a highly enantiotopic selective manner to give the mono-epoxide **18** preferentially but the second epoxidation of **18** is slow. Therefore, the mono-epoxide **18** can be obtained as a major product in a highly enantiopure form (98% ee) together with a small amount of the diepoxide.

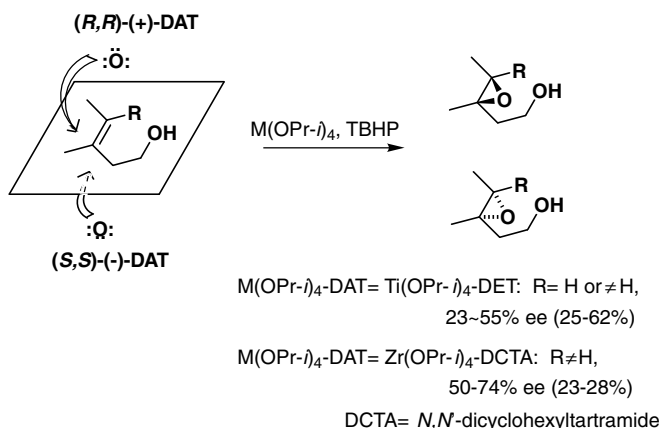


2.5

Asymmetric Epoxidation of Homo- and Bishomoallylic Alcohols

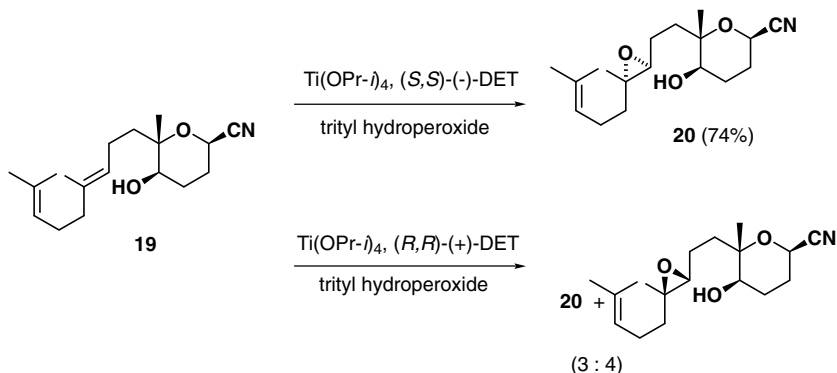
Titanium-tartrate complexes also catalyze the epoxidation of homo- and bishomoallylic alcohols but their reactions are considerably slower as compared with reactions of allylic alcohols [55]. Enantioselectivity also drops to moderate levels (Scheme 10). When the substrates are *cis*-homoallylic alcohols, use of the zirconium *N,N'*-dicyclohexyltartramide complex as catalyst improves the enantioselectivity to some extent [56].

High stereoselectivity, however, can be realized when the substrate is chiral and substrate control matches control by titanium-tartrate. Selection of the alkyl hydroperoxide is also important for achieving high stereoselectivity. For example, epoxidation of compound **19** proceeds with high diastereoselectivity when



Scheme 10

(*S,S*)-tartrate and trityl hydroperoxide are used as a chiral source and an oxidant, respectively, while diastereoselectivity is poor when (*R,R*)-diethyl tartrate is used [57].



Olefins with no pendant hydroxy group do not undergo epoxidation under the present conditions.

3

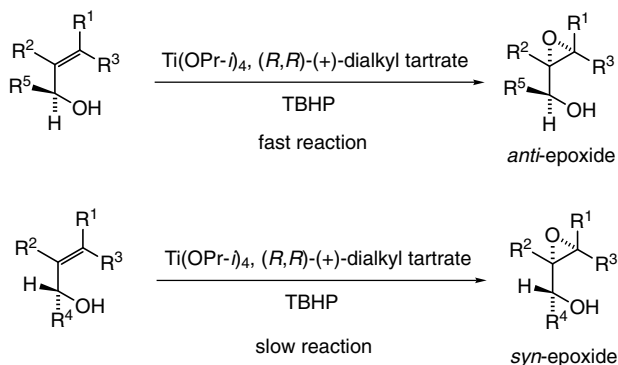
Asymmetric Epoxidation and Kinetic Resolution of Secondary Allylic Alcohols and Related Compounds

3.1

Asymmetric Epoxidation and Kinetic Resolution of Secondary Allylic Alcohols

In the epoxidation of racemic secondary alcohols, there are two stereochemical problems to be considered: (i) differentiation of enantiomers (kinetic resolution) and (ii) diastereoface selection in epoxidation.

When a racemic allylic alcohol is subjected to epoxidation using (*R,R*)-(+)-tartrate as the chiral source, the (*S*)-enantiomer of the alcohol reacts faster than the (*R*)-enantiomer while the (*R*)-enantiomer reacts faster when (*S,S*)-(–)-tartrate is the chiral source [19]. The fast reacting enantiomer gives the *anti*-epoxy alcohol with high stereoselectivity, while the slow reacting isomer shows a lower diastereoselectivity, giving a mixture of *syn*- and *anti*-epoxy alcohols (Scheme 11). This stereochemistry in the epoxidation of secondary allylic alcohols is also reasonably explained by the transition state model **8** described in Fig 1 [3, 4, 6]. In general, the relative rate constants (k_{rel}) between fast and slow isomers exceed 50 and the enantiomeric excesses of unreacted slow isomers amount to >99% ee at 55% conversion of starting materials (Fig. 2) [58]. However, it should be noted



Scheme 11

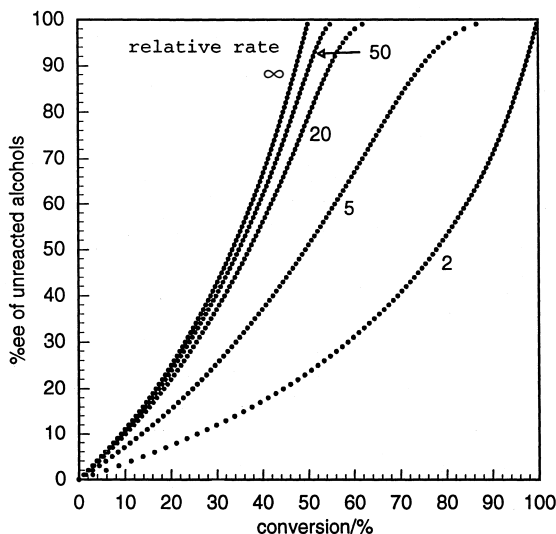


Fig. 2

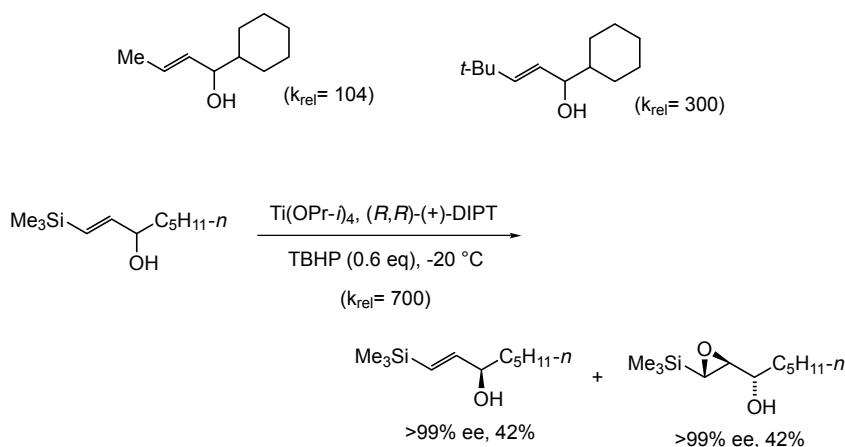
that the optimum relative rate constant is attained only when the appropriate reagents are used. Use of $\text{Ti}(\text{O}i\text{Bu})_4$ instead of $\text{Ti}(\text{OPr-}i)_4$ lowers the relative rate constants [21]. The choice of tartrate ester is also important: k_{rel} is improved as the bulkiness of the ester alkyl moiety increases ($\text{DMT} < \text{DET} < \text{DIPT}$). DIPT is generally used in the stoichiometric procedure and gives acceptable k_{rel} [19]. In the catalytic procedure, use of more bulky dicyclohexyl and dicyclododecyl tartrates is recommended [18].

In analogy with primary allylic alcohols, a secondary allylic alcohol bearing a bulky *E*-substituent (R^1) is a good substrate for kinetic resolution. For example, the k_{rel} for (*E*)-1-cyclohexyl-2-buten-1-ol is 104 and that for 1-cyclohexyl-4,4-dimethyl-2-penten-1-ol is 300 [59]. Best substrates are those in which the *E*-substituent is trimethylsilyl, iodo, or trimethylstannyl. The relative rate constant for (*E*)-1-trimethylsilyl-1-octen-3-ol is 700 and, at 50% conversion, both the unreacted alcohol and the *anti*-epoxy alcohol have more than 99% ee (Scheme 12) [60].

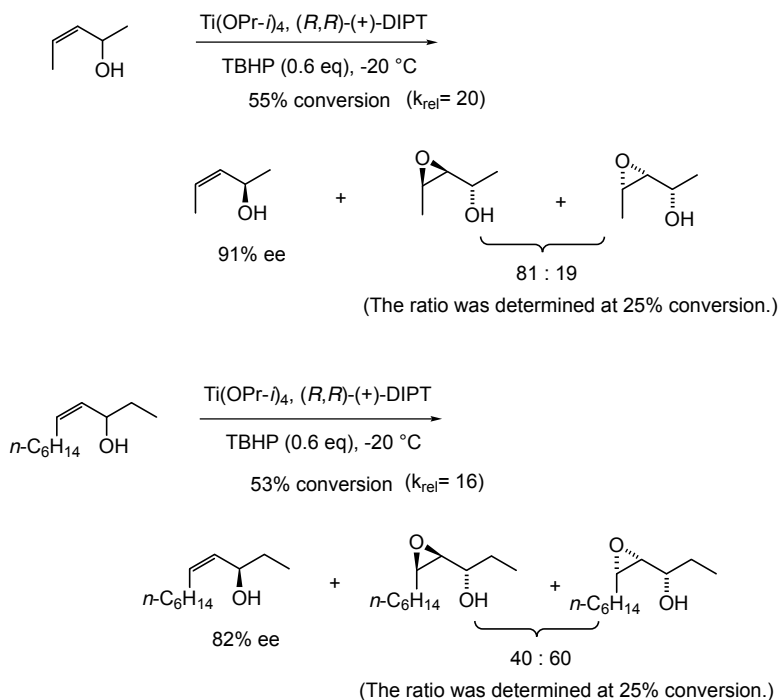
On the other hand, substrates bearing a *Z*-substituent ($\text{R}_3 \neq \text{H}$) show considerably low k_{rel} and modest diastereoselectivity. In contradiction to the empirical rule, substrates bearing a bulky *Z*-substituent often exhibit *syn*-selectivity even in the epoxidation of the fast isomers (Scheme 13) [19].

The efficiency of kinetic resolution of cyclic allylic alcohols depends on the ring size: For example, enantiomeric excesses of unreacted cyclohexenol and cycloheptenol are 30 and 80% ee, respectively, when they are exposed to the usual reaction conditions using (+)-DIPT as a chiral source for 40 h [19]. The low selectivities are attributed to the fixed dihedral angles of $\text{C}=\text{C}-\text{C}-\text{O}$ in these substrates, which are much larger than the desired one (*vide supra*).

As discussed in the Sect. 2.2, the efficiency of kinetic resolution is related to the steric repulsion between the tartrate ligand and the C1 alkyl group (R^4) in the slow isomers (Fig. 1). Therefore, kinetic resolution of the substrate bearing



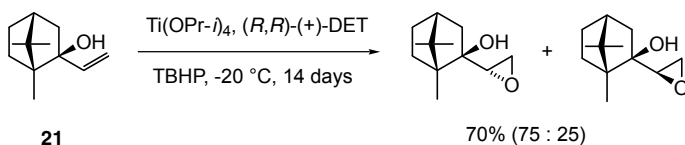
Scheme 12



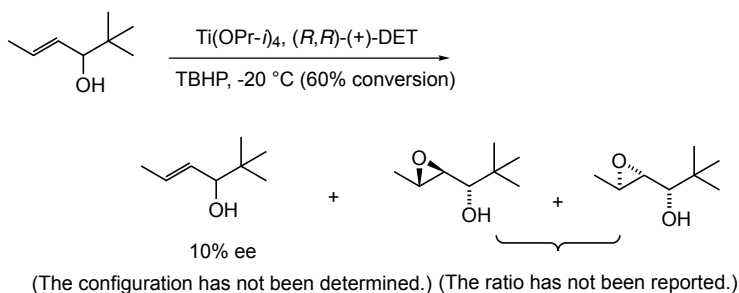
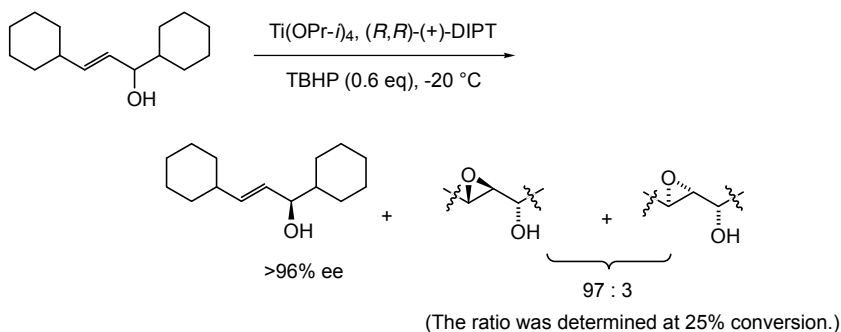
Scheme 13

branched (aryl or secondary) substituent can be performed very efficiently [19]. However, when the substituent is a tertiary one, epoxidation is slow with low diastereoselectivity, and the efficiency of kinetic resolution also drops remarkably (Scheme 14) [28].

The epoxidation of tertiary allylic alcohol **21** is also slow and low diastereoselective [61].

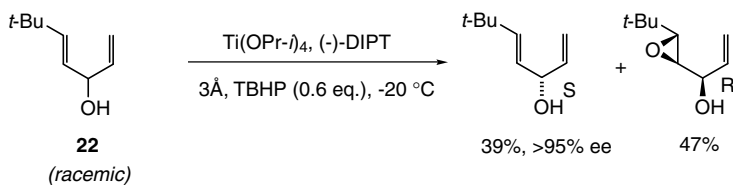


The reactivity of the double bond rises as its electron density increases (*vide supra*). Therefore, the increase in the number of substituents at the double bond enhances its reactivity, as long as the introduced substituent does not cause an unfavorable effect on AE. This reactivity difference allows the efficient kinetic resolution of racemic 6,6-dimethyl-1,4-heptadien-3-ol **22**. When (-)-diisopropyl tartrate is used as a chiral source, the (*R*)-isomer is epoxidized prior to the (*S*)-isomer because the chiral source dictates the epoxidation of the less substituted



Scheme 14

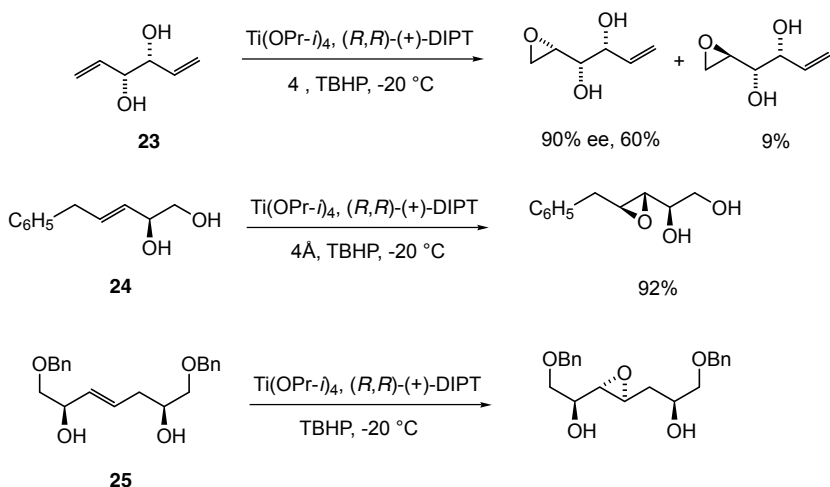
1,2-double bond in the (*S*)-isomer and of the more substituted 4,5-double bond in the (*R*)-isomer [62].



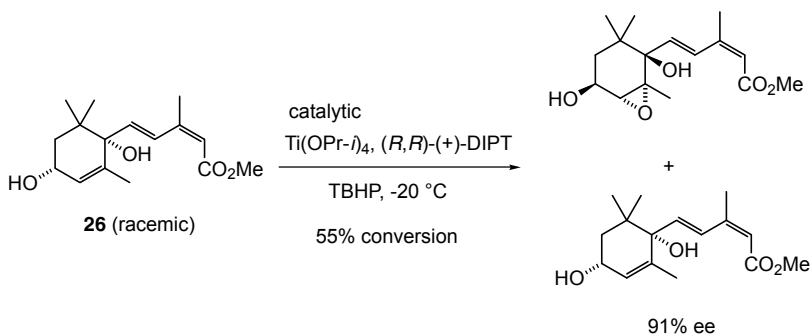
On the other hand, when an epoxy alcohol is the desired product, the reaction must be stopped before the fast isomer is consumed completely. Usually the reaction is stopped at 40 to 45% conversion. Although the direct epoxidation of racemic allylic alcohols gives the epoxides in good enantiomeric excesses, the epoxidation of the recovered unreacted allylic alcohols obtained by kinetic resolution provides epoxides of much high enantiopurity.

Epoxidation of most substrates follows the empirical rules described in Scheme 11, but some substrates show unusual stereochemistry, especially when the substrates carry a free hydroxy group in the vicinity of the allylic alcohol. Coordination of the non-allylic hydroxy group to the titanium ion influences the conformation of the loaded substrate at the transition state and affects the sense

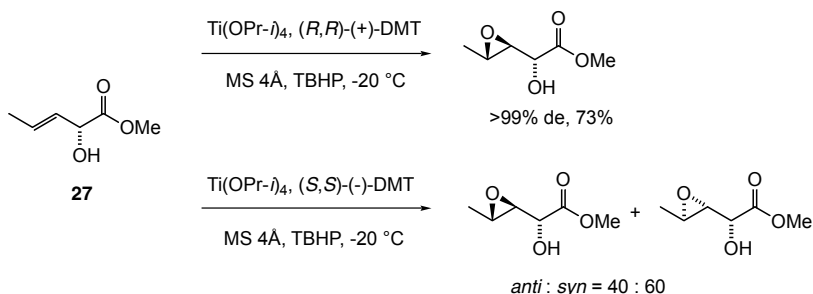
and the magnitude of enantioselection. For example, epoxidation of 1,5-hexadiene-3,4-diol **23** and 6-phenyl-4-hexene-1,3-diol **24** showed the reversed *syn*-selectivity [63, 64]. A hydroxy group remote from the allylic alcohol center does not affect diastereoface selectivity to a large extent. Compound **25** shows the usual *anti*-selectivity [65].



In some substrates, the bystander hydroxy group plays a favorable role. Cyclohexenol is a poor substrate for kinetic resolution as discussed before but kinetic resolution of methyl 1',4'-*cis*-dihydroxy- α -ionylideneacetate **26** proceeds with good selectivity. A *cis*-tertiary hydroxy group has been considered to play some synergistic role in this kinetic resolution [66].



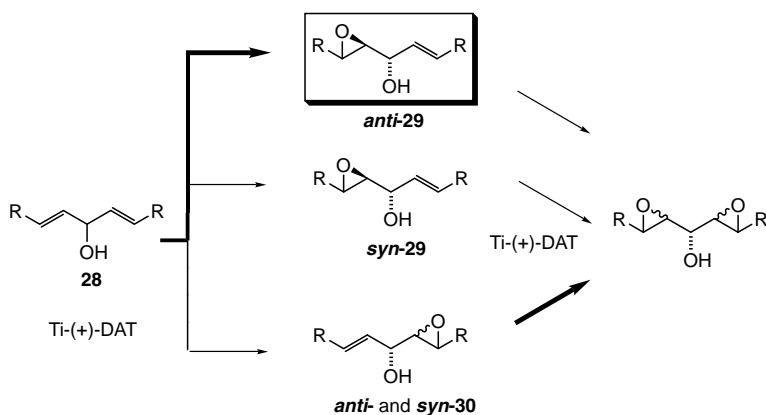
It should be noted that epoxidation of the α -hydroxy ester **27** which carries a pre-coordinating ester group at the carbinol carbon shows standard selectivity: Epoxidation of (*R*)-**27** with (+)-DMT shows excellent *anti*-selectivity, while that with (–)-DMT shows modest *syn*-selectivity [67]. This is consistent with the empirical rule.



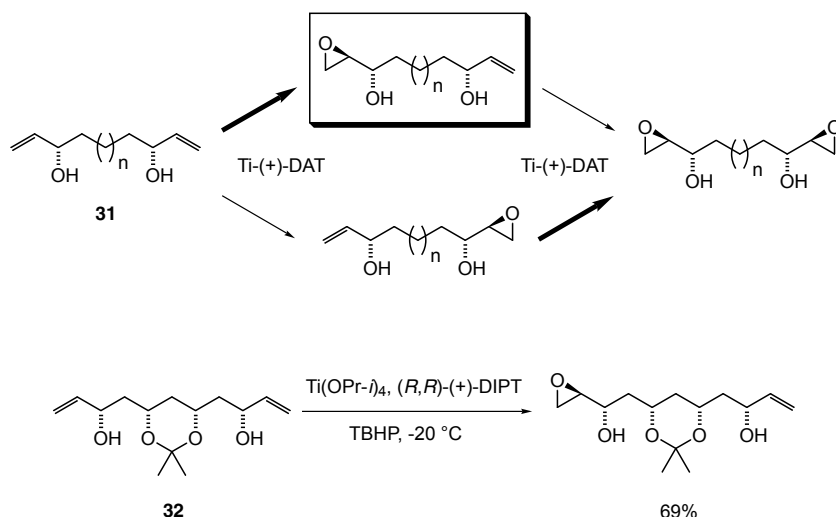
3.2

Epoxidation of Prochiral Dialkenyl Carbinols and of *meso*-Secondary Diallylic Alcohols

Epoxidation of prochiral dialkenyl carbinols **28** provides the *anti*-epoxide **29** of extremely high optical purity [68, 69, 70]. The first epoxidation occurs in an enantiotopic selective manner while the second one proceeds in an enantiomer-differentiating manner (kinetic resolution). In the second step, the minor (*R*)-monoepoxides **30** are consumed faster than the major (*S*)-enantiomers **29** and therefore the enantiomeric excess of the major *anti*-monoepoxide **29** increases as the reaction proceeds. If a reaction proceeds with a $k_{\text{fast}}/k_{\text{slow}}=104$, *anti-syn* selectivity for the fast reaction=98:2 and for the slow reaction=38:62, as observed in the epoxidation of racemic (*E*)-1-cyclohexyl-2-buten-1-ol, the enantiomeric excess of *anti*-**29** on calculation is 99.4, 99.96, and 99.994% ee at 50, 99, and 99.9% conversion, respectively. Yields of *anti*-**29** are 48, 93 (maximum), and 91% at the respective conversions. Actually, in the epoxidation of 1,4-pentadien-3-ol using (+)-DIPT as a chiral source, the enantiomeric excess of the major *anti*-**29** (R=H) was observed to increase (84, 93, >97% ee) as the reaction time was extended (3, 24, 140 h) [68]. It has recently been reported that catalytic AE of 1,4-pentadien-3-ol provides *anti*-**29** (R=H) of 97% ee and 98% de (*anti* : *syn*=99:1) in 65% yield [71].



The enhancement of the enantiomeric excess of the mono-epoxide can be expected also in the epoxidation of the *meso*-secondary diallylic alcohol **31**. Epoxidation of **32** gives the desired *anti*-epoxide of high enantiomeric excess in good yield [72]. However, some *meso*-substrates bearing two hydroxy groups in close vicinity to each other may show unusual stereochemistry as discussed in the preceding section.

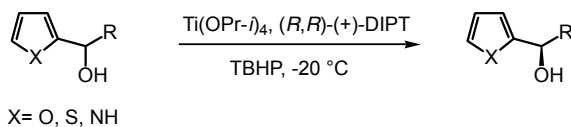


3.3

Kinetic Resolution of Furyl, Pyrrolyl, and Thienyl Alcohols

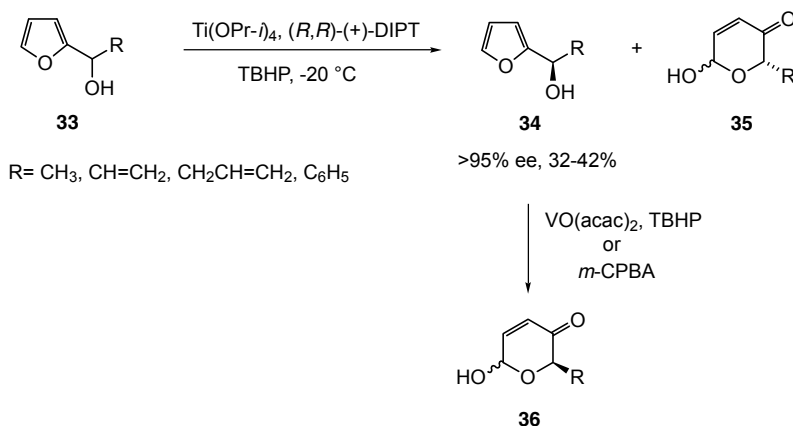
Heterocyclic compounds such as furan, thiophene, and pyrrole are subject to oxidation. Similar to secondary allylic alcohols, 2-(1-hydroxyalkyl) derivatives of these heterocyclic compounds are also good substrates for kinetic resolution using a titanium-tartrate and TBHP system (Scheme 15).

The oxidation of 2-furyl alcohols **33** using $(+)\text{-DIPT}$ as a chiral source provides (*R*)-furyl alcohols of >95% ee and pyranone when 0.6 equivalents of TBHP are used [73, 74]. This stereochemistry is consistent with the empirical rules for kinetic resolution of secondary allylic alcohols (Scheme 11). Both the optically

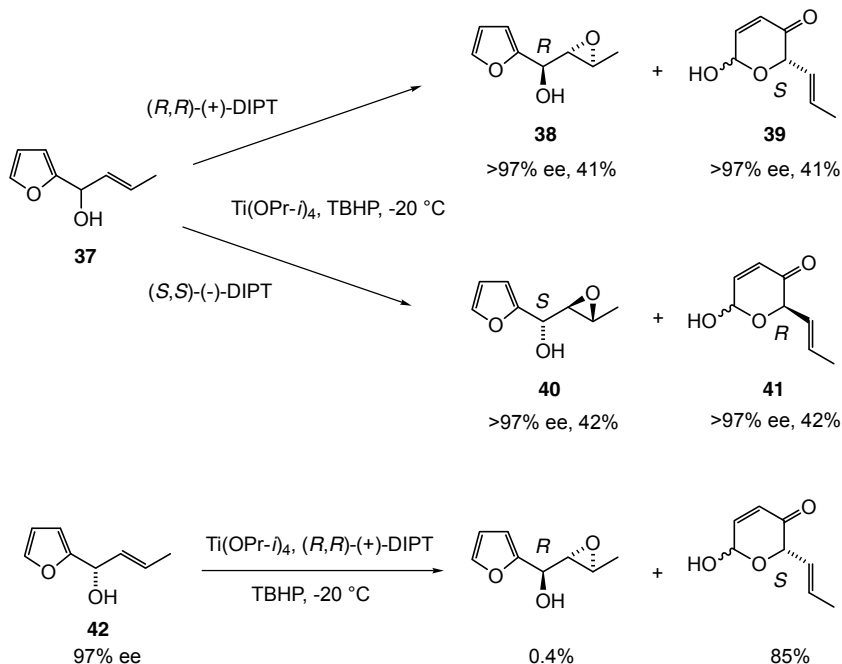


Scheme 15

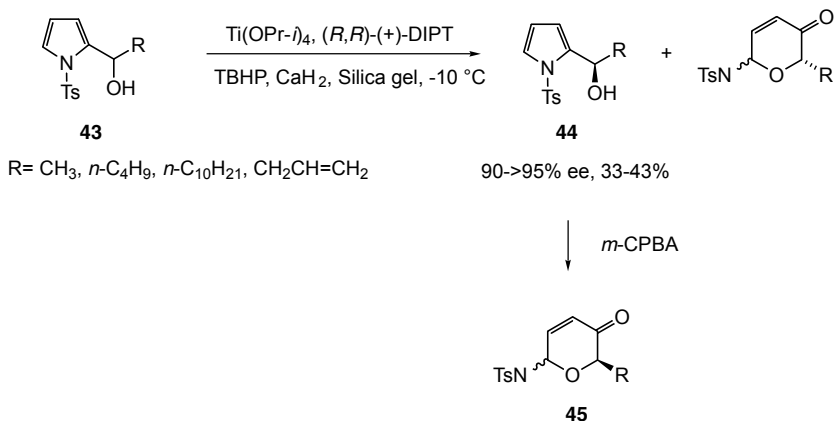
active furyl alcohols **34** and pyranones **35** are useful building blocks. When the pyranone is a desired product, the reaction must be stopped before the fast isomer is consumed completely. Although the direct oxidation product of racemic furyl alcohols is well enantiomerically enriched, a much more enantiopure product **36** can be obtained by oxidation of the recovered unreacted furyl alcohol **34** which is obtained by kinetic resolution of the racemic starting material. Needless to say, the use of chiral oxidant or catalyst is not necessary for the last oxidation step.



As described in the preceding Scheme, the furan ring is oxidized prior to the vinyl group. However, the reactivity of double bonds toward oxidants is generally enhanced as the number of the olefinic substituents increases and the reactivity of *E*-disubstituted double bond is comparable with that of the furan ring. In such a case, the chemoselectivity of the reaction is controlled by the chirality of the catalyst. For example, oxidation of racemic (*E*)-1-(2-furyl)-2-buten-1-ol **37** using (+)-DIPT as a chiral source provides (*R*)-epoxy alcohol **38** of $>97\%$ ee and (*S*)-pyranone **39** of $>97\%$ ee in 41 and 41% yields, respectively, while oxidation using (–)-DIPT provides the (*S*)-epoxy alcohol **40** of $>97\%$ ee and the (*R*)-pyranone **41** of $>97\%$ ee in 42 and 43% yields, respectively [75, 76]. Naturally, oxidation of (1*S*,2*E*)-1-(2-furyl)-2-buten-1-ol **42** of 97% ee using (+)-DIPT gives the (*S*)-pyranone exclusively. The minor (*R*)-epoxy alcohol should be derived from the minor (*R*)-enantiomer of the starting material.

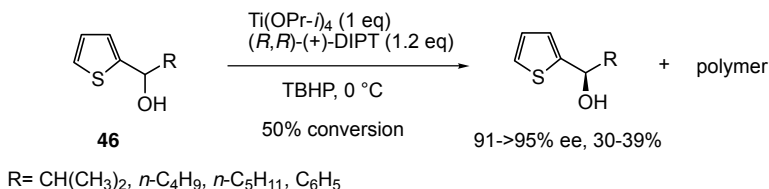


Kinetic resolution of racemic *N*-tosylpyrrol alcohol **43** using the modified titanium-tartrate system with calcium hydride and silica gel also proceeds with high efficiency. Oxidation of the recovered unreacted alcohols **44** with *m*-CPBA gives 2-*N*-tosylaminopyranones **45** of high optical purity, which are also useful building blocks for organic synthesis [77].

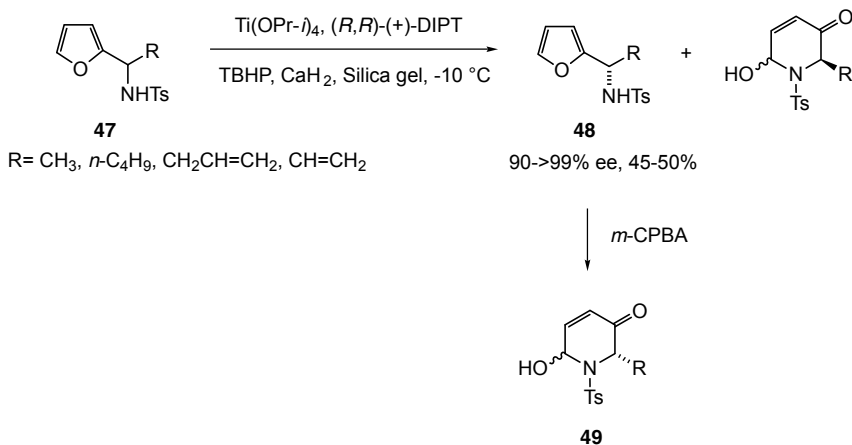


Kinetic resolution of 2-thienyl alcohols **46** is also performed efficiently [78]. Differing from kinetic resolution of racemic 2-furyl alcohols, however, a stoichi-

ometric amount of the titanium-tartrate complex is required for this reaction. The catalytic reaction shows a considerably lower efficiency. Furthermore, the oxidation of **46** does not give the corresponding 2-mercaptopyranones but the polymerized materials.



The scope of kinetic resolution of this type is not limited to alcohol derivatives but can be extended to *N*-tosylamino derivatives when the titanium-tartrate catalyst modified with calcium hydride and silica gel is used. Resolution of *N*-tosylamines **47** is effected with high efficiency but the configuration of the slow reacting isomer is opposite to that expected from the empirical rules for kinetic resolution (Scheme 11): The (*R*)-isomer of **47** is oxidized prior to the (*S*)-isomer when (+)-DIPT is used as a chiral auxiliary. Again, the Δ^4 -piperidone **49** of high enantiopurity can be obtained by oxidation of the enantioenriched furylamines **48** with *m*-CPBA [79].



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Chapter 18.2

Epoxidation of Alkenes Other than Allylic Alcohols

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Keywords: Epoxide, Salen complexes, Porphyrin, Dioxirane

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1 Introduction

The enormous success of the Sharpless epoxidation reaction helped inspire widespread efforts to identify more general catalytic systems which might be effective for the asymmetric epoxidation (AE) of unfunctionalized olefins. The question of whether substrate precoordination through a pendant functional group is required for a highly enantioselective catalytic reaction of a prochiral olefin had been answered in the negative with the discoveries of enantioselective cyclopropanation (Chapt. 16) in the 1970s and dihydroxylation (Chapt. 20) reactions in the 1980s. Nonetheless the search for effective asymmetric epoxidation catalysts for simple olefins did not meet with success until relatively recently [1, 2].

The first advances came with the discovery of chiral metal complexes that effect highly enantioselective oxo-transfer to unfunctionalized olefins [3, 4]. Such oxo-transfer catalysts have been designed to mimic the exquisite stereoselectivity found in several biological oxidation systems [5, 6, 7]. A detailed mechanistic understanding of these complexes has begun to emerge that bears importance for both synthetic and enzymatic oxo-transfer catalyst systems. More recently, chiral dioxiranes have been developed as effective epoxidation catalysts. These systems have addressed several important gaps in asymmetric epoxidation (AE) methodology with metal oxo catalysts with respect to substrate scope.

This chapter presents an overview of existing strategies for asymmetric catalytic epoxidation of unfunctionalized olefins with synthetic catalysts. The significant progress in metal-catalyzed oxo transfer and dioxirane epoxidation has increased the accessibility of several classes of optically active epoxides and concurrently highlighted important problems yet to be solved.

2 Epoxidation by Oxo-Transfer

2.1 Oxo-Transfer Mechanisms

Oxo-transfer from metal complexes to olefins results in a net two-electron reduction at the metal center. As a result, only metals capable of shuttling between oxidation states can be effective oxo-transfer catalysts. Iron, manganese, ruthenium, and chromium have proven effective for catalytic epoxidation via oxo-transfer [8, 9], and in synthetic systems studied thus far for enantioselective catalysis, these metals are most commonly coordinated by tetradentate porphyrin (1) and salen (2) ligand frameworks (Fig. 1).

Two fundamentally different proposals for the mechanism of oxygen-atom transfer from high-valent metal oxo complexes have been considered. One proposal invokes substrate attack at both the metal and oxo centers to generate an oxametallacycle intermediate (3, Fig. 2). Such a mechanism was first advanced

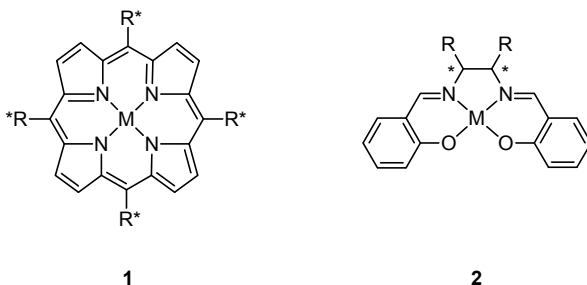


Fig. 1

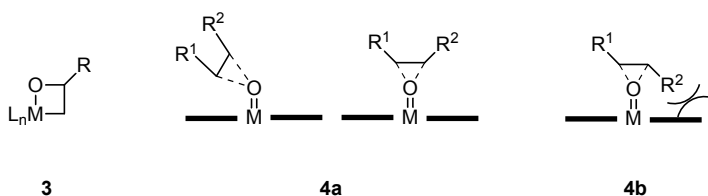


Fig. 2

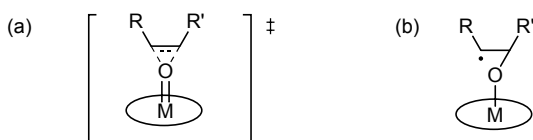


Fig. 3

in the literature by Sharpless in 1977 in the context of chromyl chloride oxidations [10]. While analogous proposals have been made for olefin epoxidation reactions catalyzed by porphyrin and salen complexes [11, 12, 13], substantial evidence has been accumulated that indicates that oxametallacycle intermediates do not participate in these reactions [14, 15, 16].

The more widely accepted mechanism for oxo-transfer involves direct substrate attack at the oxo ligand with concerted or sequential C-O bond formation. In 1985, Groves proposed a transition state geometry for epoxidation by porphyrin complexes involving a side-on, perpendicular approach of the olefin to the metal-oxygen bond [17]. This trajectory accounted for the enhanced reactivity of *cis*- over *trans*-alkenes (**4a** vs. **4b**) in porphyrin and other metal oxo catalyst systems (Fig. 2). This model has also helped explain the observed enantioselectivities in AE reactions with successful chiral catalysts [18, 19].

The lack of complete stereospecificity in the epoxidation of certain olefin classes offers compelling evidence for a stepwise mechanism for oxo-transfer [20, 21]. Alkyl-substituted olefins generally undergo stereospecific epoxidation, with *cis*-olefins affording *cis*-epoxides exclusively (Fig 3a) [22]. In contrast, acyclic olefins conjugated to aryl, vinyl, or alkynyl groups undergo nonstereospecific epoxidation, with *cis*-olefins affording mixtures of *cis*- and *trans*-epoxide products. Radical clock experiments carried out with sensitive radical probes are generally consistent with this mechanistic duality (*vide infra*) [23, 24]. Non-polar radical intermediates are implicated by the observed electronic and reactivity trends in the case of non-concerted epoxidations with Mn(salen) catalysts (Fig. 3b) [19, 25].

2.1.1

Stoichiometric Oxidants

A wide variety of stoichiometric oxidants have been identified to be effective oxygen atom donors in oxo-transfer reactions with (salen)-metal and (porphyrin)-metal catalysts. These include NaOCl [26, 27, 28], alkyl hydroperoxides [29, 30, 31], peroxy acids [32], amine *N*-oxides [33, 34], oxaziridines [35], ozone [36], potassium hydrogen persulfate (Oxone) [37], hydrogen peroxide [38, 39], periodate [40, 41], and magnesium monoperoxyphthalate [42]. In addition, the use of molecular oxygen with [43, 44] or without [45] a stoichiometric reductant has been reported in epoxidations employing synthetic heme mimics. Among all of these oxidant systems, NaOCl has been studied particularly closely [46], and it has been used most widely in asymmetric catalytic epoxidations [47, 48, 49].

In many cases, the addition of Lewis bases capable of coordinating to the metal center during epoxidation catalysis has been found to have a beneficial effect on catalyst turnover rate and number as well as epoxide yield. Commonly used additives include pyridine, imidazole, and pyridine *N*-oxide derivatives. The proposed roles of *N*-oxide derivatives in [Cr(salen)]-catalyzed and [Mn(salen)]-catalyzed epoxidation reactions include activation of the intermediate metal-oxo complex [15, 50], dissociation of unreactive μ -oxo dimer complexes to reactive monomeric species [19, 25], and/or solubilization of the active oxidant in biphasic reaction media [51].

2.1.2

Characterization of Catalytically Active Metal-Oxo Complexes

Although participation of discrete, high-valent oxo intermediates in olefin epoxidations by metal-oxo complexes is widely accepted, unambiguous assignment of the electronic configuration of the metal center in these intermediates has presented a difficult challenge. High-valent iron and manganese porphyrin complexes prepared by addition of *m*-CPBA to the corresponding [M^{III}(porphyrin)] complexes have been characterized spectroscopically [52, 53, 54]. Electrospray tandem mass spectrometry has also provided evidence for discrete [Mn^V(salen)] complexes with a terminal oxo group [55]. An important feature of these metal-oxo characterization studies has been the demonstration of stoichiometric reactivity with olefin substrates in epoxidation reactions.

A series of five- and six-coordinate chiral [Mn^{III}(salen)] complexes known to be effective AE catalysts has been characterized by X-ray crystallography [56]. Comparison of some of these structures revealed that the ligand geometry around the metal center and the chiral diimine backbone remained remarkably constant, while the salicylidene regions of the complexes adopted a wide range of conformations. The conformational variations observed in the solid state likely reflect accessible solution conformations of the [Mn^{III}(salen)] complexes and possibly their oxo counterparts.

2.2

[Mn^{III}(salen)] Complexes

The development of chiral [Mn^{III}(salen)] complexes for asymmetric epoxidation of unfunctionalized olefins has been reviewed extensively [1, 2, 57, 58]. Systematic variation of the steric and electronic environment of the complexes has led to the discovery of catalysts that are particularly effective for the epoxidation of several important classes of olefins.

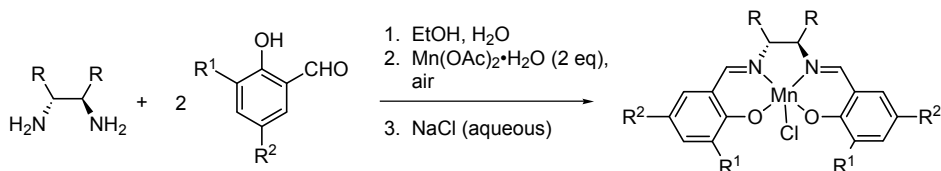
Catalyst exploration has been greatly facilitated by the ease of preparing chiral [Mn^{III}(salen)] complexes from Mn(OAc)₂·H₂O, the chiral diamine, and the appropriate salicylaldehyde (Scheme 1) [59, 60]. Using this procedure, several hundred optically active Mn complexes have been synthesized and demonstrated to exhibit a wide range of reactivity and selectivity [1, 2].

2.2.1

Ligand Design

In simplest terms, the incorporation of only two structural properties into the ligand system is required for attainment of good enantioselectivity in olefin epoxidation by [Mn^{III}(salen)] complexes: (i) a dissymmetric diimine bridge derived from a C₂-symmetric 1,2-diamine; and (ii) bulky substituents on the 3- and 3'-positions of the salicylide ligand. This is illustrated in Table 1 for the epoxidation of *cis*- β -methylstyrene by various [Mn^{III}(salen)] catalysts.

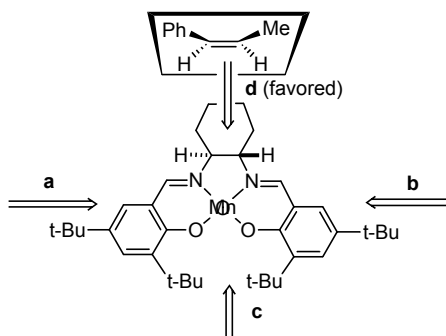
The optimal balance of steric and electronic ligand properties is apparently achieved in complex **11**. However, the considerably greater synthetic accessibility of complex **8** has made it the most widely used catalyst in this class. A highly simplified analysis for the mode of action of this catalyst is presented in Fig. 4 within the context of the side-on approach mechanism. The sterically-hindered *tert*-butyl groups are proposed to block approaches **a**–**c**, thereby enforcing approach **d** wherein stereochemical communication with the dissymmetric diimine backbone is maximized. A variety of olefin trajectories are accommodated within this general framework, with the possibility of a skewed side-on approach along one of the Mn–N vertices having gained particularly compelling support [61, 62]. Catalyst **8** has been employed widely on both laboratory and industrial scales for the epoxidation of *cis*-disubstituted and trisubstituted olefins (vide in-



Scheme 1

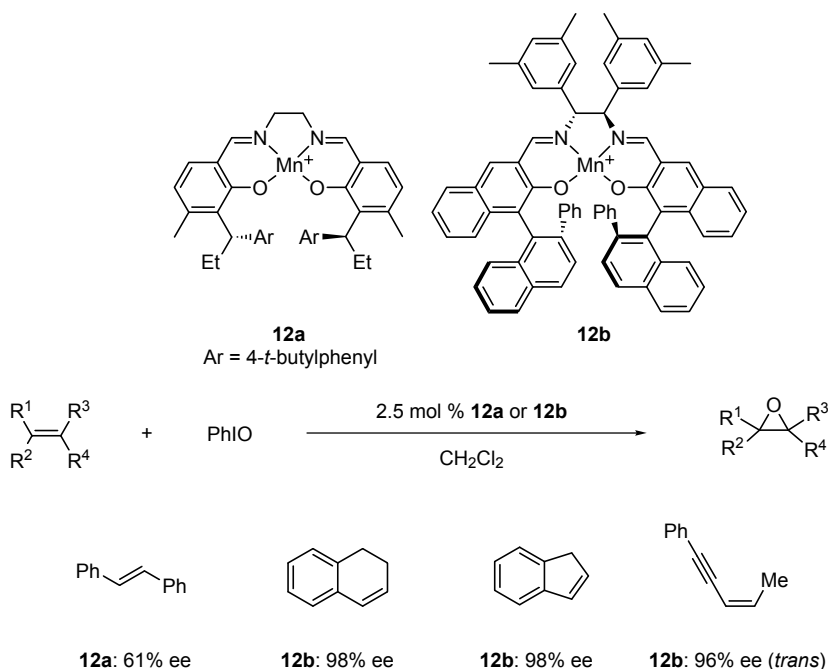
Table 1. [Mn(salen)]-catalyzed epoxidation of *cis*- β -methylstyrene

Catalyst	R, R	R ¹	R ²	ee (%)
5	Ph, Ph	H	H	<10
6	Ph, Ph	H	<i>t</i> -Bu	84
7	-(CH ₂) ₄ -	Me	<i>t</i> -Bu	80
8	-(CH ₂) ₄ -	<i>t</i> -Bu	<i>t</i> -Bu	90
9	-(CH ₂) ₄ -	OMe	<i>t</i> -Bu	86
10	-(CH ₂) ₄ -	NO ₂	<i>t</i> -Bu	46
11	-(CH ₂) ₄ -	OSi(<i>i</i> -Pr) ₃	<i>t</i> -Bu	92

**Fig. 4**

fra), and its synthesis has been commercialized on the multi-hundred kg scale [59, 60].

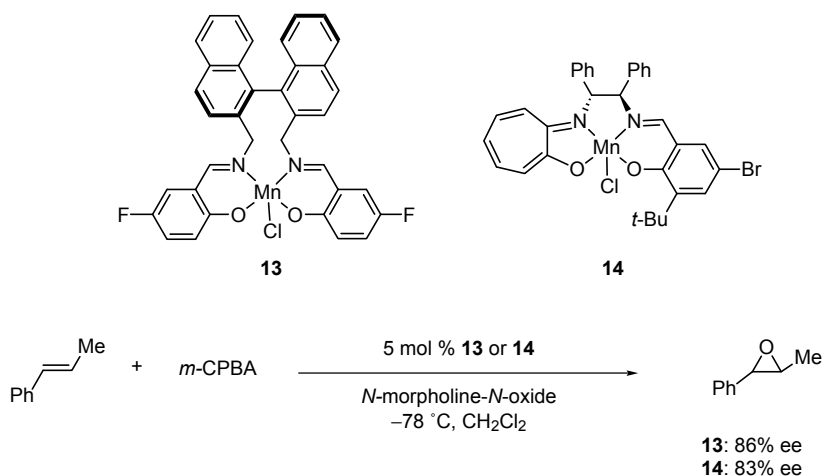
Katsuki and co-workers have examined AE with Mn(salen) catalysts **12a**, **b** bearing stereogenic centers on the 3- and 3'-positions of the salen ligand [63, 64]. The importance of these substituents was dramatically demonstrated with complex **12a**. Even with an achiral ethylenediamine backbone, catalyst **12a** effected the epoxidation of *trans*-stilbene in 61% ee (Scheme 2) [65]. Further optimization of the 3,3'-substituents led to the discovery of the more elaborate catalyst **12b**, which incorporates axial dissymmetry into the aromatic portion of



Scheme 2

the ligand. Complex **12b** represents the most enantioselective Mn(salen) catalyst known to date for the AE of several *cis*-disubstituted and trisubstituted olefins [66]. The sterically-demanding 3,5-dimethylphenyl groups on the ethylenediamine bridge together with the phenylnaphthalene substituents are believed to reinforce catalyst electronic effects to induce approach of the olefin substrate along one of the Mn-N vertices towards the metal-oxo bond.

trans-Olefins remain a particularly challenging substrate class for AE with oxo-transfer catalysts. Very recently, two novel Schiff base complexes have been developed by Jacobsen to address this issue [67]. Complex **13** replaces the conventional 1,2-diamine backbone with an axially dissymmetric diamine, and this catalyst exhibited improved enantioselectivity in the epoxidation of *trans*- β -methylstyrene (Scheme 3). Whereas electron-donating and sterically-demanding substituents are generally favored for catalysts 5-11, the fluoro-substituted complex **13** lacking 3,3'-substituents afforded the epoxide in 86% ee. In a different approach, replacing one of the salicylide units in a 1,2-diphenylethylenediamine-derived system with a tropolone ring afforded the non C_2 -symmetric Mn complex **14**. An X-ray structural analysis of **14** revealed a significant distortion of the metal center that placed the manganese atom 0.38 Å above the ligand plane. This pyramidalization might permit an unhindered approach towards the metal-oxo reactive site, a key consideration with sterically-demanding substrates such as *trans*-olefins. In fact, *trans*- β -methylstyrene was epoxidized in 83% ee

**Scheme 3**

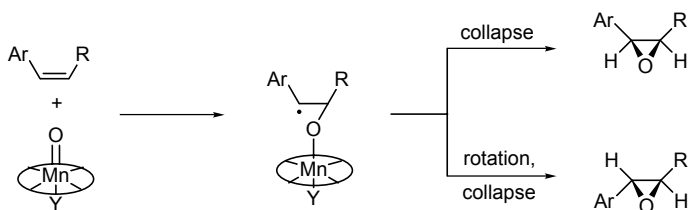
using catalyst **14**. The reversal of absolute stereoselection in the formation of product compared to the C_2 -symmetric complexes strongly suggested a fundamentally different mechanism for chiral recognition using these novel catalysts.

2.2.2

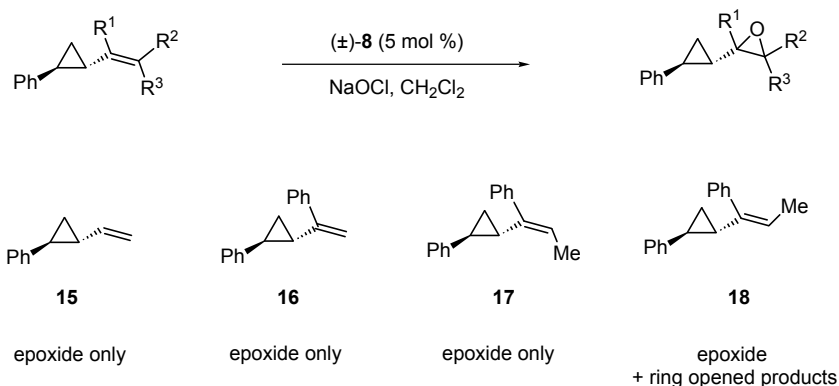
Mechanism of Olefin Epoxidation by Mn(salen) Complexes

Compelling evidence for stepwise C-O bond formation in [Mn(salen)]-catalyzed epoxidation is found in the formation of both *cis*- and *trans*-epoxides as primary products from acyclic *cis*-olefins [68]. The extent of *trans*-epoxide formation depends strongly on the nature of the substrate. Whereas simple alkyl-substituted *cis*-olefins are epoxidized stereospecifically, aryl-substituted *cis*-olefins afford mixtures of *cis*- and *trans*-epoxides with the *cis*-isomers being formed selectively. Epoxidations of conjugated dienes and enynes also afford *cis/trans* mixtures, with the *trans*-epoxide product predominating. These observations may be interpreted according to a stepwise mechanism in which a discrete radical intermediate undergoes competitive collapse to *cis*-epoxide and rotation/collapse to *trans*-epoxide (Scheme 4).

Epoxidation of radical probe substrates was examined to ascertain the viability of intermediates generated from stepwise C-O bond formation. The absence of radical rearrangement products in the [Mn(salen)]-catalyzed epoxidation of **15** strongly suggested that alkyl-substituted olefins are epoxidized in a concerted fashion (Scheme 5) [23]. This finding holds true for alkyl-substituted olefins in general, including those lacking radical probes. Aryl-substituted olefins have been more recently examined in the context of radical clock experiments [24]. The surprising absence of products derived from cyclopropane ring fragmentation was used to dispute the existence of radical intermediates derived from con-



Scheme 4



Scheme 5

jugated olefins **16** and **17**. Concerted bond formation to form an oxametallacycle intermediate was then argued to account for the product observed. However, this negative result is inconsistent with many examples of nonstereospecific epoxidation by Mn(salen) catalysts of aryl-substituted olefins [68]. In fact, olefin **18** does undergo cyclopropane rearrangement under identical epoxidation conditions.

The oxametallacycle mechanism places an unusual constraint on the coordination environment of the manganese center. Whereas the formation of a radical intermediate requires only the presence of the apical oxo ligand, formation of oxametallacycle **19** requires that a coordination site is available for formation of the Mn-C bond and that this coordination site is adjacent to the oxo ligand (Fig 5a). The availability of these coordination sites is seriously drawn into question when one takes into account the established enhancing effect of Lewis basic additives on the outcome of the reaction. Additives such as pyridine *N*-oxide positively influence the rate, yield, *cis/trans* ratio, and enantioselectivity of the [Mn(salen)]-catalyzed epoxidation with a range of terminal oxidants [19, 25, 50, 69]. The binding of *N*-oxide to the manganese center is thought to facilitate the rate-limiting oxidation to the metal-oxo, as well as stabilize the high-valent Mn(V) species. Further evidence that *N*-oxide additives function as beneficial

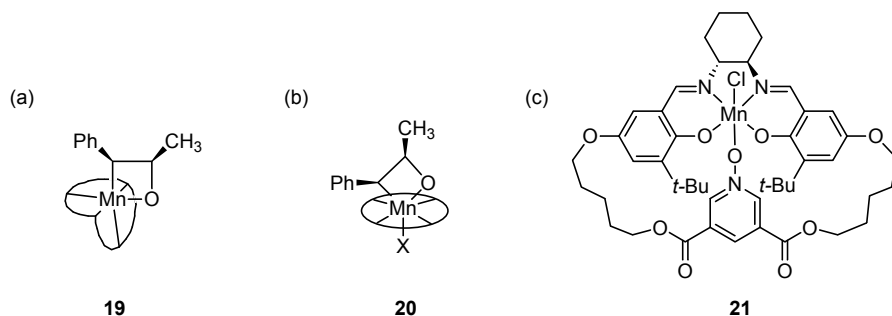


Fig. 5

axial ligands was provided by a study of catalyst **21** covalently strapped with a pyridine *N*-oxide derivative (Fig. 5c) [15]. An X-ray crystal structure analysis established axial coordination of the tethered *N*-oxide, and epoxidation reactions with this catalyst showed no dependence on external *N*-oxide additives.

Axial binding of *N*-oxide throughout the catalytic cycle implies that the adjacent coordination sites required for oxametallacycle formation are unavailable. The 7-coordinate intermediate **20** (Fig. 5b) would suffer from severe steric interactions between the oxametallacycle and the ligand, and seems unlikely given the success of hindered Mn(salen) catalysts such as **8**. While dissociation of *N*-oxide during oxametallacycle formation cannot be categorically excluded, the body of evidence supports a simpler mechanism involving direct attack of the olefin substrate at the metal-oxo bond.

The profound electronic influence of substituents, particularly at the 5- and 5'-positions of the salicylide ligand, on the enantioselectivity of Mn(salen) catalysts has also provided essential information on the reaction mechanism [70]. Dramatic catalyst electronic effects were first reported by Jacobsen in 1991, who found that electron-donating substituents on the ligand led to higher levels of asymmetric induction [71]. A range of electron-donating to electron-withdrawing substituents at the 5- and 5'-positions were evaluated with three representative olefin substrates, and a direct correlation between product enantiopurity and the σ_p values of the 5,5'-substituents on catalysts **22a–e** was observed (Fig. 6). The linear relationship was interpreted to reflect changes in the reactivity of the Mn(V)-oxo intermediate imparted by the substituents on the catalyst, where electron-donating substituents were thought to stabilize the high oxidation state and, in turn, attenuate the reactivity of the Mn(V)-oxo species. In accord with the Hammond postulate, a milder oxidant should lead to oxygen atom transfer to an olefin via a more product-like transition state, where stereochemical communication between the catalyst and substrate is maximized (Fig. 7).

The relative position of the transition state along the reaction coordinate was evaluated directly by examining secondary kinetic isotope effects as a function of the electronic character of the catalyst. The relative rates of epoxidation of styrene and β -deuteriostyrene were examined in competition experiments using

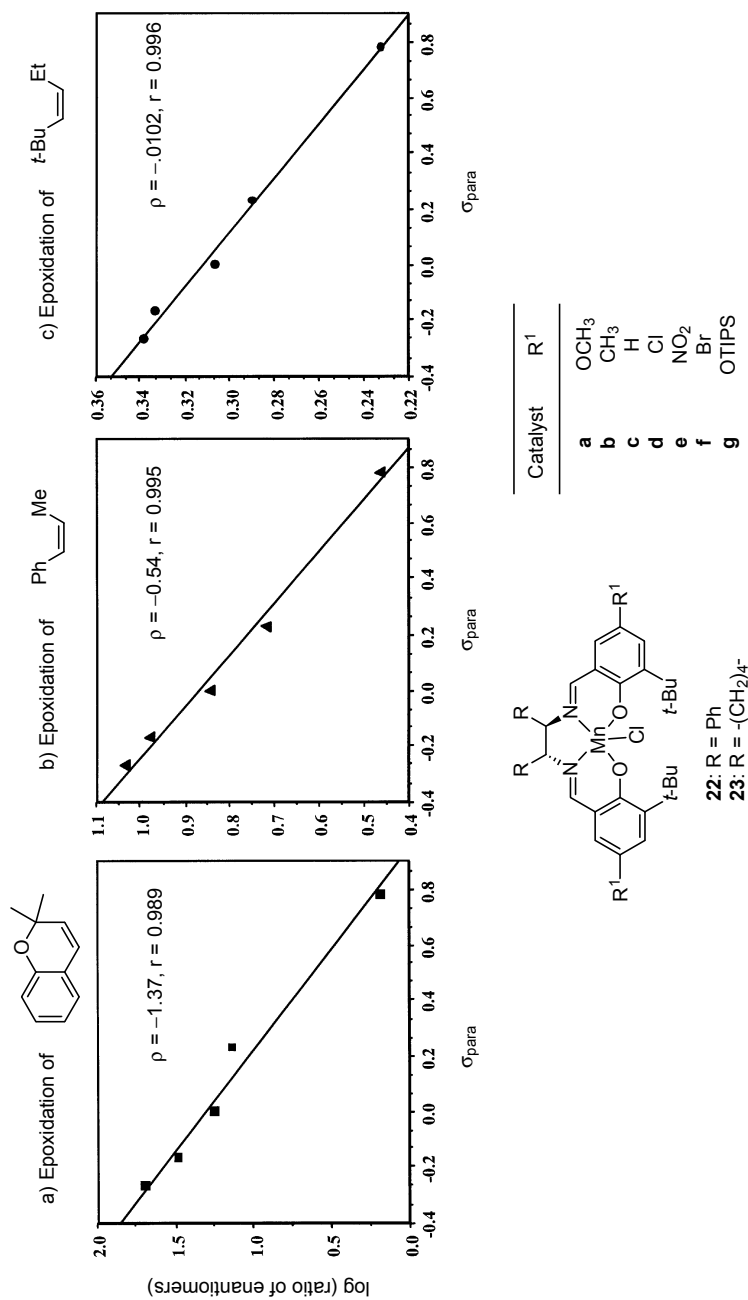


Fig. 6

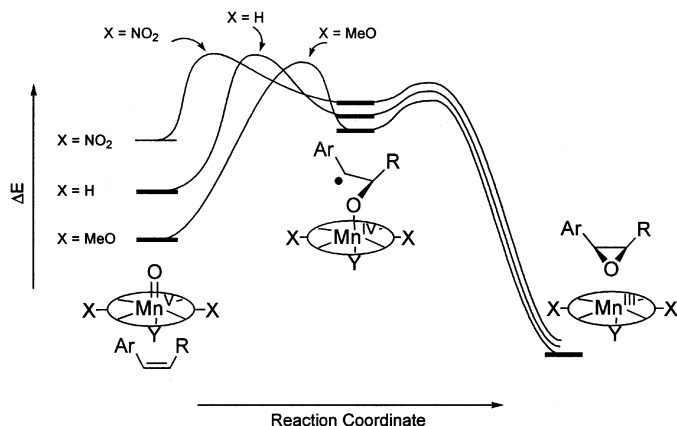


Fig. 7

Mn(salen) catalysts **23a–e** [70]. On transformation to the radical intermediate, the β -carbon of styrene undergoes a formal rehybridization from sp^2 to sp^3 which, in principle, should lead to the observation of an inverse secondary isotope effect ($k_H/k_D < 1$) for the epoxidation (Fig. 8a) [72]. Further, the magnitude of k_H/k_D should vary in concert with the position of the transition state, whereby later transition states in which the β -carbon has more sp^3 character should exhibit smaller values of k_H/k_D . A direct correlation between k_H/k_D and σ_p was observed, indicating that the electronic character of the catalyst does indeed alter the degree of rehybridization at the β -carbon and thus the position of the transition state leading to formation of the radical intermediate (Fig. 8b).

Examination of the reactivity of catalysts **22a–c** and **22e–g** at various reaction temperatures helped to shed additional light on the origin of the dramatic electronic effects on catalyst enantioselectivity. Over a 100 °C temperature range, a linear relationship between enantioselectivity and σ_p was observed. An important finding was that the Hammett plots intersected at a single “isoelectronic point”, suggesting that varying the electronic character of the catalyst influenced only one type of interaction in the system (Fig. 9) [73]. This isoelectronic relationship was inferred to reflect the degree of the first C–O bond formation and thus the position of the enantiodifferentiating transition state along the reaction coordinate.

Evaluation of activation parameters for the diastereomeric transition states leading to product revealed an interesting trend whereby the enthalpic contribution ($\Delta\Delta H^\ddagger$) dominated in the more enantioselective reactions effected by electron-rich catalysts, while conversely the entropic contribution ($\Delta\Delta S^\ddagger$) became more important with less enantioselective catalysts bearing electron-withdrawing substituents. This correlation between relative activation parameters for the diastereomeric transition states and the electronic properties of the catalysts is consistent with the Hammond postulate arguments presented above. If electron-

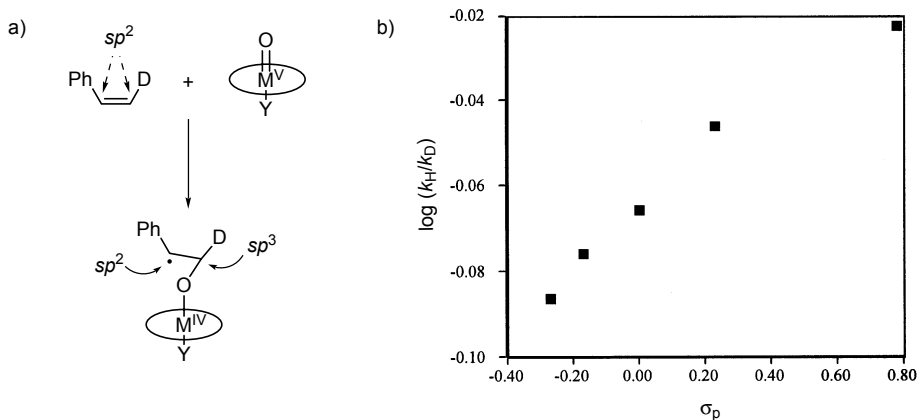


Fig. 8

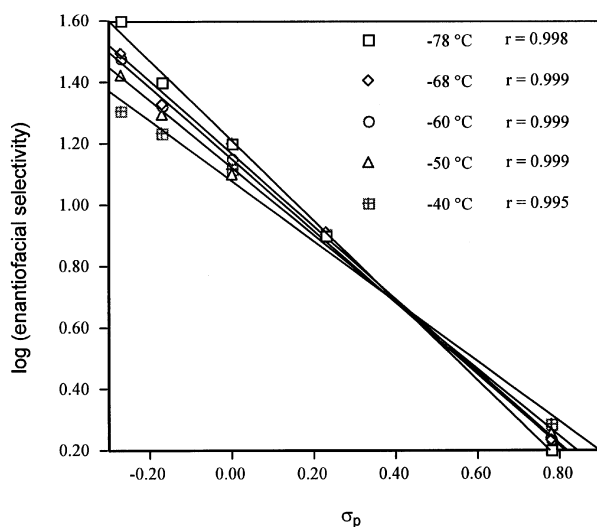


Fig. 9

donating substituents do lead to a later transition state with a more highly developed C-O bond, the energetic differences between the diastereomeric transition states should depend more strongly on the degree of bond formation (reflected by $\Delta\Delta H^\ddagger$). Similarly, in the case of electron-deficient catalysts, the differences in energies of an earlier transition state which is less-ordered and characterized by a lower degree of C-O bond formation should derive primarily from entropic factors.

In short, the experimental results presented above collectively form a more coherent understanding of the [Mn(salen)]-catalyzed epoxidation of unfunctionalized olefins. Side-on approach of the substrate at the metal-oxo species leading to stepwise C-O bond formation offers a straightforward explanation for product selectivity and additive effects. The degree of C-O bond formation reflects the position of the transition state along the reaction coordinate, and it is this position that is critical to the level of asymmetric induction in the [Mn(salen)]-catalyzed epoxidation.

2.2.3

Substrate Scope

Cyclic and acyclic *cis*-disubstituted olefins have traditionally been the best substrates for the [Mn(salen)]-catalyzed epoxidation reaction. A predictive stereochemical mnemonic for the epoxidation of *cis*-olefins by catalyst **8** is provided in Fig. 10 [19]. Especially high enantioselectivity is observed in the epoxidation of 2,2-dimethylchromene derivatives, which seem to combine several steric and electronic elements that lead to enhanced selectivity (Fig. 11) [74].

Two successful strategies for the enantioselective synthesis of *trans*-epoxides by means of oxo-metal catalysis have been discovered. The stereospecific epoxidation of *trans*-olefins offers a direct route to *trans*-epoxides, although progress in this area has been limited (see Sect. 2.2.1). Alternatively, the [Mn(salen)]-catalyzed epoxidation of *cis*-disubstituted olefins in the presence of alkaloid-derived phase-transfer catalysts such as **24** resulted in the formation of the *trans*-epoxide as the major, and in some cases nearly exclusive, product (Scheme 6) [75]. Although the mechanistic basis for the effect of added alkaloid derivatives remains quite unclear, this methodology provided a useful method for the prep-

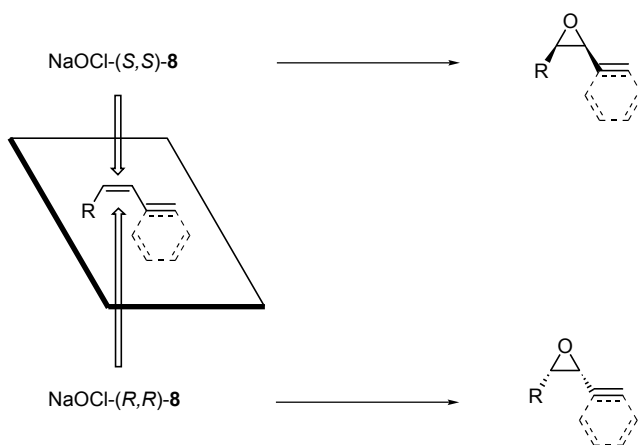
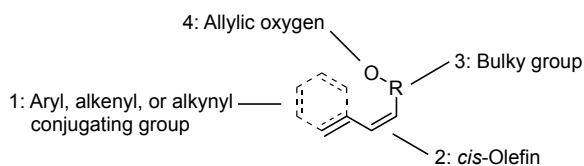


Fig. 10

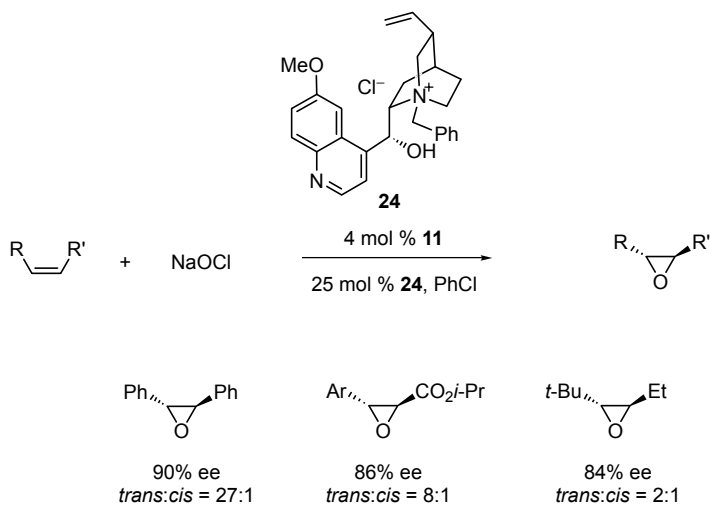


Substrate	ee (%)	Properties
	97	1,2,3,4
	88	1,2
Ar-CH=CH-CO ₂ Me	72-85	1,2,4
	93	1,2,3
	78	1,2
	94	2,3,4
	25	2,3

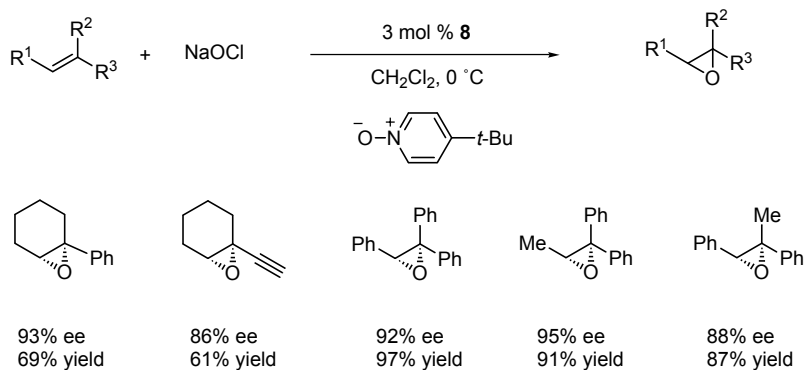
Fig. 11

ation of *trans*-epoxides with high enantioselectivity from synthetically-accessible *cis*-olefins.

Given the difficulties encountered in the epoxidation of *trans*-olefins by Mn(salen) complexes, it is intriguing that a wide range of trisubstituted olefins are outstanding substrates for asymmetric epoxidation (Scheme 7) [62, 76]. The absolute stereochemistry of the epoxide products is inverted at the benzylic carbon when compared with the sense of induction seen with *cis*-disubstituted olefins. A qualitative transition state model has been suggested wherein the trisubstituted substrate reacts with the metal-oxo complex via a skewed side-on approach (Fig. 12). The distortion of trisubstituted olefins from planarity resulting from $A_{1,2}$ or $A_{1,3}$ interactions may be critical in this context.



Scheme 6



Scheme 7

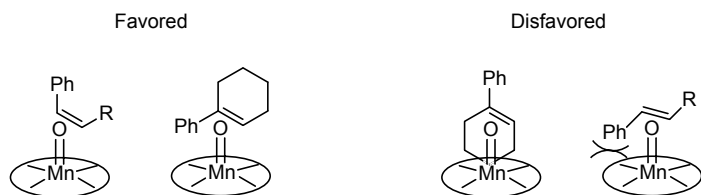
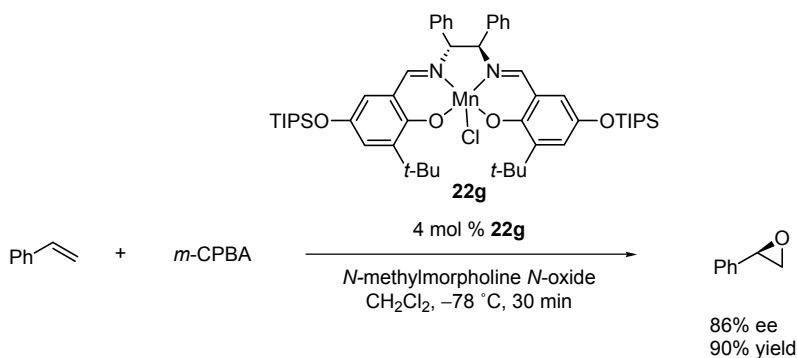


Fig. 12



Scheme 8

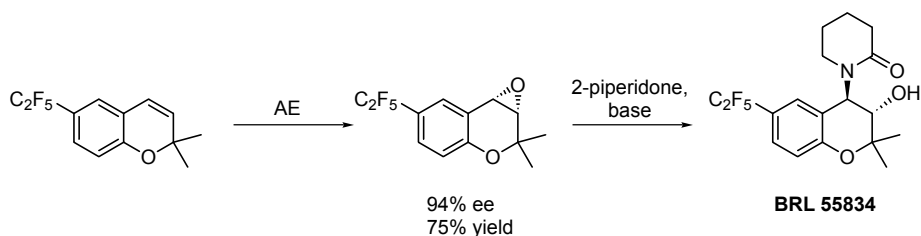
Terminal olefins represent another challenging substrate class. For olefins such as styrene, *cis-trans* partitioning leads to diminished catalyst enantioselectivity (60–70% ee). A viable solution was reported through an efficient low-temperature Mn(salen) epoxidation protocol employing *N*-methylmorpholine *N*-oxide and *m*-CPBA [77]. Improved enantioselectivities were attainable for most substrates under low-temperature conditions, but the effect was especially pronounced in the case of terminal olefins. Epoxidation of styrene, for instance, occurred rapidly to afford the epoxide in 86% ee using catalyst **22g** (Scheme 8). Deuterium-labelling experiments revealed that the improved enantioselectivity derived from enhancement of olefin facial selectivity in initial C–O bond formation as well as suppression of deleterious *cis-trans* partitioning.

2.2.4

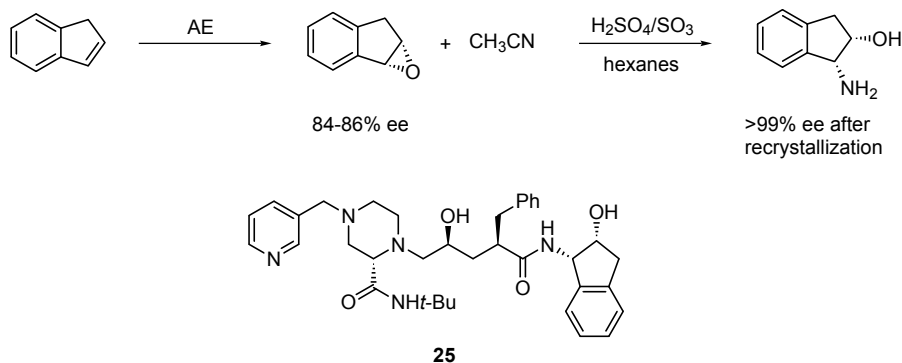
Synthetic Applications

The high enantioselectivities attained with several olefin substrate classes have allowed the [Mn(salen)]-catalyzed epoxidation to become a widely used reaction in asymmetric synthesis. Several recent examples from the literature serve to illustrate the synthetic utility of this catalytic transformation.

The [Mn(salen)]-catalyzed epoxidation of chromene derivatives was discovered to occur with exceptional enantioselectivity [74]. Chromene derivatives bearing 2,2-disubstitution appear to combine all the important substrate characteristics required for a highly enantioselective epoxidation. The synthetic utility of the enantioenriched epoxychroman products is increased by the predictable regio- and stereochemical outcome of epoxide ring opening with a variety of nucleophiles. These two features were highlighted in the synthesis of the selective potassium channel activator BRL 55834 [78]. Catalyst loadings as low as 0.2 mol % of **8** in the presence of catalytic amounts of an *N*-oxide additive afforded the epoxide in 94% ee, which underwent regioselective ring opening to produce BRL 55834 in 81% yield (Scheme 9) [79].



Scheme 9

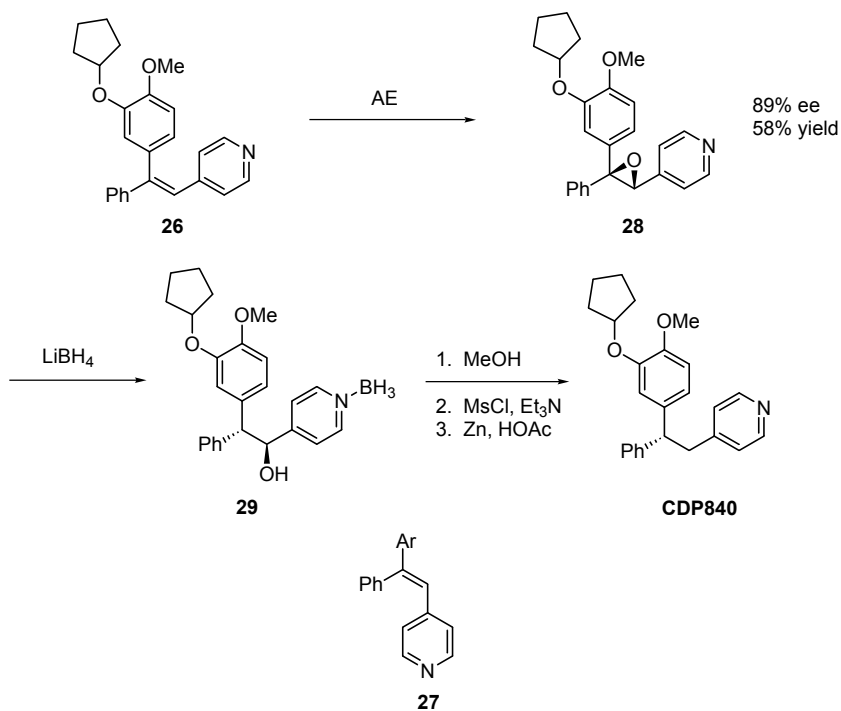


Scheme 10

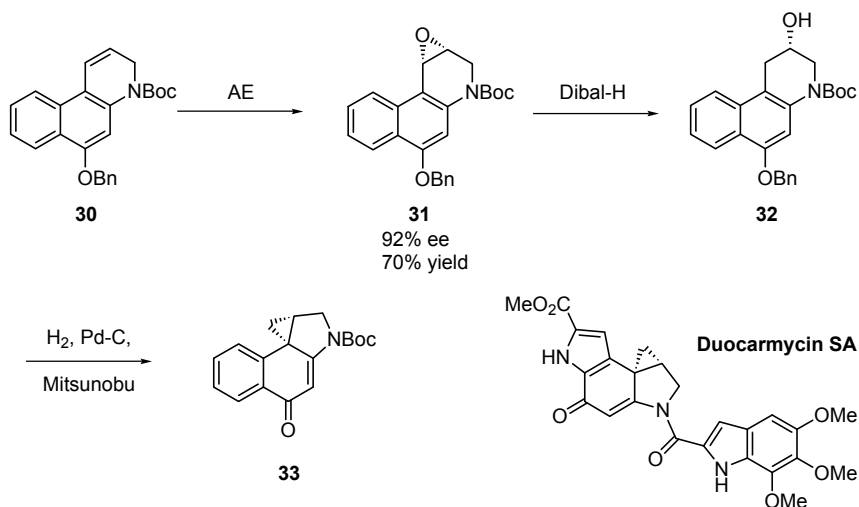
The $[\text{Mn}(\text{salen})]$ -catalyzed epoxidation of indene has also proven to be synthetically useful in various contexts. Enantio-enriched indene oxide, produced in 84–86% ee by AE of the corresponding olefin, is a precursor to important building blocks including *cis*-aminoindanol through a Ritter reaction (Scheme 10) [80]. *cis*-2-Aminoindan-1-ol has been incorporated into structures ranging from HIV-protease inhibitors (Indinavir, **25**) [81] to ligands for selective metal catalysts [82,83].

The AE of unfunctionalized olefins has also been featured in less obvious applications where neither C–O bond is retained in the final product. In the synthesis of CDP840, for instance, $[\text{Mn}(\text{salen})]$ -catalyzed epoxidation of the pyridine-containing trisubstituted olefin **26** afforded the epoxide **28** in 89% ee (Scheme 11) [84]. Poor selectivities were observed with the olefin isomer **27**, which can be explained using the proposed “skewed side-on approach” model (*vide supra*) [62]. The epoxide was then reductively opened to afford the secondary alcohol **29**, which underwent clean deoxygenation to afford the target structure.

The alkylation subunit of CC-1065 and duocarmycin has been efficiently synthesized using $[\text{Mn}(\text{salen})]$ -catalyzed epoxidation [85]. AE of intermediate **30** using low-temperature *m*-CPBA epoxidation conditions [77] afforded the epoxide **31** in 70% yield and 92% ee (Scheme 12). Reductive cleavage of the epoxide



Scheme 11

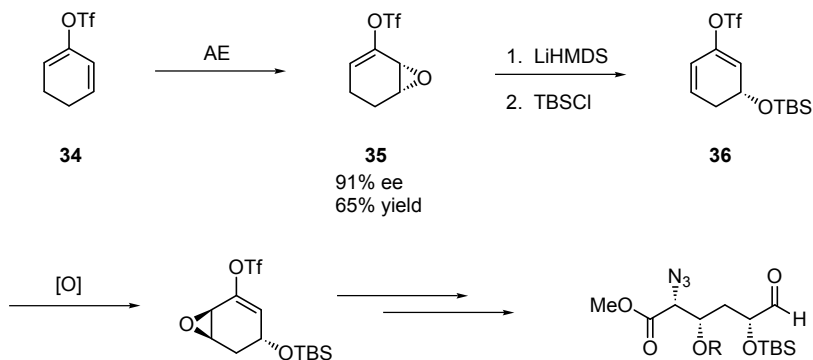


Scheme 12

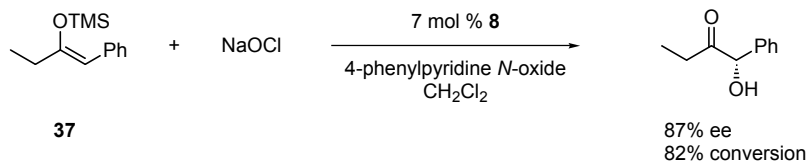
was followed by transannular spirocyclization to afford the activated cyclopropane **33** in an efficient fashion.

The above examples highlight how enantioselective olefin epoxidation coupled with stereospecific ring opening transformations can provide access to enantioenriched products difficult to synthesize using more direct stereoselective methods. Fuchs has developed another interesting application of [Mn(salen)]-catalyzed epoxidation, using 1,3-cyclohexadiene derivatives as AE substrates [86]. Regio- and enantioselective epoxidation of the cyclohexadienyl triflate **34** afforded the monoepoxide **35** in 65% yield and 91% ee (Scheme 13). Base-induced ring opening of the epoxide generated the dienyl triflate **36** in good yield, which can undergo a series of stereoselective transformations to access densely-functionalized cyclic and acyclic products.

The Mn(salen) complex **8** has also been applied towards the synthesis of α -hydroxy carbonyl compounds from enol ethers and ketene acetals [87, 88, 89]. These substrates are a special class of trisubstituted olefins, previously demonstrated to be excellent substrates for AE. Indeed, the observed sense of stereoinduction in the oxidation of enol ether derivatives adheres to the skewed side-on approach model developed for trisubstituted olefins. In the presence of 7 mol % of **8**, silyl enol ether **37** was oxidized under bleach conditions to afford the α -hydroxy ketone in 87% ee (Scheme 14) [89].



Scheme 13



Scheme 14

2.3 Chiral Porphyrin Complexes

The design of viable, highly enantioselective epoxidation catalysts based on porphyrin ligands is confronted by the inherent difficulty associated with inducing dissymmetry from remote parts of an sp^2 -hybridized coordination sphere, and the relative difficulties in constructing the chiral porphyrin rings. As research in this field has been the subject of an insightful review [90], only more recent developments will be covered here.

Collman has developed two of the more effective porphyrin-based enantioselective epoxidation systems. Catalyst **38** incorporates a threitol-derived strap that spans only one of the non-equivalent faces of the porphyrin ring (Fig. 13) [91]. In order to prevent competitive and non-selective reaction of the olefin at the unhindered face of the ligand, a bulky ligand (1,4-dicyclohexylimidazole) is incorporated to bind to the metal center on this open face during the reaction. The oxo ligand in the active complex was thus suggested to reside within the asymmetric cavity, leading to optimal stereochemical communication between substrate and ligand in the epoxidation event.

The dicyclohexylimidazole additive could be omitted when the threitol-strapped ligand was replaced with complex **39** containing a pseudo- C_2 axis of symmetry bisecting the porphyrin plane (Fig. 13) [92]. This ligand offers ample space for olefin approach while at the same time creating a dissymmetric environment in close proximity to the metal center. Catalyst loadings as low as 0.1 mol % were sufficient to effect the epoxidation of several terminal olefins us-

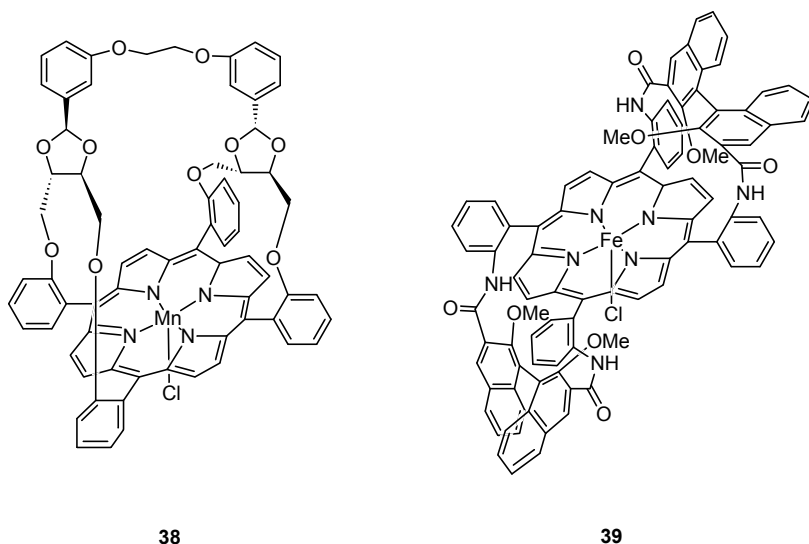
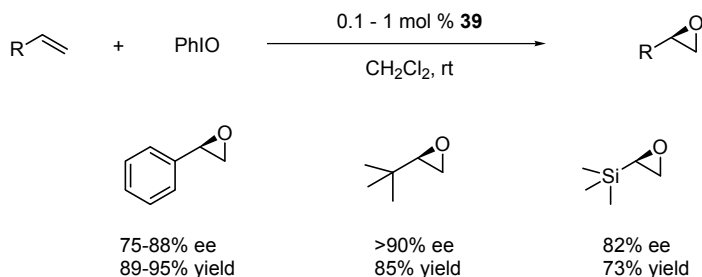


Fig. 13



Scheme 15

ing iodosyl benzene as the oxidant. The epoxidation of styrene, for instance, afforded the epoxide in 75–88% ee, where the enantioselectivity of **39** varied in the presence of additives or with portion-wise addition of the terminal oxidant (Scheme 15). Non-conjugated terminal olefins such as 3,3-dimethylbutene and vinyltrimethylsilane were also found to be excellent substrates.

3

Epoxidation with Chiral Dioxiranes

The oxidation of organic compounds with dioxirane reagents has emerged as an important synthetic method [93, 94, 95]. The effective use of dimethyldioxirane and methyl(trifluoromethyl)dioxirane for the mild and efficient oxidation of olefins, sulfides, amines, and saturated hydrocarbons naturally raised the question whether chiral versions of these reagents can be developed.

Dioxiranes are most conveniently prepared in situ by treatment of a ketone with potassium peroxomonsulfate (Oxone) [96, 97]. Either of the oxygen atoms can be transferred to an olefin, which presents an important challenge towards designing a stereoselective dioxirane epoxidation method. Regeneration of the ketone precursor following oxygen atom transfer creates the possibility of employing catalytic amounts of ketone for epoxidation.

3.1

Mechanistic Considerations

Denmark has recently disclosed results that help address the question of whether dioxirane (**A**) or Criegee-type (**B**) intermediates are involved in ketone-catalyzed epoxidation reactions (Fig. 14) [98]. [¹⁸O]-Labeling experiments using ketone **40** showed 80% of the expected isotope label was incorporated into the epoxide product, providing compelling evidence that dioxiranes are indeed the active oxidizing species [99].

Within the context of dioxirane-mediated oxygen transfer, the orientation of the dioxirane with respect to the substrate olefin has important implications for potential stereinduction models. Spiro (**A**) and planar (**B**) transition states rep-

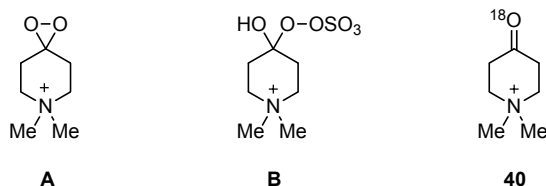


Fig. 14

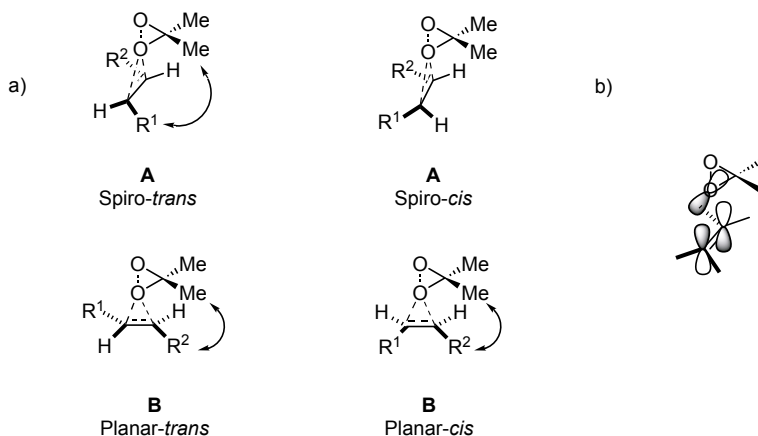


Fig. 15

resent two mechanistic extremes (Fig. 15a). A spiro orientation was proposed by Baumstark et al based on the observation that *cis*-olefins were epoxidized 7–9 times faster than their corresponding *trans*-isomers with dimethyldioxirane [100,101]. The absence of steric interactions between *cis*-olefin substituents and the methyl groups on the dioxirane in the spiro transition state was used to support the relative rate of *cis*- versus *trans*-substrates as well as the spiro arrangement. Subsequent theoretical treatment of the spiro and planar transition states by Houk has provided additional evidence that the spiro orientation is lower in energy [102]. An important molecular orbital consideration that contributes to this stability is the interaction of the oxygen lone pair with the π^* orbital of the olefin (Fig. 15b) [103].

3.2

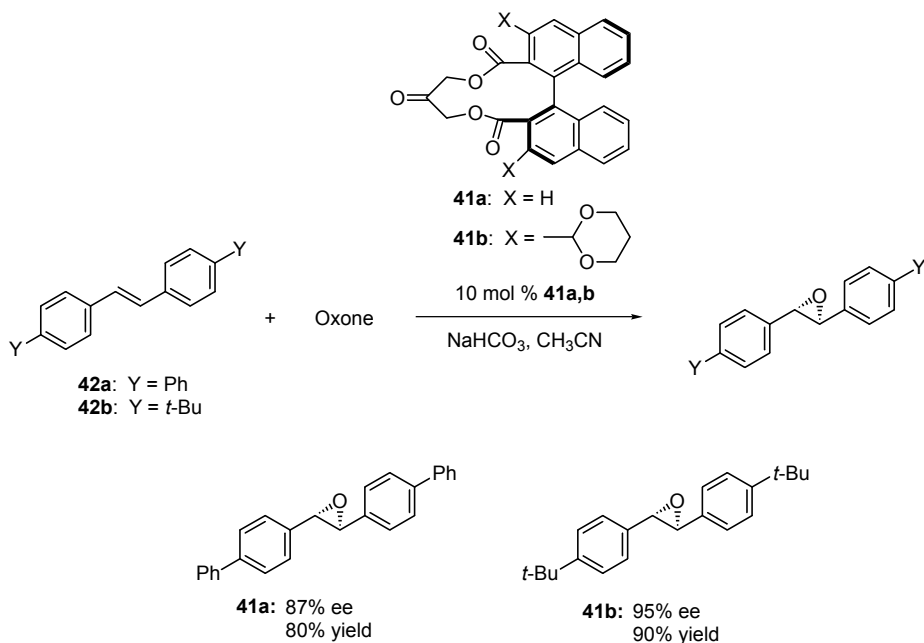
Chiral Dioxiranes

The potential for chiral ketones to effect the catalytic asymmetric epoxidation of olefins was first demonstrated by Curci in 1984 [104]. Since then, moderately selective catalytic [105, 106] and stoichiometric examples have emerged [107, 108,

109], but only recently has significant progress been made in effective asymmetric epoxidation methods using catalytic amounts of chiral ketone.

An important advance was made by Yang in 1996, who discovered that ketones bearing electron-withdrawing groups such as halogen atoms and OAc adjacent to the carbonyl showed higher catalytic activity in epoxidations of *trans*-olefins with Oxone [110]. This discovery led to the design of the C_2 -symmetric chiral ketone **41a** which effected the catalytic epoxidation of unfunctionalized olefins with moderate levels of enantioselectivity (Scheme 16). Ketone **41a** incorporated the necessary electron-withdrawing substituents required for catalytic activity, and also relied on axial chirality to avoid complications from epimerization of α -stereogenic centers. High enantioselectivities were obtained in the epoxidation of *trans*-stilbene derivative **42a**, which was produced in 80% yield and 87% ee [111]. Further optimization established that the 2,2'-substituted ketone catalyst **41b** catalyzed epoxidation of **42b** in 95% ee [112].

Yang has also developed the chiral ketone **43** derived from carvone that has allowed the investigation of electronic effects of remote nonconjugated substituents on catalyst enantioselectivity (Fig. 16) [113]. In comparing two possible transition states A and B, Yang identified n - π electronic repulsion between the 2-chloro substituent on the ketone catalyst and the phenyl ring on the substrate as a likely controlling element that favored transition state A leading to the observed product. This electronic repulsion was believed to be more pronounced



Scheme 16

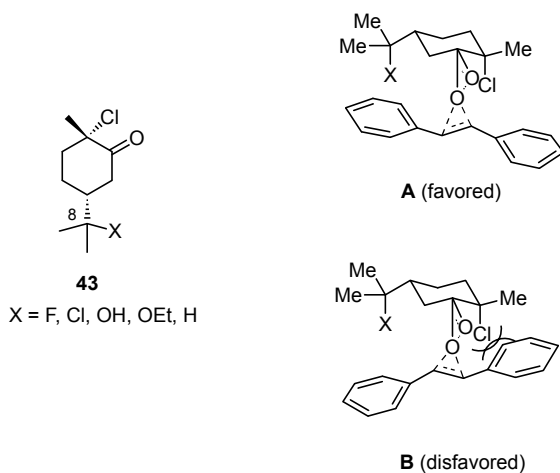
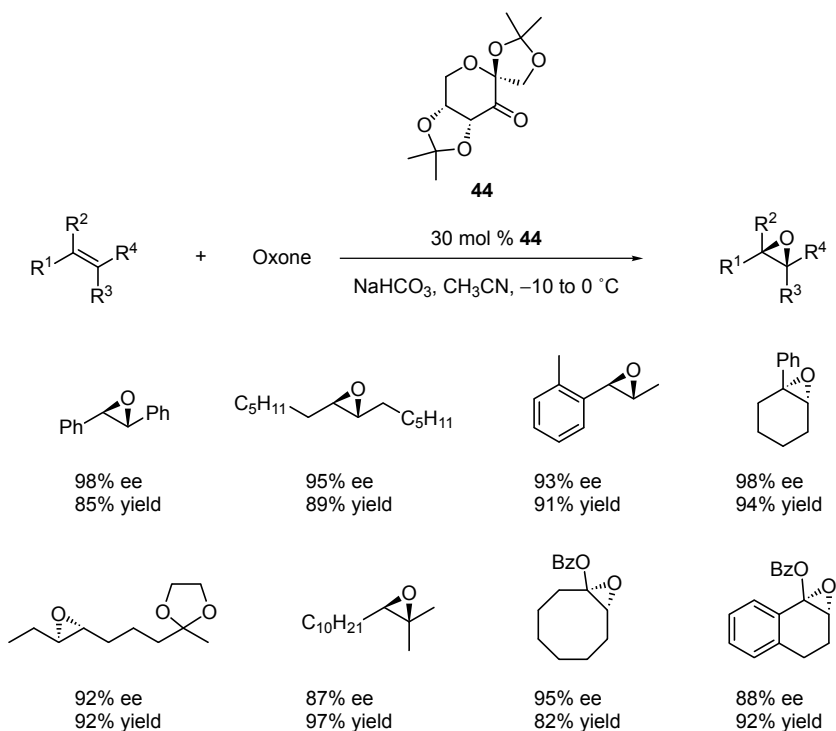


Fig. 16

with electron-rich olefins, which are epoxidized in higher ee than electron-deficient substrates. Moreover, a linear relationship between σ_m or σ_p and the enantiomeric ratio of epoxide products was obtained. Substitution at the quaternary C8 position of ketone **43** allowed further exploration of electronic field effects in the catalytic epoxidation of olefins with these dioxiranes.

The ability of non- C_2 symmetric ketones to promote a highly enantioselective dioxirane-mediated epoxidation was first effectively demonstrated by Shi in 1996 [114]. The fructose-derived ketone **44** was discovered to be particularly effective for the epoxidation of *trans*-olefins (Scheme 17). *trans*-Stilbene, for instance, was epoxidized in 95% ee using stoichiometric amounts of ketone **44**, and even more impressive was the epoxidation of dialkyl-substituted substrates. This method was rendered catalytic (30 mol %) upon the discovery of a dramatic pH effect, whereby higher pH led to improved substrate conversion [115]. Higher pH was proposed to suppress decomposition pathways for ketone **44** while simultaneously increasing the nucleophilicity of Oxone. Shi's ketone system has recently been applied to the AE of enol esters and silyl enol ethers to provide access to enantio-enriched enol ester epoxides and α -hydroxy ketones [116]. Another recent improvement of Shi's fructose-derived epoxidation reaction is the development of inexpensive synthetic routes to access both enantiomers of this very promising ketone catalyst [117].



Scheme 17

4 Conclusion

Despite the significant improvements that have been made in metal-oxo- and dioxirane-catalyzed oxidation of unfunctionalized olefins, a completely general approach to asymmetric epoxidation remains elusive. This has inspired the development of alternative, indirect methods for the preparation of enantio-enriched epoxides. These include kinetic resolution of epoxides by synthetic catalyst-mediated [118] or enzymatic [119, 120, 121, 122] hydrolysis, asymmetric alkene dihydroxylation followed by conversion of diol to epoxide [123, 124], and asymmetric reduction of α -halo ketones followed by base-induced ring closure [125]. Nonetheless, despite the high level of practicality displayed by some of these methods, there is no question that direct epoxidation of prochiral olefins is the most attractive approach. It remains to be seen whether the next breakthrough in asymmetric olefin epoxidation will emerge from further tuning of existing (salen)-metal, (porphyrin)-metal, or dioxirane methodologies, or perhaps from completely novel catalyst systems [126].

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Chapter 18.3

Epoxide Formation of Enones and Aldehydes

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Keywords: Sulfur ylides, Carbenes, Betaines, Polyamino acids, Nucleophilic oxidation, Metal peroxides, Epoxidation

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1

Introduction

Chiral epoxides frequently play a key role as intermediates in organic synthesis and the development of methods for the catalytic asymmetric synthesis of such compounds therefore remains an area of intensive research. Methods have focused principally on the asymmetric electrophilic oxidation of alkenes and good enantioselectivity has been achieved [1]. An alternative to oxidative processes for the synthesis of epoxides is the reaction of sulfur ylides with aldehydes and ketones [2, 3, 4, 5, 6]. Sulfur ylide epoxidation is a carbon-carbon bond forming reaction and is complementary to oxidative methods. The standard conditions for this reaction utilize the original Corey method: treatment of a sulfonium salt with a strong base in the presence of or followed by the addition of an aldehyde

[2]. This reaction gives epoxides in good yield and returns the corresponding sulfide. In order to render this process catalytic in sulfide, it is necessary to find conditions for converting the sulfide back into the sulfur ylide in the presence of the carbonyl compound. Two procedures have been developed to achieve this: (i) sulfide alkylation in the presence of base and (ii) reaction of a sulfide with a diazo compound in the presence of a suitable metal catalyst. These methods are discussed in more detail in this chapter.

Nucleophilic oxidation of electron-deficient alkenes provides an alternative route to epoxides and asymmetric developments in this area are also discussed.

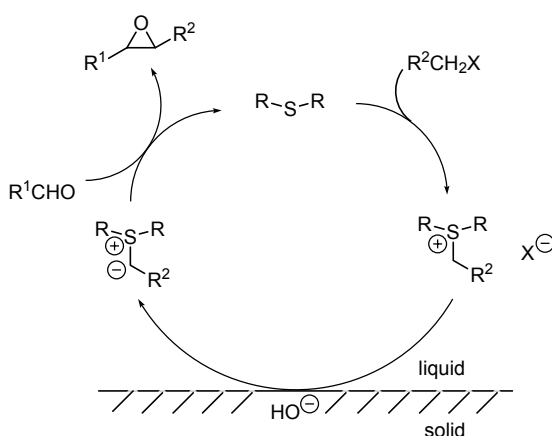
2 Sulfur Ylide Epoxidations

2.1 Ylide Generation by Alkylation under Basic Conditions

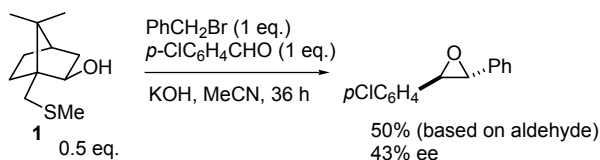
Furukawa first reported a one-pot synthesis of epoxides using a reaction system composed of alkyl sulfides, alkyl halides, and aldehydes in the presence of solid KOH in MeCN (Scheme 1) [7]. Using chiral sulfide **1** enantiomerically enriched epoxides were obtained but with only moderate enantioselectivity and yield (Scheme 2).

Considerably higher yields, slightly higher enantioselectivity, and moderate levels of turnover have been achieved by Dai using the same catalytic process but with different sulfides, e.g., **2** (Scheme 3) [8].

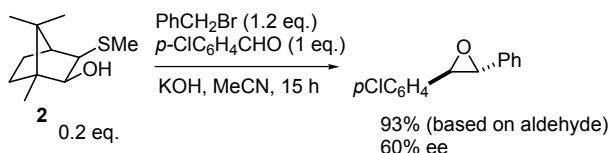
To date only benzyl transfer has been achieved and the reaction has only been applied to aromatic aldehydes [9]. Thus, this system is limited to the formation of stilbene oxides.



Scheme 1



Scheme 2



Scheme 3

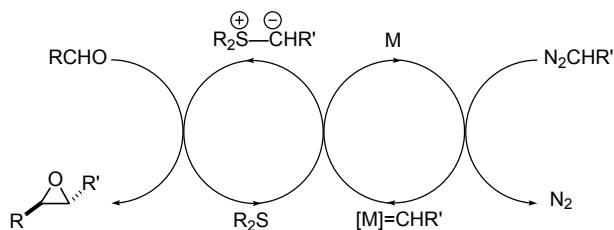
2.2

Ylide Generation from Carbenoids

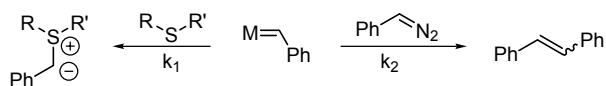
An alternative method for converting a sulfide into an ylide involves the reaction of the sulfide with a carbene or metal carbenoid [10]. We recently reported the successful application of this strategy to carbonyl epoxidation using catalytic quantities of sulfide (Scheme 4) [11, 12, 13].

In this catalytic cycle, a diazo compound is decomposed by a transition metal salt [either $\text{Cu}(\text{acac})_2$ or $\text{Rh}_2(\text{OAc})_4$] to give a metalcarbene which then reacts with a sulfide to give a sulfur ylide. Subsequent reaction of the sulfur ylide with an aldehyde gives the epoxide and returns the sulfide to the catalytic cycle. To obtain good yields of epoxides it is necessary to maintain a low concentration of the diazo compound to minimize dimerization to stilbene side products [14] (Scheme 5; $k_2 > k_1$). This is achieved by slow addition of the diazo compound using syringe pump techniques. Surprisingly, there is no direct reaction between the diazo compound and aldehyde to give homologated products; this process must therefore be much slower than formation of the metal carbenoid.

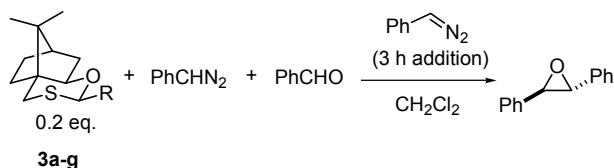
Chiral sulfides based on camphor (**3a-g**) have been tested in the catalytic process for the preparation of non-racemic epoxides (Scheme 6) [15]. It was found that high enantioselectivity could be obtained provided that the thioacetal was substituted at the 2 position (R, **3b-g**). Sterically hindered or electron-withdrawing groups resulted in lower yields in the epoxidation process. The optimum sulfide in terms of yield (73%) and enantioselectivity (93%) was **3b** (R = Me) which underwent highly enantioselective epoxidations with a range of both aromatic and aliphatic aldehydes (Scheme 7). Aliphatic aldehydes gave lower yields (paraformaldehyde did not work) compared to aromatic aldehydes and resulted in a mixture of *trans*- and *cis*-epoxides whereas aromatic aldehydes only



Scheme 4



Scheme 5

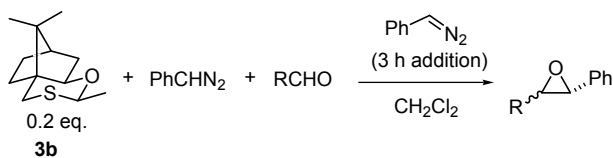


R		yield [%]	ee [%]	dr (<i>trans</i> : <i>cis</i>)
3a	H	83	41 (<i>R,R</i>)	>98:2
3b	Me	73	93 (<i>R,R</i>)	>98:2
3c	<i>i</i> -Pr	45	93 (<i>R,R</i>)	>98:2
3d	<i>t</i> -Bu	0	–	–
3e	CH ₂ Ph	56	88 (<i>R,R</i>)	>98:2
3f	CH ₂ OPh	43	83 (<i>R,R</i>)	>98:2
3g	CH ₂ OMe	70	92 (<i>R,R</i>)	>98:2

Scheme 6

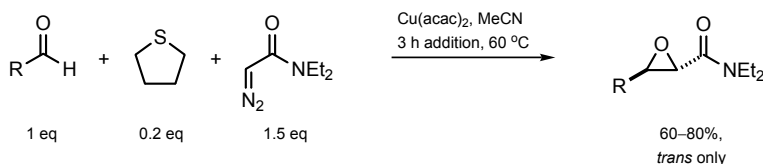
gave *trans*-epoxides. This contrasts with simple sulfides (Me₂S and tetrahydrothiophene) which afford mixtures of *trans*- and *cis*-epoxides in the catalytic cycle with benzaldehyde [12].

The range of diazo compounds that can be used in this catalytic cycle is limited. Diazomethane is not compatible with the system as diazodimerization occurs instead of ylide formation [16, 17]. Diazoacetates cannot be used as the corresponding sulfur ylides are too stable and are known not to react with simple aldehydes [18, 19, 20, 21]. As it was known that sulfur ylides stabilized by amides are sufficiently reactive to add to aldehydes [18, 22, 23, 24, 25], diazoacetamides



R	yield [%]	ee [%]	dr (<i>trans</i> : <i>cis</i>)
Ph	73	93 (<i>R,R</i>)	>98:2
4-Cl-C ₆ H ₄	72	92 (<i>R,R</i>)	>98:2
4-CH ₃ -C ₆ H ₄	64	92 (<i>R,R</i>)	>98:2
PhCH=CH	73	89 (<i>R,R</i>)	>98:2
C ₄ H ₉	35	68 (<i>R,R</i>)	92:8
cyclo-C ₆ H ₁₁	32	90 (<i>R,R</i>)	70:30

Scheme 7



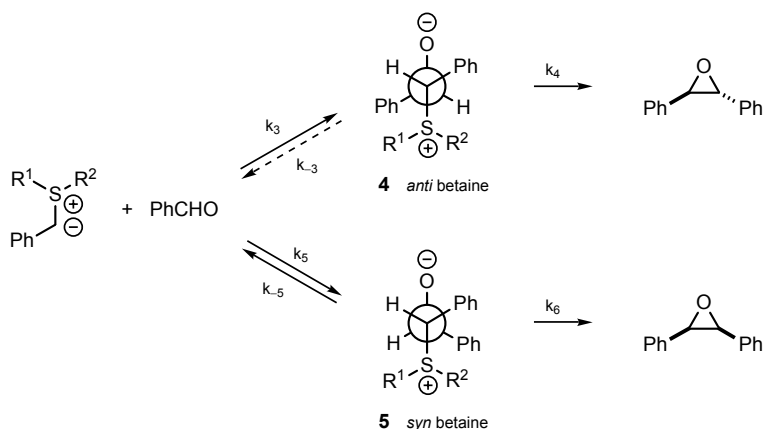
Scheme 8

were tested in the catalytic cycle and proved successful, the corresponding epoxy amides being obtained in good yield (Scheme 8) [26]. This sequence represents a catalytic Darzens reaction and attempts to find suitable chiral sulfides to render this process asymmetric are underway [27].

2.2.1

Origin of Diastereoselectivity

In order to account for the origin of the enantioselectivity and diastereoselectivity of benzylidene transfer, it is necessary to know whether the sulfur ylide reactions are under kinetic or thermodynamic control. From cross-over experiments it was found that the addition of benzylsulfonium ylide to aldehydes was remarkably finely balanced (Scheme 9) [28]. The *trans*-epoxide was derived directly from irreversible formation of the *anti*-betaine 4 and the *cis*-epoxide was derived from partial reversible formation of the *syn*-betaine 5. The higher *trans*-selectivity observed in reactions with aromatic aldehydes compared to aliphatic aldehydes was due to greater reversibility in the formation of the *syn*-betaine.



Scheme 9

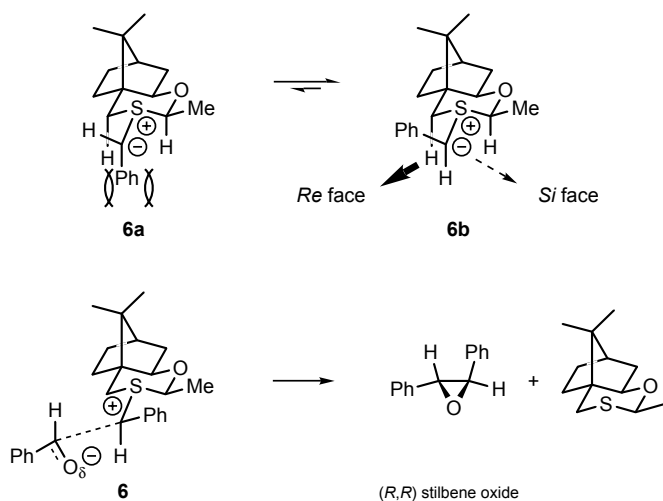
2.2.2

Origin of Enantioselectivity

As the *trans* epoxides are derived from irreversible formation of *anti*-betaines, the observed enantioselectivity must arise from different activation energies associated with the possible transition states leading to betaine formation. The number of transition states which need to be considered can be reduced by gaining information on the structure of the ylide.

A single sulfonium ylide is believed to be formed as alkylation of oxathiane **3a** gave the equatorial sulfonium salt exclusively [29]. Ylide conformation has been studied by X-ray, NMR, and computation [30]. All of these studies indicate that the preferred conformation of sulfur ylides is one in which the filled orbital on the ylide carbon is orthogonal to the lone pair on sulfur. The barrier to rotation around the C-S bond of the semi-stabilized ylide, dimethylsulfonium fluorenone, has been found to be 42 ± 1.0 kJmol⁻¹ [30]. This implies that the ylide will adopt conformations **6a** and **6b** and that these will be in rapid equilibrium at room temperature. Of these two, conformation **6b** will be favored as **6a** suffers from 1,3-diaxial interactions between the phenyl ring and the axial protons of the oxathiane. The aldehyde can approach either face of the ylide but the *Re*-face is more accessible as the *Si*-face is hindered by the equatorial methyl group (Scheme 10).

The aldehyde can react in an end-on or a [2+2] mode but there is no evidence, experimental or theoretical, to indicate which is preferred [31]. An end-on transition state is shown in Scheme 10 and this satisfactorily accounts for the high enantioselectivities observed [32].



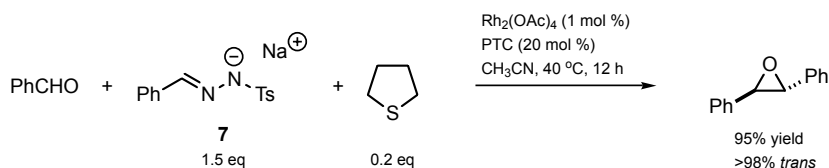
Scheme 10

2.2.3

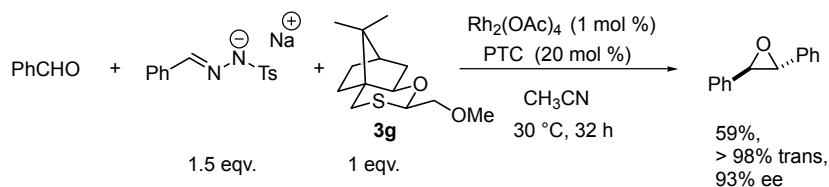
In Situ Generation of Diazo Compounds

The reactions described above have only been conducted on 1 mmol scale. Larger-scale reactions suffer from the significant operational problems associated with the handling and manipulation of large quantities of diazo compounds. However, it has recently been found that the diazo compound can be generated *in situ*, thus circumventing these problems. Thus, simply warming a suspension of tosyl hydrazone salt **7** [33] in the presence of a phase-transfer catalyst (PTC) [34], $\text{Rh}_2(\text{OAc})_4$, tetrahydrothiophene, and benzaldehyde resulted in clean epoxidation, furnishing stilbene oxide in excellent yield and diastereoselectivity (Scheme 11) [35].

The use of the camphor-derived oxathiane **3b**, which gave excellent yields and enantioselectivities in the *ex situ* process, was unsuccessful. However, the corresponding methoxy derivative **3g** was compatible with the reaction conditions; use of a stoichiometric quantity of this compound with the tosylhydrazone salt, benzaldehyde, and benzyltriethylammonium chloride (PTC) furnished a good yield of epoxide with excellent enantioselectivity (Scheme 12) [35]. Use of 0.2 equivalents of homochiral sulfide in the *in situ* catalytic cycle furnished the epoxide in a similar selectivity but in reduced yield (26%). The reduction in yield is probably due to hydrolytic cleavage of the thioacetal moiety and clearly the *in situ* process requires more stable sulfides.



Scheme 11



Scheme 12

2.3

Principal Alternatives: Stoichiometric Process for Epoxidation

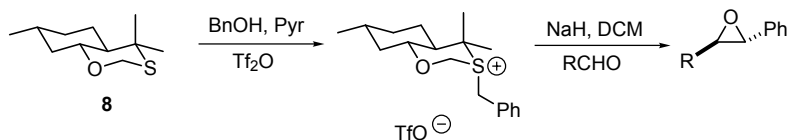
Solladié-Cavallo has used Eliel's pulegone-derived oxathiane **8** to generate terminal epoxides in up to 96% ee and diaryl epoxides in up to 99.9% ee (Scheme 13) [36, 37, 38, 39]. Good *trans:cis* ratios (95:5) were also obtained.

The high enantioselectivities obtained have been attributed to a metal-complexed ylide binding to the incoming aldehyde (Fig. 1).

2.4

Conclusions and Future Outlook

Highly enantioselective epoxidations of carbonyl compounds have been achieved using either stoichiometric amounts of sulfides under standard sulfur ylide conditions (Solladié-Cavallo) or using catalytic amounts of sulfides under the conditions described in Sect. 2.2 (Aggarwal). Only benzylidene transfer has been reported to date for asymmetric epoxidation but the range of diazocompounds that can be used in the catalytic cycle (using tetrahydrothiophene) include a number of different aryldiazomethanes [35] and diazoacetamides [26]. It should be possible to expand this range still further to include diazoalkanes using the *in situ* process. More stable chiral sulfides are required, particularly for the *in situ* formation of diazo compounds, as they should lend themselves to lower loadings and higher levels of turnover. Methylene transfer using diazomethane has not been successful but it has been found that methylene transfer can be achieved using Simmons-Smith reagents (Scheme 14) [40]. The application of chiral sulfides to this new catalytic cycle should provide a new route to enantiomerically enriched terminal epoxides.



R	yield [%]	ee [%]
H ^a	73	96
Ph	80	99.0
4-Me-C ₆ H ₄	56	99.6
4-Cl-C ₆ H ₄	76	99.0
4-NO ₂ -C ₆ H ₄	77	97.9
2-F-C ₆ H ₄	84	99.9

^a This result was obtained using the 3,4-dichlorobenzyl ylide

Scheme 13

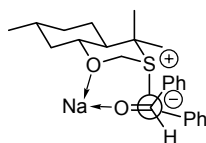
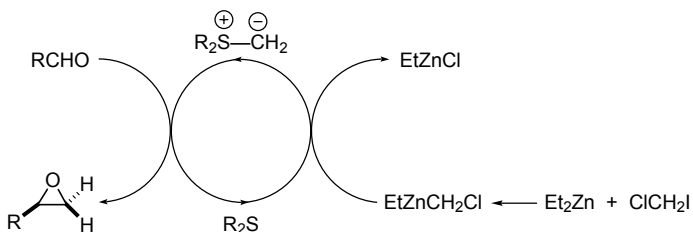


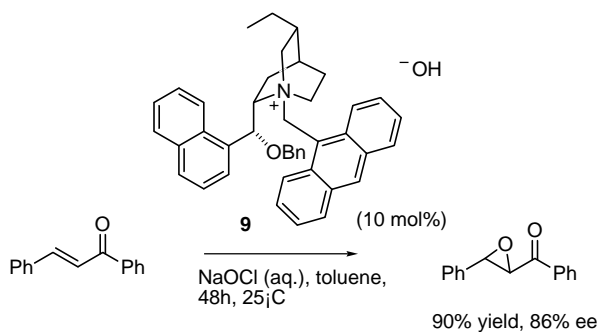
Fig. 1



Scheme 14

3 Nucleophilic Oxidations

Nucleophilic oxidation of electron-deficient alkenes is another route to epoxides. For example, reaction of enones with hydrogen peroxide and sodium hydroxide provides epoxides in good yield. The first attempt to turn this into an asymmetric transformation utilised the benzylchloride salt of quinine as a chiral phase transfer catalyst but only moderate enantioselectivity was obtained (55% with

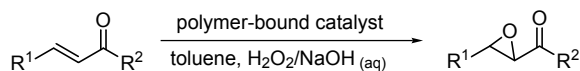
**Scheme 15**

chalcone [41], 78% with quinone derivative [42]). Further modifications of the catalyst have resulted in significant increases in enantioselectivity and scope of the reaction (Scheme 15) [43].

3.1 Polyamino Acid Catalysis

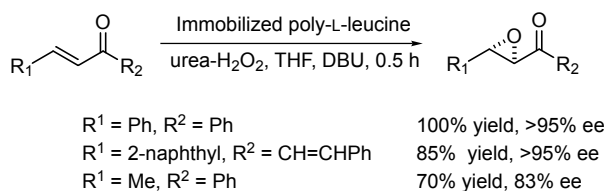
Juliá discovered that the use of polyalanine as a 'phase-transfer catalyst' gave very high enantioselectivities in the epoxidation of chalcone [44,45]. The reaction consists of a triphasic system composed of water, toluene and polyalanine (which does not dissolve in either solvent) and it is believed that the reaction occurs on the surface of the polymer. An equal weight of polymer to substrate is generally used. This reaction has been scaled up by SKB (they used poly-L-leucine) and applied in the synthesis of the leukotriene antagonist SK&F 104354 [46]. Following Juliá's work, Itsuno and coworkers developed polymer-supported polyamino acids (alanine or leucine) allowing easier work-up and catalyst recovery (Scheme 16) [47]. The catalyst was used up to twelve times in the triphasic system without significant loss of activity.

It has recently been demonstrated that this reaction could be used for the epoxidation of a broader class of enones and excellent enantioselectivities were obtained provided the enone was substituted at the β -position [48, 49, 50]. However, essentially no asymmetric induction was observed with cyclic enones [51]. Further practical improvements in this reaction have recently been made. Roberts found that the use of anhydrous urea-hydrogen peroxide with DBU in THF as a two-phase system (polymer and organic phase) resulted in rapid epoxidation with high levels of asymmetric induction [52]. This modification solves many of the problems associated with the original procedure (oxidant decomposition, long reaction times, work up) and provides a very practical oxidation system (Scheme 17).



R ¹	R ²	yield [%]	ee [%]
Ph	Ph	94	97
Ph	4-NO ₂ -C ₆ H ₄	90	99
Ph	4-MeO-C ₆ H ₄	56	76
4-MeO-C ₆ H ₄	Ph	83	87
4-Cl-C ₆ H ₄	Ph	98	99

Scheme 16



Scheme 17

3.2

Chiral Metal Hydroperoxides

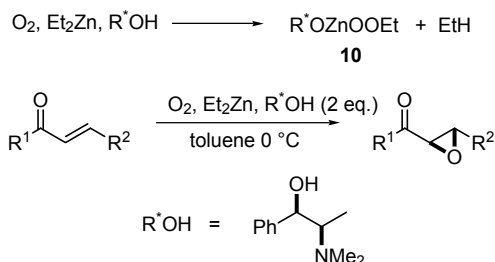
An obvious extension of the application of metal alkyl peroxides for epoxidation of electron-deficient alkenes is to use chiral ligands on the metal for asymmetric epoxidations. However, this extension has only very recently met with success.

Enders found that the use of diethylzinc, oxygen and *N*-methylephedrine converted enones into epoxides with enantiomeric excesses of up to 92% in excellent yields (Scheme 18) [53, 54]. It is believed that the zinc peroxide **10** is the intermediate in the epoxidation process. Cyclic and *s-trans*-enones cannot be epoxidized under these conditions.

The transition states shown in Scheme 19 have been proposed to account for the enantioselectivity observed and for the fact that the process is limited to *s-cis*-enones. The long distance between the carbonyl oxygen and β-carbon of *s-trans*-enones makes the simultaneous attack by zinc at the carbonyl oxygen and by the ethylperoxy group on the β-position very difficult.

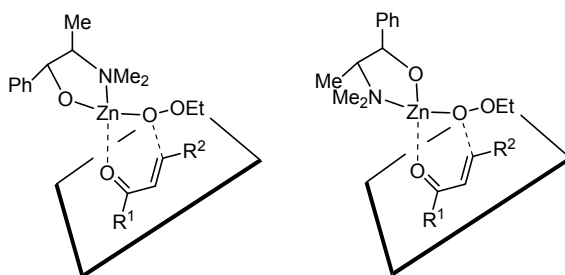
This is a remarkably simple and efficient system for the asymmetric epoxidation of unsaturated ketones which, in addition, uses cheap chemicals (Et₂Zn, O₂) together with a cheap and reusable ligand.

Jackson has reported a similar process using tartrate ligands, magnesium as the metal and *tert*-butyl hydrogen peroxide as the oxidant [55]. Enantiomeric



R ¹	R ²	yield [%]	ee [%]
Ph	Me	96	85
Ph	Et	99	91
Ph	<i>n</i> -Pr	99	87
Ph	<i>i</i> -Pr	97	92
Ph	Ph	94	61
<i>t</i> -Bu	PhCH ₂ CH ₂	99	90
2,4,6-Me ₃ -C ₆ H ₂	Et	94	82

Scheme 18

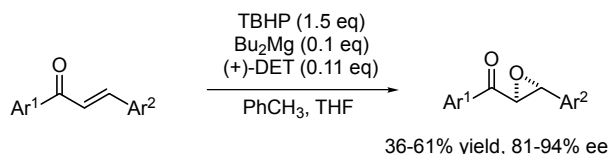


Scheme 19

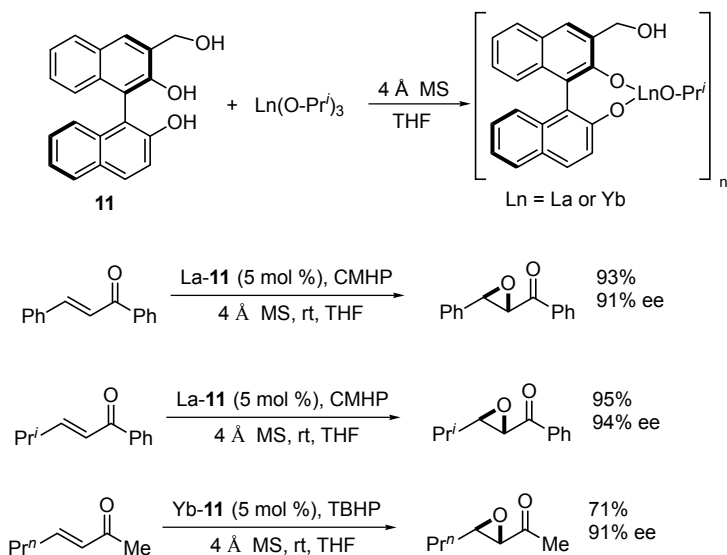
excesses of up to 94% were obtained for the oxidation of chalcones (Scheme 20). This process has the advantage that it is catalytic in the metal and ligand used. Although not indicated, this process is likely to be limited to the same class of enones as the Enders system.

Shibasaki has recently described a process for epoxidation of electron-deficient alkenes catalyzed by chiral lanthanoid-BINOL complexes (5–8 mol %) using *tert*-butyl hydrogen peroxide [or cumene hydroperoxide (CMHP)] [56]. Epoxides were obtained in excellent yields and enantioselectivities as shown in Scheme 21.

It is believed that the catalysts are oligomeric and that the Ln-alkoxide moiety activates the hydroperoxide to form an Ln-peroxide which promotes the Michael



Scheme 20



Scheme 21

addition. At the same time the Ln metal center may act as a Lewis acid activating the enone.

Of the metal-based catalysts, the method of Shibasaki provides the highest yields and enantioselectivities for the lowest catalyst loading.

3.3

Conclusions and Future Outlook

High enantioselectivity and good yields have been obtained in asymmetric epoxidation of enones. Roberts' modification of the Juliá epoxidation using an immobilized polyleucine catalyst now represents a simple, practical method for enone epoxidation. Of the metal-based systems, the most economical and practical method is probably Enders' protocol, despite the fact that it uses stoichiometric amounts of metal and ligand, as all the reagents are commercially available and cheap. It is difficult to compare the polypeptide-based catalysts with the metal based catalysts in terms of overall efficiency.

All of the methods are limited to *s-cis*-enones (chalcones generally seem to work best) and much work remains to be done to expand the range of alkenes to include *s-trans*-enones, unsaturated esters, and unsaturated nitriles. There is, therefore, considerable scope for future research in this area.

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Chapter 19

Oxidation of Sulfides

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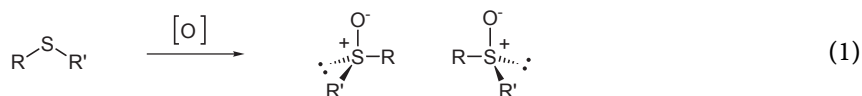
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Keywords: Sulfoxides, Sulfones, Sulfimides, Sulfoximines, Chiral metal complexes

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1 Introduction

Upon oxidation by single oxygen transfer sulfides are converted into sulfoxides, and the originally disubstituted divalent sulfur atom now becomes a center bearing four substituents, the original two R-groups, the oxygen atom and one electron lone pair. In the case of oxidations of unsymmetrical sulfides the structures of the resulting sulfoxides are no longer superimposable with their mirror images and are therefore chiral (Eq. 1).



Chiral sulfoxides have been shown to be efficient auxiliaries in asymmetric synthesis [1], and their relevance in pharmaceutical research due to their biolog-

ical activity has been demonstrated [2]. Consequently, various approaches to obtain these compounds in optically active form have been introduced [3, 4]. Many of these methods involve chemical [4] or enzymatic [5] resolutions of racemic mixtures and multistep syntheses with stoichiometric amounts of chiral auxiliaries [6]. Among the latter, Andersen's method using as key step a diastereoselective substitution of optically pure sulfinates with Grignard reagents is particularly noteworthy [7]. Other attempts involve various stoichiometric enantioselective and diastereoselective oxidations [4, 8, 9].

The most efficient way to generate optically active sulfoxides is via enantioselective catalysis [10, 11]. For this purpose enzymes and metal catalysts can be used. In this chapter, the various approaches to metal-catalyzed formation of sulfoxides based on oxidation chemistry are described. All of these methods rely on chiral transition metal complexes and, therefore, special focus will be given to a discussion of the structures of these metal-containing compounds.

2

Oxygen Transfer Catalyzed by Chiral Metal Complexes

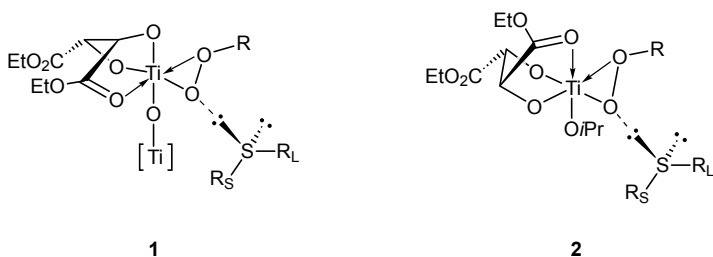
2.1

Chiral Titanium Catalysts

An early example of a catalytic asymmetric sulfide oxidation was reported by Kagan in 1987 [12], and it was based on his pioneering work on the *stoichiometric*, enantioselective oxidation of sulfides [10, 13]. The original procedure utilized a modification of the titanium reagent introduced by Sharpless for the enantioselective epoxidation of allylic alcohols, and it employed titanium tetraisopropoxide, diethyl tartrate, and water in a ratio of 1:2:1. In order to make the process catalytic only a slight modification was required. Before catalyst formation 4 Å molecular sieves had to be added. The molecular sieves act as moisture scavenger and, therefore, control the amount of water present in the reaction mixture. In addition, the formation of other, undesired titanium species which lead to non-enantioselective pathways is diminished. Recently, a further decrease of catalyst loading to 10 mol % has been achieved by replacing water with isopropanol [14]. In a typical run, the oxidation of *p*-tolyl methyl sulfide by 10 mol % of $\text{Ti}(\text{O}i\text{Pr})_4$, 40 mol % (*R,R*)-DET, and 40 mol % isopropanol in the presence of 1 weight equivalent of 4 Å molecular sieves and 2 equivalents of cumyl hydroperoxide as terminal oxidant provides the corresponding sulfoxide with 95% enantiomeric excess in 77% yield. The enantiomeric excesses of other sulfoxides vary between 75 and 95%.

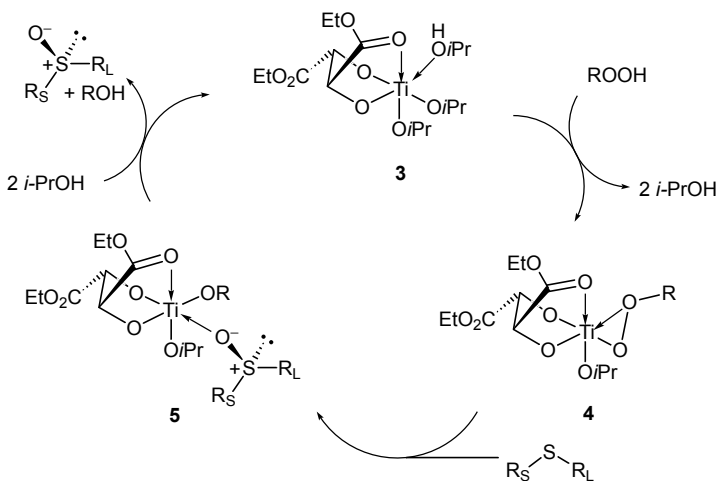
While the catalytically active titanium species in the original system was proposed to be dimeric with two titaniums being connected via a η -oxo bridge (1), the active species in the catalytic version is assumed to be a monomeric titanium compound of type 2 bearing a simple isopropoxide instead of the η -oxo group. In both intermediates, one tartrate is bound in a tridentate fashion and the peroxo group is attached in a η^2 -coordination ensuring that the approach of the in-

coming sulfide is determined by an efficient distinction between the larger and the smaller rest at the sulfur atom (R_L and R_S , respectively). As a consequence, high enantiotopic discrimination generally requires sulfides with two substituents being significantly different in size.



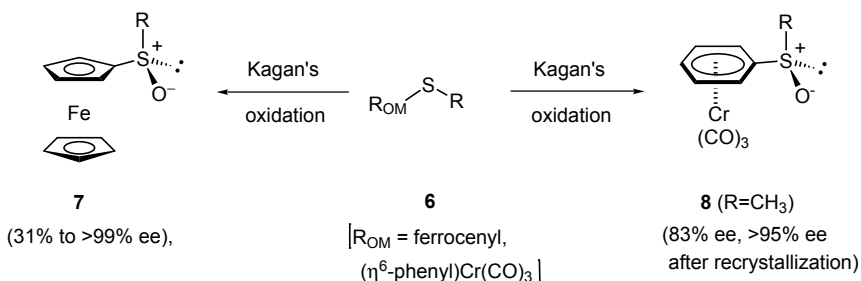
The overall catalytic cycle is believed to involve various titanium complexes which all have at least one isopropoxy ligand attached to the metal (Scheme 1). Given this fact, it is evident that kind and structure of the alkoxide can influence the catalysis, in particular the chirality transfer step ($4 \rightarrow 5$, via 2) and the displacement of the product sulfoxide from 5 to regenerate 3 . Evidence for this assumption was obtained in studies with both other titanium alkoxides and alcohols such as methanol. In all cases less efficient catalyst systems resulted.

Particularly interesting applications of Kagan's asymmetric oxidation procedure are transformations of sulfides 6 carrying an organometallic rest such as ferrocene or tricarbonyl(η^6 -arene)chromium(0). For example, Kagan reported enantioselectivities of up to 99% ee for the oxidation of phenyl or *p*-tolyl ferrocenyl sulfide [15]. Interestingly, the corresponding methyl and *n*butyl substituted sulfides gave much lower ees. In the benchtorene series, Gibson *n*è Thomas



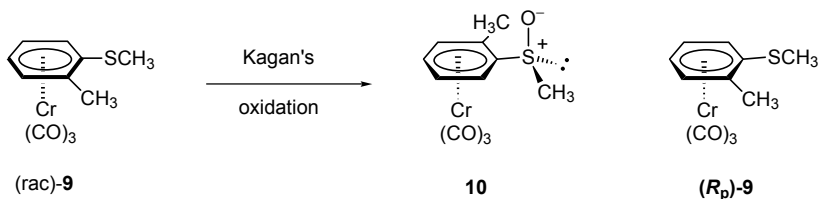
Scheme 1. Enantioselective sulfide oxidation with Ti(IV)/DET complexes in the presence of *i*-PrOH

employed the Kagan protocol for the oxidation of tricarbonyl(η^6 -thioanisole)chromium(0) and two of its derivatives and obtained enantiomeric excesses of up to 86% (90 to 95% ee after a single recrystallization) [16].



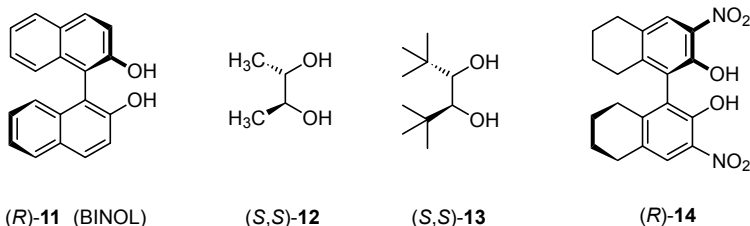
Enantiopure **7** and **8** are of major importance because the sulfoxide moiety can act as an effective anchor group in a directed *ortho*-metalation. Thus, a variety of diastereomerically pure compounds has been synthesized and found synthetic application [17, 18, 19].

If the asymmetric oxidation is applied on racemic thioethers diastereomeric products result. In the case of an efficient kinetic resolution [20] both sulfide and sulfoxide can be obtained in optically active form. An elegant application of this principle was described by Gibson *nèe* Thomas in the resolution of planar chiral racemic **9** [21].



With 0.55 equivalents of the oxidant the two enantiomers of **9** reacted at different rates leading to sulfoxide **10** in 38% yield with an ee of 60%. Unreacted sulfide **9** of opposite absolute planar chirality was obtained in 34% yield with 59% ee. Also other examples have been reported [4].

Uemura described use of a Ti(*Oi*Pr)₄/*(R)*-BINOL complex for the oxidation of alkyl aryl sulfides with aqueous *tert*-butyl hydroperoxide as stoichiometric oxidant [22]. At room temperature *p*-tolyl methyl sulfide was converted into the corresponding sulfoxide with 96% ee in 44% yield with as little as 5 mol % of the chiral ligand. The reaction is insensitive to air, while the presence of water seems to be essential for the formation of the catalytically active species, long catalyst lifetime, and high asymmetric induction. The authors observed a large positive non-linear effect which indicates that the actual catalyst consists of a titanium species with more than one (*R*)-BINOL ligand (**11**) coordinated to the metal.



A study on the time course of the enantiomeric excess of the sulfoxide revealed that it was highly dependent on the reaction time. In addition, as the reaction proceeded, the formation of sulfone was observed. With the gradually increasing amounts of sulfone the ee of the sulfoxide was raised. This dependence of the enantiomeric excess on time and sulfone formation indicated that a kinetic resolution process of the newly formed sulfoxide took place. Chiral recognition of the (*S*)-sulfoxide by the $\text{Ti}(\text{O}i\text{Pr})_4/(\text{R})\text{-BINOL}$ complex led preferably to consumption of this enantiomer and thereby raised the enantiomeric excess of the (*R*)-sulfoxide.

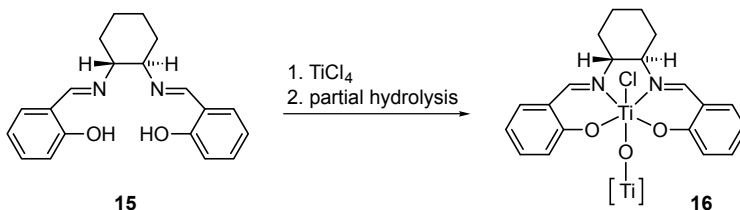
The Uemura system found application in an approach by Hutton towards members of the ustiloxin family of cyclic peptides. While the oxidation employing DET as ligand showed only little selectivity, the desired sulfoxide was obtained with a diastereomeric ratio of greater than 50:1 by changing to the (*R*)-BINOL ligand [23].

Rosini adapted the reaction conditions developed by Uemura and reported on a system using 10 mol % of (*S,S*)-1,2-diphenylethane-1,2-diol (**12**) as chiral ligand and *tert*-butyl hydroperoxide as the terminal oxidant. After optimization of the process, phenyl methyl sulfoxide was obtained in 60% yield with an ee of 80% [24].

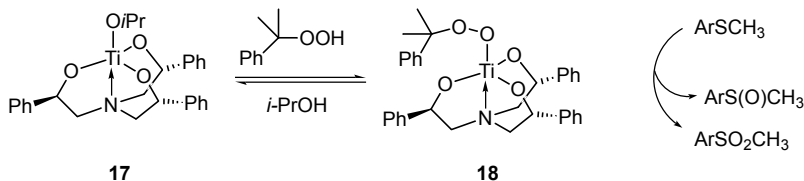
A new modification was recently described by Imamoto who employed a combination of (*S,S*)-2,2,5,5-tetramethyl-3,4-hexane diol (**13**) and $\text{Ti}(\text{O}i\text{Pr})_4$ as catalyst. The active species was proposed to be monomeric with two diols and one cumyl hydroperoxide ligand leading to an octahedral coordination sphere around titanium. Under conditions similar to those reported by Kagan, *p*-tolyl methyl sulfoxide was obtained with 95% ee in 42% yield. Sulfone formation was a dominant, albeit beneficial side reaction giving in a kinetic resolution process ($s=3.0$) the sulfoxide with higher enantiomeric excess than originally formed [25].

Another noteworthy adaptation was published by Reetz who reported the synthesis of (*R*)-3,3'-dinitrooctahydrobinaphthol (**14**) and its subsequent use in the asymmetric oxidation of *p*-tolyl methyl sulfide under various conditions [26]. Optimum reaction conditions were found to consist of a 2:1-mixture of **14** and titanium tetraisopropoxide together with cumyl hydroperoxide as the terminal oxidant thus giving *p*-tolyl methyl sulfoxide in 86% ee. The nitro groups of the ligand proved to be of major importance since the enantiomeric excess dropped to only 10% when the corresponding octahydrobinaphthol was used as ligand. Interestingly, when **14** was employed under conditions identical to Uemura's protocol, the absolute stereochemistry of the sulfoxide was found to be reverse.

Previously, Pasini [27] and Colonna [28] had described the use chiral titanium-Schiff base complexes in asymmetric sulfide oxidations, but only low selectivities were observed. Fujita then employed a related chiral salen-titanium complex and was more successful. Starting from titanium tetrachloride, reaction with the optically active C_2 -symmetrical salen **15** led to a (salen)titanium(IV) dichloride complex which underwent partial hydrolysis to generate the η -oxo-bridged bis[(salen)titanium(IV)] catalyst **16** whose structure was confirmed by X-ray analysis. Oxidation of phenyl methyl sulfide with trityl hydroperoxide in the presence of 4 mol % of **16** gave the corresponding sulfoxide with 53% ee [29].



A different approach is based on the C_3 -symmetrical triol amines introduced by Nugent [30]. Together with titanium tetraisopropoxide they afford titanium species of type **17** which react further with cumyl hydroperoxide to give a rigid monomeric titanium peroxide **18** [31]. The latter (with R=Ph) was characterized by NMR spectroscopy and ESI-MS studies [32].



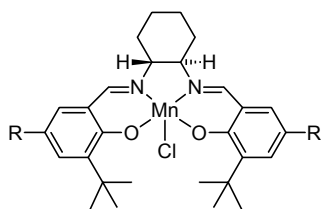
Bonchio, Licini and Nugent showed that with complex **17**, chiral sulfoxides were obtained with up to 84% ee. Even sterically demanding sulfides bearing a *tert*-butyl group were converted with enantioselectivities between 60 and 70% ee. Again, a kinetic resolution was found to increase the enantiomeric excesses. On the basis of several kinetic studies, however, the generally accepted mechanism of such a process, which involves two consecutive electrophilic oxygen transfer steps to sulfur, was questioned for this catalysis because the reaction rates for both sulfide and sulfoxide oxidation were nearly identical [33]. Depending on the substrate formation of sulfoxide or sulfone could dominate. For example, in the reaction of *p*-tolyl methyl sulfide the ratio of the rates for sulfide versus sulfoxide oxidation was three to one. In contrast, reactions with electron-poor substrates afforded more sulfone than sulfoxide. This behavior was attributed to a biphilic character of the titanium-peroxo species. Thus, the general electrophilic pathway via a η^2 -bridged peroxo species is similar to the one assumed in the Kagan oxidation competes with a simultaneous intramolecular nu-

cleophilic oxygen transfer. As an intermediate of this process, a peroxo-titanium complex with an octahedral surrounding being formed from **18** by coordination of the sulfoxide was suggested. Theoretical *ab initio* calculations [RHF/3-21G(*)] support this assumption.

2.2

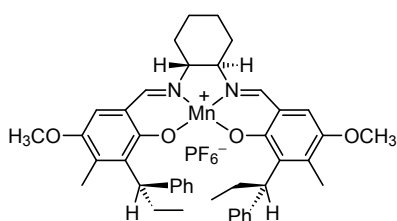
Chiral Manganese Catalysts

In 1992, Jacobsen reported the adaption of his well-established (salen)manganese(III) epoxidation system to enantioselective sulfide oxidations [34]. A catalyst loading of 2 mol % of a (salen)manganese(III)-complex was sufficient to observe chirality transfer. Hydrogen peroxide as the terminal oxidant proved to be superior to iodosylbenzene with respect to sulfoxide yields. Overoxidation to the sulfones was diminished. Commercial bleach (NaOCl) was too reactive for efficient enantiodifferentiation. The standard complex for asymmetric olefin epoxidation **19a** gave only 24% ee in the oxidation of thioanisole but the enantiomeric excess could be raised to 47% when a complex with a modified ligand bearing electron-donating methoxy groups (**19b**) was employed.



19a (R = *t*-Bu)

19b (R = OCH₃)



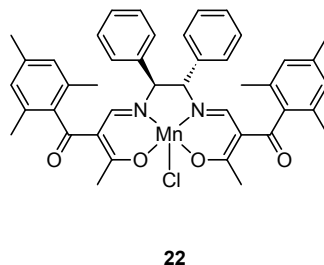
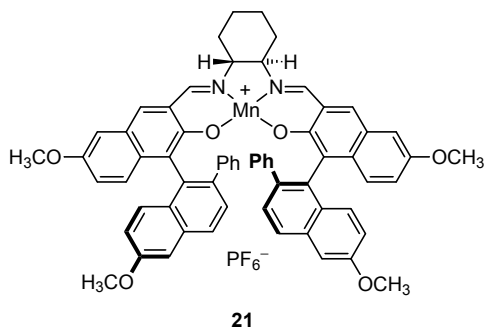
20

Electron-deficient aryl alkyl sulfides, which are less reactive than their counterparts bearing electron-donating groups, gave the best results in the oxidation with **19b**, even though enantioselectivity remained only moderate for all substrates (ee_{\max} : 68%). As in the asymmetric epoxidation with the (salen)manganese complexes the actual catalyst is believed to be an oxomanganese(V) species.

A similar (salen)manganese(III) catalyst was used by Katsuki for asymmetric sulfide oxidations [35]. Chiral complex **20** bears additional asymmetric carbons in the salicylidene part of the salen. In this system, hydrogen peroxide, which was the preferred oxidant in the Jacobsen procedure, turned out to be inefficient. Instead, iodosylbenzene was chosen, and in the presence of only 1 mol % of catalyst several aryl alkyl sulfides were oxidized in acceptable yields having enantiomeric excesses in the range of 8% to 90%. As in the Jacobsen-Katsuki-epoxidation, the presence of additives such as pyridine *N*-oxide has a beneficial effect on chemical and optical yields. In addition, such co-ligands suppress the overoxidation of sulfoxides to the corresponding sulfones so that a sulfoxide : sulfone ratio of 47:1 can be achieved. Consequently, as shown for the case of thioanisole,

a kinetic resolution of the sulfoxide via sulfone formation is not very effective ($s=2$).

More recently, investigations by Katzuki on the use of (salen)manganese complexes with additional axial chirality revealed that catalysts like **21**, which gave excellent results in asymmetric epoxidations of conjugated olefins [36], also showed improved enantioselectivities in sulfide oxidations. Again, electron-poor substrates such as 2-nitrophenyl methyl sulfide gave the best results (94% ee). Various aryl ethyl sulfoxides were obtained with enantiomeric excesses of up to 89% indicating a widening of the substrate range [37]. Finally, Katzuki reported the use of an achiral ligand in combination with (-)-sparteine as chiral axial coligand. For this system an ee of 25% was reported in the oxidation of thioanisole [38].



A combination of molecular oxygen and pivaldehyde together with (β -oxoaldiminato)manganese(III) catalyst **22** had been introduced by Mukaiyama for aerobic asymmetric epoxidations of unfunctionalized olefins [39]. In enantioselective sulfide oxidations this system gave optically active aryl methyl sulfoxides with up to 72% ee [40]. Sulfone formation was only observed with aryl alkyl sulfides bearing electron-deficient groups in the *para*-position of the aromatic ring. Taking advantage of this process, kinetic resolution in the oxidation of 4-nitrophenyl methyl sulfide afforded the sulfoxide in 79% ee, although in very low chemical yield. No sulfones were obtained from *ortho*-substituted substrates. This surprising observation was explained by an intramolecular coordination of the *ortho*-substituent to the sulfur atom of the sulfoxide which thereby blocks overoxidation. As in the epoxidation the reaction was proposed to proceed via an acylperoxo-manganese intermediate. Collapse of this species in the presence of an appropriate axial donor ligand would then form an oxomanganese(V) complex which is considered to be the actual oxygen-transfer catalyst.

For manganese-porphyrin complexes, a first example leading to very low enantiomeric excesses was reported by Groves [41]. Additionally, Halterman described a D_4 -symmetrical tetraphenylporphyrin-manganese(III) complex [42]. Employing a catalyst loading of 0.25 mol % with respect to the sulfide and with 0.5 equiv. of iodosylbenzene as the oxidant, the corresponding sulfoxides were obtained in good to excellent yields together with only a small amount of sul-

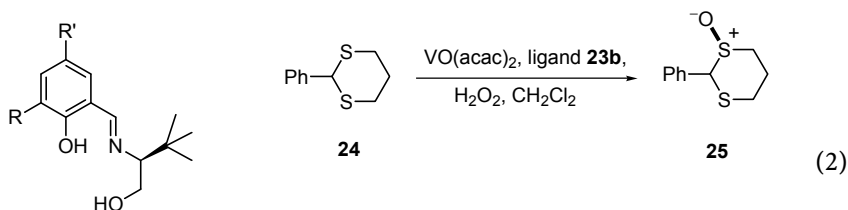
rones derived from overoxidation. However, the optical purity of the sulfoxides was only in the range of 40 to 68% ee. An attempted kinetic resolution of thioanisole proved to be unsuccessful, since the obtained phenyl methyl sulfoxide was racemic.

2.3

Chiral Vanadium Catalysts

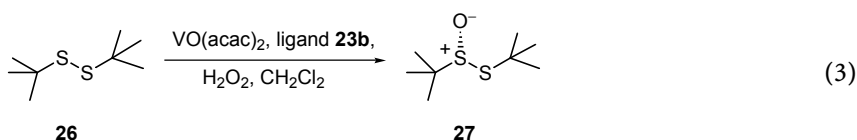
Chiral (salen)oxovanadium complexes for sulfide oxidation were first investigated by Fujita [29, 43]. In the presence of 4 mol % of the catalyst optically active sulfoxides were obtained in good yields, however, the enantiomeric excesses remained only moderate (up to 40%).

In 1995, Bolm and Bienewald introduced a new, very practical method for the asymmetric catalytic oxidation of sulfides [44]. In the presence of ≤ 1 mol % of a chiral vanadium complex prepared *in situ* from $\text{VO}(\text{acac})_2$ and **23** reactions of various sulfides or dithianes like **24** with aqueous hydrogen peroxide afforded the corresponding sulfoxides with enantiomeric excesses of up to 85% (Eq. 2). Only traces of the corresponding sulfones were observed. The transformation can easily be carried out in open vessels at room temperature using inexpensive H_2O_2 as oxidant.



23a (R = *t*-Bu, R' = NO_2)

23b (R = *t*-Bu, R' = *t*-Bu)



The preparation of ligands **23** is straightforward, and modifications by varying the substitution pattern are easily accomplished. Comparison of a series of ligands led to the conclusion that all substituents of the ligand affect the enantioselectivity [45]. Depending on the substrate the catalyst has to be fine-tuned by selecting the appropriate ligand (**23a** or **23b**).

This vanadium-catalyzed oxidation is an example of a ligand accelerated catalysis [46]. As revealed by ^{51}V -NMR-studies various vanadium species are formed

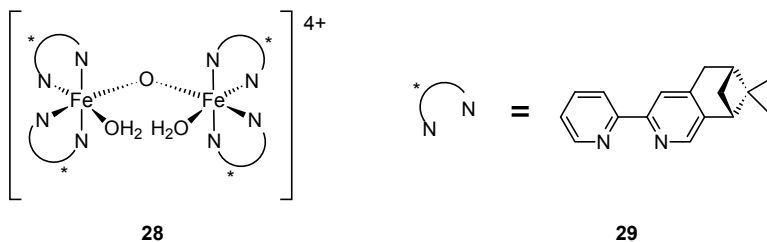
in the course of the reaction [45]. Most of them seem to have low reactivity and only a minor influence on the enantioselectivity. An asymmetric amplification has not been observed indicating that the active catalyst is a vanadium species with just one ligand coordinated to the metal. The catalyst can be partially recovered but a slight decrease in enantioselectivity occurs when it is reused.

Bolm's VO(acac)₂/chiral Schiff base oxidation system was recently adapted by Ellman in the large-scale synthesis of α -branched amines [47]. Here, *tert*-butyl disulfide **26** was oxidized to the corresponding thiosulfinate **27** employing ligand **23b**. The oxidation was carried out using as little as 1 mol % of catalyst giving *tert*-butyl *tert*-butanethiosulfinate (**27**) with 91% ee (Eq. 3). Further transformations of the thiosulfinate led to optically active amines in high yields.

2.4

Chiral Iron Catalysts

Use of the chiral iron catalyst **28** for asymmetric sulfide oxidation was recently reported by Fontecave [48]. The complex is a dimer with two iron centers which are connected via a η -oxo bridge. Two bidentate (-)-4,5-pinene-bipyridine ligands **29** and one molecule of water are coordinated to each iron atom thus completing the octahedral environment of this diferric complex. Complex **28** can be isolated as a green solid with four perchlorates as counterions.



Hydrogen peroxide is used as oxidant, and although sulfoxide yields are satisfying, enantiomeric excesses remain rather low (ee_{\max} : 40%). Interestingly, the complex can be recovered intact after oxidation indicating that its dimeric nature might actually be maintained during the course of the reaction.

Further iron containing catalysts are based on porphyrin ligands [10]. Original systems were introduced by Groves [41] and Naruta [49] who reported on modified tetraphenylporphyrin ligands bearing chiral binaphthalene groups. In their systems iodosylbenzene served as terminal oxidant. In Groves' study a catalyst loading of 0.1 mol % resulted in enantioselectivities of up to 48% ee, while Naruta obtained up to 73% ee by additionally employing 1-methylimidazole as axial ligand. A mechanistic model for the stereoselection was presented by Naruta who suggested the formation of chiral cavities from the two binaphthyl groups located above the porphyrin macrocycle [50]. Since the intermediary oxo-iron porphyrin is of C₂-symmetry, the approach of the incoming sulfide is

directed predominantly by steric interactions between the binaphthyl moieties and the larger substituent of the sulfide.

Further work on iron porphyrins including studies on the addition of imidazole is known from other groups [51,5 2]. With these systems enantioselectivities remained very low.

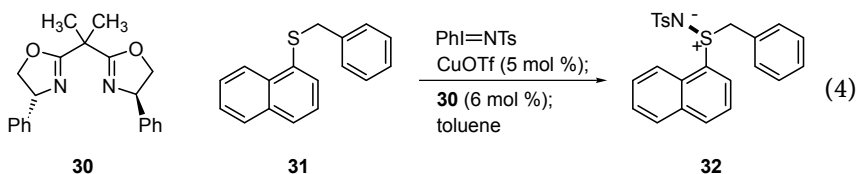
3

Nitrogen Transfer Catalyzed by Chiral Metal Complexes

3.1

Chiral Copper Catalysts

A completely different oxidative transformation of sulfides was presented by Uemura and Taylor who developed an efficient asymmetric sulfimination protocol [53]. Thereby, various sulfides were converted into the corresponding sulfimides in good chemical yields and with moderate to good enantiomeric excesses. The reaction is catalyzed by a copper salt together with a chiral bisoxazoline ligand employing *N*-(*p*-tolylsulfonyl)imino]phenyliodinane as the nitrogen-transfer reagent. Upon several screening processes, copper(I) triflate performed best, while bisoxazoline **30** derived from (*R*)-phenylglycinol was found to be the ligand of choice. Applying this combination, 1-naphthyl benzyl sulfide (**31**) was oxidized to sulfimide **32** in 75% yield and 71% ee (Eq. 4).



The reaction is proposed to proceed via an intermediary copper nitrenoid species as known from the related copper-catalyzed aziridination of olefins [54]. A tentative transition state model for the stereochemical outcome of the oxidation of *p*-tolyl methyl sulfide was suggested in which the approach of the sulfide was directed by a π - π interaction between the phenyl ring of ligand **30** and the aryl group of the sulfide. However, to date the exact mechanism remains unclear.

4

Special Applications of Sulfoxides

With a few exceptions [55], sulfoxides themselves have not been used as ligands in asymmetric catalysis so far. However, their sulfur atom can easily be oxidized further to give the corresponding sulfoximines. With appropriate substrates and mesitylenesulfonylhydroxyimine (MSH) as nitrogen-transfer reagent this reaction proceeds in a stereospecific manner [45, 56, 57]. In contrast to sulfoxides, optically active sulfoximines have found wide application in asymmetric catalyt-

ic processes including diethylzinc additions [58], borane reductions of prochiral ketones and imine derivatives [59], allylic substitutions [60], and trimethylsilylations of aldehydes [61]. Also, a chiral vanadium complex prepared from a C₂-symmetrical bisulfloximine salen-type ligand precursor has been employed in catalytic sulfur oxidation, albeit, no enantiomeric excess could be obtained so far [62].

5

Conclusion

In summary, we have presented a variety of metal-based catalysts which are able to mediate the asymmetric oxidations of sulfides to the corresponding sulfoxides and sulfimides. Although very different approaches relying on distinct metal complexes are known, there is still a demand for an appropriate system which would allow the transformation of any sulfide to occur with high enantioselectivity. Especially the rational design of chiral complexes able to selectively oxidize substrates, in particular, those compounds other than aryl methyl sulfides is still a major challenge.

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Chapter 20

Dihydroxylation of Carbon-Carbon Double Bonds

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Keywords: Asymmetric dihydroxylation, Osmium tetroxide, Cinchona alkaloid, Ligand accelerated catalysis

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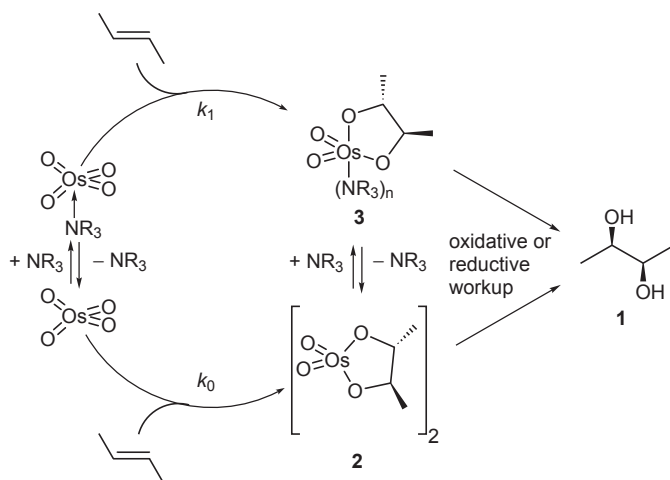
Introduction

If a reagent could be classified according to scope, reactivity, and selectivity, it could easily be argued that osmium tetroxide should hold a distinguished position by combining the seemingly mutually exclusive properties of high reactivity and scope, being able to dihydroxylate virtually any alkene with mildness, and tolerance of almost any other functional group present. Based on these credentials it seems obvious that a catalytic asymmetric dihydroxylation based on osmium tetroxide would assume an eminent position in the repertoire of synthetic methods available to the organic chemist.

1.1

Discovery of Osmium Tetroxide-Mediated Dihydroxylation

Osmium tetroxide has since its discovery probably been the most reliable reagent known for transforming an alkene to the corresponding *cis*-diol (**1**) [1]. The reaction between osmium tetroxide and an alkene (Scheme 1) usually takes place smoothly in almost any solvent with all types of carbon-carbon double bonds, with the general trend that the reaction proceeds faster with electron-rich alkenes



Scheme 1

than in electron-deficient systems. The products of such an osmylation reaction are insoluble dark dimeric osmium(VI) glycolates (2) [2] which can be transformed by a range of oxidative or reductive methods [1] to the desired *cis*-diol (1).

Criegee was the first to report that certain tertiary amines such as pyridine accelerate the reaction between osmium tetroxide and an alkene [3] and that the products formed were monomeric osmium(VI)-glycolate bispyridine complexes (3, NR₃=py, n=2) [4]. It was later shown that the number of amine ligands in the osmium(VI)-glycolate complexes is dependent upon the nature of the amine employed; when quinuclidine (1-azabicyclo[2.2.2]octane) which has strong affinity for osmium tetroxide, is used as tertiary base, monoquinuclidine complexes are formed (3, NR₃=quinuclidine, n=1) [5].

1.2

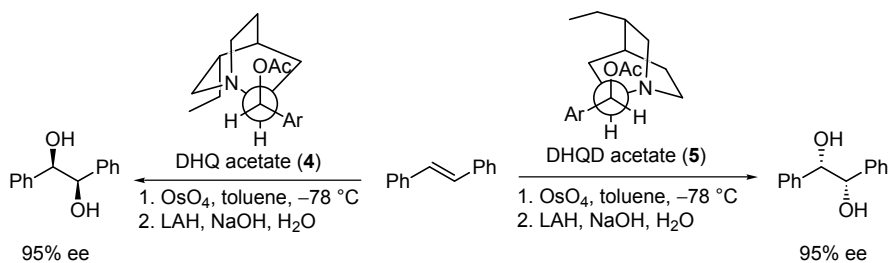
Asymmetric Dihydroxylation (AD)

Criegee's pioneering observation of the pyridine ligand acceleration effect in the osmium tetroxide addition was the direct inspiration for the asymmetric dihydroxylation reaction discovered by Hentges and Sharpless nearly 40 years later [6]. Hentges and Sharpless argued that the rate-accelerating effect of pyridine was most probably due to a coordination to the metal center in osmium tetroxide, producing a more reactive osmium tetroxide-pyridine complex. This reasoning paved the way for an asymmetric dihydroxylation process by the use of chiral rate-accelerating ligands. In a ligand-accelerated process, the rate of reaction is increased when a ligand binds to a metal center. In processes with rapidly exchanging ligands, both the microscopic rate constants k_0 (no ligand) and k_1 (with ligand(s)) and the magnitude of the catalyst/ligand binding constant (K_{eq}) are important in determining the ligand acceleration effect [Scheme 1 and Eq. (1)] [7]. The goal for an asymmetric ligand-accelerated process is to utilize the ligand-accelerating effect to channel all product formation through the chiral pathway.

$$k_1 K_{eq} [L] / k_0 > 1 \quad (1)$$

At first, Hentges and Sharpless used chiral pyridine derivatives with only modest success, a result which is at least partly due to a low binding constant (K_{eq}) for these ligands. The breakthrough came with the introduction of the quinuclidine-containing *Cinchona* alkaloid ligands; dihydroquinidine acetate (DHQD-Ac, 4) and dihydroquinine acetate (DHQ-Ac, 5) (Scheme 2). Due to the quinuclidine ring in these alkaloids, these ligands coordinated much more strongly with osmium tetroxide than the chiral pyridine derivatives, and gave chiral diols with usually fair to good optical purity. It was later shown that the enantiomeric purities originally reported were underestimated, and that an enantiomeric excess above 95% is obtained for *trans*-stilbene using these ligands.

One of the most appealing features with the *Cinchona* alkaloids as chiral ligands, is the pseudoenantiomeric relationship between dihydroquinine (DHQ)

**Scheme 2**

and dihydroquinidine (DHQD). Although DHQ and DHQD are diastereoisomers, both possess *erythro*-stereochemistry in the crucial C8 and C9 positions, but with opposite absolute configuration at these atoms as shown in Scheme 2. This near-mirror image relationship between DHQ and DHQD can be observed in reactions where these alkaloids are used as chiral ligands [8]. When DHQD acetate is used as chiral ligand in the stoichiometric dihydroxylation of *trans*-stilbene the *(R,R)*-diol is formed, whereas when DHQ acetate is used the *(S,S)*-diol is formed [9]. The fact that these ligands are not true enantiomers, but diastereoisomers, is manifested by the observation that the DHQ derivative almost invariably shows lower enantiomeric excess in the diol product than when the DHQD derivative is used.

The use of *Cinchona* alkaloid derivatives as chiral adjuvants in asymmetric dihydroxylation went largely unnoticed by the chemical community due to two important developments; Katsuki and Sharpless' simultaneous discovery of the titanium-based asymmetric epoxidation of allylic alcohols taking the focus and the resources in the Sharpless laboratory, and the discovery of a new and superior class of chiral ligands – the chiral diamines (Fig. 1). The success of the chiral diamines as ligands for osmium tetroxide-based asymmetric dihydroxylation leans heavily on the much stronger interaction between the metal center and these chelating ligands. Apart from a few exceptions, these ligands have a C₂-symmetry and give greater steric discrimination in the asymmetric dihydroxylation than their *Cinchona* counterparts, and within a few years, a range of diamine ligands were prepared and tested. The most important diamine ligands are compiled in Fig. 1, and their efficiency as chiral selectors in the AD process are compared (with the *Cinchona* ligand) in Table 1. The first diamine in this series was the *trans*-cyclohexanediamine derivative **6** prepared by Tokles and Snyder [10]. Even though the enantioselectivities obtained with ligand **6** are only modest, this ligand gives better results for alkyl-substituted terminal alkenes, such as *(R)*-1,2-heptanediol of 86% ee from 1-heptene, than for *trans*-stilbene, a substrate that almost invariably gives the highest ee in all asymmetric dihydroxylation. Hanessian [11] simplified the *trans*-cyclohexanediamine motif by preparing the bis-neohexyl secondary amine derivative **13** with much improved enantioselectivity compared with **6**. A series of 1,4-diamines derived from tartaric acid was investigated by Yamada and Narasaka [12] who found that the non

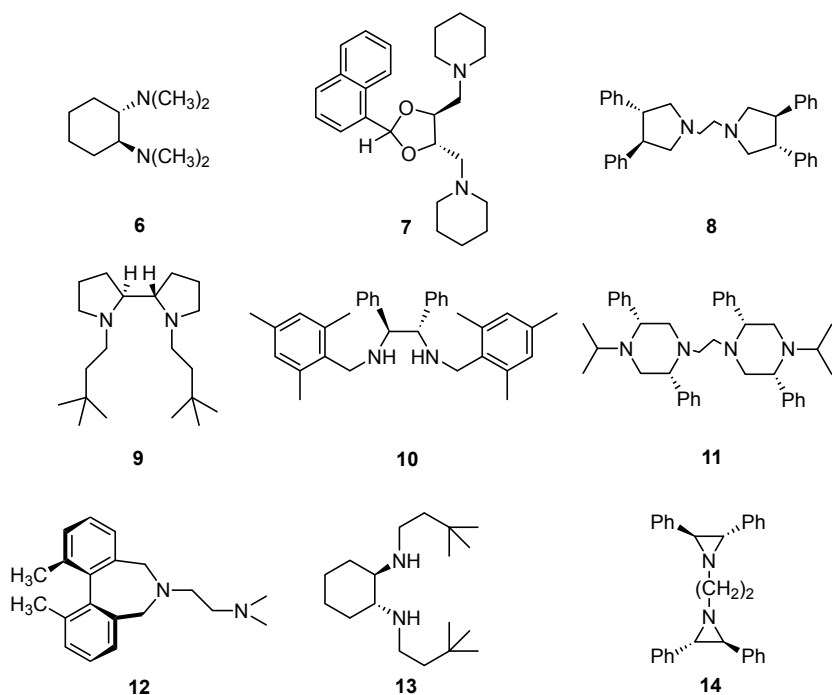


Fig. 1. Chiral diamine ligands for stoichiometric asymmetric dihydroxylation, diamine **6** (Tokles and Snyder) [10], **7** (Yamada and Narasaka) [12], **8** (Tomioka et al.) [13, 14, 15, 16, 17], **9** (Oishi and Hirama) [18, 19, 76], **10** (Corey et al.) [20], **11** (Fuji et al.) [21], **12** (Haubenstock and Subashinghe) [23], **13** (Hanessian et al.) [11] and **14** (Tanner et al.) [22]

Table 1. Comparison of enantioselectivities in the stoichiometric AD of alkenes as a function of ligand

15

Alkene	4	6	7	8	9	10	11	12	13	14
R ¹ R ² R ³										
Ph H H	61			90	88	92	89		99	
Ph H Me	49			99	92	93	95		95	
Ph H Ph	83	34	90	97	100	92	98	96		95
Et H Et	50			90	96	98			90	
Ph (CH ₂) ₄	68	66		83			71		90	

C_2 -symmetric diamine derivative **7** gave superior results. Excellent enantioselectivities over a range of substrates were, however, first obtained by Tomioka and Koga [13, 14, 15, 16, 17] with the D_2 -symmetric ligand **8**. All the reactions were performed with a 1:1 complex between **8** and osmium tetroxide at $-100\text{ }^\circ\text{C}$, and gave superior results for alkyl-substituted alkenes compared with the DHQD/DHQ acetates.

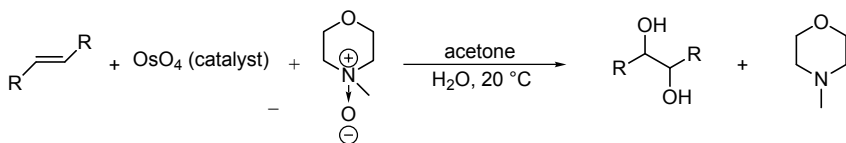
Even better results were obtained by Oishi and Hirama using their N,N' -dineohexyl-2,2'-bipyrrolidine **9** [18, 19]. The Hirama ligand proved to be especially effective in the asymmetric dihydroxylation of *trans*-dialkyl-substituted alkenes. Just after the report of Hirama, Corey described a new stilbenediamine derivative **10** which gave unsurpassed enantioselectivities on monosubstituted (terminal) alkenes [20]. The Fuji ligand **11** [21] and the Tanner ligand **14** [22] are two more recent examples of diamine ligands for AD. Ligand **12**, prepared by Haubenstock and Subasinghe [23], is an example of a diamine ligand with a chiral bi-phenyl as chiral controller.

It should, however, be noted that none of these ligands is an effective chiral selector for the AD of *cis*-disubstituted alkenes and tri- or tetrasubstituted alkenes.

1.3

Catalysis

One of the major concerns with stoichiometric osmium tetroxide dihydroxylation is the considerable cost of the reagent, and a number of catalytic variants of the reaction have been developed employing less expensive cooxidants for the reoxidation of the osmium(VI) glycolate products [1]. The first cooxidants were of inorganic origin, such as chlorates [24] or hydrogen peroxide [25], but these cooxidants often furnished variable yields of α -hydroxy ketones, 1,2-diketones, or even cleavage products. Organic cooxidants have been used with far more success, and among the most important are alkaline *tert*-butyl hydroperoxide [9] and *N*-methylmorpholine *N*-oxide (NMO) [26] (Scheme 3). Recently, inorganic cooxidants have had a renaissance with the utilization of potassium ferricyanide in aqueous potassium carbonate as a particularly effective and mild cooxidant system for osmium tetroxide dihydroxylation [27].

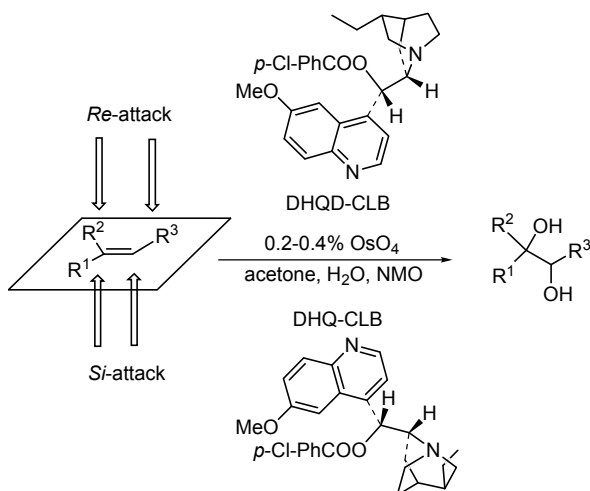


Scheme 3

2 Catalytic Asymmetric Dihydroxylation

On this background the obvious question that arises is: Is it possible to combine a known chiral ligand from the asymmetric dihydroxylation process with a suitable cooxidant, creating a catalytic asymmetric dihydroxylation process? This question was addressed in the late 1980s using the most efficient cooxidant system known at the time, the NMO system. In the catalytic NMO system, as little as 2–0.2% osmium tetroxide is sufficient as catalyst with 2 equivalents of the NMO cooxidant to produce *cis*-diols in good yield. The experimental procedure calls for the use of a homogenous acetone:water solvent mixture, where all ingredients are present from the start. This experimental convenience later proved to have unforeseeable consequences. The first obstacle was that the chiral diamine ligands that were so successful in the stoichiometric asymmetric dihydroxylation discussed in Sect. 1.2, inhibited turnover in a catalytic process using NMO as cooxidant. This serious drawback proved to be inherent to the bidentate nature of these ligands; not only do these ligands bind strongly to osmium tetroxide, they also form stable chelate complexes with the osmium(VI) glycolate (3), and thus precluding the reoxidation of osmium(VI) to osmium(VIII) necessary to complete a catalytic cycle. Consequently, the affinity of the ligand to osmium must be delicately balanced; the ligand should have a sufficient binding constant, K_{eq} (and a ligand-acceleration effect) to osmium tetroxide to secure that an optimum amount of the product is formed through the chiral pathway, however the affinity for the osmium(VI) glycolate complex must simultaneously be sufficiently low for the reoxidation and hence catalytic turnover to take place. In 1988 it became clear that this balance could be found in the *Cinchona* alkaloid ligands, when Sharpless and coworkers [28] reported that the *para*-chlorobenzoates of dihydroquinidine (DHQD-CLB) or dihydroquinine (DHQ-CLB) could be added to the NMO catalytic system and produce optically active *cis*-diols (Scheme 4) in moderate to good enantiomeric excesses as shown in Table 2.

The Sharpless group measured the total rate of reaction as a function of ligand concentration and obtained the plot shown in Fig. 2. This plot shows the gradual increase in the second-order rate constant for the catalytic AD of styrene at 25 °C, and reveals that not only is the DHQD-CLB capable of inducing optical activity in the diol product, but the presence of the chiral ligand also induces a substantial rate increase compared to the non-ligand reaction (performed under the standard NMO conditions). The ceiling rate increase is about twenty-fold at 25 °C, a figure that increases to nearly a hundred-fold at 0 °C. The kinetic experiments clearly showed that the ligand-acceleration effect was solely due to an increased rate of addition of the osmium tetroxide-ligand complex to the alkene [29]. With higher concentrations of the DHQD-CLB ligand, the rates of hydrolysis and reoxidation were slightly decreased. The overall rate of reaction is, however, greatly enhanced due to the fact that the rate acceleration in the addition step is much greater than the insignificant retardation of the hydrolysis/reoxidation step. This delicate balance appears to be almost unique for the *Cinchona* lig-



Scheme 4

Table 2. Enantiomeric excess obtained for representative substrates in the catalytic AD with DHQD-CLB as ligand and NMO as cooxidant

Entry	Alkene R ¹	R ²	R ³	ee (%)	Reaction time (h)
1	Ph	H	H	62	3
2	Ph	H	Me	65	5
3	Ph	H	Ph	88	17
4	Et	H	Et	20	17
5	Ph	Me	H	33	1.5
6	Bz	H	H	20	1.5
7	Chx	H	H	46	1
8	Ph	(CH ₂) ₄		8	1 week

ands; quinuclidine (see insert in Fig. 2) gives a much lower rate increase in the addition step than the *Cinchona* based ligands [30]; furthermore, quinuclidine inhibits turnover (as does the chelating diamine ligands) at nearly every concentration due to the formation of stable complexes between the osmium(VI) glycolates and these ligands.

The enantioselectivities obtained in the first catalytic AD process (Table 2) reveal that the best results are obtained with *trans*-substituted alkenes with at least one aromatic substituent (entries 2 and 3). If the aromatic substituent is moved further away from the alkene, the ee drops sharply (entry 6). Furthermore, terminal alkenes give moderate ee provided a directly bond aryl group is present (entry 1). 1,1-Disubstituted (entry 4) and *trans*-dialkyl-substituted alkenes

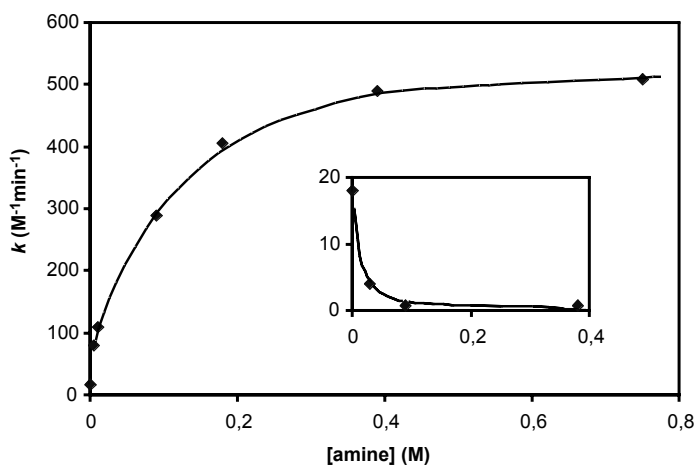


Fig. 2. Plot of the second order rate constant, k , for the catalytic dihydroxylation of styrene at 25 °C using DHQD-CLB as chiral ligand. Inserted is a plot of the second order rate constant, k , for the catalytic dihydroxylation of styrene at 25 °C using quinuclidine as ligand

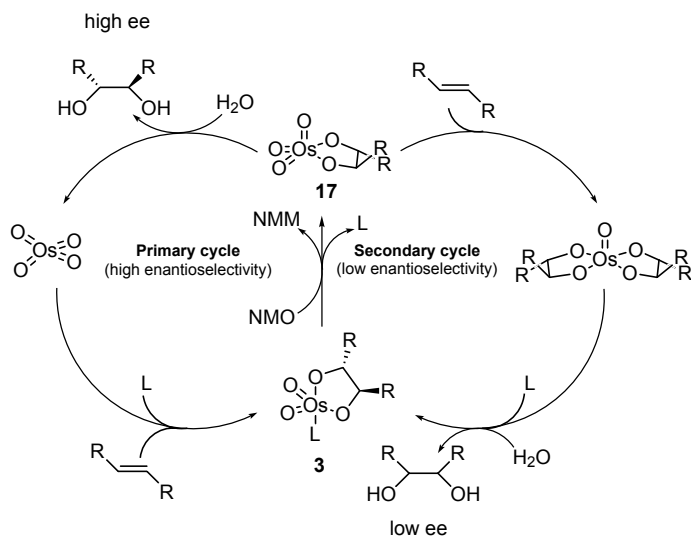
Table 3. Enantioselectivity in the AD using DHQD-CLB as chiral ligand under different conditions

Entry	Alkene			Stoichiometric	Original catalytic	Catalytic+ acetate	Catalytic slow addition
	R ¹	R ²	R ³				
1	Et	H	Et	69	20	64	70
2	Ph	(CH ₂) ₄		79	8	52	78(81)
3	Ph	H	Me	87	65	73	86
4	Ph	H	Ph	99	88	92	85
5	Ph	H	CH ₂ OH	66	7	52	66
6	<i>i</i> Pr	H	<i>i</i> Pr	80	12	61	46(76)

(entry 5) are dihydroxylated with poor enantioselectivity. The lowest enantioselectivity was obtained for the trisubstituted alkene phenylcyclohexene (entry 8); furthermore, this alkene hardly turned over in the catalytic process, requiring one week to reach completion. This result was puzzling because osmium tetroxide is known to act like an electrophile and hence the trisubstituted alkene was expected to react faster than the di- and monosubstituted olefins (cf. Table 2). Even more mysterious was the extreme gain in enantioselectivity obtained when 1-phenylcyclohexene was dihydroxylated using DHQD-CLB under stoichiometric conditions (Table 3, entry 2).

It could readily be anticipated that the bottleneck in the catalytic dihydroxylation of sterically hindered alkenes could be the slow breakdown of the os-

mium(VI) glycolate intermediate **3**. Previously, several acetate salt additives such as NaOAc or Et₄NOAc had been employed for increasing the rate of hydrolysis/reoxidation [31, 32], and in an effort to increase the catalytic turnover in the asymmetric dihydroxylation of 1-phenylcyclohexene in the presence of DHQD-CLB, two equivalents of Et₄NOAc were added. As expected, the rate of reaction increased and the reaction was complete within 17 h instead of one week. More unexpected was the optical purity of the product that had increased to 52% ee from the meager 8% ee in the absence of the acetate additive. The observation that the enantioselectivity of the product was linked to the rate of hydrolysis, strongly suggested that the osmium(VI) glycolate complex (**3**) participated in a low- or non-enantioselective diol-forming catalytic pathway. It was thus discovered that two catalytic cycles are present in the catalytic AD using NMO as cooxidant, with a putative osmium(VIII) trioxoglycolate complex (**17**) occupying the pivotal position linking the two catalytic cycles (Scheme 5) [33]. The primary cycle proceeds with high enantioselectivity and turns over by hydrolysis of the osmium(VIII) trioxoglycolate complex, while the secondary cycle proceeds with poor enantiocontrol and turns over by an alkene addition to the same osmium(VIII) trioxoglycolate complex. The distribution between the two cycles is hence determined by the rate difference between hydrolysis and addition. The acetate effect operates by increasing the rate of hydrolysis, shuttling more of the catalysis into the enantioselective primary cycle. A different approach to circumvent the secondary cycle is to limit the amount of alkene present in the reaction mixture. The original NMO procedure called for the inclusion of all ingredients from the start, thereby leaving a vast excess of alkene (relative to osmium compounds) for the osmium(VIII) trioxoglycolate complex to react with. If instead



Scheme 5

the alkene is added slowly to the reaction mixture, the amount of alkene present to react with the osmium(VIII) complex will be negligible and the only fate for complex 17 will be hydrolysis, thus completing the primary cycle [33].

One paradoxical characteristic with the slow addition procedure is observed for the most hydrolytically resistant alkenes, where the reaction proceeds faster the slower the reagent is added. As can be deduced from the discussion above, the slow addition and the acetate effect are not mutually exclusive, and can be used in combination for the most arduous alkenes (Table 3, entries 2 and 6). With the mechanistic insight into the details of the asymmetric dihydroxylation, and the remedies to maintain the enantioselectivity in the addition step, the enantioselectivity in the chiral selectors (DHQD-CLB and DHQ-CLB) became limiting factors in the AD process.

At this point, aromatic *trans*-disubstituted and trisubstituted alkenes gave good to excellent enantioselectivity in the catalytic AD (given the necessary precautions discussed above). Terminal alkenes and aliphatic alkenes still remained an elusive goal (as did *cis*-disubstituted and tetrasubstituted alkenes). Two almost simultaneous discoveries pointed out the direction for the solution of the problem with aliphatic alkenes. The first of these was the discovery of Minato et al. [27] that potassium ferricyanide ($K_3Fe(CN)_6$) in a basic two phase *tert*-butanol:water solution was an excellent stoichiometric cooxidant for an osmium-based catalytic dihydroxylation. Using this cooxidant system, catalytic AD with DHQD-CLB as chiral ligand gave unsurpassed enantioselectivities compared to the NMO system [34]. As shown in Table 4, styrene was dihydroxylated to the corresponding diol in 74% ee (compared with 62% under the original NMO conditions), *E*-5-decene afforded decenediol in 79% ee (NMO: 69% ee), and 1-phenylcyclohexene was transformed to the diol in 91% ee (NMO, slow addition: 78% ee).

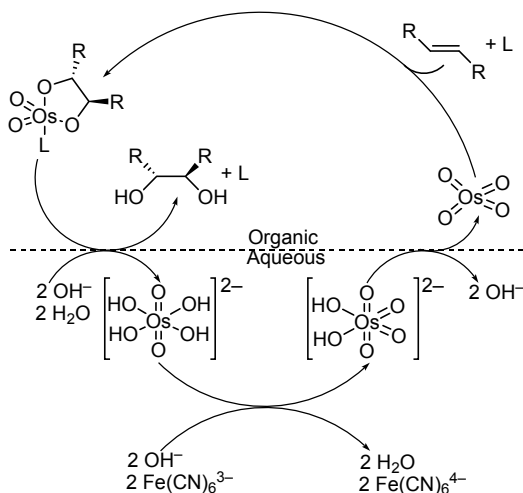
Using the potassium ferricyanide cooxidant system, the non-enantioselective secondary cycle appears to have been suppressed, consequently higher enantiomeric excesses are obtained. The mechanism for the catalytic process is outlined

Table 4. Enantioselectivity in the AD using different DHQD-ligands with NMO or $K_2Fe(CN)_6$ cooxidant systems

Entry	Alkene			NMO	$K_2Fe(CN)_6$	$K_2Fe(CN)_6$	$K_2Fe(CN)_6$
	R ¹	R ²	R ³	CLB	CLB	MEQ	PHN
1	Ph	H	H	62	74	87	78
2	Nap	H	H		88	93	83
3	H	(CH ₂) ₆			64	85	93
4	Oct	H	H		45	65	74
5	Ph	H	Ph	95	99	98	99
6	Bu	H	Bu	69	79	90	95
7	Ph	(CH ₂) ₄		78	91	92	93

in Scheme 6. Under the two-phase conditions the only oxidant in the organic layer is the OsO_4 -ligand complex, which is contrary to the homogenous NMO system, where the reactive trioxoosmium(VIII) glycolate complex also can be present. The reaction between the alkene and the OsO_4 -ligand complex takes place in the organic layer producing the osmium(VI) glycolate complex which hydrolyses and liberates the diol before osmium(VI) enters the aqueous phase and become reoxidized. This two-phase system secures that hydrolysis takes place before reoxidation, and thereby precludes the secondary cycle. An added benefit is that non-volatile $\text{K}_2\text{OsO}_2(\text{OH})_4$ is used as the source of reactive osmium in this system. The preclusion of the secondary system is, however, not the whole explanation of the increased selectivities obtained under the *tert*-butanol:water conditions. Kwong et al. reported that the enantioselectivities for asymmetric dihydroxylations varied as a function of solvents used, and that *tert*-butanol was the supreme solvent [34].

The second discovery that advanced the catalytic AD was the introduction of two new ligand classes, the 9-*O*-(4'-methyl-2'-quinolyl) ether (MEQ) and the 9-*O*-(9'-phenanthryl) ether (PHN) ligands (Fig. 3) [35]. Although it had been considered important that an *sp*² atom should be present as a substituent on the C9 hydroxy group of the *Cinchona* alkaloids (the DHQD and DHQ esters were more effective ligands than their ether counterparts), the decision to make phenolic ether derivatives was postponed due to their anticipated difficult synthesis [36]. With the advent of the MEQ and PHN ligands, major improvements were seen in the catalytic AD. This was particularly the case for *trans*-disubstituted aliphatic alkenes (Table 4, entry 6) and terminal alkenes (Table 4, entries 1–3). The MEQ class of ligands proved to be superior for terminal alkenes, especially those with an aromatic substituent, while the PHN ligands were the choice for



Scheme 6

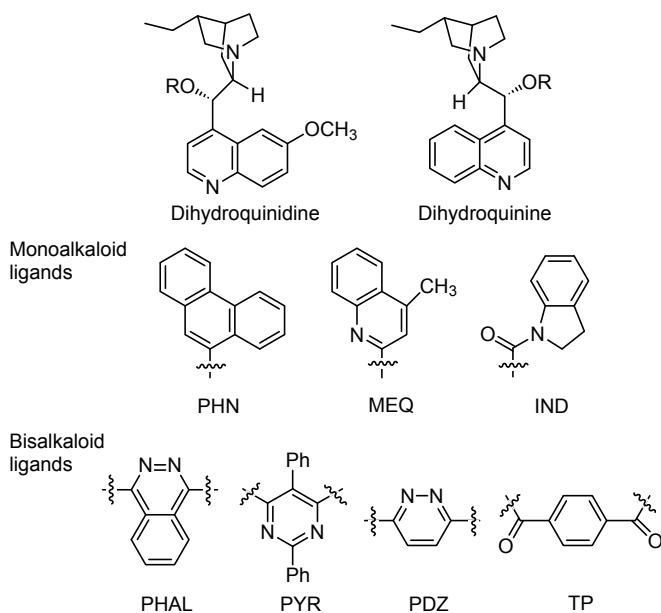


Fig. 3. Different classes of *Cinchona* alkaloid-derived ligands used in the AD process

terminal aliphatic alkenes and aliphatic *trans*-disubstituted alkenes. For the first time excellent enantioselectivities (>95% ee) in catalytic dihydroxylation of aliphatic alkenes were available. A representative example is *trans*-5-decene, which is catalytically dihydroxylated with 95% ee using DHQD-PHN as ligand.

Despite the great enhancement provided by the MEQ and the PHN ligands, they only became a transition on the road to the third generation ligands, namely the bis-*Cinchona* ligands (Fig. 3). The first of these, the phthalazine bis-dihydroquinidine ((DHQD)₂-PHAL) and its dihydroquinine analog ((DHQ)₂-PHAL) [37], have totally superseded the earlier ligand classes thanks to the superb enantioselectivity usually obtained with these ligands for nearly any type of alkene (Table 5). Simultaneously with the introduction of the PHAL class of ligands, another improvement was reported; the hydrolysis acceleration provided by methanesulfonamide. This additive allowed the reaction to be performed at a reasonable rate at 0 °C instead of the normal 25 °C, a modification which boosted the enantioselectivity even further. The increased rate of hydrolysis obtainable through the addition of methanesulfonamide combined with a higher load of osmium tetroxide, opened for the first time the possibility of catalytic dihydroxylation of tetrasubstituted alkenes. Tetrasubstituted alkenes are generally unsuitable substrates for catalytic AD reactions due to the difficult cleavage of the strongly hindered osmate ester. Apart from the difficulties of catalytic turnover, one can easily imagine that face discrimination of a tetrasubstituted alkene can be exceedingly difficult. However, with a new class of bis-alkaloid ligands

Table 5. Enantioselectivity in the AD using bis-alkaloid ligands

Entry	Alkene			(DHQD) ₂ -PHAL	(DHQD) ₂ -PYR
	R ¹	R ²	R ³		
1				97	80
2	Oct	H	H	84	89
3	Chx	H	H	88	96
4	<i>t</i> -Bu	H	H	64	92
5	Bu	H	Bu	98	88
6	Ph	H	Ph	>99.5	
7	Ph	Me	H	94	69
8	Ph	(CH ₂) ₄		99	

with a pyrimidine spacer [38], even this elusive class of alkenes is amenable to catalytic AD [39]. Given their superiority in the face discrimination of tetrasubstituted alkenes, it is surprising that these ligands also are superior for terminal aliphatic alkenes [38] (Table 5, entries 2–4).

3

Ligand Structure and Ligand Acceleration

In a synthetic context, the enantioselectivity in a process is often of greater importance than the ceiling rate of the reaction. As have been discussed previously, the amount of product originating from the chiral pathway is proportional to $k_1 K_{\text{eq}}[\text{ligand}]$, whereas the achiral pathway (leading to the racemic product) is proportional to k_0 . Due to the ligand acceleration effect [7] ($k_1 \gg k_0$), and the high affinity between osmium tetroxide and the ligand ($K_{\text{eq}}[\text{ligand}] \gg 1$) virtually all of the alkene is shuttled through the chiral pathway at much lower ligand concentration than necessary for the onset of rate saturation [29]. The effect of this can be seen in Fig. 4, where the ceiling enantioselectivity is reached at a ligand concentration of 0.01 M, whereas rate saturation requires a ligand concentration ten times higher. A consequence of this relationship is that the process can proceed with very low ligand concentration without loss of enantioselectivity. The effect can be quite staggering, as can be seen in the following imaginary experiment [7]: In the AD of *trans*-stilbene the reaction can be performed with as low as 0.01 mol % ligand and 0.2 mol % osmium tetroxide and still obtain an ee >96% in the diol product. This ee corresponds to a ratio between the chiral and the achiral pathway of 24:1. Given the osmium to ligand ratio of 20:1, the approximate ratio of rate constants, $k_1:k_0$, is 480:1, or expressed as number of molecules: of 10,000 molecules of stilbene, 20 molecules of osmium tetroxide and just 1 molecule of the chiral ligand, only 400 molecules of *trans*-stilbene are dihydroxylated with unbound osmium tetroxide, the 9600 molecules are transformed enantioselectively via the osmium tetroxide-ligand complex.

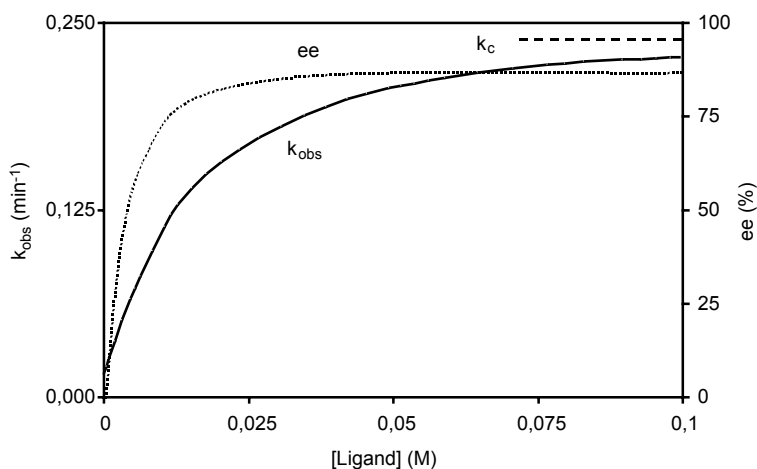
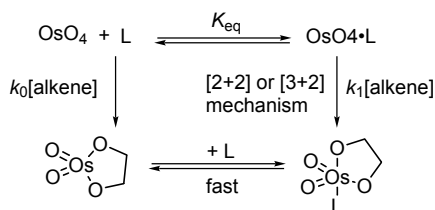


Fig. 4. Plot of the observed rate constant, k_{obs} , and the enantiomeric excess, ee , as a function of DHQD-CLB concentration in a catalytic AD of stilbene using NMO as cooxidant



Scheme 7

The stoichiometric asymmetric dihydroxylation obeys a rate law which is first order in osmium tetroxide and alkene, but shows saturation behavior in ligand (cf Fig. 2). The kinetic behavior of the reaction is shown in Scheme 7 and Eq. (2). This kinetic scheme is also valid for a discussion of the factors governing the enantioselectivity in the catalytic asymmetric dihydroxylation, since the hydrolysis and reoxidation steps does not affect the selectivity of the AD reactions under the normal two-phase reaction using $\text{K}_3\text{Fe}(\text{CN})_6$ as cooxidant.

$$r = \frac{(k_0 + k_1 K_{\text{eq}} [L])}{1 + k_{\text{eq}} [L]} \quad \Rightarrow \quad k_c = k_1 = \frac{k_2 (1 + K_{\text{eq}} [L]) - k_0}{K_{\text{eq}} [L]} \quad (2)$$

k_2 observed second order rate constant

Due to the ligand acceleration effect the $k_1 K_{\text{eq}} [\text{ligand}]$ term is larger than k_0 by several orders of magnitude [30], particularly at saturation ($k_2 = k_c$). Under saturation conditions, $K_{\text{eq}} [\text{ligand}]$ is also much larger than unity so that k_c does

not have a K_{eq} component, and is in fact equal to k_1 . Thus, the saturation rate constants are directly related to the activation energy of each ligand/alkene combination [30].

3.1

Ligand Structure and K_{eq}

The binding constants in toluene to osmium tetroxide of a series of quinuclidine derivatives have been determined [30], and it was found that the ligands generally have to adopt an “open” conformation [40] (Fig. 5) upon binding to osmium tetroxide. This conformation reduces the steric crowding around the quinuclidine nitrogen and allows complexation towards osmium tetroxide. The importance of the “open” conformation is evident in the low binding constant observed for *threo-Cinchona* analogs, where the open conformation requires the OR group and the quinoline moiety to switch places (Fig. 5) leading to a serious destabilization and a subsequent substantial drop in binding constant (Table 6).

The binding constant is extremely sensitive for steric bulk in the vicinity of the quinuclidine ring, and acyloxy substituents and flat aromatic rings are better tolerated than alkyl groups. Among the more subtle structural variations, with nonetheless profound effects on the binding constants, are the location of the ethyl substituent on the quinuclidine ring distal to the nitrogen. The binding constant is higher when the ethyl substituent is located as in the DHQD system compared to the DHQ system. This effect may be connected with the greater twist in the quinuclidine ring of the dihydroquinidine ligand [40, 41] causing one of the two adjacent methylene hydrogens to move farther away from the osmium center [30]. One more of these subtle effects is the lowering of the binding constant when the methoxy substituent on the quinoline ring is removed. Despite these subtleties, the conclusion is that to a first approximation K_{eq} can be regarded as a measure of the steric bulk around the quinuclidine nitrogen of the ligand.

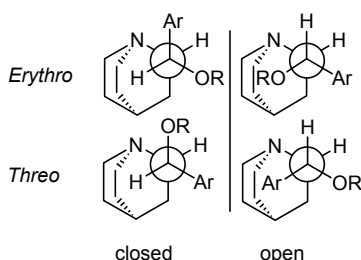


Fig. 5. Schematic depiction of the open and the closed conformations of *erythro*- and *threo*-*Cinchona* alkaloids

Table 6. Binding constants (K_{eq}) and ceiling rate constants (k_c) for different ligands measured in toluene and *tert*-butanol


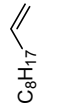
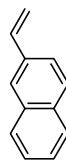
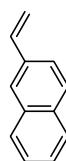
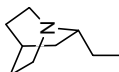
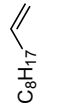
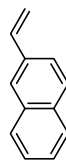
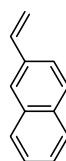
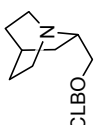
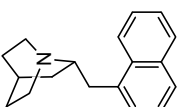
Ligand	Toluene		<i>tert</i> -Butanol	
	K_{eq}	k_c	K_{eq}	k_c
	80,000	 C_8H_{17}	 C_8H_{17}	
	235	 C_8H_{17}	 C_8H_{17}	
 CLBO	81	60	103	189
	292	115	18.3	242
			76	131
			29.2	164
			32.2	256
			125	374
			2,630	147

Table 6. Continued

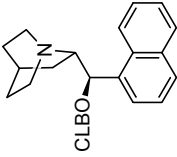
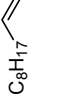
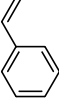
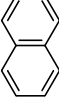
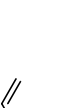
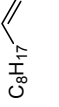
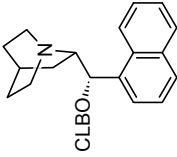
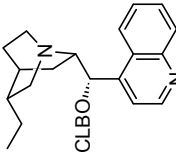
Ligand	Toluene K_{eq}	k_c C_8H_{17}	K_{eq}	k_c C_8H_{17}	<i>tert</i> -Butanol K_{eq}	k_c C_8H_{17}
	0.9					
	16.9	182	437	535		
	19.5	212	448	548		

Table 6. Continued

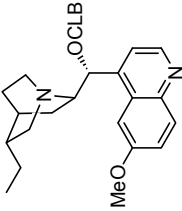
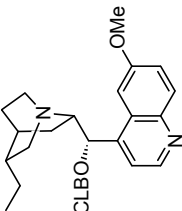
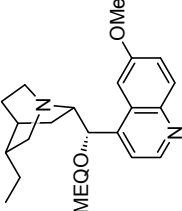
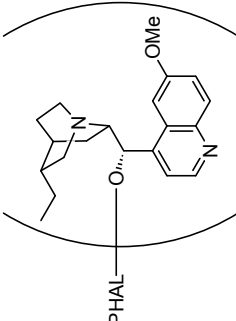






Ligand	Toluene K_{eq}	k_c C_8H_{17}	K_{eq} k_c C_8H_{17}	K_{eq} k_c C_8H_{17}	K_{eq} k_c C_8H_{17}
	25.6	246	787	1135	
	56	234	688	1000	1089
				19.6	335
				22.7	331
					1907
					2287

Table 6. Continued

Ligand	Toluene K_{eq}	k_c C_8H_{17}	K_{eq}	k_c C_8H_{17}	<i>tert</i> -Butanol K_{eq}	k_c C_8H_{17}
						
			27.7	1065	7320	35,600

3.2

Ligand Structure and Ceiling Rate Constants

When the ceiling rate constants are compared with the binding constants (Table 7), there is no direct correlation between the K_{eq} and K_c . However, some features necessary for high rate acceleration are apparent. Branching of the quinuclidine side chain leads to higher rate constants despite the fact that such branching decreases the binding constant towards osmium tetroxide. The beneficial effect of an acyloxy branching is evident by observing that this ligand gives higher ceiling rate constant than ethyl- and isopropylquinuclidines [30]. It is also apparent that even though an aromatic branching is better than an aliphatic branching, the electronic nature of the aromatic substituent has only minor influence. More striking is the importance of the quinoline methoxy group, especially for aromatic alkenes. The ceiling rate constants were also measured in *tert*-butanol, and in this solvent there is an even more pronounced difference in rate between aromatic alkenes and aliphatic alkenes, with 2-vinylnaphthalene as the fastest and 1-decene and vinylcyclohexane as the slowest substrates. The beneficial effect of the quinuclidine side chain branching, and the importance of the *O*-9-substituent is also evident in *tert*-butanol. These results show that *O*-9-substituents with flat aromatic moieties give much higher ceiling rate constants than what is obtained for the acetyl-substituted analog. Especially striking are the rate constants obtainable with the phthalazine system for aromatic alkenes, suggesting interactions between the aromatic groups of the substrate and the aromatic *O*-9-substituent. This interaction is obviously greater for the larger aromatic alkenes (2-vinylnaphthalene vs. styrene), and it is noteworthy that this interaction is limited to aromatic alkenes, vinylcyclohexane reacts much slower than styrene. The data show that the effect of variations in the *O*-9-substituent have much more profound effects upon the ceiling rate constants than almost any other variation in the ligand structure.

It is also important to note that not only the ceiling rate constants, but also the enantioselectivities are influenced by the nature of the *O*-9-substituent suggesting a relationship between the ceiling rate constant and the enantioselectivity as shown in Table 7.

The rate acceleration can either be interpreted as a destabilization of the ground state due to steric effects, or alternatively as transition state stabilization. The lack of correlation of k_c , and K_{eq} which is a first approximation of the steric

Table 7. Enantioselectivity and ceiling rate constants

Ligand	1-Decene		Styrene		2-Vinylnaphthalene	
	%ee	k_c	%ee	k_c	%ee	k_c
DHQD-CLB	45	331	74	1089	88	1907
DHQD-MEQ	65	335	87	1210	93	2287
(DHQD) ₂ -PHAL	84	1065	94	7320	98	33,600

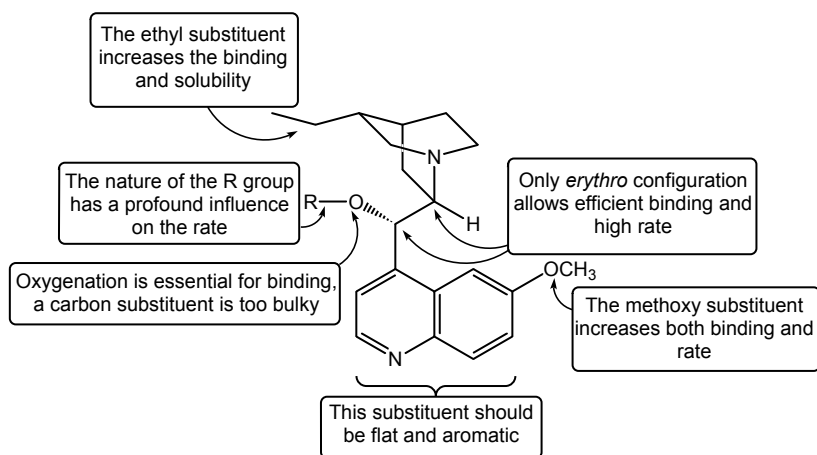


Fig. 6. Summary of different features in cinchona alkaloid ligands and their effect on osmium tetroxide binding and ligand acceleration

environment around the osmium tetroxide, together with the small influence of *O*-9-substituents on K_{eq} is consistent with effects contributing to a stabilization of the transition state, and that this stabilization at least partly originates from attractive interactions between flat aromatic groups in the substrate and aromatic groups in the ligand. Solvent effects also contribute to the interaction between the substrate and the ligand since both ceiling rates as well as relative rates with respect to 1-decene, drop when changing from *tert*-butanol to toluene. This effect which is probably due to solvophobic interactions is especially pronounced for the combination of a large aromatic substrate (2-vinylnaphthalene) and a large aromatic *O*-9-substituent (PHAL-spacer).

A summary of the different features in the *Cinchona* series of ligands and their effect on ligand acceleration are shown in Fig. 6, and reveal that the *cinchona* alkaloid skeleton is nearly ideally set up to ensure high ligand acceleration (high K_{eq} and k_1). Combined with the fact that the ligand shows great face selectivity in osmium tetroxide additions and has sufficiently low affinity for osmium(VI) glycolates for a catalytic reaction to turn over, this is indeed a remarkable feat for a simple molecule.

4

The Mechanism of the AD Reaction

The mechanism of the AD reaction, discussed in the limited context of what exact events take place during the chiral amine accelerated osmium tetroxide addition to alkenes, has been a subject of passionate debate for a number of years. The controversy is mostly concerned with two aspects of the alkene addition step in the AD process; the exact mechanism of the amine-accelerated osmium

tetroxide addition, and the origin of the enantioselectivity in the chiral amine accelerated osmium tetroxide addition.

4.1

On the Mode of Amine-Accelerated Osmium Tetroxide Addition

The first mechanism suggested for the addition of osmium tetroxide to an alkene was suggested by Blöseken as early as 1922 [42], and was further refined by Criegee during his seminal investigation of ligand-accelerated osmium tetroxide addition [2, 3, 4]. Their proposal is the textbook (3+2) mechanism, which has lately been reiterated and refined by Corey [43, 44, 45, 46, 47, 48]. The ligand-acceleration effect stems from favorable interactions between the alkene and the osmium tetroxide-ligand complex. An alternative two-step mechanism for the osmium tetroxide addition involving a (2+2) formation of an osmaoxetane intermediate followed by ligand-assisted ring expansion to the osmium glycolate complex was suggested by Sharpless et al [49] in 1977 and has later been refined to cover the aspects of ligand acceleration [50]. The Sharpless mechanism finds analogy in chromyl chloride oxidations of alkenes [49] and the metallacyclobutanes found in alkene metathesis processes. In the stepwise (2+2) mechanism, the alkene coordinates to the osmium center, and this coordinated complex undergoes a rapid and reversible rearrangement to the osmaoxetane intermediate which subsequently rearranges in a rate-limiting step to the well known osmium(VI) glycolate complex. The ligand-acceleration effect which is so essential for the successful outcome of the AD originates from ligand coordination to the osmaoxetane intermediate which is then more likely to rearrange to the osmium(VI) glycolate complex. Both the (3+2) and the (2+2) mechanisms are presented schematically in Fig. 7.

Despite considerable efforts, it has proven difficult to distinguish between these two mechanisms, partly because the (3+2) and (2+2) pathways are kinetically indistinguishable. Experimental support for a multi-step mechanism primarily stems from two experimental areas; non-linear Eyring plots and analysis of the electronic effects in the amine acceleration, whereas theoretical studies of

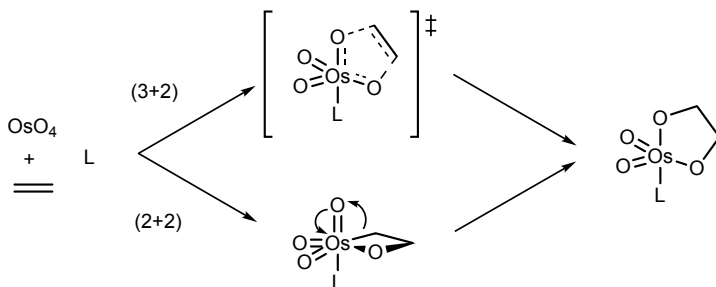


Fig. 7. Schematic representation of the concerted (3+2) and the stepwise (2+2) addition of osmium tetroxide to an alkene

proposed transition states and the observed kinetic isotope effect lend more credit to a (3+2) pathway.

4.1.1

Enantioselectivity as a Function of Temperature

A distinct feature of a stepwise osmium tetroxide addition is the presence of two transition states, one leading to the formation of the intermediate osmaoxetane, and one for the consumption of the intermediate leading to the osmium(VI) glycolate complex. In the presence of a chiral ligand, the total reaction will thus proceed through two different pairs of diastereomeric transition states, and non-linear temperature effects on the observed enantioselectivity can be expected. In the modified Eyring formalism [50, 51]: $\ln P = -(\Delta\Delta H^\ddagger/RT) + (\Delta\Delta H^\ddagger/R)$, where $P = k(\text{major diol})/k'(\text{minor diol})$ and k and k' are the overall rate constants. In the AD reaction each alkene/chiral ligand combination shows two linear regions in the Eyring plot as shown in Fig. 8 [50].

A characteristic inversion point connects these linear regions, and the temperature corresponding to this point is called the inversion temperature of the system. The presence of an inversion temperature can be explained by a reaction mechanism with at least two enantioselective steps which are weighted differently according to the temperature (i.e., the two steps have different $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$), and is hence consistent with a stepwise (2+2) mechanism. In the Sharpless proposal, the selectivity defining steps are the binding of the ligand to the osmaoxetane intermediate (Scheme 8) and the subsequent rearrangement of the ligand bound osmaoxetane to the osmium(VI) glycolate. Recently, Corey and

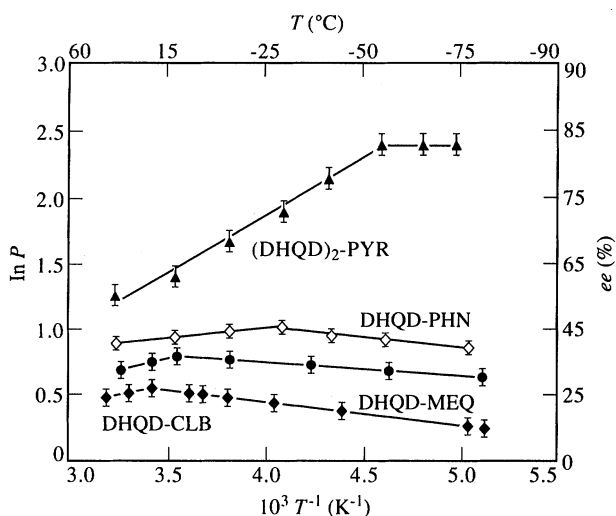
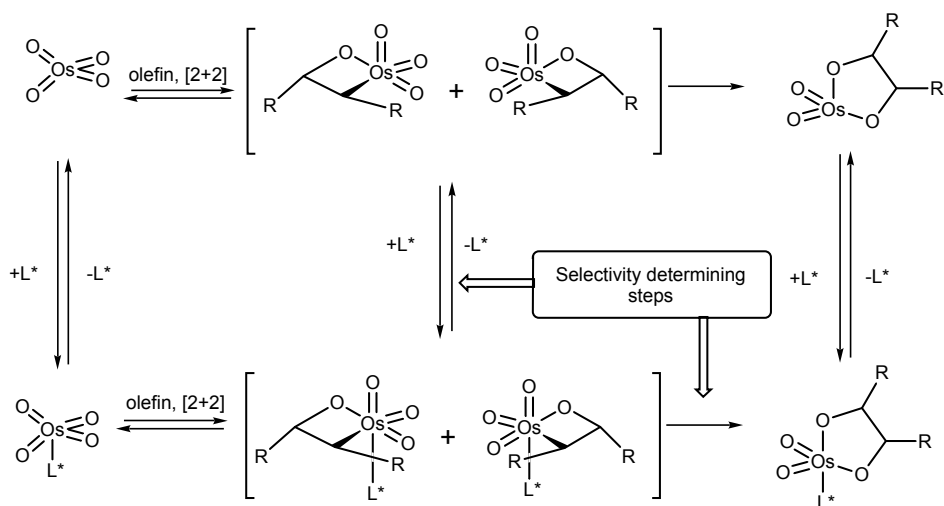


Fig. 8. Eyring plot of the asymmetric dihydroxylation of 1-decene using different ligands



Scheme 8

Noe have proposed a variation on the (3+2) pathway, including a rapid and reversible equilibrium between the alkene and the osmium tetroxide-ligand complex prior to the rate determining addition step, yielding Michaelis-Menten kinetics and subsequent non-linearity in the Eyring plots [44]. This view has been challenged by Nelson et al [52].

4.1.2

Theoretical Studies of the Reaction Mechanism

The elusive osmaoxetane intermediate has never been isolated and characterized, but has been a favored playground for theoretical studies. Jørgensen and Hoffmann performed early theoretical studies of the mechanism of osmium tetroxide addition using extended Hückel calculations [53] and concluded that the orbitals of osmium tetroxide and the alkene were well set up for a (3+2) cycloaddition, via an avoided crossing of the osmium d_{z^2} and the π -orbital of the alkene. The frontier molecular orbitals of osmium tetroxide were not directly set up for a (2+2) cycloaddition, but this mechanism could not be excluded. Higher level *ab initio* calculations have been performed on the osmaoxetane and the osmium(VI) glycolate both in the absence and the presence of an amine [54]. The osmaoxetane intermediate has also been addressed by molecular mechanics calculations [55, 56]. These theoretical studies conclude that the formation of the osmium(VI) glycolate is exothermic, and that the osmaoxetane was not too high in energy to be excluded. However, more recent calculations on the different transition states using intrinsic reaction coordinates (IRC) with the density functional theory (DFT) formalism clearly favor the (3+2) mechanism with a low calculated activation barrier [57, 58, 59, 60]. The (2+2) addition mechanism

appears to have high calculated activation barriers, suggesting that the reactions are symmetry forbidden [60].

4.1.3

Kinetic Isotope Effects in Osmylations

A completely different approach in the investigation of the reaction mechanism is the determination of kinetic isotope effects (KIE). Two such investigations have been reported lately [45, 61]. In the first study, the $^{12}\text{C}/^{13}\text{C}$ kinetic isotope effects were measured for styrene, 4-nitrostyrene, and allyl 4-methoxybenzoate (Fig. 9). Similar $^{12}\text{C}/^{13}\text{C}$ isotope effects were found for the methine and the terminal methylene carbon atoms, suggesting a symmetrical transition state structure, i.e., a (3+2) transition state [45]. The conclusion of this analysis should however be interpreted with care; it is difficult to predict what the $^{12}\text{C}/^{13}\text{C}$ KIE would have been for a less symmetrical (2+2) transition state, furthermore the analysis does not take into consideration the possible formation of regioisomeric osmaoxetanes, a possibility that would ruin any interpretation of the measured kinetic isotope effects (Scheme 9).

The second study of the kinetic isotope effect in the asymmetric dihydroxylation measures both $^1\text{H}/^2\text{H}$ as well as $^{12}\text{C}/^{13}\text{C}$ isotope effects in the dihydroxylation of *tert*-butylethylene under standard AD conditions using $(\text{DHQD})_2\text{-PYR}$ as ligand. The substrate was chosen in order to minimize the formation of regioisomeric osmaoxetanes and hence the ambiguity in which carbon of the alkene will be associated with osmium, because the transition states which locates the *tert*-butyl group next to osmium will be greatly disfavored. Furthermore, the observed kinetic isotope effects were compared with high-level transition state structure and KIE calculations performed on a model system where propene was used as alkene, ammonia as ligand, and solvent effects were omitted. The calcu-

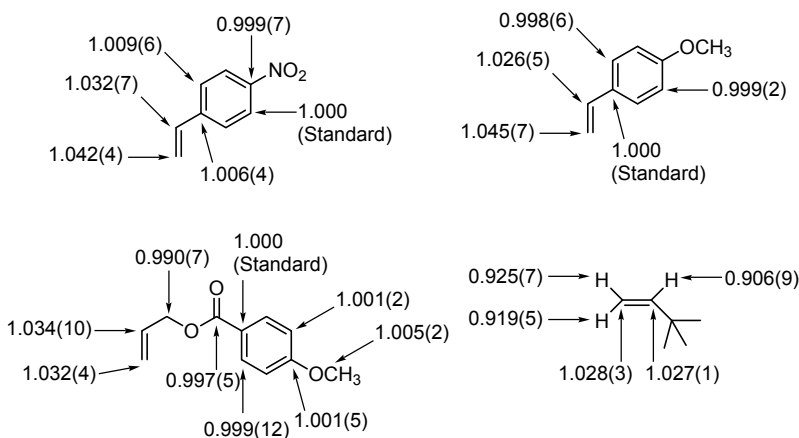
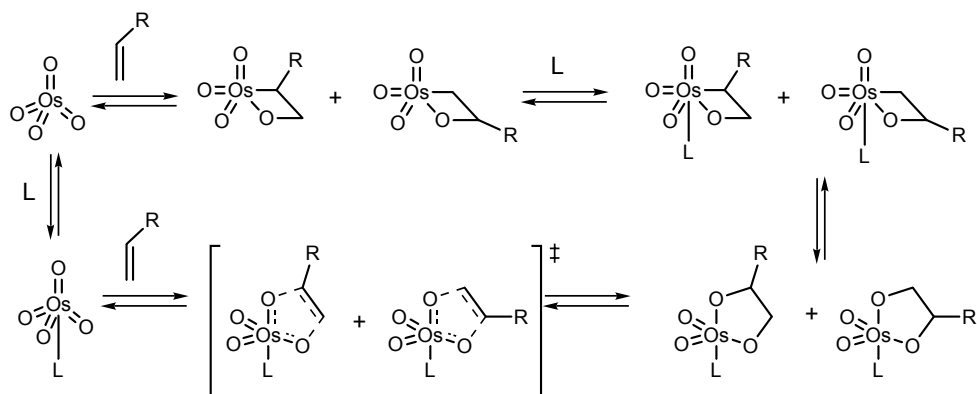


Fig. 9. Observed kinetic isotope effects in the AD process



Scheme 9

lated KIE for a (3+2) transition state are in remarkable agreement with the measured KIE, considering the substantial simplifications in the theoretical model. The calculations does not match for a rate-limiting ring expansion, and sheds doubt about a rate-limiting formation of an osmaoxetane intermediate [61].

4.1.4

Electronic Effects in Amine-Accelerated Osmylations

A classical method for the study of organic reaction mechanisms is the determination of linear free energy relationships, where the effect of electronic perturbation on thermodynamic or kinetic phenomena is addressed, usually in the form of the σ and the ρ parameters of Hammett. Both the ligand-binding ability and the electronic effects in the alkene have been analyzed in the Hammett formalism [52]. The results show that electron-donating substituents on simple pyridine or quinuclidine ligands increase K_{eq} , and decrease the N-Os bond distance. The simple linearity in the Hammett plots of the binding constants is not transferred into the ceiling rate constants for the reaction with alkenes. In the pyridine series the ρ -value is negative, whereas in the quinuclidine series, the ρ -parameter is positive, indicating that the weaker binding amines afford greater rate enhancement.

Measurement of the substrate electronic effects afforded curved Hammett plots as shown in Fig. 10. The degree of curvature was stronger causing parabolic plots for strongly coordinating amines, whereas less efficient binding ligands such as DHQD-CLB caused only moderate curvature. Non-linear Hammett plots are normally seen when there is a change in mechanism due to the change in substrate electronic properties.

Negative ρ -values are observed with substrates containing electron-releasing substituents, but the ρ -parameter gradually shifts to positive when electron-withdrawing groups are introduced into the alkene. It should be noted that the non-

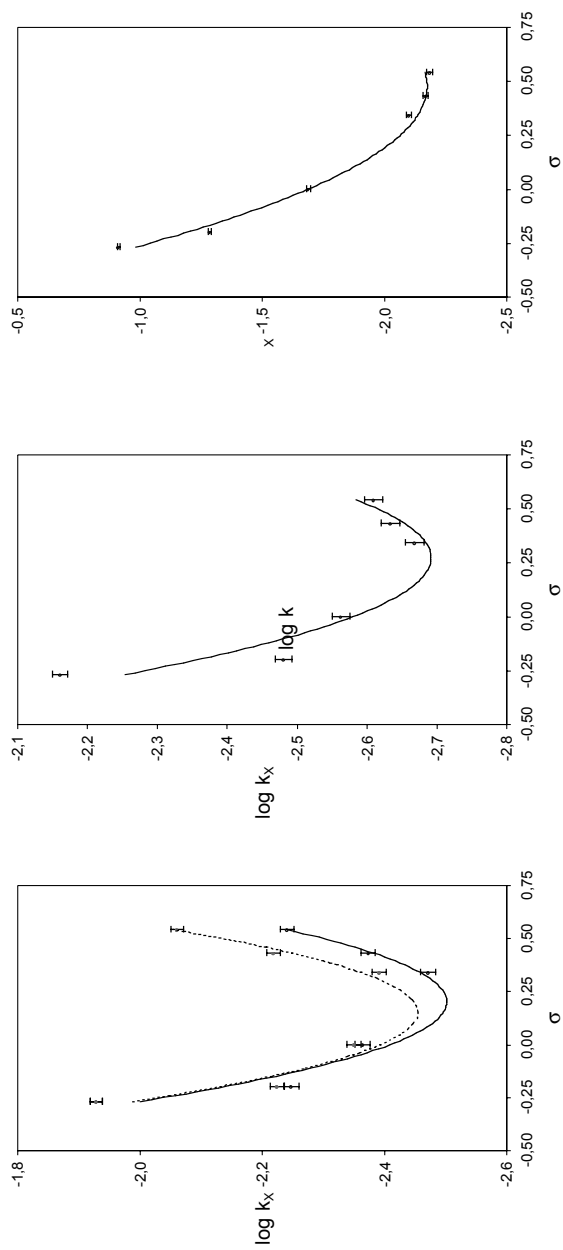


Fig. 10. Hammett plots of osmium mediated dihydroxylations of substituted stilbenes using pyridine (*left*), quinucidine (*middle*) and DHQD-CLB (*right*) as ligands

linearities in the Hammett plots are caused by the inclusion of accelerating tertiary amines, since osmylations in the absence of accelerating ligands give linear Hammett plots with a negative ρ -value [62]. In addition, the extent of curvature is also dependent on the ligand concentration. The curvature in the Hammett plots cannot be rationalized by different variations of the (2+2) mechanism, because a change in the rate-limiting step in a sequential mechanism cannot afford a Hammett relationship with a distinct minimum. If the (3+2) mechanism resembles a type II 1,3-dipolar cycloaddition [63, 64], where the HOMOs and the LUMOs of both the dipole and the dipolarophile are of approximate energy, parabolic Hammett plots with a distinct minimum can be envisaged. There are however several inconsistencies between the measured kinetic data and the reactivity predicted from the FMO model, but the (3+2) pathway is definitely a possible explanation for the part of the Hammett plot with a positive ρ -value, an area which corresponds to electron-deficient alkenes and strongly binding ligands. A stepwise (2+2) mechanism is more consistent with a negative ρ -value, in an area where electron-rich alkenes and less strongly binding ligands prevail.

4.1.5

Conclusion

From the results presented so far, it is evident that the apparent simplicity of the overall transformation is not transposed into the actual reaction mechanism of the osmylation process. There is ample evidence discrediting each mechanism, suggesting that none of the presented mechanisms are satisfactory for explaining the sequence of events that take place during the addition of osmium tetroxide to an alkene. In fact some of the investigations performed casts doubt on the presence of a single mechanism in the process. At the present stage we will have to conclude that despite an enormous effort from several research groups, the jury is still out on the case.

4.2

On the Origin of the Enantioselectivity in the AD Process

As with the mechanism of osmium tetroxide addition, the origin of the enantioselectivity in the AD process has also been a subject of much debate. An early proposal by Corey et al. [48], suggested that the AD reaction proceeded through the μ -oxo-bridged bis-osmium(VIII) complex shown in Fig. 11.

This proposal was later refuted by Kolb et al. [65] based on the fact that the rate of the AD reaction is first order in both osmium tetroxide and alkene, while Corey's proposal would require a second-order component for osmium tetroxide. Furthermore, Kolb et al. showed that the second alkaloid moiety in the bis-alkaloid ligands is not necessary for high enantioselectivity, precluding any interaction between both quinuclidine nitrogen atoms and osmium tetroxide. The two prevalent models for explaining the introduction of enantioselectivity in the AD process both operate with one active osmium tetroxide molecule per ligand,

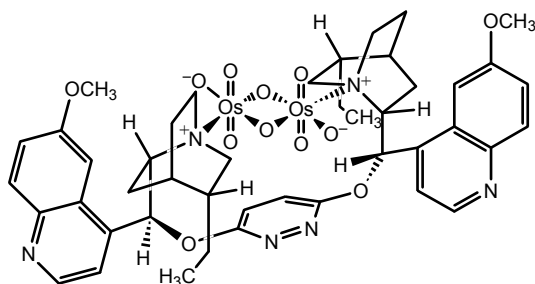


Fig. 11. Proposed μ -oxo-bridged osmium(VIII) complex

in accordance with the results of Kolb et al. The explanation of the high enantioselectivity in the AD reaction has been divided into two proposals, one by Sharpless and one by Corey. These proposals differ mainly in the view of the mechanistic details in the amine-accelerated osmium tetroxide addition and the orientation of the alkene in the transition state complex(es). These proposals are presented below in their latest iterations.

4.2.1

The Sharpless Model

The key point of the Sharpless model is the two-step mechanism for the addition of osmium tetroxide to an alkene. The basis for this suggestion is the presence of inversion points in the Eyring plots (Sect. 4.1.1). The most viable proposal for this mechanism is outlined in Fig. 12.

It should be noted that the formation of the four-membered ring most probably does not proceed via a concerted [2+2] cycloaddition mechanism. Analogous reactions between alkene-alkylidene metal complexes do not proceed by [2+2] cycloadditions [66]. All equilibria prior to the irreversible rearrangement of the ligated osmaoxetane are rapid and reversible under the AD reaction conditions. The rearrangement of the osmaoxetane is ligand-accelerated, i.e., the rearrangement of the ligated osmaoxetane is much faster than for the unligated species. The ligand acceleration reaches saturation at high ligand concentration, requiring free and rapid reversibility of all steps prior to the rate-determining step (RDS). If any of the steps prior to the RDS should become slowed down to a degree that makes it kinetically significant the rate law would change. The kinetic consequence of the mechanism presented in Fig. 12 is thoroughly discussed in the literature [67].

The two levels of enantioselection required by the inversion points in the Eyring plots are a result of the binding of the enantiomeric osmaoxetanes to the chiral ligand, and the rearrangement of the ligated osmaoxetanes to the osmium(VI) glycolate. The Sharpless group has performed density functional theory (DFT) calculations of the putative osmaoxetane complexes [68], using ru-

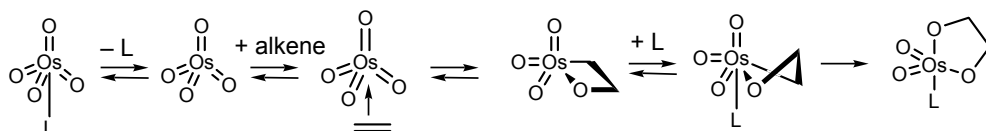


Fig. 12. Schematic representation of the stepwise mechanism for osmium tetroxide addition

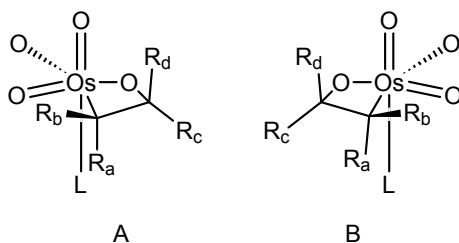


Fig. 13. Isomeric forms of the osmaoxetane intermediate

thorium as a model for osmium. The validity of this computational simplification is supported by the observation that ruthenium tetroxide dihydroxylations in the presence of AD ligands give the same facial selectivities, although with lower yield and lower enantioselectivity than osmium tetroxide dihydroxylations. Structures calculated on ruthenium agree closely with X-ray crystallographic structures of the corresponding osmium complexes. Furthermore, a series of DFT calculations on the osmium complexes using effective core potential (ECP) basis sets yield very similar structures [54, 57, 59, 60]. The calculations reveal that the four-membered osmaoxetane ring displays only a small amount of puckering, but upon the binding of a ligand, the puckering of the four-membered ring increases significantly as depicted in Fig. 13.

The amount of puckering is dependent on the substitution pattern at the osmaoxetane ring, and increases when going from *cis*-disubstituted via 1,1-disubstituted to *trans*-disubstituted osmaoxetanes, a trend that correlates with the observed increasing relative rates (Fig. 14) and enantioselectivities for the same alkene classes. In addition, the calculations strongly suggest that the pseudoaxial position *a* in the osmaoxetane complex is severely sterically crowded, leaving little more space than what is needed for a hydrogen.

When the ligand is achiral, complexes A and B in Fig. 13 are enantiomeric, but when the ligand L is chiral, A and B are diastereoisomers. The AD ligands are *Cinchona* derived and could be anticipated to display significantly more steric crowding than the ammonia ligand used in the calculations. As discussed in Sect. 3.1, the binding constant for osmium tetroxide is extremely sensitive for steric bulk in the chiral ligand. It can easily be envisioned that this dramatic effect is transferred to the osmaoxetane, where the steric crowding of position *a* in the osmaoxetane is much more severe with the AD ligands than with quinuclid-

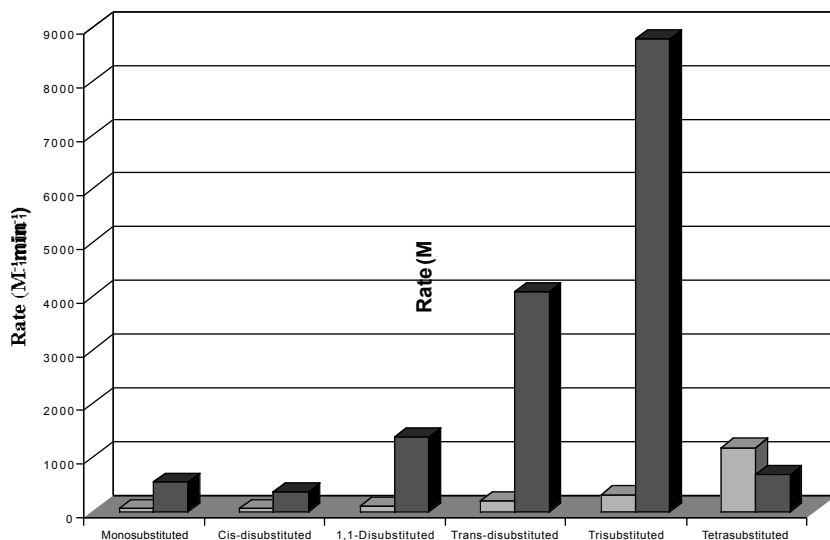


Fig. 14. Relative rates of osmium tetroxide addition with different alkene substitution classes (Gray bars: quinuclidine, white bars: (DHQD)₂-PHAL)

ine. In the following discussion, where the DHQD based ligands will be used as an example, the osmaoxetane ligand **A** will be preferred over its diastereoisomer **B** due to its non-bonded stabilization between the substituent in position *c* and *O*-9 substituent in the ligand (Fig. 15). This stabilization is especially effective when complementary large groups are present such as a large aromatic moiety in the *c* position in the osmaoxetane and a PHAL *O*-9 spacer in the ligand. The effect of this substrate-ligand stabilization is manifested as a large ligand acceleration effect for the PHAL-class of ligands with large aromatic alkenes as discussed in Sect. 3.2. This stabilizing interaction is much greater in the bis-alkaloid ligands than in the first generation ligands, leading to much higher rate constants, and hence enantioselectivities in the AD process. A molecular mechanics model for the qualitative assessment for the selectivity trends observed for several of the alkene substitution classes has been developed [55].

The ring-puckering of the osmaoxetane is also expected to influence the rate of rearrangement to the osmium(VI) glycolate, as rearrangement from isomer **A** should proceed without steric hindrance, while rearrangement from isomer **B** should experience repulsion between the hydrogen in position *a*, and the hydrogen atom on C9 of the *Cinchona* alkaloid. The expected rate difference of rearrangement adds a second level of selection in the AD process. All in all, according to the Sharpless model, the enantioselectivity observed in the AD reaction is an outcome of two factors; stabilizing stacking interactions between the (aromatic) substituents and the aromatic *O*-9 substituent in the chiral ligand, and destabilizing, repulsive interactions between the *a* substituent in the osmaoxetane and the H-9 of the ligand. A 3-dimensional model of the (DHQD)₂-PHAL

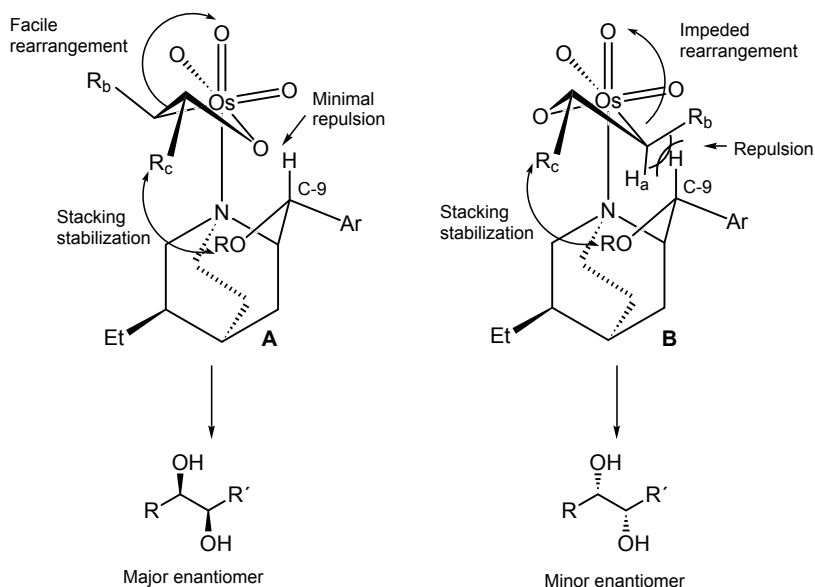


Fig. 15. Proposed intermediates in the AD process using DHQD ligands

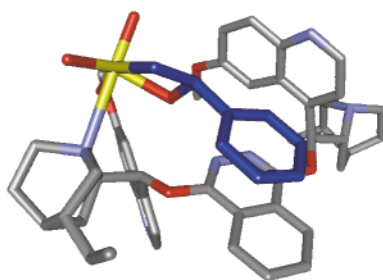


Fig. 16. 3-Dimensional model of the (DHQD)₂-PHAL bound osmaoxetane derived from styrene

bound osmaoxetane is shown in Fig. 16. A corollary of the different interactions between the ligand and substrate has led to a memorizing model for rationalizing face selectivity described in Sect. 4.2.1.1.

4.2.1.1

Mnemonic Device for Rationalizing Face Selectivity

A hallmark of the AD reaction is the wide range of substrates giving high ee values in the process, where all alkene substitution patterns from monosubstituted to tetrasubstituted represents viable substrates for the process. A second appeal-

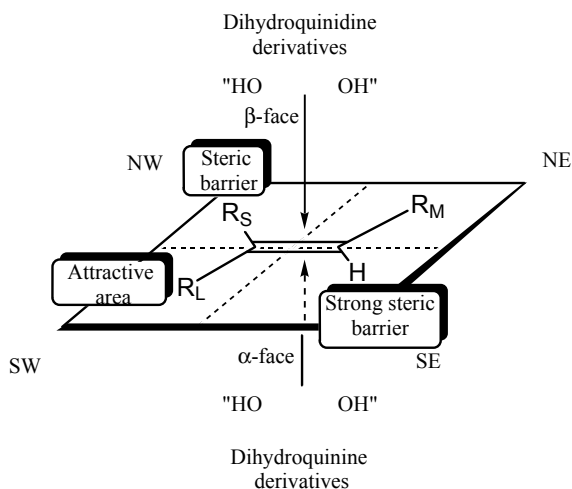


Fig. 17. Mnemonic device for predicting enantiofacial selectivity in the AD process

ing feature with the AD process is the predictability of the stereochemical outcome of the reaction. This predictability is summarized in Sharpless' mnemonic device [37], which in its refined form is depicted in Fig. 17.

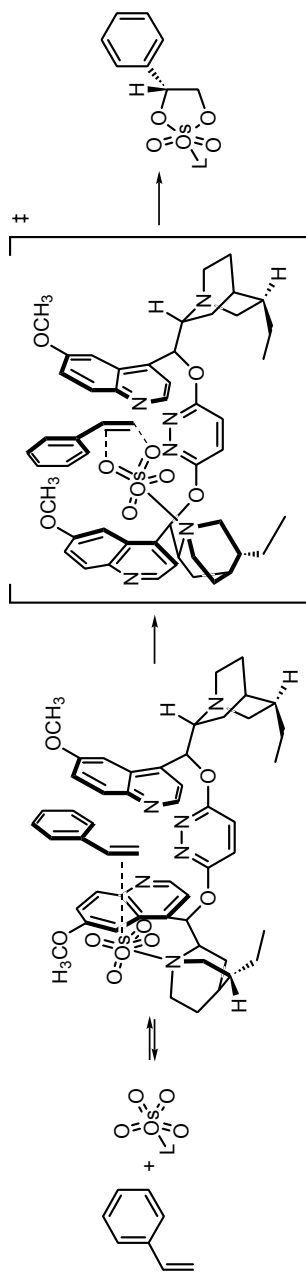
The device is a plane divided into four quadrants representing different features that the ligand imposes on the substrate. The southeast (SE) and, to a much lesser extent, the northwest (NW) quadrants represent steric barriers (with the exception that the NW quadrant can play an attractive role for certain allylic or homoallylic alcohols). The northeast (NE) quadrant represents an open area allowing considerable steric bulk in the alkene substrate, while the southwest (SW) quadrant is regarded as an attractive area, especially well suited to accommodate flat aromatic substituents. To use this device, the alkene is superimposed onto the plane taking the different properties of each quadrant into consideration. When the alkene is positioned according to these constraints, the dihydroxylation will take place from the top face when DHQD ligands are employed, or from the bottom face, in the case of DHQ ligands.

4.2.2

The Corey Model

The Corey model, presented in Scheme 10, is based on the formation of an osmium tetroxide-chiral ligand ternary complex through a rapid and reversible equilibrium. Inside this complex, the osmium tetroxide is added to the alkene via a (3+2) addition mechanism forming the ligand-bound osmium (VI) glycolate complex.

It is well known that the *Cinchona* alkaloids derivatives are conformationally flexible in solution [40, 44]. Binding of osmium tetroxide, protonation, or meth-



Scheme 10

ylation of the quinuclidine nitrogen atom rigidifies the structure forcing the alkaloid to adopt the open conformation [40, 44]. The seminal observation in the development of Corey's model was the observation that a rigid $(\text{DHQD})_2$ -PDZ derivative with an adipate linker between the quinuclidine ethyl substituents gave very similar enantioselectivities as the unlinked and flexible PDZ derivative [69]. The adipate-linked PDZ ligand was supposed to be locked in a conformation where the aromatic PDZ ring forms the bottom of a U-shaped cleft and the quinoline rings from the two alkaloids form the walls (Fig. 18). The structure of the ligand-osmium tetroxide complex is deduced from X-ray and ^1H NMR studies of the bis-methiodide derivative of the $(\text{DHQD})_2$ -PDZ and the adipate-linked $(\text{DHQD})_2$ -PDZ derivative [70] and led to a revised conformation of the pyridazine ring where the aromatic nitrogen atoms are close to coplanar with the C9 carbon of the alkaloids leading to a less clear U-shaped cleft. The orientation of the PDZ linker is expected to be quite rigid [44, 71].

The Corey mechanistic proposal is founded on the ability of the alkene substrate to bind between the two quinoline ring walls which are spaced parallel with a separation of 7.2 Å. When the substrate binds in this elongated cleft, the alkene complexes to the osmium center in the *N*-complexed osmium tetroxide through a donor-acceptor ($d-\pi$) interaction (Scheme 10). The interaction between the alkene and osmium tetroxide is also complemented with favorable van der Waals interactions between the alkene and the binding cleft. These interactions are implied by the Michaelis-Menten kinetics [72] observed in the process. The observation of Michaelis-Menten kinetics in the AD process has however been questioned as an experimental artifact by the Sharpless group [73]. The (3+2) addition takes place between the axial and one of the equatorial oxygen atoms in osmium tetroxide which are in close proximity with the alkene. This represents the minimum motion pathway in the formation of the pentacoordinate osmium(VI) glycolate ester. In the Corey model the rate acceleration observed in

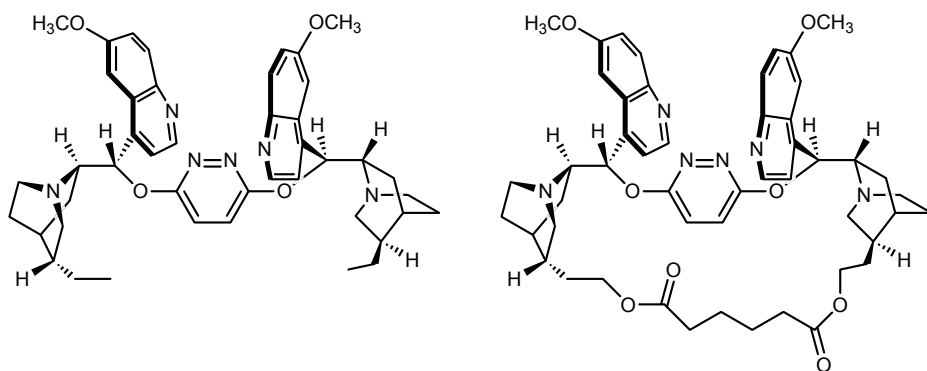


Fig. 18. AD ligands prepared by Corey, $(\text{DHQD})_2$ -PDZ (*left*) and adipate linked $(\text{DHQD})_2$ -PDZ (*right*)

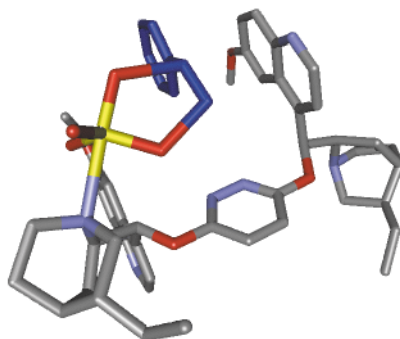


Fig. 19. A 3-dimensional representation of the transition state for styrene in the (DHQD)₂-PDZ-osmium tetroxide complex calculated by combined quantum mechanics: molecular mechanics

the AD process originates from a shortening of the quinuclidine N-Os bond during the reaction, rotation of this bond from the eclipsed to the more energetically favored staggered geometry and reduced entropic cost by the van der Waals binding between the alkene substrate and the catalyst. A 3-dimensional representation of the transition state calculated by combined quantum mechanics: molecular mechanics [IMOMM(BECKE3LYP:MM3)] is depicted in Fig. 19. The calculation sheds doubt on the donor-acceptor (d- π) interaction, and claims that most of the stabilization in the Michaelis-Menten intermediate is caused by (π - π) interaction between the styrene aromatic ring and one of the methoxyquinoline rings of the *Cinchona* ligand [74].

One of the advantages with the Corey model is the heuristic value incorporated in this simple transition state model, where ligand modifications open the possibility of increasing and changing the selectivity for certain substrates. One of these is exemplified below, the others which are represented in enhanced selectivity in the AD of allylic 4-methoxybenzoates [75] and increased selectivity for terminal dihydroxylation of polyenes [46], can be found in the literature [44].

4.2.2.1

Kinetic Resolution

Based on the transition state model, Corey has argued that the PDZ ligands (and the other bis-alkaloid ligands by analogy) are ineffective in producing kinetic resolution for substituted allyl benzoates. A docking of allyl 4-methoxybenzoate into the binding cleft of (DHQD)₂-PDZ is shown in Fig. 20. According to the Corey model, the lack of sensitivity in the ligands to preexisting chirality in the allylic position in the alkene substrates is due to the fact that the ligands obstruct any additional allylic substituent at either of the two prochiral positions A and B in the substrate. What is obviously needed to obtain kinetic resolution is a modified ligand that sterically allows an allylic substituent in one of the positions while retaining the ligand-induced obstruction in the other position.

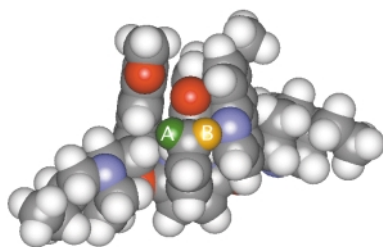


Fig. 20. A 3-dimensional representation of allyl 4-methoxybenzoate bound in the (DHQD)₂-PDZ-osmium tetroxide complex

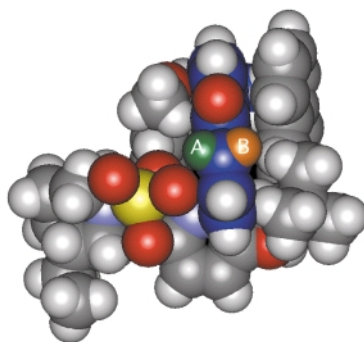


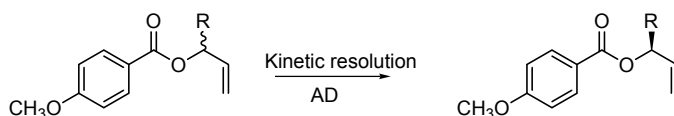
Fig. 21. A 3-dimensional representation of allyl 4-methoxybenzoate bound in the DHQD-PDZ-(S)-anthryl-osmium tetroxide complex

Table 8. Kinetic resolution in the AD of racemic allylic 4-methoxybenzoates

R	Ligand	$k_{rel[a]}$
Me	(DHQD) ₂ -PDZ	3.1
	DHQD-PDZ-(S)-anthryl	20
Ph	(DHQD) ₂ -PDZ	1.9
	DHQD-PDZ-(S)-anthryl	79

^[a] k_{rel} is the relative rate of reaction between the *R*- and the *S*-enantiomer of the substrate

Corey has argued that the quinoline ring of the inactive alkaloid had to be removed and replaced with a different aromatic wall that projected rearwards from the pyridazine linker. Such a candidate was found for the DHQD-PDZ-(S)-anthryl ligand in Fig. 21. While the rearward projecting wall is expected to decrease the stabilization of the aromatic part of the alkene substrate, and hence lower enantioselectivity in the binding of normal alkenes, the aromatic wall no longer renders steric hindrance to a substituent in the position B of an allylic benzoate, while the A position is obstructed. The DHQD-PDZ-(S)-anthryl ligand should then be capable of distinguishing the two enantiomers of a racemic allylic substrate as shown in Scheme 11, Table 8, and Fig. 21.



Scheme 11

4.3

Conclusion

Two different models have been proposed to explain the enantioselectivity in the AD process. The models are mutually exclusive, and differ in both the mechanism of the osmium tetroxide addition and in the way the chiral information of the ligand is transferred by the orientation of the alkene in the alkaloid ligand. The Sharpless model calls for a stepwise addition of osmium tetroxide, and that the enantiotropic face of the alkene is fixed in the ligand by an attractive interaction between the alkene substrate and the *O*-9 substituent in the ligand, whereas the Corey model is based on a one-step addition (disregarding any equilibria formed prior to the rate-determining step) and a binding of the alkene between the quinoline rings of the alkaloids. While both models have their merits, none of the models available today are capable of satisfactorily explaining every feature of the reaction, and only further investigations can resolve this enigma of the AD reaction. It could be pointed out that other mechanistic possibilities should be considered. Perhaps one should pose the question concerning (3+2) or (2+2) addition to be disconnected from the binding mode of the alkene in the ligand, opening, for instance, the way for a (3+2) addition to an alkene bound in the “Sharpless mode” in the ligand as a new mechanistic alternative.

5

Synthetic Applications of the Chiral Diols

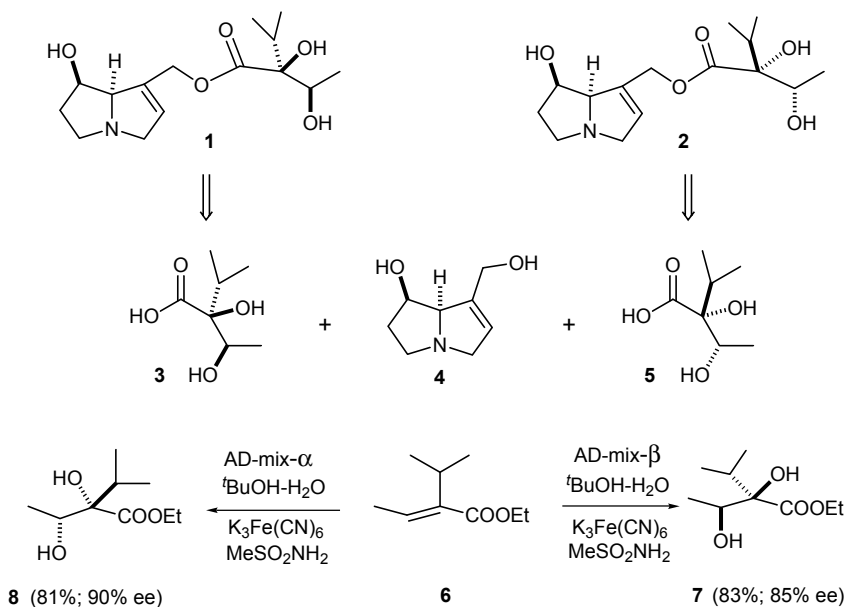
Whilst synthetic chemists wholeheartedly welcomed and rapidly applied the titanium-catalyzed Asymmetric Epoxidation of allylic alcohols to construct complex structures bearing numerous chiral centers [77], it took them much longer to use the Asymmetric Dihydroxylation for their synthetic ventures, despite the broader substrate tolerance of the AD reaction. Although several reasons might explain this reluctance, such as the variation of enantioselectivity as a function of the alkene substrate, the necessity of using different ligands for different olefin substitution patterns and the lack of efficient processes to selectively functionalize the resulting chiral diols, it is quite clear that this trend has been reversed over the past few years and that the AD of olefins has now acquired a prominent place as one of the key synthetic tools for the construction of a wide range of optically active products. Several reviews have already dealt with synthetic aspects of the AD process [78]. This chapter will only cover some of the most pertinent and up-to-date applications of the AD reaction.

5.1

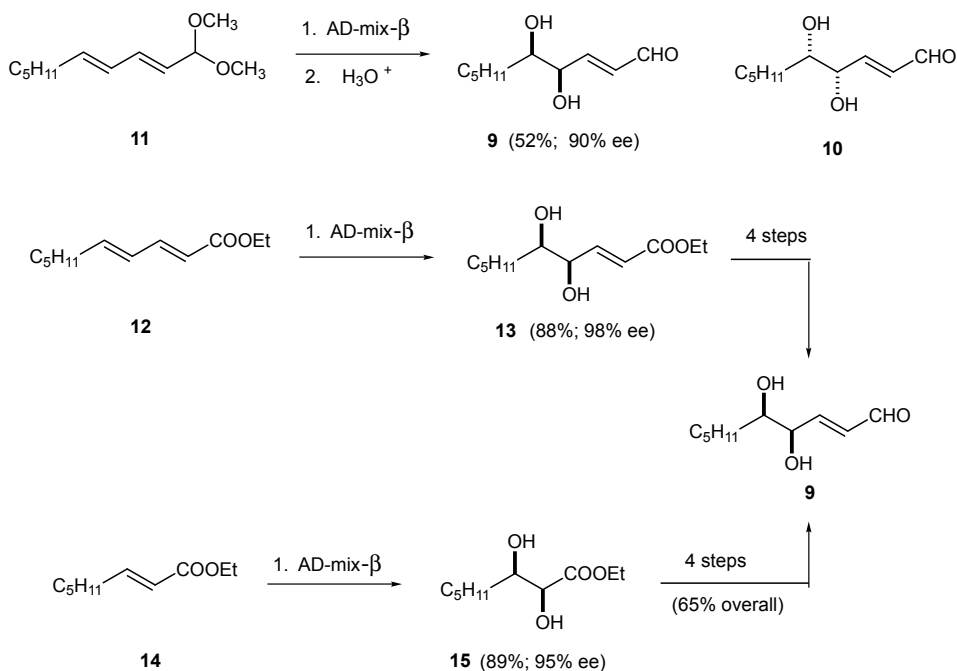
Direct Use of the Chiral Diols

The chiral diol moiety is only rarely present as such in the final compound to be synthesized. Usually, the 1,2-diol unit is further functionalized and sometimes, can be quite difficult to find in the end-product. Nevertheless, a few natural products possess, embedded in their complex structures, an optically active vicinal diol function which has been created using the AD reaction. Such is the case for the alkaloids indicine **2** and intermedine **1**, which were obtained by condensation of the nitrogen heterocycle **4** with (+)- and (-)-trachelanthic acid **3** and **5** respectively (Scheme 12) [79]. The desired optically active esters **8** and **9** were rapidly accessed by the AD reaction of the trisubstituted alkene **6**. Dihydroxylation using the AD-mix- β generated ester **7** in 83% yield and 85% *ee* whilst AD-mix- α gave the antipode **8** with slightly better enantioselectivity (90% *ee*). Hydrolysis and recrystallization furnished the optically pure acids **3** and **4** which were further transformed into the desired natural products.

(*E*)-4,5-Dihydroxydec-2-enals **9** and **10** are cytotoxic aldehydes, identified in liver microsomal lipids submitted to NADPH-Fe induced peroxidation (Scheme 13) [80]. The synthesis of *syn*-**9** and **10** was initially reported by Sharpless and coworkers and involved the AD of (*E,E*)-2,4-decadienal [81]. Unfortunately, the recovery of **9** proved to be unsatisfactory as was also the case from the corresponding acetal **11** [82]. A longer route was thus devised, starting from the (*E,E*)-



Scheme 12



Scheme 13

ester **12**. Dihydroxylation using AD-mix- β afforded the desired diol **13** in good yield and excellent enantioselectivity (98% ee). Further functional group manipulations provided aldehyde **9** of 98% ee. Enal **10** of 96% optical purity was prepared using the same sequence but starting with AD-mix- α instead of AD-mix- β . It is interesting to note that the dihydroxylation reaction selectively took place at the C-C double bond further remote from the electron withdrawing ester function, an observation that has already been amply documented in the literature [83]. Finally, a third route was investigated, starting from the α,β -unsaturated ester **14**. Dihydroxylation using AD-mix- β afforded diol **15** in 89% yield and 95% ee [84]. A four step sequence, involving an interesting one-pot reduction-Horner-Emmons condensation [85], then gave the final product **9** in an impressive 65% overall yield.

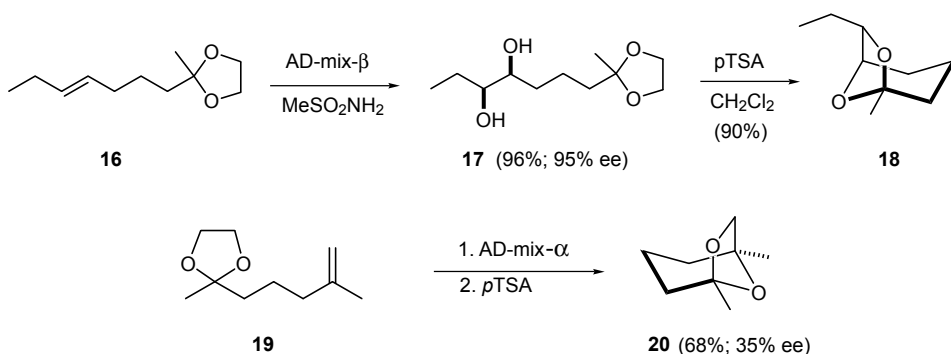
5.2

Masked Diols

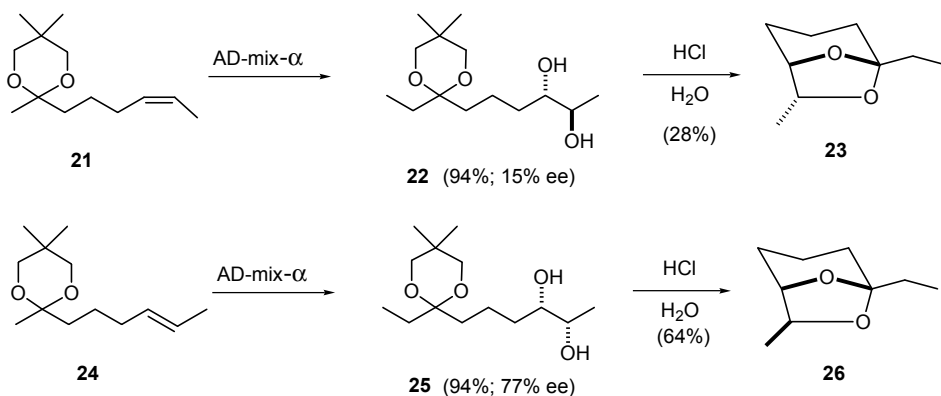
The asymmetric dihydroxylation provides an easy entry into a range of bicyclic natural products possessing an intramolecular ketal function. Members of this family are, for example, (+)-*exo*-brevicommin **18**, (–)-frontalin **20** and the (–)-*endo*- and (–)-*exo*-isobrevicommins **23** and **26**. Usually, these bicyclic ketals are prepared by acid-catalyzed intramolecular cyclization of an optically pure vicinal

diol with a ketone function. The strategies employed typically revolved around the judicious choice of the ketone protecting group. Thus, Soderquist prepared (+)-*exo*-brevicomins **18** and (-)-frontalin **20** via AD of ketal **16** and **19** followed by subsequent acid-catalyzed cyclizations (Scheme 14) [86]. However, whilst dihydroxylation of the (*E*)-alkene **16** proceeded with high enantioselectivity (95% ee), the same reaction on the 1,1-disubstituted olefin **19** proved particularly inefficient (35% ee).

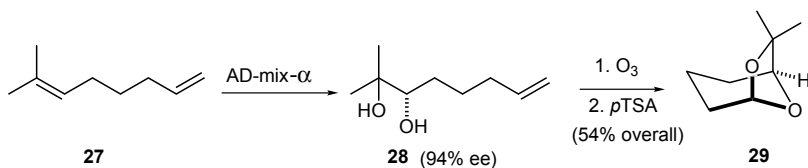
In a similar approach [87], Mori synthesized both the (-)-*endo*- and (-)-*exo*-isobrevicomins **23** and **26** by AD of (*E*)- and (*Z*)-ketals **21** and **24** respectively (Scheme 15). In both cases, however, the enantioselectivity of the AD reaction was poor. The (*E*)-alkene **24** afforded diol **25** of 77% ee and the (*Z*)-olefin **21** gave diol **22** of only 15% ee. The acid-catalyzed cyclization proceeded in this latter case in a mediocre 28% yield! An interesting kinetic resolution, using an Amano lipase, was then employed to raise the ee's of **22** to 98%.



Scheme 14



Scheme 15



Scheme 16

The use of an alkene as a masked carbonyl function was employed by Sharpless and Crispino [88] to prepare optically active 7,7-dimethyl-6,8-dioxabicyclo[3,2,1]-octane **29** (Scheme 16). Based upon the recognition that trisubstituted alkenes could be chemoselectively dihydroxylated with AD-mix- α or - β , in the presence of terminal olefins, these authors reacted diene **27** with AD-mix- α . Subsequent ozonolysis and intramolecular ketalization afforded bicycle **29** in 59% yield and 94% ee.

5.3

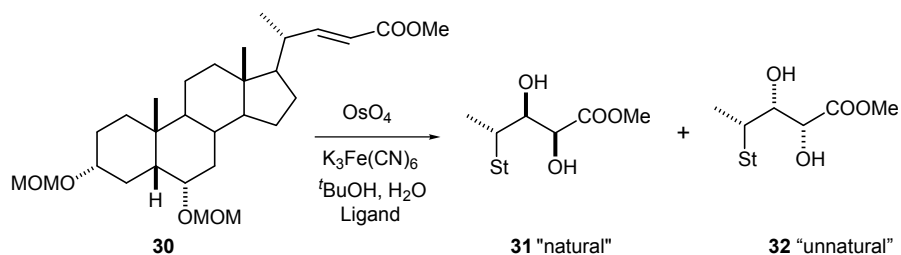
Diastereoselective AD Reactions

The high levels of enantioselectivities usually displayed in the AD reaction of prochiral olefins strongly suggested that the chiral osmium reagent should also be quite effective in the case of chiral alkenes. Several reports on double diastereoselection in the asymmetric dihydroxylation of chiral olefins have indeed revealed that exquisite levels of diastereocontrol could be achieved in the “matched” cases [78]. Moreover, it was also shown that the chiral osmium reagent was able in most cases to override the intrinsic stereochemical bias of the olefin substrate in the “mismatched” cases. However, high diastereocontrol still depends strongly upon minute changes in the alkene structure.

The AD reaction has proven to be particularly useful in the synthesis of steroids, such as brassino steroids, ecdysteroids and metabolites of vitamin D, possessing a 1,2-diol function in their C_{17} side chain [89]. The natural 22*R*, 23*R* absolute stereochemistry of the vicinal diol moiety cannot easily be obtained by diastereocontrolled osmylation using achiral osmium reagents. Typically, the unnatural 22*S*, 23*S* stereoisomer is obtained using OsO_4 [90]. However, in the presence of a chiral *cinchona* alkaloid ligand, good to excellent levels of diastereo selection could be achieved, even in mismatched cases.

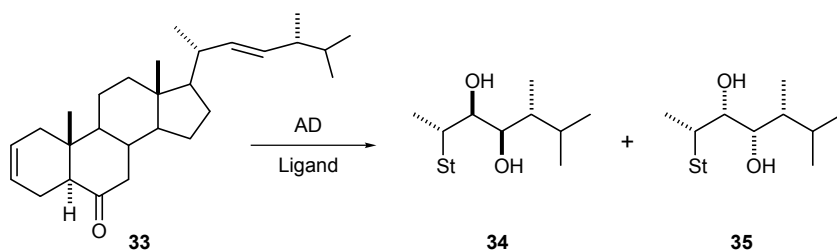
For example, the dihydroxylation of the steroid derivative **30** using OsO_4 ·pyridine gave a 1:8 mixture of diastereomeric diols in favour of the unnatural isomer **32** [91]. Using DHQD-CLB, a 4:1 ratio in favor of the natural isomer **31** could be obtained (Scheme 17).

Even greater diastereocontrol could be achieved in the asymmetric dihydroxylation of other steroid derivatives such as **33**, irrespective of the stereochemistry of the adjacent chiral substituents (Scheme 18). It is noteworthy that, in these cases, $(\text{DHQD})_2$ -PHAL is only marginally more effective than the simpler DHQD-CLB ligand [92].



Ligand	ratio 31/32
pyridine	1 : 8
DHQD-CLB	4 : 1

Scheme 17

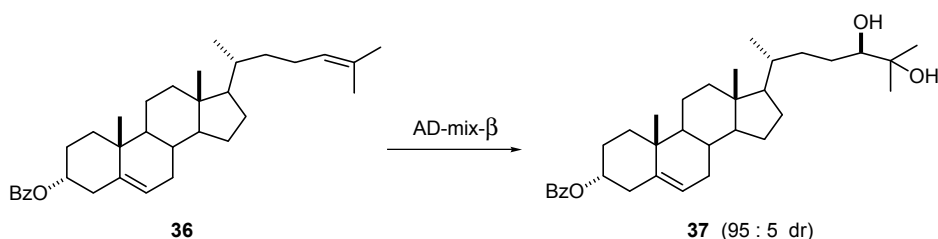


Ligand	ratio 34/35
—	1 : 1.6
DHQD-CLB	9 : 1
$(\text{DHQD})_2\text{-PHAL}$	10 : 1

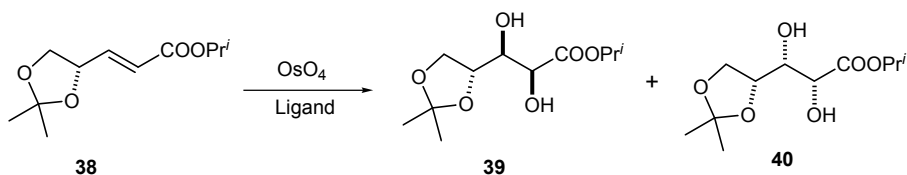
Scheme 18

When the chiral center is further remote from the alkene to be dihydroxylated, as in **36**, its stereodirecting influence is greatly reduced and the PHAL-ligands become again the preferred adjvants (Scheme 19) [93].

A number of experiments were performed by the Sharpless group [94] to assess the efficiency of different ligands in the diastereocontrolled dihydroxylation of the carbohydrate derived olefin **38** (Scheme 20). Though the PHAL ligand performed exceedingly well in the matched case, it proved to be totally inefficient in the mismatched series (Entries 4 and 5). Remarkably, the simpler CLB ligand, though displaying a more modest stereocontrol in the matched case, was able to



Scheme 19



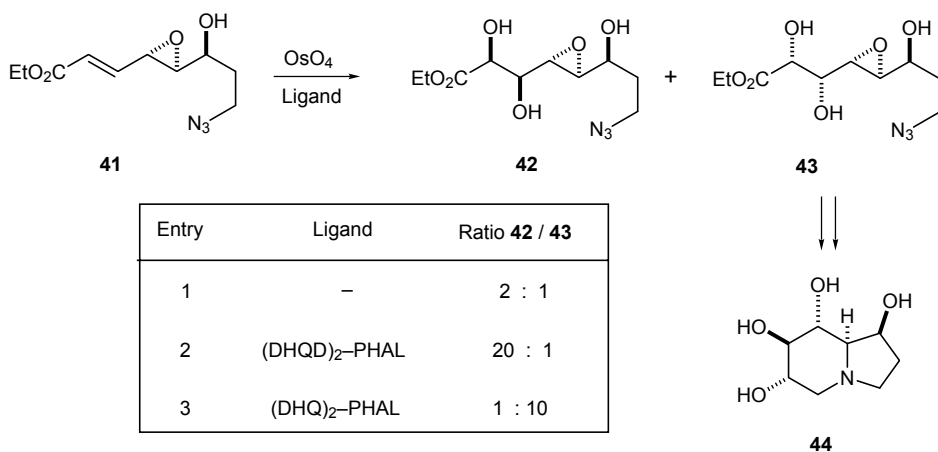
Entry	Ligand	Ratio 39/40	Yield
1	Quinuclidine	2.6 : 1	85 %
2	DHQD - CLB	10 : 1	87 %
3	DHQ - CLB	1 : 10	85 %
4	(DHQD) ₂ -PHAL	39 : 1	84 %
5	(DHQ) ₂ -PHAL	1 : 1.3	52 %

Scheme 20

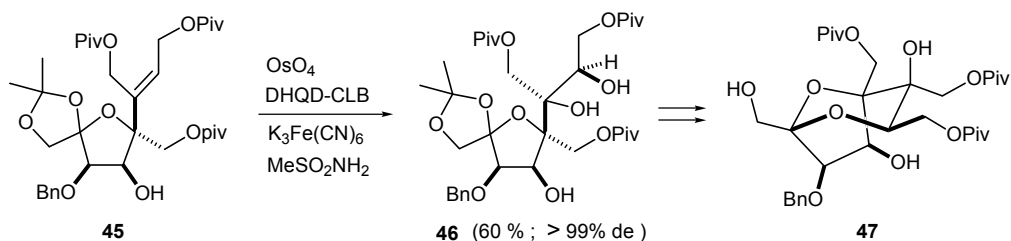
strongly override the intrinsic diastereofacial bias of the alkene substrate in the mismatched case (Entries 2 and 3).

Several total syntheses rely on the diastereoselective AD of chiral olefins. For example, an elegant approach to the indolizidine alkaloid, castanospermine **44** [95], employs as a key-step, the asymmetric dihydroxylation of enoate **41** (Scheme 21). Using (DHQD)₂-PHAL, a high selectivity in favour of the matched product **42** is observed. In this case, (DHQ)₂-PHAL is able to overcome the inherent preference of the alkene substrate and a good ratio (10:1) of the mismatched diol **43** can be obtained. Vicinal diol **43** was subsequently transformed into castanospermine **44**, providing one of the most efficient synthesis of this natural product.

The diastereoselective AD was also elegantly utilized to set up the correct stereochemistry of two crucial chiral centers in the key-intermediate **46** required for the preparation of the core of squalastatin **1 47** (Scheme 22). In this matched



Scheme 21

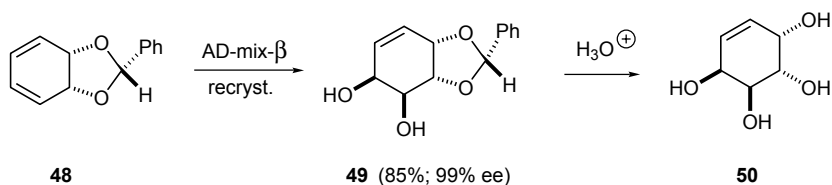


Scheme 22

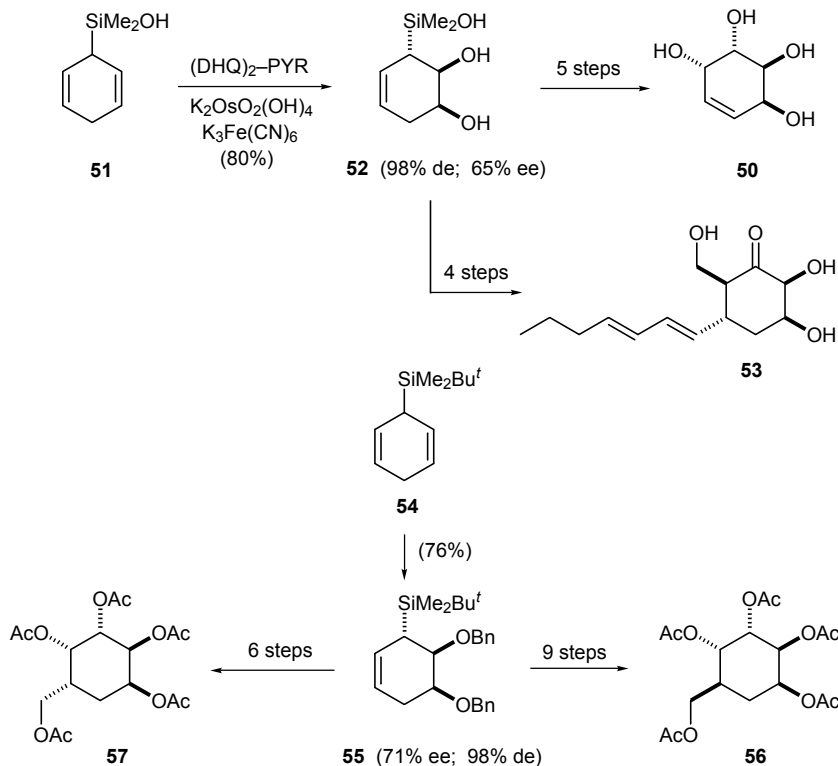
case, the use of the simple DHQD-CLB ligand led to the formation of **46** as a single diastereoisomer [96].

In contrast to the AD of prochiral cyclic dienes of various sizes, which usually turns out to be quite inefficient, probably owing to the *cis*-geometry of the alkene, double diastereocontrol generally affords the dihydroxylated product with good to excellent levels of selectivity. This methodology has been used by several groups in the total synthesis of various natural products. A short and efficient route towards (+)-conduritol E **50** [97] relies upon the AD of the benzylidene protected cyclohexadiene **48** (Scheme 23). Using AD-mix- β , *exo*-diol **49** was obtained in about 85% ee. Recrystallization afforded enantiomerically pure product **49** in an overall yield of 85%. This intermediate was further transformed into (+)-conduritol E **50** by simple acid catalyzed hydrolysis of the acetal protecting group.

A similar diastereoselective AD reaction was used by Landais in his approach towards several cyclitols [98], including (+)-conduritol E **50**, (–)-palitantin **53**,



Scheme 23

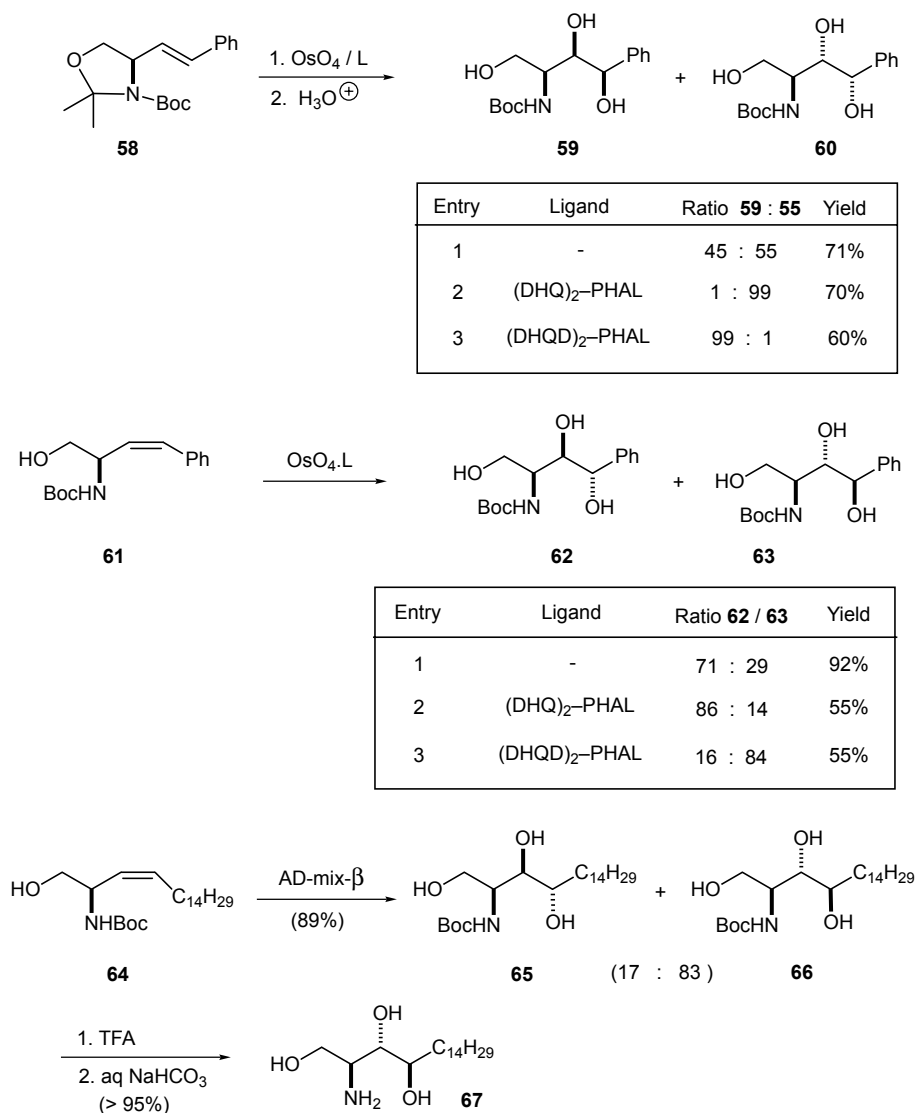


Scheme 24

pseudo- α -D-altropyranose pentaacetate **56** and pseudo-(α -D-galactopyranose pentaacetate **57** (Scheme 24). Thus, readily available allylsilane **51** [99] was submitted to asymmetric dihydroxylation using OsO_4 and $(\text{DHQ})_2\text{-PYR}$ affording the *cis*-diol **52** with high diastereo control (>98% de) but moderate enantiomeric excess (65% ee). Rather short reaction times were necessary in order to minimize the formation of unwanted tetraols. Simple functional group modifications of **52** led to the efficient preparation of **50** and **53**. In an analogous fashion, AD reaction of diene **54** afforded, after benzylation, the key-intermediate **55** in

71% ee and 98% de. Cyclohexene **55** was subsequently converted into the natural products **56** and **57**.

The presence of the *anti*-vicinal diol unit in the phytosphingosine **67** strongly suggests the application of the double diastereocontrolled AD to the *Z*-alkene **64** (Scheme 25). However, in order to access the desired product **64**, the mismatched diol should be obtained. Horikawa and coworkers studied both the achiral and the chiral dihydroxylation of the optically active (*E*)- and (*Z*)-allylic



Scheme 25

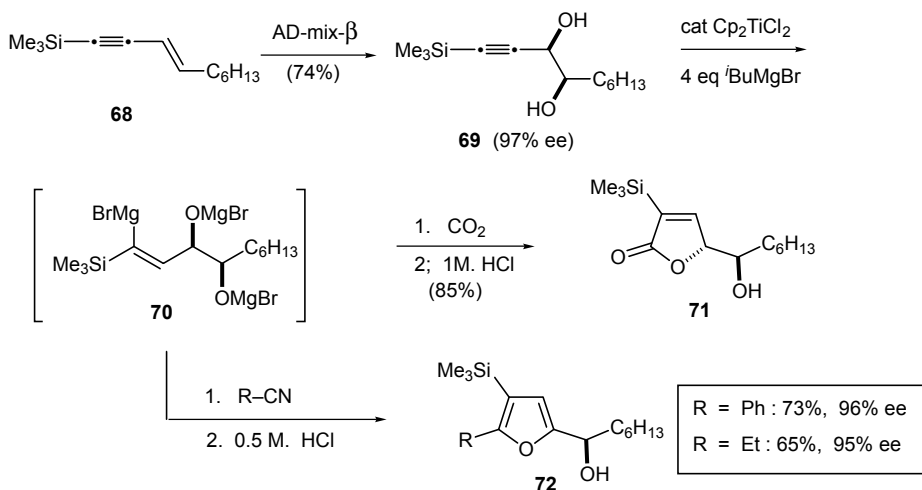
amines **58** and **61** [100]. Remarkably, and in contrast to what could have been anticipated based upon the well-known $A^{1,3}$ strain effect, the (*E*)-isomer **58** reacted with both AD-mix- α and AD-mix- β with essentially complete diastereocontrol. It is also noteworthy that in this case, the chiral reagents completely dictate the facial selectivity. Asymmetric dihydroxylation of the (*Z*)-isomer **61** proved to be less diastereoselective; the matched diol **62** being obtained with a modest enhancement (86:14 compared to 71:29). The mismatched diol **63** was produced with the opposite selectivity, showing the AD-mix- β to be more efficient than its α -counterpart. Finally, replacing the phenyl substituent of (*Z*)-alkene **61** by the requisite C_{14} aliphatic chain, did not significantly modify the levels of diastereocontrol. Deprotection of the 2,3-anti-diol **66** (mismatched isomer) afforded the desired product **67**.

5.4

Internal Capture of the Diol

A key-problem pertaining to the diol products resides in the selective differentiation of both alcohol functions. As will be discussed later, efficient methods have been delineated to accomplish such a selective discrimination [78]. One elegant way to distinguish between the two alcohol groups involves the intramolecular lactonization reaction. This methodology has been applied to the synthesis of numerous optically active natural products.

The asymmetric dihydroxylation followed by internal lactonization has been used by Sato and coworkers [101] in their efficient preparation of enantiomerically pure butenolides and furans (Scheme 26). AD of enyne **68** using AD-mix- β , afforded diol **69** in 74% yield and 97% ee. Hydromagnesiation generated the vi-



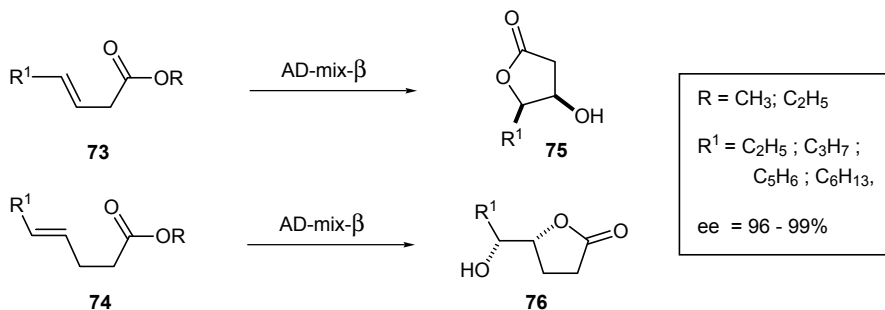
Scheme 26

nyl Grignard species **70** which was immediately treated with CO₂ and 1 M HCl, affording, after spontaneous lactonization, the optically pure butenolide **71** in 85% yield. Similarly, reaction of **70** with a nitrile instead of CO₂ followed by acid catalyzed lactonization-dehydration resulted in optically active furans **72**.

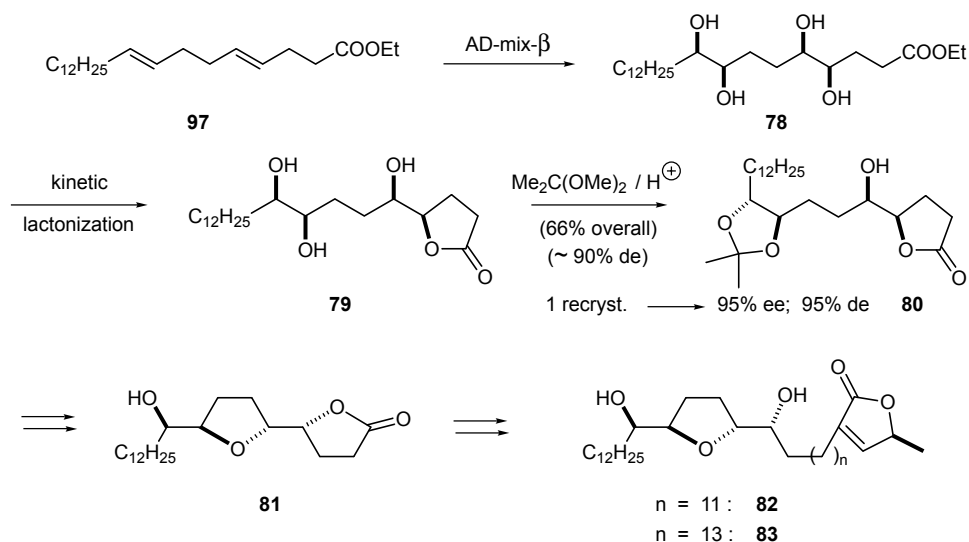
Functionalized γ -lactones are important synthetic intermediates for a number of biologically active natural products [102]. An interesting strategy based upon the AD reaction of unsaturated esters or carbamates, combined with the spontaneous kinetic cyclization to form five-membered ring lactones, has recently been established (Scheme 27). Thus, asymmetric dihydroxylation of β,γ - and γ,δ -unsaturated esters **73** and **74** results in the hydroxyl-substituted lactones **75** or the side-chain functionalized system **76** respectively, in high optical purity. This strategy was applied to the synthesis of numerous natural products.

For example, an elegant approach towards the acetogenin derivatives solamin **82** and reticulatacin **83** has been reported by Keinan (Scheme 28) [103]. Asymmetric bis-dihydroxylation of the unsaturated ester **77** resulted in the initial formation of tetraol **78**. Selective discrimination between these various hydroxyl functions was made possible by taking advantage of the kinetic lactonization of the proximal diol unit, leading to the triol **79**. Acetonide protection of the distal diol moiety, afforded lactone **80**, possessing a single, untouched, alcohol substituent. Further manipulation of the functional groups eventually delivered the key-intermediate **81** which was transformed into the final products **82** and **83**.

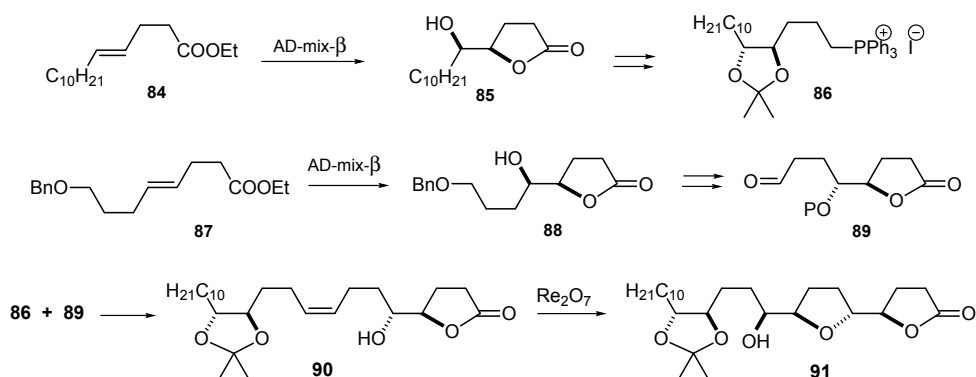
This strategy, coupled with a stereodirected epoxidation/cycloetherification allowed the combinatorial synthesis [104] of various acetogenins (Scheme 29). By carefully selecting the epoxidation reagent, either the *trans*- or the *cis*-tetrahydrofurans can be obtained at will. Starting from the γ -unsaturated ester **84**, dihydroxylation with AD-mix- β generated the hydroxy-lactone **85**. Further transformations produced the Wittig reagent **86** which was coupled with aldehyde **89**, itself derived from the ester **87** by dihydroxylation/lactonization followed by deprotection and oxidation. Coupling of the two partners afforded the (*Z*)-alkene **90** which underwent the tandem epoxidation-cyclization under the conditions described by Kennedy [105]. Combinations of these different reagents and synthons allowed the rapid construction of a whole host of varied acetogenin derivatives.



Scheme 27



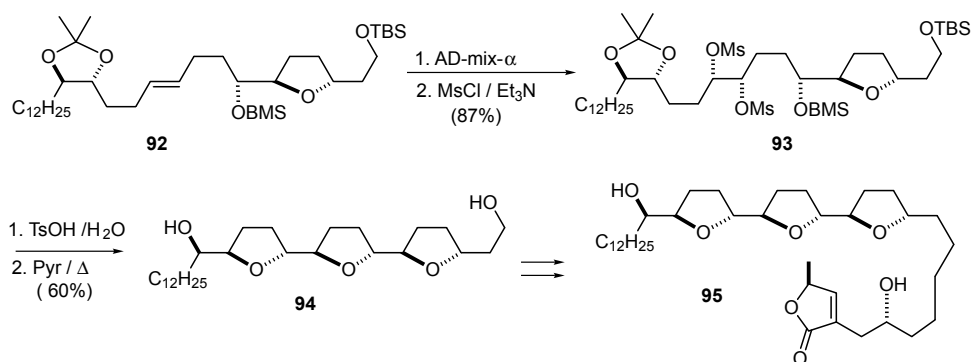
Scheme 28



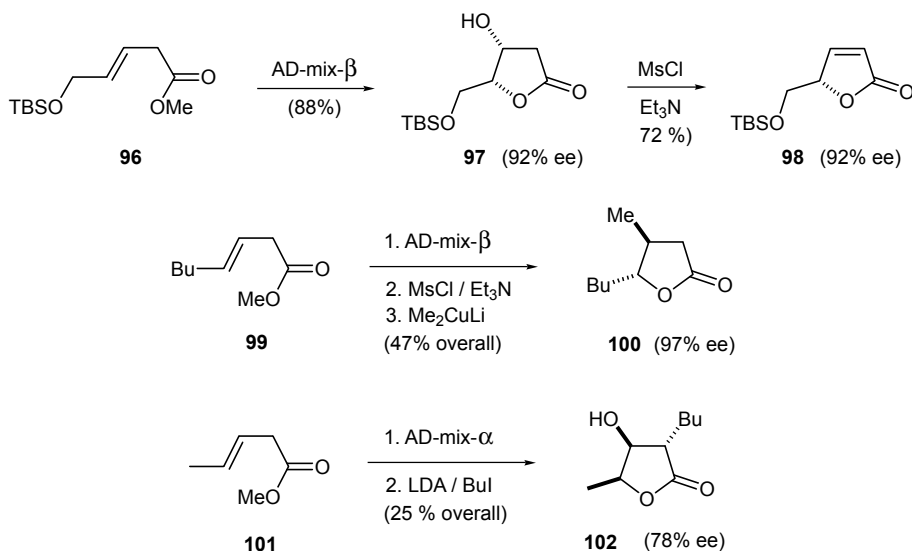
Scheme 29

A slightly different strategy was employed by Keinan [106] to synthesize another member of the acetogenin family, goniocin **95** (Scheme 30). In this case, rather than a kinetic lactonization, a double cycloetherification was performed on the dimesylate **93**, itself obtained in good yield and high ee by AD of the (*E*)-alkene **92**.

Whilst all the above-mentioned examples involve the use of γ,δ -unsaturated esters, Brückner [107] studied in detail the AD of the β,γ -unsaturated analogues (Scheme 31). Dihydroxylation followed by lactonization yielded ring substituted lactones such as **97**. A whole host of optically active lactones and butenolides



Scheme 30

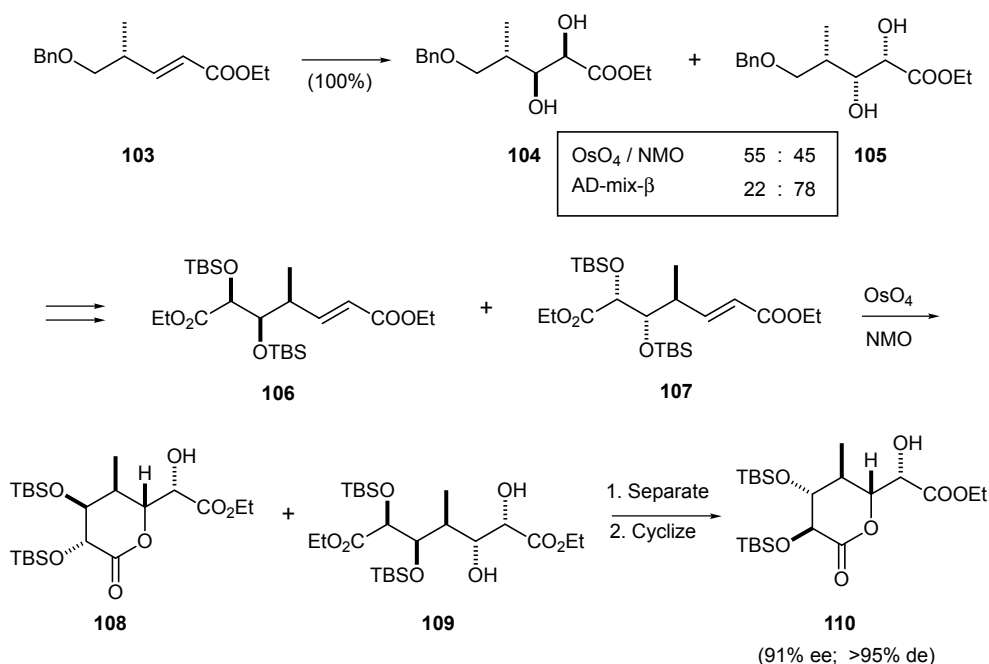


Scheme 31

could be readily assembled via this simple strategy. Subsequent modifications allowed the efficient preparation of a range of simple natural products, such as pheromones and fragrance components as well as key-intermediates for more complex syntheses. For example, AD-lactonization of unsaturated ester **99** followed by dehydration and cuprate addition gave the trans whisky lactone **100** in an overall yield of 47% and an ee of 97%. A similar sequence was employed to prepare the trisubstituted lactone **102**, an epimer of blastmycinone. In this case, however, the enantiomeric excesses of the final product were significantly lower (78% ee), reflecting the importance of the degree of substitution of the alkene substrate on the facial selectivity of the AD reagent.

5.6 Diastereoselective AD Coupled to Lactonization

The dihydroxylation of chiral olefins followed by the chemoselective intramolecular lactonization of the resulting diastereomeric diols is also a powerful strategy for the construction of various optically active 5- and 6-membered lactones. As discussed previously, the AD of alkenes bearing chiral centers can be particularly effective. By the judicious choice of the chiral ligand, either the matched or mismatched diol can be obtained with good to excellent levels of diastereocontrol. As a route towards a portion of the antitumour agent spongistatin 1, Vogel [108] studied the diastereoselective dihydroxylation of the enoates **104** and **105** (Scheme 32). These intermediates were prepared by another AD of the chiral alkene **103**. In accord with previous examples, the use of OsO_4 resulted in essentially no facial selectivity. Whilst the OsO_4 ·(DHQD)₂-PHAL catalyst was able to provide the mismatched diol **105**, though with modest preference, other chiral ligands, such as (DHQ)₂-PHAL and (DHQD)₂-PYR resulted in no selectivity whatsoever. Silylation and chain extension afforded the two α,β -unsaturated esters **106** and **107**. Dihydroxylation of the mixture of isomers **106** and **107**, using OsO_4 ·NMO, produced open diol **109** and lactone **108** as single diastereoisomers. The dihydroxylation had thus occurred with virtually complete facial selectivity in both cases. Interestingly, one diastereoisomer spontaneously cyclized to lac-

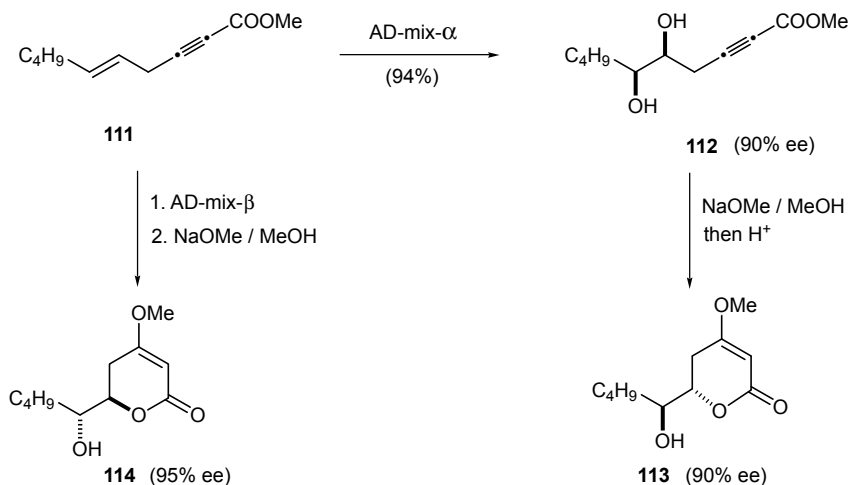


Scheme 32

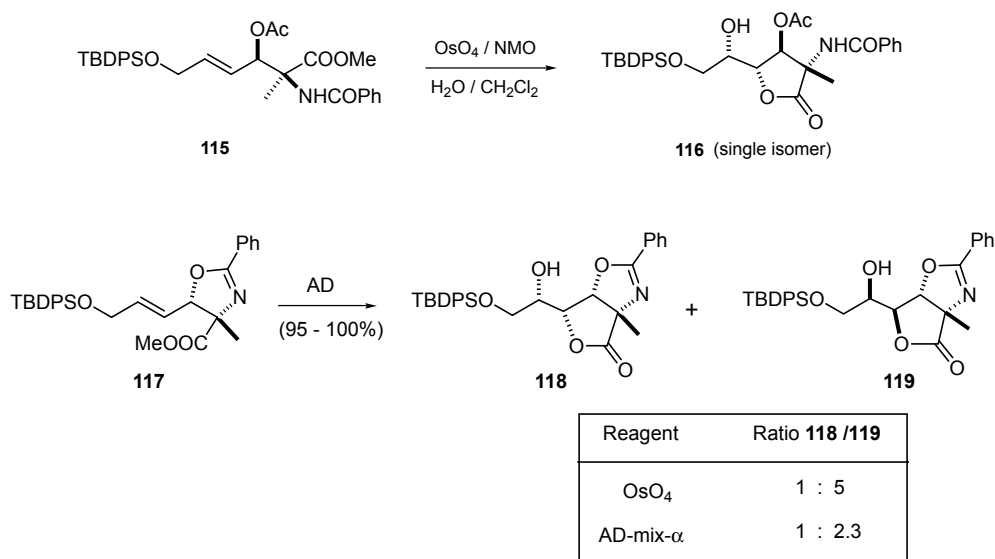
tone **108**, allowing an easy separation of the two products. Further treatment of the open-chain diol **109** ultimately gave the desired synthon **110** in 91% ee.

A slightly different combination of asymmetric dihydroxylation/lactonization sequence [109] formed the basis of an elegant route to (+)- and (-)-pestalotin **114** and **113**, a gibberellin synergistic agent (Scheme 33). Chemoselective dihydroxylation of enyne **111** using AD-mix- α afforded diol **112** in excellent yield and good enantiopurity. Michael-type addition of methoxide ion triggered the concomitant lactonization reaction, leading directly to (-)-pestalotin **113** of 90% ee, in what is probably the shortest synthesis ever reported for this natural product. An identical sequence, starting with AD-mix- β , produced the (+)-isomer **114** possessing a slightly higher optical purity.

During an approach towards sphingosine analogues, Trost [110] noticed a severe limitation in the use of the diastereoselective AD reaction (Scheme 34). Whilst the asymmetric dihydroxylation of the flexible alkene **115** using OsO₄-NMO produced lactone **116** as a single diastereoisomer, an identical reaction on the more rigid derivative **117** resulted in a complete reversal of the facial selectivity, largely favoring the undesired isomer **119**. Even the use of AD-mix- α was unable to overcome the strong substrate -controlled diastereoselectivity.



Scheme 33



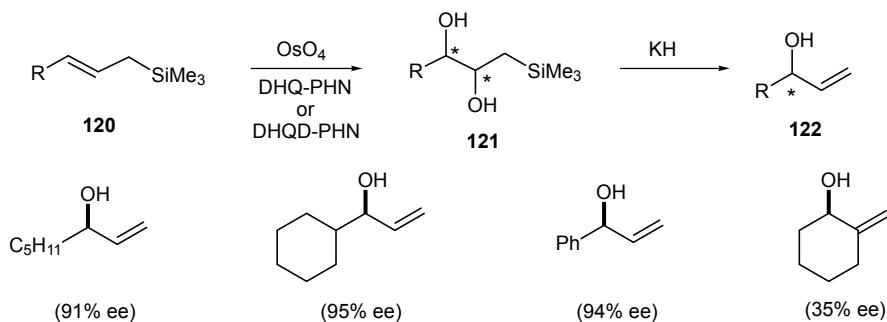
Scheme 34

5.7

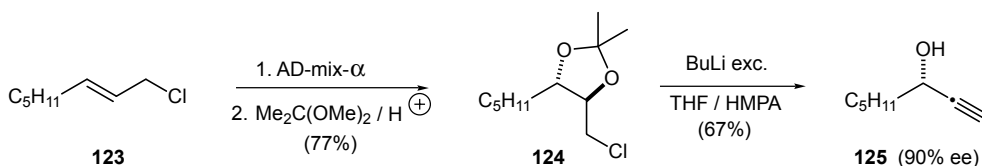
Preparation of Allylic and Propargylic Alcohols

In view of their high synthetic interest, easy and versatile access to optically active allylic and propargylic alcohols are always needed. A particularly elegant route to allylic alcohols of high ee was devised by Sharpless, Soderquist and Yu [111] based upon the AD of readily available allylsilanes (Scheme 35). Chemoselective Peterson elimination on diol **121** then gave the optically active allylic alcohols **122**. In this particular context, DHQD-PHN and DHQD-PHN proved to be the ligands of choice, giving high ee's with a range of substrates. In contrast, the PHAL ligands only performed poorly in the same reaction.

An interesting base-induced fragmentation of 1-chloro-2,3-acetonides **124** forms the basis of an efficient entry [112] into enantiomerically enriched propargylic alcohols (Scheme 36). Asymmetric dihydroxylation of allylic chloride **123** followed by acetonide formation generates the desired acetonide **124** in good yield and high ee. Addition of an excess of *n*BuLi triggers the fragmentation reaction, leading ultimately to propargylic alcohol **125** of 90% ee. This sequence was utilized in a formal total synthesis of vitamin E [112].



Scheme 35



Scheme 36

5.8

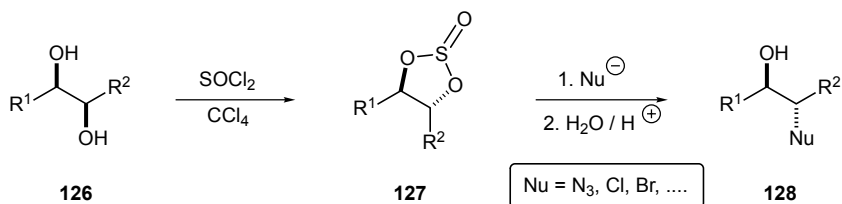
Cyclic Sulfites and Sulfates

The activation of a diol function could be performed in many different ways. As will be discussed later, vicinal diols can be easily transformed into epoxides, halohydrins and cyclic sulfates, all of them reacting readily and with high stereoselectivity with a range of nucleophiles. An intermediate typically generated during the formation of cyclic sulfates [113] is the corresponding cyclic sulfite (Scheme 37). Several nucleophiles, e.g. N_3^- , Cl^- and Br^- react readily with activated cyclic sulfites to afford in good yield and with clean inversion of stereochemistry, the substitution products.

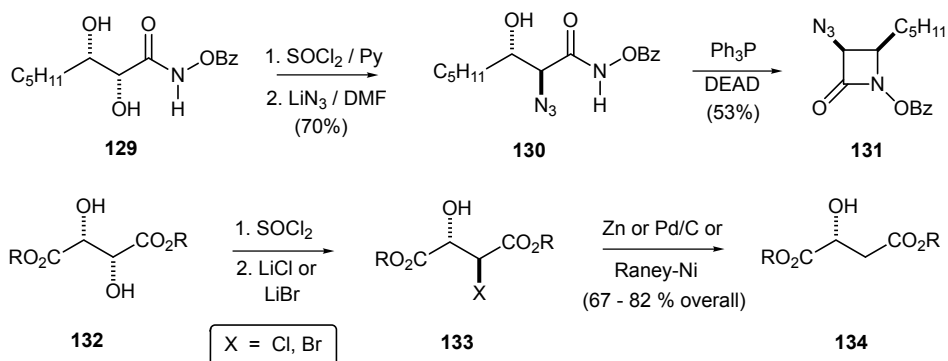
This approach provided a concise route to optically active β -lactams [114], such as **131** and malic acid derivatives **134** [115] (Scheme 38).

In addition, Svendsen [116] has studied the reaction of cyclic sulfites with various malonates and found that, in some cases, the substitution products could be obtained in good yields (Scheme 39). Unfortunately, the use of cyclic sulfites appears to be limited to a restricted number of nucleophiles and activated substrates.

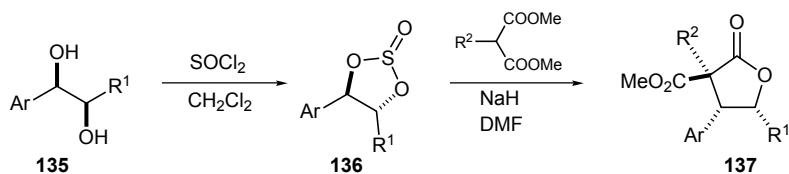
Like the epoxides, cyclic sulfates can be opened with inversion of configuration by nucleophilic attack at a carbon center (Scheme 40). The cyclic sulfates are easily prepared by oxidation of the corresponding sulfites using stoichiometric amounts of NaIO_4 and catalytic quantities of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ [117]. Simple filtration



Scheme 37

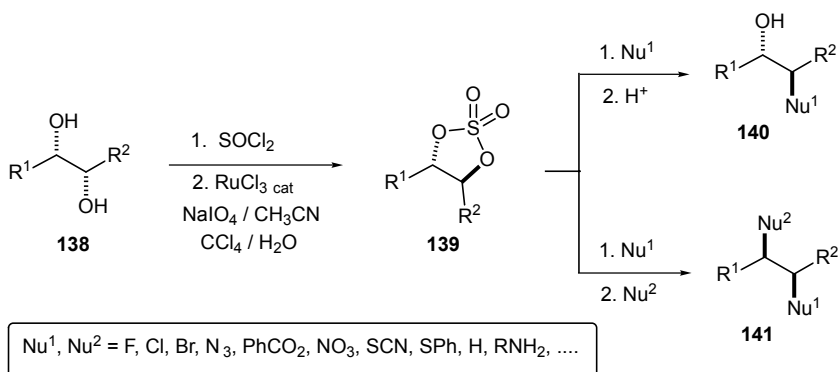


Scheme 38

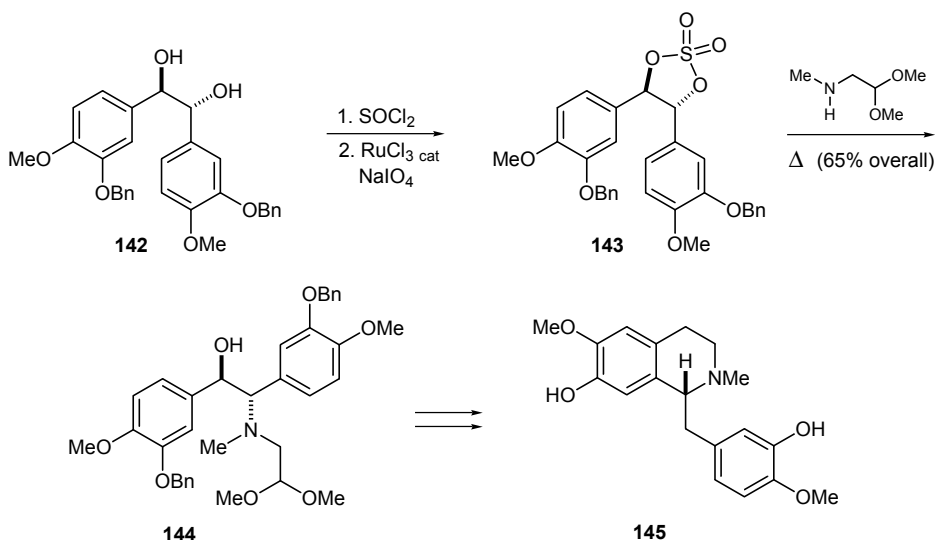


Entry	Ar	R ¹	R ²	yield
1	Ph	H	H	63%
2	Ph	H	Me	77%
3	pMeO ₂ CPh	H	H	14%
4	2-Nphth	H	H	5%

Scheme 39



Scheme 40



Scheme 41

through a pad of silica gel usually gives the pure sulfates in good to excellent yields. In contrast to the epoxides, the sulfate monoesters resulting from the first nucleophilic substitution reaction can undergo further transformations, making cyclic sulfates more versatile than the corresponding epoxides.

Numerous nucleophiles have been reacted successfully with cyclic sulfates and excellent reviews are available that detail these reactions [78a, 113]. From the synthetic viewpoint, the mono- and di-substitution reactions of cyclic sulfates have been employed to establish with complete stereocontrol, useful functional groups present in a range of natural products (Scheme 41). For example,

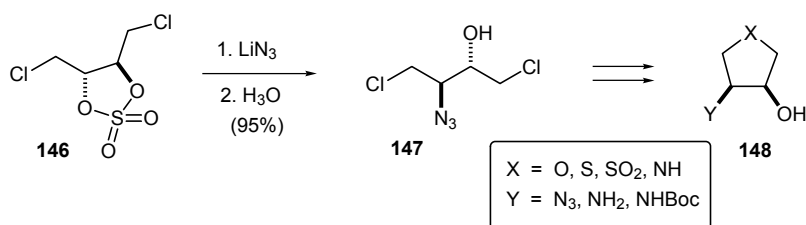
(*R*)-reticuline **145** was efficiently synthesized starting from the optically active diol **142** [118]. Formation of the cyclic sulfate, followed by nucleophilic opening with a functionalized secondary amine gave amino-alcohol **144** in an overall yield of 65%. Subsequent modifications afforded (*R*)-reticuline **145**.

The stereoselective opening of the chiral cyclic sulfate **146** derived from (*E*)-1,4-dichloro-2-butene by lithium azide afforded the azido-alcohol **147** which is a useful precursor to a range of functionalized heterocycles **148** [119] (Scheme 42).

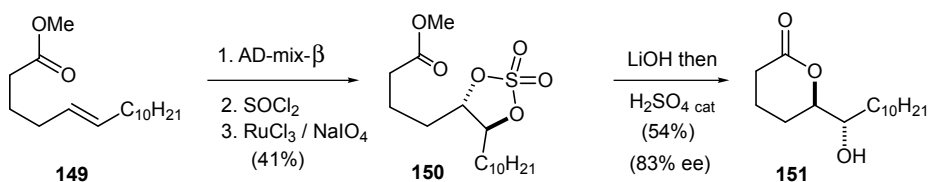
The pheromone **151** possesses an anti-relationship between the two hydroxyl functions built in its structure (Scheme 43). The establishment of such an anti-stereochemistry requires the AD of a (*Z*)-olefin, a process which usually proceeds with moderate enantiocontrol. To overcome this difficulty, Lohray [120] performed the asymmetric dihydroxylation of the isomeric (*E*)-alkene **149** and inverted selectively one of the chiral center via an intramolecular lactonization reaction on the derived cyclic sulfate **150**.

A similar strategy was followed by Allevi [82] in order to access the cytotoxic aldehydes **160** and **161** possessing an anti-diol arrangement (Scheme 44). Unfortunately, the opening of the readily available *syn*-cyclic sulfate **152** by the benzoate anion proved to be less than satisfactory.

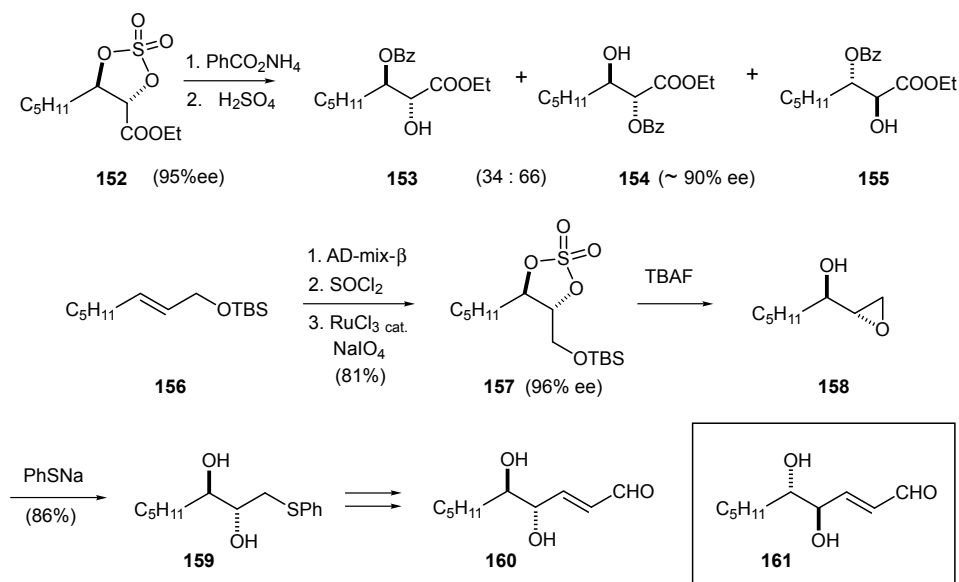
Moreover, a competitive benzoyl shift from the α - to the β -hydroxyl function, generating a 34:66 mixture of **153** and **154** made the situation even more complicated. An elegant solution to these problems relied upon the use of the corresponding silyl ether **156**. AD of **156**, followed by reaction with SOCl_2 and ruthenium-catalyzed oxidation, produced the cyclic sulfate **157** in high optical purity. An intramolecular cyclization afforded epoxide **158** which underwent a regioselective opening, generating the optically active sulfide **159**. Further transforma-



Scheme 42



Scheme 43



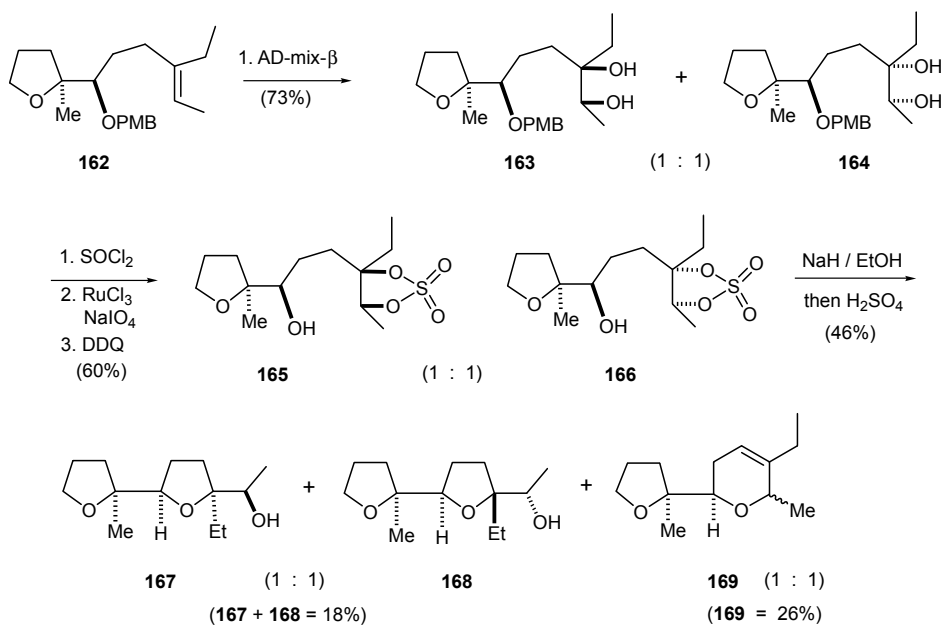
Scheme 44

tions resulted eventually in the desired aldehyde **160**. An identical route was employed to prepare the antipode **161**. This efficient strategy formed the basis of an elegant total synthesis of (+)-disparlure [121].

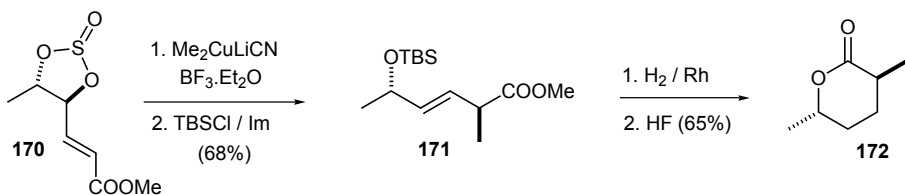
Trisubstituted alkenes are usually the best substrates for the asymmetric dihydroxylation reaction, affording the corresponding diols in high enantiopurity. During his synthetic approach towards salinomycin (Scheme 45), Brimble [112] encountered an example of extremely poor facial selectivity in the AD of the trisubstituted olefin **162**. In fact, reaction of **162** with $\text{OSO}_4(\text{DHQD})_2\text{-PHAL}$ gave a 1:1 ratio of the two diols **163** and **164**. Attempted transformation of the inseparable diols into the corresponding epoxides failed and so did the subsequent intramolecular cyclization of the derived cyclic sulfites or sulfates **165** and **166**, under a variety of conditions. The cycloetherification was eventually realized using NaH in ethanol. Unfortunately, it proceeded in poor yields and regioselectivity, affording a mixture of all four possible isomers **167**, **168** and **169** in a 1:1:1.5:1.5 ratio.

In analogy to the chemistry of epoxides, α,β -unsaturated cyclic sulfites undergo efficient $\text{S}_\text{N}2'$ opening with organocopper reagents (Scheme 46). Remarkably, in the case of γ,δ -dihydro- α,β -enoates, the opening of the cyclic sulfite proceeds faster than the alternative Michael addition of the organocuprate [123]. This methodology was used to prepare, in a few steps and in high ee, the carpenter bee pheromone **172**.

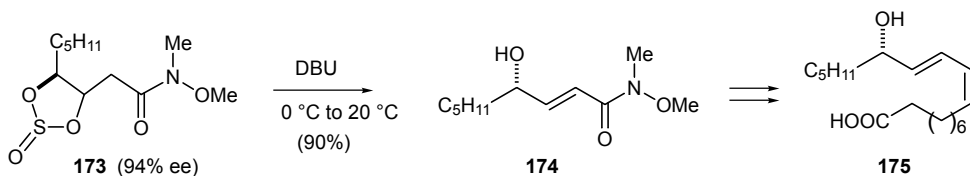
When acidic β -hydrogens are present, eliminative fragmentation of the cyclic sulfite can also occur [124], leading to optically active γ -hydroxy- α,β -unsaturat-



Scheme 45



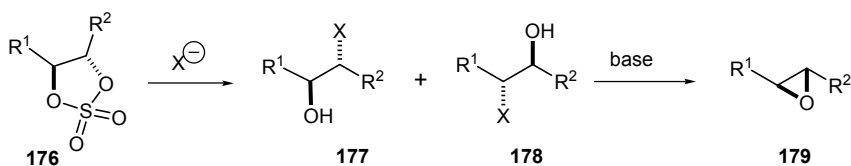
Scheme 46



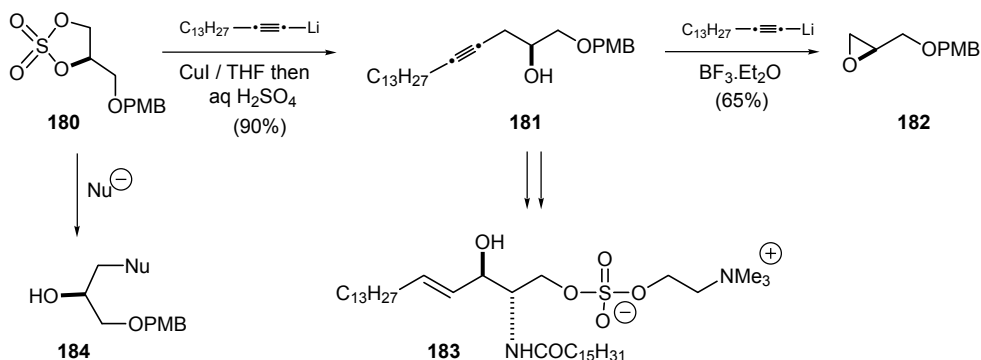
Scheme 47

ed carbonyl derivatives (Scheme 47). This strategy was employed as a key-step in an elegant synthesis of (+)-coriolic acid **175**.

The opening of cyclic sulfates **176** by halide ions proceeds with inversion of configuration and provides a stereocontrolled route to optically active halo-



Scheme 48



$Nu = C_{16}H_{33}O$ (90%); $C_{16}H_{33}S$ (94%); $C_{16}H_{33}NH$ (95%); N_3 (95%)

Scheme 49

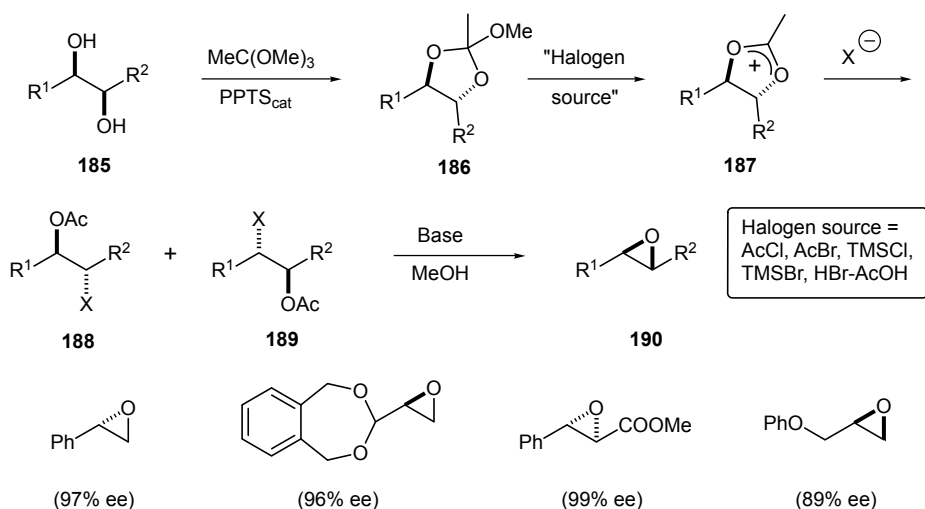
drins **177** and/or **178** (Scheme 48). Treatment with mild bases produces the corresponding epoxides **179** which, resulting from a double inversion sequence, retains the same absolute stereochemistry as the initial diol substrate [125]. Interestingly, no regiocontrol is required in the opening of the cyclic sulfate, since both diastereomeric halohydrins ultimately provide the same epoxide.

During its synthesis of 3-deoxy-sphingomyelin **183**, Bittman [126] had the opportunity to compare the reactivity of epoxide **182** and the corresponding cyclic sulfate **180** towards various nucleophiles (Scheme 49). In all cases, he observed that the cyclic sulfate **180** was more reactive than the epoxide **182**, affording in high yield the monosubstitution products **181** and **184**.

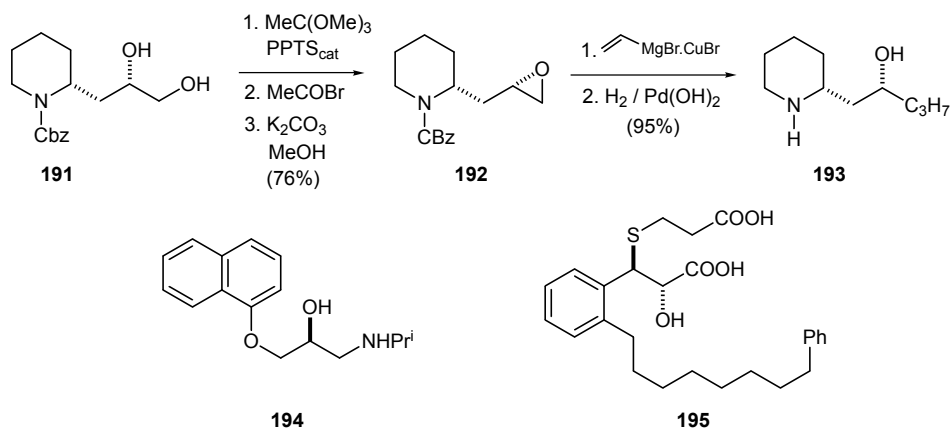
5.9

Epoxides from Diols

An alternative, one-pot, procedure (Scheme 50) for the preparation of optically pure epoxides **190** from the corresponding diols **185** involves the following sequence of reactions: (1) reaction of the diol **185** with trimethylorthoacetate, generating the cyclic orthoester **186**; (2) addition of a halogen source such as $HBr \cdot AcOH$ [127], $AcCl$, $AcBr$, $TMSCl$ or $TMSBr$ [128] to form, via oxonium ion **187**,



Scheme 50



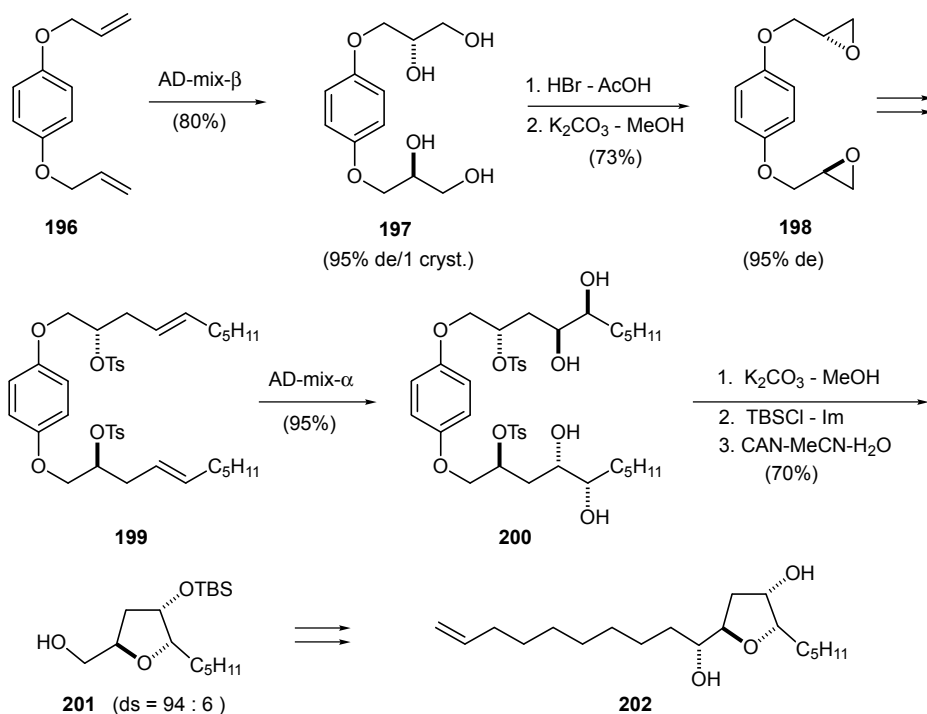
Scheme 51

the halohydrins **188** and **189** and (3) saponification of the acetate function followed by intramolecular cyclization. Using this one-pot process, a range of simple, optically active, epoxide building blocks could be easily prepared. A few examples are shown in Scheme 50.

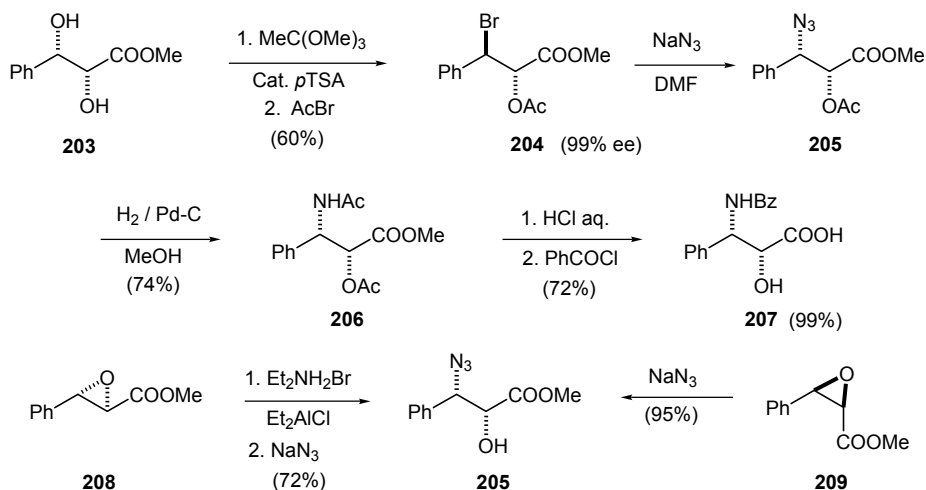
This procedure was subsequently employed in a number of total syntheses (Scheme 51). For example, Momose [129] devised a short route to (-)-halosarine **193** based upon the conversion of the readily available piperidine derivative **191** into epoxide **192**. Several other compounds, such as (*S*)-propranolol **194** [130] and SKF 104353 **195** [125] were prepared along these lines.

A double epoxidation reaction served as a key step in the synthesis of the marine natural product **202** by Wang and coworkers [131] (Scheme 52). Dihydroxylation of the bis-alkene **196** with AD-mix- β generated tetraol **197** in good yield and high enantiopurity. A single recrystallization afforded product **197** of 95% de. Direct conversion of the tetraol **197** into the bis-epoxide **198** was accomplished using the HBr-AcOH protocol. A few steps converted **198** into the homologated bis-olefin **199** which was subjected to a second asymmetric dihydroxylation. Base-catalyzed cyclization of tosylate **200** followed by oxidation of the protecting group, then released the key-intermediate **201** which was subsequently transformed into the final product **202**.

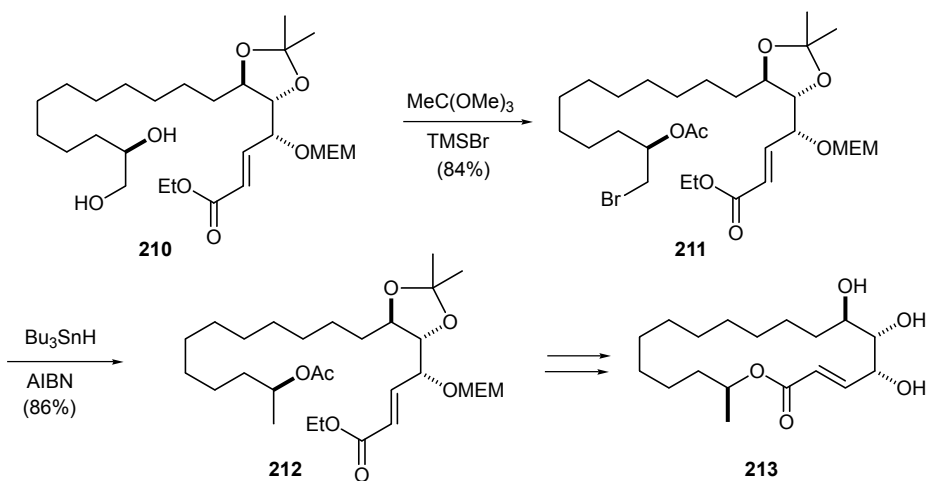
In some cases, the conversion of the diol into the corresponding halohydrin proceeds with high or even complete regiocontrol, allowing for further useful functionalization of the intermediate halohydrin (Scheme 53). This strategy was employed in a short and elegant approach to the taxol side-chain **207** [132]. Thus, diol **203**, readily obtained by AD of methyl cinnamate underwent smooth conversion into the single bromohydrin acetate **204** which reacted with sodium azide to give the azido-derivative **205**. Further transformation afforded the fully protected taxol sidechain **207** in good overall yield and high ee (99% ee). In this particular case, the opening of the *trans*- or the *cis*-epoxide **208** and **209** by azide



Scheme 52



Scheme 53



Scheme 54

ion also proved to be highly regioselective [133], generating azido-alcohol **205** and thus providing another route to the taxol side-chain **207**.

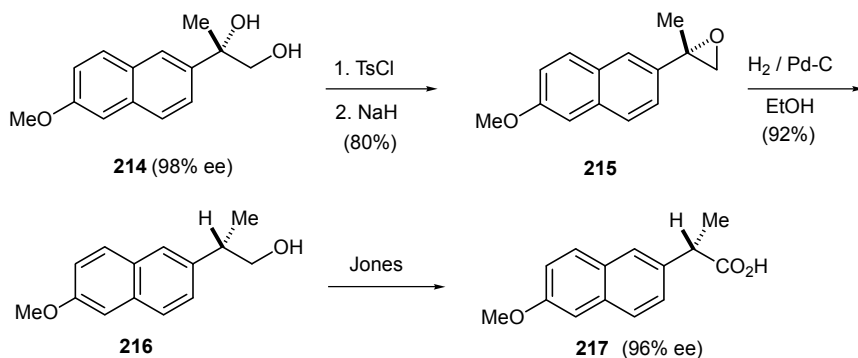
The high regioselectivity observed in the transformation of some chiral diols into halohydrins allows various selective reactions to be performed on these intermediates. For example, the reduction of the halide substituent affords an easy entry into optically active carbinols (Scheme 54). This methodology was used by Keinan [134] in his approach towards aspicillin **213**. Thus, the enantiomerically pure diol **210** was transformed into the bromohydrin **211** which was reduced to

the alcohol **212**. Further elaboration of the other functional groups and macrocyclization ultimately afforded aspiceillin **213**.

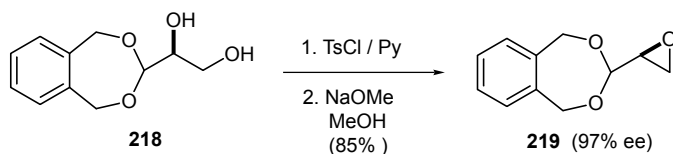
In some cases, a simple tosylation can be equally regioselective, especially when one of the hydroxyl substituents is more sterically hindered than the other. This approach served as a key step in an expeditious approach towards naproxen **217** (Scheme 55). The primary alcohol function of the optically active diol **214**, of 98% ee, was selectively activated with tosyl chloride [135]. The resulting tosylate, upon treatment with NaH, underwent smooth cyclization to the epoxide **215**. Hydrogenolysis proved to be highly facial selective, delivering the primary alcohol **216** in high enantiopurity. A final Jones oxidation then furnished naproxen **217** of 96% ee.

When the reactivity difference between the two hydroxyl functions is not sufficient to attach selectively the tosyl group on one of the alcohol substituents, recourse to triisopropylphenyl sulfonylchloride generally provides a useful solution [136]. This strategy has been employed in numerous cases. For example, selective monotosylation of diol **218** followed by base-catalyzed cyclization gave the useful glyceraldehyde building block **219** [137] (Scheme 56).

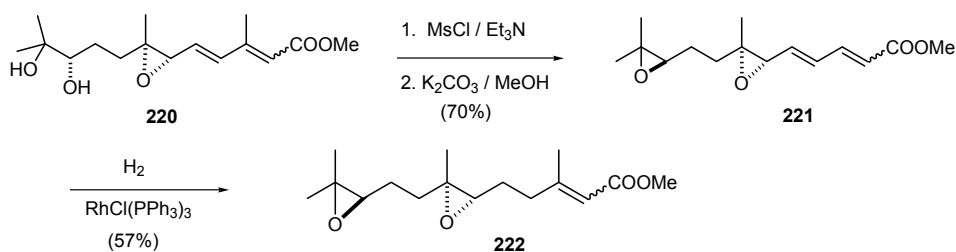
A similar set of reactions formed the basis of a short route to optically active juvenile hormone III bisepoxide **222** [138] (Scheme 57). Since tertiary alcohols can be easily differentiated from primary and secondary hydroxyl functions, the cheaper and more reactive mesylate could be used in this case instead of a tosylate.



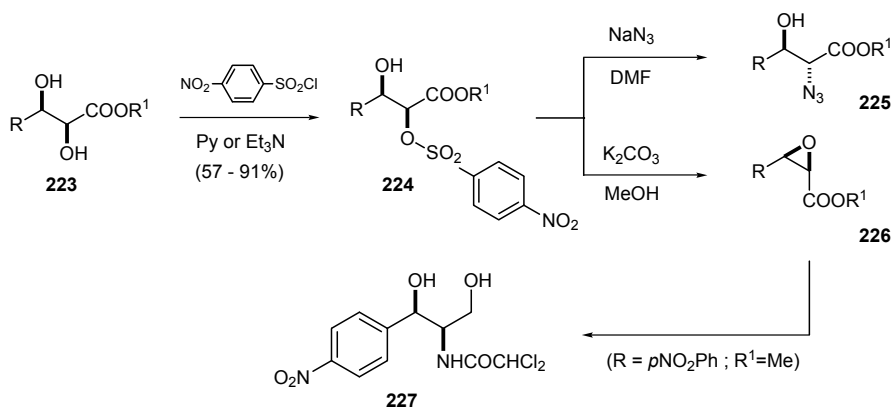
Scheme 55



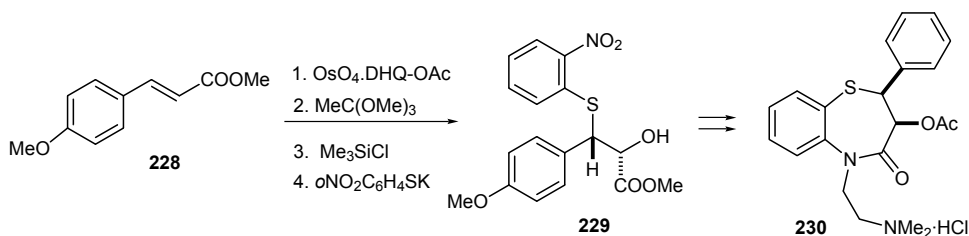
Scheme 56



Scheme 57



Scheme 58



Scheme 59

Subtle differences in acidity can sometimes be used to discriminate between two hydroxyl functions (Scheme 58). In these cases, *p*-nitrobenzenesulfonyl chloride appears to be the reagent of choice. Not only does it display improved chemoselectivity for the most acidic hydroxyl function, but it also acts as a better leaving group. This strategy was employed to prepare, inter alia, substituted α -amino acids **225** [127a], glycidic esters **226** [127a] and chloramphenicol **227** [139].

This approach also forms the basis of an elegant synthesis of diltiazem **230** as shown in Scheme 59 [128c].

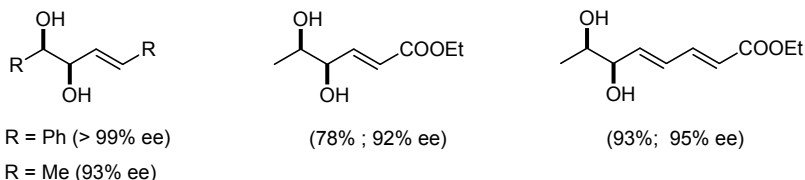
5.10 Dihydroxylation of Dienes

The asymmetric dihydroxylation of dienes tends to be highly regio- and chemo-selective. Indeed, in most cases and without special control of the reaction conditions, selective monohydroxylation of the diene takes place [83], affording enediols which are useful precursors to a range of optically active intermediates (Scheme 60). It appears that the presence of the diol moiety significantly lowers the reactivity of the remaining olefin towards further dihydroxylation. Moreover, we have already seen earlier that the addition of the diol unit typically occurs on the most electron-rich alkene. Furthermore, it was also shown that unsubstituted olefins reacted more sluggishly than disubstituted or conjugated olefins.

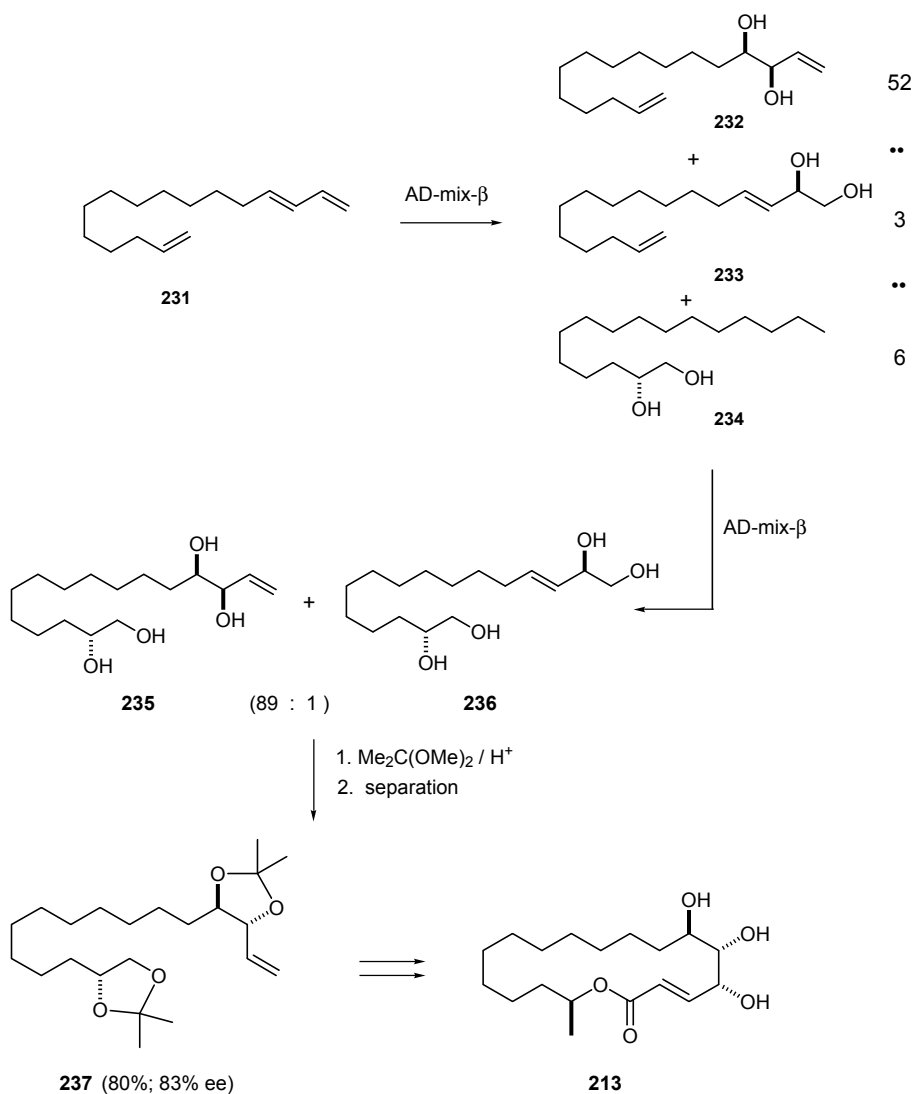
These reactivity differences were exploited by Keinan [134] in his synthesis of aspicillin **213** (Scheme 61). Thus, the asymmetric dihydroxylation of triene **231**, using 1 equivalent of AD-mix- α , resulted in a mixture of diols **232** to **234** in a 52:3:6 ratio. A second AD reaction enhanced the selectivity, affording an 89:1 mixture of the two tetraols **235** and **236**. Protection and separation then gave the aspicillin precursor **237** in decent yield but only in 83% ee. This material was further transformed into the desired natural product.

Double AD of dienes is an interesting way to enhance the enantioselectivity of the first dihydroxylation reaction. This amplification process, which has been applied to many other asymmetric reactions, usually results in significant improvement of the enantiopurity of the bis dihydroxylated product. Momose [140] has studied in detail the double AD of several non-conjugated dienes, during his elegant synthesis of a range of optically active nitrogen heterocycles (Scheme 62).

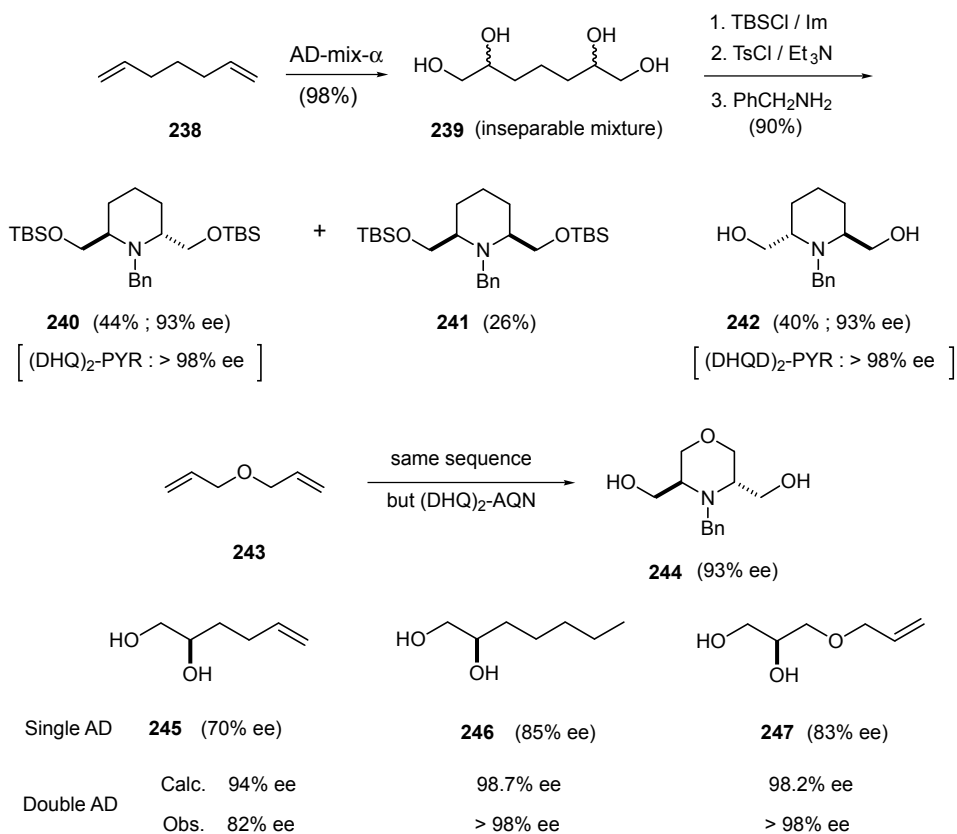
Thus, single AD of dienes **238** and **243** gave diols **245** to **247** with moderate ee's. A second dihydroxylation then generated the corresponding tetraols of considerably higher enantiopurity. It is interesting to note that the calculated values for the ee's of the second dihydroxylation correlate well with the observed enantioselectivities. Further reactions of these tetraols then afford the disubstituted heterocycles **240** to **242** in high ee. In the case of these terminal alkenes, the (DHQD)₂-PYR and the (DHQ)₂-PYR ligands proved to be the best.



Scheme 60



Scheme 61



Scheme 62

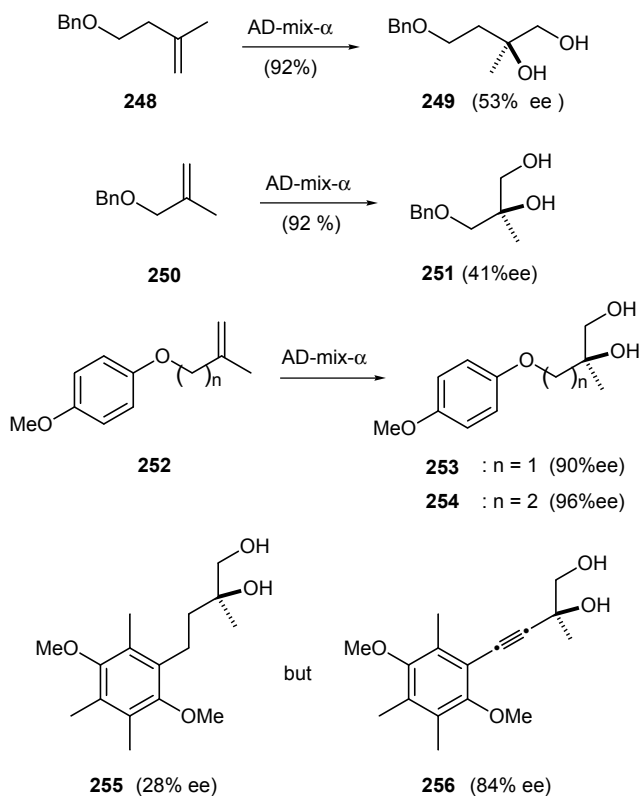
5.11

Conclusions

The growing interest manifested by synthetic chemists towards the use of the asymmetric dihydroxylation of olefins has resulted in so many varied applications that it is beyond the scope of this limited review to enumerate them all. Throughout this concise review, the specificities of the catalytic AD of alkenes have been discussed and the salient features of the almost limitless transformations of the resulting chiral diols have been illustrated through the use of selected examples. Whilst the AD of olefins is now considered as one of the most important tools in asymmetric synthesis, let us not forget that the enantioselectivity displayed by the asymmetric dihydroxylation process can depend upon subtle steric, electronic or conformational effects that are far less pronounced in other asymmetric catalytic reactions. Such is the case in our last example [141], featuring an elegant approach towards vitamin E by Tietze and coworkers

(Scheme 63). They noticed that the AD of olefins **248** and **250** proceeded with poor enantioselectivity. However, by adjusting the electronics of the protecting group (**252**) or by decreasing the conformational freedom of the linking chain (compare **255** with **256**), good to excellent levels of enantioselectivities could be reached.

Clearly, in order to take maximum advantage of the power of the AD reaction, it is up to the synthetic chemists to devise novel and imaginative routes to their desired compounds that will either avoid or capitalize on these subtle effects.



Scheme 63

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Chapter 21

C-H Oxidation

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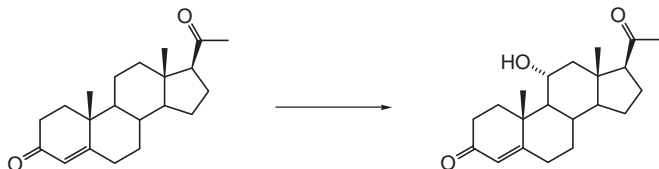
Keywords: C-H oxidation, Benzylic hydroxylation, Allylic oxidation, Desymmetrization of *meso* compound, Kharash-Sosnovsky reaction, Iron-porphyrin complex, (Salen)manganese(III) complex

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1 Introduction

C-H oxidation is the most direct and useful method for the functionalization of organic compounds and also plays very important roles in many biological transformations [1]. For example, progesterone is converted into 11 α -hydroxyprogesterone stereospecifically with aid of a mutant strain of *Aspergillus ochraceus* (Scheme 1) [2]. However, such high stereoselective C-H oxidation has long been limited to biochemical reactions using oxidizing enzymes or microorganisms. On the other hand, high enantioselectivity has already been achieved in C=C oxidation by using well-designed molecular catalysts.

The difficulty of stereoselective C-H oxidation originates in the natures of C-H bond: σ -bonds are generally much more stable than π -bonds and, therefore,



Scheme 1

C-H bonds are less reactive as compared with C=C bond. Thus, oxidation of C-H bond requires harsh reaction conditions and/or a highly reactive oxidizing agent and this makes stereocontrol of C-H oxidation difficult. Furthermore, the precise mechanisms of C-H oxidation are still surrounded by uncertainty. For example, two mechanisms have been postulated, (a) concerted oxygen atom insertion and (b) stepwise oxidation including hydrogen atom abstraction and radical rebound steps, for C-H oxidation by cytochrome P-450 [3, 4, 5, 6] but the argument remains unsettled. Limited knowledge on the mechanism has hampered the design of the appropriate catalyst for asymmetric C-H oxidation. Despite these difficulties, recent developments of asymmetric synthesis have also facilitated progress in asymmetric C-H oxidation, especially asymmetric oxidation of activated C-H bonds. Considering the reactivity of C-H bonds, it is natural that the study of asymmetric C-H oxidation began with benzylic and allylic C-H oxidations. Although the scope of C-H oxidation is still limited, high enantioselectivity has recently been achieved in the oxidation of this class of substrates, which will be dealt with in this chapter.

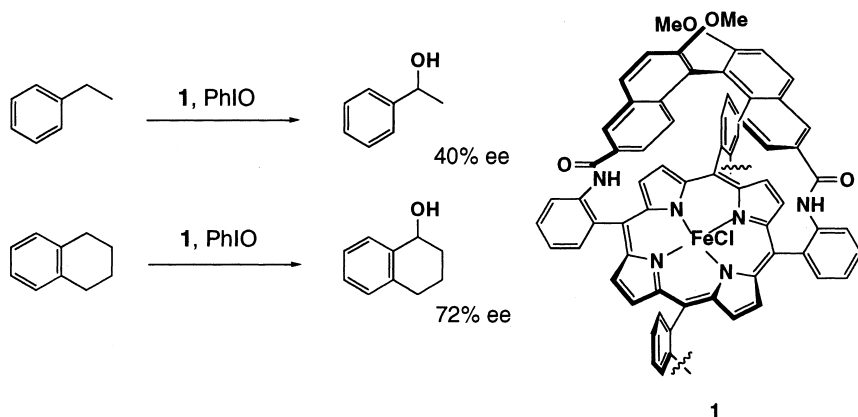
2

Asymmetric Benzylic Hydroxylation

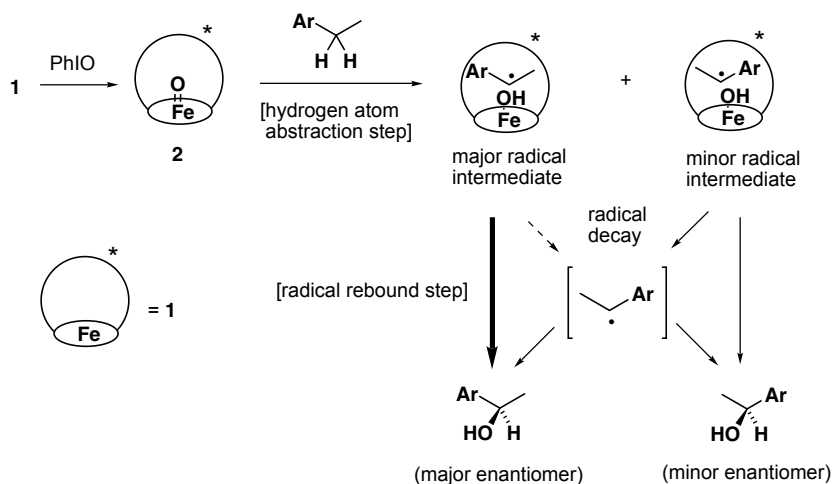
As described above, biological C-H oxidation is generally highly stereoselective. These biological reactions are catalyzed by various monooxygenases bearing a metal complex in their active sites. For example, the representative monooxygenase, cytochrome P-450, carries an iron-porphyrin complex at its active site, in which molecular oxygen is converted into “iron-oxo” species and then transferred to substrates. Thus, many optically active iron-porphyrin complexes have been synthesized to effect enantioselective oxygen transfer reactions. In 1990, Groves and Viski reported the first asymmetric benzylic oxidation using the sophisticated chiral iron-porphyrin complex **1** as a catalyst and iodosylbenzene as an oxidant (Scheme 2) [7]. A good enantioselectivity of 72% ee was achieved when tetralin was used as a substrate.

In this reaction, iodosylbenzene oxidizes complex **1** to the corresponding oxo species **2** which, in turn, abstracts the benzylic hydrogen atom giving enantiomerically enriched radical intermediates. The enantioselectivity attained in the hydrogen abstraction step is further enhanced in the following radical rebound step (Scheme 3). The major radical intermediate undergoes radical-rebound smoothly to give the major enantiomer of benzylic alcohol, while the minor radical intermediate undergoes radical decay to a considerable extent, probably due to the unfavorable interaction between the radical species and the surrounding chiral binaphthyl bridge moiety [7, 8]. This radical decay process brings about further enhancement of the enantioselectivity. For example, the enantioselectivity in hydrogen atom abstraction from ethylbenzene is 33% ee but the enantiomeric excess of the resulting phenethyl alcohol is 40% ee.

(Salen)manganese(III) complexes (hereafter referred to as Mn-salen complexes) show catalytic activity similar to metalloporphyrin complexes. Jacobsen



Scheme 2

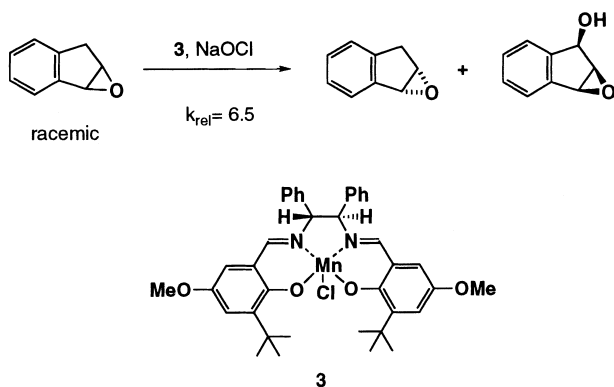


Scheme 3

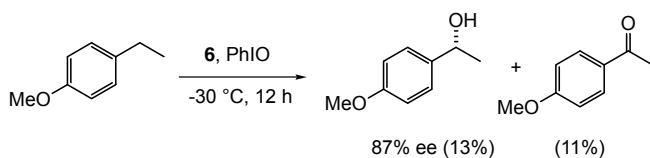
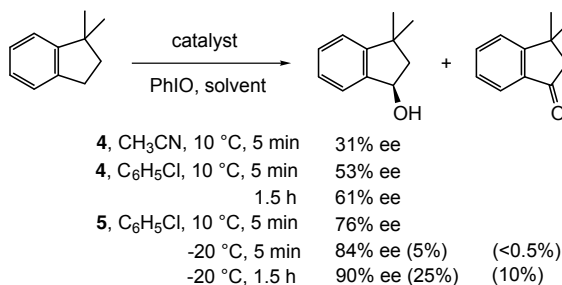
and the present author have independently reported that optically active Mn-salen complexes are excellent catalysts for asymmetric epoxidation of conjugated olefins [9, 10, 11]. These Mn-salen complexes also catalyze benzylic hydroxylation.

Larrow and Jacobsen have reported that the kinetic resolution of racemic indene oxide with Mn-salen complex **3** proceeds with a moderate level of relative rate constant ($k_s/k_r=6.5$) (Scheme 4) [12].

Katsuki and coworkers have examined the enantioselective benzylic hydroxylation of 1,1-dimethylindane with the Mn-salen complex **4**, which is a good catalyst for asymmetric epoxidation, but the reaction in acetonitrile showed only a



Scheme 4



Scheme 5

modest enantioselectivity of 31% ee (Scheme 5) [13,14]. This salen-catalyzed hydroxylation also proceeds through a radical intermediate. In contrast to the porphyrin-catalyzed reaction, however, stereoselective radical decay cannot be ex-

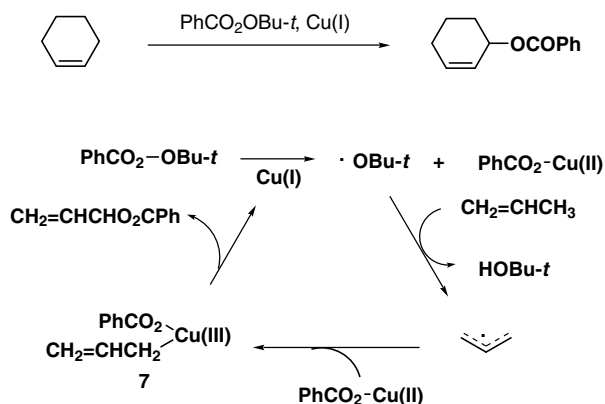
pected in this reaction because **4** lacks a chiral bridge architecture. Participation of non-stereoselective radical decay causes a deterioration of enantioselectivity. The undesired radical decay is suppressed to some extent by the use of a solvent with high viscosity which can construct a strong solvent cage, thus increasing enantioselectivity. Actually, enantioselectivity is improved up to 53% ee when the reaction is carried out in chlorobenzene. Further improvement up to 84% ee is realized by the use of complex **5** at a lower reaction temperature. Complex **5** carries the bulky 4-(*tert*-butyldiphenylsilyl)phenyl group on the naphthyl ring that hangs over the manganese ion and suppresses the undesired radical decay. The resulting benzylic alcohol is slowly oxidized to the corresponding ketone. Fortunately, the minor enantiomer of the alcohol is oxidized preferentially and the enantiomeric excess of the alcohol increases to 90% ee when the reaction time is prolonged to 1.5 h. Hydroxylation of *p*-methoxyethylbenzene with complex **6** also proceeds with high enantioselectivity.

3

Allylic Oxidation

Several methods are now available for allylic oxidation. Among them, the ene-type oxidation reaction with, e.g., SeO_2 or $^1\text{O}_2$ oxidation have been the most widely used for the purpose [15] but their asymmetrization has not met with success. Another widely used method is the Kharash-Sosnovsky reaction using a peroxide and Cu(I) salt system [16]. This reaction has been considered to proceed through a Cu(III)-allyl complex **7** (Scheme 6) [17].

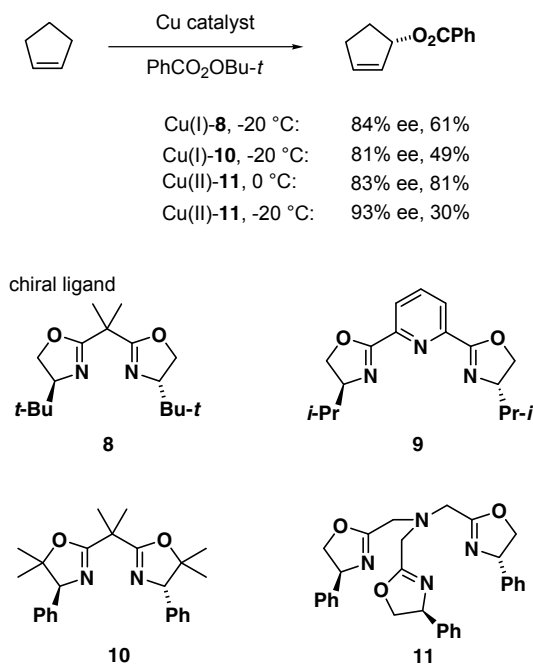
This mechanism suggests that the reaction can be performed in an enantioselective manner, if the copper ion is appropriately modified by chiral ligand(s). In 1965, the Cu(II)- α -ethyl camphorate complex was found to promote the asymmetric Kharash-Sosnovsky reaction, although the enantioselectivity was only modest [18]. Thirty years later, this chemistry was followed by three highly enan-



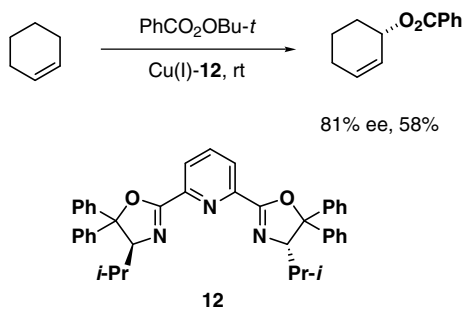
Scheme 6

tioselective reactions. Pfalz and coworkers have reported that the Cu(I)-bis(oxazoline) **8** complex is an efficient catalyst for this purpose [19]. For example, treatment of cyclopentene with *tert*-butyl peroxybenzoate in the presence of the Cu(I)-**8** complex gives 2-cyclopentenyl benzoate of 84% ee in 61% yield. Acetonitrile is the solvent of choice (Scheme 7). The Cu(II)-**8** complex is less efficient than the Cu(I)-**8** complex. Pyridine-2,6-bis(oxazoline) (**9**, Nishiyama ligand) is also an equally efficient chiral ligand. Andulus and coworkers have independently reported that Cu(I)-bis(oxazoline) complex **10** is also an efficient catalyst for allylic oxidation [20].

On the other hand, Kawasaki and Katsuki have synthesized the copper-tris(oxazoline) ligand **11** complex which mimics the active site structure of non-heme monooxygenase and examined its use in allylic oxidation [21, 22]. It is interesting to note that the Cu(II)-**11** complex is more effective as a catalyst than the corresponding Cu(I)-**11** complex, in contrast to the copper complexes of bis(oxazolines). Contamination of water adversely affects the enantioselectivity and the oxidation of cyclopentene in the presence of molecular sieves in acetone shows a high enantioselectivity of 93% ee, although the chemical yield is moderate. However, the enantioselectivity of these reactions using **8-11** is substrate-dependent and the oxidation of other cyclic olefins with these chiral ligands shows a somewhat diminished enantioselectivity. In contrast to this, DattaGupta and Sih



Scheme 7



Scheme 8

have demonstrated that the Cu(I) complex bearing the modified Nishiyama ligand 12 as a chiral source is a good catalyst for allylic oxidation of cyclohexene (81% ee, 58% yield) in the presence of molecular sieves, while the reaction of cyclopentene shows only modest enantioselectivity of 59% ee (Scheme 8) [23].

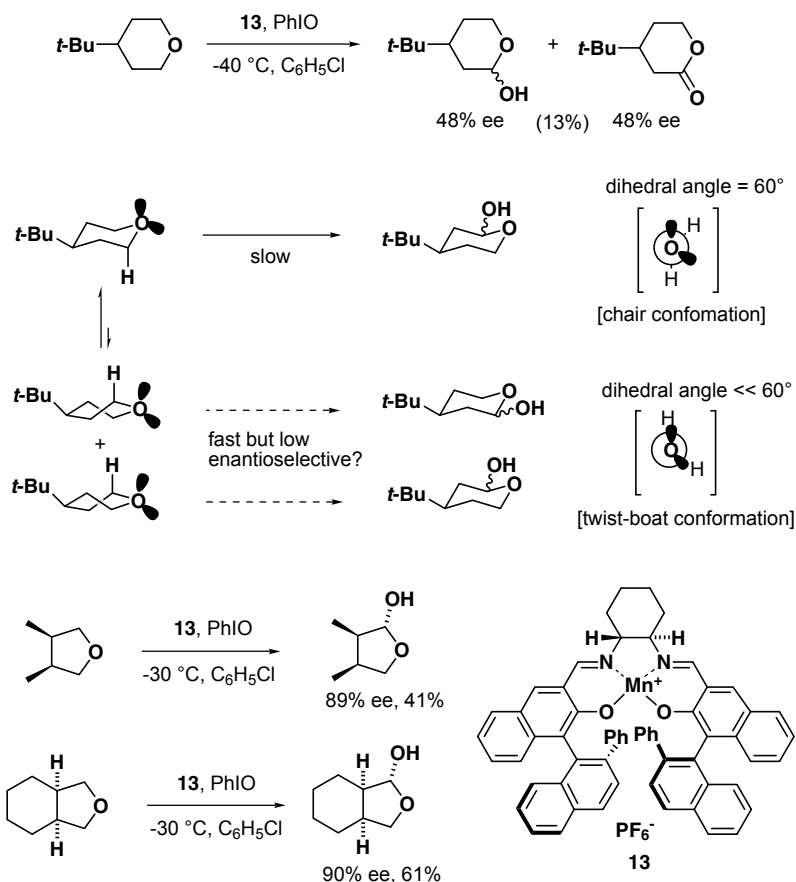
4

Desymmetrization of Prochiral or *meso*-Cyclic Ethers

Although it is well known that cyclic ethers are readily oxidized to the corresponding lactols or lactones, their asymmetric desymmetrization was not examined until quite recently. However, desymmetrization of prochiral or *meso*-cyclic ethers is expected to be a useful tool for organic synthesis, since many prochiral or *meso*-cyclic ethers are available in bulk. Recently, Miyafuji and Katsuki have reported the desymmetrization of 4-*tert*-butylcyclohexane and *meso*-tetrahydrofurans with the chiral (salen)manganese(III) complex 13 as catalyst (Scheme 9) [24, 25]. The oxidation of the former shows only the modest enantioselectivity, while the reaction of the latter exhibits excellent enantioselectivity. The low enantioselectivity (48% ee) observed in the oxidation of 4-*tert*-butyltetrahydrofuran has been attributed to the participation of enantiomeric twist-boat conformers. Although 4-*tert*-butyltetrahydrofuran exists in an equilibrium mixture of chair and enantiomeric twist-boat conformers and the equilibrium ratio of the latter is very small, the latter is considered to be more reactive than the former for stereoelectronic reasons. One of α -C-H bonds in the twist-boat conformer almost eclipses the *n*-orbital while those in the chair conformer are *gauche* or *anti* to the *n*-orbital.

In contrast to this, 3,4-dimethyltetrahydrofuran having a more planar structure is readily oxidized and shows high enantioselectivity of 89% ee. Oxidation of 8-oxabicyclo[4.3.0]nonane also proceeds with a high enantioselectivity of 90% ee.

In conclusion, the recent achievements in asymmetric C-H oxidation demonstrate that stereocontrol of C-H oxidation is not a formidable but rather a rewarding task remaining to be solved in oxidation chemistry.



Scheme 9

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Chapter 22

Baeyer-Villiger Reaction

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Keywords: Baeyer-Villiger oxidation, [1,2]-Rearrangement, Copper, Platinum, Titanium

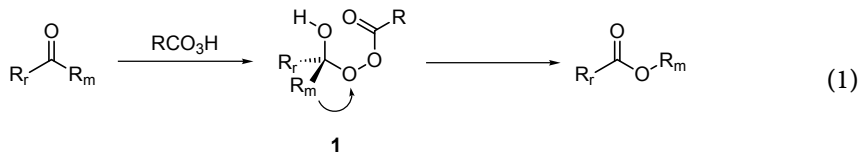
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1 Introduction

A Baeyer-Villiger oxidation implies the formation of an ester or lactone starting from an acyclic carbonyl compound or a cyclic ketone. In 1899, Alfred Baeyer and Victor Villiger discovered this previously unknown oxidative transformation while investigating the oxidation of cyclic terpenoid ketones with Caro's reagent, peroxomonosulfuric acid [1]. The unexpected outcome of their experiments was that the cyclic ketones they used inserted an oxygen atom in the α -position to the carbonyl carbon atom under cleavage of the C-C-bond, affording lactones as oxidation products. Since then, the Baeyer-Villiger oxidation (also known as the 'Baeyer-Villiger rearrangement') has become a precious synthetic tool in organic chemistry. Its distinguishing characteristics include the intrinsic regioselectivity as to which side of the carbonyl group the oxygen atom will insert and the complete retention of configuration during the rearrangement [2, 3, 4].

Criegee proposed a two-step mechanism (Eq. 1) for the Baeyer-Villiger oxidation which is widely accepted, at least for the reaction with organic peracids as oxidizing agent [5]: as first step the reversible acid- or base-catalyzed addition of

a peroxide to a carbonyl function gives a tetrahedral peroxyhemiketal, the so-called Criegee-intermediate **1**. The subsequent step, which will be the rate-determining one in most cases, comprises the migration of a substituent R_m from the carbonyl carbon to the next oxygen atom of the peroxy bridge and, simultaneously, the cleavage of the O-O-bond along with the release of the acid moiety.



The aforementioned regioselectivity stems from a substituent-dependent rearrangement in the second step of Criegee's mechanism: like in other [1,2]-rearrangements, that α -C-atom will preferably migrate which is best able to stabilize a positive charge developing in the migration step, i.e., a *tert*-butyl substituent, for example, is more prone to migrate than a methyl group. This capability to stabilize positive charge is often a dominant but not the only factor that dictates the migratory aptitude of the substituents. Other electronic and steric effects, the pH of the reaction media, or the structure of the peroxide used have to be taken into account. Thus, particularly in complex molecules, the migration of different substituents α to the carbonyl group can become rather unpredictable [6,7,8,9,10,11,12]. Even so, the migrating substituent's configuration is preserved in any case.

Apart from peracids various other peroxy compounds including hydrogen peroxide and alkyl peroxides can be used as oxidants in the Baeyer-Villiger reaction. *Tert*-butyl hydroperoxide, for instance, is able to oxidize cyclobutanones to γ -butyrolactones, yet fails to do so with larger ring ketones due to their lack of ring strain that cyclobutanones are endowed with in great extent. To circumvent work with these hazardous, highly oxygenated compounds and, in addition, to open up the perspective of rendering the Baeyer-Villiger oxidation enantioselective, the use of metals has proved to be decisive.

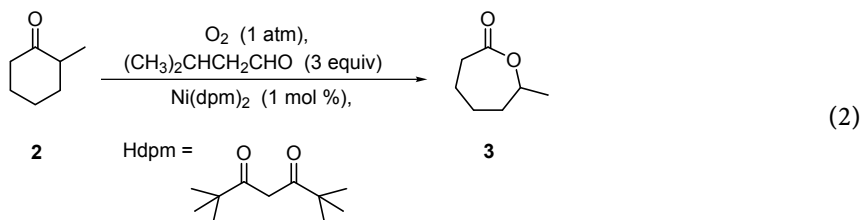
2

Metal-Catalyzed Baeyer-Villiger Oxidation

Metals can be used as Lewis acids – like SnCl_4 – in the Baeyer-Villiger oxidation, catalyzing the addition of a peroxy species to the carbonyl group and promoting the subsequent rearrangement of the resulting Criegee intermediate [13,14,15]. Another feature the use of metals can bring about is the metal-catalyzed in situ formation of peroxy species. Thus, in combination with an aldehyde and dioxygen, metals such as nickel and copper have been found to effect Baeyer-Villiger oxidations.

In 1991, Yamada and Mukaiyama presented bis(dipivaloylmethanato)nickel(II) as catalyst for the Baeyer-Villiger oxidation with dioxygen and an aliphatic aldehyde as coreductant (Eq. 2) [16]. In the optimized version of this catalysis a

cyclic or acyclic ketone dissolved in 1,2-dichloroethane was oxidized in the presence of 3 equivalents of isovaleraldehyde and 1 mol % of the nickel(II) catalyst under an atmosphere of oxygen. After several hours' reaction at room temperature the corresponding Baeyer-Villiger product was obtained in high yield and, furthermore, regioselectively. Thus, the nickel catalyzed Baeyer-Villiger oxidation of ketone **2** (Eq. 2) solely afforded lactone regioisomer **3**, as opposed to the oxidation with *m*-CPBA which gave a mixture of regioisomers in a ratio of 10 to 1.



Murahashi revealed that the Baeyer-Villiger oxidation with dioxygen in the presence of aldehyde could also be catalyzed by Fe_2O_3 [17]. It is proposed that in an Fe_2O_3 -mediated reaction between dioxygen and aldehyde a transient acylperoxy radical is generated which is involved in the formation of a peracid-ketone adduct like **1**; such an intermediate will give, after the usual rearrangement, the corresponding lactone.

As to the mechanistic pathway of aerobic oxidations of this type little evidence of any details has emerged as yet [18]. However, it seems quite reasonable to assume the intermediacy of peracids being formed by autoxidation of the aldehydes [19, 20]. Metals can be involved in various stages of oxidation processes like the described nickel(II)- or iron(III)-catalyzed reactions [21]: acyl radicals may be produced by metals from aldehydes which then participate in the autoxidation of the aldehydes. Metals can direct the oxygen insertion itself, too, or promote other catalytic pathways as well as even inhibit catalytic turnover.

3

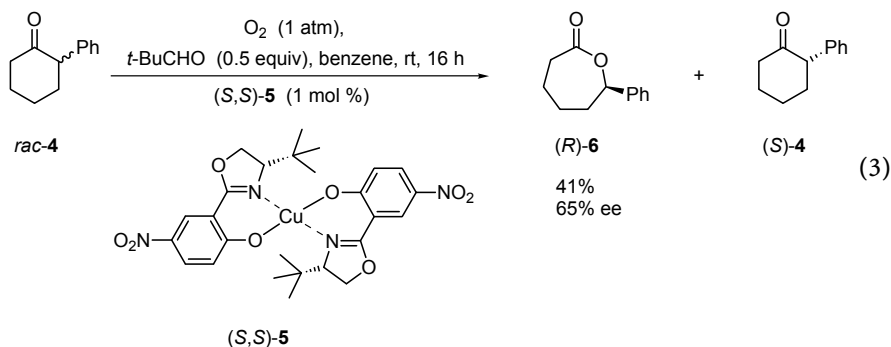
Asymmetric Metal-Catalyzed Baeyer-Villiger Oxidation

3.1

Copper-Catalyzed Asymmetric Baeyer-Villiger Oxidation

In Baeyer-Villiger oxidations catalyzed by (achiral) copper or nickel salts substituted cyclohexanones like **4** (Eq. 3) had been shown to be reactive substrates for the conversion to the corresponding (racemic) lactones in the presence of aldehyde and molecular oxygen [22]. The next step was to develop a chiral catalyst in order to make this reaction proceed in an enantioselective manner, giving optically active oxepanones. Various copper complexes were screened in a search for asymmetric induction in the aerobic Baeyer-Villiger oxidation. The most active and selective catalyst that was eventually found was the copper complex

(*S,S*)-**5**, bearing two bidentate oxazoline-type ligands. Its X-ray structure revealed a distorted tetrahedral coordination geometry [23,24,25,26].

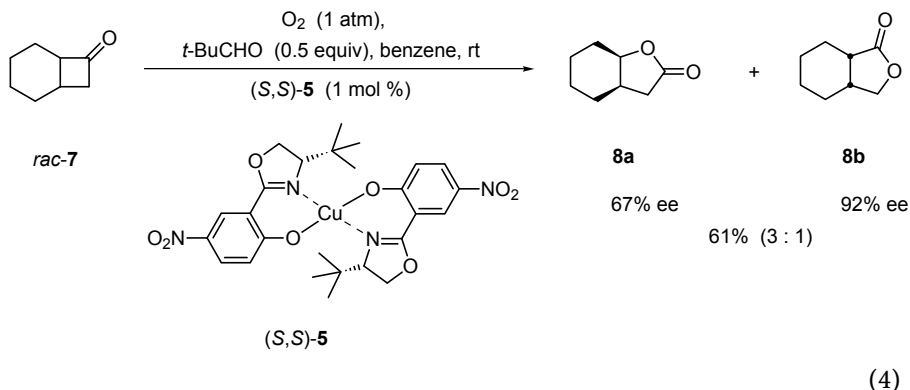


By using the chiral catalyst (*S,S*)-**5** racemic cyclohexanones with different aromatic substituents in the α -position were converted into lactones enantioselectively (Eq. 3). Catalyses of this type are carried out according to a quite convenient protocol: substrate, 0.5 to 3 equiv of pivaldehyde, and 1 mol % of catalyst (*S,S*)-**5** are dissolved in benzene and filled in an oxygen-ventilated Schlenk-type flask, bearing a balloon of oxygen gas affixed to its tap. After 16 to 20 hours of vigorous stirring at ambient temperature the mixture is diluted with diethyl ether. Extraction with an aqueous solution of NaHCO_3 is followed by drying of the organic layer over MgSO_4 , evaporation of the solvent, and purification of the product by column chromatography on silica gel. Analysis by GC or HPLC using chiral columns reveals the enantiomeric excess of the lactones, e.g., 65% ee for lactone (*R*)-**6** obtained from racemic 2-phenylcyclohexanone (**4**) in 41% yield.

For an efficient catalysis the bulky *tert*-butyl group at the aromatic ring as well as the electron-withdrawing *p*-nitro substituent of the catalyst have proved essential. Furthermore, the synopsis of EPR (electron paramagnetic resonance) coupling constants of several oxazoline-copper(II) complexes similar to (*S,S*)-**5** and their respective catalytic performance suggests that a lower electron density at the metal center and, hence, a weaker ligand-copper bond parallel a better outcome as to yield and enantioselectivity. Tetradentate salen-copper complexes have shown no catalytic activity and thereby affirm the necessity of rather loosely bound bidentate oxazoline ligands which may be easily exchanged by an in situ formed peroxy agent during catalysis. The assumption, in turn, of peroxy radicals or peracids being involved in the metal catalysis is reinforced by the direct use of a peracid instead of dioxygen/aldehyde: peroxolauric acid (90%) in combination with copper catalyst (*S,S*)-**5** also enantioselectively transforms the ketone *rac*-**4** into the optically active lactone (*R*)-**6** (48% ee; 76% yield).

An as yet unexplicable drawback of the described catalytic system (*S,S*)-**5**/pivaldehyde/dioxygen is its limitation to 2-aryl substituted cyclohexanones; the positional isomer 4-phenylcyclohexanone or 2-alkyl substituted cyclohexanones are not converted. The strained cyclobutanones, however, will almost always react under the catalytic conditions. Thus, the racemic bicyclic cyclobu-

tanone **7** (Eq. 4) affords two isomeric γ -lactones **8a** and **8b** in a ratio of 3 to 1 (61%) with enantiomeric excesses of 67 and 92%, respectively [24].



Apparently, the reaction proceeds in an enantiodivergent manner, i.e., the regioisomeric lactones **8a** and **8b** emanate from opposite enantiomeric ketones and show different ee values. Transformations of this kind are rare, and the most significant examples of these have been summarized by Kagan [27].

Monocyclic cyclobutanones **9** (Fig. 1) with alkyl, aryl, or carboxylato substituents at C3 gave under the usual catalytic conditions optically active lactones with only moderate enantiomeric excesses (up to 47% ee) [25]. Increasing the amount of pivaldehyde used in the catalysis led to higher yields without a significant decline in enantioselectivity. For instance, 3-phenylcyclobutanone (**9**, R=Ph) was converted to the corresponding (*S*)-lactone in 66% yield with either 0.5 equiv pivaldehyde added two times during 40 hours, but in 88% yield with 3 equiv pivaldehyde added portionwise over 3 days; the enantiomeric excesses (44% ee) were identical in either catalysis.

Contrary to the prochiral monosubstituted cyclobutanones **9**, Kelly's tricyclic ketone **10** afforded the corresponding lactone with 91% ee highly enantioselectively (62% yield) [26]. The significantly greater asymmetric induction in this case has been proposed as being the result of an extraordinary high diastereofacial control during the presumed addition of a peroxy species to the tricyclic ketone **10**.

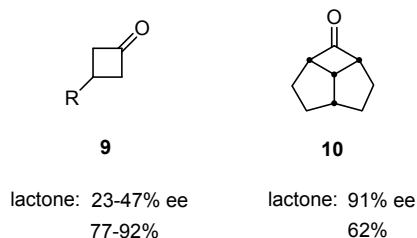
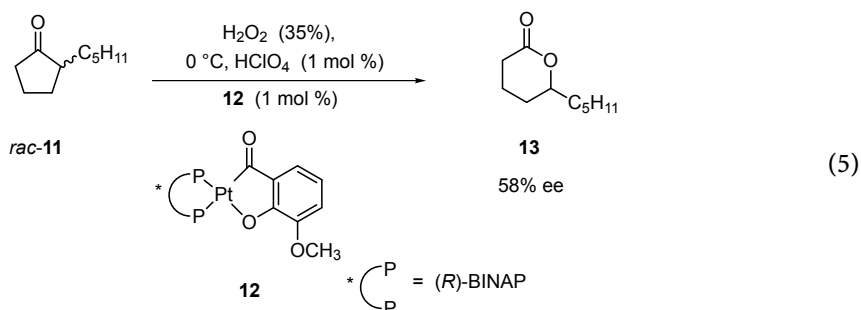


Fig. 1

3.2

Platinum-Catalyzed Asymmetric Baeyer-Villiger Oxidation

Another method for enantioselective Baeyer-Villiger oxidations was developed by Strukul [28, 29]. His catalytic system is based on cationic platinum-diphosphine complexes which activate H_2O_2 to oxidize cyclic ketones (Eq. 5).



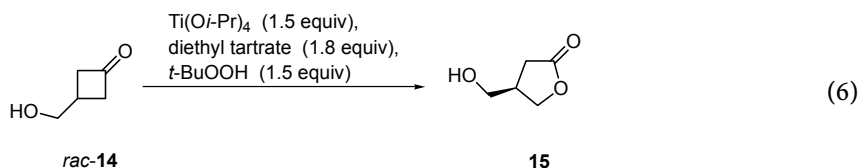
The highest enantiomeric excess of 58% was achieved with 2-(*n*-pentyl)cyclopentanone (**11**) as substrate and BINAP/2-vanillin platinum complex **12** as catalyst (Eq. 5). As a comparison with the reaction of 2-methylcyclopentanone revealed, a shorter side chain in the substrate led to a slightly faster reaction but significantly decreased the enantioselectivity at the same time. Also, a six-membered cyclic ketone, 2-methylcyclohexanone, was converted under identical conditions to the corresponding (*S*)-lactone with 45% ee.

The catalytically active cationic complex is preformed by reaction of complex **12** with the strong acid HClO_4 : the phenolic oxygen is protonated and the coordinative bond of the bidentate vanillin ligand to platinum is cleaved at this end. In contrast to the treatment of **12** with HCl , which gives an inactive chloroplatinum complex, the non-coordinating anion $[\text{ClO}_4]^-$ leaves a vacant coordination site on the central metal, thus rendering it catalytically active.

3.3

Titanium-Catalyzed Asymmetric Baeyer-Villiger Oxidation of Cyclobutanones

A third variant of a metal-catalyzed enantioselective Baeyer-Villiger oxidation of cyclobutanones was reported by Lopp [30]. Up to 75% ee was achieved using the system for the epoxidation of allylic alcohols developed by Sharpless, i.e., $\text{Ti}(\text{O}i\text{-Pr})_4$, chiral diethyl tartrate, and *tert*-butyl hydroperoxide (Eq. 6).

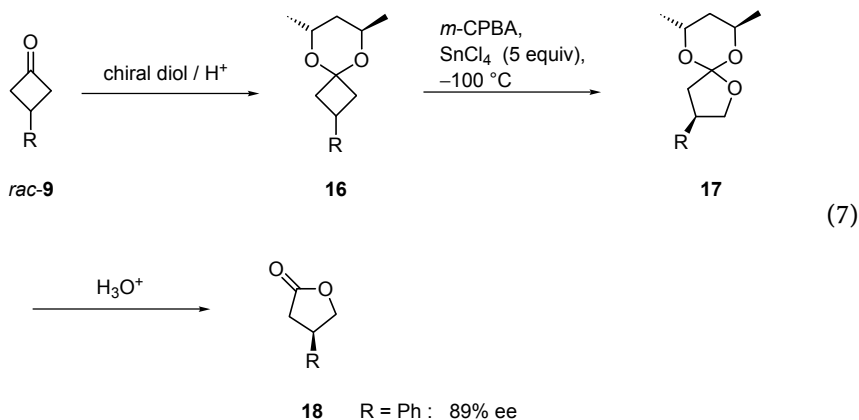


In this oxidation the maximum conversion of the substrates remained moderate (with *tert*-butyl hydroperoxide 49%, with *m*-CPBA 20%).

4

Other Approaches to an Asymmetric Baeyer-Villiger Oxidation

Sugimura introduced a diastereotopic differentiating peracid oxidation of ketals **16** prepared from prochiral ketones **9** with an optically active, C₂-symmetrical diol (Eq. 7) [31].



Although the reaction of ketals **16** with an overstoichiometric amount of *m*-CPBA in dichloromethane under reflux did not proceed at all, the presence of SnCl₄ promoted the oxidation and the ketals were smoothly converted into chiral lactones **18** even at low temperatures. The best result was achieved at -100 °C with the ketal derived from 3-phenylcyclobutanone (**9**, R=Ph) and 2,4-pentane-diol. By using 5 equiv of SnCl₄ the corresponding lactone was obtained with 89% ee.

Apart from the asymmetric metal catalysis, enantioselective Baeyer-Villiger oxidations mediated by enzymes have been known for some time [32,33,34]. Both whole-cell cultures and isolated enzymes, usually flavin-dependent monooxygenases, can be used to oxidize ketones enantioselectively. For future improvements in the asymmetric Baeyer-Villiger oxidation the use of chiral Lewis acids in combination with an appropriate oxidant seems worthy of intensive investigation.

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Chapter 23

Isomerization of Carbon-Carbon Double Bonds

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Keywords: Allyl alcohol, Allylamine, Aza-allyl, Azomethine, BINAP, BIPHEMP, Citronellal, Cobalt, DIOP, Enol, Enamine, Imine, Isomerization, Kinetic resolution, Nitrogen-triggered, Rhodium, Ruthenium

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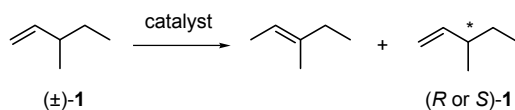
1 Introduction

Olefinic compounds are isomerized under a great variety of conditions; catalysts such as acids, bases, and organometallic complexes are effective in promoting the migration of double bonds [1, 2]. Thermodynamically, the migration of simple prochiral olefins to less substituted ones is not favored. The methylene-azomethine rearrangement is a typical example where thermodynamic stability decides the reaction pathway [3]. Provided that well-designed catalysts are available, the reactions possess a high potential for obtaining enantiopure amines. When the less substituted olefin gains relative stability, the migration of a mult-substituted inner double bond would occur as seen like that observed in func-

tionalized allylic systems. Various complexes of iron, cobalt, palladium, rhodium, ruthenium, osmium, iridium, platinum, and strong bases have been proposed as catalysts for such allylic migrations [4]. Typically, the allyl group is commonly used for the protection of hydroxy or amino groups in organic synthesis. Removal of this protecting group involves a two-step sequence: isomerization of the allyl group to a propenyl derivative followed by the acid catalyzed hydrolysis [5, 6]. The asymmetric isomerization of a prochiral allyl system obviously has high synthetic utility for obtaining chiral aldehydes or ketones. In 1978 an enantioselective hydrogen migration of prochiral allylamines to enamines was reported by using Co(I)-DIOP complexes as catalysts [7]. When the reaction was catalyzed by a cationic rhodium complex of BINAP, surprisingly high chemical and enantiomeric selectivities of 99% and 98%, respectively, were obtained [8]. A new nitrogen-triggered mechanism has been proposed to explain such high catalytic activities and reaction selectivities [9]. This isomerization has revealed a wide range of applications including the world's largest asymmetric synthesis of (-)-menthol [10]. This article summarizes mainly the asymmetric isomerization of allylic oxygen and nitrogen systems. Brief introductions to recent achiral reactions are also included where they are promising for applications in asymmetric catalysis.

2 Isomerization of Simple Olefins

In 1970s, much effort was devoted to the kinetic resolution of racemic 1-alkenes (Scheme 1, an asterisk will be used throughout this article to denote optically active entities). The enantiomeric excesses, though poor, were observed in the unreacted olefins **1**. The results are surprising in that the asymmetric induction occurred in simple substrates with only primitive chiral catalysts [11, 12, 13, 14].



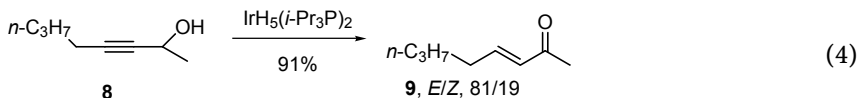
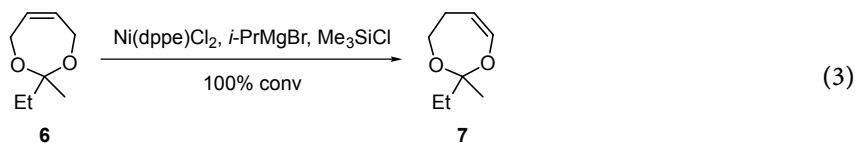
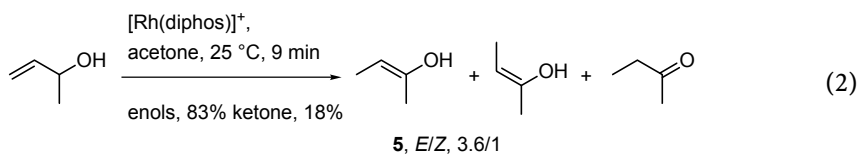
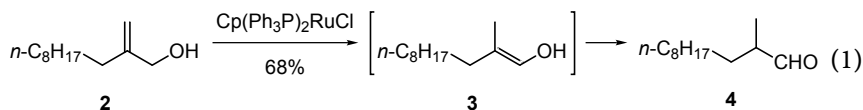
Catalyst	Conv [%]	ee [%] of unreacted olefin
Ti[(-)-menthoxide] ₄ , DIBALH	65	2.20
Ni[P(OEt) ₂ Ph] ₄ , (R)-(-)-PMe(<i>n</i> -Pr)(Ph)	50	23
[RuH{(R)-(-)-phenylglycolato}(PPh ₃) ₃]	22	0.7
[Ni(<i>N</i> -methylsalicylaldimene) ₂], (-)-DIOP, <i>i</i> -Bu ₃ Al	24	0.57
[Ni(<i>N</i> -methylsalicylaldimene) ₂], (R)- <i>N,N</i> -dimethyl-1-phenylethylamine, <i>i</i> -Bu ₃ Al	35	0.32

Scheme 1

3 Isomerization of Oxygen Functions

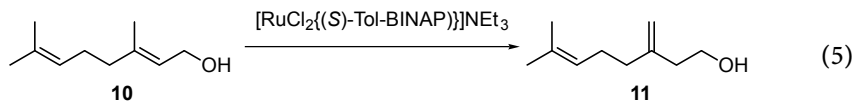
3.1 General

It is well known that the isomerization of allyl alcohols to the corresponding saturated aldehydes and ketones is induced by a variety of transition metal catalysts [15]. Studies using pentacarbonyliron suggested that the reaction occurred in an intramolecular fashion and required a *syn*-relationship between the transferred hydrogen and the catalyst for a 1,3-suprafacial-hydrogen shift [16]. Typically, the isomerization of allyl alcohol **2** proceeds through enol form **3** which rapidly transforms to the corresponding aldehydes **4**, Eq. (1) [17, 18]. When the reaction was carried out under mild conditions, it was possible to obtain the fugacious enol molecules **5**, Eq. (2) [19]. Allyl ethers were isomerized to propenyl derivatives by (naphthalene)chromium tricarbonyl [20], or $[\text{Ru}(\text{H}_2\text{O})_6]^+$ catalysts [21]. The smooth isomerization of cyclic but-2-ene-1,4-diol derivatives **6** to but-1-ene-1,4-diol derivatives **7** was mediated by nickel complexes, Eq. (3) [22]. Propargyl alcohol derivatives **8** were isomerized to α,β -enones **9** by iridium complexes in which the coordination of basic phosphines was required, Eq. (4) [23].



In the study of Ru-BINAP catalyzed asymmetric hydrogenation of geraniol **10**, a striking isomerization to γ -geraniol **11** was observed, Eq. (5) [24]. The reaction is noteworthy in that it promotes the olefin migration from an inner to an *exo* position. Originally the presence of **11** was supposed to be an intermediate

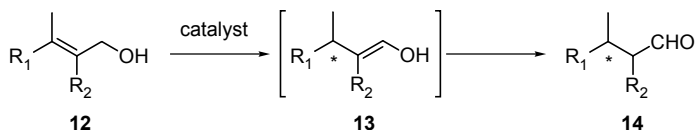
for the hydrogenation, but now this alcohol can also be isolated on a preparative scale [25].



3.2

Allyl Alcohols to Carbonyl Compounds

In 1976 the first example of the asymmetric isomerization of prochiral allyl alcohols to aldehydes was reported [26]. The isomerization proceeds by migration of the olefinic double bond of allyl alcohol **12** from the 2,3 position to the 1,2 position to give enol **13**, which transforms rapidly to aldehyde **14** (Scheme 2). It was claimed that DIOP (**15**)-modified rhodium catalysts (Fig. 1) exemplified the enantioselectivity in 2 to 4% ee. After their successful use for allylamines, BINAP (**16**)-coordinated rhodium catalysts (Fig. 1) were applied for the isomer-



R1	R2	Catalyst	Conv [%]	ee [%]	Confign
Me	Me	RhH(CO)(PPh ₃) ₃ , DIOP	91	4	(S)
Et	H	RhH(CO)(PPh ₃) ₃ , DIOP	63	2	(R)
Me	H	[Rh{(R)-BINAP}(COD)] ⁺	64	-	
H	H	[Rh{(R)-BINAP}(COD)] ⁺	87	-	
Me ₂ C=CH(CH ₂) ₂	H	[Rh{(R)-BINAP}(COD)] ⁺	70	37	(S)
Me ₂ C=CH(CH ₂) ₂	H	[Rh{(S)-BINAP}(COD)] ⁺	68	36	(R)
Ph	H	[Rh{(R)-BINAP}(COD)] ⁺	47	53	(S)

Scheme 2

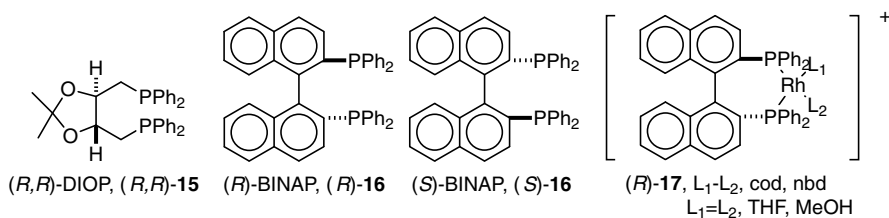
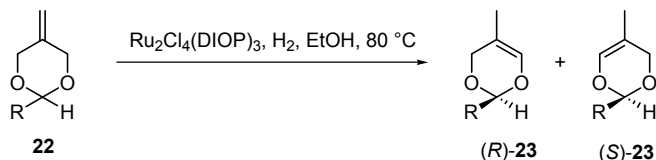
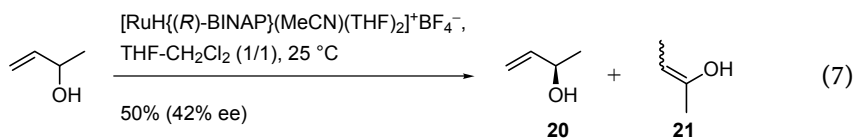
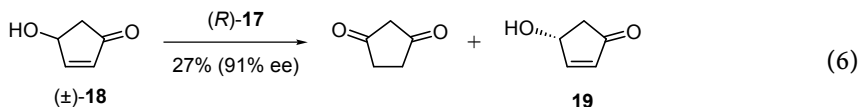


Fig. 1. Structures of **15**, **16**, and **17**

ization. The prochiral allyl alcohols geraniol and 3-methylcinnamyl alcohol, were isomerized in the presence of 1 mol % of **17** (Fig. 1; throughout this article the counter anion omitted is perchlorate) to citronellal and 3-methylcinnamyl aldehyde, respectively. In these acyclic systems, reaction selectivities were fairly low compared to those obtained in their amine counterparts [27].

However, the isomerizations of cyclic allyl alcohols to ketones proceeded more cleanly, for example, an effective kinetic resolution of racemic 4-hydroxy-2-cyclopentenone **18** was observed, Eq. (6). In the presence of (*R*)-**17**, the reaction proceeded with a five to one enantiomeric discrimination to give 1,3-cyclopentanedione. At a conversion of 83%, the optical purity of remaining 4-hydroxy-2-cyclopentenone **19** was 91% in the (*R*)-configuration, thus providing a useful building block for prostaglandin synthesis [28]. Recently, a kinetic resolution of acyclic allyl alcohols has been carried out with the Ru-BINAP catalysts, Eq. (7). A fairly good discrimination was observed, namely with a conversion of 50%, the enantiomeric purity of the remaining allyl alcohol **20** was 42%. A mixture of stereoisomers of enol intermediates **21** were also isolated under the limiting conditions ($[C]=2.6 \text{ mmol L}^{-1}$, 2.2 min) [29].



R	Time [h]	Yield [%]	ee [%]
<i>t</i> -Bu	2	75	12.8
Et	1	77	17.3
<i>i</i> -Pr	1.5	73	18.2
3-Me-C ₆ H ₄	5	47	18.6
C ₆ H ₅	4	77	37.6
Et ₂ NCH ₂	3	80	22.6
Et ₂ N(CH ₂) ₂	6	68	18.3
<i>i</i> -Pr ₂ NCH ₂	2	90	23.4
<i>i</i> -Pr ₂ N(CH ₂) ₂	2	85	30.8

Scheme 3

A unique asymmetric isomerization of 2-substituted 5-methylene-1,3-dioxanes **22** to 5-methyl-4*H*-1,3-dioxins **23** was catalyzed by a ruthenium complex of DIOP under a hydrogen atmosphere (Scheme 3). Although the enantiomeric purity remained in the range of 35 to 50%, cyclic acetals obtained are promising starting materials for the synthesis of macrolide antibiotics and other polyketide-derived natural products [30].

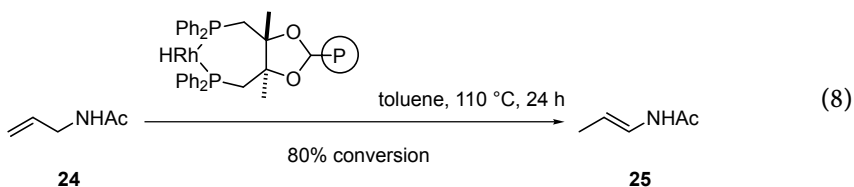
4 Isomerization of Nitrogen Functions

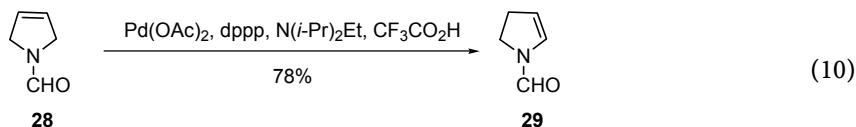
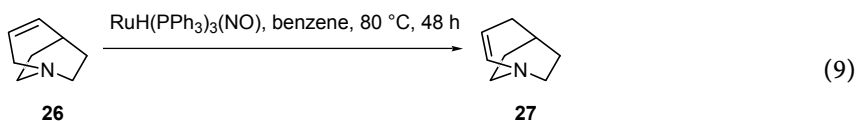
4.1 General

The development of an efficient access to enantiopure amines is highly important in organic synthesis. One of the approaches is the asymmetric hydrogenation of imines (see chapter 6.2). An alternative route is the imine isomerization reaction (methylene-azomethine rearrangement), which was extensively studied by Ingold et al. in 1930s and by Cram et al. in the 1960s and 1970s using achiral bases [3, 31]. Several reports on the asymmetric [1,3]-proton shift of imines by chiral catalysts have appeared and are aimed at the synthesis of enantiopure amines.

The isomerization of allylamines could be more selective compared to their oxygen homologues due to the higher coordination property of nitrogen. This assumption was clearly exemplified by the discovery of the cobalt-catalyzed isomerization of allylamines to enamines. With the introduction of cationic rhodium complexes of BINAP, the reaction has become one of the most successful asymmetric reactions [32].

Systematic studies on the isomerization of *N*-allylamides **24** and -imides to aliphatic enamides **25** were carried out with iron, rhodium, and ruthenium complexes as catalysts, Eq. (8). Regrettably, no prochiral substrate was applied for the rhodium catalyst bearing polymer-anchored DIOP [33]. In the framework of a study on the conjugative interaction in the isomerization of 1-azabicyclo[3.2.2]non-2-ene **26** to orthogonal enamine **27**, catalyzed by either *t*-BuOK or RuH(NO)(PPh₃)₃, the enamine formation was calculated to be favored by ~4 kcal mol⁻¹, Eq. (9) [34]. Recently, the palladium-catalyzed isomerization of the *N*-acyl-2,5-dihydropyrroles **28** to *N*-formyl-2,3-dihydropyrroles **29** was reported, Eq. (10) [35].



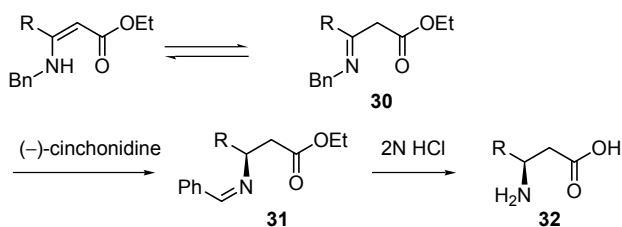


4.2

Methylene-Azomethine Rearrangement

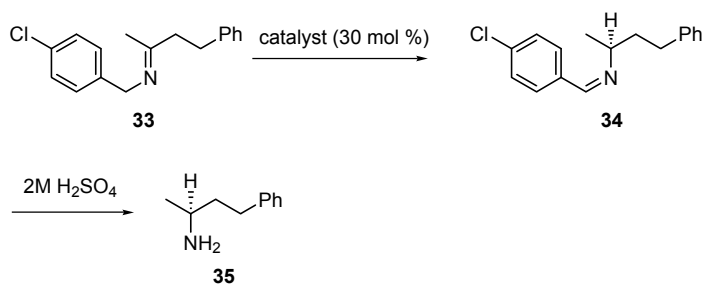
A new kind of enantioselective [1,3]-proton transfer in aza-allylic systems was reported, namely, the *N*-benzylimines **30** were converted to the more thermodynamically favored *N*-benzylidene derivatives **31** as shown in Scheme 4. Among the chiral bases (*R*)-(+)-*N,N*-dimethyl-1-phenylethylamine, (1*R*,2*S*)-(-)-*N*-methylephedrine, and (-)-cinchonidine employed as catalysts, only (-)-cinchonidine showed an asymmetric induction. A series of optically active β -polyfluoroalkyl- β -amino acids **32**, which are of great pharmaceutical interest, was prepared in 87 to 93% yields with ee's in the range of 15 to 36% [36].

Another example was the transformation of the aza-allylic system of *N*-benzylimine **33**, which resulted in the formation of the *N*-benzylidene derivatives **34** as outlined in Scheme 5 [37]. Upon hydrolysis, the chiral amine **35** was produced. The chiral bases **36**, **37**, and **38** (Fig. 2) were tested as the catalysts. Presumably, the bulkiness of the base controlled the reaction selectivities.



R	Catalyst, mol %	Temp [°C]	Time [h]	Yield [%]	ee [%]
CF ₃	9	100	50	93	16
CF ₃	5	100	50	21	15
C ₂ F ₅	10	100	40	89	29
H(C ₂ F ₄)	10	100	26	88	36
C ₃ F ₇	12	100	65	91	30
H(C ₄ F ₈)	13	100	65	88	20

Scheme 4



Catalyst	Solvent	Temp [°C]	t1/2 [min]	ee [%]	Config
36	THF	66	60	7	(R)
36	toluene	105	450	10	(R)
37	toluene	105	400	2	(R)
38	THF	66	100	22	(S)
39	toluene	105	300	44	(S)

Scheme 5

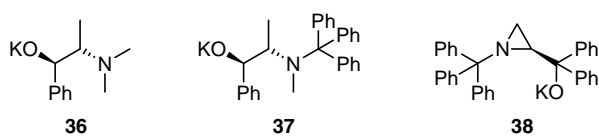
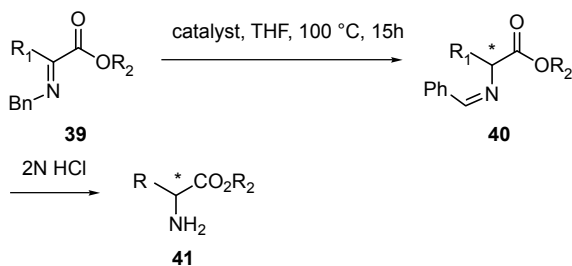


Fig. 2. Structures of 36, 37, and 38



R1	R2	Catalyst	Yield [%]	ee [%]
<i>i</i> -Pr	Et	Co(acac) ₂ , DIOP, DIBALH	78	20.0
<i>i</i> -Pr	Et	Co(acac) ₂ , BINAP, DIBALH	60	6.7
Et	<i>i</i> -Pr	Co(acac) ₂ , DIOP, DIBALH	51	4.5
Bn	Et	Co(acac) ₂ , DIOP, DIBALH	40	9.7

Scheme 6

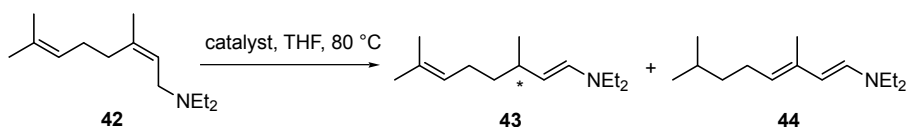
We obtained some preliminary results in the isomerization of the benzylimine derivative **39** to benzylidene derivative **40**. The catalyst solution was prepared by reducing $\text{Co}(\text{acac})_2$ with DIBALH in the presence of DIOP or BINAP. This isomerization may open a new access to the enantiopure α -amino acids **41** by introducing the modern concept of homogeneous catalysis, (Scheme 6) [38].

4.3

Allylamines to Enamines

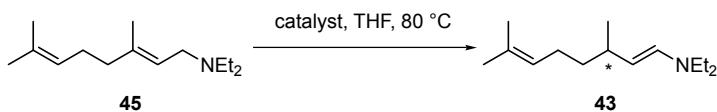
The transition metal catalyzed isomerization of prochiral allylamines to the corresponding enamines has presented an interesting problem in enantioselection. Various types of catalysts such as bases, solid bases, metal complexes of titanium, and cobalt promoted the migration of the multiply substituted inner double bonds of *N,N*-diethylnerylamine **42** (Scheme 7) [39]. The first asymmetric isomerization was performed with a cobalt catalyst comprised of $\text{Co}(\text{II})$, (+)-DIOP, and DIBALH and afforded citronellalenamine **43** in 35% ee (39% chemical yield). However, the migration of the double bond at carbon 6 also occurred to give a considerable amount of dienamine **44**. Monodentate chiral ligands gave low optical yields for the isomerization of *N,N*-diethylnerylamine.

Extensive studies on the asymmetric isomerization of *N,N*-diethylgeranylamine **45** to citronellalenamine were carried out using $\text{Rh}(\text{I})$ -diphosphine catalysts (Scheme 8) [40]. Although neutral rhodium complexes were inert to the reaction, cationic rhodium complexes of diphosphines were very active. The catalytic activity varied considerably with the nature of the ligands. Interestingly, a fully alkyl-substituted diphosphine, CyDIOP **46** (Fig. 3) gave 77% ee, representing a considerable gain compared to its prototype DIOP (22%). Disappoint-



Catalyst	Conv [%]	Products [%]	ee [%]	Confign
<i>t</i> -BuOK, DMSO	100	44 (100)		
BuLi, TMEDA	100	44 (100)		
MgO, calcined, 400 °C	45	44 (100)		
Cp_2TiCl_2 , <i>i</i> -PrMgBr	95	44 (100)		
$\text{CoH}(\text{N}_2)(\text{PPh}_3)_3$	22	43 (85), 44 (15)		
$\text{Co}(\text{acac})_2$, PPh_3 , DIBALH	20	43 (81), 44 (19)		
$\text{Co}(\text{acac})_2$, (+)-DIOP, DIBALH	45	43 (87), 44 (13)	35	(<i>R</i>)
$\text{Co}(\text{acac})_2$, (-)-Ph ₂ P-menthyl, DIBALH	20	43 (80), 44 (20)	7	(<i>S</i>)
$\text{Co}(\text{acac})_2$, (<i>R</i>)-BINAP, DIBALH	15	43 (97)	20	(<i>R</i>)

Scheme 7



Catalyst	Conv [%]	Selectivity [%]	ee [%]	Confign
$[\text{Rh}\{\text{(R)-BINAP}\}\text{Cl}]_2$	0			
$[\text{Rh}\{(+)\text{-DIOP}(\text{COD})\}]^+$	71	100	22	(R)
$[\text{Rh}\{(-)\text{-CyDIOP}(\text{THF})_2\}]^+$	18	80	77	(S)
$[\text{Rh}\{\text{(R)-BINAP}\}(\text{COD})]^+$	100	100	97	(S)
$[\text{Rh}\{\text{(S)-BINAP}\}(\text{COD})]^+$	100	100	97	(R)
$[\text{Rh}\{\text{(S)-BINAP}\}(\text{MeOH})_2]^+$	100	100	97	(R)
$[\text{Rh}\{\text{(S,S)-BPPM}\}]^+$	69	91	14	(S)
$[\text{Rh}\{\text{(S,R)-BPPFA}\}]^+$	0			
$[\text{Rh}\{\text{(R)-BINAP}\}_2]^+$	100	100	97	(S)
$[\text{Rh}\{\text{(S)-BINAP}\}_2]^+$	100	100	98	(R)
$[\text{Rh}\{\text{(S)-BIPHEMP}\}(\text{COD})]^+$	98	100	97	(R)
$[\text{Rh}\{\text{(R)-BIPHEMP}\}(\text{COD})]^+$	98	100	97	(S)

Scheme 8

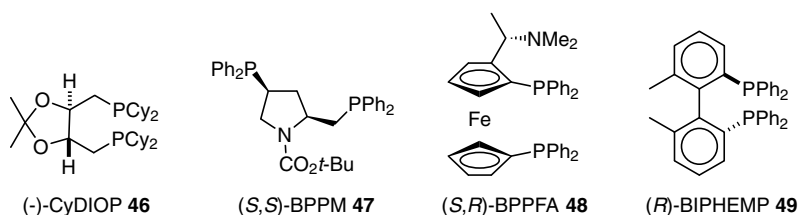


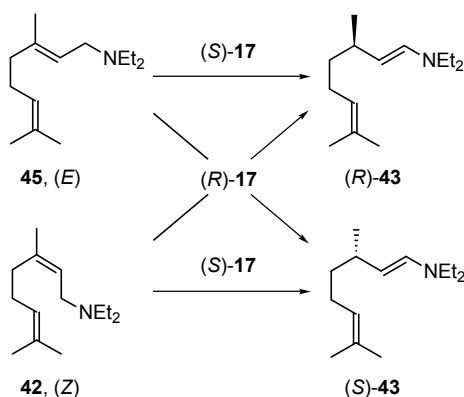
Fig. 3. Structures of **46**, **47**, **48**, and **49**

ingly, BPPM **47** (Fig. 3), which is an excellent ligand for asymmetric hydrogenation, gave a poor result in enantioselection. A diphosphine bearing a tertiary amine substituent, BPPFA **48** (Fig. 3), was totally inactive. This is probably due to the tridentate chelation of the ligand preventing substrate coordination. The ligands BINAP and BIPHEMP **49** (Fig. 3) [41] showed excellent enantioselectivity, chemoselectivity, and catalytic activity for the isomerization. These characteristics of BINAP and BIPHEMP-based catalysts may be due to their structures, in which all substituents on both phosphorous atoms are aromatic groups. It was serendipity to discover the rhodium-bis BINAP complex $[\text{Rh}\{\text{(R- or S)-BINAP}\}_2]^+ \text{ClO}_4^-$. This complex was first isolated and elucidated from a reaction mixture of **45** catalyzed by $[\text{Rh}(\text{BINAP})(\text{COD})]^+$, presumably through disproportionation [42]. This thermally stable complex was suitable for the industrial

uses and provided a very high turnover number without impairing chemo- and enantioselectivities.

The exclusive formation of the (*E*)-enamine in spite of the double bond geometry of the starting substrate is another noticeable feature of the isomerization. The present enantioselective isomerization requires prochiral allylamines free from geometrical isomers. In the isomerization, one specific feature is the stereochemical correlation between substrate geometries, product configurations, and the ligand chirality, as shown in Scheme 9.

Effects of additives in the isomerization of substrate **45** by catalyst **17** were studied under the conditions of $[S]=0.24 \text{ mol L}^{-1}$, $[S] [C]^{-1}=100$ at $60 \text{ }^{\circ}\text{C}$ in THF. The results are briefly summarized in Table 1, and are important both for mechanistic studies and improvements of the catalyst activity. Simple tertiary amines retard the reaction drastically, which suggests the coordination order of amines to Rh-BINAP species to be proportional with the order of basicity of simple tertiary amines, allylamines and enamines. Without the presence of simple tertiary amines, this phenomenon enables the fast replacement of the enamine formed from the catalyst by a substrate molecule that permits a smooth catalytic cycle. The presence of chelate diolefins like COD also disturbs the catalytic cycle. An over-isomerized by product, dienamine **44**, acts as a strong catalyst poison.



Scheme 9

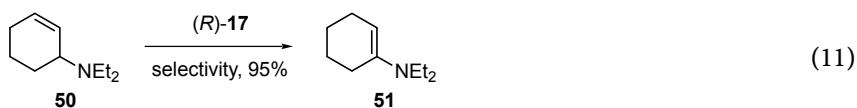
Table 1. Effect of additive

Additive	[additive] [catalyst] ⁻¹	k _{obs} [mol L ⁻¹ min ⁻¹]
none	0	37.0
NEt ₃	4	20.0
COD	2	8.5
dienamine 44	2	1.8

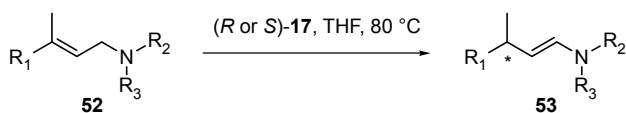
4.3.1

Scope and Applications

Scope and limitation of allylamine substrates were studied extensively by employing Rh-BINAP complexes **17** as the catalyst (THF, 60 °C). The structure of the substrates influenced the reaction drastically. The first limitation is β -substituted allylamines, thus *N,N*-dimethyl-2-methyl-2-butenylamine was not isomerized, presumably due to the thermodynamic stability of the substrate. The second is the α -substitution, namely *N,N*-dimethyl-1-methyl-2-propenylamine gave polymeric products. This fact is in accordance with the thermal instability of enamines derived from small acyclic methyl ketones. However, the cyclic allylamine, 3-diethylaminocyclohex-1-ene **50** was isomerized selectively to the corresponding enamine **51**, Eq. (11).



This isomerization is most effectively applicable to allylamines substituted at the γ,γ' -positions. In the presence of a catalytic amount of **17**, prochiral tertiary allylamines **52** were isomerized to enamines **53** (Scheme 10). The basicity of the amine nitrogen appears an important factor for the catalytic activity. Phenyl substituents on the nitrogen atom greatly retarded the reaction rate. Allylamides were slow-reacting substrates, which required the high temperature of 150 °C to give the corresponding enamides. Interestingly, an allylamine having a styrene-type conjugated olefin, *N,N*-diethyl-3-phenyl-2-butenylamine was isomerized to

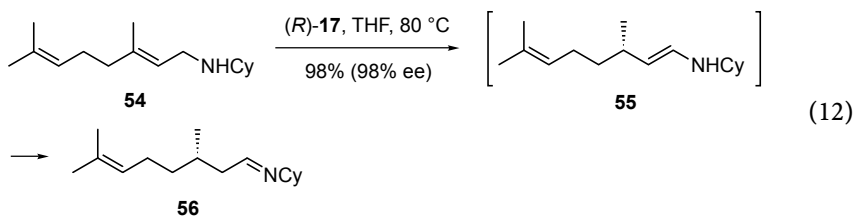


R1	R2	R3	BINAP	Yield [%]	ee [%]	Confign
Me ₂ C=CH(CH ₂) ₂	H	Ph	(<i>R</i>)	15	80	(<i>S</i>)
Me ₂ C=CH(CH ₂) ₂	Ph	Ph	(<i>R</i>)	0	–	–
Me ₂ C=CH(CH ₂) ₂	H	Ac	(<i>R</i>)	30	95	(<i>S</i>)
Ph	Et	Et	(<i>R</i>)	83	90	(<i>S</i>)
Ph	Et	Et	(<i>S</i>)	84	90	(<i>R</i>)
Me ₂ C(OH)(CH ₂) ₃	Et	Et	(<i>R</i>)	98	97	(<i>S</i>)
Me ₂ C(OMe)(CH ₂) ₃	Et	Et	(<i>S</i>)	97	98	(<i>R</i>)
Me ₂ C(OH)(CH ₂) ₃	Et	Et	(<i>S</i>)	100	97	(<i>R</i>)
Me ₂ C=CH(CH ₂) ₂	Me	cyclo-C ₆ H ₁₁	(<i>R</i>)	100	98	(<i>S</i>)

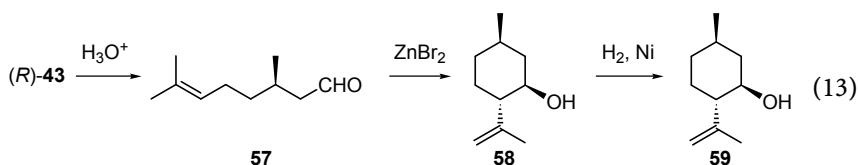
Scheme 10

give the enamine. Up to then, this substrate was known to be resistant against a variety of homogeneous catalysts. The presence of either hydroxy or methoxy group in the substrate did not affect the isomerization. Accordingly, *N,N*-diethyl-7-hydroxygeranylamine was converted to 7-hydroxycitronellal enamine which, on hydrolysis, gave 7-hydroxycitronellal, a valuable fragrance material with a scent of lily of the valley. Similarly, under catalysis by (*R*)-17, *N,N*-diethyl-7-methoxygeranylamine gave (*S*)-7-methoxycitronellal, which is a key intermediate for the synthesis of an artificial insect growth regulator (see chapter 41.4). For all these substrates the stereochemical relationship shown in Scheme 9 remains unaffected.

Secondary allyl amines **54**, although less basic than their tertiary alkyl homologues, are also good substrates for the isomerization. This fact is explained by the rapid transformation of enamine **55** to imine **56**, a more stable valence tautomer, Eq. (12).

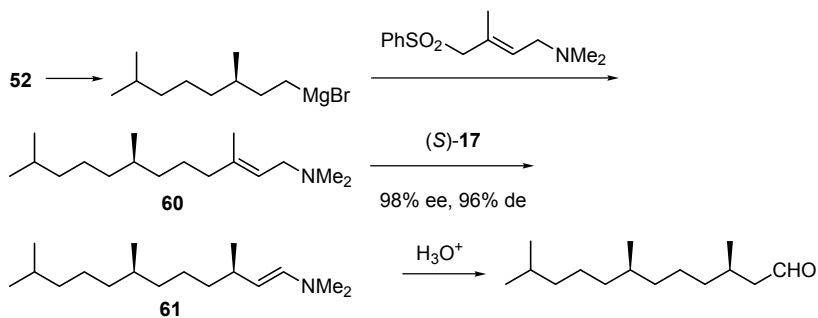


The most successful application of this isomerization is the manufacture of (–)-menthol on a 1,500 ton scale annually. As shown in Eq. (13), the synthetic sequence is composed of the hydrolysis of (*R*)-43 to (*R*)-citronellal **57**, the zinc bromide-catalyzed ene-reaction to (–)-isopulegol **58**, and hydrogenation to (–)-menthol **59** (see chapter 41.4 for details).

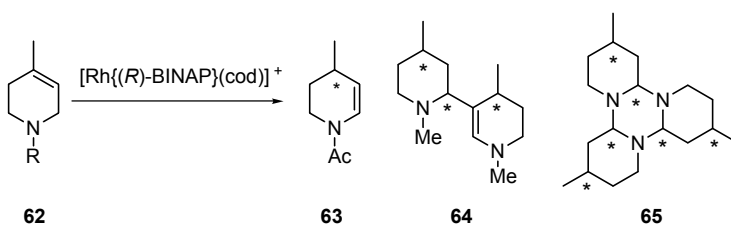


Another example is the synthesis of the enantiopure α -tocopherol side chain [43]. Thus, the C15 allylamine, (*E*)(7*R*)-1-dimethylamino-3,7,11-trimethyl-2-dodecene **60**, was isomerized to the corresponding C15 (*R,R*)-enamine **61** with very high selectivities of 98% ee and 96% de (Scheme 11).

Besides acyclic allyl amines, cyclic allyl amines that should yield (*Z*)-enamines, were also active substrates. In the isomerization of tetrahydropyridine derivatives **62** by the Rh-BINAP catalyst at 150 °C, the cyclic allyl amide gave selectively the enamide **63**. In the case of a tertiary allylamine, the isomerization occurred at 60 °C with 100% conversion. However, the corresponding (*Z*)-enamines could not be detected in the monomeric form, only the dimer **64** was isolated. Similarly, a secondary amine gave the trimer of enamine **65** in a low yield.



Scheme 11



R in 62	product	yield [%]	ee [%]
Ac	63	72	98
Me	64	90	ND
H	65	26	ND

Scheme 12

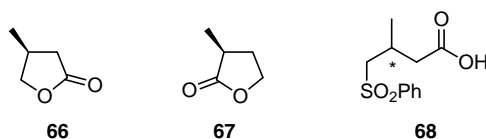
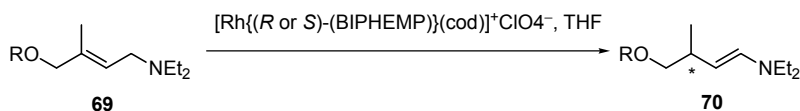


Fig. 4. Structures of 66, 67, and 68

Though these dimers and trimers showed optical rotatory values, their configuration and optical purity were not determined (Scheme 12) [27].

The present asymmetric isomerization was applied for the synthesis of the chiral isoprenoid synthons **66**, **67**, and **68** (Fig. 4) [44]. These bifunctional isoprenoids are useful building blocks for the syntheses of natural-type vitamins E and K as well as related biologically active compounds.

Prochiral allyl amines bearing an oxygen function at the γ -position, **69**, were isomerized to enantiopure enamines **70** by cationic rhodium complexes of BI-

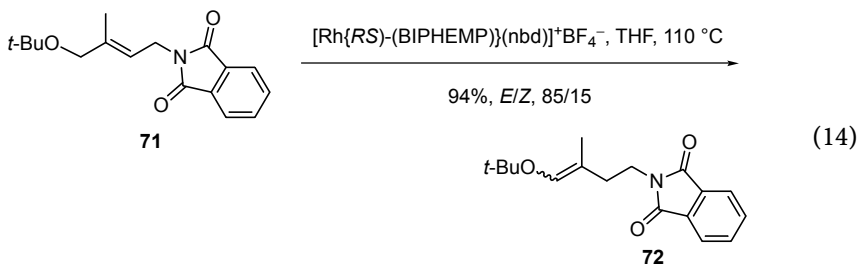


R	Conditions				Products		
	BIPHEMP	[S] [C] ⁻¹	Temp [°C]	Time [h]	Yield [%]	ee [%]	Confign
PhCH ₂ OCH ₂	(R)	200	75	64	73	99	(R)
PhCH ₂ OCH ₂	(S)	85	85	59	54	98.5	(S)
<i>t</i> -BuOCH ₂	(R)	180	110	24	60	94	(R)
<i>t</i> -BuOCH ₂	(S)	200	110	40	64	92.5	(S)
Me ₃ SiOCH ₂	(R)	50	80	48	50	96	(R)
MeOCH ₂ OCH ₂	(R)	65	80	48	19	96	(R)
CH ₂ =CHCH ₂ OCH ₂	(R)	100	75	87	30	70	(R)
(MeO) ₂ CH	(S)	100	90	40	34	90	(S)

Scheme 13

PHEMP. The isomerizations occurred regioselectively towards the allylic amino function to afford enamines (Scheme 13).

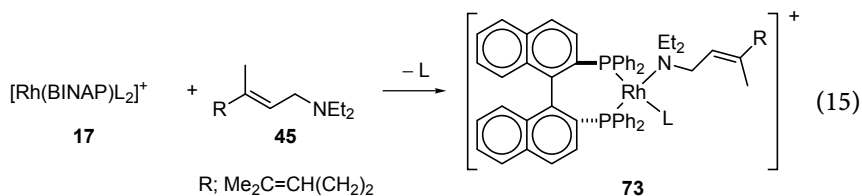
The presence of the second allylic functionality (alkoxy moiety) apparently did not interfere in the reaction pathway. However, when the diethylamino group was replaced by an imido (or an amido) function, i.e., **71**, a move in the direction of the O-function to give **72** occurred, Eq. (14).



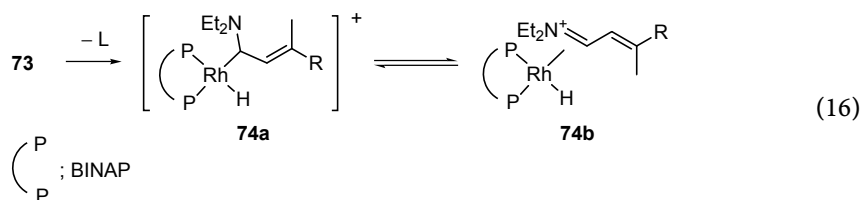
4.3.2

Mechanistic Studies

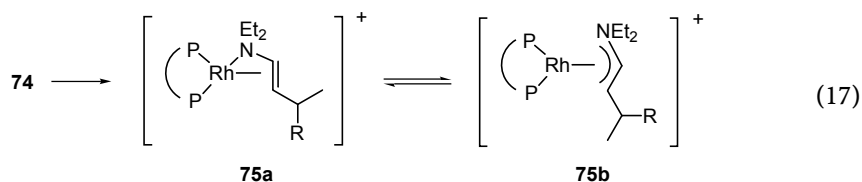
The mechanism of the Rh-BINAP complex-promoted isomerization of *N,N*-diethylgeranylamine is briefly summarized, which is a digested abstract of literature [2, 9, 27, 45, 46]. The reaction starts from the simple nitrogen-coordinated cationic rhodium complex **73** generated by ligand exchange between the complex **17** and the substrate **45** (L denotes solvent molecules, THF, MeOH, CH₂Cl₂, or BINAP), Eq. 15.



The square planar complex **73** undergoes β -elimination via liberation of L to form a transient equilibrium of the iminium-rhodium hydride σ -complex **74a** and the π -complex **74b**, Eq. 16. These complexes **74a** and **74b** represent a unique nitrogen-triggered mechanism that is different from either the hydride addition-elimination pathway or the π -allyl mechanism resulting in the intramolecular 1,3-hydrogen shift.



These complexes **74** are converted to the η^3 -enamine complex **75** by the transfer of the hydrogen atom from Rh to C3. The replacement of the coordinated enamine in **75** by a substrate molecule liberates enamine and complex **73**, thus completing the catalytic cycle.



By using a deuterium-labeled substrate, (*R*)-*N,N*-diethylgeranylamine-1-*d* **76** (Fig. 5) the migrating hydrogen atom was identified. When (*R*)-**76** was treated with **17** in THF at 40 °C, a clean intramolecular migration of the C1 proton took place to give the (*R,E*)-enamine. The enantiomeric purity was greater than 97%. No isotope effect on the selectivity was observed.

The 1,3-hydrogen transfer occurs in a suprafacial fashion with strict differentiation between the pro-(*S*) and pro-(*R*) hydrogens at C-1 of the allylic amines,

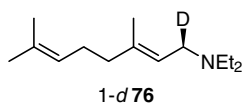
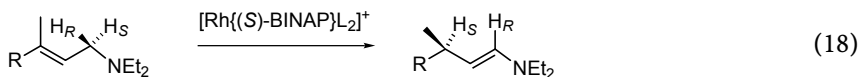


Fig. 5. Structure of **76**

Eq. (18). The Rh^+ -BINAP complexes differentiate efficiently between the enantiotopic C-1 hydrogen of the *N,N*-diethylgeranyl group through interaction with the adjacent nitrogen atoms. The overall 1,3-hydrogen shift occurs in a suprafacial manner from the *s-trans* type chiral conformer, leading to (*R,E*)- or (*S,E*)-citronellaldiethyleneamine.



This stereospecificity is caused by the structural features of the BINAP ligand; C2 chirality, full aromatic substitution, the flexible atropisomeric skeletal backbone, and phenyl rings attached to the phosphorous atoms that align the transition states.

5 Conclusions

Isomerization of olefins is a thermodynamically favored energy-saving reaction. Certainly, the reactions are performed simply by the interaction of substrates and catalysts, without using another reagent. Allyl oxygen or nitrogen functions can provide carbonyl products through intramolecular redox (reduction-oxidation) transformations. In general, asymmetric hydrogenation and isomerization are complements to each of the other. Frequently, one metal complex can catalyze both reactions effectively.

Future perspectives within the scope of this article are:

- (1) the application of modern homogeneous metal catalysts towards the methylene-azomethine rearrangement,
- (2) the design of efficient ligands matching with allyl oxygen function (oxygen-triggered reactions), and
- (3) the expansion of the scope of the isomerization to allylamines bearing alkoxy or siloxy groups at the γ -position.

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Chapter 24

Allylic Substitution Reactions

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Keywords: Allylic substitution, Allylation, Allylic alkylation, π -Allyl complexes, Palladium, Molybdenum, Tungsten, Iridium

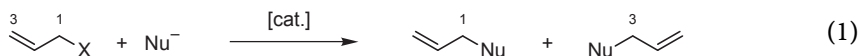
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1

Introduction

Transition metal-catalyzed allylic substitutions or, as these reactions are also called, ‘allylic alkylations’ or ‘allylations’, Eq. (1), are highly versatile reactions that have become part of the standard repertoire of modern organic synthesis [1, 2, 3, 4, 5, 6]. They often proceed under much milder conditions than ordinary S_N2 or S_N2' reactions and with different chemo-, regio- and stereoselectivities. Typical leaving groups are acetates or carbonates, rather than the more reactive halides or sulfonates, which may be a considerable advantage in the synthesis of complex multifunctional compounds. By changing the metal or the ligand, it is often possible to tune the reactivity or selectivity of the catalyst according to the specific requirements of a particular application. A variety of transition metal complexes derived from palladium, nickel, ruthenium, rhodium, iridium, molybdenum, tungsten, and other elements are known to catalyze allylic substitutions. The most widely used catalysts are palladium complexes and their structure and mode of action are well-understood. The properties and scope of other transition metal catalysts have not been explored in such depth, although, in certain cases they can offer distinct advantages over Pd complexes, e.g., by reversal of regioselectivity [7, 8, 9, 10, 11].



The first example of an enantioselective metal-catalyzed allylic substitution was reported by Trost and Strege [12] in 1977. Since their original findings that $\text{Pd}(\text{PPh}_3)_4$ in the presence of the chiral diphosphine diop can induce moderate ees, strong efforts have been made to develop practically useful enantioselective catalysts for this important class of reactions. It took many years to reach that goal, which is not surprising because the problem of enantiocontrol in allylic substitutions is more complex than in most other metal-catalyzed reactions, as will be shown in the following discussion. However, during the last few years, a number of efficient chiral catalysts have been found which considerably expand the scope of enantioselective C-C and C-heteroatom bond formation [13, 14, 15].

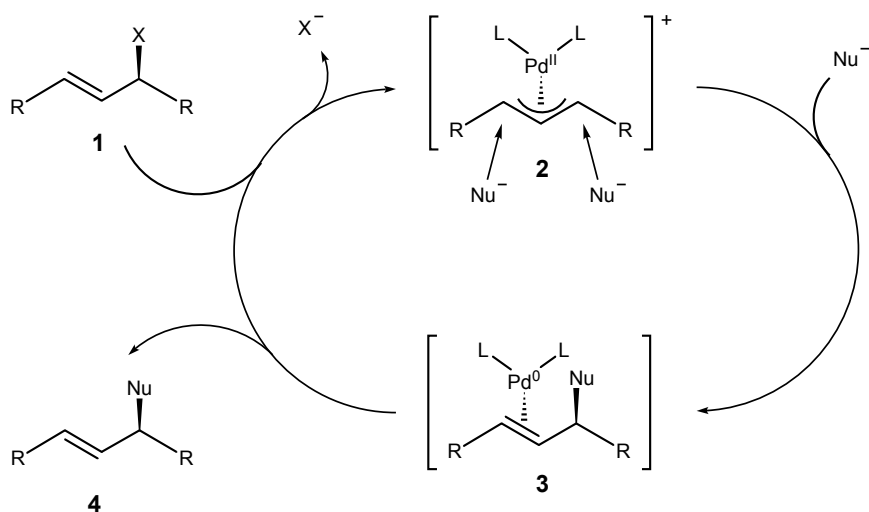
In addition, structural and mechanistic studies have considerably improved the understanding of how these catalysts work. Hence, a more rational approach to catalyst design has become possible which will certainly stimulate further progress in this field.

2 Mechanism

2.1 Catalytic Cycle

The most important class of allylic substitutions are palladium-catalyzed reactions with so-called 'soft' nucleophiles such as stabilized carbanions or amines, and with few exceptions, the enantioselective transformations discussed in this chapter belong to this category. The mechanism of these reactions has been firmly established and a detailed picture of the catalytic cycle can be drawn [1, 2, 3, 4, 5, 6, 13, 14, 15]. The course of allylic substitutions catalyzed by metals other than palladium is less clear and information about the intermediates involved is scarce.

The generally accepted mechanism of palladium-catalyzed allylic substitutions is shown in Scheme 1. An allylic substrate **1**, typically an acetate or a carbonate, reacts with the catalyst, which enters the catalytic cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes can be used as precatalysts, because Pd(II) is easily reduced *in situ* to the active Pd(0) form. Presumably, the reaction is initiated by formation of a π -complex which eliminates X^- to produce an $(\eta^3\text{-allyl})\text{palladium(II)}$ complex. The product of this oxidative addition can



Scheme 1

be a cationic complex **2**, as shown in Scheme 1, or a neutral complex if the resulting anion X^- coordinates with palladium. The equilibrium between the neutral and the cationic form depends on the nature of the ligands as well as on other factors such as the solvent and the anion. With catalysts containing a bidentate ligand, and most chiral ligands that have been used are bidentate, the cationic complex, which is more reactive toward nucleophiles, usually predominates. Besides coordination of additional ligands or ligand exchange reactions, allyl complexes **2** can isomerize in various ways (see Sect. 2.2) and this can have important consequences for the course of a reaction.

In the absence of nucleophiles, the intermediate allyl complexes are stable and can be isolated. This is an attractive, quite unique feature of palladium-catalyzed allylic substitutions, because in most catalytic processes it is difficult to isolate or even merely detect intermediates of the catalytic cycle. The vast amount of data on the structure and reactivity of (allyl)palladium complexes that is available, has led to valuable insights into the mechanism of allylic substitutions and the origin of enantioselection in reactions with chiral catalysts (see Sect. 7).

The electrophilic Pd(II) center activates the allyl system for nucleophilic attack at the allyl termini. Attack at the central carbon atom is rarely observed [16]. Addition of the nucleophile at C1 or C3 generates an unstable Pd(0)-olefin complex **3** which readily releases the final product **4** and undergoes oxidative addition to another substrate molecule. Although the occurrence of π -complexes has been generally accepted, only recently, has such an intermediate been detected and characterized by NMR spectroscopy [17].

Both the oxidative addition leading to **2** and subsequent nucleophilic attack normally occur stereoselectively with inversion of configuration at the reacting allylic carbon atom. Thus, if the intermediate allyl complex does not undergo any isomerization that changes its configuration, the overall process **1**→**4** proceeds with retention of configuration, i.e., the nucleophile is introduced at the same side of the allyl plane that was originally occupied by the leaving group X.

In contrast to 'soft' nucleophiles which attack the allyl face opposite the palladium complex, 'hard' nucleophiles (e.g., organozinc reagents) first coordinate to the metal center and then are transferred intramolecularly to the allyl ligand (see, e.g., Table 1 in [13]). Therefore, the reaction of allyl-palladium complexes with 'hard' nucleophiles usually involves retention of configuration. However, the classification as 'soft' and 'hard' nucleophiles is not always unambiguous. With acetate as the nucleophile, e.g., the stereoselectivity depends on the reaction conditions and both overall inversion as well as retention have been observed [18].

2.2

Structure and Reactivity of Allyl-Palladium Complexes

(η^3 -Allyl)Pd(II) complexes play a central role as key intermediates in the catalytic cycle of allylic substitutions. Therefore, knowledge of their structure and reactivity is crucial, especially for designing new catalysts or for selecting suitable

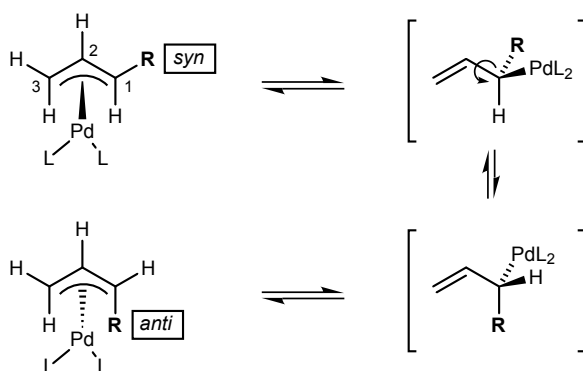
ble catalysts for new types of substrates. The chemistry of allyl complexes has been extensively studied and is well-understood. In addition, a wealth of structural information is available from crystal structures as well as from NMR spectroscopy [19]. As expected from the strong preference of Pd(II) for a square-planar coordination geometry, in most complexes the Pd(II) center is surrounded by the allyl system and two other ligands located in a plane defined by the two allyl termini and the metal center. Allyl complexes can show very complex dynamic behavior in solution which makes the analysis or prediction of the outcome of allylic substitutions often difficult. They can undergo fast structural changes by ligand association-dissociation processes or by π - σ - π isomerization, a process leading from a η^3 -complex via a generally unstable, short-lived η^1 -intermediate to a different η^3 -complex.

2.2.1

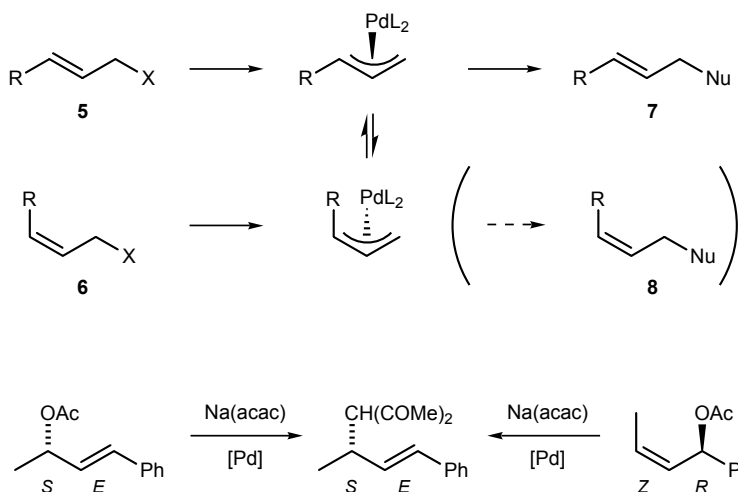
π - σ - π Isomerization

As shown in Scheme 2, π - σ - π isomerization can result in *syn-anti* interconversion by rotation around the σ -(C-C) bond in the η^1 -intermediate (*syn* and *anti* refer to the positions *syn* and *anti* to the substituent at C2). The *syn* position is sterically favored and, consequently, in 1-monosubstituted allyl systems the *syn*-isomer is more stable than the *anti*-isomer. In general, the thermodynamic equilibrium lies far on the side of the *syn*-isomer and only if a substituent is sufficiently small (e.g., R=Me) is the *anti*-isomer present in notable amounts. However, certain ligands, that exert strong steric hindrance in the coordination plane toward the *syn*-substituent, can strongly destabilize the *syn*-isomer and reverse the equilibrium in favor of the *anti*-isomer [20, 21].

If *syn-anti* isomerization of the intermediate allyl complexes is fast compared to nucleophilic attack, then both the *cis*- and the *trans*-isomers 5 and 6 (Scheme 3) afford the same ratio of *cis*- and *trans*-products with the more stable *trans*-isomer 7 predominating. The relative rates of *syn-anti* isomerization and nucle-



Scheme 2



Scheme 3

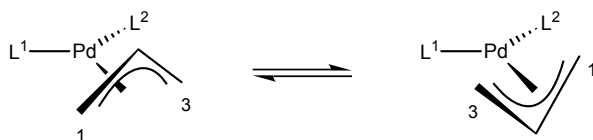
ophilic addition depend on the specific conditions such as the nature and concentration of the nucleophile, the type of catalyst, the solvent or coordinating additives. The stereochemical consequences of *syn-anti* isomerization are illustrated by the reaction of (*E*)-1-methyl-3-phenyl- and (*Z*)-1-phenyl-3-methyl-2-propenyl acetate with sodium acetylacetonate as nucleophile [22] (Scheme 3). In this case the *anti-syn*-allyl-palladium complex derived from the (*R*)-(*Z*)-isomer isomerizes to the more stable *syn-syn*-allyl complex. In this process the palladium atom shifts to the opposite face of the allyl system and, therefore, the (*S*)-(*E*)-product is formed as in the reaction of the (*S*)-(*E*)-acetate.

There are also other isomerization processes that can occur by a π - σ - π mechanism, e.g., racemization (or epimerization, if the Pd complex is derived from a chiral ligand, see Sect. 3.3) or a rearrangement of the allyl system which is often referred to as apparent allyl rotation.

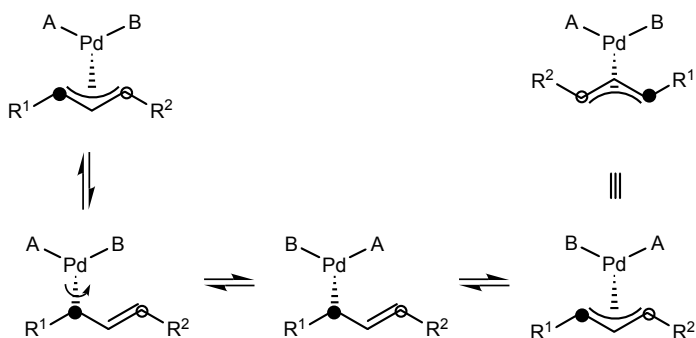
2.2.2

Apparent Allyl Rotation

In this process the two termini of the allyl system switch position with respect to the other two coordination sites (Scheme 4). At the same time, the central allyl C atom moves from one side of the coordination plane to the other. If the two ligands L^1 and L^2 are different and chiral as, e.g., in complexes with unsymmetrical chiral bidentate ligands, this isomerization leads to a diastereoisomeric complex even if the allyl system has structurally identical termini (see, e.g., Scheme 24). The two diastereoisomeric allyl complexes can undergo nucleophilic addition with different rates and different regioselectivities and, consequently, the relative rate of apparent allyl rotation can strongly influence the product distribu-



Scheme 4

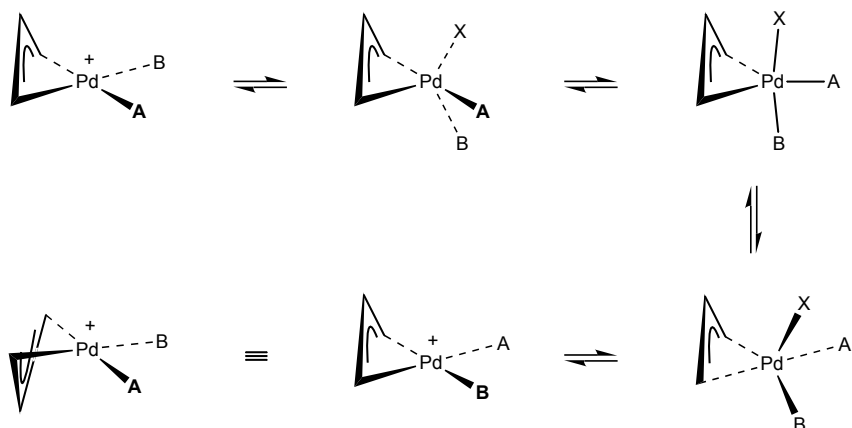


Scheme 5

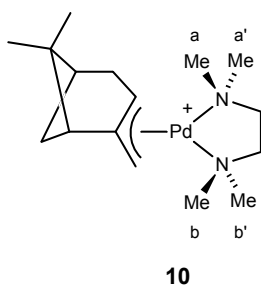
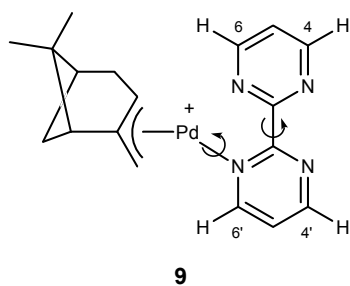
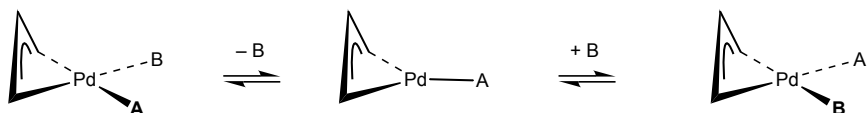
tion of allylic substitutions, including the enantiomer ratio in reactions with chiral catalysts. However, if L^1 and L^2 are identical as, e.g., in C_2 -symmetrical chiral bidentate ligands, allyl rotation generates two identical structures and, therefore, has no consequences.

As the name suggests, apparent allyl rotation probably does not involve a simple rotation around the Pd-allyl axis. Such a process seems energetically unfavorable because it would require simultaneous breaking of two Pd-C bonds or a severe geometrical distortion of the preferred planar coordination geometry. Several mechanisms of apparent allyl rotation have been proposed [19, 23, 24]. One of them involves π - σ - π isomerization with concomitant rotation around the Pd-C bond in the η^1 -intermediate as shown in Scheme 5.

Catalytic amounts of anions such as chloride or fluoride [23, 25] or polar solvents like DMSO and acetonitrile [26] that can coordinate to palladium have been found to accelerate apparent allyl rotation. Stabilization of the η^1 -intermediates by coordination of an external ligand could account for these observations. The anion effect has also been explained by the pseudorotation mechanism shown in Scheme 6 [23]. Addition of an external ligand to a pseudo-square-planar allyl-Pd(II) complex (the allyl system is considered as a bidentate ligand coordinating with its two terminal C atoms) leads to a 'pentacoordinated' complex, that undergoes geometrical changes in which the two ligands A and B can switch positions. In contrast to the π - σ - π mechanism, the η^3 -allyl-palladium bond remains intact during the whole process.



Scheme 6



Scheme 7

A third pathway has been proposed involving dissociation of one of the ligands A or B to form a tricoordinated intermediate (Scheme 7) [24, 27]. Readdition of this ligand can occur from two sides leading either back to the starting complex or to the isomer corresponding to the product of formal allyl rotation. Support of this mechanism comes from NMR studies of allyl complexes with chelating bidentate nitrogen ligands. Breaking of one of the Pd-N bonds has been demonstrated in complexes with 2,2'-bipyrimidine (**9**) or TMEDA (**10**) [24]. $^1\text{H-NMR}$ exchange spectroscopy of complex **9** revealed that in addition to an ex-

change of the two proton sets corresponding to the two pyrimidine rings, an exchange between H4 and H6 in one ring and H4' and H6' in the other ring takes place. This implies that rotation around the central bond in the bipyrimidine ligand must occur which is only possible if one of the pyrimidine rings dissociates from palladium. The TMEDA complex (10) showed an analogous dynamic behavior with all four methyl groups switching between positions a, a', b, and b'.

2.2.3

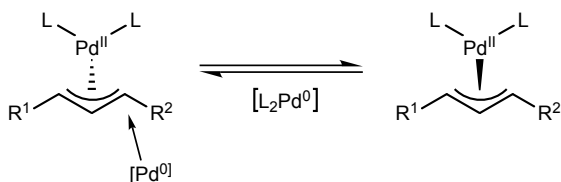
Palladium(0)-Catalyzed Allyl Exchange

A different type of isomerization is shown in Scheme 8. Similar to the nucleophilic addition step in allylic substitutions, the electrophilic allyl system bound to Pd(II) can react with a Pd(0) complex. The Pd(0) complex adds to the free π -face of the allyl ligand and displaces the Pd(II) complex on the backside. Therefore, this process results in an inversion of configuration at all three allyl carbon atoms in contrast to apparent allyl rotation which does not change the configuration of the allyl ligand. As both allyl-Pd(II) and Pd(0) complexes are generated in the catalytic cycle, allyl exchange can occur during catalytic allylic substitutions [28, 29, 30]. However, because the concentration of palladium species in catalytic reactions is much lower than that of the substrate and the nucleophile, isomerization by allyl exchange is usually slow compared to product formation or does not take place at all.

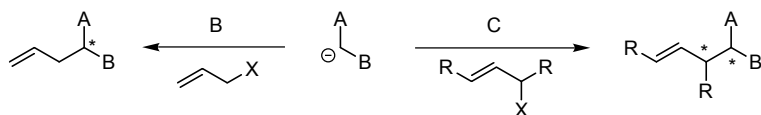
3

Substrates

Using a chiral catalyst, an achiral or racemic substrate can be converted to an optically active product by allylic substitution. In this process a new stereogenic center may be created in the allyl fragment (A), in the moiety derived from the nucleophile (B) or in both parts (C) (see Scheme 9). Most reactions described in



Scheme 8



Scheme 9

this chapter belong to type A. Examples of categories B and C are rare but recently very promising results have been obtained for some transformations of this type (see Sect. 9.6).

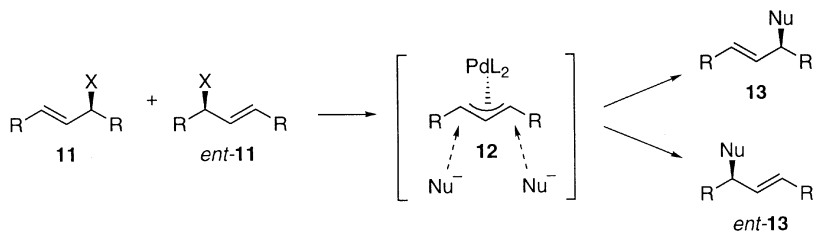
A wide variety of structurally very different substrates has been used for enantioselective allylic substitutions of type A. These substrates can be divided into the following classes according to their substitution pattern and the nature of the corresponding allyl-metal complexes [14] (for a classification scheme based on the nature of the enantioselection process, see [15]).

3.1

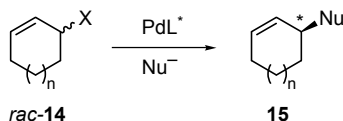
Substrates with Identical Substituents at C1 and C3 (RCH=CH-CHXR)

Allyl derivatives **11** with identical substituents at C1 and C3 are an important class of substrates for enantioselective allylic substitution (Scheme 10). Starting from either enantiomer (**11** or *ent*-**11**) the same allyl-palladium complex **12** is formed. Therefore, the first part of the catalytic cycle leading to this intermediate usually is irrelevant for the stereoselectivity of the overall reaction [31]. The two termini of the free allyl system are enantiotopic. If the catalyst is chiral, they become diastereotopic in the allyl-metal complex and, therefore, may exhibit different reactivities toward nucleophiles. Under the influence of a suitable chiral ligand attached to palladium, nucleophilic attack can be rendered regioselective leading preferentially either to product **13** or its enantiomer *ent*-**13**.

In this way racemic starting materials **11** or the synthetically important cycloalkenyl derivatives **14** (Scheme 11) can be converted to enantiomerically enriched products. The most widely studied derivative is 1,3-diphenyl-2-propenyl acetate **11** (R=Ph, X=OAc) which has become the standard test substrate for evaluating enantioselective catalysts (see Sect. 9.1).



Scheme 10

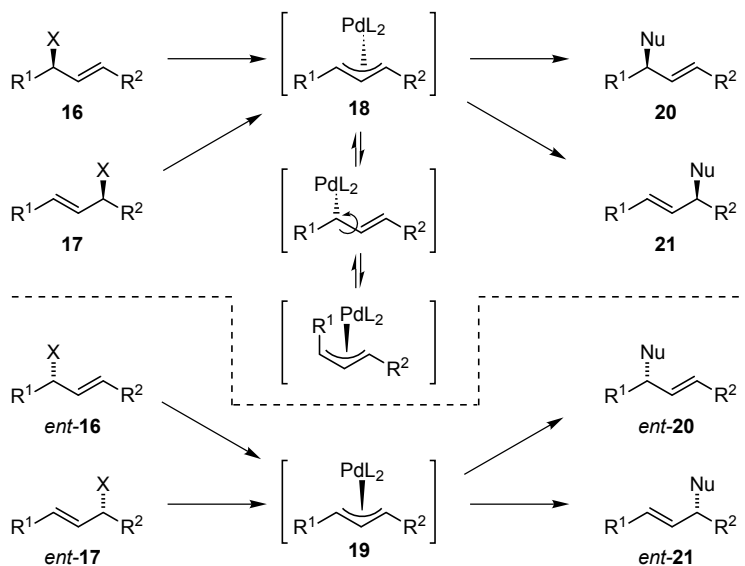


Scheme 11

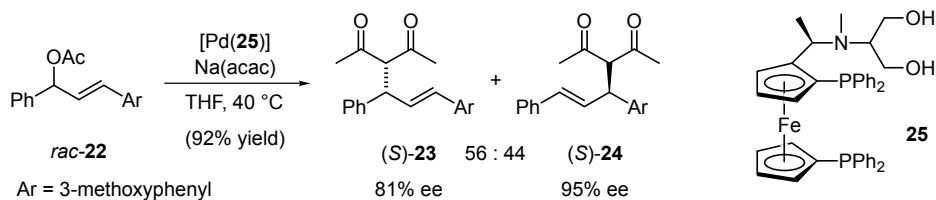
3.2

Substrates with Different Substituents at C1 and C3 ($R^1CH=CH-CHR^2X$)

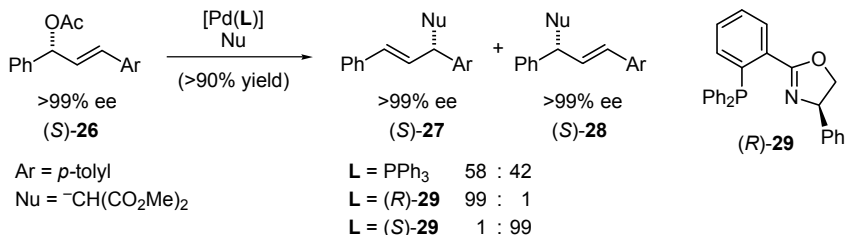
The reaction scheme for substrates **16** bearing different substituents at the two allylic termini is more complex (Scheme 12). In this case **16** and the enantiomer *ent*-**16** are converted to different allyl complexes **18** and **19** with opposite absolute configuration at the allyl C-atoms. Nucleophilic addition to **18** with 'soft' nucleophiles leads to the regioisomers **20** and **21** whereas **19** affords the corresponding enantiomeric products *ent*-**20** and *ent*-**21**. The two allyl complexes **18** and **19** cannot interconvert by a π - σ - π process which solely results in *syn-anti* isomerization. Isomerization of **18** to **19** would be possible by Pd(0)-catalyzed allyl transfer (see Sect. 2.2.3) or a mechanism proposed for allylic acetates involving metal-centered addition of acetate to the allyl system with retention [32]. However, if **18** and **19** do not interconvert, it is not possible to transform a racemic mixture of **16**/*ent*-**16** (or **17**/*ent*-**17**) selectively to one of the product enantiomers (e.g., **20**) as described for substrate **11** (Scheme 10). In this case, the configuration of the products is determined by the configuration of the substrate because the overall process proceeds with retention. A chiral catalyst can only influence the regioselectivity of nucleophilic attack, as shown in Scheme 10 for the allyl complex **12**, but not the stereoselectivity of the reaction. In the ideal case, when the regioselectivity is completely controlled by the chiral catalyst while the influence of the substituents R^1 and R^2 is negligible, a racemic substrate is converted to a 1:1 mixture of enantiopure regioisomers (**20** and *ent*-**21** or **21** and *ent*-**20**).



Scheme 12



Scheme 13



Scheme 14

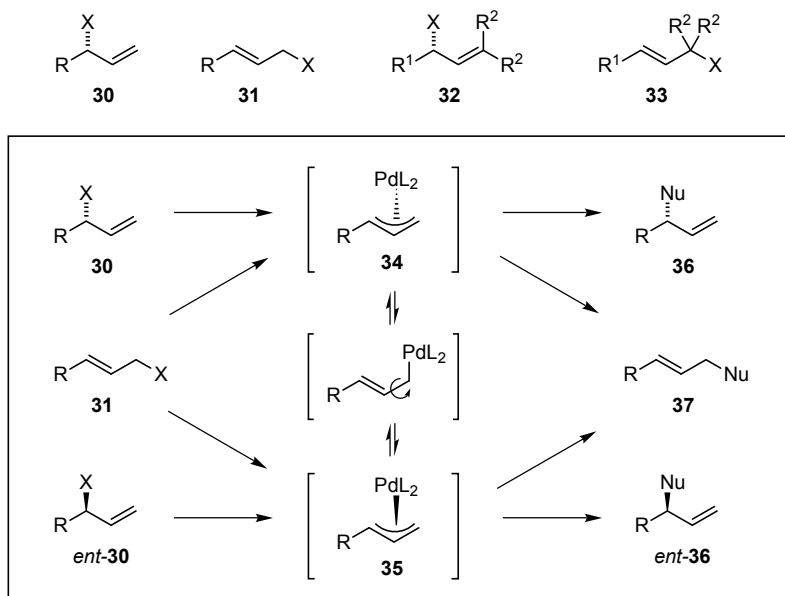
This is illustrated by the reaction shown in Scheme 13. The two regioisomers **23** and **24** are formed in similar quantities with moderate to high enantiomeric excess [33]. Kinetic resolution of racemic substrates of this type has also been described [34].

If an enantiopure substrate is chosen, then the chiral catalyst can be used to control the regioselectivity of the reaction (Scheme 14). Depending on the configuration of the chiral ligand either one of the regioisomers, **27** or **28**, can be obtained with very high selectivity [35]. There is no loss of enantiomeric purity, implying that racemization of the starting material or inversion of configuration at the allylic carbon atoms in the intermediate allyl-palladium complex does not occur. The use of chiral catalysts in combination with optically active substrates is a useful new concept for solving the difficult problem of regiocontrol in allylic substitutions (see also Sect. 9.2).

3.3

Substrates with Identical Geminal Substituents at C1 or C3 ($\text{R}^1\text{HC}=\text{CH-C}(\text{R}^2)_2\text{X}$ or $(\text{R}^1)_2\text{C}=\text{CH-CHR}^2\text{X}$)

In allyl systems such as **30–33** (Scheme 15) bearing two identical geminal substituents at one of the termini, π - σ - π isomerization can result in racemization of the allyl-palladium intermediate (or epimerization if the Pd catalyst is chiral). The relative rates of π - σ - π isomerization and nucleophilic attack at the allyl system are of crucial importance for the stereochemical course of allylic substitutions with this type of substrates. If π - σ - π isomerization is fast compared to nu-



Scheme 15

cleophilic attack, all three substrates **30**, its enantiomer *ent-30*, and **31** give the same equilibrium mixture of allyl intermediates and, therefore, the same product distribution. In this case, nucleophilic attack is the turnover-limiting and selectivity-determining step. If a chiral palladium catalyst is used which discriminates between the two pathways leading from intermediates **34** and **35** to the enantiomeric products **36** and *ent-36*, respectively, then a racemic mixture **30**/*ent-30* or the achiral isomer **31** can be converted to an optically active substitution product. The kinetic scheme can be further complicated by *syn-anti* isomerization of the allyl complexes but this is not discussed here.

If the interconversion of the π -allyl intermediates **34** and **35** is much slower than nucleophilic attack, the product distribution depends on the nature of the substrate. In this case the two enantiomeric chiral substrates **30** and *ent-30* are converted to the corresponding product enantiomers **36** and *ent-36* with overall retention of configuration. Starting from a racemic mixture of **36** and *ent-36*, the two product enantiomers **36** and *ent-36* are formed in a 1:1 ratio and, therefore, a chiral catalyst cannot induce enantioselectivity (except for kinetic resolution). However, the analogous reaction of the linear, achiral substrate **31** can be rendered enantioselective if a chiral catalyst is used that adds preferentially to one of the enantiotopic faces of **31** to give either complex **34** or **35**. In this case, the enantioselectivity is determined in the oxidative addition of the substrate to the catalyst while nucleophilic addition to the π -allyl intermediate is irrelevant for the enantiomeric excess of the overall reaction. The relative rates of π - σ - π isomerization and the other processes shown in Scheme 15 strongly depend on

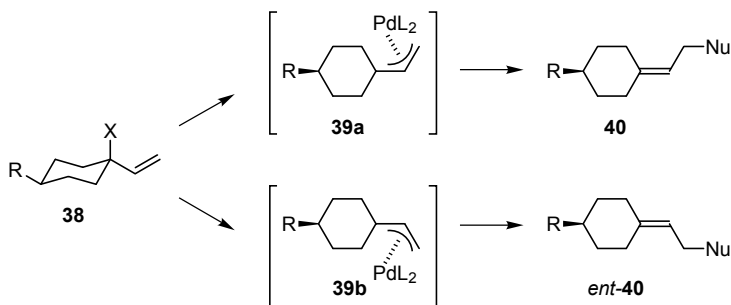
the reaction conditions and, therefore, proper choice of the reaction parameters can be crucial for achieving satisfactory enantioselectivity.

In addition to enantiocontrol, the problem of regiocontrol arises in these reactions. There are various factors that influence the regioselectivity of allylic substitutions [3, 4, 13, 36, 37, 38, 39]. Electronic effects exerted by the catalyst and the allylic substituents, steric interactions between the nucleophile, the allyl system and the catalyst, and the relative stabilities of the π -olefin complexes formed after nucleophilic addition, can all play a role. The relative importance of these factors varies with the catalyst, the substrate, the nucleophile, the solvent and other reaction parameters and is difficult to predict.

With substrates of type **32** and **33** (e.g., R^2 =phenyl) the chiral products are usually formed with high preference over the achiral isomers, whereas in analogous reactions of monosubstituted allyl derivatives **30** or **31** the achiral linear isomer **37** is the major product with most palladium catalysts (exceptions are crotyl derivatives; R =Me). The use of less electron-donating ligands, which render the palladium center more electrophilic, has been shown to change the product ratio in favor of the chiral product **36** [3, 4, 37, 39]. This may be rationalized by an increase of the cationic character of the allyl system making nucleophilic attack at the substituted terminus more favorable, similar to the trend observed, e.g., in nucleophilic epoxide openings. A reversal of regioselectivity has also been observed with molybdenum [8], tungsten [7], iridium [9], rhodium [10], and ruthenium [11] complexes.

Although enantiocontrol combined with regiocontrol in favor of the chiral product **36** is still a problem, recent progress in this area is encouraging. It has been shown that the regioselectivity in palladium-catalyzed reactions of arylpropenyl acetates **30** and **31** (R =aryl) can be reversed using special chiral ligands (Sects. 6 and 9.3). In addition, chiral molybdenum [40], tungsten [41], and iridium catalysts [42] have been found that favor nucleophilic attack at the substituted terminus of 1-arylallyl systems (see Sects. 6 and 9.3).

A related but rather special type of substrate is shown in Scheme 16. Achiral cycloalkyl derivatives such as **38** can be converted to alkylidene-cycloalkanes **40** possessing axial chirality. The reaction of various derivatives **38** ($R=t$ -Bu) and



Scheme 16

the corresponding *trans*-isomers with different leaving groups X was studied in detail, using a chiral BINAP-Pd catalyst [43] (see Sect. 9.3). The enantioselectivity was found to be induced in the ionization step by enantioface selection. No interconversion of the intermediates **39a** and **39b** was observed in this case. Isomerization to the corresponding allyl complexes with the Pd atom *cis* relative to the R group is likely to take place but, as long as equilibration between **39a** and **39b** is slow relative to nucleophilic addition, has no stereochemical consequences.

3.4

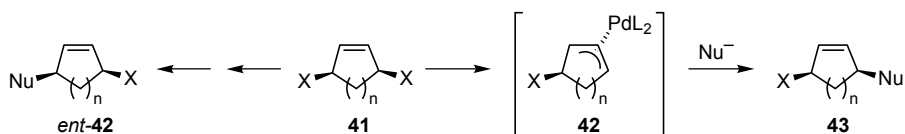
meso-Substrates with Two Enantiotopic Leaving Groups

Substrates derived from *meso*-cycloalkenediols such as **41** are a highly versatile starting materials for enantioselective allylic substitutions [15]. Regioselective displacement of one of the enantiotopic leaving groups by the chiral catalyst leads to a chiral allyl intermediate **42** which is attacked regioselectively at the sterically less hindered position to afford product **43** (Scheme 17). Products of this type can be converted to variety of useful compounds by a second allylic substitution reaction.

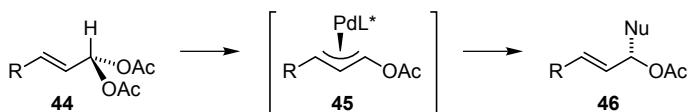
3.5

Substrates with two Geminal Enantiotopic Leaving Groups

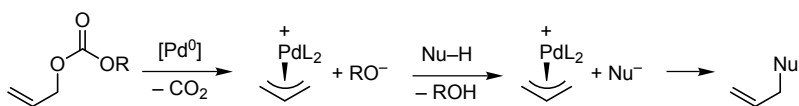
The only examples of this class of substrates, that have been studied, are geminal dicarboxylates **44** which are readily prepared from aldehydes [44, 45]. Enantioselective displacement of one of the enantiotopic carboxylate groups by the chiral catalyst leads to the chiral allyl complex **45** (Scheme 18). This intermediate which is of the same type as **18** (Scheme 12) has been shown to undergo regioselective nucleophilic addition at the acetoxy-bearing terminus with inversion of configuration (see Sect. 9.5).



Scheme 17



Scheme 18



Scheme 19

4 Leaving Groups

It is an attractive feature of transition metal-catalyzed allylic substitutions that rather unreactive leaving groups can be used which are usually inert toward nucleophiles in the absence of a catalyst [3]. The reactivity of the leaving group can have a significant effect on the enantiomeric excess, especially if enantioselection occurs in the oxidative addition step (see, e.g., [43]). The most common substrates are allylic acetates and carbonates. Carbonates have the advantage that an alkoxide is liberated in the ionization step that can serve as a base for generating the nucleophile Nu^- from the precursor $Nu-H$ (Scheme 19) [46, 47]. Therefore, it is not necessary to add stoichiometric quantities of a base. This allows the base concentration to be kept at low levels which may be important if base-sensitive compounds are involved. In addition, the reaction mixture remains homogeneous even with anionic nucleophiles that are only sparingly soluble. Other examples that belong to this category are vinyl epoxides [47, 48, 49] and carbamates [46, 47]. High base concentration can also be avoided by replacing the external base by *N,O*-bis(trimethylsilyl)acetamide (BSA, see Sect. 8).

Allylic halides are often too reactive to be useful because the uncatalyzed (non-enantioselective) substitution may compete with the catalytic process. However, there are examples of enantioselective reactions with chlorides and due to their high reactivity, remarkable turnover numbers have been achieved [50]. Reactive carboxylic esters such as trifluoroacetates can cause problems because they can also react by acylating the nucleophile. In cases where more reactive leaving groups rather than acetates or carbonates are needed, phosphates may be a good choice [41].

5 Nucleophiles

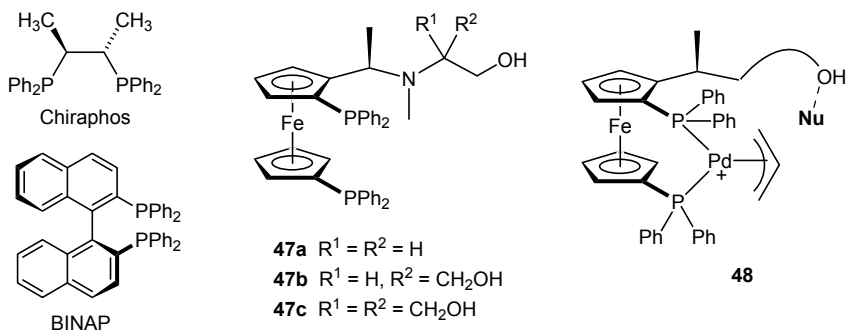
A wide range of carbon and heteroatom nucleophiles have been employed in transition-metal catalyzed allylic substitutions [3]. The *C*-nucleophiles most frequently used in enantioselective Pd-catalyzed allylations are stabilized carbanions described by the general formula $RXYC^-$ with X and Y being π -acceptors. Besides the anion of dimethyl malonate, which has become the standard nucleophile for testing new catalysts, many other stabilized carbanions bearing carbonyl, sulfone, nitrile, or nitro groups have been used [15]. Nitroalkanes, including nitromethane, also belong to this category of so-called 'soft' nucleophiles

with a pK_a below 20 [51, 52]. As mentioned before, the terms ‘soft’ and ‘hard’ are not well defined. The main purpose of this rather empirical classification is to distinguish between nucleophiles that react with inversion of configuration at the allyl system, and others that react with retention (cf. Sect. 2.2). There are only a few examples of enantioselective reactions with ‘hard’ C-nucleophiles such as organozinc or Grignard reagents [15]. Clearly, this area deserves more attention in future research. In view of the great importance of optically active amines in nature and as pharmaceuticals, enantioselective allylation of nitrogen nucleophiles is of considerable interest. The range of N-nucleophiles that have been used includes simple primary amines such as benzylamine, phthalimide, sulfonamides, benzoylhydrazine, $\text{NaN}(\text{Boc})_2$, and azides [15, 53, 54]. Enantioselective reactions of O-nucleophiles (carboxylates [55] and phenols [56]) and S-nucleophiles (*p*-TolSO₂Na [57]) have also been described. The Pd-catalyzed reduction of allylic esters with formate can be regarded as an allylic substitution with hydride as the nucleophile and an enantioselective version using chiral monodentate phosphine ligands has been recently reported [58].

6 Catalysts and Ligands

Initially, chiral bidentate phosphines, which proved to be so efficient in enantioselective hydrogenations, were used as ligands. Although high *ees* could be obtained in certain cases (e.g., with chiraphos and BINAP, Scheme 20), the scope of standard diphosphines in allylic substitutions with ‘soft’ nucleophiles seems limited (cf. [14, 15] and Sect. 9). One reason why these ligands are not as effective as in other areas of asymmetric catalysis has been attributed to the fact that the crucial bond-forming process, the nucleophilic addition to the allyl system, is taking place outside the coordination sphere and, therefore, cannot be directly controlled by the chiral ligand.

As a possible solution to this problem, the bifunctional ligand system 47 (Scheme 20) was developed by Hayashi et al. [14, 59, 60]. The side chain was pos-

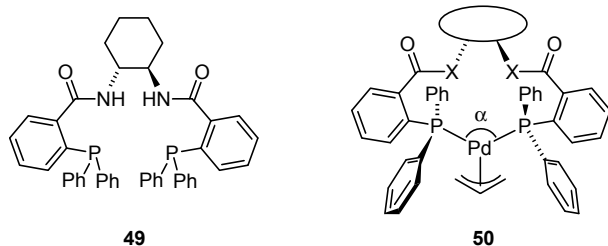


Scheme 20

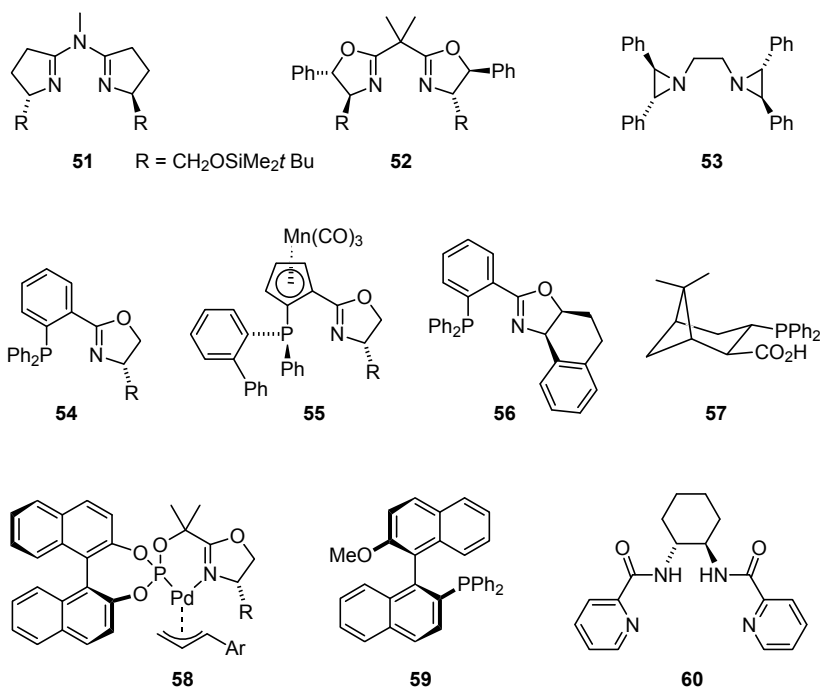
tulated to reach over the allyl system and interact with the nucleophile by hydrogen bonding and, in this way, direct the approach to one of the allylic termini (cf. formula 48). The experimental results supported this assumption. The functionality and the length of the side chain were found to be crucial. Ligands with longer or shorter hydroxyalkyl chains and derivatives lacking the hydroxy group were ineffective. This concept of incorporating an additional binding site for the nucleophile was very successful and good enantioselectivities were obtained in a number of reactions of acyclic allyl esters with C- and N-nucleophiles (see Sect. 9.1). For the first time, respectable ees could be achieved with these ligands in the alkylation of prochiral 1,3-dicarbonyl compounds such as 2-acetoxycyclohexanone with allyl acetate (81% ee with 47a) [14, 61].

However, a secondary interaction between the catalyst and the nucleophile is not a prerequisite for high enantioselectivity, as demonstrated by the diphosphine ligand 49 (Scheme 21) developed by Trost [15, 62]. Trost's concept was to increase the bite angle and, as a consequence, create a chiral cavity in which the allyl system is embedded (see formula 50, Scheme 21). In this case *trans*-1,2-diaminocyclohexanone is used as a chiral scaffold to induce a specific chiral arrangement of the four P-phenyl groups. In addition, a number of related ligands has been reported which are derived from other chiral diols, diamines, or dicarboxylates. In one case, the structure of an allyl-Pd complex was elucidated by X-ray analysis and, indeed, the bite angle α was measured to be 111° rather than the usual 90° [62]. These diphosphines derived from 2-(diphenylphosphino)benzoic acid (DPPBA) are the most versatile ligands for Pd-catalyzed allylic alkylation available today, giving excellent enantioselectivities for many classes of substrates including cycloalkenyl esters, geminal diacetates, and *meso*-substrates with two enantiotopic leaving groups. DPPBA-based ligands have also been used to control the stereoselectivity in reactions of prochiral nucleophiles. Interestingly, 1,3-dimethylallyl acetate and related di(*n*-alkyl) derivatives also react with good enantioselectivity, whereas the sterically more demanding 1,3-diaryl and dicyclohexyl analogues give poor ees [63], in contrast to the general trend observed with other ligands (for a possible explanation, see Sect. 7).

There are other classes of ligands (Scheme 22) which do not form a chiral cavity like 49 and also lack a functionalized side chain like 47 but still can induce



Scheme 21



Scheme 22

high enantioselectivity. For a number of C_2 -symmetric bidentate nitrogen ligands, e.g., very high ees have been recorded in the reaction of dimethyl malonate with 1,3-diphenylallyl acetate (see Sect. 9.1). The origin of the enantioselection in this case has been revealed by X-ray structural data (see Sect. 7). Based on the encouraging results with azasemicorrins and bisoxazolines such as **51** (95% ee) and **52** (97% ee) [64, 65], many other types of nitrogen ligands have been tested including the diaziridine **53** (>99% ee) [66]. Despite these impressive selectivities, the scope of N,N -ligands is limited. 1,3-Diarylallyl esters give the best results whereas less reactive substrates react more sluggishly and with low enantioselectivity. Nucleophiles such as amines or acetylacetonate, that coordinate more strongly to Pd than the anion of dimethyl malonate, cannot be used because they can displace the chiral ligand with obvious detrimental consequences.

The search for more reactive and more stable catalysts that overcome these limitations has led to chiral phosphino-oxazoline (PHOX) ligands such as **54** [67, 68, 69, 70, 71, 72]. Several short and efficient syntheses have been developed, making these ligands readily accessible from commercially available precursors. Compared to C_2 -symmetric ligands, the phosphino-oxazolines provide an additional means of controlling the selectivity based on electronic effects. In contrast to allyl complexes with C_2 -symmetric ligands, complexation of the metal by P, N -

ligands should result in electronic discrimination of the two allylic termini due to the different *trans* influences of phosphorus and nitrogen (see Sect. 7). Phosphinooxazolines can induce high enantioselectivities with acyclic substrates such as 1,3-diarylallyl and 1,3-diisopropyl acetate [67] or 3,3-diphenyl-2-propenyl acetate [73, 74]. Their application range seems to be complementary to the diphosphines of type 50, since they give poor results with cycloalkenyl acetates and only moderate ees with 1,3-bis(*n*-alkyl)allyl systems.

Based on mechanistic and structural knowledge, Helmchen has optimized the phosphinooxazoline structure for allylic alkylations with cycloalkenyl esters [71]. With ligand 55 enantioselectivities between 93 and >99% ee could be induced in the reaction of dimethyl malonate with cyclopentenyl, cyclohexenyl, and cycloheptenyl acetate. Similarly high ees were obtained with the six- and seven-membered ring substrates using the phosphino-carboxylate ligand 57 [75]. Helmchen also optimized the ligand structure for 1,3-dimethylallyl acetate as substrate and reported >85% ee in the reaction with dimethyl sodiomalonate using the phosphinooxazoline 56 [76]. These results illustrate one advantage of P,N-ligands of this type. Their modular construction allows extensive and independent variation of the phosphine part, the back-bone, and the oxazoline ring and makes it possible to optimize the ligand structure for a particular reaction.

Recently, special ligands and catalysts have been developed for allylic substitutions with 1- or 3-monosubstituted allyl substrates 30 and 31 such as 1- or 3-phenylallyl acetate (cf. Scheme 15). Normally, Pd-catalysts afford mainly the achiral linear product with this type of substrate. However, ligand 58 induces the opposite regioselectivity and the chiral branched regioisomer is obtained with good enantioselectivity [77, 78] (see Sect. 9.3). Two factors are thought to be responsible for this unusual regioselectivity. The phosphite group is less electron-donating than a phosphine group resulting in a more electrophilic Pd center. Therefore, the cationic character of the transition state should be enhanced, facilitating nucleophilic attack at the substituted allyl terminus. The sterically demanding binaphthyl system forces the substituted end of the allyl ligand to the less hindered position *trans* to the phosphite group (cf. the X-ray structure in [78]). In this geometry, nucleophilic addition at the substituted terminus is favored for electronic reasons, because it involves attack *trans* to the Pd-P bond [17, 79, 80].

Similar regio- and enantioselectivities were obtained with the monodentate phosphine 59 [81]. In contrast to phosphinooxazoline-palladium complexes which afford mainly the linear product, analogous W and Ir catalysts favor formation of the branched isomer with high ee and good to excellent regioselectivity in the reaction of dimethyl malonate with 3-arylallyl esters [41, 42]. A powerful catalyst for this class of substrate, a Mo complex derived from the dipyridine ligand 60, was recently reported by Trost [40]. With various 1- and 3-arylallyl esters regio- and enantioselectivities of up to 99:1 and 99% ee have been observed. For allylic substitutions with organozinc and Grignard reagents, chiral nickel complexes proved to be efficient catalysts and in some cases, good ees could be obtained [13, 14, 15].

7 Mechanistic Models for Enantioselection

As discussed in Sect. 3, the mechanism of Pd-catalyzed allylic substitutions is often highly complex, involving numerous intermediates and competing reaction pathways. Enantioselection can occur early in the catalytic cycle, e.g., by enantioface discrimination in the substrate, or later in the nucleophilic addition step. There are reactions where the enantioselectivity-determining step changes when the substrate structure or the reaction conditions are altered. Therefore, the origin of enantioselectivity may vary from one case to another and no general mechanism of enantioselection can be proposed.

The simplest enantioselective process is the reaction of a racemic substrate with two identical substituents at the allylic termini (Scheme 10). Here, the enantioselectivity originates from regioselective nucleophilic attack at the two enantiotopic termini of the allyl system. If a C_2 -symmetric ligand is used, only one allyl-Pd intermediate has to be considered (if we disregard *syn-anti* isomerism) and an analysis of the possible regioselectivity-determining factors becomes relatively straightforward.

X-ray and NMR structural studies of allyl-Pd complexes with bisoxazoline ligands led to important clues on the origin of enantioselection [35, 64, 70]. Crystal structures of (bisoxazoline)Pd(II)(1,3-diphenylallyl) complexes revealed that one of the Pd-C bonds is significantly lengthened as a consequence of the repulsive interaction between the bisoxazoline ligand and one of the allylic phenyl groups (see Fig. 1). From the absolute configuration of the product it can be concluded that the nucleophile preferentially attacks the longer, more strained Pd-C bond, suggesting that the release of strain associated with the cleavage of this bond may be one of the factors responsible for enantioselection. During the reaction with the nucleophile leading to a Pd(0)-olefin complex, the allyl system has to rotate out of the coordination plane (cf. Scheme 23). Rotation in the direction indicated in A (Scheme 23) is more favorable than rotation in the opposite

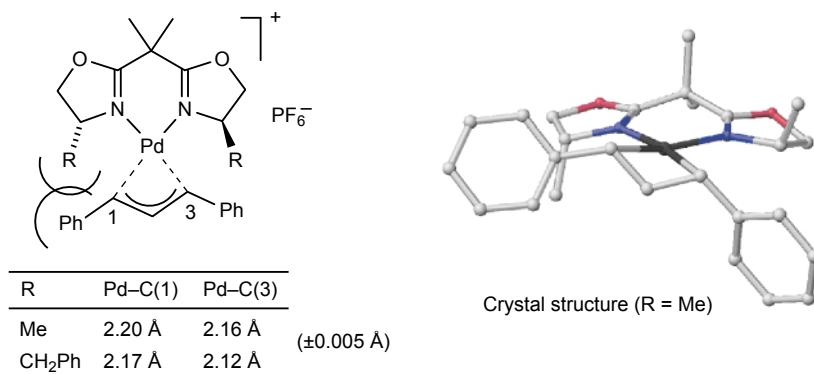
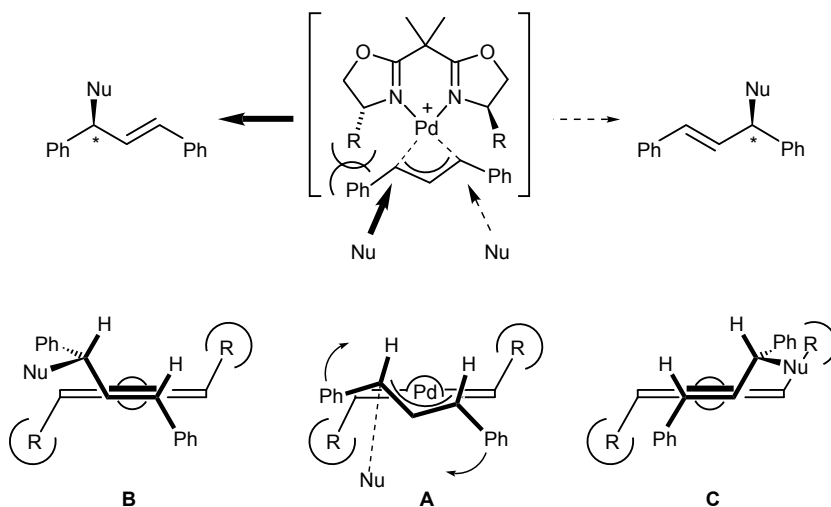


Fig. 1

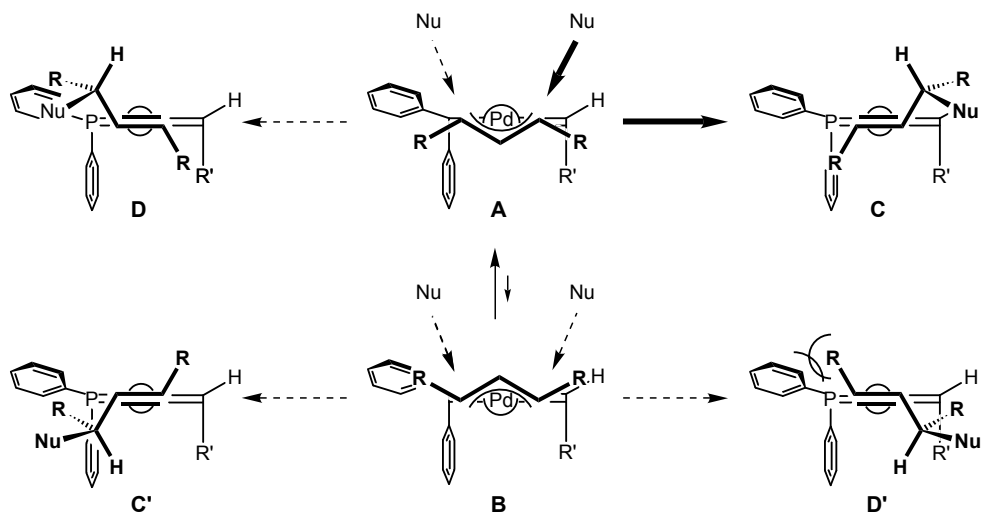


Scheme 23

direction, which would be induced by nucleophilic attack at the other terminus and would increase the repulsive steric interaction between the allyl system and the bisoxazoline ligand. A rotation of ca. 15° in this direction has actually been observed in the crystal structure of a bisoxazoline-Pd complex (Fig. 1) [70]. Thus, there are two likely factors responsible for regiocontrol: strain-induced selective activation of one of the allylic termini and sterically controlled rotation of the allyl ligand during nucleophilic attack. This mechanistic model is also consistent with results obtained with other types of C_2 -symmetric N,N- and P,P-ligands [66, 82, 83].

In the literature, it has been discussed whether allylic substitutions of this type proceed via an early or late transition state [26, 29, 71]. As illustrated in Scheme 23, during the transformation of an allyl-Pd complex to an olefin π -complex of type B or C the allyl fragment has to undergo a rotation of only 30° (starting from a planar coordination geometry) and, therefore, the transition state (cf. formula A) structurally resembles the starting allyl complex as well as the product complex. Thus, valid conclusions on the transition state should be possible from both the corresponding allyl and olefin complexes and the distinction between early and late transition states does not seem to be so important in this case.

A mechanistic rationalization of the enantioselectivity observed with non-symmetric ligands such as the phosphinooxazolines **54** is more difficult. In this case, two isomeric allyl-Pd intermediates are formed (Scheme 24, structures A and B) and this obviously complicates the analysis. However, from the results of extensive NMR studies [17, 84] and X-ray analyses [71, 85] a plausible mechanistic model can be derived. A typical crystal structure of a phosphinooxazoline-Pd-allyl complex is shown in Fig. 2 [86]. The electronic differentiation of the al-



Scheme 24

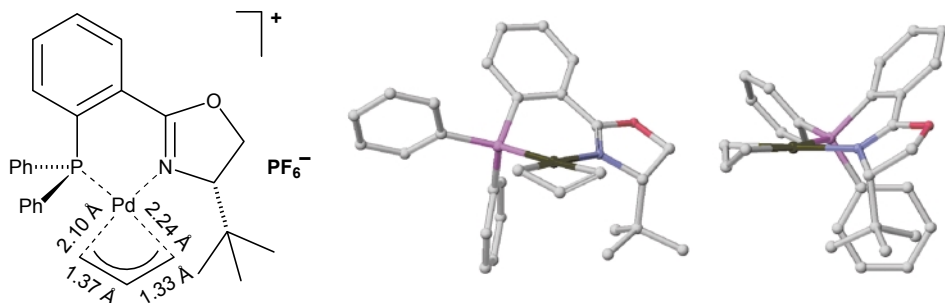


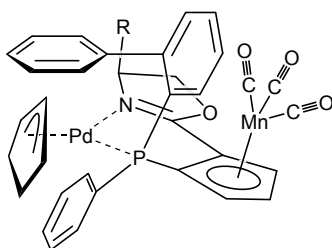
Fig. 2

lylic termini by the chiral ligand is clearly reflected in the different Pd-C bond lengths. Computational studies [79, 80] as well as NMR investigations [17, 21] provide strong evidence that the nucleophile preferentially attacks the longer Pd-C bond *trans* to the P atom. The structure shows that the *tert*-butyl group at the stereogenic center in the oxazoline ring and the axially oriented *P*-phenyl group are both quite remote from the allyl ligand. Therefore, the interaction with the equatorial *P*-phenyl group is assumed to be the principal factor responsible for enantiocontrol [71, 76].

NMR studies have shown that allyl intermediates A and B (Scheme 24) are in rapid equilibrium [87] and that isomer A is more stable [17, 84, 85]. The higher stability of A is explained by crystal structure data (see, e.g., Fig. 2) which suggest that isomer B suffers from steric repulsion between the equatorial *P*-phenyl

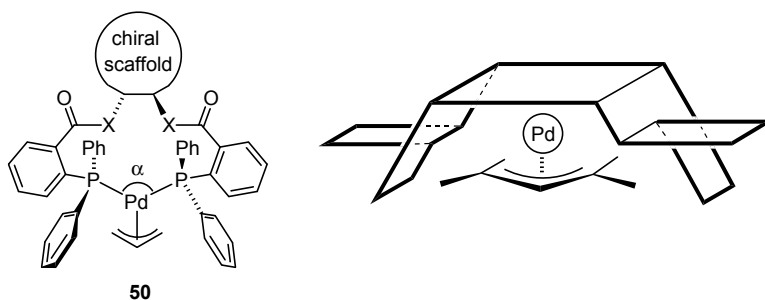
group and the adjacent *syn* substituent at the allyl terminus. However, the energy difference between **A** and **B** is not the origin of the enantioselectivity induced by these ligands because nucleophilic attack is slow compared to the interconversion of **A** and **B**. Therefore, the product distribution depends on the energy differences between the four transition states leading to **C**, **C'**, **D**, and **D'** (Curtin-Hammett principle [88]). In a remarkable NMR analysis, Steinhagen, Reggelin and Helmchen [17] have shed light on this complex reaction scheme. In the reaction between dimethyl malonate and 1,3-diphenylallyl acetate, they were able to characterize the so far elusive primary product of nucleophilic addition, a π -olefin complex of type **C**. The results are consistent with a pathway via **A** leading to **C**. Among the four pathways shown in Scheme 24, this is the only one that is electronically as well as sterically favored (nucleophilic attack *trans* to the Pd-P bond, no steric repulsion between the equatorial phenyl group and the allyl system).

The structural properties of phosphinooxazolines also explain why these ligands are not suited for reactions with cycloalkenyl esters such as cyclohexenyl acetate. In the corresponding allyl intermediates, the *syn* substituents, which are postulated to play a crucial role in the enantioselection observed with acyclic substrates (cf. Scheme 24), are lacking. Based on such considerations, Helmchen was able to develop a modified ligand that induces high enantioselectivities in the reaction with cycloalkenyl acetates [71]. In the corresponding Pd complex, an *o*-phenyl group, which was specifically introduced for this purpose, forces the allyl system to adopt the geometry shown in **61**. The observed enantioselectivities are consistent with an intermediate of type **61** reacting preferentially at the position *trans* to the Pd-P bond.



61

As discussed in Sect. 6, the chiral DPPBA-based diphosphines described by the general formula **50** are highly efficient and versatile ligands for many classes of allylic substitutions [15, 62]. The remarkable properties of this family of ligands is related to the bite angle α which is significantly larger than in unstrained Pd-diphosphine complexes. As a consequence, the *P*-aryl groups are positioned very close to the coordination sites *trans* to the P atoms and form a chiral pocket around the allyl ligand. Based on molecular modeling and X-ray structural data, Trost and coworkers have devised a cartoon model of the chiral pocket [63] (cf. Scheme 25; for a mnemonic that can be used to predict the sense of chiral induction, see [15, 62]). The relatively small size and the particular shape of this pocket



Scheme 25

et explain why 1,3-disubstituted allyl systems with large substituents (e.g., phenyl or cyclohexyl) in the *syn* positions react very slowly and with low enantioselectivity whereas the corresponding bis(*n*-alkyl) derivatives give faster rates, good yields, and high ees. The excellent results obtained with cycloalkenyl esters are also consistent with this model. Cyclic allyl systems lacking substituents at the two *syn* positions fit very well into the catalyst's chiral pocket. The same model has also been used to explain the stereoselectivity of other classes of allylic substitutions [89].

It should be mentioned that many other structural and mechanistic studies of Pd catalysts with chiral P,P-, P,N-, and other P,X-ligands have been reported [19, 21, 25, 26, 29, 66, 83, 90, 91, 92, 93]. These investigations have considerably enhanced our understanding of enantioselective Pd-catalyzed allylic substitution. The example of catalyst **61** [71] shows that the detailed structural and mechanistic knowledge accumulated over the last few years makes it possible to design new chiral ligands in a rather straightforward, rational way, at least in some cases [94]. Nevertheless, for many other classes of allylic substitutions, the development of suitable chiral catalysts remains a challenge.

8

Practical Aspects

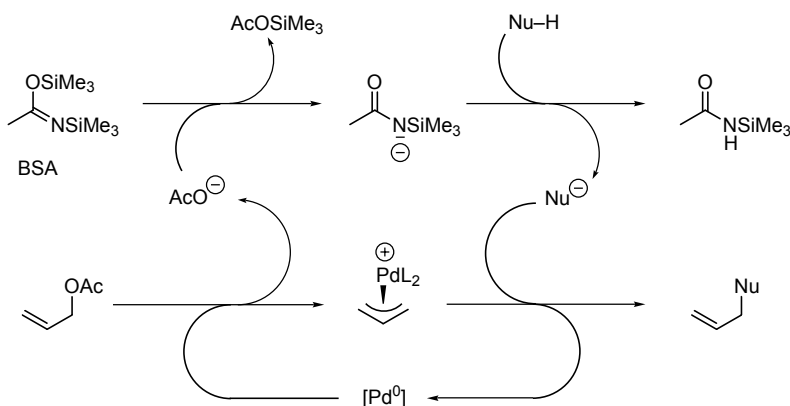
Palladium-catalyzed allylic substitutions are easy to carry out. In general, reactions are run under an inert atmosphere, however, special techniques or special equipment are not necessary. Both Pd(0) and Pd(II) complexes may serve as catalyst precursors, although a Pd(0) species is required to start the catalytic cycle. Palladium(0)-dibenzylideneacetone complexes [95] (e.g., commercially available Pd₂dba₃·CHCl₃) or the chloro(allyl)Pd(II) dimer [96] are convenient catalyst precursors. When an allyl-Pd(II) complex is used, the reaction is initiated by nucleophilic addition to the allyl system leading to a catalytically active Pd(0) complex. Other Pd(II) complexes such as Pd(OAc)₂ can be activated by reducing agents, e.g., excess phosphine ligand, certain nucleophiles or other components present in the reaction mixture. In most cases, the chiral Pd complex is prepared

in situ from the Pd precursor and the chiral ligand which is usually added in excess (1.1 equiv. or more).

Most reactions can be carried out at temperatures between 20 and 50 °C using 1–5 mol % of catalyst. At least for reactive substrates, it seems possible to lower the amount of catalyst. The highest S/C ratio has been reported for the reaction of 2-cyclopentenyl chloride with dimethyl sodiomalonate (0.02 mol % cat.; 89% yield; >4000 turnovers in 3 h at –35 °C) [50]. So far no industrial applications of enantioselective allylic substitutions are known and most reactions described in the literature were carried out on a small scale.

A variety of solvents can be used ranging from benzene and dichloromethane to more polar media like THF or DMF. Sometimes the solvent strongly influences the rate and ee, but there are also reactions that are quite insensitive to the nature of the solvent. In allylic substitutions with anionic nucleophiles, the counter ion can have a strong effect on the enantioselectivity. In the reaction of 2-cyclopentenyl acetate with the anion of dimethyl malonate and a catalyst derived from ligand **49** (Scheme 21) in THF, e.g., the tetrahexylammonium and the cesium salt gave ees of 68 and 76%, respectively, whereas the sodium salt afforded 39% ee and the lithium salt 63% ee of the opposite enantiomer [97]. The best enantioselectivity (>98% ee) was obtained with the tetrahexylammonium and cesium salts in dichloromethane. Unfortunately, no general rules for selecting the best solvent and counterion can be given.

Instead of an anionic nucleophile, the protonated neutral form can be used in combination with *N,O*-bis(trimethylsilyl)acetamide (BSA; see Scheme 26) [65, 98, 99, 100]. The reaction is initiated by catalytic amounts of acetate ions. Silyl transfer from BSA to the acetate generates the anion of *N*-(trimethylsilyl)acetamide which then deprotonates dimethyl malonate. In the subsequent allylic substitution, one equivalent of acetate is generated which, as before, reacts with BSA. The use of BSA has the advantage that only catalytic amounts of a base are present in the reaction mixture and that the neutral protonated nucleophile can



Scheme 26

be used which is more soluble in apolar solvents than the corresponding sodium salt. With this procedure it is possible to run reactions in dichloromethane or benzene under essentially homogeneous conditions. As mentioned in Sect. 4, the use of allylic carbonates rather than acetates also allows reactions to be carried out with only catalytic amounts of a base.

9

Survey of Reactions

Each of the classes of substrates and the nucleophiles used with this class is discussed in the sections that follow. The best ligand(s) for each substrate class was(were) selected rather than a comprehensive listing of all ligands reported. When possible, ligands which give >90% ee are listed but in the absence of this level of selectivity the best results obtained to date with a specific ligand are presented. In addition, the utility of the alkylation products is illustrated by showing how the enantioselective alkylation has been applied in the synthesis of a specific natural product or pharmaceutically important target. The vast majority of reactions have been investigated using palladium catalysts but in some cases, chiral molybdenum, tungsten, iridium, and nickel complexes have been used with moderate to very good results.

9.1

Substrates with Identical Substituents at C1 and C3 (RCH=CH-CHXR)

Substrates bearing identical substituents at C1 and C3 are the most thoroughly studied, in part, because these were among the first class of substrates examined and a benchmark level of enantioselectivity has been established. Recent history has shown that almost all newly designed ligands are first tried with 1,3-diphenylpropenyl acetate prior to investigating some of the substrates that provide more significant challenges. The interpretations of the factors responsible for highly selective reactions have arisen from these studies which can then be applied to other substrates. However, it should be pointed out that in general there is little or no correlation between the enantioselectivities obtained with 1,3-diphenylpropenyl acetate and other substrates. Acyclic and cyclic substrates have both been examined and yielded good results.

Representative data for the standard test substrate, 1,3-diphenylprop-2-enyl acetate, are listed in Table 1. Trost's review [15] provides a comprehensive list of the ligands that were examined up to 1996 and the best of these ligands plus any new and useful ones are included here, Fig.3. All these ligands give the product in >90% ee. In general both C₂ symmetric and unsymmetrical bidentate ligands work well with this substrate. Many of the ligands reported contain one or two phosphine groups but in addition dinitrogen ligands such as **53**, **63**, **65**, and **72** have been reported, that give high ees with this substrate. Many classes of nucleophiles react with this substrate including 'soft' carbon nucleophiles (malonate and substituted malonates, cyclic and acyclic 1,3-diketones and 2-substituted

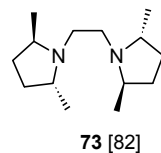
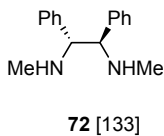
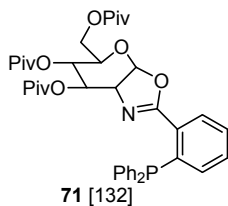
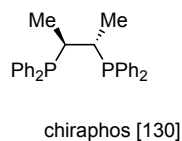
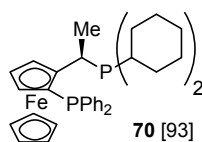
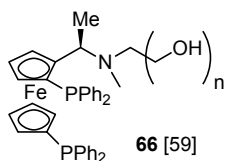
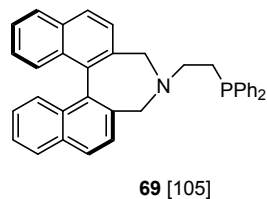
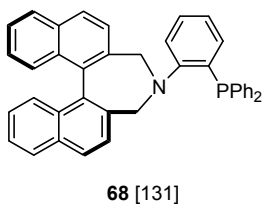
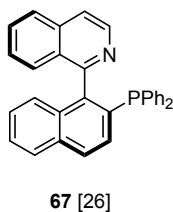
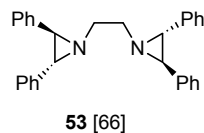
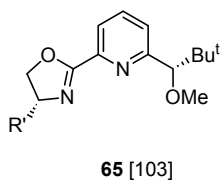
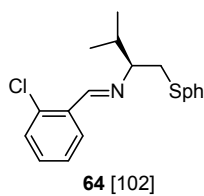
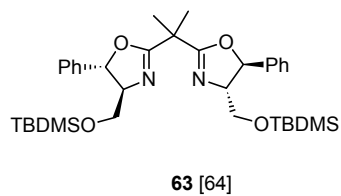
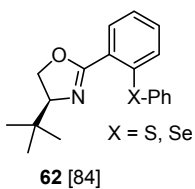
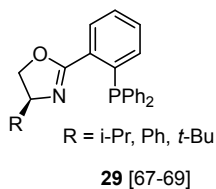
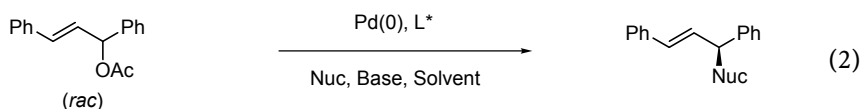


Fig. 3. List of ligands in Pd-catalyzed reactions of 1,3-diphenylpropenyl acetates

Table 1

Nu	Ligand	Yield	ee (%)	Ref.
NaCH(CO ₂ CH ₃) ₂	53	89	99	[66]
NaCH(CO ₂ CH ₃) ₂	Chiraphos	86	90	[130]
NaCH(CO ₂ CH ₃) ₂	62	84–99	92–96	[68]
NaCH(CO ₂ CH ₃) ₂	66 (n=2)	40	92	[59]
NaCH(COCH ₃) ₂	66 (n=3)	97	90	[59]
NaCH(CO ₂ CH ₃) ₂	68	95	96	[131]
NaCH(CO ₂ CH ₃) ₂	69	95	96	[105]
15-crown-5/NaCH(CO ₂ CH ₃) ₂	29 (R=Ph)	98	97	[67]
15-crown-5/NaCH(CO ₂ CH ₃) ₂	67	–	90	[26]
NaCH(SO ₂ Ph) ₂	29 (R= <i>i</i> -Pr)	98	98	[72]
BSA/CH ₂ (CO ₂ CH ₃) ₂	63	97	97	[64]
BSA/CH ₂ (CO ₂ CH ₃) ₂	29 (R=Ph)	98	98	[64]
BSA/CH ₂ (CO ₂ CH ₃) ₂	62 (X=S)	95	96	[72]
BSA/CH ₂ (CO ₂ CH ₃) ₂	70	57	93	[64]
BSA/CH ₂ (CO ₂ CH ₃) ₂	64	87	94	[102]
BSA/CH ₂ (CO ₂ CH ₃) ₂	73	98	91	[82]
BSA/CH ₂ (CO ₂ CH ₃) ₂	BINAP	85	90	[26]
BSA/CH ₂ (CO ₂ CH ₃) ₂	66 (n=2)	97	90	[59]
BSA/CH ₂ (CO ₂ CH ₃) ₂	65	97	99	[103]
BSA/CH ₂ (CO ₂ CH ₃) ₂	72	83	95	[133]
BSA/CH ₂ (CO ₂ CH ₃) ₂	71	94	98	[132]

1,3-diketones), nitrogen nucleophiles (benzylamine, NaN(Boc)₂, TosNHNa, PhCON(Na)NH₂, and veratrylamine) and sulfur nucleophiles (sulfinate).



Unfortunately it is not possible to simply extrapolate from the diphenyl series to other 1,3-disubstituted propenyl subunits. For example, replacing the phenyl groups by alkyl moieties usually gives much poorer results. Until recently the best ee obtained when R=Me was 87% using dimethyl methylmalonate and one of Trost's chiral DPPBA-type ligands [15] which are based on the diaminocyclohexane scaffold. Unfortunately, much poorer ees were obtained with amines, phenylsulfinate, and malonate itself. Trost has recently disclosed that a DPPBA-type ligand bearing polyether chains on the diarylphosphine group leads to ees in the range of 90–99% for R=Me using nucleophiles such as dibenzyl sodiomalonate, and sodium benzenesulfinate, Eq. (3) and Table 2 [106]. For R=*n*-Pr, ees of up to 69% have been achieved using malonate and ligand **29** but the ee decreases to 59–66% when an amide or sulfonamide nucleophile is used. In con-

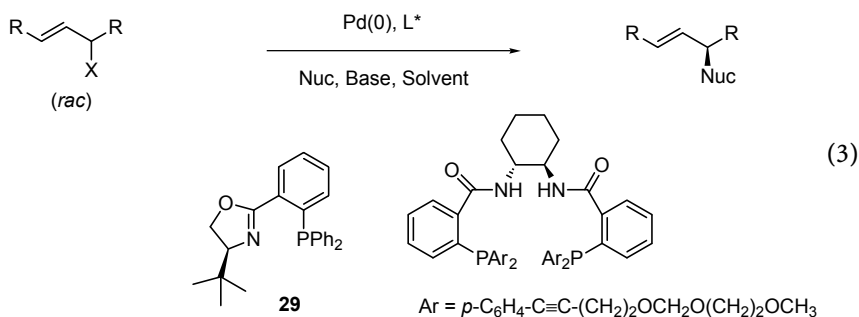
Table 2

R	X	Nu	Yield	ee (%)	Ref.
CH ₃	OAc	NaN(Boc) ₂	44	75 ^[a]	[53]
CH ₃	OAc	NaNHTs	61	66 ^[a]	[53]
CH ₃	OAc	NaCH(CO ₂ CH ₃) ₂	96	71 ^[a]	[67]
CH ₃	OAc	NaCH(CO ₂ CH ₃) ₂	97 (21)	85 (89.5@-40 °C)	[76]
CH ₃	OAc	NaCH(CO ₂ Bn) ₂	90	96	[106]
CH ₃	OAc	PhSO ₂ Na	81	99	[106]
CH ₃	OAc	NaCH(CO ₂ CH ₃) ₂	93	87 ^[b]	[116]
<i>n</i> -Pr	OAc	NaCH(CO ₂ CH ₃) ₂	96	69 ^[a]	[67]
<i>n</i> -Pr	OAc	NaNHTs	90	66 ^[a]	[53]
<i>i</i> -Pr	OPO(OEt) ₂	NaNHTs	57	90 ^[a]	[53]
<i>i</i> -Pr	OPO(OEt) ₂	NaN(Boc) ₂	29	97 ^[a]	[53]
<i>i</i> -Pr	OAc	NaCH(CO ₂ CH ₃) ₂	88	96 ^[a]	[67]

^[a]With ligand **29** (R=*t*-Bu).

^[b]With the DPPBA-type ligand shown

trast, when R=*i*-Pr, ees of 90–97% have been obtained with carbon and nitrogen nucleophiles including amines, amides, and sulfonamides and ligand **29**. In general, *N*-nucleophiles are less reactive than malonate and require longer reaction times and/or higher temperatures. The most successful ligands when R=*n*-alkyl are the BPPFA analogues but these give lower ees when R=Ph.



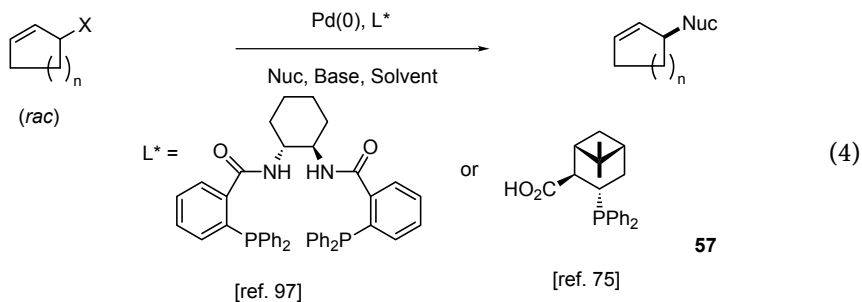
Cyclic alkenyl acetates and carbonates have also been examined in the enantioselective alkylation reaction, Eq. (4) and Table 3 [15, 71, 75]. Since the π -allyl complex produced from a cyclic precursor must have the *anti,anti* configuration, direct extrapolation from the results with the acyclic precursor cannot be assumed. In the event, five-, six-, and seven-membered rings all give ees >94% with phthalimide as the nucleophile in the presence of Trost's DPPBA-based ligands (the best results are obtained when the linker is a *trans*-cyclohexyl diamine unit, **49**). Typical soft carbon nucleophiles like malonate anions react to give the alkylated products in >90% ee using Trost's ligand **49**. Oxygen nucleophiles such

Table 3

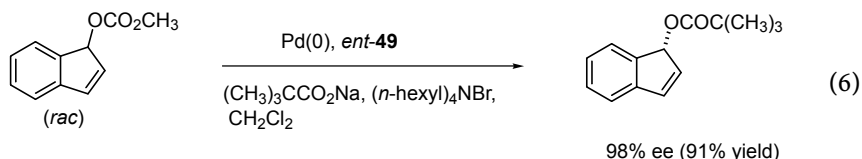
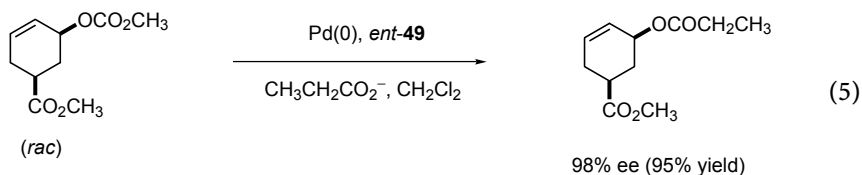
Nuc	X	n	Yield	ee (%)	Ref.
PhthN ⁻	OAc	1	87	94	[97]
	OAc	2	95	97	[97]
	OAc	3	84	98	[97]
LiCH(CO ₂ CH ₃) ₂	OAc	1	81	98	[97]
	OAc	2	86	96	[97]
	OAc	3	93	93	[97]
LiCH(CO ₂ CH ₃) ₂	OAc	1	76	83	[75]
	OAc	2	91	98	[75]
	OAc	3	75	98	[75]
(CH ₃) ₃ CCO ₂ ⁻	OCO ₂ CH ₃	1	91	97	[55]
	OCO ₂ CH ₃	2	94	92	[55]
	OCO ₂ CH ₃	3	98	98	[55]
PhSO ₂ ⁻	OCO ₂ CH ₃	1	99	98	[134]
	OCO ₂ CH ₃	2	95	98	[134]
	OCO ₂ CH ₃	3	95	98	[134]

as carboxylates and phenols react with high selectivity as well to give ethers and esters with ees typically in the 92–98% range. A sulfinate nucleophile also gives the corresponding five-, six-, and seven-membered allylic sulfones in up to 98% ee. Typically these reactions were carried out in the presence of a tetraalkylammonium salt. In the alkylation of cyclopentenyl acetate with malonate, the best results were obtained in dichloromethane as solvent and with cesium or tetrahexylammonium as the counterion. The ee increased with increasing size of the tetraalkylammonium ion. Using the polyether-containing DPPBA ligand developed by Trost [cf. Eq. (3)], as little as 0.25 mol % of palladium is required and no tetraalkylammonium salt is needed to achieve high rates. It has been proposed that the polyether complexes the metal cation and increases the reactivity of the nucleophile which is in proximity to the π -allyl moiety. A correlation was noted between metal ion and the ee which supports this proposal [106].

As discussed in Sects. 6 and 7 (cf. structures 55 and 61), Helmchen has optimized the structure of phosphinooxazolines for cyclic substrates. Using ligand 55, he has achieved excellent enantioselectivities (93 to >99% ee) in reactions of dimethyl malonate with cyclopentenyl-, -hexenyl, and -heptenyl acetates [71]. In addition, he has obtained similar results with the phosphinocarboxylate ligand 57 (Scheme 22) [75].

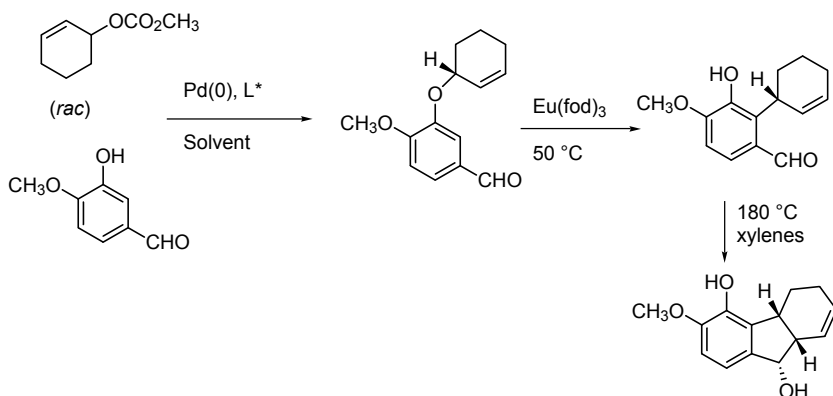


A particularly attractive approach is the deracemization reaction of cyclic alkenyl carbonates since easily prepared racemic starting materials can be converted into synthetically useful enantiomerically enriched products [55]. For example, indenyl carbonate and a cyclohexenyl carbonate have been deracemized to give the products in 98% ee using the enantiomer of ligand **49**. In both cases the nucleophile was a carboxylate salt (propionate and pivalate, respectively), Eqs. (5) and (6).

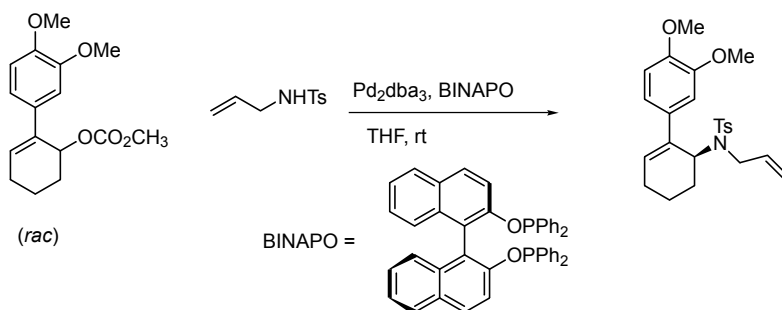


The products of the asymmetric alkylation have been used as key building blocks in syntheses of morphanes, phyllanthocin, and periplanone B natural products. In the case of the synthesis of the morphane skeleton, a phenolic nucleophile was reacted with cyclohexenyl methyl carbonate and the resulting ether was subjected to a europium-induced Claisen rearrangement followed by an intramolecular aldehyde-ene reaction to generate the key tricyclic intermediate, Scheme 27 [56].

Mori et al. have shown that asymmetric alkylation with an allylic tosyl amide followed by a zirconium-promoted cyclization provides an efficient route to mesembrine and mesembrane alkaloids [107]. The best ee was obtained with BINAPO as the ligand, Scheme 28. The product was obtained in 86% ee and following recrystallization the sulfonamide was obtained in 99% ee.



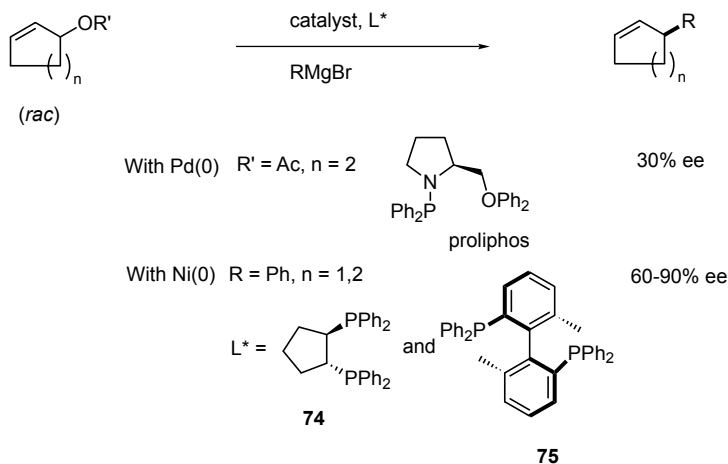
Scheme 27



Scheme 28

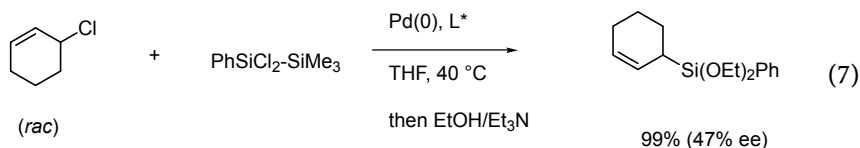
Hard nucleophiles also react with cyclic allylic acetates and halides. For example, cyclohexenyl acetate reacts with a vinylmagnesium species in the presence of PROLIPHOS to give the product of allylic alkylation in 30% ee [108].

Nickel catalyzed reactions of Grignard reagents with allyl ethers have also been carried out in the presence of chiral ligands to furnish enantiomerically pure cycloalkenes, Scheme 29. The ligands examined to date include chiraphos, BINAP, enantiomerically pure 1,2-*trans* diphenylphosphinocyclopentane **74**, and **75**. The best results were obtained with **74** and **75** but significant differences were noted as a function of nucleophile and ring size. For instance, ethylmagnesium bromide gave much better results than the methyl-, *n*-propyl-, and *i*-propyl analogues in reactions with the five-membered ring compound. In general higher ees were obtained for the five-membered ring compared to the six-membered ring for a given nucleophile and ligand. Reaction of a secondary Grignard reagent (phenethylmagnesium bromide) with allyl phenyl ether using a nickel catalyst and chiraphos gave the alkylated product in good yield but modest ee (58%) [13, 14].



Scheme 29

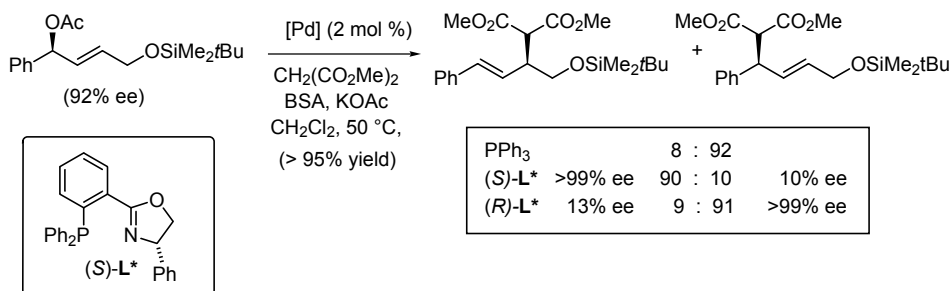
On changing from a carbon nucleophile to one based on silicon the ee was 47% using a palladium catalyst and a ferrocenyl ligand, Eq. (7) [115].



9.2

Substrates with Different Substituents at C1 and C3 (R¹CH=CH-CHR²X)

When the substituents are different at C1 and C3 (and neither is a CH₂ group), formation of the π -allyl complex from a racemic mixture of alkenyl acetates generates diastereomeric complexes in the presence of a chiral ligand. In fact many pairs of complexes may be formed depending on the geometry of the π -allyl moiety since there are several *syn/anti* isomers possible. Furthermore, a π - σ - π sequence does not lead to epimerization at the allylic C-atoms and other isomerization reactions that interconvert the diastereomeric allyl intermediates derived from the two substrate enantiomers are usually not observed (cf. Sect. 3.2). Therefore, conversion of a racemate to one product enantiomer is usually not possible. However, chiral catalysts can be used for kinetic resolution or for regiocontrol in reactions of racemic (Scheme 13) and optically active substrates (Scheme 14). If the regioselectivity is induced by the catalyst rather than the substituents present in the substrate, then the combination of an optically active substrate with a chiral enantiopure catalyst is a powerful concept for achieving



Scheme 30

regiocontrol, especially for transformations which with achiral catalysts afford mixtures or mainly the undesired regioisomer. Scheme 30 illustrates such a case [109]. Depending on which enantiomer of the catalyst is used, either one of the two regioisomers can be selectively prepared. Because the overall reaction proceeds with retention, enantiopure substrates are transformed into enantiopure products (cf. Scheme 14). Even substrates of only 80–90% ee afford products of high enantiomeric purity because the minor substrate enantiomer is converted to the regioisomer and not to the enantiomer of the main product.

9.3

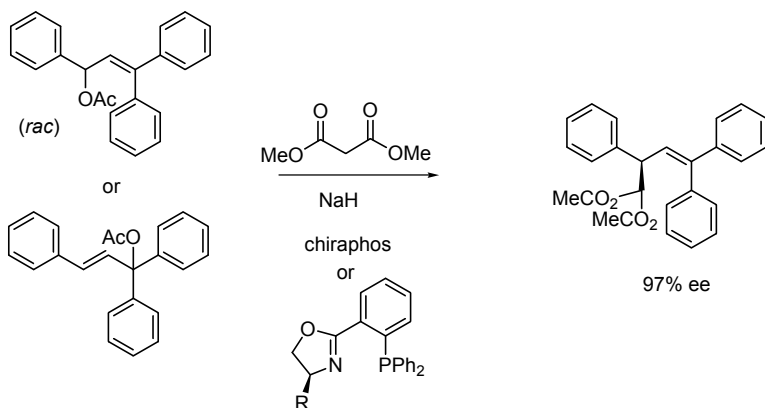
Substrates with Identical Geminal Substituents at C1 or C3 ($R^1HC=CH-C(R^2)_2X$ or $(R^1)_2C=CH-CHR^2X$)

For substrates bearing identical geminal substituents at either C1 or C3, the issues that become important are regiocontrol (since alkylation at the carbon bearing the identical substituents would give rise to achiral product) and the rate of π - σ - π interconversion vs the rate of alkylation (cf. Sect. 3.3).

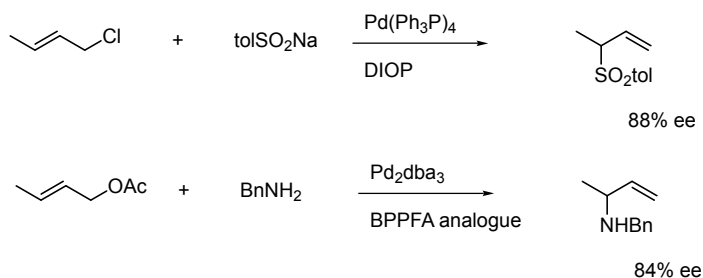
Two types of substrate have been most thoroughly examined. The first are substrates bearing three aryl groups (two at C1 and one at C3) in which case the alkylation can occur at the less substituted carbon *but* can still generate a stereocenter, Scheme 31. Bosnich reported some useful results with this system in 1985 where ees up to 86% were obtained with chiraphos as the ligand [110]. More recently, Williams showed that an oxazoline-phosphine ligand **29** produced better results (up to 97% ee) [73, 74, 111, 112].

The second class of substrate of importance bears a CH₂ group at one of the termini of the π -allyl unit. Until recently this family of substrates presented the biggest challenge because the vast majority of palladium-catalyzed reactions deliver the nucleophile to the less substituted carbon unless there are some special additional factors (i.e., ring size in an intramolecular reaction, substituent effects, etc.).

Early results with crotyl chloride and the sodium salt of toluene sulfinic acid in the presence of DIOP gave the allyl sulfone in 88% ee and with a ratio of 5.3:1 for the regioisomers favoring the chiral product [113]. A BPPFA analogue com-



Scheme 31



Scheme 32

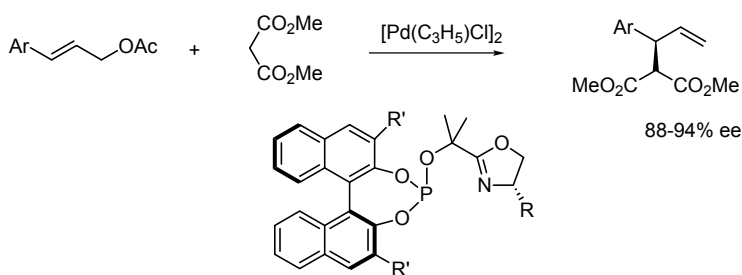
plexed to palladium also catalyzed the allylic amination of crotyl acetate with benzylamine and gave the product in 84% ee and 32.3:1 in favor of the chiral product, Scheme 32 [114]. However reaction with the chiral but racemic compound, 3-acetoxy-1-butene, gave the same product but in only 64% ee.

More recently, it was found that by careful design of the catalyst and choice of reaction conditions, it is possible to obtain good results with some monosubstituted allyl systems and a carbon nucleophile like malonate. Hayashi showed that 1-aryl-1-acetoxy-3-propene reacts with dimethyl methylmalonate using a palladium chloride complex in the presence of the MOP ligand to give a mixture of regioisomers containing predominantly the branched isomer. The ee of the adducts was 85–87% for various aryl groups [81]. A key requirement for good regioselectivity was that a neutral π -allyl complex be generated rather than a cationic species. Thus, $[\text{PdCl}(\pi\text{-C}_3\text{H}_5)]_2$ was the best palladium complex and a monodentate and bulky ligand like MOP was essential. Typical monodentate or bidentate ligands (dppe, Ph₃P) gave predominantly the linear isomer since a cationic palladium π -allyl intermediate was presumably generated and this complex prefers to react at the less substituted carbon. Pfaltz [77, 78] showed that the

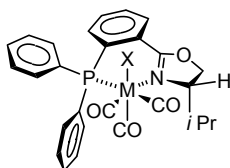
palladium complex of a new binol-oxazoline phosphite ligand promotes the regio- and enantioselective reaction of malonate and cinnamyl acetate and other aryl acetates, Scheme 33. Modest to excellent regioselectivity is observed and the ees are typically above 90%. An examination of ligand effects revealed that increasing the steric demands of the binol portion (i.e., $R' \neq H$) improved the ee but at the expense of regioselection. The matching of the chirality of the oxazoline and binol was also shown to be important to the ee and regioselectivity. Both the ee and regioselectivity were significantly lower for when the Ar group was replaced by an alkyl or alkenyl moiety.

A reversal of regioselectivity in favor of the branched product can also be achieved by using Mo, W, or Ir instead of Pd catalysts. Pfaltz has shown that a tungsten complex containing a chiral phosphinooxazoline leads to regio- and enantioselective alkylation, Fig. 4 [41, 78].

Recently, a more general solution to the challenge of high ee and high regioselectivity in this class of substrates was found by Trost [40]. A molybdenum catalyst and a chiral dipyrindine ligand **76** based on the diaminocyclohexyl scaffold provided very good results, Eq. (8) and Table 4. Molybdenum complexes have been known for some time to favor reaction at the more substituted carbon of the π -allyl moiety but all previous ligands were ineffective at generating active catalysts or giving good enantioselectivity. All the substrates reported to date



Scheme 33



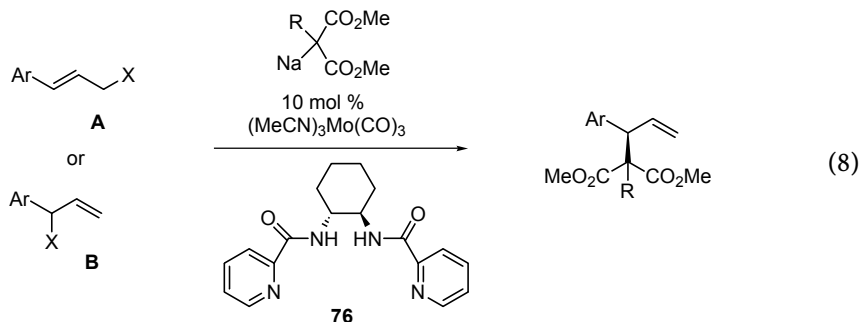
X = THF, CH₃CN

Fig. 4

Table 4

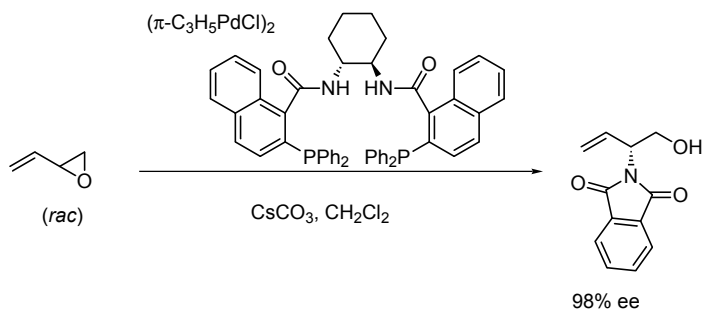
Substrate	Ar	R	Ratio	Yield (%)	ee (%)
A, X=OCO ₂ CH ₃	Ph	H	49:1	70	99
B, X=OCO ₂ CH ₃	Ph	H	32:1	61	97
B, X=OCO ₂ CH ₃	2-thienyl	H	19:1	78	88
B, X=OCO ₂ CH ₃	2-pyridyl	H	8:1	69	96
B, X=OCO ₂ CH ₃	1-naphthyl	H	99:1	82	87
A, X=OAc	Ph	CH ₃	24:1	67	98
A, X=OAc	2-furyl	CH ₃	32:1	71	97
B, X=OAc	2-furyl	CH ₃	32:1	65	87 (95@rt)
B, X=OCO ₂ CH ₃	2-pyridyl	CH ₃	5:1	71	94
B, X=OCO ₂ CH ₃	2-thienyl	CH ₃	13:1	71	75

have an aromatic group at C3 but groups other than substituted benzenes have been successfully used (thiophene, pyridine, furan). The level of regioselectivity varies from 5–99:1 and is typically >10:1 for malonate and substituted malonates. The amount of catalyst is higher than typically used for palladium-catalyzed reactions (10 mol % vs 1–2 mol %) but the lower cost of the metal partially offsets this shortcoming.

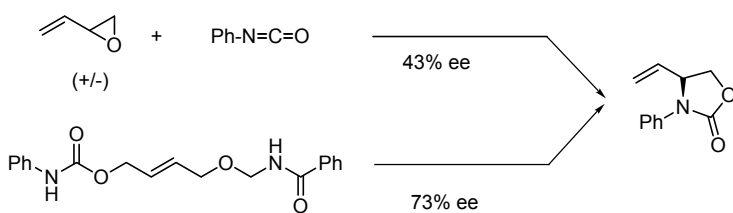


Helmchen has also shown that iridium complexes with certain phosphinooxazoline ligands react with cinnamyl acetate or an aryl-substituted cinnamyl acetate to produce the alkylation products in ees up to 95% and with regioselectivities of 19–99:1 in favor of the branched product [42].

Chiral racemic vinyloxydes react with phthalimide at the more substituted end of the π -allyl intermediate to give the chiral allylamine in up to 98% ee, Scheme 34 [116]. Some modification of the standard DPPBA-type ligand was required in order to achieve this level of selectivity. In particular, increased steric bulk in the form of a naphthyl moiety was claimed to restrict the number of rotamers and thereby increase the selectivity. This sequence was used to prepare vinylglycinol and a related reaction was used to synthesize a key intermediate for the synthesis of some anti-fungal agents [117].



Scheme 34



Scheme 35

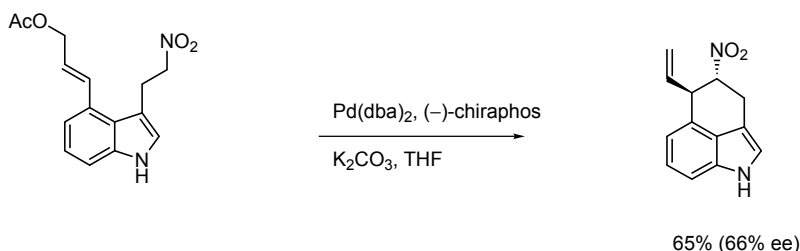
More modest levels of selectivity were obtained with an intramolecular nucleophile produced by reaction of the alkoxide with phenyl isocyanate. However, when the achiral precursor was used, the ee improved by 30%, Scheme 35 [118].

The increase in ee for the achiral starting material can be understood if there is enantioselectivity in the ionization step and if transfer of the palladium from one face of the π -allyl to the other occurs by the π - σ - π process. In the former reaction a mixture of diastereomeric π -allyl complexes is formed and the rate of cyclization is competitive with the rate of interconversion (via the π - σ - π process).

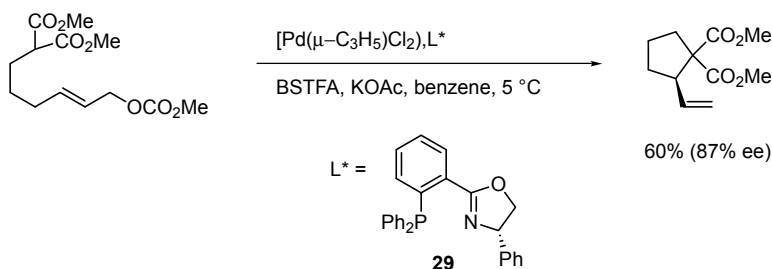
Intramolecular alkylations have also been performed on substrates so that the preference for one ring size over another leads to reaction at the more substituted carbon and generates a stereocenter. Although no general solution for intramolecular reactions has emerged, some good to excellent results have been obtained for specific cases.

Genét investigated the intramolecular reaction of a nitroalkane and an allylic acetate in the indole nucleus and obtained the cyclized product in 65% yield and 66% ee using chiraphos as the ligand, Scheme 36 [52].

Pfaltz has examined intramolecular reactions and found that ligand, leaving group, and solvent all play a role in the regioselectivity of the cyclization and the C/O alkylation ratios. The best results were obtained with allyl carbonates in dichloromethane and the phosphinooxazoline ligand **29** where ees up to 87% are possible. The stereochemistry of the alkene does not affect the ee of the re-



Scheme 36



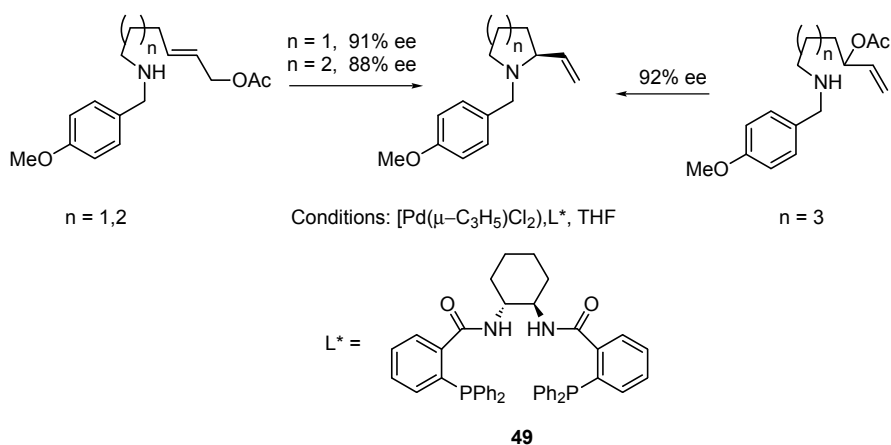
Scheme 37

action supporting the notion that equilibration of the π -allyl species is faster than alkylation, Scheme 37 [119].

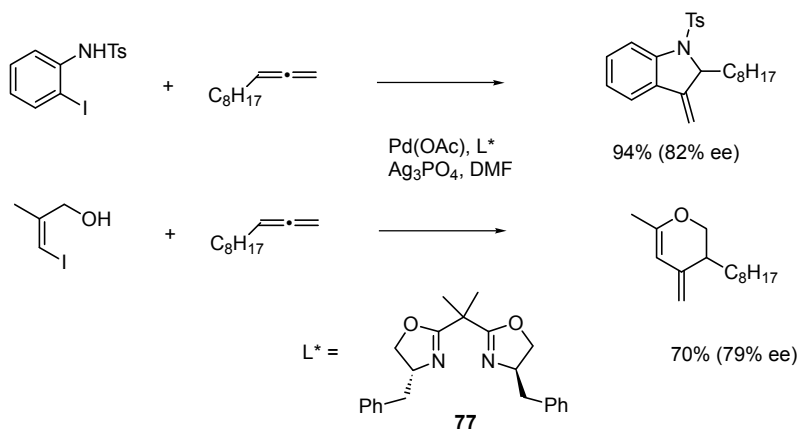
Trost has shown that heterocyclic compounds can be prepared using an intramolecular cyclization of a benzylamine onto an allylic acetate. Enantiomeric excesses of 80–92% were observed using the DPPBA-based ligand **49** developed in his laboratory, Scheme 38. The size of the ring and the position of the allylic leaving group played a role in the reactivity and enantioselectivity [120].

Although somewhat different, Larock's annulation reactions of allenes with aryl halides also belong to this category, as they involve an intermolecular carbopalladation followed by an intramolecular allylation as the key step. The best results were obtained with the bisoxazoline ligand **77** where ees of up to 82% were observed, Scheme 39 [121].

Alkylation of cyclic substrates bearing tertiary allylic acetates occurs at the less substituted primary carbon and the resulting product is chiral by virtue of the substituent on the ring, Scheme 40 (cf. Sect. 3.3 and Scheme 16). Reaction with malonate in the presence of a palladium-BINAP complex gives the product in up to 90% ee [43]. A strong correlation between the leaving group ability and the ee was noted with good leaving groups leading to lower ees. Olefin complexation and subsequent π -allyl formation are key processes influencing the selectivity. It is interesting to note that reaction of the enantiomerically enriched ac-

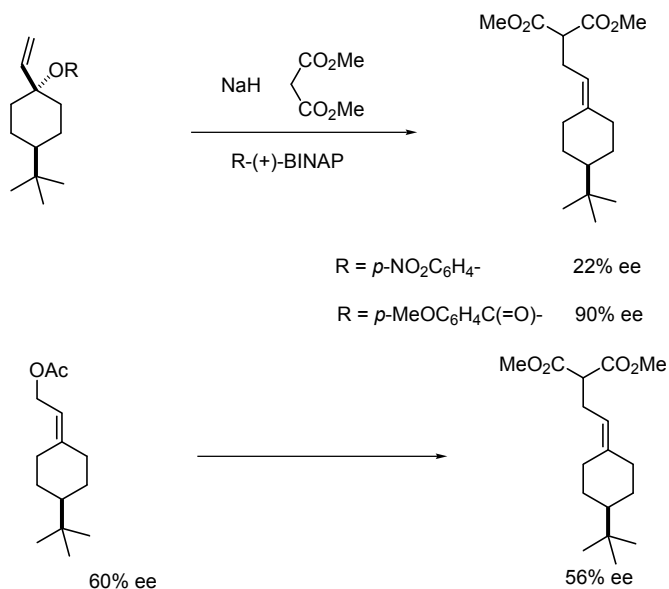


Scheme 38



Scheme 39

ate gives products of similar ee, Scheme 40. This result strongly supports the notion that exchange from one enantioface to the other does not occur once the π -allyl species is formed.

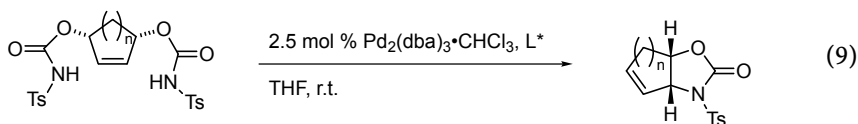


Scheme 40

9.4

meso-Substrates with Two Enantiotopic Leaving Groups

Trost and van Vranken carried out extensive investigations on the intramolecular cyclization of *meso*-compounds and obtained synthetically useful results, Eq. (9) and Table 5 [122, 123]. Five-, six-, and seven-membered *meso*-dicarbamates undergo cyclization with ees up to 97% using the ligands **78** and **79** shown in Fig. 5. The key step to achieve good ees is an enantioselective ionization step induced by complexation of the catalyst to the olefin on the face opposite the leaving group. Fused *N*-tosyloxazolidinones are produced in excellent yield and are useful building blocks in organic synthesis. Most recently, Trost has shown that adding triethylamine leads to a significant improvement in the enantioselectivity of these reactions and ees up to 99% have been observed [124].



The analogous intermolecular process has also been investigated with a variety of nucleophiles [15, 125]. In these studies the nature of the leaving group was found to be important to the ultimate enantioselectivity. For example, bulky

Table 5

n	Yield (%)	ee (%)	Ligand
1	94	88	78
1	99	88	78
2	82	97	79
3	82	95	79

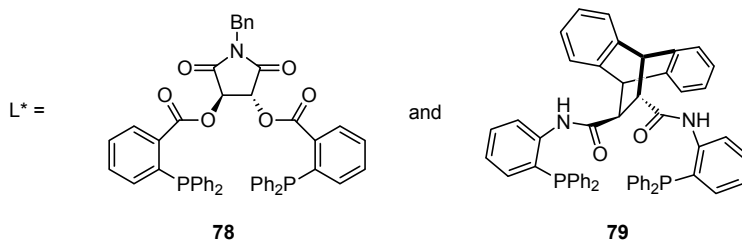
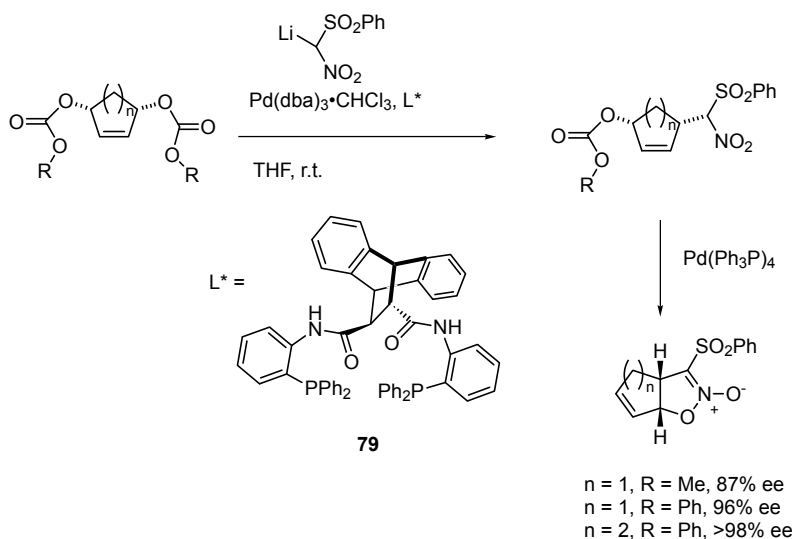


Fig. 5



Scheme 41

leaving groups gave higher ees than did small leaving groups such as the methyl carbonate. The five- and six-membered rings underwent a second cyclization following the alkylation step, providing access to oxazoline *N*-oxides whereas the reaction of the seven-membered ring stopped after step 1. Of the ligands examined **79** gave the best results, Scheme 41. Trost has found that in some cases

when the cyclization step is slow, addition of $\text{Pd}(\text{PPh}_3)_4$ accelerates the ring formation. The “mismatch” between the chiral catalyst and the chiral product which inhibits the cyclization is no longer present when an achiral palladium complex is used.

The oxazoline *N*-oxides have been converted into cyano alcohols or hydroxy esters which were known precursors to carbanucleosides such as carbovir, aristeromycin, and valienamine which is a glycosidase inhibitor.

Other nucleophiles have also been shown to react with the *meso*-diester. Among the most successful are cyclic 1,3-diketones, malonate, amines, and azide, Eq. (10) and Table 6 [15, 126]. In all cases the ee exceeds 90% and is often above 95% with ligand **49**.

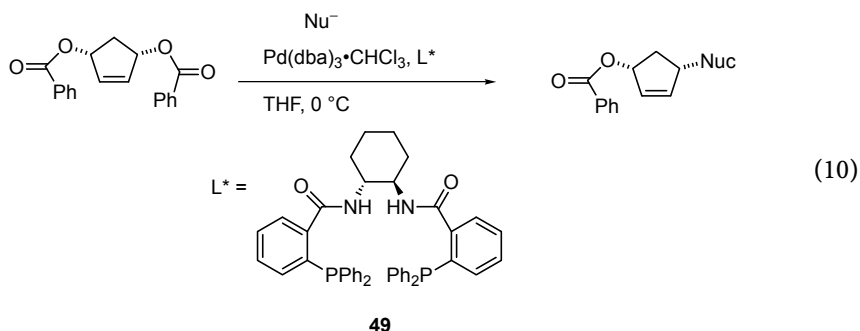
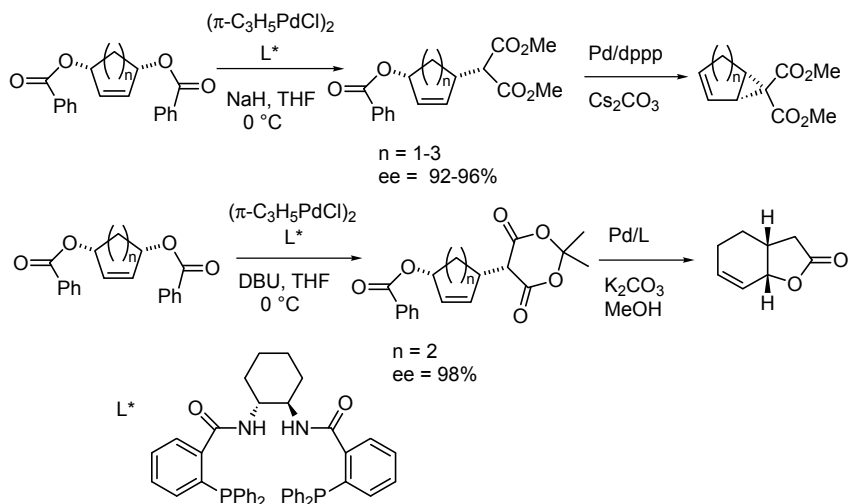


Table 6

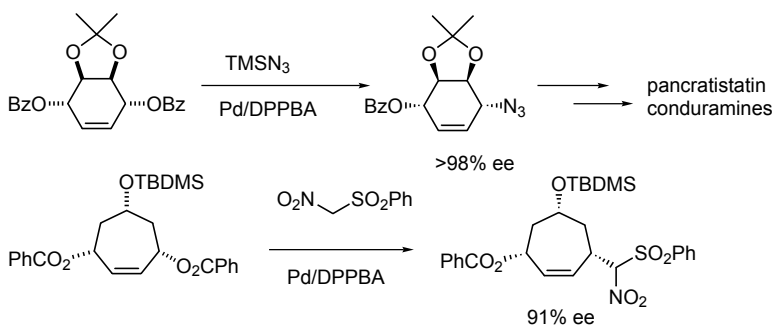
Nu	Base	Yield (%)	ee (%)
2-methyl-1,3-cyclohexadione	DBU	84	98
$\text{CH}_3\text{CH}(\text{CO}_2\text{CH}_3)_2$	NaOH	80	93
$\text{MeNHCH}_2\text{C}_6\text{H}_5$	–	71	95

A variation on this sequence used malonate or Meldrum's acid to form cyclopropanes and lactones, respectively, Scheme 42 [127]. An important observation in this sequence was that the second reaction was very poor in the presence of the chiral ligand since the allylic ester that remained was mismatched to the chirality of the ligand so ionization was very slow. The best way to overcome this problem in the cyclopropane series was to use a palladium catalyst with an achiral ligand for the second step. The choice of base was crucial to the eventual mode of cyclization with Cs_2CO_3 being most effective for the cyclopropane forming reaction and K_2CO_3 the best base for the lactone formation.

The desymmetrization of *meso*-compounds has also been carried out on more highly functionalized substrates and the products have been used as building blocks for biologically active targets. For example, pancratistatin and conduramines have been prepared from an intermediate arising from a palladium-catalyzed displacement by TMSN_3 , Scheme 43 [54].



Scheme 42



Scheme 43

9.5

Substrates with Two Geminal Enantiotopic Leaving Groups

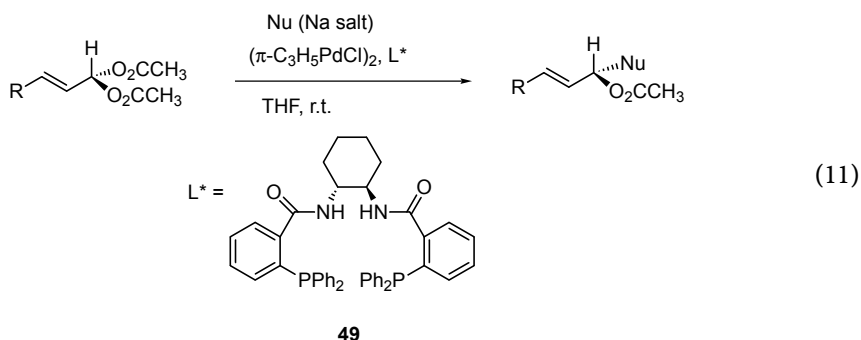
The reaction of substrates bearing geminal enantiotopic leaving groups has not been thoroughly investigated but the preliminary results have been very encouraging. In the presence of palladium and ligand **49**, geminal acetates undergo asymmetric ionization and reaction with nucleophiles including malonate and substituted malonates, substituted Meldrum's acid, and substituted bis-sulfones, Table 7 [44]. A variety of substituents on the alkene of the substrate has also been examined and good results were obtained with aryl, hindered alkyl,

Table 7

R	R'	Nu	Yield (%)	ee (%)
Ph	CO ₂ CH ₃	CH ₃ CH(CO ₂ CH ₃) ₂	92	>95
<i>i</i> -Pr	CO ₂ CH ₃	CH ₃ CH(CO ₂ CH ₃) ₂	75	>95
<i>i</i> -Pr	CO ₂ CH ₃	Meldrum's acid	58	90
TBDPSOCH ₂	CO ₂ CH ₃	CH ₃ CH(CO ₂ CH ₃) ₂	85	91
Me	CO ₂ CH ₃	CH ₃ CH(CO ₂ CH ₃) ₂	99 ^[a]	92
Me	CO ₂ CH ₃	CH ₃ CH(SO ₂ PH) ₂	99	67

^[a]2.9:1 mixture of regioisomers was produced.

and siloxymethyl moieties. Much poorer ees were obtained with a simple crotyl geminal acetate.



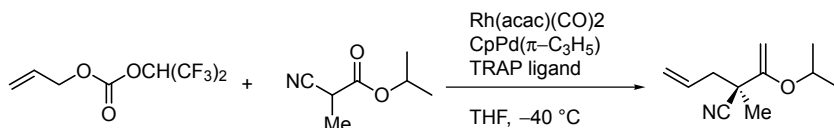
9.6

Reactions of Prochiral Nucleophiles

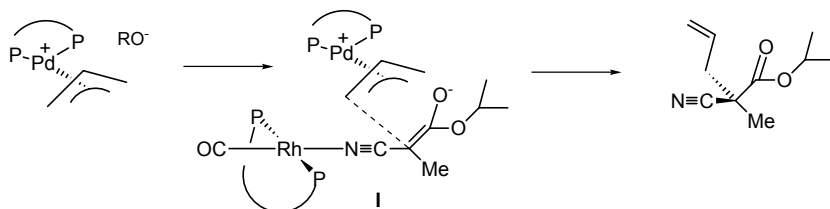
A two component catalyst system has provided promising results in the alkylation of a π -allyl moiety with a prochiral nucleophile (Scheme 44).

Ito and Sawamura showed that the use of rhodium and palladium in the presence of the TRAP-type ligand generates an effective catalyst combination for the reaction of an allyl carbonate with a cyanopropionamide [128]. The palladium-TRAP complex is proposed to generate a cationic π -allyl species. In addition, a rhodium-TRAP species complexes the cyano group of the nucleophile and induces formation of the enolate. Reaction of the enolate with the π -complex in assembly I generates the observed product, Scheme 45. The notion that enolization is caused by complexation to the cyano group is based on previous results in the enantioselective rhodium-catalyzed Michael addition.

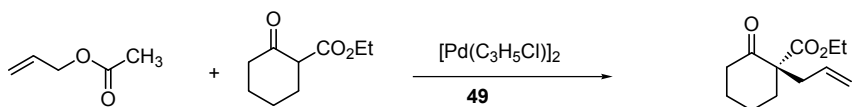
The ee of the reaction is as high as 99% when the alkylation is carried out at low temperature (-40 °C). Control experiments showed that while the alkylation



Scheme 44



Scheme 45



Scheme 46

occurs in the absence of rhodium, the ee is 0%. The structure of the allyl carbonate also had a significant effect on the ee with ethyl allyl carbonate giving 32% ee under the optimized conditions but hexafluoroisopropyl allyl carbonate gave 93–99% ee as a function of the substituents on the TRAP ligand. The leaving group effect was attributed to its better coordination to the rhodium. It seems to be essential for the rhodium alkoxide to carry out the deprotonation rather than direct generation of the nucleophile by the alkoxide, otherwise coordination of the nucleophile to the rhodium is slow compared to direct and non-enantioselective alkylation of the π -allyl species. More electron-rich TRAP ligands gave superior results to electron-poor ligands, indicating that the TRAP is bound to the rhodium and is influencing the rate of nucleophilic attack.

It has recently been demonstrated that alkylation of allyl acetate and symmetrical allylic carbonates with a β -ketoester is an efficient route to products containing a quaternary carbon center and one or two new stereocenters, respectively [129]. The best ee for the alkylation of 2-carboethoxycyclohexanone was 86% using toluene (75% ee in CH_2Cl_2) as the solvent, N,N,N',N' -tetramethylguanidinium ion as the cation, and **49** as the ligand (Scheme 46). The product was used as a key intermediate in the synthesis of the spiroalkaloid (–)-nitramine.

A 2-carbobenzyloxytetralone nucleophile also worked well with several different 2-substituted allyl acetates to yield the final products in 89–94% ee, Eq. (12) and Table 8.

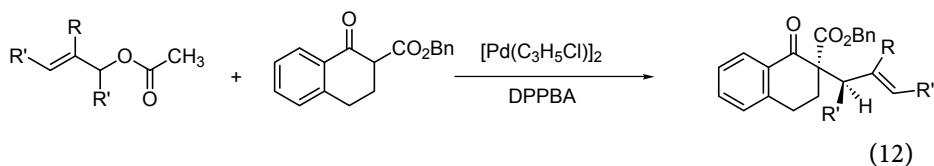
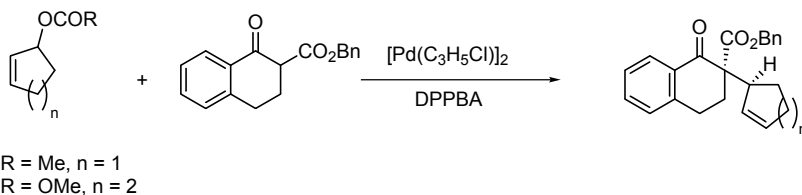


Table 8^[a]

R'	R	Time	Yield (%)	ee (%)
H	H	15 min	94	89
H	CH ₃	3 h	81	95
H	CH ₂ OAC	1.5	80	94
CH ₃	H	3 h	71	97 (dr=94:6)

^[a]0.4 mol % Pd, 1.2 equiv. DMG in toluene at 0 °C.

In addition, cyclic alkenyl acetates and carbonates react in an enantio- and diastereoselective fashion with the carbobenzyloxytetralone to give the alkylated products in 96 and 99% ee for the five- and six-membered rings, respectively. The diastereomeric ratios were typically greater than 98:2 (Scheme 47).



Scheme 47

10 Outlook

During the last few years metal-catalyzed allylic substitution has become one of the most versatile methods for the enantioselective formation of C-C and C-heteroatom bonds. The mild reaction conditions, the compatibility with many functional groups and the often high enantioselectivities make this method attractive for application in the synthesis of complex natural products or pharmaceuticals. For industrial applications, however, the productivity of the catalysts needs to be further improved in order to achieve high turnover numbers and frequencies. Other challenges for future research include the problem of regioselectivity in reactions of unsymmetrically substituted allyl derivatives and the still unsatisfactory enantioselectivities obtained with some classes of substrates. Moreover, enantioselective reactions with non-stabilized carbanions such as organozinc or Grignard reagents remain a largely unexplored field that deserves attention. Future research will certainly profit from the recent advances in understanding the mechanism of Pd-catalyzed allylic substitution and, therefore, the next years are likely to bring further significant progress in this important area of asymmetric catalysis.

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Chapter 25

Cross-Coupling Reactions

Tamio Hayashi

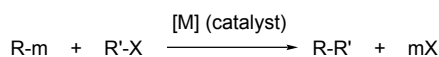
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Keywords: Hydrosilylation, Olefins, 1,3-Dienes, Platinum catalyst, Nickel catalyst, Rhodium catalyst, Palladium catalyst, Secondary alcohols, Allylsilanes

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1 Introduction

Nickel and palladium complexes are known to catalyze the reaction of organometallic reagents (R-m) with alkenyl or aryl halides and related compounds (R'-X) to give cross-coupling products (R-R'), which provides one of the most useful synthetic means for making a carbon-carbon bond [1, 2, 3, 4, 5] (Scheme 1). The catalytic cycle of the reaction is generally accepted to involve an unsymmetrical diorganometal complex LnM(II)(R)R' as a key intermediate. From this intermediate the product R-R' is released by reductive elimination to leave an LnM(0) species that undergoes oxidative addition to R'-X generating an intermediate LnM(II)(X)R' . Transfer of an alkyl group from R-m to this intermediate by transmetallation reproduces the diorganometal complex. Since most of the nickel and palladium catalysts used successfully for the cross-coupling have tertiary phosphines as ligands, optically active phosphine ligands have been conveniently used to make the metal complexes function as chiral catalysts. As organometallic reagents (R-m), relatively reactive organomagnesium and -zinc reagents have been often used for the asymmetric cross-coupling. The organic electrophiles (R'-X) used for the catalytic cross-coupling are aryl and alkenyl halides or pseu-

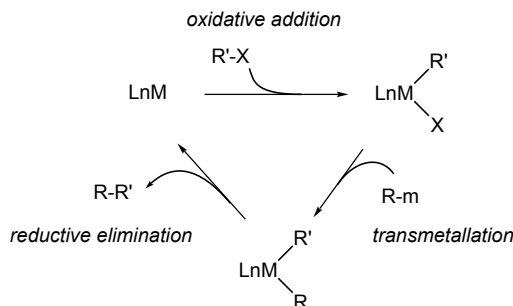


M = Ni, Pd

m = Mg, Zn, Al, Zr, Sn, B, Si, etc.

R' = aryl, alkenyl

X = Cl, Br, I, OSO₂CF₃, OPO(OR)₂, etc.



Scheme 1

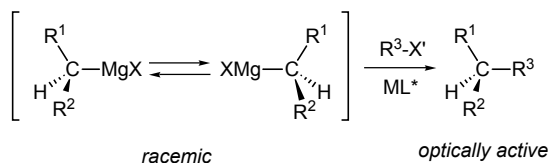
do halides, such as triflates, in which the new carbon-carbon bond is formed on the sp^2 carbon center, indicating that the creation of chiral carbon centers or chiral molecules by the catalytic cross-coupling is not always easy. For the asymmetric synthesis by this cross-coupling process, special systems have been designed. One is the reaction of secondary alkyl Grignard reagents where a kinetic resolution of the racemic reagents is expected and the other is the asymmetric synthesis of axially chiral molecules such as biaryls (vide infra).

2

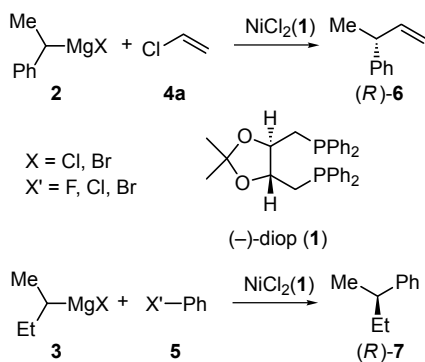
Asymmetric Cross-Coupling of Secondary Alkyl Grignard and Zinc Reagents

Asymmetric synthesis by the catalytic cross-coupling reaction has been most extensively studied with secondary alkyl Grignard reagents. The asymmetric cross-coupling with chiral catalysts allows transformation of a racemic mixture of the secondary alkyl Grignard reagent into an optically active product by a kinetic resolution of the Grignard reagent. Since the secondary alkyl Grignard reagents usually undergo racemization at a rate comparable to the cross-coupling, the enantiomerically enriched coupling product is formed even if the conversion of the Grignard reagent is 100% (Scheme 2).

In the first reported examples of the asymmetric Grignard cross-coupling, a nickel complex coordinated with (-)-DIOP (**1**) was used as catalyst [6, 7]. Reaction of 1-phenylethyl (**2**) and 2-butyl (**3**) Grignard reagents with vinyl chlo-



Scheme 2

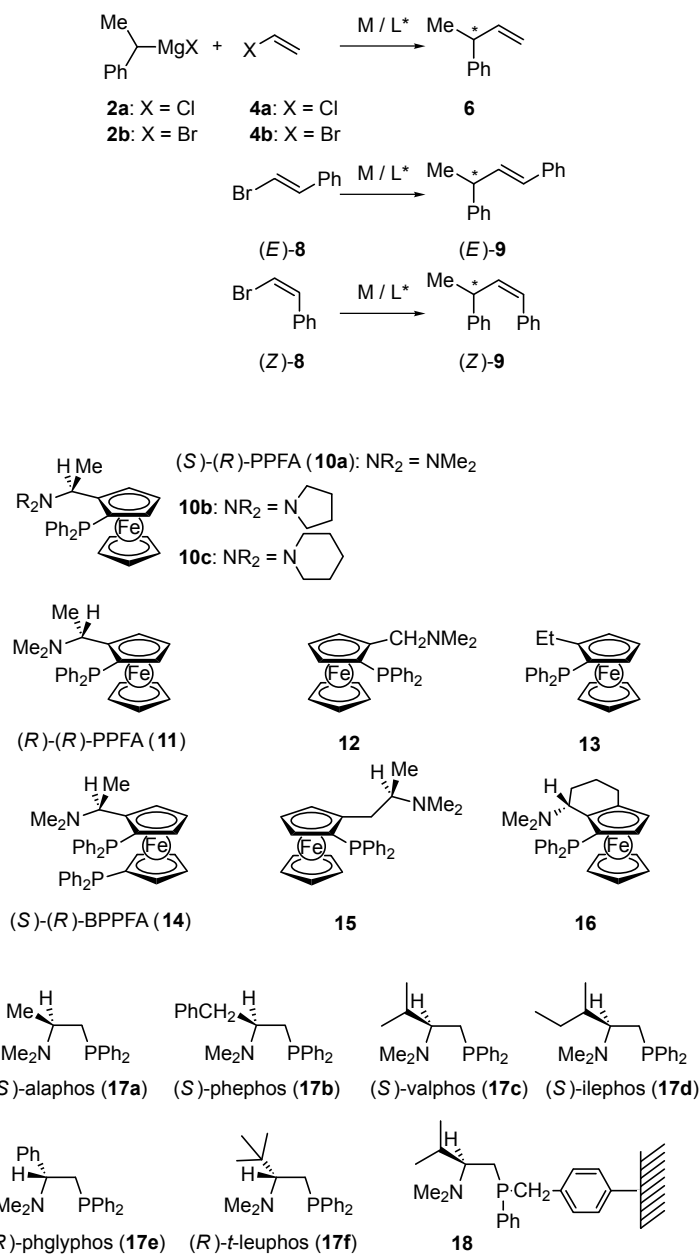


Scheme 3

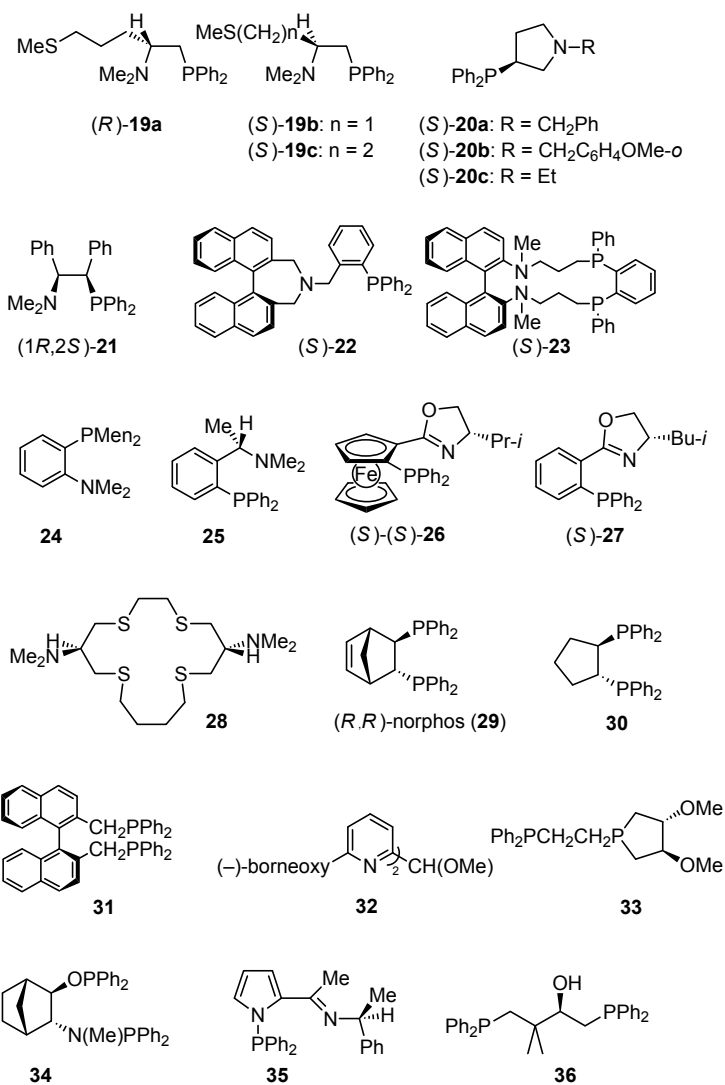
ride (**4a**) and phenyl halides (**5**), respectively, gave the corresponding coupling products, (*R*)-3-phenyl-1-butene (**6**) and (*R*)-2-phenylbutane (**7**) (Scheme 3). The enantioselectivity was slightly dependent on the halide atoms of both the Grignard reagents and organic halides, the highest being 13% ee for **6** and 17% ee for **7**.

After these findings, asymmetric cross-coupling of the secondary alkyl Grignard reagents has been attempted using various kinds of optically active phosphine ligands. The reaction most extensively studied so far is that of 1-phenylethylmagnesium chloride (**2a**) with vinyl bromide (**4b**) or bromostyrene (**8**) forming 3-phenyl-1-butene (**6**) or 1,3-diphenyl-1-butene (**9**), respectively (Scheme 4). Some of the representative results are summarized in the table of this scheme. The cross-coupling proceeds generally in high yields in diethyl ether at 0 °C or lower temperature in the presence of not more than 1 mol % of the nickel-phosphine complex NiCl₂P* or an in situ catalyst generated from NiX₂ (X=Cl or Br) and a phosphine ligand L*. The preformed palladium complex PdCl₂L* also catalyzes the asymmetric cross-coupling.

It was found that the ferrocenylphosphines containing an (dialkylamino)alkyl group on the side chain are effective for the cross-coupling of **2a** catalyzed by nickel or palladium complexes [8, 9, 10]. Ferrocenylmonophosphine, (*S*)-(*R*)-PPFA (**10a**) and -bisphosphine, (*S*)-(*R*)-BPPFA (**14**) gave the coupling product **6** with 68% ee and 65% ee, respectively. The presence of the (dialkylamino)alkyl side chain is of primary importance for the high selectivity and the enan-



Scheme 4. Asymmetric cross-coupling of 1-phenylethylmagnesium halides **2** with alkenyl halides **4** or **8**



Scheme 4. Continued

Entry	Halide 4 or 8	PhCH(Me)MX (eq to halide)	Catalyst (mol %)	Reaction conditions			Yield (%)	% ee	Ref.
				Solvent	Temp. (°C)	time (h)			
1	4a	2a	(-)-diop (1)/Ni (0.4)	Et ₂ O	-80	20	74 (6)	7 (R)	6
2	4a	2a (3-9)	(-)-diop (1)/Ni (0.1)	Et ₂ O	0	1	81 (6)	13 (R)	7
3	4b	2a (4)	(S)-(R)-PPEA (10a)/Ni (0.5)	Et ₂ O	-20	24	>95 (6)	68 (R)	8, 9
4	4b	2a (3)	(S)-(R)-10b/Ni (0.5)	Et ₂ O	0	24	>95 (6)	62 (R)	9
5	4b	2a (3)	(S)-(R)-10c/Ni (0.5)	Et ₂ O	0	24	43 (6)	42 (S)	9
6	4b	2a (2)	(R)-(R)-PPEA (11)/Ni (0.5)	Et ₂ O	-20	24	>95 (6)	54 (R)	9
7	4b	2a (4)	(S)-12/Ni (0.5)	Et ₂ O	0	24	>95 (6)	65 (6)	8, 9
8	4b	2a (3)	(R)-13/Ni (0.5)	Et ₂ O	0	24	86 (6)	5 (S)	8, 9
9	4b	2a (3)	(S)-(R)-PPEA (10a)/Pd (0.5)	Et ₂ O	25	70	82 (6)	61 (R)	9
10	4b	2a (4)	(S)-(R)-BPPEA (14)/Ni (0.5)	Et ₂ O	0	24	73 (6)	65 (R)	9
11	4b	2a (2)	(R)-(S)-15/Ni (0.5)	Et ₂ O	0	40	77 (6)	17 (R)	10
12	(E)-8	2a (2)	(S)-(R)-PPEA (10a)/Ni (0.5)	Et ₂ O	0	24	62 ((E)-9)	52 (R)	9
13	(E)-8	2a (2)	(S)-(R)-PPEA (10a)/Pd (2)	Et ₂ O	25	20	- ((E)-9)	73	11
14	4a	2b (1,2)	(S)-(R)-BPPEA (14)/Ni (0.5)	Et ₂ O	25	-	~100 (6)	60-70 (R)	12
15	4b	2a (2)	16/Pd (0.4)	Et ₂ O	0	24	95 (6)	79 (R)	13
16	4b	2a (2)	(S)-alaphos (17a)/Ni (0.5)	Et ₂ O	0	48	>95 (6)	38 (S)	14, 15
17	4b	2a (2)	(S)-phephos (17b)/Ni (0.5)	Et ₂ O	0	48	>95 (6)	71 (S)	14, 15
18	4b	2a (2)	(S)-valphos (17c)/Ni (0.5)	Et ₂ O	0	48	>95 (6)	81 (S)	14, 15
19	4b	2a (2)	(S)-ilephos (17d)/Ni (0.5)	Et ₂ O	0	48	>95 (6)	81 (S)	15
20	4b	2a (2)	(R)-phglyphos (17e)/Ni (0.5)	Et ₂ O	0	48	>95 (6)	70 (R)	14, 15
21	4b	2a (2)	(R)-t-leuphos (17f)/Ni (0.5)	Et ₂ O	0	48	>95 (6)	83 (R)	14, 15
22	4b	2a (2)	18/Ni (0.5)	Et ₂ O	0	40	73 (6)	49 (S)	16
23	4b	2a (2)	(R)-19a/Ni (0.8)	Et ₂ O	-5	16	(6)	88 (R)	17

Scheme 4. Continued

Entry	Halide 4 or 8	PhCH(Me)MX (eq to halide)	Reaction conditions			Yield (%)	% ee	Ref.
			Solvent	Temp. (°C)	time (h)			
24	4b	2a (2)	Et ₂ O	-5	14	>90 (6)	38 (S)	18
25	4b	2a (2)	Et ₂ O	-5	14	>90 (6)	65 (S)	18
26	4a	2a (1.2)	Et ₂ O	-78→rt	20	68 (6)	89 (R)	19,20
27	4b	2a (1.2)	Et ₂ O	-78→rt	20	96 (6)	73 (R)	19,20
28	4a	2a (1.2)	Et ₂ O	-78→rt	20	64 (6)	75 (R)	19
29	4a	2a (1.2)	Et ₂ O	-78→rt	20	82 (6)	72 (R)	19,20
30	4b	2a (2)	Et ₂ O	0	48	91 (6)	66	21
31	(E)-8	2a (2)	Et ₂ O	0	48	95 ((E)-9)	94	21
32	4b	2a	Et ₂ O	0	20	67 (6)	46 (R)	22,23
33	4b	2a (1.7)	Et ₂ O	0	20	54 (6)	16 (R)	24
34	(E)-8	2a (1.5)	Et ₂ O	-45	20	65 ((E)-9)	11 (R)	25
35	(E)-8	2a (2)	Et ₂ O	-45→0	20	>95 ((E)-9)	40 (R)	26
36	(E)-8	2a (1.5)	Et ₂ O	0	6	74 ((E)-9)	45 (S)	27
37	(Z)-8	2a (2.5)	Et ₂ O	-19	17	95 ((Z)-9)	45 (S)	28
38	4b	2a (2)	Et ₂ O	-10→0	2	50 (6)	46 (R)	29,30
39	4b	2a (2)	Et ₂ O	-40→rt	2	95 (6)	67 (S)	31
40	4a	2a (2)	Et ₂ O	0	24	45 (6)	47 (S)	12,32
41	4b	2a	Et ₂ O	0	24	(6)	11 (S)	33
42	4b	2a	Et ₂ O	-10	12	46 (6)	11 (R)	34
43	4b	2a (2)	Et ₂ O	-78→rt	20	52 (6)	17 (S)	35
44	(E)-8	2a (2)	Et ₂ O	-45→20	20	90 ((E)-9)	13 (S)	36
45	4b	2a	Et ₂ O	0	18	66 (6)	32 (R)	37
46	4b	2a (1.5-2)	Et ₂ O	-78→25		<53 (6)	22 (S)	38

Scheme 4. Continued

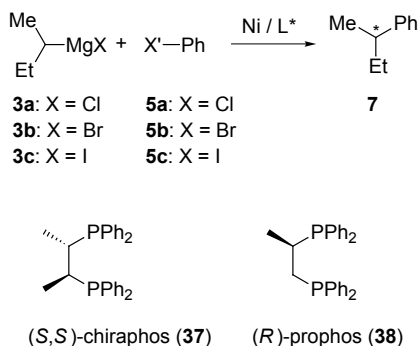
tioselectivity is strongly affected by the structure of the dialkylamino group (entries 3–11 in table of Scheme 4). The ferrocene planar chirality in **10a** plays an important role in the enantiocontrol rather than the carbon central chirality on the ferrocene side chain, which is shown by comparison of the enantioselectivity with that observed with its diastereoisomer (*R*)-(*R*)-PPFA (**11**) or **12** that lacks the central chirality. The amino group is proposed to coordinate with the magnesium atom in the Grignard reagent at the transmetalation step in the catalytic cycle, where the coordination occurs selectively with one of the enantiomers of the racemic Grignard reagent to bring about high selectivity, although the coordination has not been supported by NMR studies of a palladium complex [11]. The influence of the extent of conversion on enantioselectivity has been studied in the reaction of the Grignard reagent **2b** with **4a** catalyzed by the nickel complex of (*S*)-(*R*)-BPPFA (**14**) [12]. A ferrocenylphosphine **16** which is analogous to PPFA but has a tetrahydroindenyl moiety was more enantioselective than PPFA (**10a**) for the palladium-catalyzed asymmetric cross-coupling of **2a** with **4b** to give (*R*)-**6** of 79% ee [13] (entry 15).

Based on the high efficiency of the (dialkylamino)alkyl side chain on the ferrocenylphosphines, a series of β -(dialkylamino)alkylphosphines **17** was prepared and used for the cross-coupling. Those substituted with a sterically bulky alkyl group at the chiral carbon center are more effective than the ferrocenylphosphine ligands. Valphos (**17c**), ilephos (**17d**), and *t*-leuphos (**17f**), which were prepared starting with valine, isoleucine, and *tert*-leucine, respectively, gave the product **6** with over 81% ee [14, 15] (entries 16–22). Use of the polymer-supported β -(dialkylamino)alkylphosphine ligand **18** which is analogous to valphos (**17c**) gave 3-phenyl-1-butene (**6**) in somewhat lower enantiomeric purity [16]. A comparable enantioselectivity was observed with the β -(dialkylamino)alkylphosphines **19** containing a sulfide group on the alkyl chain [17, 18] (entries 23–25). The sulfur-bearing alkyl group is more effective than the simple alkyl side chain, highest (88% ee) being obtained with **19a** which is derived from homomethionine. Several 3-diphenylphosphinopyrrolidine-type ligands **20** were prepared and used for the nickel-catalyzed Grignard cross-coupling of 1-phenylethylmagnesium chloride (**2a**) [19, 20] (entries 26–29). The *N*-benzyl derivative **20a** is most effective giving (*R*)-**6** of 89% ee in the reaction with vinyl chloride (**4a**). An asymmetric amplification was observed to some extent in the asymmetric cross-coupling with ligands **20**. High enantioselectivity (94% ee) was reported in the cross-coupling of **2a** with (*E*)-**8** in the presence of a nickel or palladium catalyst coordinated with the new chiral (β -aminoalkyl)phosphine ligand (1*R*,2*S*)-**21** which was derived from *erythro*-2-amino-1,2-diphenylethanol [21] (entries 30–31). Some other (aminoalkyl)phosphines, those based on the axially chiral 1,1'-binaphthyl skeleton, **22** [22, 23] and **23** [24], dimethylphosphine **24** [25], and the 1-phenylethylamine derivative **25** [26] have been also used, though the enantioselectivity was not always high (entries 32–35). The phosphinoferrocenyloxazoline (*S*)-(*S*)-**26** was a more stereoselective ligand than its diastereomeric isomer for the palladium-catalyzed reaction of 1-phenylethylmagnesium chloride (**2a**) with (*E*)-**8** to give (*E*)-**9** of 45% ee [27] (entry 36). A nickel complex co-

ordinated with phosphinophenylloxazoline (*S*)-27 was studied with regard to its structure and its use as a catalyst for the asymmetric cross-coupling with (*Z*)- β -bromostyrene (*Z*)-8 [28] (entry 37). Interestingly, the enantioselectivity observed with (*E*)-8 was much lower (8% ee) than that (45% ee) with (*Z*)-8.

Several chiral macrocyclic sulfides have been prepared and examined as chiral ligands for the nickel-catalyzed coupling reaction, although the enantioselectivity was not so high (46% ee with the tetrasulfide ligand 28) [29, 30] (entry 38). Nickel catalysts complexed with the unfunctionalized chelating bisphosphine ligands, (*R,R*)-norphos (29) [31] and 30 [12, 32], also induced a high selectivity in the reaction shown in Scheme 4 (entries 39–40). The results reported with the other phosphine ligands 31 to 36 [33, 34, 35, 36, 37, 38] are summarized in the table to Scheme 4 (entries 41–46).

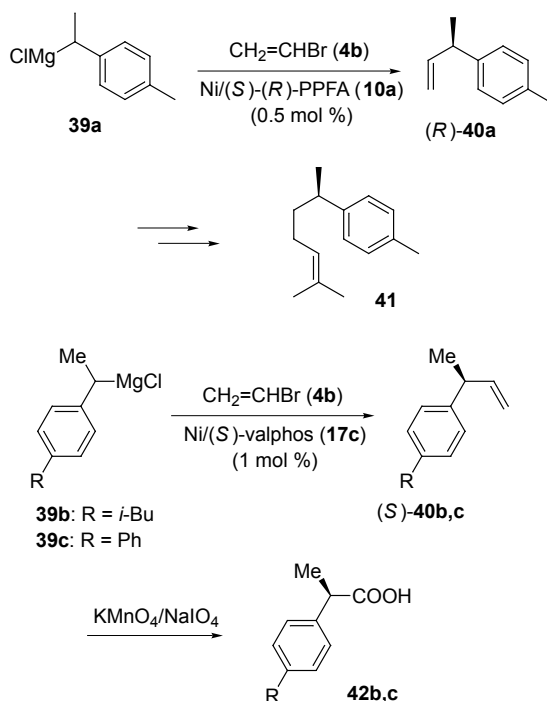
The asymmetric cross-coupling of secondary alkyl Grignard reagents that do not contain an aryl group such as phenyl on the chiral carbon center has not been so successful in terms of enantioselectivity as that of the 1-arylethyl Grignard reagent. The reaction of the 2-butyl Grignard reagents 3 with phenyl halides 5 was mainly studied with nickel catalysts complexed with chiral homologues of 1,2-bis(diphenylphosphino)ethane [31, 39, 40] (Scheme 5). The highest enantiomeric purity (55% ee) of the product, 2-phenylbutane was obtained in the reaction of 3b (X=Br) with 5b (X'=Br) in the presence of a nickel complex coordinated with 1,2-bis(diphenylphosphino)cyclopentane (30). Use of (*S,S*)-chiraphos (37) as a chiral ligand produced (*S*)-7 of 43% ee. Detailed studies on the reaction of 3 (X=Cl, Br, I) with 5 (X'=Cl, Br, I) in the presence of the nickel/(*R*)-prophos (38) catalyst revealed that the absolute configuration of the coupling product as well as the enantioselectivity is dependent on the halogen atoms in both the Grignard reagent and phenyl halides. For examples, reaction of 3b (X=Br) with 5b (X'=Br) gave (*R*)-2-phenylbutane (7) of 40% ee whereas that of 3a (X=Cl) with 5c (X=I) gave (*S*)-7 of 15% ee. In the reaction of substituted phenyl halides, the enantioselectivity was found to be strongly influenced by steric factors but only slightly by electronic factors.



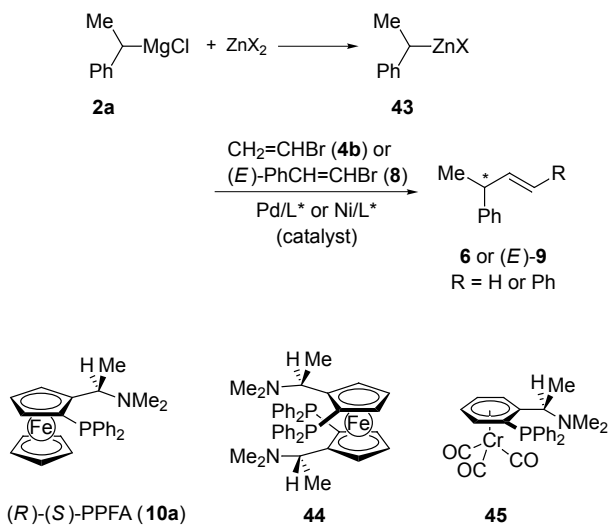
Scheme 5

The chiral ferrocenylphosphine (*S*)-(*R*)-PPFA (**10a**) and β -(dialkylamino)alkylphosphines **17** are used for the nickel-catalyzed asymmetric cross-coupling of 1-aryl-substituted ethyl Grignard reagents **39** with vinyl bromide (**4b**) (Scheme 6). The enantioselectivity is as high as that for the reaction of the 1-phenylethyl Grignard reagent (**2a**). The coupling product (*R*)-**40a** which was obtained in the cross-coupling of 1-(*p*-tolyl)ethylmagnesium chloride was converted by a sequence of reactions into α -curcumene (**41**) of 66% ee [41]. Oxidation of the coupling products **40b** and **40c** gave optically active 2-(4-isobutylphenyl)propionic acid (ibuprofen) (**42b**, 80% ee) and its biphenyl analogue (**42c**, 82% ee), both of which are anti-inflammatory agents [15].

Use of 1-phenylethylzinc reagents in place of the corresponding Grignard reagents sometimes increases the stereoselectivity (Scheme 7). The results are summarized in the table of Scheme 7, which also contains the data obtained with the Grignard reagents for comparison. The reaction of zinc reagents **43** prepared from **2a** with a zinc halide in THF in the presence of a palladium catalyst coordinated with a chiral ferrocenylphosphine [(*R*)-(*S*)-PPFA (**10a**)] proceeded with 85–86% enantioselectivity [42] (entries 1 and 2). The selectivity is higher than that observed for the reaction with 1-phenylethyl Grignard reagent (entry 3, see also entry 3 in the table of Scheme 4). The highest enantioselectivity in the for-



Scheme 6



Scheme 7. Asymmetric cross-coupling of 1-phenylethylzinc halides **43** with alkenyl halides **4** or **8**

Entry	Halide 4 or 8	PhCH(Me)MX (eq to halide)	Catalyst (mol %)	Reaction conditions			Yield (%)	% ee	Ref.
				Solvent	Temp. (°C)	time (h)			
1	4a	2a+ZnI ₂ (3)	(R)-(S)-PPFA (10a)/Pd (0.5)	THF/Et ₂ O	0	21	>95 (6)	86 (S)	42
2	4a	2a+ZnCl ₂ (3)	(R)-(S)-PPFA (10a)/Pd (0.5)	THF/Et ₂ O	0	40	>95 (6)	85 (S)	42
3	4a	2a (3)	(R)-(S)-PPFA (10a)/Pd (0.5)	Et ₂ O	0	21	>95 (6)	65 (S)	42
4	(E)-8	2a+ZnCl ₂ (3)	(R)-(S)-PPFA (10a)/Pd (0.5)	THF/Et ₂ O	0	22	88 ((E)-9)	60 (S)	42
5	4a	2a+ZnCl ₂ (3)	44/Pd (0.5)	THF/Et ₂ O	0	20	>95 (6)	93 (R)	43
6	4a	2a+ZnCl ₂ (3)	45/Pd (0.5)	THF/Et ₂ O	0	18	67 (6)	61 (S)	45
6	4a	2a (3)	45/Pd (0.5)	THF/Et ₂ O	0	18	56 (6)	13 (S)	45
8	4a	2a+ZnBr ₂ (2)	(S)-19a/Ni (0.1)	Et ₂ O	-34	21	73 (6)	70 (R)	46, 47
9	4a	2a (2)	(S)-19a/Ni (0.1)	Et ₂ O	0	20	95 (6)	61 (S)	46, 47
10	4a	2a+ZnBr ₂ (2)	(S)-19b/Ni (0.1)	Et ₂ O	2	16	88 (6)	52 (R)	46, 47
11	4a	2a (2)	(S)-19b/Ni (0.1)	Et ₂ O	4	96	>95 (6)	60 (S)	46, 47

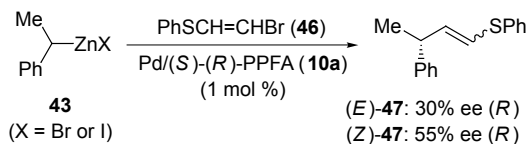
Scheme 7. Continued

mation of (*R*)-**6**, 93% ee, was obtained with the C_2 -symmetric ferrocenylphosphine ligand **44** containing two phosphorus atoms and two aminoalkyl side chains on the ferrocene skeleton [43, 44] (entry 5). An aminoalkylphosphine **45** ligand which is analogous to PPFA (**10a**) but having the (η^6 -benzene)chromium structure in place of ferrocene showed a slightly lower selectivity (61% ee) in the reaction of 1-phenylethylzinc reagent [45] (entries 6 and 7). Reversal of absolute configuration of the coupling product **6** by addition of the zinc salt was observed in the reaction catalyzed by **19-Ni** [46, 47] (entries 8–11). Thus, the cross-coupling of the Grignard reagent **2a** with **4a** in the presence of a nickel catalyst coordinated with aminoalkylphosphine (*S*)-**19a** gave (*S*)-**6** of 61% ee while the reaction of the organozinc reagent generated from **2a** and zinc bromide gave its enantiomer (*R*)-**6** in 70% ee.

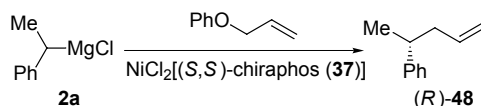
The asymmetric cross-coupling of zinc reagent **43** with (*E*)- and (*Z*)-1-bromo-2-(phenylthio)ethenes (**46**) catalyzed by Pd/(*S*)-(*R*)-PPFA (**10a**) gave optically active alkenyl sulfides **47**, which could undergo the second cross-coupling, the sulfide being replaced by the Grignard reagent in the presence of a nickel catalyst [48] (Scheme 8).

Kinetic resolution of the racemic 1-phenylethyl Grignard reagent **2a** was also observed in the cross-coupling with allylic substrates such as allyl phenyl ether in the presence of $\text{NiCl}_2[(S,S)\text{-chiraphos}(\mathbf{37})]$ which gave (*R*)-4-phenyl-1-butene (**48**) of 58% ee [49] (Scheme 9).

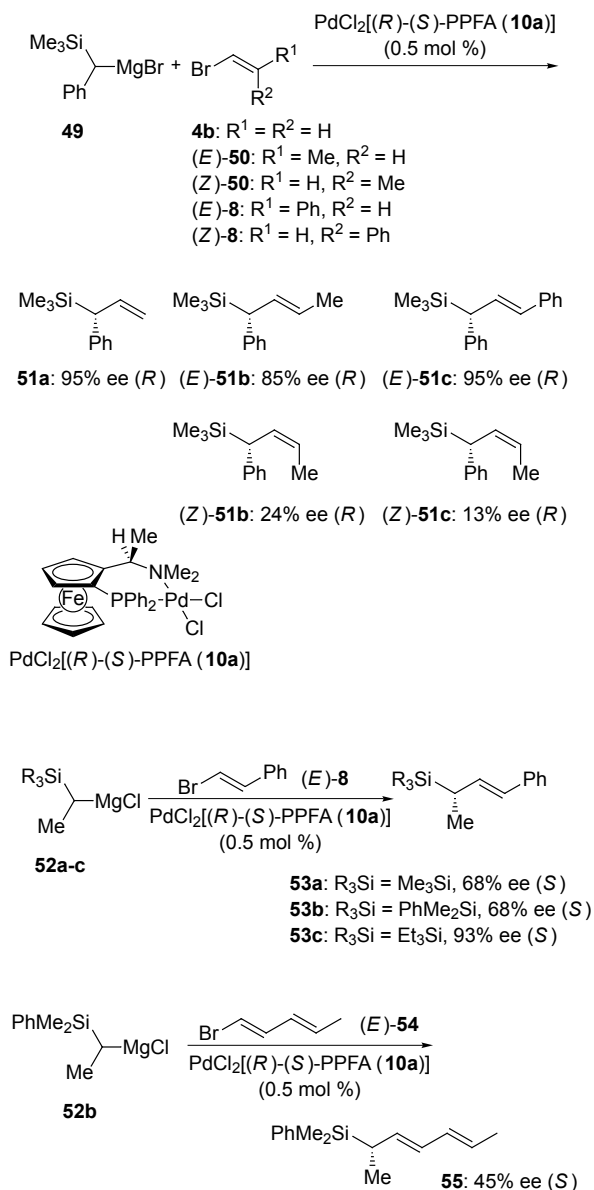
The asymmetric cross-coupling was successfully applied to the synthesis of optically active allylsilanes [50, 51] (Scheme 10). The reactions of α -(trimethylsilyl)benzylmagnesium bromide (**49**) with vinyl bromide (**4b**), (*E*)-bromopropene ((*E*)-**50**), and (*E*)-bromostyrene ((*E*)-**8**) in the presence of 0.5 mol % of a palladium complex coordinated with chiral ferrocenylphosphine, (*R*)-(*S*)-PPFA (**10a**), gave the corresponding (*R*)-allylsilanes (**51**) with 95%, 85%, and 95% ee, respectively, which were substituted with phenyl group at the chiral carbon center bonded to the silicon atom. These allylsilanes were used for the S_E'



Scheme 8



Scheme 9



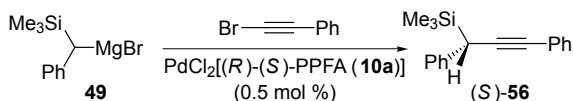
Scheme 10

reactions forming optically active homoallyl alcohols and π -allylpalladium complexes. A lower stereoselectivity was observed with the (*Z*)-alkenyl bromides (*Z*)-**50** and (*Z*)-**8**. The palladium/PPFA catalyst was also effective for the reaction of 1-(trialkylsilyl)ethylmagnesium chlorides **52** with (*E*)-bromosty-

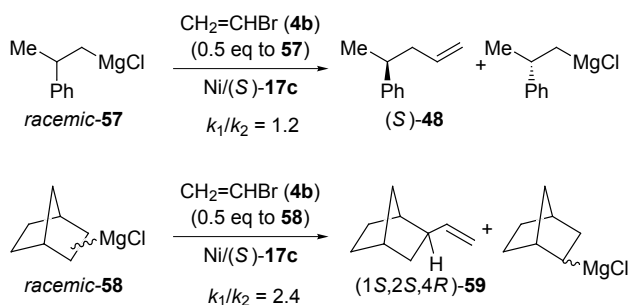
rene ((*E*)-**8**). The enantioselectivity was dependent on the trialkylsilyl group, triethylsilyl being the best to produce (*S*)-1-phenyl-3-silyl-1-butene (**53c**) of 93% ee. The dienyilsilane (*S*)-**55** which is 45% enantiomerically pure was also prepared by asymmetric cross-coupling with the dienyil bromide (*E*)-**54**. The palladium-catalyzed asymmetric cross-coupling of α -(trimethylsilyl)benzylmagnesium bromide (**49**) was also applied for the synthesis of the optically active propargylsilane **56** (18% ee) by using 1-bromo-2-phenylacetylene as a coupling partner [52] (Scheme 11).

The Grignard reagents, 2-phenylpropylmagnesium chloride (**57**) and the norbornyl Grignard reagent (**58**), that do not undergo the racemization have been kinetically resolved by asymmetric cross-coupling with less than 1 equiv of vinyl bromide, although the efficiency of the resolution is not high [53] (Scheme 12). One of the enantiomers of the racemic **58** underwent the coupling reaction in the presence of the (*S*)-valphos (**17c**)/Ni catalyst 2.4 times faster than the other enantiomer. The enantiomeric purity of the coupling product **59** was 37% ee at 19% conversion. Interestingly, all of the coupling products **59** have vinyl group in an *exo*-position.

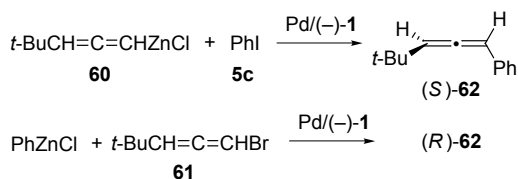
A chiral allene compound has been prepared by a palladium-catalyzed cross-coupling reaction of 4,4-dimethylpenta-1,2-dienylzinc chloride (**60**) with phenyl iodide (**5c**) or of 1-bromo-4,4-dimethylpenta-1,2-diene (**61**) with phenylzinc chloride [54] (Scheme 13). The highest enantiomeric purity (25% ee) of the allene (*S*)-**62** was obtained in the former coupling with (*R,R*)-diop (**1**) as chiral ligand. Interestingly, the enantiomeric purity was independent of the ratio of the reagents although the reaction seems to involve a kinetic resolution of the racemic **60**.



Scheme 11



Scheme 12



Scheme 13

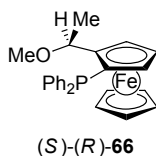
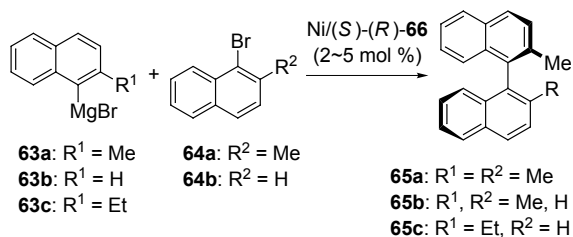
Several chiral ferrocenyl sulfides, which are analogous to PPFa (10a) or BPPFA (14) but have a sulfide group instead of a diphenylphosphine group, were used for the reaction of allylmagnesium chloride with 1-phenylethyl chloride in the presence of nickel or palladium catalysts to give 4-phenyl-1-pentene with up to 28% ee [55, 56].

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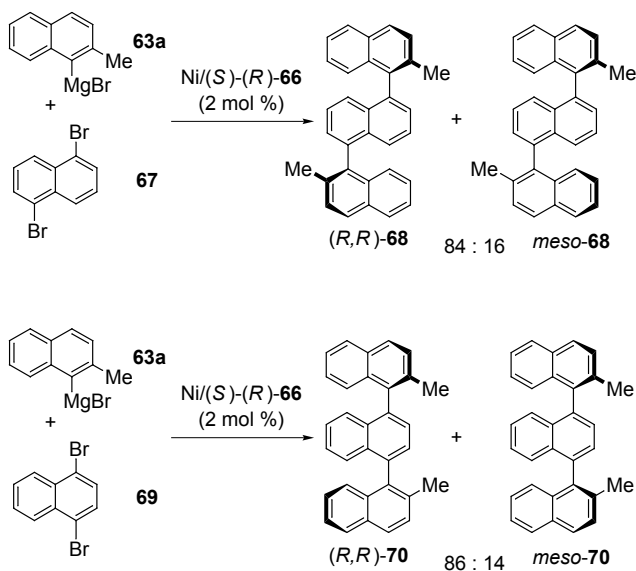
Asymmetric Cross-Coupling of Aryl Grignard Reagents Forming Axially Chiral Biaryls

The preparation of axially chiral binaphthyls is one of the most exciting applications of catalytic asymmetric cross-coupling reactions in organic synthesis. The reaction of 2-methyl-1-naphthylmagnesium bromide (**63a**) with 1-bromo-2-methylnaphthalene (**64a**) forming 2,2'-dimethyl-1,1'-binaphthyl (**65a**) has been examined using nickel catalysts coordinated with several chiral phosphine ligands (Scheme 14). Initial studies with (-)-diop (**1**), (S)-(R)-BPPFA (**14**), or (S)-**31** gave rather poor enantioselectivities (2%, 5%, and 13% ee, respectively) [33, 57]. Use of the ferrocenylphosphine ligand (S)-(R)-**66**, which is a chiral monophosphine ligand containing a methoxy group on the side chain, dramatically increased the selectivity to produce a high yield of (R)-**65a** with 95% ee [58]. High enantioselectivity was also attained in the reaction of **63a** with 1-bromonaphthalene (**64b**) which gave (R)-2-methyl-1,1'-binaphthyl (**65b**) with 83% ee. The binaphthyl (R)-**65b** was produced with a much lower % ee in the reaction of the other combination, that is, cross-coupling of 1-naphthylmagnesium bromide (**63b**) with 1-bromo-2-methylnaphthalene (**64a**). The 2-ethyl-1-naphthyl Grignard reagent **63c** was also successfully used for the reaction with **64b**, which gives **65c** of 77% ee.

The nickel-catalyzed cross-coupling of 2-methyl-1-naphthylmagnesium bromide (**63a**) was extended to the asymmetric synthesis of ternaphthalenes [59] (Scheme 15). Reaction of 1,5-dibromonaphthalene (**67**) with 2 equiv of **63a** in the presence of a nickel catalyst coordinated with (S)-(R)-**66** gave a high yield of ternaphthalene **68** consisting of chiral and *meso* isomers in a ratio of 84/16. The chiral isomer turned out to be 98.7% enantiomerically pure with the (R,R) configuration. The very high enantiomeric excess can be rationalized by the double asymmetric induction at the first and the second cross-couplings. The reaction



Scheme 14



Scheme 15

of **63a** with 1,4-dibromonaphthalene (**69**) gave ternaphthalene (*R,R*)-**70** of 95.3% ee together with a small amount of *meso*-**70**.

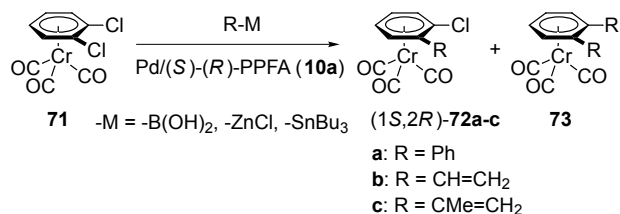
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Enantioposition-Selective Asymmetric Cross-Coupling

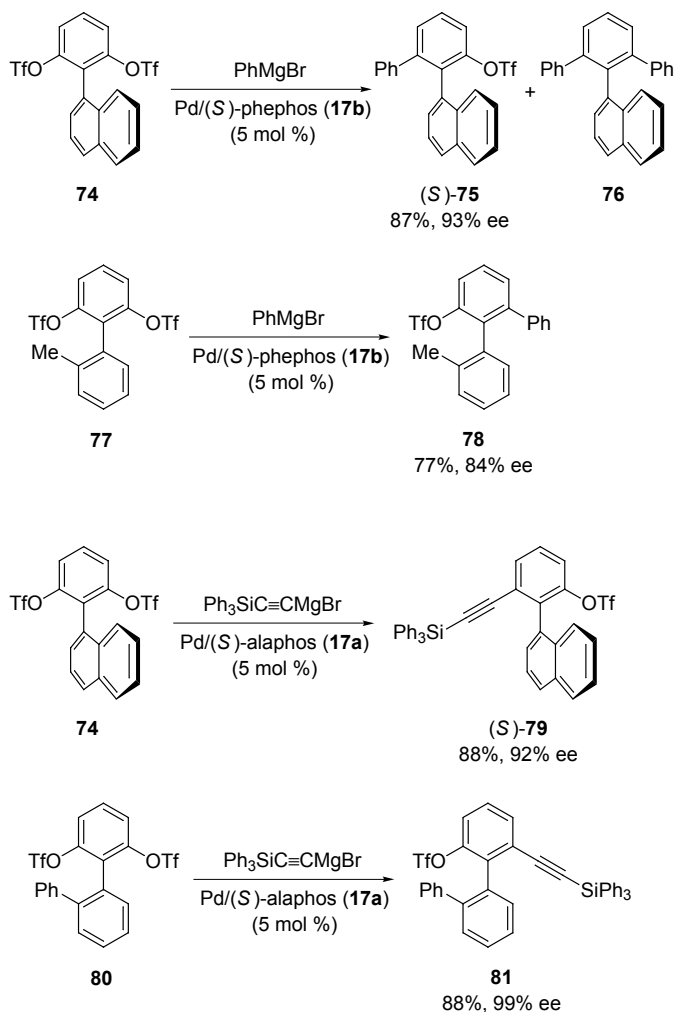
Planar chiral tricarbonyl(η^6 -arene)chromium complexes were prepared by catalytic asymmetric cross-coupling of tricarbonyl(η^6 -*o*-dichlorobenzene)chromi-

um (71) with alkenyl- or arylmetal reagents [60, 61] (Scheme 16). In the presence of 10 mol % of a palladium catalyst generated from $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ and ferrocenylmonophosphine (*S*)-(*R*)-PPFA (10a), an enantioselective substitution of one of the chloride atoms takes place to give the planar chiral monosubstitution products 72 together with a minor amount of the disubstitution products 73 which are achiral. The highest enantiomeric excess of the monosubstitution product is 69% ee which was reported for the phenylation of 71 with phenylboronic acid to afford (1*S*,2*R*)-72a. Alkenylation with ethenylboronic acid or propen-2-ylboronic acid also proceeded enantioselectively to give the corresponding monoalkenylation product 72b (38% ee) or 72c (44% ee). Interestingly, use of ethenyltributyltin as the vinylation reagent in place of ethenylboronic acid resulted in the formation of the racemic product 72b while use of ethenylzinc chloride gave 72b of 42% ee.

The enantioselective asymmetric cross-coupling has been also successfully applied to the synthesis of axially chiral biaryl molecules [62] (Scheme 17). Reaction of the achiral ditriflate 74 with 2 equiv of phenylmagnesium bromide in the presence of lithium bromide and 5 mol % of $\text{PdCl}_2[(\text{S})\text{-phephos (17b)}]$ at -30°C for 48 h gave an 87% yield of the monophenylation product (*S*)-75 which is 93% ee and a 13% yield of the diphenylation product 76. The enantiomeric purity of the monophenylation product (*S*)-75 is dependent on the yield of the diphenylation product 76. A kinetic resolution is demonstrated to take place at the second cross-coupling forming 76. The minor isomer at the first cross-coupling, that is (*R*)-75, is consumed five times faster than the major isomer (*S*)-75 at the second cross-coupling, which causes an increase in the enantiomeric purity of (*S*)-75 as the amount of 76 increases. High enantioselectivity was also reported in the reaction of the *o*-tolyl analogue 77 which gave the monophenylation product 78 of 84% ee. For enantioselective alkynylation, the (*S*)-alaphos (17a) ligand is more enantioselective than (*S*)-phephos (17b) [63]. For example, the reactions of achiral ditriflates 74 and 80 with (triphenylsilyl)ethynylmagnesium bromide in the presence of a palladium catalyst coordinated with (*S*)-alaphos (17a) gave the corresponding monoalkynylation products (*S*)-79 (92% ee) and 81 (99% ee), respectively.



Scheme 16



Scheme 17

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Chapter 26.1

Alkylation of Carbonyl Groups

Kenso Soai · Takanori Shibata

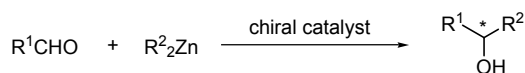
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Keywords: Amino alcohol, Dialkylzinc, Alkylation, Alcohol, Asymmetric autocatalysis

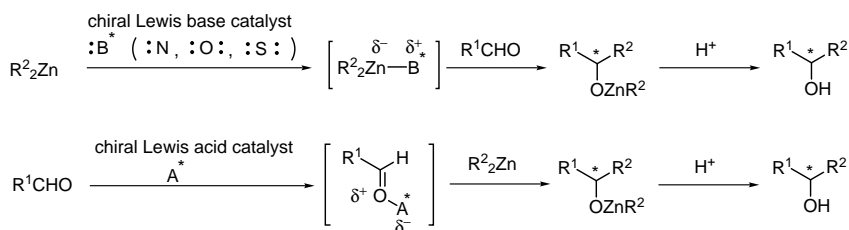
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1 Introduction

One of the most useful methods for the synthesis of optically active *sec*-alcohols is catalytic enantioselective alkylation of aldehydes using organometallic reagents. The advantages of enantioselective alkylation of aldehydes over enantioselective reduction of ketones are as follows: (1) Elongation of the carbon skeleton is possible in combination with the generation of a chiral center. (2) *Ee*'s of the enantioselective alkylation of aliphatic aldehydes are usually higher than those of the reduction of aliphatic ketones. Among the organometallic reagents,



Scheme 1



Scheme 2. Chiral catalysts for the enantioselective addition of dialkylzinc species to aldehydes

dialkylzinc is utilized most frequently in catalytic enantioselective alkylation of aldehydes [1, 2]. Enantio- and chemoselective alkylations of functionalized aldehydes with dialkylzinc reagents using chiral catalysts (Scheme 1) afford optically active functionalized *sec*-alcohols with high ee's [1]. Asymmetric autocatalytic alkylation has been achieved with nitrogen-containing heterocyclic aldehydes [3].

2

The Mechanism of Catalysis for the Alkylation of Aldehydes with Dialkylzincs

There are two mechanisms of catalysis for the alkylation of aldehydes with dialkylzinc reagents. One is Lewis base-promoted catalysis and another is Lewis acid-promoted catalysis (Scheme 2). Dialkylzinc reagents do not usually react with aldehydes in the absence of catalysts, because their nucleophilicity is not sufficiently high. However, Lewis bases (atoms as electron donor are nitrogen, oxygen, and sulfur) such as a β -amino alcohol [4] activate dialkylzinc reagents by the formation of zincates, which are able to react with aldehydes. Thus, enantioselective alkylation using a chiral Lewis base as a catalyst affords optically active *sec*-alcohols. On the other hand, a chiral Lewis acid enhances the electrophilicity of aldehydes by coordination to the oxygen atoms of the aldehydes, thus dialkylzincs could make an addition to aldehydes.

3

Asymmetric Alkylation of Aldehydes Catalyzed by Chiral Lewis Base

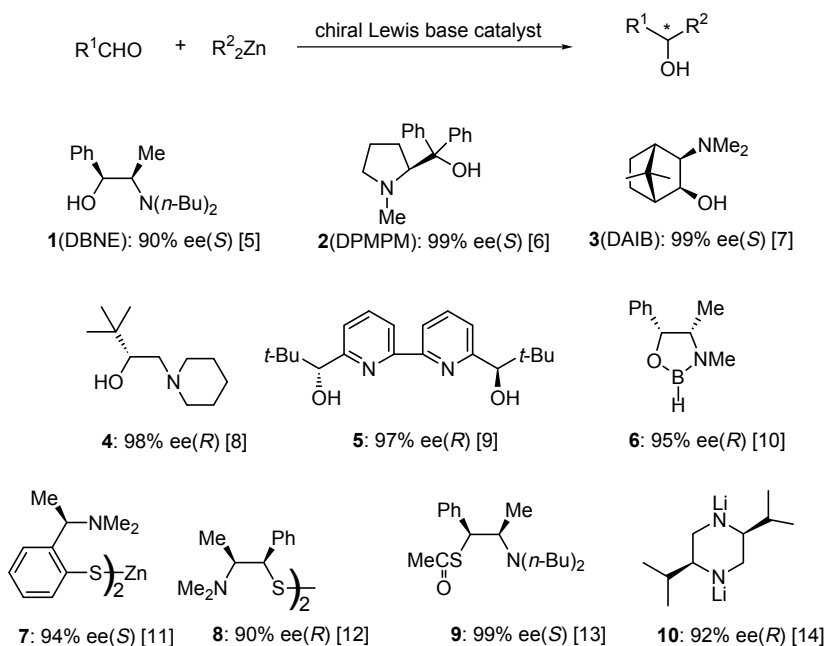
In the presence of a catalytic amount of a chiral β -amino alcohol, the enantioselective ethylation of benzaldehyde with diethylzinc affords enantiomerically en-

riched 1-phenylpropanol. Some representative β -amino alcohols **1** to **4** as highly enantioselective chiral catalysts are shown in Scheme 3.

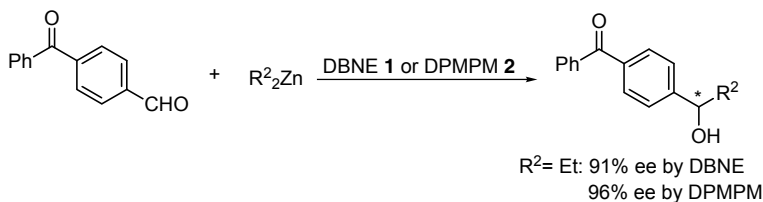
The chiral catalysts **1** to **4** are highly enantioselective in the addition of di(*prim*-alkyl)zincs to aromatic aldehydes. (1*S*, 2*R*)-*N,N*-dibutylnorephedrine [**1** (DBNE)] [**5**] possesses the advantage of its utility as a highly enantioselective catalyst even for the alkylation of aliphatic aldehydes to afford aliphatic *sec*-alcohols with up to 93% ee [**5**]. DBNE is also an appropriate chiral catalyst for the addition of diisopropylzinc [di(*sec*-alkyl)zinc] (98% ee) [**15**]. (*S*)-Diphenyl(1-methylpyrrolidin-2-yl)methanol [**2** (DPMPM)] [**6**] catalyzes the enantioselective ethylation of aromatic aldehydes to afford almost enantiomerically pure *sec*-alcohols [**6**]. 3-*exo*-(Dimethylamino)isoborneol [**3** (DAIB)] [**7**] and **4** [**8**] are also highly enantioselective catalysts for the alkylation of aromatic aldehydes [**7**, **8**].

Highly enantioselective chiral catalysts other than β -amino alcohols for the addition of diethylzinc to aromatic aldehydes include the chiral bipyridylalkanol **5** [**9**], the oxazaborolidine **6** [**10**], the amino thioate **7** [**11**], the amino disulfide **8** [**12**], the amino thioester **9** [**13**], and the lithium amide of piperazine **10** [**14**]. The chiral amino thioester **9**, a thioester analog of DBNE, does not form a zinc amide or a zinc thioate because it does not possess an acidic hydrogen atom. Simple coordination of nitrogen and sulfur atoms to the zinc atom of diethylzinc may generate an efficient chiral catalyst.

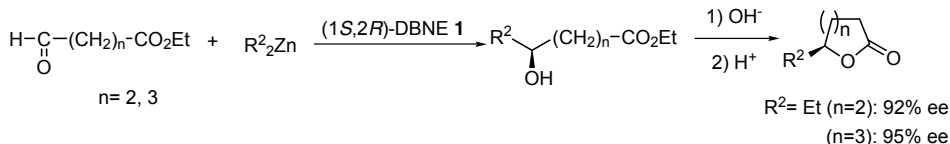
Enantio- and chemoselective alkylations of ketoaldehydes and formylesters using the chiral catalysts DBNE and DPMPM give enantiomerically enriched hy-



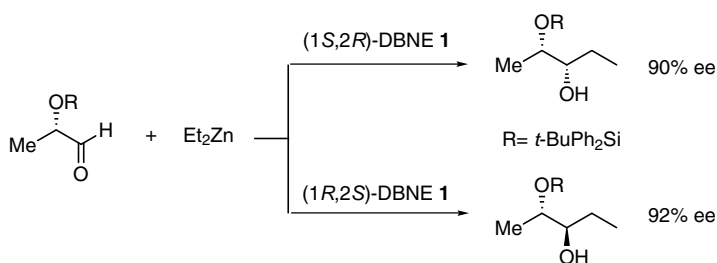
Scheme 3



Scheme 4



Scheme 5



Scheme 6

droxyketones [16] and hydroxyesters which are readily transformed into chiral lactones [17] with high ee's (Scheme 4 and Scheme 5). These reactions are not usually possible with alkylolithiums and Grignard reagents since these reagents could even react with ester and ketone moieties.

In the asymmetric alkylation of α -chiral aldehydes using dialkylzinc reagents, the stereochemistry is controlled by the configuration of the chiral catalyst, not by the stereochemistry in the α -position. It is different from the diastereoselective alkylation using other organometallic reagents where the stereochemistry follows from Cram's rule or the Felkin-Ahn model. Each diastereomer with high ee was obtained by the choice of the appropriate enantiomer of chiral catalyst [(1*S*, 2*R*)- or (1*R*, 2*S*)-DBNE 1] (Scheme 6) [18].

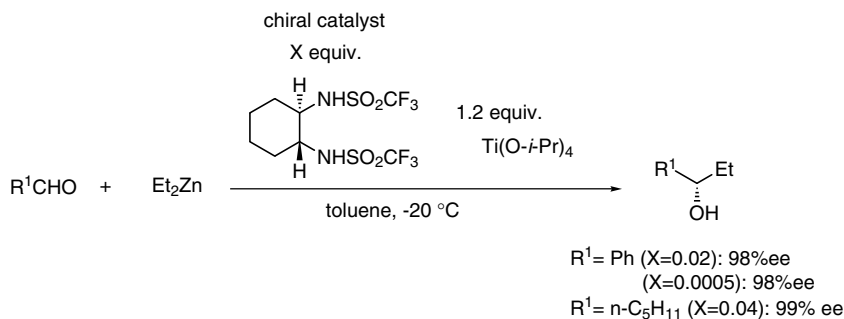
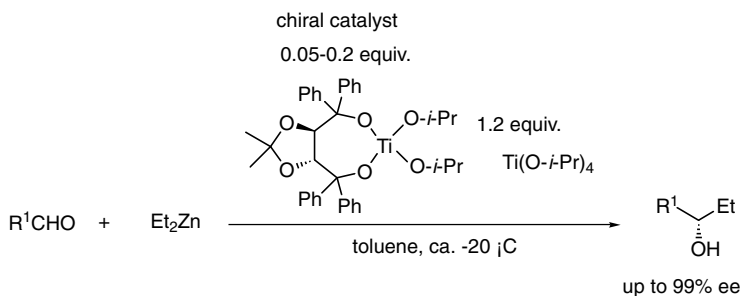
4

Asymmetric Alkylation of Aldehydes Catalyzed by Chiral Lewis Acid

The addition of dialkylzinc to aldehyde proceeds smoothly in the presence of a Lewis acid. Several catalytic asymmetric alkylations catalyzed by chiral titanium complexes have been reported using dialkylzinc reagents.

Ohno et al. developed an enantioselective alkylation by the use of a C₂-symmetric disulfonamide as a chiral ligand [19, 20, 21]. They designed the chiral catalyst based on the concept that coordination of an electron-withdrawing chiral ligand to the Lewis acid, Ti(O-*i*-Pr)₄, enhances the catalytic activity. Actually, the acidity of the disulfonamide has an influence on the enantioselectivity and fluorine-containing disulfonamides, especially trifluoromethylsulfonamide, were found to be the best choice of chiral catalyst (Scheme 7). It should be noted that a decrease in the amount of chiral ligand from 0.02 equiv. to 0.0005 equiv. has no effect on the yield and ee and the turnover reached 2,000. Also in the alkylation of aliphatic aldehydes, very high enantioselectivities can be attained.

Seebach et al. have comprehensively examined the use of a chiral diol (TADDOL) derived from tartaric acid as a chiral ligand [22]. The titanium-TADDOL system also catalyzes the asymmetric addition of diethylzinc to various aldehydes (Scheme 8) [23, 24]. This system is applicable to the alkylation of various

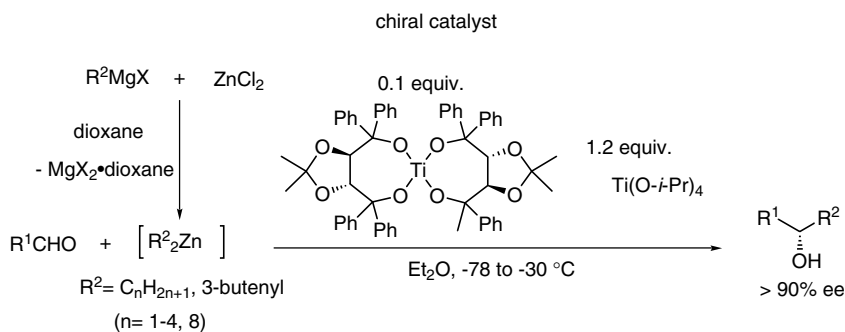
**Scheme 7****Scheme 8**

dialkylzinc reagents prepared in situ from Grignard reagents and ZnCl_2 by excluding MgX_2 as a dioxane complex (Scheme 9) [25, 26]. Commercially available dialkylzinc reagents are limited, therefore, the preparation of the dialkylzinc reagents from the respective Grignard reagents, which are more accessible than the dialkylzinc species, could widen the utilization of asymmetric alkylation.

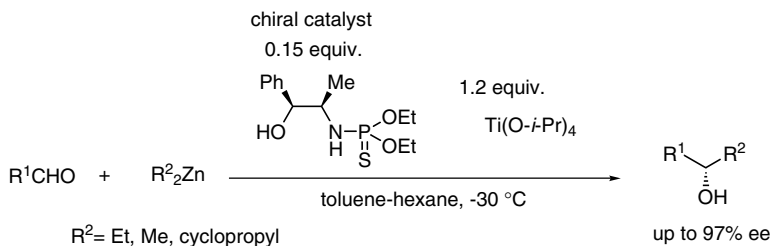
Recently, Chan and Nakai et al. independently reported that a chiral binaphthol-titanium complex is also an effective catalyst in the asymmetric ethylation by diethylzinc to afford chiral *sec*-alcohols in good ee's [27, 28].

The utilization of chiral thiophosphoramidate derivatives as chiral catalysts is almost unexplored. Soai et al. found that a chiral thiophosphoramidate derived from norephedrine is an effective catalyst for the enantioselective alkylation of aldehydes with dialkylzinc reagents with the aid of $\text{Ti}(\text{O}-i\text{-Pr})_4$ (Scheme 10) [29, 30]. Only moderate ee's can be achieved by the corresponding phosphoramidate (oxygen analogue) or thiophosphinamide. This means that thiophosphoramidate component is indispensable for the highly enantioselective induction. Recently, it was found that the $\text{Ti}(\text{O}-i\text{-Pr})_4$ -chiral thiophosphoramidate ligand catalyzed the asymmetric cyclopropylation of various aldehydes by dicyclopropylzinc (up to 97% ee) [31]. This is the first example of a highly enantioselective cycloalkylation using a dicycloalkylzinc reagent.

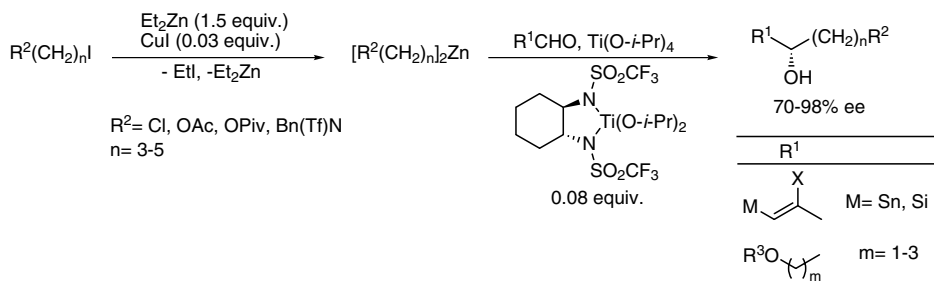
Knochel et al. comprehensively studied the preparation of functionalized organozinc species [32] and their application for an enantioselective alkylation of various aldehydes. An iodine-zinc exchange reaction in the presence of a cata-



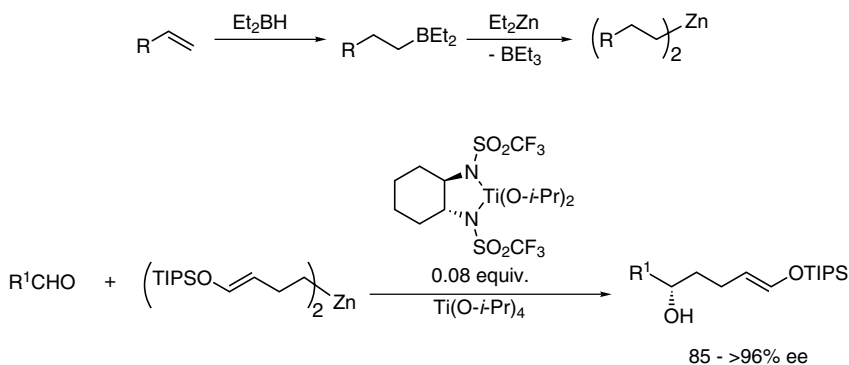
Scheme 9



Scheme 10



Scheme 11



Scheme 12

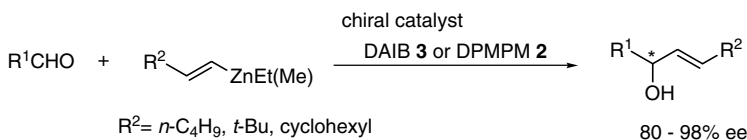
lytic amount of CuI provides dialkylzinc reagents possessing halogen, oxygen, nitrogen functionalities at the terminal positions. By use of these functionalized dialkylzincs, asymmetric alkylations of various aldehydes were examined in the presence of the chiral disulfonamide-titanium complex [19, 20, 21] as an asymmetric catalyst. Synthetically useful chiral compounds, such as γ -silylated or γ -stannylated allyl alcohols and diols, were obtained in high ee's (Scheme 11) [33, 34, 35].

A more convenient method for the preparation of functionalized organozinc species is hydroboration of an alkene followed by transmetalation with Et_2Zn [36]. In this scheme, a wider range of functional organozincs is readily synthesized. For example, Knochel et al. reported that a dialkylzinc, prepared from a dienic silyl enol ether, enantiomerically added to various aldehydes in the presence of the chiral disulfonamide-titanium system (Scheme 12) [37].

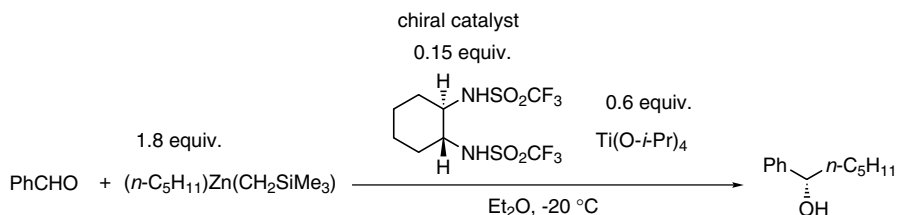
5

Asymmetric Alkylation Using Unsymmetrical Dialkylzincs

One of the drawbacks of alkylation using a dialkylzinc reagent is that only one R^2 group in R^2_2Zn is transferred to the aldehyde and the other is wasted. When



Scheme 13



Scheme 14

an unsymmetrical dialkylzinc (R^2ZnR^3) is utilized, however, only the more reactive site operates as an alkylation reagent. For an example, asymmetric alkenylation overwhelmingly proceeded on the use of an alkenylalkylzinc in the presence of a catalytic amount of chiral amino alcohols to afford chiral allyl alcohols (Scheme 13) [38, 39]. Also, in the case of an alkynylalkylzinc, alkynylation proceeds to give chiral propargyl alcohols in moderate ee [40].

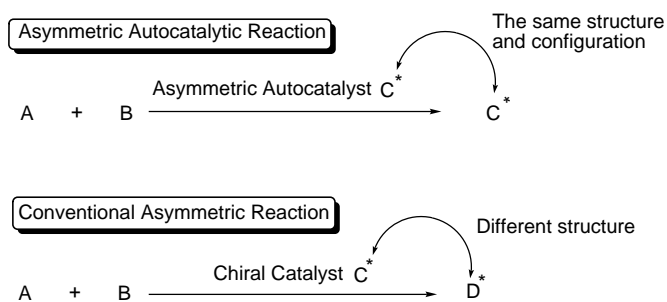
Recently, the trimethylsilylmethyl group was found to work as a dummy site in the alkylation using an unsymmetrical dialkylzinc. Highly enantioselective and chemoselective pentylation proceeds on use of pentyl(trimethylsilylmethyl)zinc (Scheme 14) [41]. This concept will probably exhibit its utility when a very valuable R^2 group must be transferred.

6

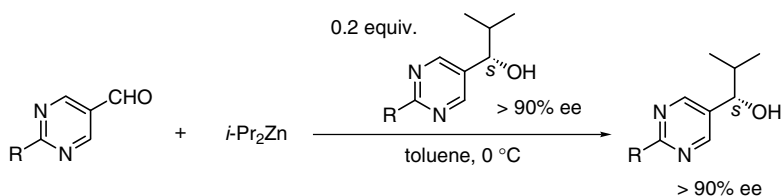
Asymmetric Autocatalytic Alkylation

Asymmetric autocatalysis, where the structures of chiral catalyst and the product are identical, i.e., the chiral product plays the role of the chiral catalyst, is a very intriguing system from both scientific and synthetic standpoints (Scheme 15) [42, 43]. From the latter standpoint, it intrinsically possesses the following advantages over conventional asymmetric reactions, where the structures of the chiral catalyst and product are different from each other: 1) The number of multiplication is practically infinite. 2) the chiral catalyst is semipermanently active without deterioration. 3) A separating process for catalyst and the product is not needed.

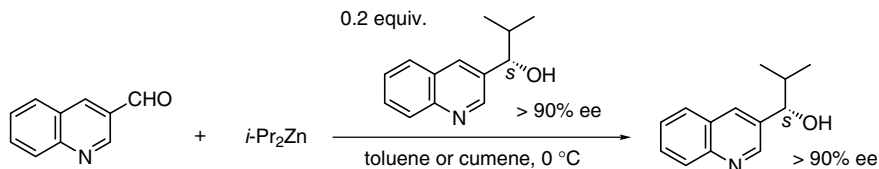
Several scientists had pointed out the importance of asymmetric autocatalysis but it remained a theoretical system until Soai found an asymmetric alkylation of pyridine-3-carbaldehyde: the 3-pyridylalkanol functions as an asymmetric autocatalyst in an enantioselective alkylation of pyridine-3-carbaldehyde us-



Scheme 15



Scheme 16



Scheme 17

ing dialkylzinc reagents to provide the 3-pyridylalkanol of the same configuration as the catalyst [44]. Chiral diols and ferrocenyl alcohol were also found to have asymmetric autocatalytic activity [45, 46], but enantioselectivities in these reactions remained low to moderate. Recently, a highly enantioselective autocatalytic alkylation was established in asymmetric isopropylation of pyrimidine-5-carbaldehyde and quinoline-3-carbaldehyde (Scheme 16 and Scheme 17) [47, 48]. When 0.2 equiv. of chiral alkanols (>90% ee) were employed, they automultiplied without any loss of ee to afford themselves (>90% ee).

Moreover, when these alkanols with low ee are utilized as asymmetric autocatalysts, pyrimidyl- and quinolylalkanol with higher ee were obtained [49, 50]. The reactions were performed in succession in order to make the best use of the autocatalysis, that is, the products of one run served as the asymmetric autocatalyst for the next. In the case of pyrimidylalkanol, starting from (*S*)-alkanol with only 2% ee, the ee reached almost 90% after 4 runs [49].

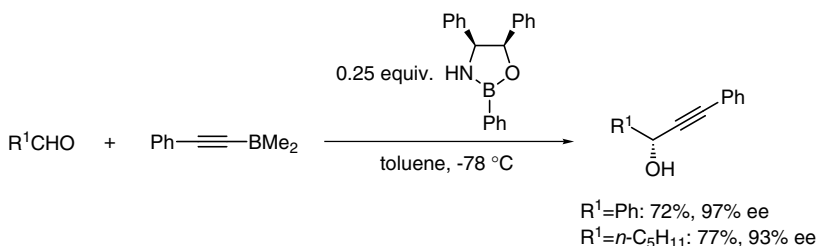
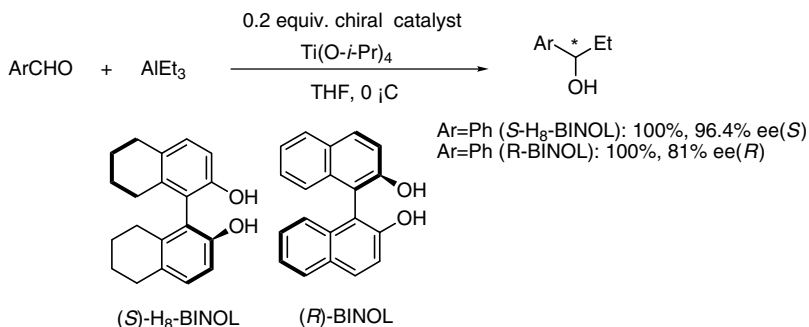
7

Asymmetric Alkylation Using Alkynylborane and Trialkylaluminum

Diorganozinc reagents have a monopoly as alkylation reagents in catalytic asymmetric alkylations of aldehydes. But a few catalytic asymmetric alkylations were reported by the use of alkynylborane and trialkylaluminum species.

Corey et al. reported a highly enantioselective alkylation using a chiral oxazaborolidine as catalysts [51] in a manner analogous to asymmetric reduction of ketones with borane [52]. The alkylation reagent is alkynyldimethylborane which is prepared in situ from bromodimethylborane and the corresponding alkynylstannane. A catalytic cycle was realized by the use of an oxazaborolidine possessing a phenyl group on the boron atom (Scheme 18).

Various trialkylaluminum reagents can be obtained on an industrial scale. However, their utilization in asymmetric alkylation is limited, for example, an enantioselective allylation of aldehydes by allyldialkylaluminum [53]. Recently, Chan et al. reported the first example of a catalytic alkylation of aldehyde using triethylaluminum [54]. Asymmetric ethylations of various aromatic aldehydes proceed in very high yields and ees in the presence of a chiral titanium alkoxide prepared from $\text{Ti}(\text{O}-i\text{-Pr})_4$ and chiral 5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (H_8 -BINOL) (Scheme 19). It is noteworthy that H_8 -BINOL is a more efficient chiral catalyst than BINOL. High enantioselectivity can be attained only in the

**Scheme 18****Scheme 19**

combination of aromatic aldehydes and triethylaluminum but this research should open a broader perspective in asymmetric alkylations.

8 Principal Alternatives

Several methods have been reported for the enantioselective alkylation of aldehydes using a stoichiometric amount of chiral ligands. Organometallic reagents utilized in these methods include alkyllithium species, Grignard reagents, and dialkylmagnesium reagents [4, 55, 56, 57, 58, 59].

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Chapter 26.2

Alkylation of Imino Groups

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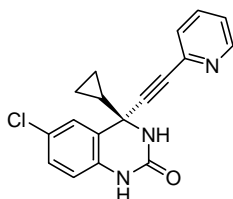
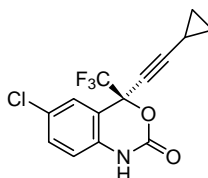
Keywords: Auxiliary, Ligand, Controller, Catalyst, Alkylation, Allylation, Mannich reaction, Azomethine function, C=N bond, Imine, Nitron, Oxime, Organometallic compound, Organolithium reagents, Grignard reagents, Organozinc reagents, Organoboron reagents, π -Allylpalladium complexes, Lithium enolates, Silyl ketene acetal, Silyl enol ether, Homoallylic amine, Amine, α -Amino acid

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1

Introduction

One of the most economical ways of generating single enantiomers of chiral compounds is by asymmetric catalysis, for recent reviews, see Refs. [1a, 1b, 1c]. Over the past few years, much emphasis has been placed on the design and development of cost-effective chiral catalysts that display a high degree of reactivity and enantioselectivity. One of the stronger arguments for asymmetric catalysis is without any doubt its use in industrial asymmetric synthesis. In the context of this chapter, the development of a commercially viable, highly enantioselective process for manufacturing a promising antiviral drug is noteworthy [2a, 2b]. The drug candidate, DMP-266, is actually one of two compounds that belong to two new classes of potent non-nucleoside HIV-1 reverse transcriptase inhibitors recently reported [3a, 3b]. The synthesis of DMP-266 was achieved using a highly enantioselective (96–98% ee) lithium cyclopropylacetylide addition to a trifluoroacetophenone in the presence of a lithiated ephedrine derivative [2b].

**L-738,372****DMP-266**

The routes to enantiomerically pure compounds (resolution notwithstanding) represent two modes of asymmetric synthesis: (1) chiral auxiliary-based asymmetric synthesis (asymmetric diastereoselective synthesis), (2) external chiral ligand-controlled asymmetric synthesis (asymmetric enantioselective synthesis) which includes asymmetric catalysis. All of these methods have been applied to the asymmetric synthesis of amines and amine derivatives via the asymmetric alkylation of the C=N function. An excellent general review on the alkylation of the C=N function is given in Ref. [4a; for recent reviews on the asymmetric synthesis of amines, see Refs. 4b, and 4c. Reviews on the asymmetric synthesis of amines and their derivatives via stabilized carbanion additions to the C=N bond of azomethines bearing a chiral auxiliary are given in Refs. 5a, 5b, 5c. For reviews on the asymmetric synthesis of amines and amine derivatives via non-stabilized carbanion additions to the C=N bond of azomethines bearing a chiral auxiliary, see Refs. 6a, 6b, 6c, 6d]. Enantiomerically pure amines [7] are indeed important compounds utilized extensively in organic synthesis as resolving agents [8], raw materials or intermediates in the production of biologically active substances [9], and chiral auxiliaries for asymmetric synthesis [10]. The objective of this review is to provide a comprehensive overview of the current state of the art of asymmetric catalysis in the addition of nucleophiles to the azome-

thine function [11a, 11b]. The scope is all encompassing for C=N function (imines, oximes, nitrones) as well for nucleophiles (alkyl and allyl organometallics, enolates and enol silanes). Certain cases wherein external chiral adjuvants have been used in stoichiometric quantities are included for completeness and because these cases are likely to provide the foundation for the development of catalytic processes. For reviews on the use of external chiral ligands in asymmetric synthesis, see Refs. [12a, 12b, 12c, 12d].

2

C=N vs C=O Catalytic Asymmetric Alkylation

The asymmetric addition of organometallic reagents to the azomethine group in the presence of chiral ligands is quite underdeveloped in comparison to the effort on record in the area of stoichiometric, enantioselective alkylation of carbonyl groups [13a, 13b, 13c]. This disparity is primarily due to the poor electrophilicity of the C=N function and the tendency of enolizable azomethines to undergo deprotonation rather than addition. Recently, however, Kobayashi et al. have discovered the remarkable ability of lanthanide triflates to reverse the normal reactivity trends for aldehydes and their derived aldimines. Kobayashi found that at low temperature, catalytic amounts of Yb(OTf)₃ effected the reaction of trimethylsilyl enol ethers of ketones with aldimines even in the presence of the corresponding aldehyde [14a]. Similarly, Sc(OTf)₃ catalyzed the condensation of an aldehyde, an amine and allyltributylstannane to afford homoallylic amines in good yield [14b]. Here again the in situ generated aldimine reacted preferentially over the aldehyde in the reaction mixture. Thus, important strategies for successful catalytic enantioselective additions are to: amplify the nucleophilicity of the alkylating agent, attenuate the basicity of the alkylating agent or find specialized catalysts that particularly activate azomethine functions.

The ultimate goal of using an external, chiral ligand in a chemical reaction is the potential for a catalytic, asymmetric synthetic transformation, [1a, 1b, 1c]. Thus, the substoichiometric, asymmetric alkylation of aldehydes with organozinc reagents represents a major accomplishment [1a, 15a, 15b, 15c, 15d], whereas a similar catalytic process for azomethine derivatives has only recently been achieved.

3

Mechanism of Catalysis in the Ligand-Mediated Addition of Organometallic Reagents to the C=N Bond

One must be well aware of the characteristic features concerning the addition of organometallic reagents to carbon-heteroatom multiple bonds such as the carbon-oxygen and the carbon-nitrogen double bonds in order to develop a catalytic asymmetric process for this type of reaction.

With regard to the mechanism of addition of Grignard reagents (RMgX) to aldehydes and ketones, it has been proposed that the initial stages of this mechanism involve the formation of various complexes composed of the carbonyl com-

pound and a species such as RMgX , R_2Mg , or MgX_2 , via $\text{O}\cdots\text{Mg}$ interaction. This type of complexation appears to be required prior to the addition of the nucleophile to the carbonyl group. In the case of organolithium additions to carbonyl compounds, a similar activation of the substrate prior to nucleophilic addition has been also invoked. For example, in their work on the use of organolithium compounds with ketones in the presence of a cryptand, Perraud and co-workers have demonstrated the need of electrophilic catalysis by the Li^+ ion in the nucleophilic addition of organolithiums [16a, 16b]. In the context of amines and amine derivatives synthesis, these remarks on the complexation of carbonyl compounds prior to nucleophilic addition indicate, in the same way, the very likely complexation of the azomethine function to the metal atom of the organometallic compound before the transfer of the alkyl group to the $\text{C}=\text{N}$ bond. The development of a catalytic asymmetric alkylation of an azomethine function will therefore require the complexation of the sp^2 hybridized nitrogen atom to the metal atom of the chiral catalyst-complexed organometallic compound before the transfer step.

For most azomethine functions and organometallic compounds examined in this review, the challenge of developing a successful catalytic asymmetric alkylation process resides in controlling the competition that exists between the chiral ligand-catalyzed reaction and the non-catalyzed reaction. This is a fundamental feature of all ligand-accelerated processes including the chiral amino alcohol-catalyzed addition of organozinc compounds to aldehydes [15a, 15b, 15c, 15d, 17]. The catalytic enantioselective alkylation of azomethine functions is a typical example in which ligand-acceleration effects will be essential for the catalyzed reaction to occur in a rapid and highly enantioselective manner. This ligand-accelerated catalysis will be even more critical when a substoichiometric amount of the chiral ligand is used. The major course of the alkylation reaction will be expected to proceed from the chiral ligand-complexed substrate-organometallic compound combination which should have a higher reactivity than the substrate-organometallic compound combination itself.

The major concern with respect to the mechanism of catalysis of such asymmetric alkylation reactions is to assure the continuous presence in solution of the more reactive complex. The addition of an organometallic compound to a $\text{C}=\text{N}$ bond will produce indeed a new metallated species in solution: a metal amide. This metal amide will be strongly coordinated to the chiral ligand [18], and will compete with the organometallic compound toward complexation with the chiral ligand. Regeneration of the more reactive chiral ligand-complexed substrate-organometallic compound combination, through ligand exchange from the chiral ligand-complexed metal amide and the organometallic compound, is an essential step in the catalytic asymmetric alkylation of azomethine functions. Tomioka and co-workers, pioneers in the field of enantioselective alkylation of imines, have discussed this fundamental issue of catalytic reactive species regeneration, in the context of their findings as illustrated in Fig. 1 [19d].

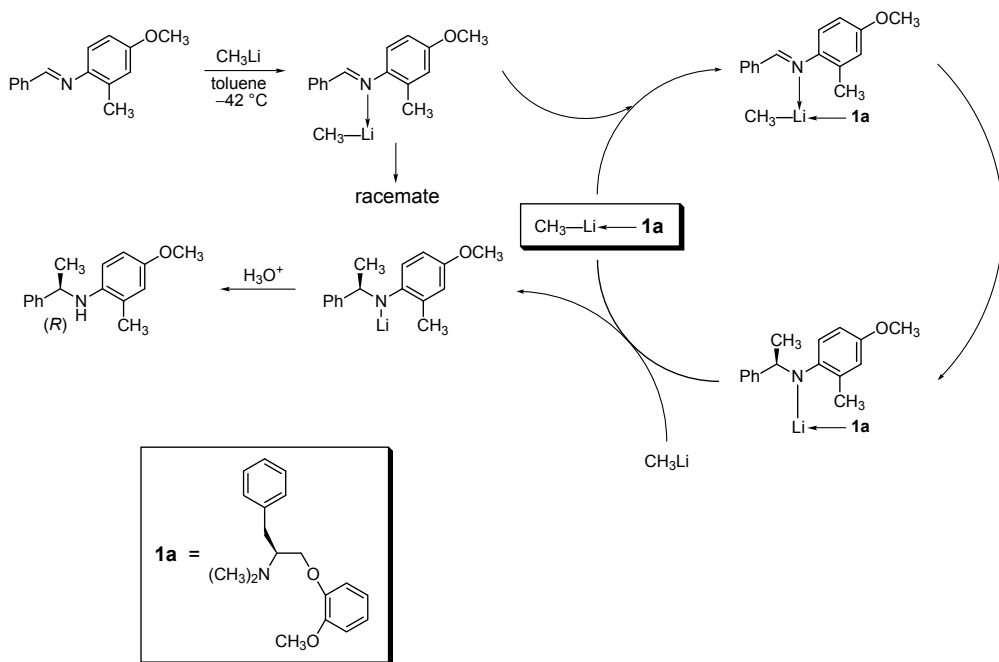


Fig. 1

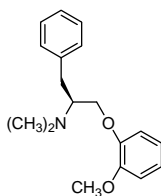
4

Basis for Stereinduction in the Ligand-Mediated Addition of Organometallic Reagents to the C=N Bond

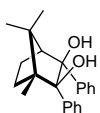
As highlighted in the previous section, the C=N containing substrate will most likely need to become coordinated to the metallic catalyst or reagent to observe the addition reaction. This prerequisite is responsible for the initial recognition process between these two reactive species. The orientation of the chiral catalyst in close proximity to the coordination site will be expected to have a strong influence on the course of the reaction.

Whereas all reactions using organozinc reagents employed chiral amino alcohols as catalysts, the use of organolithium reagents, and Grignard reagents to a lesser extent, has required a greater level of variety of chiral ligand structure. The various catalysts used in the catalytic enantioselective additions to imines and imine derivatives reported in this review are highlighted in Fig. 2 and Fig. 3. Those employed for alkylation with organolithium, -zinc, and -magnesium reagents are collected in Fig. 2 and those catalysts suitable for allylation and Manich-type reaction are found in Fig. 3.

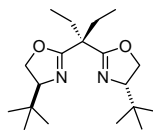
Catalytic Asymmetric Alkylation with Organolithium Reagents:



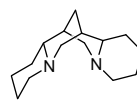
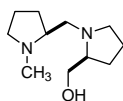
Tomioka et al. (Ref. 19)



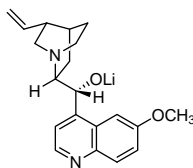
Itsuno et al. (Ref. 23a)



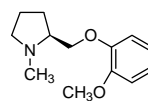
Denmark et al. (Ref. 25a)

Denmark et al. (Ref. 25a)
Itsuno et al. (Ref. 23b)

Itsuno et al. (Ref. 23b)

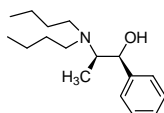
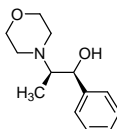


Huffman et al. (Ref. 31a)

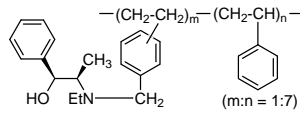


North et al. (Ref. 32)

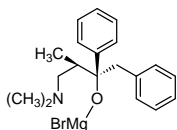
Catalytic Asymmetric Alkylation with Organozinc Reagents:

Katritzky et al. (Ref. 34)
Soai et al. (Refs. 35a, 35b)

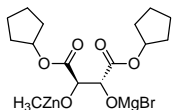
Soai et al. (Refs. 35a, 35b)



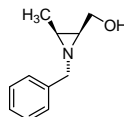
Soai et al. (Ref. 35c)



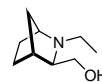
Ukaji et al. (Ref. 39a, 39b)



Ukaji et al. (Ref. 40)

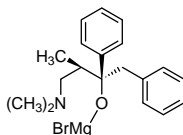


Andersson, Tanner et al. (Refs. 37c, 37d)



Andersson et al. (Ref. 38)

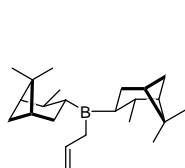
Catalytic Asymmetric Alkylation with Grignard Reagents:



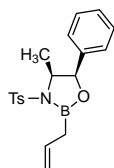
Ukaji et al. (Refs. 39a, 39b)

Fig. 2

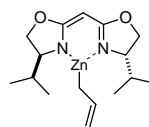
Catalytic Asymmetric Allylation



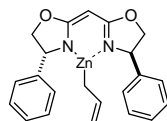
Itsuno et al. (Ref. 42a)



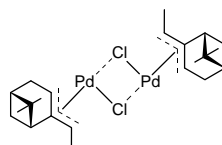
Itsuno et al. (Ref. 42b)



Nakamura et al. (Ref. 43)

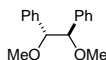


Hanessian et al. (Ref. 45)

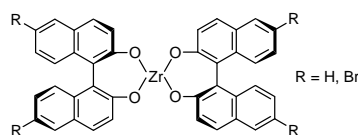


Yamamoto et al. (Ref. 46)

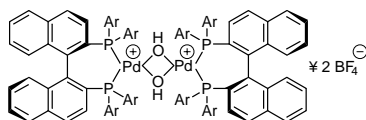
Catalytic Asymmetric Mannich-Type Reaction



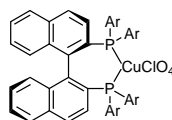
Tomioka et al. (Ref. 50)



Kobayashi et al. (Ref. 51)



Sodeoka et al. (Ref. 53)



Lectka et al. (Ref. 54)

Fig. 3

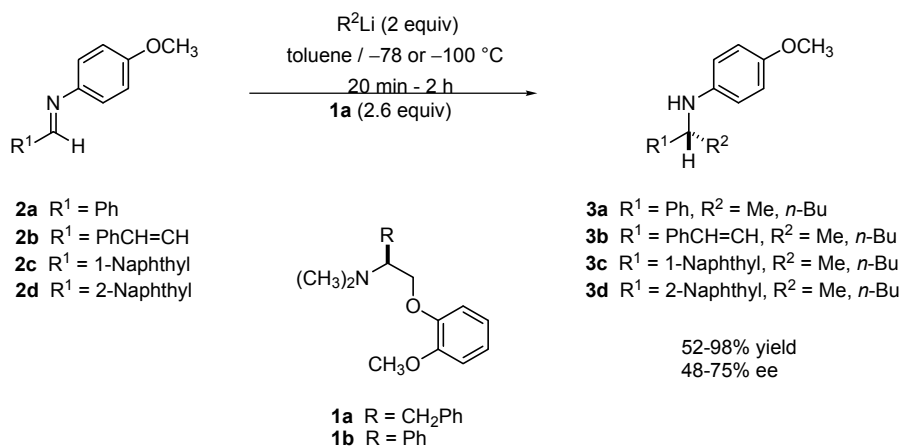
5

Catalytic Enantioselective Alkylation of Imines with Organolithium Reagents

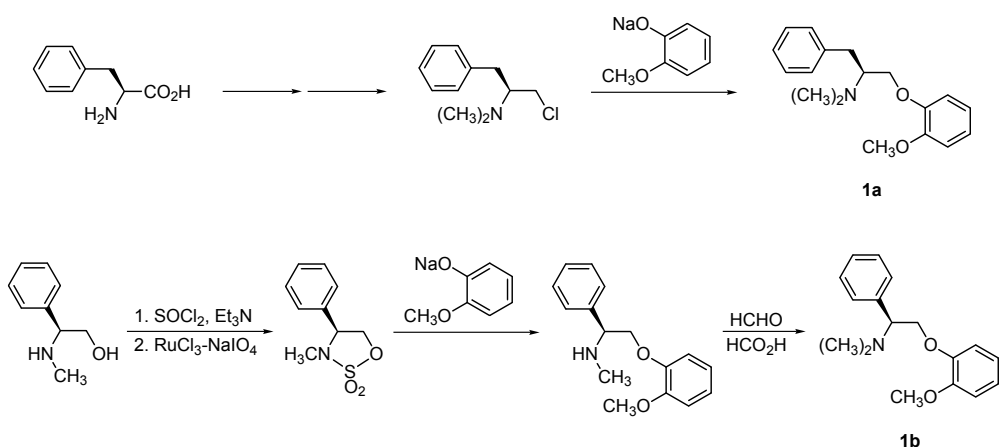
The first report of enantioselective addition of organometallic reagents to an azomethine function appeared in 1990. Tomioka and co-workers reported the addition of organolithium compounds to *N*-arylimines in the presence of a stoichiometric amount of a chiral β -amino ether as the asymmetric controller [19a]. This significant contribution resulted from an observation made earlier in the context of a related synthetic project [20a]. Tomioka et al. studied the addition of methyl lithium (MeLi) and *n*-butyllithium (*n*-BuLi) to unsaturated *N*-(4-methoxyphenyl)imines derived from benzaldehyde (2a), cinnamaldehyde (2b),

and 1-/2-naphthalenecarboxaldehydes (**2c,d**). The 1,2-addition reactions were performed in the presence of an excess (2.6 equiv per equiv of **2**) of the chiral β -amino ether **1a** as the chiral promoter (Scheme 1). For previous uses of the chiral β -amino ether **1a** in various stereoselective reactions by Tomioka and co-workers, see Refs. [21a, 21b, 21c].

The syntheses of the chiral, tridentate β -amino ethers **1a,b** have also been reported [19e]. Amino ether **1a** was prepared from commercially available L-phenylalanine via the acyl chloride, and amino ether **1b** was prepared from commercially available L-2-phenylglycine (Scheme 2). Other ligands (bidentate chiral ethers and amino ethers) were also prepared, and these authors carried out a structure-enantioselectivity relationship study with these various chiral ami-



Scheme 1



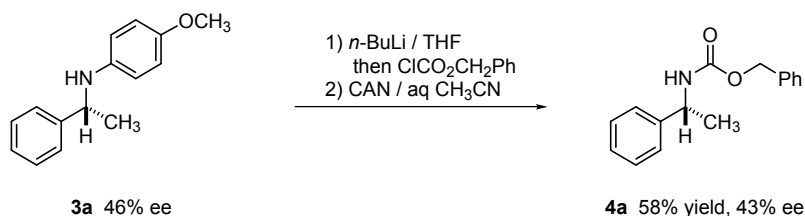
Scheme 2

no ethers. The optimization of ligand structure was performed using the methylolithium addition (2 equiv of MeLi in toluene at $-78\text{ }^{\circ}\text{C}$) to imine **2a**. The ligands **1a,b** were selected because they exhibited the same high level of enantioselectivity (70% ee).

The reactions were run in toluene (<0.5 g of imine, ca. 0.05 M), at -78 or $-100\text{ }^{\circ}\text{C}$, with varying reaction times (20 min \rightarrow 2 h). Using a twofold excess of the alkyllithium, the secondary amines **3a–d** were isolated in good yields (up to 98%) and with moderate to good enantiomeric purities (48–75% ee). The formation of the 1,4-addition product was not observed. It is important to note that the chiral ligands **1a,b** were recovered quantitatively for reuse, without any loss of enantiomeric purity. The highest enantioselectivities were observed with the imines derived from benzaldehyde and naphthalenecarboxaldehydes (65–75% ee). The additions of MeLi consistently provided the highest enantioselectivities for every substrate examined, compared to the use of *n*-BuLi. The authors have mentioned that toluene and diethyl ether were the solvents of choice, whereas THF and DME afforded the amines **3a–d** in nearly racemic form. They also noted that the enantioselectivity of the reaction of imine **2a** with lithium bromide (LiBr)-complexed MeLi at $-42\text{ }^{\circ}\text{C}$ was not significantly affected [19e]. However, a study by Tomioka and co-workers on the effects provided by the change of the *N*-phenyl ring substitution in the starting imines has shown that higher enantioselectivities (up to 90% ee) could be obtained, particularly in the case of the alkylation of imines derived from 2-methylanisidine, in the presence of **1a** [19c].

The synthetic utility of this enantioselective alkylation of an arylimine relies on a practical method for the dearylation of the resulting chiral amine. A two-step procedure was illustrated for amine **3a** ($R^2=\text{Me}$), which begins with a protection step (*n*-BuLi/ $\text{ClCO}_2\text{CH}_2\text{Ph}$) followed by oxidative cleavage of the aryl moiety (ceric ammonium nitrate: CAN). The *N*-protected amine **4a** was isolated in only 58% overall yield without significant loss of enantiomeric purity (Scheme 3).

Tomioka and co-workers have also disclosed a catalytic enantioselective process for the alkylation reaction described just above, by the use of a substoichiometric amount of the chiral tridentate ligand **1a** [19b]. To compare the data obtained from both stoichiometric and substoichiometric processes, MeLi and *n*-BuLi were used as the carbon nucleophiles in additions to the imines **2a–d**. Sub-



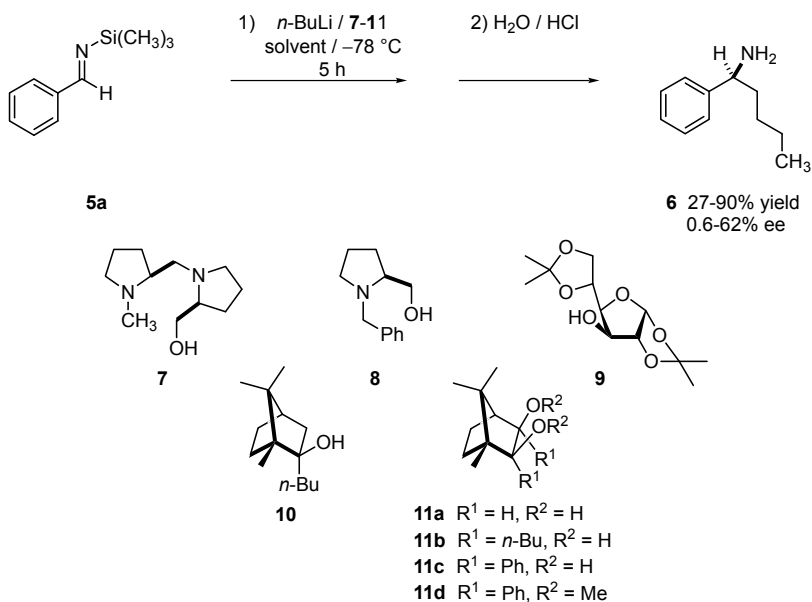
Scheme 3

stoichiometric amounts of **1a** (0.05–0.5 equiv) were used in these addition reactions. Most of the reactions were run in toluene, at -42 or -78 °C depending on the nucleophile, with varying reaction times (20 min \rightarrow 5 h). In a similar manner to the previous study, 2 equiv of the organolithium compound was employed, and uniformly high yields of the secondary amines **3a–d** were obtained (81–99%). A significant level of enantioselectivity was observed in the addition of MeLi and *n*-BuLi to the naphthalenecarboxaldehyde-derived imines **2c,d**: 50–59% ee with 0.3 equiv of **1a**. At comparative loadings of the ligand **1a**, the additions of MeLi again provided the highest enantioselectivities compared to the additions of *n*-BuLi. The results of the experiments conducted with MeLi and the imine **2a** were particularly interesting with regard to the catalytic activity of the ligand **1a**. Indeed, while practically no reaction occurred with 0.05 equiv of **1a** at -78 °C, when the reaction was carried out at -42 °C, the resulting amine **3a** ($R^2=$ Me) was isolated in 96% yield and 40% ee. It is noteworthy that the reaction proceeded as well at -42 °C in the absence of **1a** to afford 91% yield of racemic **3a** ($R^2=$ Me). In the case of *n*-BuLi additions, the choice of the solvent was critical for asymmetric catalysis. Indeed, the reaction with **2a** and 0.3 equiv of **1a** in toluene, at -78 °C, afforded the corresponding amine **3a** ($R^2=$ *n*-Bu) in only 25% ee whereas the use of Et₂O or *i*-Pr₂O as solvent afforded the chiral amine in 45 and 60% ee, respectively. The use of LiBr-complexed MeLi for the addition to imine **2a** at -42 °C significantly decreased the enantioselectivity of the reaction [19e], but the catalytic enantioselective alkylation of imines derived from 2-methylansidine resulted again in higher enantioselectivities [19d].

Although the level of enantioselectivity reported in this study remained moderate, the chiral agent **1a** still exhibited a remarkable catalytic effect on asymmetric induction to produce the enantiomerically enriched secondary amines **3a–d**. Tomioka and co-workers have applied the use of chiral ligand-mediated addition of organolithium reagents to imines for the synthesis of biologically active compounds, see Refs. [19f, 19g]. For reports by Tomioka and co-workers on the use of other chiral ligands for the catalytic enantioselective addition of other organolithium compounds, see Refs. [22a, 22b].

The second report of catalytic enantioselective organolithium additions to the imine group came in 1991 from the laboratories of Itsuno and co-workers [23a]. These researchers studied the addition of *n*-BuLi to *N*-(trimethylsilyl)benzaldehyde imine **5a** in the presence of chiral modifiers such as alcohols, diols, and amino alcohols (<1 g of imine, ca. 0.13 M). The chiral ligands used were easily prepared according to literature procedures. The enantiomerically enriched primary amine **6** was obtained in 27–90% yield after appropriate workup, depending on the nature of the chiral ligand and the reaction solvent (Scheme 4).

Since the formation of a chiral lithium alkoxide is likely to be involved in the asymmetric addition process, various ratios of the components (chiral ligand:*n*-BuLi:**5a**) were examined. The results of this study revealed a remarkable solvent effect on both efficiency and selectivity for *n*-BuLi additions, and a dependence of the absolute configuration of the amine **6** on the solvent employed. The amino alcohols such as **7** and **8** gave only poor enantioselectivities in the butyl addition



Scheme 4

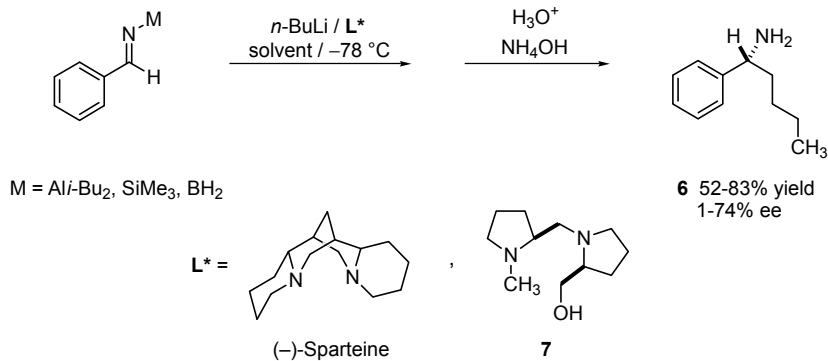
to **5a**: 4 and 14% ee, respectively, whereas the chiral alcohols **9–11** proved to be superior ligands in all respects; they could be easily separated from the reaction mixture, resulting in high isolated yields of the amine, and were re-used. Whereas the chiral ligands **9**, **10** and **11a,b** afforded the amine **6** in 3–25% ee, the use of the chiral diol **11c** in Et_2O (**11c**:*n*-BuLi:**5a**=2:5:0.5) gave the best results (62% ee) favoring the *S*-enantiomer. It should be noted that the use of the chiral diether **11d** afforded a racemic compound. The authors proposed that a chiral lithium alkoxide could act as a chiral modifier of *n*-BuLi during the addition step.

The same group has recently reported new findings on the reaction of *n*-BuLi with *N*-(metallo)imines [23b]. They examined the addition of *n*-BuLi to an *N*-aluminumimine, *N*-borylimine, and *N*-silylimine in the presence of chiral nitrogen ligands including (–)-sparteine and proline-derived amino alcohols (Scheme 5).

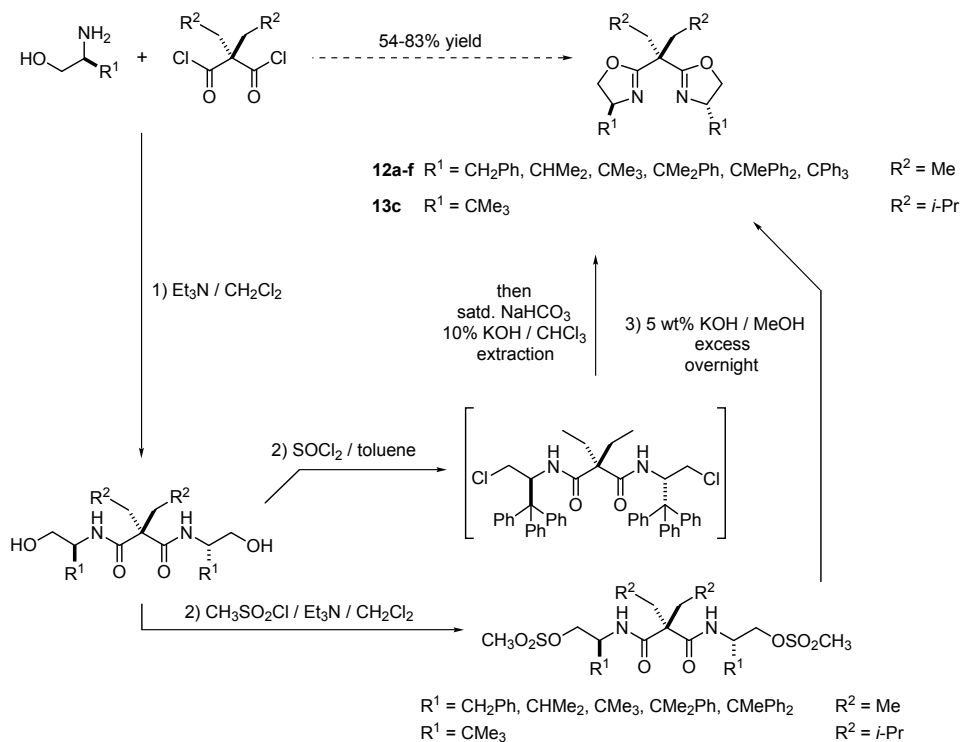
The reaction of the preformed (–)-sparteine·*n*-BuLi complex (1 equiv) with benzaldehyde *N*-(diisobutylaluminum)imine (1 equiv) at $-78\text{ }^{\circ}\text{C}$ in pentane gave the best result; 70% yield and 74% ee favoring the *R*-enantiomer. On the other hand, a preformed (–)-sparteine·benzaldehyde *N*-borylimine complex (1 equiv) was treated with *n*-BuLi (1 equiv) at $-78\text{ }^{\circ}\text{C}$ in Et_2O to give the corresponding primary amine in 68% yield and 50% ee, favoring also the *R*-enantiomer.

Although quite specific, these two contributions of Itsuno and co-workers constitute an interesting example of organometallic/chiral ligand interaction for the catalytic enantioselective alkylation of imines [24].

In 1994, Denmark et al. described the use of readily available C_2 -symmetric 2,2'-bis(oxazolino)methanes **12** and **13** for enantioselective addition of organo-



Scheme 5

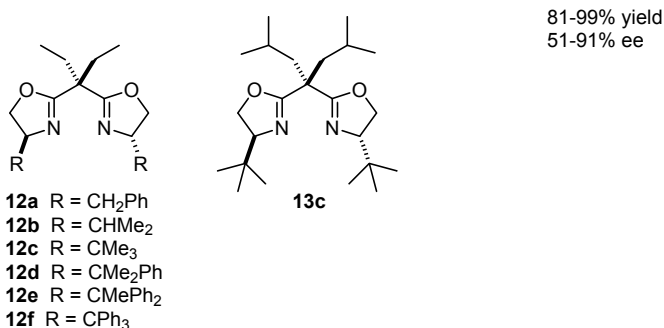
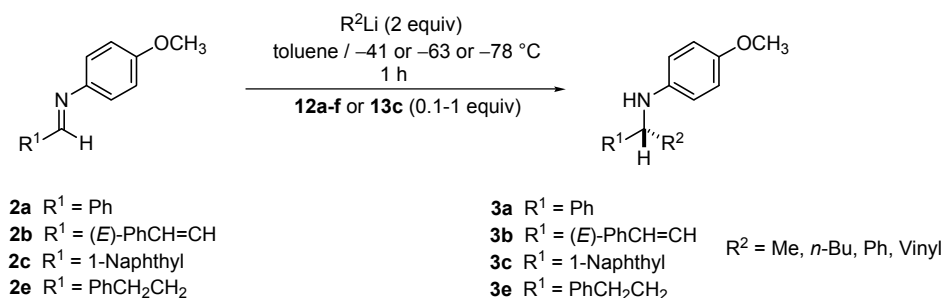


Scheme 6

lithium reagents (Scheme 6) [25a, 25b]. This class of compounds has been extensively employed as ligands in a variety of transition metal-catalyzed asymmetric reactions – for recent reviews, see Refs. [26a, 26b, 26c, 26d, 26e, 26f]. The chiral C_2 -symmetric bis(oxazoline) ligands **12a-f** and **13c** used in this work were easily

synthesized from naturally-derived or synthetic amino alcohols and malonyl dichloride derivatives [27a, 27b].

The first stage of this study focused on the optimization of ligand structure using the addition of MeLi (2 equiv of MeLi in toluene at -63 or -78 °C) to imine **2a** (<0.5 g of imine, ca. 0.06 M) in the presence of a stoichiometric amount of the ligand (1 equiv based on **2a**). The secondary amine **3a** ($R^2=Me$) was isolated in good yields: up to 99% with **12e**, and with good enantiomeric purities: up to 85% ee with **13c** (Scheme 7) [28]. Since the *tert*-butyl series is more readily available, **12c** and **13c** were selected for the survey of substrate and nucleophile generality. In all stoichiometric additions using **12c** and **13c**, the ligand was recovered in enantiomerically pure form in 91–100% yield. The highest enantioselectivities in the MeLi addition to other imines were observed with aliphatic imines **2e** compared to aromatic **2a,c** and conjugated imines **2b**: 91% vs 85% ee. To assay the generality of this procedure for the addition of other organolithium nucleophiles, the aliphatic imine **2e** was selected. Methyl lithium consistently provided the highest enantioselectivities (91% ee) compared to *n*-BuLi (51% ee), PhLi (30% ee), and vinyl lithium (89% ee). The effect of solvent was evaluated using the addition of *n*-BuLi to imine **2e** in the presence of the ligand **12c** [29]. The use of *i*-Pr₂O as solvent afforded amine **3e** ($R^2=n$ -Bu) in 86% yield and 69% ee, whereas toluene, Et₂O, and *tert*-butyl methyl ether (TBME) gave the same compound in 82–90% yield and 48–57% ee.

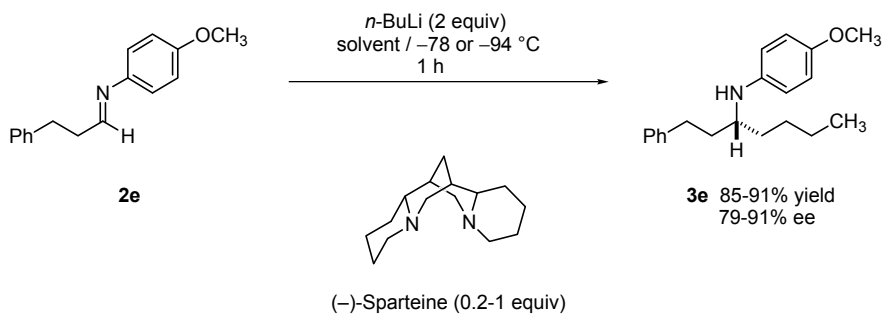


Scheme 7

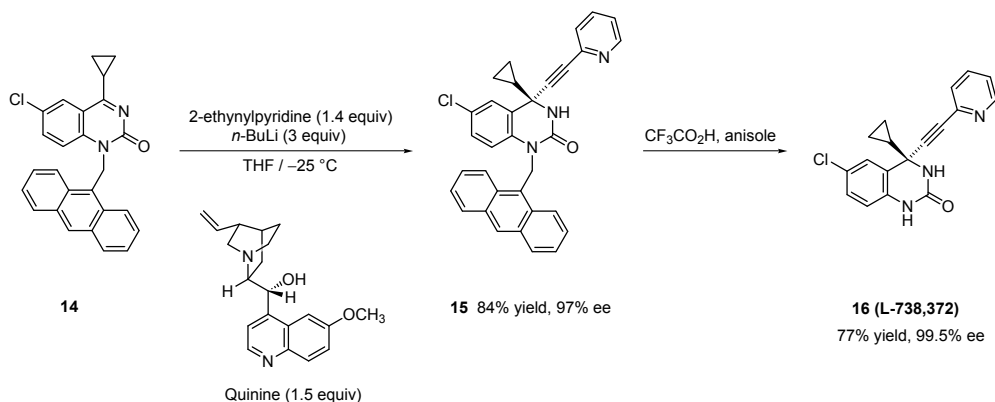
The potential use of a substoichiometric amount of the promoter was suggested by the observation that the reaction of MeLi with **2a** in the absence of an added ligand hardly proceeded in toluene at $-78\text{ }^{\circ}\text{C}$, affording **3a** ($\text{R}^2=\text{Me}$) in only 6% yield after 4 h. Indeed, the addition of MeLi to imines **2a-c**, **e** with substoichiometric amounts of **12c** (0.1–0.2 equiv), in toluene at -41 or $-63\text{ }^{\circ}\text{C}$, proceeded in excellent yield (81–98%), albeit with somewhat reduced enantioselectivity (60–82% ee). The addition of vinylolithium to **2e** using **12c** (0.2 equiv) afforded the corresponding amine with a comparable level of enantioselectivity (82% ee). The lesser selectivities observed in the stoichiometric and substoichiometric modes of the *n*-BuLi addition to **2e** suggested that a stronger chelating ligand was necessary. The bidentate tertiary amine (–)-sparteine was found to serve effectively as the external ligand (Scheme 8). (–)-Sparteine is an inexpensive and commercially available chiral diamine that has found applications in asymmetric transformations of organolithium reagents [30a, 30b, 30c, 30d, 30e, 30f].

The use of (–)-sparteine had a dramatic effect on the rate of reaction, in both stoichiometric and substoichiometric quantities, allowing complete conversion of **2e** with *n*-BuLi between -78 and $-94\text{ }^{\circ}\text{C}$. The enantioselectivity of *n*-BuLi addition to **2e** significantly improved, affording **3e** ($\text{R}^2=n\text{-Bu}$) in 90% yield and 91% ee (in Et_2O). The presence of (–)-sparteine (1 equiv) also affected the enantioselective addition of PhLi to **2e**, affording **3e** ($\text{R}^2=\text{Ph}$) in 82% ee compared to 30% ee using **12c** (1 equiv).

In seeking an efficient, economic, and scaleable route to the new potent non-nucleoside HIV-1 reverse transcriptase inhibitor **16** (L-738,372) [**2a**], process chemists at the Merck Research Laboratories have significantly contributed to the field of asymmetric alkylation of imines. Huffman and co-workers have reported a very efficient asymmetric route to **16** via the addition of a lithium acetylide to the cyclic *N*-acylketimine **14** in the presence of the lithium alkoxide of the alkaloid quinine as a stoichiometric chiral additive (Scheme 9) [31a]; the previous route to the inhibitor **16** included a resolution step [31b]. Whereas other types of chiral additives were screened (e.g., diamines, diethers), only β -amino alkoxides were enantioselective. The search for readily available amino alcohols was dictated by the necessity of developing a practical process. The commer-



Scheme 8

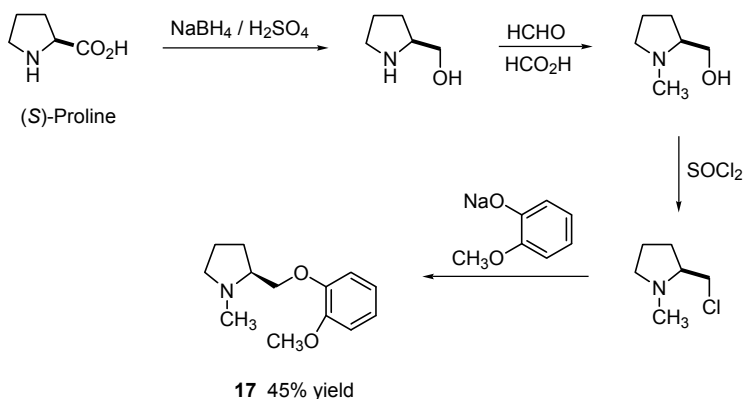


Scheme 9

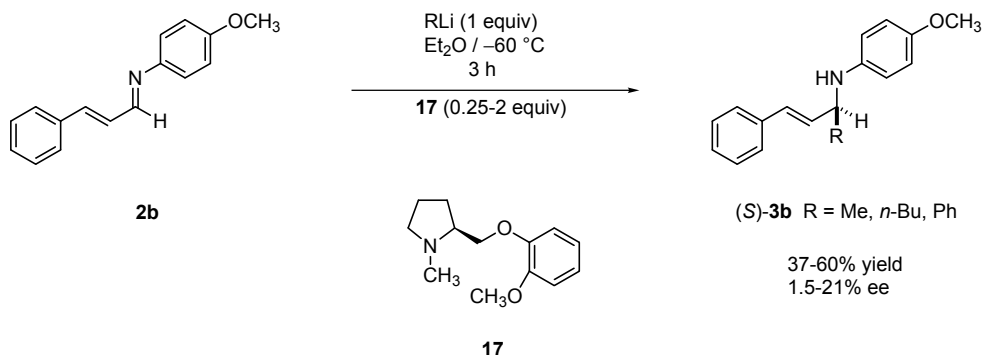
cially available *Cinchona* family of alkaloids afforded the best selectivities; quinine and dihydroquinine both favored the required (*S*)-enantiomer, but quinine was ultimately selected for reaction optimization because of a substantial advantage in cost and availability. Quinidine could be used to give the opposite enantiomer. Lithium alkoxides and acetylides (*n*-BuLi deprotonation) gave better results than the corresponding sodium or magnesium salts, and the use of THF rather than toluene or Et₂O gave better selectivities. The electronic and steric effects on stereoselectivity of the protecting group on the *sp*³ nitrogen of **14** were also investigated; a high level of selectivity was obtained with the 9-anthrylmethyl group, affording **15** in 94% ee (<0.2 g of **14**, 0.10 M **14**, 0.15 M acetylide, 0.16 M quinine alkoxide). A large scale reaction (>1 kg of **14**) was also carried out at the optimum temperature of -25 °C, and the crude free base **15** was isolated in 97% ee. The corresponding (+)-camphorsulfonic acid salt was isolated in 98% ee, and deprotection of the 9-anthrylmethyl group, followed by crystallization, gave the RT inhibitor **16** in 99.5% ee (Scheme 9).

North and co-workers required a convenient, catalytic asymmetric synthesis of specifically the (*S*)-enantiomer of allylic amines [32]. They prepared a new catalyst, **17**, by modifying Tomioka's tridentate amino ether **1a** [19a], but utilizing only readily available (*S*)-amino acids. Catalyst **17** was prepared in 45% yield overall from commercially available (*S*)-proline according to a procedure very similar to that described for the preparation of **1a** (Scheme 10).

The addition of MeLi, *n*-BuLi, and PhLi to cinnamaldehyde *N*-(4-methoxyphenyl)imine **2b** was then studied in the presence of varying amounts (0.25, 1.0, and 2.0 equiv per equiv of **2b**) of catalyst **17**. The reactions were run in Et₂O, at -60 °C for 3 h and then warmed to room temperature for 18 h (Scheme 11). The highest, but still moderate enantiomeric purities were obtained using MeLi as the nucleophile (up to 21% ee) and the secondary amines **3b** were isolated in moderate yields, too: up to 60%; this trend is comparable with that previously observed for catalyst **1a** [19a, 19b, 19c, 19d]. Most of the secondary amines **3b**



Scheme 10



Scheme 11

were shown to possess the (*S*)-configuration as wanted, but in all cases, the enantiomeric purities were lower than those previously reported for catalyst **1a**. Catalyst **17** could be recovered from the reaction mixture by chromatographic separation.

6

Catalytic Enantioselective Alkylation of Imines with Organozinc Reagents

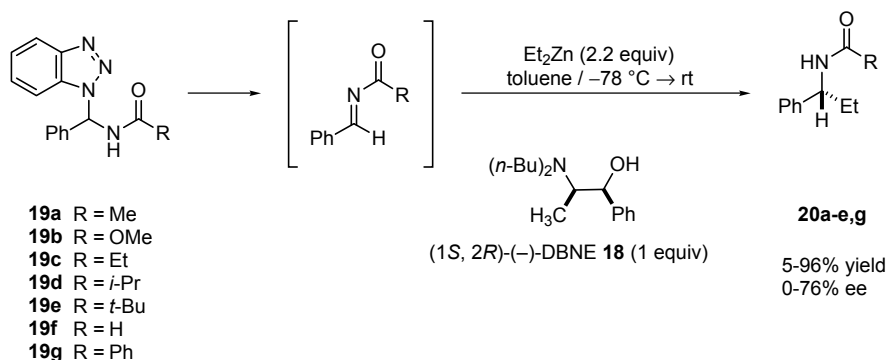
The tremendous success in the catalytic asymmetric addition of organozinc reagents to aldehydes spurred Itsuno and co-workers to examine the reactivity of diethylzinc with silyl imines in the presence of chiral amino alcohols and diols. Unfortunately, this type of azomethine function failed to react [23a]. The use of activated *N*-acyl- and *N*-phosphinoylimines turned out to be crucial as evidenced by the following reports on the alkylation of these functions using di-

alkylzinc reagents in the presence of a stoichiometric and substoichiometric amount of a chiral amino alcohol.

In the context of their study of the reactions of *N*-(aminoalkyl)benzotriazoles [33], Katritzky and Harris reported in 1992 the use of diethylzinc for the chiral amino alcohol-mediated enantioselective addition to the C=N bond in these compounds (Scheme 12) [34]. These substrates act as masked activated *N*-acylimines. Of the large variety of ligands available for the catalytic asymmetric reactions of dialkylzinc reagents, the sterically constrained β -dialkylamino alcohol, (-)-*N,N*-dibutylnorephedrine (DBNE) **18**, prepared by alkylation of commercially available norephedrine, was selected for this study. Some preliminary experiments conducted with the use of *N*-(aminobenzyl)benzotriazoles gave the ethylated product, but with no enantioselectivity. Diethylzinc (Et_2Zn) was found to react even in the absence of a chiral promoter. The behavior of the less reactive *N*-(amidobenzyl)benzotriazoles **19a–g** was then investigated.

Orienting experiments were carried out with the benzotriazole derivative **19a**. Initially, the use of a substoichiometric amount (0.2 equiv) of DBNE in toluene afforded the *N*-(1-phenylpropyl)amide **20a** in only 13% ee. In the presence of an equimolar mixture of **19a** and DBNE **18**, the amide **20a** was isolated in 14% yield and 55% ee. It is important to note that no ethyl addition occurred at -78°C . With 3 equiv of Et_2Zn , and 1 equiv of DBNE, the amide **20a** was isolated in 46% yield, and 76% ee. With these optimal conditions (>2 g of benzotriazole derivative, ca. 0.25 M), the reactivity of the other substrates **19b–g** was examined. In these cases, the excess of Et_2Zn was found to have no additional effect, and 2 equiv of Et_2Zn was employed. With the exception of the formamide derivative **19f**, all the other substrates afforded the corresponding amides **20b–e,g**, with however a wide range of chemical yields (5–96%) and with moderate enantioselectivities (0–42% ee). The absence of selectivity observed for **19e** was attributed to steric hindrance.

Although the level of enantioselectivity observed in this study was modest, this contribution has documented for the first time the use of a dialkylzinc reagent for the stereoselective addition of a carbon nucleophile to the imine function.

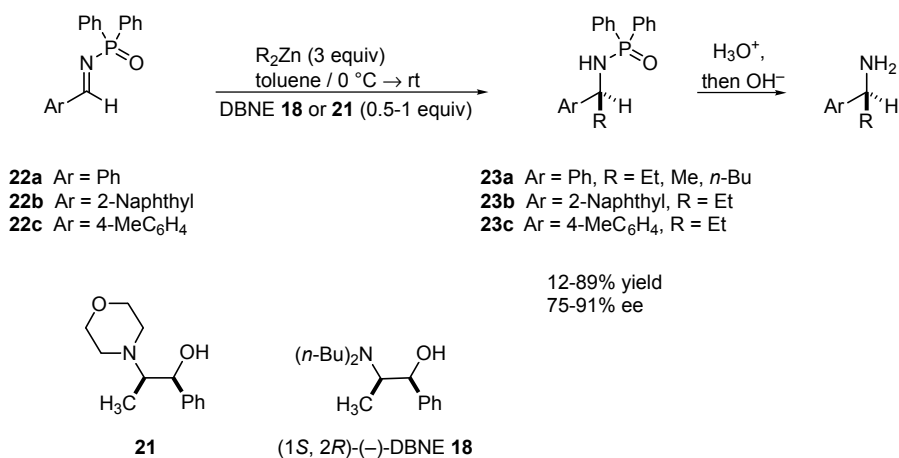


Scheme 12

In 1992, Soai reported the synthesis of enantiomerically enriched amines by the reaction of organozinc reagents with *N*-diphenylphosphinoylimines [35a, 35b, 35c]. The diphenylphosphinoyl moiety provided the necessary activation of the C=N bond to observe dialkylzinc additions. The reactivity of a series of three *N*-diphenylphosphinoylimines **22a–c** was examined in the presence of Et₂Zn and a substoichiometric or a stoichiometric amount of the chiral β-amino alcohols **18** or **21** (<0.1 g of phosphinoylimine, ca. 0.17 M) (Scheme 13).

When the chiral ligand **21** was used stoichiometrically (**22**:R₂Zn:**21**=1:3:1), the reaction of imine **22a** with Et₂Zn afforded the corresponding (*S*)-phosphoramidate **23a** (R=Et) in 89% yield and 90% ee. In the presence of DBNE **18**, (*S*)-**23a** (R=Et) was obtained in 61% yield and 84% ee. The highest enantioselectivity was recorded with the use of imine **22b**, affording the phosphoramidate **23b** in 84% yield and 91% ee. In the presence of a substoichiometric amount of the chiral ligand **21**, i.e., 0.5 equiv, the phosphoramidates **23a–c** (R=Et) were obtained in 85–87% ee. However, a significant drop of the chemical yield was observed (57–69%). With a substoichiometric amount of DBNE **18** (0.1 equiv), only 12% yield of **23a** (R=Et) was obtained, but a good level of enantioselectivity was preserved: 75% ee. Finally, the methyl and butyl addition of the imine **22a** using 1 equiv of **21** gave the phosphoramidates **23a** (R=Me) and **23a** (R=*n*-Bu) in 46% yield and 85% ee, and 56% yield and 87% ee, respectively. The acidic hydrolysis of the phosphoramidates liberated the corresponding aromatic primary amines with no loss of enantiomeric purity.

Soai and co-workers have continued their studies as described in two recent communications. One report details the synthesis of enantiomerically enriched ferrocenylamines by the catalytic, asymmetric dialkylzinc alkylation of a ferrocenylimine [35b], and the other report introduces the use of heterogeneous chiral catalysts in the enantioselective diethylzinc alkylation of a phosphinoyl imine [35c].



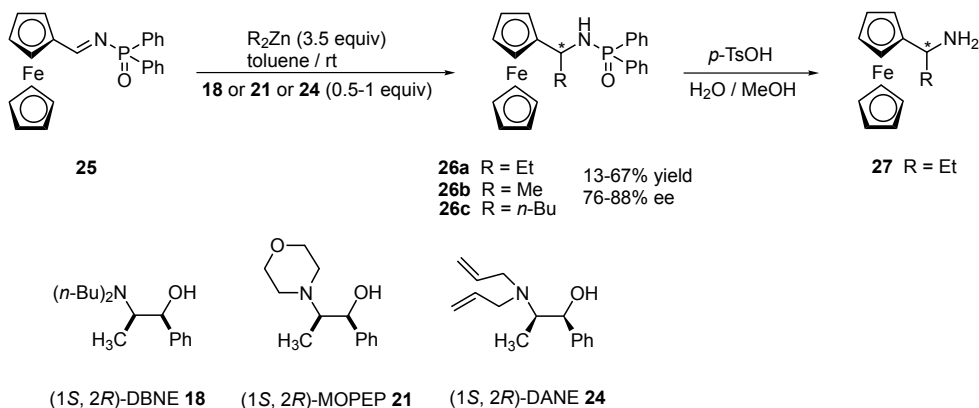
Scheme 13

The importance of enantiomerically pure ferrocenylamines derives from their use as key synthetic intermediates for the synthesis of chiral catalysts. Soai et al. studied the addition of Et_2Zn , Me_2Zn , and $n\text{-Bu}_2\text{Zn}$ to ferrocenyl-*N*-diphenylphosphinoylimine **25** (<0.2 g of phosphinoyl imine, ca. 0.10 M) in the presence of a stoichiometric amount of the chiral β -amino alcohols **18** (DBNE), **21** ((1*S*, 2*R*)-2-morpholino-1-phenyl-1-propanol, MOPEP), or **24** ((1*S*, 2*R*)-*N,N*-diallylnorephedrine, DANE) (Scheme 14) [35b]. When Et_2Zn and imine **25** were reacted in toluene at room temperature, the use of **21** gave the best results, affording (+)-*N*-(diphenylphosphinoyl)-1-ferrocenylpropylamine **26a** in 67% yield and 88% ee. Me_2Zn and $n\text{-Bu}_2\text{Zn}$ afforded the alkylated products **26b,c** in lower yields, but with similar enantioselectivities. In the presence of a substoichiometric amount (0.5 equiv) of the chiral ligand **21**, a significant drop of the chemical yield was observed (34%), however, there was almost no decrease of the enantioselectivity (86% ee). This effect is comparable with that reported earlier by these same authors [35a]. Subsequent hydrolysis of amine **26a** afforded (+)-1-ferrocenylpropylamine **27** without loss of enantiomeric purity.

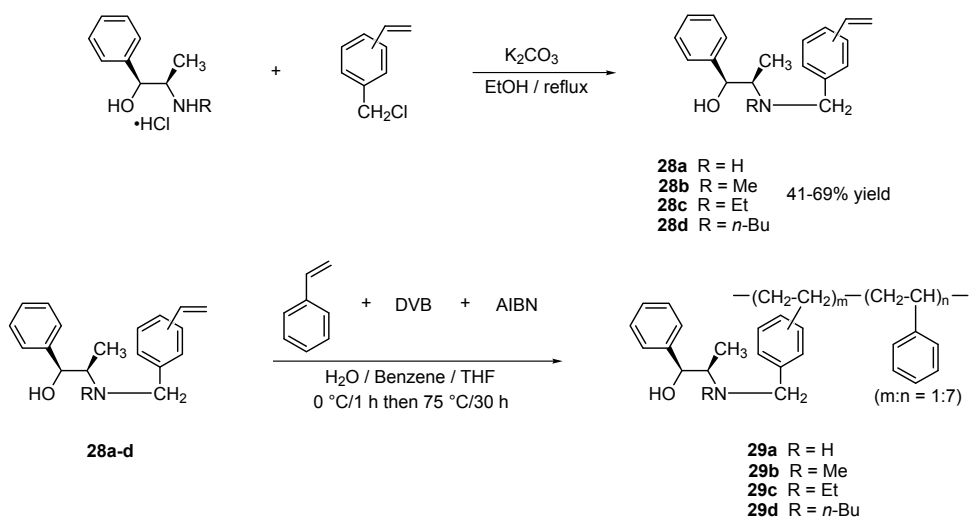
All of catalytic enantioselective alkylations of imines that have been described up to this point used homogeneous chiral catalysts. In an effort to facilitate the separation process of the product from the reaction mixture, Soai and co-workers have employed copolymers of norephedrine for the enantioselective addition of diethylzinc to a phosphinoyl imine [35c].

Chiral monomeric ligands **28a–d** were first prepared in 41–69% yield by the reaction of *N*-(alkyl)norephedrine hydrochloride with vinylbenzyl chloride. The chiral ligands **29a–d** were synthesized by the copolymerization of the chiral monomers **28a–d** with styrene and divinylbenzene (DVB) (Scheme 15).

The chiral monomeric ligands **28a–d** were tested in diethylzinc alkylation reactions with *N*-diphenylphosphinoylimine **22a**. In all cases, the corresponding phosphinamide **23a** ($\text{R}=\text{Et}$) was obtained with a high enantiomeric purity ($\geq 88\%$ ee); the use of a stoichiometric amount of chiral ligand **28b** gave the best



Scheme 14



Scheme 15

enantioselectivity (95% ee). The copolymerized chiral ligands **29a–d** were used with Et_2Zn and **22a** in toluene at room temperature rather than at $0\text{ }^\circ\text{C}$, and for a longer reaction time. Phosphinamide **23a** (R=Et) was obtained with a good to high enantiomeric purity (64–88% ee), but the yields were lower (30–60%). The copolymer **29b**, easily separated from the reaction mixture by filtration was recovered and re-employed to afford **23a** (R=Et) with the same level of enantioselectivity, i.e., 86% ee.

As part of an ongoing research program directed toward the use of chiral aziridines in asymmetric synthesis [36], Andersson, Tanner and co-workers have recently reported the detailed results of their own findings in the field of catalytic asymmetric dialkylzinc alkylation of imines [37d]. Tanner et al. had previously communicated their success in the catalytic asymmetric addition of organolithium reagents to imines with C_2 -symmetric bis(aziridines) [37a, 37b]. This was followed by a preliminary report on the use of aziridino alcohols as well as simple aziridines for the addition of diethylzinc to *N*-diphenylphosphinoylimines [37c]. The most recent report is an extension of this study, and includes the detailed preparation of the ligands [37d].

The aziridino alcohols that have been prepared and tested as chiral promoters for the catalytic asymmetric dialkylzinc alkylation of imines are shown in Fig. 4. The authors have investigated three different approaches to obtain the ligands in enantiomerically pure form: (1) the use of the chiral pool, (2) the Sharpless asymmetric aminohydroxylation, and (3) the Sharpless asymmetric dihydroxylation. The starting materials for the preparation of the aziridino alcohols **30**, **31a–h**, **32a,b**, and **33** were the readily available amino acids *L*-serine, *L*-threonine, and *allo-L*-threonine.

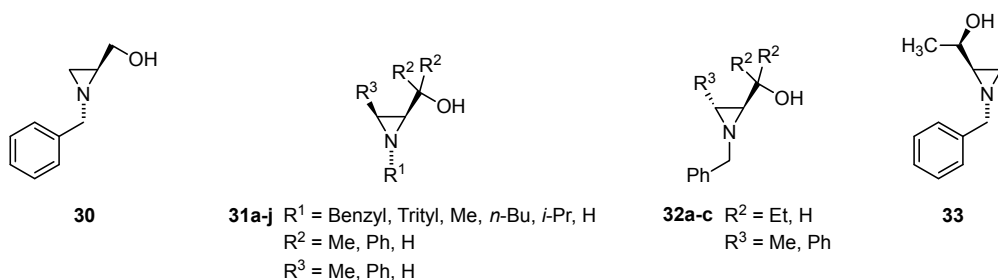
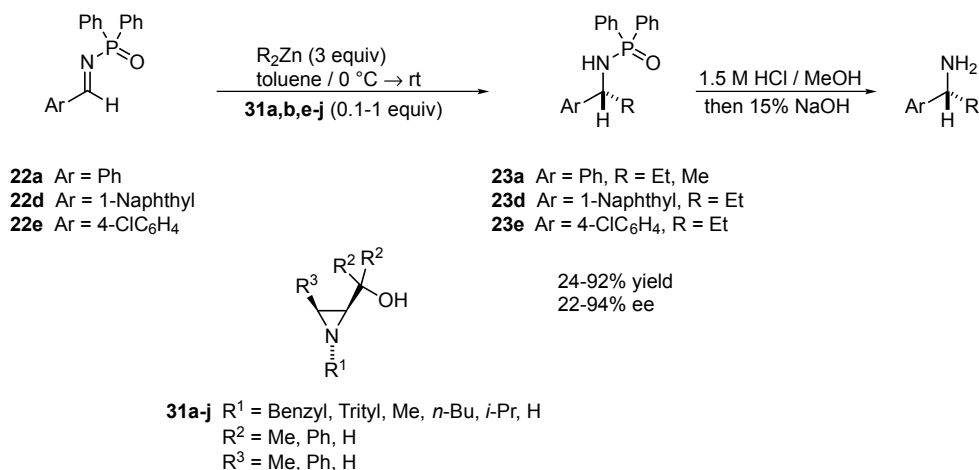


Fig. 4



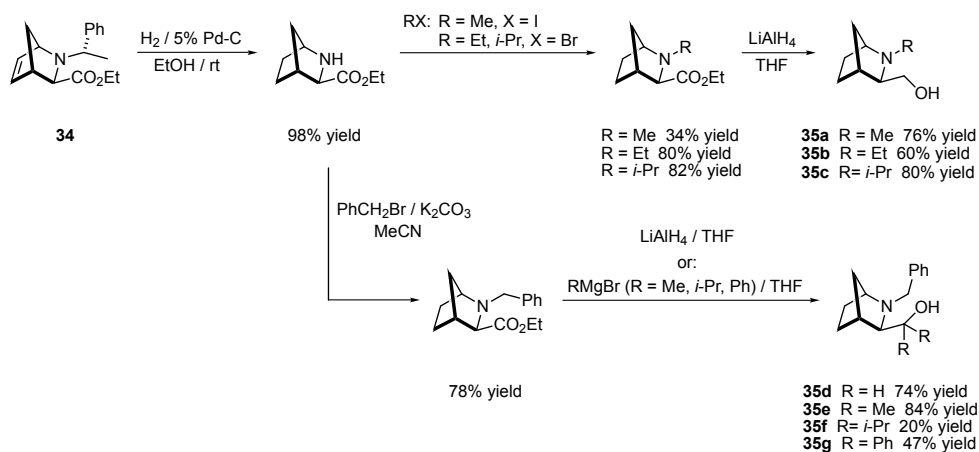
Scheme 16

The reactivity of a series of three *N*-diphenylphosphinoylimines **22a,d,e** was examined in the presence of Et₂Zn or Me₂Zn and a stoichiometric amount of the chiral aziridino alcohols **30–33** (<0.1 g of phosphinoylimine, ca. 0.17 M) (Scheme 16). The imine **22a** proved to be the best substrate for the addition reaction (using Et₂Zn): 63% yield/94% ee with **31a**, 72% yield/91% ee with **31h**, 57% yield/86% ee with **31i**, and 78% yield/80% ee with **31f**. The corresponding phosphinamide **23a** (R=Et) was formed as the (*R*)-enantiomer. Dimethylzinc turned out to be much less reactive than Et₂Zn, and low to moderate enantioselectivities were obtained. In all cases, up to 90% of the chiral aziridino alcohol could be recovered during the workup in a typical experiment, and the recovered ligand could be used again without loss of enantioselectivity. The good enantioselectivities obtained with some of the ligands prompted the authors to use them in a substoichiometric amount. The addition of Et₂Zn to imine **22a** with substoichiometric amounts of **31a** (0.1–0.5 equiv), in toluene from 0 °C to

room temperature, proceeded in moderate yield (37–76%), and with somewhat reduced enantioselectivity (49–87% ee). Finally, acidic hydrolysis of the initially formed phosphinamides **23a,d,e** led to the corresponding free amines without racemization.

The β -amino alcohols **35a–g** represent the latest variation on the theme of chiral promoters for the enantioselective addition of dialkylzinc reagents to imines (Scheme 17) [38]. Andersson and co-workers' interest in the use of chiral, sterically constrained β -amino alcohols with the 2-azanorbornyl skeleton led them to consider such bicyclic β -amino alcohols as chiral catalysts in the above-mentioned addition reaction. One important feature of these ligands is the fact that both enantiomers are equally available. The common precursor for all the ligands was **34** which could be constructed via an aza-Diels-Alder reaction. The synthesis of the bicyclic amino alcohols **35a–g** is depicted in Scheme 17.

The reactivity of *N*-diphenylphosphinoylimines **22a** and **22d** was examined in the presence of Et_2Zn or Me_2Zn and a stoichiometric amount of the chiral bicyclic amino alcohols **35a–g** under the same reaction conditions as those reported for the ligands **30–33** [37d]. Both imines proved to be good substrates for the addition reaction (using Et_2Zn): 63% yield/91% ee with **22a** and 65% yield/92% ee with **22d** in the presence of ligand **35d**. The corresponding phosphinamides **23a,d** (R=Et) were formed as the (*S*)-enantiomer. Again, dimethylzinc turned out to be much less reactive than Et_2Zn , but a high level of enantioselectivity was still observed (83% ee). In all cases, up to 90% of the chiral bicyclic amino alcohol could be recovered during the workup in a typical experiment. The addition of Et_2Zn to imine **22a** with substoichiometric amounts of **35d** (0.1 and 0.25 equiv) proceeded in moderate yield (38 and 46%), but with very promising levels of enantioselectivity (68 and 85% ee, respectively). Acidic hydrolysis of the phosphinamides **23a,d** also led to the corresponding free amines without racemization.



Scheme 17

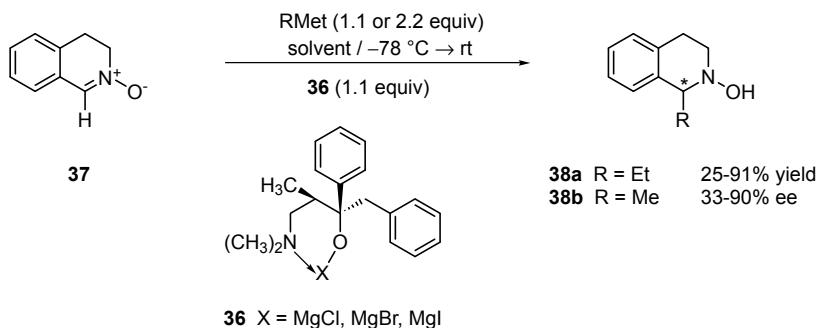
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Catalytic Enantioselective Alkylation of Nitrones with Grignard and Organozinc Reagents

In 1993, Ukaji, Inomata and co-workers documented the enantioselective alkylation of a nitron as the acceptor [39a]. It was anticipated that the oxygen atom of the nitron would strongly coordinate a metal incorporated in a chiral environment to activate the nucleophilic addition of an organometallic reagent. Using the in situ generated metal alkoxide of (2*S*, 3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-butan-2-ol (Chirald) (**36**, X=H) as the external chiral ligand, the authors studied the reaction of alkylmetals such as EtMgX (X=Cl, Br, I), MeMgBr, Et₂Zn, and Me₂Zn with nitron **37** as the substrate (Scheme 18).

The addition reactions using Grignard reagents were performed as follows: RMgCl (2.2 equiv) was treated with Chirald (1.1 equiv) to generate magnesium alkoxide **36** (X=MgCl) (1.1 equiv), and the nitron **37** (1.0 equiv) was added to the solution at -78 °C. Of the three ethyl Grignard reagents surveyed, the reaction using EtMgBr in Et₂O in the presence of magnesium alkoxide **36** (X=MgBr) afforded the alkylated product (*S*)-**38a** in 54% yield and with the best enantioselectivity (75% ee). The enantioselectivity of the reaction was further improved, by the use of MgBr₂ (1.1 equiv) as an additive. In dimethoxyethane (DME), the addition of EtMgBr to **37** afforded (*S*)-**38a** in 90% ee. In contrast, the addition reactions using dialkylzinc reagents gave rise to a reversal of the enantioselectivity. The use of Et₂Zn (2.2 equiv) in THF at 25 °C in the presence of magnesium alkoxide **36** (X=MgBr) afforded the alkylated product (*R*)-**38a** in 74% yield and 57% ee. The same trends as above were observed when the addition reactions were performed with MeMgBr ((*S*)-**38b** in 80% ee) and Me₂Zn ((*R*)-**38b** in 66% ee). Although the reaction mechanism remains obscure, the reversal of the enantioselectivity obtained by the simple change of the organometallic species is of great interest.

Ukaji, Inomata and co-workers have also disclosed a similar catalytic asymmetric process for the alkylation of nitrones using solely dialkylzinc reagents and a substoichiometric amount of the bromomagnesium alkoxide **36** (X=Mg-



Scheme 18

Br) [39b]. In this report, the authors have found a 74% yield and 65% ee for the ethylated product (*R*)-**38a**, using 1.1 equivalents of **36** (X=MgBr). In the presence of 0.2 equivalents of **36**, the enantioselectivity of the addition was reduced to 33% ee. It was found that the addition of another bromomagnesium alkoxide improved the enantioselectivity. Bromomagnesium triphenylmethoxide (0.3 equiv) was shown to be the most effective and gave the alkylated product (*R*)-**38a** in 91% yield and 62% ee. Under the same reaction conditions, the use of Me₂Zn afforded (*R*)-**38b** in 93% yield and 58% ee. Other nitrones possessing the dihydroisoquinoline skeleton were also tested (Fig. 5). Addition of diethylzinc to **39a** and **39b** in the presence of the chiral bromomagnesium butoxide **36** (0.2 equiv) and bromomagnesium triphenylmethoxide (0.3 equiv) as the additive afforded the alkylated products (*R*)-**40a** (R²=Et) and (*R*)-**40b** in 97% yield/70% ee and 89% yield/78% ee, respectively; in both cases, higher enantioselectivities were obtained in comparison with the stoichiometric asymmetric reaction (58% ee and 57% ee, respectively). The reaction of Me₂Zn with **39a** afforded the alkylated product (*R*)-**40a** (R²=Me) in 84% yield, and the enantioselectivity was again higher than that in the stoichiometric reaction (63 vs 50% ee). The authors have suggested that the role of bromomagnesium triphenylmethoxide is to react with the in situ generated chiral ligand **36**-complexed alkylated product to regenerate the chiral bromomagnesium butoxide **36** and give a non-chirally complexed alkylated product.

The most recent publication in the field of catalytic asymmetric alkylation of nitrones with organozinc reagents has documented the use of bis-alkoxides derived from (*R,R*)-tartaric acid esters as new chiral catalysts for this reaction (Scheme 19) [40]. Ukaji, Inomata and co-workers were interested in further improving their own method for practical use especially in regard of catalyst availability. Both enantiomers of tartaric acid esters **41** are readily available.

The addition reaction of Et₂Zn to nitrone **37** (<0.2 g of nitrone, ca. 0.09 M) in the presence of 0.2 equivalents of in situ generated bis-alkoxide **41** was examined in CH₂Cl₂ at 25 °C. Ukaji et al. essentially studied the influence of the ester group (R¹) in magnesium zinc alkoxide **41** (M¹=MgBr, M²=ZnR, R=Me, Et). Some esters derived from acyclic secondary alcohols afforded the alkylated product (*S*)-**38a** in high yield and with a good enantioselectivity; 86% yield and 72% ee using **41a**. It is noteworthy that in the case of *tert*-butyl ester, the enanti-

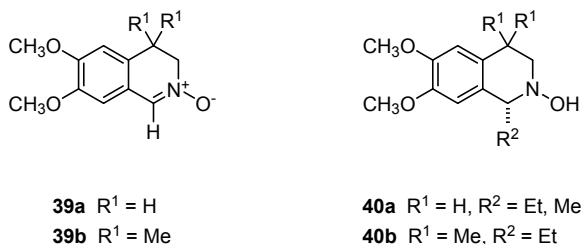
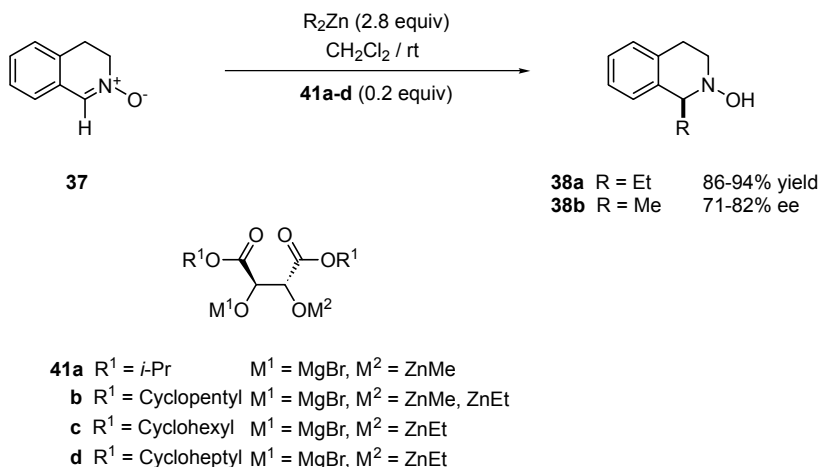


Fig. 5



Scheme 19

oselectivity was lower (34% ee). The esters derived from cyclic secondary alcohols were found to be the esters of choice; 94% yield/74% ee using **41b** ($M^2 = ZnEt$) and 89% yield/82% ee using **41b** ($M^2 = ZnMe$); 89% yield/71% ee using **41c**; and 94% yield/71% ee using **41d**. The bromomagnesium methylzinc alkoxide **41b** ($M^2 = ZnMe$) was selected to carry out addition reactions to other nitrones. The addition of Et_2Zn to **39a** afforded hydroxylamine **40a** ($R^2 = Et$) in 88% yield and 83% ee. The highest enantioselectivities were obtained when Et_2Zn , Me_2Zn , and $i\text{-Pr}_2Zn$ were added to nitron **39b**; the corresponding hydroxylamines were isolated with 94, 85, and 88% ee, respectively. The authors have suggested that, in the catalytic asymmetric addition of Et_2Zn , ethyl group transfer to the nitron predominantly comes from Et_2Zn associated with **41**, and not from an ethyl group in the zinc alkoxide of tartrate. This present method described by Ukaji et al. is also quite innovative in comparison with their original publication [39a]. The easy availability of (*R,R*)- and (*S,S*)-tartaric acid esters makes this method very attractive for practical use.

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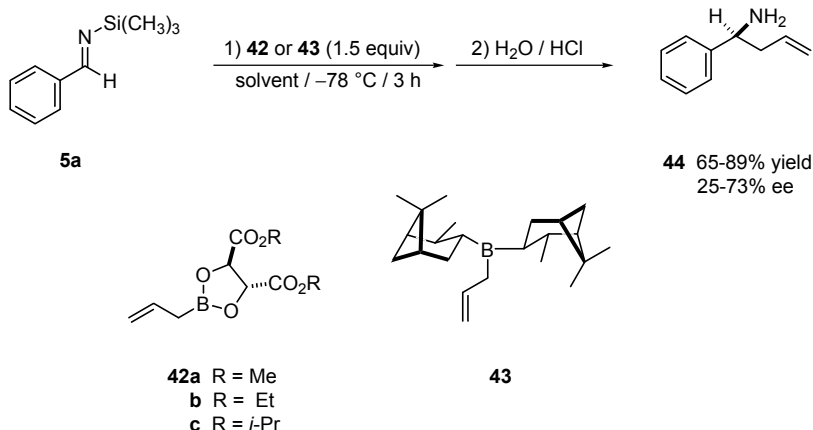
Catalytic Enantioselective Allylation of Imines and Oximes

Enantiomerically pure homoallylic amines are very important chiral building blocks for the synthesis of pharmacologically important molecules and natural products. The enantioselective synthesis of these compounds initially involved the chiral auxiliary-based asymmetric allylation of imines [41a, 41b, 41c], and it is just recently that a few enantioselective variants have been reported. Although still in the regime of stoichiometric asymmetric synthesis, the first methods described below merit discussion for their synthetic utility and for establishing the groundwork for future development.

The first example of enantioselective allylation of an azomethine function was reported in 1995 by Itsuno and co-workers [42a]. These researchers studied the addition of preformed chiral allylboranes to *N*-(trimethylsilyl)benzaldehyde imine (**5a**) (<2 g of imine, ca. 0.27 M). Of the wide range of chiral allylboron reagents reported in the literature, the use of chiral allylboronates **42a-c** and *B*-allyldialkylborane **43** were logical first choices given their utility in the enantioselective addition to carbonyl substrates (Scheme 20).

The chiral allylboronates **42a-c** were readily obtained from enantiomerically pure tartrate esters and triallylborane. These reagents reacted with the silyl imine at $-78\text{ }^{\circ}\text{C}$ to give the corresponding primary homoallylamine (*R*)-**44** in 70–89% yield and 25–39% ee. The dialkyl tartrates could be recovered almost quantitatively. The chiral *B*-allyldialkylborane **43** was also easily prepared by one-pot reaction of commercially available (–)-*B*-chlorodiisopinocampheylborane [(–)-DIP-Chloride], allyl chloride, and magnesium. The reaction of the silylimine with **43** in THF at $-78\text{ }^{\circ}\text{C}$ afforded the primary homoallylamine in 64% ee, favoring the (*S*)-enantiomer. The use of Et_2O as solvent gave somewhat a better enantioselectivity; 73% ee.

Itsuno and co-workers have continued their efforts in a second report wherein the chiral reagent **43** is used in combination with a variety of imines **2a**, **5a**, **45**, and **46** (Fig. 6) [42b]. The reaction of **43** with *N*-(4-methoxyphenyl)benzaldehyde imine **2a** at $25\text{ }^{\circ}\text{C}$ afforded the chiral homoallylamine in 22% ee. Under similar reaction conditions, sulfenimine **45** reacted with **43** to give the corresponding homoallylamine in 92% yield and 32% ee; a higher selectivity (79% ee) was obtained at $-78\text{ }^{\circ}\text{C}$, but the reaction was slower (36% yield). The reaction of oxime ether **46** was more sluggish; a 46% yield with 63% ee was obtained at $0\text{ }^{\circ}\text{C}$ whereas no reaction occurred at $-78\text{ }^{\circ}\text{C}$. These results prompted the authors to investigate the reactivity of *N*-trimethylsilylimine derivatives such as **5a-c** with a variety of preformed, chiral allylboron reagents.



Scheme 20

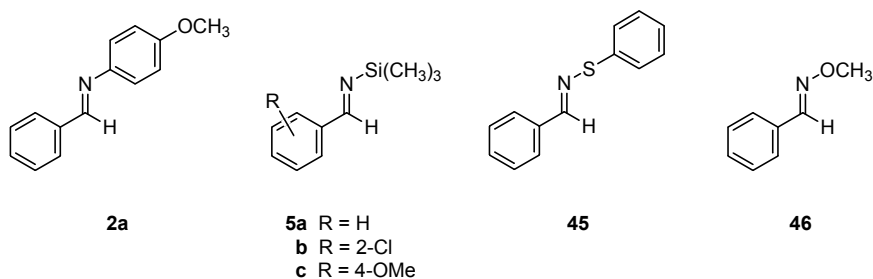
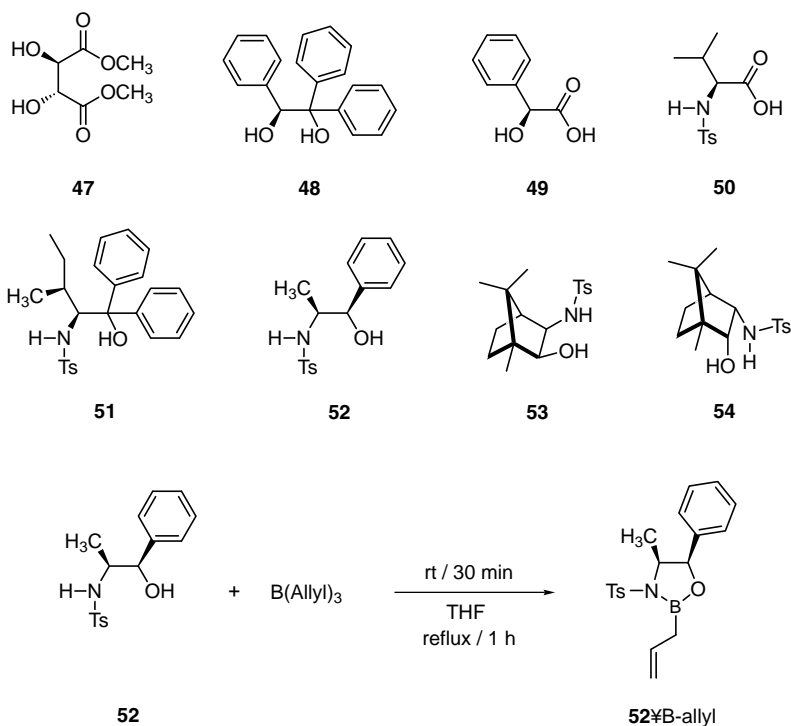


Fig. 6



Scheme 21

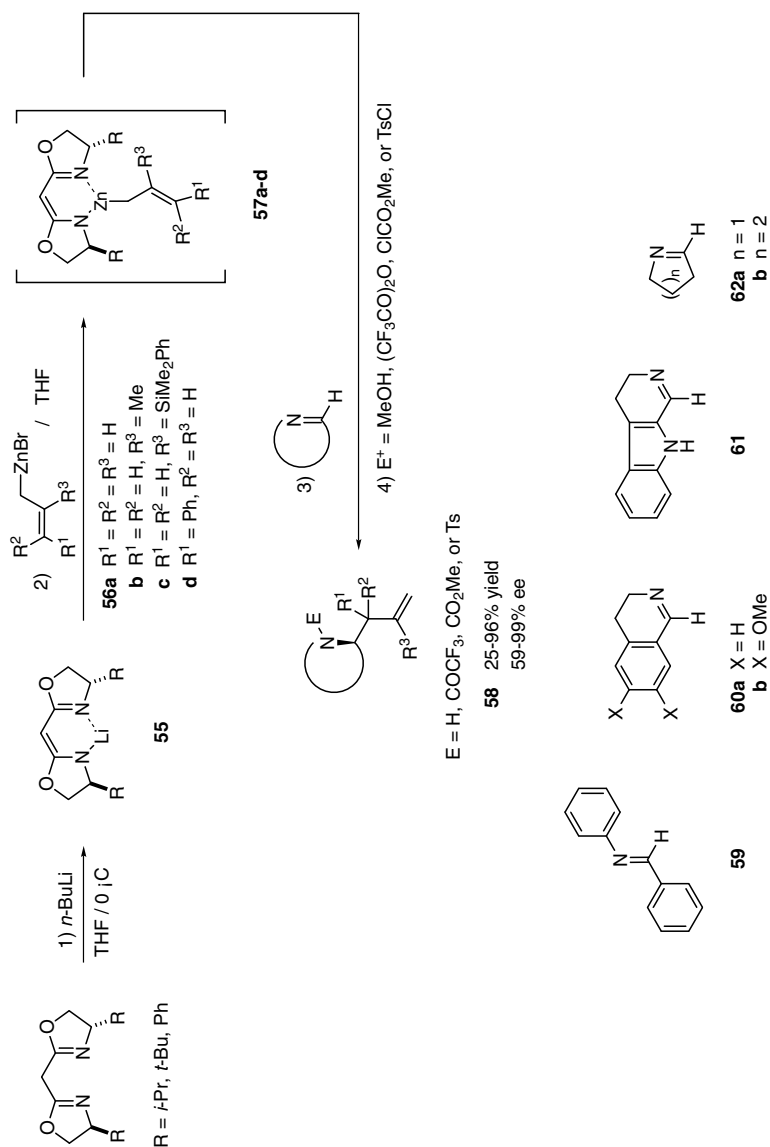
The chiral allylboration reagents employed by Itsuno et al. in this study were prepared by mixing triallylborane (1 equiv) with the appropriate chiral modifier in THF. A variety of chiral modifiers, including chiral diols **47** and **48**, chiral hydroxy acid **49**, *N*-sulfonylated amino acid **50**, and *N*-sulfonylamino alcohols **51**–**54** was evaluated (Scheme 21). The chiral modifiers **47**–**54** used in this study could be prepared easily and efficiently, and were easily recovered and recycled.

The best result (92% ee) was obtained when *N*-trimethylsilylimine **5a** was treated with *B*-allyloxazaborolidine **52**·*B*-allyl derived from (–)-norephedrine (**52**). The chiral allylboration reagent derived from **53** also provided a high level of enantioselectivity (89% ee) when combined with imine **5a**. These reactions favored the formation of (*S*)-**44** as had been observed with the use of reagent **43**. No attempt was made to rationalize the origin of enantioselectivity [42c].

Following their earlier findings on the enantioselective allylzincation of cyclopropenone acetals [43], Nakamura and co-workers investigated the same reaction with imines of aromatic aldehydes [44]. In an initial experiment, (*E*)-benzaldehyde *N*-phenyl imine (**59**) was treated with preformed chiral allylic zinc reagent **57a** (R=*i*-Pr) obtained by mixing a lithiated bis(oxazoline) (**55**, R=*i*-Pr) with an allylic zinc bromide (**56a**) (Scheme 22). The allylation product was obtained in 95% yield, but the enantioselectivity was only 6% ee. Fortunately, the enantioselective allylzincation of *Z*- (i.e., cyclic) aldimines was more successful.

A series of cyclic aromatic imines (**60a,b** and **61**, <1 g of imine, ca. 0.41 M) was first tested. Their reaction with the chiral allylic zinc reagent **57a** (R=*i*-Pr) followed by trapping with either MeOH, (CF₃CO)₂O, ClCO₂Me, or TsCl gave the corresponding homoallylic secondary amines **58** (E=H) in 54–90% yield and 90–95% ee, favoring the (*S*)-enantiomer. A change of substituent (R=*t*-Bu, Ph) on the bis(oxazoline) ligand was found to affect the reactivity and the selectivity of the allylic zinc reagent; the ligand derived from valinol (R=*i*-Pr) was selected for the ensuing reactions. The use of other chiral allylic zinc reagents (**57b,c**, R=*i*-Pr) with imines **60b** and **61** gave the allylation products with a high level of enantioselectivity, too (95–98% ee). The reaction of cyclic aliphatic imines (**62a,b**) was found to also take place smoothly. When treated with the allylzinc reagent **57a** (R=*i*-Pr), imines **62a,b** afforded the corresponding allylation products with 88 and 89% ee, respectively. The addition of methallylzinc reagent **57b** (R=*i*-Pr) to **62b** occurred with the highest level of enantioselectivity ever recorded in this study (99% ee). The bis(oxazoline) ligand was recovered without racemization upon basic aqueous workup of the reaction mixture. The authors have proposed a chair-like transition structure (similar to that advanced in their previous studies [43]) to account for the origin of asymmetric induction observed in this study.

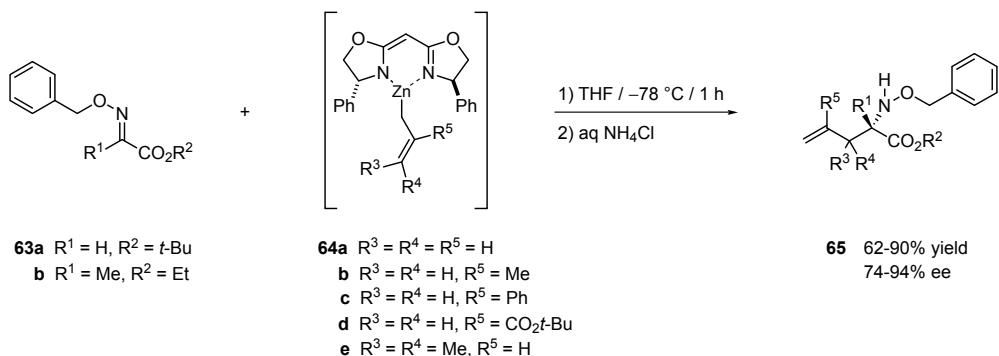
The use of a preformed, chiral bis(oxazoline)-based allylic zinc reagent was also investigated by Hanessian and Yang [45]. These authors examined the enantioselective allylation of α -keto ester *O*-benzyl oximes, to provide a one-step synthesis of immediate precursors to *D*- and *L*-allylglycines. The chiral allylation reagent **64a** was prepared according to Nakamura [43], and was combined with oxime **63a** (<0.5 g of oxime, ca. 0.1 M) to afford *N*-benzyloxyallylglycine derivative (*S*)-**65** in 82% yield and 93% ee (Scheme 23). Other chiral bis(oxazoline) ligands gave essentially no enantioselectivity. The use of substituted allyl bromides for the in situ generation of chiral reagents **64b–e** gave good to excellent selectivities (74–94% ee) when these reagents were reacted with oxime **63a**. The reaction of ketoxime **63b** was found to also take place smoothly, and led to the corresponding α -methyl substituted *L*-allylglycine derivative with high enantioselectivity (91% ee). The chiral bis(oxazoline) ligand could be easily recovered un-



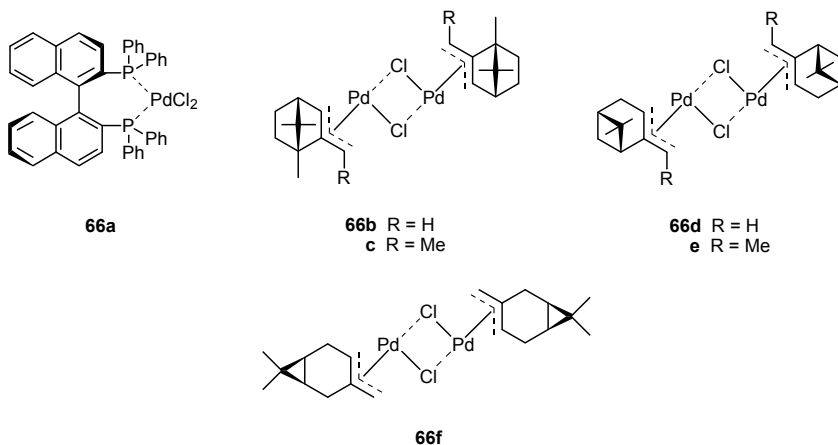
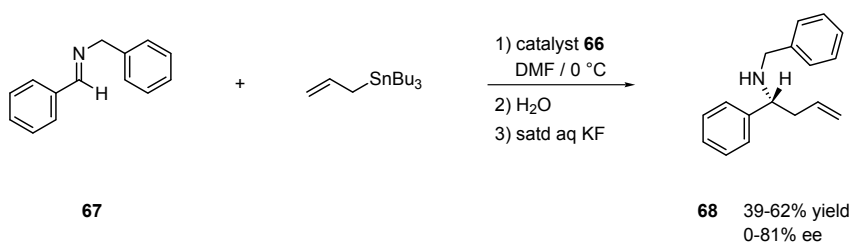
Scheme 22

changed. The synthetic value of this asymmetric transformation was illustrated by the isolation of L-allylglycine following simple functional manipulation of the corresponding precursor.

The first example of truly catalytic, enantioselective allylation of imines has been reported by Yamamoto [46a]. These authors had first discovered that imines could undergo allylation reaction via a palladium-catalyzed allylstannane reaction to afford the corresponding homoallylamines in high yields [47a, 47b,



Scheme 23



Scheme 24

47c]. A bis- π -allylpalladium complex was shown to be an important intermediate for the catalytic cycle reacting with imines as a nucleophile. The proper choice of a chiral nontransferable π -allyl group has enabled these researchers to develop an enantioselective variant of this allylation reaction. Various chiral palladium complexes (**66a–f**) were screened (5 mol %) in the reaction of imine **67** with allyltributylstannane in DMF (Scheme 24). Chiral BINAP-palladium com-

plex **66a** gave the homoallylamine **68** in 39% yield, in racemic form. Although very low levels of enantioselectivity were observed with the use of chiral π -allylpalladium chloride complexes **66b,c**, the chiral catalyst **66d** gave (*R*)-**68** in 62% yield and 50% ee. The chiral catalyst **66e** was obtained following a minor structural modification of **66d**, and the allylation of **67** using this catalyst afforded the homoallylamine **68** in 62% yield and 81% ee. The catalyst **66f** was not effective for this asymmetric allylation. The generality of the reaction of allyltributylstannane [46b] with various imines in the presence of **66e** was then examined. The corresponding homoallylamines were isolated in 30–83% yield and 40–82% ee.

A plausible mechanism for this asymmetric allylation has been formulated (Fig. 7). The first step involves the transmetalation of allyltributylstannane to palladium. The resulting bis- π -allylpalladium complex **69** would react with imine **67** to give the π -allylpalladium complex **70**; this coordination stage is the key step for the asymmetric induction observed in this reaction. The addition step would produce the π -allylpalladium amide **71**, and another transmetalation of allyltributylstannane to palladium would lead to the formation of the desired product and the regeneration of complex **69**.

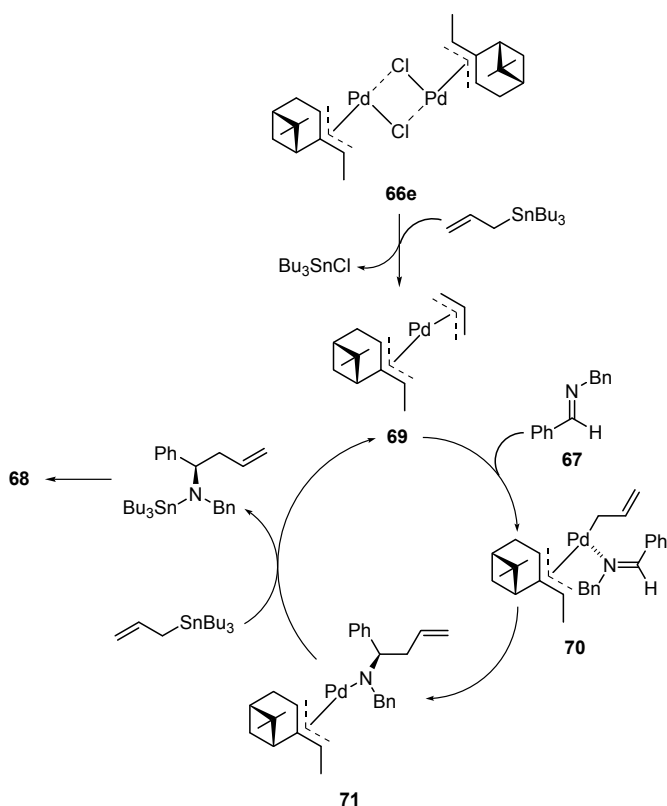


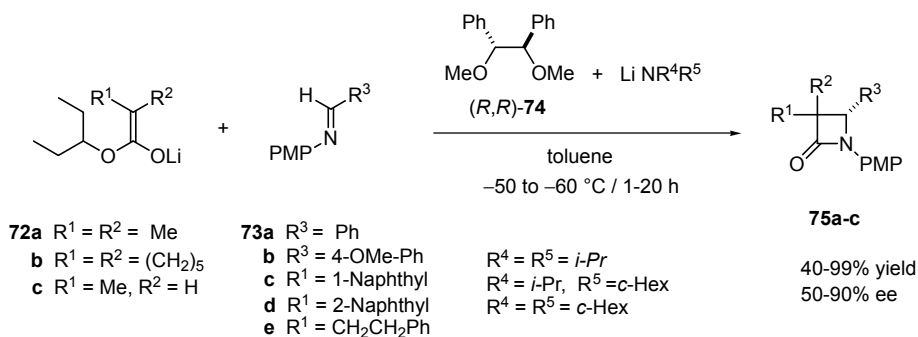
Fig. 7

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Catalytic Enantioselective Mannich-Type Reactions

Asymmetric Mannich-type reactions provide useful routes for the synthesis of enantiomerically enriched β -amino ketones or esters [48a, 48b]. For the most part, these methods involve the use of chirally modified enolates or imines. Only a handful of examples has been reported on the reaction of imines with enolates of carboxylic acid derivatives or silyl ketene acetals in the presence of a stoichiometric amount of a chiral controller [49a, 49b, 49c]. Reports describing the use of a substoichiometric amount of the chiral agent are even more scarce. This section contains some of the most recent advances in the field of catalytic enantioselective additions of lithium enolates and silyl enol ethers of esters and ketones to imines.

The association of chiral ligands with lithium enolates of esters and ketones as well as the consequences on reactivity has been well documented. The influence of an external ligand on the stereochemical course of addition to an imine was first reported by Tomioka and co-workers [50a, 50b]. These authors surveyed the addition of a variety of lithium ester enolates **72** to a selection of 4-methoxyphenylaldimines **73** in the presence of a full equivalent of hydrobenzoin bis(methyl ether) ((*R,R*)-**74**) (Scheme 25). Although the initial results were promising (60% ee and 95% yield), they were unable to improve the selectivity for formation of lactam **75** until the critical observation of the importance of a lithium amide as a co-activator. For example, addition of 2.2 equivalents of LDA accelerated the reaction and improved the enantioselectivity to 87% ee. Similar effects were reported for lithium cyclohexylisopropylamide (LICA) and lithium dicyclohexylamide, but the bulkier amides lithium tetramethylpiperidide and lithium *tert*-butylcyclohexylamide gave significantly poorer selectivities. Under these conditions even enolizable aldimines such as **73e** gave high yield (90%) and enantioselectivity (90%) of the lactam. The diastereoselectivity with the unsymmetrically substituted enolate **72c** was modest (ca. 4/1) favoring the *cis*-lactam. Interestingly, both *cis*- and *trans*-isomers displayed similar enantiomer-



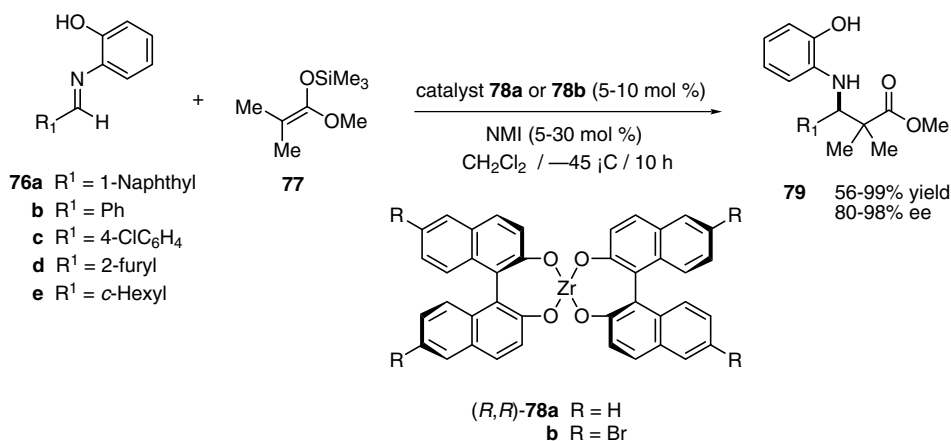
Scheme 25

ic excesses (73–76%). On the basis of empirical observations with many combinations of reagents, the authors propose the existence of a ternary complex between **72**, (*R,R*)-**74**, and the lithium amide. Moreover, they noted the enhanced reactivity of the ternary complex compared to the activation of **72** by the lithium amide alone. This led to the successful demonstration of enantioselective catalysis by (*R,R*)-**74**. Thus, reaction of **72a** with **73a** in the presence of LICA (2.4 equiv) and (*R,R*)-**74** (0.2 equiv) afforded **75a** in 80% yield and 75% ee [50c].

The development of a catalytic, enantioselective Mannich-type reaction of silyl ketene acetals lagged far behind the now-well-established enantioselective Mukaiyama directed aldol addition. The major consideration for the invention of such a transformation is obviously the selection of an appropriate Lewis acid activator. This is a challenging problem in view of the basicity of the imine nitrogen, the ambiguity in complexation geometry, and most importantly the release of the catalyst to effect turnover. Thus, it is not surprising that the first successful catalytic, enantioselective Mannich reaction was reported only in 1997.

To address the design criteria listed above, Kobayashi and co-workers prepared the mildly Lewis acidic zirconium[BINOL]₂ complexes **78a,b** from Zr(*Ot*-Bu)₄ and (*R*)-BINOL and the imines **76** derived from 2-aminophenol [51a, 51b, 51c, 51d] (Scheme 26). In the presence of catalytic amounts of **78a** the trimethylsilyl ketene acetal of methyl 2-methylpropanoate (**77**) reacted with **76a** to afford the adduct **79** quantitatively and with 34% ee. The use of *N*-methylimidazole (NMI) in equal amounts markedly improved the selectivity to 70% ee as did the use of **78b** which provided **79** in 90% ee. By chemical correlation the products were shown to be of the *R*-configuration. The reaction displayed some generality with aromatic aldimines (83–98% ee), but the one enolizable aldimine gave only modest results (56% yield, 80% ee) [51e].

The hydroxy group of the 2-hydroxyphenylimine moiety serves several critical roles. First, it allows for easy oxidative removal (1: MeI; 2: CAN) of the nitro-

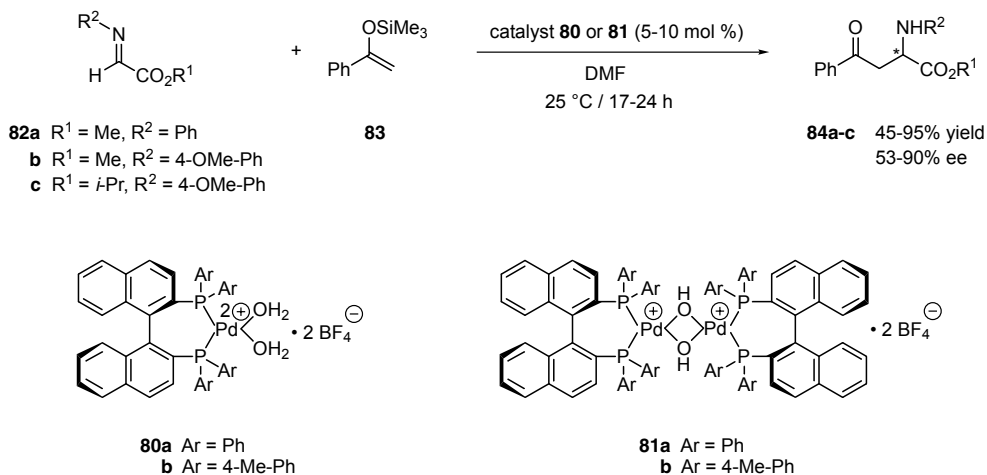


Scheme 26

gen protecting group to generate primary amines. Second, it is supposed to assist in the binding of the zirconium catalyst to fix the geometry of the complex and third, it is believed to provide the proton needed to release the Lewis acid from the product and receive the silyl group from **77**. The authors have proposed a catalytic cycle to account for these features, though the paucity of structural information precluded any insight in the origin of enantioselection. *N*-Methylimidazole is believed to be a deaggregation agent for the catalyst [51f].

The search for a catalyst suitable to promote addition of the less reactive silyl enol ethers of ketones has identified a novel class of cationic transition metal complexes in two independent laboratories. The use of a chiral palladium(II) diaquo complex in the catalytic asymmetric addition of silyl enol ethers to aldehydes (first demonstrated by Shibasaki, Sodeoka et al. [52a, 52b]) provided a clear precedent for their subsequent use with α -imino esters [53] (Scheme 27). Initial experiments focused on the reaction of various α -imino esters **82a–c** with silyl enol ether **83** (1.5 equiv) in the presence of the Pd diaquo complex **80a** (10 mol %) in DMF. Extensive experimentation led to the formation of **84c** in 67% ee, and also underscored the importance of suppressing the generation of tetrafluoroboric acid during the course of the reaction.

Towards that end, binuclear μ -hydroxo complexes **81a,b** could be made by the treatment of the diaquo complexes **80a,b** with 4 Å molecular sieves in acetone. These complexes were expected to prevent the formation of HBF_4 when treated with silyl enol ether **83**. In the presence of the novel complex **81b** (5 mol %), the reaction of silyl enol ether **83** with α -imino ester **82c** proceeded smoothly at 25 °C to give the acylalanine derivative (*S*)-**84c** in 95% yield and 90% ee (Scheme 27). The reaction of other silyl enol ethers with α -imino ester **82c** afforded the corresponding acylalanine derivatives with good asymmetric induction (53–84% ee).



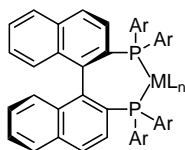
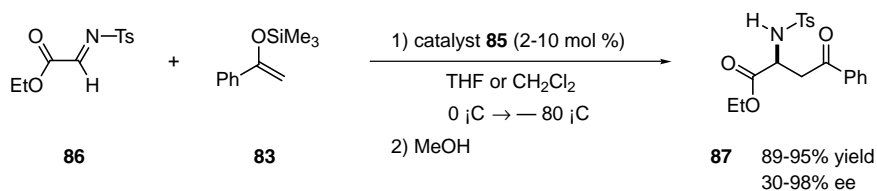
Scheme 27

This catalytic asymmetric Mannich-type reaction of silyl enol ethers with α -imino esters is notable because it proceeds under neutral conditions.

Lectka and co-workers have simultaneously developed similar phosphine-transition metal catalysts for the same transformation [54a, 54b, 54c, 54d]. These researchers were interested in testing the reactivity of α -imino esters toward enol silane nucleophiles upon chelation with a late transition metal (Ag(I), Cu(I), Ni(II), and Pd(II)) as a means of substrate activation. This ultimately led to the development of a catalytic, enantioselective alkylation of α -imino esters with enol silanes in up to 98% ee and in high chemical yields (Scheme 28).

α -Imino ester **86** reacted with enol silane **83** (1.1 equiv) in the presence of 10 mol % of (*R*)-BINAP-AgSbF₆ (**85a**) to afford the desired product **87** in 95% yield and 90% ee. The complex **85b** afforded **87** in 80% ee (at -80 °C) whereas complex **85c** gave **87** in 91% yield and 98% ee (at 0 °C). Catalyst (**85c**) loading as low as 2 mol % afforded **87** in 96% ee (at 0 °C). The complex **85d** was the least selective catalyst (30% ee at -80 °C). The use of other enol silanes was also examined in combination with either complex **85a**, **85b**, or **85c**, and the corresponding addition products were isolated in 65–94% yield and 61–98% ee. Recrystallization of most of these reaction products afforded virtually enantiomerically pure materials (>99% ee). The tosyl and ethyl groups could be easily removed to yield substituted amino acids in good chemical yields with no detectable racemization.

These two recent communications of a high-yielding catalytic asymmetric alkylation of α -imino esters provide access to a variety of non-natural α -amino acids as well as to precursors for natural products, and therefore should prove to be extremely useful. In addition they serve to set expand the palette of metal complex types and catalysis modes for future investigations in this young field.



- 85a** Ar = Ph, ML_n = AgSbF₆
b Ar = Ph, ML_n = Pd(ClO₄)₂
c Ar = 4-Me-Ph, ML_n = CuClO₄
d Ar = Ph, ML_n = Ni(SbF₆)₂

Scheme 28

10

Conclusions

The very encouraging and exciting results disclosed during these past nine years and reported in this review have contributed to the emergence of an interesting new area of research. The stereoselective synthesis of amines and amine derivatives starting from an achiral substrate and using a nucleophilic reagent in the presence of an external chiral auxiliary has become a viable process. While several types of carbon nucleophiles have been already examined, new methods of enantioselective addition might originate from the choice of different azomethine functions and/or different chiral promoters. The search for a new and practical catalytic, enantioselective alkylation of azomethine functions will remain a challenge in modern synthetic chemistry for some time to come.

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Chapter 27

Allylation of Carbonyl Groups

Akira Yanagisawa

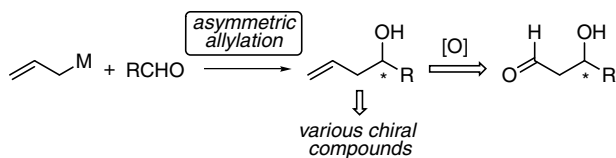
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Keywords: Allylation, Allylsilanes, Allylstannanes, Carbonyl compounds, Chiral Lewis acid catalysts, Chiral Lewis base catalysts

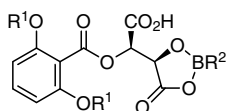
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1 Introduction

Asymmetric allylation of carbonyl compounds to prepare optically active secondary homoallylic alcohols is a useful synthetic method since the products are easily transformed into optically active β -hydroxy carbonyl compounds and various other chiral compounds (Scheme 1). Numerous successful means of the reaction using a stoichiometric amount of chiral Lewis acids or chiral allylmethyl reagents have been developed and applied to organic synthesis; however, there are few methods available for a catalytic process. Several reviews of asymmetric allylation have been published [1, 2, 3, 4, 5] and the most recent [5] describes the work up to 1995. This chapter is focussed on enantioselective allylation of carbonyl compounds with allylmethyls under the influence of a catalytic amount of chiral Lewis acids or chiral Lewis bases. Compounds **1** to **19** [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39] shown in Fig. 1 are the chiral catalysts reported to date that have been successfully used for the catalytic enantioselective allylation of carbonyl compounds. Some of these have also been applied to enantioselective propargylation or the Mukaiyama aldol reaction. Chiral compounds **20** to **25** [40, 41, 42,



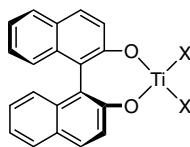
Scheme 1



1, $\text{R}^1 = i\text{-Pr}$; $\text{R}^2 = \text{H}$ [6,7]

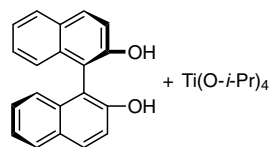
2, $\text{R}^1 = i\text{-Pr}$; $\text{R}^2 = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$ [7]

3, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{H}$ [8]



4, $\text{X} = \text{Cl}$ [9, 10]

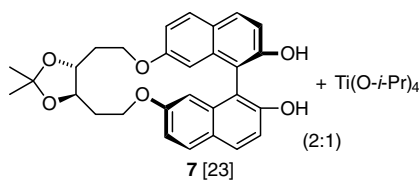
5, $\text{X} = \text{Br}$ [9]



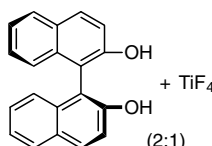
6A (1:1) [11, 13-16, 22]

6B (2:1) [12, 13, 16, 23]

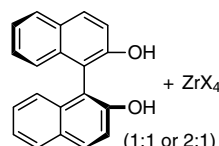
ent-6B (2:1) [17-21]



7 [23]

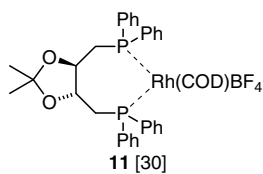


8 [24, 25]

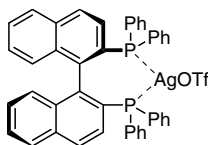


9, $\text{X} = \text{O-}i\text{-Pr}$ [19, 27, 28]

10, $\text{X} = \text{Cl}$ [29]

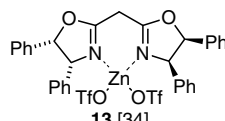


11 [30]

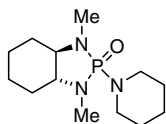


12 [31-33]

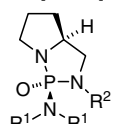
ent-12 [31, 33]



13 [34]



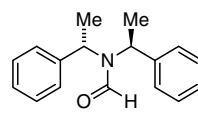
14 [35]



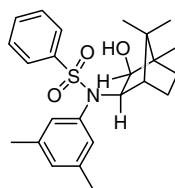
15, $\text{R}^1 = \text{-(CH}_2)_5\text{-}$; $\text{R}^2 = 1\text{-naphthyl}$ [36, 37]

16, $\text{R}^1 = n\text{-Pr}$; $\text{R}^2 = 1\text{-naphthyl}$ [36, 37]

17, $\text{R}^1 = n\text{-Pr}$; $\text{R}^2 = 1,2,3,4\text{-tetrahydro-1-naphthyl}$ [37]



18 [38]



19 [39]

Fig. 1

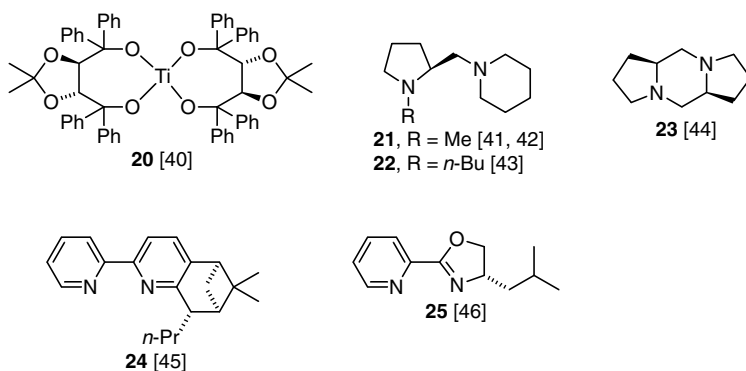


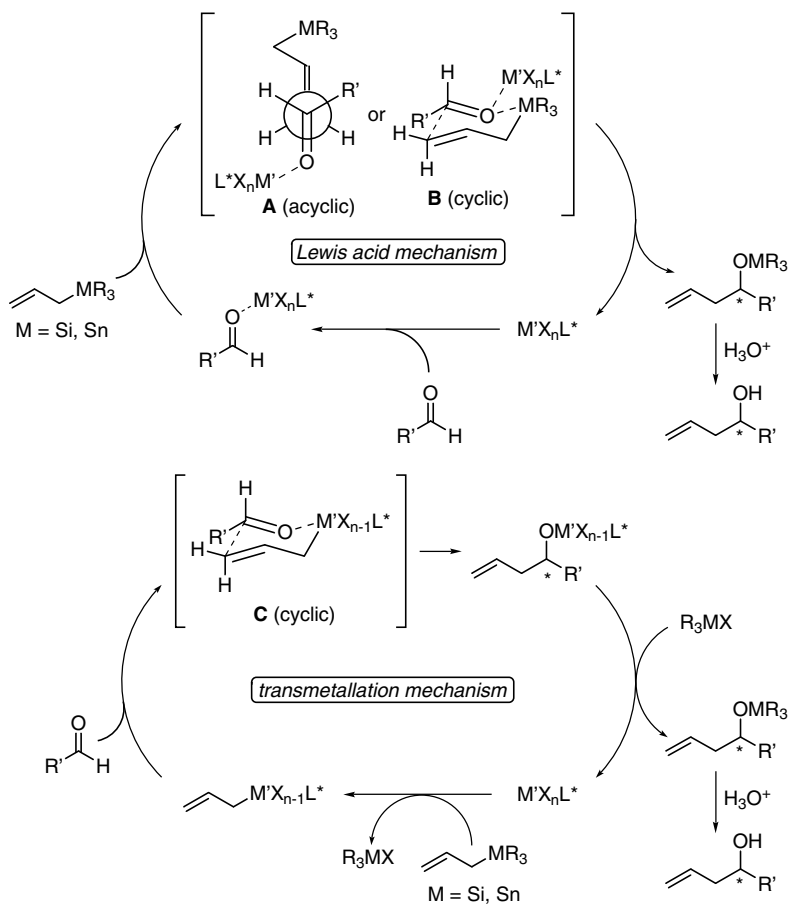
Fig. 2

43, 44, 45, 46], which have been used for the stoichiometric allylation, also have great potential for utilization in catalytic allylation (Fig. 2).

2

Mechanism of Catalysis

Most of the catalytic methods reported so far are the chiral metal compound-catalyzed allylation reactions using allylic silanes or allylic stannanes. Two types of catalytic mechanism, Lewis acid mechanism and transmetallation mechanism, can be considered for these reactions as illustrated in Scheme 2. If the chiral metal catalyst $M'X_nL^*$ acts as a Lewis acid in the asymmetric allylation, an aldehyde is coordinated to this catalyst first and then reaction by an allylmetal ($M=Si$ or Sn) takes place via an acyclic antiperiplanar transition-state structure **A**; this was proposed by Y. Yamamoto to explain the high *syn*-selectivity obtained by addition of crotyltributyltin to aldehydes in the presence of $BF_3 \cdot OEt_2$, irrespective of the double-bond geometry of the crotyltin [47, 48]. A cyclic transition-state model **B** is also a possible alternative for a Lewis acid mechanism. Nishigaichi and Takuwa proposed a similar cyclic model for $ZnCl_2$ -promoted *anti*-selective γ -allylation of aldehydes with γ -substituted allylstannanes [49]. Chiral (acyloxy)borane (CAB) complexes **1** to **3** [6, 7, 8] conceivably react by the Lewis acid mechanism. In contrast, a cyclic transition-state structure **C** containing a chiral ligand-coordinated metal atom $M'X_{n-1}L^*$ instead of a trialkylsilyl or trialkylstannyl group is a probable model when transmetallation to an allyl- $M'X_{n-1}L^*$ occurs rapidly. The chiral catalyst $M'X_nL^*$ is reproduced by reaction of the resulting metal alkoxide of homoallylic alcohol with R_3MX ($M=Si$ or Sn). For chiral transition metal catalysts including binaphthol-titanium complexes and the BINAP-silver(I) complex, both catalytic reaction pathways are possible.



Scheme 2

3

Catalytic Allylation of Carbonyl Compounds

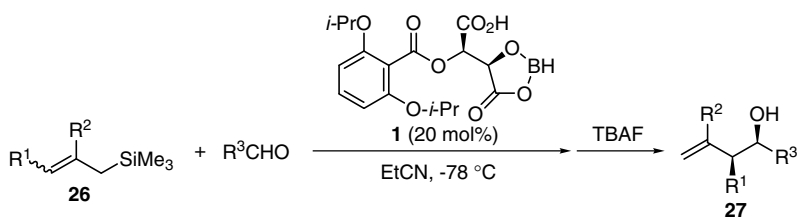
Catalytic enantioselective allylations of aldehydes already published can be classified into two methods carried out under the influence of chiral Lewis acid catalysts and chiral Lewis base catalysts. The process by chiral Lewis acid catalysts generally uses allyltrimethylsilane or allyltrialkylstannane as an allylating agent, both of which show low reactivity toward aldehydes without these catalysts. The process by chiral Lewis base catalysts employs allyltrichlorosilane or allylmetals possessing relatively higher reactivity. Both processes can be successfully applied to various substituted allylmetal compounds or allenylmetal compounds.

3.1

Allylation by Chiral Lewis Acid Catalysts

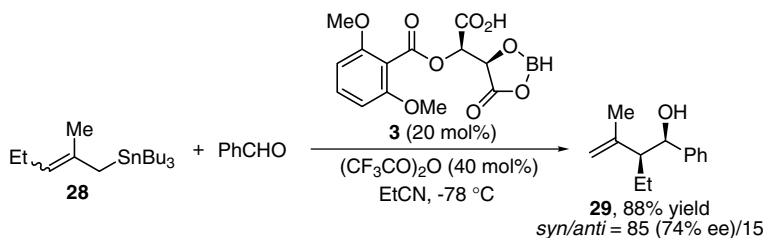
The first example of catalytic enantioselective allylation of aldehydes was achieved using CAB complex **1** by our group (Scheme 3) [6, 7]. We have also found that the CAB complex is a powerful catalyst for enantioselective Diels-Alder and aldol-type reactions. We then attempted the CAB-catalyzed Sakurai-Hosomi allylation of aldehydes with allylic silanes **26**. The CAB complex **1** can be prepared *in situ* from reaction of (2*R*,3*R*)-mono(2,6-diisopropoxybenzoyl) tartaric acid and $\text{BH}_3 \cdot \text{THF}$ in propionitrile at 0 °C. In the presence of 20 mol % of the CAB catalyst, various allylic trimethylsilanes **26** reacted with achiral aldehydes in propionitrile at -78 °C followed by desilylation with TBAF to afford the corresponding optically active homoallylic alcohols **27** enantioselectively in good yields. γ -Methylated allylsilanes exhibit excellent diastereoselectivity in addition to high enantioselectivity, up to 96% ee. Noteworthy is the fact that *syn* (*erythro*) alcohols are selectively obtained in the reactions regardless of the *E/Z* stereochemistry of the γ -alkylated allylsilanes. An exclusive 1,2-selectivity is observed when allylic silanes are added to α,β -unsaturated aldehydes. The reactivity of allylation can be improved without decreasing the enantioselectivity by using the CAB catalyst **2** derived from 3,5-bis(trifluoromethyl)phenylboronic acid and a tartaric acid derivative. The extended transition-state model is proposed to explain the observed preference for *syn* selectivity [7].

Later, Marshall extended the scope of the CAB catalyst system to allylic stannanes (Scheme 4) [8]. Under the influence of a catalytic amount of CAB complex **3** and trifluoroacetic anhydride, allylic tributylstannane **28** can be added to



R ¹	R ²	R ³	Yield [%]	<i>syn/anti</i>	ee [%]	Config
H	H	Ph	46		55	<i>R</i>
H	Me	Ph	68		82	<i>R</i>
H	Me	(<i>E</i>)- <i>n</i> -PrCH=CH	50		80	
Me (<i>E/Z</i> =61/39)	Me	Ph	63	96/4	92 (<i>syn</i>)	
Me (<i>E/Z</i> =36/64)	Me	Ph	64	96/4	92 (<i>syn</i>)	
Me (<i>E/Z</i> =65/35)	Et	Ph	74	97/3	96 (<i>syn</i>)	<i>R</i>
Me (<i>E/Z</i> =65/35)	Et	<i>n</i> -Pr	36	95/5	86 (<i>syn</i>)	<i>S</i>

Scheme 3



Scheme 4

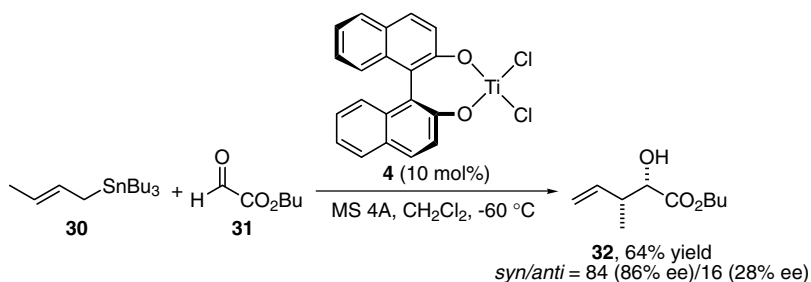
a variety of aldehydes. For example, the addition to benzaldehyde gave the homoallylic alcohol **29** in 88% yield with a *syn/anti* ratio of 85/15. The *syn* isomer indicated 74% ee.

Chiral titanium complexes **4** and **5**, which were developed as chiral catalysts for asymmetric carbonyl-ene reactions with prochiral glyoxylate esters [50], were first applied to the catalytic asymmetric allylation of carbonyl compounds by Mikami and Nakai (Scheme 5) [9]. The titanium catalysts are prepared from (*S*)-binaphthol and diisopropoxytitanium dihalide (X=Cl and Br) in the presence of 4 Å molecular sieves. Using these catalysts, glyoxylates are enantio- and diastereoselectively allylated with allylic trimethylsilanes or allylic tributylstannanes. High levels of enantioselectivity and *syn* selectivity are observed for (*E*)-crotylsilane and -stannane. The *syn* selective allylation reaction is believed to proceed mainly through an antiperiplanar transition state.

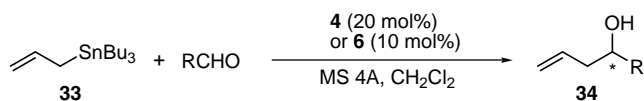
Thereafter, the BINOL-Ti complex-catalyzed asymmetric allylation was extensively and individually studied by Tagliavini and Umani-Ronchi's group and by Keck's group. Tagliavini and Umani-Ronchi have shown that various achiral aldehydes can be highly enantioselectively allylated with allyltributyltin by a 20 mol % of chiral titanium complex **4** (Scheme 6) [10]. In this procedure, straight-chain aliphatic aldehydes proved to be suitable substrates affording high enantiomeric excesses.

Keck almost simultaneously reported two procedures using chiral titanium catalysts **6A** and **6B** for the enantioselective addition of allyltributyltin to aldehydes [11]. In the first procedure, the catalyst **6A** is prepared from a 1:1 mixture of (*R*)-binaphthol and titanium tetraisopropoxide. The second procedure for the preparation of **6B**, in contrast, requires a 2:1 mixture of BINOL, Ti(O^{*i*}Pr)₄, and a catalytic amount of CF₃SO₃H or CF₃CO₂H. Using 10 mol % of the catalyst **6A** or **6B**, a variety of aromatic, aliphatic, and α,β-unsaturated aldehydes are efficiently transformed into the corresponding optically active homoallylic alcohols with high enantioselectivity. An improved procedure was later published for the catalytic asymmetric allylation reactions using the 2:1 BINOL/Ti catalytic system [12].

The catalytic process was also applied to enantioselective additions of methallyltributylstannane and allenyltributylstannane to aldehydes [13, 14]. The methyl group of methallytin compound does not affect the chemical yield or enantioselectivity in the reaction [13]. A positive nonlinear effect was observed for



Scheme 5



R	Catalyst	Temp. [°C]	Yield [%]	ee [%]	Config	Reference
C ₅ H ₁₁	4	-20	75	98	<i>R</i>	10
PhCH ₂ CH ₂	6B	-78 to -20	98	96		11
<i>c</i> -C ₆ H ₁₁	4	r.t.	75	93	<i>S</i>	10
<i>c</i> -C ₆ H ₁₁	6A	-78 to -20	66	94	<i>R</i>	11
Ph	4	r.t.	96	82	<i>S</i>	10
Ph	6B (without MS)	-20	98	96	<i>R</i>	12
(<i>E</i>)-PhCH=CH	4	-20	38	94	<i>S</i>	10
(<i>E</i>)-PhCH=CH	6B (without MS)	0	62	90	<i>R</i>	12

Scheme 6

the methallyl addition. For example, the product was obtained in 88% ee when (*R*)-BINOL of 50% ee was used in the reaction at -20 °C [13]. The chiral amplification phenomenon was further examined in detail by Faller and coworkers, and they also found the chiral poisoning phenomenon in a racemic BINOL/Ti catalyst system [15]. The addition of allenylstannane requires a stoichiometric or nearly stoichiometric amount of the chiral titanium catalyst **6A** to realize good yields of isolated product due to the lower reactivity of allenylstannane [14].

Functionalized allyltributylstannanes can also be used in the BINOL/Ti-catalyzed reaction and addition of β -substituted allyl groups with heteroatoms in the side chain to aldehydes has been achieved with a high degree of enantiocontrol [16]. The catalytic asymmetric allylation has been successfully applied to total syntheses of the macrolides (*R*)-(+)-ricinelaidic acid lactone and (-)-gloeosporone [21].

Yu and co-workers reported that $i\text{PrSSiMe}_3$ accelerates the catalytic asymmetric allylation of aldehydes with BINOL-Ti complex *ent*-**6B** [17]. For example, the

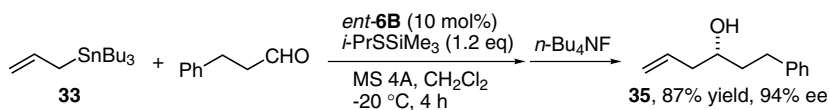
reaction of allyltributyltin **33** with hydrocinnamaldehyde in the presence of 10 mol % of *ent*-**6B** and 1.2 equiv of *i*-PrSSiMe₃ in CH₂Cl₂ at -20 °C for 4 h followed by desilylation with *n*-Bu₄NF gave the homoallylic alcohol **35** in 87% yield with 94% ee (Scheme 7). If the accelerator is absent, a longer reaction time (70 h) is necessary to gain a comparable chemical yield in the reaction at -20 °C. The *i*-PrSSiMe₃ is thought to dissociate the product from the transition state by taking advantage of the strong affinities of Sn-S and Si-O bonds, and to regenerate the chiral titanium catalyst. The same group further showed that Et₂BS^{*i*}Pr [18, 19], Et₂AlS^{*i*}Pr [18], and B(OMe)₃ [20] are also good accelerators for the catalytic asymmetric allylation of aldehydes. The alkylthioborane is superior to other reagents with respect to reactivity, enantioselectivity, and is applicable to other systems such as propargylation with allenyltributylstannane [19].

Another noteworthy attempt to improve the catalytic asymmetric allylation was carried out employing a tin(II)-mediated Barbier-type reaction [22]. An allyltin reagent, generated *in situ* from allyl bromide, a Sn(II) compound, and a catalytic amount of CuCl, was allowed to react with aldehydes under the influence of the BINOL-Ti catalyst **6A** to provide the product with up to 63% ee.

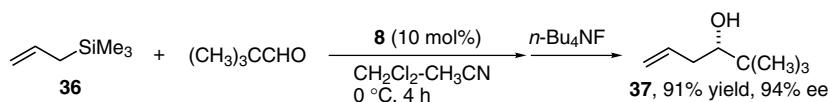
Lipshutz and coworkers synthesized an optically active BINOL analog by copper-catalyzed intramolecular biaryl coupling and applied the complex with Ti(O^{*i*}Pr)₄ **7** to Keck's asymmetric allylation [23]. In the reaction with benzaldehyde or cyclohexanecarboxaldehyde, almost identical results were obtained with regard to both yields of isolated product and enantiomeric excesses.

A catalytic enantioselective addition of allylsilane to aldehydes was achieved using a chiral Ti catalyst **8**, which was prepared from (*S*)-BINOL and TiF₄ [24, 25]. Although allylic trialkylsilanes are inexpensive and nontoxic allylating agents, they are less reactive nucleophiles than the corresponding allylic stannanes. Carreira found that the TiF₄-derived chiral catalyst **8** has sufficient reactivity to mediate the allylation with allyltrimethylsilane [24]. For the catalytic asymmetric reaction, α,α -dialkylated aldehydes are suitable substrates which can acquire high enantioselectivity. For example, when the allylation of pivalaldehyde was performed with 10 mol % of the chiral Ti catalyst **8** in CH₃CN/CH₂Cl₂ at 0 °C for 4 h, the adduct **37** was formed in 94% ee (Scheme 8). The catalytic process also showed a nonlinear relationship between the ee of BINOL and the ee of the product.

Regarding the origin of the high level of asymmetric induction by CAB or BINOL-Ti catalyst, Corey and coworkers postulated that the C-H \cdots O hydrogen bond occurring in the transition-state assembly seems to be a key factor in determining the absolute stereochemical course of the allylation reactions of alde-



Scheme 7



Scheme 8

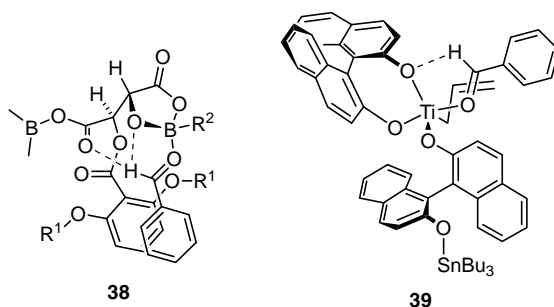
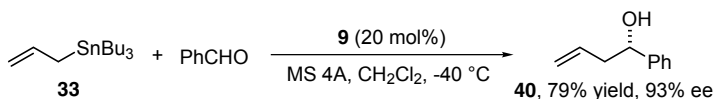


Fig. 3

hydres (Fig. 3) [26]. For the CAB catalyst derived from (*R,R*)-tartrate, structure **38** is believed to be formed preferentially, and to contain two hydrogen bonds between a formyl hydrogen of benzaldehyde and two oxygens of the chiral ligand. An allylic silane can thus react with the aldehyde selectively at the *re*-face to afford the *R*-enriched homoallylic alcohol. For the allylation catalyzed by BINOL-Ti complex **6B**, benzaldehyde-coordinated bis-BINOL titanate ester **39** has been proposed as a preferred transition-state structure.

Tagliavini and Umani-Ronchi found that chiral BINOL-Zr complex **9** as well as the BINOL-Ti complexes can catalyze the asymmetric allylation of aldehydes with allylic stannanes (Scheme 9) [27]. The chiral Zr catalyst **9** is prepared from (*S*)-BINOL and commercially available $\text{Zr}(\text{O}^i\text{Pr})_4 \cdot i\text{PrOH}$. The reaction rate of the catalytic system is high in comparison with that of the BINOL-Ti catalyst **4**, however, the Zr-catalyzed allylation reaction is sometimes accompanied by an undesired Meerwein-Ponndorf-Verley type reduction of aldehydes. The Zr complex **9** is appropriate for aromatic aldehydes to obtain high enantiomeric excess, while the Ti complex **4** is favored for aliphatic aldehydes. A chiral amplification phenomenon has, to a small extent, been observed for the chiral Zr complex-catalyzed allylation reaction of benzaldehyde.

Yu and coworkers reported that use of $i\text{PrSB}(\text{Et})_2$ as an additive accelerates the chiral Zr-catalyzed asymmetric allylation reaction and suppresses the concomitant Meerwein-Ponndorf-Verley reduction. The presence of the additive is thought to dissociate the product from the reaction complex and to regenerate the chiral catalyst [28]. This method was further extended to asymmetric propargylation with allenyltributylstannane by the same group [19]. In contrast, Tagliavini and Umani-Ronchi and their group have shown that an enantioselective allylation of



Scheme 9

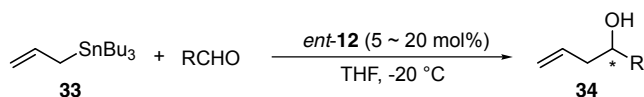
aldehydes with allyltributyltin is catalyzed by a new zirconium-BINOL complex **10**, and that a catalytic amount of 4-*tert*-butylcalix[4]arene activates the reaction, thus allowing the use of only 2 mol % of the chiral Zr catalyst **10** [29].

Most commonly used chiral Lewis acids have been derived from main group and early transition series elements. An initial attempt at utilizing optically active catalysts of late transition metal complexes for the enantioselective addition of allyltributylstannane to aldehydes was made by Nuss and Rennels [30]. Employment of Rh(COD)[(-)-DIOP]BF₄ (**11**) as a catalyst, however, resulted in only a small degree of asymmetric induction (17% ee).

We found that a BINAP·silver(I) complex also catalyzes the asymmetric allylation of aldehydes with allylic stannanes, and high γ -, *anti*-, and enantioselectivities are obtained by this method [31, 32, 33]. The chiral phosphine-silver(I) catalyst can be prepared simply by stirring an equimolar mixture of chiral phosphine and silver(I) compound in THF at room temperature. Scheme 10 shows the results obtained by the reaction of a variety of aldehydes with allyltributyltin (**33**) under the influence of 5 to 20 mol % of (*S*)-BINAP·silver(I) triflate (*ent*-**12**) in THF at -20 °C [31]. The reaction furnishes high yields and remarkable enantioselectivities not only with aromatic aldehydes but also with α,β -unsaturated aldehydes, with the exception of an aliphatic aldehyde which gives a lower chemical yield. In the reaction with α,β -unsaturated aldehydes, 1,2-addition takes place exclusively. Enantioselective addition of methallyltributylstannane to aldehydes can also be achieved using this method [31, 32].

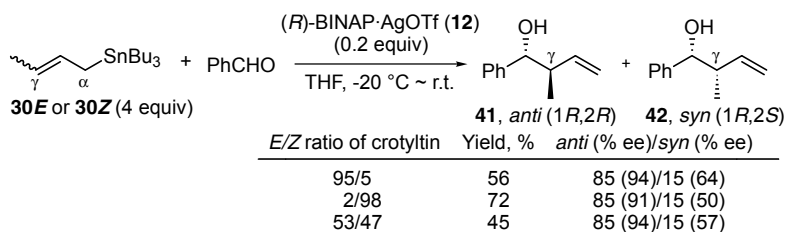
Condensation of γ -substituted allylmetals with aldehydes is a fascinating subject with respect to regioselectivity (α/γ) and stereoselectivity (*E/Z* or *anti/syn*). Addition of (*E*)-crotyltributyltin (**30E**, *E/Z*=95/5) to benzaldehyde in the presence of 20 mol % of (*R*)-BINAP·AgOTf (**12**) in THF at -20 °C to room temperature exclusively gives the γ -adducts **41** and **42** with an *anti/syn* ratio of 85/15 [32]. The *anti*-isomer **41** indicates 94% ee with a 1*R*,2*R* configuration (Scheme 11). Use of (*Z*)-crotyltributyltin (**30Z**, *E/Z*=2/98) or a nearly 1:1 mixture of the (*E*)- and (*Z*)-crotyltributyltin also results in a similar *anti/syn* ratio and enantioselectivity (Scheme 11).

Reactions of aldehydes with 2,4-pentadienylstannanes are also catalyzed by the BINAP·silver(I) complex, and the corresponding γ -pentadienylated optically active alcohols are obtained with high enantioselectivity [33]. When benzaldehyde is reacted with 1 equiv of pentadienyltributyltin (**43**, *E/Z*=97/3) and 0.1 equiv of (*S*)-BINAP·AgOTf (*ent*-**12**) at -20 °C, the γ -product **44** is obtained in 61% yield with 90% ee (Scheme 12). Pentadienyltrimethyltin offers a chemical yield and enantioselectivity comparable to those of pentadienyltributyltin. Ketones are inert under the standard reaction conditions.

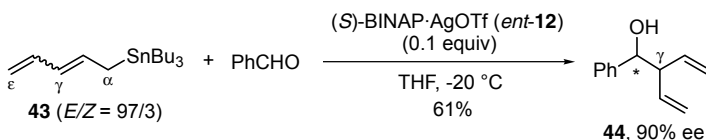


R	Yield [%]	ee [%]	Config
Ph	88	96	S
<i>p</i> -MeOC ₆ H ₄	59	97	
<i>p</i> -BrC ₆ H ₄	95	96	
2-furyl	94	93	
(<i>E</i>)-PhCH=CH	83	88	S
(<i>E</i>)- <i>n</i> -PrCH=CH	72	93	
PhCH ₂ CH ₂	47	88	

Scheme 10



Scheme 11



Scheme 12

Chiral bis(oxazoline) is an excellent chiral ligand as is BINAP for asymmetric reactions catalyzed by chiral metal complexes and has been applied to catalytic enantioselective allylation of aldehydes with allyltributyltin (**33**) by Cozzi, Umami-Ronchi and their colleagues [34]. Among various combinations of chiral bis(oxazolines) and metal salts, they found that the zinc complex **13** is the most effective and the ee values are in the range of 40 to 46%.

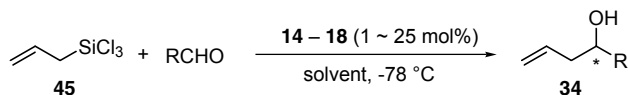
3.2

Allylation by Chiral Lewis Base Catalysts

The first example of chiral Lewis base-catalyzed allylation of carbonyl compounds was shown by Denmark et al. [35]. They surveyed a variety of achiral and chiral Lewis bases as stoichiometric reagents to promote the addition of allyltrichlorosilane to benzaldehyde and found that the chiral phosphoramidate **14** was a superior chiral promoter. When crotyltrichlorosilane was employed, the diastereoselectivity (*anti/syn*) of the product was dependent on the geometry of the crotylsilane. Based on the stereochemical outcome, the reaction was proposed to proceed via closed transition structures involving hexacoordinate silanates. The potential for catalysis was proved using a 25 mol % of **14** at $-78\text{ }^{\circ}\text{C}$ and a moderate enantiomeric excess was obtained (Scheme 13).

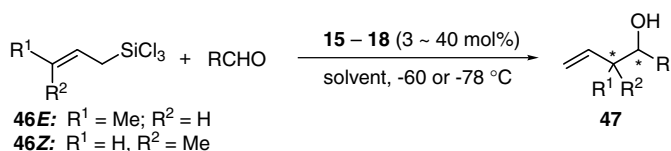
Iseki et al. later improved the catalytic process and showed that chiral phosphoramidates **15**, **16**, and **17**, prepared from (*S*)-proline, are suitable to catalyze the asymmetric allylation of aromatic aldehydes to give chiral homoallylic alcohols **34** with up to 88% ee (Scheme 13) [36, 37]. The same group has also developed a chiral formamide **18** as a chiral Lewis base catalyst [38]. This catalyst is convenient for the allylation of aliphatic aldehydes with high enantioselectivity. A typical aromatic aldehyde, benzaldehyde, gives a low enantiomeric excess (Scheme 13).

The *anti/syn* ratios and enantiomeric excesses of the reaction with (*E*)- and (*Z*)-crotyltrichlorosilanes, **46E** and **46Z**, respectively, catalyzed by the Lewis bases **15** to **18** are summarized in Scheme 14 [36, 37, 38]. In every case, the *anti* and



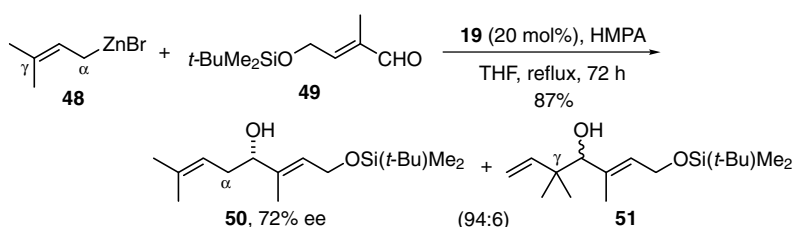
R	Catalyst	Time [h]	Solvent	Yield [%]	ee [%]	Config	Reference
Ph	14 (0.25 equiv)	24	CH ₂ Cl ₂	74	59	<i>R</i>	35
Ph	15 (0.1 equiv)	168	THF	67	85	<i>R</i>	36,37
Ph	16 (0.1 equiv)	168	THF	83	88	<i>S</i>	36,37
Ph	17 (0.01 equiv)	336	THF	98	88	<i>S</i>	37
Ph	18 (0.2 equiv)	168	C ₂ H ₅ CN	94	8		38
<i>c</i> -C ₆ H ₁₁	18 (0.2 equiv)	336	C ₂ H ₅ CN	80	98	<i>R</i>	38
PhCH ₂ CH ₂	18 (0.2 equiv)	504	C ₂ H ₅ CN	84	95	<i>S</i>	38

Scheme 13



R	Silane	Catalyst	Solvent	Yield [%]	<i>anti/syn</i>	ee [%]	Config	Reference
Ph	46E	15	THF	68	97/3	73	1R,2R	36,37
Ph	46Z	15	THF	95	2/98	76	1R,2S	36,37
Ph	46E	16	THF	90	98/2	83	1S,2S	36,37
Ph	46Z	16	THF	80	2/98	77	1S,2R	36,37
Ph	46Z	17	THF	63	<1/99	88	1S,2R	37
<i>c</i> -C ₆ H ₁₁	46E	18	C ₂ H ₅ CN	92	>99/1	98	1S,2R	38

Scheme 14



Scheme 15

syn homoallylic alcohols **47** are formed diastereoselectively from (*E*)- and (*Z*)-crotylsilanes, respectively.

Hong and coworkers have achieved a regio- and enantioselective addition of a prenylzinc reagent to an aldehyde and applied it to the synthesis of (–)-rosiridol [39]. They found that when prenylzinc bromide (**48**) was allowed to react with aldehyde **49** in the presence of HMPA, the α adduct **50** was obtained predominantly, while the γ adduct **51** was formed nearly exclusively without HMPA. Addition of 1.5 equiv of chiral amino alcohol derivative **19** to the reaction mixture induced a high degree of enantioselectivity without losing the α-regioselectivity. The use of 20 mol % of the chiral Lewis base **19** did not affect the yield or product ratio (**50**:**51**) of the reaction, and the α-adduct indicated 72% ee (Scheme 15).

4

Principal Alternatives

Various methods which use a stoichiometric amount of chiral Lewis acids or chiral Lewis bases are available for enantioselective allylation and related reactions

of aldehydes: e.g., chiral spiro titanate **20**/allylmagnesium bromide [40], tin(II) triflate/chiral diamine **21**/RAL(*t*Bu)₂ (R=allyl, methallyl, and allenyl) [41, 42], chiral diamine **22**/diallyltin dibromide [43], chiral diamine **23**/allylmagnesium bromide [44], chiral 2,2'-dipyridyl **24**/CrCl₂/allyl bromide [45], and chiral pyridinylloxazoline **25**/(*E*)-crotyltrichlorosilane [46]. Enantioselective allylation of carbonyl compounds with chiral allylmetal compounds, to which chiral auxiliaries are covalently bonded, is also a convenient route to the corresponding optically active homoallylic alcohols and numerous excellent chiral allylating agents have been developed [1, 2, 4, 5]. No enzymatic approaches to an enantiofacially selective allylation of carbonyl compounds have yet been reported.

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Chapter 28

Cyanation of Carbonyl and Imino Groups

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Keywords: α -Cyanohydrin, α -Aminonitrile, Hydrogen cyanide, Acetone cyanohydrin, TMSCN, Lewis acid, Cyclic dipeptide, Peptide-metal complex, Strecker synthesis

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1 Introduction

Cyanation has become a useful C_1 homologation methodology in organic synthesis. In particular, asymmetric cyanation of carbon-oxygen or carbon-nitrogen double bonds is of considerable importance since the optically active cyanated products have been used as intermediates for pyrethroid insecticides such as esfenvalerate [1], and liquid crystalline materials [2]. In addition, the introduced cyano group of an α -cyanohydrin or α -aminonitrile can easily be transformed without loss of the optical purity into various other functional groups such as carboxylic acid, ester, aldehyde, and amine, which serve as important chiral pools in the design of asymmetric catalysts as well as in syntheses of various biologically active materials.

Thus, the preparation of the optically active cyanohydrins and aminonitriles has been a major topic of interest in the field of asymmetric synthesis. However, a practical method for cyanation was not reported until the early 1980's, except for the use of an enzyme, oxynitrilase; a flavoprotein isolated from seeds and blossoms of various Prunaceae species, which catalyzes the addition of hydro-

gen cyanide to benzaldehyde to give (*R*)-mandelonitrile exclusively [3, 4, 5, 6, 7, 8].

Concerning the cyanating agent, hydrogen cyanide and its alkaline metal salts are frequently used to effect cyanation in the presence of a catalytic or a stoichiometric amount of a base, such as amines, phosphines, and metal alkoxides. Acetone cyanohydrin, which serves as an alternative to hydrogen cyanide, also promotes the cyanation of carbonyl and imino compounds (transhydrocyanation) to yield the corresponding cyanohydrins or aminonitriles along with the formation of acetone.

Cyano(trimethyl)silane (TMSCN) also plays a significant role in cyanations. The reactions proceed both in the presence of (Lewis) acids [9] and bases [10]. Hence, chiral Lewis acid-catalyzed cyanation reactions have been frequently performed by using TMSCN.

Accordingly, the design of the catalyst for asymmetric cyanation has mainly been performed using natural alkaloids, amino acid derived compounds with a basic moiety in the substituent, and Lewis acidic organometallics modified with optically active compounds [11].

On the other hand, only few studies have been successful in the asymmetric cyanation of imines compared with that of carbonyl compounds since imines, in general, themselves promote the cyanation reaction without a catalyst.

2

Asymmetric Cyanation of C=O Bonds

2.1

Base-Catalyzed Asymmetric Cyanation of C=O Bonds

In 1912, an attempt to realize asymmetric induction in the addition of hydrogen cyanide to carbonyl compounds by using an optically active natural alkaloid as a catalytic base was reported [12, 13]. Cyclodextrins were also reported by Jackson et al. [14] to catalyze asymmetric hydrocyanation. However, their enantioselectivities were disappointing. Tsuboyama designed poly-(*S*)-isobutylethyleneimine (**1**; Fig. 1), which was prepared by ring-opening polymerization of the optically active aziridine derived from (*S*)-leucine, to give (*R*)-(-)-mandelonitrile in 20% ee in the reaction of benzaldehyde with HCN [15, 16]. The asymmetric induction is suggested to be based on the helical structure of the polymer. Danda reported the asymmetric addition of HCN to 3-phenoxybenzaldehyde catalyzed by polymer-supported alkaloids. Among a variety of alkaloids examined, poly(quinidine-co-acrylonitrile) (**2a**; Fig. 1) afforded (*S*)-cyanohydrin in 46% ee; in contrast, poly(quinine-co-acrylonitrile) (**2b**; Fig. 1) gave (*R*)-cyanohydrin in 20% ee [17]. The use of (5*R*)-5-(4-imidazolylmethyl)-imidazolidine-2,4-dione (**3**; Fig. 1) as a catalyst yielded optically active (*S*)-cyanohydrins with an enantioselectivity up to 37% [18]. Cyanation of aldehydes catalyzed by (*S*)- α -dimethylamino- ϵ -caprolactam (**4**; Fig. 1) also furnished the optically active cyanohydrins in up to 26% ee [19]. In the reactions using **4**, acetone cyanohydrin was

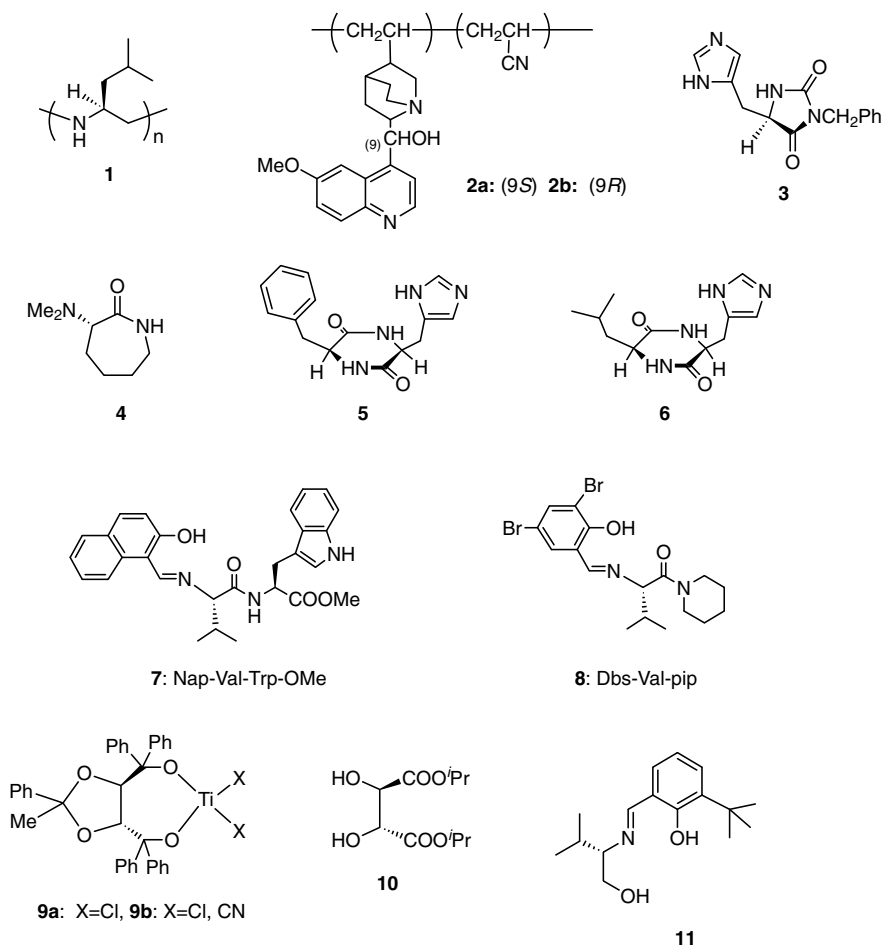


Fig. 1. Structures of compounds 1 to 11

employed as a cyanating agent and aliphatic aldehydes generally resulted in better selectivities than aromatic aldehydes.

Some peptides bearing a basic moiety in the side chain of the amino acid are also candidates as a catalyst for cyanation [20, 21, 22, 23]. Among the acyclic as well as the cyclic peptides examined, a cyclic dipeptide (**5**; Fig. 1) composed of (*S*)-phenylalanine (Phe) and (*S*)-histidine (His) was found to be effective [24, 25, 26]. The reaction of benzaldehyde with hydrogen cyanide in the presence of 2 mol % of the catalyst in toluene at $-20\text{ }^{\circ}\text{C}$ for 8 h furnished the corresponding (*R*)-cyanohydrin in 97% yield and an enantioselectivity of 97%. The asymmetric cyanation of various aromatic and heteroaromatic aldehydes similarly proceeded to give the optically active cyanohydrins, although aromatic aldehydes with electron withdrawing groups such as NO_2 and CN and aliphatic aldehydes

resulted in lower enantioselectivities. In contrast, hydrocyanation of benzaldehyde catalyzed by the cyclic peptide of (*S*)-leucine and (*S*)-histidine, cyclo[(*S*)-Leu-(*S*)-His] (**6**; Fig. 1) afforded (*S*)-mandelonitrile in 55% ee [27]. Higher enantioselectivities were observed in the reactions with aliphatic aldehydes (61 to 81% ee). The results are summarized in Table 1.

In cyanations catalyzed by the cyclic peptides, the reaction should not be performed in a homogeneous medium. When the reaction was carried out in benzene as a solvent, the state of the mixture changed from heterogeneous to homogeneous [24]. Indeed, the optical purity of the product decreased along with the increase of the conversion although a high ee was observed at the initial stage of the reaction (10% conversion; 90% ee). In contrast, a high enantioselectivity at a high conversion was realized when toluene was used as solvent in which the reaction proceeded under heterogeneous conditions (gel-like state) throughout the reaction [25].

The catalytic activity and selectivity in the hydrocyanation also depend on the method of purification. When the catalyst was purified by a non-aqueous solvent, high catalytic activity and asymmetric induction were realized. In addition, viscosity and thixotropy of the reaction mixture were also reported to influence the enantioselectivity [28]. Thus, it seems difficult to explain how the asymmetric induction occurs on a unimolecular level. Mechanistic studies on the asymmetric catalysis by NMR [29, 30, 31], calculation [30, 31], and X-ray diffraction patterns [25] were reported by several groups.

Table 1. Asymmetric hydrocyanation of aldehydes catalyzed by chiral base

Substrate	Catalyst	% ee (Confign)	ref
PhCHO	1	20 (<i>R</i>)	15
3-PhOC ₆ H ₄ CHO	2a	46 (<i>S</i>)	17
	2b	20 (<i>R</i>)	17
	3	37 (<i>S</i>)	18
	4	26 (<i>S</i>)*	19
CH ₃ (CH ₂) ₃ CHO	4	26 (<i>S</i>)*	19
PhCHO	(<i>S</i>)-His	5 (<i>S</i>)	20
	<i>Z</i> -(<i>S</i>)-Ala-(<i>S</i>)-His-OMe	~0 (<i>S</i>)	21
	<i>Z</i> -(<i>S</i>)-His-(<i>S</i>)-Phe-OMe	~0 (<i>S</i>)	21
	<i>cyclo</i> -[(<i>S</i>)-His-(<i>S</i>)-Ala]	10 (<i>R</i>)	21
	<i>cyclo</i> -[(<i>S</i>)-His-(<i>S</i>)-His]	3 (<i>R</i>)	21
	5	97 (<i>R</i>)	25
3-MeOC ₆ H ₄ CHO	5	97 (<i>R</i>)	25
4-O ₂ NC ₆ H ₄ CHO	5	53 (<i>R</i>)	25
CH ₃ (CH ₂) ₄ CHO	5	56 (<i>R</i>)	25
PhCHO	6	55 (<i>S</i>)	27
CH ₃ (CH ₂) ₄ CHO	6	74 (<i>S</i>)	27

*Acetone cyanohydrin was used as a cyanating agent.

It is remarkable that Danda reported enantioselective autoinduction in asymmetric cyanation. When a small amount of the optically pure cyanohydrin was added to the reaction mixture, highly enantioselective cyanation occurred even by using almost racemic catalyst **5**, Fig. 1 (2% ee) [32].

Some effort has been devoted to support the cyclic dipeptide with a polymer side chain. However, the selectivities for the cyanation by the supported catalyst were not as high as those catalyzed by **5** or **6**, Fig. 1 [33, 34].

2.2

Asymmetric Cyanation of C=O Bonds by Metal-Catalyzed Reactions

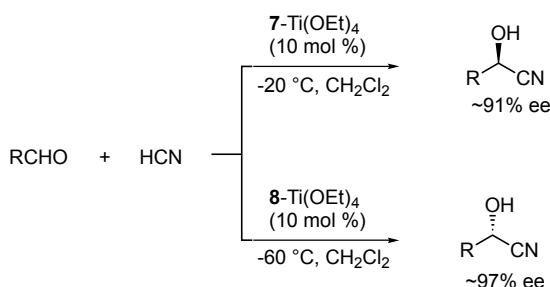
2.2.1

Peptide-Metal Complex

Since the addition of HCN to carbonyl compounds proceeds in the presence of a catalytic base, asymmetric cyanation should also be possible by using metal alkoxides such as boron, aluminum, titanium, zirconium, and lanthanoids through modification with an optically active substituent or ligand. Mori and Inoue reported that the titanium complex of an acyclic dipeptide composed of (*S*)-valine, whose amino terminal was modified with phenolic Schiff base of 2-hydroxy-1-naphthaldehyde (Nap), and (*S*)-tryptophan methyl ester, [**7**: Nap-(*S*)-Val-(*S*)-Trp-OMe; see reaction (1) in Scheme 1] catalyzed the addition of HCN to various aldehydes to yield (*R*)-cyanohydrins with up to 90% ee.[35, 36, 37].

The reactions proceeded in highly enantioselective manners with aromatic aldehydes and in relatively high selectivities with aliphatic aldehydes. Since the modulation of the catalyst can easily be performed by switching amino acid residues, several catalysts were surveyed as shown in Table 2. Consequently, the selectivity was found to be mainly controlled by the structure of the N-terminal amino acid residue, however, the stereochemistry of the second amino acid was also important to obtain the optically active cyanohydrins in highly selective manners.

The idea in the design of the peptide ligand was recently applied to combinatorial chemistry. Snapper and Hoveyda applied the technique of combinatorial

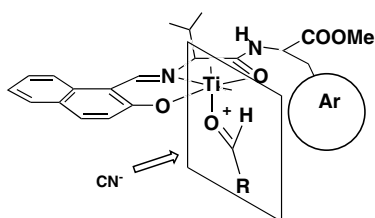


Scheme 1

Table 2. Asymmetric hydrocyanation of benzaldehyde catalyzed by a peptide-titanium complex

peptide (10 mol %)	% ee (Confign)
Nap-(<i>S</i>)-Val-(<i>S</i>)-Phe-OMe	86 (<i>R</i>)
Nap-(<i>S</i>)-Ile-(<i>S</i>)-Phe-OMe	85 (<i>R</i>)
Nap-(<i>S</i>)-Leu-(<i>S</i>)-Phe-OMe	75 (<i>R</i>)
Nap-(<i>S</i>)-Phe-(<i>S</i>)-Phe-OMe	67 (<i>R</i>)
Nap-(<i>S</i>)-Ala-(<i>S</i>)-Phe-OMe	59 (<i>R</i>)
Nap-(<i>S</i>)-Phgly-(<i>S</i>)-Phe-OMe (*)	59 (<i>R</i>)
Nap-(<i>S</i>)-Val-(<i>S</i>)-Trp-OMe	90 (<i>R</i>)
Nap-(<i>S</i>)-Val-(<i>S</i>)-Val-OMe	87 (<i>R</i>)
Nap-(<i>S</i>)-Val-(<i>S</i>)-Leu-OMe	59 (<i>R</i>)
Nap-(<i>S</i>)-Val-(<i>S</i>)-Phgly-OMe (*)	24 (<i>R</i>)
Nap-(<i>R</i>)-Val-(<i>S</i>)-Phe-OMe	38 (<i>S</i>)
Nap-(<i>S</i>)-Val-OMe	0
Nap-(<i>S</i>)-Val-NHBzl	30(<i>R</i>)

* Phgly: phenylglycine

**Fig. 2.** The complex to afford (*R*)-cyanohydrin

chemistry to the design of a peptide-titanium complex for enantioselective ring opening of epoxides [38, 39].

The structure of the peptide-titanium complex is considered to be as shown in Fig 2, where coordination of the substrate aldehyde is also given. The structure shows that the isopropyl group of the valine residue controls the coordination site of the carbonyl and the second amino acid residue effectively covers the *re*-face of the carbonyl. The cyano group subsequently attacks the *si*-face of the aldehyde to form the *R*-cyanohydrin predominantly. Based on the above working hypothesis, the catalyst to effect the opposite enantioface selection was designed as follows. Preference of *re*-face attack of the cyano group to give the *S*-cyanohydrin can be realized by removal of the second amino acid residue and by adding a bulky substituent at the 3-position of the aromatic ring as illustrated in Fig. 3. Dbs-(*S*)-Val-pip (**8**: 3,5-dibromosalicylideneimino-(*S*)-valine-piperidine amide, see Fig. 1) was accordingly designed to satisfy the above requirements. Indeed,

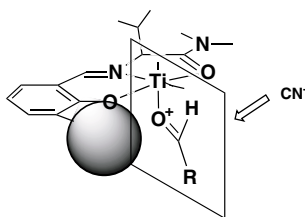


Fig. 3. The complex to afford (*S*)-cyanohydrin

the reaction catalyzed by a titanium complex of **8** afforded the *S*-cyanohydrin with high enantioselectivity up to 97% ee [36].

2.2.2

Asymmetric Cyanation Catalyzed by Chiral Lewis Acids

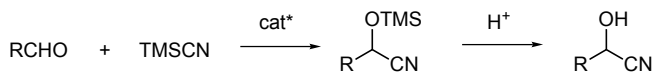
Cyano(trimethyl)silane (TMSCN) serves as a cyanating agent for carbonyl groups in the presence of a catalytic or stoichiometric amount of a Lewis acid such as boron trifluoride, titanium(IV) chloride, tin(IV) chloride, etc. Thereby, a wide variety of chiral ligands was designed and used for asymmetric cyanation reactions. Among them, titanium complexes have mostly been employed as the catalysts.

Narasaka reported that, although the reactions proceeded in a stoichiometric manner, the mixture of $\text{TiCl}_2(\text{O}i\text{-Pr})_2$ with chiral diol (**9a**, see Fig. 1) derived from tartaric acid promoted the addition of TMSCN to aromatic aldehydes in the presence of 4 Å molecular sieves to yield the corresponding cyanohydrins with an ee of up to 96%[40].

High enantioselectivities were observed in the reactions of aromatic aldehydes compared with several aliphatic aldehydes (Scheme 2). Higher selectivity in the reaction of the aliphatic aldehyde was realized when the titanium reagent and TMSCN were mixed at room temperature to generate the titanium cyanide (**9b**; Fig. 1) prior to the addition of the aldehyde [41].

Catalytic asymmetric cyanation using 20 mol % of the complex of $\text{Ti}(\text{O}i\text{-Pr})_4$ with diisopropyl tartrate (**10**; Fig. 1) was reported by Oguni [42, 43]. The mixture of $\text{Ti}(\text{O}i\text{-Pr})_4$ and **10** (Fig. 1) did not exhibit high enantioselectivity. Moreover, the selectivity and the reactivity were still low when the formed isopropyl alcohol was removed under reduced pressure using the freeze-dry method. High reactivity and an enantioselectivity of up to 90% were observed when the isopropyl alcohol was again added to the freeze-dried titanium complex.

Oguni also reported that the titanium complex of a chiral amino alcohol whose amino group was modified with a salicylal-type Schiff base as shown in **11** (Fig. 1) catalyzed the cyanosilylation of aromatic and aliphatic aldehydes [44, 45, 46, 47, 48]. The selectivity in the reactions of aromatic or α,β -unsaturated aldehydes was relatively higher to yield the corresponding cyanohydrins in 91% ee



Scheme 2

with *p*-anisaldehyde or in 96% ee with *trans*-2-methyl-2-butenal. Aliphatic aldehydes showed relatively lower selectivities (65 to 66% ee.)

The use of a chiral sulfoximine (**12**, Fig. 4) as a ligand of $\text{Ti}(\text{O}i\text{-Pr})_4$ was reported by Bolm [49]. The reaction of benzaldehyde afforded mandelonitrile in 91% ee when a stoichiometric amount of the complex was used. However, the selectivity decreased to 44% by using 20 mol % of the catalyst.

In 1986, Reetz reported that the TiCl_4 complex of optically active (*R*)- or (*S*)-1,1'-bi-2-naphthol (BINOL- TiCl_2 ; **13a**, Fig. 4) promoted the catalytic asymmetric silylcyanation to furnish the corresponding cyanohydrin in 82% ee [50]. However, details of the reaction have not been investigated so far, presumably due to the poor experimental reproducibility. Nakai recently reported the asymmetric catalytic cyanosilylation of aldehydes with the structure of the BINOL-titanium complex being studied in detail [51]. The stoichiometric use of the (*R*)-BINOL- $\text{Ti}(\text{O}i\text{-Pr})_2$ (**13b**, Fig. 4) complex in toluene yielded (*S*)-cyanohydrin in 78% ee. However, catalytic use (20 mol %) of the same complex significantly decreased the selectivity to 0%. High selectivity (72% ee) by using a catalytic amount of the titanium complex was obtained when the reaction was carried out in CH_2Cl_2 at 0 °C. Under these conditions, the titanium complex was found to possess two cyano groups as the substituents, the structure of the complex being confirmed by an NMR study. Thus, the reactive and enantioselective species in the catalytic asymmetric cyanosilylation of aldehydes was found to be **13c** (Fig. 4). The chiral salen-titanium complex **14** (Fig. 4) was also reported to be an efficient catalyst for asymmetric silylcyanation by Jiang [52]. The reaction using 5 mol % of the catalyst **14** afforded mandelonitrile in 87% ee. The titanium complex of (*S*)-3,3-dimethyl-1,2,4-butanetriol (**15**, Fig. 4) was recently reported to catalyze the asymmetric silylcyanation of ketones such as acetophenone (60% ee) under high pressure (0.8 GPa) [53].

Several metallic species other than titanium have been reported. Kobayashi showed that the tin(II) complex (**16**, Fig. 4) modified by cinchonine, a natural alkaloid, catalyzed the reaction to give the chiral cyanohydrin of cyclohexanecarbaldehyde in 90% ee [54]. Corey applied a magnesium complex of chiral bisoxazoline (**17**, Fig. 4) to the asymmetric silylcyanation. High selectivity of up to 95% ee was observed in the reactions of aliphatic aldehydes compared with benzaldehyde (52% ee) [55]. An aluminum complex of a peptide containing the phenolic Schiff base (**7**) was shown by Mori and Inoue to be an efficient catalyst for the addition of TMSCN to aldehydes [56, 57].

Mori and Inoue reported that the peptide complex of lanthanum isopropoxide also exhibited high catalytic activity towards asymmetric cyanosilylation [58]. Although the reaction proceeded in the presence of only 1 mol % of the catalyst, the enantioselectivity was moderate to good (up to 71% ee). Abiko recently re-

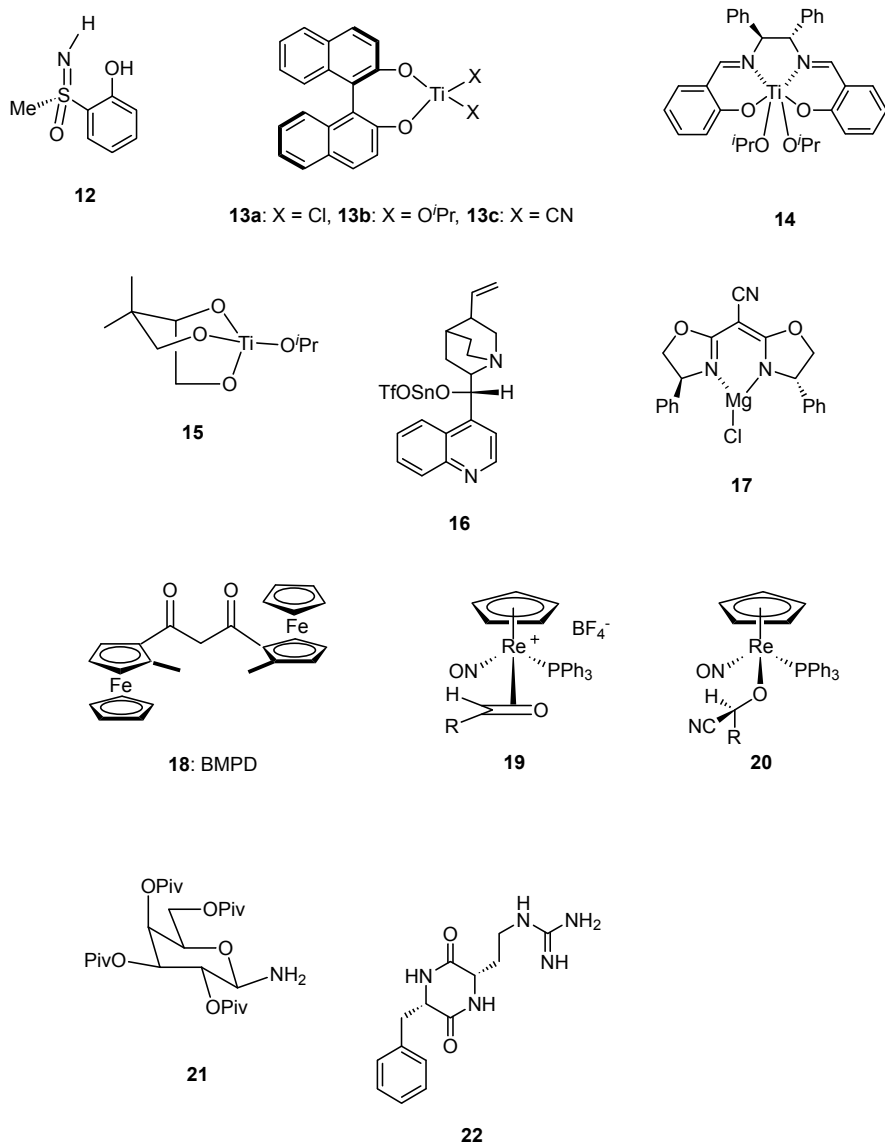


Fig. 4. Structures of compounds 12 to 22

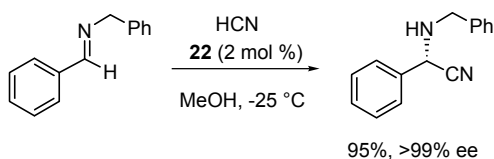
ported that the yttrium alkoxide complex of 1,3-dionate with a chiral ferrocenyl moiety (**18**: BMPD, Fig. 4) was an efficient catalyst for the cyanosilylation of aldehydes [59]. The catalyst proved to be highly enantioselective (90% ee) for the addition of TMS-CN to benzaldehyde and, in addition, to be highly reactive, effecting the reaction even with the use of 0.2 mol % of the complex. Although the reaction was not catalytic, Gladysz showed that the chiral rhenium π -aldehyde

complex (**19**, Fig. 4) effected the cyanation by $\text{Et}_4\text{N}^+\text{CN}^-$ to give the corresponding cyanohydrin alkoxide **20** (Fig. 4) in a highly diastereoselective manner. Since the structure of **19** has been clarified by X-ray crystallography, the study should be helpful for the understanding of the course of the enantioface selection in the cyanation reactions [60, 61].

3

Asymmetric Cyanation of C=N Bonds (Strecker Type Synthesis)

In contrast to the large number of asymmetric cyanation of carbonyl groups that have been reported, studies on the catalytic asymmetric cyanation of the carbon-nitrogen double bond are rather sparse. Diastereoselective reactions of cyanide to chiral imino groups, which were prepared from carbonyl compounds with a variety of chiral primary amines, were studied to introduce the new chiral center to the product.[62] Several systems are amenable to the one-pot synthesis of the α -aminonitriles by the reaction of a carbonyl compound, chiral primary amines, and cyanating agent. For example, Kunz reported a one-pot synthesis using the chiral amino sugar **21** (Fig. 4) to yield the corresponding aminonitrile with high diastereoselectivity [63]. However, the highly enantioselective reaction of a non-chiral imine with a cyanating agent in the presence of an asymmetric catalyst has not been reported. The first highly selective and practical asymmetric cyanation of an imine was reported by Lipton, where a cyclic dipeptide composed of (*S*)-phenylalanine and (*S*)- α -amino- γ -guanidinobutyric acid (**22**, Fig. 4) was shown to be highly effective [64]. The reaction of the *N*-benzylimine of benzaldehyde with HCN catalyzed by 2 mol % of **22** at $-25\text{ }^\circ\text{C}$ in MeOH (Scheme 3) afforded the corresponding α -aminonitrile in 95% yield with >99% ee. The BINOL-Ti complex **13c** was also reported to catalyze the addition of TMSCN to imines with ~30% ee [51].



Scheme 3

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Chapter 29.1

Mukaiyama Aldol Reaction

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Keywords: Aldol, Enol silane, Transition metal

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1

Introduction

The asymmetric aldol addition reaction has emerged as one of the most powerful stereoselective transformations available to the synthetic chemist for complex molecule synthesis [1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n]. A new carbon-carbon bond is formed with concomitant generation of up to two new stereogenic centers. Thus, the aldol addition reaction has proved to be of great synthetic utility since it allows for fragment coupling in the assembly of complex structures. Numerous aldol addition methods have been developed for the stereocontrolled construction of molecules containing the characteristic β -hydroxycarbonyl retron [2]. The reaction methodology spans the range of processes utilizing chiral substrates (aldehydes or enolates), stoichiometric quantities of optically active additives, or, more recently, chiral catalysts. Additionally, impressive advances in biocatalysis have afforded enzyme and antibody-catalyzed processes that furnish products in high enantioselectivity and yield [3a3b, 4a, 4b, 4c, 4d]. A large, continually-expanding body of work on asymmetric aldol methodology renders comprehensive coverage of the area well beyond the scope of a single chapter. Consequently, this review is focused on the presentation and discussion of the recent advances specifically related to transition metal-catalyzed, enantioselective aldol addition reactions. The success of this methodology is already evident in the increasing number of applications of catalytic methods to the asymmetric synthesis of stereochemically complex natural products [5a, 5b, 5c, 5d, 5e, 5f].

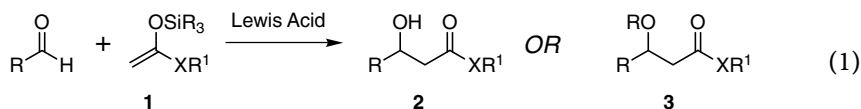
The rapid evolution of catalytic reaction methods for enantioselective aldol additions affords newer processes that are increasingly practical in their execution for a broad range of substrates prescribing minuscule amounts of catalyst. However, when compared to other catalytic asymmetric processes such as hydrogenation, dihydroxylation, and epoxidation it is evident that there is much room for further optimization. Without doubt, discovery and innovation in this area of C-C bond-forming reactions will lead to the development of catalysts and processes indispensable to the synthesis of optically active, stereochemically complex structures with applications in materials science and medicine.

2

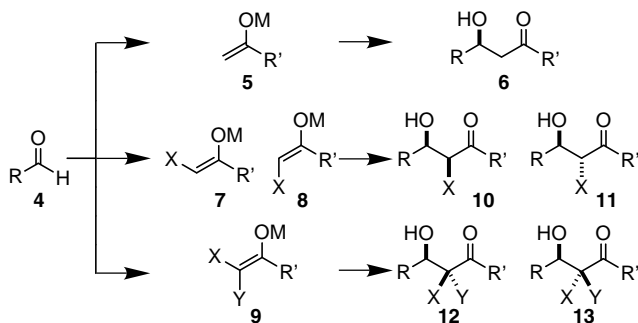
Background

The discovery of the Lewis acid-mediated addition of enol silanes to aldehydes and acetals by Mukaiyama and coworkers pioneered a novel approach to the construction of molecules via the crossed aldol reaction (Eq. 1) [6a6b]. Importantly, this development proved to be a key lead for the subsequent evolution of this C-C bond forming reaction into a catalytic Si atom-transfer process. Typical enol silanes derived from esters, thioesters, and ketones are unreactive towards aldehydes at ambient temperatures. However, stoichiometric quantities of Lewis acids such as TiCl_4 , SnCl_4 , AlCl_3 , BCl_3 , $\text{BF}_3 \cdot \text{OEt}_2$, and ZnCl_2 were found to pro-

mote aldehyde addition to give β -hydroxycarbonyl adducts. Innumerable electrophilic promoters and catalysts have been investigated for this reaction including Sn(IV) [7], Sn(II) [8a, 8b, 8c, 8d, 8e, 8f, 8g, 8h, 8i, 8j, 8k, 8l, 8m, 8n, 8o, 8p, 8q, 8r, 8s, 8t, 8u, 8v, 8w, 8x, 8y, 8z], Mg(II) [9], Zn(II) [10a,10b,10c,10d,], Li(I) [11a, 11b, 11c], Bi(III) [12a, 12b, 12c, 12c], In(III) [13], Ln(III) [14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h, 14i, 14j, 14k, 14l, 14m, 14n, 14o], Pd(II) [15], Ti(IV) [16a, 16b, 16c, 16d, 16e, 16f, 16g], Zr(IV) [17a, 17b], Ru(II) [18a, 18b], Rh(II) [19a, 19b], Fe(II) [20a, 20b, 20c, 21a, 21b, 21c, 21d], Al(III) [22a, 22b, 22c], Cu(II) [23a, 23b, 24], Au(I) [25], R_3SiX [26a, 26b, 26c, 26d, 26e, 26f], $Ar_3C^{(+)}$ [27a, 27b, 27c, 27d, 27e, 27f, 27g], acridinium salts [28], and clay [29]. Additionally, the aldol reaction of silyl enol ethers has also been conducted utilizing Lewis bases as catalysts or promoters. These include fluoride [30a, 30b, 30c, 30d], for which naked enolates are proposed as the reactive species, and, more recently, phosphoramidate bases [31a, 31b]. Since the trail-blazing report by Mukaiyama, many examples of stereoselective additions between chiral aldehydes and enol silanes have been documented and applied to the total syntheses of stereochemically complex natural products [32]. The stereochemical features of these processes have been analyzed in detail utilizing transition-state models incorporating steric, dipolar, and stereoelectronic effects [33].



The methods that have been reported for the crossed aldol addition reaction may be classified on the basis of the enolate employed and, correspondingly, on the structure of the substituted products generated (Scheme 1). Following this rubric, two general aldol addition processes may be identified: the first includes the reaction of unsubstituted acetate-derived enolates **5** and aldehydes, which generates a single new stereogenic center in the form of a secondary alcohol **6**; the second comprises the reactions of α -mono- or disubstituted enolates **7**, **8**, **9**, which furnish adducts containing up to two new stereogenic centers. In this lat-



Scheme 1

ter category, the use of a substituted enolate leads to additional complexity since 1,2-*syn* **10** or 1,2-*anti* **11** diastereomeric adducts may be formed, a stereochemical feature referred to as simple diastereoselection [1a]. The extent to which the simple diastereoselection is correlated to the geometric isomer of the starting enolate (*E* versus *Z*) depends on the mechanism of the process and structure of the transition states which, in turn, are a function of reaction parameters including the substrates, metals, counterions, and solvents. Aldol addition methods abound in which the *syn/anti* stereochemistry of products is stereospecifically determined by the choice of enolate used [1g], and, for selected examples, [34a, 34b]; however, examples have been reported in which either *Z*- or *E*-enolates afford the same product in a stereoconvergent manner, for selected examples in which simple diastereoselectivity in the products is not correlated to the enolate geometry, see Refs. [35a, 35b].

The structural details of the transition states in the Mukaiyama aldol addition reaction have been the subject of intense experimental and theoretical investigations [36a, 36b, 36c, 36d, 36e, 36f, 37a, 37b, 37c, 37d, 37e]. The proposed models of the transition-state structures for the addition of enol silanes to an aldehyde-Lewis acid complex may be categorized into two general classes: (1) those for which open, extended transition states **14**, **15**, **16** have been proposed; and (2) those for which closed, cyclic transition state structures **17** to **20** have been invoked (Fig. 1). It is worthwhile to scrutinize the diverse models; however, it is important to recognize that a classification based on putative transition-structure types has its limitations. An understanding of the catalytic Mukaiyama aldol at such resolution is tenuous as a result of the fact that the rate at which preparative synthetic methodology is being discovered has outpaced the rate of the accompanying structural and mechanistic studies. By contrast, there exists a wealth of empirical and theoretical data for the corresponding non-catalytic, asymmetric aldol addition reactions [1]. While the study of such processes is daunting, it can provide useful insight in the parallel analysis of the catalytic methodology.

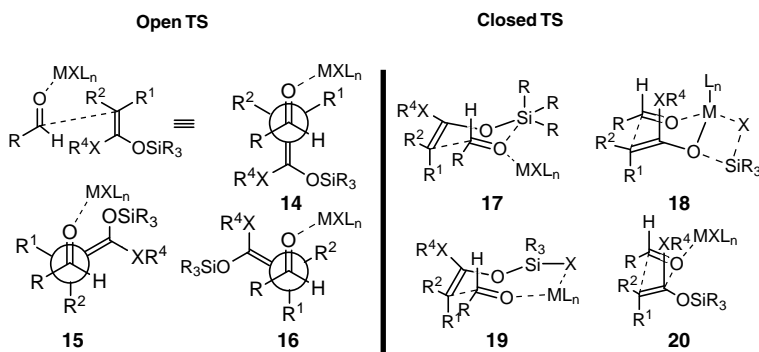


Fig. 1. Proposed transition state structures for the addition of silyl enol ethers and aldehydes

2.1 Analysis of Transition States

2.1.1 Extended, Open Structures

In a landmark study of Mukaiyama aldol addition reactions, Heathcock proposed that the observed stereochemical outcome of the products in the Lewis acid-mediated addition of silyl ketene acetals to aldehydes was consistent with extended, open transition-state structures [38a, 38b]. This analysis has gained wide acceptance as a consequence of its predictive power. Alternative models involving cyclic, closed structures have also been postulated, in particular, the latter have been invoked with increasing regularity in the analyses of catalytic, enantioselective aldol addition reactions [7, 30b, 39a, 39b].

The conformational degrees of freedom associated with the aldehyde and enolate in extended, open transition state structures complicates any detailed analysis of the reaction (Fig. 2). Accordingly, the free energy difference between *synclinal* arrangements (15, 16, 22, or 24) and *anticlinal* arrangements (14 and 23) are not always readily discerned on the basis of steric interactions [40a, 40b]. Studies aimed at factoring any inherent stereoelectronic preference that may favor *synclinal* or *anticlinal* dispositions have underscored the delicate, intricate balance of dipolar, inductive, and steric effects which exist in these addition reactions (for an investigation of Lewis acid aldehyde complexes, see Refs. [41a, 41b, 41c]. In this regard, given the diversity of reaction conditions reported for the Mukaiyama aldol addition, it may not be feasible to reduce this multifarious reaction into a single mechanistic construct [42a, 42b, 42c].

A number of structural and mechanistic studies of related nucleophilic addition processes deserve close scrutiny since they provide relevant parallels that are useful in the analysis of the Mukaiyama aldol addition reaction [43, 44].

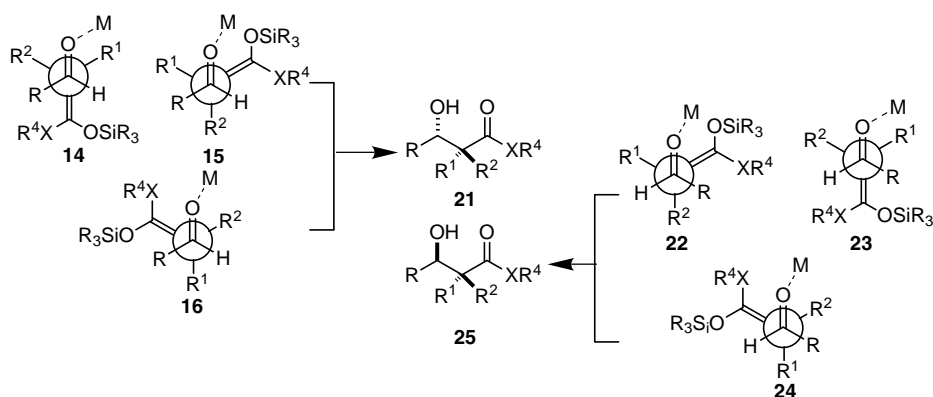


Fig. 2. Analysis of open transition states

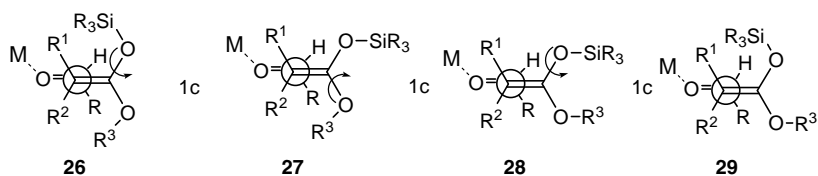


Fig. 3. The diversity of rotamers that may be populated by silyl ketene acetals

Their integration into the study of mechanistic models for the addition of enol silanes to aldehydes may allow a more detailed understanding of the stereochemical features of this reaction. For example, the subtle interplay of steric interactions ($A_{1,3}$) and stereoelectronic effects ($Lp_O \rightarrow \sigma^*_{C-O}$) can bias the conformational profile of enol silanes in the ground state (Fig. 3). When operating in synergy, such effects can result in well-defined minima having pin wheel-type conformations [45]. Wilcox has obtained an X-ray crystal structure of a propionate-derived enol silane that displays structural features similar to those reported for alkyl vinyl ethers and reveals the inherent stereoelectronic preference for the *s-cis* isomer in the ground state in the absence of overriding steric effects [46, 47a, 47b]. The consequences of the various available conformations of the enol silane on the relative energies of the extended transition-state structures that may be populated, 26 to 29, have received little attention. Structural features such as these will need to be incorporated into models since the energetic consequences of such effects impact the reaction stereoselectivity and are likely to be augmented in the transition state.

Other topological features that are important to consider in the context of enol silane additions to aldehydes were proposed by Seebach to account for the diastereoselective Michael additions of enamines to nitroolefins [48]. These have been generalized in the form of rules for C-C bond forming processes between prochiral centers and can be utilized in an analysis of the Mukaiyama aldol addition reaction. The preferred approach of the two reacting components is such that: (1) all bonds are staggered, (2) a gauche arrangement exists between the enol silane C=C and the aldehyde C=O and C-H bonds (cf. 32 Fig. 4), (3) the smaller of the substituents of the enolate (R^1 vs R^2) is *anti* with respect to the acceptor bond C=O, and (4) the enolate and aldehyde oxygen atoms which develop charges as the reaction progresses are positioned proximal to one another. Importantly, the approach of the two reactants is necessarily governed by a Bürgi-Dunitz alignment between the aldehyde LUMO and enol silane HOMO [49a, 49b, 49c]. Optimization of these orbital interactions conspire to enforce a non-parallel arrangement of the planes defined by each of the trigonal carbons in the electrophilic and nucleophilic partners 30, 31, 32 (Fig. 4). Such an arrangement further augments any steric interactions between the aldehyde substituent and the substituent on the enolate C_α as the reacting partners proceed to product.

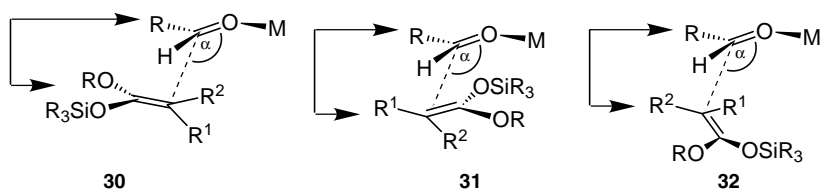


Fig. 4. The Seebach model as applied to enol silane additions to aldehydes emphasizes the incipient steric interactions that result from Bürgi-Dunitz constraints

2.1.2

Closed Structures

The most intensely studied aldol addition mechanisms are those believed to proceed through closed transition structures, which are best understood within the Zimmerman-Traxler paradigm (Fig. 5) [1d]. Superposition of this construct on the Felkin-Ahn model for carbonyl addition reactions allows for the construction of transition-state models impressive in their ability to account for many of the stereochemical features of aldol additions [50a, 50b, 50c, 51]. Moreover, consideration of dipole effects along with remote non-bonding interactions in the transition-state have imparted additional sophistication to the analysis of this reaction and provide a bedrock of information that may be integrated into the further development and refinement of the corresponding catalytic processes [52a, 52b]. One of the most powerful features of the Zimmerman-Traxler model in its application to diastereoselective additions of chiral enolates to aldehydes is the correlation of enolate geometry (*Z*- versus *E*-) with simple diastereoselectivity in the products (*syn* versus *anti*). Consequently, the analyses of catalytic, enantioselective variants that display such stereospecificity often invoke closed, cyclic structures. Further studies of these systems are warranted, since it is not clear to what extent such models, which have evolved in the context of diastereoselective aldol additions via chiral auxiliary control, are applicable in the Lewis acid-catalyzed addition of enol silanes and aldehydes.

The closed transition-state structures that have been proposed for the Lewis acid-mediated addition of enol silanes to aldehydes are of two general specifications (Fig. 6). The first includes models in which the metal complex plays an integral role in the closed structure through its incorporation into the cyclic array (Fig. 6, 18 and 19). The second includes models in which the metal is exocyclic to the ring (Fig. 6, 17 and 20). These include six-membered rings 17 [36a], fused bicyclic 4- to 6-membered rings 18 [6b, 14b, 53a, 53b, 53c, 54], eight-membered rings 19 [6, 55], and four-membered rings 20 [56a, 56b, 56c, 57]. All of these models share a common mechanistic feature: the intact enol silane is the reactive nucleophilic species in the addition to the aldehyde.

Recently, catalytic, enantioselective aldol addition reactions have been reported which are proposed to proceed through mechanistic pathways involving

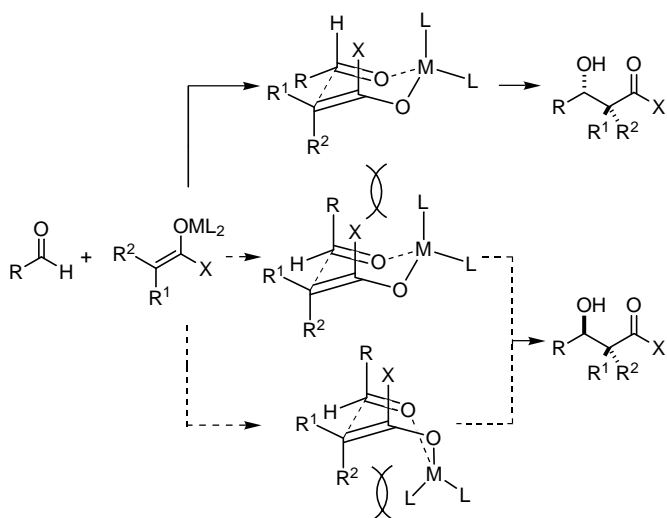


Fig. 5. The Zimmerman-Traxler transition states for aldol addition reactions

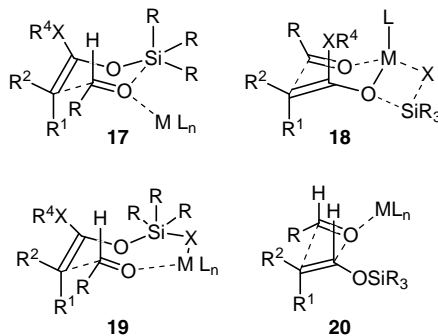
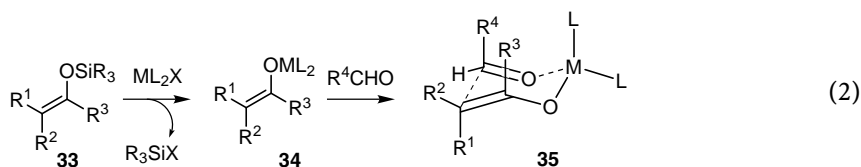
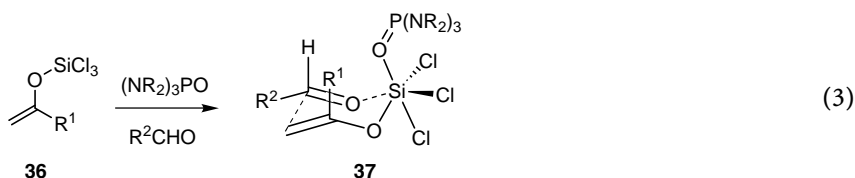


Fig. 6. Proposed closed transition-state structures for the Mukaiyama aldol addition of enol silanes

a metalloenolate intermediate **34** (Eq. 2). The metalloenolate intermediate is formed upon reaction of the enol silane with a metal complex or, alternatively, upon deprotonation of an acidic C-H compound. Regarding the latter, Hayashi and Ito have reported the addition reaction of isocyanoacetates to aldehydes that is mediated by a chiral Au(I) complex [25]. Mechanistic investigations by these researchers implicate an Au-enolate as a catalytically important species. More recently, Shibasaki and Carreira have reported enantioselective processes in which optically active Pd(II) and Cu(II) enolates, respectively, are generated in a catalytic manner and undergo addition to aldehydes [15, 24].



A second distinct process disclosed by Denmark involves the Lewis base-catalyzed addition of enol trichlorosilanes **36** to aldehydes (Eq. 3) [30b]. Remarkably, despite the fact that the uncatalyzed addition of such enol silanes to aldehydes is rapid at $-78\text{ }^{\circ}\text{C}$, the use of optically active phosphoramides substantially accelerates the addition reaction and leads to the formation of optically active products. As a consequence of stereochemical studies involving substituted enol trichlorosilanes, Denmark has proposed a hexacoordinated silicon atom as the organizational locus about which enolate and aldehyde are arranged in a cyclic array **37**.



2.1.3

Aldehyde-Metal Complexes

A number of excellent studies have been conducted that examine the structural features and energetics of bonding in complexes formed between aldehydes and Lewis acid [41a, 58, 59a, 59b, 59c, 59d, 59e]. The work has been meticulously reviewed and represents an important resource in understanding the important complexation phenomena between aldehyde and Lewis acid and its relationship to asymmetric catalysis. The coordination of an aldehyde or ketone to a Lewis acid leads to the enhancement of the electrophilicity of the carbonyl towards nucleophilic addition by the otherwise unreactive enol silane. Of particular importance in the analysis of such processes is the conformation about the M-O dative bond in the active complex formed between aldehyde and Lewis acid (Fig. 7). Models that account for the energetic preference for aldehyde binding in an orientation that exposes or blocks an aldehyde diastereoface have factored in non-bonded steric interactions or attractive dipolar interactions (cf. **40**) and stereoelectronic effects (**39**) [60, 61a, 61b]. It has been suggested that the non-bonded aldehyde lone pair opposite the formyl C-H can interact in an energetically favorable manner with the M-X antibonding orbital $\sigma^*_{\text{M-X}}$ as in **39**. Although there is only scant evidence that corroborates such a model, a stereoelectronic effect would lock in place a conformation about the M-O bond such that the dihedral angle C-O-M-X is 0° . Additional stabilizing features that serve to accentuate the

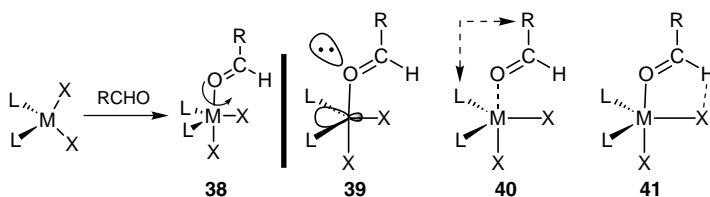


Fig. 7. Postulated bonding models for aldehyde-Lewis acid complex

difference between the aldehyde diastereofaces include dipole-induced, charge-transfer effects that have been generically referred to as π - π or π -stacking interactions. In the prototypical model such energetically stabilizing features are optimal when the polarized metal-bound aldehyde is proximal to a polarizable aromatic moiety [62].

Recently, a fundamentally new approach to understanding the bonding in aldehyde-metal complexes has been proposed and discussed by Corey (Fig. 7) [63a, 63b, 63c, 63d, 63e]. The Corey model incorporates a hydrogen bond between the formyl C-H on the bound, polarized aldehyde moiety and one of the metal-bound, ligating heteroatoms (41). This bonding arrangement is suggested to lead to increased organization in the aldehyde-Lewis acid complex which enforces and further augments any inherent steric and dipolar effects of the ligand. In its most generalized form, the construct provides an elegant explanation that accounts for the observation of highly stereoselective processes in a broad range of aldehyde addition reactions.

3

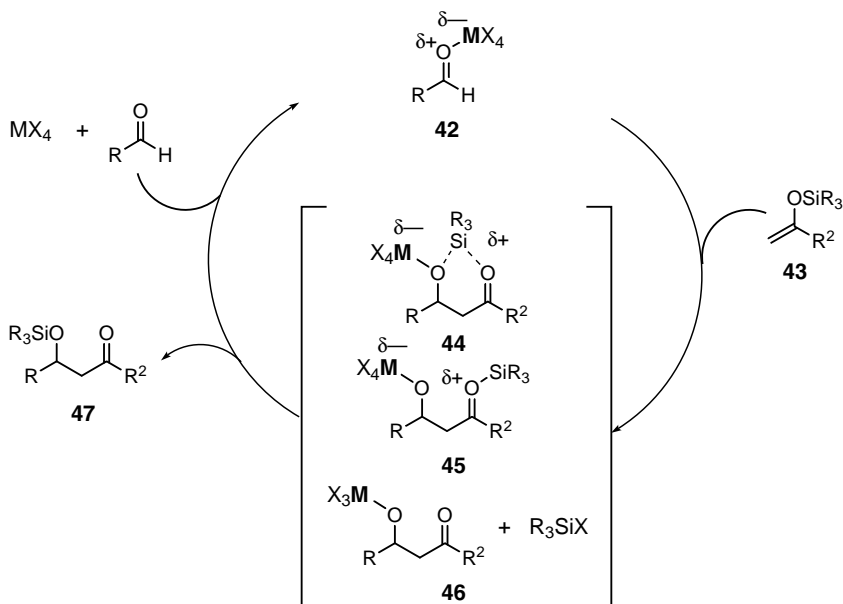
Catalysis of Mukaiyama Aldol Additions

3.1

General Mechanistic Aspects

The nucleophilic addition of enol silanes with aldehydes to produce β -silyloxy carbonyl adducts 47 is an example of a group-transfer process (Scheme 2), for applications in polymer synthesis, see: [64a, 64b, 64c]. In its simplest mechanistic rendition the reaction proceeds upon coordination of the aldehyde to Lewis acid MX_4 to afford an activated electrophilic species 42. Addition of the nucleophilic enol silane 43 to 42 leads to C-C bond formation and generation of the aldol adduct. Various intermediate structures 44, 45, 46 have been postulated to be formed concomitant with or following C-C bond formation. The generation of intermediates 45 and 46 necessitates subsequent silylation of the β -alkoxide furnishing aldol adduct 47 and regenerating catalyst MX_4 .

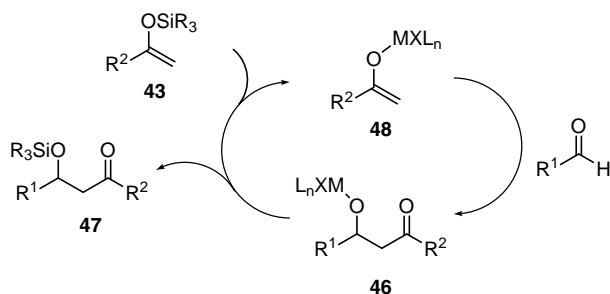
The initial studies on the reaction of enol silanes and aldehydes implicated the stoichiometric metal promoter, such as TiCl_4 , as a Lewis acid. Subsequent investigations confirmed this hypothesis, ruling out a reaction between ketone- or ester-derived enol silane and TiCl_4 under the typical conditions employed for



Scheme 2

the process [65]. For example, on the basis of ^{29}Si -NMR experiments Chan concluded that silylketene acetals did not undergo metallation by TiCl_4 . These results were validated in subsequent investigations by Kuwajima and Nakamura [66a, 66b]. These investigators demonstrated that the stereochemistry of aldol adducts derived from propionate-derived titanium enolates differed from that obtained from TiCl_4 -mediated addition of silyl enol ethers to aldehydes.

The results of these key studies, however, do not preclude catalytically competent metalloenolate intermediates in a process that complements the traditional Lewis acid-mediated Mukaiyama aldol addition. Evidence for such a process has been rigorously documented, leading to the successful development of catalytic, enantioselective versions (Scheme 3). In this regard, Bergman and Heathcock documented the reaction chemistry of Rh(I), W(I), and Re(I) enolates and their ability to sustain catalytic C-C bond forming addition reactions [67a, 67b, 67c, 67d, 67e]. Importantly, this study documented the ability of metal aldolates such as **46** to undergo *O*-silylation by the starting enol silane **43**. Additional mechanistic investigations provided insight into the kinetic profile of the individual steps of the process. The formation of the metal aldolate adduct was shown to be reversible with subsequent alkoxide silylation as the rate-determining step. It was suggested that the development of an enantioselective variant of these processes would necessitate that the *O*-silylation step effect a kinetic resolution of the diastereomeric metal aldolates **46**. Recent disclosures by Shibasaki and Carreira have documented the feasibility of developing enantioselective



Scheme 3

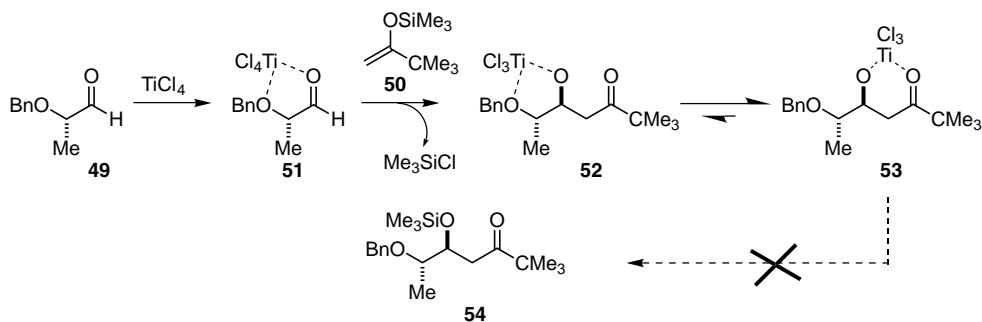
processes based on this general type of mechanistic construct involving a catalytically competent metalloenolate intermediate.

3.2

The Atom Transfer Step: Silylation of Metal Aldolate

In its original formulation, the procedure for the Mukaiyama aldol prescribed stoichiometric quantities of a strong Lewis acid such as $\text{BF}_3 \cdot \text{OEt}_2$, TiCl_4 , or ZnCl_2 . Upon completion, the reaction mixture was typically quenched under conditions that would not allow the exact identity of the aldol adduct to be established: metal aldolate **46**, *O*-silyl ether **47**, or a mixture of both. Subsequent mechanistic studies have suggested that, for some of these processes, a metal aldolate **45** or **46** is the product directly formed from the metal-mediated C-C bond-forming reaction [36b, 68, 69a, 69b]. This mechanistic feature is of great importance in understanding the overall catalytic atom-transfer process. In this regard, Reetz's elegant NMR studies on the TiCl_4 -mediated addition of pinacolone-derived enol silane **50** to α -benzyloxypropionaldehyde **49** are informative (Scheme 4) [35]. In the spectroscopic experiment, consumption of **49** and **50** was observed to be rapid at -78°C with concomitant formation of a metal aldolate adduct **53** and Me_3SiCl . In preceding studies, Reetz had documented that additions to substrates such as α -benzyloxypropionaldehyde proceeded from the chelated reactive intermediate **51** formed upon binding TiCl_4 by the aldehyde. It is important to note that **53** was observed as the only product of the addition reaction. The investigators suggested that although chelate **52** may be the first-formed adduct, it rapidly rearranged giving **53**. Additionally, an important observation in these experiments germane to understanding catalysis of this reaction is the fact that the corresponding β -*O*-silylated product **54** was not observed within the time-scale of the experiment. In related studies, Denmark has studied spectroscopically the TiCl_4 -promoted reactions of allylsilanes and aldehydes wherein the only observed product was the Ti(IV)-alkoxide and not the corresponding *O*-silyl ether [70a, 70b].

The generation of a discreet metal aldolate such as **53** may produce a reactive silylating agent as co-product that is itself a competent catalyst for the Mukaiya-



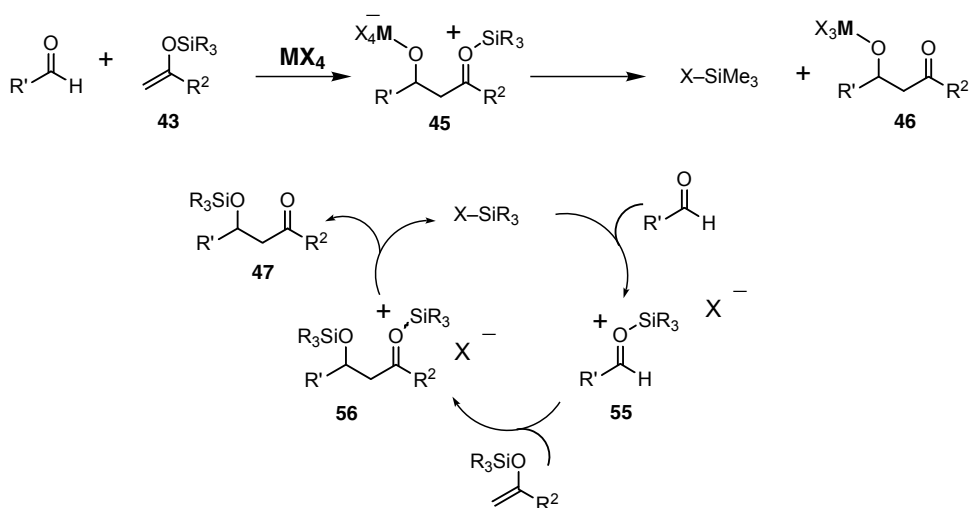
Scheme 4

ma aldol addition reaction. The relative rates of metal aldolate silylation versus the silyl-catalyzed aldol addition reaction becomes critical to the metal mediated enantioselective process and to the extent that metal complex functions as the true catalytic entity.

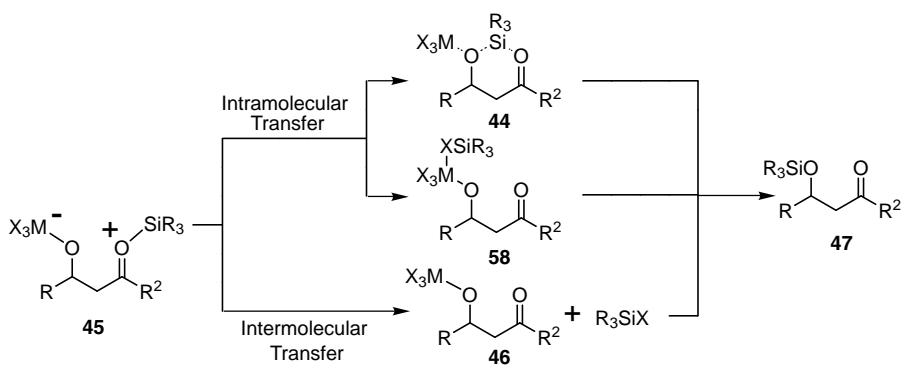
Recent mechanistic studies of the Mukaiyama aldol addition reaction by Bosnich and Carreira suggest that some of the processes that have been proposed to proceed by metal catalysis may only be metal initiated with the observed rapid reaction catalyzed by a silylating species generated in situ (Scheme 5) [69a, [69b, 70a, 70b]. Thus, in the presence of the metal promoters, the generation of adventitious Brønsted acid or Lewis acidic silyl species can be problematic. This is likely to be particularly important with strong Lewis acid promoters, wherein a strong M-O bond is generated in the aldolate adduct. The production of reactive silylating agents in the reaction mixture can lead to rapid silyl-catalyzed aldol addition reaction $55 \rightarrow 56 \rightarrow 47$ that outpaces the metal catalyzed process. In this regard, caution is warranted in the analyses of these systems since the formation of silylated adducts is not a sufficient condition to validate the claim that metal catalysis is operative. The use of optically active complexes along with the observation of optically active products represents the most direct test of metal complex participation. For such cases, the extent of participation by the metal catalyst can be correlated to the optical purity of the product. The proportion of racemic product generated can result from either the inherent limitation of the chiral metal catalyst or the extent to which a competing, stereorandom Brønsted acid or silane catalyzed process is occurring.

In a metal-catalyzed process, the catalytically active Lewis acid complex is only regenerated upon silylation of the metal aldolate intermediate **45**. Silylation of **45** can occur through a variety of mechanisms which are represented in their simplest forms in Scheme 6: (1) direct intramolecular Si-transfer ($45 \rightarrow 44 \rightarrow 47$); (2) intramolecular silyl transfer mediated by a transient intermediate which is produced upon silylation of the ligand ($45 \rightarrow 58 \rightarrow 47$); or (3) intermolecular silylation ($45 \rightarrow 46 \rightarrow 47$).

Experimental evidence that corroborates the existence of a putative zwitterionic intermediate analogous to **45** has been provided by Bosnich and coworkers

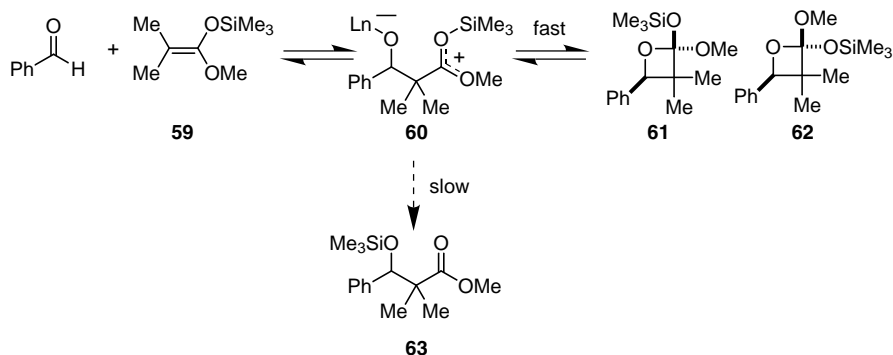


Scheme 5

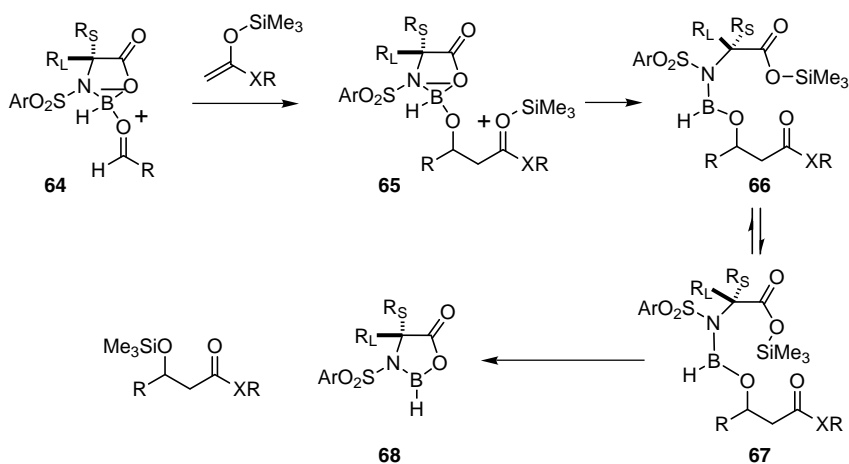


Scheme 6

in a study of the Eu(III)-catalyzed addition of **59** to benzaldehyde (Scheme 7) [71]. Spectroscopic data has been obtained that is consistent with the formation of four-membered ring adducts **61/62** as the kinetic products of the reaction. The step leading to these cyclic products has been shown to be reversible: prolonged exposure of **61/62** to the reaction conditions led to the conversion of these metastable oxetanes to **63**, the thermodynamic product of the reaction. The investigators have speculated that the formation of oxetane adducts in this study is a consequence of a slow silyl transfer step **60**→**63**. Thus, these observations highlight the fine balance that can exist between the various reaction pathways available to the adduct of the C-C bond-forming step (cf **60**).



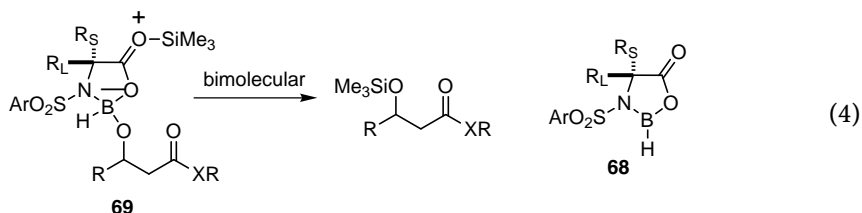
Scheme 7



Scheme 8

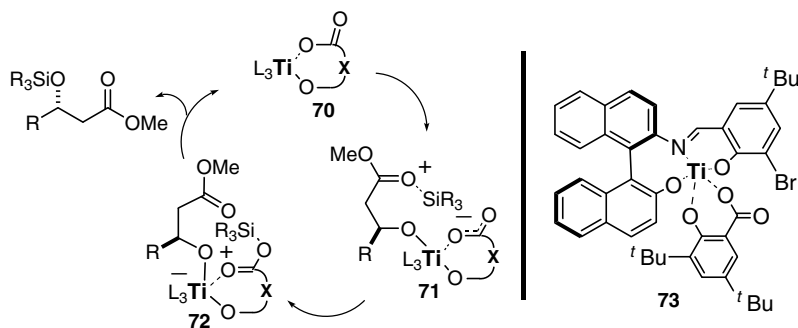
Inspection of the reported enantioselective catalytic aldol addition reactions reveals some general mechanistic trends that provide useful considerations in the design of catalysts for C=O additions. A number of examples of asymmetric aldol additions have been proposed to proceed through an intermediate in which ligand has undergone silylation. One of the earliest examples is the oxazaborolidene-catalyzed aldol addition reactions reported by Masamune [72a, 72b, 72c]. A novel mechanistic model was postulated which featured an intermediate boron aldolate wherein the carboxylate ligand has undergone silylation (**66/67**, Scheme 8). In the course of the study the investigators observed that extent of asymmetric induction (% ee) of the product varied with the addition rate of reactants, with optimal induction observed when enol silane is added over 48 h. Two critical assumptions were made in the interpretation of the data: (1) boronate **66/67** may be a competent Lewis acid catalyst for the aldol addition re-

action, albeit furnishing products with attenuated enantioselectivity since the chiral ligand is bound in a monodentate manner; and (2) intramolecular silyl transfer to the β -alkoxyboronate is the rate determining step in the overall process (Eq. 4). The observed sensitivity of the product enantiomeric excess to the rate of addition is elegantly accounted for by Masamune's mechanistic scheme. Thus, under conditions that involve slow addition of substrates, intramolecular or intermolecular aldolate silylation can occur competitively at the expense of the undesired process catalyzed by **66/67**. This mechanistic paradigm may be quite general; in this regard, it is interesting to note that a preponderance of catalytic enantioselective group-transfer processes have been reported which utilize optically-active ligands that feature carboxylate donor ligands prominently.

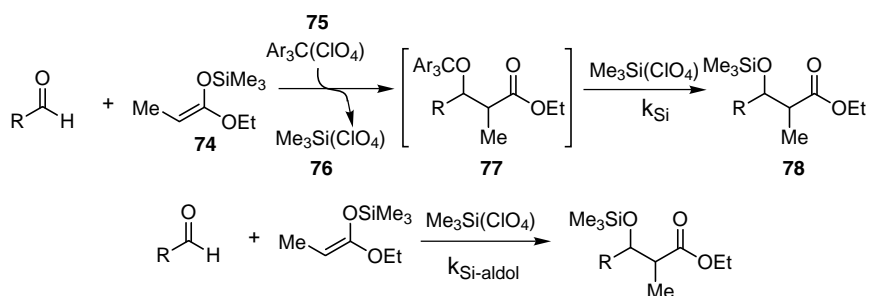


Carreira has utilized a related mechanistic construct in the design of a Ti(IV) complex **73** that is catalytically active (Scheme 9) [68]. The use of a metal-bound salicylate ligand proved critical to the development of a workable catalytic, enantioselective process. Thus, the Ti(IV) complex **73** effects the addition of unsubstituted acetate-derived silyl ketene acetals to a broad range of aldehydes utilizing as little as 0.2 mol % catalyst. Importantly, the operational aspects of the process are greatly simplified since the reaction may be conducted at -10 – 23 °C without the requirement of slow addition. The efficiency of this process has been attributed to the operation of a silyl-shuttle mediated by a carboxyl ligand. In the context of an octahedral metal complex **72**, the silyl-transfer step is suggested to benefit from the proximity of the silylcarboxylate to the alcoholate with concomitant activation of this silylating agent by coordination to the Lewis acidic metal center.

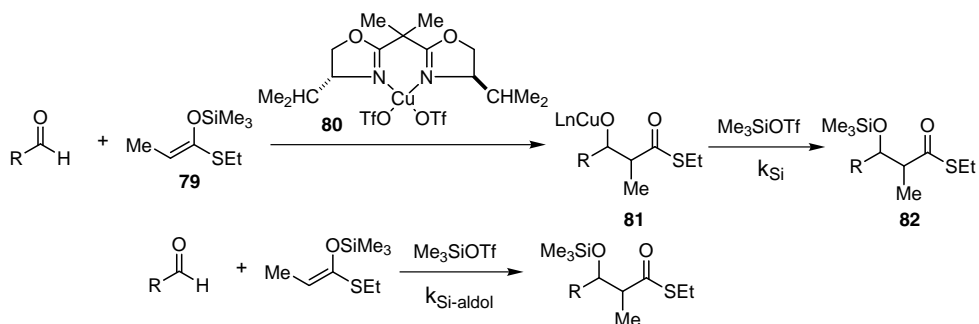
In contrast to the mechanism discussed in the previous section, catalytic, enantioselective aldol addition processes have been described which proceed through an intermediate aldolate that undergoes subsequent intermolecular silylation. Denmark has discussed this possibility in a study of the triarylmethylation-catalyzed Mukaiyama aldol reaction (Scheme 10) [73]. The results of exploratory experiments suggested that it would be possible to develop a competent catalytic, enantioselective Lewis-acid mediated process even when strongly Lewis acidic silyl species are generated transiently in the reaction mixture. A system of this type is viable only if the rate of silylation of the metal aldolate is faster than the rate of the competing silyl-catalyzed aldol addition reaction ($k_{\text{Si}} \gg k_{\text{Si-aldol}}$ Scheme 10). A report by Chen on the enantioselective aldol addition reaction catalyzed by optically active triaryl cations provides support for the mechanistic conclusions of the Denmark study [74].



Scheme 9



Scheme 10



Scheme 11

An enantioselective process which provides a powerful illustration of this phenomena has been documented by Evans (Scheme 11) [24]. In this work, the addition of enol silanes **79** to α -benzyloxyacetaldehyde is catalyzed by the optically active Cu(II)-bis(oxazoline) complex **80**, furnishing adducts **82** in excellent

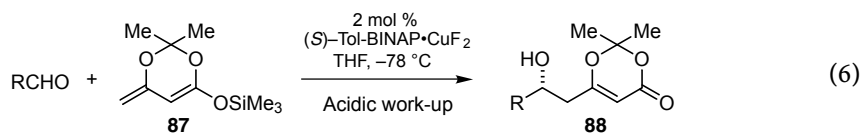
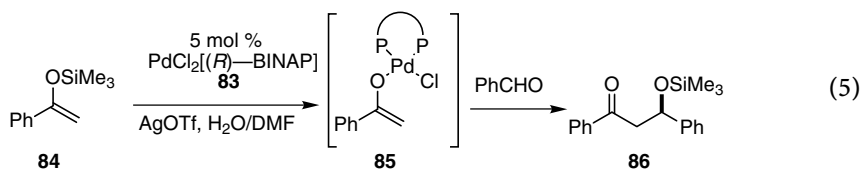
enantio- and diastereoselectivity. Two noteworthy features of this system merit consideration in the context of this mechanistic discussion:

- (1) the reaction was shown to be accelerated in the presence of added Me_3SiOTf without a corresponding deleterious effect in the product enantioselectivity;
- (2) silylation of the metal aldolate occurs in an intermolecular fashion.

The first phenomenon implicates silylation of a metal aldolate intermediate as the rate-determining step wherein the presence of added silylating agent at -78°C selectively accelerates metal aldolate silylation. The second phenomenon was demonstrated using double-labeling experiments and attests to the efficiency of the process. Importantly, the viability of this system probably results from the fact that the metal alkoxide generated undergoes rapid silylation as a consequence of a weak Cu-O metal bond. This is to be contrasted to the metal alkoxides generated as intermediates when strong oxophilic Lewis acids are used when silyl transfer has been suggested to be considerably slower.

Advances in the development of metal-catalyzed Mukaiyama aldol addition reactions have primarily relied on a mechanistic construct in which the role of the Lewis acidic metal complex is to activate the electrophilic partner towards addition by the enol silane. Alternate mechanisms that rely on metallation of enol silane to generate reactive enolates also serve as an important construct for the design of new catalytic aldol addition processes. In pioneering studies, Bergman and Heathcock documented that transition-metal enolates add to aldehydes and that the resulting metallated adducts undergo silylation by the enol silane leading to catalyst turnover.

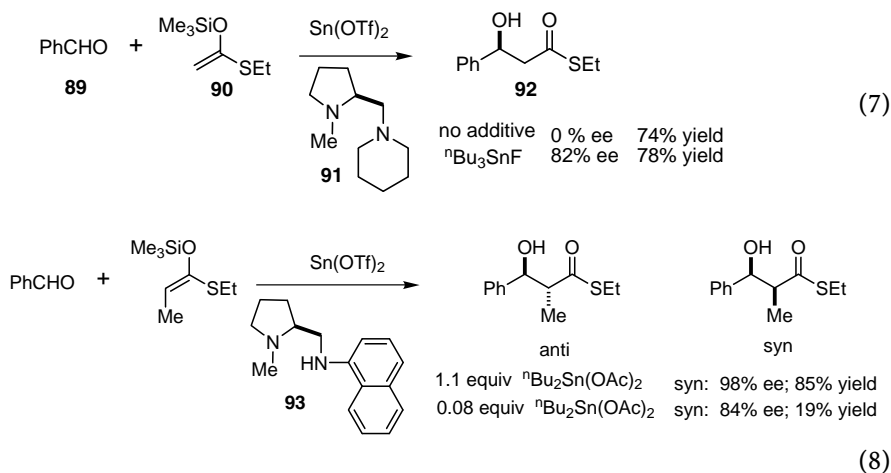
Two systems have been reported that may be operating through the intermediacy of a transition-metal enolate intermediate (Eqs. 5 and 6). Although extensive mechanistic information is lacking, experimental and spectroscopic evidence is consistent with the turn-over step in the catalytic cycle occurring from silylation of a metalloaldolate by the starting enol silane. In this regard, Shibasaki has described a Pd(II)-catalyzed addition of ketone-derived silyl enol ethers to aldehydes [15]. Carreira has also described a process which utilizes a Cu(II) complex that is proposed to initiate the catalytic cycle by metallation of the starting enol silane which subsequently participates in a catalytic aldol addition reaction [24].



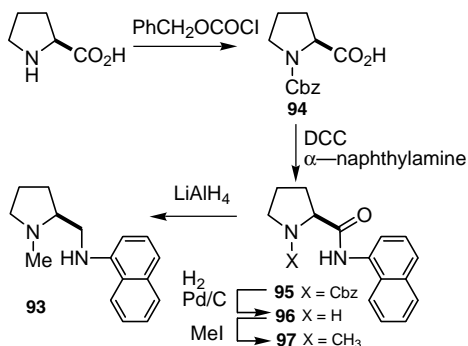
4 Lewis Acid-Catalyzed Aldol Addition Reactions

4.1 Tin(II)

Pioneering studies of stoichiometric Sn(II)-promoted additions of enol silanes to aldehydes by Mukaiyama and Kobayashi are valuable resources in understanding the catalytic versions of the reaction. Stoichiometric quantities of optically active Sn(II) complexes prepared from diamines mediate a collection of aldol addition reactions (Eqs. 7 and 8) [7, 75a, 75b, 75c]. Thus, the addition of the *S*-ethyl thioacetate-derived enol silane **90** with benzaldehyde promoted by a complex generated in situ by mixing 1 equivalent each of Sn(OTf)₂ and Bu₃SnF along with 1.2 equiv. of diamine **91** produced adduct **92** (2:1 1,3,5-trimethylbenzene/CH₂Cl₂, -78 °C) in 82% ee. Importantly, in the absence of added Bu₃SnF, the product was isolated in racemic form [76]. Subsequent intensive investigation of this process identified the optimal ligands for a broad range of carbonyl additions such as those derived from the aminonaphthalene substituted ligand **93**. Additionally, the aldol addition reactions performed with Sn(II) complex **93** display considerably less sensitivity to the reaction conditions in providing optically active aldol adducts. However, even with this ligand, the high levels of stereoselectivity in the products were observed when the reactions were conducted in the presence of additives, such as 1.1 eq of Bu₂Sn(OAc)₂ [7 h].



A diverse family of optically active diamine ligands have been prepared by Mukaiyama and Kobayashi commencing with proline. The diamine ligands are readily available in either enantiomeric form from (*R*)-(+)- or (*S*)-(-)- proline through a short synthetic sequence (Scheme 12) [77a, 77b]. The versatility of this proline-derived ligand class has been elegantly documented by Mukaiyama and Kobayashi. Subtle structural modifications of ligands derived from a single



Scheme 12

proline enantiomer allow the preparation of the corresponding Sn(II) complexes which behave as pseudo-enantiomers [7, 78a, 78b, 78c, 78d, 78e, 78f]; for example, in the aldol additions of silyl thioketene acetal **100** with aldehydes in the presence of stoichiometric quantities of the Sn(II) complexes derived from **98** or **99** adducts **101** and their enantiomers **102**, respectively, were isolated in up to 99% ee and >99:1 *syn* diastereoselectivity (Fig. 8).

The working mechanistic model crafted by these investigators invokes an intermediate metal aldolate **104** whose silylation was proposed to be slow. Formation of Me_3SiOTf **105** as a by-product in the reaction was expected to be problematic since **105** is known to function as a catalyst in a competitive, stereorandom aldol addition reaction (Scheme 13). This analysis suggested that the ameliorative effects of Bu_3SnF and $\text{Bu}_2\text{Sn}(\text{OAc})_2$ as additives in the stoichiometric Sn(II)-catalyzed aldol reactions were due to the ability of such additives to suppress the competing Me_3SiOTf -catalyzed additions. This analysis suggested two critical modifications of the Sn(II)-promoted reaction that would facilitate the subsequent evolution of this stoichiometric process into the corresponding enantioselective Sn(II)-catalyzed version. In this regard, when a dichloromethane solution of cyclohexanecarboxaldehyde and thioketene silyl acetal was added slowly over 3.5 h to a solution of the catalyst **103** at -78°C , the adduct was isolated in 76% yield and 73% ee. By contrast, when the addition was performed over 6 h, an improvement (80% ee) in the enantioselectivity was observed [8j]. Additionally, the use of a polar, aprotic, Lewis-basic propionitrile as solvent was found to lead to further improvement in the enantioselectivity of the process affording the adduct of cyclohexanecarboxaldehyde in 92% ee. Slow addition of the reactants maintains the concentration of the reactants low, thereby allowing the rate of Sn-aldolate silylation and catalytic turnover to compete with the rate of the competing Si-catalyzed process. Mukaiyama has suggested that the polarity of the solvent propionitrile (dielectric constant=28.86) as well as its ability to function as a coordinating ligand for the active Sn(II) complex **103** is key to the success of the catalytic process. For the Sn(II)-mediated aldol process, it can be speculated that coordination of propionitrile to the metal aldolate complex may

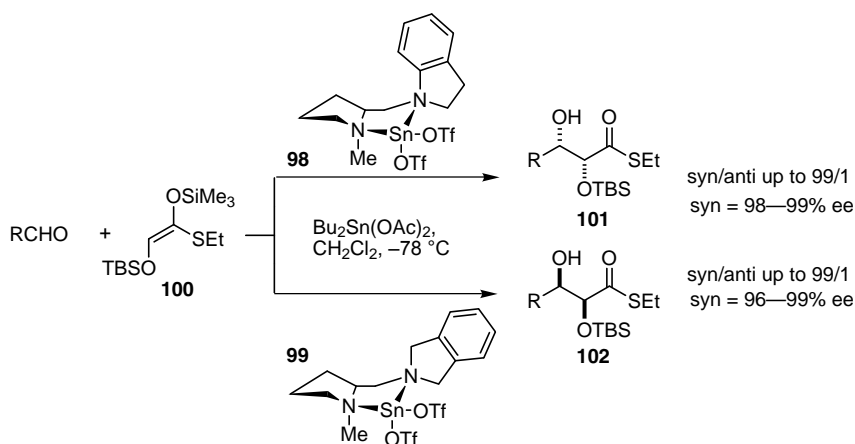
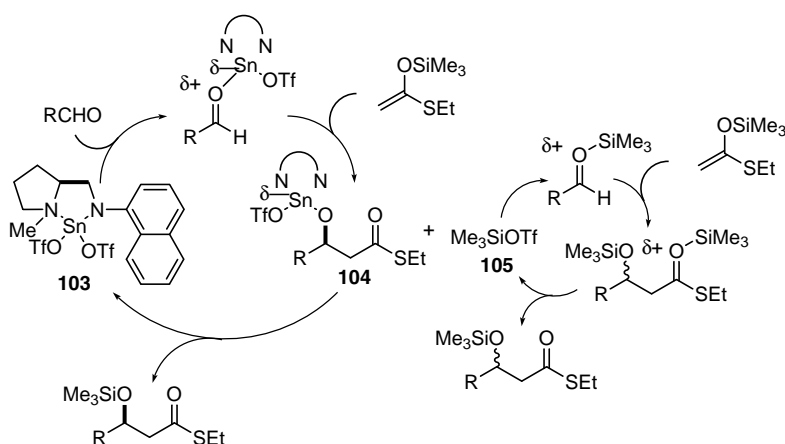


Fig. 8. The use of diamines derived from (*R*)-proline as pseudo-enantiomers

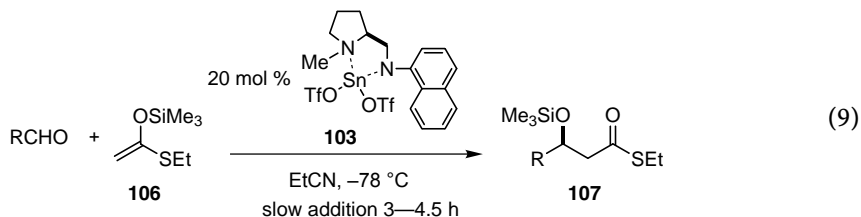


Scheme 13

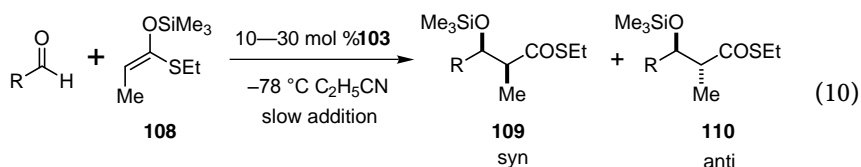
increase the electron density at the metal and thereby increase the reactivity of the metal alkoxide towards silylation. Working in synergy, these effects lead to selective acceleration of the metal aldolate silylation and catalyst turnover.

The additions of acetate, propionate, and other substituted enolates following the optimized protocol have been reported. The typical set of conditions prescribe the use of 10 to 30 mol % catalyst in propionitrile at -78°C and slow addition of reactants. For the acetate-derived silyl thioketene acetals **106** adducts are obtained in up to 93% ee and 90% yield (Eq. 9) [8j]. The addition of thiopropionate-derived *Z*-silyl ketene acetal **108** to a range of aldehydes delivered aldol

adducts with high levels of simple diastereoselectivity (89/11→99/1 **109/110**) and up to 98% ee (Eq. 10) [79]. Further studies of these processes has led to the observation that the addition of Sn(II) oxides (40 mol %) can lead to improvements in *syn/anti* ratio along with the enantioselectivity of the aldol product [80].

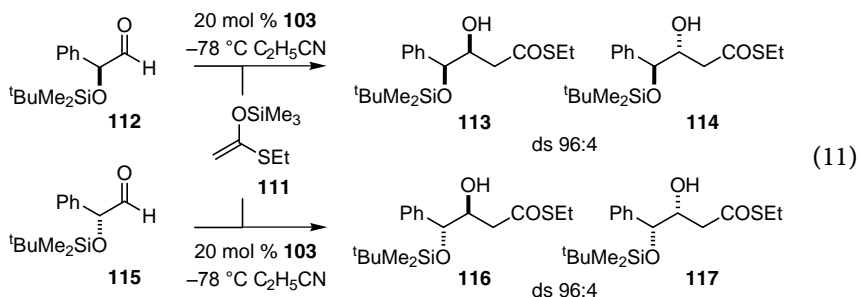


Entry	Aldehyde	Yield	% ee
1	$\text{H}_3\text{C}(\text{CH}_2)_5\text{CHO}$	79%	93 %
2	$\text{o-C}_6\text{H}_{11}\text{CHO}$	81%	92 %
3	$(\text{CH}_3)_2\text{CHCHO}$	48%	90 %
4	$\text{H}_3\text{C}(\text{CH}_2)_3\text{CH=CHCHO}$	65%	72 %
5	$\text{Bu-C}\equiv\text{C-CHO}$	68%	88 %
6	$\text{Me}_3\text{Si-C}\equiv\text{C-CHO}$	75%	77 %
7	$\text{Ph-C}\equiv\text{C-CHO}$	71%	79 %
8	$\text{C}_6\text{F}_5\text{CHO}$	90%	68 %



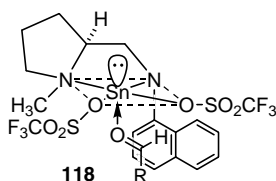
Entry	Aldehyde	Yield	syn/anti	% ee
1	PhCHO	77%	93/7	90%
2	$p\text{-ClC}_6\text{H}_4\text{CHO}$	83%	87/13	90%
3	$p\text{-MeC}_6\text{H}_4\text{CHO}$	75%	89/11	91%
4	$\text{H}_3\text{C-CH=CH-CHO}$	76%	96/4	93%
5	$\text{H}_3\text{C}(\text{CH}_2)_5\text{CHO}$	80%	>99/1	>98%
6	$\text{o-C}_6\text{H}_{11}\text{CHO}$	71%	>99/1	>98%

Experiments using optically active aldehyde substrates in combination with optically active catalysts can provide insight into the structure of the active complex. Moreover, the data generated may corroborate and help to further refine the putative catalyst model. By pitting the inherent stereochemical bias of the substrate against that of the catalyst for control of the stereochemical outcome of the reaction such a study provides a measure of the extent to which each dictate the product stereochemistry. For the Sn(II)-diamine-mediated addition reactions of enol silane **111** and enantiomeric aldehydes **112** and **115**, the resident chirality of the substrate had no measurable effect on the magnitude of asymmetric induction (Eq. 11) [81]. Thus, the product stereochemistry is exclusively controlled by the absolute stereochemistry of the chiral Sn(II) complex (**112**→**113**, 96:4 diastereoselectivity; **115**→**116**, 96:4 diastereoselectivity). This feature is of practical significance in the fragment coupling of chiral subunits for complex molecule assembly [8x, 78a, 78b, 78c, 78d, 78e, 78f, 82].



The structures of the functional catalyst or relevant intermediates in the proposed catalytic cycle in solution are presently unknown; however, the available spectroscopic experiments are informative [78f]. In CD_2Cl_2 at -78°C , $^1\text{H-NMR}$ spectra of a 1:1 mixture of the silyl enol ether and $\text{Sn}(\text{OTf})_2$ -diamine **102** did not show evidence of metallation of the enol silane to give the corresponding Sn(II) enolate. Although the catalytic reactions were conducted in propionitrile and not dichloromethane, these experiments support the contention that a metaloenolate is not involved as an intermediate in the catalytic cycle.

Mukaiyama and Kobayashi have postulated the Sn(II)-diamine complex **118** to possess square pyramidal geometry. The optically active diamine ligand forms a chelate to tin with the stereochemically relevant lone-pair residing in the sterically demanding position proximal to the pyrrolidine ring. Aldehydes are proposed to bind at the site *trans* to the lone pair and *syn* to the aminonaphtha-



lene moiety. It is possible that a stabilizing dipolar interaction between the bound polarized aldehyde and the electron-rich aminonaphthalene ring may be locking the aldehyde in place and leading to effective blocking of one of the aldehyde diastereofaces.

Evans has recently reported the use of structurally well-defined Sn(II) Lewis acids **119** and **120** (Fig. 9) for the enantioselective aldol addition reactions of α -heterosubstituted substrates [83]. These complexes are easily assembled from Sn(OTf)₂ and C₂-symmetric bisoxazoline ligands **124** and **126** (Fig. 10). The facile synthesis of these ligands commences with optically active 1,2-amino alcohols **122**, which are themselves readily available from the corresponding α -amino acids **121** [84, 85]. The Sn(II)-bis(oxazoline) complexes were shown to function optimally as catalysts for enantioselective aldol addition reactions with aldehydes and ketone substrates that are suited to putatively chelate the Lewis acid. For example, using 10 mol % of **119**, thioacetate and thiopropionate derived silyl ketene acetals add at -78 °C in CH₂Cl₂ to glyoxaldehyde to give hydroxy diesters **130** in superb yields and enantioselectivities as well as diastereoselectivities (Eq. 12). The process represents an unusual example wherein 2,3-*anti*-aldol adducts are obtained in a stereoselective manner.

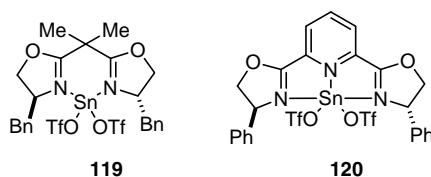


Fig. 9. Chiral bisoxazoline complexes utilized as catalysts for enantioselective additions to chelating aldehydes

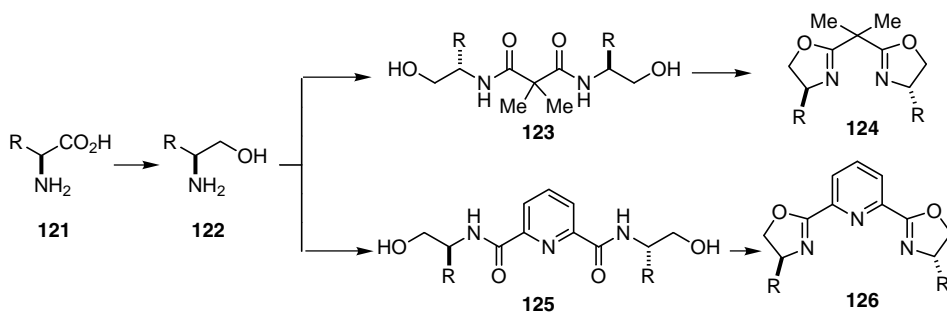
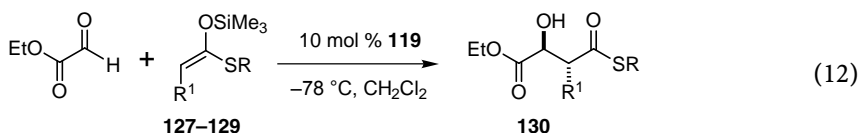
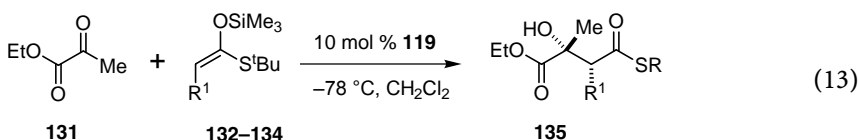


Fig. 10. Synthesis of bisoxazoline ligands

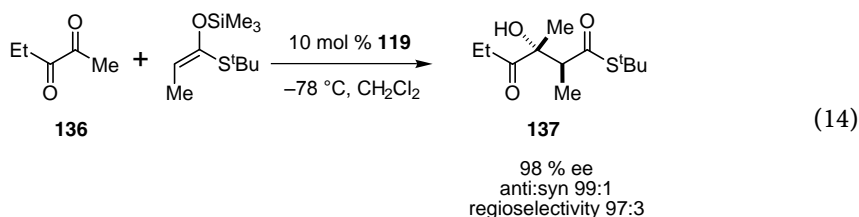


Entry	SR	R ¹	anti:syn	Yield	% ee
1	SPh	H	—	90%	98%
2	SPh	Me	90:10	87%	95%
3	SPh	Et	92:8	90%	95%
4	SPh	ⁱ Pr	93:7	72%	95%

Aldol additions to ethyl pyruvate **131** by silyl ketene thioacetals **132**, **133**, **134** have been shown to proceed in high yields and superb levels of induction (Eq. 13). This process represents an uncommon example of catalytic, asymmetric aldol additions to ketones, providing access to synthetically useful compounds such as **137**. The remarkable ability of the catalyst to differentiate between subtle steric differences of substituents flanking a 1,2-diketone was elegantly demonstrated in the highly enantioselective additions to 2,3-pentanedione **136** (Eq. 14). The aldol adduct of *S*-*tert*-butyl thiopropionate derived silyl ketene acetal afforded 2,3-*anti*-aldol adduct (>99:1 *anti/syn*) in 98% ee and 97:3 chemoselectivity for the methyl ketone [86].



Entry	R ¹	anti:syn	Yield	%ee
1	Me	99:1	84%	96%
2	Et	98:2	84%	97%
3	ⁱ Bu	99:1	81%	99%



An important feature of the Evans system is the ability to provide insight into the catalyst structure. The X-ray crystal structure of the (bisoxazoline)·Sn(OTf)₂

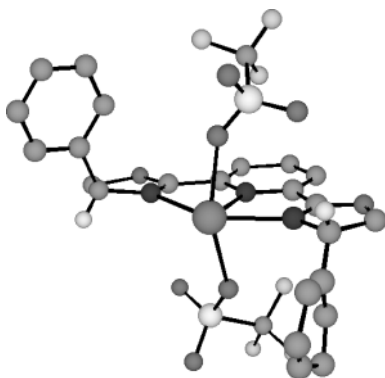


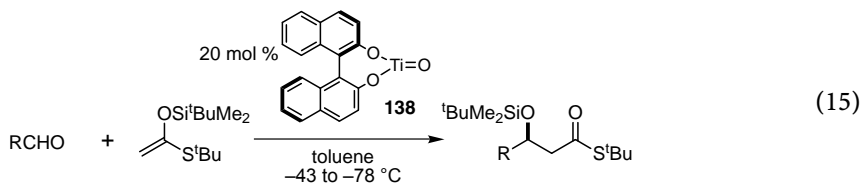
Fig. 11. X-ray crystal structure of the Sn(II)•bisoxazoline adducts

complex displays the central Sn(II) atom in square pyramidal geometry (Fig. 11). The three amino donors occupy a meridional position with the triflate counterions *trans*-diaxially bound. These exhibit some distortion away from the stereochemically relevant, Sn-centered lone pair that resides in the meridional plane. Electrospray ionization studies reveal that the cationic complex is readily generated by dissociation of the triflate counterions, underscoring the kinetic lability of **119** and **120** towards ligand exchange, the sine qua non of a catalytic processes. This structural information has already proven valuable in the design of additional processes, and promises to lead to further advances in the development of other catalytic systems.

4.2

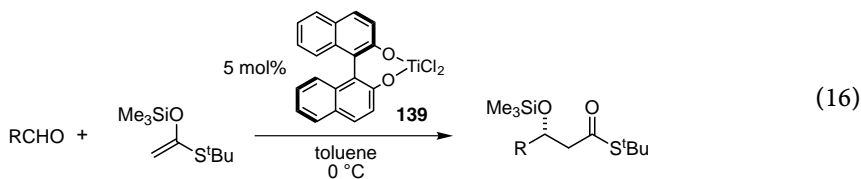
Titanium(IV)

Mukaiyama and coworkers have utilized complexes prepared from (*R*)- or (*S*)-1,1'-2,2'-binaphthol (BINOL) and Ti(IV) precursors generated upon treating $\text{Ti}(\text{O}^i\text{Pr})_4$ with an equivalent of H_2O in benzene [87, 88]. The catalytically active species is suggested to be a BINOL·Ti=O complex **138**. However, given the proclivity of related Ti(IV)=O complexes to exist as dimers centered about a $(\text{Ti}(\mu\text{-O}))_2$ core coupled with the inherent instability of group IV oxo complexes, it is likely that the structure of the Ti(IV) species is not monomeric. Using the catalyst generated upon combining 20 mol % each of BINOL, $\text{Ti}(\text{O}^i\text{Pr})_4$, and H_2O in toluene, the aldol addition reaction of unsubstituted silyl ketene thioacetals with a variety of aromatic aldehydes afforded products in 91–98% yield and 36–85% enantiomeric excess (Eq. 15). Subtle effects on the enantioselectivity were noted as a function of the aromatic solvent employed with enantioselectivity decreasing along the series: toluene (60% ee), ethylbenzene (54% ee), *m*-xylene (50% ee), 1,3,5-trimethylbenzene (41% ee), and chlorobenzene (16% ee) [89].



Entry	Aldehyde	Yield	% ee
1	PhCHO	91%	60%
2	(<i>E</i>)-PhCH=CHCHO	98%	85%
3	β -NaphthylCHO	98%	80%
4	α -NaphthylCHO	97%	36%

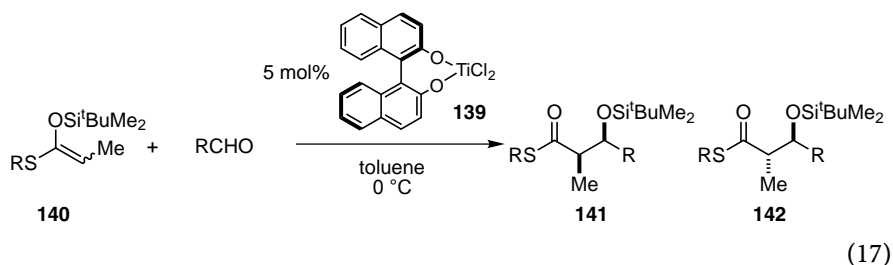
Mikami has examined a BINOL-TiCl₂ complex **139** that effectively catalyzes the addition of methyl ketone-, thioacetate-, and thiopropionate-derived enol silyl ethers and aldehydes, giving adducts in impressive yields and enantioselectivity [38a, 90] (Eq. 16). The protocol prescribes the use of 5 mol % of a catalyst generated by treating TiCl₂(O^{*i*}Pr)₂ and (*R*)- or (*S*)-BINOL in toluene. The synthesis of TiCl₂(O^{*i*}Pr)₂ is effected by disproportionation reaction of a 1:1 mixture of Ti(O^{*i*}Pr)₄ and TiCl₄ followed by distillation. In general, an important advantage of processes such as these in catalytic asymmetric processes that utilize BINOL as ligand is the fact that both enantiomeric forms are commercially available [91].



Entry	Aldehyde	Yield	% ee
1	BnO-CH ₂ -CHO	81%	96%
2	Cl-CH ₂ -CHO	61%	91%
3	BocNH-CH ₂ -CHO	64%	88%
4	C ₆ H ₁₇ -CH ₂ -CHO	60%	91%
5	Me-CH=CH-CHO	61%	81%
6	ⁿ BuO ₂ C-CHO	84%	95%
7	Me-CH(Me)-CHO	61%	85%

The addition reaction of *tert*-butyl thioacetate-derived silyl ketene acetal produces the corresponding aldol adducts in 84% yield and up to 96% enantiomeric excess (Eq. 16). The enantioselectivity of the products was observed to be optimal with toluene as solvent; the use of the more polar dichloromethane consistently produced adducts with 10–15% lower enantiomeric excess. The bulkier *tert*-butylthioacetate-derived enol silane was found to lead to uniformly higher levels of enantioselectivity than the smaller *S*-ethyl thioacetate acetal. This process is impressive in that it tolerates a wide range of aldehyde substrates; for instance, the aldol addition reaction has been successfully conducted with aldehydes substituted with polar functionality such as *N*-Boc amides, chlorides, esters, and *O*-benzyl ethers. A key feature of this system when compared to previously reported processes was the ability to achieve high levels of stereoselectivity at 0 °C, in contrast to other processes that commonly prescribe operating temperatures of –78 °C.

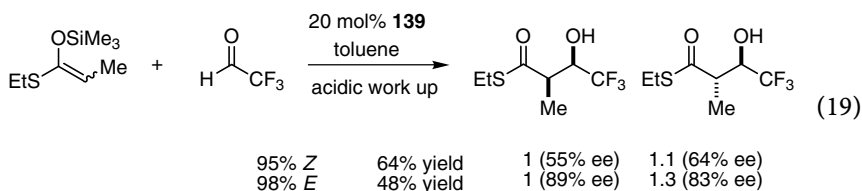
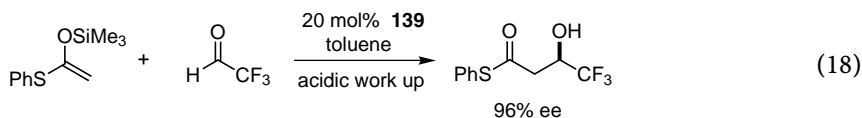
The addition of propionate-derived enol silanes **140** delivered 1,2-disubstituted aldol adducts **141** and **142** in useful yields and selectivities (Eq. 17) [90]. As in the acetate-derived additions, the selectivity of the process was dependent on the thioalkyl substituent of the silyl ketene acetal **140**. The 1,2-*syn* adduct was obtained from the addition of *E*-enolsilane and *n*-butyl glyoxylate (Eq. 17, entry 3). Correspondingly, the formation of 1,2-*anti* adduct was observed in the addition of α -benzyloxy acetaldehyde and the *Z*-enol silane derived from the *tert*-butyl thioester.



Entry	Enol silane	Aldehyde	E/Z	Yield	syn/anti	% ee
1	R = Et		77% <i>E</i>	85%	72:28	90%
2	R = Et		95% <i>Z</i>	80%	48:52	86%
3	R = Et		77% <i>E</i>	64%	92:8	98%
4	R = ^t Bu		93% <i>Z</i>	81%	8:92	90%

The Mikami catalyst (**139**) has been utilized in numerous interesting applications. For example, the addition reaction has been extended to include trifluor-

oacetaldehyde as substrate, giving optically active fluorinated adducts which are of increasing importance in medicinal chemistry as well as materials science [92]. The addition of thioacetate-derived silyl ketene acetals to trifluoroacetaldehyde affords adduct in 96% ee (Eq. 18). The corresponding aldol addition of substituted enolates produces a mixture of *syn/anti* adducts 55%–89% enantiomeric excess (Eq. 19).



Mikami has conducted a series of mechanistic studies that provide insight into the structural details of the transition-state structure and the Si-atom-transfer step (Fig. 12) [93]. Experiments involving two enol silanes, such as **143** and **144**, incorporating minor differences in the *O*-silyl and *O*-alkyl substituents allow the nature of the key atom-transfer step to be probed. Such double-label experiments can effectively determine whether the Si atom-transfer step proceeds via an intra- or intermolecular process. When α -benzyloxyacetaldehyde was allowed to react with 0.5 equiv each of **143** and **144**, only aldol adducts **145** and **147** were isolated from the reaction mixture. The absence of adducts **146** and **148** was consistent with a mechanism involving intramolecular metal aldolate silylation. Mikami has suggested a transition-state structure **149** in which C-C bond formation and aldolate silylation occur concomitantly in a silatropic ene-like process. For such an arrangement, the migrating trialkylsilyl group serves to anchor the six-membered ring, with the metal complex residing exocyclic to the array. The results of additional experiments with optically active aldehydes by Mikami is suggested to provide additional validation for the working model **149**.

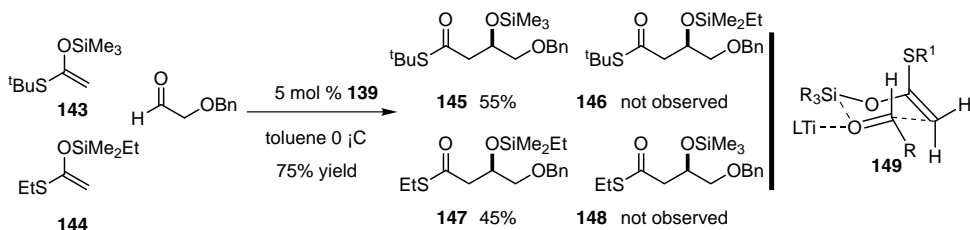


Fig. 12. Double labeling experiments by Mikami supporting a silatropic ene transition-state

Although this analysis of the transition state structure is consistent with the experimental observations, other mechanistic pathways may be postulated (Fig. 13) [94]. The mechanistic analysis of a related carbonyl addition process involving the BINOL-Ti(O^{*i*}Pr)₂-catalyzed addition of allylstannanes to aldehydes offers insight to an alternate mechanistic pathway that may account for the results of the double labeling experiments by Mikami. In an in-depth analysis of the Keck catalytic, enantioselective aldehyde allylation reaction by allyltributyltin, Corey has proposed an intermediate **152** wherein the BINOL ligand is transiently *O*-stannylated. In a subsequent step, intramolecular *trans*-stannylation occurs releasing product **154** with regeneration of catalyst. The operation of an analogous mechanistic step in the Mikami aldol process wherein the ligand participates as a temporary repository of the silyl group (**155**) would account for the observed results in the double-labeling experiments.

A related Mukaiyama aldol catalyst system reported by Keck prescribes the use of a complex that is prepared in toluene from (*R*)- or (*S*)-BINOL and Ti(O^{*i*}Pr)₄ in the presence of 4 Å molecular sieves. In work preceding the aldol addition reaction, Keck had studied this remarkable catalyst system and subsequently developed it into a practical method for enantioselective aldehyde allylation [95a, 95b, 95c, 96]. Because the performance of the Ti(IV) complex as an aldol catalyst was quite distinct from its performance as a catalyst for aldehyde allylation, a careful examination of the reaction conditions was conducted. This meticulous study describing the use of (BINOL)Ti(O^{*i*}Pr)₂ as a catalyst for aldol additions is noteworthy since an extensive investigation of reaction parameters, such as temperature, solvent, and catalyst loading and their effect on the enantiomeric excess of the product was documented. For example, when the reaction of benzaldehyde and *tert*-butyl thioacetate-derived enol silane was conducted in dichloromethane (10 mol % catalyst, -10 °C) the product was isolated in 45% yield and 62% ee; by contrast, the use of toluene as solvent under otherwise identical conditions furnished product of higher optical purity (89% ee), albeit in 54% yield. For the reaction in toluene, increasing the amount of catalyst from 10 to 20 mol %

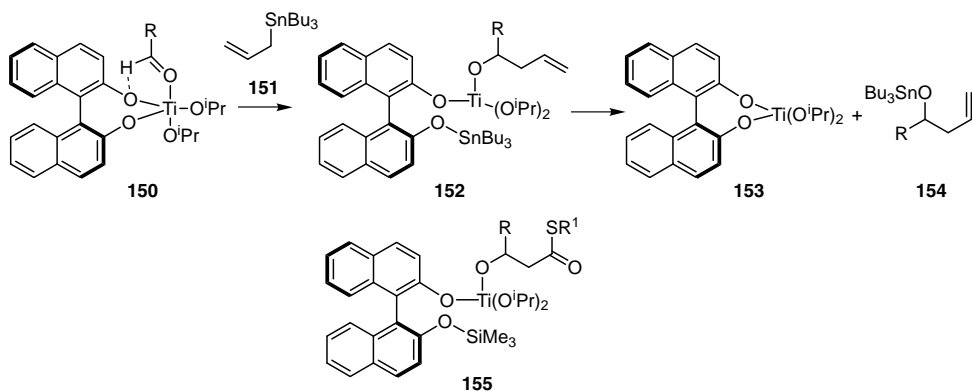
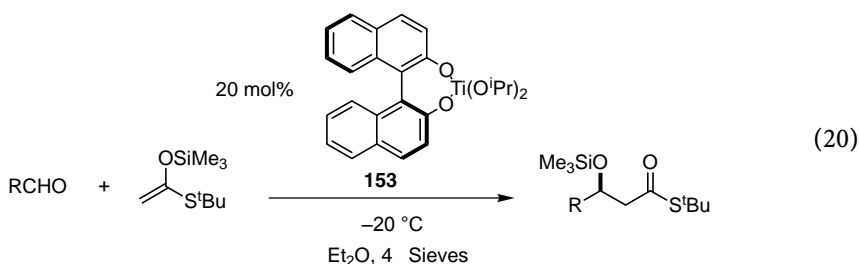


Fig. 13. Alternate proposal to account for the absence of silyl scrambling in the Mikami system

resulted in further amplification in the enantioselectivity of the products (95% ee); however, further increasing in the catalyst load to 50 mol % produced a diminution in asymmetric induction to 87% ee. Additional studies of solvent effects identified Et₂O as the optimal medium for the catalytic process.

Treatment of the thioacetate-derived enol silane with aldehyde and 20 mol % catalyst **153** at -20 °C in Et₂O gave the product in high optical activity (Eq. 20). Hydrolytic work-up of the crude reaction products afforded the β-hydroxy aldol adducts in excellent enantioselectivity (97–99% ee) [97]. The addition reaction in Et₂O also displayed some sensitivity to concentration, temperature, and catalyst loading. Thus, the aldol addition with benzaldehyde at two different substrate concentrations, 0.25 and 0.5 M, gave product in 97 and 92% ee, respectively. Decreasing the catalyst load to 10 mol % afforded the product in identical % ee's, albeit in diminished yields (71% after 16 h) when compared to the corresponding yield (90% after 10 min) with 20 mol % catalyst. An important conclusion from this study is that the variation in product yield and selectivity as a function of catalyst concentration and catalyst loading are correlated to the known non-linear effects in these systems.



Entry	Aldehyde	Yield	%ee
1	PhCHO	90%	97%
2	PhCH ₂ CH ₂ CHO	80%	97%
3	2-FurylCHO	88%	>98%
4	<i>c</i> -C ₆ H ₁₁ CHO	79%	89%
5	PhCH=CHCHO	76%	89%
6	PhCH ₂ OCH ₂ CHO	82%	>98%

Carreira has reported a series of studies that have led to the development of a family of optically active tridentate ligands **156** and their corresponding derived Ti(IV) complexes **157** and **158** (Fig. 14). Tridentate ligands were selected for study on speculation that greater control over catalyst design and structure would be available with a ligand able to coordinate through more than two heteroatom donors. The ligand family is derived from the unsymmetrical, chiral 2,2'-amino-hydroxy-1,1'-binaphthalene, a ligand fundament not previously investigated in

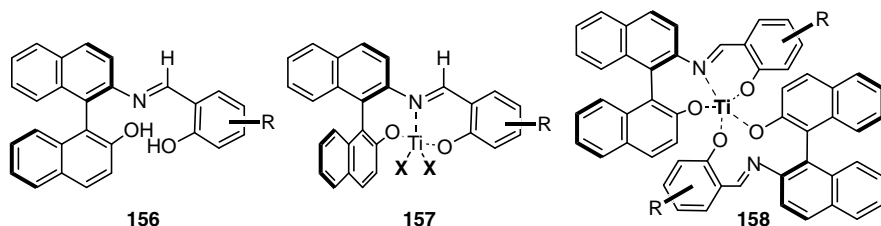


Fig. 14. Tridentate ligand and the derived complexes employed by Carreira

inorganic coordination chemistry. Racemic 2,2'-aminohydroxy-1,1'-binaphthalene is readily prepared by oxidative heterocoupling of 2-aminonaphthalene and 2-hydroxynaphthalene following a procedure developed by Kocovsky and Smcrina [98a, 98b]. Resolution of the racemate is effected with the commercially available (*R*)- or (*S*)-camphorsulfonic acids, allowing for either enantiomer of the unsymmetrically substituted binaphthyl to be readily accessed.

The ability to derivatize the amine functionality in **159** confers flexibility in the synthesis of a number of tridentate ligands (**156**) of varying electronic or steric properties (Fig. 15). Specifically, the preparation of Schiff bases derived from **159** and salicylaldehydes **160** would provide a library of tridentate ligands for Ti(IV). The tridentate ligands incorporate two aryloxy donors and a neutral imine nitrogen; consequently, coordination to Ti(IV) would necessarily generate a complex with two additional charged donor atoms **157**. Further substitution of these two remaining ligands allows for additional structural variables in the form of chelating groups whose electronic and steric properties are amenable to alteration. Thus, the overall modular design of the complex **162** allows for independent variation of several ligand variables in the optimization of the process [99]. The results of preliminary experiments that varied the nature of substituents on the salicylimine component led to the identification of the 4-*tert*-butyl-6-bromosalicylaldehyde (**163**) derived ligands as optimal in the asymmetric addition reactions for the broadest scope of aldehyde substrates.

The initial investigations of catalytic carbonyl addition processes were guided by the hypothesis that formation of the silylated aldolate product and release of the metal complex would be facilitated by incorporating into the complex an effective means for transfer of the trialkylsilyl group. Importantly, salicylate ligands were investigated since Masamune had articulated the critical role that carboxylates could play in Si-atom transfer reactions. In this regard, a number of electronically and sterically diverse salicylic acids are commercially available at a nominal price. Moreover, the replacement of the two coordinated isopropoxides in **164** could be easily achieved upon adding chelating ligands to the catalyst solution followed by azeotropic removal of the released isopropanol (Eq. 21).

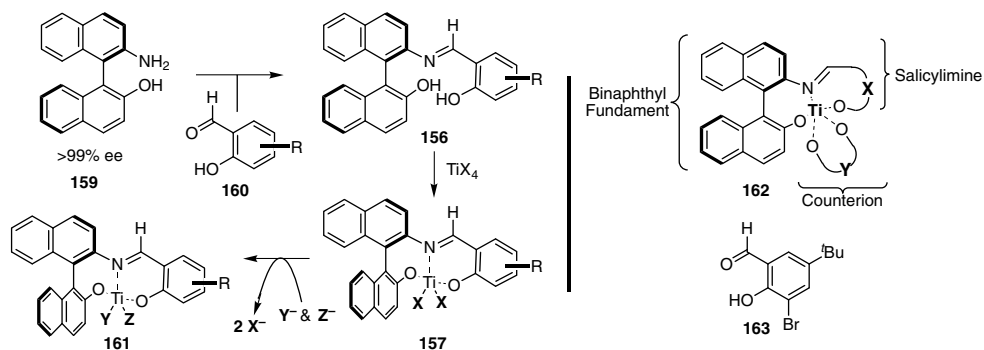
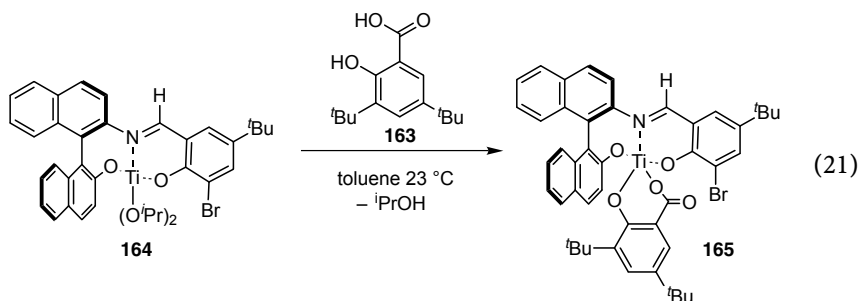
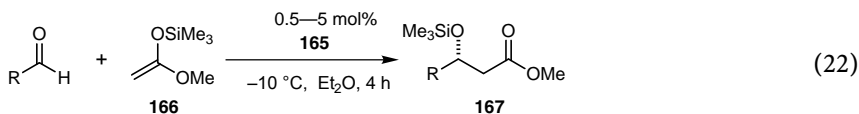


Fig. 15. Synthesis and structural analysis of the Carreira complex



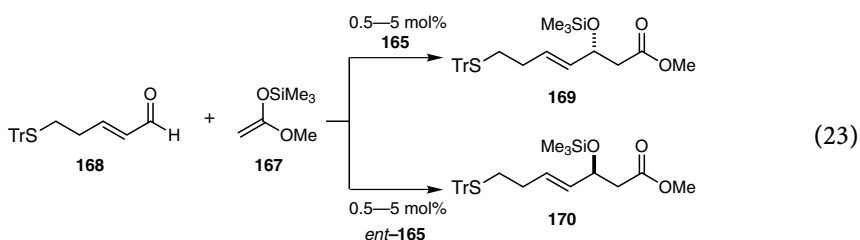
Treatment of tridentate ligand with $\text{Ti}(\text{O}^i\text{Pr})_4$ and di-*tert*-butylsalicylic acid (**163**) in toluene followed by evaporation of the solvent afforded an orange complex postulated to be **165**, which was shown to be an effective catalyst for the Mukaiyama aldol reaction. Under optimized conditions, the simple methyl acetate-derived enol silane **166** adds to aldehydes in the presence of as little as 0.5 mol % of **165** at 0 °C to give optically active adducts **167** in high yields and up to 99% ee (Eq. 22) [100]. Importantly, the reaction can be conducted with a wide range of substrates such as aliphatic, aromatic and unsaturated aldehydes as well as functionalized aldehydes.



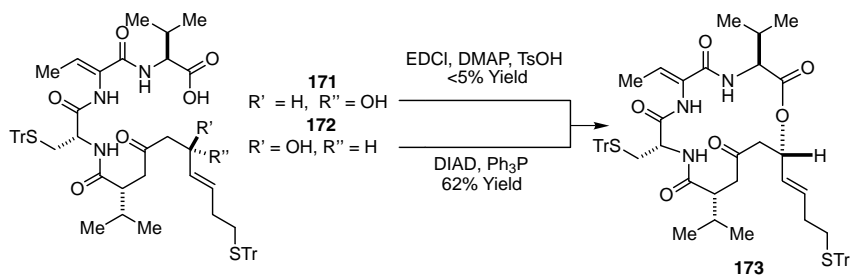
Entry	Aldehyde	Yield	% ee
1	$\text{Ph}(\text{CH}_2)_3\text{—}\equiv\text{—CHO}$	84%	96%
2	$\text{TBSOCH}_2\text{—}\equiv\text{—CHO}$	91%	96%
3	$\text{Ph—}\equiv\text{—CHO}$	96%	94%

4	$i\text{Pr}_3\text{Si}-\text{C}\equiv\text{C}-\text{CHO}$	97%	97%
5	$\text{Me}-\text{CH}=\text{CH}-\text{CHO}$	82%	98%
6	$\text{Me}-\text{CH}_2-\text{CH}_2-\text{CHO}$	76%	95%
7	$\text{Ph}-\text{CH}=\text{CH}-\text{CHO}$	99%	98%
8	$\text{Ph}-\text{CH}_2-\text{CH}_2-\text{CHO}$	98%	94%
9	$\text{Me}-\text{CH}(\text{Ph})-\text{CHO}$	84%	96%
10	$t\text{BuMe}_2\text{SiO}-\text{CH}(\text{Me})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CHO}$	87%	95%
11	$t\text{BuPh}_2\text{SiO}-\text{CH}_2-\text{CH}_2-\text{CHO}$	89%	91%
12	$\text{Ph}_3\text{CS}-\text{CH}(\text{C}_6\text{H}_{11})-\text{CH}=\text{CH}-\text{CHO}$	99%	98%
13	$\text{C}_6\text{H}_{11}-\text{CHO}$	81%	95%
14	$\text{Me}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CHO}$	83%	98%
15	$\text{Ph}-\text{CH}=\text{C}(\text{Me})-\text{CHO}$	92%	95%

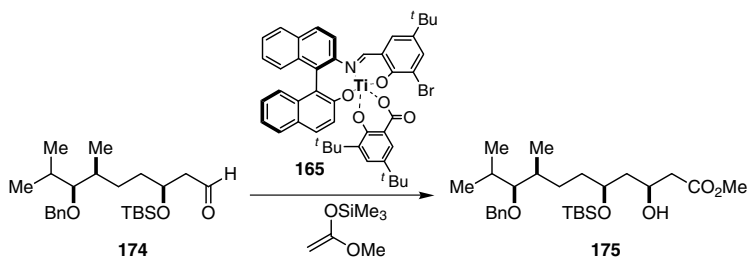
The catalytic process has found successful application in several natural product total syntheses. In 1996, Simon reported a synthesis of the antitumor depsipeptide FR-9001,228 in which the aldol addition reaction of **168** and the ethyl acetate-derived enol silane furnished a key synthetic intermediate (Eq. 23). The enantioselective aldol addition reaction of **168** was conducted with **165** and its enantiomer *ent*-**165** to separately provide both enantiomers of the aldol adducts **169** and **170** (Scheme 14). These were then utilized in the preparation of diastereomeric seco acids **171** and **172** [101]. Macrocyclization of **172** through a Mitsunobu reaction yielded the desired natural product **173**.



In a separate, elegant use of **165**, Rychnovsky and coworkers have carried out a diastereoselective addition of methyl acetate-derived silyl ketene acetal to aldehyde **174** to afford adduct **175** in high diastereomeric purity (Scheme 15) [102]. Hydroxy ester **175** was subsequently employed as an intermediate in the total synthesis of the polyene macrolide antibiotic Roflamycoin. This work highlights a novel application of the chiral catalyst system in reagent-controlled coupling of chiral functionalized substrates which by themselves display only mod-



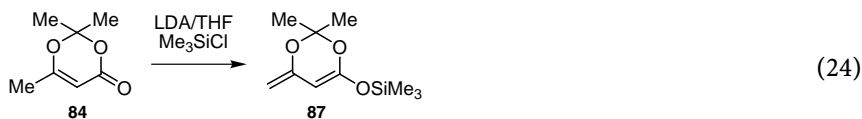
Scheme 14

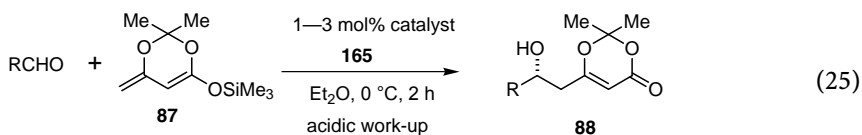


Scheme 15

est levels of asymmetric induction, thus underscoring the ability of the catalyst to function in a distereoselective synthesis.

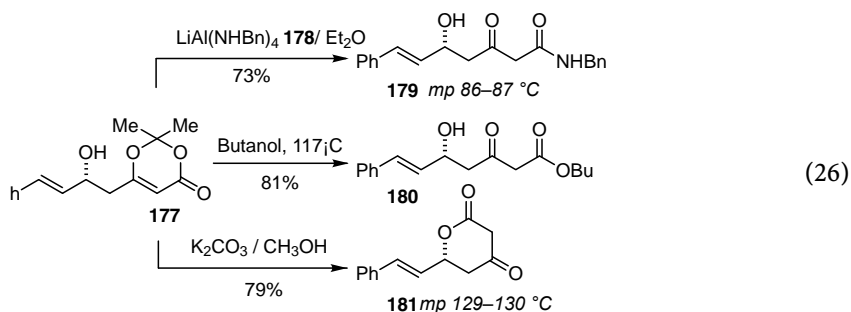
In addition to the efficiency exhibited by catalyst **165** with a broad spectrum of aldehydes in acetate aldol addition reactions, this catalyst has been shown to function competently in enantioselective additions of dienol silane **87**. The requisite dienolate is readily synthesized from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **84** (diketene+acetone adduct) by deprotonation with LDA and quenching with Me_3SiCl (Eq. 24). Dioxinone **84** is commercially available at a nominal price; in addition, the silyl dienolate **87** is easily purified by distillation and stable to prolonged storage. The addition reactions of **87** with aldehydes were conducted with 1–3 mol % of **165** at 0 °C (Eq. 25). A variety of aldehydes serve as substrates and give aldol adducts in 79–97% yields and up to 99% ee after a single recrystallization.



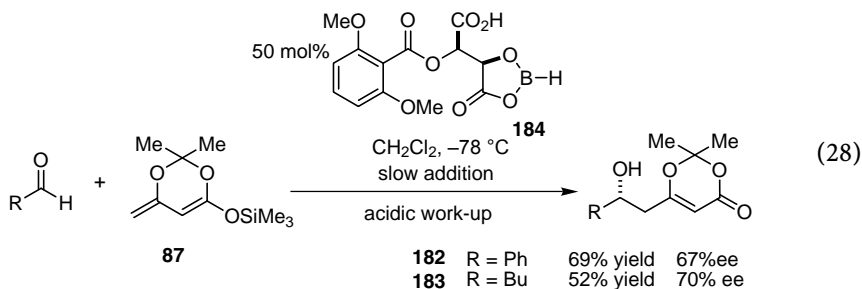
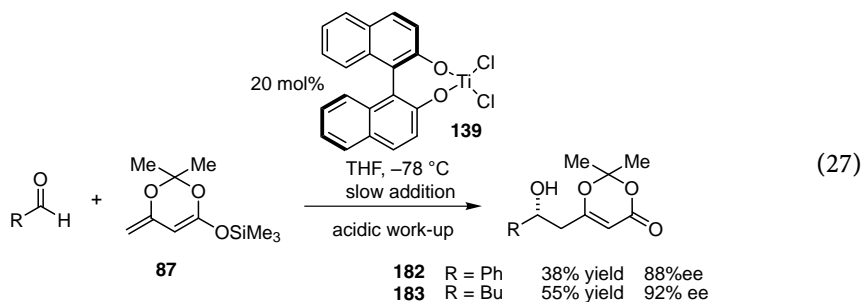


Entry	Aldehyde	Yield	% ee
1	$i\text{Pr}_3\text{Si}-\text{C}\equiv\text{C}-\text{CHO}$	86%	91%
2	$t\text{BuMe}_2\text{SiO}-\text{CH}_2-\text{CH}=\text{CH}-\text{CHO}$	97%	94%
3	$\text{Ph}-\text{CH}=\text{CH}-\text{CHO}$	88%	92% (99%)
4	$\text{Me}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CHO}$	95%	92%
5	PhCHO	83%	84% (96%)
6	$\text{Ph}-\text{CH}_2-\text{CH}_2-\text{CHO}$	97%	80%
7	$\text{Bu}_3\text{Sn}-\text{CH}_2-\text{CH}=\text{CH}-\text{CHO}$	79%	92%

The catalytic, enantioselective aldol addition reaction generates products that can serve as versatile precursors to useful building blocks for asymmetric synthesis (Eq. 26). For example, treatment of cinnamaldehyde adduct **177** with $\text{LiAl}(\text{HNBn})_4$ **178** afforded the crystalline amide **179** (73%). Heating in *n*-BuOH converted **177** to ester **180** (81%). Heating in alkaline methanol yielded (79%) the crystalline lactone **181**. The synthetic utility of adducts **179** and **180** is enhanced by the stereoselective reaction methods that have been developed for their reduction to the corresponding *syn* and *anti* 3,5-diols [103, 104].



In work concurrent with that of Carreira, Sato and coworkers reported that dienol silane **87** participated in catalytic Mukaiyama aldol addition reactions in the presence of 20–100 mol % of Mikami's Ti(IV) complex **139** or Yamamoto's CAB complex **184** (Eqs. 27 and 28). The addition of **87** to benzaldehyde and pentanal at -78°C utilizing 20 mol % of **139** afforded the corresponding adducts **182** and **183** in 38% yield/88% ee and 55% yield/92% ee, respectively. The use of **184** at 50 mol % delivered **182** and **183** in 69% yield/67% ee and 52% yield/70% ee, respectively.



4.3

Boron

Numerous boron complexes have been prepared and studied as catalysts for the Mukaiyama aldol addition reaction and related processes [105]. The types of ligands that have been generally utilized in the preparation of these complexes are derived from either *N*-sulfonyl- α -amino acids or α -hydroxy acids. Both classes share common structural features and form a five-membered chelate involving the carboxylate moiety and the corresponding α -heteroatom (Fig. 16). As discussed above, Masamune has postulated an important mechanistic role for the acyloxy group in facilitating silyl-group transfer [72]. In general, catalytic aldol addition reactions utilizing borane-derived complexes require 20–30 mol % catalyst in propionitrile as solvent at low temperature with slow addition of the reactants.

Yamamoto has documented the use of boryl complexes prepared with a tartaric acid-derived ligand class [106]. The modified tartrate ligands are conven-

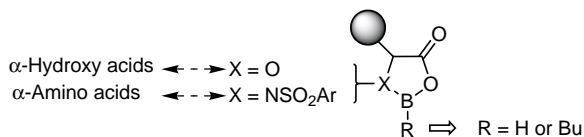
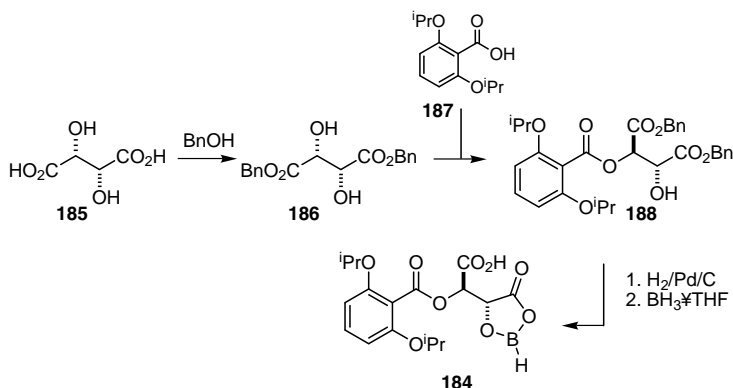


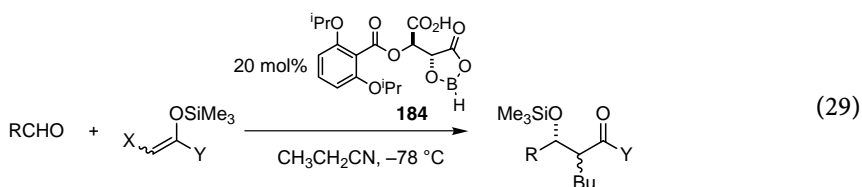
Fig. 16. The general structural characteristics of amino acid and tartrate derived ligands for boron catalysts



Scheme 16

iently prepared from (*R*)- or (*S*)-tartaric acid following a three-step sequence of reactions: (1) formation of the tartrate bisbenzyl ester **186**; (2) monoacylation **186**+**187**→**188**; followed by (3) hydrogenolysis of the *O*-benzyl esters to afford **184** (Scheme 16). In the initial studies these complexes were employed as catalysts for the Diels-Alder cycloaddition reactions [107, 108]. Subsequent investigations have documented the use of the Lewis-acidic boryl complex **184** in aldehyde addition reactions [109].

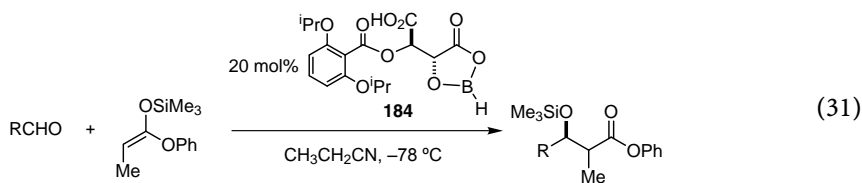
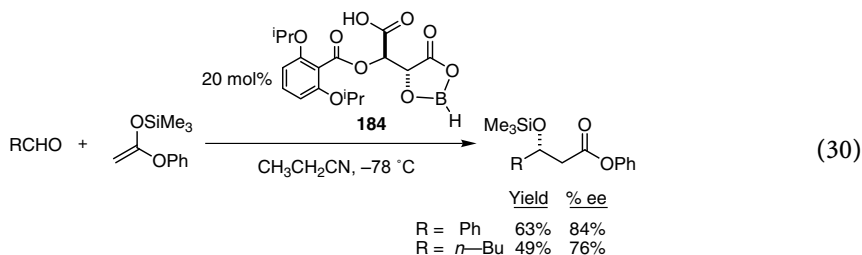
The addition of ketone-derived enol silanes and aldehydes in the presence of **184** at -78°C in propionitrile afforded the aldol adducts in excellent yields as well as diastereo- and enantioselectivity (Eq. 29) [106]. The versatility of this catalyst is evidenced by the fact that enol silanes derived from aliphatic methyl and ethyl ketones as well as acetophenone are substrates for the aldol addition reaction.



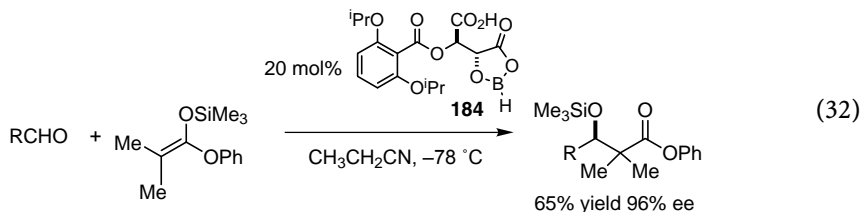
Entry	Enol silane	Aldehyde	Yield	syn/anti	% ee
1		PhCHO	81%	-	85%
2		<i>n</i> -BuCHO	70%	-	80%
3		PhCH=CHCHO	88%	-	83%

4		PhCHO	96%	94:6	96%
5		<i>n</i> -PrCHO	79%	>94:6	93%
6		MeCH=CHCHO	79%	>94:6	93%
7		PhCHO	97%	93:7	94%

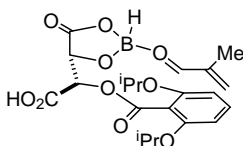
The use of these boryl complexes in catalytic, enantioselective additions to aldehydes by silyl ketene acetals has also been the subject of intense investigation by Yamamoto (Eq. 30) [108]. Although ethyl and benzyl acetate-derived enol silanes furnished racemic products, the phenyl acetate-derived trimethylsilyl ketene acetals proved optimal, giving adducts in up to 84% ee. Additionally, Yamamoto has documented the use of **184** in aldol addition reactions of propionate- and isobutyrate-derived enol silanes (Eqs. 31 and 32). Thus, the addition of the phenyl acetate derived (*E*)-enol silane afforded adducts as diastereomeric mixtures with the *syn* stereoisomer displaying up to 97% ee (Eq. 32).



Entry	Aldehyde	Yield	syn/anti	%ee (syn)
1	PhCHO	83%	79/21	92%
2		57%	65/35	88%
3		45%	64/36	79%
4		97%	96/4	97%
5		86%	>95/5	94%



Although detailed structural data on the active catalysts in the Mukaiyama aldol addition processes is lacking, related studies of the complex as a catalyst for the Diels Alder cycloaddition reaction provided important insight [110]. In this regard, Yamamoto has conducted $^1\text{H-NMR}$ spectroscopic experiments that display a strong NOE between the aromatic ring protons of the aroyl moiety and the enal β -protons. This observation has led Yamamoto to postulate a structure which positions the bound electrophilic component proximally to the 2,6-diisopropoxybenzene ring. The NOE data suggest a structure wherein the bound aldehyde is positioned proximally to the aroyl moiety. Yamamoto has also carried out molecular weight measurements of a solution of the complex generated from phenyl boronic acid; in benzene the formula weight corresponds closely with that for a well defined monomeric species. Additional infrared spectroscopic data are consistent with a complex possessing a five-membered chelate formed between the alkoxy and acyloxy functional groups (Fig. 17).



Kiyooka and coworkers have reported a boron catalyst prepared from $\text{BH}_3\cdot\text{THF}$ and *N-p*-toluenesulfonyl-L-valine [111]. These boron complexes were first reported as stoichiometric reagents which promote the Mukaiyama aldol addition reaction. The outcome of the addition reaction exhibits a dramatic dependence

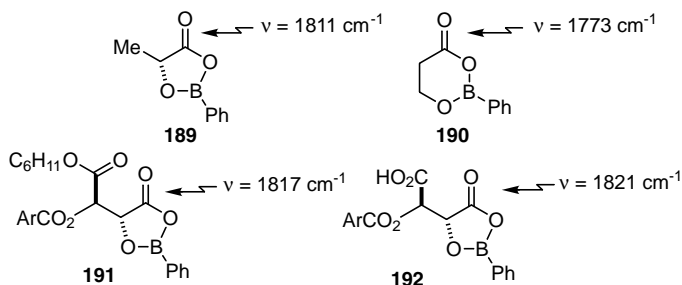
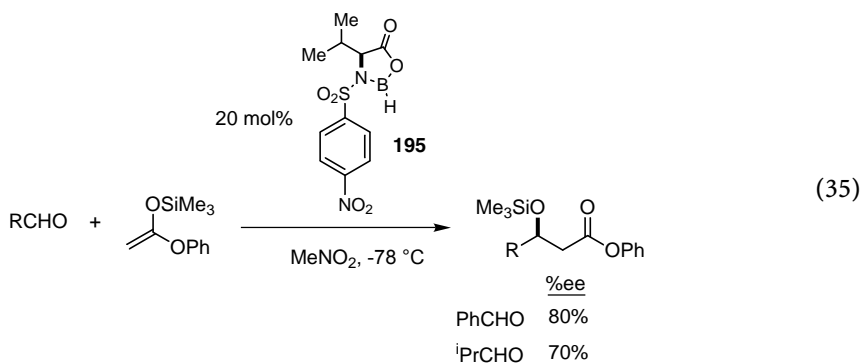
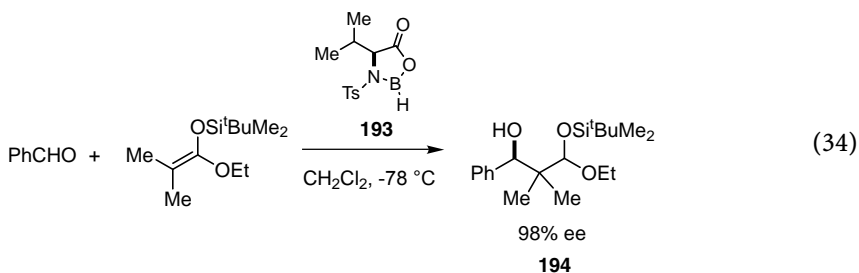
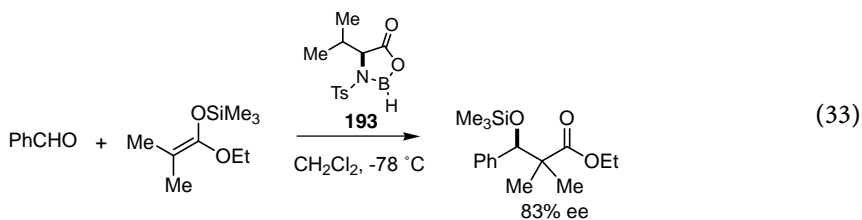


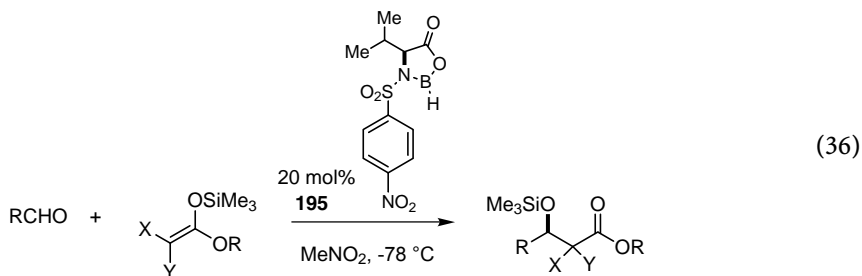
Fig. 17. IR data of a various boryl complexes

on the nature of the trialkylsilyl moiety (Me_3Si versus ${}^t\text{BuMe}_2\text{Si}$) of the enol silane. The enol silane derived from the trimethylsilylketene acetal afforded the expected aldol addition adducts in 77–87% yields with 83–92% ee (Eq. 33). By contrast, the bulkier *tert*-butyldimethylsilylketene acetal furnished the reduced adduct **194** (Eq. 34). This latter product is suggested to be formed by addition of the silyl ketene acetal to the activated aldehyde-promoter complex followed by hydride transfer by the borane to the putative *O*-silylated ester intermediate. This result highlights the fine balance that exists in group transfer reactions such as these between silyl transfer (catalyst turn over) and alternate reaction pathways [112, 113, 114, 115]. Two important modifications made it possible to convert the process into a corresponding catalytic aldol addition: the use of nitromethane as solvent and the *N*-*p*-nitrobenzenesulfonyl derived ligand (Eq. 35).

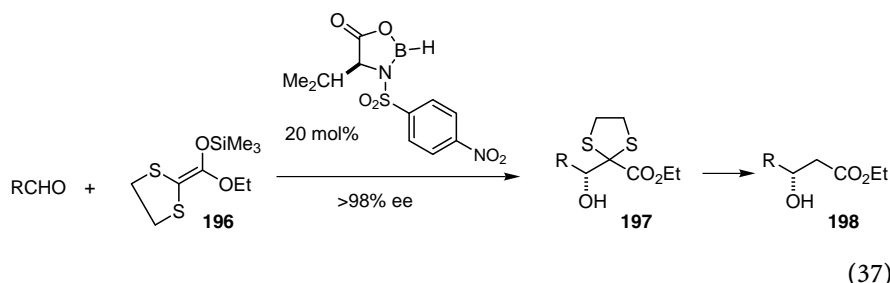


The addition of phenyl acetate-derived enol silane to benzaldehyde and *iso*-butyraldehyde in nitromethane utilizing 20 mol % catalyst **195** provided the silylated aldol adducts in 80 and 70% ee, respectively. Kiyooka has also document-

ed the ability of **195** to mediate the addition of substituted enolates (Eq. 36). The *E*-propionate derived enol silane afforded the adducts in 60–91% yield, albeit in modest levels of simple diastereoselectivity. The enantiomeric excess for the *anti* adduct was observed to be of uniformly higher optical purity. Addition reactions of hetero-substituted enol silanes **196** (Eq. 37) have also been studied. The reductive removal of the dithiane following aldol addition reaction provides an alternative to the acetate aldol addition reaction.



Entry	Enol silane	Aldehyde	Yield	syn/anti	%ee
1			65%	-	96%
2			92%	-	90%
3			97%	-	95%
4			63%	-	81%
5			91%	76:24	syn: 66% anti: 90%
6			60%	60:40	syn: 60% anti: 91%
7			64%	65:35	syn: 90% anti: 97%



An AM1 optimized structure of the chiral borane complex has been utilized as the centerpiece of the model that is proposed to account for the stereochemical outcome of the reaction (Fig. 18). The aldehyde is suggested to coordinate to the boron on the face opposite the isopropyl substituent thereby minimizing steric interactions. The Kiyooka model **199** places the formyl-H over the five-membered ring chelate subtending an obtuse H-B-O-C dihedral angle. Analogous modes of binding have been proposed in other chiral Lewis acid boron compounds that have been ingeniously utilized for Diels-Alder cycloaddition reactions [116a, 116b]. The preference for such orientation may result from the presence of a stabilizing anomeric interaction. Alternatively, the bound aldehyde may be locked in the conformation invoked by Kiyooka as a result of a formyl C-H hydrogen bond to the acyloxy donor following the bonding model proposed by Corey (Fig. 18) [63a, 63b, 63c, 63d, 63e].

Masamune has examined a number of oxazaborolidines derived from a series of simple α -amino acid ligands derivatized as the corresponding *N-p*-toluenesulfonamides [72a, 72b, 72c]. A dramatic improvement in the reaction enantioselectivity was observed when the complex prepared from α,α -disubstituted glycine arylsulfonamides were employed (Eq. 38). Thus, using 20 mol % of **200** the aldol adduct of benzaldehyde and *O*-phenyl isobutyrate-derived enol silane was isolated in 98% ee. In subsequent studies the product enantioselectivity was optimized as a function of substitution of the arylsulfonamide (Eq. 39). Thus, for complexes possessing the general structure **201** the enantiomeric excess of the benzaldehyde adduct varies along the series: Ar=3,5-bis(trifluoromethyl)phenyl (52% ee); mesityl (53% ee); 1-naphthyl (67% ee); 2-naphthyl (78% ee); 4-*tert*-butylphenyl (81% ee); phenyl (83% ee); 4-methoxyphenyl (86% ee); 4-acetamidophenyl (86% ee).

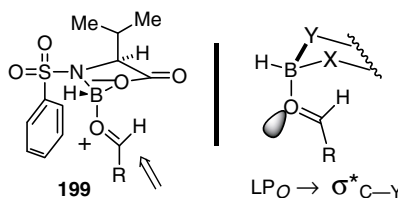
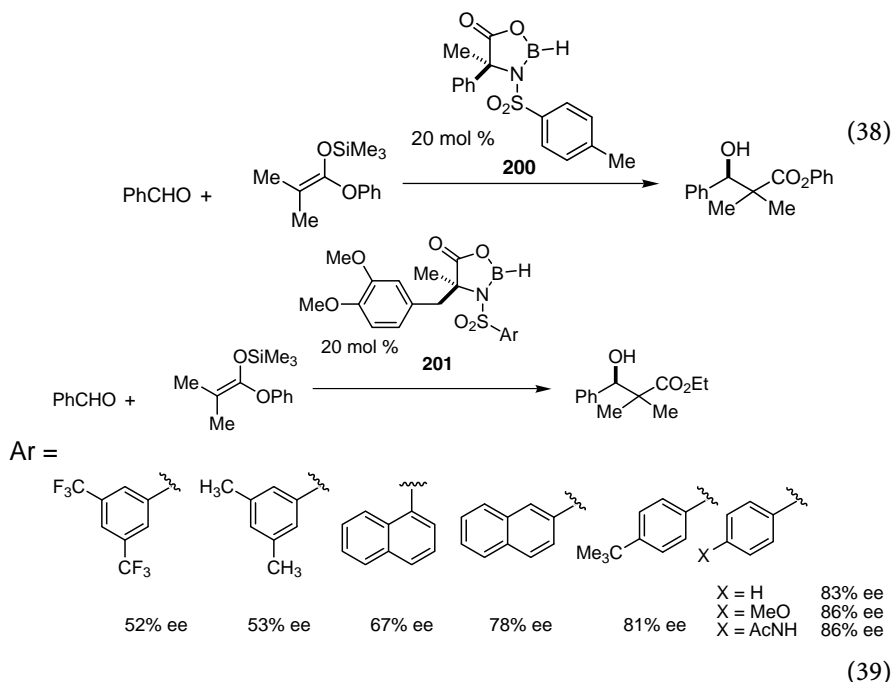
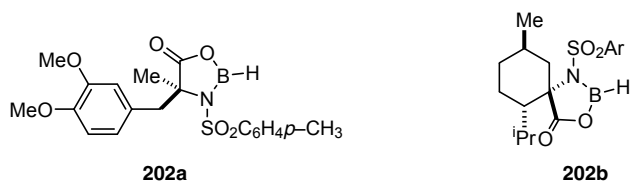


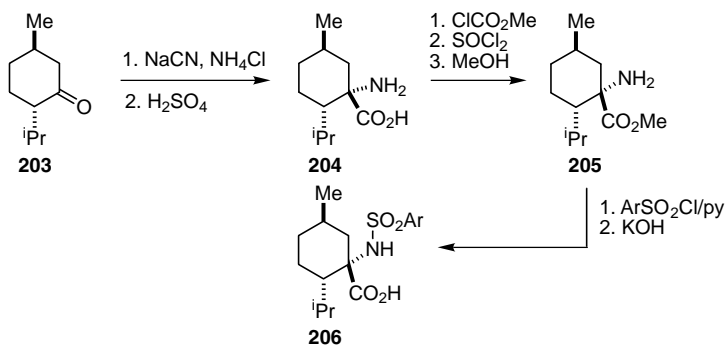
Fig. 18. Kiyooka's model of the aldehyde-Lewis acid complex



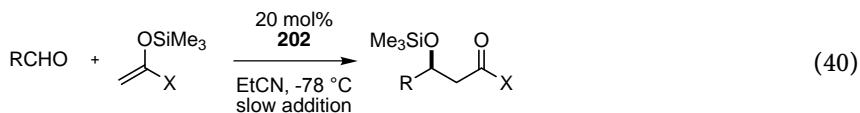
The preparation of the novel ligand **202b** illustrates the general synthetic approach to this class of quaternary α,α -disubstituted glycine sulfonamides (Scheme 17). Menthone (**203**) is converted to **204** using the Strecker amino acid synthesis procedure. A short sequence of synthetic manipulations subsequently yields the desired amino acid ligand **206**.



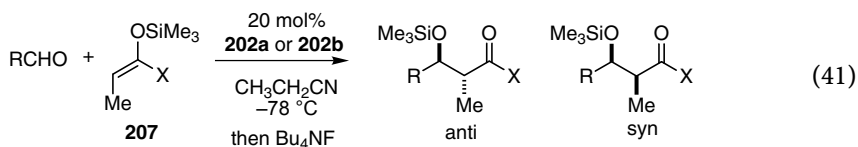
In analogy to the Yamamoto and Kiyooka catalysts, Mukaiyama aldol addition reactions catalyzed by **202a** and **202b** are optimal for *O*-phenyl acetate-derived enol silanes under conditions wherein the aldehyde substrates are added slowly to the reaction mixture in propionitrile at $-78\text{ }^{\circ}\text{C}$. The aldol adducts are isolated for a broad range of aldehydes in excellent yields and up to 92% ee (Eq. 40). The propionate aldol adducts are isolated in good yields, with preference for the *syn* diastereomer in up to 98% ee (Eq. 41) [117].



Scheme 17



Entry	Aldehyde	X	Yield	%ee
1	PhCHO	SEt	86%	87%
2		S ^t Bu	89%	89%
3		OPh	77%	93%
4	PrCH=CHCHO	S ^t Bu	91%	82%
5	PhCH ₂ CH ₂ CHO	SEt	82%	89%
6		OPh	78%	85%
7	PrCHO	S ^t Bu	91%	92%
8	C ₆ H ₁₁ CHO	S ^t Bu	75%	81%
9		OPh	87%	84%
10	2-furylCHO	S ^t Bu	98%	85%

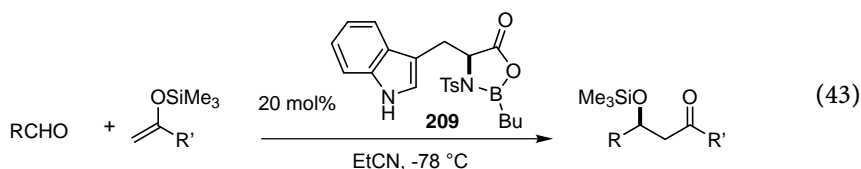
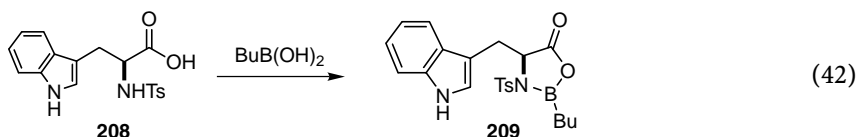


Entry	Aldehyde	Catalyst	X	Yield	syn/anti	% ee syn	% ee anti
1	PhCHO	202b	SEt	89%	87:13	80%	94%
2		202b	S ^t Bu	78%	94:6	82%	66%
3		202b	OPh	77%	77:23	87%	>98%
4	PrCH=CHCHO	202b	SEt	80%	80:20	60%	73%
5	PhCH ₂ CH ₂ CHO	202a	SEt	85%	91:9	82%	81%
6		202a	OPh	72%	90:10	75%	>98%
7	PrCHO	202a	SEt	81%	88:12	70%	81%
8		202b	SEt	94%	66:33	89%	90%
9		202b	SEt	78%	89:11	75%	>98%

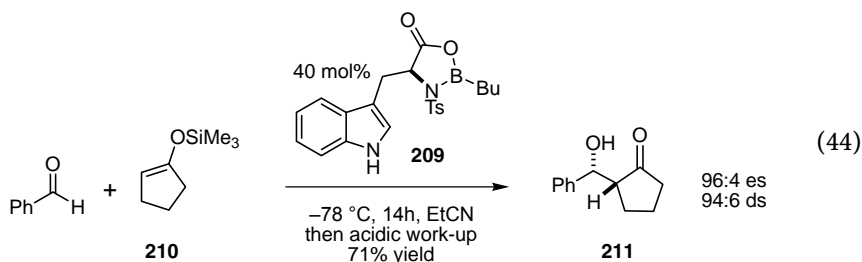
The Masamune analysis of the acyloxyborane-catalyzed Mukaiyama aldol addition reactions underscores an important structural feature of acyloxy ligands in metal complexes that mediate Si-atom transfer reactions. At short reaction times when the reaction is run with 1 equiv of complex, the β -hydroxy ester is isolated as the major product from the reaction mixture, while with prolonged reaction times the product mixture becomes enriched in the silylated product. The analysis suggests a critical role for the acyloxy ligand wherein it is silylated during the nucleophilic addition of enol silane to the coordinated aldehyde. In a subsequent step, transilylation from the carboxyl group to the metal aldolate occurs, leading to product release and catalyst regeneration. The use of α -alkyl-substituted α -amino acid ligands was postulated to lead to more rapid transilylation reaction as a consequence of the Thorpe-Ingold effect. Moreover, the slow addition of substrates would allow this intermediate to undergo transilylation at a rate that is more rapid than the boryl-catalyzed aldol addition reaction (Scheme 8).

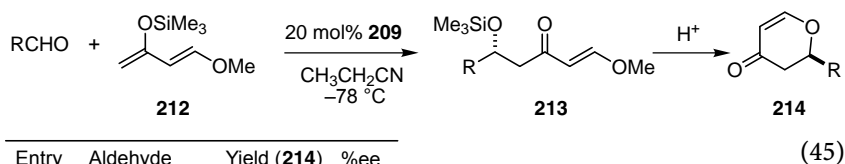
Corey has developed an interesting class of Lewis acidic boron complexes prepared from *N*-aroylsulfonyl-L-tryptophan **208**. The active complex is conveniently prepared from **208** and BuB(OH)₂ (Eq. 42). This same complex catalyzes the enantioselective addition of methyl ketone derived trimethylsilylenol ethers and 1-methoxy-3-trimethylsilyloxybutadiene (Eq. 43) [118, 119]. Using 20 mol %

of **209** in propionitrile at $-78\text{ }^{\circ}\text{C}$ the acetophenone and 2-hexanone-derived enol silanes add to aldehydes to give aldol adducts in up to 90% ee and useful yields. Moreover, the cyclopentanone-derived enol silane adds to benzaldehyde to give **211** in an impressive 92% ee and 88% diastereoselection (Eq. 44). Upon completion of the reaction, the *N*-tosyltryptophan ligand can be conveniently extracted in alkaline aqueous wash, facilitating isolation of the desired aldol adduct; subsequently, the ligand may be recovered by extraction of the acidified aqueous solution. This same complex has been shown to effectively catalyze the addition of 2-trimethylsilyloxy-4-methoxybutadiene **212** and aldehydes giving the corresponding aldol adducts **213** in good yields and up to 82% ee (Eq. 45). The dienolate adducts can be converted in high yields to the corresponding dihydro-4*H*-pyran-4-ones **214** upon treatment with trifluoroacetic acid in Et_2O [116b].



Entry	R'	Aldehyde	Yield	%ee
1	Ph	PhCHO	82%	89%
2	Ph	<i>o</i> -C ₆ H ₁₁ CHO	67%	93%
3	Ph	<i>n</i> -C ₃ H ₇ CHO	94%	89%
4	Ph	2-furylCHO	100%	92%
5	<i>n</i> -Bu	PhCHO	100%	90%
6	<i>n</i> -Bu	<i>o</i> -C ₆ H ₁₁ CHO	56%	86%





Entry	Aldehyde	Yield (214)	%ee
1	PhCHO	100%	82%
2	PhCH ₂ CH ₂ CHO	57%	69%
3	2-furylCHO	83%	67%
4	<i>c</i> -C ₃ H ₇ CHO	87%	73%
5	<i>c</i> -C ₆ H ₁₁ CHO	80%	76%

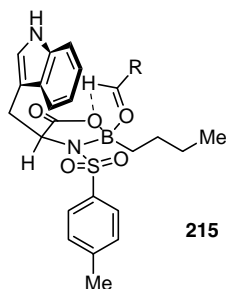


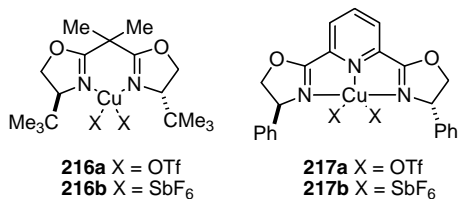
Fig. 19. Corey's model for the aldehyde-Lewis acid complex

In related studies of the tryptophan-derived oxazaborolidene complex as a catalyst for Diels-Alder cycloaddition reactions, Corey has provided insight into the structure of the methacrolein complex **215** (Fig. 19). The results of ¹H-NMR NOE experiments indicate the presence of a well-defined aldehyde complex in which the enal is in close contact with the indole ring. The presence of this interaction is supported by the observation of a broad UV absorption band (400–600 nm) that is reversibly formed by successive warming (250 K) and cooling (210 K) of a methylene chloride solution of the aldehyde and complex. Moreover, replacement of the indolyl subunit with a β-naphthyl group leads to a diminution on the product enantioselectivity. When the *N*-tosyl group is replaced with an *N*-mesitylsulfonyl, little enantioselectivity is observed, suggesting that the interaction between the indole and aldehyde has been disrupted due to steric demands of the methyl-substituted aromatic group.

4.4

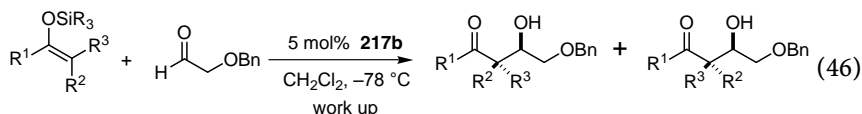
Copper(II)

The use of Cu(II) complexes as Lewis acid catalysts for the Mukaiyama aldol addition reaction has been documented and studied by Evans [120a, 120b, 121a,

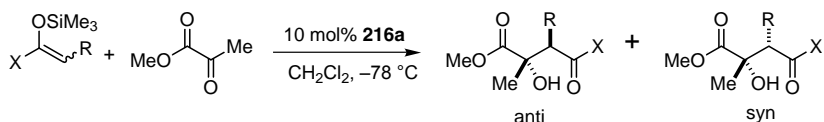


121b]. The catalysts **216** and **217** are generated upon treatment of Cu(OTf)₂ with bisoxazolone ligands. These have been shown to function effectively in the addition of enol silanes with α -heteroatom-substituted aldehydes and ketones such as benzyloxyacetaldehyde and pyruvates in superb yields and selectivities.

The addition of substituted and unsubstituted enolsilanes at -78 °C utilizing 5 mol % catalyst was shown to be very general for various nucleophiles including silyl dienolates along with enol silanes prepared from butyrolactone as well as acetate and propionate esters (Eqs. 46 and 47). It is noteworthy that the addition of both propionate-derived *Z*- and *E*-silylketene acetals stereoselectively forms the *syn* adduct in 97% and 85% ee, respectively.



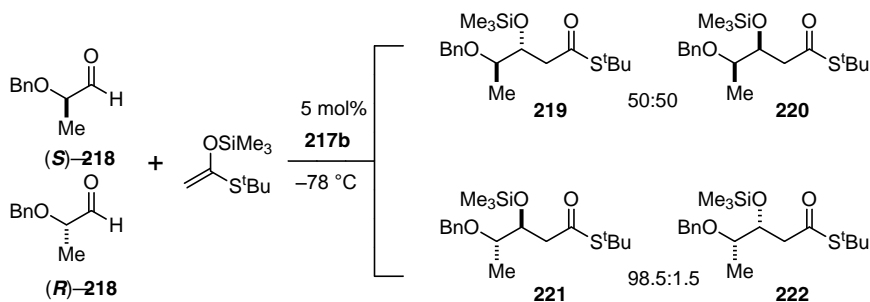
Entry	Nucleophile	mol% 217b	Yield	syn/anti	%ee
1		0.5	96%	-	99%
2		0.5	95%	-	98%
3		0.5	99%	-	98%
4		5	94%	-	92%
5		10	90%	97:3	97%
6		10	48%	86:14	85%
7		10	95%	96:4	95%



(47)

Entry	Nucleophile	Yield	syn/anti	%ee(syn)
1		99%	-	99%
2		76%	-	93%
3		99%	-	77%
4		96%	94:6	96%
5		98%	95:5	88%

The results of addition reactions with related substrate types provide important insight into the structural and mechanistic aspects of the Cu(II)-catalyzed process. Thus the reaction of α -*tert*-butyldimethylsilyloxyacetaldehyde furnished the corresponding adduct in only 56% ee; moreover, additions to β -(benzyloxy)propionaldehyde yielded only racemic adduct. These two critical observations suggest the important role of the substrate binding to the Lewis-acid center in producing a complex possessing a five-membered ring chelate that leads to aldehyde-face differentiation. This is further underscored in a series of experiments in which aldol addition to enantiomeric α -benzyloxy-propionaldehydes (*R*)-**218** and (*S*)-**218** was investigated (Scheme 18). The addition of *tert*-butyl thioacetate-derived enol silane to (*R*)-**218** furnished adduct in 98.5:1.5 diastereoselectivity; by contrast, addition to the enantiomeric substrate (*S*)-**218**



Scheme 18

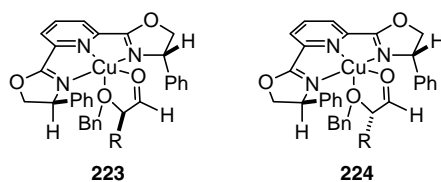
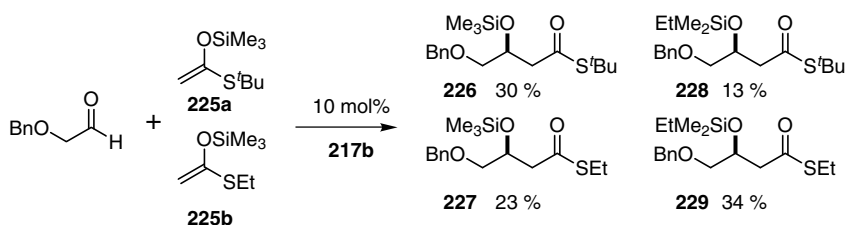


Fig. 20. Stereoanalysis of the metal-bound aldehyde complexes



Scheme 19

under otherwise identical conditions afforded adducts as a 50:50 mixture of diastereomers. These experimental observations provide evidence for matched/mismatched substrate/catalyst pairing and further substantiate the presence of a chelated aldehyde in the activated complex. In this regard, analysis of the putative chelates formed from (*R*)-**218** and (*S*)-**218** reveal that the stereocontrolling features of the ligand operate in concert with only one of the two enantiomeric aldehydes (Fig. 20).

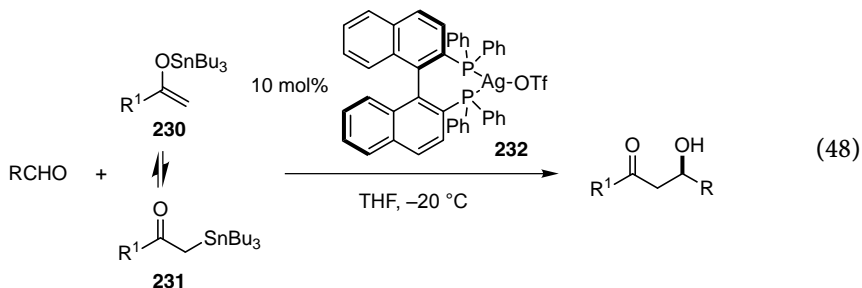
Studies employing doubly-labeled, sterically and electronically similar enol have revealed additional interesting mechanistic details on the nature of the silyl-transfer or turnover step [39a, 39b]. In the experiment, a 1:1 mixture of the two silyl ketene acetals **225a** and **225b** were allowed to react with α -benzyloxyacetaldehyde in the presence of 5 mol % **217b** (Scheme 19). The reaction mixture yields a mixture of products in which the trialkylsilyl group has been scrambled, a result consistent with a turnover step in which silyl transfer occurs in an intermolecular fashion. The remarkable success of this system stems from the ability of a labile Cu(II) alkoxide to undergo silylation at a faster rate than the competing deleterious processes involving silyl-catalyzed aldol addition reaction.

4.5

Silver(I)

Yamamoto has pioneered the use of Ag(I) complexes as Lewis acids for aldehyde allylation [122] and aldol addition [123]. For the aldol addition process, ketone-derived tributyltin enolates have been employed as the nucleophilic component (Eq. 48). These enolates are readily prepared from the corresponding enolates upon treatment with Bu_3SnOMe . Importantly, although the resulting Bu_3Sn -enolates are known to exist as a mixture of *C*- and *O*-bound tautomers **230/231**,

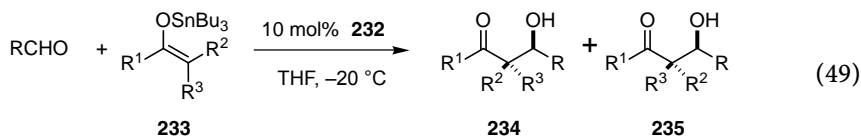
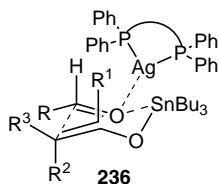
this mixture can be used directly in the addition reaction. Control experiments had previously shown that tributylstannyl enolates undergo nucleophilic addition to aldehydes at ambient temperature over 14 h. Remarkably, however, Yamamoto has documented that the addition of Ag(I)-bisphosphine complex **232** substantially accelerate the addition reaction yielding adducts in up to 95% ee and 83% yield (Eq. 48).



Entry	Nucleophile	Aldehyde	Yield	%ee
1		PhCHO	73%	77%
2			83%	53%
3			61%	59%
4		PhCHO	78%	95%
5			69%	86%
6			75%	94%
7		PhCHO	57%	71%
8			33%	41%
9			40%	50%

Yamamoto has also examined the reactions of substituted *E*- and *Z*-enol stannanes derived from cycloalkanones and acyclic *tert*-butylethyl and -propyl ketones (Eq. 49). The addition reactions of cyclic enolates afforded the adducts in excellent yields (92–96%) and 89/11 to 93/7 *anti/syn* diastereomeric ratio with the enantiopurity of the major diastereomer **234** uniformly high (92–95% ee). The use of acyclic *Z*-enol stannanes delivered the complementary *syn* adducts in superb diastereoselectivities (<1/99 *anti/syn*) and enantioselectivity (91–95% ee). The high degree of stereospecificity of the addition process with respect to the

enolate component led the investigators to propose a closed transition state structure **236** wherein the chiral Ag(I) complex is exocyclic to the heterocyclic stannacyclohexane.

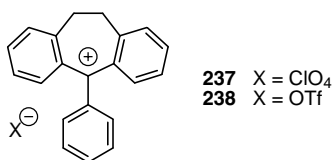


Entry	Nucleophile	Aldehyde	Yield	syn/anti	%ee
1		PhCHO	92%	89/11	92%
2		PhCHO	94%	92/8	93%
3		PhCHO	90%	85/15	96%
4		PhCHO	81%	<1/99	95%
5		Ph-CH ₂ -CH ₂ -CHO	77%	<1/99	95%
6		PhCHO	98%	<1/99	91%

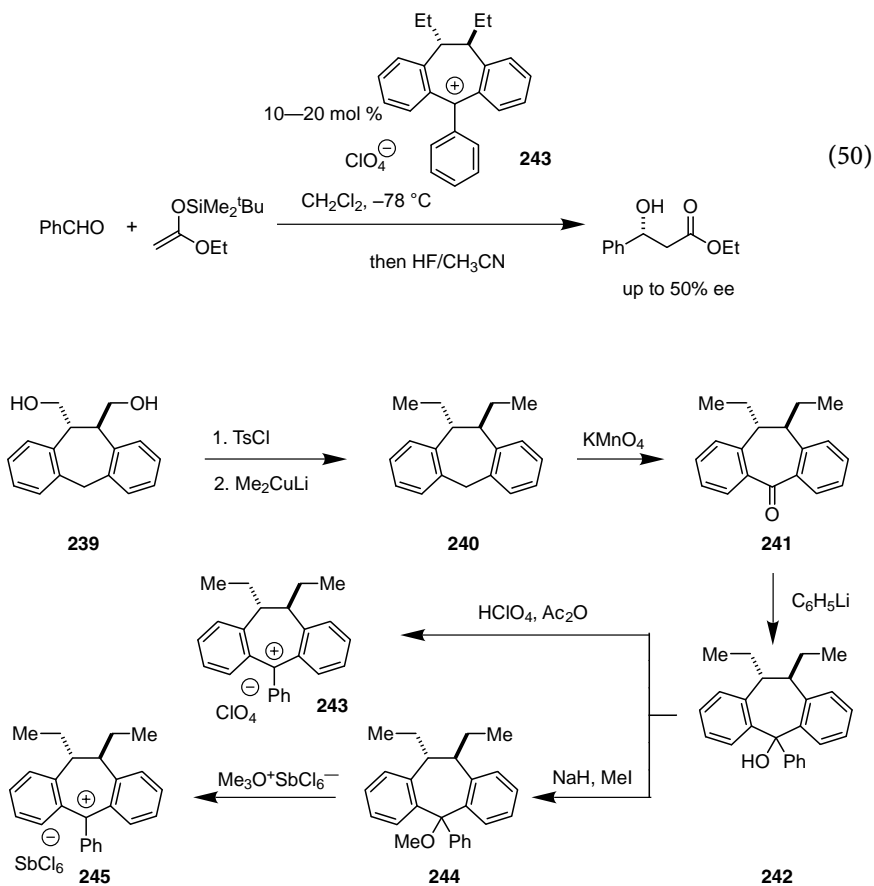
4.6

Carbocationic Lewis Acids

A series of reports by Mukaiyama and coworkers have highlighted the ability of triarylmethyl cations to function as promoters for the aldol addition reaction of enol silanes and aldehydes [27a, 27b, 27c, 27d, 27e, 27f, 27g, 90]. Subsequent studies by Denmark have provided the mechanistic and conceptual groundwork for the design of catalytic strategies utilizing 1-phenyldibenzosuberyl perchlorate **237** and triflate **238** salts as novel carbon-based Lewis acid catalysts for asymmetric aldol addition reactions [73].



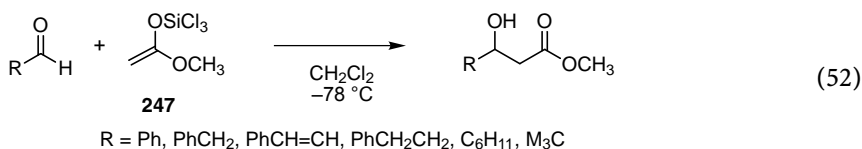
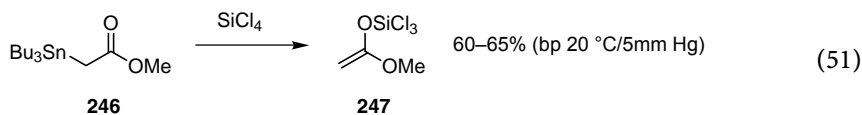
Recently, Chen has synthesized and resolved chiral suberylcarbocation ions and successfully demonstrated their use for Mukaiyama aldol addition reactions [74]. The asymmetric synthesis of the optically active triarylmethylcarbocation commences with the C₂-symmetric diol **239**, whose preparation had been reported by Platzke and Snatzke in an approach to a variety of anti-inflammatory agents [124] (Scheme 20). With the chiral Lewis acids in hand, Chen documented their use as asymmetric catalysts (Eq. 50); interestingly, both the yield and enantioselectivity of the process were shown to be sensitive to the counterion (ClO₄⁻, PF₆⁻, versus SbCl₆⁻) of the triarylmethylation.



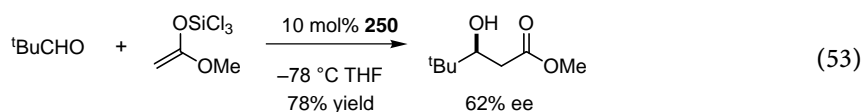
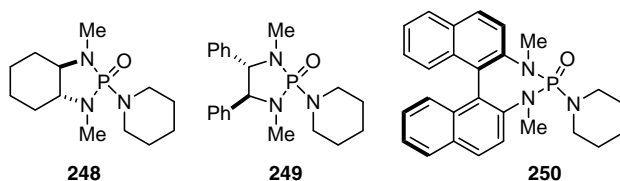
Scheme 20

5 Lewis Base-Mediated Aldol Addition Reactions

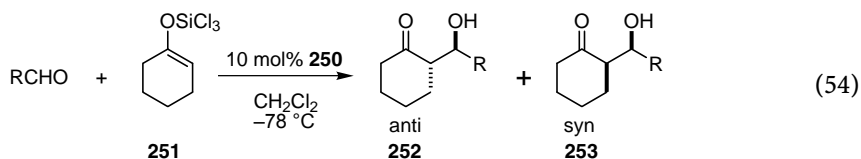
In a novel departure from the traditional approach to the asymmetric Mukaiyama aldol, Denmark has reported a Lewis base-catalyzed aldol addition reaction of enol trichlorosilanes and aldehydes. These unusual silyl ketene acetals are readily prepared by treatment of the tributylstannyl enolates **246** with SiCl_4 (Eq. 51). In the initial ground-breaking studies, the methyl acetate-derived trichlorosilyl ketene acetal **247** was shown to add rapidly to a broad range of aldehydes at -80°C to give adducts (89–99% yield, Eq. 52).



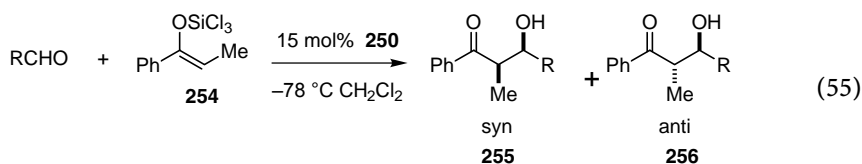
Despite the fact that the uncatalyzed reactions are reported to be very rapid at -78°C , Denmark has demonstrated that the addition reaction is dramatically accelerated in the presence of a catalytic amounts of Lewis-basic phosphoramides, such as hexamethylphosphoric triamide (HMPA). This remarkable observation coupled with mechanistic investigations has led to the successful development of chiral phosphoramides **248** to **250** as Lewis-base catalysts for enantioselective Mukaiyama aldol addition reactions. Initial investigations documented the superiority of phosphoramidate **250** in delivering products of high optical purity; for example, the addition reaction of enol trichlorosilane derived from methyl acetate with trimethylacetaldehyde at -78°C affords the aldol adduct in 62% ee and 78% yield (Eq. 53).



This system has been successfully applied to the addition reaction of substituted enol silanes to aldehydes, leading to the formation of adducts displaying useful levels of simple and absolute stereocontrol (Eqs. 54 and 55). For example, the addition of cyclohexanone-derived enol silane **251** to a broad range of aldehydes selectively affords the anti-adducts **252** in up to 95% enantiomeric excess. It is particularly interesting that the catalyzed and uncatalyzed reactions have divergent simple stereochemical outcomes. Thus, in contrast to reactions catalyzed by **250**, the reaction of **248** and benzaldehyde is predominantly *syn*-selective. The addition of acyclic *Z*-enolates **254** exhibited the opposite trend; thus, while the uncatalyzed addition of propiophenone-derived trichlorosilyl enolate with aldehydes has a modest preference for the *anti* adduct, the phosphoramidate catalyzed reaction displays *syn*-selectivity with all but one substrate (phenylpropynal). The acyclic 1,2-*syn* products were formed in 84–96% ee and 89–97% yields. The high selectivity of this process suggests a tight, well-defined transition state structure; Denmark has postulated a cyclic array organized about the silyl moiety.



Aldehyde	Yield	syn/anti	% ee (syn)
	95%	1:1	93%
	94%	1:99	97%
	94%	1:99	88%
	98%	1:99	92%
	90%	1:5	82%



Aldehyde	Yield	syn/anti	% ee (syn)
	95%	18:1	95%
	89%	12:1	96%
	96%	3:1	84%
	97%	9:1	92%
	94%	7:1	91%

6

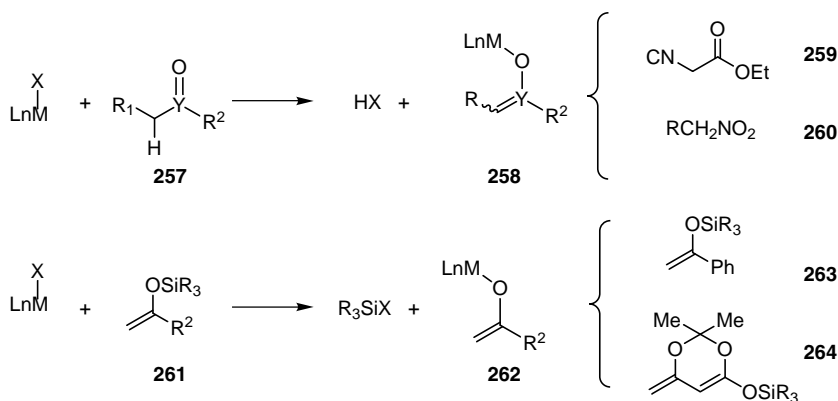
Mukaiyama Additions via Metalloenolate Intermediates

6.1

Silver(I), Copper(II), Palladium(III)

Shortly after the discovery of the Lewis acid-mediated Mukaiyama aldol addition reaction of enol silanes the general mechanistic aspects of the reaction were intensely investigated [30a, 30b, 30c, 30d]. These processes are considered to proceed by electrophilic activation of the aldehyde towards addition by the nucleophilic enol silane. However, aldol addition processes that proceed by alternative mechanistic pathways have been documented and studied. It is worth considering those systems that have been developed for catalytic, enantioselective aldehyde addition reactions through metalloenolate intermediates.

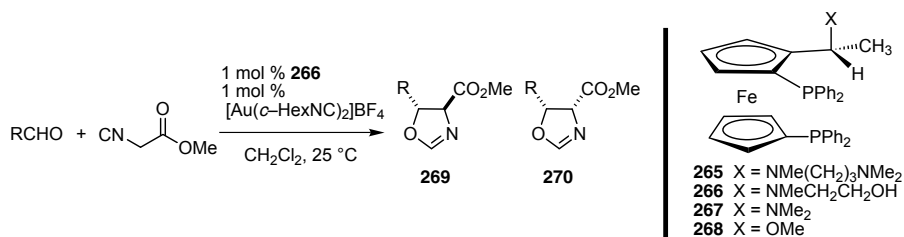
Two general type of processes that proceed by way of a putative enolate-metal complex have been documented: (1) those in which the metalloenolate nucleophile is generated following deprotonation of C-H acid $257 \rightarrow 258$, and (2) those in which the metalloenolate is generated upon desilylative metallation of an enol silane $261 \rightarrow 262$ (Scheme 21). Examples of the former processes have been documented and utilize activated C-H acids with pK_a (H_2O) < 20 such as isonitrile esters **259**, nitroalkanes **260**, and ketones. Fewer cases have been reported for the catalytic addition of enol silanes through a putative metalloenolate intermedi-



Scheme 21

ate; these include acetophenone and 2,2,3-dimethyldioxinone derived enol silanes **263** and **264**.

The pioneering work of Hayashi and Ito has set high standards for the class of carbonyl addition reactions involving the first type of aldol addition reactions (Eq. 56) [25]. These investigators documented the Au(I)-catalyzed addition of α -isocyanocarboxylic acid esters to aldehydes to afford substituted oxazoline adducts. A family of chiral ferrocenylbisphosphines ligands and the corresponding Au(I) and Ag(I) complexes were developed for this process and were the key to the success of this remarkable process. The typical procedure prescribes the use of 1 mol % of the complex in dichloromethane at 25 °C with reaction times ranging from 20 to 40 h. The product oxazolines are isolated in superb yields as a mixture of *trans*/*cis* diastereomers (70/30 to >99/1) and 74–97% enantiomeric excess. The synthetic chemistry of these oxazoline adducts has been studied and developed extensively [125a, 125b].

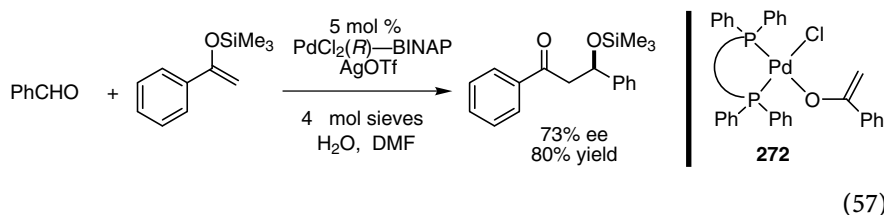


(56)

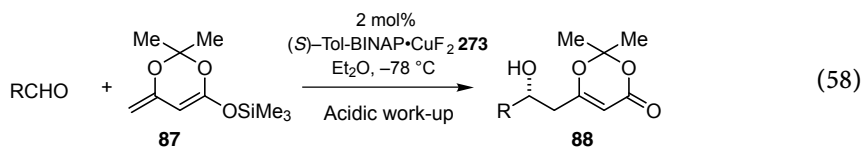
The efficiency and selectivity of this process has been explained on the basis of several critical structural parameters that are synergistically operating in this system. The coordination of an isocyanide to the soft metal center is proposed to lead to a facile deprotonation of the enolate precursor by the pendant basic alkylamino sidechain. The formation of a contact ion-pair between enolate and ammonium groups should lead to a preferred orientation of the metal-bound

enolate wherein one of the two diastereomeric enolate faces is exposed. Coordination of the aldehyde to the cationic metal center completes the coordination sphere at Au(I) leading to stereoselective C-C bond formation.

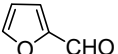
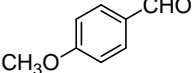
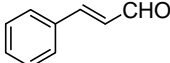
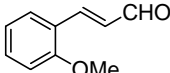
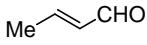
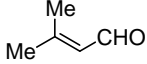
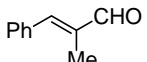
Shibasaki and coworkers have reported an asymmetric, catalytic aldol addition reaction of ketone-derived enol silanes and aromatic aldehydes that is proposed to proceed through the intermediacy of a palladium enolate [126]. The active catalyst mixture is prepared upon treating a PdCl₂ and (*R*)-BINAP in the presence of 4 Å molecular sieves and AgOTf, with the optimal formulation also prescribing the addition of 2 equivalents of water. Aromatic aldehydes constitute the ideal substrates for the reaction giving adduct in up to 80% yield and 73% ee (Eq. 57). Shibasaki and co-workers have carried out some spectroscopic investigations that provide insight into the putative catalytic cycle and have suggested a model with a Pd-enolate **272** as the catalytically active intermediate.



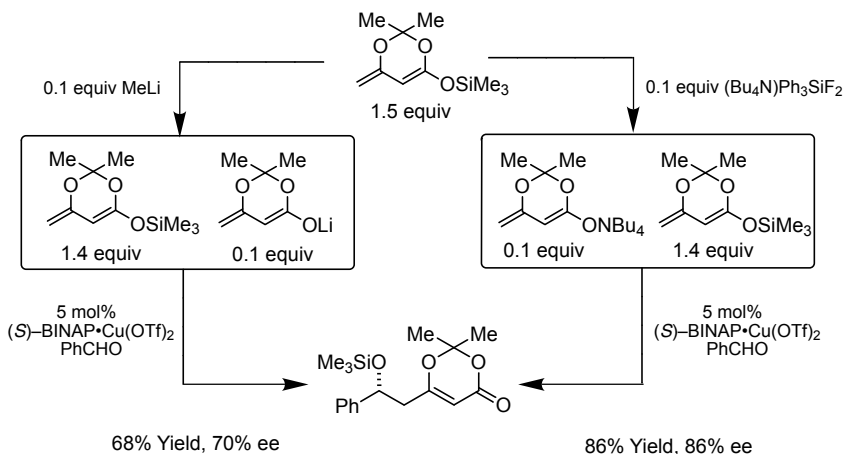
Carreira and co-workers have described a Cu-mediated process that effects the catalytic, enantioselective addition of silyl dienolates **87** to aldehydes [24]. The active complex that is believed to initiate the reaction is readily prepared in situ upon mixing optically active bisphosphine, Cu(OTf)₂ and (Bu₄)NPh₃SiF₂ in THF (Eq. 58). The addition reactions catalyzed by this system proceed with a broad range of aldehydes to afford adducts **88** in up to 95% ee and 98% yield. Moreover, the reaction may be conducted on a preparative multigram scale utilizing as little as 0.5 mol % of **273** without deleterious effects on the product enantiomeric excess or yields.



Entry	Aldehyde	Yield	% ee
1		92%	94%
2		86%	93%
3		98%	95%

4		91%	94%
5		93%	94%
6		83%	85%
7		82%	90%
8		48%	91%
9		81%	83%
10		74%	65%

In analogy to the Au(I) and Pd(II) systems of Hayashi and Shibasaki, respectively, this process is proposed to proceed through a metalloenolate intermediate. The catalytically active metalloenolate species is generated upon desilylative metallation of the enol silane by the cupric fluoride complex. In support of the hypothesis that a soft-metal enolate is an intermediate in the reaction, the investigators have observed that the reaction can be successfully executed under conditions that directly promote transmetalation of the enol silane in the absence of fluoride (Scheme 22). When a solution of enol silane is successively treated with 10 mol % of either MeLi or $(\text{Bu}_4\text{N})\text{Ph}_3\text{SiF}_2$ at 0 °C, followed by 5 mol % of (S)-BINAP-Cu(OTf)₂ at -78 °C and benzaldehyde, the aldol adduct was isolated



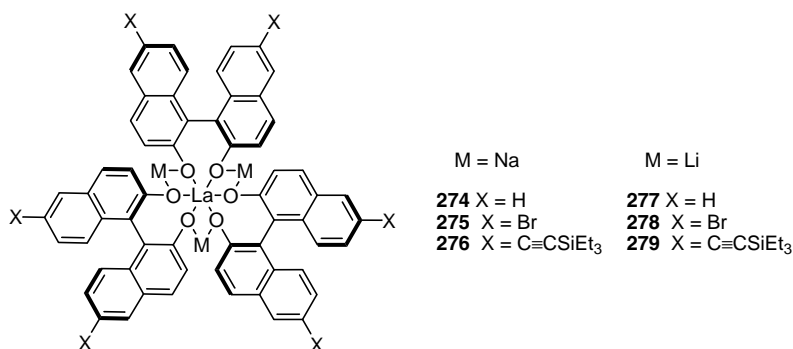
Scheme 22

in good yields and enantioselectivities. Thus, the fluoride counterion is only responsible for initiating the catalytic cycle by generation of the metalloenolate.

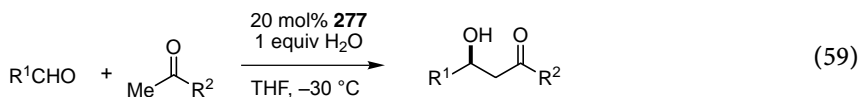
6.2

Lanthanides

Shibasaki has developed a family of heterobimetallic complexes **274** to **279** derived from the alkali metal diaryloxy salt of chiral binaphthols and lanthanide alkoxides; these complexes function as catalysts in a variety of useful enantioselective addition reactions [127, 128, 13j].



The direct addition of enolizable ketones to aldehydes in the presence of 20 mol % of **277** furnished adducts in up to 94% ee and 81% yield (Eq. 59). Although additional examination and optimization of the system is warranted, it represents an important ground-breaking advance in the field of catalytic aldol addition methodology since it obviates the preparation and use of enol silanes.



Entry	Aldehyde	R ²	Yield	%ee
1	Me ₃ CCHO	Ph	81%	91%
2		CH ₃	53%	73%
3		1-naphthyl	55%	76%
4		CH ₃ CH ₂	71%	94%
5	<i>o</i> -C ₆ H ₁₁ CHO	Ph	72%	44%
6	Me ₂ HCCHO	Ph	59%	54%
7	Ph(CH ₂) ₂ CHO	Ph	28%	52%

In-depth investigation of these systems has provided mechanistic and structural details of this remarkable catalytic system. X-ray crystal structures of the rare earth/Na/BINOL complexes have been obtained which form the basis of the structural models of the active species that have been proposed. Moreover, laser-desorption/ionization time-of-flight mass spectrometry data corroborates the solid state structural data and substantiates the proposal of a 3:3:1 ligand, alkali metal:lanthanide complex as the active species. Shibasaki and co-workers have proposed that the lanthanide alkoxide functions as a Brønsted base and, following deprotonation of the nitroalkane, furnishes a metallocenate. The nature of the alkali metal in the lanthanide complex is important to the successful production of nitro aldol adducts in high enantiomeric excesses. Thus, while the Li-derived complex furnishes adducts in excellent enantioselectivities, the sodium-derived complex gives racemic product. Shibasaki has proposed that the nitroenolate is bound to the active catalyst by coordination to the lithium site. The nature of the lanthanide metal has also been shown to be important; thus the optimal catalyst for the aldol addition with optimal selectivities obtained for La(III) (97% ee) while the complexes prepared from the smaller rare earth metals give products with diminished induction. The lanthanide center is thus postulated to function as the Lewis acid site to which the aldehyde coordinates. The resulting active complex constitutes the lithium nitronate and La-bound aldehyde complex that leads to product formation. The Shibasaki catalyst represents a remarkable example of a self-assembled bimetallic system for which it is possible to fine tune structure and function by subtle variations in three variables: alkali metal, lanthanide, and substituted binaphthol. In this regard, Shibasaki and coworkers have elegantly documented other permutations of these variables that lead to impressive catalysts for asymmetric Michael additions, hydrophosphonylation of imines, and enoate epoxidation.

7

Conclusions

The successful development of an asymmetric, catalytic reaction process is a multidimensional problem at the interfaces of inorganic, organometallic, and organic chemistry that demands the consideration and integration of a multitude of parameters such as reaction mechanism as well as catalyst design and synthesis. Additionally, environmental concerns along with the constraints of the marketplace require that newer processes be invented with attention to experimental practicality. The numerous asymmetric catalytic aldol addition processes that have been detailed in this chapter highlight the intensity of interest in the generation of practical enantioselective carbonyl addition reactions. The diversity of catalysts, reaction conditions, and mechanistic possibilities underscore the intellectual richness that this general area provides for discovery and innovation in chemistry. The breathtaking pace of developments will surely continue unabated, guaranteeing the continued evolution of this field.

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Chapter 29.2

Addition of Isocyanocarboxylates and Aldehydes

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Keywords: Isocyanocarboxylate, Aldol reaction, Gold, Silver, Ferrocenylphosphine, β -Hydroxy- α -amino acid

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1 Introduction

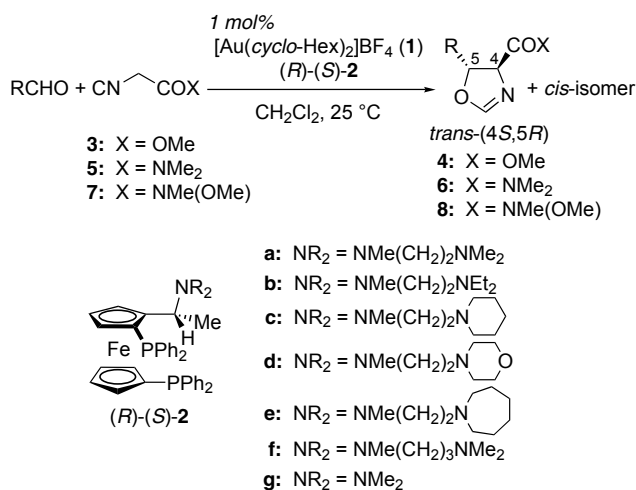
α -Isocyanocarboxylates are useful as precursors of α -amino acid enolates, which are readily generated with mild bases such as tertiary amines or K_2CO_3 . The enolates react with an electrophile to yield a variety of α -amino acid derivatives. In 1985, Ito developed an aldol-type reaction with ethyl isocyanoacetate catalyzed by CuCl together with Et_3N , which yields useful 5-alkyl-2-oxazoline-4-carboxylates as synthetic intermediates of β -hydroxy- α -amino acids [1]. In the catalytic reaction, the copper salts act as Lewis acids to activate the α -hydrogen of the isocyano group, and one of the activated α -hydrogens is abstracted by the Et_3N to generate the ammonium enolate of isocyanoacetate, which reacts with aldehyde to form the aldol adduct. Therefore, the ammonium enolate coordinated to the metal atom is expected to be a key intermediate in the stereocontrol of the aldol reaction. In 1986, Ito and Hayashi reported that chiral ferrocenylphosphine-gold(I) complexes are effective for asymmetric aldol reactions of isocyanoacetate [2]. This chapter presents an overview of gold(I)-catalyzed asymmetric aldol reactions of isocyanocarboxylates and their analogs.

2

Asymmetric Aldol Reaction of Isocyanoacetates with Aldehydes

Gold(I) complexes prepared in situ from bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**1**) [3] and chiral ferrocenylphosphine ligands (*R*)-(*S*)-**2a–e** [4, 5] bearing a 2-(dialkylamino)ethyl side chain are effective chiral catalysts for asymmetric aldol reactions of methyl isocyanoacetate (**3**) with aldehydes, which give *trans*-(4*S*,5*R*)-5-alkyl-2-oxazoline-4-carboxylates (*trans*-**4**) with high enantiomeric excess (Scheme 1, Table 1) [2, 6, 7, 8, 9, 10]. The corresponding chiral copper(I) and silver(I) catalysts are less stereoselective. Both the enantio- and *trans*-selectivity are affected by the terminal amino group on the side chain of ligands **2a–e**. Especially, enantioselectivity of the reaction with acetaldehyde is significantly improved by the modification of the terminal amino group, and six-membered ring amino groups such as piperidino (**2c**) and morpholino (**2d**) groups are superior in general (entries 1–5,10,11) [11, 12]. The 2-(dialkylamino)ethyl side chain is essential for the high degree of stereocontrol. Ferrocenylphosphine **2f** bearing a 3-(dimethylamino)propyl side chain is much less enantioselective, and **2g** without a pendant side chain gives almost racemic oxazolines with low *trans/cis* ratio (entries 12,13) [2].

Secondary and tertiary alkyl aldehydes give the corresponding *trans*-oxazolines almost exclusively with high enantioselectivity (entries 6,7). The reaction with α,β -unsaturated aldehydes catalyzed by the chiral gold complex is free of any products resulting from 1,4-additions, and proceeds with high stereoselectivity (entries 8,9). Various functional groups on aromatic aldehydes are acceptable for the highly enantio- and diastereoselective aldol reaction with **3** (entries 14–16). The reactions of highly fluorinated benzaldehydes, such as C_6F_5CHO



Scheme 1

Table 1. Gold(I)-catalyzed asymmetric aldol reaction of **3**

Entry	R	Ligand	Yield [%]	<i>trans/cis</i>	ee of <i>trans</i> - 4 [%]
1	Me	2a	94	78/22	37
2	Me	2b	100	84/16	72
3	Me	2c	100	85/15	85
4	Me	2d	99	89/11	89
5	Me	2e	100	86/14	80
6	<i>i</i> -Pr	2c	99	99/1	94
7	<i>t</i> -Bu	2d	94	100/0	97
8	(<i>E</i>)- <i>n</i> -PrCH=CH	2d	85	87/13	92
9	(<i>E</i>)-MeCH=C(Me)	2a	89	91/9	95
10	Ph	2a	91	90/10	91
11	Ph	2d	93	95/5	95
12	Ph	2f	99	89/11	23
13	Ph	2g	80	68/32	0
14	2-MeOC ₆ H ₄	2d	98	92/8	92
15	4-ClC ₆ H ₄	2d	97	94/6	94
16	4-NO ₂ C ₆ H ₄	2d	80	83/17	86
17	2-thienyl	2a	90	95/5	33
18	2-furyl	2a	62	68/32	32
19	2-pyridyl	2a	45	75/25	6

and 2,3,5,6-F₄-C₆HCHO, form preferentially the corresponding *cis*-oxazolines with high enantiomeric excesses (86% and 90% ee, respectively), however, the enantiopurity of *trans*-oxazolines is fairly low (36% and 33% ee, respectively) and the ratios of *trans*- to *cis*-**4** are about 4/6 [13, 14]. Low enantioselectivities for the *trans*-oxazoline were observed in the aldol reactions of 2-heteroaromatic aldehydes, such as 2-thiophene-, 2-furan-, and 2-pyridinecarboxaldehyde (entries 17–19) [15].

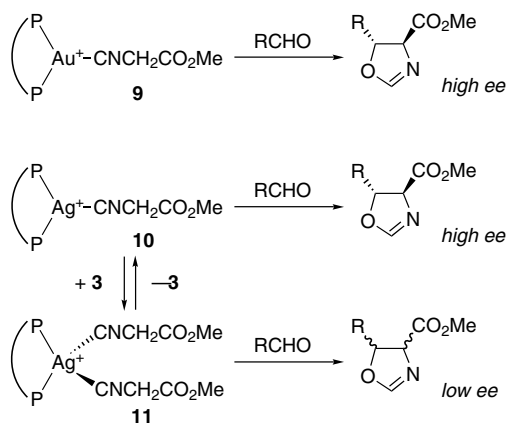
The *trans*-oxazolines with high enantiomeric excess can readily be converted to optically active *threo*-β-hydroxy-α-amino acids without epimerization by acid hydrolysis. Moreover, the aldol reaction was applied to the total synthesis of Cyclosporin's unusual amino acid MeBmt [16], and to the asymmetric synthesis of D-*threo*- and D-*erythro*-sphingosine, important membrane components [17]. The [substrate]/[catalyst] ratio can be raised to 10,000/1 without significant loss of the stereoselectivity in the reaction of **3** with 3,4-methylenedioxybenzaldehyde (91% ee, *trans/cis*=91/9), indicating that the gold-catalyzed aldol reaction may provide a practical process to produce optically active *threo*-β-hydroxy-α-amino acids [6].

Use of isocyanacetamide **5** instead of isocyanacetate **3** improves the enantioselectivity of the aldol reaction with acetaldehyde and primary alkyl aldehydes (R=Me: 99% ee, *trans/cis*=91/9, R=Et: 96% ee, *trans/cis*=95/5, R=*i*-Bu:

97% ee, *trans/cis*=94/6) [18]. A remarkable improvement in stereoselectivity attained by the use of **5** is observed for the aldol reactions with highly fluorinated benzaldehydes, which give the corresponding *trans*-oxazolines **6** with high enantio- and diastereoselectivity (80–91% ee, *trans/cis*=77/23 to 85/15) [14, 19]. Methyl 2-oxopropanoate also is a good electrophile for the asymmetric aldol reaction of **5**, producing 90% ee of *cis*-(4*S*,5*S*)-oxazoline (*cis/trans*=88/12) [20].

The asymmetric aldol reaction of the α -isocyano Weinreb amide **7** also proceeds with high enantio- and diastereoselectivity, yielding *trans*-oxazoline **8** [R=Me: 97% ee (*trans/cis*=95/5), R=*i*-Pr: 97% ee (*trans/cis*=98/2), R=Ph: 97% ee (*trans/cis*=98/2), R=(*E*)-MeCH=CH: 99% ee (*trans/cis*=97/3)] [21]. The oxazolines **8** can be transformed to optically active *N,O*-protected β -hydroxy- α -aminoaldehydes and ketones in high yield, which are useful chiral building blocks for the synthesis of highly functionalized unusual amino acids, amino polyols, and peptide mimics.

IR studies of the coordination chemistry of gold(I) and silver(I) coordinated with (*R*)-(*S*)-**2a** in the presence of **3** revealed a significant difference between these metals in the coordination number of the isocyanide to metal [22]. The tricoordinated gold(I) complex **9** coordinated with one isocyanide was observed without the formation of tetracoordinated species bearing two isocyanides, even in the presence of a large excess of isocyanide at 25 °C, while the silver complex is in equilibrium between the tricoordinated complex **10** and the tetracoordinated complex **11**, in the presence of one equivalent of **3** (Scheme 2). Consequently, it may be expected that the tricoordinated complexes **9** and **10** coordinated with two phosphorous atoms of the ligand and one isocyanide may be key intermediates for high enantioselectivity. Actually, slow addition, over 1 h, of isocyanide **3** to prevent the formation of species **11** enables the asymmetric aldol reaction with the AgClO₄/*(R)*-(*S*)-**2c** catalyst to give *trans*-oxazoline **4** with high enantiomeric excess (R=Ph: 80% ee, R=*i*-Pr: 90% ee), although the aldol reaction with **3** added in one portion gives only 37% ee (R=Ph) of *trans*-**4**.



Scheme 2

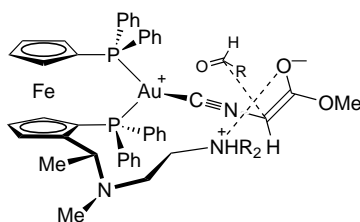


Fig. 1

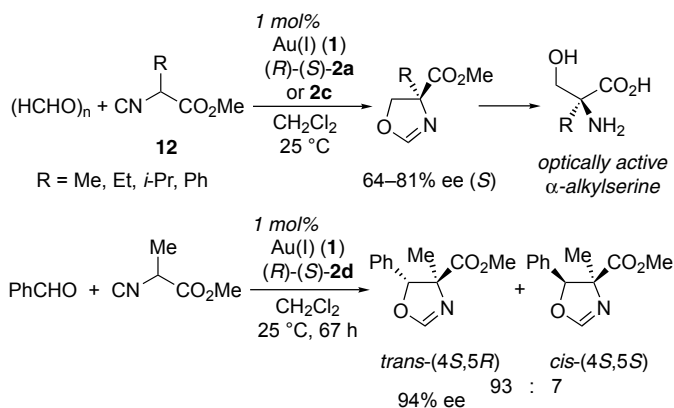
The high efficiency of the gold catalyst can be explained by a postulated transition state as shown in Fig. 1, where the terminal amino group of (*R*)-(*S*)-**2** abstracts one of the α -methylene protons of **3** activated by coordination to the gold cation, forming the ammonium enolate of the isocyanacetate [2]. Ionic interaction between the enolate anion and the ammonium cation seems to control the enantioface of the enolate reacting with aldehyde [23, 24]. The distance between the terminal amino group and the ferrocene moiety of **2a–e** will be crucially important for such conformational control. The pendant side chain tethered to **2** shields the *re*-face of the enolate, therefore, aldehydes approach the *si*-face preferentially. Such a conformation of the side chain was demonstrated by the structure of the AgOTf/(*R*)-(*S*)-**2a** complex coordinated with two molecules of **3** in a solution, which was determined by $^1\text{H}\{^1\text{H}\}$ NOE experiments [25].

Togni and Pastor reported that the combination of the carbon central chirality at ferrocenylmethyl position and the ferrocene planar chirality was also an important factor for the high enantioselectivity [26, 27]. Ferrocenylphosphine (*R*)-(*S*)-**2a**, which has *R*-central chirality along with *S*-planar chirality, attains high enantioselectivity for the aldol reaction with benzaldehyde to provide *trans*-(4*S*,5*R*)-**4**, while the diastereomeric (*S*)-(*S*)-**2a** gives much lower ee of *trans*-**4** (41% ee, *trans/cis*=84/16) with the *R*-configuration at the 4-position. NMR studies on (*R*)-(*S*)- and (*S*)-(*S*)-**2a** suggest that the directions of the aminoethyl side chains differ. The inversion of the central chirality of (*R*)-(*S*)-**2a** may bring about a conformational change from the transition state as shown in Fig. 1, so that aldehydes attack preferentially the *re*-face of the ammonium enolate of **3**.

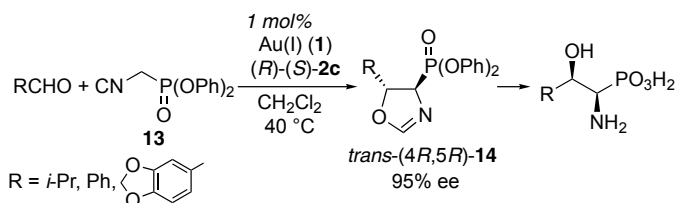
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Catalytic Asymmetric Aldol Reaction of α -Isocyanocarboxylates and Their Analogues

Gold(I)/ferrocenylphosphine **2a–d** complexes are applicable to asymmetric aldol reactions of α -alkyl substituted α -isocyanacetates **12**. Although the dependency of stereoselectivity on the structures of the substrates is fairly large, some combinations of **12** and aldehydes show high enantio- and diastereoselectivity (Scheme 3). The reaction with paraformaldehyde yields (*S*)-4-alkyl-2-oxazoline-4-carboxylates in 64 to 81% ee, which can be readily transformed to the



Scheme 3



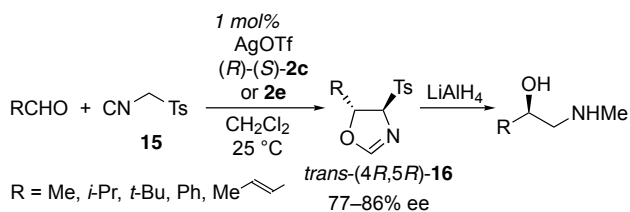
Scheme 4

corresponding optically active α -alkylserines, a class of biologically interesting compounds [23]. The combination of **12** with acetaldehyde or benzaldehyde gives the corresponding *trans*-oxazolines with high enantioselectivity, although the *trans*-selectivity is very low, except for the reaction of α -isocyanopropionate with benzaldehyde [24].

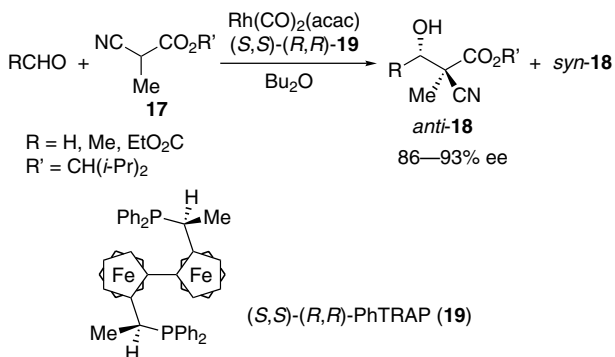
(Isocyanomethyl)phosphonate **13** reacts with aldehydes at 40 °C in the presence of gold(I)/(*R*)-(S)-**2c** to give 95% ee of *trans*-(4*R*,5*R*)-5-alkyl-2-oxazoline-4-phosphonates **14**, with no *cis*-isomer detectable by $^1\text{H-NMR}$ (Scheme 4) [28, 29]. The asymmetric reaction provides useful access to optically active (1-aminoalkyl)phosphonic acids, which are a class of biologically interesting phosphorous analogs of α -amino acids.

Interestingly, the aldol-type condensation of tosylmethyl isocyanide **15** with aldehydes is catalyzed by the silver(I)/ferrocenylphosphine **2c** or **2e** catalyst more selectively than it is catalyzed by the chiral gold catalyst (about 20% ee) under the standard reaction conditions (Scheme 5) [30]. Oxazoline **16** can be converted to optically active α -alkyl- β -(*N*-methylamino)ethanols by reduction with LiAlH_4 .

Recently, a rhodium(I)-catalyzed, highly enantioselective aldol reaction of the 2-cyanopropionate **17** has been achieved by the use of the *trans*-chelating



Scheme 5



Scheme 6

chiral diphosphine ligand (*S,S*)-(*R,R*)-PhTRAP (**19**), yielding the corresponding optically active *anti*-aldol **18** with *2S*-configuration (Scheme 6) [31].

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Chapter 29.3

Nitroaldol Reaction

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Keywords: Heterobimetallic lanthanoid catalysts, Asymmetric nitroaldol reaction, Henry reaction, Enantioselective and diastereoselective reactions, syn-Selectivity

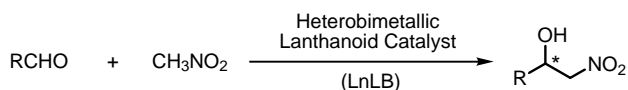
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1 Introduction

Just over 100 years ago, Henry et al. discovered the addition reaction of nitroalkanes to aldehydes with formation of compounds containing a β -nitroalcohol framework [1]. During the history of modern organic chemistry, the importance of these nitroalcohols as versatile intermediates in the synthesis of natural products and many other useful compounds has increased rapidly [2, 3, 4]. This was especially due to the easy transformation of the nitro group into other functional groups, e.g., amine derivatives. Consequently, up to now the nitroaldol reaction (Henry reaction) has developed to one of the most classical C-C bond forming processes [4]. However, in contrast to the high interest in the Henry reaction as a method to produce a wide pool of useful compounds, the lack of a synthetic tool for an enantioselective design prevented the application of the reaction to the challenging field of asymmetric synthesis for a long time.

First encouraging results for a stereoselective synthesis in general were reported by Seebach in 1982, who investigated the *syn/anti*-diastereoselectivity starting from achiral aldehydes and nitroalkanes [4, 5]. Barrett et al. examined the influence of nonchiral Lewis acids on the *syn/anti* diastereoselectivity [6]. Stoichiometric amounts of an enantiomerically pure aldehyde were used in a diastereoselective reaction with 3-nitropropionate by Hanessian et al. [7]. However, an approach to enantioselective synthesis of nitroalcohols via the route of the asymmetric Henry reaction could not be carried out until almost one hundred years after the discovery of the nitroaldol reaction.

In 1992, Shibasaki et al. [8] reported for the first time on the use of recently developed chiral heterobimetallic lanthanoid complexes (LnLB) as chiral catalysts in the catalytic asymmetric Henry reaction (Scheme 1). In the following sections, this efficient concept of an asymmetric nitroaldol reaction, its scope and limitations, and its applications to complex stereoselective synthetic topics are described.

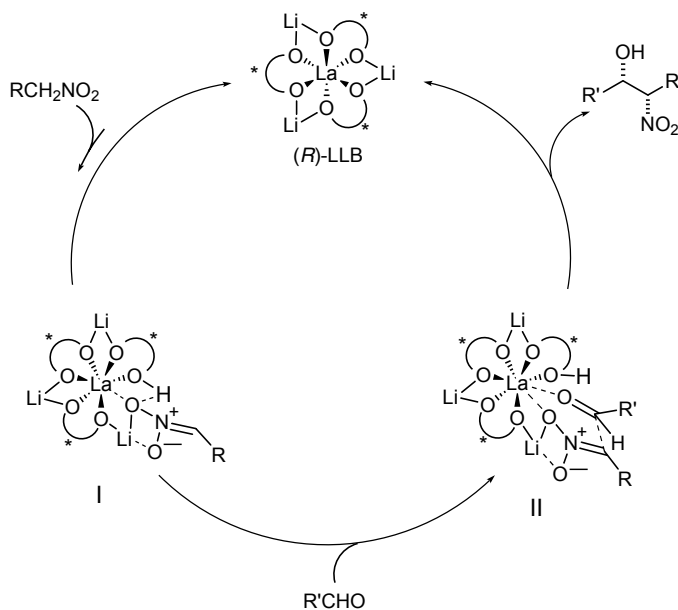


Scheme 1. Catalytic asymmetric nitroaldol reaction promoted by heterobimetallic lanthanoid catalysis LnLB

2 Mechanism

The proposed mechanism for the asymmetric nitroaldol reaction catalyzed by heterobimetallic lanthanoid complexes is shown in Scheme 2 [9]. In the initial step, the nitroalkane component is deprotonated and the resulting lithium nitronate coordinates to the lanthanoid complex under formation of the intermediate I [10]. Subsequent addition of the aldehyde by coordination of the C=O double bond to the lanthanoid(III) ionic center leads to intermediate II, in which the carbonyl function should be attacked by the nitronate via a six-membered transition state (in an asymmetric environment). A proton exchange reaction step will then generate the desired optically active nitroalkanol adduct with regeneration of the “free” rare earth complex LnLB.

The same basic principle of this catalytic cycle with slight modifications concerning the structure of several intermediates can also be proposed when using the improved, second generation catalysts of the LnLB type [11]. The Henry reaction with this type of catalysts together with detailed mechanistic considerations will be described in section 6.



Scheme 2. A possible mechanism for catalytic asymmetric nitroaldol reactions

3

The Catalytic Concept: Catalyst Design and Development of an Efficient Catalysis in Model Reactions

3.1

The First Steps and Applications in Model Reactions

The first promising investigations on the asymmetric nitroaldol reaction showed that this reaction proceeded efficiently in the presence of a catalytic amount of a chiral rare earth metal complex using optically active BINOL as a bidentate asymmetric ligand [8]. In contrast, the use of less acidic bidentate asymmetric diols as ligands led to a lack of asymmetric induction due to an undesired exchange of the asymmetric ligand for (acidic) nitromethane. The chiral BINOL based catalyst was prepared starting from anhydrous LaCl_3 and an equimolar amount of the dialkali metal salt of BINOL in the presence of a small amount of water [12].

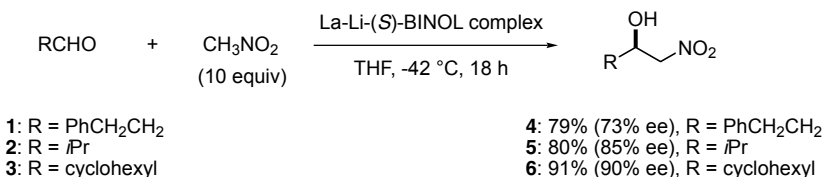
By using the catalyst prepared as described above, the first example of a catalytic asymmetric nitroaldol reaction was realized. The results are summarized in Scheme 3. Starting from prochiral aldehydes **1** to **3**, the desired products **4** to **6** were obtained in good chemical yields and with enantioselectivities up to 90% ee [8]. The amount of the catalyst is not shown in Scheme 3 due to the unknown structure of the catalyst (at this time).

3.2

Structural Requirements for an Efficient Catalysis

Investigations concerning the influence of the rare earth metal component showed pronounced differences both in the reactivity and in the enantioselectivity among the various rare earth metals used [13]. When benzaldehyde and nitromethane were used as starting materials, the corresponding Eu complex gave **7** in 72% ee (91%) in contrast to 37% ee (81%) in the case of the La complex (-40°C , 40 h). The unique relationship between the ionic radii of rare earth metals and the enantioselectivities of several nitroaldols **4**, **6**, **7** is depicted in Fig. 1.

Consequently, small changes in the structure of the catalyst (ca. 0.1 Å in ionic radius of the rare earth cation) cause drastic changes in the optical purity of the produced nitroaldols. Although in general nitroaldol reactions are regarded as



Scheme 3. The first catalytic asymmetric nitroaldol reaction catalyzed by chiral lanthanoid complexes

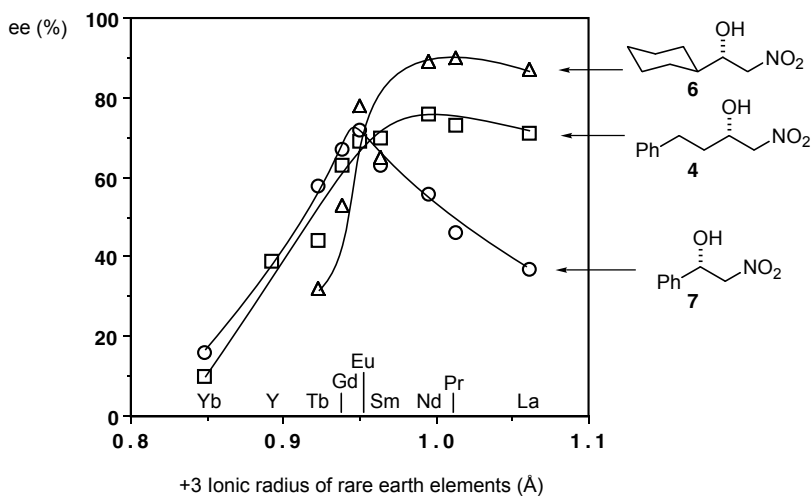


Fig. 1. Effects of the ionic radii of rare earth elements on the enantioselectivity

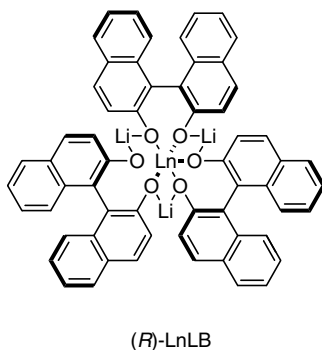


Fig. 2. The structure of (R)-LnLB

equilibrium processes, in the Ln-BINOL complex catalyzed asymmetric nitroaldol reactions no detectable retro-nitroaldol reaction was observed.

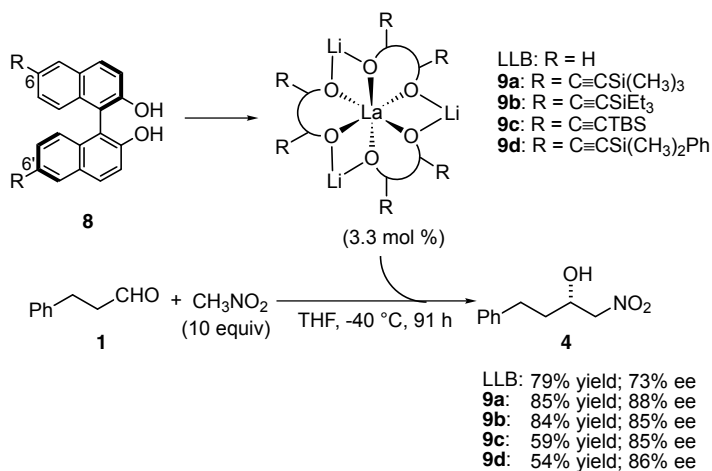
A breakthrough in the catalyst design and development of improved catalytic systems for the Henry reaction was achieved by the clarification of the catalyst structure. According to LDI-mass spectrometric investigations, the structure of the heterobimetallic complex LnLB consists of one lanthanoid, three lithiums, and three BINOL moieties (Fig. 2) [14, 15, 16]. The oligomeric structure of the catalyst in the reaction mixture was supported by a slightly positive asymmetric amplification [12, 17, 18, 19]. Thus, the LnLi_3 tris(binaphthoxide) complex (LnLB) appeared to be an effective asymmetric catalyst for nitroaldol reactions. Having succeeded in determining the structure of the LnLB complex, the conditions for

the preparation of LLB [the abbreviation LLB is used in case of lanthanum (La) as the lanthanoid component (Ln)] were further optimized with establishment of two efficient procedures for preparation, starting from $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{La}(\text{O}-i\text{-Pr})_3$, respectively [20]. On preparing the catalyst from $\text{La}(\text{O}-i\text{-Pr})_3$, it is interesting to note that the addition of 1 equiv of water to LLB was found to improve the catalyst's activity [14].

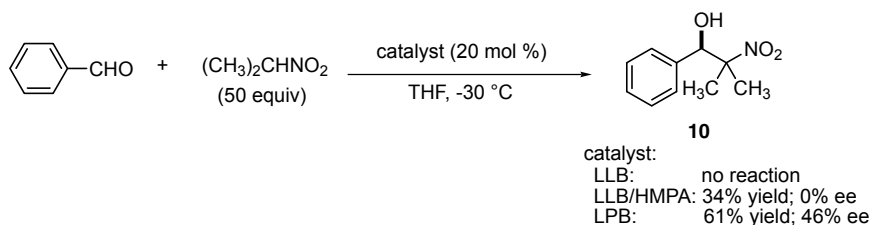
In addition to the early results of the general and effective catalytic asymmetric nitroaldol reaction (Scheme 3), which proceeds efficiently in the presence of 3.3 mol % of LLB, the knowledge of the structure of the LnLB complexes led to an extension of this catalytic method to a wide range of further applications.

However, structural modification of the BINOL ligand system also plays an important role with regard to stereoselection in the asymmetric Henry reaction. Improved enantioselectivities were obtained using a number of (*R*)-BINOL derivatives **8** (3 mol equiv) in which the 6,6'-positions were substituted [21]. Their utility as asymmetric catalysts was assessed using the nitroaldol reaction of nitromethane with hydrocinnamaldehyde **1**. Enantioselectivities up to 88% ee accompanied by chemical yields up to 85% were obtained using 3.3 mol % of various catalysts **9** and 10 equiv of nitromethane (-40°C , 91 h) (Scheme 4).

In conclusion, surprisingly the substitution at the 6,6'-positions of BINOL proved to be effective in obtaining superior asymmetric catalysts, whereas the use of complexes derived from 3,3'-disubstituted BINOL derivatives [22, 23] gave racemic **4** while the BIPOL derived catalyst [24] gave **4** in only 39% ee. The reason for the positive effect of 6,6'-substituents on BINOL might be that the introduction of 6,6'-bis(trialkylsilyl)ethynyl substituents completely suppresses undesired ligand exchange between nitroalkane and BINOL, whereas this appears to occur in the case of LLB (albeit in only small amounts) [9, 25].



Scheme 4. Catalytic asymmetric nitroaldol reactions promoted by various LLB type complexes



Scheme 5. Catalytic asymmetric nitroaldol reactions using 2-nitropropanol

Recently, Okamoto et al. showed that the reactivity and selectivity also depends on the alkali metal component in the heterobimetallic catalysts [26]. Using the bulkier 2-nitropropane as starting material in a model reaction with benzaldehyde, almost no reaction occurred at $-30\text{ }^{\circ}\text{C}$ in the presence of the lithium containing catalyst LLB, whereas higher temperatures as well as the use of HMPA as a co-solvent led to racemic product **10**. However, in the presence of the corresponding potassium containing catalyst LPB, which has been developed and applied previously by Shibasaki et al. [27, 28], the desired reaction to **10** proceeded with 46% ee in 61% yield (Scheme 5).

In contrast, the use of LLB was connected with superior enantioselectivity and chemical yield (compared to LPB) when replacing 2-nitropropane by the less bulkier nitromethane (LLB: 91% yield; 48% ee; LPB: 71% yield; 6% ee) [26].

4

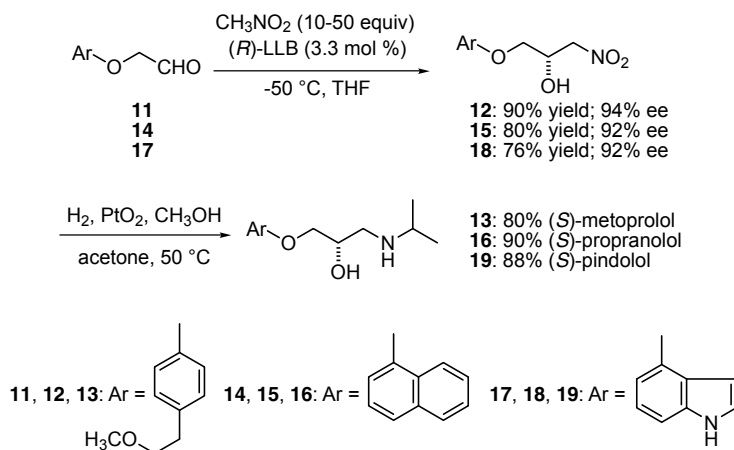
Application of LnLB Catalysis I: Enantioselective Construction of Nitroaldol Adducts with One Stereogenic Center

4.1

Asymmetric Synthesis of β -Blockers

A first example of an efficient application of the LnLB catalyzed nitroaldol reaction as key step in a multi-step syntheses was presented by Shibasaki et al. in the asymmetric approach to three kinds of optically active β -blockers **13**, **16**, and **19** (Scheme 6) [13, 29, 30, 31].

Using **17** and 10 mol equiv of nitromethane at $-50\text{ }^{\circ}\text{C}$ in the presence of 3.3 mol % of (*R*)-LLB catalyst, a 76% yield of nitroaldol **18** in 92% ee was obtained. Reductive alkylation of the nitroaldol **18** to **19** was accomplished in 88% yield by a PtO_2 catalyzed hydrogenation in the presence of 5 mol equiv of acetone in methanol. Thus, (*S*)-(-)-pindolol **19** was synthesized in only four steps from 4-hydroxyindole [30]. Interestingly, the nitroaldols **12**, **15**, and **18** were found to have (*S*)-configuration when (*R*)-LLB was used. The nitronates thus appear to react preferentially with the *Si* face of the aldehydes, in the opposite sense to the enantiofacial selectivity which might have been expected on the basis of the previous results (cf. Scheme 3). These results suggested that the presence of



Scheme 6. Catalytic asymmetric synthesis of β -blockers using (*R*)-LLB as a catalyst

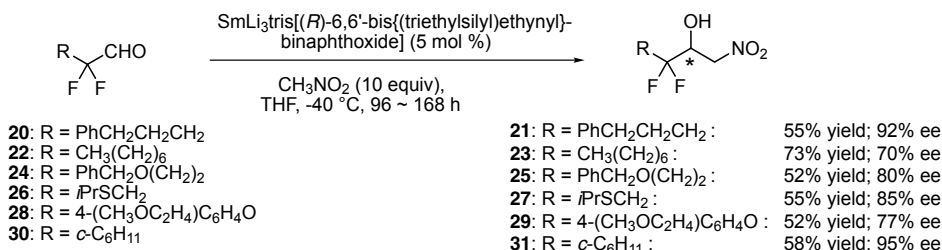
an oxygen atom at the β -position had a pronounced influence on the enantiofacial selectivity.

4.2

Asymmetric Synthesis of Fluorine-Containing Nitroaldol Adducts

The LLB type catalysts were also successfully applied in the asymmetric nitroaldol reaction of the quite unreactive α,α -difluoro aldehydes. In general, catalytic asymmetric syntheses of fluorine-containing compounds are rather difficult [32]. However, catalytic asymmetric nitroaldol reaction of a broad variety of α,α -difluoro aldehydes **20**, **22**, **24**, **26**, **28**, and **30** proceeded satisfactorily when using the heterobimetallic asymmetric catalysts with modified, 6,6'-disubstituted BINOL ligands [33] (Scheme 7). The best results were obtained with the samarium(III) complex (5 mol %) generated from 6, 6'-bis{(triethylsilyl)ethynyl}BINOL with enantioselectivities up to 95% ee.

The (*S*)-configuration of the nitroaldol adduct **21** showed that the nitronate reacted preferentially on the *Si* face of aldehyde in the presence of (*R*)-LLB (20 mol %; 74% yield; 55% ee). In previous examples (*R*)-LLB generally caused the attack of the nitronate with *Re* face preference on aldehydes. Therefore, it is noteworthy that the enantiotopic face selection for α,α -difluoro aldehydes is the reverse to that for nonfluorinated aldehydes. The stereoselectivity for α,α -difluoro aldehydes is identical with that of β -oxa-aldehydes, suggesting that the fluorine atoms at the α -position have a great influence on enantioface selection.



Scheme 7. Catalytic asymmetric nitroaldol reactions of α,α -difluoro aldehydes

5

Application of LnLB Catalysis II: Enantioselective Construction of Nitroaldol Adducts with Two or More Stereogenic Centers

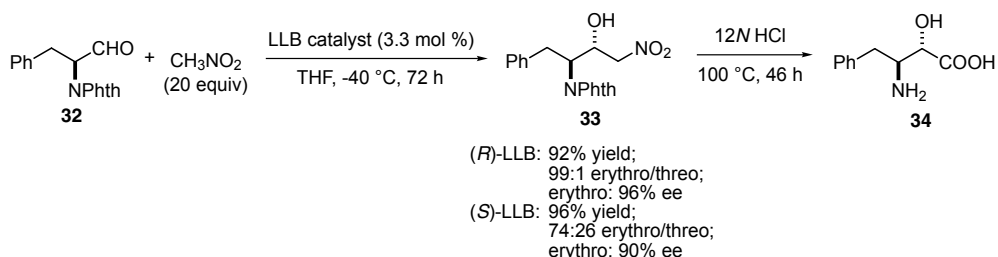
5.1

Diastereoselective Catalytic Nitroaldol Reaction Starting from Chiral Aldehydes

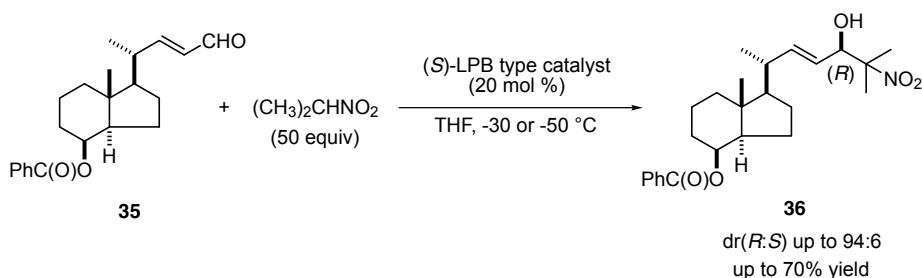
The diastereoselective catalytic nitroaldol reaction has been investigated starting from optically active α -amino aldehydes, e.g., **32**. The adducts of type **33** are attractive intermediates for the synthesis of unnatural *erythro*-amino-2-hydroxy acids, which are important components of several biologically active compounds. For example, the promising HIV-protease inhibitor KNI-272 [34, 35] contains (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (*erythro*-AHPA, **34**) as a subunit. A conventional diastereoselective synthesis in the presence of achiral bases led to limited internal induction with *erythro*/*threo* ratios of **33** in the range between 62:38 and 74:26. The use of the achiral complex La(*O-i*-Pr)₃ gave the product **33** in an 89:11 *erythro*/*threo* ratio [36]. However, this limitation of diastereoselection has been overcome by using catalytic amounts of lithium-containing heterobimetallic complexes LnLB (Scheme 8).

In the presence of (*R*)-LLB (3.3 mol %), the treatment of *N*-phthaloyl-L-phenylalanyl **32** with nitromethane at -40 °C gave practically a single stereoisomer of (2*R*,3*S*)-2-hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane **33** in 92% yield (>99:1 *erythro*-selectivity) [36]. The enantiofacial selectivity for the C-2 hydroxy group of **33** agreed with results previously observed in enantioselective nitroaldol reactions for non- β -oxa-aldehydes using LLB. Interestingly, reaction of the (*S*)-aldehyde **32** with nitromethane, using the (*S*)-LLB complex as a catalyst, led to a reduced diastereo- and enantioselectivity (96% yield; *erythro*/*threo* 74:26; 90% ee (*erythro*)). The conversion of the nitroaldol adduct **33** into **34** was achieved in a one pot process (80% yield). Investigations to study use of this type of diastereoselective asymmetric nitroaldol reaction on an industrial scale are now in progress [37].

A further example of a diastereoselective nitroaldol reaction using heterobimetallic lanthanoid complexes as catalysts was recently reported by Okamoto et



Scheme 8. Diastereoselective nitroaldol reaction as key step in the synthesis of *erythro*-AHPA **34**



Scheme 9. Catalytic diastereoselective nitroaldol reaction promoted by the LPB type catalyst

al. [26] in connection with a novel approach to $1\alpha,24(R)$ -dihydroxyvitamin D_3 [38], which is an active analogue of vitamin D_3 and induces keratinocyte differentiation [39, 40]. Here, several rare earth metal complexes were used to catalyze the nitroaldol reaction of the C/D-ring 24-aldehyde precursor **35** with 2-nitropropane (Scheme 9). In accordance with the results of the corresponding model reaction with benzaldehyde, when using 2-nitropropane as starting material (see Chapter 3.2) the best results were achieved in the presence of the potassium containing lanthanoid complex of type LPB with (*S*)-6,6'-((triethylsilyl)ethynyl)BINOL as ligand. The desired nitroaldol adduct **36** was formed in yields up to 71% and with diastereomeric ratios (dr) up to 94:6 (Scheme 9). It is noteworthy that a conjugate double bond in the aldehyde component was needed for good asymmetric induction.

The obtained nitroaldol adduct **36** was easily converted into a synthetic intermediate of $1\alpha,24(R)$ -dihydroxyvitamin D_3 by a denitration reaction using 2,2'-azobisisobutyronitrile (AIBN) and Bu_3SnH [26].

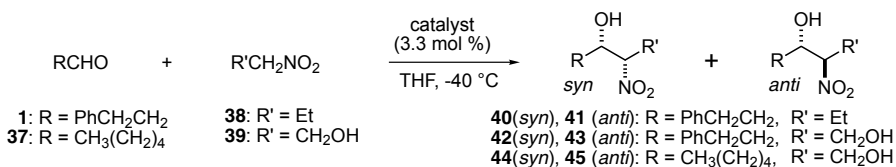
5.2

Diastereoselective and Enantioselective Synthesis: Asymmetric Construction of Two New Stereogenic Centers Starting from Prochiral Compounds

LnLB type catalysts are also able to promote diastereoselective and enantioselective nitroaldol reactions starting from prochiral materials. In preliminary work, LLB gave unsatisfactory results in terms of both diastereoselectivity (*syn/anti* ratio 63:37 to 77:23) and enantioselectivity (<78% ee) [29]. However, an effective asymmetric induction was obtained in the presence of LLB type catalysts **9** containing 6,6'-substituted BINOL.

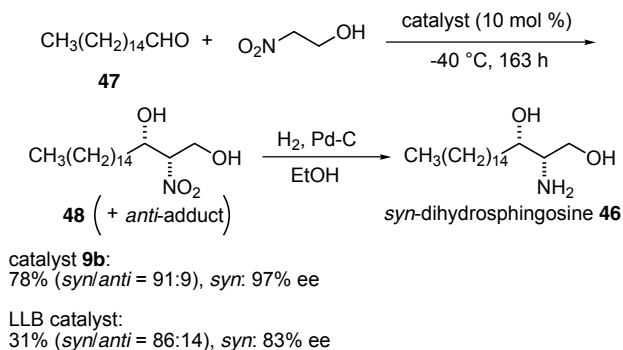
The application of the catalysts of type **9** (3.3 mol %) to diastereoselective nitroaldol reactions led to high *syn*-selectivity and enantioselectivity [41]. In all cases, much higher *syn*-selectivity (*syn/anti* ratio up to 94:6) and enantioselectivity (up to 97% ee) were obtained using the catalysts with 6,6'-substituted BINOL instead of LLB (representative results are given in Scheme 10). The optical purities of the minor *anti*-adducts **41**, **43**, and **45** were lower than those of the *syn*-adducts **40**, **42**, and **44**, indicating that the former were not generated by epimerization of the nitro group. In fact, treatment of the *syn*-adducts with catalysts such as LLB and its derivatives resulted in near-quantitative recovery of the starting materials with unchanged optical purities.

The *syn*-selective asymmetric nitroaldol reaction was successfully applied to the catalytic asymmetric synthesis of *threo*-dihydroshingosine **46**, which elicits a variety of cellular responses by inhibiting protein kinase C (Scheme 11) [42]. Nitroaldol reaction of hexadecanal **47** with 3 equiv of nitroethanol catalyzed by **9b** gave the corresponding nitroaldol adduct **48** in high *syn*-selectivity (91:9) and 78% yield, with the *syn*-adduct **48** being obtained with up to 97% ee [41]. In this case, under similar conditions the LLB-catalyzed reaction proceeded only



Reagent	Catalyst	Time [h]	Product	Yield [%]	<i>syn/anti</i>	ee (<i>syn</i>) [%]
1+38	LLB	138	40+41	89	85:15	87
1+38	9b	138	40+41	89	93:7	95
1+39	LLB	111	42+43	62	84:16	66
1+39	9b	111	42+43	97	92:8	97
37+39	LLB	93	44+45	79	87:13	78
37+39	9b	93	44+45	96	92:8	95

Scheme 10. Diastereoselective and enantioselective nitroaldol reaction



Scheme 11. Catalytic asymmetric synthesis of *syn*-dihydrosphingosine

slowly to give a 86:14 ratio of the *syn* and *anti*-adducts in 31% yield (with lower optical purity: 83% ee). The hydrogenation of **48** in the presence of 10% Pd on charcoal afforded *threo*-dihydrosphingosine **46** in 71% yield.

5.3

Tandem Inter-Intramolecular Catalytic Asymmetric Nitroaldol Reaction

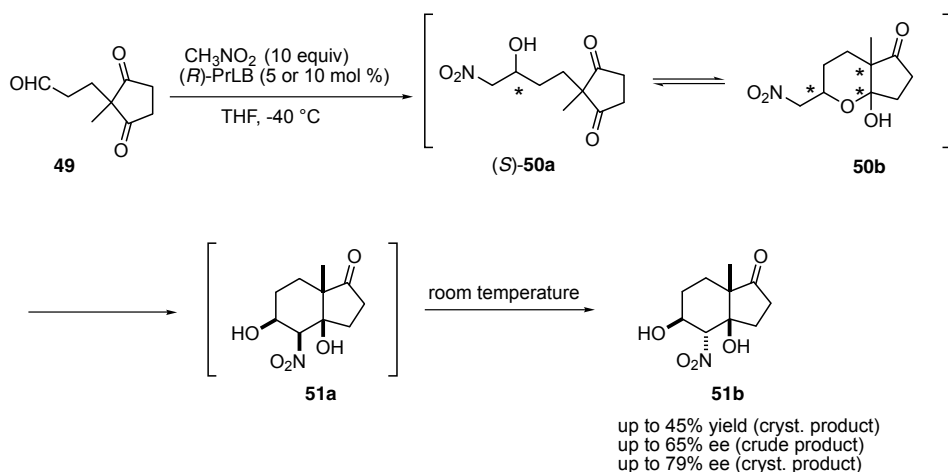
The asymmetric catalytic nitroaldol reaction was also successfully extended to the field of asymmetric tandem reactions [43]. Tandem reactions are especially useful to construct compounds with several chiral centers in a one-pot process starting from simple achiral components in the presence of a chiral catalyst. The first tandem inter-intramolecular catalytic asymmetric nitroaldol reaction was realized in the reaction of the cyclopentanedione derivative **49** with nitromethane using a catalytic amount of LnLB according to Scheme 12 [43].

In addition to temperature effects, the optical purity of the product **51b** strongly depends on the lanthanoid center ion. In the presence of the (*R*)-PrLB complex (5 mol %) as the most efficient catalyst, the hexahydro-1-indanone derivative **51b** was formed with enantioselectivities up to 65% ee [for comparison: LLB (10 mol %; -20 °C): 39% ee; YbLB (10 mol %; -20 °C): 7% ee] [43]. After crystallization, **51b** was isolated with up to 79% ee and 41% yield.

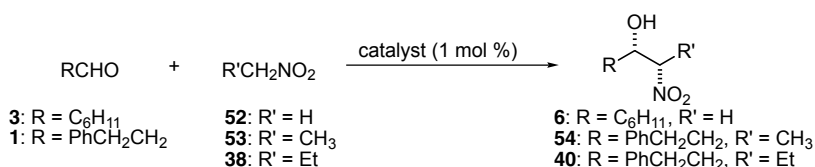
6

Recent Extensions and Improvements of the Catalytic Concept: The Second Generation of LnLB Catalysts

The catalytic asymmetric nitroaldol reactions promoted by LLB or its derivatives require at least 3.3 mol % of asymmetric catalysts for efficient conversion. However, even in the case of 3.3 mol % of catalyst, reactions are rather slow. Attempts were made to reduce the required mol % of asymmetric catalysts and accelerate the reactions, which led to a second-generation of heterobimetallic lan-



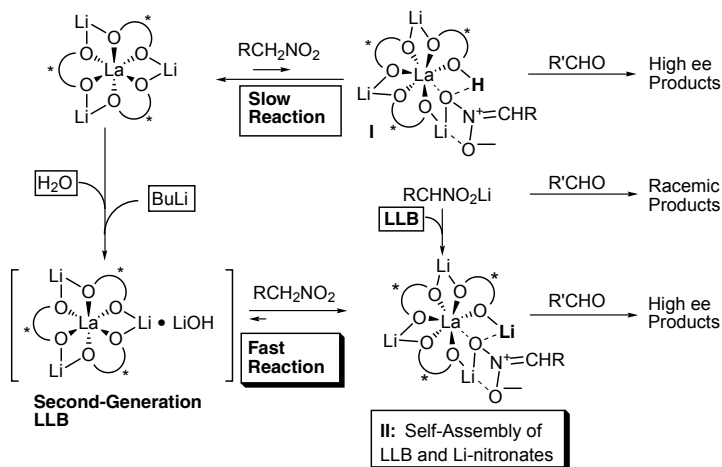
Scheme 12. Tandem inter-intramolecular catalytic asymmetric nitroaldol reaction



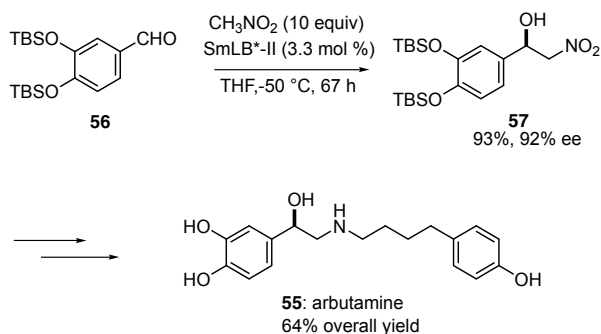
Reagent	Catalyst	Time [h]	Temp. [°C]	Product	Yield [%]	syn/anti	ee (syn) [%]
3+52	LLB	24	-50	6	5.6	-	88
3+52	LLB-II	24	-50	6	73	-	89
1+53	9b	113	-30	54	25	70:30	62
1+53	9b-II	113	-30	54	83	89:11	94
1+38	9b	166	-40	40	Trace	-	-
1+38	9b-II	166	-40	40	84	95:5	95

Scheme 13. Comparison of the catalytic activity of LLB and second-generation LLB (LLB-II) or **9b** and **9b-II**. [LLB-II: LLB+H₂O (1 mol equiv)+BuLi (0.9 mol equiv); **9b-II**: **9b**+H₂O (1 mol equiv)+BuLi (0.9 mol equiv)]

thanoid catalysts (LLB-II), prepared from LLB, 1 mol equiv of H₂O, and 0.9 mol equiv of butyllithium. The use of only 1 mol % of LLB-II efficiently promoted catalytic asymmetric nitroaldol reactions and additionally LLB-II (3.3 mol %) accelerated the catalytic asymmetric nitroaldol reaction [11]. A comparison of the efficiency of LLB and the second-generation LLB catalysts is given in Scheme 13.



Scheme 14. Proposed mechanism of catalytic asymmetric nitroaldol reaction promoted by LLB, LLB-II or LLB-Li-nitronate



Scheme 15. A catalytic asymmetric synthesis of arbutamine. [SmLB*⁻-II=SmLi₃tris((*R*)-6,6'-bis(trimethylsilylethynyl)binaphthoxide)+H₂O (1.0 mol equiv to Sm)+BuLi (0.6 mol equiv to Sm)]

The structure of LLB-II has not yet been unequivocally determined. However, it appears that it is a complex of LLB and LiOH. A proposed reaction course for the improved catalytic asymmetric nitroaldol reaction is shown in Scheme 14.

It is also noteworthy that treatment of the lithium nitronate (0.9 mol %), generated from nitropropane and butyllithium, with **9b** (1 mol %), **1**, and nitropropane **38** under similar conditions as described above gave comparable results (59% yield, *syn/anti* ratio 94:6, 94% ee), suggesting the presence of a heteropolymetallic intermediate **II** as shown in Scheme 14.

Using a second-generation LnLB catalyst consisting of 6,6'-bis(trimethylsilyl)ethynyl}BINOL and Sm, an efficient catalytic asymmetric synthesis of arbutamine **55**, a useful β -agonist [44, 45], was achieved (Scheme 15) [46]. In the key step, the nitroaldol adduct **57** was formed in 93% yield and with 92% ee [46].

7

Summary and Outlook

From its recent beginnings in 1992, Shibasaki et al. have developed the catalytic asymmetric nitroaldol reaction (Henry reaction) into a highly efficient synthetic method for the stereoselective synthesis of nitroalkanols [9]. Alkali metal-containing heterobimetallic lanthanoid complexes were applied as catalysts. Using these catalysts, a broad variety of nitroalkanol derivatives containing one, two, or more stereogenic centers has been constructed in a highly stereoselective manner. In the mean time, this new and innovative catalytic concept has been applied to the synthesis of several biologically active and pharmaceutically interesting compounds (or their precursors). Very recently, the asymmetric nitroaldol reaction catalyzed by heterobimetallic complexes was successfully carried out in 100 g scale (with 90% ee) [47]. Further extension to an industrial scale (up to 15 kg) is now in progress [47].

Concerning future work, an improvement might be the extension of the asymmetric catalytic nitroaldol reaction to the field of solid-support synthesis. An interesting contribution concerning the use of dendritic catalysts in the Henry reaction was reported very recently by Cossio et al. [48], who demonstrated that dendrimers based on achiral triethanolamine exhibit catalytic properties. Several nitroalkanols were synthesized with *syn/anti* ratio up to 2:1 (racemic *syn*- and *anti*-products). The design of enantiomerically pure dendrimers and their application to the field of asymmetric catalytic nitroaldol reaction should be of high interest.

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Chapter 30

Addition of Acyl Carbanion Equivalents to Carbonyl Groups and Enones

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Keywords: Nucleophilic acylation, triazolium salts, thiazolium salts, benzoin reaction, acyloin reaction, Stetter reaction

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1 Introduction

In the course of evolution, nature has devised a multitude of enzymes which are capable of stereoselectively forming C–C bonds *in vivo*. Depending on the kind of substrate employed, nucleophilic acylation reactions are accomplished in nature by means of different lyases such as transketolases and pyruvate decarboxylases, which all require thiamine (1) as coenzyme [1, 2, 3, 4, 5, 6]. For the synthetic organic chemist, asymmetric catalytic C–C bond formation reactions, in

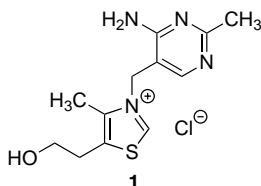
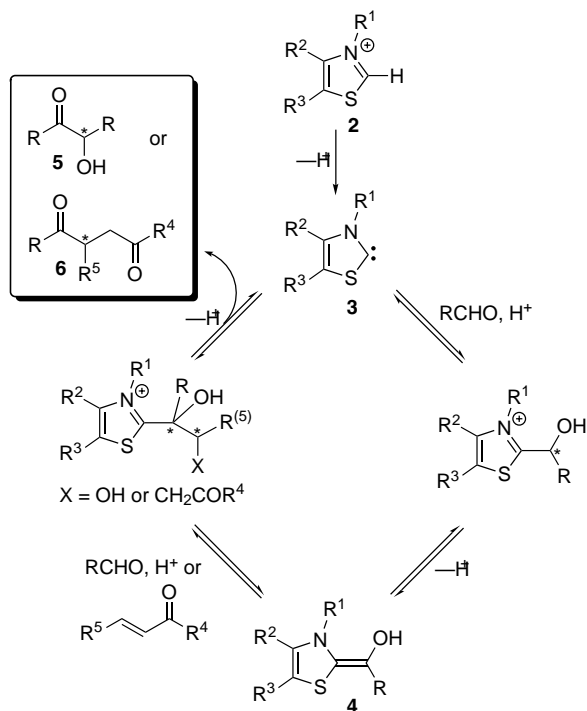


Fig. 1

general, constitute tools of prime importance for the efficient and straightforward stereoselective synthesis of chiral building blocks [7, 8, 9, 10, 11, 12]. However, only a few methods have been published that allow the asymmetric catalytic nucleophilic acylation of carbonyl compounds or activated double bonds leading to the corresponding enantiomerically pure or enriched 1,2- and 1,4-bifunctionalized compounds. All approaches described so far mimic the catalytic systems involving the naturally occurring coenzyme thiamine (1), Fig. 1.

2 The Mechanism of Heterazolium Catalysis

The basic mechanism of heterazolium catalysis was elucidated by Breslow et al. [13] in 1958 in the course of their pioneering work (Scheme 1). First the heterazolium ion **2** used as the catalyst is deprotonated affording the corresponding nucleophilic carbene **3** which represents the actual catalytically active species. This species attacks the carbonyl function of an aldehyde leading to the hydroxy-enamine-type Breslow intermediate **4**, which subsequently functions as the nucleophilic acylation reagent (d^1 -synthon). Reaction with an electrophilic substrate such as a second aldehyde molecule or Michael acceptors yields the bifunctional products **5** or **6**, respectively, and the original carbene catalyst **3**.



Scheme 1

The catalytic cycle was recently challenged by López-Calahorra et al. [14, 15, 16, 17, 18, 19, 20], who claimed that the catalysis proceeds via the corresponding dimers of the aforementioned nucleophilic carbenes leading to dimeric intermediates. However, recent investigations by Breslow et al. [21, 22] and others [23] seem to confirm the original proposal by Breslow.

3 Nucleophilic Acylation of Aldehydes

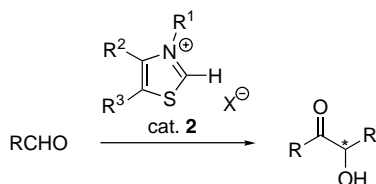
The nucleophilic acylation of aldehydes is a short and efficient pathway to 1,2-bifunctionalized building blocks. This reaction type is extremely valuable, since it allows the catalytic formation of α -hydroxy ketones, which are important synthetic intermediates in organic chemistry.

In general, the starting materials, i.e. the aldehydes, are readily accessible or even commercially available. Despite this synthetic significance, only a few catalytic asymmetric variants for the nucleophilic acylation of aldehydes have been reported.

3.1 Thiazolium Catalysts in the Nucleophilic Acylation of Aldehydes

The first investigations in the field of heterazolium-catalyzed asymmetric nucleophilic acylation go back to Sheehan et al. (Scheme 2) [24], who tried to devise an asymmetric variant of the benzoin reaction, which was known to be catalyzed by thiazolium salts from the work of Ukai et al. [25, 26] and of Mizuhara et al. [27].

Sheehan et al. [28] developed several chiral thiazolium salts, which were shown to catalyze the formation of benzoin with low to moderate enantiomeric excesses, up to 52% in the case of a 1-naphthylethyl-substituted catalyst. However, the yields were very low (6%), leading to the consumption of a stoichiometric amount of the catalyst (TTN < 1) which limited the applicability of the reaction. Tagaki et al. [29] reported chiral menthyl-substituted thiazolium salts, the best of which catalyzed the formation of benzoin with enantiomeric excesses up to 35% and slightly improved yields of 20% (TTN 4) by carrying out the reaction in a micellar two-phase system. Zhao et al. [30] combined the superior catalyst concept of Sheehan et al. with the favorable micellar reaction conditions of



Scheme 2

Tagaki et al. and obtained benzoin with enantiomeric excesses of up to 57% and yields ranging from 20 to 30% using 1-naphthylethyl-based catalysts. For some catalysts, a critical micelle concentration could be observed in several buffer solutions, which was understood as evidence of micelle formation being involved in the catalytic process. López-Calahorra et al. [31] introduced bridged *bisthiazolium* salts to the catalytic benzoin reaction, however, the enantiomeric excesses found were quite low (ee up to 26%, yields up to 21%).

In general, the unsatisfactory yields obtained in the asymmetric variants of the thiazolium-catalyzed benzoin reaction are probably caused by the low inherent activity of the thiazolium salts, which is aggravated by the steric bulk accumulated in the neighborhood of the active site.

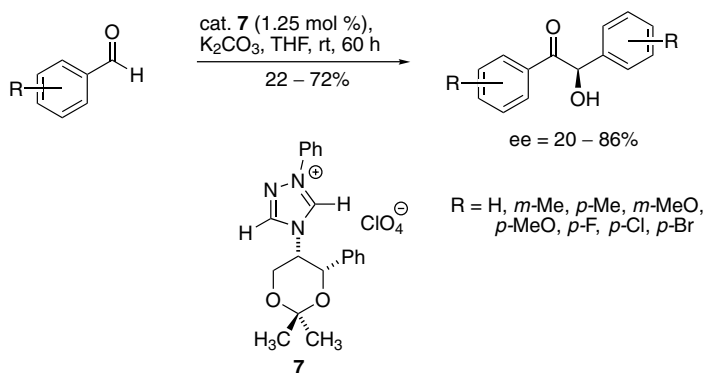
3.2

Triazolium Catalysts in the Nucleophilic Acylation of Aldehydes

Recent work by Teles et al. [32] has shown that triazolium salts are highly active catalysts for the condensation of formaldehyde affording glycolaldehyde (formoin reaction). In terms of activity, these catalysts proved considerably superior to the thiazolium salts previously used for this transformation. Investigations into the mechanism have shown that the catalytic cycle corresponds to the mechanism proposed by Breslow [32].

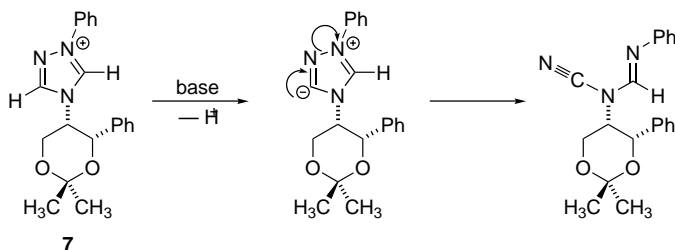
Accordingly, our research group [33] synthesized a variety of chiral triazolium salts and examined their ability to catalyze the benzoin reaction. However, the enantiomeric excesses and catalytic activities proved to vary strongly with slight structural changes in the substitution pattern of the triazolium system.

The catalyst 7, which is accessible via bisformylation of phenylhydrazine [34] and cyclization to the oxadiazolium salt [35] with subsequent ring opening ring closure substitution [36] using (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan, yielded benzoin with 75% ee and a satisfactory yield of 66% using a significantly reduced catalyst amount of 1.25 mol % allowing total turnover numbers over 50 (Scheme 3). This represents an increase in activity of almost two orders of magnitude compared with those results obtained with chiral thiazolium salts. We subsequently extended the applicability of this new catalyst type to other aromatic substrates to give the respective aromatic α -hydroxy ketones. This illustrates that electron-rich aldehydes generally furnish the respective benzoin in moderate to good enantiomeric excesses up to 86%, whereas the asymmetric inductions achieved with electron-deficient aldehydes are significantly lower. Apparently, deactivation of the aldehyde function leads to lower catalytic activity but higher enantioselectivities. Accordingly, the highest enantioselectivities of 86% (and the lowest yields) were obtained with *p*-methoxybenzaldehyde, in which the carbonyl function is considerably deactivated due to the +M effect of the methoxy group. All in all, this procedure has been routinely used to prepare different benzoin on a multigram scale. However, despite the significant improvement of the enantioselectivities and catalyst activities achieved upon use



R^1	R^2	Yield [%]	ee [%]
H	H	66	75
MeO	H	41	66
H	MeO	22	86
Me	H	54	76
H	Me	46	82
H	F	48	44
H	Cl	51	29
H	Br	72	20

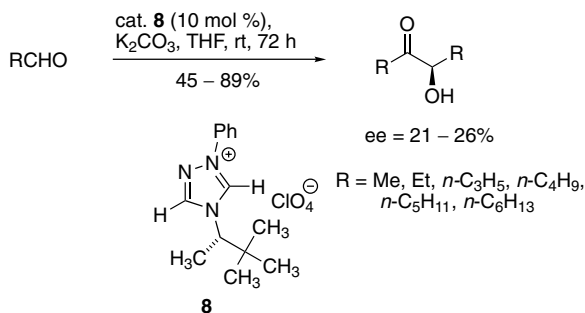
Scheme 3



Scheme 4

of triazolium salt **7**, the method does not yet present a fully satisfactory approach to the asymmetric synthesis of α -hydroxy ketones.

The major deactivation pathway of the catalyst **7** in the course of the catalytic cycle proceeds via deprotonation at C-3, since the proton at C-3 is almost as acidic as that one at C-5. After the removal of the proton, the triazol ring opens to the respective *N*-cyanobenzamidine, leading to the irreversible destruction of the catalyst (Scheme 4) [33].



R	Yield [%]	ee [%]
Me	45	23
Et	65	23
<i>n</i> -C ₃ H ₅	84	21
<i>n</i> -C ₄ H ₉	84	26
<i>n</i> -C ₅ H ₁₁	89	21
<i>n</i> -C ₆ H ₁₃	71	21

Scheme 5

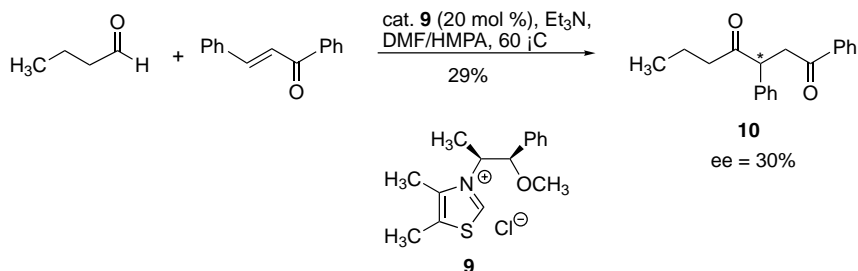
The reaction has to be carried out in the absence of oxygen and water, otherwise the intermediately formed nucleophilic carbene is oxidized to the triazolone or suffers hydrolysis with subsequent amination-type ring opening. Attempts to apply catalyst **7** to the synthesis of aliphatic acyloins gave very low yields and low enantioselectivities. Optimization of the catalyst structure with regard to activity and enantioselectivity yielded triazolium salt **8** as the best-suited system for the condensation of aliphatic aldehydes (Scheme 5) [37]. However, the enantiomeric excesses obtained, only up to 26%, and the rather low total turnover numbers, ranging from 4 to 8, are modest and a search for new, more active catalyst systems is highly desirable.

An asymmetric variant of a mixed acyloin or benzoin condensation using heterazolium catalysts has not yet been reported. However, enzymes have been shown to catalyze a number of mixed acyloin condensations efficiently [38, 39, 40].

4

Nucleophilic Acylation of Enones and Enoates (Stetter Reaction)

The Stetter reaction is an extremely useful Umpolung procedure for the synthesis of 1,4-dicarbonyl compounds [41, 42, 43]. Since its discovery in 1973, it has found widespread application in the preparation of key organic intermediates and in natural product synthesis. However, despite the importance and useful-



Scheme 6

ness of this protocol, very few asymmetric approaches have been reported and those only recently.

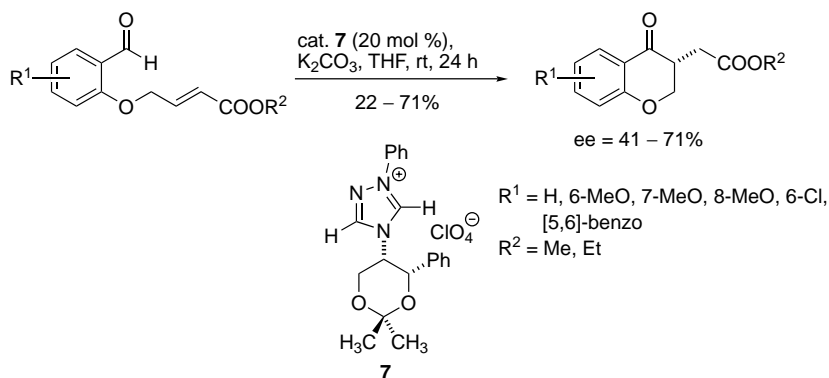
The first attempts to develop a heterazolium-catalyzed asymmetric variant of the Stetter reaction were carried out by our group [44, 45, 46], employing the chiral thiazolium salt **9** to catalyze the addition of butanal to chalcone. The resultant 1,4-dicarbonyl compound **10** was obtained in 29% yield with enantiomeric excesses up to 30% (Scheme 6).

Attempts to use triazolium catalysts instead of thiazolium salts proved to be unsuccessful, although the activity of triazolium salts in the non-enantioselective Stetter reaction had been previously reported [41]. However, some triazol-5-ylidenes have been shown to give stable adducts with several Michael acceptors and this could be the reason for their failure to react [47, 48].

We used triazolium salt **7** as the catalyst for the intramolecular Stetter reaction of 2-formylphenoxyacrylates **11** affording the corresponding 4-chromanones **12** [49], since these were known to be highly active substrates in the non-enantioselective thiazolium-catalyzed Stetter reaction [50] (Scheme 7). Apparently, the entropically favorable proximity of the reacting functionalities leads to a strong enhancement of the reactivity.

As already observed in the triazolium-catalyzed benzoin reaction, electron-donating substituents (e.g. methoxy) lead to moderate to good enantiomeric excesses, up to 71%, whereas electron-withdrawing groups cause a strong decrease in enantioselectivity. Again, deactivation of the aldehyde function leads to lower catalytic activity but higher enantioselectivities. The chromanones accessible via this method are useful intermediates for the synthesis of pterocarpans [51, 52].

In general, however, the activity of the triazolium salts in this asymmetric Stetter protocol is quite low, i.e. the total turnover numbers obtained ranged from 0.5 to 8. The development of more active catalysts which are also suitable for the intermolecular Stetter reaction is desirable.



R ¹	R ²	R ³	R ⁴	R ⁵	Yield [%]	ee [%]
H	H	H	H	Me	73	60
H	H	H	H	Et	69	56
H	H	H	MeO	Me	44	68
H	H	H	MeO	Et	69	62
H	H	MeO	H	Me	22	71
H	MeO	H	H	Me	56	61
H	Cl	H	H	Me	50	41
-CH=CH-CH=CH-		H	H	Me	51	65

Scheme 7

5 Principal Alternatives

Highly enantiomerically enriched α -hydroxy ketones are readily accessible via various stoichiometric methods, e.g. carbamoylation reactions [52], nucleophilic acylation using metalated aminonitriles [54] or the α -hydroxylation of chiral hydrazones [55] and α -silyl ketones, as well as the α -hydroxylation of ketones using chiral oxaziridines [56]. A number of catalytic approaches are based on the asymmetric dihydroxylation of enol ethers [57] and the enantioselective reduction of diketones using enzymes [58], or via catalytic hydrogenation [59]. As was mentioned earlier, a highly enantioselective enzymatic variant of the mixed acyloin condensation with aromatic aldehydes and aliphatic α -oxocarboxylic acids yielding the mixed acyloins with high enantiomeric excesses has been described [38, 39, 40].

The nucleophilic acylation of Michael acceptors can be accomplished by a number of stoichiometric methods, i.e. via the addition of metalated α -aminonitriles [60, 61] or under neutral conditions with formaldehyde-SAMP-hydrazone

acting as an aza-enamine [62, 63]. Enzymatic approaches to an asymmetric nucleophilic acylation of Michael acceptors have not been published so far.

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Note added in proof

Some more conformationally restricted thiazolium catalysts have been recently published by Leeper et al. [1, 2] and Rawal et al. [3].

Using a chiral, bicyclic Thiazolium salt Leeper et al. [1] obtained enantiometric excesses of up to 20.5% (c.y. 50%, 10 mol % catalyst, TTN ca. 2) in the benzoin reaction..A similar bicyclic catalyst gave ee's of up to 33% when used for the synthesis of butyrolin (c.y. 75%, 20 mol % catalyst, TTN ca. 4).

A novel thiazolium catalyst with a norbornane backbone gave benzoin with enantiomeric excesses of up to 26% (c.y. 100%, 5 mol % catalyst, TTN = 20) [2].

Rawal et al. [3] achieved enantiomeric excesses up to 52% for the formation of benzoin with improved yields of up to 48%, using the best thiazolium catalyst previously described by Sheehan et al. (10 mol % catalyst, TTN = 5).

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Chapter 31.1

Conjugate Addition of Organometallic Reagents

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Keywords: Ligand, Ether, Amine, Nucleophilic addition, Organolithium, Grignard reagent, Organozinc, Copper, Phosphorus, Conjugate addition, Alkylation, Phosphine, Activated olefin, β -Substituted carbonyl compound

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1 Introduction

Conjugate additions of organometallic reagents to electrophilically activated olefins constitute one of the versatile methodologies for forming carbon-carbon bonds [1]. The products are the corresponding β -substituted carbonyl com-

pounds. Because of the usefulness of the reaction as well as the products, many approaches to asymmetric conjugate addition reactions and successful achievements have been reported, especially using chirally modified olefins [2, 3]. However, the approach towards enantioselective conjugate addition reaction is currently a developing area [4, 5, 6, 7, 8, 9, 10]. In this chapter the recent progress in the enantioselective conjugate addition reactions of organolithium and organo-copper reagents with achiral activated olefins under the control of an external chiral ligand or chiral catalysts is summarized. The Michael reaction of active methylene compounds is not included in this chapter.

2

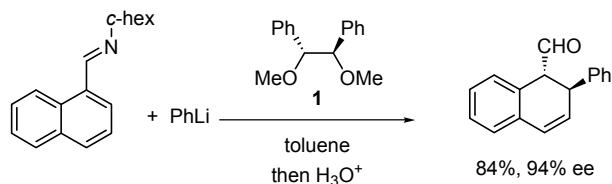
Reaction of Organolithium Reagents Using External Chiral Ligands

Organolithium compounds are highly reactive species and are used in a variety of organic transformations. Asymmetric conjugate addition of organolithium reagents to α,β -unsaturated carbonyl compounds has recently reached a useful level with the use of external chiral ligands, especially the chiral DME modification, **1**, and the chiral diamine, (-)-sparteine **2** [11]. Chiral diethers are used as ligands for lithium, and the use of a stoichiometric amount of diether **1** has shown the greatest efficiency for the asymmetric addition of organolithium reagents to α,β -unsaturated *N*-cyclohexylimines (Scheme 1) [12, 13, 14]. After hydrolysis, β -substituted aldehydes are obtained with an excellent selectivity. The ligand **1** is recoverable for reuse in high yield. The use of a poor coordinating solvent such as toluene or ether is essential for high enantioselectivity, probably because of the formation of the tight lithium-ligand chelated complex.

The diether **1** was readily prepared by dimethylation of the chiral stilbene diol which was prepared by an AD-mix reaction of stilbene in high yield.

The observed enantiofacial selection has been interpreted in terms of lithium-coordinated complex formation between the organolithium, the imine and the chiral diether **1** (Fig. 1). The R group of the organolithium is then transferred from the favored complex to the less hindered face of the double bond of the unsaturated imine.

The regioselectivity, that is 1,4- vs. 1,2-addition, is directed mainly by the larger LUMO coefficient of the corresponding reaction site [15]. A change of the cyclohexyl group of the imine moiety to an aromatic group leads to larger coefficients at the imine carbon and results in selective 1,2-conjugate addition. A cat-



Scheme 1

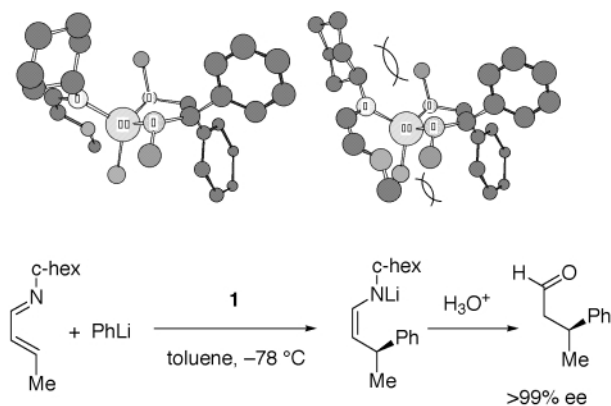
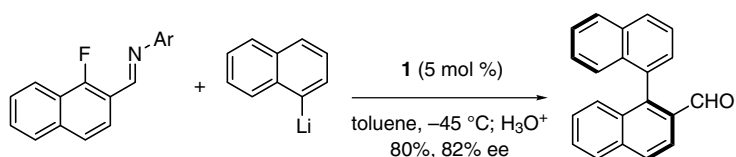


Fig. 1.



Scheme 2

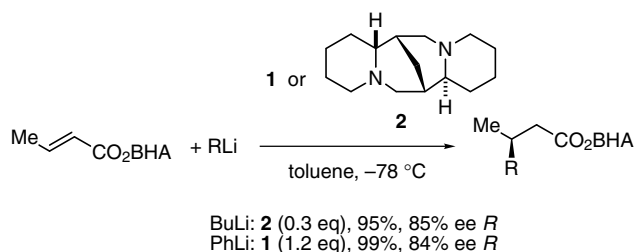
alytic asymmetric 1,2-addition reaction to provide a chiral amine is also possible [16, 17].

The first prominent catalytic asymmetric addition of an organolithium reagent was realized in the reaction of 1-naphthyllithium with 1-fluoro-2-naphthaldehyde imine in the presence of the chiral diether **1** to afford chiral binaphthyls in over 82% ee (Scheme 2). Merely a catalytic amount of **1** (5 mol %) is required to effect the reaction, in which an enantioselective conjugate addition-elimination mechanism is operative [18].

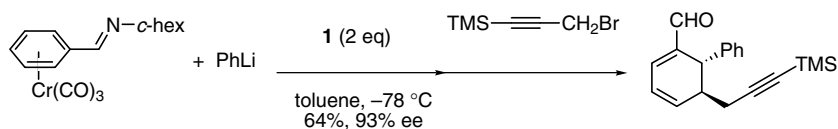
The same ligand for organolithium has been used to achieve a high level of catalytic asymmetric conjugate addition to hindered α,β -unsaturated and naphthyl esters as shown in Scheme 3 [19, 20]. The chiral diether **1** shows high efficiency for aryllithium reagents and (–)-sparteine for alkyl lithium compounds. The catalytic turnover of (–)-sparteine is superior to that of **1** [21].

The chromium complex of benzaldehyde imine is also good substrate for addition of organolithium reagents mediated by a stoichiometric amount of the chiral diether **1** in toluene to give the corresponding addition products in up to 93% ee (Scheme 4)[22].

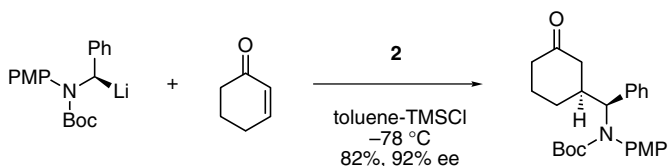
(–)-Sparteine **2** is also an excellent chiral diamine ligand in stoichiometric amounts as shown by the ligand-directed conjugate addition of chirally fixed organolithium species. The choice of ligand for lithium can provide control of 1,2- vs 1,4-addition of organolithium species to α,β -unsaturated carbonyl substrates



Scheme 3



Scheme 4



Scheme 5

(Scheme 5) [23]. Furthermore in these addition reactions, two stereocenters are constructed with high diastereo- and enantioselectivities.

3

Reaction of Heteroorganocuprates Prepared from Organolithium and Grignard Reagents

Organocopper reagents are the most reliable species for conjugate additions and a number of approaches towards chiral cuprates has been developed. The approaches are classified into two categories; one is the chiral heterocuprate obtained by treatment with chiral alcohols, amines, sulfonamides, and thiols. The other involves organocopper compounds coordinated by chiral external ligands such as phosphines, sulfides, and oxazolines.

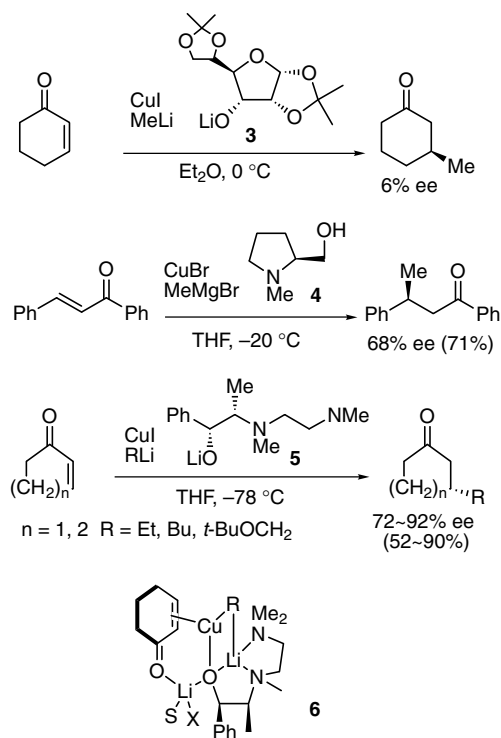
3.1

Chiral Alkoxy cuprates

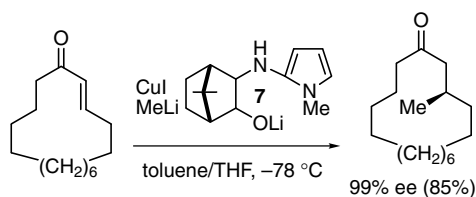
Chirally modified alkoxy cuprates can be generated from organolithium or Grignard reagents and copper(I) salt in the presence of a lithium or magnesium al-

cholate of a chiral alcohol **3**. Although in the early attempts the enantioselectivity was not high [24, 25], use of *N*-methylprolinol **4** as a chiral alkoxide source opens a new route for the asymmetric conjugate addition reaction of the Grignard reagent, methylmagnesium bromide, with chalcone to provide a relatively good enantioselectivity of 68% [26]. The reaction was optimized to afford the addition product in 88% ee [27, 28]. A breakthrough was achieved by using the ephedrine-derived chiral amino alcohol **5** to effect conjugate addition of organolithium reagents in over 90% enantioselectivity [29]. Even a small amount of alkoxide impurity in the alkyllithium solution was found to be deleterious for the enantioselectivity. The relationships between the cluster structure and the enantiofacial selection are a matter of discussion [30]. The observed enantiofacial selection was interpreted in terms of the model **6** (Scheme 6).

By use of an amino alcohol having a bornane skeleton (**7**) the conjugate addition of methyl lithium to cyclic alkenones to afford the corresponding methyl adduct in excellently high ee was realized (Scheme 7). Although these reactions need a stoichiometric amount of the chiral alcohol, batch process techniques are applicable in the reaction [31, 32].



Scheme 6



Scheme 7

3.2

Chiral Amidocuprates

Chirally modified amidocuprates can be generated from organolithium or Grignard reagents and copper(I) salt in the presence of a lithium or magnesium amide of a chiral amine. A relatively high enantioselectivity was first reported by Bertz in which a chiral amide **8** and copper iodide were used to effect the reaction of phenyllithium to afford the adduct in 50% ee (Scheme 8) [33]. The more simple prolinol derived lithium amide **9** (Scheme 8) is interesting in that it affords either enantiomers by choosing bromide or thiocyanate as a copper source in over 82% ee [34]. The linear lithium amide **10** (Scheme 8) was also introduced to effect the addition to provide the adducts in up to 97% ee [35, 36]. The observed enantiofacial selection was interpreted by means of a model assuming a dimeric structure in which the presence of the phenyl group blocks the bottom face and leads to top face reaction (Fig. 2). The dimeric structure was supported by the observation of amplification effect.

Application of the prolinol-derived lithium amide **11** (Scheme 9) in the asymmetric synthesis of (+)-confertin was successful with the addition of isopropenyllithium to 2-methylcyclopentenone being a key step [37].

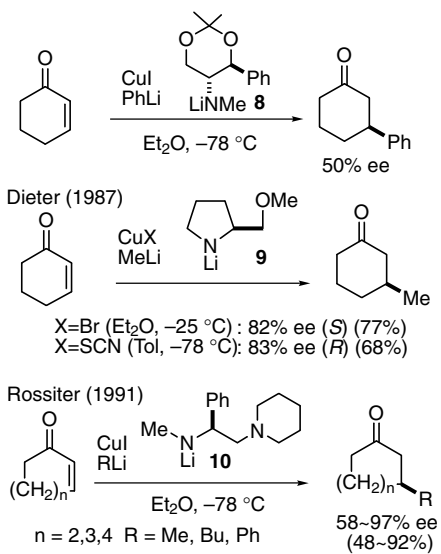
The first epoch-making catalytic process was developed using a chiral copper amide in 1990. In the presence of 3 mol % of aminotroponimine-copper **12** (Scheme 9) butylmagnesium chloride reacted with cyclohexenone to afford the corresponding adduct in 74% ee. A weakly basic nitrogen-copper structure is proposed as the reason for the success [38, 39].

3.3

Chiral Thiocuprates

Chirally modified thiocuprates are used mostly in the catalytic process, probably because of the high affinity of sulfur atom to copper and their good stability. Thiocuprates can be generated from organolithium or Grignard reagents and a copper(I) salt in the presence of the lithium or magnesium thiolate of a chiral thiol.

The reaction of the Grignard reagents is catalyzed by a catalytic amount of chiral copper thiolates **13–15** (Scheme 10) to afford the corresponding adduct in relatively high ee [40, 41, 42].



Scheme 8

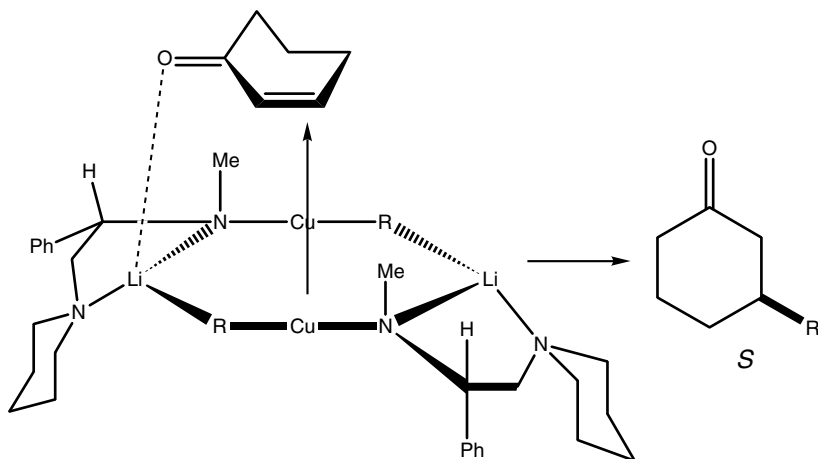
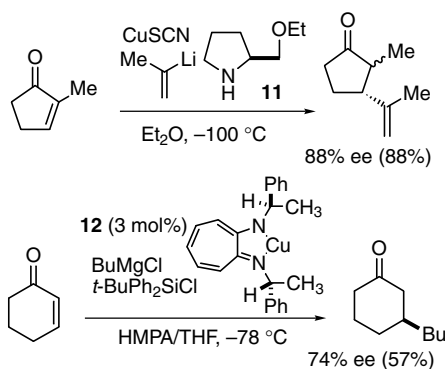
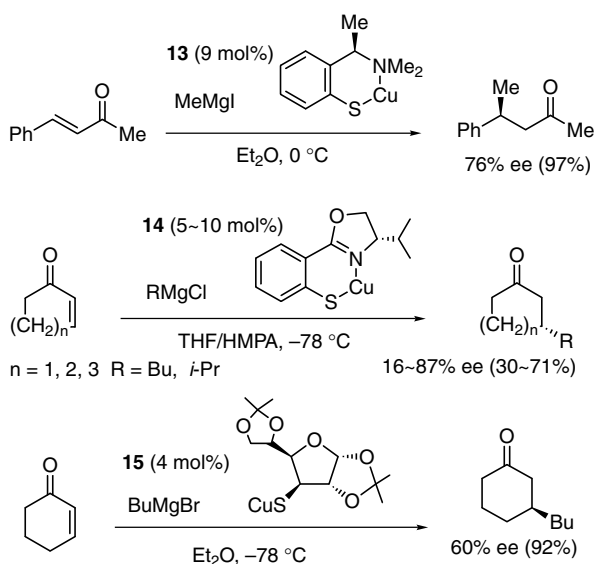


Fig. 2



Scheme 9



Scheme 10

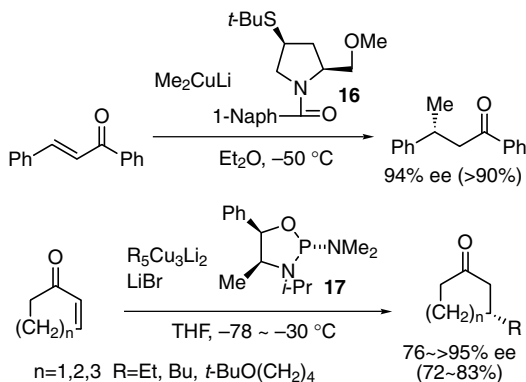
4

Reaction of Homoorganocopper Reagents Prepared from Organolithium Reagents and Grignard Reagents with External Chiral Ligands

Organocopper reagents, prepared from a copper(I) salt and organometallic species such as organolithium or Grignard reagents, contain two different metals in the cluster. A chiral modification requires a chiral ligand, the heteroatoms of which coordinate to copper and other metal. Kretschmer was the first to use the chiral diamine (–)-sparteine **2** as a ligand for methylcopper in 1972 [43]. However, the reaction with cyclohexenone gave the addition product in only 6% ee.

The breakthrough in the stoichiometric reaction was realized by Leyendecker in 1983 with the use of the hydroxyprolinol-derived sulfide **16** (Scheme 11) with three coordinating sites as shown in Fig. 3 [44, 45]. The reaction of dimethylcopper lithium with chalcone gave the product in 94% ee. In 1991, Alexakis introduced chiral phosphines as ligands **17** (Scheme 11) in the reaction of a medium-order cuprate with cycloalkenones in the presence of lithium bromide to afford the products in 76–95% ee [46]. Unfortunately, the catalytic process with an organolithium reagent was described as being unsuccessful.

The proline-derived bidentate amidophosphines **18–20** (Scheme 12) were developed by us on the basis of the concept of metal-differentiating coordination. The carbonyl oxygen and phosphorus atoms of the ligand selectively coordinate to lithium and copper of organocopper species, which discriminates the reaction face of the complex (Fig. 4). In fact the reaction of dimethylcopperlithium with chalcone gave the adduct in 84% ee [47]. Enantioselectivity was later improved to 90% with more bulky amidophosphine **20** based on the model shown [48, 49]. The metal selective coordination was supported by NMR studies [50]. The reaction with cycloalkenone was also highly efficient to give the adducts in up to 95% ee by the reaction of lithium cyanocuprate in the presence of lithium bromide [51]. However, the catalytic version of the reaction with the lithium cyanocuprate was unsuccessful. On the other hand, magnesium cyanocuprate prepared from the corresponding Grignard reagent was highly effective to afford the products in up to 98% ee. It is noteworthy that the same chiral ligand gave the products with the reversed absolute configuration on replacing lithium by



Scheme 11

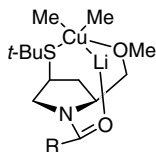
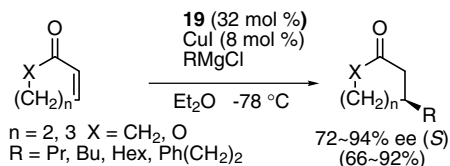
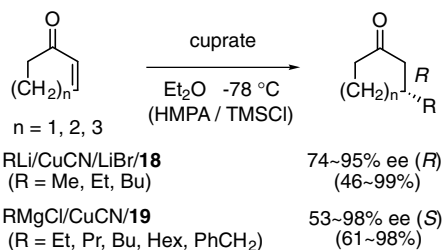
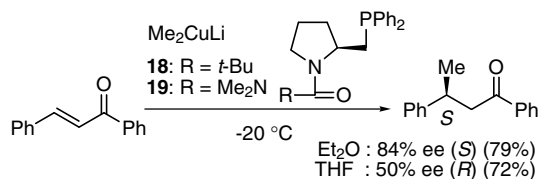


Fig. 3.



Scheme 12

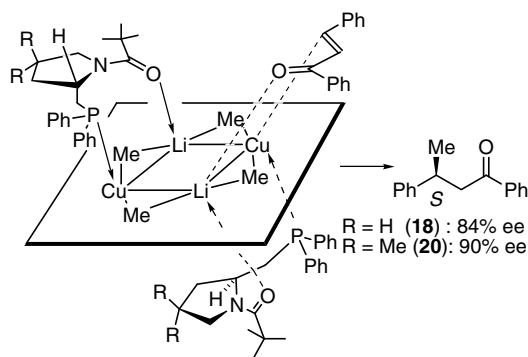
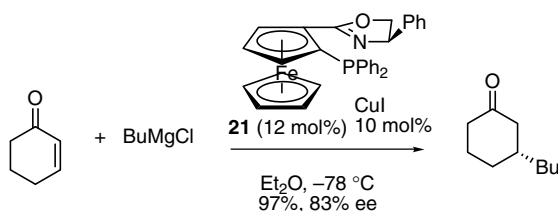


Fig. 4.

magnesium [52]. Catalytic asymmetric conjugate addition was realized by using 8 mol % of copper iodide and 32 mol % of the chiral amidophosphine **19** to afford the products in 72–94% ee [53]. The amidophosphine is recoverable for reuse in high yield.

The chiral ferrocenylphosphine oxazoline **21** (Scheme 13) was also introduced as a chiral ligand for use in catalytic amounts (12 mol %) in the reaction



Scheme 13

of Grignard reagents and 10 mol % of copper iodide with cyclohexenone to afford the product in 83% ee [54].

5

Reaction of Organocopper Reagents Prepared from Organozinc Reagents with External Chiral Ligands

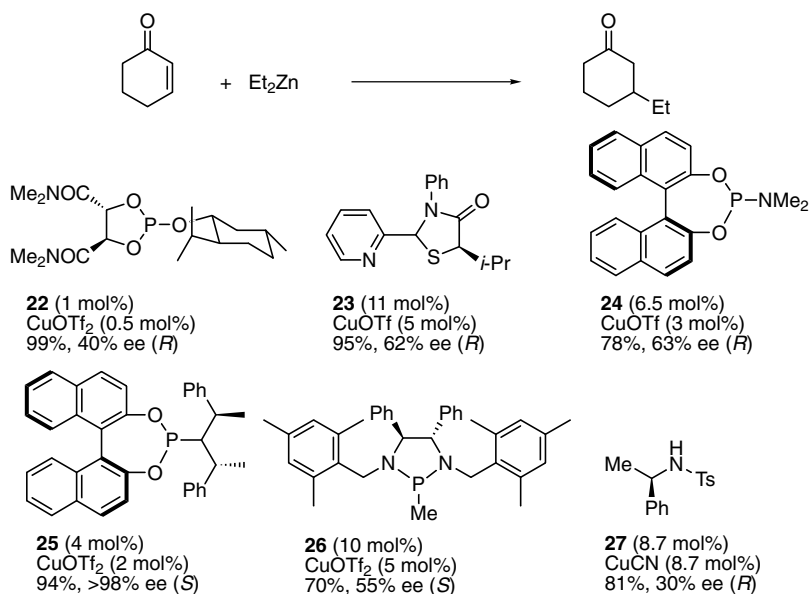
Asymmetric conjugate additions of organozinc reagents to enones in the presence of chiral ligands are a rapidly developing and exciting new field in conjugate addition chemistry. Using **17**, Alexakis discovered with the copper-catalyzed asymmetric conjugate addition of diethylzinc to cyclohexenone, giving the product in 32% ee. The binaphthol-based phosphorus amidite **24** was developed by Feringa to afford the product in 63% ee [55]. Later this ligand was greatly improved (**25**) to afford the ethylcyclohexenone adduct in over 98% ee (Scheme 14) [56]. However, high enantioselectivity is limited to cyclohexenone and rather poor selectivities were observed with cyclopentenone (10% ee) and cycloheptenone (53% ee).

The success is attributed to the use of copper triflate as the copper source. The ligand catalyzes not only the reaction of cycloalkenone but also that of acyclic enones. The chiral thiazolidinone **23** (Scheme 14) was also developed as a chiral ligand to afford the product in 63% ee [57].

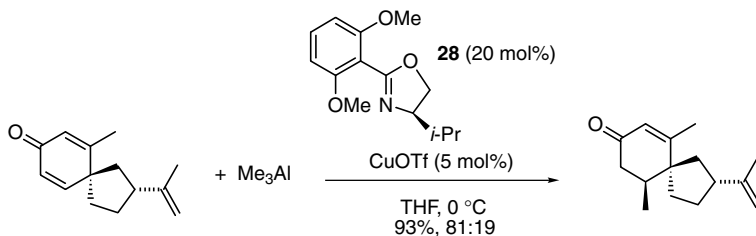
Since the bisphosphine or monophosphine greatly accelerates the copper-catalyzed reaction [58], a survey of the known diphosphines was carried out and revealed that 0.5% of copper(II) triflate and 0.5% of phosphine are sufficient, although enantioselectivity was at the most 44% [59]. The chiral phosphite ligand based on tartrate **22** (Scheme 14) was also observed to exert the same ligand acceleration [60], but the ee was not so satisfactory [61].

The symmetrical aminophosphine ligand **26** (Scheme 14) was synthesized and examined in the reaction with cyclohexenone in the presence of 5 mol % of copper triflate to afford the product in 55% ee [62].

Based on Noyori's finding that *N*-monosubstituted sulfonamide and copper(I) catalyze the addition of diorganozinc reagents to cycloalkenone [63], the effect of the chiral sulfonamide **27** (Scheme 14) was examined by Sewald; it was found that catalytic amounts of both sulfonamide and copper(I) are necessarily to effect the reaction, but the ee was at the most 32% [64].



Scheme 14



Scheme 15

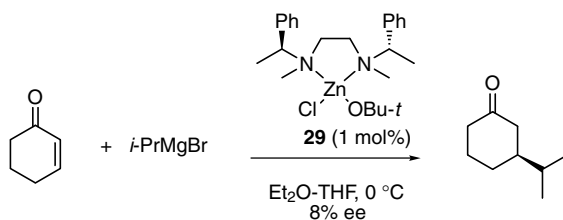
The reaction of trimethylaluminum [65, 66] with cyclohexadienone was also catalyzed by the combination of the oxazoline ligand **28** and copper(I) triflate to afford relatively high selectivity (Scheme 15) [67]. The process was successfully applied to the asymmetric total synthesis of (–)-solavetivone [68].

6

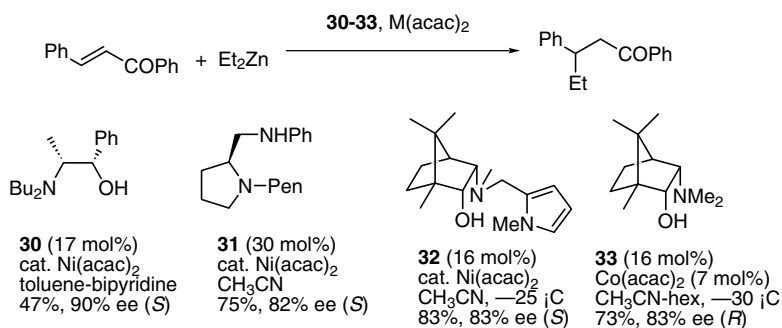
Reaction of Organometallic Reagents with External Chiral Ligands

The chiral diamine-zinc(II) complex **29** catalyzes the addition of Grignard reagent to cyclohexenone, though the ee was poor (Scheme 16) [69].

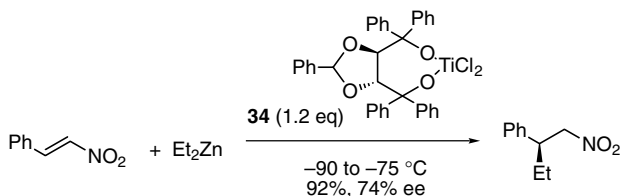
A catalytic process was achieved by using a combination of 17 mol % of amino alcohol **30** and nickel acetylacetonate in the reaction of diethylzinc and chal-



Scheme 16



Scheme 17



Scheme 18

cone to provide the product in 90% ee (Scheme 17)[70, 71, 72, 73]. The proline derived chiral diamine **31** was also effective to give 82% ee [74].

The camphor-derived tridentate amino alcohol **32** (Scheme 17) also catalyzes the conjugate addition reaction of diethylzinc in the presence of nickel acetylacetonate to afford the product in 83% ee [75]. Similarly the ligand **33**-cobalt acetylacetonate complex catalyzes the reaction to afford the product in 83% ee [76].

The combination of titanium-TADDOL **34** mediates the reaction of diethylzinc with nitroolefins to afford the products in relatively high ees (Scheme 18) [77].

7

Principal Alternatives

β -Substituted carbonyl compounds are readily accessible via conjugate addition of organometallic reagents to α,β -unsaturated carbonyl compounds [7]. Although a stoichiometric amount of chiral auxiliary is necessary, the asymmetric addition to the olefin bonded covalently by a chiral activating group has been well documented to give the adduct with high level of diastereoselectivity [78, 79, 80, 81, 82, 83, 84, 85, 86]. Removal of the chiral auxiliary provides the chiral β -substituted carbonyl compounds.

Catalytic asymmetric hydrogenation is a well-established method for the conversion of the stereochemically defined α,β -unsaturated carbonyl compounds to the chiral β -substituted carbonyl compounds in high enantioselectivity [87, 88].

Rhodium(I)-catalyzed isomerization of allylic amines is also good route to β -substituted aldehydes [89].

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Chapter 31.2

Conjugate Addition of Stabilized Carbanions

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Keywords: Michael addition, Amine, Phase transfer catalyst, Alkoxide, Crown ether, Transition metal complex, Lewis acid

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1 Introduction

Conjugate addition reactions are some of the most fundamental C-C bond-forming reactions in organic synthesis, and their asymmetric versions have been studied extensively [1]. Treated in this chapter is the catalytic conjugate addition of stabilized carbanions, especially enolate derivatives, for which the term “Michael addition and/or reaction” is used. The asymmetric Michael reactions can be categorized into two groups (Fig. 1):

- (i) enantioselective addition of prochiral donor (enolate) to acceptor; and
- (ii) Enantioselective addition of donor (enolate) to prochiral acceptor [2].

The former reaction discriminates the enantiofaces of the donor, and the asymmetric center is formed on the donor carbon atom. The latter reaction proceeds *via* enantioface discrimination of the Michael acceptor generating a chiral carbon center on the acceptor. Although both reactions are known, their mecha-

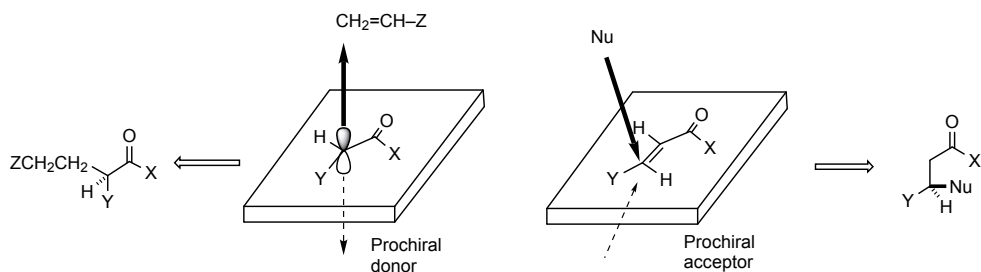


Fig. 1

nisms for asymmetric induction appear to differ. Distinct catalyst systems are generally used for the two groups of the reaction.

The mechanism of the former reactions, at least in principle, is fairly easy to understand. The anionic donor (enolate) interacts with chiral cationic species such as ammonium salts or metal cations, which differentiate the enantiofaces of the donor. In contrast, the latter reaction appears to be more complicated since the chiral enolate complex recognizes the enantiofaces of the Michael acceptor. The following discussions may be helpful in some cases for the better understanding of the prochiral acceptor reaction [2, 3].

The first aspect is the concept of the enantiofaces of the Michael acceptors. Fig. 2 shows how the *re*- and *si*-enantiofaces of the Michael acceptors can be defined. Here, the first priority is always given to the C=C group irrespective of the other substituents. This definition is relatively insensitive to changes in the substituents compared to the conventional *re*/*si*-face definitions. Since the Michael acceptors possess two prochiral centers, the α -carbon and β -carbon, an enantioface can be described as, for example, *re*(α), *si*(β), *si*(α)/*si*(β), or *re*(α)/*si*(β). The enantiofaces *si*(α) or *re*(β) indicate the *si*-face with regard to the α -carbon atom and the *re*-face with regard to the β -carbon atom, respectively.

The prochiral acceptor reactions can then be classified into the α -enantioface-discriminating reaction and β -enantioface-discriminating reaction (Fig. 3). The absolute configurations of the adducts derived from (*E*)- and (*Z*)-acceptors provide the criteria. If both isomers give *si*(α) attack products, the α -enantiofaces are discriminated. The nucleophile recognizes the chiral environments in the vicinity of the acceptor α -carbon atom rather than the β -carbon. Asymmetric Michael addition reactions utilizing chiral auxiliaries show α -enantioface discrimination [4]. Since the amide or ester auxiliaries are located in the vicinity of the α -carbon atom, the asymmetrical reaction reasonably proceeds via this mechanism. β -Enantioface-discriminating reactions would give, for example, *si*(β) attack products from (*E*)- and (*Z*)-acceptors. Reaction of the *re*(β) attack is known for a Grignard addition reaction [5].

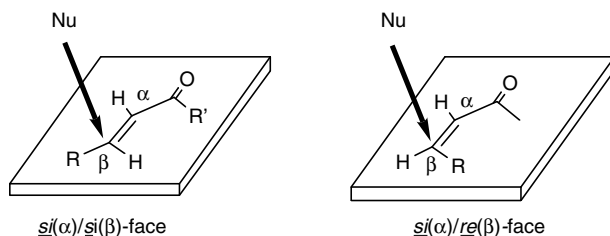


Fig. 2

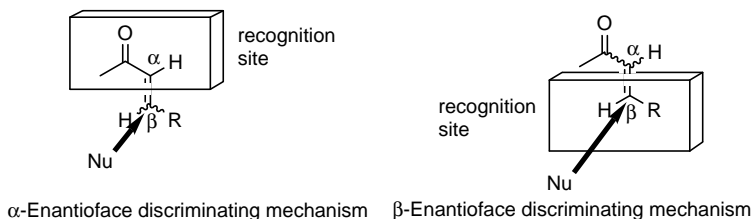


Fig. 3

2 Amine Catalysts

Early studies on the catalytic asymmetric Michael reactions were conducted with readily available amines of natural origin as listed in Fig. 4. (–)-Quinine (1) and (+)-quinidine (2) are pseudo-enantiomeric concerning the aza[2.2.2]bicyclooctane and quinoline moiety, and generally give the antipodes. The same situation holds for (+)-cinchonine (3) and (–)-cinchonidine (4) which are demethoxylated derivatives of 1 and 2.

The catalytic asymmetric Michael addition using chiral amine was first reported by Långström and Bergson [6]. Treatment of 2-methoxycarbonyl-1-indanone (6) and acrolein with 0.03 mol % of partially resolved (*R*)-2-(hydroxymethyl)quinuclidine (5, 57% ee) in benzene at room temperature gave optically active adduct, $[\alpha]_{546}^{21.0} +8.83^\circ$ (*c* 6.53, CCl_4). It clearly indicated that the cluster formed from the base and the enolate reacted with the acceptor. The enantiomeric excess and the absolute configuration of this compound, however, have not yet been determined.

Wynberg studied the catalysis by *Cinchona* alkaloids [7, 8]. Use of 1 in the addition of 6 to 3-buten-2-one (7) gave the optically active adduct (*S*)-8 in 76% ee (Scheme 1). As shown below, this prochiral donor reaction has become a standard to evaluate the efficiency of various catalysts. Several features of the reaction deserve comment:

- (i) The configuration at C(8) and C(9) of the catalyst is mainly responsible for the stereochemical outcome. The amine 1 with the (8*S*,9*R*)-configuration

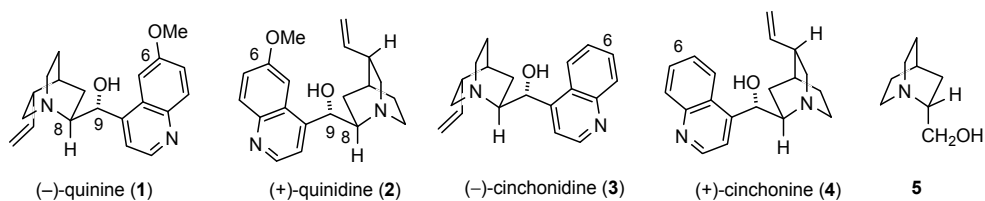
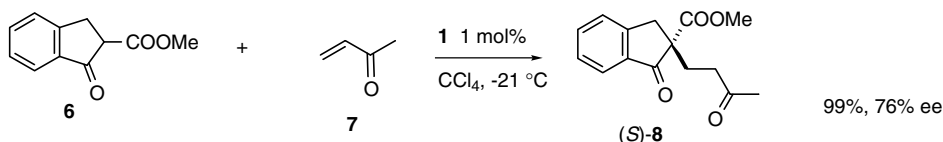


Fig. 4



Scheme 1

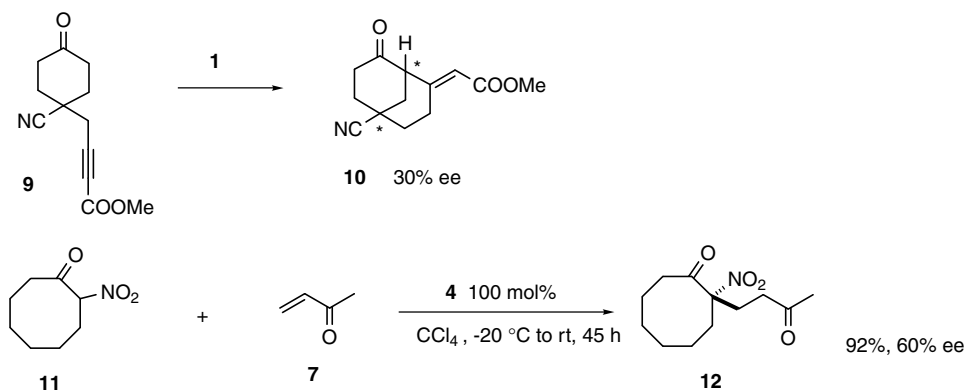
and 2 with the (8*R*,9*S*)-configuration gave the antipodes with comparable optical purities.

- (ii) The hydroxy group at the C(9) position probably participates in the transition state *via* hydrogen bonding. The reaction rate and the optical purity decreased when the corresponding acetate was employed. Addition of even a small amount of ethanol reduced the stereoselectivity.
- (iii) Use of non-polar solvents such as toluene and CCl₄ gave better results than polar or protic solvents.
- (iv) The activation by the amines is restricted to relatively acidic Michael donors such as 6, and the less acidic 2-alkoxycarboxycyclohexanone was inert under these conditions.

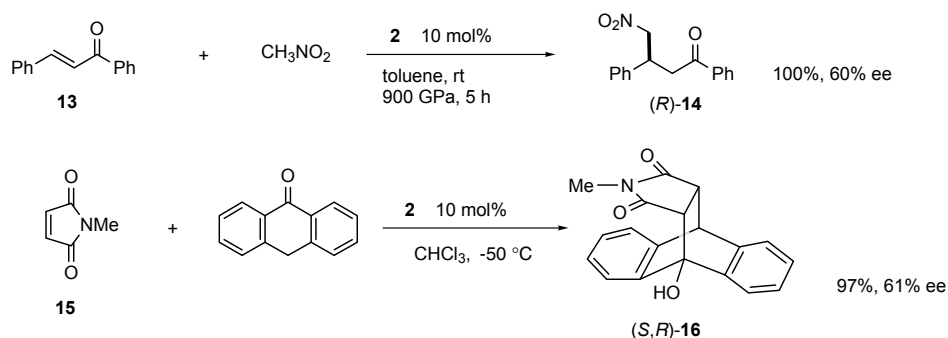
The results of Långström were considerably improved by this alkaloid methodology as judged from the optical rotation of the same adduct, $[\alpha]_{546}^{\text{rt}} -61.1^\circ$ (c 3.46, CCl₄).

The *Cinchona* alkaloids were used in other reactions of acidic prochiral donors (Scheme 2). Optically active spiro-compounds were synthesized by the double Michael addition of 1,3-cyclohexanedione to dibenzylideneacetone [9]. Trost reported a novel intramolecular addition of acetylenic ester 9 giving bicyclic 10 in 30% ee [10]. A series of 2-nitrocycloalkanones were added to 7 in the presence of 4 (100 mol %) [11]. Depending on the ring size, the enantiomeric excess and the absolute configuration differed. For example, the eight-membered ring compound 11 gave (*S*)-12 (60% ee), while the twelve-membered ring compound gave the (*R*)-adduct (25% ee). Example of the kinetic resolution have also been reported [12].

In contrast to the above prochiral donor reactions, only a limited number of prochiral acceptor reactions have been reported (Scheme 3) [13]. Nitromethane did not add to chalcone (13) in the presence of 1 in aprotic solvents. Although



Scheme 2



Scheme 3

the reaction took place in methanol, the product was racemic. Matsumoto found that nitromethane added to **13** under a high pressure of 900 GPa (Scheme 3) [14, 15]. The amine **1** and **3** gave (*S*)-**14**, while **2** and **4** gave (*R*)-**14**. The enantiomeric excesses were relatively insensitive to pressures between 400 and 900 GPa when **2** was used as the catalyst. Brucine and strychnine which lack the β -hydroxy amine moiety showed no asymmetric induction.

Kagan studied the base-catalyzed cycloaddition reaction of anthrone and *N*-methylmaleimide (**15**) [16]. In contrast to the above reactions, **2** and **3** gave (*S,R*)-**16**, while **1** and **4** gave (*R,S*)-**16**. The oxygen functionality at C(6) of the catalysts might be participating in the asymmetric induction. Besides the alkaloids, (*S*)-prolinol also gave (*R,S*)-**16** in 47% ee.

Polymer-supported chiral amine reagents represent an attractive extension of this methodology, since these catalysts can readily be recovered (Fig. 5). Succinated polystyrene-divinylbenzene (**17**) attached to **1** promoted the addition of **6** to **7** at a slower rate than the homogeneous reaction [17]. Although the absolute configuration of the adduct (*S*)-**8** was identical, the enantiomeric excess was low-

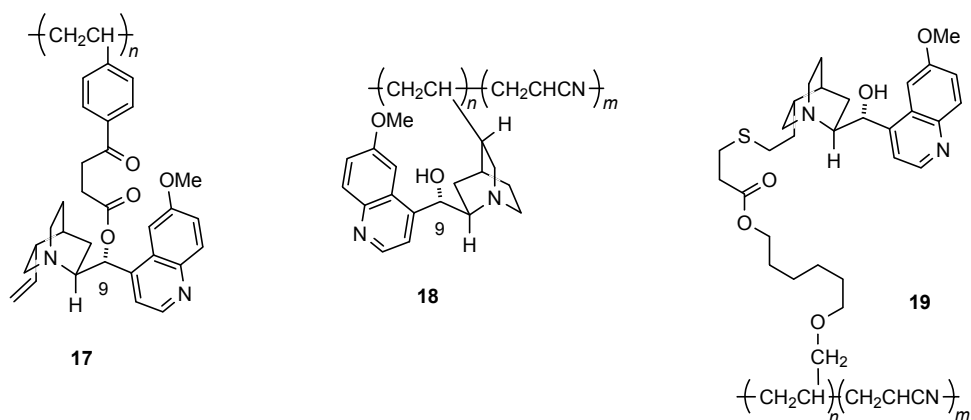
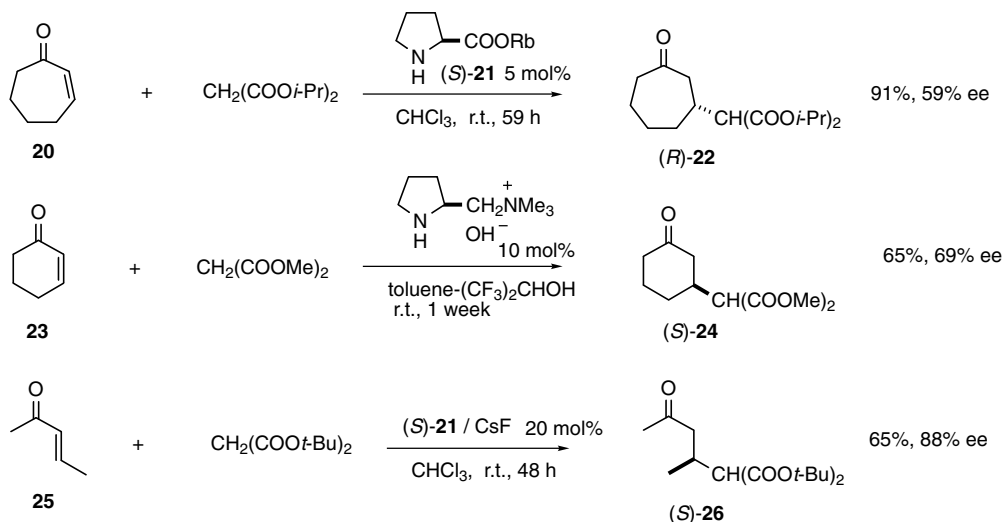


Fig. 5

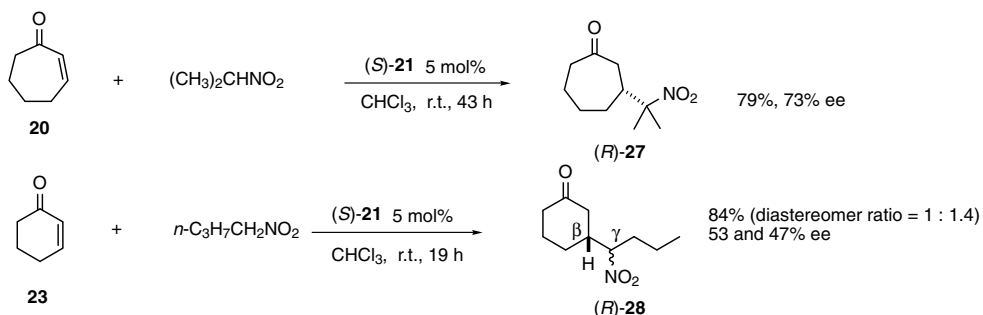
er, a maximum of 11% ee. Later, copolymers were prepared by Kobayashi from the alkaloids and acrylonitrile by olefin polymerization, which exhibited much improved enantioselectivity [18, 19, 20]. The catalyst **18** gave (*R*)-**8** in 42% ee. This could be ascribed to the presence of the free C(9) hydroxy group. The catalysts were recovered and reused. Introduction of spacers between the polymer backbone and the chiral amine, as shown in **19**, further enhanced the stereoselectivity, up to 65% ee [21]. The value was close to that obtained by the homogeneous reaction.

In order to broaden the scope of the amine-catalyzed Michael addition, Yamaguchi examined the system of amine and alkali metal salt [2]. Although amine did not promote the addition of malonate to enones, the $\text{LiClO}_4\text{-Et}_3\text{N}$ catalyst turned out to be effective. Optically active amines, however, gave racemic adducts. As an extension, the (*S*)-proline rubidium salt, (*S*)-**21**, was developed, which possessed a cation and an amine moiety in the same molecule [2, 22]. The catalyst (*S*)-**21** in chloroform promoted the asymmetric addition of malonate to a wide range of enones and enals as exemplified by the reaction of 2-cycloheptenone (**20**) giving (*R*)-**22** (Scheme 4). The role of the counter cation was important and (*S*)-**24** was obtained from 2-cyclohexenone (**23**) when (*S*)-proline lithium and tetrabutylammonium salts were employed. Taguchi used (*S*)-pyrrolidylalkylammonium hydroxide derived from (*S*)-proline and obtained (*S*)-**24** [23]. Changes in the side chain and cation structure dramatically varied the reaction course. Higher asymmetric induction was attained by reacting di(*t*-butyl) malonate in the presence of (*S*)-**21** and CsF, and (*S*)-**26** was obtained in 88% ee from acyclic (*E*)-enone **25**.

The amino acid salt (*S*)-**21** (5–10 mol %) catalyzed the asymmetric Michael addition of nitroalkanes (Scheme 5) [24, 25]. Substituted nitromethanes exhibited higher enantiomeric excesses, and addition of 2-nitropropane to cycloheptenone **20** gave (*R*)-**27** in 73% ee. In case of primary nitroalkane, two diastereomers of **28** were formed in comparable amounts, both of which possessed the



Scheme 4



Scheme 5

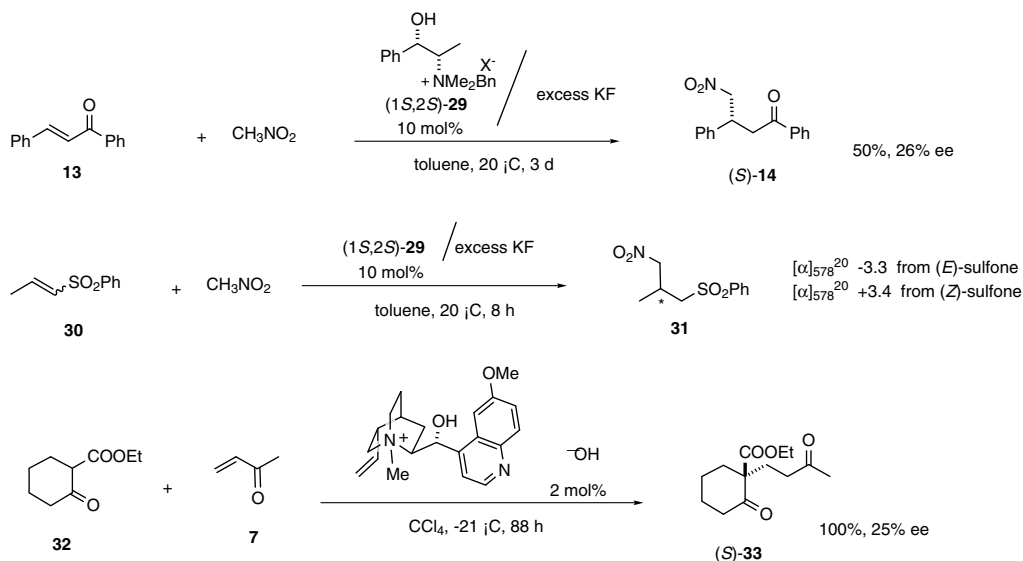
(*R*)-configuration at the β -carbon atom. This implied that (*S*)-21 controlled the stereochemistry of the C-C bond forming β -carbon atom, and marginally affected that of the γ -carbon atom.

These malonate and nitroalkane reactions gave the adducts with the predicted absolute configurations: (*R*)-adducts were obtained from cyclic (*Z*)-enones and (*S*)-adducts from acyclic (*E*)-enones when (*S*)-21 was employed. The stereochemical outcome can be summarized as *si*(α)-attack. The involvement of the α -enantioface-discriminating mechanism suggests that the chiral catalysts are located in the vicinity of the enone carbonyl group at the transition state. The reaction of the primary nitroalkane mentioned above also supports this explanation.

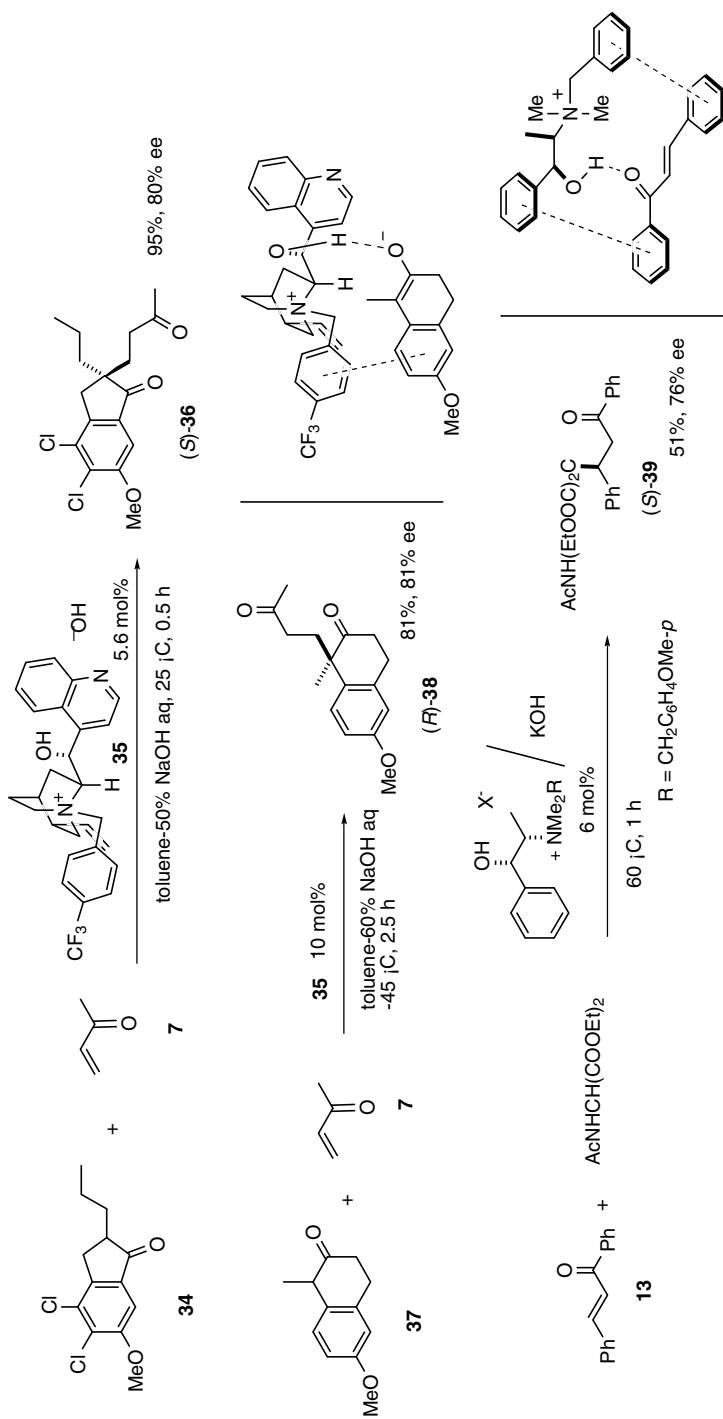
3 Phase Transfer Catalysts

Chiral phase transfer catalysis involves a similar concept as chiral amine catalysis in the sense that the enolate forms an ion pair with chiral ammonium cation. The former, however, has an advantage of being a stronger base compared to the latter [12, 26, 27, 28]. Although the addition of nitromethane to **13** did not take place with **1**, it proceeded with ammonium fluoride generated *in situ* by treating *N*-benzyl-*N*-methylephedrinium bromide, (1*S*,2*S*)-**29**, with excess KF (Scheme 6). Nitroketone (*S*)-**14** was obtained in 26% ee. When nitromethane was added to (*E*)- and (*Z*)-2-propenylsulfone (**30**), the antipodes **31** were obtained. This phase transfer reaction appears to proceed *via* the α -enantioface-discriminating mechanism, and the enolate-ammonium cation ion pair probably is interacting with the sulfonyl group at the transition state. Tetraalkylammonium hydroxide was also used for the asymmetric addition of **32** to **7** giving (*S*)-**33** [8, 29, 30].

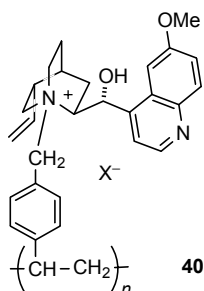
Conn reported that *N*-(*p*-trifluoromethylbenzyl)cinchoninium bromide (**35**) catalyzed the addition of 2-propylindanone **34** to **7** exhibiting (*S*)-selectivity in 80% ee (Scheme 7) [31]. The antipode (*R*)-**36** was obtained in 52% ee when *N*-benzylcinchonidium bromide was used. Although the salt is not soluble in toluene, a homogeneous toluene solution obtained by partition between the organic solvent and the aqueous base exhibited the activity. Related reactions were conducted with **37**, and asymmetric inductions of higher than 80% ee were attained in the synthesis of (*R*)-**38** [32]. The *p*-trifluoromethylbenzyl group was considered to participate in a π - π interaction with the substrate aromatic ring. Hydro-



Scheme 6



Scheme 7

**Fig. 6**

gen bonding between the catalyst hydroxy group and enolate oxygen was also shown to be critical.

Solid-liquid phase transfer without solvent was reported for a prochiral acceptor reaction. In the presence of *N*-(*p*-methoxyphenylmethyl)ephedrinium salt, aminomalonate underwent addition to **13** giving (*S*)-**39** in 76% ee [33, 34, 35]. The selectivity was higher in the absence of solvent than in toluene or chloroform. Introduction of the electron-donating group at the *N*-benzyl arene moiety enhanced the selectivity. A π - π interaction between **13** and the aromatic ring of the catalyst was suggested, since the enantiomeric excesses correlated with the Hammett's factor.

The cationic polymer **40**, prepared from chloromethylated polystyrene and **1**, was subjected to ion-exchange to give the hydroxide or fluoride derivatives, and used in the asymmetric addition of **6** to **7** giving (*S*)-**8** in 27% ee (Fig. 6) [36].

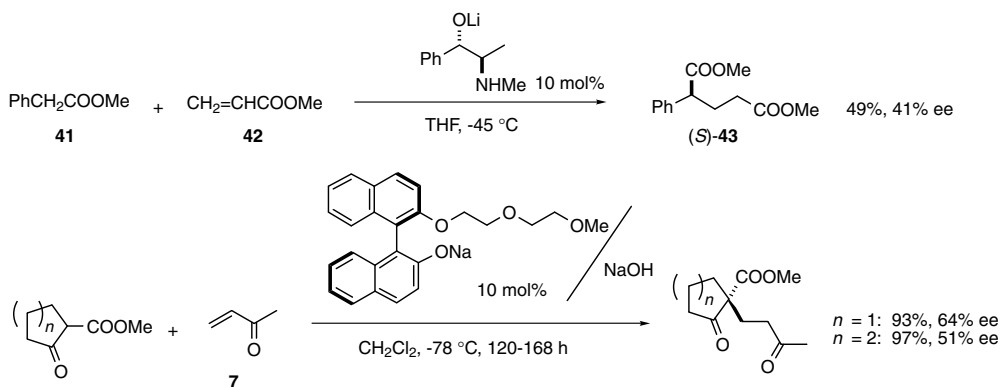
4

Alkoxide and Phenoxide Catalysts

In 1953, chemists in Russia reported the asymmetric induction in the Michael addition of cyclohexanone and 2-methylcyclohexanone to acrylonitrile in the presence of optically active quartz coated with EtOLi, EtOK, or EtONa [37]. Maximum rotations of 0.07 and 0.157 were obtained, respectively.

Chiral metal alkoxides are apparently attractive candidates for the asymmetric catalyst since they are readily available. A very low level of asymmetric induction, however, was observed when lithium (*S*)-1-phenylethoxide was used in the reaction of phenylacetate **41** and acrylate **42**. Koga showed that a stoichiometric amount of the lithium alkoxide derived from an amino alcohol promoted the asymmetric addition giving (*S*)-**43** in 84% ee [38]. Use of sodium or potassium salts resulted in racemic **43**. A catalytic reaction (10 mol %) still exhibited a selectivity of 41% ee (Scheme 8).

As indicated by Miyano, alkali metal phenoxides derived from (*R*)-1,1'-bi-2-naphthol (BINOL) possessing an oligoether moiety promoted the asymmetric addition of ketoesters to **7** [39]. Simple BINOL or its monomethyl derivative gave the racemic product, and the appropriate length of the polyoxyethylene chain

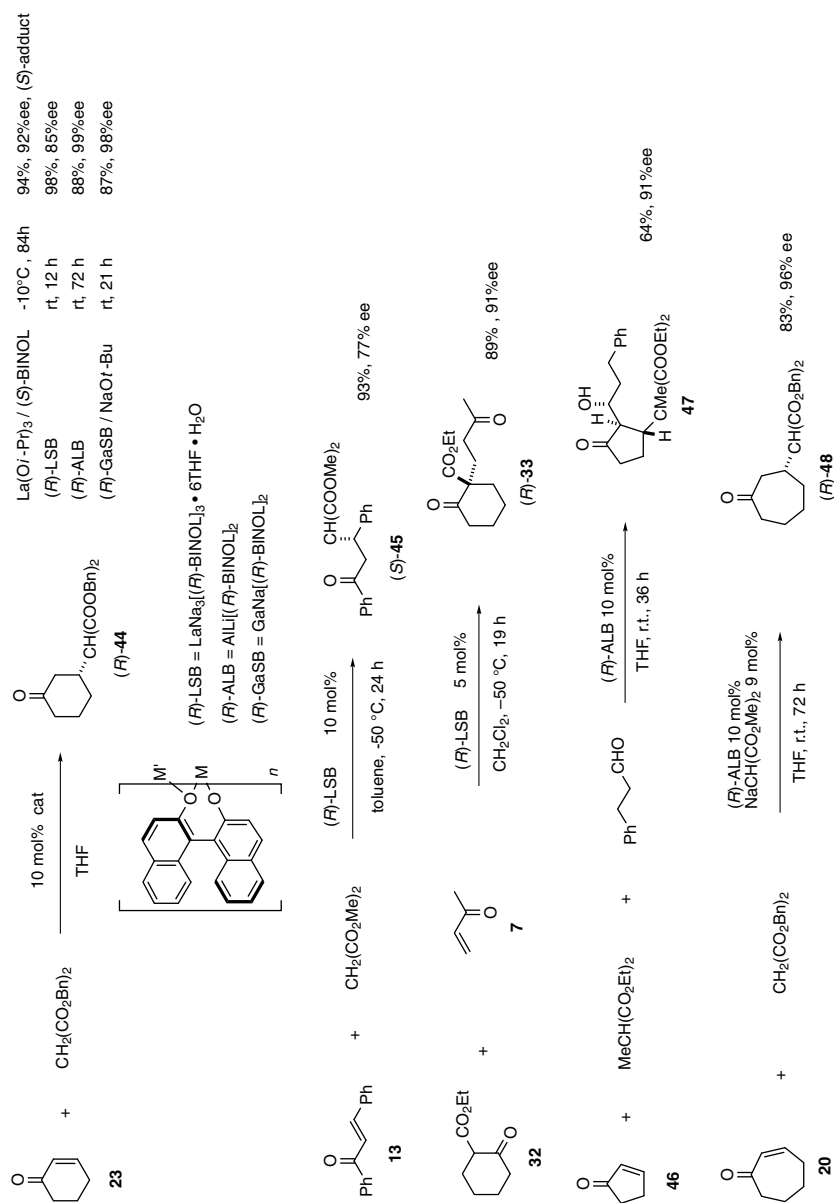


Scheme 8

was required. Sodium and potassium salts gave higher asymmetric induction than lithium, rubidium, or cesium salts, probably reflecting the affinity of the oligoether chain to the metal cation.

The most successful example of this approach has been provided by Shibasaki and Sasai using optically active phenoxides derived from BINOL (Scheme 9) [40, 41, 42, 43, 44, 45]. Four catalyst systems consisting of group 3 or group 13 elements were developed for the asymmetric Michael addition of malonates to prochiral enones. Three of them were associated with alkali metal cations, which also played an important role in the effective asymmetric induction. The oligomeric structure formed from BINOL and two metal components was named “heterobimetallic catalyst”. Their initial work was conducted with lithium free lanthanoid complex prepared from $\text{La}(\text{O}i\text{-Pr})_3$ and (*S*)-BINOL, and addition of dibenzyl malonate to **23** with 10 mol % of the (*S*)-catalyst at -10 °C gave (*S*)-**44** in 92% ee. The composition of the complex was $\text{La}:\text{BINOL}=2:3$. Addition of *t*-BuONa to this complex generated lanthanum-sodium-(*R*)-BINOL, (*R*)-LSB catalyst, whose structure was determined by X-ray analysis as $\text{LaNa}_3(\text{BINOL})_3 \cdot 6\text{THF} \cdot \text{H}_2\text{O}$. Of the possible combinations of lanthanoids and alkali metals, the lanthanum/sodium system gave the best results in terms of the stereoselectivity. NMR and computational studies suggested that the *si*-face of **23** was effectively shielded by the catalyst, which resulted in the formation of (*R*)-**44**. Both the basic and the Lewis acid nature of the catalyst is important. The LSB catalyst can be used for the reaction of **13** giving (*S*)-**45** provided that it is conducted at -50 °C in toluene. The LSB catalysts also promoted the asymmetric reaction of prochiral donor **32** and **7**.

An aluminum-lithium catalyst, (*R*)-ALB, prepared from (*R*)-BINOL, and lithium aluminium hydride promoted the addition of malonate to **23** giving (*R*)-**44** in 99% ee. X-ray analysis of the ALB catalyst showed an aluminum ate complex structure with Li coordination to the oxygen atom. The asymmetric tandem Michael-aldol reaction of **46** was conducted with this catalyst giving a single isomer **47** containing three asymmetric centers. The aluminum enolate under-



Scheme 9

went aldol reaction more rapidly than protonation. Another catalyst, (*R*)-GaNa-BINOL generated from GaCl₃, NaO*t*-Bu (4 equivalents), and (*R*)-BINOL (2 equivalents), was less active than (*R*)-ALB. However, addition of one mol equivalent of *t*-BuONa dramatically accelerated the reaction. Since the optical activity was not reduced by the presence of the added base, the sodium salt of malonate bound to the catalyst much more rapidly than it reacted with enone. A related method using malonate sodium salt was applied to the less reactive **20** giving (*R*)-**48** in 96% ee.

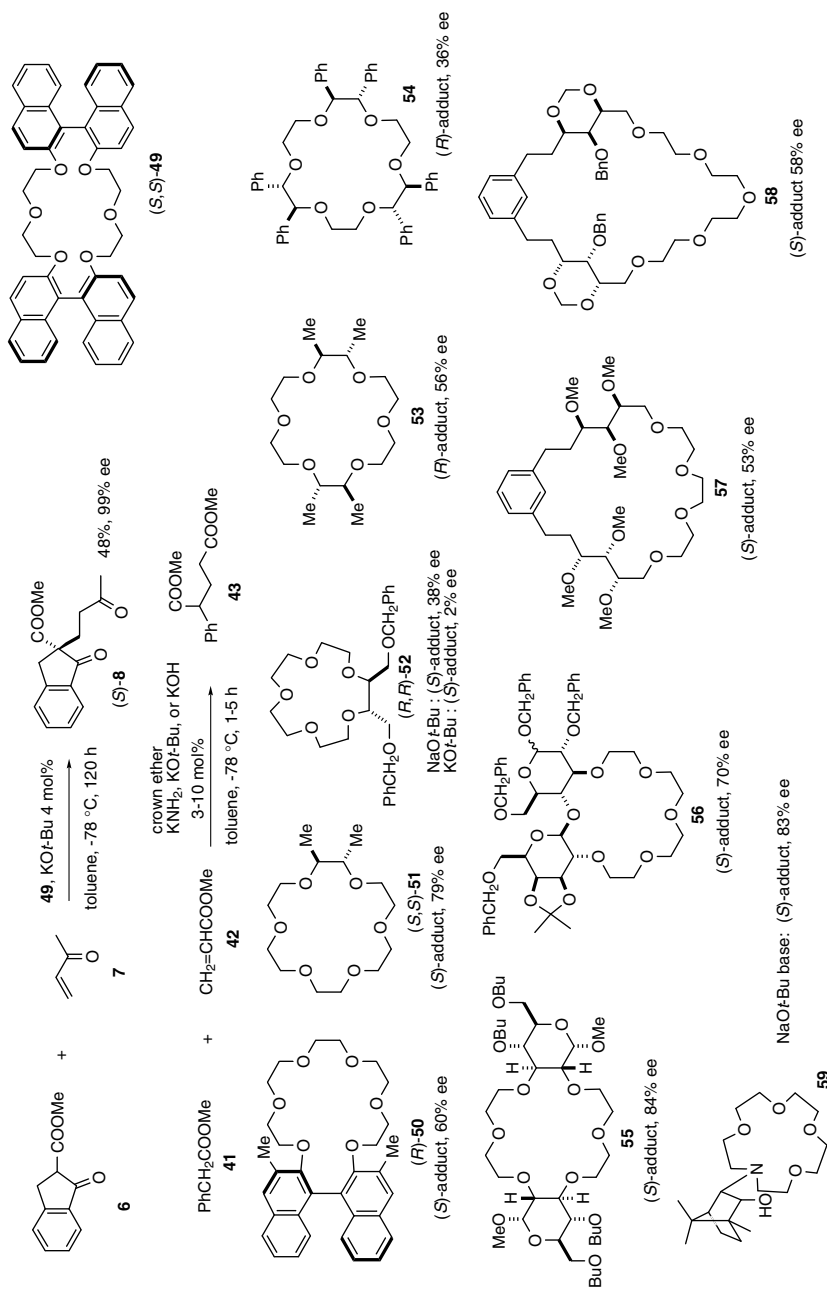
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Crown Ether/Alkali Metal Base Catalysts

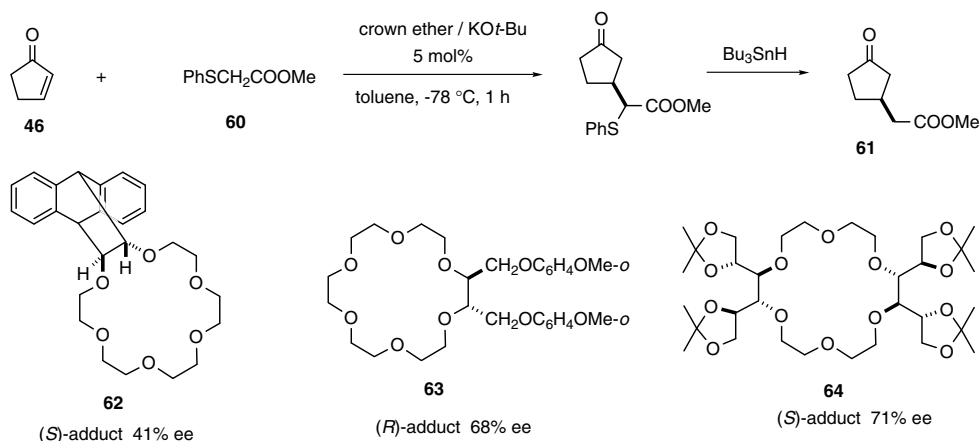
Cram found that chiral crown ethers in the presence of alkali metal bases catalyzed the asymmetric Michael addition [46]. Ketoester **6** underwent addition to **7** in more than 99% ee in the presence of (*S,S*)-**49** and KO*t*-Bu (4 mol %). Another crown ether, (*R*)-**50**, and KNH₂ promoted the addition of **41** to **42** giving (*S*)-**43** in 60% ee. Since then, this reaction was examined using various optically active crown ethers [47, 48, 49, 50, 51, 52, 53, 54, 55, 56], which are summarized in Scheme 10 showing the configuration and enantiomeric excess of **43**. Slight changes in the structure of the crown ethers drastically affected the stereochemistry of the reaction. A brief structure-activity relationships may be presented.

A simple derivative, (*S,S*)-1,2-dimethyl-18-crown-6 (**51**), and KO*t*-Bu gave (*S*)-**43** with a considerable level of asymmetric induction, 79% ee [49]. It is presumed that vicinal dimethyl group occupies a diaxial arrangement thus constructing an effective chiral environment. (*R,R*)-15-Crown-5 **52** gave (*S*)-**43** when NaO*t*-Bu was used as the base, and a very low ee was obtained with the potassium salt [50]. It may be due to a weaker interaction between the cation and the crown ether in the latter. Notably, the (*S,S,S,S*)-1,2,7,8-tetramethyl and (*R,R,R,R,R,R*)-hexaphenyl derivatives, **53** and **54**, gave the antipode (*R*)-**43** [49, 50, 51]. Crown ethers containing a disaccharide moiety such as **55** and **56** were also developed [52, 53, 54]. Deracemization phenomena were observed in which (\pm)-**43** was converted to (*S*)-**43** in the presence of KO*t*-Bu and **55**. The reaction took place under thermodynamic control. In the reactions of the 25-membered ring polyether **57** and the 27-membered compound **58**, the protecting group played an important role [55]. The structure of the ion pair consisting of **59**, enolate, and metal cation was discussed on the basis of theoretical calculations [56].

Asymmetric Michael additions of the prochiral acceptors using crown ethers are rare. The reaction of **60** and **46** using chiral crown ethers **62**, **63**, **64**, etc., was reported by Yamamoto and other researchers (Scheme 11) [57, 58]. The phenylthio group could be removed under radical conditions giving **61**.



Scheme 10



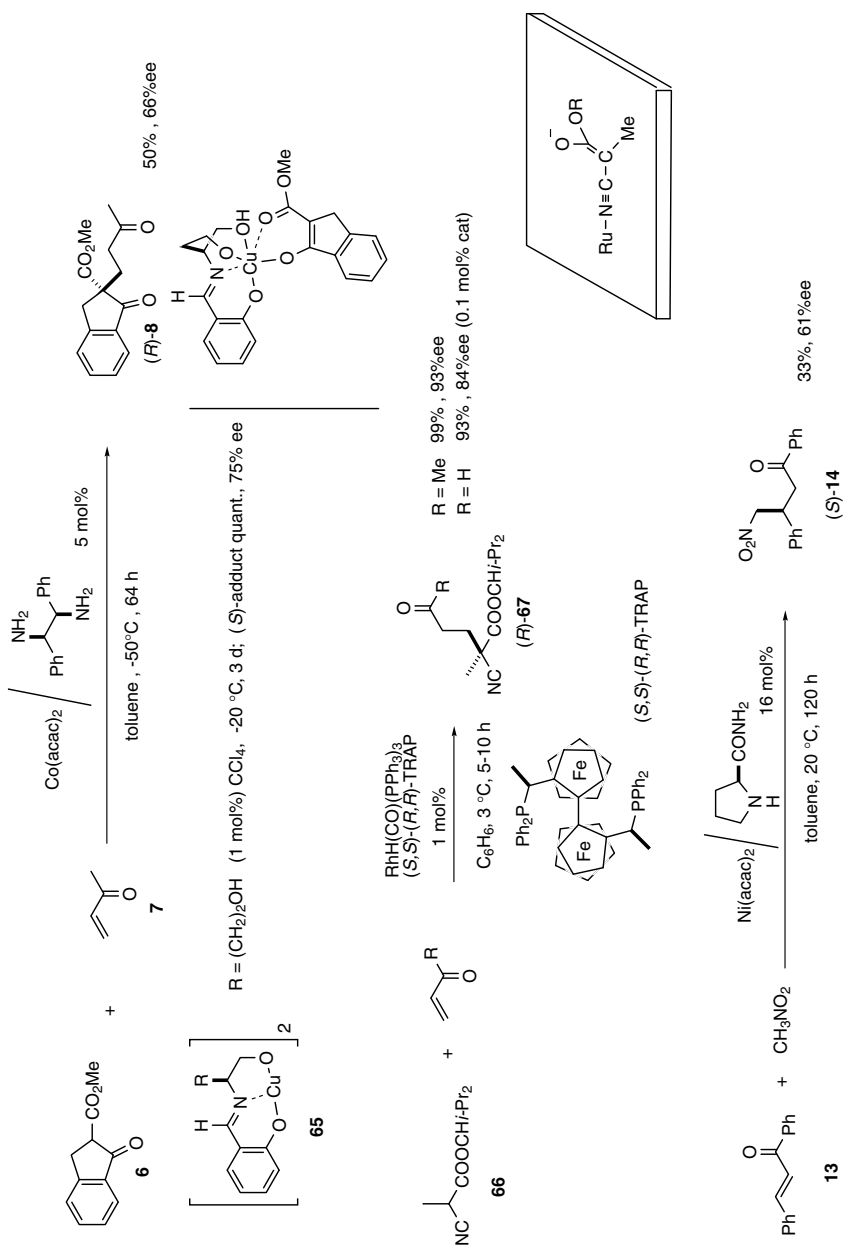
Scheme 11

6 Transition Metal Complexes

The transition metal-catalyzed asymmetric Michael addition reaction was first reported by Brunner employing the complex of Co(acac)₂ and (*S,S*)-1,2-diphenyl-1,2-ethylenediamine (Scheme 12) [59, 60]. An enantiomeric excess of 66% was attained in the reaction of **6** and **7** giving (*R*)-**8** at -50 °C in toluene. The dimeric copper complex **65** derived from salicylaldehyde and optically active (*S*)-hydroxyamines also promoted the reaction giving (*S*)-**8** in 75% ee [61, 62, 63]. The second hydroxy group is considered to occupy the axial position of the monomeric intermediate.

Based on the finding that ruthenium complexes catalyzed the Michael addition of cyanoesters, Ito developed a system of RhH(CO)(PPh₃)₃ and chiral bidentated phosphine, (*S,S*)-(*R,R*)-TRAP. The catalyst promoted the asymmetric addition of **66** to **7** giving (*R*)-**67** [64, 65, 66]. In the case of a reactive acceptor, acrolein, even 0.1 mol % of the complex effectively catalyzed the reaction. An enantiomeric excess of up to 93% was attained with the diisopropylmethyl ester. Since BINAP, DIOP, CHIRAPHOS, *etc.*, did not induce such high stereoselectivities, the *trans*-coordinated structure constructed by the TRAP was considered to be critical. The structure of the ruthenium complex obtained by X-ray analysis indicated the interaction of the metal with the nitrile nitrogen atom. The *trans*-coordinated ligand might be required to affect the remote reaction site.

The combination of (*S*)-prolinamide and Ni(acac)₂ promoted the asymmetric addition of nitromethane to **13** in the selectivity up to 61% ee [67, 68, 69].

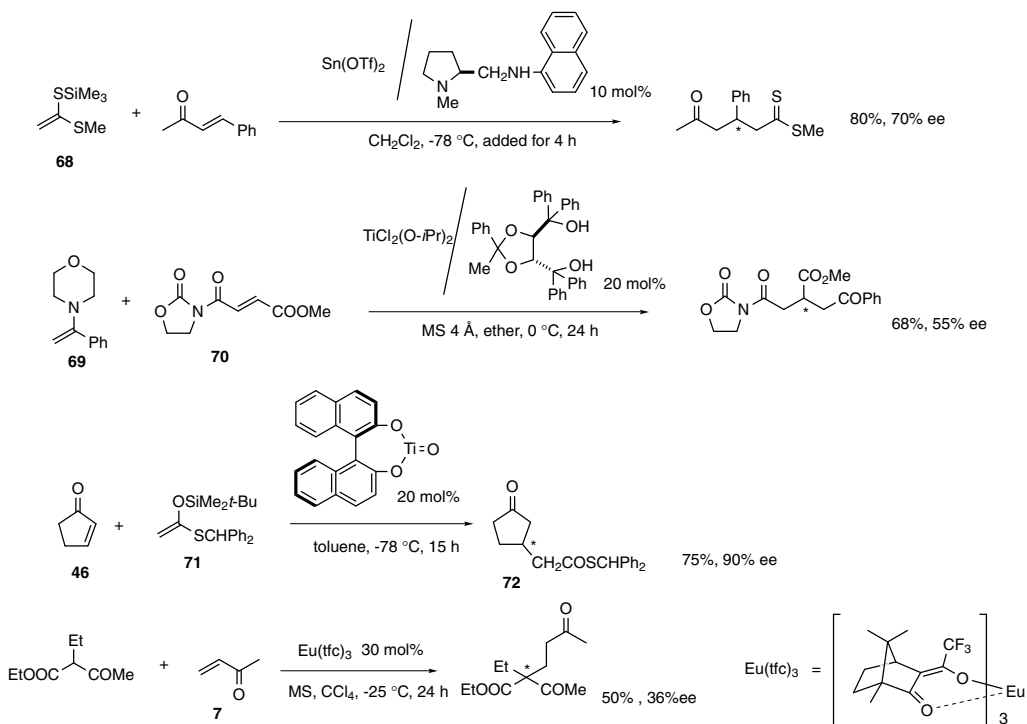


Scheme 12

7 Metal Complexes with Lewis Acid Properties

Metal compounds possessing Lewis acid character are often used in the Michael addition reaction, and the methodology is reasonably applied to the asymmetric reaction in the presence of chiral ligands. The mechanism could involve either purely Lewis acidic activation of the Michael acceptor or generation of new organometallic species by the transmetalation or C-H activation, although they were not clear in many cases. The system of $\text{Sn}(\text{OTf})_2$ and chiral (*S*)-diamine developed by Mukaiyama promoted the asymmetric addition of trimethylsilyl enthiolate **68** to β -arylvinyl ketones (Scheme 13) [70, 71]. The diamine-coordinated tin enolate was considered to be involved, and slow addition of **68** was essential to inhibit the racemate formation process.

Narasaka reported that the titanium compound generated from $\text{TiCl}_2(\text{O}i\text{Pr})_2$ and an optically active diol in the presence of 4 Å molecular sieve promoted the asymmetric addition of enamine **69** to the activated fumarate **70** [72]. Cyclobutane derivatives were formed when β,β -disubstituted enamines were employed. Titanium oxide derived from (*R*)-BINOL and $(i\text{PrO})_2\text{Ti}=\text{O}$ catalyzed the asymmetric addition of silyl thioenol ether **71** to enones [73]. The sulfur derivative ex-



Scheme 13

hibited a much higher enantiomeric excess than simple ester, and addition to **47** gave **72** in 90% ee. Reaction of the lanthanoid shift reagent, europium tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) was also reported [74].

Several successful examples appeared for the catalytic asymmetric Michael addition reaction. It may be apparent, however, that they are not yet quite satisfactory in terms of stereoselectivity, catalyst efficiency, and applicability. Development of new methods is still required, which would also deepen the fundamental understanding of the Michael addition reaction, a very important reaction in organic synthesis.

Acknowledgments: I would like to thank Ms. Mie Tomizawa for the preparation of drawings.

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Chapter 32

Ene-Type Reactions

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Keywords: Ene reaction, Hetero-Diels-Alder reaction, Ene cyclization, Desymmetrization, Kinetic resolution, Non-linear effect, Asymmetric activation, Metallo-ene, Carbonyl addition reaction, Aldol-type reaction, Titanium, Aluminum, Magnesium, Palladium, Copper, Lanthanides, Binaphthol, Bisoxazoline, Diphosphine, TADDOL, Schiff base.

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List of Abbreviations

BINOL: 1,1'-bi-2-naphthol
TADDOL: $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
MPM: 4-methoxyphenylmethyl

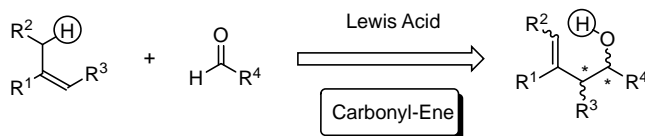
1 Introduction

Asymmetric catalysis of organic reaction to provide enantiomerically enriched products is of central importance for modern synthetic and pharmaceutical chemistry. In particular, enantioselective catalysis is an economical and environmentally benign process, since it achieves “multiplication of chirality” [1] thereby affording a large amount of the enantio-enriched product, while producing a small amount of waste material, due to the very small amount of chiral catalyst employed. Thus, the development of enantioselective catalysts is a most challenging and formidable endeavor for synthetic organic chemists [2,3]. Highly promising candidates for such enantioselective catalysts are metal complexes bearing chiral organic ligands. The degree of enantioselectivity should be critically influenced by metal-ligand bond lengths, particularly metal-oxygen and -nitrogen bond lengths in the cases of metal alkoxide and amide complexes [4,5], as well as the steric demand of the organic ligands. Therefore, boron and aluminum are the main group elements of choice, and titanium is one of the best early transition metals with hexa- and pentacoordination, lanthanides are similarly useful. The Lewis acidity of the metal complexes is generally proportional to the value of $(\text{charge density}) \times (\text{ionic radius})^{-3}$ [6].

2 Carbonyl-Ene Reaction

C-H bond activation [7] and C-C bond formation are the key issues in organic synthesis. In principle, the ene reaction is one of the simplest methods for C-C bond formation, which converts readily available olefins, via activation of an allylic C-H bond and allylic transposition of the C=C bond, into more functionalized products. The ene reaction encompasses a vast number of variants in terms of the enophile used. Comprehensive reviews on ene reactions are given in Refs. [8a, 8b, 8c, 8d].

The class of ene reactions involving a carbonyl compound as the enophile, which we refer to as the carbonyl-ene reaction [8c], constitutes a useful synthetic method for the stereocontrolled construction of carbon skeletons using a stoichiometric or catalytic amount of various Lewis acids (Scheme 1) [9, 10]. From the synthetic point of view, the carbonyl-ene reaction should, in principle, constitute a more efficient alternative to the carbonyl addition reaction of allylmetal

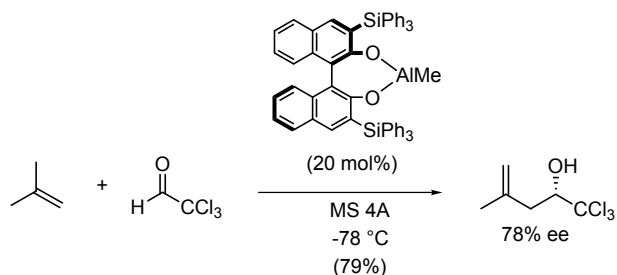


Scheme 1. Carbonyl-ene reaction catalyzed by chiral Lewis acids

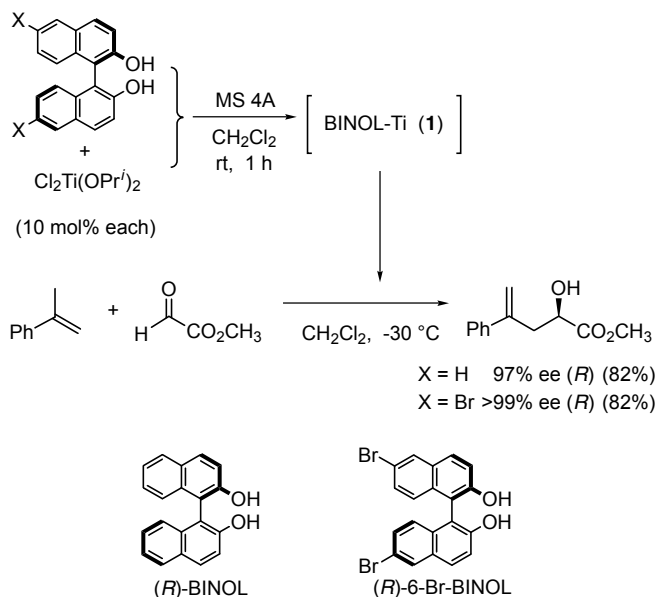
species which has now become one of the most useful methods for stereocontrol [11a, 11b, 11c, 11d, 11e, 11f, 11g].

Yamamoto et al. have reported an asymmetric catalysis of carbonyl-ene reaction, which employs chloral as the enophile using an optically pure 3,3'-bissilylated binaphthol (BINOL) aluminum catalyst (Scheme 2) [12]. The 3,3'-diphenyl BINOL-derived aluminum catalyst provides the racemic product in low yield.

We have developed a chiral titanium catalyst for the glyoxylate-ene reaction which provides α -hydroxy esters of biological and synthetic importance [13] in an enantioselective fashion (Scheme 3) [14, 15a, 15b]. Various chiral titanium catalysts were screened [16]. The best result was obtained with the titanium catalyst



Scheme 2. Asymmetric carbonyl-ene reaction catalyzed by chiral Al complex



Scheme 3. Asymmetric carbonyl-ene reaction catalyzed by BINOL-Ti complex


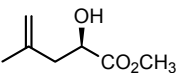

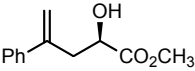

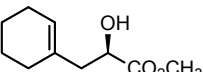

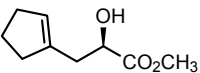
(1) prepared in situ in the presence of 4 Å molecular sieves (MS 4A) from diisopropoxytitanium dihalides ($X_2Ti(O^iPr)_2$, X=Br [17] or Cl [18]) and optically pure BINOL or 6-Br-BINOL [19a, 19b, 19c, 19d]. (This ligand is now commercially available in either (*R*)- or (*S*)-form.) The remarkable levels of enantioselectivity and rate acceleration observed with these BINOL-Ti catalysts (1) [20] stem from the favorable influence of the inherent C_2 symmetry and the higher acidity of BINOLs compared to those of aliphatic diols. The reaction is applicable to a variety of 1,1-disubstituted olefins to provide the ene products in extremely high enantiomeric excess (Table 1).

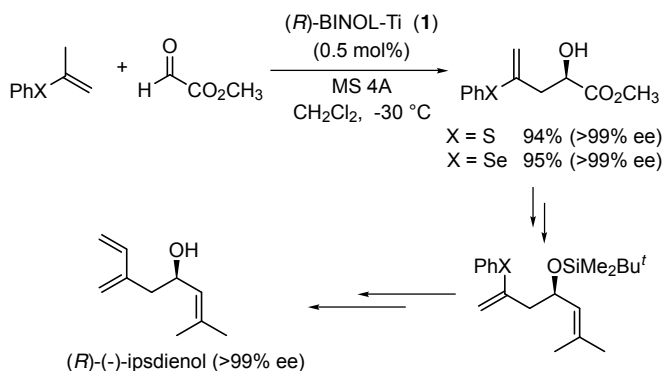
In the reactions with mono- and 1,2-disubstituted olefins, however, no ene product was obtained. This limitation has been overcome by the use of vinylic sulfides and selenides instead of mono- and 1,2-disubstituted olefins. With these substrates, the ene products are formed with virtually complete enantioselectivity and high diastereoselectivity [21]. The synthetic utility of the vinylic sulfide and selenide approach is exemplified by the synthesis of enantiopure (*R*)-(-)-ipsdienol, an insect aggregation pheromone (Scheme 4), [22a, 22b, 22c].

We [23] and others [24] have also reported the lanthanide complex-catalyzed asymmetric glyoxylate-ene reaction (Scheme 5). Although the reaction of glyoxylate and α -methylstyrene proceeds catalytically under the influence of the lanthanide $Ln(NTf_2)_3$ or $Ln(OTf)_3$ [25] complexes with chiral ligands, the enantioselectivity is low-to-moderate.

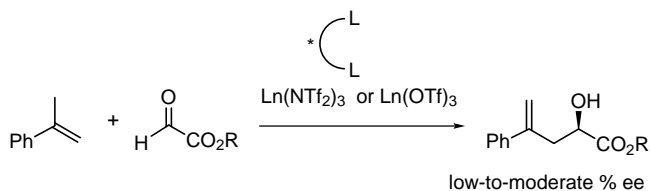
The synthetic potential of the asymmetric catalytic carbonyl-ene reaction depends greatly on the functionality that is possible in the carbonyl enophile. How-

Table 1. Asymmetric catalytic glyoxylate-ene reaction with various olefins

Run	olefin	$X_2Ti(O^iPr)_2$ (X)	catalyst (mol %)	products	% yield	% ee
A		Cl	10		72	95
		Cl	1.0		78	93
		Br	10		87	94
B		Cl	1.0		97	97
		Br	1.0		98	95
C		Cl	10		82	97
		Br	5		89	98
D		Cl	10		87	88
		Br	5		92	89



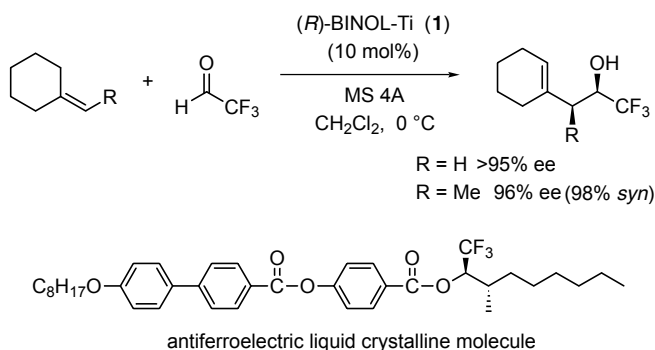
Scheme 4. Asymmetric carbonyl-ene reaction of vinylic sulfides and selenides



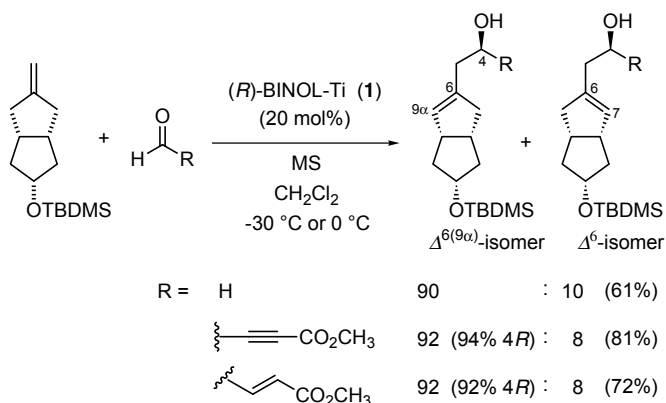
Scheme 5. Asymmetric carbonyl-ene reaction catalyzed by chiral lanthanide complexes

ever, the types of enophile that can be employed in the asymmetric catalytic ene reaction have previously been limited to aldehydes such as glyoxylate [15, 16, 26] and chloral [12, 27a, 27b]. Thus, it is highly desirable to develop other types of carbonyl enophiles to provide enantio-enriched molecules with a wider range of functionalities. We have developed an asymmetric catalytic fluoral-ene reaction [28], which provides an efficient approach for the asymmetric synthesis of some fluorine-containing compounds of biological and synthetic importance [29]. The reaction of fluoral with 1,1-disubstituted and trisubstituted olefins proceeds quite smoothly under catalysis by the BINOL-Ti complex (1) to provide the corresponding homoallylic alcohol with extremely high enantioselectivity (>95% ee) and *syn*-diastereoselectivity (>90%) (Scheme 6). The sense of asymmetric induction in the fluoral-ene reaction is exactly the same as that observed for the glyoxylate-ene reaction; *(R)*-BINOL-Ti (1) provides the *(R)*- α -CF₃ alcohol. The *syn*-diastereomers of α -trifluoromethyl- β -methyl-substituted compounds thus synthesized with *two stereogenic centers* show anti-ferroelectric properties preferentially to the *anti*-diastereomers [30a, 30b, 30c, 30d].

The BINOL-Ti catalyst can also be used for the carbonyl-ene reaction with formaldehyde or vinyl and alkynyl analogues of glyoxylates in an asymmetric catalytic desymmetrization (*vide infra*) approach to the asymmetric synthesis of isocarbacycline analogues (Scheme 7) [31a, 31b].



Scheme 6. Asymmetric carbonyl-ene reaction of fluoral



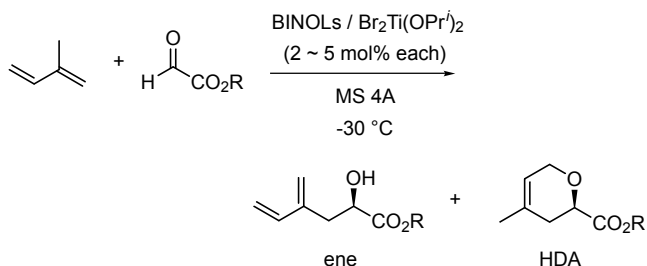
Scheme 7. Asymmetric carbonyl-ene reaction of formaldehyde or vinyl and alkynyl analogues of glyoxylate

2.1

Ene vs Hetero-Diels-Alder Reaction

In the reaction of a carbonyl compound with a conjugated diene having an allylic hydrogen, such as isoprene, there is the problem of the so-called periselectivity, arising from the formation of both the ene product and the hetero-Diels-Alder (HDA) product. In the reaction of glyoxylate with isoprene under catalysis of the BINOL-Ti complex (1) the ratio of ene/HDA product is dependent not only on the solvent employed but also on the chiral ligand of the titanium complex and further on the steric bulkiness of alkyl group (R) in glyoxylate (Scheme 8, Table 2) [19c].

The more polar solvent CH₂Cl₂ is more favorable than toluene for the formation of the ene product (Run 1 vs 2). The modification of the BINOL-ligand, 6-



Scheme 8. Ene vs hetero Diels-Alder reaction catalyzed by BINOL-Ti complex

Table 2. The reaction of glyoxylate with isoprene

Run	R	BINOLs (mol %)	% yield	ene (% ee)/HDA (% ee)
1	Me	BINOL (2)	94	79 (97):21 (97)
2 ^a	Me	BINOL (2)	85	74 (98):26 (-)
3	Me	6-Br-BINOL (2)	95	83 (99):17 (-)
4	ⁿ Bu	6-Br-BINOL (2)	86	85 (>99):15 (-)
5	ⁱ Pr	6-Br-BINOL (5)	61	90 (92):10 (-)
6	CH ₂ CF ₃	6-Br-BINOL (2)	95	92 (>99):8 (-)

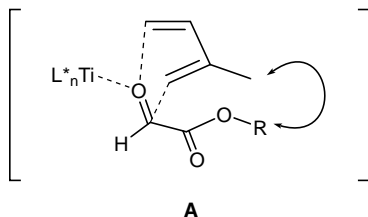
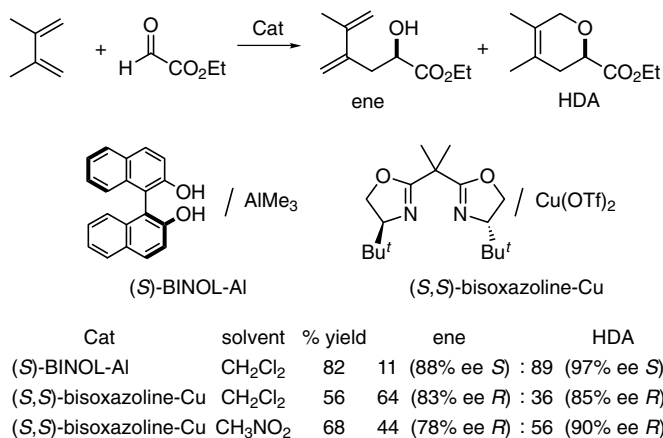


Fig. 1. Endo transition state of hetero-Diels-Alder reaction

Br-BINOL, is quite effective for enhancement of both the ene-selectivity and enantioselectivity as compared with those by the parent BINOL-Ti catalyst (1) (Run 1 vs 3). An increase in the steric bulkiness of the alkyl group (R) [32] in the glyoxylate leads to a substantial increase in the periselectivity for the ene product (Runs 3 to 6): With the more bulky alkyl group (R), the *endo* orientation of the ester moiety becomes less favorable through repulsive interaction between the alkyl group (R) and the methyl substituent of isoprene in the transition state (A) for the HDA reaction (Fig. 1), resulting, in turn, in the predominant formation of the ene products. Thus, the periselectivity for the ene reaction is increased up to 92%, particularly with the trifluoroethyl glyoxylate, accompanied by a high chemical yield (84%) and again complete enantioselectivity (Run 6) [33]. The



Scheme 9. Ene vs hetero Diels-Alder reaction catalyzed by BINOL-Al or bisoxazoline-Cu complex

enhanced ene-selectivity is presumably due not only to the steric but also to the electronic effect of the electron-withdrawing CF₃ group [32, 34].

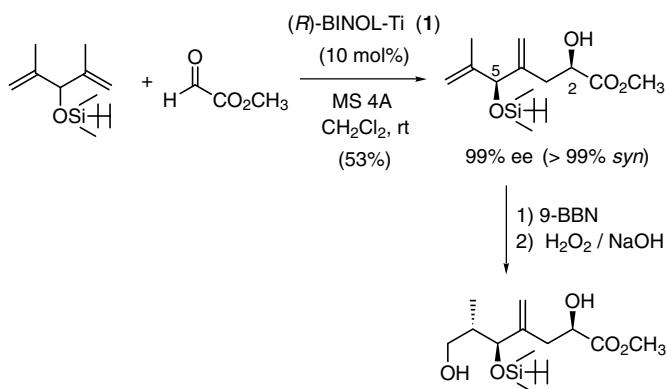
A dramatic changeover is observed not only in the ene/HDA product ratio but also in the absolute stereochemistry when the central metal is changed from Ti to Al. Jørgensen and coworkers thus reported the HDA selective reaction of ethyl glyoxylate with 2,3-dimethyl-1,3-butadiene catalyzed by a BINOL-derived Al complex [35], where the HDA product was obtained in up to 89% periselectivity with high ee (Scheme 9). The absolute configuration was opposite to that observed when using the BINOL-Ti catalyst.

They have also reported on a solvent effect in the reaction of ethyl glyoxylate and 2,3-dimethyl-1,3-butadiene catalyzed by the cationic bisoxazoline-Cu complex (Scheme 9) [36]. In the less polar solvent CH₂Cl₂, the ene product is obtained predominantly. In contrast, the reaction in the more polar solvent CH₃NO₂ leads to a preference for the HDA product over the ene product.

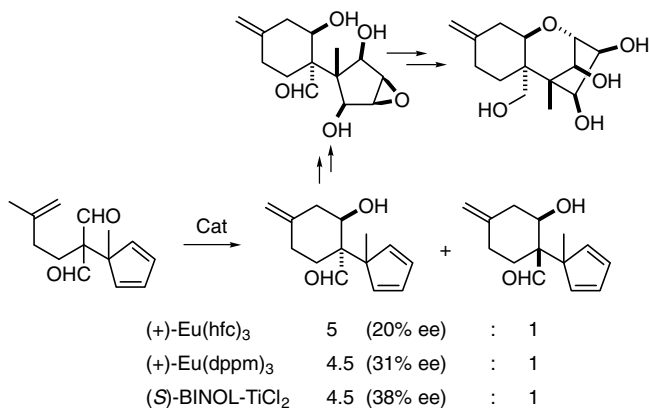
2.2

Asymmetric Catalytic Desymmetrization

Desymmetrization of an achiral, symmetrical molecule through a catalytic process is a potentially powerful but relatively unexplored concept for asymmetric synthesis. While the ability of enzymes to differentiate between enantiotopic functional groups is well known [37a, 37b, 37c, 37d], little is known about a similar ability of non-enzymatic catalysts, particularly for carbon-carbon bond forming processes. Desymmetrization by the catalytic glyoxylate-ene reaction of prochiral ene substrates with the planar symmetry provides an efficient access to remote [38] and internal [39] asymmetric induction which is otherwise difficult to attain (Scheme 10) [40]. The (2*R*,5*S*)-*syn*-product is obtained in >99% ee along



Scheme 10. Asymmetric desymmetrization in carbonyl-ene reaction catalyzed by BINOL-Ti complex



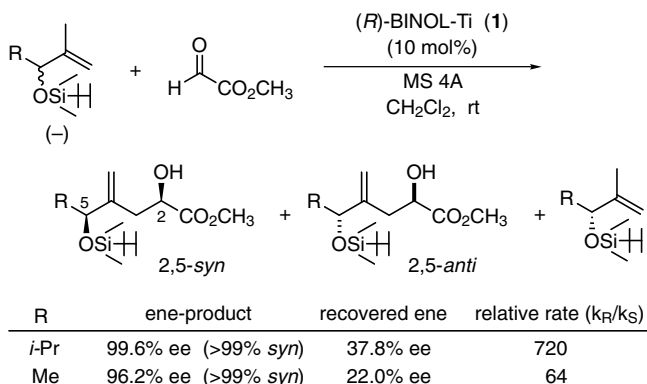
Scheme 11. Asymmetric desymmetrization in asymmetric ene cyclization

with more than 99% diastereoselectivity. The diene thus obtained can be transformed to a more functionalized compound in a regioselective and diastereoselective manner.

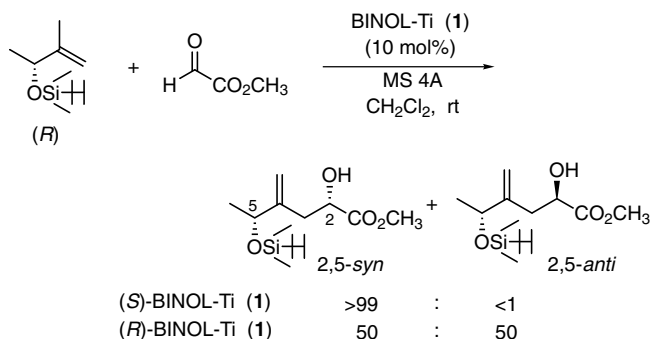
Ziegler and Sobolov have reported an asymmetric desymmetrization approach to the synthesis of the tricothecene, anguidine, via an ene cyclization (Scheme 11) [41]. The (2,4) ene cyclization (vide infra) of the prochiral aldehyde on silica gel gives a 1:1 diastereomeric mixture. Cyclization with purified Eu(fod)_3 as Lewis acid catalyst gives an 8:1 mixture. The major isomer is a potential intermediate for the synthesis of anguidine. However, use of $(+)\text{-Eu(hfc)}_3$, $(+)\text{-Eu(dppm)}_3$, or $(S)\text{-BINOL-TiCl}_2$ complex as chiral Lewis acid affords only 20~38% ee.

2.3 Kinetic Optical Resolution

On the basis of the desymmetrization concept, the kinetic optical resolution of a racemic substrate [42a, 42b] might be recognized as an intermolecular version of the desymmetrization. The kinetic resolution of a racemic allylic ether by the glyoxylate-ene reaction also provides an efficient access to remote but relative [40] asymmetric induction. The reaction of allylic ethers catalyzed by the (*R*)-BINOL-derived complex (1) provides the 2*R*,5*S*-*syn*-products with >99% diastereoselectivity along with more than 95% ee (Scheme 12). The high diastereoselectivity, coupled with the high ee, strongly suggests that the catalyst/glyoxylate complex efficiently discriminates between the two enantiomeric substrates to accomplish effective kinetic resolution. In fact, the relative rates between the



Scheme 12. Kinetic optical resolution in asymmetric carbonyl-ene reaction catalyzed by BINOL-Ti complex



Scheme 13. Double asymmetric induction in carbonyl-ene reaction catalyzed by BINOL-Ti complex

reactions of the either enantiomers, calculated by the equation $\ln[(1-c)(1-ee_{\text{recov}})] \times \{\ln[(1-c)(1+ee_{\text{recov}})]\}^{-1}$, $c=(ee_{\text{recov}}) \times (ee_{\text{recov}}+ee_{\text{prod}})^{-1}$, $0 < c, ee < 1$ where c is the fraction of consumption, were ca. 700 for $R=i\text{-Pr}$ and 65 for $R=\text{Me}$. As expected, the double asymmetric induction [43a, 43b, 44] in the reaction of the (*R*)-ene component using the catalyst (*S*)-1 (“matched” catalytic system) leads to the complete (>99%) 2,5-*syn*-diastereoselectivity in high chemical yield, whereas the reaction of the (*R*)-ene using (*R*)-1 (“mis-matched” catalytic system) produces a diastereomeric mixture in quite low yield (Scheme 13).

2.4

Positive Non-Linear Effect of Non-Racemic Catalysts

A chiral catalyst is not necessarily in an enantiopure form. Deviations from the linear relationship, namely “non-linear effects” are sometimes observed between the enantiomeric purity of chiral catalysts and the optical yields of the products (Fig. 2). Among these, the convex deviation, which Kagan [45a] and Mikami [46] independently refer to as a positive non-linear effect, (abbreviated as (+)-NLE (asymmetric amplification [45c]) has attracted current attention by achieving a higher level of asymmetric induction than the enantio-purity of the non-racemic (partially resolved) catalysts [45a, 45b, 45c]. In turn, (-)-NLE stands for the opposite phenomenon of concave deviation, namely a negative non-linear effect.

We have observed a remarkable level of (+)-NLE in the catalytic ene reaction. For instance, in the glyoxylate-ene reaction, the use of a catalyst prepared from BINOL of 33.0% ee provides the ene product with 91.4% ee in 92% chemical yield (Scheme 14) [46]. The ee thus obtained is not only much higher than the ee of the BINOL employed, but also very close to the value (94.6% ee) obtained using enantiomerically pure BINOL (Fig. 3).

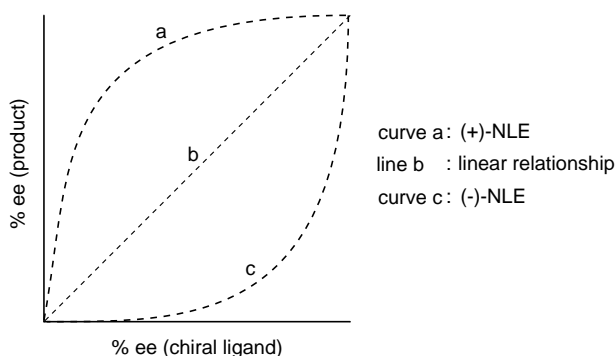
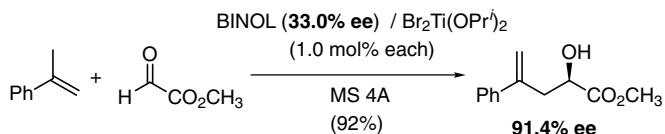


Fig. 2. Relationship between the enantiomeric purity of chiral ligands and the optical yield of products



Scheme 14. Positive non-linear effect in asymmetric carbonyl-ene reaction

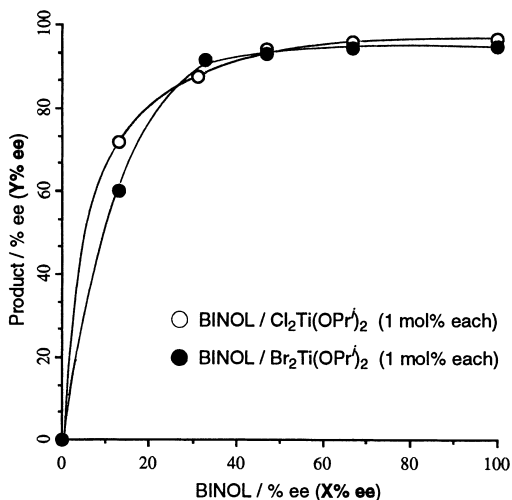


Fig. 3. Positive non-linear effect in asymmetric glyoxylate-ene reaction

2.5 Asymmetric Activation of Racemic Catalysts

While non-racemic catalysts can generate non-racemic products with or without NLE, racemic catalysts inherently produce only racemic products. A strategy whereby a racemic catalyst is enantiomer-selectively de-activated by a chiral molecule has been shown to yield non-racemic products [47, 48]. However, the level of asymmetric induction does not exceed the level attained by the enantiopure catalyst (Fig. 4a). Recently, “chiral poisoning” [49] has been named as such a *deactivating* strategy. In contrast, we have reported an alternative but conceptually opposite strategy to asymmetric catalysis by racemic catalysts. A *chiral activator* selectively activates one enantiomer of a racemic chiral catalyst. Higher enantioselectivity might be attained than that achieved by an enantiopure catalyst ($\% ee_{\text{act}} \gg \% ee_{\text{enantiopure}}$), in addition to a higher level of catalytic efficiency ($k_{\text{act}} \gg k_{\text{enantiopure}}$) (Fig. 4b).

Catalysis with racemic BINOL-Ti(O^tPr)₂ (2) achieves extremely high enantioselectivity by adding another diol for the enantiomer-selective activation (Scheme 15, Table 3) [50a, 50b, 50c, 50d]. Significantly, a remarkably high enan-

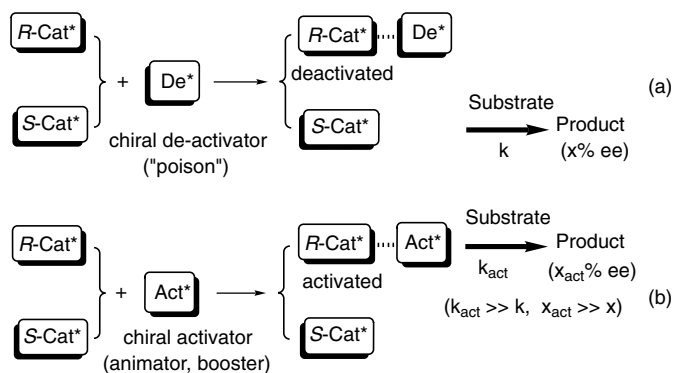


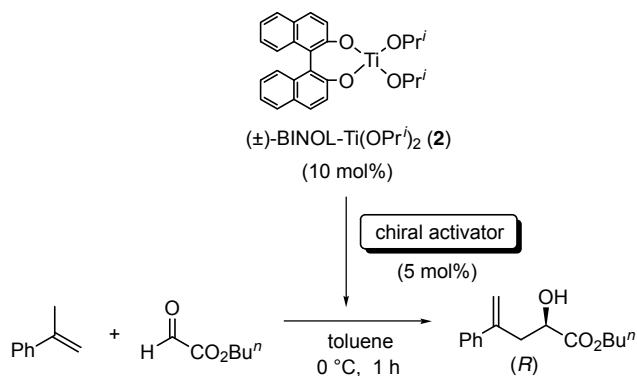
Fig. 4. Asymmetric activation vs de-activation

tioselectivity (90% ee, *R*) was achieved using just a half-molar amount (5 mol %) of (*R*)-BINOL activator added to a *racemic* (\pm)-BINOL-Ti(O^{*i*}Pr)₂ complex (**2**) (10 mol %).

The activation of the enantiopure (*R*)-BINOL-Ti(O^{*i*}Pr)₂ [51] catalyst (**2**) was investigated by further addition of (*R*)-BINOL (Scheme 16, Table 4). The reaction proceeded quite smoothly to provide the carbonyl-ene product in higher chemical yield (82%) and enantioselectivity (97% ee) (Run 3) than without additional BINOL (95% ee, 20%) (Run 1). Comparing the results of enantiomer-selective activation of the *racemic* catalyst (90% ee, *R*) (Table 3, Run 4) with those of the enantiopure catalyst [with (97% ee, *R*) or without activator (95% ee, *R*)], the reaction catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(R)*-BINOL complex (**2'**) is calculated to be 27 times faster than that catalyzed by (*S*)-BINOL-Ti(O^{*i*}Pr)₂ (**2**) in the *racemic* case (Fig. 5a). Indeed, kinetic studies involving a rapid-quench GC analysis show that the reaction catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(R)*-BINOL complex (**2'**) is 26 times faster than that catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂ (**2**). These results imply that the *racemic* (\pm)-BINOL-Ti(O^{*i*}Pr)₂ (**2**) and half-molar amount of (*R*)-BINOL assemble preferentially into the (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(R)*-BINOL complex (**2'**) and unchanged (*S*)-BINOL-Ti(O^{*i*}Pr)₂ (**2**). In contrast, the enantiomeric form of the additional chiral ligand (*(S)*-BINOL) activates the (*R*)-BINOL-Ti(O^{*i*}Pr)₂ (**2**) to a smaller degree (Run 6), thus providing the carbonyl-ene product in lower optical (86% ee, *R*) and chemical (48%) yields than (*R*)-BINOL does.

The great advantage of asymmetric activation of the *racemic* BINOL-Ti(O^{*i*}Pr)₂ complex (**2**) is highlighted in a catalytic version (Table 3, Run 5). High enantioselectivity (80.0% ee) is obtained by adding less than the stoichiometric amount (0.25 molar amount) of additional (*R*)-BINOL. A similar phenomenon of enantiomer-selective activation has been observed in aldol and (hetero-) Diels-Alder reactions catalyzed by a *racemic* BINOL-Ti(O^{*i*}Pr)₂ catalyst (**2**) [52].

Another possibility was explored using *racemic* BINOL as an activator. *Racemic* BINOL was added to the (*R*)-BINOL-Ti(O^{*i*}Pr)₂ (**2**) (Run 8), giving higher



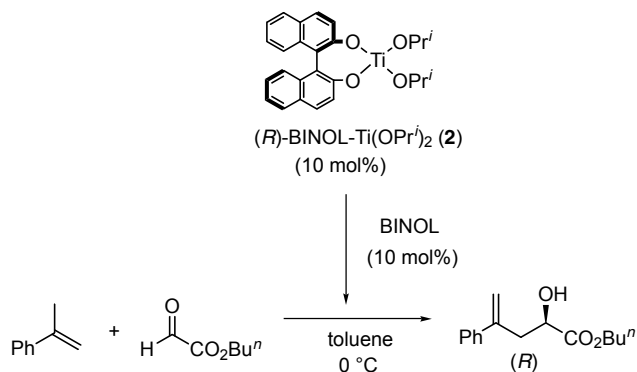
Scheme 15. Enantiomer selective activation of racemic BINOL-Ti(O^{*i*}Pr)₂

Table 3. Enantiomer selective activation of racemic BINOL-Ti(O^{*i*}Pr)₂ (**2**)

Run	chiral activator	% yield	% ee
1	none	1.6	0
2		20	0
3		38	81
4		52	90
5 ^a		35	80

^a 2,5 mol% of (R)-BINOL as an activator

yield and enantioselectivity (96% ee, 69%) than those obtained by the original catalyst (*R*)-BINOL-Ti(O^{*i*}Pr)₂ (**2**) without additional BINOL (95% ee, 20%) (Run 1). Comparing the results (96% ee, *R*) with the racemic activator with those of enantiopure catalyst, (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(R)*-BINOL (**2'**) (97% ee, *R*) or (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(S)*-BINOL (86% ee, *R*), the reaction catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂ catalyst/*(R)*-BINOL complex (**2'**) is calculated to be 10 times faster than that catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(S)*-BINOL (Fig. 5b). A rapid-quench GC analysis revealed the reaction catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(R)*-BINOL complex (**2'**) to be 9.2 times faster than that catalyzed by the (*R*)-BINOL-Ti(O^{*i*}Pr)₂/*(S)*-BINOL.



Scheme 16. Asymmetric activation of enantiopure BINOL-Ti(O^{*i*}Pr)₂

Table 4. Asymmetric activation of enantiopure (R)-BINOL-Ti(O^{*i*}Pr)₂ (2)

Run	BINOL	time (min)	% yield	% ee
1	none	60	20	95
2		1	1.6	95
3	(R)-BINOL	60	82	97
4		1	41	97
5		0.5	24	97
6	(S)-BINOL	60	48	86
7		0.5	2.6	86
8	(±)-BINOL	60	69	96

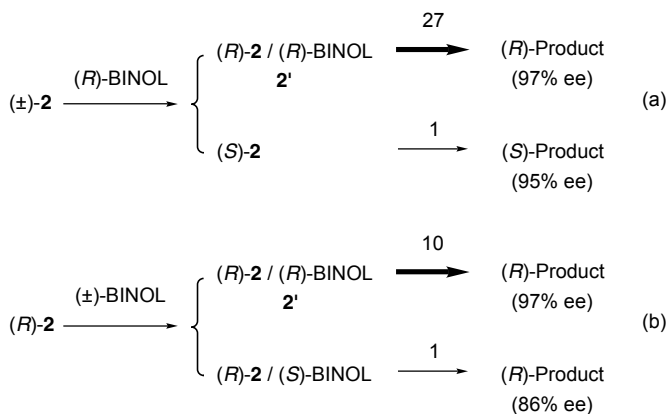


Fig. 5. Kinetic feature of asymmetric activation of BINOL-Ti(O^{*i*}Pr)₂

3 Ene Cyclization

Conceptually, intramolecular ene reactions [53a, 53b, 53c, 53d] (ene cyclizations) can be classified into six different modes (Fig. 6) [8a, 54]. In the ene cyclizations, the carbon numbers where the tether connects the [1,5]-hydrogen shift ring system, are expressed in (m,n) type. A numerical prefix stands for the forming ring size.

Asymmetric catalysis of ene reactions was initially explored in the intramolecular cases, since the intramolecular versions are much more facile than their intermolecular counterparts. The first example of an enantioselective 6-(3,4) carbonyl-ene cyclization was reported using a BINOL-derived zinc reagent [55]. However, this was successful only when using an excess of the zinc reagent (at least 3 equivalents). Recently, an enantioselective 6-(3,4) olefin-ene cyclization has been developed using a stoichiometric amount of a TADDOL-derived chiral titanium complex (Scheme 17) [56]. In this ene reaction, a hetero Diels-Alder product was also obtained, the ratio depending critically on the solvent system

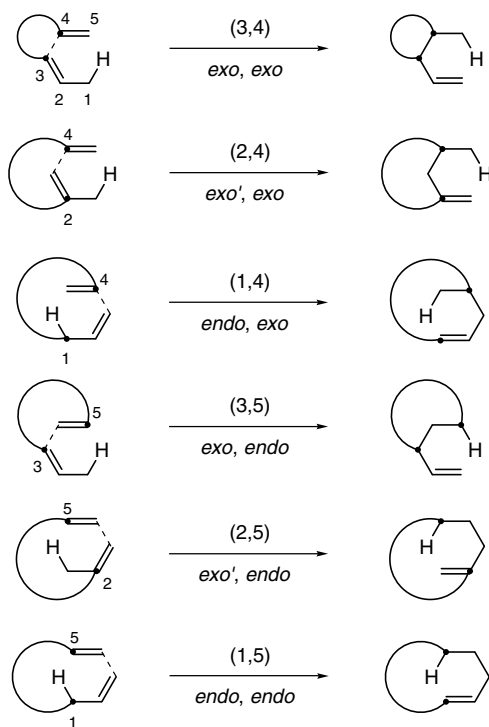
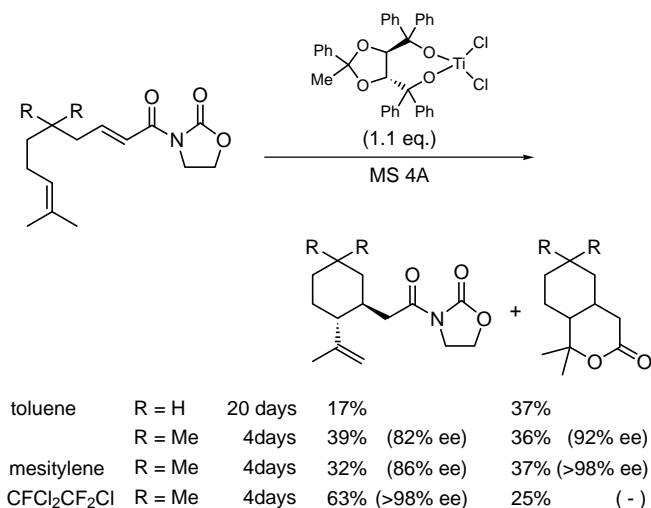
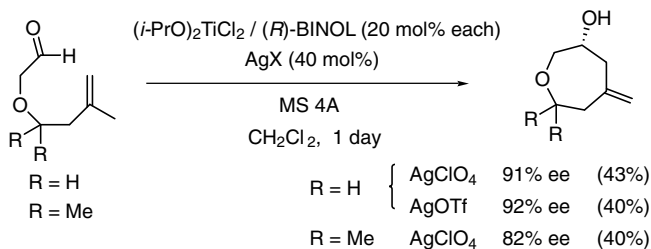


Fig. 6. Classification of ene cyclization



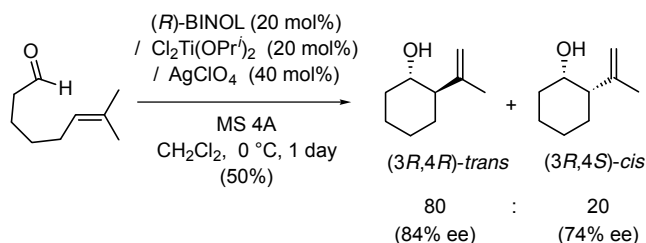
Scheme 17. Asymmetric ene cyclization catalyzed by TADDOL-Ti complex



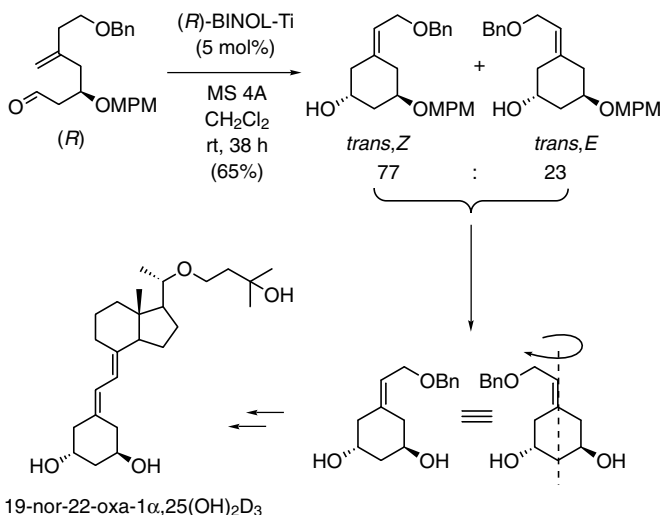
Scheme 18. Asymmetric 7-(2,4) carbonyl-ene cyclization catalyzed by BINOL-Ti complex

employed. In both cases, geminal disubstitution is required in order to obtain high ee's. However, neither reaction constitutes an example of a truly catalytic asymmetric ene cyclization.

We reported the first examples of asymmetric catalysis of intramolecular carbonyl-ene reactions of types (3,4) and (2,4), using the BINOL-derived titanium complex (1) [54, 57]. The catalytic 7-(2,4) carbonyl-ene cyclization gives the oxepane with high ee, and *gem*-dimethyl groups are not required (Scheme 18). In a similar catalytic 6-(3,4) ene cyclization, the *trans*-tetrahydropyran is preferentially obtained with high ee (Scheme 19). The sense of asymmetric induction is exactly the same as observed for the glyoxylate-ene reaction: the (*R*)-BINOL-Ti catalyst provides the (*R*)-cyclic alcohol. Therefore, the chiral BINOL-Ti catalyst works efficiently for both the chiral recognition of the enantioface of the aldehyde and the discrimination of the diastereotopic protons of the ene component in a truly catalytic fashion.



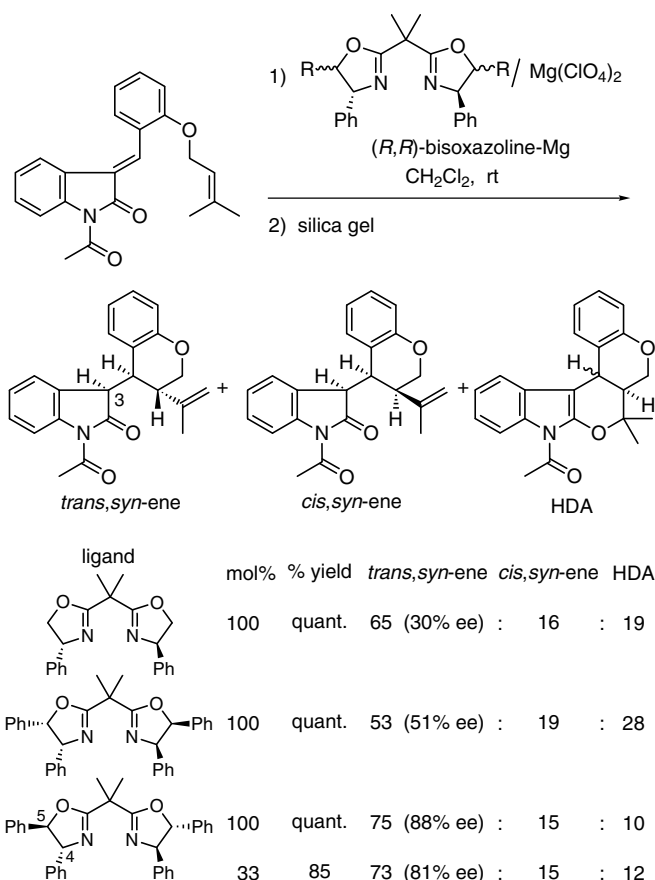
Scheme 19. Asymmetric 6-(3,4) carbonyl-ene cyclization catalyzed by BINOL-Ti complex



Scheme 20. “Symmetry”-assisted enantiospecific synthesis of A-ring of Vitamin D analogues based on asymmetric ene cyclization

Basic research on the synthesis of analogues of the biologically active form of vitamin D $_3$, 1 α ,25-dihydroxyvitamin D $_3$ [1 α ,25(OH) $_2$ D $_3$] has brought about the development of an important new field in medicinal chemistry [58, 59]. We have reported “symmetry”-assisted enantiospecific synthesis of the A-ring of the vitamin D hybrid analogues, 19-nor-22-oxa-1 α ,25(OH) $_2$ D $_3$ (Scheme 20) [60]. It should be noted here that the “*gem*-dialkyl” substituents are not necessary in obtaining a high level of enantioselectivity.

Desimoni and coworkers reported on the enantioselective ene cyclization using a stoichiometric or catalytic amount of a bisoxazoline-Mg(ClO $_4$) $_2$ complex (Scheme 21) [61]. In all cases, although a hetero-Diels-Alder product was formed, an ene product was obtained predominantly in *trans,syn* fashion as the major kinetic product. The minor kinetic ene products, the *trans,anti* and *cis,anti* products, were readily isomerized at the C3 atom by silica gel to give the thermodynamically stable products, the *trans,syn* and *cis,syn* isomers, respectively. The



Scheme 21. Asymmetric ene cyclization catalyzed by bisoxazoline-Mg complex

ratio of ene/HDA products and the enantioselectivity were critically dependent on the substituent at the 5 position of the chiral bisoxazoline ligand. A 4,5-*trans* disubstituent is important to obtain the ene product predominantly and in high % ee. When the reaction was performed with a reduced the amount of bisoxazoline-Mg complex, the product distribution and enantioselectivity were close to those of the corresponding stoichiometric reaction.

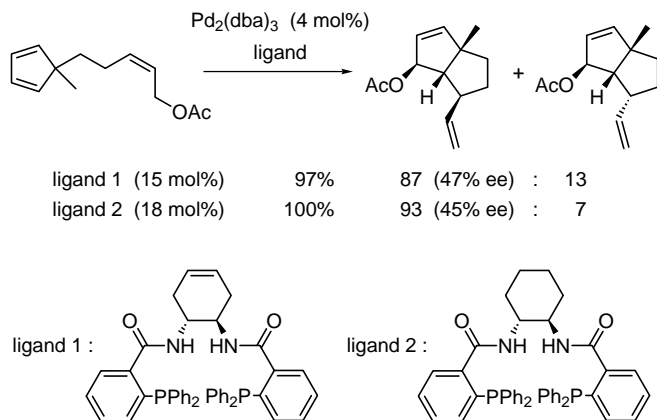
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Metallo-Ene Cyclization

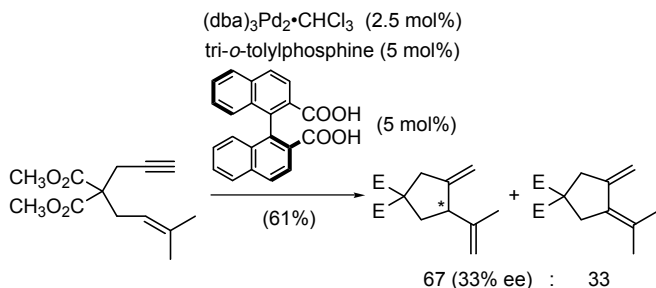
Metallo-ene cyclizations, intramolecular Pd(0), Ni(0), Rh(I), Zn(0) catalyzed alkene (or alkyne) allylations [62, 63, 64], have been recognized as a powerful tool in organic synthesis due to the synthetically useful functionalizations such as carbonylation or C-C coupling. The high regio- and stereoselectivities also al-

low the application of the metallo-ene cyclization to the syntheses of a variety of natural products. However, the enantioselective version of the catalytic metallo-ene cyclization, where the absolute stereochemistry of newly created stereogenic centers is controlled by chiral metal complexes, remains to be explored. Recently, Oppolzer and coworkers reported the enantioselective metallo-ene cyclization catalyzed by chiral palladium, nickel, and rhodium complexes (Scheme 22) [65]. Moderate enantioselectivity in terms of differentiation between the enantiotopic olefin functionality of prochiral ene substrate with planar symmetry was observed by using a chiral palladium complex. The use of a chiral bidentate ligand with a large bite angle [66] is effective for this type of enantioselective catalytic metallo-ene cyclizations.

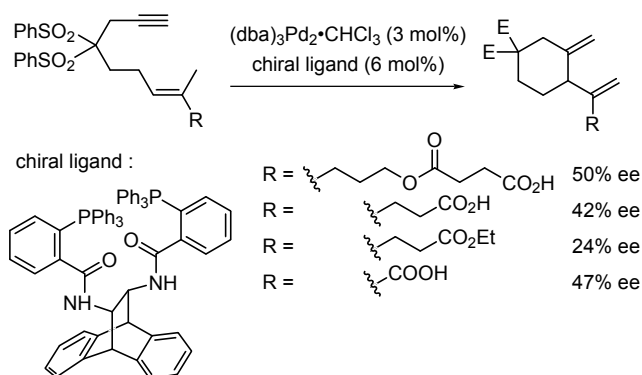
Pd complexes also catalyze the cyclization of the 1,6-enyne system to provide carbo- or heterocyclic compounds. The catalytic enantioselective version was reported by Trost and coworkers using chiral binaphthylidicarboxylic acid ligands [67] or cyclohexyldiamine-derived diphosphine [68] to provide moderate level of % ee (Schemes 23 and 24).



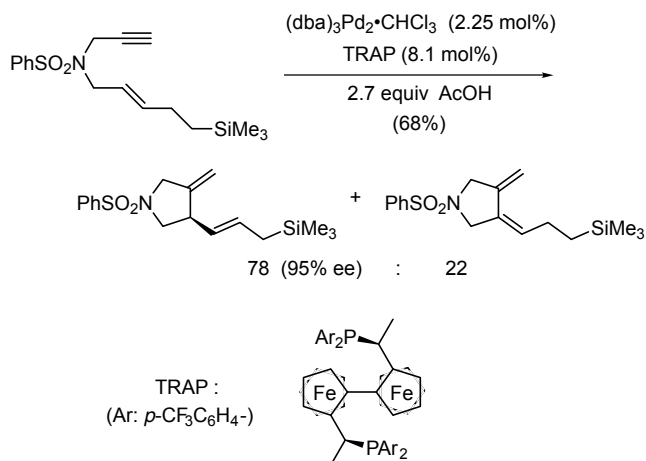
Scheme 22. Asymmetric metallo-ene cyclization catalyzed by chiral Pd complex



Scheme 23. Asymmetric cyclization of 1,6-enyne catalyzed by Pd/chiral acid



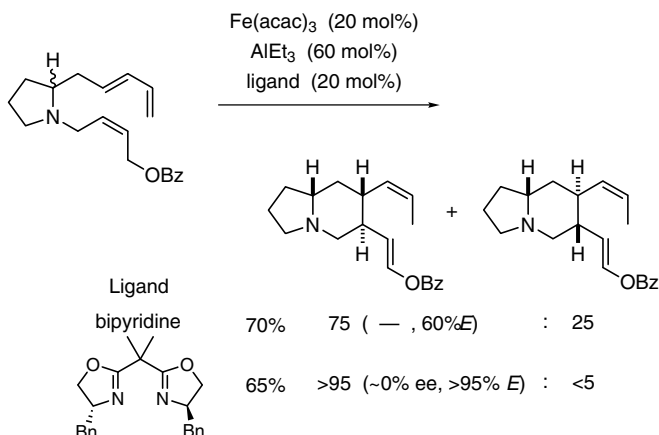
Scheme 24. Asymmetric cyclization of 1,7-enyne catalyzed by chiral Pd complex



Scheme 25. Asymmetric cyclization of 1,6-enyne catalyzed by TRAP-Pd complex

Extremely high enantioselectivity was attained by using the *trans* chelate diphosphine ligand, TRAP (Scheme 25) [69]. There are strong implications in the catalytic efficiency between electron density at the phosphine atom and the enantioselectivity: Increasing the electron-withdrawing ability of the ligand *P*-aryl substituents resulted in higher enantioselectivity and also higher catalytic activity. The best enantioselectivity, up to 95% ee, was obtained in the reaction of the silicon-substituted 1,6-enyne with a *para*-CF₃-substituted arylphosphine as a chiral ligand.

Iron complexes can also be employed for ene cyclization of triene systems (Scheme 26). Though a chiral bisoxazoline complex exhibits not only higher 1,3-stereoselection but also diastereoselection, no asymmetric induction was observed by the use of chiral bisoxazoline iron complex [70].



Scheme 26. Ene-type cyclization of triene system catalyzed by iron complex

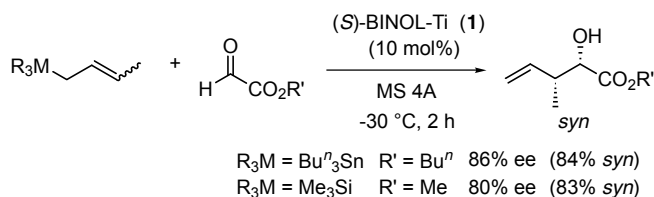
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Carbonyl Addition Reaction

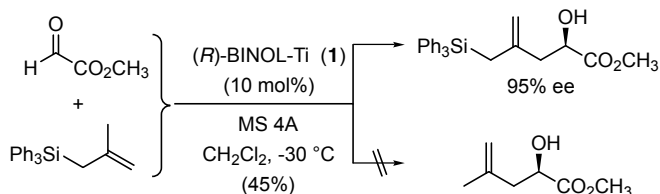
During the course of our research project on asymmetric catalysis of the carbonyl-ene reaction, we have found that the BINOL-Ti complexes (**1**) catalyze rather than promote stoichiometrically the carbonyl addition reaction of allylic silanes and stannanes [11, 71]. The addition reactions to glyoxylate of (*E*)-2-butenylsilane and -stannane proceed smoothly to afford the *syn*-products in high enantiomeric excess (Scheme 27) [71]. The *syn*-product thus obtained could readily be converted to the lactone portion of verrucaline A [72].

We have further found that BINOL-Ti (**1**) catalyzes the Sakurai-Hosomi reaction of methallylsilanes with glyoxylates (Scheme 28) [73]. Surprisingly, however, the products were obtained in the allylic silane (ene product) form with high enantioselectivity.

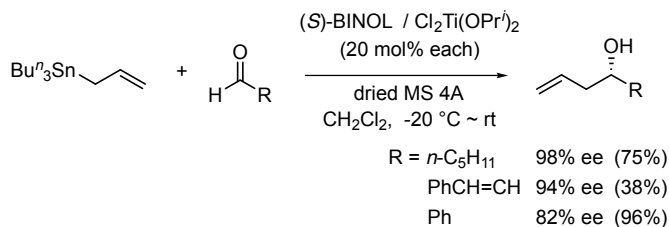
Asymmetric catalysis by BINOL-Ti complexes of the reaction of aliphatic and aromatic aldehydes with an allylstannane has been reported independently by Umani-Ronchi/Tagliavini [74] and Keck [75]. In Ronchi/Tagliavini's case [74], a new complex generated by reaction of the BINOL-Ti complex with allylstannane has been suggested to be the catalytic species which provides the remarkably high enantioselectivity (Scheme 29). Interestingly enough, no reaction occurs if 4 Å molecular sieves are not present during the preparation stage of the chiral catalyst, and 4 Å molecular sieves affect the subsequent allylation reaction. 4 Å molecular sieves dried for 12 h at 250 °C and 0.1 torr were recommended. Keck reported that addition of $\text{CF}_3\text{CO}_2\text{H}$ or $\text{CF}_3\text{SO}_3\text{H}$ strongly accelerates the reactions catalyzed by the BINOL-Ti(O^iPr)₂ complex (**2**) [75].



Scheme 27. Asymmetric carbonyl addition reaction catalyzed by BINOL-Ti



Scheme 28. Asymmetric ene-type reaction of methallylsilanes



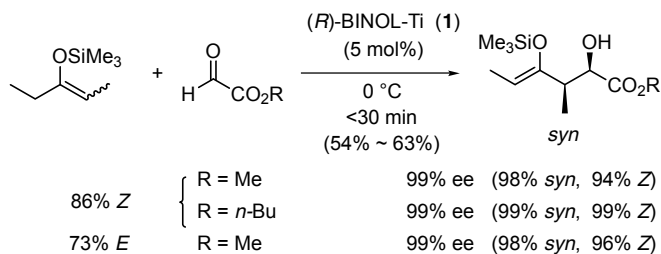
Scheme 29. Asymmetric carbonyl addition reaction of aliphatic and aromatic aldehydes

6

Aldol-Type Reaction

The aldol reaction constitutes one of the most fundamental bond construction processes in organic synthesis [76a, 76b]. Therefore, much attention has been focused on the development of asymmetric catalysts for aldol reactions using silyl enol ethers of ketones or esters as storable enolate components, the so-called Mukaiyama aldol condensation.

We have found that the BINOL-derived titanium complex serves as an efficient catalyst for the Mukaiyama-type aldol reaction of ketone silyl enol ethers with good control of both absolute and relative stereochemistry (Scheme 30) [77]. Surprisingly, however, the aldol products were obtained in the silyl enol



Scheme 30. Asymmetric aldol (prototropic ene-type) reaction

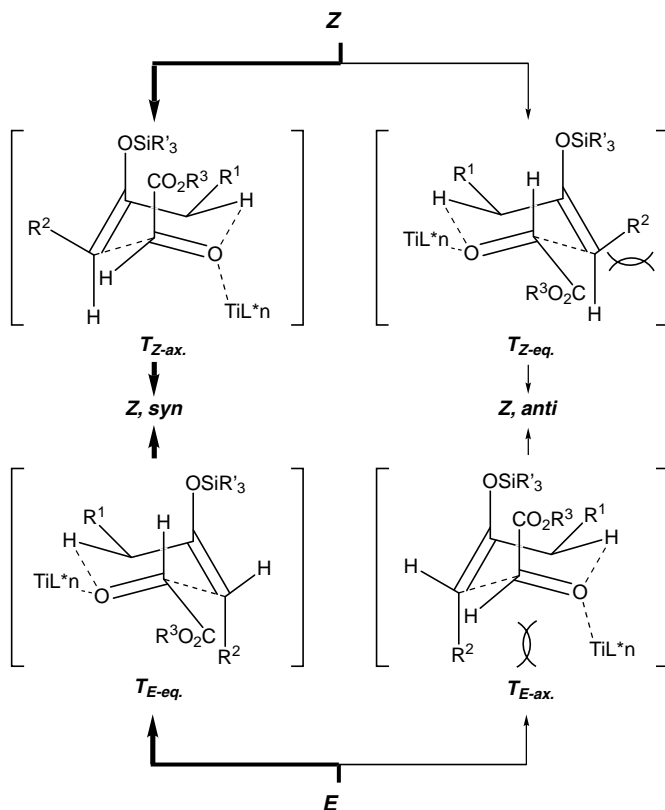


Fig. 7. Transition states of Mukaiyama-type aldol reaction of ketone silyl enol ether

ether (ene product) form, with high *syn*-diastereoselectivity from either geometrical isomer of the starting silyl enol ethers.

It appears likely that the reaction proceeds through an ene reaction pathway. Such an ene reaction pathway has not been previously recognized as a possible mechanism in the Mukaiyama aldol condensation. Usually, an acyclic antiperi-

planar transition state model has been used to explain the formation of the *syn*-diastereomer from either (*E*)- or (*Z*)-silyl enol ethers [78a, 78b]. However, the cyclic ene mechanism now provides another rationale for the *syn*-diastereoselection irrespective of the enol silyl ether geometry (Fig. 7).

The aldol reaction of a silyl enol ether proceeds in a double and two-directional fashion – upon addition of an excess amount of an aldehyde – to give the silyl enol ether in 77% isolated yield and in more than 99% ee and 99% de (Scheme 31) [79]. The present asymmetric catalytic aldol reaction is characterized by a kinetic amplification phenomenon of the product chirality on going from the one-directional aldol intermediate to the two-directional product (Fig. 8). Further transformation of the *pseudo* C_2 symmetric product whilst still being protected as the silyl enol ether leads to a potent analogue of an HIV protease inhibitor.

The silatropic ene pathway, that is, direct silyl transfer from an enol silyl ether to an aldehyde, may be involved as a possible mechanism in the Mukaiyama aldol-type reaction. Indeed, *ab initio* calculations show the silatropic ene pathway involving the cyclic (boat and chair) transition states for the BH_3 -promoted aldol reaction of the trihydrosilyl enol ether derived from acetaldehyde with formaldehyde to be favored [80]. Recently, we have reported the possible intervention of a silatropic ene pathway in the asymmetric catalytic aldol-type reaction of silyl enol ethers of thioesters [81]. The chloro and amino compounds thus obtained are useful intermediates for the synthesis of carnitine and GABOB (Scheme 32) [82a, 82b].

There is a dichotomy in the sense of *syn*- vs *anti*-diastereofacial preference, dictated by the bulkiness of the migrating group [80]. The sterically demanding silyl group shows *syn*-diastereofacial preference but the less demanding proton leads to *anti*-preference (Scheme 33). The *anti*-diastereoselectivity in carbonyl-

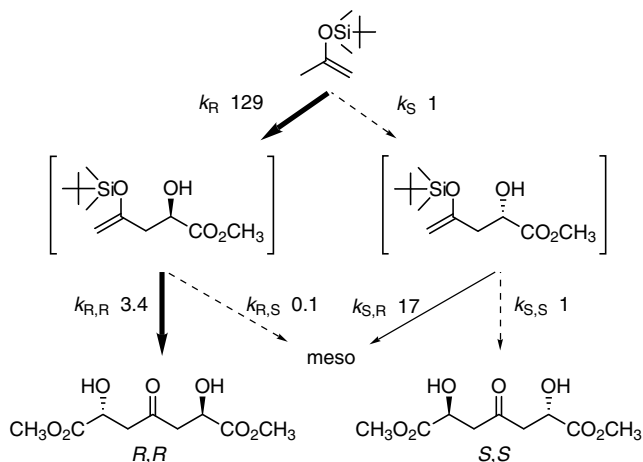
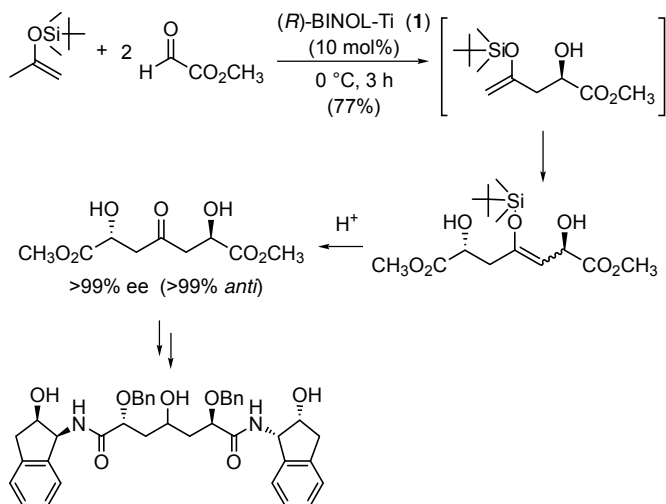
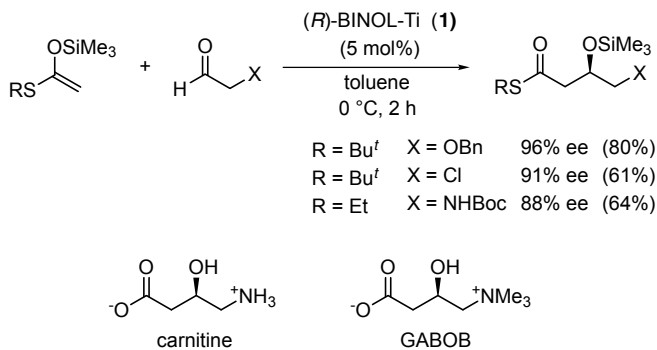


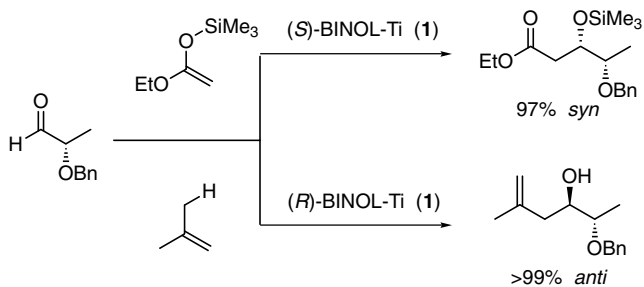
Fig. 8. Kinetic feature of two-directional aldol reaction



Scheme 31. Tandem and two-directional aldol-type reaction



Scheme 32. Asymmetric aldol (metallotropic ene-type) reaction



Scheme 33. Asymmetric carbonyl-ene vs aldol-type reaction of α -benzyloxy aldehyde

ene reactions can be explained by the Felkin-Anh-like cyclic transition state model (T_1) (Fig. 9). In the aldol reaction, by contrast, the inside-crowded transition state (T_1') is less favorable than T_2' , because of the steric repulsion between the trimethylsilyl group and the inside methyl group of aldehyde (T_1'). Therefore, the *syn*-diastereofacial selectivity is visualized by the *anti*-Felkin-like cyclic transition state model (T_2').

Keck [83] and Carreira [84a, 84b] have independently reported catalytic asymmetric Mukaiyama aldol reactions. Keck et al. also reported an aldol reaction of α -benzyloxy aldehyde with Danishefsky's diene. The aldol product was transformed to the hetero-Diels-Alder type product through acid-catalyzed cyclization. In their method, the catalyst is prepared using 1:1 and 2:1 stoichiometry of BINOL and $Ti(O^iPr)_4$ (Scheme 34) [85]. In their cases, oven dried 4 Å molecular sieves are used to generate the catalyst, which they reported to be of the BINOL- $Ti(O^iPr)_2$ structure, under refluxing conditions.

Carreira employed a chiral BINOL-derived Schiff base-titanium complex as a catalyst for aldol reactions with acetate-derived ketene silyl acetals (Scheme 35) [84a]. The catalyst was prepared in toluene in the presence of salicylic acid, which was reported to be crucial to attain a high enantioselectivity. The similar Schiff base-titanium complex is also applicable to the carbonyl-ene type reac-

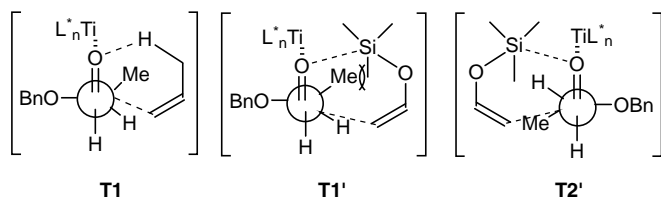
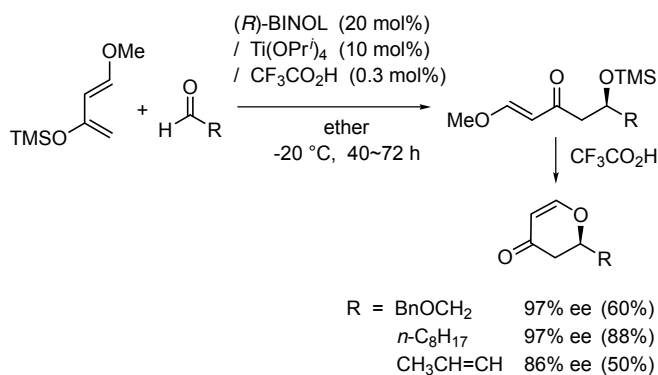
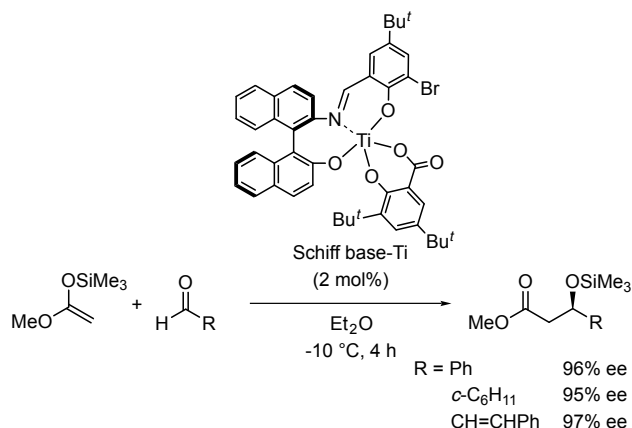


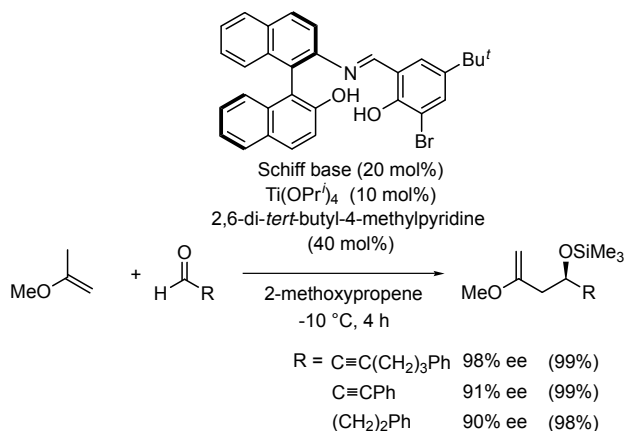
Fig. 9. Transition states of carbonyl-ene and aldol-type reaction of α -alkoxy aldehyde



Scheme 34. Asymmetric aldol-type reaction of Danishefsky's diene



Scheme 35. Asymmetric aldol-type reaction catalyzed by chiral Schiff base-Ti



Scheme 36. Asymmetric ene-type reaction of 2-methoxypropene

tion with 2-methoxypropene [84b]. Although the reaction was conducted in the toluene or ether solution to provide no addition product, excellent chemical yield and enantioselectivity were achieved by the use of 2-methoxypropene as a solvent (Scheme 36).

7

Conclusion

The class of ene reactions, the carbonyl-ene reaction in particular, has gained a wide scope for synthetic applications and a mechanistic basis for the stereocontrolled construction of carbon skeletons by catalytic amounts of various chiral

Lewis acids. For practical applications, the development of more efficient catalysts is important, for which molecular design of asymmetric catalysts is the key in view of the structure-catalytic activity relationship. Any progress along this line is highly promising and worth the effort.

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Chapter 33.1

Diels-Alder Reactions

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Keywords: Diels-Alder reaction, Cycloaddition, Lewis acids, Enantioselective catalysis

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1 Introduction

In the hierarchy of carbon-carbon bond constructions, the Diels-Alder reaction has attained a preeminent position [1]. This cycloaddition process allows for the stereoselective formation of cyclohexene rings possessing as many as four contiguous stereogenic centers while intramolecular [2] and transannular [3] variants facilitate the simultaneous formation of as many as three carbocyclic rings. It has long been recognized that the reaction facilitates the rapid development of molecular complexity and has been duly exploited in organic synthesis [4].

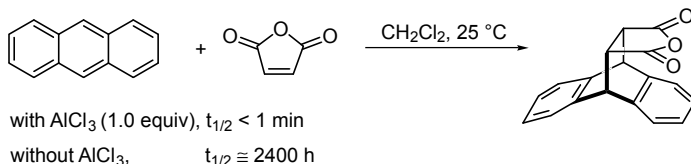
Given the prominent role of the Diels-Alder reaction in organic chemistry, it is not surprising that the search for enantioselective variants of this process has captured the attention of numerous researchers. Although chiral auxiliary-based reactions [5] retain a position of central importance, complementary catalytic variants are developing rapidly. Among these, chiral Lewis acid complexes that selectively activate one component (diene or dienophile) while providing a stereodefined environment are maturing as effective catalysts [6]. Accordingly, the ensuing discussion focuses on advances that have been made in the design and application of chiral Lewis acids for the Diels-Alder reaction.

2 Mechanistic Considerations in Lewis Acid Catalysis of the Diels-Alder Reaction [7]

2.1 General

In 1960, Yates and Eaton reported that an approximate rate acceleration of 10^5 was observed for the Diels-Alder reaction of anthracene and maleic anhydride in the presence of aluminum chloride (Scheme 1) [8]. This finding had important practical ramifications since it demonstrated that the Diels-Alder reaction could be conducted under mild conditions when an electropositive metal was used to lower the energy of activation.

In a subsequent study, Inukai and Kojima determined that the enthalpy of activation in the thermal reaction of butadiene with methyl acrylate was 18.0 ± 1.0 kcal/mol, while aluminum chloride catalysis reduced the activation energy to 10.4 ± 1.9 kcal/mol; little effect on the entropy of activation was observed [9]. Cal-



Scheme 1

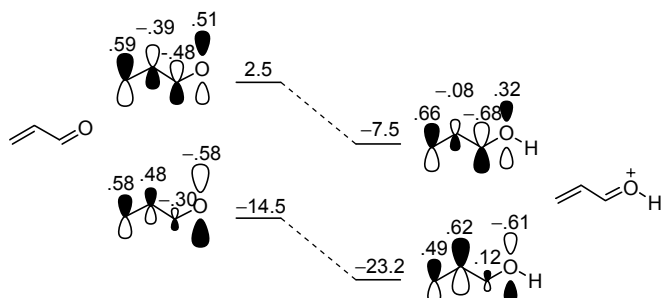
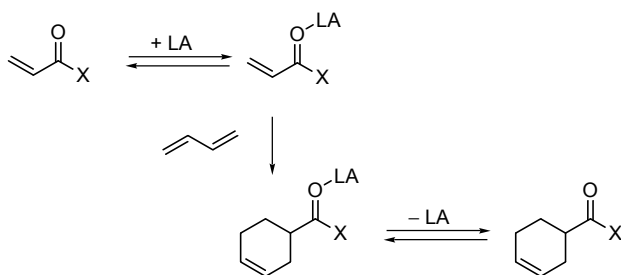


Fig. 1. Frontier orbital energies (eV) and coefficients for acrolein and protonated acrolein



Scheme 2

culations for related cycloadditions suggest that Lewis acid catalysis will usually contribute approximately a 10 kcal/mol drop in the activation energy [10]. This positive attribute of Lewis acid catalysis has been explained on the basis of frontier molecular orbital theory by Houk and Strozier who showed that the coordination of an acid (a proton in this case) to a typical dienophile substantially lowers the LUMO energy (Fig. 1), thereby enhancing interaction with the diene HOMO and lowering the activation energy for the process [11].

In a simplified catalytic cycle, reversible coordination of the dienophile to the Lewis acid (LA) activates the substrate toward diene cycloaddition. In the catalyst turnover event, the Lewis acid-product complex dissociate to reveal the decomplexed cycloadduct and regenerated catalyst (Scheme 2). While this catalytic cycle neglects issues of product inhibition and nonproductive catalyst binding for dienophiles having more than one Lewis basic site, the gross features of this process are less convoluted than many other enantioselective reactions (*e.g.*, olefin dihydroxylation, aldol reactions), a fact which may provide insight as to why this process is frequently used as a test reaction for new Lewis acid catalysts.

2.2 Diastereoselectivity and Transition State Issues

Subsequent studies have demonstrated another attractive feature of Lewis acid activation: enhanced *endo* diastereoselectivity (Fig. 2) [12,13]. Augmented secondary orbital interactions, an extension of Alder's notion of "maximum accumulation of unsaturations" [14], stemming from a "tighter" transition state for the catalyzed process relative to the thermal variant have been postulated as the source of enhanced *endo* diastereoselection [11]. However, this picture has since been refined, in particular for the Lewis acid-mediated cycloaddition. One study contends that stabilizing HOMO (diene)-LUMO (dienophile) interactions lead to destabilizing charge donation. The geometry of the *endo* transition state allows for the minimum induced charge separation and is thus favored [15]. It is generally agreed that Lewis acid dienophile activation results in a more asynchronous transition state: bond formation at the dienophile terminus is more advanced than for the internal carbon [16].

More recent research has uncovered some unusual attributes of the transition states for Lewis acid-catalyzed Diels-Alder reactions. Of note, a [4+3] transition state has been postulated as the low energy pathway for the borane-catalyzed Diels-Alder reaction between acrolein and 1,3-butadiene [17]; that is, a stabilizing interaction between the terminal carbon of the diene and the carbonyl carbon of the dienophile appears to be more important than the classically-invoked interaction between C-2 of the diene and the carbonyl carbon (Fig. 3). While this argument was originally advanced for only the *endo s-trans* transition state, it has been subsequently broadened in scope to include each of the four possible diastereomeric transition states for the boron trifluoride-promoted process [10]; thus, the energy differences for these reaction pathways are determined by the strength and number of the secondary interactions.

An even more unusual mechanistic hypothesis has arisen from calculations conducted at the Hartree-Fock level of theory which concluded that the boron trifluoride-promoted reaction of acrolein and 1,3-butadiene proceeds *via* a

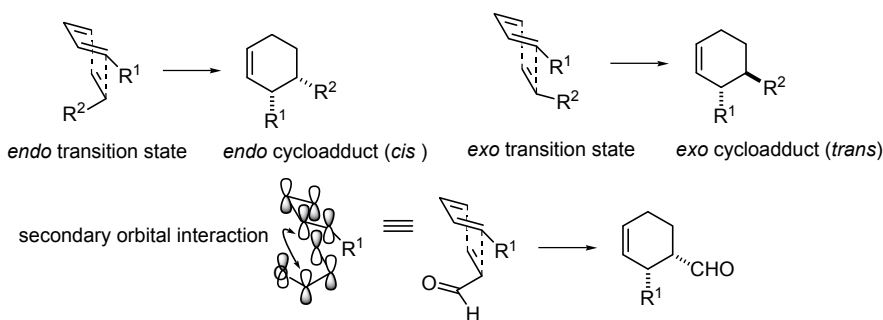


Fig. 2. Diels-Alder transition states and secondary orbital interaction for the *endo* transition state

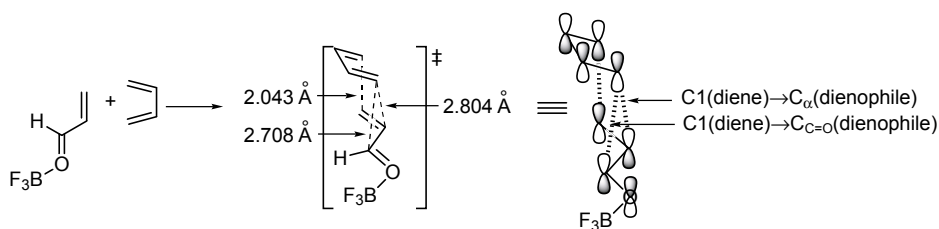


Fig. 3. Proposed [4+3] transition state

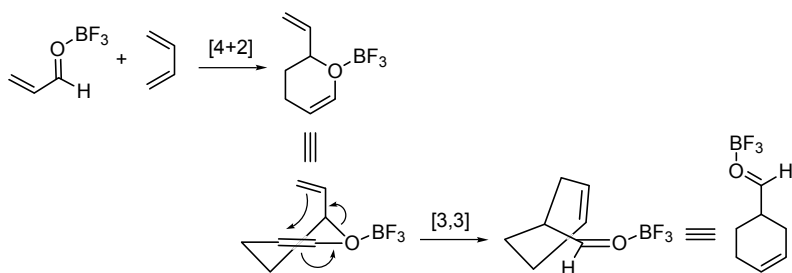


Fig. 4. Proposed hetero [2+4] cycloaddition-Claisen rearrangement mechanism

[2+4] hetero Diels-Alder reaction to afford a high energy boron-coordinated vinyl dihydropyran which undergoes a [3,3] sigmatropic rearrangement to give the observed carbocyclic Diels-Alder adduct (Fig. 4) [18]. When electron correlation effects are included by means of Density Functional Theory (DFT) calculations, however, the expected [4+2] cycloadduct is observed [10].

The preceding discussion is not meant to imply that stereoelectronic effects alone are responsible for determining diastereoselection in the Diels-Alder reaction. Indeed, examples of reactions that do not conform to the *endo* rule abound, and these cases are not easily explained without invoking alternative hypotheses. For instance, it has been demonstrated that 1,1-disubstituted dienophiles can favor formation of the *exo* product with cyclopentadiene, sometimes to the complete exclusion of the electronically favored *endo* isomer [19]. There appears to be subtle interplay between steric and electronic factors, as simply switching the diene to cyclohexadiene or an acyclic diene results in a turnover in selectivity to favor the *endo* isomer. While the exact source of stereocontrol for a given cycloaddition is still a source of debate, this review will emphasize the practical ramifications of diastereoselection, namely, prototypical dienophiles such as α -methacrolein and α -bromoacrolein can be relied on to deliver *exo* cycloadducts preferentially with cyclopentadiene (*endo* otherwise), while acrylate, crotonate, and cinnamate-derived dienophiles will generally favor the *endo* tran-

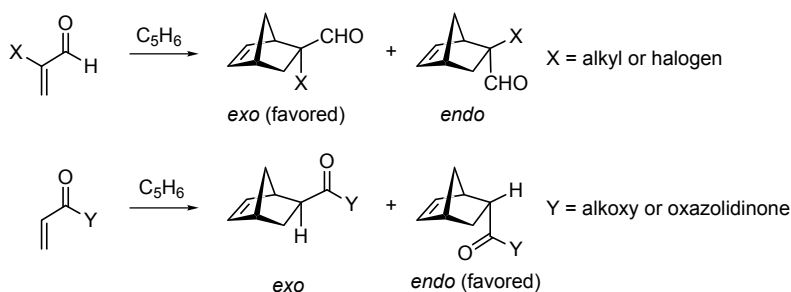


Fig. 5. Generalized stereochemical preferences as a function of dienophile

sition state in catalyzed reactions with dienes (Fig. 5). The reader is referred to reviews of this topic for a more exhaustive discussion [14, 20, 21].

2.3

The Nature of the Lewis Acid-Dienophile Complex

The realization of high enantioselectivity for the catalyzed Diels-Alder reaction (or any enantioselective process) relies on effective funneling of the reactants through a transition state that is substantially lower in energy relative to competing diastereomeric transition states. For the process at hand, a high level of transition state organization is required, necessitating control of several factors: 1) mode of binding (η^2 vs. η^1) of the carbonyl group to the Lewis acid; 2) for η^1 complexes, the regiochemistry of complexation to two or more available lone pairs; 3) conformation of the dienophile (*s-cis* vs. *s-trans*).

Control of these variables poses a formidable challenge to those engaged in reaction design, since all regiochemical and conformation issues must be addressed, independent of enantiofacial bias (Fig. 6). All three of these topics have been surveyed extensively elsewhere; the salient points will be summarized for the purpose of the ensuing discussion.

2.3.1

Mode of Complexation

Analysis of solid state and solution structures of metal-bound carbonyl complexes reveals two distinct modes of interaction. The carbonyl component may associate with the Lewis acid through its non-bonding electron pairs, or it may complex in a π sense through the C-O π bond. The interaction between an electron deficient Lewis acid and a carbonyl will likely result in a η^1 complex, while metal complexes with greater electron density have a higher propensity to form η^2 complexes with carbonyl compounds that are sufficiently π acidic [22]. For instance, Gladysz has shown that cationic rhenium complex $[(\eta^5\text{-C}_5\text{H}_5)(\text{PPh}_3)(\text{NO})\text{Re}]^+\text{PF}_6^-$ binds an aldehyde (high π acidity) η^2 , while the same complex

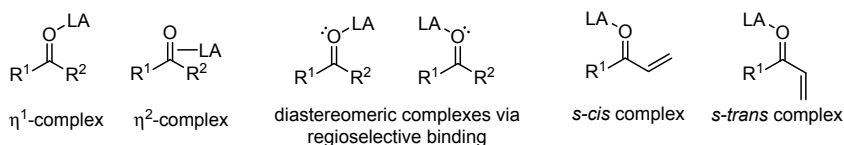


Fig. 6. Key factors in Lewis acid-dienophile complexation

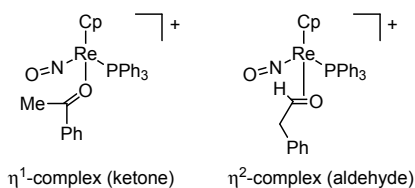


Fig. 7. Turnover in binding mode (η^1 vs η^2) as a function of carbonyl group

binds a ketone (lower π acidity) η^1 (Fig. 7) [23, 24]. Because the former case results in increased electron density on the carbonyl due to a HOMO (metal)-LUMO (carbonyl) interaction, this is less useful with respect to activation of α,β unsaturated carbonyls toward electron-rich dienes (normal electron demand). As a consequence, η^1 complexes are thought to be operative in catalytic enantioselective Diels-Alder reactions. The reader is referred to an excellent review of this topic by Schreiber and co-workers for a thorough treatment of the literature associated with Lewis acid-carbonyl complexation [25].

2.3.2

Regioselection in Lewis-Acid/Carbonyl Complexation

Extensive spectroscopic and theoretical work has laid a solid foundation for predicting how a given carbonyl compound will bind to a Lewis acid. The case of unsaturated aldehydes is the most straightforward, as Lewis acid complexation has only been observed *syn* to the formyl proton, both in the solid state and in solution. Reetz and co-workers have reported that the benzaldehyde- BF_3 complex exhibits the expected *E* geometry both in solution and the solid state by means of heteronuclear Overhauser effect (HOE) experiments and X-ray crystallography (Fig. 8A) [26], while Corey and co-workers showed crystallographically that BF_3 likewise coordinates methacrolein *syn* to the formyl proton (Fig. 8B) [27]. By the observation of an HOE between the metal center and formyl proton, Denmark and Almstead deduced that a number of aldehydes coordinate to SnCl_4 in the *E* geometry (Fig. 8C) [28]. They further observed that α,β -unsaturated aldehydes were significantly more Lewis basic than saturated or alkynyl aldehydes.

While this geometrical preference likely results from the impact of steric effects, hypotheses which suggest electronic effects as biasing elements have been

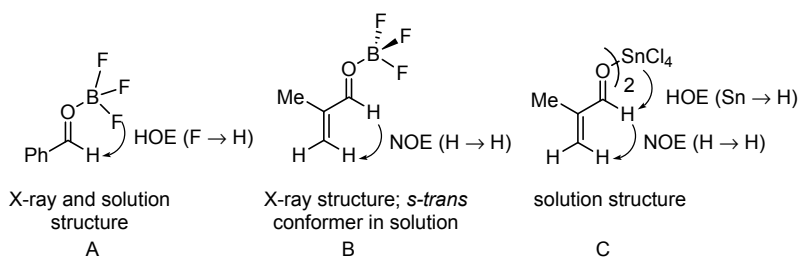


Fig. 8. *Anti* aldehyde-Lewis acid complexes

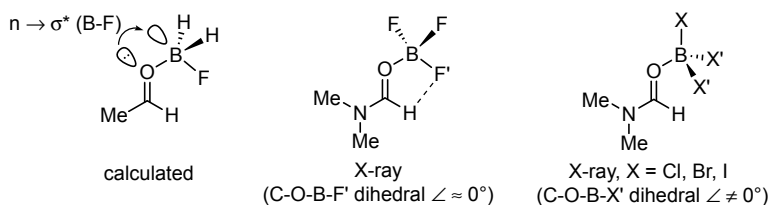


Fig. 9. Conformation of *anti* aldehyde-Lewis acid complexes; proposed anomeric effect and formyl hydrogen bond

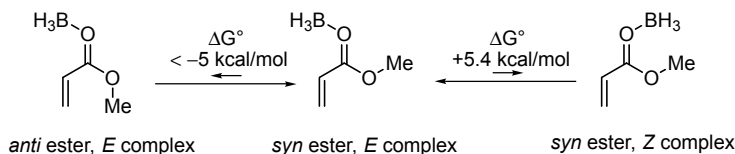


Fig. 10. Borane-methyl acrylate complexes (*ab initio*)

proposed. Goodman has suggested that the computationally-indicated conformational preference (Fig. 9) for boron-bound aldehydes is a consequence of an anomeric effect between the uncomplexed oxygen lone pair and the B-F antibonding orbital ($n \rightarrow \sigma^*$ (B-F)) [29]. Corey and co-workers have argued that the issue is not one of stereoelectronics, but rather a previously unappreciated hydrogen bond between the boron-bound fluoride and the formyl hydrogen [30]. This argument is derived from the fact that only the B-F bond eclipses the C-O bond in the X-ray structures of dimethylformamide-BX₃ complexes (Fig. 9, X = F, Cl, Br, I). The heteroatom-formyl hydrogen bond concept has been extended by analogy to explain other enantioselective processes [31].

The lack of spectroscopic evidence for Lewis acid complexation *anti* to the formyl hydrogen in aldehyde-derived complexes does not imply that such complexes do not exist. Indeed, *ab initio* molecular orbital calculations suggest that the energy difference for *E* and *Z* BF₃-aldehyde complexes can be as small as 1.2 kcal/mol, indicating that the *Z* conformer is present at equilibrium [32].

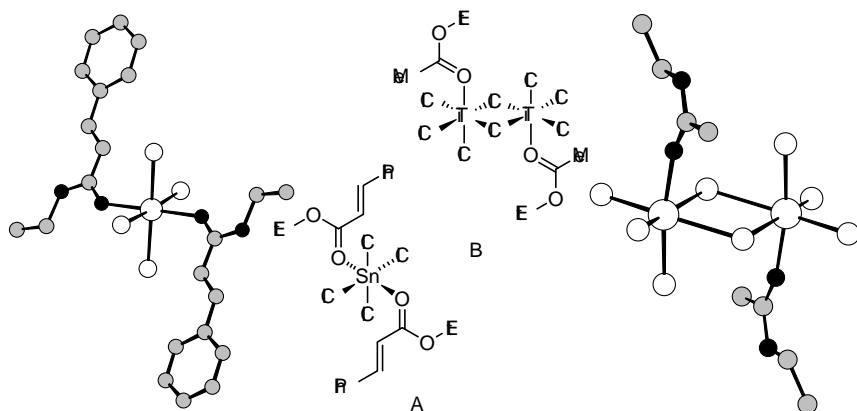


Fig. 11. X-ray structures of metal-bound esters

Ab initio calculations for the borane-methyl acrylate complex indicate that complexation of the lone pair *anti* the OMe group (*E* complex) is favored by 5.4 kcal/mol; the *syn* conformation of the ester is strongly favored over the *anti* (Fig. 10, for a discussion of the *s-cis/s-trans* issue, see Sect. 2.3.3) [33].

For the most part, the results of these calculations are reinforced by solid state structures. A structure of (ethyl cinnamate)₂·SnCl₄ indicates that both esters are disposed *syn* and favor the *E* complex (Fig. 11A) [34]. Similarly, ethyl acetate complexes with TiCl₄ to afford a dimeric structure with bridging chlorides; the esters are *syn* and complexation occurs *anti* to the ethoxy group (Fig. 11B) [35].

Those carbonyl compounds discussed above are prototypical “one-point binding” substrates. That is, coordination to the Lewis acid occurs in a monodentate fashion. In enantioselective catalysis of the Diels-Alder reaction, frequent use is made of bidentate dienophiles, substrates containing two Lewis basic sites capable of forming a chelate to the metal center (this is an extension of concepts which originated in the study of auxiliary-based Diels-Alder reactions; for leading references, see [36]). Such chelating interactions contribute an important organizational constraint to the transition state, and some effort has been made to understand the interaction of such substrates with Lewis acids. Shown in Fig. 12A is the representation of an X-ray structure of a complex between TiCl₄ and an acryloyl lactate dienophile known to afford cycloadducts in high diastereomeric excess [37]. An interesting feature of this structure is the somewhat unusual partial π coordination of the acryloyl carbonyl moiety, although the source of this out-of-plane bonding is not completely clear. While both ester groups are disposed *syn*, coordination of the acryloyl moiety is *anti* to the alkene, indicating that formation of a chelate is sufficiently favored to override the preference for the normal coordination mode *syn* to the alkene. Oppolzer's titanium-bound crotonyl sultam (Fig. 12B) also exhibits chelation in the solid state; the most convincing corroborating evidence for the existence of the chelate in solution was a

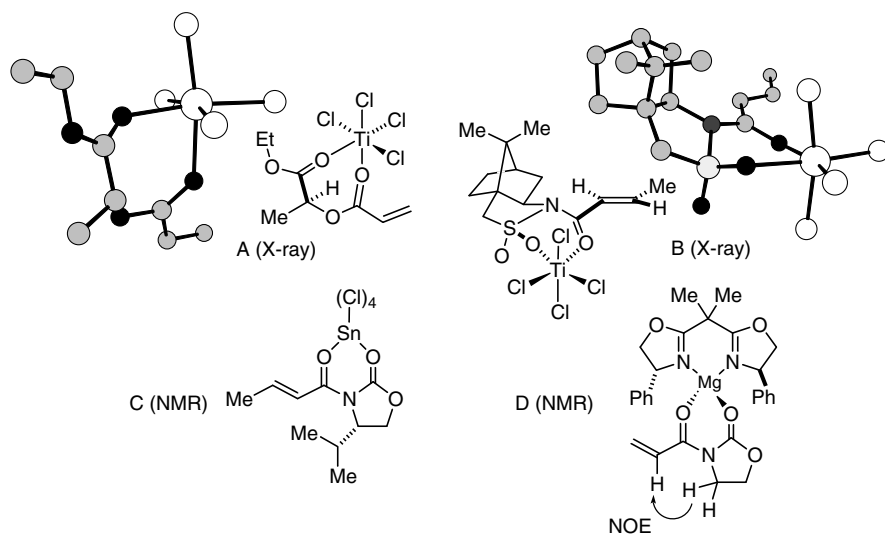


Fig. 12. Solution and solid state structures of metal-bound chelating dienophiles

decrease in IR stretching frequency for both the carbonyl and sulfonyl vibrations relative to the free sultam [38]. Castellino has performed ^1H -, ^{13}C -, and ^{119}Sn -NMR spectroscopic studies on SnCl_4 -bound crotonyl oxazolidinone and found that, to the limits of detection, only the chelated complex is formed (Fig. 12C) [39]. Achiral acyl oxazolidinones are among the most commonly employed chelating dienophiles in catalytic enantioselective Diels-Alder reactions, although in cases where the metal center cannot accommodate two additional ligands, one point-binding has been invoked in discussions of asymmetric induction.

2.3.3

Dienophile Conformation

The *s-cis/s-trans* dienophile conformational issue is critical to the analysis of any given enantioselective process since the interconversion of the two conformers in any well-defined chiral environment results in a reversal in the predicted enantiofacial bias. Consequently, considerable effort has been expended in studying this equilibrium.

Ab initio calculations and experimental measurements suggest that coordination of an α,β -unsaturated carbonyl to a Lewis acid results in an increase in the barrier to rotation about the $\text{C}_1\text{-C}_2$ single bond from 4–9 kcal/mol to 8–12 kcal/mol as a result of augmented $\text{C}_1\text{-C}_2$ double bond character (Fig. 13) [33]. This energy barrier is in the same regime as the measured energy of activation for a typical catalyzed Diels-Alder reaction.

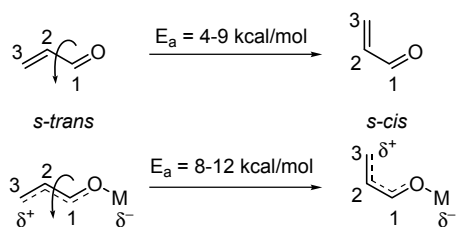


Fig. 13. Barrier to rotation of free and coordinated dienophiles

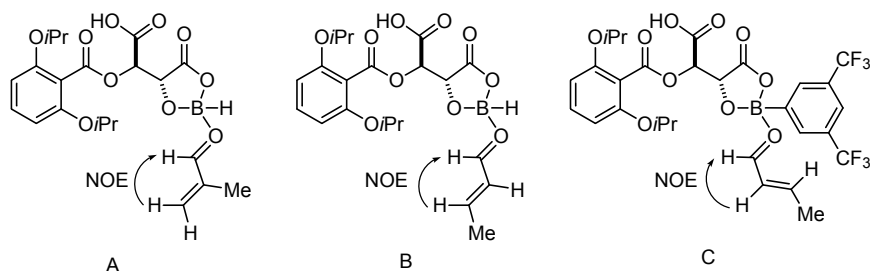


Fig. 14. Solution structures of CAB-aldehyde complexes

Uncomplexed acrolein, methacrolein, and crotonaldehyde all favor the *s-trans* conformer, and this preference is enhanced upon complexation to a Lewis acid. For example, Corey showed that the BF_3 -methacrolein complex adopts the *s-trans* conformation in the solid state as well as in solution by crystallographic and NMR spectroscopic methods (Fig. 8B) [27], while Denmark and Almstead found that methacrolein adopts the *s-trans* geometry upon complexation with SnCl_4 (Fig. 8C) [28]. Yamamoto demonstrated that methacrolein is also observed in the *s-trans* conformation upon complexation to his chiral acyloxyborane (CAB) catalyst (Fig. 14A and Sect. 3.1.2) [40]. Interestingly, with the same CAB system, crotonaldehyde exhibited varying preferences for the two possible conformers depending on the exact substituents on the boron. On the basis of NOE enhancements, the *s-trans* conformer was observed exclusively with a hydrogen substituent on boron (Fig. 14B); the *s-cis* conformer was the only one detected in the case of the aryl-substituted acyloxyborane (Fig. 14C).

The general preference for the *s-trans* conformer carries over to some extent for carboxylic esters. *Ab initio* calculations for the borane-methyl acrylate complex show a 1.4 kcal/mol preference for the *s-trans* conformer (Fig. 10), presumably due to reduced steric interactions (B-H for the *s-trans* vs. B- CH_2 for the *s-cis*) [33]. Solid state structures, however, show that both conformers can be observed for esters (Figs. 11 and 12).

The *s-cis* conformation observed for Oppolzer's chelating sultam (Fig. 12B) reflects a general dispositional preference for amides, consistent with lanthanide

metal-induced shift NMR studies by Montaudo *et al.*, who provided an empirical equation for assessing the conformational distribution for a given α,β -unsaturated carbonyl compound [41]. In the context of studies on chiral magnesium catalysts, Desimoni and coworkers disclosed that acryloyl oxazolidinones exhibit NOE enhancements between the nitrogen-bearing methylene group of the heterocycle and the α -vinyl proton (Fig. 12D) [42]. Largely on the basis of these NMR experiments and those of Collins (Sect. 3.2.4), and crystallographic data provided by Jørgensen (Sect. 3.2.4), the *s-cis* conformation of chelated acyl oxazolidinone dienophiles has been inferred.

However, as a harbinger of the danger in predicting transition state structures on the basis of preferred ground state conformations, Houk has found in *ab initio* calculations that borane-bound acrolein preferentially adopts the *s-trans* configuration, but the activation energy for reaction (with 1,3-butadiene) from the *s-cis* configuration is decidedly lower [15]. This finding has been reinforced with the DFT calculations of Garcia *et al.* [10] and foreshadows the ubiquity of the Curtin-Hammett principle in catalytic Diels-Alder reactions: numerous proposed transition structures that appear in this review are derived from higher energy dienophile-catalyst complexes.

3

Chiral Lewis Acid Catalysis of the Diels-Alder Reaction

Promotion of the Diels-Alder reaction by a substoichiometric amount of chiral Lewis acid has developed to a relatively high level of sophistication as a result of the extensive research in this field. In the interest of providing mechanistic insight into highly efficient systems, the discussion will be limited to systems which provide synthetically useful levels of enantioselection (typically greater than 90%) [43]. Even with this restriction, the reader will note remarkable breadth in the chiral complexes that have been studied. As a result of the unique characteristics different metals confer to Lewis acidic complexes, it is advantageous to discuss each metal in turn.

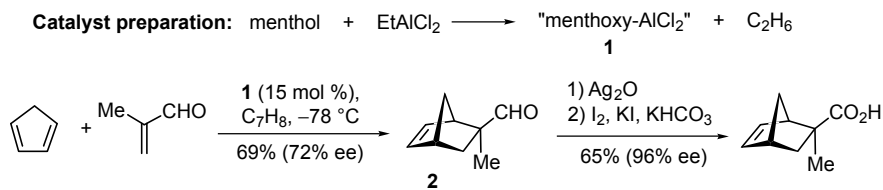
3.1

Main Group Lewis Acids

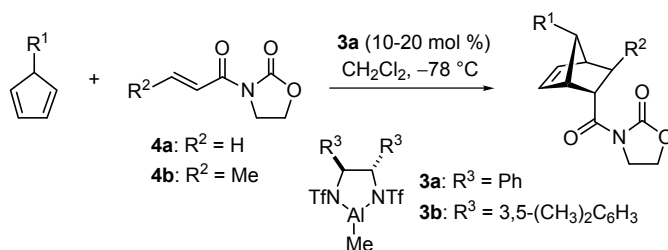
3.1.1

Aluminum

In 1979, Koga and coworkers disclosed the first practical example of a catalytic enantioselective Diels-Alder reaction [44] promoted by a Lewis acidic complex, presumed to be “menthoxyaluminum dichloride” (1), derived from menthol and ethylaluminum dichloride, whose structure remains undefined [45]. This complex catalyzed the cycloaddition of cyclopentadiene with acrolein, methyl acrylate, and methacrolein with enantioselectivities as high as 72% ee. Oxidation of 2 (predominantly *exo*) followed by recrystallization actually lowered the ee;



Scheme 3



R ¹	R ²	Yield [%]	endo/exo	ee [%]
H	H	92	>50:1	91
H	Me	88	96:4	94
CH ₂ O ₂ bn	H	94	–	95

Scheme 4

however, isolation of the mother liquors gave product of 96% ee (Scheme 3). On the basis of a proposed transition state, Koga and coworkers made systematic changes to the cyclohexanol moiety and the aluminum substituents, but the highest ee was realized for the original system [46, 47].

A decade later, Corey introduced an effective aluminum-diamine controller for Diels-Alder and aldol additions. The C₂-symmetric stilbenediamine (stien) ligands are available in good yield from substituted benzils, which are in turn derived from benzoic acids, aryl aldehydes, or aryl bromides [48]. Formation of the active catalyst **3** is achieved by treatment of the bis(sulfonamide) with trimethylaluminum; recovery of the ligand was essentially quantitative. Acryloyl and crotonyl imides **4** are particularly effective dienophiles for this system, as shown in Scheme 4.

The transition structure depicted in Fig. 15 was suggested by the authors based on a dimeric X-ray structure of the catalyst and NMR spectroscopic data showing an NOE enhancement between the α -vinyl proton of the dienophile and the benzylic proton of the catalyst. While imide **4** is typically viewed as a chelating Lewis base, the presumed tetracoordinate aluminum would prevent this mode of activation. As noted previously, imide **4** is generally assumed to pre-

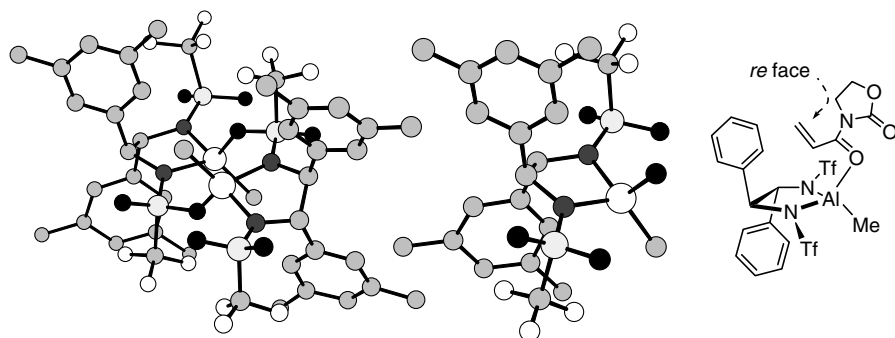
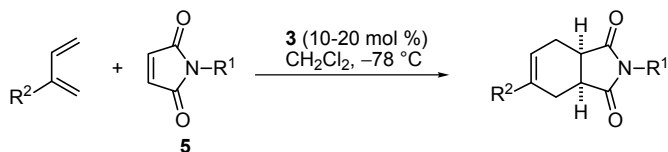


Fig. 15. X-ray structure of catalyst **3b** (dimeric); simplified view of the X-ray structure with one-half of the dimer excised; proposed transition structure for aluminum-stien catalyzed Diels-Alder reactions



R ¹	R ²	Catalyst	ee [%]
2-CH ₃ C ₆ H ₄	OMe	3b	93
2-CH ₃ C ₆ H ₄	OMe	3a	58
Ph	OMe	3b	62
2-CMe ₃ C ₆ H ₄	OMe	3b	95
2-I C ₆ H ₄	OMe	3b	93
2-Me-4-BrC ₆ H ₄	OMe	3b	>97
2-CMe ₃ C ₆ H ₄	CH ₂ SiMe ₃	3b	95

Scheme 5

for the *s-cis* conformer in the ground state; the proposed *s-trans* geometry and potential electrostatic repulsion between the two carbonyls should be noted, but the absolute stereochemistry of the adducts is consistent with Fig. 15 and the aforementioned experimental data.

Subsequent studies have expanded the scope of this catalyst to include maleimides **5** [49]. In order to obtain enantiomerically enriched cycloadducts with this symmetrical dienophile an unsymmetrical diene was used (Scheme 5); this constitutes the first example of such a process. *Ortho* substitution on the *N*-aryl group was found to be crucial to the realization of high enantioselectivity, perhaps to discourage catalyst binding the carbonyl lone pair *syn* to the *N*-aryl moiety; a transition state analogous to that depicted for the imides (Fig. 15) was invoked. The fact that the dienophile is locked in the *s-trans* conformer could lend

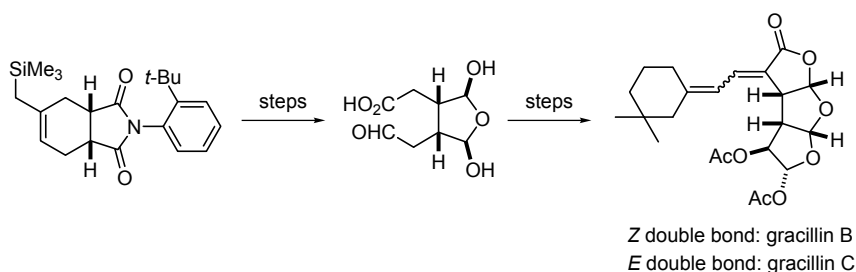
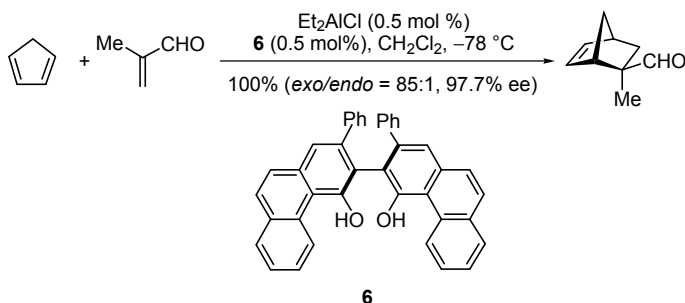


Fig. 16. Transformation of maleimide-derived cycloadduct into gracillins B and C



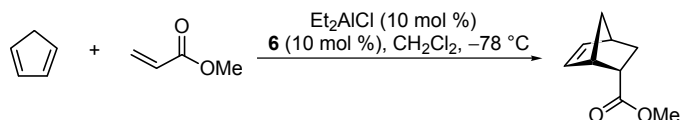
Scheme 6

support to the Curtin-Hammett scenario necessary for the transition state depicted in Fig. 11 to be operative. This methodology was exploited in elegant syntheses of gracillins B and C (Fig. 16) [50].

In 1993, Wulff and coworkers reported their finding that a complex derived from diethylaluminum chloride and “vaulted” biaryl ligand **6** catalyzed the enantioselective Diels-Alder reaction between cyclopentadiene and methacrolein (Scheme 6) [51, 52]. Although somewhat lengthy, the ligand preparation is amenable to preparative scale synthesis (11–12 mmol). This possible detraction is attenuated by the 0.5 mol % catalyst loading, which is the lowest reported for any enantioselective carbocyclic Diels-Alder reaction. Further, the chiral ligand is recovered quantitatively by silica gel chromatography.

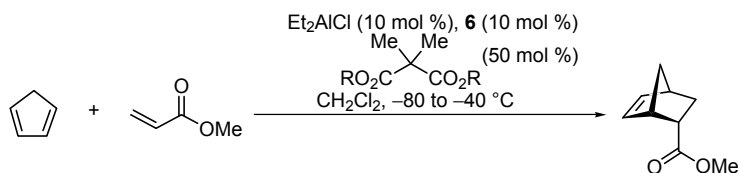
A notable feature of this catalytic system is that asymmetric induction is lower at the early stages of the reaction. A subsequent study revealed that in the reaction of methyl acrylate and cyclopentadiene, the cycloadduct interacts with the catalyst in a fashion such that the enantioselectivity is intimately tied to the percent conversion (Scheme 7).

The result of their exploratory effort was the determination that an enantioselective autoinductive mechanism is operative. Only one other example of such a mechanism exists in the context of the Diels-Alder reaction [53]. In a series of clever experiments, the authors found that achiral additives achieve the same end, facilitating uniformly high asymmetric induction throughout the course of



Conversion [%]	ee [%]
21	48
43	72
61	81
>95	82

Scheme 7



R	Temp [°C]	Yield [%]	<i>endo/exo</i>	ee [%]
Me	-80	49	99:1	98
<i>i</i> -Pr	-80	70	99:1	97.5
<i>t</i> -Bu	-80	76	99:1	>99
1-adamantyl	-40	100	98.1:1	92.5

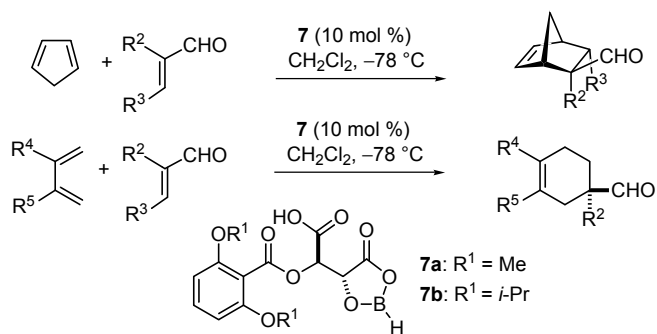
Scheme 8

the reaction (Scheme 8). The efficacy of malonate additives suggests that the catalytically active species might be a hexacoordinate aluminum center; future work is aimed at determining whether this is in fact the case. It should be noted that selective cycloadditions of acrylate esters are rarer than for their aldehyde or imide counterparts [54]; therein lies an attractive attribute of the Wulff system.

3.1.2

Boron [55]

Yamamoto and coworkers have developed a practical Diels-Alder catalyst for aldehyde dienophiles. Treatment of a monoacylated tartaric acid with borane released *ca.* 2.2 equiv of H₂ gas, affording a complex that has been assigned structure 7. Circumstantial evidence for structure 7 was found in the comparable enantioselectivity of a catalyst in which the free carboxyl group was esterified (see below). The chiral (acyloxy)borane (CAB) complex is effective in catalyzing a number of aldehyde-based Diels-Alder reactions (Scheme 9) [56]. Reactions with



Catalyst	R ²	R ³	R ⁴	R ⁵	Yield [%]	<i>exo/endo</i>	ee [%]
7a	Me	H	–	–	85	89:11	96
7a	H	H	–	–	90	12:88	84
7a	Me	Me	–	–	91	97:3	90
7b	Br	H	–	–	100	94:6	95
7b	Br	Me	–	–	100	>99:1	98
7b	Br	H	Me	Me	80	–	95
7a	Me	H	Me	Me	61	–	97
7a	Me	H	Me	H	65	–	91

Scheme 9

cyclopentadiene are fairly general with respect to the aldehyde, with the exception of crotonaldehyde (2% ee). Less reactive dienes such as isoprene and 2,3-dimethyl-1,3-butadiene may be successfully employed with bromoacrolein and methacrolein dienophiles.

A series of NMR spectroscopic experiments established that the preferred ground state conformation for both crotonaldehyde and methacrolein is *s-trans* when complexed to **7b** (Fig. 14) [40]. Additionally, NOE experiments indicated close proximity of the aldehyde and the aryl ring; π -stacking between the aryl group and aldehyde was suggested as an organizational feature which imparted high enantioselectivity to the cycloaddition event (Fig. 17) [57]. A crystal structure of the uncomplexed monoacylated tartaric acid revealed a folded rather than extended structure, further suggesting the possibility of this arrangement.

As illustrated in Scheme 10, the CAB catalyst also effectively catalyzes the intramolecular Diels-Alder reaction of trienal **8** to afford bicyclic product **9** in high diastereo- and enantioselectivity [58]. In a single step, this *endo*-selective reaction achieves the formation of a tetrahydroindane ring system containing a stereogenic quaternary center.

A tryptophan-derived oxazaborolidine has been shown to be an effective catalyst for aldehyde-based Diels-Alder reactions. Complex **10**, prepared from α -methyl tryptophan and $\text{BuB}(\text{OH})_2$ with removal of water, effects the cycloaddi-

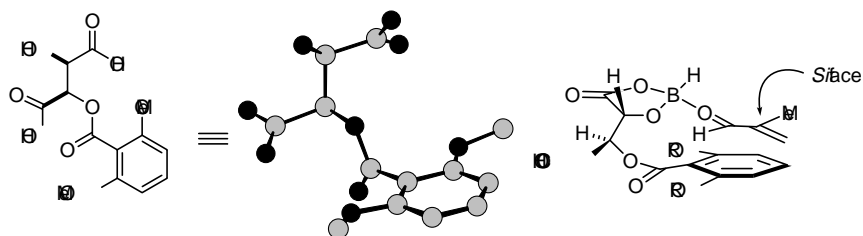
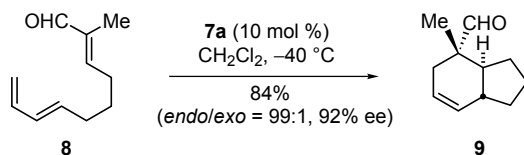
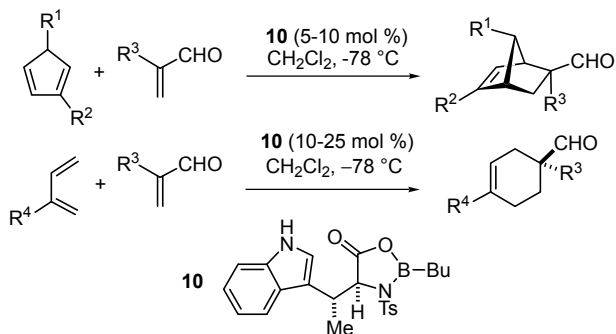


Fig. 17. X-ray structure for monoacylated tartaric acid precursor for complex **7a** and proposed transition state assembly for CAB catalyst **7** [40]

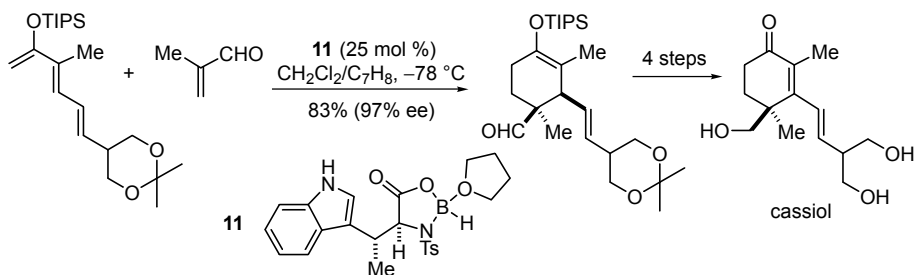


Scheme 10

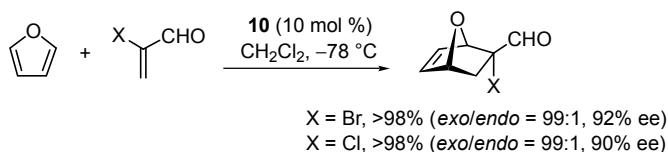


R ¹	R ²	R ³	R ⁴	Yield [%]	ee [%]
H	H	Br	–	95	99
CH ₂ OBn	H	Br	–	81–83	>92
H	CH ₂ C(Br)CH ₂	Br	–	81	99
–	–	Cl	OTIPS	–	94
–	–	Br	Me	76	92

Scheme 11



Scheme 12



Scheme 13

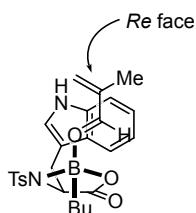


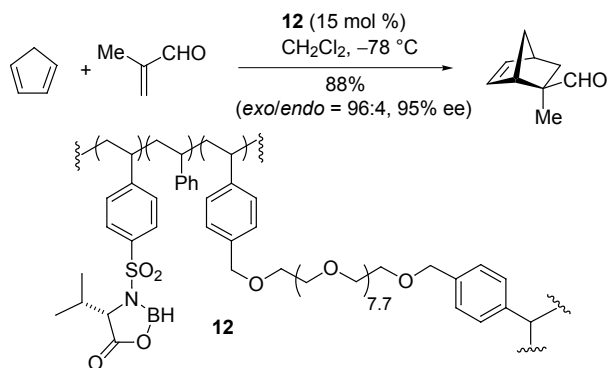
Fig. 18. Proposed transition state assembly for oxazaborolidine catalyst **10** (Me group omitted for clarity)

tion of α -halo- and α -alkylacroleins with cyclic and acyclic dienes in high stereoselectivity (Scheme 11) [59].

The utility of such cycloadditions has been demonstrated by the elaboration of the cycloadducts to complex natural products [60]. For example, the adduct derived from a cyclopentadiene having a 2-bromoallyl sidechain has been converted to an intermediate employed in a previous (racemic) synthesis of gibberellic acid. As illustrated in Scheme 12, an exceptionally efficient synthesis of cassiol is realized by the successful execution of a rather difficult *endo*-selective Diels-Alder reaction using a slightly modified oxazaborolidine (**11**). The high catalyst loading is balanced by the fact that all the carbons and the quaternary center of the natural product are introduced in a single step.

It has been further demonstrated that furan may be successfully employed as a diene using catalyst **10** and α -haloacroleins as the 2π component (Scheme 13) [61].

A rationalization for the sense of induction for this system has been advanced and is illustrated in Fig. 18 (methyl group omitted for clarity) [62]. Salient ob-

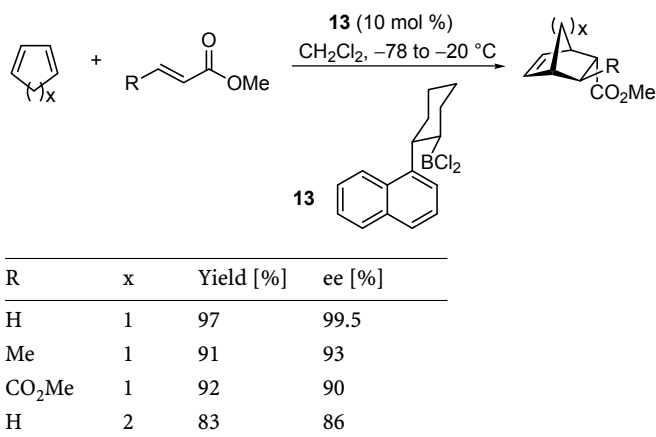


Scheme 14

servations on the ground state complex include: the appearance of a bright orange-red color on addition of methacrolein at 210 K that was attributed to an electron donor-acceptor complex; NOE's that imply a rigidified catalyst structure upon addition of the dienophile; a preferred *s-trans* conformer of the complexed aldehyde based on NMR spectroscopic observations. The Curtin-Hammett principle is invoked, and the *s-cis* conformer is proposed to be the active catalytic species. A subsequent publication has suggested a hydrogen bond between the formyl hydrogen and the carboxylate oxygen as an additional organizational feature [31a].

A related catalyst reported by Itsuno and coworkers offers some exciting practical benefits to the oxazaborolidine system. A valine-derived cross-linked copolymer, when treated with borane-methyl sulfide, serves as an effective catalyst for the methacrolein-cyclopentadiene Diels-Alder reaction (Scheme 14) [63]. The polyether in the cross-linking unit is particularly important for realizing maximum selectivity. The advantages of heterogeneous catalysis are realized: the catalyst was easily recovered from reaction mixtures and reused multiple times without deleterious effects to the enantioselectivity or yield. As an added benefit, the polymeric catalyst in some cases conferred higher levels of enantioselectivity than the solution analogs which were reported independently by Yamamoto and Helmchen [64]. The absolute configuration of the product is opposite that obtained from the tryptophan-derived oxazaborolidine catalyst **10**, suggesting that the mechanism of asymmetric induction is probably different for the two systems.

It is evident that minimization of the degrees of freedom of the dienophile in the transition state is an important criterion for reaction selectivity. A unique catalyst system designed by Hawkins and coworkers takes advantage of two distinct binding interactions to rigidify the catalyst-substrate complex [65]. The aromatic alkylidichloroborane **13** is an effective cycloaddition catalyst for acrylate dienophiles (Scheme 15) [66]; however, reports utilizing this catalyst are strictly confined to ester substrates with either cyclopentadiene or cyclohexadiene.



Scheme 15

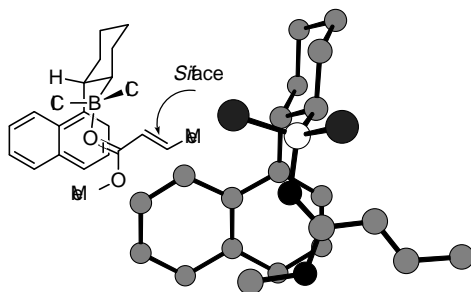
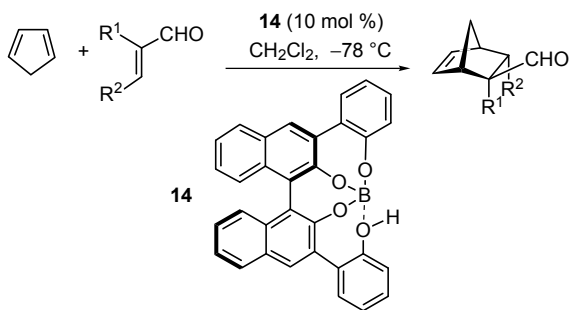


Fig. 19. Proposed transition state assembly for catalyst **13**; catalyst-methyl crotonate complex (X-ray)

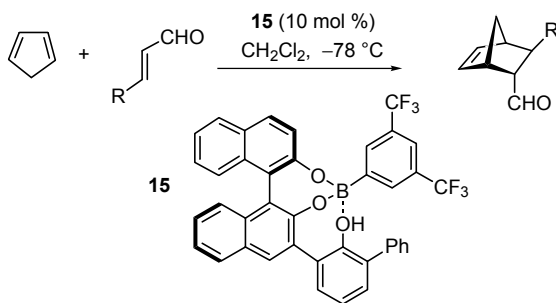
The X-ray structure of the indicated borane-methyl acrylate complex (Fig. 19) unequivocally confirms the design concept. The solid state structure shows a close contact (3.40 Å from the center of the substituted phenyl ring to the carbonyl carbon) between the electron-rich arene and boron-bound methoxycarbonyl group, an arrangement which also exists in solution. As the polarizability of the aryl group is increased, the dienophile is drawn closer to the arene, suggestive of a dipole-induced attractive interaction. The air-sensitive catalyst **13** was synthesized by way of a resolution in 5 steps.

Yamamoto and co-workers have introduced a conceptually interesting series of catalysts that incorporate an acidic proton into the active catalyst. Termed Brønsted acid-assisted chiral Lewis acid (BLA), catalyst **14** selectively catalyzes a number of diene-aldehyde cycloadditions reactions (Scheme 16) [67]. While extremely selective for the substrates shown, no aldehydes lacking an α -substituent were reported to be effective in this reaction. This feature was addressed in



R ¹	R ²	Yield [%]	<i>exo/endo</i>	ee [%]
Br	H	>99	>99:1	99
Me	H	>99	>99:1	99
Me	Me	>99	>99:1	98
(CH ₂) ₃	-	>99	98:2	93

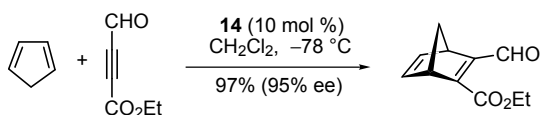
Scheme 16



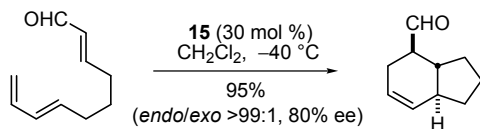
R	Yield [%]	<i>endo/exo</i>	ee [%]
H	84	97:3	95
Me	94	90:10	95
CO ₂ Et	91	98:2	95

Scheme 17

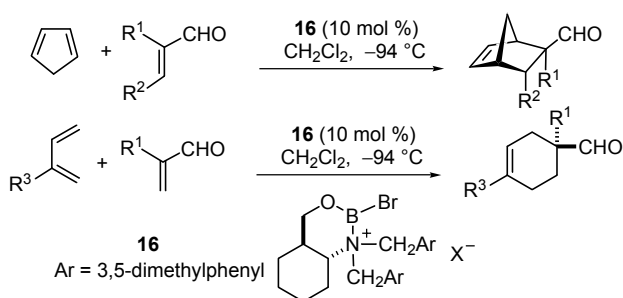
a second-generation BLA (15), which was general with respect to the aldehyde component (Scheme 17) [68]. Despite this uniformly high selectivity, the lack of spectral or solid state characterization of the active catalyst makes stereochemical models speculative at this point. One particularly relevant observation is that formation of a monoether corresponding to 14 gives a far less selective catalyst, implicating the active proton in the catalytic event. Dienes other than cyclopentadiene may be employed with both catalysts and recovery of the chiral ligand is quantitative.



Scheme 18



Scheme 19



R ¹	R ²	R ³	X	Yield [%]	<i>exo</i> : <i>endo</i>	ee [%]
Br	H	–	B(3,5-(CF ₃) ₂ Ph) ₄	99	91:9	98
Me	H	–	Br	99	88:12	90
Br	Me	–	B(3,5-(CF ₃) ₂ Ph) ₄	99	>98:2	96
Me	Me	–	B(3,5-(CF ₃) ₂ Ph) ₄	97	>98:2	89
-(CH ₂) ₄ -	–	–	Br	99	>98:2	96
Br	H	H	B(3,5-(CF ₃) ₂ Ph) ₄	99	–	94
Br	H	Me	B(3,5-(CF ₃) ₂ Ph) ₄	99	–	96

Scheme 20

Cycloadditions between acetylenic aldehydes and dienes are effected by catalyst **14**, the best case being illustrated in Scheme 18 [69]. This is one of only two reports of highly enantioselective Diels-Alder reactions using alkynes. *Ab initio* calculations propose that the reaction is proceeding via an *exo* transition state. On the basis of FMO theory, the authors suggest that a secondary antibonding interaction between the lobes on C-2 of cyclopentadiene and the carbonyl oxygen accounts for the higher relative energy of the *endo* transition state.

An enantioselective intramolecular Diels-Alder reaction of α -unsubstituted 2,7,9-decatrinal afforded the corresponding bicyclic aldehyde in high yield and

good enantioselection using BLA 15 (Scheme 19). Alternatively, when CAB catalyst 7a was employed in the same reaction, the adduct was obtained in lower yield and selectivity (74% yield, 46% ee).

Promising results have been reported by Corey using cationic oxazaborinane complex 16 as an aldehyde-diene cycloaddition catalyst (Scheme 20) [70]. α -Substituted aldehydes and four dienes are reported to undergo low-temperature ($-94\text{ }^{\circ}\text{C}$) Diels-Alder reaction to give adducts in high *exo* selectivity and excellent enantioselection. The catalyst is prepared in seven steps and ligand recovery after the reaction is 85%; catalyst decomposition occurs above $-60\text{ }^{\circ}\text{C}$.

Catalyst 16 has also been reported to effect cycloaddition of propargyl aldehydes with cyclopentadiene (Scheme 21) [71]. While simple β -alkyl substituted alkynyl aldehyde dienophiles proved to be unreactive, the derived silyl- or stan-nyl-substituted analogues proceeded with good levels of enantioselectivity. It was further demonstrated that the derived cycloadducts are useful chiral building blocks by virtue of their ability to undergo transition metal-catalyzed cross-coupling reactions. Despite the somewhat elevated catalyst loading, this system does not require two activating substituents on the alkyne, in contrast to BLA catalyst 14. As with that system, an *exo* transition state is proposed as the favored reaction pathway.

An enantioselective Diels-Alder reaction between methacrolein and cyclopentadiene with 3 mol % of borate catalyst 17 (Fig. 20) proceeds with good selectivity ($-78\text{ }^{\circ}\text{C}$, 85% yield, *exo/endo*=97.4:2.6, 90% ee) [72]. The catalyst is available in one step from BINOL and the ligand may be recovered in nearly quantitative yield after the reaction.

Proline-derived boron complex 18 catalyzes the enantioselective cycloaddition of methacrolein and cyclopentadiene ($-78\text{ }^{\circ}\text{C}$, 84% yield, *exo/endo*>99:1,

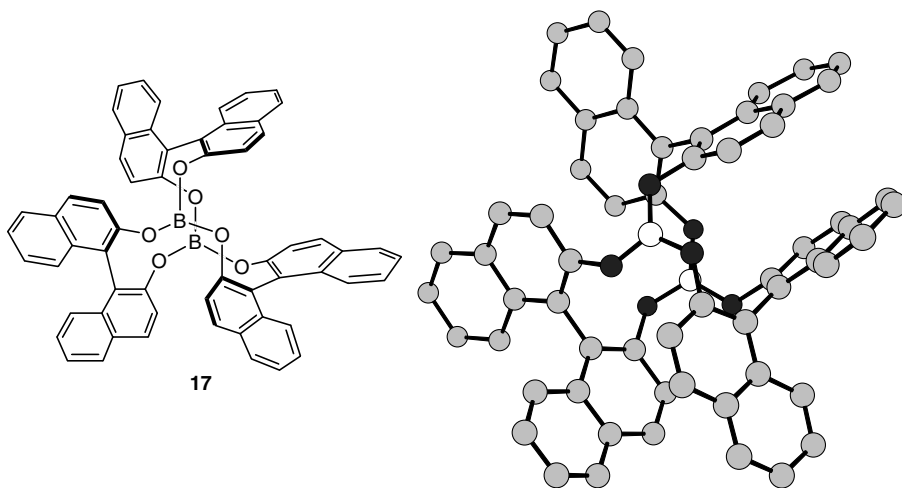
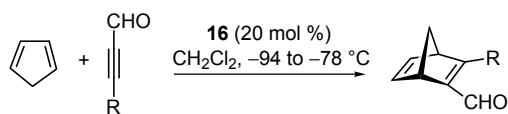


Fig. 20. Borate “propeller” catalyst 17 and X-ray structure



R	X	Yield [%]	ee [%]
SiMe ₃	B(3,5-(CF ₃) ₂ Ph) ₄	68	87
SiEt ₃	B(3,5-(CF ₃) ₂ Ph) ₄	37	85
SiMe ₂ Ph	B(3,5-(CF ₃) ₂ Ph) ₄	50	87
SnBu ₃	B(3,5-(CF ₃) ₂ Ph) ₄	83	80

Scheme 21

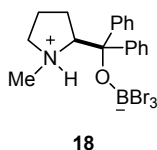


Fig. 21. Zwitterionic proline-based Lewis acid

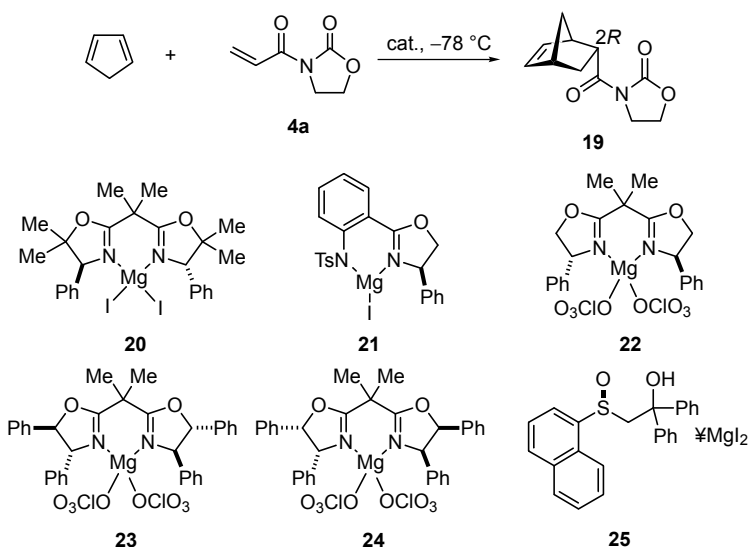
97% ee) [73]. ¹¹B-, ¹H-, and ¹³C-NMR spectroscopy were instructive in assigning the structure of **18** (Fig. 21): the methyl group appeared as a doublet and was shifted downfield from its position in the prolinol ligand. Efforts to study complexation between methacrolein and **18** were not successful due to the unfavorable equilibrium. It is evident that further work will be needed to elucidate the role that **18** plays in this reaction.

3.1.3

Magnesium

Magnesium-derived Lewis acids, while not attracting as much attention as their boron counterparts, have been developed as selective Diels-Alder catalysts. A significant point of divergence between the two metals in their applications should be noted: enantioselective Diels-Alder reactions with boron Lewis acids utilize aldehyde or ester dienophiles without exception, while successful cycloadditions with magnesium complexes always employ a dicarbonyl compound as the activating moiety of the 2π component. The magnesium center is typically viewed as being amenable to chelating substrates, while the boron center is attractive for single-point binding dienophiles.

Bis(oxazoline)-magnesium complex **20** (10 mol %) catalyzes the indicated cycloaddition (Scheme 22) to give **19** (2*R*) in 82% yield and 91% ee (*endo/exo*=97:3) [74]. The absolute stereochemistry of the product is consistent with bidentate activation of the substrate through a tetrahedral metal geometry with reaction out of the *s-cis* conformer. Complex **21**, derived from the opposite enantio-



Scheme 22

meric series of chiral amino alcohol provides the same enantiomer (*2R*) as **20**, proceeding in 81% yield (50 mol % **21**) and 91% ee [75]. Hydroxysulfoxide-derived catalyst **25** mediates the same reaction (10 mol %) and delivers *ent*-**19** (*2S*) in 88% ee [76]. Structural and mechanistic investigations on these complexes are less developed than for many boron catalysts; accordingly, hypotheses pertaining to selectivity issues are still quite speculative.

The most detailed work for magnesium catalysts has been performed by Desimoni and coworkers with complexes **22**, **23**, and **24** [42, 77]. NMR spectroscopic studies with **22** and imide **4a** suggest that the metal center in the dienophile-catalyst complex adopts the expected tetrahedral coordination geometry, with the imide disposed in an *s-cis* configuration. Upon addition of 2 equivalents of methanol-*d*₁, the complex is transformed to an octahedral geometry with the endocyclic carbonyl bound out of the plane of the chiral ligand (based on chemical shift data and observed NOE's). The practical consequence of this geometry change is an alteration of the exposed enantioface of the dienophile with the addition of auxiliary ligands (Fig. 22). In support of this hypothesis, complex **23** catalyzes (5 mol %) the reaction of cyclopentadiene and acryloyl imide to afford *ent*-**19** (*2S*) in 97% ee (*endo/exo*=199:1). The enantiomeric product **19** (*2R*, 89% ee, *endo/exo*=94:6) was obtained using complex **24** (5 mol %) with water as the auxiliary ligand (10 mol %). In the absence of water, catalyst **24** preferentially delivers the *2S* product (22–43% ee), making **24** one of two Diels–Alder catalysts which can deliver either product enantiomer with proper choice of addend (see also Sect. 3.3). Complicating mechanistic analysis somewhat is the fact that no turnover in stereochemistry occurs using complex **23** and auxiliary ligands. The importance of the *cis* or *trans* relationship of the phenyl groups in complex-

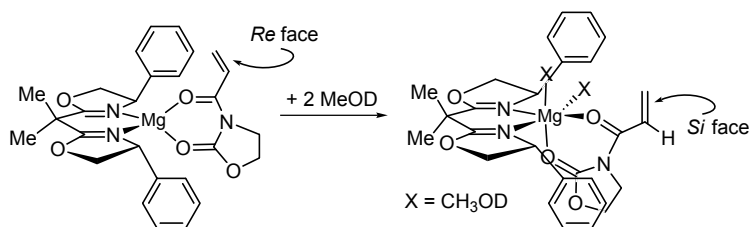
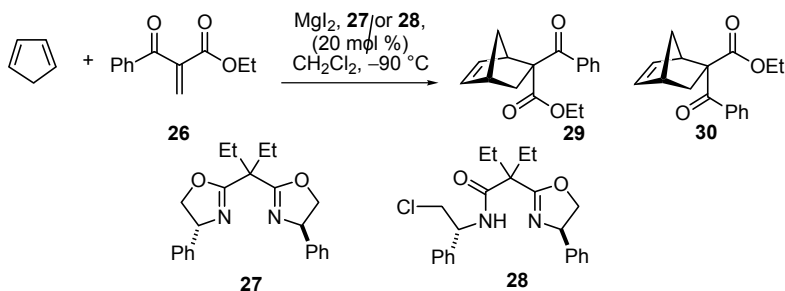


Fig. 22. Turnover in selectivity for Mg(bisoxazoline) catalysts with the addition of coordinating ligands (tetrahedral→octahedral transposition)



Ligand	Yield [%]	29:30	ee of 29 [%]
26	81	>99:1	85.3
27	88	>99:1	87.0

Scheme 23

es 23 and 24 points to possibility of an electronic effect which could either reinforce or partially cancel the steric bias provided by the proximal phenyl group. While not mentioned explicitly by the authors, the relative stereochemistry of the phenyl groups could also play a significant role in gearing that could significantly affect the chiral environment about the metal center (for general references on gearing effects, see [78]). As a final note on mechanism, no nonlinear effects were observed with catalyst 22, indicative of a putative mononuclear catalyst-dienophile complex.

A magnesium-based catalyst system which employs either a bis(oxazoline) or amido-mono(oxazoline) ligand derived from phenylglycine has been reported to effect an interesting Diels-Alder between unsymmetrical alkylidene 26 and cyclopentadiene (Scheme 23) [79]. The reaction generates a quaternary center and is noteworthy in its ability to preferentially deliver cycloadduct 29, despite a superficial similarity between the two carbonyl substituents (OEt vs. Ph). This selectivity has been rationalized on the basis of an inferred steric preference for the phenyl group to reside perpendicular to the alkylidene, thus creating a marked bias in the diastereomeric transition states [80].

3.2

Transition Metal Lewis Acids [81]

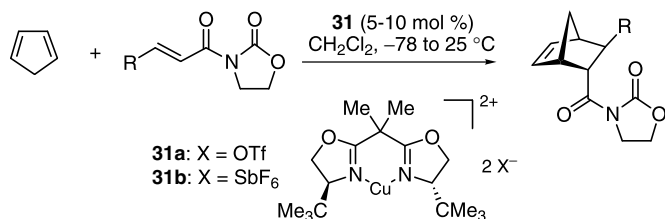
3.2.1

Copper

Evans and coworkers have reported that cationic copper(II)-bis(oxazoline) complexes derived from *tert*-leucine are effective Lewis acids for a wide range of enantioselective Diels-Alder reactions. While initial investigations employed cyclopentadiene as the diene and triflate catalyst **31a** (Scheme 24) as the Lewis acid [82], subsequent studies revealed that the reaction rate is strongly dependent on the counterion X [83]. The hexafluoroantimonate catalyst **31b** is approximately 20 times more reactive than **31a** and is typically more stereoselective. The heightened reactivity and selectivity conferred by catalyst **31b** allows access to more substituted adducts in uniformly high enantioselectivity. The active catalyst is easily prepared and robust: exposure to air is not deleterious and the reactions may be conducted in the presence of free hydroxy groups. However, reduction of the metal center can be problematic with electron-rich dienes; this side reaction may be controlled by a judicious choice of temperature.

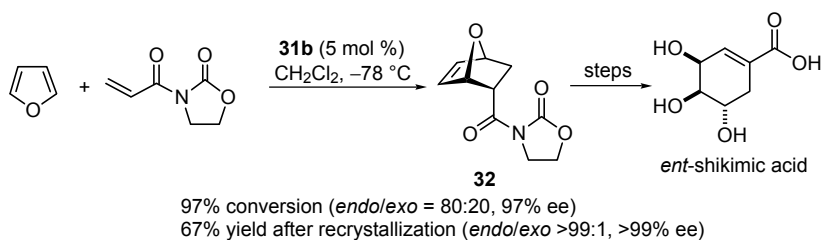
A stereoselective Diels-Alder reaction between furan and acrylimide yielded bicyclic adduct **32** that could be recrystallized to isomeric purity (Scheme 25) [84]. The cycloaddition reaction was reversible at higher temperatures and resulted in preferential formation of racemic *exo* isomer. Cycloadduct **32** was elaborated in six steps to *ent*-shikimic acid.

The synthetic utility of this copper(II) system has been subsequently expanded to include a number of less reactive dienes, several of which have not been previously used in enantioselective Diels-Alder reactions [85]. Functionalized buta-

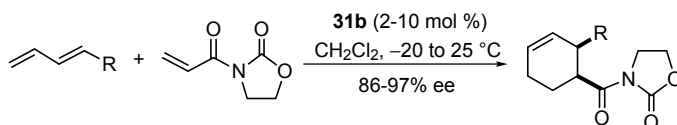


R	Catalyst	Yield [%]	<i>endo/exo</i>	ee [%]
H	1a	86	98:2	>98
CO ₂ Et	1a	92	94:6	95
Me	1a	85	96:4	97
Ph	1b	96	91:9	96
Cl	1b	96	86:14	95

Scheme 24



Scheme 25



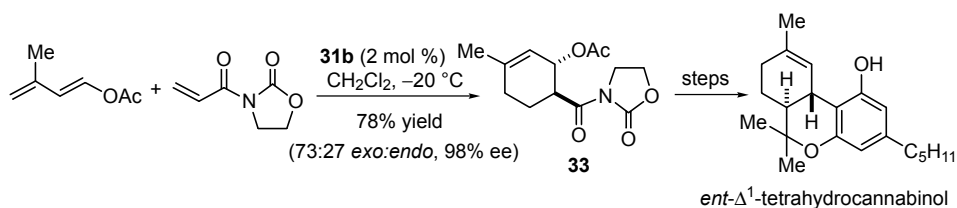
R	Yield [%]	<i>endo/exo</i>	ee [%]
Me	70	91:9	94
OAc	75	85:15	96
Ph	95	85:15	97
SPh	84	98:2	98
NHCbz	54	72:28	90

Scheme 26

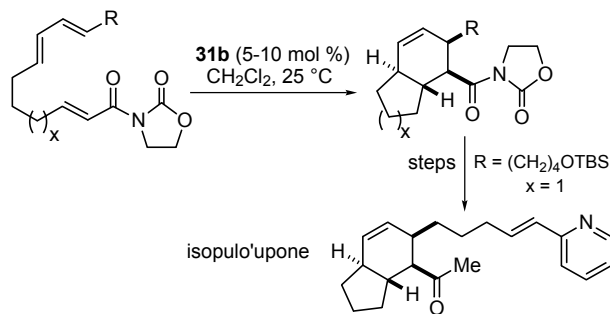
dienes are particularly good substrates: alkyl, aryl, oxygen, nitrogen, and sulfur substitution at the terminal position may be tolerated with no loss in stereoselectivity for the favored *endo* product (Scheme 26). The adducts also exhibit a high incidence of crystallinity which greatly simplifies purification efforts. Catalyst loadings of 2 mol % are generally sufficient to achieve complete reaction and scale-up occurs without incident, making this one of the more efficient Diels-Alder catalysts. A study by Jørgensen disclosed an apparent accelerating effect using nitromethane as a solvent (vs. dichloromethane) for this catalyst system [86].

The reaction between 1-acetoxy-3-methylbutadiene preferentially affords *exo* adduct **33** in high enantioselectivity (Scheme 27); **33** was elaborated in four steps to *ent*- Δ^1 -tetrahydrocannabinol [87]. The turnover in diastereoselectivity is thought to be a result of a steric interaction between the 3-methyl group of the diene and the chiral ligand, a repulsion which is not present for the parent 1-acetoxybutadiene (an *endo* selective diene).

Hexafluoroantimonate catalyst **31b** mediates a number of enantioselective intramolecular Diels-Alder reactions as well (Scheme 28) [88]. The marine natural product isopulo'upone was assembled in a straightforward fashion from the bicyclo[6.5.0] skeleton possessing a functionalized side chain. From an acyclic



Scheme 27



R	X	Yield [%]	<i>endo/exo</i>	ee [%]
H	1	89	>99:1	86
Ph	1	86	>95:5	92
Ph	2	97	84:16	97
$(\text{CH}_2)_4\text{OTBS}$	1	81	>99:1	96

Scheme 28

precursor, all four of the natural product's contiguous stereocenters are correctly installed in a single step.

In every case for copper catalyst **31**, the absolute stereochemistry of the cycloadducts is accounted for by the intervention of the substrate-catalyst complex depicted in Fig. 23, in which the *s-cis* configured dienophile is bound to the catalyst in the plane of the ligand in a bidentate fashion. The *tert*-butyl group shields the top face and cycloaddition occurs from the exposed *si* enantioface. Support for this model derives from X-ray structures of aquo complexes of catalysts **31a** and **31b** which show that the complex possesses a distorted square planar geometry; EPR spectroscopy on the binary catalyst-dienophile complex indicates that this geometry carries over from the solid state into solution. Calculations at the PM3 level of theory further favor the indicated reactive assembly [85].

Double stereodifferentiating experiments [89] using chiral dienophiles have effectively ruled out the intervention of a tetrahedral copper center or a reactive *s-trans* conformer (Scheme 29) [82]. It is noteworthy that in the mismatched

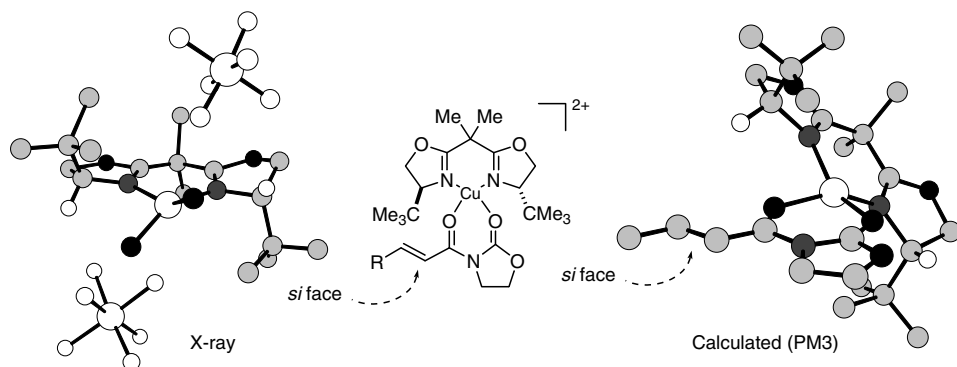
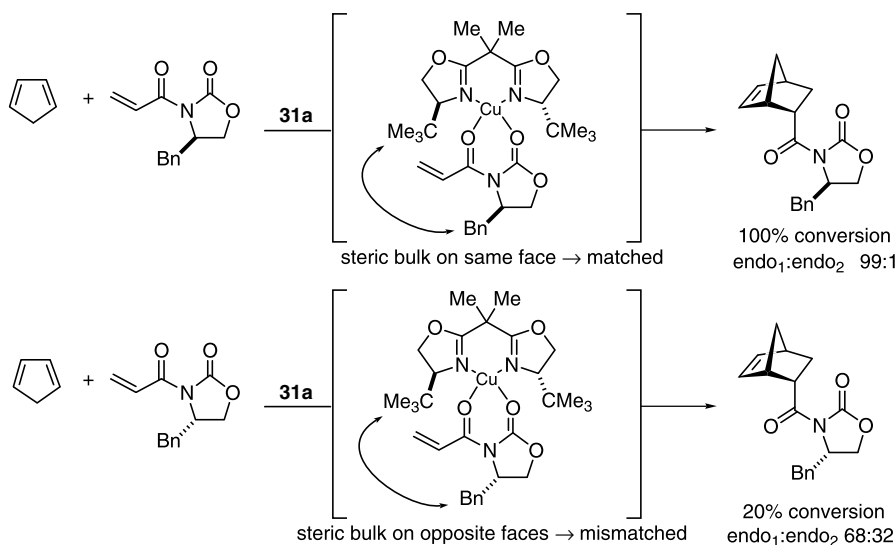


Fig. 23. X-ray structure of **31b**·(H₂O)₂, proposed transition state assembly for bis(oxazoline)Cu catalyst **31**, and PM3 calculated structure of the substrate-catalyst complex



Scheme 29

case, the stereochemical preference exhibited by the catalyst overrides that of the auxiliary.

Modifications to the parent bis(oxazoline) structure have been subsequently disclosed (Fig. 24). Spirobis(oxazoline) **34** derived from amino indanol catalyzes (10 mol %) the enantioselective cycloaddition between cyclopentadiene and acrylamide (−78 °C) in 96.3% ee (*endo/exo*=44:1) [90]. When the size of the spiro ring (e.g., cyclobutyl, -pentyl, -hexyl) is increased, the resulting structural change progressively degrades the reaction enantioselectivity, demonstrating a relation-

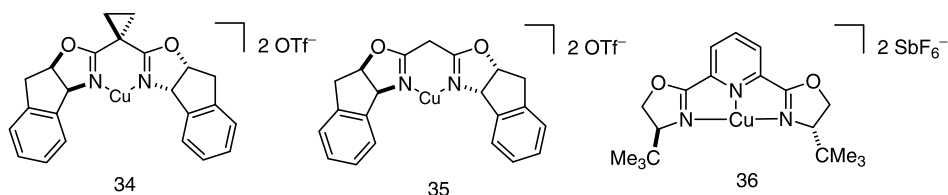
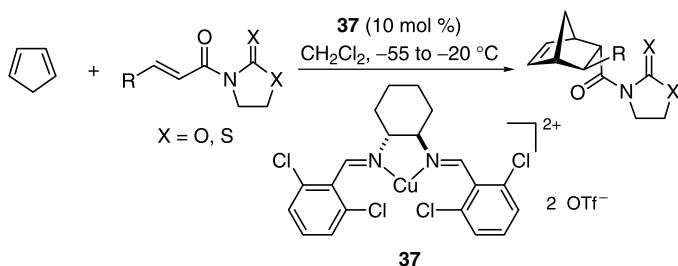


Fig. 24. Bis(oxazoline)Cu complexes for Diels-Alder reactions



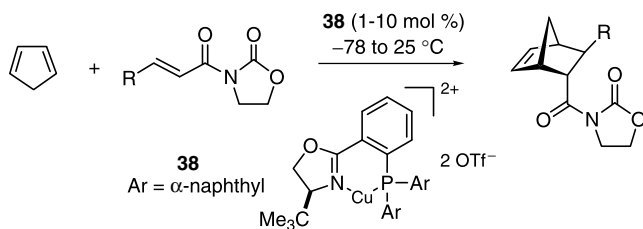
R	X	Yield [%]	<i>endo/exo</i>	ee [%]
H	O	87	80:20	92
Me	S	86	93:7	91
Ph	S	84	92:8	92
CO ₂ Et	S	99	90:10	88

Scheme 30

ship between ligand bite angle and enantiomeric excess. A simple *gem*-dimethyl bridge (rather than cycloalkane) delivers the adduct in 95% ee [91], while unsubstituted **35** has been shown to catalyze the same reaction in 99% ee (dr>99:1) [92]. In spite of the ligand modifications introduced in complexes **34** and **35**, it is not evident their performance is superior to the parent *tert*-butyl-bis(oxazoline)Cu(SbF₆)₂ complex **31b** (Scheme 24). Finally, bis(oxazoliny)pyridine (pybox) complex **36** is a selective catalyst for Diels-Alder reactions between unsaturated aldehydes and cyclopentadiene [83].

Cationic copper(II) complex **37** derived from a chiral bis(imine) ligand has also been shown to be an effective catalyst for reactions between cyclopentadiene and acylated thiazolidine-2-thione dienophiles, albeit with slightly lower selectivities than for the bis(oxazoline) complex **31** (Scheme 30) [93]. The bis(2,6-dichlorophenylimine) was found to be optimal among a number of electron-rich and -poor aryl imines screened. The reaction exhibits a positive non-linear effect which suggests that the minor ligand enantiomer can be sequestered by the formation of a catalytically less active (*R,R*)/(*S,S*)Cu(II) dimer.

A recent disclosure by Helmchen has demonstrated that (phosphino-oxazoline)copper(II) complexes are also good chiral templates for asymmetric cataly-



R	Catalyst (mol%)	Solvent	Yield	<i>endo:exo</i>	ee [%]
H	10	CH ₂ Cl ₂	92	94:6	97
H	1	EtNO ₂	86	95:5	92
Me	10	CH ₂ Cl ₂	98	88:12	86
Ph	10	EtNO ₂	74	40:60	85
CO ₂ Et	10	CH ₂ Cl ₂	95	60:40	75

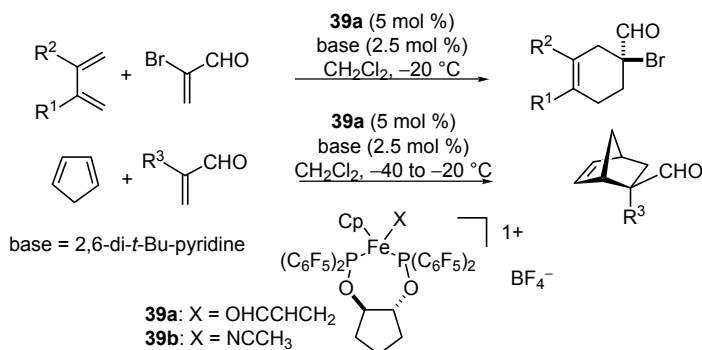
Scheme 31

sis of the Diels-Alder reaction (Scheme 31) [94]. As with the bis(oxazoline)Cu(II) complex **31**, the *tert*-leucine-derived variant was found to be optimal, and bulky aryl groups on the phosphorous center were crucial as well. Dichloromethane and nitroethane were found to function well as solvents, allowing access to cycloadducts of good enantiomeric excess with acryloyl, crotonyl, cinnamoyl, and fumaroyl imide dienophiles. A turnover in diastereoselectivity occurs with the cinnamoyl imide dienophile, and the *exo* cycloadduct is formed in moderate excess. Interestingly, for this system the more associating triflate counterion was found to afford a more selective catalyst than the hexafluoroantimonate-derived catalyst, in contrast to **31**. Additionally, it appears that more sterically restrictive catalysts are more active catalysts.

3.2.2

Iron

Kündig's cationic iron(II) complex **39a**, derived from *trans*-1,2-cyclopentanediol, is a stable, isolable brown solid that possesses sufficient Lewis acidity to catalyze Diels-Alder reactions between unsaturated aldehydes and dienes [95]. The highest selectivities and yields were realized using bromoacrolein as the dienophile (Scheme 32). Further inspection reveals that dienes less reactive than cyclopentadiene give cycloadducts in higher yield and enantioselectivity, a characteristic that is even more impressive when one considers that the *endo* and *exo* transition states produce enantiomeric products for isoprene and 2,3-dimethylbutadiene. Cyclohexadiene may be used in the reaction with bromoacrolein to afford the cycloadduct in 80% de and >99% ee. In the case of cyclopentadiene,



R ¹	R ²	R ³	Yield [%]	ee [%]
Me	H	–	99	96
Me	Me	–	92	97
–	–	Me	62	90
–	–	Br	87	95

Scheme 32

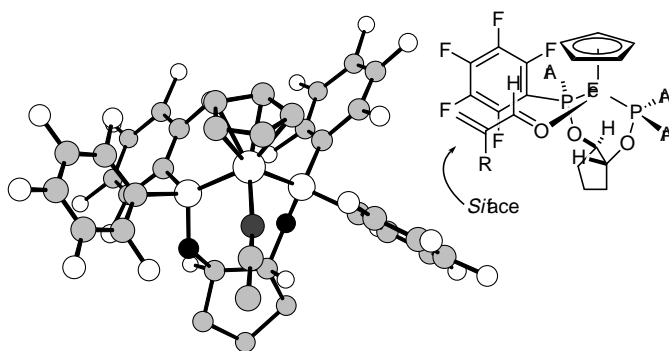
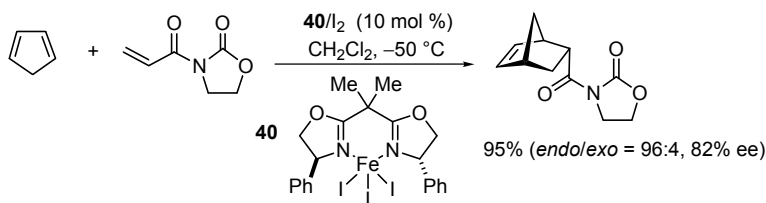


Fig. 25. X-ray structure of **39b** and proposed transition state assembly for cationic iron complex **39a**

diastereomeric excesses are greater than 90% for the two cases shown. In all cases, low catalyst loadings are feasible.

An undefined catalyst is recovered after the conclusion of the reaction by precipitation with hexane and filtration, but no mention is made of recycling. The presence of the acid scavenger is important, as irreproducible results (variable reaction rate, diminished selectivity) are obtained in the absence of the pyridine base. While **39a** gradually decomposes in solution above -20°C , spectroscopic observations ($^1\text{H-NMR}$ and IR) support the assigned structure and the mode of binding (Fe-O=C η^1 complex). An X-ray structure of **39b** wherein acetonitrile



Scheme 33

has replaced acrolein as a ligand has provided the basis for a transition state model (Fig. 25) which suggests that the *Re* face of the aldehyde is blocked by the pentafluorophenyl ring of the ligand. The presence of this electron-poor moiety lies in contrast to oxazaborolidine catalyst **10** and dichloroalkylborane catalyst **13** which employ electron-rich aromatics as key constituents of the complexes. That these three electronically diverse catalysts are all able to deliver cycloadducts in high enantioselectivities highlights that our understanding pertaining to substrate-catalyst interaction is still in its infancy.

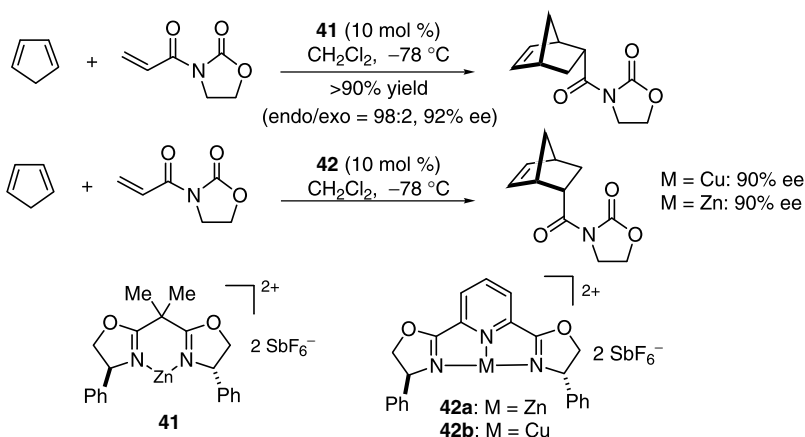
A bis(oxazoline)Fe(III) complex has also been shown to function as an effective catalyst for an enantioselective Diels-Alder reaction between cyclopentadiene and acryloyl imide (Scheme 33) [96]. Recovery of the chiral ligand proceeded in >85% yield. The scope of this catalyst has not been evaluated against less reactive dienes and dienophiles that require higher reaction temperatures.

3.2.3

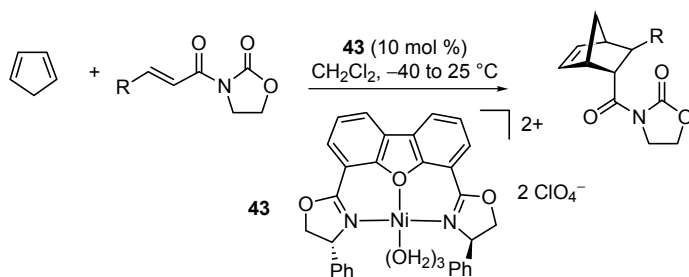
Other Late Transition Metal Catalysts

While copper and iron Lewis acids are the most prominent late transition metal Diels-Alder catalysts, there are reports on the use of other chiral complexes derived from ruthenium [97, 98], rhodium [99], and zinc [100] in enantioselective cycloaddition reactions, with variable levels of success. As a comparison study, the reactions of a zinc(II)-bis(oxazoline) catalyst **41** and zinc(II)-pyridylbis(oxazoline) catalyst **42** were evaluated side-by-side with their copper(II) counterparts (Scheme 34) [101]. The study concluded that zinc(II) Lewis acids catalyzed a few cycloadditions selectively, but, in contrast to the [Cu(*t*-Bubox)](SbF₆)₂ complex **31b** (Sect. 3.2.1), enantioselectivity was not maintained over a range of temperatures or substitution patterns on the dienophile. An X-ray crystal structure of [Zn(Ph-box)](Cl)₂ revealed a tetrahedral metal center; the absolute stereochemistry of the adduct was consistent with the reaction from that geometry and opposite that obtained with Cu(II) complex **31**.

A C₂-symmetrical tridentate ligand that employs a benzofuran backbone, recently reported by Kanemasa, is also an effective chiral controller for asymmetric Diels-Alder reactions [102]. Dubbed DBFOX, the ligand forms catalytically competent complexes with a wide range of transition metal salts. Remarkably, complexes derived from Fe(ClO₄)₂, Co(ClO₄)₂·6H₂O, Ni(ClO₄)₂·6H₂O, Ni(ClO₄)₂,



Scheme 34



R	Yield [%]	endo/exo	ee [%]
H	95	98:2	96
Me	90	92:8	93
Pr	90	93:7	94
Ph	52	–	74

Scheme 35

$\text{Cu}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$, and $\text{Zn}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$ all catalyze the reaction of acryloyl imide and cyclopentadiene in >96% ee (Scheme 35). This generality with respect to the metal center of the Lewis acid complex is unprecedented and quite extraordinary. The results also point to a typical advantage of transition metal catalysts over boron complexes: insensitivity to moisture. Catalyst **43** can be stored at ambient temperature and atmosphere for weeks with no deleterious effects and may also be used with dienophiles bearing an alkyl group at the β -position.

An X-ray structure of catalyst **43** reveals the nickel disposed in an octahedral geometry. From this solid state structure a transition state model was fashioned

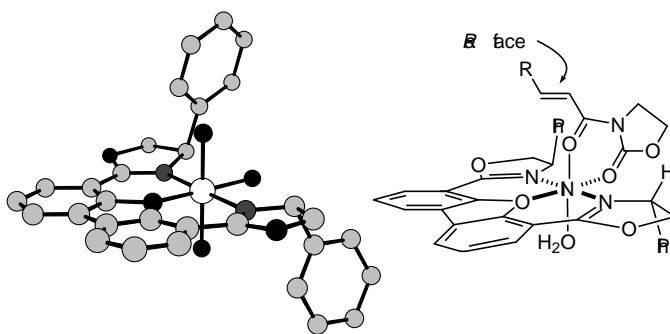


Fig. 26. X-ray structure and proposed transition state assembly for DBFOX-Ni(II) complex 43

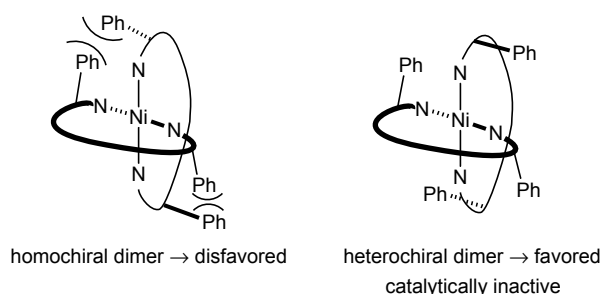


Fig. 27. Dimeric DBFOX complexes; formation of the heterochiral dimer is irreversible and sequesters the minor enantiomer as a catalytically inactive complex

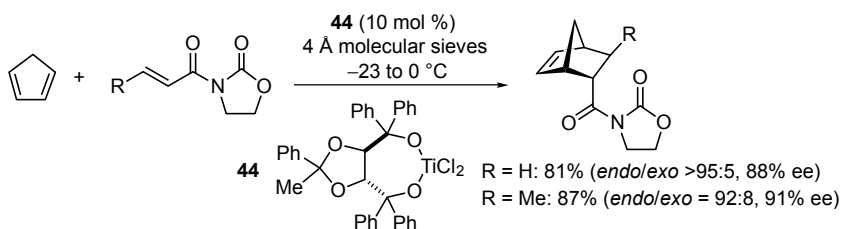
(Fig. 26) in which the exocyclic carbonyl group is bound in the apical position and the dienophile reacts out of the *s-cis* conformation. Steric shielding of the *Si* face by the ligand phenyl group would favor diene attack on the exposed *Re* face. As with Mg(II)bis(oxazoline) complexes (Sect. 3.1.3), the presence of ligands other than the dienophile appear to be important in the creation of a stereodefined environment about the metal center.

Dramatic nonlinear effects are observed for this system, as the employment of ligand at 20% ee affords the cycloadduct in 91% ee. Preferential formation of a heterochiral dimer serves to sequester the minor enantiomer and it has been proposed that this amplification is augmented by aggregation of the heterochiral dimeric complex in solution (Fig. 27).

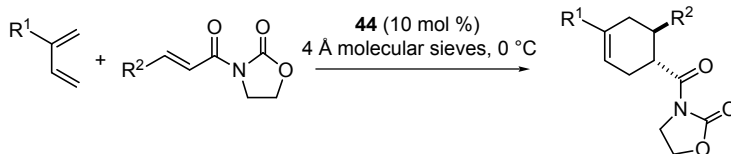
3.2.4

Early Transition Metal Lewis Acids

Titanium rivals boron for the amount of attention it has received in the development of catalytic enantioselective Diels-Alder reactions (for enantioselective Diels-Alder reactions promoted by stoichiometric amounts of chiral titanium



Scheme 36

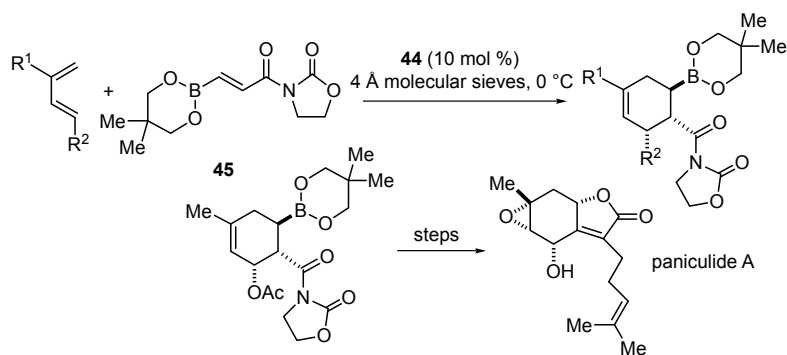


R ¹	R ²	Yield [%]	ee [%]
H	CO ₂ Me	84	91
Me	CO ₂ Me	94	94
H	H	81	93
Me	H	93	96
SEt	H	72	91

Scheme 37

complexes, see [103]); however, the similarities between the two metals cease at that point. While many boron complexes exhibit tetracoordination and have been shown to be monomeric in solution, titanium(IV) accommodates up to six ligands, and the derived complexes frequently feature bridging ligands and attendant aggregation. As will be noted, such behavior has frustrated efforts to probe catalyst structure and address issues of stereoinduction. It has been demonstrated that a wealth of ligands create an effective chiral environment around boron to induce asymmetry; in contrast, primarily one ligand has proven successful for titanium. As a consequence, this particular system has been studied quite extensively.

Tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligands synthesized from tartaric acid have been extensively employed by Narasaka as the chiral control element in selective Diels-Alder reactions. Initial experiments were conducted with simple dienes and α,β -unsaturated imides using complex **44** (Scheme 36) [104, 105]. Several rather subtle features have contributed to the success of these endeavors: 1) the use of the acetophenone-derived dioxolane rather than the acetonide resulted in an increase of 20% ee; 2) the use of alkyl-substituted benzenes as solvent augmented enantioselectivities relative to more common organic solvents (e.g., CH₂Cl₂, THF) [106]; 3) use of 4 Å molecular sieves was typically required to achieve maximum enantioselectivity.



R ¹	R ²	Yield [%]	ee [%]
H	H	76	>98
Me	H	74	>98
Me	Me	92	94
Me	OAc	71	95

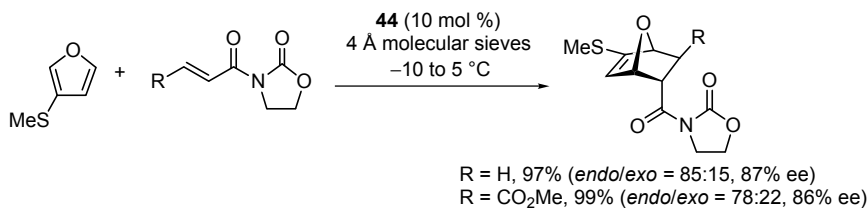
Scheme 38

The titanium-TADDOL system is notable for its breadth of reacting partners. Fumaroyl [104b] and acryloyl [107] imide dienophiles may be employed with substituted and unsubstituted butadienes to afford cyclohexenes in high enantiomeric excess (Scheme 37). In the case of 2-thioethylbutadiene, the lower yield is accounted for by the intervention of a competing [2+2] cycloaddition pathway.

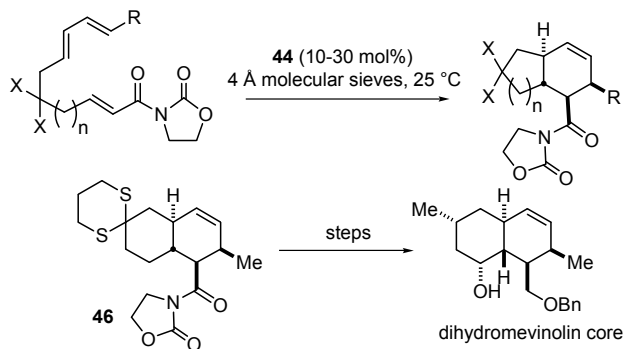
As noted in Scheme 38, 3-borylpropenoic acid derivative **45** functions as an effective dienophile with several butadienes [108]. The impetus for the development of this particular dienophile was the low reactivity observed for the corresponding 3-acetoxypipropenoic acid derivative. Subsequent to cycloaddition, the boryl moiety may be stereospecifically oxidized to the corresponding alcohol and, as such, dienophile **45** effectively functions as a β -hydroxyacrylic acid surrogate. An asymmetric synthesis of (+)-paniculide A relied on this strategy as the key transformation [109].

A substituted furan has been demonstrated to afford oxabicyclo[2.2.1]heptene cycloadducts in high enantioselectivity under the influence of the Ti-TADDOL catalyst (Scheme 39) [110]. Reversibility at elevated temperatures was apparently not a problem in this case, in contrast to the reaction mediated by complex **31** (Sect. 3.2.1).

Titanium(IV)-TADDOL complexes are competent catalysts for intramolecular Diels-Alder reactions as well (Scheme 40) [111]. While a highly functionalized product is obtained, reaction times are on the order of days (68–257 h). The presence of the dithiane in the alkyl tether appears to be necessary not only for reasonable reactivity but also for high diastereoselectivity; the latter apparently results from unfavorable interactions between the dithiane and the diene in the



Scheme 39



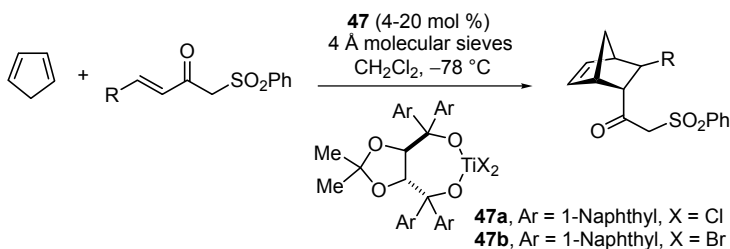
R	X	n	Yield [%]	ee [%]
H	H	1	87	87
H	S(CH ₂) ₃ S	1	62	95
H	S(CH ₂) ₃ S	2	64	86
Me	S(CH ₂) ₃ S	2	70	87

Scheme 40

exo transition state, while the former is thought to be a manifestation of the Thorpe-Ingold effect [112]. As a demonstration of the synthetic utility of the process, cycloadduct **46** (R=Me, n=2, X=S(CH₂)₃S) was elaborated to the hydro-naphthalene core of the mevinic acids.

The only highly enantioselective (>90% ee) Diels-Alder reaction using a ketone as a dienophile has been reported by Wada using the modified Ti(IV)-TAD-DOL catalyst **47** (Scheme 41) [113]. The important design feature is the use of a β-sulfonyl ketone, which presumably provides a chelating substrate to enhance catalyst-dienophile organization. The only diene used in this study was cyclopentadiene, and a limited number of dienophiles were employed, but the selectivities observed are noteworthy. As an added bonus, the phenylsulfonyl group may be excised to afford the corresponding methyl ketone in good yield.

As a result of the high level of success enjoyed by this family of catalysts, substantial effort has been invested in the study of the mechanism of asymmetric



Catalyst	R	Yield [%]	endo/exo	ee [%]
47a	Me	80	>99:1	>99
47b	Pr	90	>99:1	94
47b	Ph	65	83:17	78

Scheme 41

induction. $^1\text{H-NMR}$ spectral studies have shown that catalysts such as **44** (typically formed from $\text{TiCl}_2(\text{OiPr})_2$ and the chiral diol) are in fact in equilibrium with the starting materials [114]. Not unexpectedly, $\text{TiCl}_2(\text{OiPr})_2$ promotes the reaction between a fumaroyl imide and isoprene at a substantially higher rate than complex **44**. In toluene- d_8 at 25°C , the ratio of complex **44** to free diol is 87:13; the addition of 4 Å molecular sieves changes this ratio to 94:6, perhaps pointing to the role this addend is playing.

A 1:1 complex of a Ti-TADDOL catalyst and imide dienophile has been crystallographically characterized and implicated as the reactive species in enantioselective Diels-Alder reactions [115]. The imide is chelated to the metal center in the same plane as the chiral ligand (**48**, Fig. 28); this arrangement places the prochiral alkene in a position remote from the resident chirality and would presumably result in little stereochemical communication between the ligand and approaching diene. From the X-ray structure, Jørgensen has proposed that the pseudoequatorial phenyl group shields the *Si* face of the olefin in the *endo* transition state (*i.e.*, **49**) [116]; however, others have argued (*vide infra*) that binary complex **48** may simply be the most thermodynamically stable species (and most likely to crystallize from solution), not the dominant reactive species.

$^1\text{H-NMR}$ spectral studies of a 1:1 mixture of imide dienophile and $[\text{Ti}(\text{TADDOL})\text{Cl}_2]$ have revealed the presence of three species in solution, the geometry of the major complex being **49**, the same as in the solid state structure [117]. Complex **50** is proposed as one of the minor components, owing to shielding effects observed for some of the oxazolidinone protons and hindered rotation for the pseudoaxial aryl group of the ligand; such a complex is further postulated to be the reactive species. DiMare has convincingly argued that intermediate **50** in which the activated carbonyl is *trans* to a chloride ligand should experience a higher level of Lewis acid activation than in **49** where the *trans* substituent is an alkoxy group.

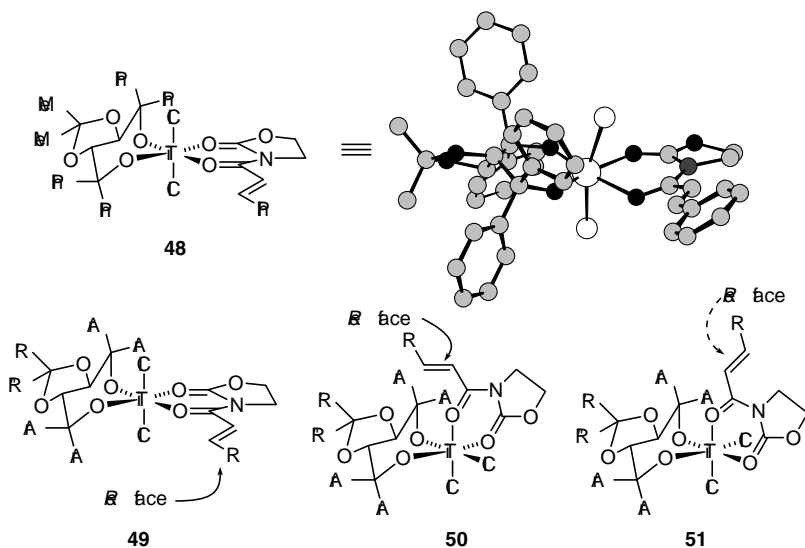


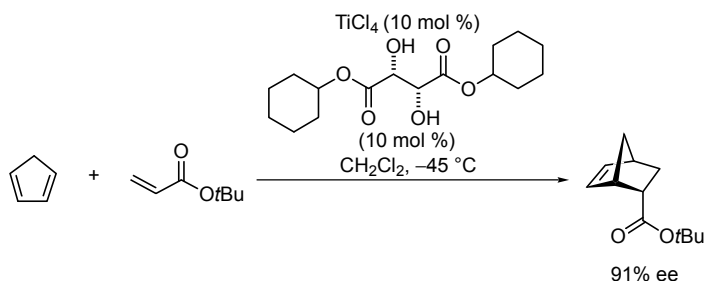
Fig. 28. X-ray structure of Ti-TADDOL-bound cinnamoyl imide **48** and proposed transition state assemblies for Ti-TADDOL mediated Diels-Alder reactions

Corey has proposed that the dienophile is activated in the apical position, but reacts via an *s-trans* configuration as illustrated in **51**. A donor-acceptor interaction between the pseudoequatorial aryl group and the bound dienophile was proposed as an organizational element due to the correlation between enantiomeric excess and aryl substituents [118]. It becomes necessary to invoke the Curtin-Hammett principle twice to validate this transition state: reaction occurs from the less favored metal geometry and the higher energy dienophile conformation. Incorporation of a *gem*-dimethyl group on the nitrogen-bearing carbon of the oxazolidinone led to nearly racemic product and was interpreted as evidence for reaction out of the *s-trans* conformer. While it appears that double stereodifferentiating experiments of the type carried out with catalyst **31** (Sect. 3.2.1) would be informative in differentiating transition structure **51** from **49** and **50**, no such studies have been disclosed.

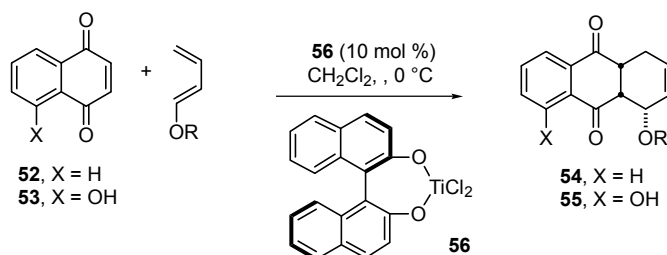
As a final cautionary note regarding mechanistic interpretation of this system, Seebach has noted positive non-linear effects for the Diels-Alder reaction using Ti(IV)-TADDOL, indicating the possibility of either an aggregated transition state or the formation of catalytically inactive 1:1 (*R,R*)/(*S,S*)-titanium complexes [119].

Another tartaric acid-derived complex catalyzes the Diels-Alder reaction of *tert*-butyl acrylate and cyclopentadiene with good levels of enantiomeric excess (Scheme 42) [120]. The use of a smaller ester substituent resulted in lower enantioselectivity for the derived cycloadduct.

Despite their high reactivity as dienophiles and the potential utility of the derived cycloadducts, quinones have rarely been utilized in catalytic enantioselective



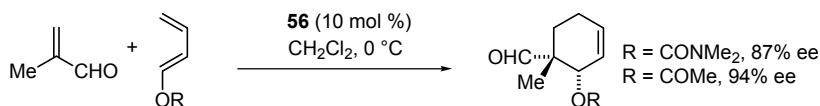
Scheme 42



X	R	ee [%]	Comment
H	Me	86	Molecular sieves added
OH	COMe	76–96	Molecular sieve-free catalyst

Scheme 43

tive Diels-Alder reactions (for enantioselective quinone-diene Diels-Alder reactions with stoichiometric amounts of a chiral Lewis acid, see [121]). This is interesting in light of the fact that one of the variables which could contribute to low selectivity has been effectively deleted: quinones must react out of an *s-trans* configuration since the dienophile is locked in a ring. One of the few successful examples of an enantioselective quinone-Diels-Alder reaction was realized by Mikami using naphthoquinone (**52**, X=H) and a Ti(IV)-binaphthol complex in the presence of 4 Å molecular sieves (Scheme 43) [122, 123]. Tricyclic product **54** was formed with complete *endo* selectivity in 85% ee using catalyst **56**. When a similar reaction was attempted with juglone (**53**, X=OH), the cycloadduct **55** was obtained in only 9% ee. It was speculated that the molecular sieves were aiding in a deleterious phenol/chloride exchange; NMR experiments did seem to suggest that the phenol was bound to the catalyst. Accordingly, an alternate catalyst was prepared in which the molecular sieves were removed by centrifugation prior to the start of the reaction. With this modification, the desired cycloaddition could be executed between juglone and 1-acetoxybutadiene with high levels of selectivity, although the authors report that the enantioselectivity is vari-



Scheme 44

able and catalyst batch-dependent. The derived cycloadducts are noteworthy as they provide a potential entry into the asymmetric syntheses anthracycline and tetracycline families of antibiotics.

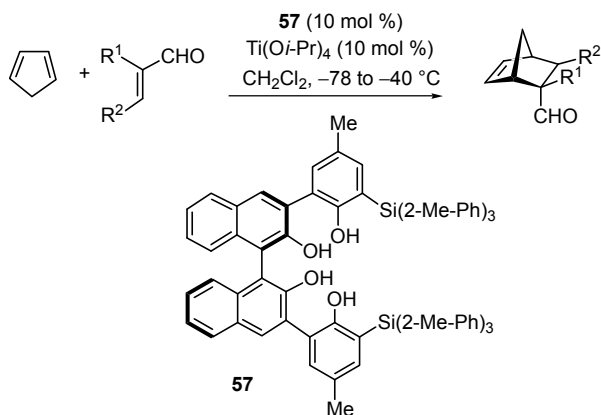
Further work with the molecular sieve-free Ti(IV)-binaphthol catalyst **56** showed that 1-alkoxydienes react with methacrolein to afford cyclohexene products possessing a quaternary center adjacent to a stereochemically defined secondary urethane in near diastereomeric purity and high enantiomeric excess (Scheme 44).

Mikami and coworkers conducted the Diels-Alder reaction with a catalyst prepared by mixing enantiomerically pure (*R*)-**56** and racemic **56** and observed a positive nonlinear effect; however, they found no asymmetric amplification when they prepared the catalyst by mixing enantiomerically pure (*R*)-**56** and enantiomerically pure (*S*)-**56** (*i.e.*, linear correlation between catalyst and product ee). Introduction of molecular sieves restores the asymmetric amplification in the latter case, apparently by equilibration of (*R*)(*R*) and (*S*)(*S*) dimers into catalytically less active (*R*)(*S*) dimers. As expected, the reaction rate was faster for (*R*)-**56** than for (\pm)-**56** derived from racemic binaphthol ligand (*ca.* 5-fold faster).

Yamamoto has disclosed that another binaphthol-derived complex is an effective catalyst for enantioselective Diels-Alder reactions of aldehydes and cyclopentadiene (Scheme 45). Azeotropic removal of 2-propanol from a mixture of ligand **57** and Ti(O*i*Pr)₄ affords a Lewis acid capable of catalyzing Diels-Alder reactions between cyclopentadiene and acrolein, methacrolein, and crotonaldehyde, delivering cycloadducts with enantioselectivities in excess of 94%; however, diastereoselectivity is moderate in two cases [124].

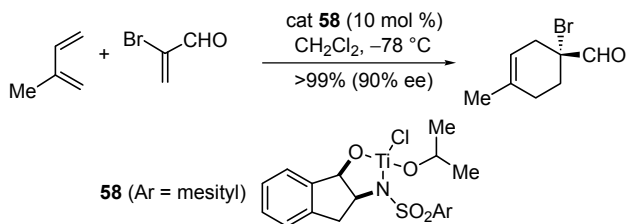
The authors contend that the Lewis acid complex is helical, but characterization of the catalyst is limited to cryoscopic molecular weight measurements of a related complex in benzene. Two attributes of this system deserve attention: 1) the tetraalkoxytitanium species still possesses sufficient Lewis acidity to catalyze the reactions of interest at low temperatures; 2) the catalyst exhibits a fairly flat enantioselectivity-temperature profile (88% ee at 0 °C for the acrolein-cyclopentadiene reaction). The ligand was synthesized in five steps from (*R*)-(+)-3,3'-dibromobinaphthol dimethyl ether, and while other groups may be used in lieu of the tri-*o*-tolylsilyl group, the highest levels of enantioselectivity were realized with ligand **57**.

A rather different titanium(IV) Diels-Alder catalyst employed a *cis*-amino indanol, prepared in five steps from indene, as the chiral control element [125]. The amino indanol is regioisomeric to the one incorporated into a bisoxazolonyl



R ¹	R ²	Yield [%]	<i>endo/exo</i>	ee [%]
H	H	70	85:15	96
Me	H	75	1:99	94 (2S)
H	Me	76	70:30	95

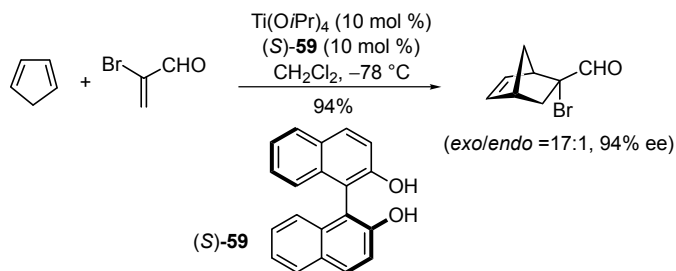
Scheme 45



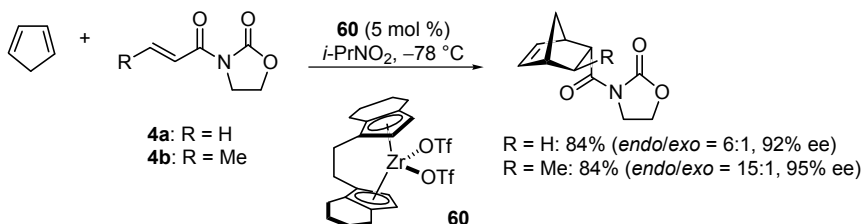
Scheme 46

ligand for copper(II) Lewis acids (**34**, **35**). Treatment of the ligand with Ti(OiPr)₄ in toluene at elevated temperature, followed by azeotropic removal of 2-propanol and subsequent treatment with one equivalent of SiCl₄ yielded a metal complex, tentatively formulated as **58**, as an amorphous yellow solid. By spectroscopic inspection the complex was not monomeric in solution, but aggregated. Nonetheless, **58** functioned as a stereoselective Lewis acid, catalyzing the cycloaddition of bromoacrolein with cyclopentadiene (93% ee) or isoprene (Scheme 46).

Keck and Krishnamurthy have shown that the Diels-Alder reaction of cyclopentadiene and bromoacrolein is facilitated by a Lewis acid derived from titanium tetrakisopropoxide and *S*-BINOL (**59**) (Scheme 47) [126]. The cycloaddition may be conducted with isoprene at slightly lower levels of enantioselectivity; methacrolein-cyclopentadiene Diels-Alder reactions are only moderately selective.



Scheme 47



Scheme 48

While metallocenes are ubiquitous in organometallic and polymer chemistry, few such complexes have been reported to catalyze the Diels-Alder process in high enantioselectivity [127, 128, 129]. The bis(tetrahydroindenyl)zirconium triflate **60** and the corresponding titanocene are electrophilic to the extent that they catalyze the low-temperature cycloadditions of acrylate and crotonate imides with cyclopentadiene with good diastereoselectivity and excellent enantioselectivity (Scheme 48). The reactivity of **60** is noteworthy since the corresponding reaction using the crotonyl imide with highly reactive catalysts **31a** or **44** requires temperatures of -15 and 25°C , respectively.

Collins and coworkers uncovered a truly dramatic solvent effect during these investigations. In the most telling example, the reaction of **4a** with cyclopentadiene proceeded in CH_2Cl_2 to afford racemic material, while the same reaction, conducted in 2-nitropropane, allows the adduct to be prepared in 92% ee. Only slightly lower enantiomeric excess was observed in nitromethane. ^1H - and ^{19}F -NMR spectroscopy of an equimolar mixture of **60** and acryloylimide **4a** in CD_3NO_2 established that very little unbound **4a** was present in solution; rather, at -30°C , two complexes in a 2:1 ratio were observed. On the basis of the ^{13}C -NMR spectrum, it was concluded that the carbonyls in both complexes were bound to the metal center. In CD_2Cl_2 , the ratio of complexes was altered (6:1), leading the authors to surmise that the dramatic shift in selectivity resulted from a change in stability of the catalyst-dienophile complexes, which could be assigned on the basis of NOE enhancements (Fig. 29). Further NOE studies showed that the unsaturated imide resided in the *s-cis* conformation for both bound

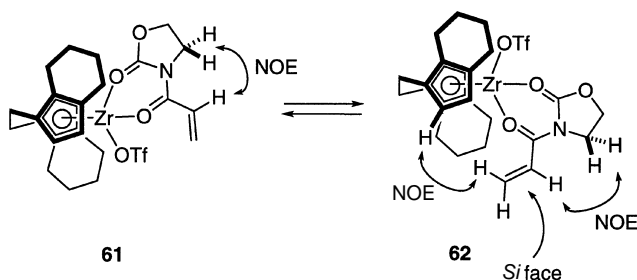


Fig. 29. Diastereomeric complexes formed between zirconocene **60** and imide **4a**

complexes. Since the unsaturated imide lies in a more defined chiral environment in **62**, it may be reasonably assumed that this is the species which leads to the enantioenriched product; the absolute configuration of the adduct is consistent with shielding of the *Re* face by the cyclohexyl ring and reaction from the exposed *Si* face.

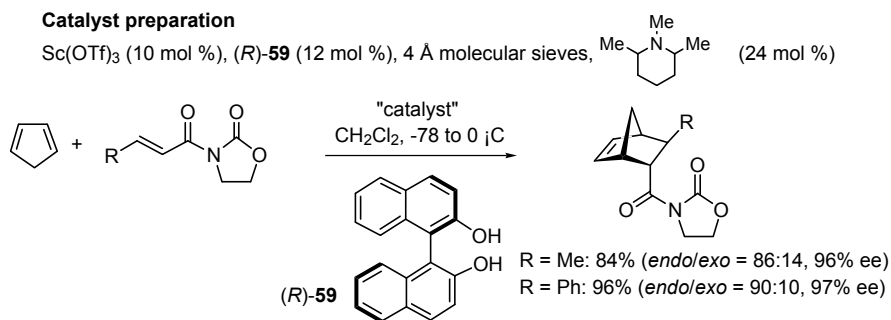
3.3

Lanthanide Lewis Acids

Many researchers have refrained from using lanthanide complexes in stereoselective Diels-Alder reactions, perhaps due to large coordination spheres which can accommodate up to a dozen ligands. The rather daunting task of interpreting the identity of active catalysts and substrate-catalyst complexes among the myriad possible options has not hampered the development of some quite useful chiral lanthanide catalysts.

Kobayashi and coworkers have reported that a chiral complex derived from scandium(III)triflate, *R*-(+)-BINOL ((*R*)-**59**), and 1,2,6-trimethylpiperidine in the presence of 4 Å molecular sieves catalyzes the reaction of unsaturated imides with cyclopentadiene in 96–97% ee (Scheme 49) [130].

The particular trialkylamine additive was uniquely effective in securing maximum enantioselectivity, as both more and less steric demand on the amine afforded products having lower ee. ¹³C-NMR and IR spectral studies have shed some light on the role of the amine additive. Rather than acting as a ligand, it has been suggested that the basic amines are interacting weakly with the acidic hydrogens of the phenols to form a hydrogen bond. The working hypothesis is that this hydrogen bond extends the axial chirality of the binaphthol (Fig. 30). In principle, this organizational motif provides an attractive alternative to the covalent modification the binaphthol ligand, since the amine additive can be easily varied, but the singular effectiveness of 1,2,6-trimethylpiperidine is not apparent from the working model. A second experimental nuance that merits mention is that the enantiomeric excess of the product is eroded as the catalyst ages [131]. While the cause is not known, the diminution in selectivity can be arrested with the addition of certain dicarbonyl additives. As with some other catalyst systems



Scheme 49

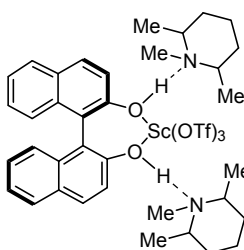
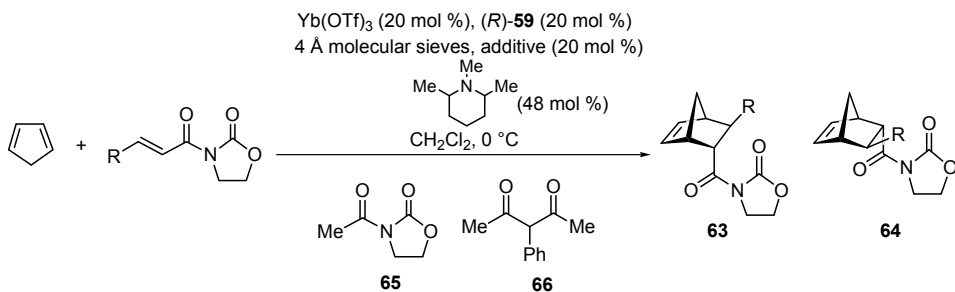


Fig. 30. Proposed extended axial chirality by interaction of amine base with binaphthol- $\text{Sc}(\text{OTf})_3$ catalyst

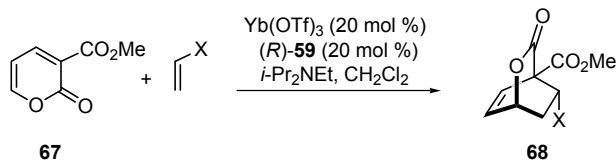
presented previously, asymmetric amplification was observed with catalysts prepared from optically impure binaphthol ligand, suggesting aggregative catalyst behavior.

An exciting result with a related system ($\text{Yb}(\text{OTf})_3$ [132] vs. $\text{Sc}(\text{OTf})_3$) is illustrated in Scheme 50. If, in addition to the amine additive, one equivalent (relative to metal salt) of a dicarbonyl compound was included in the reaction, a turnover in enantioselectivity was observed [133]. In the case of the crotonyl imide, without added ligand the *2S,3R* enantiomer **63** was obtained selectively (95% ee); however, with the addition of 3-phenylacetylacetone (**66**), the *2R,3S* isomer **64** was formed in 81% ee. As was noted previously, the addition of dicarbonyl compounds to the scandium(III) triflate catalyst deters catalyst aging, but no turnover in enantioselectivity was observed. The difference between the two systems is thought to lie in a change in coordination number. To rationalize the reversal in facial bias, it has been postulated that the imide and the acetylacetone possess differential affinity for diastereotopic binding sites. It is conjectured that the stronger binding acetylacetone ligand forces the dienophile into a site in which the opposite enantioface is exposed, but no spectroscopic evidence supporting this turnover in binding has been disclosed. In contrast to the $\text{Sc}(\text{III})$ -binaphthol catalyst, the $\text{Yb}(\text{III})$ -binaphthol catalyst with added 3-phenylacetylacetone exhibits a negative nonlinear effect, while in the absence of any added ligand, no



R	Comment	Yield [%]	<i>endo/exo</i>	er (63:64)
Me	no additive	77	89:11	97.5:2.5
Me	Added 66	83	93:7	9.5:90.5
<i>n</i> -Pr	no additive	81	80:20	91.5:8.5
<i>n</i> -Pr	added 66	81	91:9	10:90

Scheme 50



X	Yield [%]	ee [%]
Oet	90	27
OC ₆ H ₁₁	90	92
Oadamantyl	91	93
SPh	91	>95

Scheme 51

nonlinear effects are observed (at >60% ee) [134]. Thus, it appears that the active catalyst possesses a different degree of aggregation for each case.

A conceptually different [4+2] cycloaddition catalyzed by a chiral lanthanide complex has been disclosed. The inverse electron demand Diels Alder reaction of 3-methoxycarbonyl-2-pyrone (**67**) and enol ethers or sulfides [135] was catalyzed by a chiral ytterbium(III) triflate-binaphthol complex in the presence of diisopropylethylamine (Scheme 51) [136]. Thermal decarboxylations of bicyclic lactones such as **68** are known to yield dienes which may undergo subsequent pericyclic reactions [137]; thus, the adducts of this process are potentially useful chiral building blocks. The nature of the substituent on the 2π component was found to be crucial for the realization of high enantioselectivity.

4

Alternative Methods

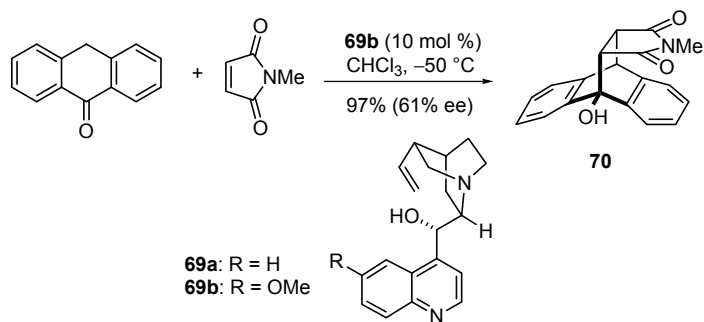
The vast majority of strategies aimed at effecting enantioselective Diels-Alder reactions rely on complexation of an unsaturated carbonyl compound to a chiral Lewis acid, but this is not the only catalytic method for achieving enantiofacial bias. A unique approach outlined in Scheme 52 takes advantage of a diene (or precursor) possessing an acidic proton [138]; treatment with a catalytic amount of a chiral base results in transient formation of an oxidodiene which undergoes oxyanion-accelerated cycloaddition with a maleimide [139].

Asymmetric induction is thought to arise from an organized transition state in which the chiral amine base is associated with the oxidodiene (ion pairing) and the dienophile (hydrogen bonding, Fig. 31).

Mechanistic studies have discounted the possibility that cycloadduct **70** arises from a tandem Michael-aldolization pathway [140]. Stereospecificity is observed using fumaronitrile (*trans* double bond) or maleonitrile (*cis* double bond) as dienophiles, indicating either a concerted reaction or a rapid second step (aldol) relative to internal bond rotation. Upon treatment with triethylamine in methanol, ring opening to the formal Michael adduct, a thermodynamic sink, is observed; this Michael adduct was not formed in the enantioselective catalytic reaction. Further, the Michael adduct was not converted to cycloadduct **70** upon treatment with quinidine in chloroform; in fact, access to **70** from the Michael product could be achieved only under fairly special conditions.

The only other example of an enantioselective base-catalyzed Diels-Alder reaction is illustrated in Scheme 53. A hydroxypyrene (**71**) is the substrate which undergoes activation by a catalytic amount of cinchonine (**69a**, R=H), subsequently reacting with *N*-methylmaleimide to form the derived tricyclic adduct with good selectivity [141].

Use of a *Cinchona* alkaloid in which the hydroxy group had been acylated resulted in formation of cycloadducts of low enantiomeric excess, leading the authors to conclude that bidentate activation (Fig. 32) was important in providing



Scheme 52

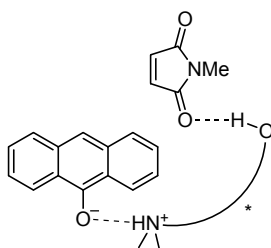
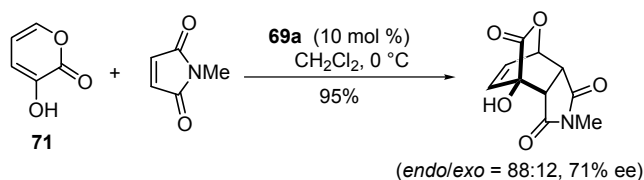


Fig. 31. Postulated ion-pairing in chiral base-catalyzed Diels-Alder reactions



Scheme 53

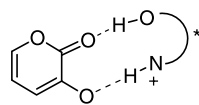


Fig. 32. Postulated ion pairing of hydroxy pyrone 71 with *Cinchona* alkaloid base

a high level of transition state organization. It is important to note that the control experiments which were performed in the anthrone/maleimide system (Scheme 52) were not performed for the reaction in Scheme 53; thus, a tandem Michael-aldolization pathway, while unlikely, has not been strictly excluded.

Enantiocontrol in the base-catalyzed Diels-Alder reaction has not yet reached the level of its Lewis acid-catalyzed counterpart; time will tell if the method can be generalized to a wider scope of substrates.

A fundamentally different approach to asymmetric induction in the Diels-Alder process entails the use of catalytic antibodies generated from transition state analogs [142]. Outlined conceptually in Fig. 33, haptens mimicking the *endo* and *exo* transition states were separately utilized to elicit catalytic antibodies which were used as Diels-Alder catalysts [143]. Bicyclo[2.2.2]hexanes modeling the boat-like Diels-Alder transition state were designed to minimize product inhibition, since the low energy product conformation is the twist chair, which presumably will not bind competitively to the catalytic site.

The catalytic antibodies were found to be exceptionally selective for the indicated cycloaddition reactions (Scheme 54). It is remarkable that either diastereomeric product may be obtained enantiomerically pure simply by selecting the

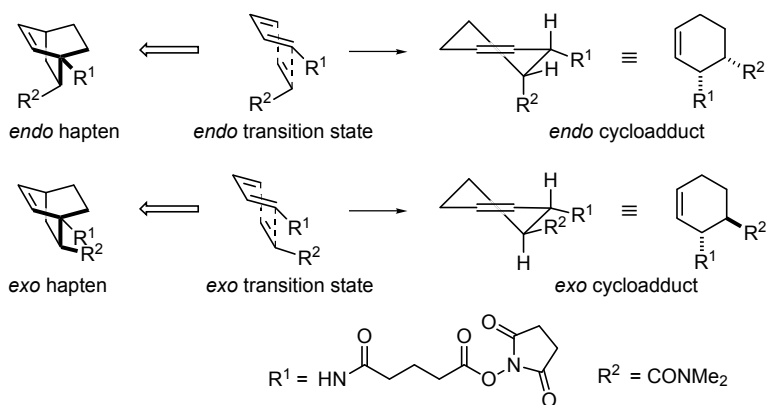
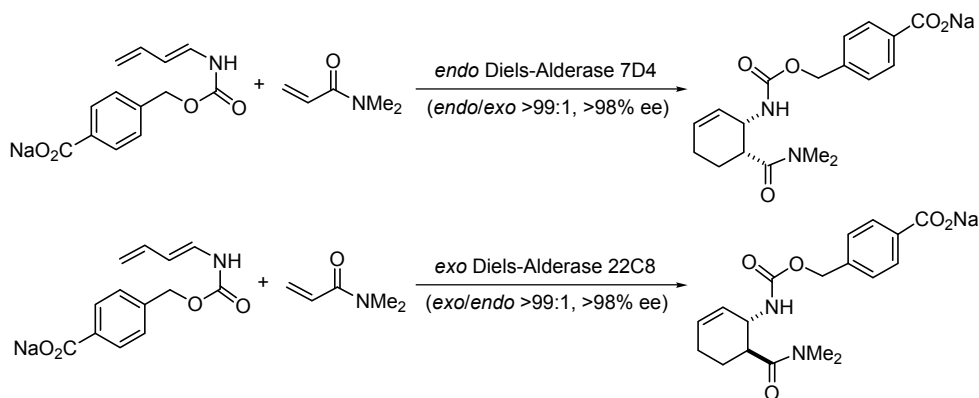


Fig. 33. Generation of catalytic antibodies by haptens designed to mimic the Diels-Alder transition state geometry, but not the product conformation



Scheme 54

correct catalytic antibody (for structural studies of Diels-Alderase antibodies, see [144]). Especially interesting is the fact that the energetically disfavored *exo* product may be obtained preferentially. This type of selectivity is rare in enantioselective Lewis acid-catalyzed processes [145, 146]. Based on the reported reaction conditions, it appears that the catalytic antibody turns over roughly four times for the *endo* adduct and five times for the *exo* [147]. With regard to practical considerations, separate antibodies must be prepared for each desired cycloadduct and it is not clear whether this process is amenable to large scale (20 μM of antibody reported); nonetheless, the levels of stereoselectivity render this concept immediately useful.

5 Conclusions

From the preceding discussion, some generalizations may be drawn with respect to the development of catalytic enantioselective Diels-Alder reactions and some conservative predictions pertaining to the future of the field may be proffered.

While astonishing diversity has been realized in the development of chiral complexes which will catalyze the Diels-Alder reaction with high attendant enantioselection (Fig. 34), the pool of reactions which has been sampled is relatively small. A plethora of catalysts has been reported to catalyze the cycloaddition of cyclopentadiene with acrolein or acrylate derivatives, but realization of generality with respect to reacting partners has been more difficult. The goal of this chapter is to provide a comprehensive review of advances in the field and in so doing suggest to the reader the untapped potential which remains. Those interested in executing these enantioselective processes must take into account factors of ligand synthesis, scalability, selectivity, and generality. For unsaturated aldehydes, oxazaborolidine (**10**), CAB (**7**) and BLA (**14**, **15**) catalysts distinguish themselves in their general applicability. A similar demarcation is possible for two-point binding substrates, as both Ti-TADDOL (**44**) and Cu(II)bis(oxazoline) (**31**) systems are both effective for a wide range of dienes and dienophiles and are amenable to preparative scale processes. A potential marker for synthetic utility of catalytic systems is actual application in multistep natural product synthesis. The aforementioned oxazaborolidine **10**, Cu(II)-bis(oxazoline) **31**, and Ti-TADDOL **44** have been successfully used in that context, as well as the aluminum-stien complex **3**.

Despite the development of a multitude of efficient, selective catalysts, the field is still at a fledgling stage. What does the future hold? In answering this query, it is important to consider two critical issues which are inexorably intertwined: mechanism and synthetic utility.

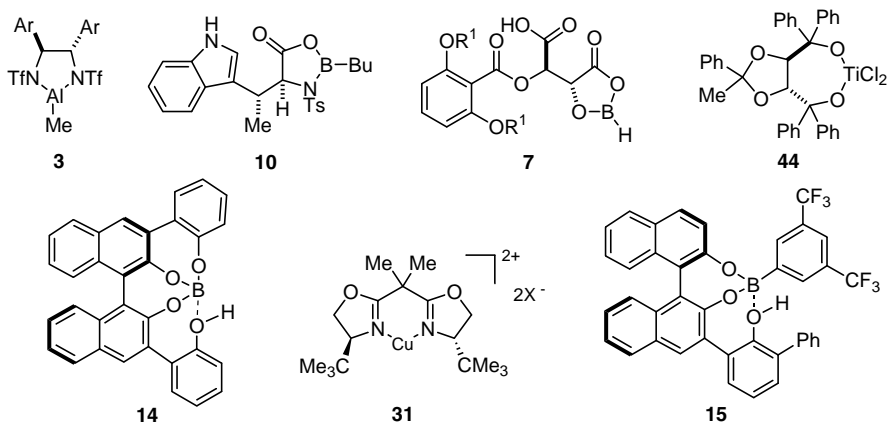


Fig. 34. Diels-Alder catalysts applicable to a breadth of diene/dienophile combinations

Mechanism. A strong argument can be made that the rigor that characterized earlier physical organic studies of the Diels-Alder reaction (and others) has been at least partially supplanted by more qualitative approaches. While exceptions certainly exist, kinetic analyses and isotopic labeling are no longer *de rigueur* and a brief survey of the literature reveals that structural characterization of catalysts and catalyst-substrate complexes does not appear to be a prerequisite for the formulation of transition structures. It is not coincidence that the mostly broadly useful Diels-Alder catalysts are those which are best understood mechanistically. As the field continues to expand, it will become even more critical to obtain a complete understanding of the minute details and nuances of each new catalyst system. Spectroscopic and solid state characterization of catalysts and activated complexes, as well as solution behavior from reaction kinetics will be indispensable in this regard. Without this rigor, mechanistic understanding and advances that extend from such insight will be slow coming, but with innovative approaches to the study of the intimate details of these processes, the field should continue to flourish.

Synthetic Utility. The enantioselective catalytic Diels-Alder reaction will continue to grow in usefulness to the synthetic organic chemist. Broadly speaking, current endeavors seek to expand the scope of this reaction through the development of complexes that effectively catalyze the cycloaddition of an entire spectrum of reacting partners. In simplest terms, more reactive catalysts and dienophiles will provide access to more highly functionalized products and facilitate the rapid assembly of molecular complexity. Even as this development occurs, questions will arise which will demand creative solutions. For example, can catalysts be designed to differentiate between the lone pairs of a simple α,β -unsaturated ketone and deliver cycloadducts in high enantioselectivity? Can alkenes lacking a carbonyl substituent be activated by chiral complexes in a face-selective fashion toward cycloaddition with dienes? Mechanistic studies will be crucial in assessing the feasibility of these and other processes. Practical considerations will lead to the development of more robust catalysts which can operate over a broad temperature range without special experimental precautions (inert atmosphere and the like). The Diels-Alder reaction will likely benefit from general advances being made in the field of asymmetric synthesis: generation of new catalyst leads will be facilitated by the continuing evolution of combinatorial chemistry, while catalyst immobilization in the solid and liquid phase can serve to greatly simplify product isolation and catalyst recycling. Additionally, the aforementioned simplicity of the catalytic cycle assure the continued prominence of the Diels-Alder process as an attractive test reaction for newly developed chiral catalysts. In this context, successful application of chiral Lewis acids to the Diels-Alder reaction is frequently a reliable indicator of potential utility to other classes of reactions. Notably, facile extension to aldol, ene, Michael, dipolar cycloaddition, and hetero-Diels-Alder reactions are a common outgrowth of studies in the enantioselective catalysis of the carbocyclic Diels-Alder reaction. The reader need only briefly scan other chapters of this monograph to find corroborating evidence for this point.

Undoubtedly, the axiom that *the constraints of the multistep synthesis experience provide the impetus for reaction development* will continue to be pertinent to the Diels-Alder reaction. The realization of more reactive and more general catalysts will continue to be a goal for the field and will yield an ever-growing arsenal of tools for use in the synthetic endeavors which require highly functionalized, enantioenriched carbocyclic building blocks.

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Chapter 33.2

Hetero-Diels-Alder and Related Reactions

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Keywords: Cyclocondensation, Danishefsky's diene, Aldehydes, Pyrone derivatives, Chiral Lewis acids, Enantioselectivity

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1

Introduction

Since Danishefsky demonstrated that activated dienes, such as siloxydiene (commonly referred to as Danishefsky's diene) react with a wide spectrum of aldehydes to afford 5,6-dihydro- γ -pyrones in 1982 [1], the hetero-Diels-Alder reaction has attracted a great deal of attention over the last two decades [2, 3]. The use of asymmetric catalysis in these reactions is overwhelmingly associated with heterodienophiles. Especially, the cyclocondensations of activated dienes with aldehydes or their derivatives are of particular importance, providing a multitude of opportunities for the highly efficient regio- and stereoselective construc-

tion of various heterocycles in enantiomerically pure form. In spite of the great potential of this synthetic methodology, its development was for a long time restricted to only a few efforts. However, during the last decade this field has been the subject of intense and successful research [4, 5, 6].

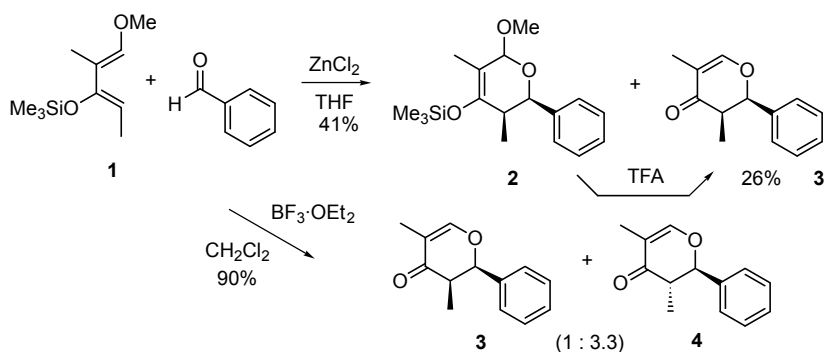
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The Mechanistic Aspect of the Hetero-Diels-Alder Reactions

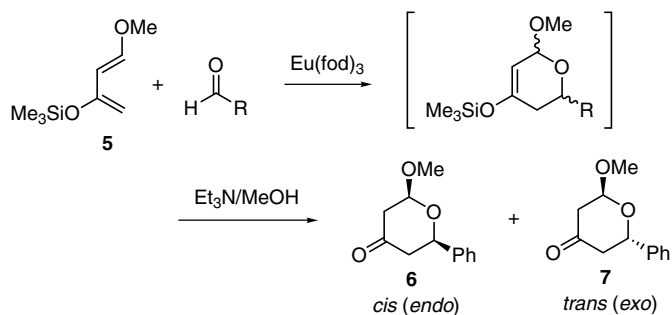
The first set of rigorous mechanistic investigations on the hetero-Diels-Alder reaction was performed by Danishefsky and co-workers. When the cyclocondensation between siloxydiene **1** and benzaldehyde was catalyzed by ZnCl_2 in THF and quenched with NaHCO_3 without aqueous workup conditions, enol ether **2** was isolated in addition to pyrone **3**, indicating a pericyclic mechanistic pathway. The enol ether **2** could then be transformed into **3** by acidic treatment. Thus, the reaction catalyzed by ZnCl_2 exhibits strong preference for *cis* (*endo*) stereochemistry. With $\text{BF}_3 \cdot \text{OEt}_2$, the reaction proceeds through Mukaiyama aldol like process, giving a diastereomeric mixture of pyrones **3** and **4** (Scheme 1) [7, 8]. Moreover, Danishefsky demonstrated that lanthanide(III) complexes catalyzed the cycloaddition of activated dienes with aldehydes [9]. The stereoselectivity increases dramatically using these catalysts. When diene **5**, for example, reacts with a variety of aldehydes with $\text{Eu}(\text{fod})_3$ as catalyst, virtually complete *cis* (*endo*) selectivity is observed. The aldehydes that function as dienophiles can be aliphatic or aromatic, see Table 1.

The Lewis acid complexes to the lone electron pair of the aldehyde *anti* to the R group, forcing the R group into an *endo* position in the transition state. In the case of lanthanide catalysts, the large steric bulk of the lanthanide metal-ligand complex causes the increase in *cis* selectivity (Scheme 2).

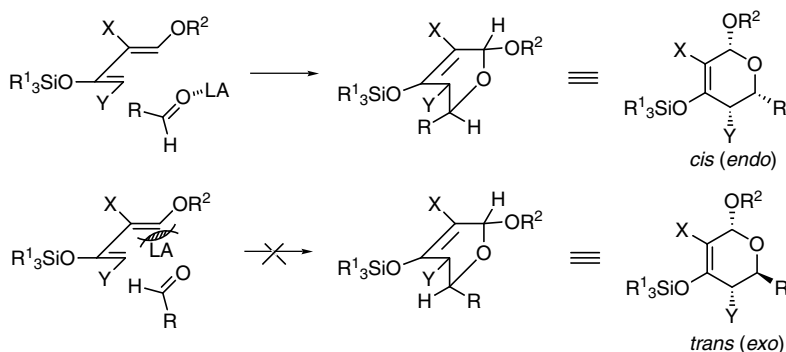
With the achievement of high stereochemical control resulting from nearly exclusive *endo* topography in the Lewis acid catalyzed reactions, the effect of chiral Lewis acid complexes on the enantiofacial selectivity of the cyclocondensation reaction should be documented. As an example, one can consider the cycloaddi-



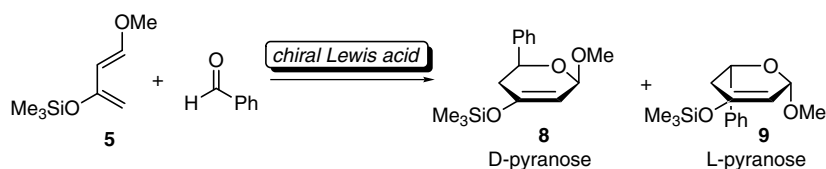
Scheme 1

**Table 1.** $\text{Eu}(\text{fod})_3$ -catalyzed hetero-Diels-Alder reaction

Entry	Aldehyde (R)	6	7
1	Ph	12	1
2	2-Furyl	6	1
3	<i>trans</i> -Styryl	8	1
4	Me	2.8	1
5	<i>n</i> -C ₅ H ₁₁	1.2	1
6	<i>i</i> -Pr	1.5	1

**Scheme 2**

tion of benzaldehyde to diene **5** under the influence of a chiral catalyst. Assuming a pericyclic reaction mode and high *endo* selectivity, a mixture of two possible products can result. Compound **8** is designated as a D-pyranose and compound **9** as an L-pyranose, based on carbohydrate nomenclature (**8** and **9** are enantiomers). A simple and practical method to synthesize compounds such as **8** and **9** in either enantiomeric form and in high optical purity is of great synthetic value (Scheme 3).



Scheme 3

3

Chiral Eu(hfc)₃ Catalysis

The first asymmetric catalyst to be evaluated was the commercially available chiral lanthanide β -diketonate complex $\text{Eu}(\text{hfc})_3$ [10]. The initial result was obtained from the reaction of benzaldehyde with diene **5**, which showed 18% enantiomeric excess [11]. Attempts to improve the asymmetric induction by varying the substituents on the diene were undertaken (Scheme 4). Substitution at either C2 or C4 of the diene seemed to increase the asymmetric induction. By using the 2,4-dimethyldiene **10a**, for example, the ee is increased to 36% [11]. Interestingly, both the 2-methyldiene **10b** and 2-acetoxydiene **10c** show no significant improvement in facial selectivity over the parent diene.

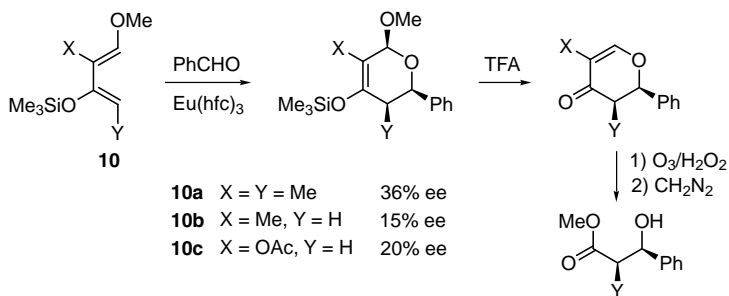
Since the dienes with different C1 functionalities were obtained by enol silylation of the corresponding alkoxyenones [12] which, in turn, are readily prepared by acid catalyzed exchange with the commercially available *trans*-1-methoxy-1-buten-3-one, investigations were focused on the effects of the C1 alkoxy variation on the asymmetric induction. The presence of a large achiral alkoxy group at C1 of the diene results in a significant increase in facial selectivity [11]. When using the 2-acetoxydiene and the corresponding 2-siloxydiene, substantial increases in ee are observed on replacing the methoxy group with the *t*-butoxy group (Scheme 5).

Finally, with two of the dienes the induction was maximized by modifying the experimental conditions. By conducting the reaction of dienes **11b** and **11d** in the absence of solvent and at reduced temperature up to 55% and 58% ee's, respectively, could be obtained [11].

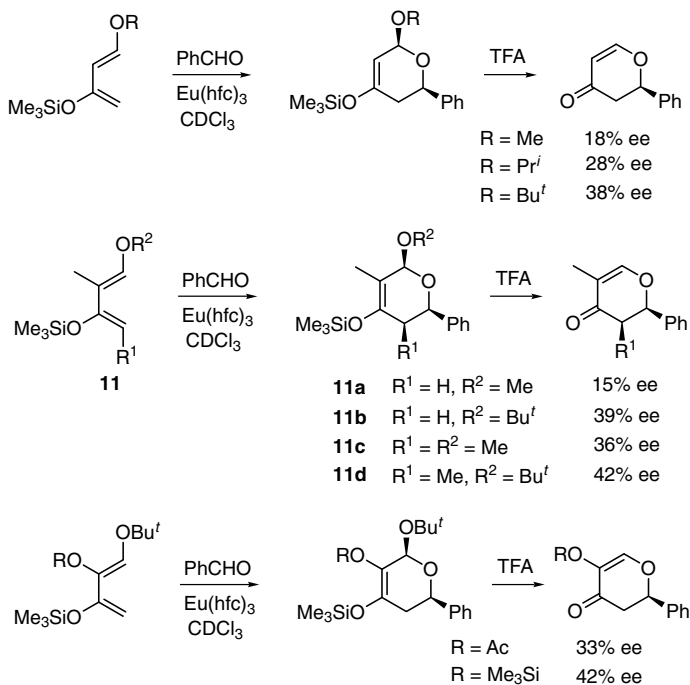
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Chiral Aluminum Catalysis

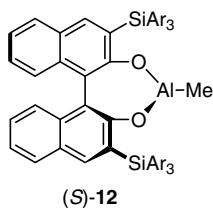
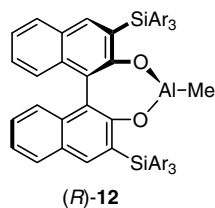
The asymmetric hetero-Diels-Alder reaction, which is apparently quite powerful in natural product syntheses, had not been developed to a useful level due to the lack of the well-designed asymmetric catalysts until Yamamoto and Maruoka reported a first solution to the problem by using chiral organoaluminum catalysts of type (*R*)-**12** and (*S*)-**12** (see Structure 1), which were newly devised on the basis of studies on the exceptionally bulky Lewis acid, MAD [13, 14].



Scheme 4



Scheme 5

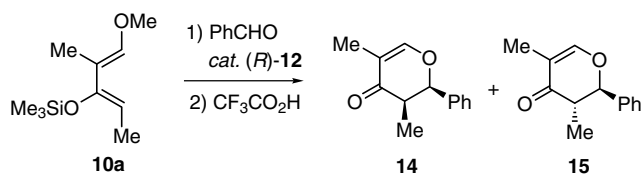


Structure 1

The optically pure (*R*)-(+)-3,3'-bis(triarylsilyl)binaphthol, (*R*)-13, requisite for preparation of (*R*)-12 can be synthesized in two steps from (*R*)-(+)-3,3'-dibromobinaphthol [15]. Reaction of (*R*)-13 in toluene with Me₃Al produced the chiral organoaluminum reagent (*R*)-12 as a pink to wine-red solution. Treatment of a mixture of benzaldehyde and siloxydiene **10a** in toluene under the influence of catalytic (*R*)-12 (Ar=Ph: 10 mol %) at -20 °C for 2 h furnished, after exposure of the resulting hetero-Diels-Alder adducts to trifluoroacetic acid in CH₂Cl₂, *cis*-dihydropyrone **14** (77%) and its *trans* isomer **15** (7%) (Scheme 6). The major *cis* adduct **14** was shown to exist in 95% ee. Furthermore, use of the sterically more hindered aluminum reagent (*R*)-12 (Ar=3,5-xylyl) has proved to exhibit excellent *cis*- and enantioselectivities (93% yield; *cis/trans*=30:1; 97% ee in **14**), indicating the importance of the choice of the bulky triarylsilyl moiety in **12** for obtaining the high enantioface differentiation of prochiral aldehydes.

Use of nonpolar solvents such as toluene produced higher enantioselectivities than polar solvents such as CH₂Cl₂ and ether solvents, and lowering the temperature gradually increased the optical yield.

The chiral oxygenophilic organoaluminum catalyst **12** bearing such a sterically hindered chiral auxiliary unit may form a stable 1:1 complex with benzaldehyde, allowing enantioselective activation of the carbonyl moiety as illustrated in Fig. 1. Then the diene **10a** would approach benzaldehyde with an *endo* alignment of the aldehyde phenyl residue and **10a** in order to minimize the steric



Scheme 6

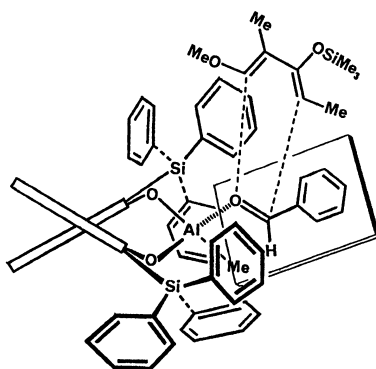
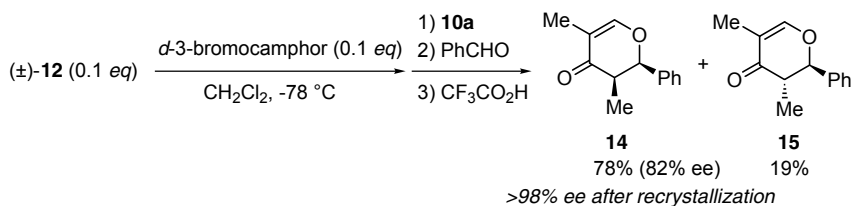


Fig. 1

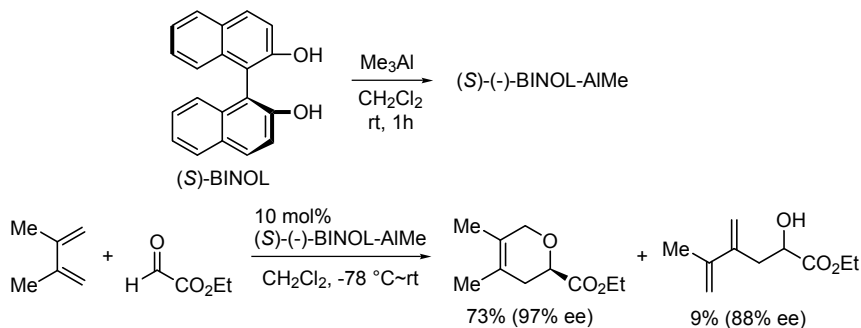
repulsion between the incoming diene and the front triarylsilyl moiety, thereby yielding the *cis* adduct **14** predominantly in accord with the experimental findings. It was emphasized that the hetero-Diels-Alder adduct, once formed, readily split off from the aluminum center in view of the steric release between the adduct and the aluminum reagent, resulting in regeneration of the catalyst **12** for further use in the catalytic cycle of the reaction [13].

Yamamoto and Maruoka also reported a conceptually new method of in situ generating the chiral catalyst **12** for asymmetric hetero-Diels-Alder reactions by discrimination of the racemic **12** with a chiral ketone [16]. As shown in Scheme 7, sequential treatment of (\pm)-**12** (0.1 equivalent) with *d*-3-bromocamphor (0.1 equivalent), the diene **10a** (1.05 equivalent), and benzaldehyde (1 equivalent) at $-78\text{ }^{\circ}\text{C}$ in CH_2Cl_2 and stirring of the mixture at this temperature for 3 h afforded the hetero-Diels-Alder adducts **14** and **15**, after acidic workup, in 78% and 19% yields, respectively. The optical yield of the major *cis* isomer **14** was 82%. Although the extent of asymmetric induction is not as satisfactory as that with optically pure **12**, one recrystallization of the *cis* adduct **14** of 82% ee from hexane gave the essentially pure **14** (>98% ee with ~60% recovery), thereby enhancing the practicability of this method.

Jorgensen and co-workers achieved the first Lewis acid-catalyzed chemoselective reaction of conjugated dienes having allylic C-H bonds with glyoxylate esters, which mainly leads to formation of the hetero-Diels-Alder product with



Scheme 7



Scheme 8

very high enantioselectivity [17]. The choice of catalyst is crucial for the hetero-Diels-Alder selectivity and it was found that a combination of Me_3Al and BINOL gives a very high chemo- and enantioselective complex [(S)-(-)-BINOL-AlMe] (Scheme 8).

5 Chiral Boron Catalysis

In 1989, Yamamoto introduced the chiral (acyloxy)borane (CAB) complex for catalytic asymmetric Diels-Alder reactions [18], which has been utilized as a magic hand catalysis for the aldol synthesis and for the Sakurai-Hosomi reaction so far [19, 20]. In contrast to $\text{R}=\text{H}$ of **17**, which is both air and moisture sensitive, the *B*-alkylated catalyst, $\text{R}=\text{Ph}$ or alkyl, is stable and can be stored in closed containers at room temperature. This catalyst is easily prepared from phenyl- or alkylboric acid and **16**: simple mixing of a 1:1 molar ratio of the ester **16** and phe-

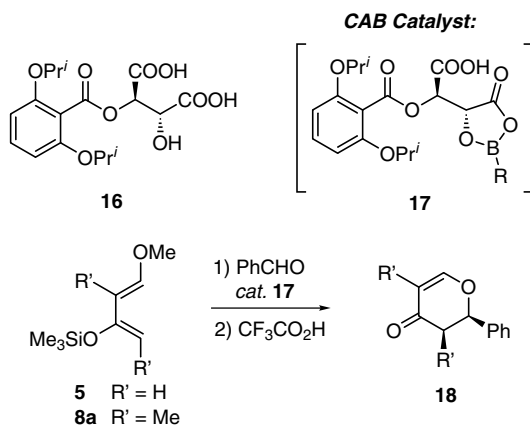
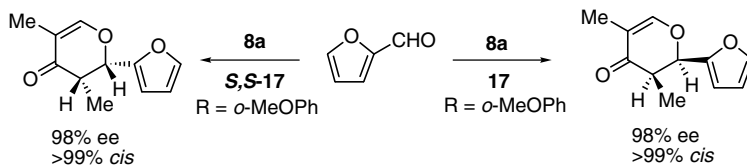
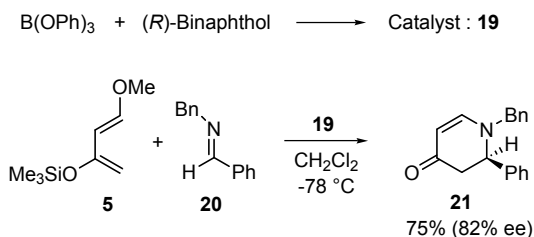


Table 2. CAB-mediated asymmetric hetero-Diels-Alder reaction

Entry	Diene	R of boric acid	Product yield [%]	% ee (confign)
1	5	Bu	67	73 (<i>R</i>)
2		Ph	63	75 (<i>R</i>)
3		2,4,6- Me_3Ph	47	95 (<i>R</i>)
4		2,4,6- <i>i</i> - Pr_3Ph	55	95 (<i>R</i>)
5		<i>o</i> -MeOPh	80	79 (<i>R</i>)
6		<i>o</i> - <i>i</i> -PrOPh	63	84 (<i>R</i>)
7	8a	Bu	56 (12)	93 (2 <i>R</i> ,3 <i>R</i>)
8		Ph	65 (29)	87 (2 <i>R</i> ,3 <i>R</i>)
9		2,4,6- Me_3Ph	<5	
10		<i>o</i> -MeOPh	95 (5)	97 (2 <i>R</i> ,3 <i>R</i>)



Scheme 9



Scheme 10

nylboric acid in freshly distilled propionitrile at room temperature for 0.5 h smoothly produced the reactive catalyst. This catalyst solution is sufficiently reactive and catalyzes hetero-Diels-Alder reaction of aldehydes with Danishefsky diene to yield dihydropyrones of excellent optical purity (Table 2) [21].

The power of the CAB catalytic reaction for the enantioselective route to carbon-branched pyranose derivatives is also seen from the following example (Scheme 9).

Yamamoto also reported an asymmetric aza Diels-Alder reaction of an imine mediated by a stoichiometric amount of the chiral boron complex **19** which is conveniently prepared in situ simply by mixing a 1:1 molar ratio of optically active binaphthol and triphenyl borate in CH_2Cl_2 at room temperature [22]

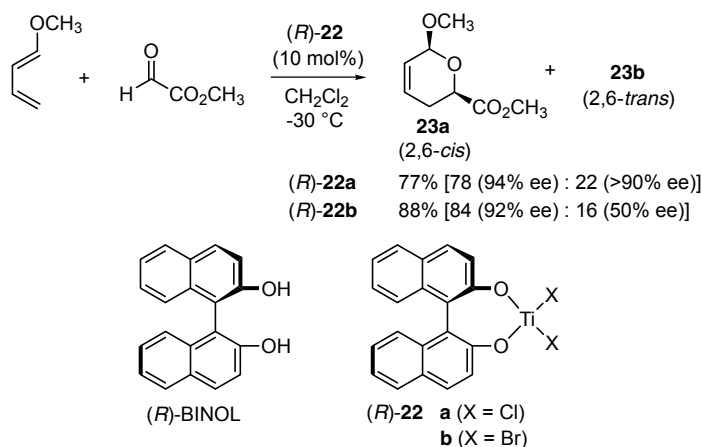
For example, the reaction of aldimine **20** with Danishefsky's diene **5** is promoted by **19** in the presence of 4 Å molecular sieves at -78°C , producing dehydropyridone **21** in 75% yield and 82% ee (Scheme 10). This method is successful with several aldimines and affords products of up to 90% ee.

6

Chiral Titanium Catalysis

Based on their early study in the enantioselective carbonyl-ene reaction [23], Nakai, Mikami, and Terada have found that the asymmetric hetero-Diels-Alder reaction of prochiral glyoxylate with methoxydiene can be catalyzed by the chiral titanium complex, producing the *cis*-dihydropyran carboxylate as a major product in high enantiomeric purity (Scheme 11) [24].

The observed *cis*-selectivity provides a mechanistic insight into the state of complexation between glyoxylate and the chiral titanium catalyst. Of the two



Scheme 11



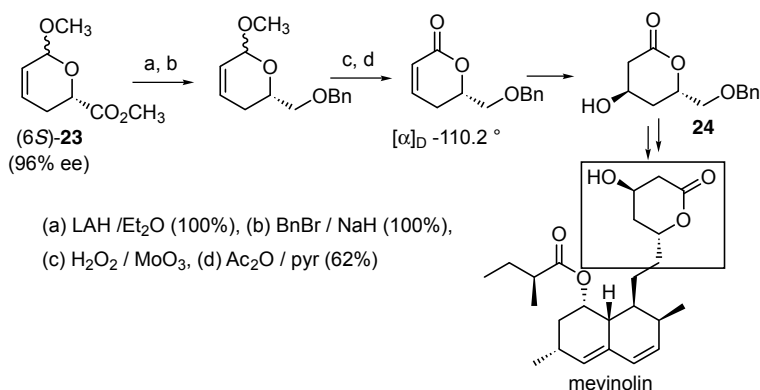
Structure 2

transition states leading to the *cis*-product, the *syn-endo* transition state **B** should be less favorable because of the steric repulsion in the sterically demanding titanium complex. Thus, the titanium catalyst should be complexed in an *anti* fashion and then the reaction proceeds through an *endo*-orientation (Structure 2).

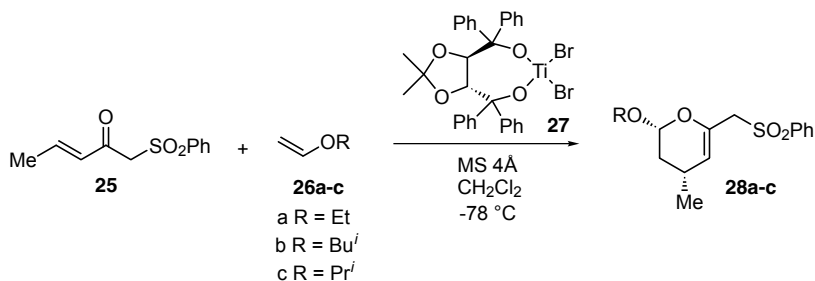
The hetero-Diels-Alder adduct thus obtained by the use of (*S*)-**22a** can readily be converted not only to monosaccharides but also to the lactone portion **24** of mevinolin or compactin in a short step as shown in Scheme 12.

Hetero-Diels-Alder reactions of 1-oxa-1,3-butadienes with vinyl ethers, which lead to 3,4-dihydro-2*H*-pyran derivatives, are synthetically equivalent to Michael type conjugate additions. Wada and coworkers presented the first examples of a catalytic asymmetric intermolecular hetero-Diels-Alder reaction by the use of (*E*)-2-oxo-1-phenylsulfonyl-3-alkenes **25** and vinyl ethers **26** (Table 3) [25].

The reaction of enone **25** with a large excess of ethyl vinyl ether **26a** was performed in the presence of titanium catalyst **27** (10 mol %) at -78 °C for 20 h to give *cis*-isomer **28a** as a single isomer in 59% yield (59% ee). The enantioselectivity was effectively enhanced by increasing the bulkiness of the alkoxy substituent R of the dienophiles **26a-c** (Table 3). This methodology offers a very effective synthetic route for the enantiomers of 4-substituted 2,4-*cis*-2-alkoxy-3,4-dihydro-2*H*-pyrans.

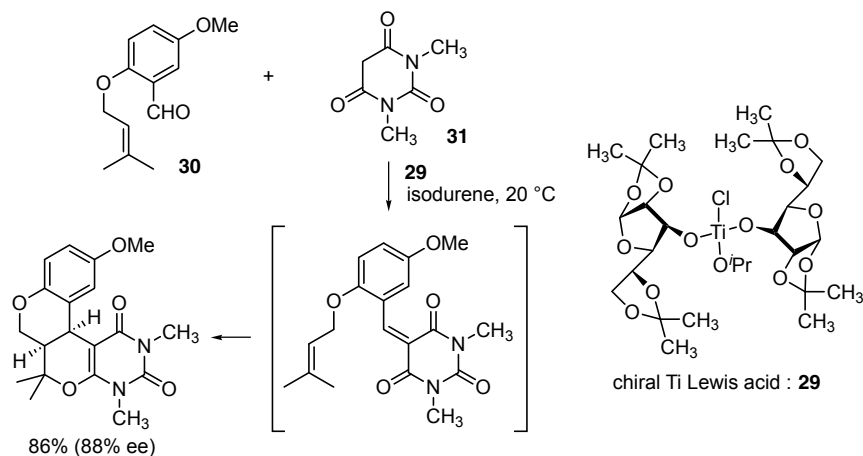


Scheme 12

**Table 3.** Chiral Lewis acid-catalyzed asymmetric hetero-Diels-Alder reactions of enones with vinyl ethers **26a-c**

Entry	Vinyl ether	Yield [%]	% ee (config)
1	26a	28a (91)	59 (2 <i>R</i> ,4 <i>R</i>)
2	26b	28b (92)	88 (2 <i>R</i> ,4 <i>R</i>)
3	26c	28c (90)	97 (2 <i>R</i> ,4 <i>R</i>)

Although it is a stoichiometric procedure, the intramolecular hetero-Diels-Alder reaction of 1-oxa-1,3-butadienes, obtained in situ by a Knoevenagel condensation of aromatic aldehydes and *N,N*-dimethylbarbituric acid, is mediated by a chiral titanium Lewis acid **29** which has 1,2:5,6-di-*O*-isopropylidene- α -D-glucopyranose as a ligand. The highest ee-value was obtained in the reaction of **30** with **31** in isodurene as illustrated in Scheme 13[26].



Scheme 13

7

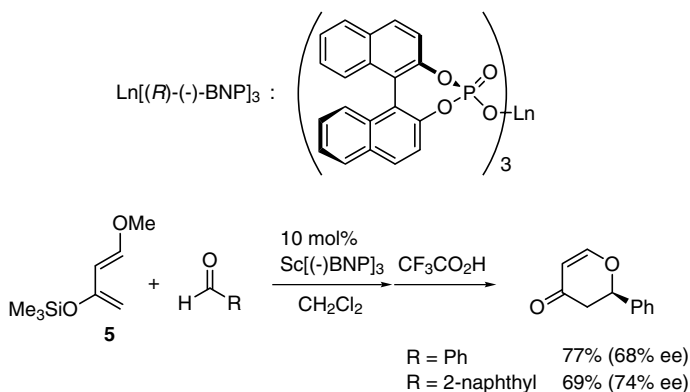
Chiral Lanthanide Catalysis

Although the utility of rare earth metal complexes as Lewis acid catalysts in organic synthesis has received much attention, only a limited number of investigations has been reported on isolable chiral rare earth metal complex-catalyzed asymmetric reactions [11, 27, 28, 29, 30].

Inanaga and coworkers prepared a series of tris[(*R*)-(-)-1,1'-binaphthyl-2,2'-diylphosphato]lanthanides(III) $\text{Ln}[(\text{-})\text{BNP}]_3$ as new chiral and stable Lewis acids by the simple treatment of lanthanide(III) chlorides with three equivalent of the optically active sodium phosphate at room temperature, and reported the observed catalytic activity [31, 32]. The asymmetric hetero-Diels-Alder reactions of the Danishefsky diene 5 with benzaldehyde or with 2-naphthaldehyde were successfully performed at 0 °C in the presence of 10 mol % of $\text{Sc}[(\text{-})\text{BNP}]_3$ to give the corresponding adducts in 77 and 69% chemical yields with 68 and 74% enantiomeric excesses of (*R*)-(-)-isomers, respectively (Scheme 14).

When the reaction was conducted at room temperature under the catalysis of $\text{Yb}[(\text{-})\text{BNP}]_3$, the asymmetric induction was improved to 73% ee. The effect of the central metal ion of the chiral catalysts on the optical yield of the product, 2-phenyl-2,3-dihydro-4*H*-pyran-4-one, is shown in Fig. 2. The degree of enantioselection is highly sensitive to and dependent on the ionic radius of lanthanide ions [31].

Since the reaction proceeded under heterogeneous conditions, further elaboration was made to make a clear solution by adding a variety of ligands and the efficacy of them was tested for the above reaction by analyzing the enantiomeric excess of the final product. The best result was obtained when the reaction was carried out at room temperature using 10 mol % each of the Yb-catalyst and 2,6-



Scheme 14

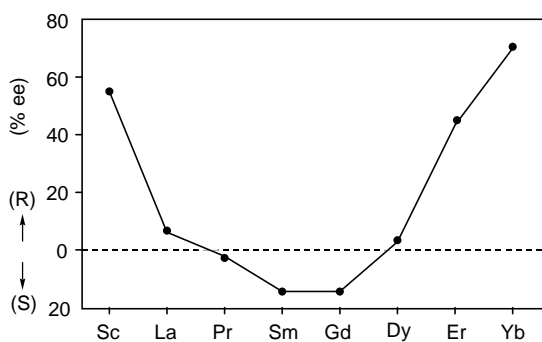
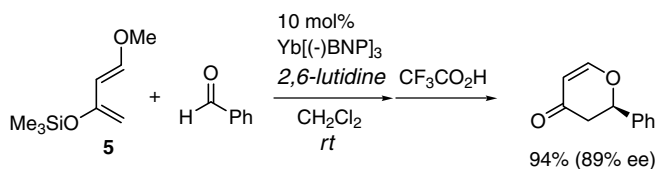


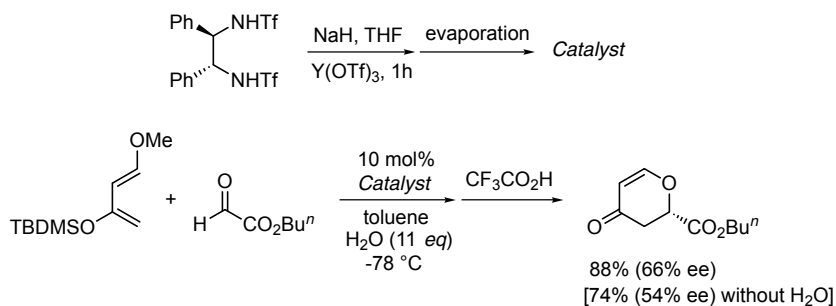
Fig. 2



Scheme 15

lutidine as an additive (Scheme 15). It should be noted that the observed enantiomeric excess of 89% is rather high for the reaction temperature (23 to 25 °C), since most catalytic asymmetric hetero-Diels-Alder reactions required a rather low temperature (usually -78 °C) to attain this level of enantioselection [32].

The precise structure of the catalyst is not clear. Since the addition of two equivalents of 2,6-lutidine to the catalyst slightly diminished the enantiomeric



Scheme 16

excess, the active catalyst which leads to high enantioselection is thought to be the 1:1 lutidine-ytterbium complex rather than the 2:1 complex at the stage where enantioselection is made.

Mikami and coworkers also reported the development of lanthanide bis(trifluoromethanesulfonyl)amides (bistriflylamides) as a new type of asymmetric catalysts for the hetero-Diels-Alder reaction of Danishefsky's diene, wherein the significant effect of water as an additive is observed in increasing not only the enantioselectivity but also the chemical yield. Bistriflylamides can be used as effective bidentate ligands to increase the Lewis acidity of their chiral metal complexes on account of the higher acidity of the conjugated acids than those of aliphatic and aromatic diols, which are commonly used as chiral bidentate ligands [33].

Chiral lanthanide bistriflylamides were prepared through the reaction of lanthanide(III) triflates and chiral bistriflylamides, which are deprotonated with 2 equivalents of sodium hydride in THF for 1 h. Dichloromethane or toluene was introduced, after evaporation of THF, to the residual complex. The resultant suspension of the lanthanide complex was then used for the hetero-Diels-Alder reaction (Scheme 16).

8

Chiral Transition Metal Catalysis

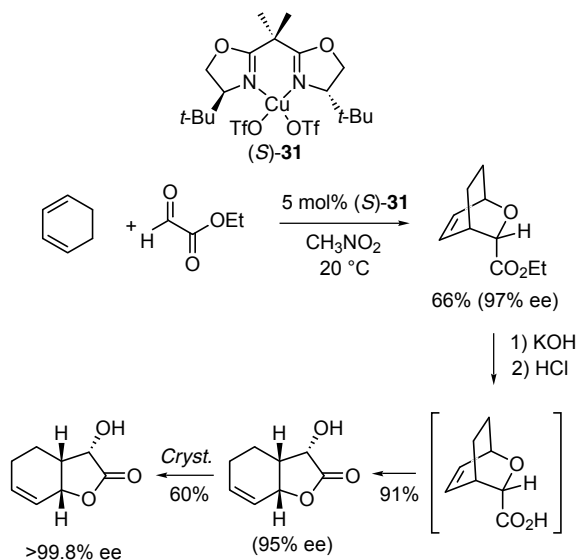
The reaction between a diene, such as 2,3-dimethylbuta-1,3-diene, and a carbonyl compound can lead to the formation of both the hetero-Diels-Alder product and the ene product. Copper(II) bisoxazoline-catalyzed reactions of glyoxylate esters with dienes leading to the hetero-Diels-Alder product and the ene product in high yield and with a high enantiomeric excess, have been developed by Johannsen and Jorgensen [34]. The hetero-Diels-Alder product:ene product ratio is in the range 1:0.6 to 1:1.8 and is dependent on both the chiral ligand attached to the metal, the glyoxylate ester, and the reaction temperature. Notably, the use of a polar solvent such as nitromethane leads to a significant improvement of the catalytic properties of a cationic copper-Lewis acid in the hetero-Diels-Alder reaction of alkyl glyoxylates with dienes.

For instance, the reaction of cyclohexa-1,3-diene and ethyl glyoxylate in the presence of (*S*)-**31** proceeds smoothly to give the cycloadduct in 66% yield with 97% ee. The synthetic application of this process was demonstrated by the preparation of a highly interesting synthon for sesquiterpene lactones in high yield and diastereoselectivity, and with a very high ee as illustrated in Scheme 17 [35].

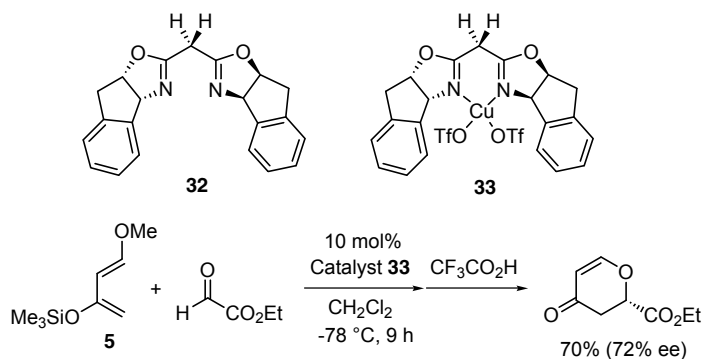
Ghosh and coworkers also reported that the reaction of Danishefsky's diene **5** and the glyoxylate esters catalyzed by a (*1R,2S*)-bis(oxazoline)-metal complex afforded the corresponding aldol adduct which, on treatment with TFA, furnished the enantiomerically enriched hetero-Diels-Alder product in good yield [36]. Among various ligand-metal complexes examined, conformationally constrained bis(oxazoline)-Cu(II)-triflates of type **33** afforded 72% ee and 70% isolated yield. Such constrained ligands like **32** are particularly attractive because of their ready availability in both enantiomeric forms from the corresponding commercially available optically active *cis*-1-amino-2-indanols (Scheme 18).

This methodology was also found to be very effective for the hetero-Diels-Alder reaction of benzyloxyacetaldehyde with Danishefsky's diene **5** producing dihydropyran derivatives appropriately functionalized for the synthesis of the C₃-C₁₄ segment of the novel antitumor agent laulimalide (Scheme 19) [37].

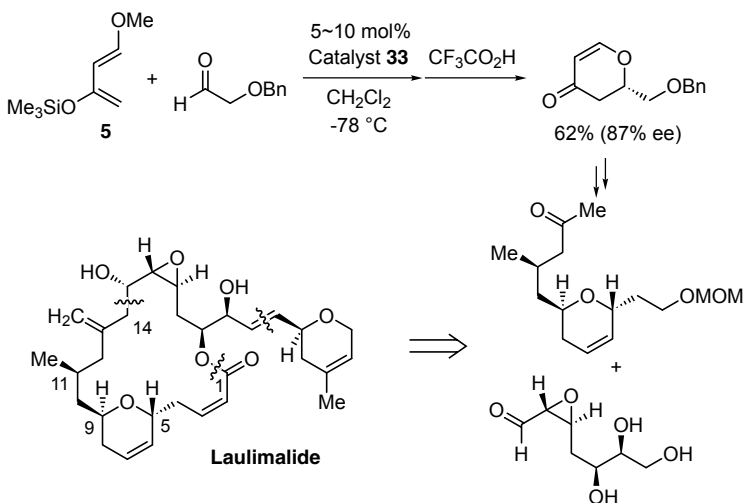
Novel optically active oxovanadium(IV) complexes bearing camphor-derived 1,3-diketono ligands have been prepared by Togni [38]. The complex bis(3-heptafluorobutyl)camphorato)oxovanadium (**34**) was found to be a very efficient catalyst for the cycloaddition of aldehydes to activated dienes to give pyrone derivatives. Thus, the reaction of benzaldehyde with 1-methoxy-2,4-dimethyl-3-(triethylsiloxy)butadiene in the presence of 5 mol % of (+)-**34** at -78 °C



Scheme 17



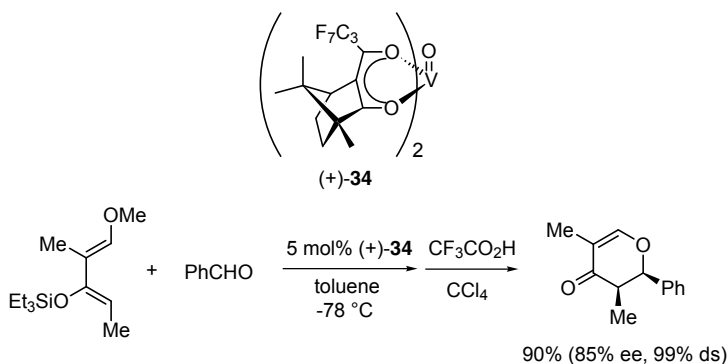
Scheme 18



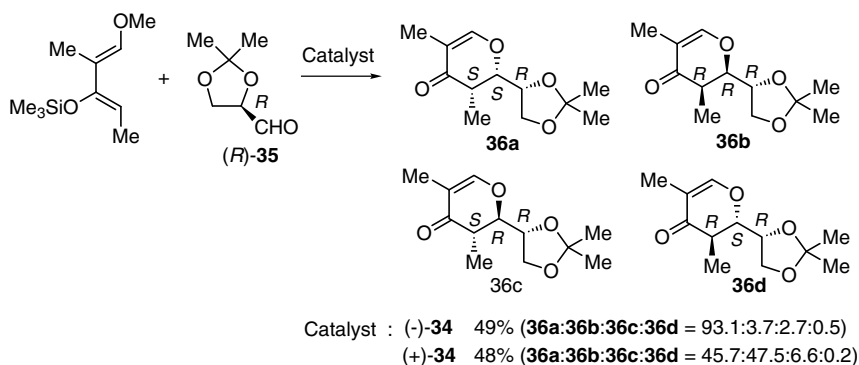
Scheme 19

gave, after protolytic workup, *cis*-3,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-pyran-4-one with 99% diastereoselectivity and 85% ee (Scheme 20).

Interestingly, the reactions of (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**35**) with 1-methoxy-2,4-dimethyl-3-(trimethylsilyloxy)butadiene, catalyzed by (+)-**34** and (–)-**34**, respectively, involved a high degree of double stereodifferentiation. The matched combination of (–)-**34** with (*R*)-**35** gave one of the four possible diastereomeric pyrone products in 93.1% selectivity. On the other hand, the mismatched pair showed almost no selectivity (Scheme 21) [38].



Scheme 20



Scheme 21

9 Alternatives

Asymmetric hetero-Diels-Alder reactions utilizing chiral substrates or stoichiometric amounts of chiral auxiliaries constitute an indispensable part of this field and also are very useful methods with potential synthetic importance. Selected recent advances are included in the following references [6, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48].

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Chapter 33.3

[2+2] Cycloaddition Reactions

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Keywords: [2+2] Cycloaddition, Cyclobutane, Chiral titanium catalyst, Propionolactone, Cinchona alkaloid

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1 General Introduction

[2+2] Cycloaddition reaction is one of the powerful synthetic methods for the construction of 4-membered carbo- and heterocyclic rings [1, 2, 3, 4, 5, 6, 7]. In spite of the potential utility for the 4-membered ring compounds as synthetic in-

intermediates, there have been only a few reports on catalytic asymmetric [2+2] cycloaddition reaction, which can be categorized into two reaction types. One is the Lewis acid-catalyzed [2+2] cycloaddition for the preparation of cyclobutanes, and the other is the [2+2] cycloaddition of ketenes and aldehydes catalyzed by chiral tertiary amines or chiral Lewis acid for the preparation of β -propiolactone derivatives.

2

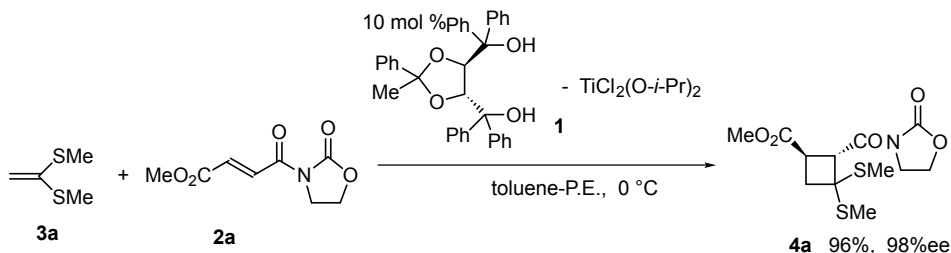
[2+2] Cycloadditions of Alkenyl Sulfides and Electron-Deficient Alkenes

2.1

Introduction

Photochemical [2+2] cycloaddition reactions and [2+2] cycloaddition reactions of ketenes have been widely used for the preparation of cyclobutane derivatives. The thermal [2+2] cycloaddition reaction is known to proceed between highly electrophilic and nucleophilic alkenes; alkenes having cyano, fluoro, and trifluoromethyl groups react with electron-rich alkenes such as alkenyl ethers and sulfides [8]. As for the catalyst-mediated [2+2] cycloaddition reactions, Lewis acids are known to promote [2+2] cycloadditions [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. However, the applicability of this cycloaddition is rather limited because of the side reactions such as ene reactions, conjugate addition reactions, and ring opening reactions of the produced cyclobutane derivatives. There was no general Lewis acid-catalyzed [2+2] cycloaddition reaction, until Takeda [25] and Narasaka et al. [26, 27, 28, 29, 30, 31, 32, 33] found that alkenyl sulfides react with a wide variety of electron-deficient olefins in the presence of a Lewis acid.

The first catalytic asymmetric [2+2] cycloaddition reaction was reported in 1989 by the use of the chiral titanium reagent prepared from the tartrate-derived chiral 1,4-diol **1** and $\text{TiCl}_2(\text{O}-i\text{-Pr})_2$ [26]. Treatment of methyl (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenate (**2a**) and 1,1-bis(methylthio)ethylene (**3a**) with a 10 mol % amount of the chiral titanium reagent in a mixed-solvent of toluene and petroleum ether (P.E.) at 0 °C afforded the cyclobutane derivative **4a** in 96% yield in nearly optically pure form (98% ee) (Scheme 1). In this section we



Scheme 1

describe the chiral titanium reagent-promoted asymmetric [2+2] cycloaddition reaction between electron-deficient alkenes and alkenyl sulfides.

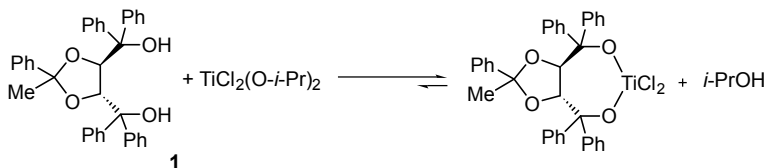
2.2

Mechanism of the Catalytic Reactions and Basis of Stereinduction

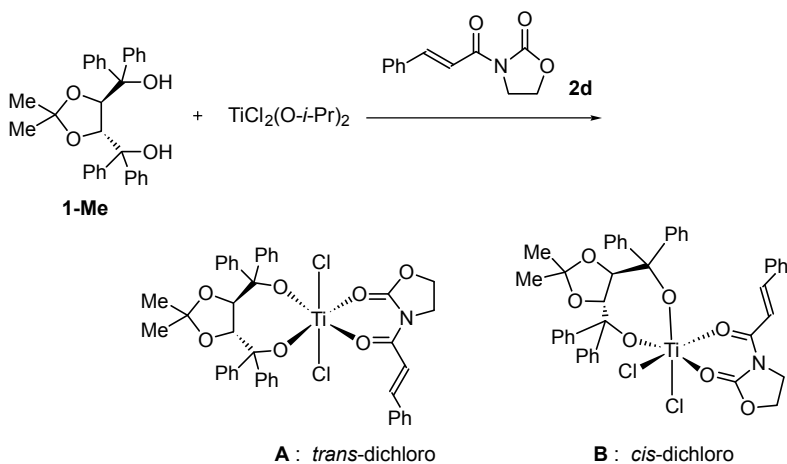
The titanium catalyst is prepared in situ by mixing the chiral 1,4-diol **1** and $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ in toluene in the presence of 4 Å molecular sieves (MS) (Scheme 2). Because of the high asymmetric induction observed in the asymmetric [2+2] cycloaddition reaction described above, $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ is supposed to be converted completely to the chiral titanium species. An NMR study of a mixture of equimolar amounts of $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ and the 1,4-diol **1** in toluene- d_8 , however, reveals that the mixture consists of a chiral titanium complex and achiral $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ and that the ratio of the complexed **1** to free **1** is about 84:16 at a concentration of 0.17 mol/l.

This observation does not coincide with the high enantioselectivity in the asymmetric reactions, since the remaining achiral $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ is considered to be a more effective Lewis acid than the chiral titanium complex. When $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ and the diol **1** are mixed together, alkoxy exchange takes place and a chiral cyclic titanium alkoxide is generated with elimination of isopropyl alcohol. In the NMR spectrum of the mixture in toluene- d_8 , the methine proton of isopropyl alcohol appears at lower field as compared with that of isopropyl alcohol itself. This lower field shift suggests the complexation of isopropyl alcohol with $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$. It is considered that the coordination of isopropyl alcohol causes aggregation of the achiral titanium species [$\text{TiCl}_2(\text{O-}i\text{-Pr})_2$] which decreases its activity as a Lewis acid [34].

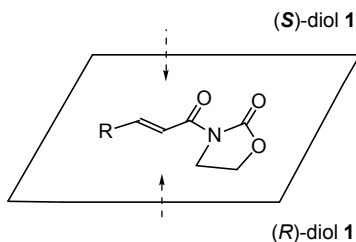
A chiral titanium complex with 3-cinnamoyl-1,3-oxazolidin-2-one (**2d**) was isolated by Jørgensen et al. from a mixture of $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ with (2*R*,3*R*)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (**1-Me**) which is an isopropylidene acetal analogue of **1** [35]. The structure of the complex was determined by X-ray methods. The complex consists of the isopropylidene diol **1-Me** and the cinnamoyloxazolidinone **2d** in the equatorial plane and the two chloride ligands in the apical (*trans*) position as depicted in structure A (Scheme 3). It appears from this structure that the pseudo-axial phenyl group of the chiral ligand seems to block one face of the coordinated **2d**. In contrast, from an NMR study of the complex in the solution, Di Mare et al. reported that the above *trans*



Scheme 2



Scheme 3



Scheme 4

dichloro complex **A** is a major complex in the solution. He proposes another minor complex **B** (Scheme 3) with the two chlorides facing *cis* to each other to be the most reactive intermediate in this chiral titanium-catalyzed reaction [36].

At the present stage, it is not clearly confirmed whether the *trans* and/or the *cis* complex are the real reactive intermediate. The absolute configuration of the cycloadducts is, however, predicted by both models. When the (*R*)-1,4-diol **1** is employed as a chiral auxiliary, the *Re* face of the α carbon of the alkenoyl moiety of **2** is attacked so far without exception (Scheme 4).

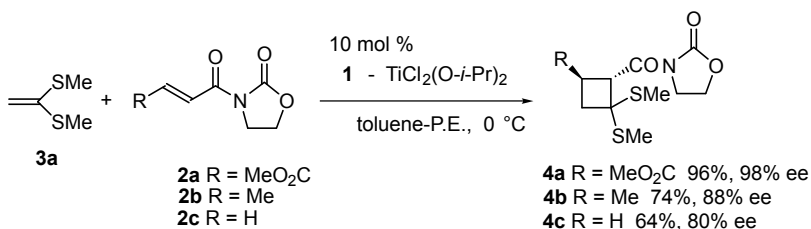
2.3

Practical Aspects

2.3.1

Reaction of Ketene Dithioacetal [26, 29]

As mentioned in the introduction, the chiral titanium-catalyzed asymmetric [2+2] cycloaddition reaction proceeds between methyl (*E*)-4-oxo-4-(2-oxo-1,3-



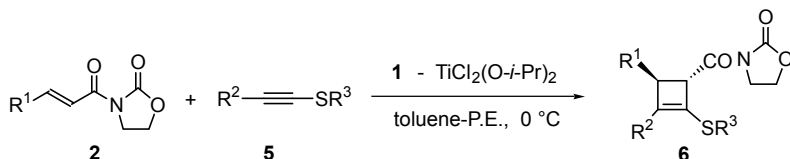
Scheme 5

oxazolidin-3-yl)-2-butenolate (**2a**) and ketene dimethyldithioacetal to afford the cyclobutane derivative **4a** in high optical purity. Ketene dimethyldithioacetal (**3a**) also reacts with 3-acryloyl- or 3-crotonoyloxazolidinone **2b** or **2c**, giving the corresponding cyclobutanone dimethylthioacetals **4b** and **4c** in 88% ee and 80% ee, respectively (Scheme 5). Optically pure cyclobutanes **4a** and **4c** are easily prepared by recrystallization. The chiral auxiliary **1** is completely recovered without loss of the optical purity. Since a 5% molar amount of the catalyst is enough for completion of the reaction, the total turnover number of the catalyst in this reaction is ranging from 10 to 20.

2.3.2

Reaction of Alkynyl Sulfides [27, 29]

As is shown in Scheme 6 and Table 1, alkynyl sulfides can be employed in the asymmetric [2+2] cycloaddition reaction; however, the reactivity of alkynyl sulfides is largely dependent on the substituent at sulfur. A phenyl sulfide, 1-phenylthio-1-hexyne (**5e**), does not react with **2a**, while the alkynyl methyl sulfides **5a-d** react smoothly with fumaric and acrylic acid derivatives **2a,c**, yielding cyclobutenes **6**. Trisubstituted cyclobutenes are prepared in good yield and in almost enantiomerically pure forms with only a catalytic amount of the chiral titanium reagent. For the preparation of tetrasubstituted cyclobutenes, however, an equimolar amount of the chiral titanium is required for the reaction to go to completion. Compared with the ketene dimethyldithioacetal **3a**, alkynyl methyl sulfides **5** are less reactive and the reaction between the crotonoyloxazolidinone **2b** and **5** fails even in the presence of an equimolar amount of the catalyst.



Scheme 6

Table 1. Asymmetric cycloaddition of alkynyl sulfides **5**

2 R ¹	5 R ²	R ³		Amount of Ti [mol. amount]	Yield [%]	ee of 6 [%]
CO ₂ Me (2a)	<i>n</i> -Bu	Me	(5a)	1.1	92	>98
	Me	Me	(5b)	1.1	90	>98
	cyclohexyl	Me	(5c)	1.1	84	>98
	H	Me	(5d)	0.1	83	>98
	<i>n</i> -Bu	Ph	(5e)	1.1	0	
Me (2b)	<i>n</i> -Bu	Me	(5a)	1.1	0	
H (2c)	<i>n</i> -Bu	Me	(5a)	0.1	80	>98
	cyclohexyl	Me	(5c)	0.3	65	>98

2.3.3

Reaction of Alkenyl Sulfides [27, 29]

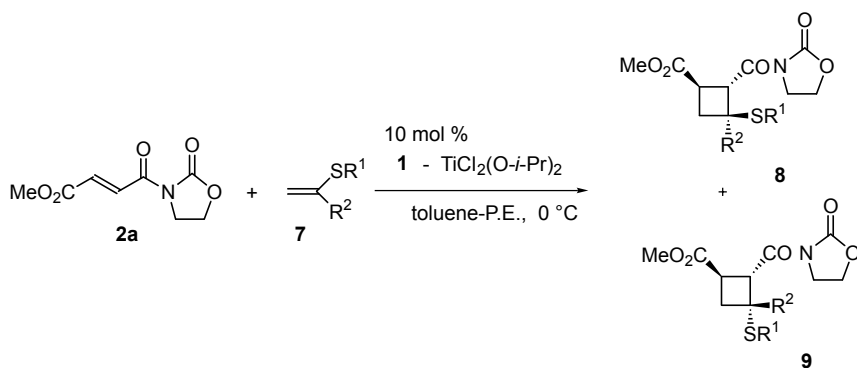
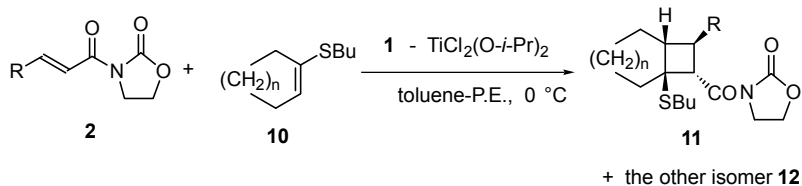
Alkenyl sulfides are known to react with some labile electron-deficient olefins such as methyl vinyl ketone in the presence of AlCl₃ to form cyclobutanes [25]. In the present chiral titanium-promoted asymmetric reaction, alkenyl sulfides can also be employed as electron-rich components. 2-Ethylthio-1-propene (**7a**) reacts with **2a** in the presence of a catalytic amount of the chiral titanium reagent, giving the diastereomeric [2+2] cycloaddition products **8a** and **9a** in 51% (>98% ee) and 19% (79% ee) yields, respectively (Scheme 7 and Table 2). Although 2-ethylthio-1-propene (**7a**) is known as a good ene component in the reaction with carbonyl compounds, 3-(3-(methoxycarbonyl)-5-ethylthio-5-hexenoyl)-1,3-oxazolidin-2-one, an ene product, is obtained only in 16% yield as a side product.

The reaction of **2a** with an allylsilane-type sulfide, 3-trimethylsilyl-2-methylthio-1-propene (**7b**), also afforded the cyclobutanes **8b** and **9b** in 54% (>98% ee) and 17% yields, respectively, without any formation of allylation and ene reaction products. The diastereoselectivity of these two reactions using 2-alkylthio-propene derivatives **7a,b** is not high, but the major isomers **8a,b** are obtained in nearly enantiomerically pure forms.

Cycloalkenyl sulfides **10** are converted into bicyclo[n.2.0]alkane compounds with almost complete enantioselectivity by the reaction with the fumaric or acrylic acid derivatives **2a,c** as listed in Scheme 8 and Table 3. As the reactivity of **10** is not as high as that of acyclic alkenyl sulfides, the use of an equimolar amount of the chiral titanium reagent is required to attain a good chemical yield in some cases. Diastereoselectivity is generally excellent and no ene product is detected.

Table 2. Asymmetric [2+2] cycloaddition reaction of alkenyl sulfides **7**

R ¹	R ²	Sulfide	Yield [%]		ee of [%]	
			8	9	8	9
Et	Me	(7a)	51 (8a)	19 (9a)	>98	79
Me	CH ₂ SiMe ₃	(7b)	54 (8b)	17 (9b)	>98	-

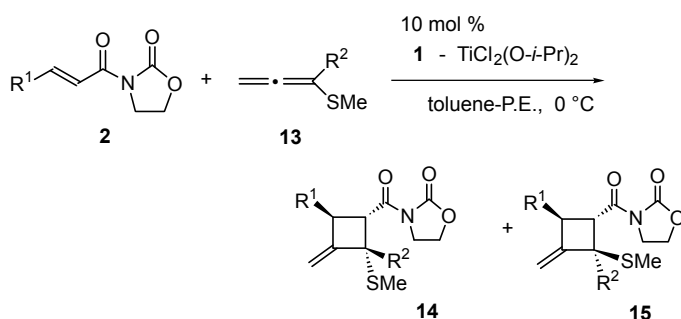
**Scheme 7****Scheme 8****Table 3.** Reaction of cyclic alkenyl sulfides **10**

R	10 n	Amount of Ti [mol. amount]	Yield (11+12) [%]	11:12	ee of 11 [%]
CO ₂ Me (2a)	2 (10a)	1.1	96	>99:1	>98
		0.15	92	>99:1	>98
	3 (10b)	1.1	97	92:8	>98
	4 (10c)	1.1	89	91:9	>98
H (2c)	2 (10a)	0.25	74	82:18	>98

2.3.4

Reaction of 1,2-Propadienyl Sulfides [28, 29, 32]

1,2-Propadienyl sulfides having an α -trimethylsilyl, trimethylstannyl, or benzyl substituent, **13a,b,c**, react with **2a,c** to give methylenecyclobutane derivatives **14** and **15** in good chemical yields in nearly enantiomerically pure forms (Scheme 9 and Table 4). The diastereoselectivity is high in the reactions of **2a** with the α -trimethylsilyl- and α -trimethylstannylallenes **13a,b**, in which these bulky substituents and the oxazolidinylcarbonyl group have a *trans* geometry in the products. Although the trimethylstannylallene **13b** reacts in high yield, the corresponding tributylstannyl analogue does not react with **2a**, presumably because of the steric hindrance.



Scheme 9

Table 4. Asymmetric [2+2] cycloaddition reaction of propadienyl sulfides **13**

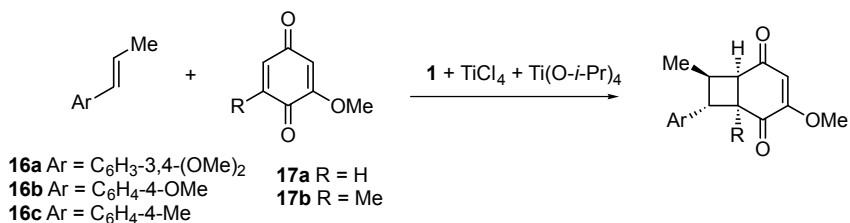
R ¹	R ²	Yields [%]		ee's [%]		
		14	15	14	15	
CO ₂ Me	(2a)	SiMe ₃ (13a)	quant. ^a	–	>98	–
		SnMe ₃ (13b)	93 ^a	–	96	–
		SnBu ₃	0	0		
		CH ₂ Ph (13c)	30	57	94	>98
H	(2c)	SiMe ₃ (13a)	41	21	>98	–

^a**15** was not detected by ¹H-NMR spectroscopy

2.3.5

Reaction of Styrenes and 1,4-Benzoquinones

The chiral titanium catalyst prepared by mixing the diol **1**, TiCl_4 , and $\text{Ti}(\text{O-}i\text{-Pr})_4$ in a 1:1:1 ratio promotes the asymmetric [2+2] cycloaddition reaction between styrenes **16** and 1,4-benzoquinones **17** to afford cyclobutane derivatives in good optical purity (Scheme 10 and Table 5) [37]. This reaction is not a truly catalytic reaction because excess amounts of the catalyst (5 molar amounts) have to be employed in order to obtain a high enantiomeric excess. The catalyst in this reaction is thought to be different from the one prepared from the diol **1** and $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ in a 1:1 ratio as described previously.



Scheme 10

Table 5. Asymmetric [2+2] cycloaddition of styrenes and quinones

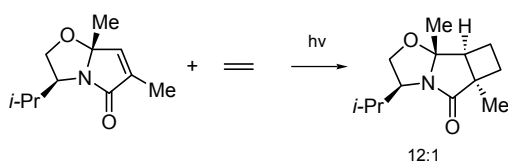
Styrene	Quinone	Yield [%]	ee [%]
16a	17a	88	92
16b	17a	86	90
16c	17a	71	86
16a	17b	43	88
16b	17b	72	90

2.4

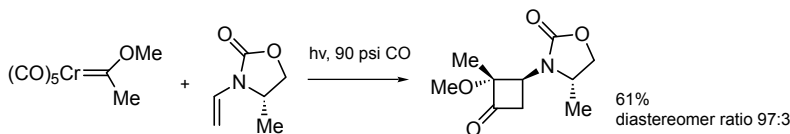
Principle Alternatives

Highly enantiomerically enriched cyclobutane derivatives are prepared via diastereoselective [2+2] cycloaddition reactions of chiral ethylene derivatives; for instance, by photochemical (Scheme 11 and Scheme 12) [38, 39] and thermal [2+2] cycloaddition (Scheme 13) [40, 41] reactions of chiral alkenes and by the [2+2] cycloaddition of chiral keteneiminium ions (Scheme 14) [42].

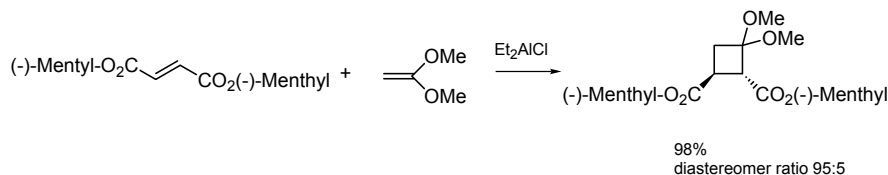
Chiral cyclobutane derivatives are also synthesized by the enantioselective alkylation [43], by the chemical [44] and enzymatic [45] resolution of racemic precursors (Scheme 15), and by the ring enlargement of the corresponding chiral cyclopropylidene oxide (Scheme 16)[46].



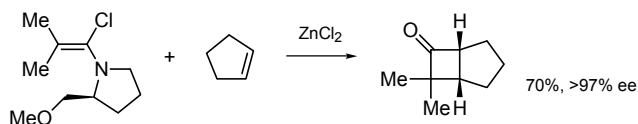
Scheme 11



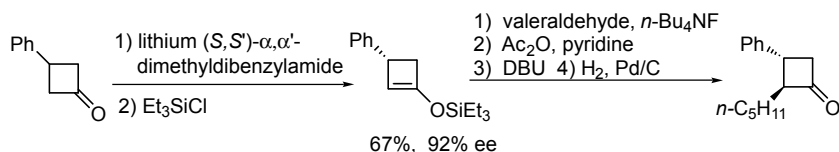
Scheme 12



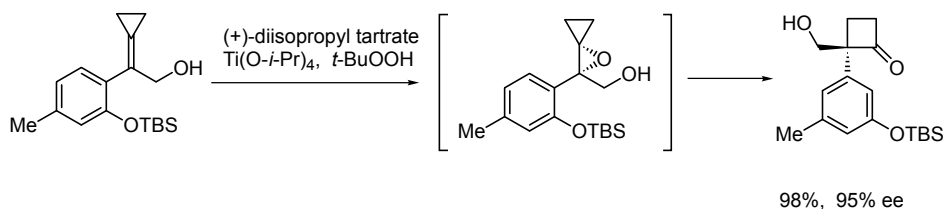
Scheme 13



Scheme 14



Scheme 15



Scheme 16

3

[2+2] Cycloadditions of Ketenes and Aldehydes

3.1

Introduction

The hetero [2+2] cycloaddition reaction is a synthetically important reaction for the construction of 4-membered heterocyclic compounds. As far as the catalytic asymmetric reaction is concerned, however, only the cycloaddition between ketenes and aldehydes has been reported. The thus synthesized chiral oxetan-2-ones are employed as monomer precursors for the biologically degradable copolyesters and also as chiral building blocks for natural product synthesis. Two types of catalysts, *Cinchona* alkaloids and a chiral Lewis acid, are known to promote this reaction.

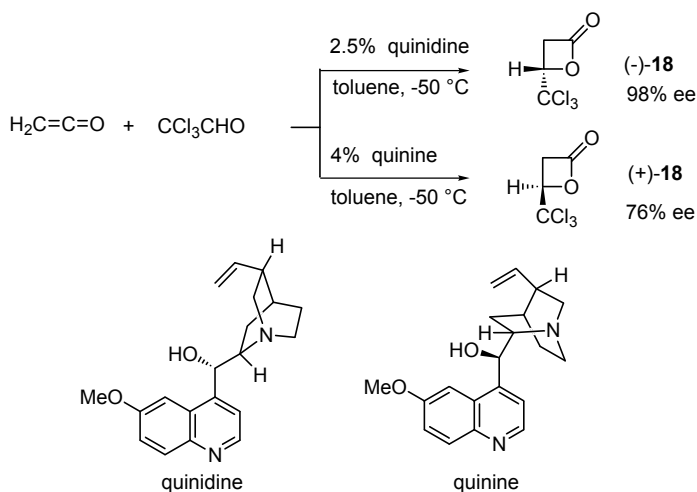
3.2

Cinchona-Alkaloids-Catalyzed Reaction

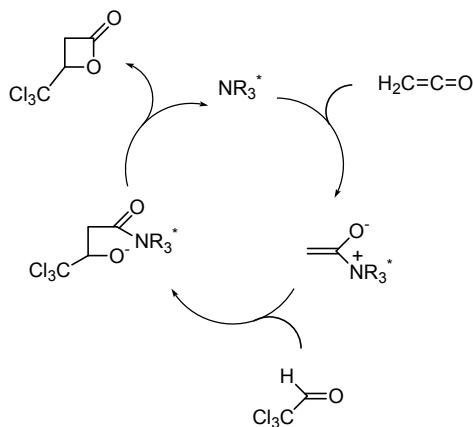
3.2.1

Mechanism of the Catalytic Reaction

Cinchona alkaloids are the effective asymmetric catalysts in the [2+2] cycloaddition reaction of ketenes and aldehydes [47]. That is, the reaction between ketenes and chloral proceeds with a catalytic amount (2.5 mol %) of quinidine in toluene at -50°C to provide the β -propiolactone (–)-18 in quantitative yield with 98% ee (Scheme 17).



Scheme 17



Scheme 18

By the use of quinine instead of quinidine, the opposite enantiomer $(+)\text{-18}$ can be synthesized with good optical purity (76% ee) (Scheme 17). It is also noteworthy that exceedingly simple catalysts such as 1,2-dimethylpyrrolidine and *N,N*-dimethyl- α -phenylethylamine gave good enantiomeric excess (60 and 77% ee's, respectively). Although the reaction mechanism and the basis of the stereoselection are not clear, the reaction is thought to proceed in a stepwise manner via a tertiary amine-ketene complex as initial intermediate and not via a tertiary amine-chloral complex (Scheme 18).

3.2.2

Generality of the Reaction

Not only chloral but also other polyfunctionalized aldehydes can be employed in this reaction to afford chiral 4-substituted-2-oxetanones **19** (Scheme 19) and the results are listed in Table 6 [48]. Highly electron-deficient ketones react with ketene, for example, trichloroacetophenone does not react with ketene but the reaction does proceed when an electron-withdrawing substituent such as a chloro or nitro group is introduced into the phenyl group.

3.2.3

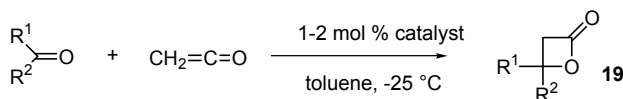
Principle Alternatives

The alternative procedure for chiral 4-substituted-2-oxetanones is the ring closure of optically active β -hydroxycarboxylic acid derivatives [49].

3.3

Chiral Lewis Acid-Catalyzed Reaction

A C_2 -symmetric N,N' -di-3,5-bis(trifluoromethyl)benzenesulfonyl-(1*R*,2*R*)-1,2-diphenylethylenediamine **20**- Et_3Al complex promotes the [2+2] cycloaddition reaction between ketene and aldehydes to afford optically active 4-substituted oxetan-2-ones **21** (Scheme 20) [50]. The catalyst is prepared by mixing the bis-sulfonamide **20** and Et_3Al , and the reaction proceeds by the coordination of the aldehyde to the chiral Lewis acid.



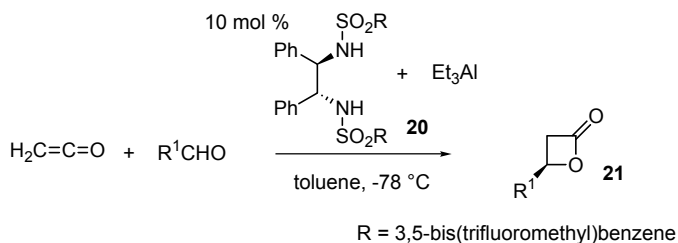
Scheme 19

Table 6. Reaction catalyzed by *Cinchona* alkaloids

R ¹	R ²	Yield [%]	ee [%] ^a	ee [%] ^b
CCl ₃	H	89	98 (<i>R</i>)	76 (<i>S</i>)
CCl ₂ CH ₃	H	95	91 (<i>R</i>)	76 (<i>S</i>)
CCl ₂ C ₆ H ₅	H	89	90	68
CCl ₃	CH ₃	72	94 (<i>R</i>)	85 (<i>S</i>)
CCl ₃	C ₆ H ₄ Cl- <i>p</i>	68	90	65
CCl ₃	C ₆ H ₄ NO ₂ - <i>p</i>	95	89	65

^aCatalyst is quinidine

^bCatalyst is quinine

**Scheme 20****Table 7.** Reaction catalyzed by chiral aluminum reagent

R ¹	Yield [%]	ee [%]
Me	59	30
Et	77	33
<i>n</i> -Bu	82	41
<i>i</i> -Pr	76	56
cyclohexyl	75	74
<i>t</i> -Bu	77	65
Ph	11	14

In the presence of 10 mol % of the chiral catalyst, aldehydes react with ketene at $-78\text{ }^{\circ}\text{C}$ in toluene for 1 h to afford oxetan-2-one derivatives **21** in 14 to 74% ee as listed in Table 7. This suggests that the reactions of bulkier aldehydes proceed in better optical purity. Although the obtained enantioselectivity is not high, there is a room for the future improvement.

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Chapter 34.1

Alkylation of Enolates

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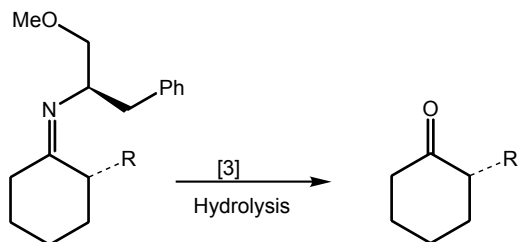
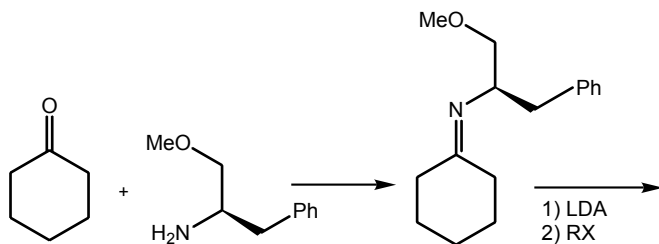
Keywords: Phase transfer, Chiral ligand, Chiral base, Allylic alkylation, Cinchonine, Enolate alkylation, Asymmetric deprotonation, Asymmetric arylation, Radical alkylation

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1 Introduction

Reaction of enolates with alkylating agents is one of the oldest methods of forming carbon-carbon bonds in synthetic organic chemistry. Progress in selective alkylations of enolates has been steadily advancing over the past four decades. Interest in selective alkylations arose in the 1960s with studies directed toward understanding axial vs. equatorial diastereoselective alkylations of cyclohexanones [1], and *erythro* vs. *threo* alkylations of acyclic enolates [2]. The concept of diastereoselective alkylations was taken a step further in the 1970s to provide the first indirect methods for asymmetric alkylations of enolates, with the pio-

neering studies of Meyers [3], Koga [4], Whitesell [5], and Enders [6]. These methods involved a three-step sequence which included reaction with a stoichiometric covalent chiral auxiliary, deprotonation and alkylation to form product enriched in one diastereomer, and cleavage to produce the enantioenriched product with release of the chiral auxiliary, Eq. (1). Over the past two decades a wide variety of chiral auxiliaries have been introduced that are applicable to substrates of diverse structures [7].



On the other hand, asymmetric enolate alkylation via catalytic methods is rare, and the technology for doing so can still be considered in its infancy. While many other catalytic C-C bond forming methods for enolates have been achieved, such as aldol and Michael reactions, progress has been slow for alkylation reactions. Part of the reason for this is that, for typical alkylations, no organized transition state exists which involves all three components of the reaction: the enolate, the chiral catalyst, and the alkylating agent. Instead, for enantioselective alkylation to occur, tight binding between the catalyst and enolate must occur, and the alkylating agent will simply attack the least hindered face. Since achieving a single tightly bound complex requires a perfect match between substrate and enolate (3-point binding essential for chiral recognition), catalytic enantioselective alkylations are rare. On the other hand, to use an aldol reaction as an example, all components of the reaction, including the aldehyde, the organometal species, and chiral catalyst, can be organized in a 6-membered transition state held in place by metal coordination, which facilitates an enantiotopic reaction. In this case, organization of the TS is the key, not organization of the ground state molecules, as in an alkylation reaction.

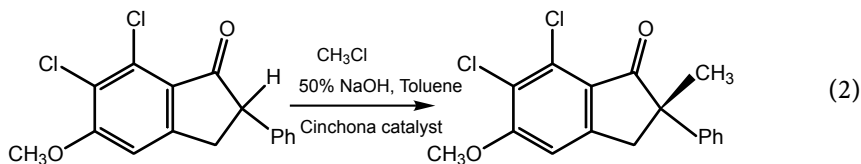
The following sections review the work on catalytic asymmetric alkylations of enolates that has primarily been carried out in the past decade. Each approach

has seen its successes, although none has found widespread use due to drawbacks which range from narrow substrate specificity to difficult catalyst preparation. The primary alternatives to catalytic routes involve diastereoselective alkylations using a chiral auxiliary, as described briefly above, and enantioselective protonations, described in the following chapter.

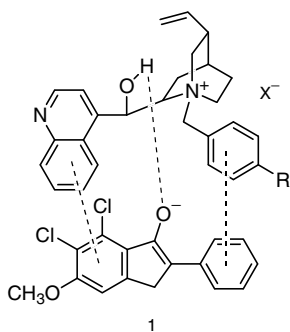
2 Phase Transfer Catalysis

In the late 1970s Wynberg and coworkers pioneered the use of *Cinchona* alkaloids as catalysts for asymmetric reactions, demonstrating 76% ee's for both an epoxidation of a naphthoquinone [8] and the Michael reaction of an indanone derivative with methyl vinyl ketone [9]. On the other hand, asymmetric enolate alkylations using chiral catalysts had limited success during this period. An asymmetric alkylation of an enolate using chiral phase transfer catalysts was first reported in 1975 by Fiaud [10] for the reaction of 2-acetylcyclohexanone with allyl bromide using 10% aq. NaOH and a catalyst derived from ephedrine. An optical yield of 6% was reported, based on the magnitude of the optical rotation in comparison with a pure sample of the enantiomer. Likewise, ee's of 5 to 7% were reported in 1979 and 1980 for the alkylation of ethyl 2-oxocyclohexanecarboxylate using chiral phase transfer catalysts [11, 12]. However, even these modest enantioselectivities were challenged by Dehmlov and coworkers [13], who determined that, in some cases, most or all of the optical rotations were due to decomposition products of the catalyst, and that no optical rotation was observed in products that had been purified by chromatography.

The first breakthrough in asymmetric alkylation came in 1984 when Dolling and coworkers [14] reported a 94% ee in the phase-transfer alkylation of indanone derivatives using *Cinchona* alkaloids as catalysts, Eq. (2).



The key to the excellent enantioselectivity was finding conditions to maximize tight ion pairing between the enolate and the catalyst such that only one face was available for alkylation. The authors proposed that three-point binding was necessary for high ee. A hydrogen bond between the alkaloid hydroxy group and the enolate oxygen provided the directional handle, with additional stabilization and directionality being furnished by π -bonding interactions between the aromatic rings (complex 1). Several experiments supported the ion-pair hypothesis. First of all, the selectivity was highest in nonpolar solvents such as toluene, which should enhance tight ion pair formation. Secondly, the selectivity increased as the concentration of NaOH was increased from 30% to 50%. With 30% NaOH the water content in the organic layer is much higher compared to



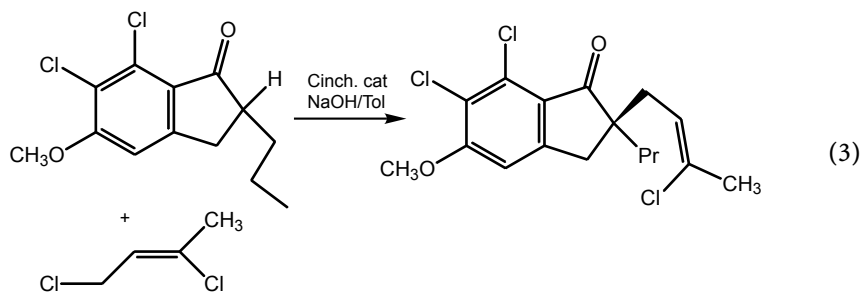
50% NaOH, and the higher level of water would be expected to disrupt the hydrogen bond of the ion pair. Finally, the electronics of the catalyst had a significant impact on the selectivity. A Hammett plot of $\log ee/ee_0$ vs. the substituent constant of the *N*-benzyl group of the catalyst gave a reaction constant ρ of 0.21 with a range of *ee*'s from 60% for *p*-MeO to 92% for *p*-CF₃. This suggests that electron-withdrawing substituents enhance the binding of the enolate and catalyst, as might be expected for a charge-transfer complex between the electron-rich phenyl group of the enolate and the increasingly electron-poor benzyl portion of the catalyst.

A mechanistic study of this reaction produced a number of unanticipated findings [15]. While *N*-benzylcinchoninium bromide is virtually insoluble in toluene ($<10^{-5}$ M), millimolar quantities were detected by HPLC analysis of the organic layer of aliquots removed from the reaction. Based on titration experiments (acid-base and bromide) and methylation experiments, it was proposed that the species in the organic layer was a dimer comprised of the catalyst and its deprotonated zwitterion. Subsequently, solution NMR experiments [16] corroborated this proposal. The NMR spectrum of a dimer solution in benzene compared to that of the octanesulfonate salt of the monomeric catalyst revealed that the protons on the quinoline rings were shifted downfield while those on the phenyl ring were shifted upfield. This is consistent with the dimer having a structure wherein the quinoline is opposite the phenyl ring, and the NMR shifts indicate the quinoline donates electrons to the phenyl ring. The protons on the face of the quinuclidine ring also shift, while those in the back remain unchanged. Thus, the structure of the catalyst dimer appears to be quite similar to that proposed for the indanone carbanion-catalyst ion pair. Subsequently, an X-ray structure of the catalyst dimer was obtained which was consistent with the proposed solution structure [16].

Due to the low solubility of the catalyst itself, formation of the dimer appears to be a critical part of the chiral alkylation process since it greatly enhances solubility of the catalyst. Kinetic measurements of the alkylation step revealed an order of 0.5 in catalyst, indicating the dimer dissociates to the monomer before complexation with the indanone enolate.

Another curious aspect of these reactions was the differences observed depending on the concentration of the aq. NaOH. Using 50% NaOH, the ee of product was measurably the same regardless of the amount of catalyst used. In contrast, for 30% NaOH, the ee of the product decreased as the catalyst concentration increased. Calculation of the rates of formation of the racemic and chiral product revealed that the order in catalyst was 0.5 for the asymmetric process, analogous to that found with 50% NaOH, but the order for the racemic process was 1.0. Thus, in this case, the racemic and asymmetric reactions must proceed through different mechanisms.

The asymmetric phase transfer reaction was extended by the Merck group to a substrate which lacked the phenyl group, Eq. (3) [17].



Using the same catalyst (*p*-CF₃ benzylcinchoninium) a 92% ee was obtained with yield >95%, while use of the diastomeric catalyst, *p*-CF₃-benzylcinchonidinium, provided an ee of 76%, but 30 mol% catalyst was required for the reaction to reach completion. While having opposite configurations at the critical C8 and C9 positions, cinchonidine and cinchonine are diastereomers (Fig. 1, since they have the same configuration at the two other chiral centers, C3 and C4). Examination of space-filling models suggested the preferred conformation of cinchonine had the vinyl group behind the hydroxy group, leaving only one face available for hydrogen bonding. On the other hand, cinchonidine appears to be more flexible, and the vinyl group does not block one side of the hydroxy group, which may account for the lower enantioselectivity observed with this catalyst.

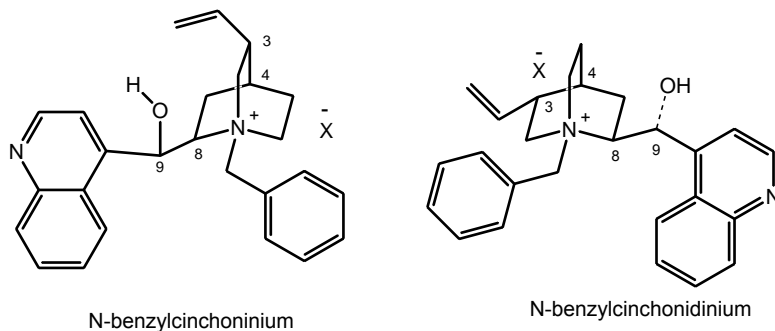
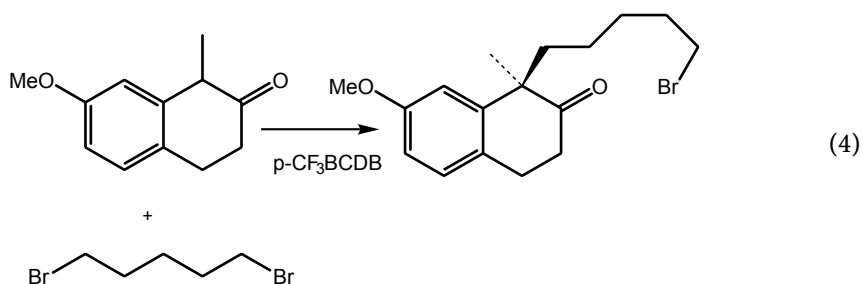


Fig. 1

The equivalent enantioselectivity for the phenylindanone and propylindanone is somewhat surprising since the propyl group can only provide van der Waals interaction with the benzyl group of the catalyst and this might not be expected to provide adequate interaction to secure the two substrates in an ion-pair complex of the type shown with the phenyl enolate. However, extensive computational studies on enolate:cinchoninium complexes have led to the conclusion that dispersion forces play an important role in determining the shape of the intermolecular complexes, and that Coulombic attractions simply augment the strength of the intermolecular attraction [18]. Thus, these calculations suggest that replacement of phenyl with propyl might not cause major differences in binding, which concurs with the experimental results. In addition, the absence of the phenyl group means that the negative charge is more localized, leading to enhanced Coulombic attraction.

A novel dual catalytic process was also discovered for the reaction with the propylindanone substrate [16]. Since the cinchonidinium catalyst is unstable, 30 mol % was required for the reaction to reach completion using the standard phase-transfer conditions. However, employing a nonionic poly(ethylene oxide) surfactant (Triton X-405) and solid KOH along with the chiral catalyst, the level of the cinchona catalyst could be reduced to 7 mol % with no loss in enantioselectivity. In this process, the Triton X-405 plays two roles. Firstly, it extracts KOH into the organic layer (as measured by titration), where the indanone is deprotonated, as detected by formation of the yellow anion. In addition, the surfactant draws the monomeric catalyst into the organic phase. The apparent strong binding of the enolate and catalyst then causes a tight ion-pair to form such that no racemic alkylation of the Triton-K⁺-indanone anion occurs.

The asymmetric phase transfer alkylation has been applied to a few other cyclic substrates, all of which can form planar enolate anions conducive to ion pairing with the cationic catalysts. Nerinckx and Vandewalle reported that tetralones could be alkylated with 1,5-dibromopentane with a yield of 74% and an ee of >70% in benzene/50% NaOH using the *p*-CF₃-benzylcinchonidinium catalyst, Eq. (4) [19]. The configuration of the

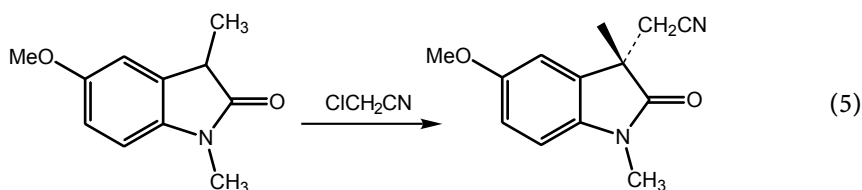


resulting alkylated product is consistent with an ion-pair in which the benzyl group of the catalyst interacts with the aromatic portion of the enolate; with the hydrogen bond between the catalyst hydroxy group and the enolate oxygen, two-

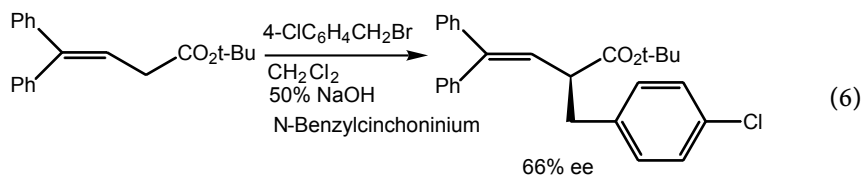
point binding is invoked to rationalize the product configuration. With the non-fused cyclic substrates 2-phenylcyclopentanone and 2-phenylcyclohexanone, ee's for methylation at ambient temperature with MeBr were only 13% and 36%, respectively.

These results are consonant with the ion-pair proposal of Dolling, since the more flexible non-fused substrates would have more degrees of freedom and hence would not be expected to provide a selective ion pair from one conformer. On the other hand, Michael reactions with methyl vinyl ketone of these substrates at $-20\text{ }^{\circ}\text{C}$ provided the adducts in $>80\%$ ee. Although the authors provide no rationale, the TS for the Michael reaction may be organized by the cationic alkaloid binding to both the anionic enolate and the developing negative charge in the Michael acceptor.

A further example that demonstrates the usefulness of the phase transfer chemistry for fused aromatic substrates is the cyanomethylation of a physostigmine precursor, Eq. (5) [20]. High selectivity (78%) was observed only for cinchoninium catalysts with electron-withdrawing groups in the benzyl group, as the unsubstituted benzyl catalyst gave only 10% ee and *ortho* substituents in the benzyl group also gave minimal enantioselectivity.



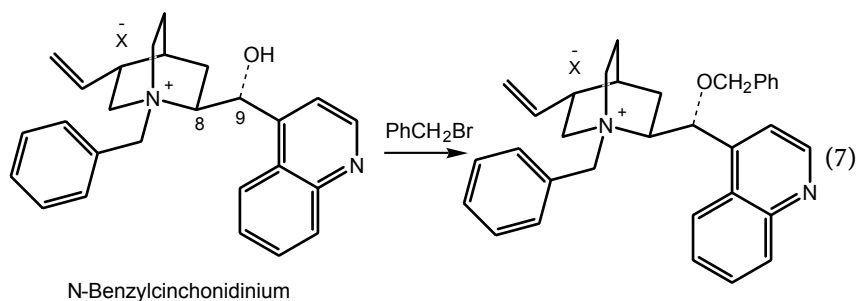
Based on the above results and rationalizations of enantioselectivities, expectations would be low for success in the enantioselective alkylation of flexible, acyclic enolates via chiral phase transfer catalysis. However, in 1989 O'Donnell and coworkers reported the asymmetric alkylation of acyclic Schiff bases with ee's up to 66%, Eq. (6) [21]. Critical to obtaining high enantioselectivity was use of the *t*-Bu ester, 50% NaOH as base, methylene chloride as solvent, and bromide as the leaving group. Further optimization, including 70% toluene/30% dichloromethane as solvent, 4:1 ratio of organic:aqueous, high agitation, and a temperature of $5\text{ }^{\circ}\text{C}$ resulted in an improved enantioselectivity of 81% [22]. In contrast to Dolling's work, either enantiomer could be obtained in nearly equal selectivity by simply changing the catalyst from cinchoninium to cinchonidinium, and no effect was observed by addition of electron-withdrawing groups into the benzyl group of the catalyst.



Besides being acyclic, another confounding factor with this substrate is that it is secondary, so the product still contains an active proton such that racemization and dialkylation are concerns. However, neither of these potential obstacles were problems in this chemistry since the monoalkylated product is 4 pKa units less acidic than the starting active methylene compound [23]. A further complication of the acyclic enolate is that both *Z*- and *E*-enolates can be formed, and these are likely to complex differently with the catalyst. A computational study suggested that the *Z*-enolate complexes to the cinchoninium catalyst more strongly than the *E*-enolate, and this enolate fits into a groove of the catalyst rather than directly in a face-to-face orientation. However, calculations could not determine any trends or patterns to explain the enantioselectivity [18].

The phase transfer alkylation of Schiff bases has been extended to several other alkyl bromides as a route to new amino acids [24], and the enantioselectivities in these cases are comparable (50 to 70% ee) to those reported by O'Donnell. In addition, the methodology has been used for the synthesis of α -methylamino acids, with ee's of about 50% [25]. Further optimization using an *O*-alkylated catalyst and a no solvent process with solid KOH/K₂CO₃ led to improved ee's of 70% [26].

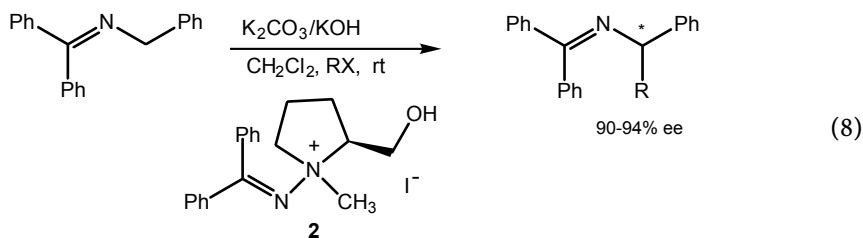
Further work by the O'Donnell group led to an unexpected finding that the free OH of the cinchona catalyst is not required for high enantioselectivity [27a]. Under phase transfer conditions using *N*-benzylcinchonidinium bromide, the hydroxy group of the catalyst reacts with the alkylating agent, Eq. (7). When this *O*-alkylated catalyst was prepared independently and used as a catalyst, the enantioselectivity in the asymmetric alkylation of the benzophenone Schiff base was the same (60% ee) as in the reaction using the free OH catalyst. Since all hypotheses for the mechanism of enantioselectivity involve hydrogen-bonding from the catalyst OH group to the enolate, this result indicates that other modes of chiral recognition must be occurring, at least in some cases.



While O'Donnell and co-workers offered no explanation for these unusual observations, recent work by Corey [27b] and Lygo [27c] has provided a rationale along with the most impressive results in this field to date. As with the O'Donnell work, the catalyst used by the Corey group is *O*-alkylated (allyl), while the new twist is introduction of an *N*-anthracenylmethyl group on the quinuclidine nitrogen of cinchonidine. The Lygo group also used the anthracenylmethyl cata-

lyst, and showed no difference whether the hydroxy group was alkylated or not, the assumption being that alkylation occurred during the reaction. Using solid cesium hydroxide as base at $-60\text{ }^{\circ}\text{C}$ to $-78\text{ }^{\circ}\text{C}$ and the same substrate as shown in Eq. 6, enantioselectivities in the 95–99.5% range were achieved by the Corey group. The Lygo group used liquid-liquid phase transfer conditions with KOH as base and achieved ee's up to 94%. With the hydroxy group allylated, no possibility of hydrogen bonding exists, so an explanation different from that of Dolling must be invoked. That provided by Corey [27b] involves a tight ion-pair held in a rigid 3-dimensional geometry by van der Waals and coulombic attractions, with the large anthracenyl group providing steric screening and rigidity. The most stable geometry of the ion pair allows for approach of the electrophile from only one face of the enolate.

In the work described thus far, the chiral catalysts that have been effective have all been derived from *Cinchona* alkaloids, most specifically, cinchonine and cinchonidine. Efforts to use other catalysts have been described, but most have met with very limited success [28, 29]. One extraordinary exception has been reported by Eddine and Cherqaoui, who found that the pyrrolidiniumhydrazonium salt (2) catalyzed the phase transfer alkylation of the imine shown in Eq. (8). with enantioselectivities up to 94% [30]. Due to the low acidity of the imine substrate, the solid base medium of KOH/ K_2CO_3 was used which allowed reaction within 24 hours with 2–5% catalyst. Notably, no reaction occurred with standard ammonium phase transfer catalysts. When the hydroxy group of the catalyst was alkylated, the ee in the phase transfer reaction was reduced from 91% to 58%, demonstrating the need for hydrogen bonding for tight enolate-catalyst binding.



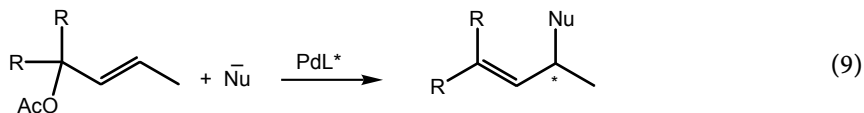
Summary. Asymmetric catalytic phase transfer alkylations are effective within a limited pool of substrates. No generalized catalyst is effective with a wide range of substrates; instead, catalyst and conditions must be tuned for each reaction. The rationale for enantioselectivity has been probed by theory and experiment, but much work remains to unravel the details of the chemistry.

3

Transition Metal-Catalyzed Asymmetric Allylic Alkylations of Enolates

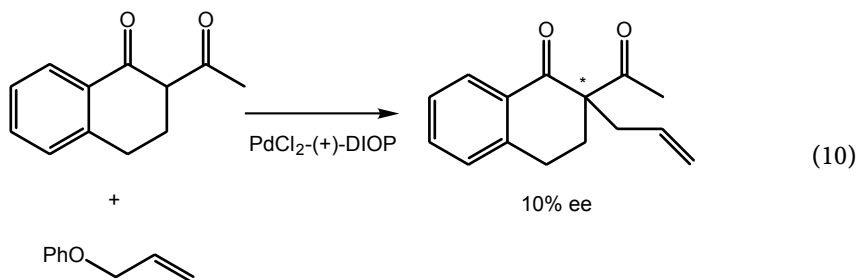
Using palladium metal complexed with chiral ligands, allylic alkylations of stabilized enolates have been developed in recent years into highly enantioselective

processes [31]. The majority of the work in this area has focused on selectivity at the electrophilic allylic center, not at the prochiral enolate center, Eq. (9).



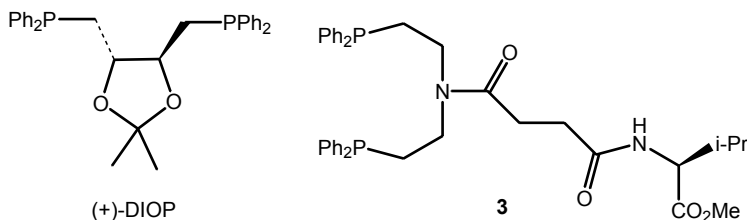
As outlined in the Trost and van Vranken review [31], selectivity can result from a number of different processes, depending on the substrate. In general, a π -allyl-metal-ligand complex is formed, with the chiral ligand binding such that it can influence enantioselectivity at the allylic center. Three X-ray crystal structures have been published of π -allyl-palladium complexes coordinated with chiral ligands which shed light on the enantioselective process [32, 33]. The structure of a Chiraphos-palladium complex with a triarylallyl substrate indicates that the phosphane ligand has steric interactions with the phenyl groups of the allyl moiety, creating a chiral environment around the allyl group such that enantioselectivity can be induced at the allylic center [32]. In the other examples, sparteine was complexed with either cyclohexenyl or 1,1,3-triphenylallyl groups. In both cases palladium complexes with one face of the allyl group, although the orientation of the cyclohexenyl and triarylallyl groups was different for the two substrates. In all three cases the palladium atom and the chiral ligand block one face of the allyl group, leaving the other face open for nucleophilic attack. From these examples, one can see that the incoming nucleophile would have little or no interaction with the chiral ligand, since they are on opposite sides of the allyl group. Thus, expectations are low that conventional chiral ligands could induce asymmetry at the nucleophilic center.

Kagan was the first to study reactions in which enantioselectivity at a prochiral nucleophile was examined. In the reaction of 2-acetyltetralone with allylic ethers in the presence of a chiral DIOP-Pd catalyst, Eq. (10), the allylated products were obtained with ee's of only 10% [34].



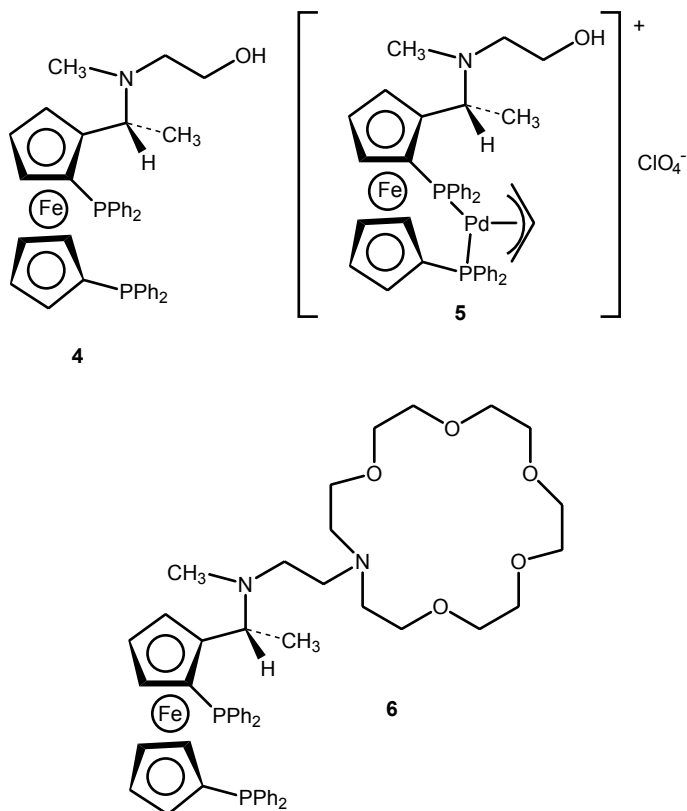
This reinforced the expectation that simple chiral ligands would not be able to produce useful levels of enantioselectivity at the nucleophilic center. Since then a number of workers have devised chiral ligands specifically designed for inducing enantioselectivity at the nucleophilic center of prochiral nucleophiles in allylic alkylations [35]. In 1982 Kumada and coworkers constructed a series of lig-

ands with a chiral group remote from the phosphane ligand such that the chiral group could possibly interact with nucleophilic enolate [36]. The best ligand for the allylation of the sodium salt of 2-acetylcyclohexanone was **3**, which afforded a 52% ee for a reaction at $-50\text{ }^{\circ}\text{C}$. For comparison the DIOP ligand only gave a 2% ee. The enantioselectivity was rationalized assuming the amide and methoxycarbonyl groups chelate to the sodium ion, which essentially connects the nucleophile to the asymmetric Pd complex and provides an increased ability to differentiate between the enantiotopic faces of the nucleophile.



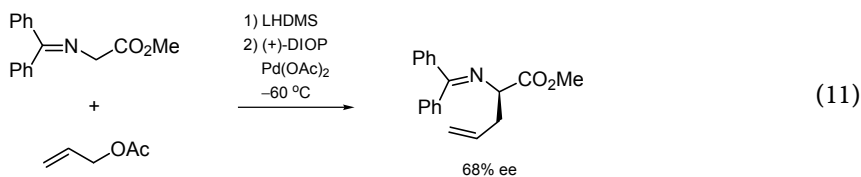
This concept was further expanded to the design of ferrocenylphosphane ligands which possessed functional groups designed to interact with the approaching nucleophile. The design of these ligands differed from the previous example since the phosphane groups are at the center of asymmetry in the catalyst while the pendant group which is to interact with the counterion is achiral. With catalyst **4**, an ee of 81% [37] (later revised to 70% [38]) was reported for allylation of 2-acetylcyclohexane. Interestingly, 2-acetylcyclopentanone provided an ee of <5%. The acyclic substrates, phenylacetaldehyde (53% ee) and benzoylacetone (60% ee) gave reasonable enantioselectivities, indicating that a cyclic substrate is not required. The fused-ring substrate, 2-acetyltetralone, gave the highest ee in the series of 82%. Hydrogen-bonding between the hydroxy group on the catalyst ligand and the enolate oxygen was proposed to explain the high selectivity. A X-ray structure of the π -allylpalladium complex with the hydroxylated ligand **4** provided support for this hypothesis [39]. In this structure (**5**) the hydroxy group is located over the allyl group and is close to one of the allyl carbons; thus, coordination to the metal cation would bring the nucleophile into close proximity to one of the allyl carbon centers.

The idea of using a secondary interaction with the counterion to connect the nucleophile and electrophile was taken a step further in a catalyst design that included an aza-crown ether appended to the chiral ferrocenylphosphane ligand, **6**. As in the previous example, the chirality of the ligand is in close proximity to the palladium binding site, while the pendant group is achiral. Introduction of the crown ether was designed to enhance coordination to the counterion. A ternary complex including the crown ether, potassium cation, and the enolate anion was proposed in which the bulky crown ether blocks approach of the enolate to C1 and provides a chiral pocket around carbon C3 [40]. Enantioselectivities up to 75% were reported [40], which were later revised to 65% [38].

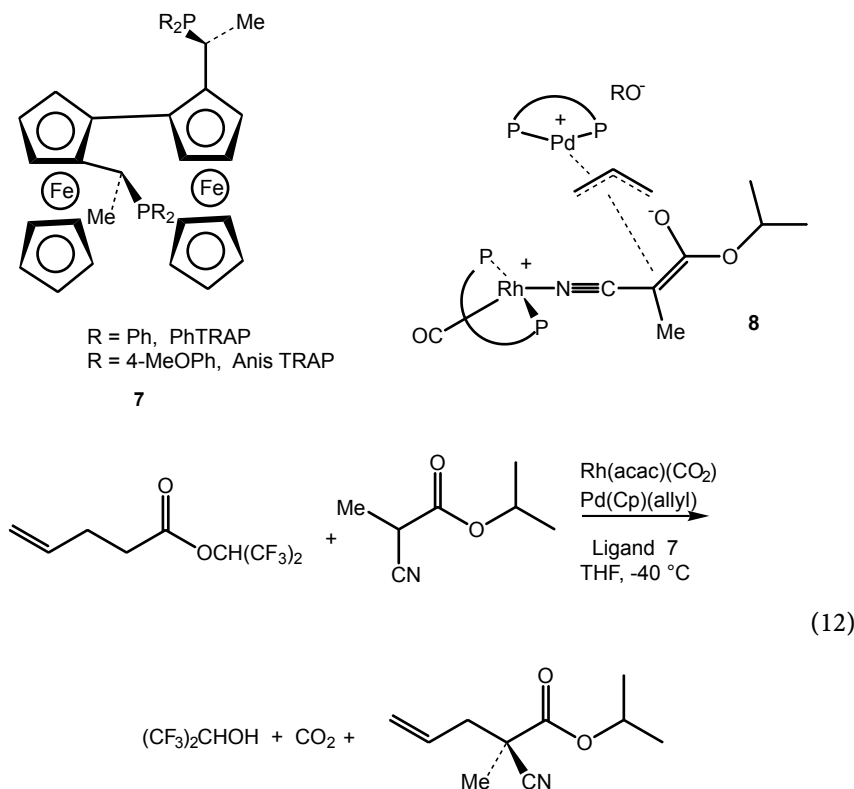


Allylations of α -nitroketones and α -nitroesters were also carried out with the crown ether ligands using fluoride salts as base. Moderate ee's in the 40–50% range were obtained using rubidium fluoride and ferrocenylphosphane ligands bearing monoaza-15-crown-5 or 18-crown-6 pendants. With the nitroesters, enantioselectivity increased with increased steric hindrance of the ester alkyl group, with an 80% ee realized in the best case using rubidium perchlorate as co-catalyst, which was proposed to increase the ratio of cation bound ligand to free ligand [41].

Genet has studied the enantioselective allylation of acyclic Schiff bases. Given the discussion and results above, one would not expect significant selectivity to result from use of simple chiral ligands. However, a respectable ee of 57% was determined for the reaction at $-60\text{ }^{\circ}\text{C}$ using chiral DIOP as ligand with the lithium enolate of the imine, Eq. (11) [42]. Further work indicated that use of two moles of DIOP vs. Pd, use of palladium acetate as catalyst precursor, and lithium hexamethyldisilazide instead of LDA as base provided an increase in ee to 68% [43, 44]. When the amount of DIOP ligand was reduced to 1 mol equiv. vs. Pd, the opposite enantiomer was formed, but with lower enantioselectivity [45]. No explanation of this unusual finding was given.

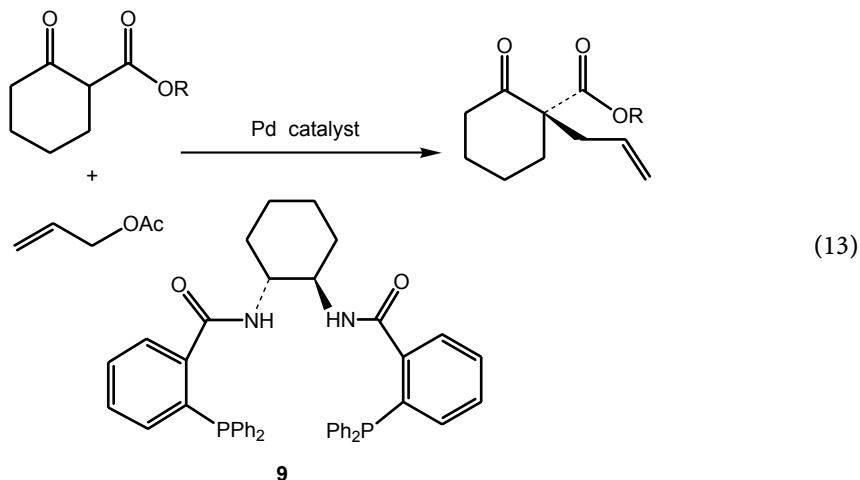


Enantioselective allylic alkylation of α -cyanoesters was accomplished using a two-component system of Pd and Rh and the chiral ferrocenyl ligand, PhTRAP (7) [46]. The cyanopropanoate is coordinated to the rhodium atom, which is also coordinated to the chiral ligand, via the cyano nitrogen atom, while the allyl group is activated by forming the π -allyl complex with palladium, as depicted in the transition state structure **8**. Nucleophilic attack of the enolate on the allyl complex then occurs enantioselectively to produce the allylated product. Ee's up to 99% were obtained using allyl hexafluoro-2-propyl carbonate and the electron-rich Anis-TRAP ligand at -40 °C, Eq. (12).



A different approach has been recently reported by the Trost group, which involves investigating whether a chiral pocket can transfer its chirality to the nu-

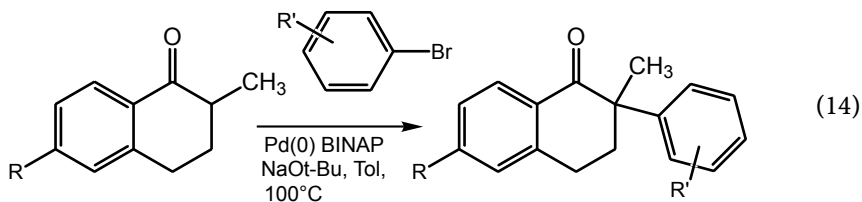
cleophile just through geometric constraints [47]. Success was achieved using the diphosphane catalyst **9** with a series of β -ketoesters. Enantioselectivity of 86% ee was obtained for 2-alkoxycarbonylcyclohexanone, Eq. (13), the first time a high ee has been observed for a ketoester substrate. The examples shown previously in this section were all diketones or imine derivatives. Higher ee's (90–95%) were obtained for the reactions involving the more rigid tetralone substrates.



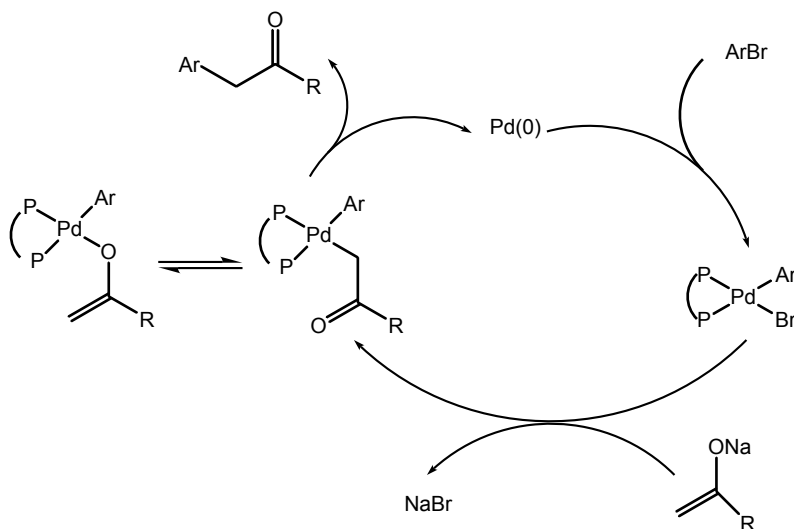
4

Transition Metal-Catalyzed Asymmetric Arylation of Enolates

Palladium-catalyzed regioselective arylation of enolates was disclosed by Hartwig [48] and Buchwald [49] in 1997, closely followed by a report by Buchwald that high levels of enantioselectivity could be attained in this catalytic process [50]. The enolate is generated using NaOt-Bu in toluene, while the arylation is accomplished using an aryl bromide, chiral BINAP, and either Pd₂(dba)₃ or Pd(OAc)₂ as catalyst. Using 2-methyltetralone as substrate, ee's ranged from 61–88% with variously substituted aryl bromides, Eq. (14).



With 2-methyl-1-indanone, high ee's were obtained with some aryl bromides, but very low ee's with *p*-substituted aryl bromides, a result with no ready explanation. The postulated reaction pathway is shown below (Scheme 1), although it is unclear where the enantioselective-determining step occurs.



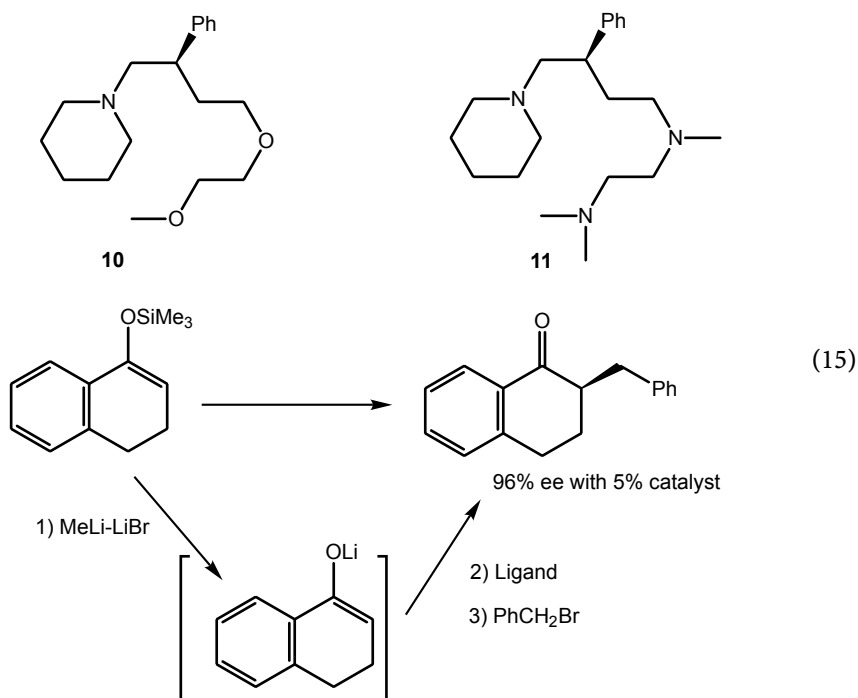
Scheme 1. Catalytic cycle for enolate arylation

5

Asymmetric Alkylation of Enolates Using Chiral Ligands

Koga has pioneered the use of chiral amine ligands in the enantioselective reactions of lithium enolates with achiral electrophiles [51]. In the initial work, a full equivalent of the chiral ligand **10** was used for the benzylation of cyclohexanone and 1-tetralone, Eq. (15) [52]. Rationale for the enantioselectivity was coordination of the lithium ion by the tridentate ligand which provides a chiral environment around the enolate, leading to an enantioselective reaction.

The lithium enolate was generated from the corresponding silyl enol ether using MeLi, then the ligand was added to complex the lithium ion, followed by reaction with the alkyl halide. Since the ee increased as the reaction proceeded, LiBr, which is formed during the reaction, was hypothesized to be important in the enantioselection. This was proven by addition of LiBr initially, which gave an overall higher ee and resulted in a constant ee over the course of reaction. When the chiral amine was added at 20 mol %, less than 1% reaction occurred. It was proposed that the chiral ligand was inactivated by complexation with LiBr. Thus, LiBr was shown to be necessary for high enantioselectivity, yet prevented use of the ligand catalytically. This constraint was overcome by addition of achiral diamines, such as *N,N,N',N'*-tetramethylethylenediamine or *N,N,N',N'*-tetramethylpropylenediamine, which were added as traps for LiBr via 5- or 6-membered chelates of Li⁺ [53]. An optimized ee of 96% was realized using just 5 mol % of catalyst **11** and 2 equiv. of tetramethylpropylenediamine in toluene. That high ee's can be obtained in the presence of a large amount of an achiral amine indicates that the chiral amine-lithium enolate complex must be significantly more



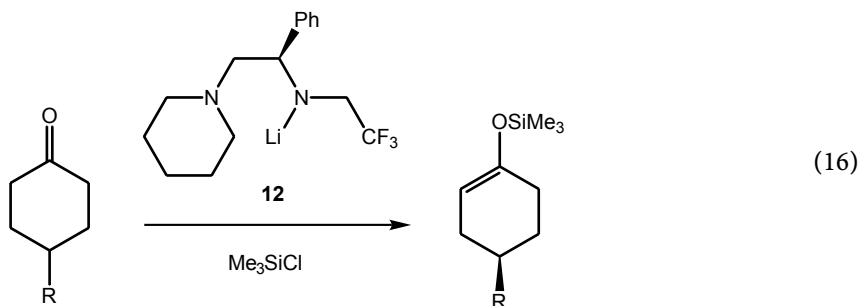
reactive than the bidentate achiral ligand-lithium enolate complex. The catalytic reaction was successfully extended to cyclohexanone enolate, with a yield of 52% and an ee of 90%.

6 Deprotonation by Chiral Lithium Amide Bases

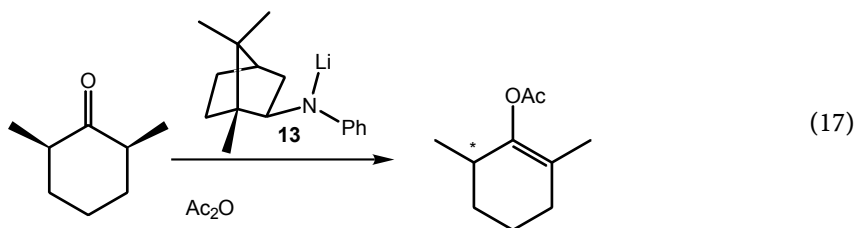
Deprotonation of carbonyl compounds by chiral lithium bases to generate chiral lithium enolates is another method toward asymmetric alkylation of enolates. This method is similar to that discussed in the previous section, in that both generate lithium enolates with the lithium ion complexed to a chiral amine base. In the method described in the previous section, the lithium enolate is generated from the corresponding silyl enol ether using MeLi, then a neutral tertiary amine ligand is added. This differs from chiral deprotonation in that a chiral amide base derived from a secondary amine is used to generate the lithium enolate, and the resulting protonated secondary amine then becomes the chiral ligand associated with the lithium enolate.

The first successful chiral deprotonation was reported in 1980 by Whitesell, who found that epoxides could be deprotonated with chiral amide bases to generate optically active allylic alcohols with ee's up to 31% [54]. In 1986 Simpkins and Koga independently reported stoichiometric asymmetric deprotonations of ketones. Koga studied the deprotonation of prochiral 4-alkyl-cyclohexanones

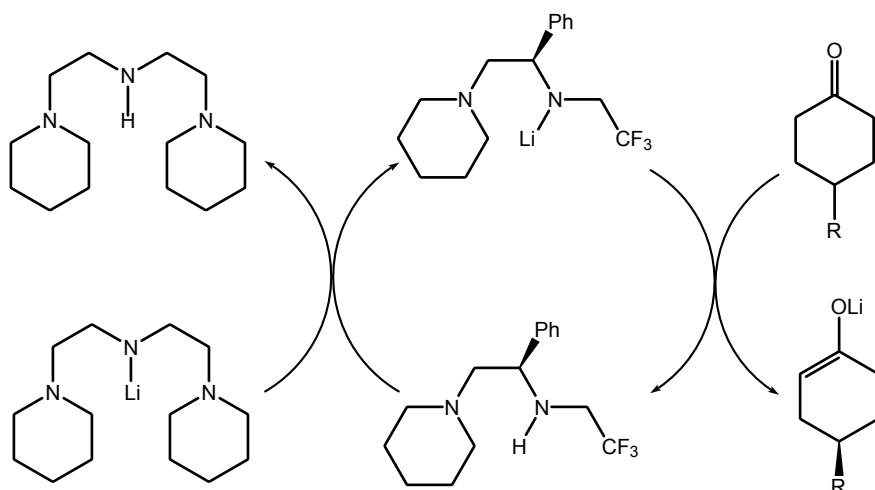
using a series of chelating amide bases, Eq. (16), with the best ee of 97% at $-105\text{ }^{\circ}\text{C}$ using 4-*t*-butylcyclohexanone [55]. The use of HMPA increased enantioselectivity, which was shown by NMR to be due to the ability of HMPA to convert the dimeric form to the more reactive monomeric form [56].



Simpkins examined the deprotonation of 2,6-dimethylcyclohexanone using a series of chiral amide bases. Enantioselectivity up to 74% was achieved using the bicyclic base 13, Eq. (17) [57].



Koga has recently devised a catalytic asymmetric deprotonation of 4-substituted cyclohexanones using the same substrates and amide bases shown in Eq. (15) [58]. The strategy conceived by Koga is as follows. Since deprotonation of carbonyl compounds is thought to involve coordination of the carbonyl oxygen to lithium, a tridentate base should be inferior to a bidentate base, since the former has an additional coordination ligand that will prevent coordination of lithium to the carbonyl group. The idea was then to use a catalytic amount of chiral bidentate ligand along with a large excess of an achiral tridentate ligand. The chiral base will serve to asymmetrically deprotonate the carbonyl group, and the achiral base will react with the resulting protonated chiral amine to regenerate the chiral base due to the greater acidity of the chiral base induced by the electron-withdrawing trifluoromethyl group (Scheme 2). With 30 mol % chiral base, chemical yields of 83% with 79% ee were achieved.



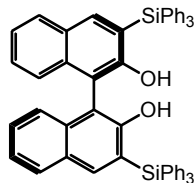
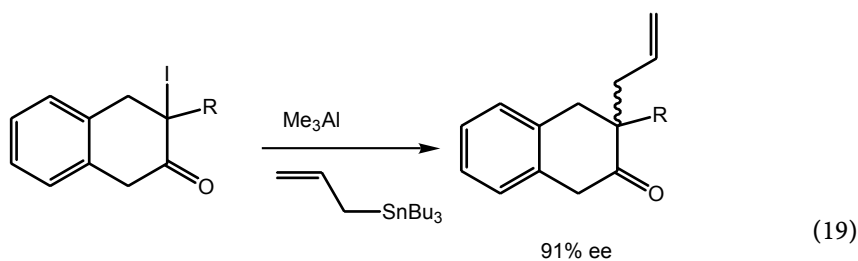
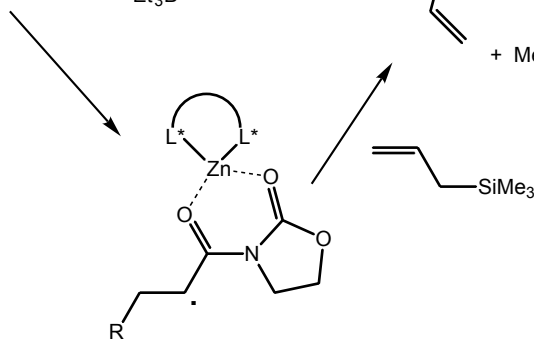
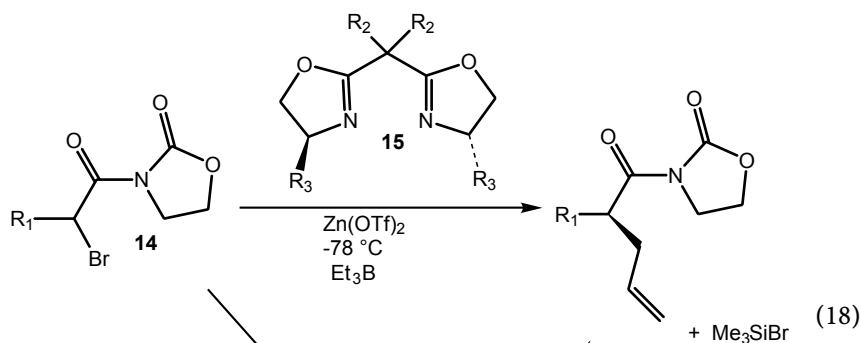
Scheme 2

7

Enantioselective α -Alkylation of Carbonyl Groups via Free Radicals

Within the past decade, diastereoselective radical reactions have become feasible and the factors controlling selectivity defined. Chiral auxiliaries for radical reactions have been recently developed in analogy to those developed for carbanion chemistry in the 1970s and 1980s. The first example of stoichiometric use of a chiral ligand for enantioselective radical additions was recently reported by Porter and coworkers [59, 60, 61]. Reaction of the amide **14** with allyltrimethylsilane at $-78\text{ }^\circ\text{C}$, initiated by triethylborane, in the presence of 1 equiv. each of zinc triflate and the chiral bidentate ligand **15**, provided the allylated product in a yield up to 88% and ee of 90%, Eq. (18). The presumed intermediate is the α -keto radical complexed to the chiral Lewis acid.

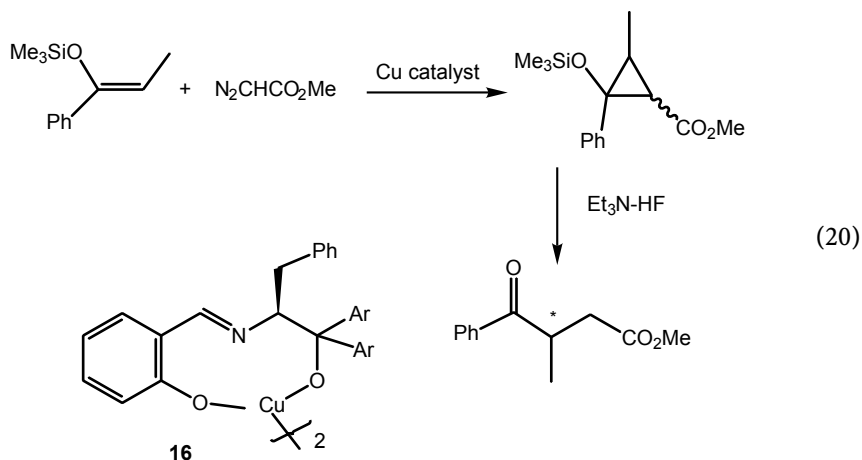
The first catalytic asymmetric radical-mediated allylation was reported in late 1997 by Hoshino and coworkers, who studied the allylation of an α -iodolactone substrate, Eq. (19) using trimethylaluminum as Lewis acid and a silylated binaphthol as the chiral catalyst, with triethylborane as radical initiator [62]. Use of one equiv. of diethyl ether was crucial for high enantioselectivity, providing an ee up to 91% in the presence of one equiv. of catalyst, with only a 27% ee in the absence of ether, and poorer ee's when other ethers were employed. In the catalytic version, the ee's dropped off vs. the stoichiometric reaction, with an ee of 81% with 0.5 equiv., and 80% with 0.2 equiv., and 72% with 0.1% catalyst. As in the above example, the presumed chiral intermediate involves complexation of the lactone radical with the Lewis acid-binaphthol complex, with the diethyl ether perhaps as a ligand on the aluminum.



8

Enantioselective Alkylation via Cyclopropanation of Silyl Enol Ethers

Reissig and coworkers have devised an indirect method of enantioselective alkylation of ketones via cyclopropanation of silyl enol ethers in the presence of the chiral copper catalyst **16**, followed by ring opening to provide the substituted ketones. Overall, the transformation corresponds to alkylation of ketones using methyl diazoacetate as the electrophile. Enantioselectivities up to 88% were realized in the cyclopropanation of aryl substituted olefins, Eq. (20) [63, 64].



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Chapter 34.2

Protonation of Enolates

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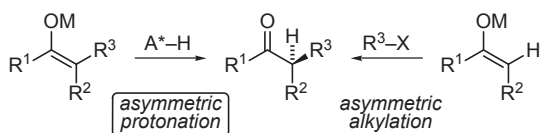
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Keywords: Protonation, Metal enolates, Chiral proton sources, Achiral proton sources

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1 Introduction

Asymmetric protonation of enols or enolates is an efficient route as is asymmetric alkylation of enolates to prepare carbonyl compounds which possess a tertiary asymmetric carbon at the α -position (Scheme 1). Numerous successful methods have been developed and applied to organic synthesis. Several reviews of asymmetric protonation have been published [1, 2, 3, 4, 5] and the most recent [4, 5] describe the work in detail up to early in 1995. This chapter is focussed on enantioselective protonation of prochiral metal enolates by a catalytic amount of chiral proton sources. Compounds 1 to 40 [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62]



Scheme 1

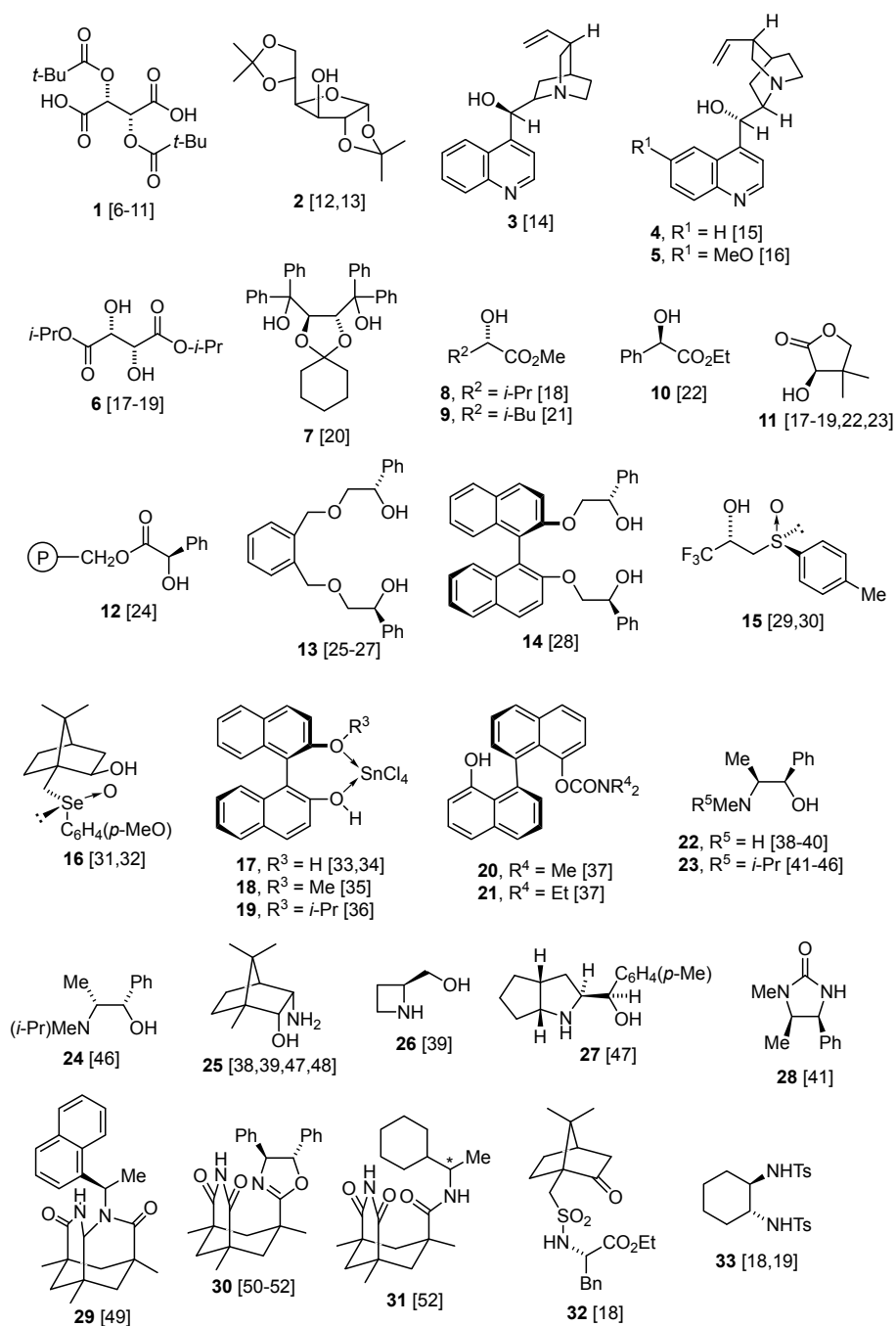


Fig. 1

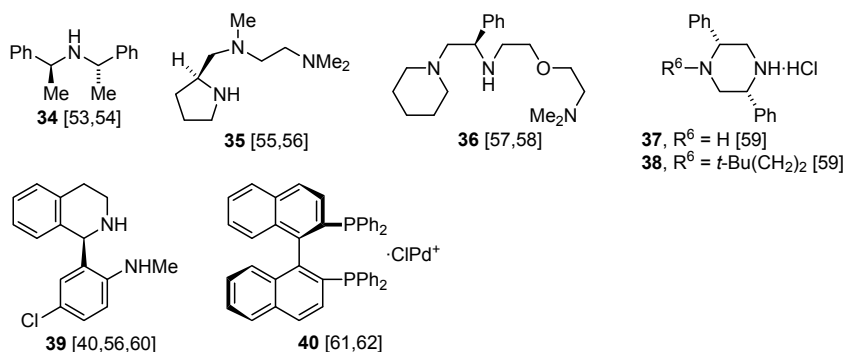


Fig. 1 (continued)

shown in Fig. 1 are the chiral proton sources or chiral catalysts reported to date which have been successfully used for the stoichiometric protonation of metal enolates. Some of these have been used to realize the catalytic process in combination with achiral proton sources as described in Section 3. The rest also have great potential for utilization in catalytic protonation.

2

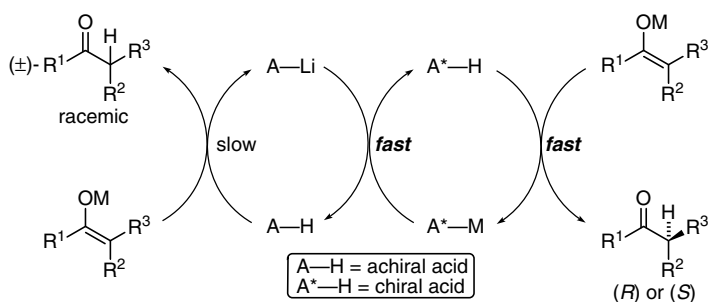
Mechanism of Catalysis

Asymmetric protonation of a metal enolate basically proceeds catalytically if a coexisting achiral acid A-H reacts with the deprotonated chiral acid A^{*}-M faster than with the metal enolate, a concept first described by Fehr et al. [44]. A hypothesis for the catalytic cycle is illustrated in Scheme 2. Reaction of the metal enolate with the chiral acid A^{*}-H produces (*R*)- or (*S*)-ketone and the deprotonated chiral acid A^{*}-M. The chiral acid A^{*}-H is then reproduced by proton transfer from the achiral acid A-H to A^{*}-M. Higher reactivity of A^{*}-M toward A-H than that of the metal enolate makes the catalytic cycle possible. When the achiral acid A-H protonates the enolate rapidly at low temperature, selective deprotonation of one enantiomer of the resulting ketone by the metallated chiral acid A^{*}-M is seen as an alternative possible mechanism.

3

Catalytic Protonation of Metal Enolates

Catalytic enantioselective protonations of metal enolates already published can be roughly classified into two methods carried out under basic conditions and acidic conditions. The process under basic conditions is, for example, the protonation of reactive metal enolates such as lithium enolates with a catalytic amount of chiral acid and an excess of achiral acid. The process under acidic conditions employs silyl enol ethers or ketene silyl acetals as substrates. Under the influence



Scheme 2

of a chiral Lewis acid or chiral Brønsted acid catalyst, the silyl ethers are transformed into optically active carbonyl compounds by an achiral acid.

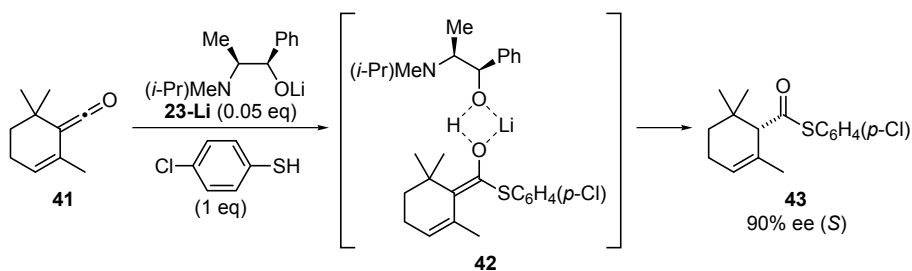
3.1

Protonation under Basic Conditions

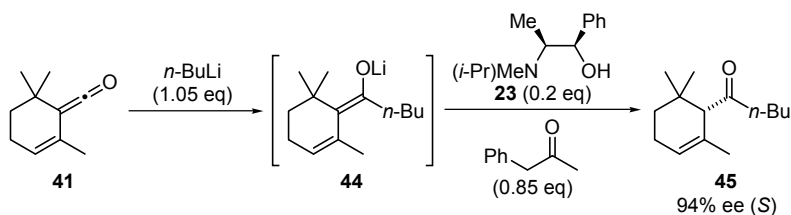
The first example of catalytic enantioselective protonation of metal enolates was achieved by Fehr and coworkers (Scheme 3) [44]. They found the enantioselective addition of a lithium thiolate to ketene **41** in the presence of an equimolar amount of (-)-*N*-isopropylephedrine (**23**) with up to 97% ee. Based on the results, they attempted the catalytic version; for example, slow addition of *p*-chlorothiophenol to a mixture of ketene **41** (1 equiv) and lithium alkoxide of (-)-*N*-isopropylephedrine **23-Li** (0.05 equiv) gave thiol ester **43** with 90% ee. First, the thiol is deprotonated by **23-Li** to generate lithium *p*-chlorothiophenoxide and **23**. The thiophenoxide adds to the ketene **41** leading to *Z*-thiol ester enolate which is presumed to react with the chiral amino alcohol **23** via a four-membered cyclic transition state **42** to form the product **43** and **23-Li**. The lithium alkoxide **23-Li** is reused in the catalytic cycle. The key to success in the catalytic process is that the rate of introduction of thiophenol to a mixture of the ketene **41** and **23-Li** is kept low, avoiding the reaction of the thiol with the intermediate lithium enolate.

Later, the same group showed that an asymmetric protonation of preformed lithium enolate was possible by a catalytic amount of chiral proton source **23** and stoichiometric amount of an achiral proton source [45]. For instance, when lithium enolate **44**, generated from ketene **41** and *n*-BuLi, was treated with 0.2 equiv of **23** followed by slow addition of 0.85 equiv of phenylpropanone, (*S*)-enriched ketone **45** was obtained with 94% ee (Scheme 4). In this reaction, various achiral proton sources including thiophenol, 2,6-di-*tert*-butyl-4-methylphenol, H₂O, and pivalic acid were used to provide enantioselectivity higher than 90% ee. The p*K*_a value of the achiral acid must be smaller than that of **45** to accomplish a high level of asymmetric induction. The catalytic cycle shown in Scheme 2 is the possible mechanism of this reaction.

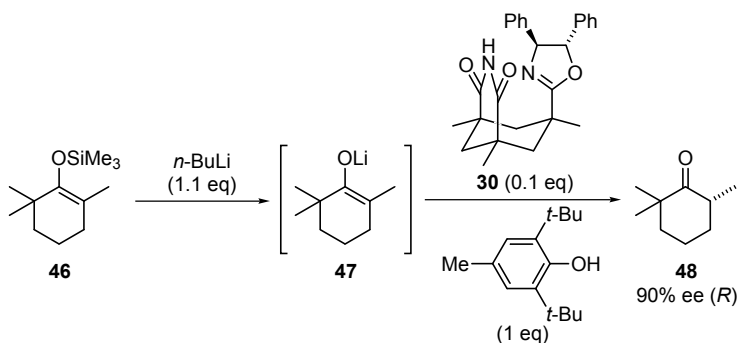
Our research group independently found a catalytic enantioselective protonation of preformed enolate **47** with (*S,S*)-imide **30** founded on a similar concept (Scheme 5) [51]. The chiral imide **30**, which has an asymmetric 2-oxazoline ring and is easily prepared from Kemp's triacid and optically active amino alcohol, is an efficient chiral proton source for asymmetric transformation of simple metal enolates into the corresponding optically active ketones [50]. When the lithium enolate **47** was treated with a stoichiometric amount of the imide **30**, (*R*)-enriched ketone **48** was produced with 87% ee. By a ¹H-NMR experiment of a mixture of (*S,S*)-imide **30** and lithium bromide, the chiral imide **30** was found to form a complex rapidly with the lithium salt. We envisaged that a catalytic asym-



Scheme 3



Scheme 4

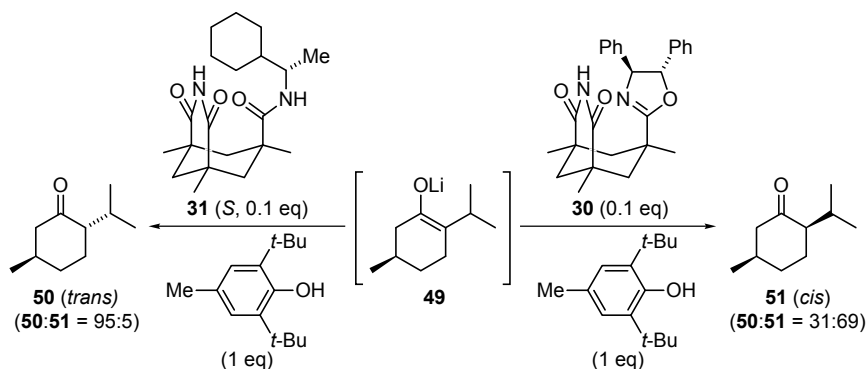


Scheme 5

metric protonation might be possible if the lithium enolate **47** forms a complex with (*S,S*)-imide **30** more rapidly than with the coexisting achiral proton source and the achiral acid is selectively deprotonated by the resulting lithiated (*S,S*)-imide. The catalytic reaction has been realized by addition of 0.1 equiv of (*S,S*)-imide **30** to the lithium enolate **47**, generated from the corresponding silyl enol ether **46** and *n*-BuLi, prior to the addition of a stoichiometric amount of an achiral acid over a period of 2 h. Among the achiral acids examined, 2,6-di-*tert*-butyl-*p*-cresol (BHT) gave the best result (90% ee, Scheme 5).

The aforementioned catalytic process was further applied to diastereoselective protonation of a chiral enolate of (–)-menthone (Scheme 6) [52]. When the lithium enolate **49** was quenched with BHT at –78 °C, an 86:14 mixture of *trans*-product **50** and *cis*-product **51** was obtained. Reaction of the enolate **49** with (*S*)-imide **31** (0.1 equiv), which was derived from (*S*)-1-cyclohexylethylamine, followed by slow addition of BHT (1 equiv) at the same reaction temperature furnished a higher *trans*-selectivity (**50**:**51**=95:5). The enantiomer of (*S,S*)-imide **30** showed a similar level of *trans*-selectivity, while *cis*-isomer **51** was produced as a major product (**50**:**51**=31:69) in reaction with (*S,S*)-imide **30**. This is an example of diastereoselective protonation in which a new stereogenic center is formed under the influence of a chiral proton source rather than of the asymmetric carbon of the enolate **49**.

The chiral tetradentate amine **36** was shown to be an efficient chiral source for enantioselective protonation of prochiral lithium enolate **53** by Koga's group [57]. The corresponding silyl enol ether **52** was treated with methyl lithium-lithium bromide complex to generate the lithium enolate **53** containing LiBr. Asymmetric synthesis of 2-methyl-1-tetralone (**54**) was achieved with up to 91% ee by protonation of **53** with a stoichiometric amount of the chiral amine **36** and achiral Brønsted acid. LiBr is necessary for attaining high asymmetric induction in the reaction and a ternary complex formed from the enolate **53**, the chiral amine **36**, and LiBr is assumed to be a reactive intermediate. The catalytic version was achieved using 0.2 equiv of the amine **36** and a large excess of powdered

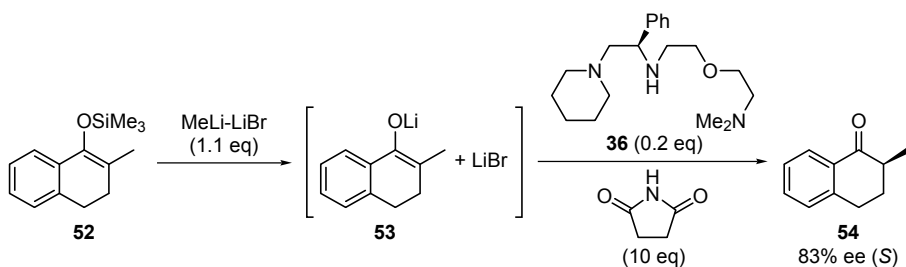


Scheme 6

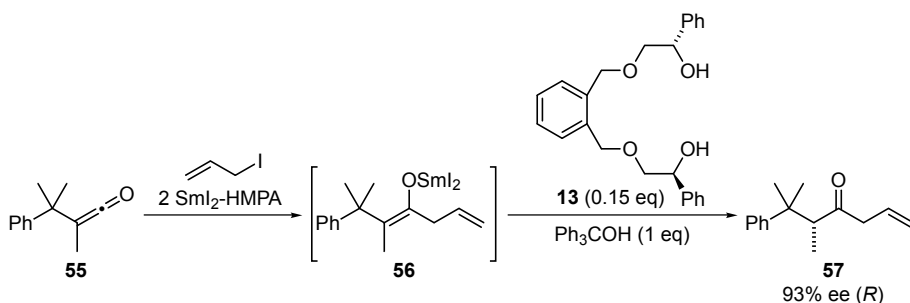
succinimide, and thus (*S*)-enriched ketone **54** was obtained with 83% ee (Scheme 7) [58].

A C_2 -symmetric homochiral diol **13** (DHPEX) is a chiral proton source developed by Takeuchi et al., for samarium enolates which are readily prepared by SmI_2 -mediated allylation of ketenes [25, 26]. In the stoichiometric reaction using DHPEX **13**, they found that -45°C was the best reaction temperature for the enantioface discrimination, e.g., when methyl (1-methyl-1-phenylethyl)ketene **55** was used as a substrate, the product exhibited 95% ee [27]. The catalytic reaction was carried out using trityl alcohol as an achiral proton source which was added to a mixture of *in situ* generated samarium enolate **56** and DHPEX **13** (0.15 equiv) slowly so as not to exceed the ratio of the achiral proton source to DHPEX **13** of more than 0.7. The highest ee (93% ee) of product **57** was gained when the achiral proton source was added over a period of 26 h (Scheme 8) [27].

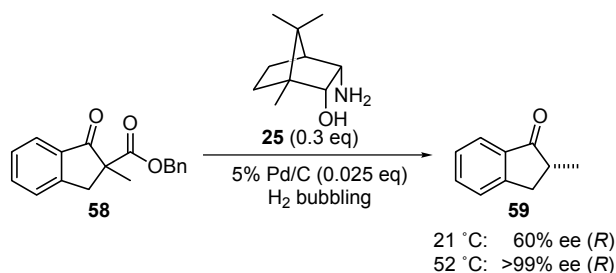
Muzart and coworkers have succeeded in a catalytic asymmetric protonation of enol compounds generated by palladium-induced cleavage of β -ketoesters or enol carbonates under nearly neutral conditions [47, 48]. Among the various optically active amino alcohols tested, (+)-*endo*-2-hydroxy-*endo*-3-aminobornane (**25**) was effective as a chiral catalyst for the enantioselective reaction. Treatment of the β -ketoester of 2-methyl-1-indanone **58** with a catalytic amount of the amino alcohol **25** (0.3 equiv) and 5% Pd on charcoal (0.025 equiv) under bubbling of hydrogen at 21°C gave the (*R*)-enriched product **59** with 60% ee



Scheme 7



Scheme 8



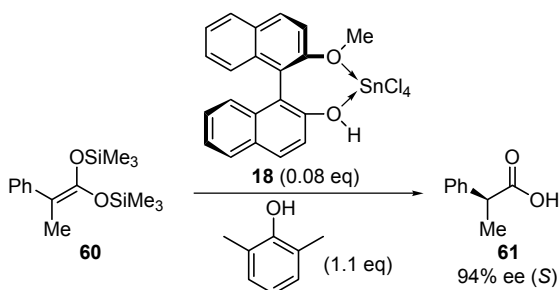
Scheme 9

(Scheme 9) [48]. The enantioselectivity was highly dependent on the reaction temperature and almost enantiopure 2-methyl-1-indanone (**59**) was obtained at 52 °C. The reaction was assumed to proceed via an enol or palladium enolate intermediate which was produced by cleavage of the benzyl-oxygen bond and the subsequent decarboxylation.

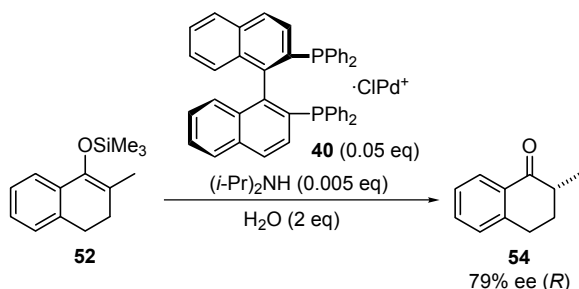
3.2 Protonation under Acidic Conditions

Silyl enol ethers, known as chemically stable and easy handled enolates, can be protonated by a strong Brønsted acid. Our group demonstrated that a Lewis acid-assisted Brønsted acid (LBA **17**), generated from optically pure binaphthol and tin tetrachloride, was a chiral proton source of choice for asymmetric protonation of silyl enol ethers possessing an aromatic group at the α -position [33, 34]. Binaphthol itself is not a strong Brønsted acid, however, LBA **17** can protonate less reactive silyl enol ethers since the acidity of the phenolic protons of **17** is enhanced by complexation with tin tetrachloride. The catalytic asymmetric protonation of silyl enol ethers was accomplished for the first time by LBA **18**. Treatment of ketene bis(trimethylsilyl)acetal **60** with 0.08 equiv of LBA **18** and a stoichiometric amount of 2,6-dimethylphenol as an achiral proton source afforded (*S*)-2-phenylpropanoic acid (**61**) with 94% ee (Scheme 10) [35]. LBA **19** derived from binaphthol monoisopropyl ether has been successfully applied to the enantioselective protonation of *meso* 1,2-enediol bis(trimethylsilyl) ethers under stoichiometric conditions [36].

Nakai and a coworker achieved a conceptually different protonation of silyl enol ethers using a chiral cationic palladium complex **40** developed by Shibasaki and his colleagues [61] as a chiral catalyst and water as an achiral proton source [62]. This reaction was hypothesized to progress via a chiral palladium enolate which was diastereoselectively protonated by water to provide the optically active ketone and the chiral Pd catalyst regenerated. A small amount of diisopropylamine was indispensable to accomplish a high level of asymmetric induction and the best enantioselectivity (79% ee) was observed for trimethylsilyl enol ether of 2-methyl-1-tetralone **52** (Scheme 11).



Scheme 10



Scheme 11

4

Principal Alternatives

Various methods using a stoichiometric amount of chiral proton sources or chiral ligands are available for enantioselective protonation of metal enolates: e.g., protonation of metal enolates preformed by deprotonation of the corresponding ketones or by allylation of ketenes [6, 7, 8, 9, 10, 11, 13, 17, 18, 19, 21, 22, 25, 26, 29, 30, 31, 32, 37, 40, 41, 42, 43, 49, 50, 53, 54, 55, 56, 57, 59, 60, 63], the Birch reduction of α,β -unsaturated acids in the presence of a sugar-derived alcohol **2** [12], a SmI_2 -mediated reduction of an α -diketone or 2-aryl-2-methoxyketones with chiral proton sources [16, 28], deracemization of 2-alkylcyclohexanones with chiral diol **7** in alkaline conditions based on host-guest inclusion complexation [20], and decarboxylation of malonic acid derivatives with Cu(I) /alkaloid catalysts of **3** and **4** [14, 15]. A ketene silyl acetal derived from racemic mandelic acid can be enantioselectively protonated by (*R*)-pantolactone (**11**) in the presence of LiCl [23] or by polymer-supported chiral alcohol **12** [24], which is a substitute for LBA **17–19**. The method employing **12** is temperature dependent and exhibits the highest enantioselectivity (94% ee) at -40°C [24]. Optically active 2-methyl-1-indanone and 2-methyl-1-tetralone can be synthesized from the corresponding prochiral enol carbonates or racemic β -ketoesters by a multistep

reaction: palladium-catalyzed cleavage/decarboxylation/chiral amino alcohol-mediated enantioselective ketonization [38, 39]. Enantioselective photodeconjugation of α,β -unsaturated carbonyl compounds with chiral amino alcohols is a convenient route to the corresponding optically active β,γ -unsaturated carbonyl compounds [64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76]. Irradiation of α -disubstituted indanones under analogous reaction conditions has led to Norrish type II cleavage followed by asymmetric tautomerization of the resulting enols [77, 78]. Addition of alcohols or amines to ketenes [79, 80, 81, 82, 83, 84, 85, 86] and Michael addition of thiocarboxylic acids or thiols to α,β -unsaturated esters [87, 88] are alternative ways of generating enols. Some other processes of asymmetric protonation of enols have been reported [89, 90]. Racemic ketones can be deracemized via enamines which are converted into optically active enriched ketones by protonation with chiral acids and subsequent hydrolysis [91, 92, 93, 94, 95, 96]. Enzymatic enantiofacially selective hydrolysis of enol esters is also a promising route to optically active carbonyl compounds [97, 98, 99, 100, 101]. Antibodies are attractive optically active proteins for asymmetric catalysis of stereogenic transformation. Prochiral enol ethers and enol acetates are protonated to produce enantiomerically pure carbonyl compounds by antibody-catalyzed hydrolysis [102, 103, 104, 105, 106]. Multi gram-scale synthesis is possible with catalytic antibodies [107].

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Chapter 35

Ring Opening of Epoxides and Related Reactions

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Keywords: Epoxide, Ring opening, Desymmetrization, Kinetic resolution

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1 Introduction

The ready availability of achiral and racemic epoxides from simple alkene precursors renders epoxide ring-opening an appealing approach to asymmetric synthesis. The inherent strain-induced reactivity of epoxides can be enhanced by coordination of the epoxide oxygen to a Lewis acid, thereby creating the possibility for chiral Lewis acids to catalyze enantioselective ring opening events.

The asymmetric ring opening (ARO) of *meso*-epoxides has the potential to generate two contiguous stereogenic centers from an achiral starting material. The wide variety of nitrogen, sulfur, oxygen, carbon, and halogen nucleophiles that have been reported in epoxide desymmetrization reactions underscores the versatility of epoxides and their ring-opened derivatives. Catalytic approaches

to effect the enantioselective deprotonation of *meso*-epoxides have also emerged as viable synthetic methods.

The ability to couple ARO with the kinetic resolution of a racemic mixture of epoxides offers another powerful strategy in asymmetric synthesis. Kinetic resolution is an attractive approach when the epoxide is easily accessed in racemic form, and becomes even more valuable when effective enantioselective routes to these epoxides are lacking. The most appealing scenario is one where both the ring-opened product and the unreacted epoxide are valuable chiral products.

The number of catalytic asymmetric transformations involving epoxides has grown considerably, even since this topic was last reviewed in 1996 [1, 2]. This chapter will highlight recent progress in asymmetric catalytic ring-opening methods and their increasing importance in the stereoselective synthesis of entio-enriched compounds.

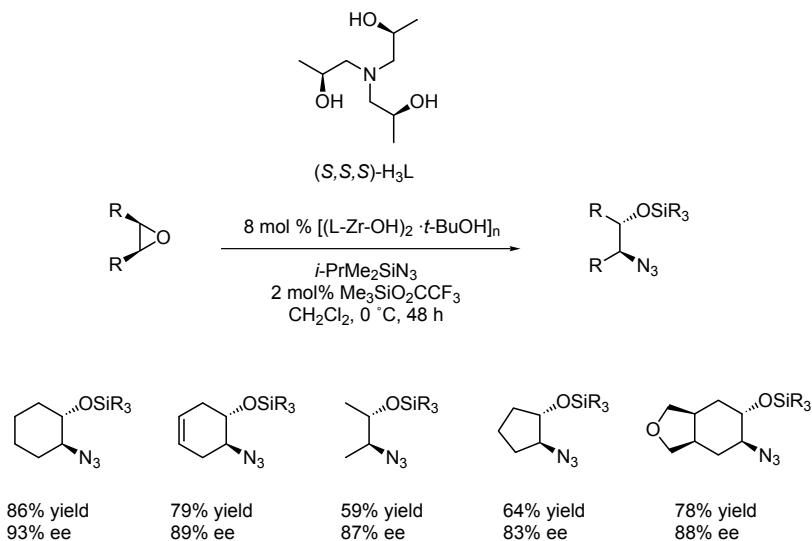
2

Enantioselective Ring Opening of *meso*-Epoxides

2.1

Nitrogen Nucleophiles

Highly enantioselective catalytic desymmetrization of *meso*-epoxides through nucleophilic ring opening was first effectively demonstrated by Nugent, who found that a zirconium trialkanolamine complex catalyzed the addition of azidosilanes to *meso*-epoxides (Scheme 1) [3]. Azide has been the most widely explored nitrogen nucleophile [4, 5, 6, 7], in part due to its utility as an amine sur-

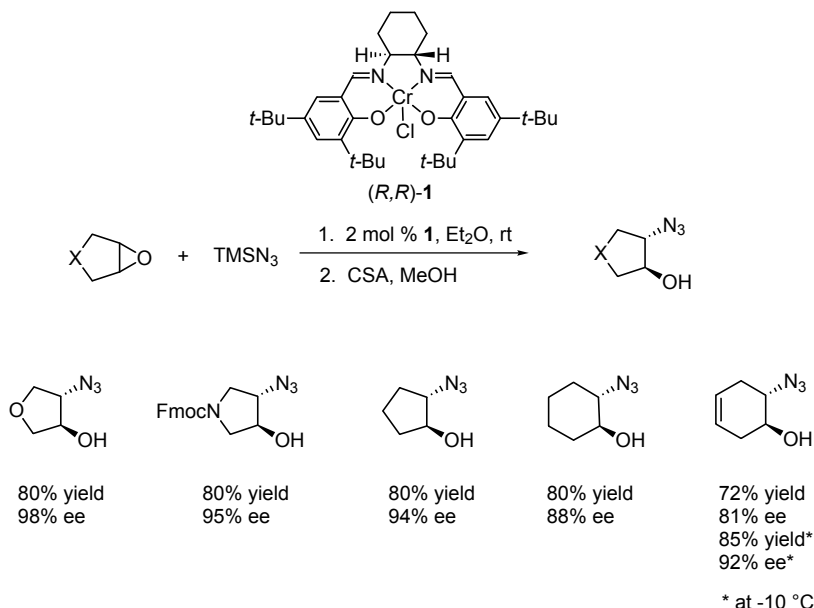


Scheme 1

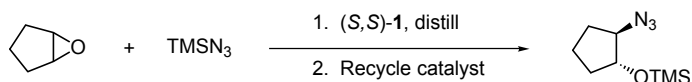
rogate that requires no protection for subsequent chemical elaboration. The useful levels of optical purity as well as the relatively broad substrate scope validated the ARO of epoxides as a worthy goal in asymmetric catalysis.

A very efficient chiral Cr(salen) catalyst that promoted the enantioselective addition of TMSN_3 was reported subsequently by Jacobsen [8]. The Cr complex **1** was conveniently prepared by insertion of CrCl_2 or alternatively a CrCl_3/Zn mixture into the (salen) ligand and subsequent air oxidation to the stable Cr(III) species. Low catalyst loadings (2 mol %) of this complex effected epoxide ring-opening of a wide variety of *meso*-epoxides containing carbamate, amide, or ester functionality (Scheme 2). In addition to its functional group tolerance, other practical advantages of the Cr(salen) catalyst include its indefinite stability under catalytic conditions which allowed for its repeated recycling. The discovery that the Cr(salen)-catalyzed ARO performed equally well in the absence of solvent rendered the process even more appealing, as simple distillation of the product mixture afforded the azido silyl ether with the highest possible volumetric productivity and no by-products generated (Table 1).

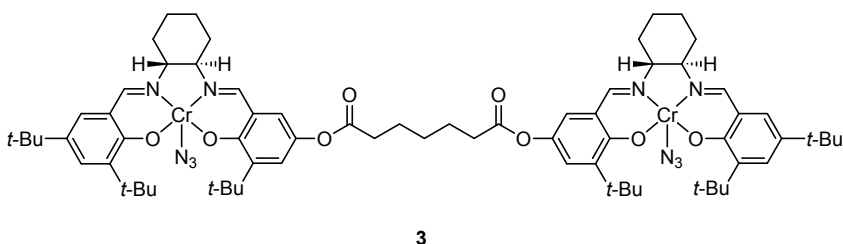
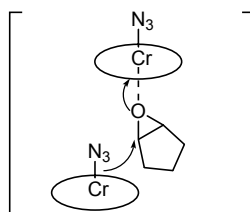
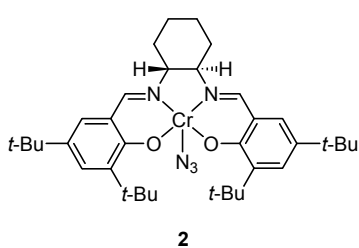
A novel mechanism was elucidated in the Cr(salen)-catalyzed ARO reaction in which the catalyst was discovered to perform dual roles [9]. The synthesis and characterization of the Cr(salen)N_3 complex **2** allowed the identification of this species as the active catalyst in the ARO reaction, suggesting that one role of the Cr catalyst was to deliver the azide nucleophile. X-ray crystallographic and IR spectroscopic analysis of **2** revealed a 6-coordinate geometry with the Lewis acid-



Scheme 2

Table 1. Recycling of Cr(salen) complex **1** in the ARO with TMSN_3 

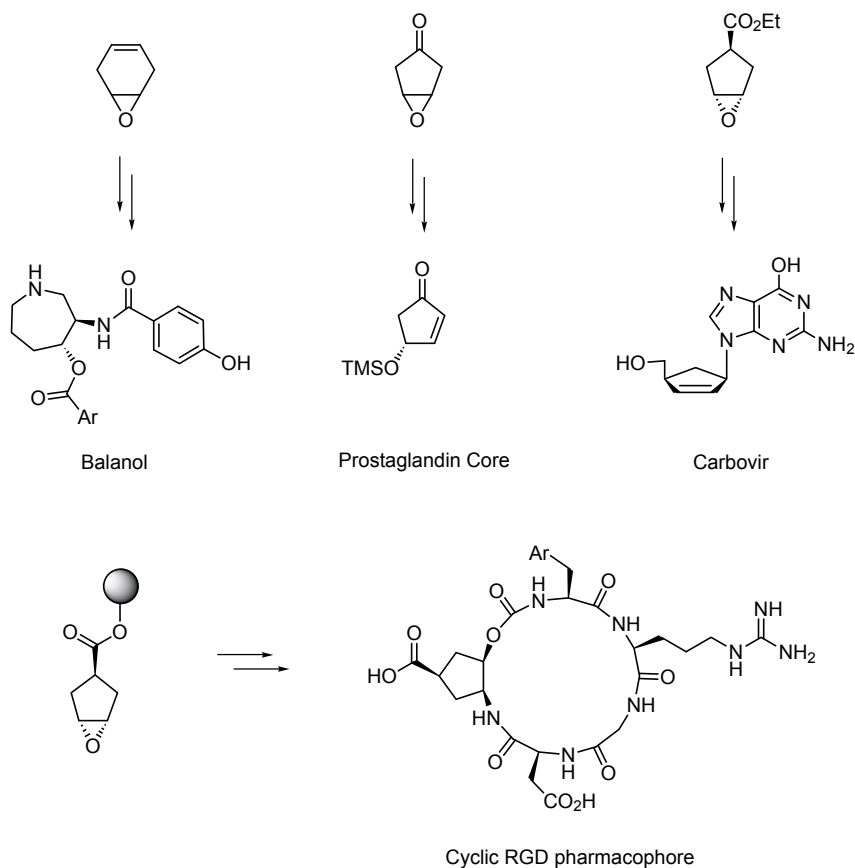
Cycle	Yield (%)	ee (%)
1	84	93
2	92	94
3	93	94
4	95	94
5	91	94
6	95	94
7	95	94
8	94	94
9	95	94
10	95	95
11	92	95

**Fig. 1**

ic Cr center bound to ligands such as THF or cyclopentene oxide. Kinetic analysis of the reaction established a rate law where the reaction rate was proportional to $[\text{Cr}]^2$. This was consistent with epoxide opening occurring through a bimetallic rate- and enantioselectivity-determining step where the Cr-activated

azide is delivered to the coordinated epoxide of another Cr(salen) catalyst (Fig. 1). Additional evidence for a cooperative mechanism was provided by constructing dimeric catalysts such as **3** in which two Cr(salen) units were covalently linked. This led to a dramatic rate enhancement in the ARO with TMSN_3 with similar levels of enantioselectivity to those obtained with monomeric catalyst **2** [10].

The Cr(salen)-catalyzed ARO could be applied to prepare a range of chiral building blocks useful for the synthesis of biologically important compounds. Practical routes to cyclic *cis*- and *trans*-1,2-amino alcohols have been developed using Cr(salen) catalysis [11]. ARO methodology also enabled the enantioselective synthesis of the core structures of balanol [12], prostaglandin derivatives [13], and a series of carbocyclic nucleoside analogs such as aristeromycin and carbovir (Scheme 3) [14]. The enantioselective addition of TMSN_3 to polymer-immobilized epoxides catalyzed by **1** also allowed the facile construction of cyclic RGD peptide derivatives on a solid phase [15].



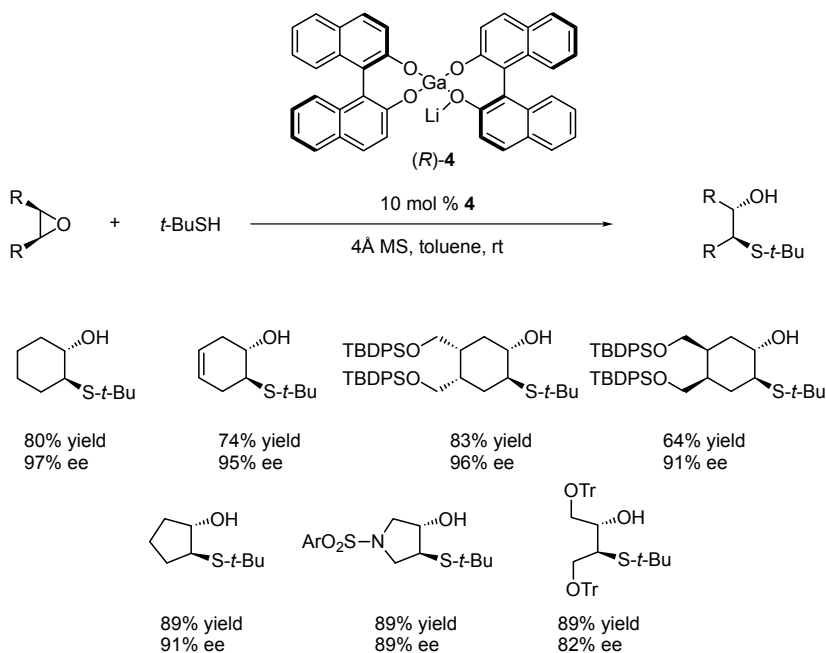
Scheme 3

2.2 Sulfur Nucleophiles

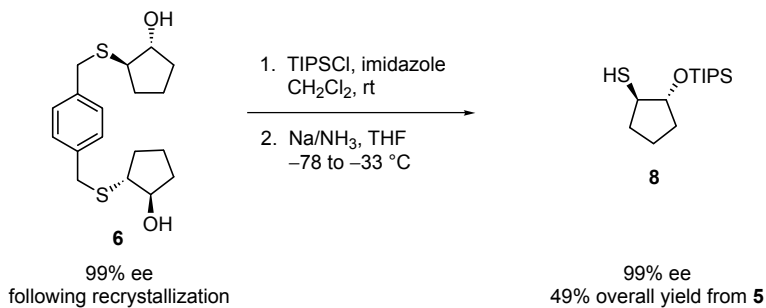
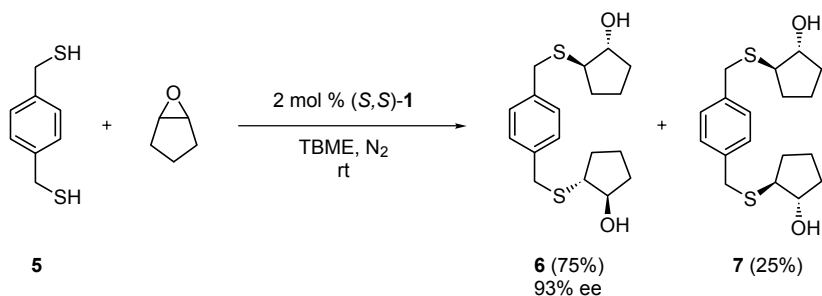
A breakthrough in the ARO with sulfur nucleophiles was made by Shibasaki, who discovered that the Ga-Li-bis(binaphthoxide) complex **4** catalyzed the addition of *tert*-butyl thiol to cyclic and acyclic epoxides in 82–97% ee (Scheme 4) [16]. Ten mol % of the heterobimetallic catalyst promoted the ring opening of a wide range of substrates, and the *tert*-butyl thiol adducts could be converted to enantio-enriched allylic alcohols through an oxidation/elimination sequence.

The addition of other sulfur nucleophiles was reported by Jacobsen to be catalyzed by the same Cr(salen) complex **1** initially reported for the ARO with TMSN₃. Benzyl mercaptan afforded the ring-opened hydroxy sulfides in excellent yield and 59–70% ee [17]. The moderate levels of enantioselectivity were improved by use of the dithiol **5**, which afforded mixtures of bishydroxy sulfides in which the ee of the chiral product **6** was substantially enriched (Scheme 5). The sulfide products could be easily elaborated into the free thiols by reductive debenylation, providing access to the β -silyloxy thiol **8** in optically pure form.

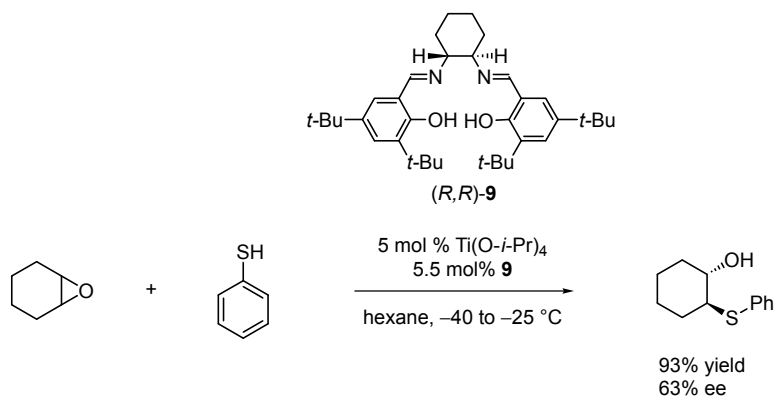
A titanium (IV) complex with the identical (salen) ligand was reported recently to effect the addition of thiophenol with moderate enantioselectivity [18]. The complex was formed *in situ* from 5 mol % Ti(O-*i*-Pr)₄ and 5.5 mol % of the chiral ligand **9**, and this catalyst promoted the ring opening of cyclohexene oxide in 93% yield and 63% ee at –40 to –25 °C (Scheme 6).



Scheme 4



Scheme 5



Scheme 6

2.3

Oxygen Nucleophiles

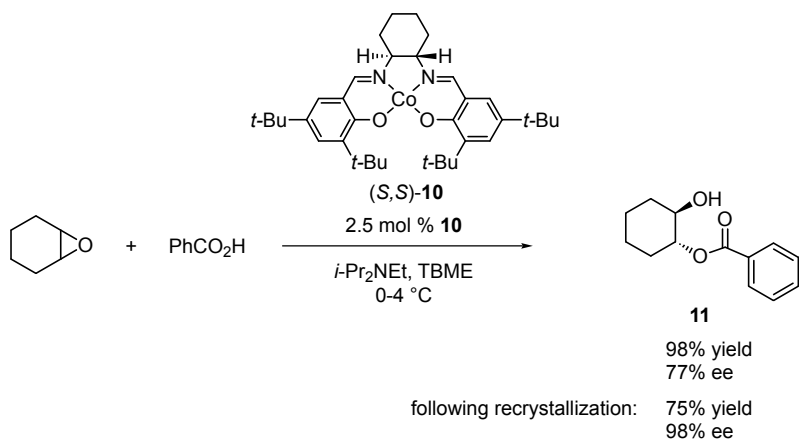
The reaction of oxygen-containing nucleophiles including alcohols, phenols, and carboxylic acids allows the generation of a 1,2-diol equivalent in which the oxygen atoms are differentially protected. Given the synthetic utility of 1,2-diols

[19], the ability to selectively functionalize either oxygen atom would render these ARO products even more versatile.

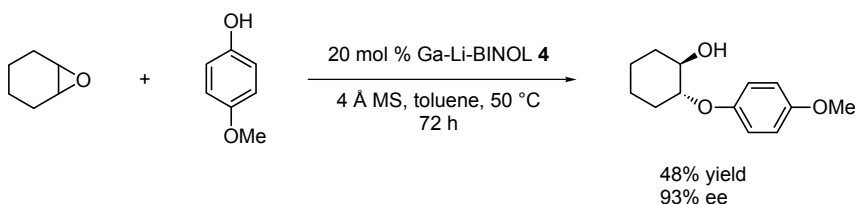
Jacobsen reported that the Co(salen) complex **10** catalyzed the addition of carboxylic acids to *meso*-epoxides [20]. An initial screen revealed that benzoic acid and its derivatives were the most useful nucleophiles from the perspective of reactivity and selectivity. Although optical purities exceeding 90% ee were observed only with selected substrates, the crystallinity of the benzoate esters in some cases allowed enhancement of their enantiopurity by recrystallization. The ring opening of cyclohexene oxide, for instance, proceeded on a multigram scale in quantitative yield and 77% ee; subsequent recrystallizations of the monobenzoate ester **11** then afforded 98% ee material isolated in 75% yield (Scheme 7).

The Ga-Li-BINOL complex **4** was discovered by Shibasaki to catalyze the ring opening of epoxides with 4-methoxyphenol. Elevated temperatures and high catalyst loadings render this catalyst system less practical than the *tert*-butyl thiol counterpart, but the hydroxy aryl monoethers produced in this reaction do offer access to valuable monoprotected 1,2-*trans*-diols (Scheme 8) [21].

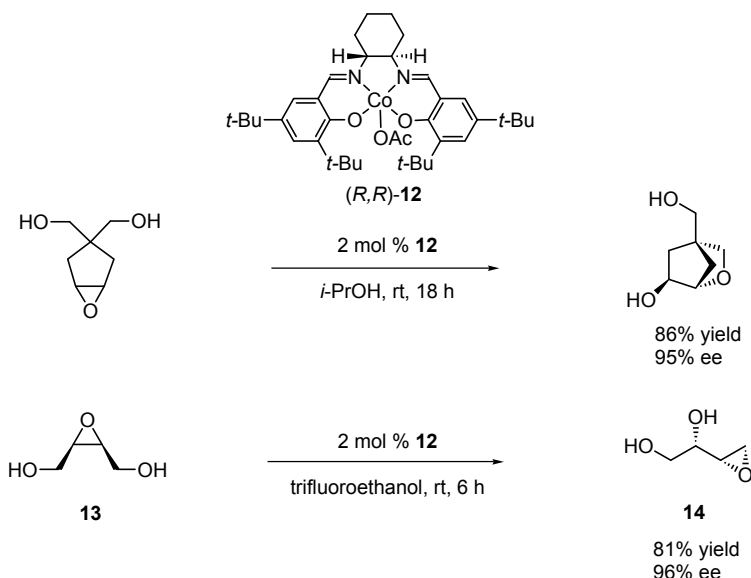
An intramolecular ring-opening reaction with oxygen nucleophiles was discovered by Jacobsen to be catalyzed by the Co(salen)OAc catalyst **12** [22]. The



Scheme 7



Scheme 8



Scheme 9

cyclization of *meso*-epoxy diols produced novel cyclic and bicyclic products in good yields and >95% ee. Complex **12** also catalyzed an asymmetric Payne rearrangement of the *meso*-epoxy diol **13** to afford the enantio-enriched C₄ building block **14** in 81% yield and 96% ee (Scheme 9).

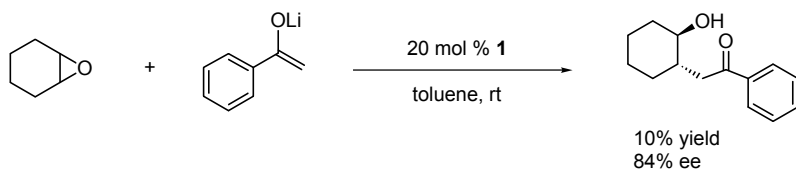
2.4

Carbon Nucleophiles

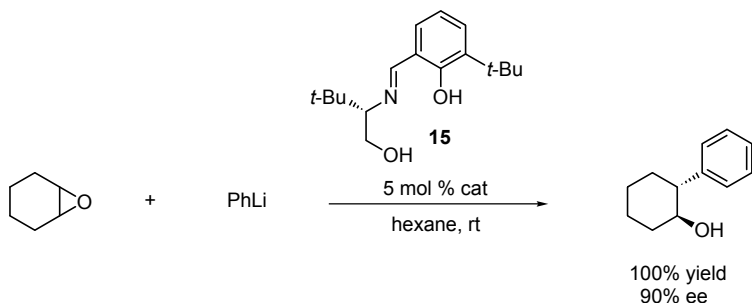
A difficult challenge in developing ARO reactions with carbon nucleophiles is identifying a reagent that is sufficiently reactive to open epoxides but at the same time innocuous to chiral metal catalysts. A recent contribution by Crotti clearly illustrates this delicate reactivity balance. The lithium enolate of acetophenone added in the presence of 20 mol % of the chiral Cr(salen) complex **1** to cyclohexene oxide in very low yield but in 84% ee (Scheme 10) [23]. That less than one turnover of the catalyst was observed strongly suggests that the lithium enolate and the Schiff base catalyst are not compatible under the reaction conditions.

Oguni discovered that phenyllithium in the presence of 5 mol % of chiral Schiff base ligands created a stable and efficient catalyst system. The addition to cyclohexene oxide occurred in quantitative yield to form the phenylcyclohexanol in 90% ee (Scheme 11) [24]. Oguni proposed that deprotonation of the phenol and/or 1,2-addition to the imine ligand **15** formed the catalytically-active species.

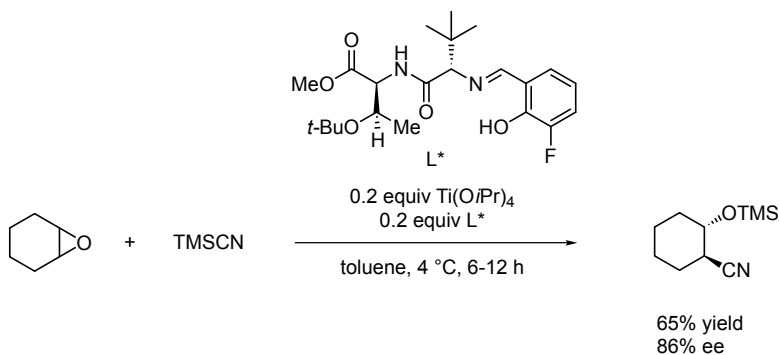
Cyanide stands as an appealing candidate for ARO reactions, given its stability toward a variety of metal-ligand complexes, its reactivity toward epoxides



Scheme 10



Scheme 11



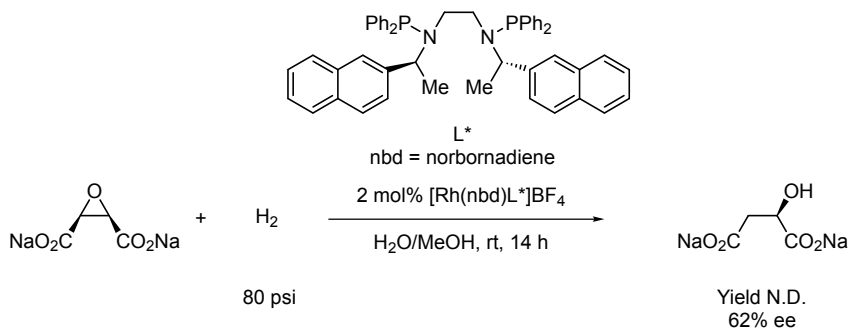
Scheme 12

under catalytic conditions, and the synthetic utility of the ring-opened products. The Ti(O-*i*-Pr)₄-catalyzed addition of TMSCN was discovered by Oguni to be dramatically accelerated by achiral tridentate Schiff base ligands [25]. Snapper and Hoveyda subsequently developed an asymmetric version of this reaction using chiral amino alcohol backbones. In addition, this work demonstrated the solid phase assembly of ligands for the rapid synthesis of potential catalysts (Scheme 12) [26].

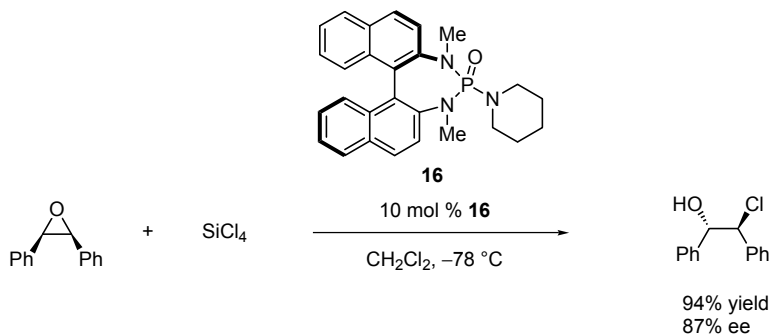
2.5 Hydrogen and Halogen Nucleophiles

The asymmetric reduction of *meso*-epoxides with hydrogen or hydrides has been scarcely explored, despite the synthetic utility of the chiral secondary alcohol products. The lone example has been provided by Chan, who treated the disodium salt of epoxysuccinic acid with H₂ or MeOH as the reducing agent in the presence of a chiral rhodium catalyst (Scheme 13) [27]. Deuterium labeling experiments established that the reduction proceeded through direct cleavage of the epoxide C-O bond, rather than isomerization to the ketone followed by carbonyl reduction.

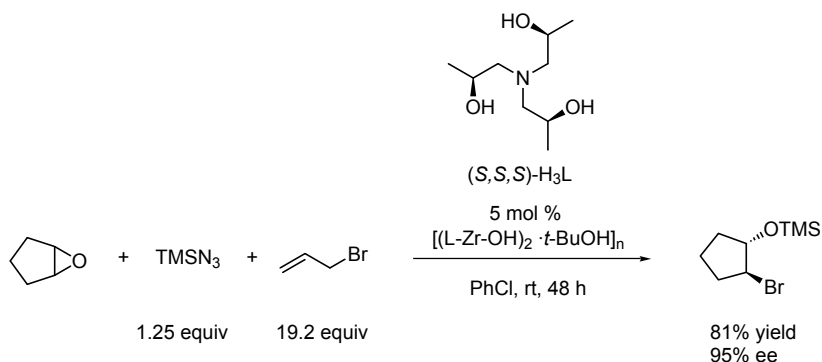
Desymmetrization with halogen nucleophiles was effectively demonstrated with two mechanistically-divergent chiral catalysts. Denmark disclosed a Lewis-base activated delivery of chloride that was catalyzed by the enantiopure phosphoramidate **16**. Binding of the phosphoramidate was believed to induce dissociation of SiCl₄ into the chiral phosphorus/silicon cation and chloride anion, which subsequently ring-opened the activated epoxide. The best enantioselectivity was observed with *cis*-stilbene oxide, which was formed in 94% yield and 87% ee (Scheme 14) [28].



Scheme 13



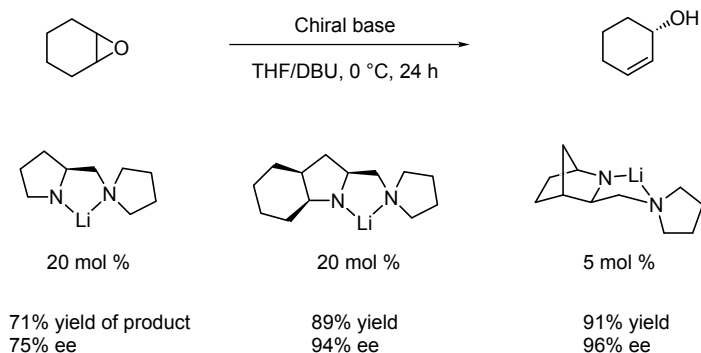
Scheme 14

**Scheme 15**

Nugent adapted the zirconium trialkanolamine complex developed for the enantioselective addition of TMSN_3 (Scheme 1) to catalyze the addition of bromide, where substitution of bromide for azide at the metal center was proposed to account for the epoxide halogenation product (Scheme 15) [29]. When a large excess of the bromide source was used to suppress azido alcohol formation, a wide range of cyclic epoxides reacted with 5 mol % of the catalyst to afford good yields of the bromohydrins in 84–96% ee.

2.6 Enantioselective Deprotonation

While several stoichiometric chiral lithium amide bases effect the rearrangement of *meso*-epoxides to allylic alcohols [1], few examples using catalytic amounts of base have been reported. Asami applied a proline-derived ligand to the enantioselective deprotonation of cyclohexene oxide to afford 2-cyclohexen-

**Scheme 16**

1-ol in 71% yield and 75% ee [30]. Investigation of a related diamine ligand led to an improvement of product ee to 94% [31], but the lack of substrate generality and the limited availability of both enantiomers of the catalyst restrict its application (Scheme 16). A bicyclic variant was discovered by Andersson to display slightly broader substrate scope, as catalytic amounts of this lithium amide base afforded high levels of enantiopurity for cyclohexene and cycloheptene oxide [32]. In addition to accessing high levels of asymmetric induction, this diamine ligand has the additional advantage of being readily prepared as either enantiomer.

3 Kinetic Resolution of Racemic Epoxides

The use of kinetic resolution as a strategy in asymmetric synthesis has been reviewed extensively [33, 34]. The availability of epoxides in racemic form and the lack of effective enantioselective methods for preparing several important epoxide structural classes renders kinetic resolution by ARO a potentially powerful tool. For kinetic resolutions in which recovery of unreacted substrate is targeted, a cheap and easily handled reagent is desirable for effecting the resolution. Ideally, the ring-opened product would be of synthetic value, and each component of the kinetic resolution (unreacted substrate, product, and catalyst) would be easily isolated in pure form.

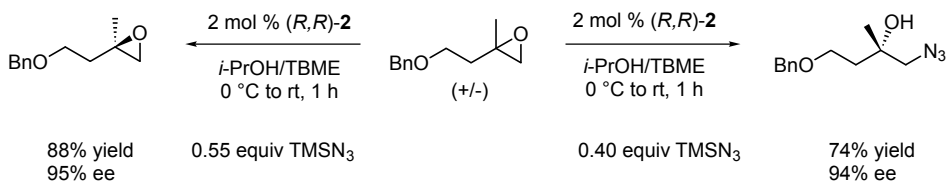
3.1 Kinetic Resolution with TMSN_3

Jacobsen successfully extended the Cr(salen)-catalyzed ARO of *meso*-epoxides with TMSN_3 to the reaction of terminal epoxides, generating valuable 1-amino-2-alkanol precursors [35]. The Cr(salen) complex **1** effectively distinguished between substrate enantiomers with k_{rel} ranging from 44 to 230, reflecting a very high level of chiral recognition by this catalyst system. Most notable, simple aliphatic substrates such as propylene oxide in which the catalyst must differentiate between only a hydrogen and a methyl group were efficiently resolved (Table 2).

The Cr(salen) catalyst was shown to catalyze the resolution of 2,2-disubstituted epoxides, in which a methylene and a methyl group were distinguished by the chiral catalyst. The ARO of this difficult substrate class demonstrated a useful feature of kinetic resolution, in that the enantiopurity of the unreacted epoxide could be improved through higher substrate conversion (Scheme 17). Alternatively, allowing the reaction to proceed to only 40% conversion allowed production of the tertiary alcohol in 74% yield and 94% ee [36, 37, 38].

Table 2. Kinetic resolution of terminal epoxides with TMSN_3 catalyzed by **1**

R	ee (%)	Yield (%) ^[a]	K_{rel} ^[b]
CH_3	97	98	230
CH_2CH_3	97	83	140
$(\text{CH}_2)_3\text{CH}_3$	97	89	160
CH_2Cl	95	94	100
$\text{CH}_2\text{C}_6\text{H}_5$	93	94	71
<i>c</i> - C_6H_{11}	97	84	140
$(\text{CH}_2)_2\text{CH}=\text{CH}_2$	98	94	280
$\text{CH}(\text{OEt})_2$	89	96	44
CH_2CN	92	80	45

^[a] Isolated yield based on TMSN_3 ^[b] $k_{\text{rel}} = \ln[1 - c(1 + ee)] / \ln[1 - c(1 - ee)]$ **Scheme 17**

3.2

Hydrolytic Kinetic Resolution

The ideal kinetic resolution would require no external resolving agent, so that through an enantioselective isomerization or polymerization optically pure products are generated. In the absence of these methods [39], the possibility of an inexpensive nucleophile such as water to serve as the resolving agent could provide a very appealing alternative.

Jacobsen disclosed a chiral $\text{Co}(\text{salen})$ catalyst that promoted the hydrolytic kinetic resolution (HKR) of terminal epoxides [40]. Remarkably low levels of the $\text{Co}(\text{salen})\text{OAc}$ complex **12** effected enantioselective epoxide hydrolysis to afford mixtures of the unreacted epoxide and the ring-opened diol. Controlling the amount of water in the HKR allowed either of these chiral products to be generated in high enantiopurity (Tables 3 and 4) [41]. Significant differences in vola-

Table 3. Hydrolytic kinetic resolution catalyzed by **12** to produce terminal epoxides in $\geq 99\%$ ee

$\text{R-epoxide} + \text{H}_2\text{O} \xrightarrow[0\text{ }^\circ\text{C to rt}]{0.5-2.0\text{ mol \% (R,R)-12}}$

(+/-) 0.55 equiv $\geq 99\%$ ee

R	Catalyst (mol %)	Solvent	Time (h)	Yield (%) ^[a]
CH ₃	0.2	–	18	92
(CH ₂) ₃ CH ₃	0.5	–	18	86
CH ₂ Ph	0.5	THF	18	92
<i>c</i> -C ₆ H ₁₁	0.5	THF	18	87
<i>t</i> -Bu	2.0	1,2-hexanediol	48	82
CH ₂ Cl	0.5	THF	18	83
CF ₃	0.5	–	18	75
CH ₂ CO ₂ Et	0.5	THF	18	92
CH ₂ NHBoc	2.0	THF	38	72
CO ₂ Me	2.0	THF	24	86
COMe	2.0	THF	24	80
CH ₂ OBn	0.5	THF	18	96
<i>m</i> -Cl-C ₆ H ₄	0.8	THF	48	80

^[a]Yield based on a maximum theoretical yield of 50%**Table 4.** Hydrolytic kinetic resolution catalyzed by **12** to produce 1,2-diols

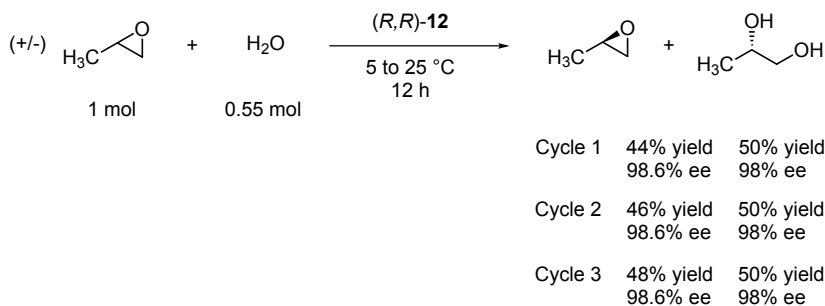
$\text{R-epoxide} + \text{H}_2\text{O} \xrightarrow[0\text{ }^\circ\text{C to rt}]{0.5-2.0\text{ mol \% (R,R)-12}}$

(+/-) 0.45 equiv ee (%) Yield (%)^[a]

R	Catalyst (mol %)	Solvent	ee (%)	Yield (%) ^[a]
CH ₃	0.2	–	99	89
(CH ₂) ₃ CH ₃	0.2	–	99	90
CH ₂ Ph	0.5	THF	95	81
<i>c</i> -C ₆ H ₁₁	0.5	THF	99	82
<i>t</i> -Bu	2.0	1,2-hexanediol	95	80
CH ₂ Cl	2.0	THF	96	100
CF ₃	0.5	–	99	82
CH ₂ CO ₂ Et	0.5	THF	96	80
OTBS	0.5	THF	98	83

^[a]Yield based on a maximum theoretical yield of 50%

tility between the product diol and the epoxide, meanwhile, facilitated the purification of each component through fractional distillation.

**Scheme 18**

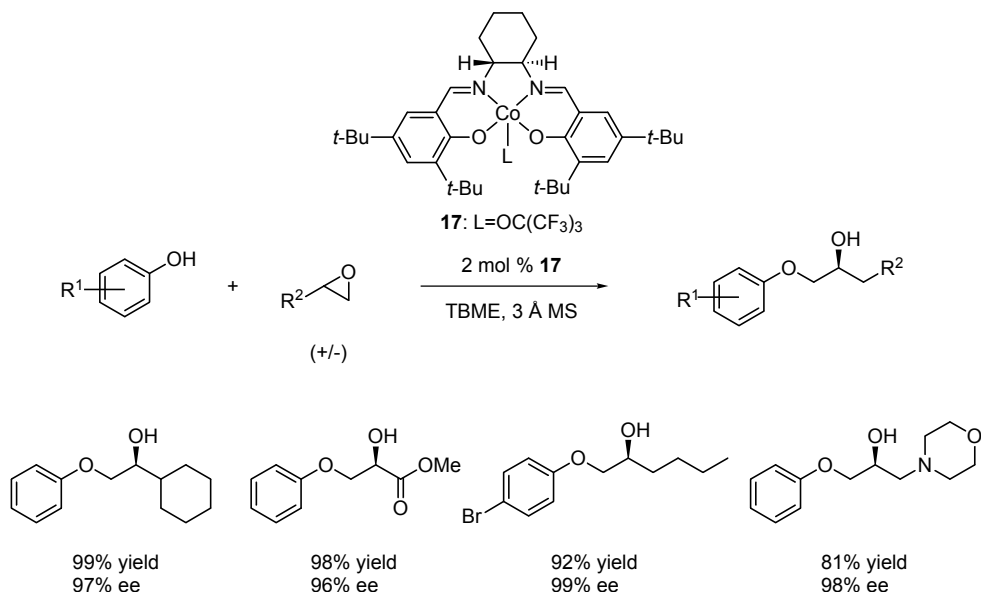
The Co(salen) catalyst is remarkably insensitive to the steric properties of terminal epoxide substrates, as substituents ranging from methyl to cyclohexyl to *tert*-butyl groups are accommodated in the kinetic resolution. Propylene oxide presented an impressive illustration of catalyst enantiocontrol, where a k_{rel} exceeding 400 was estimated for this substrate. This epoxide served to further emphasize the synthetic utility of this process, as the HKR of 1 mole of propylene oxide proceeded efficiently with catalyst that had been recycled from previous kinetic resolutions (Scheme 18). The HKR of propylene oxide has also been effected on a multi-hundred kilogram scale in the pilot plant at ChiRex.

The hydrolytic kinetic resolution addressed a long-standing problem in enantioselective epoxide synthesis. The ability to access almost any terminal epoxide or 1,2-diol in high enantiopurity greatly expanded the chiral pool of compounds available for asymmetric synthesis. Equally important was the demonstration of practicality and efficiency that renders the ARO of a racemic mixture a synthetically viable approach.

3.3

Kinetic Resolution with Phenols

While its convenience and low cost seem to make water the ideal oxygen atom source for ARO reactions, the need for mono-protected 1,2-diols prompted the investigation of other oxygen nucleophiles in kinetic resolutions. Jacobsen reported that the Co(salen) complex **17** promoted the enantioselective addition of phenols and substituted phenols to racemic mixtures of terminal epoxides [42]. A wide range of aliphatic epoxides reacted effectively with *ortho*-, *meta*-, or *para*-substituted phenols bearing electron-donating or electron-withdrawing functionality (Scheme 19). This kinetic resolution offered an enantioselective route to β -aryloxy alcohols, which are important intermediates in pharmaceutical applications [43,44]. The dynamic kinetic resolution of epibromohydrin represented a particularly useful transformation, as the ring-opened product could be further elaborated to differentiated aryl glycidyl ethers or aryloxy propanolamines. An immobilized version of catalyst **17** was efficiently prepared that



Scheme 19

enabled the enantioselective synthesis of parallel libraries containing these compounds [45,46].

4

Conclusion

The development of asymmetric ring-opening reactions has given increased priority to the stereoselective reactions of epoxides in asymmetric synthesis. While a range of heteroatom and carbon-based nucleophiles has been explored with varying amounts of success, the list of nucleophiles to be discovered is certainly likely to continue growing. The potential to couple asymmetric ring-opening transformations with asymmetric epoxidation methods by way of diastereo- and regioselective processes on chiral epoxides constitutes another important future challenge in ARO methodology.

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Chapter 36

Polymerization Reactions

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Keywords: Macromolecular stereochemistry, Main-chain chiral polymer, Atropisomeric polymer, Kinetic resolution, Anionic polymerization, Cationic polymerization, Insertion polymerization

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1 Introduction

With the notable exceptions of natural rubber and gutta-percha, almost all naturally occurring polymers are optically active. Historically, interest in optically active synthetic polymers has focused on modeling natural polymers, interpreting the conformational properties of macromolecules in solution, and investi-

gating the mechanism of polymerization reactions [1]. The synthesis of well-defined, optically active model polymers, and the understanding of their chiroptical properties, has made possible the conformational analysis of biopolymers using circular dichroism and optical rotatory dispersion [2, 3]. Isotactic polyolefins containing side-chain chirality often exhibit large, temperature-dependent optical rotations. Such characteristics provide clear experimental evidence that these polymers can maintain in solution the helical conformations that have been shown by X-ray studies to exist in the crystalline state [4, 5]. The stereoselective polymerization of racemic α -olefins has demonstrated that the chirality of the active catalytic site, not the chirality of the growing polymer chain, provides stereochemical control during polymerization using heterogeneous Ziegler-Natta catalysts [6].

Optically active synthetic polymers such as poly(trityl methacrylate) supported on silica gel [7, 8] as well as poly(ethylene glycol dimethacrylate) cross-linked in the presence of an optically active template [9] have found general use as chiral stationary phases for the optical resolution of various racemates by chromatography. A current area of investigation concerns the use of optically active polymers as reagents and catalysts for asymmetric synthesis [10, 11, 12].

Optically active polymers have been shown to exhibit different physical properties than their corresponding racemates [13]. Chiral polymers that exhibit two- or three-dimensional order [14] are valuable in applications that require piezoelectric, ferroelectric, and non-linear optical materials [15, 16]. It has been suggested that optically active polymers bearing photosensitive groups could find potential application as information storage materials, where data is preserved in the form of stereoisomeric structural variations of the polymer [17]. Polymers have several advantages over organic and inorganic materials for such applications since they exhibit mechanical stability, can be easily processed, and often permit a diverse range of functional group variation [16].

Due to the many important applications of optically active polymers, a significant goal is the development of new strategies for the synthesis of these polymers. Nature takes advantage of the ready availability of enantiopure monomers such as amino acids and sugars to construct its optically active polymers; e.g., proteins, nucleic acids and polysaccharides. For synthetic macromolecules, the analogous strategy of polymerizing optically active monomers has enjoyed considerable success, but suffers from the limited availability and/or high expense of enantiomerically enriched monomers. A far more efficient synthesis of chiral polymers is the polymerization of racemic or achiral monomers. For example, racemic monomers can be kinetically resolved using enantiopure polymerization catalysts, and achiral monomers can be enchaind using enantioselective catalysts to give optically active polymers. In the field of polymer chemistry, there is considerable debate concerning the definition of catalysis as it pertains to polymer synthesis. Molecular species that construct only one polymer chain during a chemical reaction are called initiators, while those that make more than one chain are termed catalysts. This distinction between initiation and catalysis exists since the synthesis of an individual polymer chain is emphasized, not the

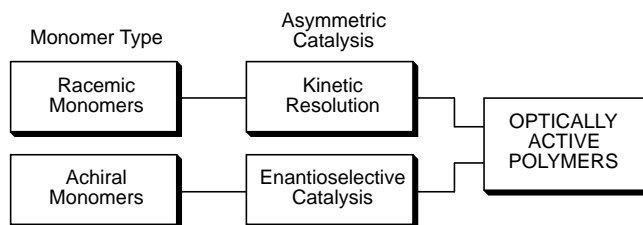


Fig. 1. Catalytic methods for the synthesis of optically active polymers from racemic and achiral monomers

addition of a monomer unit to the chain end. In contrast, if the repetitive process of monomer enchainment is the focus, then all molecular agents that produce polymer chains can be considered catalysts. The focus of this review is developments in the field of enantioselective polymerization that have occurred during the last decade [8, 18]. Therefore, all polymerization methods that involve the use of enantiopure catalysts or initiators for the direct, enantioselective synthesis of polymers from racemic or achiral monomers are reviewed (Fig. 1).

2

Chirality of Linear Macromolecules

The recognition of symmetry elements in stereoregular polymers is often much more difficult than in small molecules [19]. The identification of the symmetry properties of a conformationally flexible macromolecule is most easily carried out on the conformer exhibiting the highest symmetry. This form, most often the planar zig-zag, is conveniently represented as the Fischer projection to facilitate immediate recognition of the relative configuration of adjacent stereocenters (Fig. 2). Exactly opposite to the usual rules, horizontal lines represent bonds extending behind the plane of the paper while vertical lines depict bonds emerging from the paper [20].

Whereas small organic compounds are typically well defined with respect to their constitution, connectivity and stereochemistry, synthetic macromolecules are often inhomogeneous due to a distribution of molecular weights, defects in connectivity, different chain ends, and stereochemical defects. These impurities arise from the nature of the synthetic processes used to make the polymers, where successive steps are carried out without purification of the intermediate chain segments. In addition, it is impossible to separate polymers which differ only in minor details. For the analysis of the stereochemistry of these macromolecules, chemists are forced to use simplified models, where the polymers are assumed to have idealized structures and exist as infinitely long chains. Whereas the chirality of a finite chain can be determined using the normal criteria, an infinitely long chain contains the symmetry properties of a one-dimensional space group and translational symmetry operations must be considered. The two criteria for chirality of an infinitely long chain are (1) the absence of reflection elements of

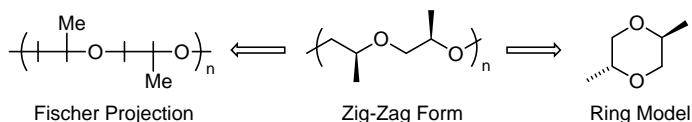


Fig. 2. Models of stereoregular polymers

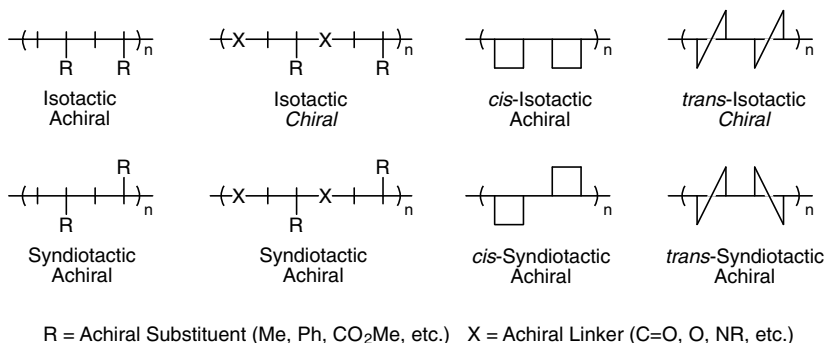


Fig. 3. Common architectures of stereoregular, linear polymers and cyclopolymers

symmetry (mirror planes) and (2) the absence of glide reflection elements (glide-mirror planes) [19].

An alternative method of identifying the chirality of a polymer modeled as an infinite chain is to draw a ring composed of the repeating unit of the polymer. If the ring has a center or plane of symmetry, then the chain is achiral (Fig. 2). For example, it is not intuitively obvious whether the polymer in Fig. 2 is chiral or achiral, but using the ring model its achirality is apparent due to the center of inversion.

The synthesis of chiral polymers from vinyl monomers requires complex architectures in order to circumvent the symmetry constraints of simple homopolymers. This was recognized in the early 1950s by Frisch [21] and Arcus [22] who examined the microstructures of stereoregular homo- and copolymers of achiral olefins. Shown above are Fischer projections for several possible stereochemical arrangements of chiral and achiral stereoregular polymers (Fig. 3). Note that simple vinyl homopolymers are achiral – only if the endgroups are different can an isotactic or syndiotactic polymer be chiral. However, the optical activity of such a polymer sample in the enantiomerically pure form will vanish as the molecular weight approaches infinity due to internal dilution [23, 24]. Such a molecule is described as being cryptochiral, where the model is chiral but the chirality of the polymer itself cannot be experimentally verified [25]. Only the structurally more complex polymers can exhibit chirality. Described in the following are synthetic strategies for the enantioselective synthesis of optically active polymers with these chiral microstructures.

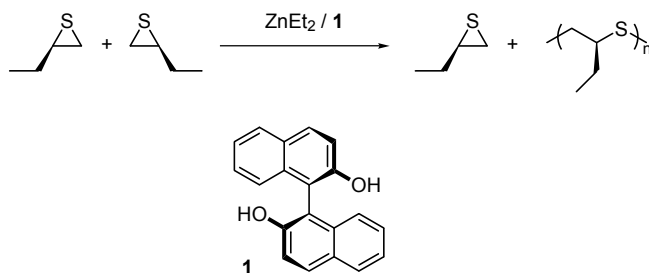
3

Kinetic Resolution Polymerization of Racemic Monomers

A kinetic resolution polymerization [26] (also called 'stereoselective', 'enantioasymmetric' and 'asymmetric-selective' polymerization) is a process where a single stereoisomer of a mixture of monomers is polymerized, giving polymers containing only one configuration of the repeating unit [27]. An example of such a process is when an enantiopure catalyst (C^*) reacts with a racemic monomer (M_S, M_R) such that C^* only reacts with M_S to make optically active poly(M_S), while M_R remains entirely unreacted (or vice-versa). In this ideal scenario, the ratio of the propagation rate constants ($k_S/k_R=R_{S/R}$) approaches infinity. The advantage of this procedure is that optically active polymers can then be synthesized directly from easily obtained racemic monomers. In addition, the remaining monomer, which has been resolved from the racemic mixture, can be used as a reagent for asymmetric synthesis. The disadvantage is that precious few catalytic systems (with the notable exception of biological systems) exhibit the ideal selectivity of the example described. As a result, the optical purity of the polymer formed is dependent on the degree of monomer conversion. Research in the area of kinetic resolution polymerization has focused on the polymerization of epoxides, episulfides, lactones, and olefins. Kinetic resolution in ring-opening polymerization has recently been reviewed [28, 29]. In general the selectivities have been poor, with the remaining monomer at half-conversion typically having an enantiomeric excess (*ee*) of less than 50% ($R_{S/R}<5$). Notable exceptions have recently been reported, though.

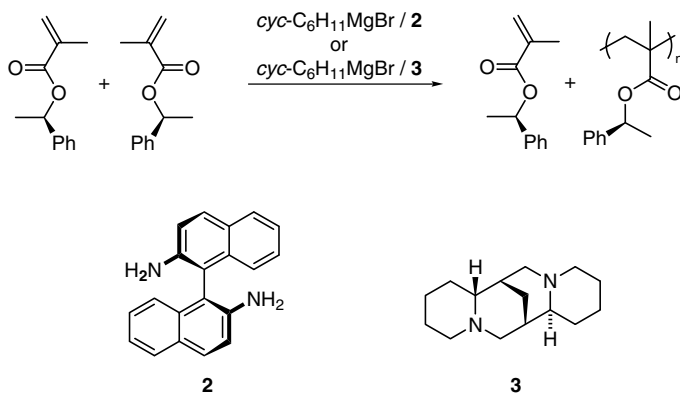
Sépulchre has reported the use of an easily prepared zinc-binaphthol (**1**) complex which gives a high degree of stereoselectivity in the polymerization of episulfides. In the polymerization of *rac*-ethylthiirane, the *ee* of the unreacted monomer is 66% at 46% conversion ($R_{S/R}=15$) (Scheme 1) [30]. Spassky and Sepulchre have previously reported the use of this compound for the highly selective polymerization of *rac*-methylthiirane, where at 50% conversion, the optical purity of the unreacted monomer is 80% ($R_{S/R}=20$) [31].

Suda has reported the polymerization of *rac*- α -methylbenzyl methacrylate by a Grignard/binaphthyl diamine (**2**) initiator where the unreacted monomer at

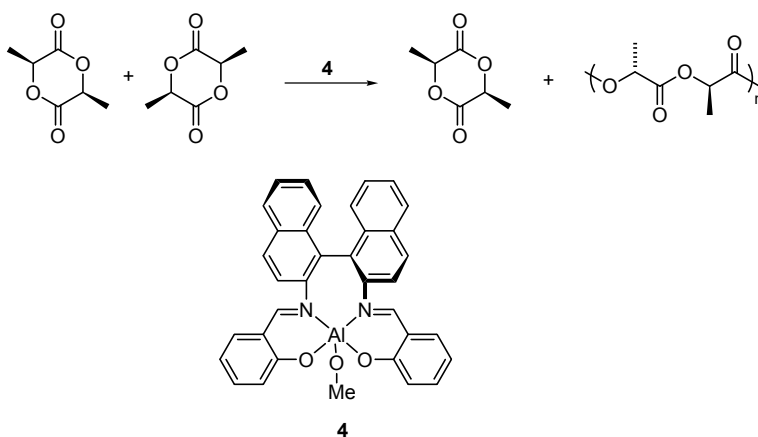
**Scheme 1**

57% conversion is 86% ee ($R_{S/R}=11$) (Scheme 2) [32]. Okamoto has previously shown that Grignard/(-)-sparteine (**3**) complexes can be used to resolve this monomer with slightly higher selectivity (monomer 94% ee at 77% conversion ($R_{S/R}=15$)) [33].

Recently, Spassky has demonstrated that the chiral Schiff base complex **4** is highly selective for the kinetic resolution polymerization of *rac*-lactide [34]. At 50% conversion, the residual monomer is approximately 80% ee ($R_{R/S}=20$) (Scheme 3). In addition, the poly(lactides) exhibit narrow molecular weight distributions, consistent with the absence of significant transesterification.



Scheme 2



Scheme 3

4 Enantioselective Polymerization of Achiral Monomers

4.1 Atropisomeric Polymers

It is well known that isotactic polyolefins often exist as equimolar mixtures of right- and left-handed helices in the crystalline state [19, 35]. Upon dissolution they typically undergo rapid conformational changes due to a lack of rotational barriers [36]. In 1974, Drenth demonstrated that polymers bearing bulky side groups exist as stable helices in solution by resolving poly(*tert*-butyl isocyanide) into optically active fractions [37].

During the two decades after this important discovery, a tremendous amount of research has been directed toward the polymerization of sterically demanding achiral monomers with chiral initiators to create enantiomerically pure helical polymers (also known as ‘helix-sense selective’ or ‘screw-sense-selective polymerization’). These polymers, known as atropisomers, are stable conformational isomers that arise from restricted rotation about the single bonds of their main chains. Key aspects of these reactions are enantiopure initiators that begin the polymerization with a one-handed helical twist, and monomers with bulky side-chains that can maintain the helical conformation due to steric repulsion. Notable examples of this fascinating class of polymers that are configurationally achiral but conformationally chiral include [8, 38, 39] poly(trityl methacrylate), polychloral, polyisocyanates, and polyisocyanides. Important advances in anionic and metal-based enantioselective polymerization methods have been reported in recent years.

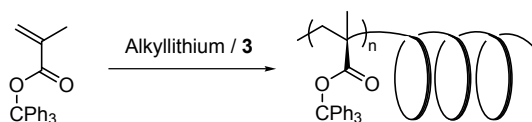
4.1.1 Anionic Polymerization

One of the most studied polymerization systems employs alkyllithium initiators that are modified by chiral amine ligands for the polymerization of sterically bulky methacrylates [8, 38, 39, 40, 41], acrylates [42], crotonates [43], and acrylamides [44]. A primary example is the reaction of triphenylmethyl methacrylate with an initiator derived from 9-fluorenyllithium and (–)-sparteine (**3**) at –78 °C (Scheme 4). The resultant isotactic polymer is optically active, and is postulated to adopt a right-handed helix as it departs from the polymerization site. This polymer has been particularly successful as a chiral stationary phase for the chromatographic resolution of atropisomers [8]. Many modifications of the organolithium initiator/chiral ligand system have been explored. Recently, Okamoto has applied enantiopure radical initiators for the enantioselective polymerization of bulky methacrylate monomers [45].

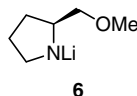
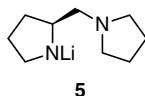
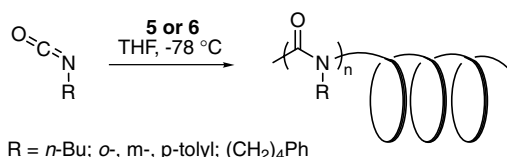
Isocyanates can be polymerized by anionic initiators to give polymers that exhibit a rigid, helical conformation in solution. Elegant studies by Green and coworkers have revealed that the copolymerization of achiral isocyanates with

small amounts (ca. 1%) of enantiopure chiral isocyanates yield polymers exhibiting unexpectedly high optical rotations [46]. Presumably the small amount of chiral side chains is sufficient to organize the dynamic helical polymer to a single screw-sense. Recently, Okamoto has polymerized bulky, achiral aliphatic and aromatic isocyanates using enantiopure lithium alkoxides and amides (**5**, **6**) to produce optically active polymers (Scheme 5) [47, 48, 49]. The optical rotations of polymers produced from a given monomer were found to be highly sensitive to the nature of the initiator used, decreased with increasing polymer molecular weight, and are temperature dependent. Thus it is proposed that the chiral chain end controls the handedness of the helix despite facile intramolecular helical reversals.

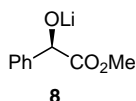
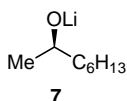
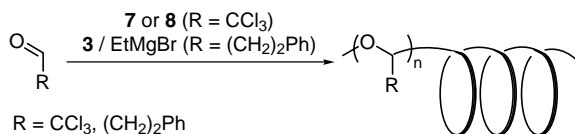
The polymerization of bulky aldehydes such as chloral using enantiopure lithium alkoxides (**7**, **8**) gives insoluble, isotactic polymers that exhibit optical activity in the solid state (Scheme 6) [8, 50, 51]. The solution and solid-state hel-



Scheme 4



Scheme 5



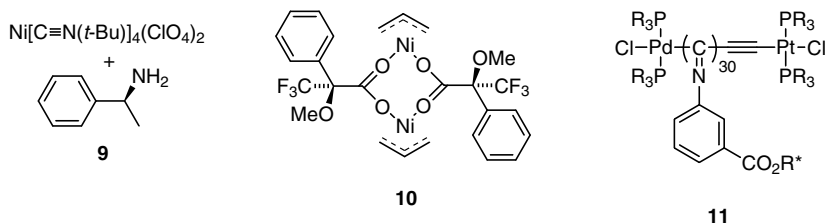
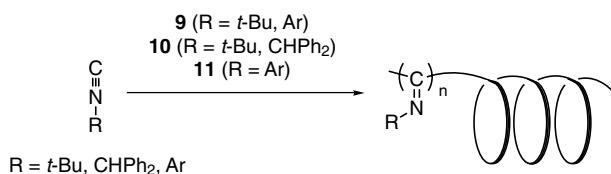
Scheme 6

ical conformation of optically active polychloral oligomers has been recently determined using NMR spectroscopic and crystallographic methods [52, 53, 54]. Okamoto has prepared optically active polymers of 3-phenylpropanal using a (-)-sparteine (3)/Grignard initiator [55]. Analysis of oligomers revealed that the growing chain-end reacts with the monomer in a Tischenko reaction to give an ester terminus.

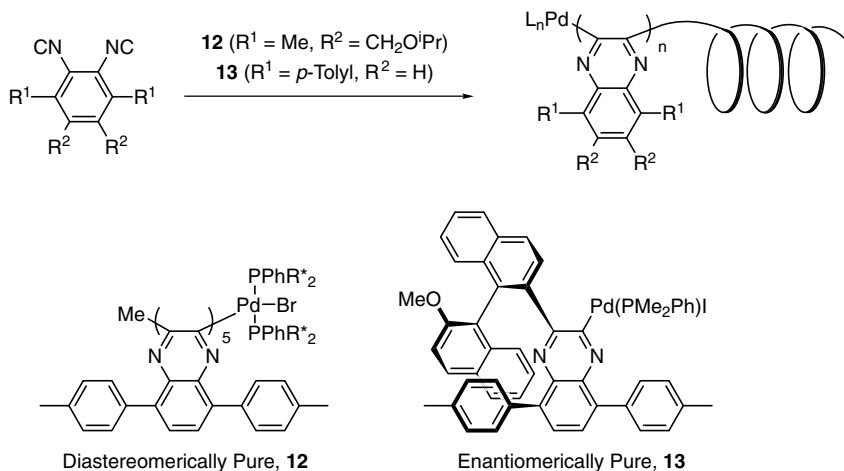
4.1.2

Metal-Catalyzed Polymerization

Poly(isocyanides) typically exhibit stable helical conformations in solution since substituents on each main-chain atom restrict helix isomerization. Nolte and Drenth have combined Ni(II) complexes with optically active amines (9) to form enantioselective catalysts for the polymerization of *tert*-butyl isocyanide and other bulky isocyanides (Scheme 7) [56]. Nickel complexes containing 2-*tert*-butylphenyl isocyanide ligands produced polymers with exceptionally high optical rotation. Novak and Deming discovered a class of nickel carboxylate catalysts (10) for the enantioselective polymerization of *tert*-butyl and diphenylmethyl isocyanide (Scheme 7) [57]. Addition of two equivalents of cyanide increased the enantioselectivity of the polymerization. Takahashi has reported a bimetallic palladium-platinum complex (11) that produces high molecular weight, monodisperse polymers from achiral aromatic isocyanides in high yield (Scheme 7) [58]. When an enantiopure menthyl-substituted monomer is first oligomerized, the resulting single-handed helical oligomer complex can be used as an enantioselective catalyst for the polymerization of achiral isocyanides.



Scheme 7

**Scheme 8**

Ito and coworkers have explored the use of enantiopure organopalladium complexes for the living cyclopolymerization of 1,2-diiisocynoarenes to poly(2,3-quinoxaline)s. Initial studies revealed that oligomers of sterically bulky diisocyanides were conformationally stable, and the diastereomerically pure oligomers could be resolved by chromatography with palladium complexes attached at the chain-end (**12**) [59, 60]. Addition of another diisocyanide monomer to the resolved oligomers yielded polymers with equal but opposite optical rotations upon cleavage of the palladium complex (Scheme 8). More recently, Ito has employed enantiopure, binaphthyl ligated palladium complexes (**13**) for the enantioselective cyclopolymerization of 1,2-diiisocyno-3,6-di-*p*-tolylbenzene (Scheme 8) [61]. X-Ray structural analysis of a pentamer revealed the rigid, right-handed helical nature of the polymer.

4.2

Main-Chain Chiral Polymers

In 1961, Natta reported one of the first examples of enantioselective catalysis using a transition metal catalyst. In this reaction, an optically active polymer was formed from 1,3-pentadiene using a chiral organoaluminum/ VCl_3 catalyst [62]. The optical activity of this polymer results from the main-chain chirality of polymer, where the methyl-substituted stereogenic centers are predominantly of one absolute configuration. Since this initial study, significant advances in the enantioselective synthesis of main-chain chiral polymers have been reported using ionic and metal-based techniques.

4.2.1

Metal-Catalyzed Polymerization

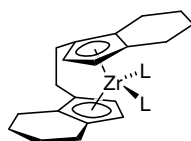
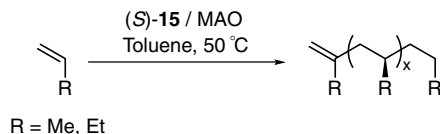
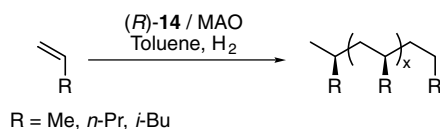
The discovery that group IV metallocenes can be activated by methylaluminoxane (MAO) for olefin polymerization has stimulated a renaissance in Ziegler-Natta catalysis [63]. The subsequent synthesis of well-defined metallocene catalysts has provided the opportunity to study the mechanism of the initiation, propagation, and termination steps of Ziegler-Natta polymerization reactions. Along with the advent of cationic palladium catalysts for the copolymerization of olefins and carbon monoxide [64, 65], these well-defined systems have provided extraordinary opportunities in the field of enantioselective polymerization.

4.2.1.1

Olefin Oligomerization

Isotactic polypropylene chains can be chiral only if their endgroups are different. Enantiomerically pure zirconocene/MAO catalysts have been employed to form isotactic polypropylene; as expected the high polymer in solution was optically inactive [66]. Anticipating that the oligomers from these catalysts should be optically active, Pino used (*R*)-14/MAO for the asymmetric oligomerization of propylene, 1-pentene, and 4-methyl-1-pentene using hydrogen as a chain transfer agent (Scheme 9) [67]. In the case of propylene, approximately 90% of the products ($x < 47$) had a measurable optical activity. The oligomeric alkane fractions were characterized by polarimetry, and their absolute configurations were used to unambiguously determine the enantiofacial preference of the metallocene catalyst for the first time [23]. Fuhrmann has recently used $MgCl_2$ -supported enantiopure titanium complexes for the synthesis of enantiomerically-enriched oligomers of 1-butene in up to 71% ee [68]. The aluminum-terminated oligomers can be hydrolyzed to the alkane, or oxidized to produce alcohols.

By raising the reaction temperature and lowering the olefin concentration, Kaminsky synthesized optically active olefin-terminated oligomers *via* β -hydrogen elimination chain transfer (Scheme 9) [24]. Propylene and 1-butene were oligomerized using (*S*)-15/MAO predominantly to products where $0 < x < 5$. Although these functionalized alkene oligomers are of greater synthetic interest than the related saturated compounds, they are typically formed in lower percent enantiomeric excess (% ee) due to higher reaction temperatures.



(S)-14; L₂ = (*S*)-binaphtholate
 (S)-15; L = *O*-acetyl-(*S*)-mandelate
 (S)-16; L = biphenyl-2,2'-diolate

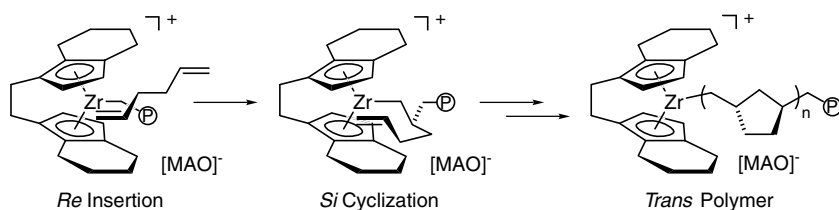
Catalyst	R	x	Temp. (°C)	ee (%)	Reference
(R)-14	Me	1	0	100	[67]
(R)-14	<i>n</i> -Pr	0	25	50	[67]
(R)-14	<i>i</i> -Bu	0	25	84	[67]
(S)-15	Et	1	50	27	[24]

Scheme 9

4.2.1.2

Diolefin Cyclopolymerization

Nonconjugated diolefins can be polymerized in an insertion and cyclization sequence, resulting in a polymer containing rings in the main chain. Whereas vinyl polymers have only two structures of maximum order (isotactic, syndiotactic), cyclopolymers are inherently more complicated. Fig. 3 shows that the *trans*-isotactic microstructure contains no mirror planes of symmetry and is thus chiral by consequence of its main-chain stereochemistry. There are two criteria for chirality of this polymer: (1) isotacticity (the same relative stereochemistry of every other stereocenter); and (2) the presence of *trans* rings. The enantiofacial selectivity of the first olefin insertion determines the tacticity of the cyclopolymer, and the diastereoselectivity of the cyclization step determines whether *cis* or *trans* rings are formed. Using homogeneous Ziegler-Natta catalysts, Coates and Waymouth have studied the effect of the catalyst geometry on the enantioselectivity and diastereoselectivity of ring formation with various α,ω -dienes [69, 70, 71]. Metallocene (*R*)-14/MAO produces an optically-active cyclopolymer of 1,5-hexadiene with $[\Phi]_{405}^{28} = +51.0^\circ$ (Scheme 10). Cyclopolymerization with (*S*)-14 afforded the enantiomeric polymer, $[\Phi]_{405}^{28} = -51.2^\circ$. Microstructural analysis of the polymer by ¹³C-NMR revealed a *trans* ring content of 72% and an enan-



Scheme 10

tiofacial selectivity for olefin insertion of 91%. The high degree of stereoregularity and predominance of *trans* rings are responsible for the optical activity of the polymer. Okamoto has recently carried out similar reactions using chromatographically resolved **16** (and the analogous hafnocene complex) and obtained comparable results [72, 73].

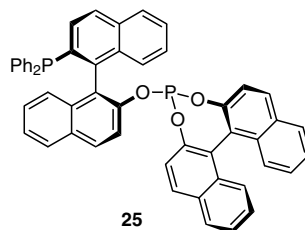
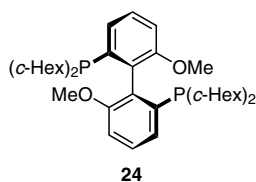
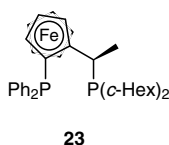
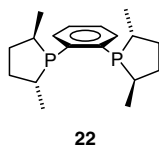
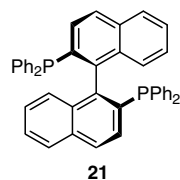
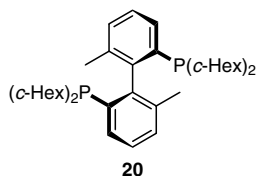
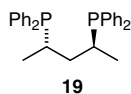
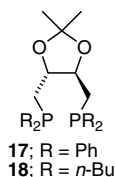
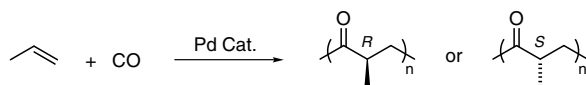
4.2.1.3

Alternating Copolymerization of Olefins and Carbon Monoxide

The synthesis of alternating copolymers from carbon monoxide (CO) and olefins using palladium catalysts is currently an area of intense research. In cases where α -olefins are used, the regiochemistry (head/tail orientations) and stereochemistry (tacticity) of olefin insertion have a strong influence on the physical and mechanical properties of the polymers. Unlike regioregular α -olefins homopolymers, these copolymers have a directionality along the polymer backbone due to the incorporation of CO. Therefore isotactic, regioregular CO/ α -olefin polymers are chiral by virtue of their main-chain stereochemistry (Scheme 11).

In the early 1980s, it was discovered that cationic palladium catalysts with bidentate tertiary phosphines exhibited remarkable reaction rates for olefin/CO copolymerization [64, 65]. Although initial studies using bidentate arylphosphines produced CO/propylene polymers with poor regioregularity, it was later revealed that bidentate alkylphosphines and/or chiral phosphines produced polymers with a much higher degree of regioregularity. In the early 1990s, the first reports concerning the use of enantiopure, C_2 -symmetrical ligated catalysts for the enantioselective copolymerization of α -olefins and CO began to appear.

In a 1990 patent, Wong briefly noted that palladium-based catalysts form optically-active propylene/CO copolymers when the enantiopure C_2 -symmetrical phosphine ligands **17** and **18** are employed [74]. In 1992, Consiglio and coworkers published several papers concerning the use of enantiopure bidentate phosphine ligands in CO/propylene copolymerization [75, 76, 77]. The copolymers formed using ligands **19** and **20** were highly regioregular, and because of the simplicity of the ^{13}C -NMR spectra it was proposed that the polymers were isotactic. Proof of the isotactic microstructure (using ligand **20**) came when a circular dichroism spectrum of the copolymer revealed an intense band in the n - π^*



Catalyst ^a	Yield (g _{poly} /g _{Pd} ⁻¹)	Comment	Reference
17/A	93	$[\alpha]_D^{25} = +6.6^\circ$ (HFIP)	[74]
18/A	703	$[\alpha]_D^{25} = +10.4^\circ$ (HFIP)	[74]
20/A	NR ^b	Highly regioregular; $\Delta\epsilon = -1.56 \text{ L mol}^{-1} \text{ cm}^{-1}$; $[\alpha]_D^{20} = +26^\circ$; $T_m = 245^\circ \text{ C}$	[77, 78]
17/B	500	78% H-T linkages; $[\alpha]_D^{20} = -7^\circ$ (CH ₂ Cl ₂)	[80]
19/B	630	76% H-T linkages; $[\alpha]_D^{20} = -29^\circ$ (CH ₂ Cl ₂)	[80]
21/B	300	66% H-T linkages; $[\alpha]_D^{20} = +36^\circ$ (CH ₂ Cl ₂)	[80]
22/B	1462	$M_n = 36,000$; $[\alpha]_D^{25} = -30^\circ$ (HFIP); $[\alpha]_D^{25} = +70^\circ$ (CHCl ₃)	[84]
23/A	2975	$M_n = 6300$; 99% H-T linkages; $\Delta\epsilon = +1.84 \text{ L mol}^{-1} \text{ cm}^{-1}$	[85]
24/A	391	$M_n = 6900$; 100% H-T linkages; $\Delta\epsilon = +1.73 \text{ L mol}^{-1} \text{ cm}^{-1}$; $[\alpha]_D^{25} = -29.1^\circ$ (HFIP); $T_m = 237^\circ \text{ C}$	[86, 83]
25/C	284	$M_n = 65,000$; 100% H-T linkages; $[\alpha]_D^{24} = +57.2^\circ$ (HFIP); $T_m = 164^\circ \text{ C}$	[82]

^a A = Pd(OAc)₂, Ni(ClO₄)₂, naphthoquinine; B = [Pd(MeCN)₂](BF₄)₂; C = Pd(1,5-cyclooctadiene)(Cl)(Me), Na[B(3,5-(CF₃)₂C₆H₃)₄].

^b Not reported.

Scheme 11

region (275 nm; $\Delta\epsilon = -1.56 \text{ L mol}^{-1} \text{ cm}^{-1}$) [77]. It was later shown that this polymer exhibits a specific optical rotation of $[\alpha]_D^{20} = +26^\circ$ [78]. Such chiroptical properties are only possible with an isotactic microstructure, where an excess of propylene units are enchainned with the same absolute configuration. Interest-

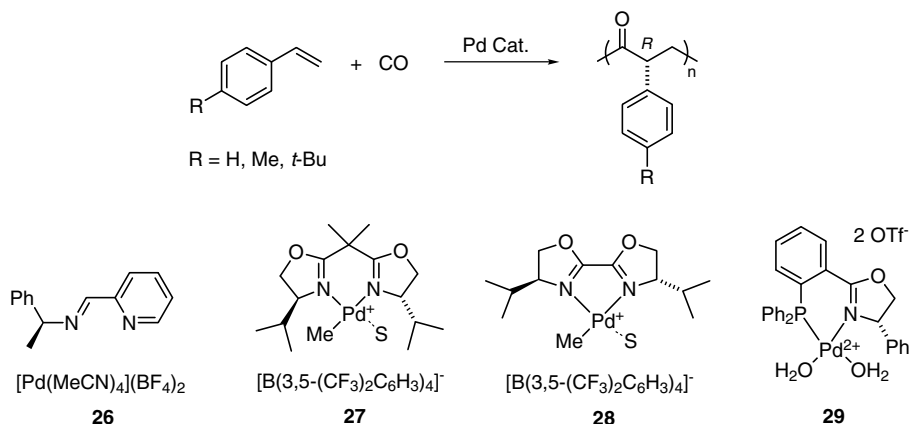
ingly, this polymer is isolated from the reaction in the spiroketal form, but is converted to the polyketone by dissolution in hexafluoroisopropanol (HFIP) followed by precipitation with methanol [79].

Sen and coworkers have synthesized optically active propylene/CO copolymers using more traditional chiral phosphines (17, 19, 21) [80]. Chien had previously carried out related polymerizations using 17 and 21 as ligands, but no chiroptical properties were reported [81]. Sen demonstrated that catalysts with ligands 17, 19, and 21 gave moderately regioregular polymers with 66–78% head-to-tail linkages. The polymer formed using the atropisomeric binaphthyl ligand exhibited the highest optical rotation, although an enantioselectivity of the reaction was not reported.

In 1995, several new catalysts were reported to exhibit very high degrees of regioselectivity, stereoselectivity, and enantioselectivity for the synthesis of propylene/CO copolymers. From these studies, there is now good evidence that the regiochemistry results from a primary insertion of propylene into the Pd-acyl bond [78, 82]. There is agreement concerning the absolute configuration of these polymers. Based on the sign of the CD band [83] and from the isolation of oligomers of known absolute configuration [82], the copolymer that is dextrorotatory in HFIP is assigned the *S*-configuration. Note that the same polymer is *levorotatory* in chlorinated solvents [84]. Therefore it is difficult to measure and compare degrees of enantioselectivity since the specific optical rotations of these polyketones are also extremely sensitive to the sample concentration, temperature, and the molecular weight of the polymer [84]. In addition, chiroptical values for the pure polymers are unknown. Nevertheless, it is clear that these catalysts exhibit excellent selectivities. Sen has reported a highly enantioselective copolymerization using a Duphos-ligated (22) catalyst [84]. By measuring the ^{13}C -NMR spectrum of the copolymer in the presence of chiral shift reagents, an enantioselectivity of greater than 90% was determined. Consiglio has exploited ferrocene-based mixed aliphatic/aromatic phosphines (23) to produce optically-active copolymers with a purported enantioface selectivity of 97% [85]. Aliphatic phosphine 24 can be used to produce polymers where the % ee of olefin insertion is as high as 98% [83, 86]. Takaya has used a phosphine-phosphite bidentate ligand (25) to produce a copolymer with the highest reported specific optical rotation in HFIP ($[\alpha]_{\text{D}}^{24} = +57.2^\circ$) [82].

In addition to propylene, other nonconjugated olefins have been copolymerized with CO using enantiopure palladium catalysts. Allylbenzene, 1-butene, 1-heptene, 4-methyl-1-pentene, and *cis*-2-butene [84, 85] as well as hydroxy- and carboxylic acid-functionalized monomers [87] have been polymerized to give optically active polymers. Waymouth, Takaya and Nozaki have recently reported the enantioselective cyclocopolymerization of 1,5-hexadiene and CO [88, 89].

The enantioselective copolymerization of styrenes and CO has also been achieved (Scheme 12). Using bidentate pyridine-imine ligands (26), Sen synthesized optically active styrene and 4-methylstyrene copolymers [80]. Based on a microstructural analysis, a 36% ee for olefin insertion was reported. Brookhart employed a C_2 -symmetrical bisoxazoline complex (27) to produce styrene-based



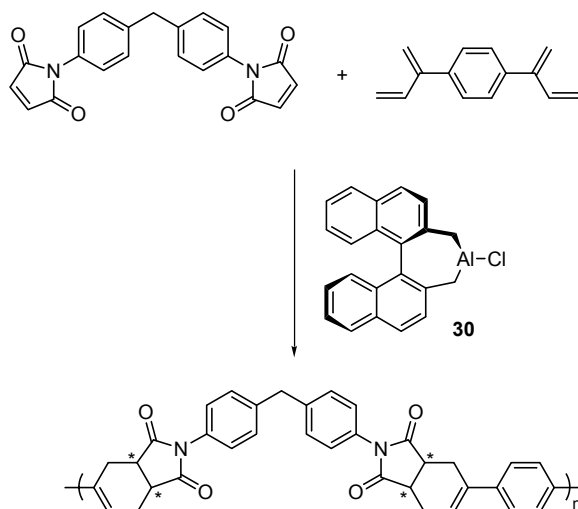
Catalyst ^a	R	Yield (g _{poly} g _{Pd} ⁻¹)	Comment	Reference
26/A	H	NR ^b	$[\alpha]_D^{20} = -16^\circ$ (CH ₂ Cl ₂); M _n =5,600	[80]
26/A	Me	NR	$[\alpha]_D^{20} = -14^\circ$ (CH ₂ Cl ₂); M _n =14,000	[80]
27	<i>t</i> -Bu	179	$[\alpha]_D^{25} = -284^\circ$ (CH ₂ Cl ₂); M _n =26,000	[90]
28	H	13	$[\alpha]_D^{25} = -348^\circ$ (Cl ₂ HCCHCl ₂)	[92]
28	Me	66	$[\alpha]_D^{25} = -350^\circ$ (CH ₂ Cl ₂)	[92]
29	H	NR	$[\alpha]_D^{25} = -403^\circ$ (HFIP/CHCl ₃)	[93]
25/B	<i>t</i> -Bu	192	$[\alpha]_D^{23} = -261^\circ$ (CH ₂ Cl ₂); M _n =4,300	[82]

^a A = [Pd(MeCN)₂](BF₄)₂; B = Pd(1,5-cyclooctadiene)(Cl)(Me), Na[B(3,5-(CF₃)₂C₆H₃)₄].

^b Not reported

Scheme 12

copolymers that exhibited extremely high specific optical rotations [90]. After consideration of previous mechanistic studies and molecular models, it was proposed that propagation occurred by a 2,1-insertion mechanism to give an *R*-stereocenter. Brookhart has also devised a clever ancillary ligand exchange, where the chiral bisoxazoline ligand is replaced with an achiral bipyridine ligand during chain formation to create an optically active stereoblock polymer [91]. Musco [92] and Consiglio [93] have used palladium-oxazoline complexes (**28**, **29**) to produce styrenic copolymers that exhibit high optical rotations. Takaya has briefly noted the use of his novel phosphine-phosphite bidentate ligands for the enantioselective production of aromatic polyketones [82].



Scheme 13

4.2.1.4

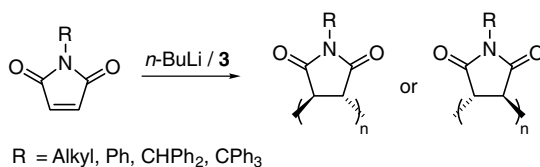
Diels-Alder Polymerization

Recently, Itsuno described the first enantioselective Diels-Alder-based polymer synthesis using a chiral Lewis acid-mediated reaction between a bisdiene and a bisdienophile (Scheme 13) [94]. The bismaleimide and bisdiene were allowed to react with the enantiopure aluminum complex **30** (20 mol %) at $-30\text{ }^{\circ}\text{C}$ to give polymers with molar optical rotations ($[\Phi]_{\text{D}}$) as high as $+243^{\circ}$. No information concerning the degree of stereochemical purity or absolute configuration of the polymer was given.

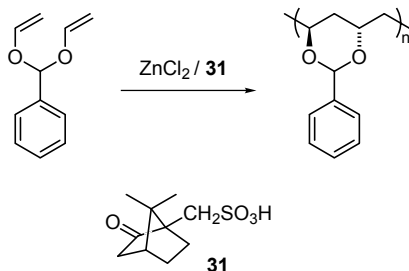
4.2.2

Anionic Polymerization

In 1960, Natta reported the first direct synthesis of an optically active polymer from an achiral monomer, where methyl sorbate was polymerized using (*R*)-2-pentyllithium [95]. Ozonolysis of the polymer (under conditions possibly allowing epimerization) produced (*S*)-methyl succinic acid in 5% ee, which provides evidence of asymmetric induction and absolute configuration of the polymer main chain. Since this initial report, a remarkable void in the literature exists concerning the synthesis of main-chain chiral polymers from achiral monomers using anionic initiators. Okamoto and Oishi have polymerized *N*-substituted maleimides with chiral anionic initiators (Scheme 14) [96, 97]. The polymer is assumed to have predominantly a *trans*-diisotactic microstructure, which adopts a secondary helical structure. The absolute configuration of the main chain has



Scheme 14



Scheme 15

not been assigned. Several studies have documented the influence of the N-substituent on the stereoselectivity of the polymerization [96, 98, 99]. More recently, Oishi has found that organolithium/bisoxazoline initiators produce polyimides that exhibit lower optical rotations [100].

4.2.3

Cationic Polymerization

Natta accomplished the first enantioselective cationic polymerization by reacting benzo- and naphthofurans with chiral cationic initiators [101, 102, 103]. Using aluminum trichloride modified with (*S*)-phenylalanine, the optical rotation of the polymer formed is independent of molecular weight, suggesting enantiomorphic site control. Autocatalytic behavior was also noted, as higher optical activities are obtained in polymerizations where a small amount of the optically active polymer is initially present. The absolute configuration of the polymer is unknown, although the microstructure is proposed to be *trans*-diisotactic.

Kakuchi and Yokota have reported the enantioselective cyclopolymerization of divinyl acetal and divinyl catechol using a chiral cationic initiator **31**/ ZnCl_2 (Scheme 15) [104, 105]. The resultant polymer contains only cyclic units, however the relative ratio of *cis* and *trans* rings is not reported. By comparing the CD spectra of the polymer and a model compound, it was suggested that the *trans* rings of the polymer were predominantly of one absolute configuration.

5 Principal Alternatives

There are several alternative methods for the synthesis of optically active polymers from achiral or racemic monomers that do not involve polymerization catalysts. Optically active polymers have been formed from achiral dienes immobilized in a chiral host lattices [106]. In these reactions, the chiral matrix serves as a 'catalyst' and can be recovered following the reaction. For example, 1,3-pentadienes have been polymerized in perhydrotriphenylene and apocholic acid hosts, where asymmetric induction occurs via through-space interactions between the chiral host and the monomer [107, 108]. The resultant polymers are optically active, and the optical purities of the ozonolysis products are as high as 36%. In addition, achiral monomers have been found to pack in chiral crystals with the orientations necessary for topochemical solid-state polymerization [109]. In these reactions, the scientist is the 'enantioselective catalyst' who separates the enantiomeric crystals. The oligomers, formed by a $[2\pi+2\pi]$ asymmetric photopolymerization, can be obtained in the enantiomeric pure form [110].

Achiral polymers synthesized from achiral monomers have been modified after polymerization using asymmetric catalysts to yield optically active polymers. For example, enantioselective ketone reduction, hydrogenation, olefin epoxidation, and olefin hydroxylation have been carried on the functional groups of achiral polymers [111, 112]. Such functionalizations, however, are often incomplete or occur with a low degree of asymmetric control.

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Chapter 37

Heterogeneous Catalysis

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Keywords. β -Functionalized ketones, α -Keto acid derivatives, Cinchona modified Pt catalysts, Chiral imprints, Chiral metal surfaces, Chiral polymers, Cyanohydrin formation, Cyclic Dipeptides, Epoxidation catalysts, Heterogeneous catalysts, Hydrogenation catalysts, Modified metal oxides, Polypeptides, Tartrate-modified Nickel catalysts

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1

Introduction/Overview

Among the various methods to selectively produce one single enantiomer of a chiral compound, enantioselective catalysis is arguably the most attractive method. At this time, homogeneous metal complexes with chiral ligands are the most widely used and versatile enantioselective catalysts [1]. From an industrial point of view, heterogeneous catalysts are of interest for a number of reasons, and

Table 1. Strong and weak points of homogeneous and heterogeneous catalysts

	Homogeneous	Heterogeneous
Strong points	defined on molecular level scope, variability (design?) (availability)	separation, recovery handling stability, re-use
Weak points	sensitivity activity, productivity (separation)	characterization reproducibility availability, preparation narrow scope

a comparison of the properties of homogeneous and heterogeneous catalysts is made in Table 1. Several recent reviews give a digest of the most relevant aspects of heterogeneous enantioselective catalysts [2, 3, 4, 5, 6]. This short overview describes the various types of chiral heterogeneous catalysts based on metals, metal oxides, and organic polymers. Special emphasis is placed on giving the synthetic chemist an impression of the present state of the art and of the substrate specificity of these heterogeneous catalytic systems. For detailed information on reaction conditions and other experimental details the cited references should be consulted.

2

Chirally Modified Hydrogenation Catalysts

Investigation of heterogeneous chiral hydrogenation catalysts started in the late fifties in Japan and has seen a renaissance in the last few years [2, 4, 6]. In spite of many efforts, only two classes of modified catalyst systems have been found that are of synthetic use at this time: nickel catalysts modified with tartaric acid [4] and platinum and, to a lesser degree, palladium catalysts modified with *Cinchona* alkaloids and analogs thereof [7, 8]. However, several laboratories are working to expand the scope of this interesting and potentially very versatile class of chiral catalysts.

2.1

Mechanism and Mode of Action

The influences of catalyst preparation, modifier and substrate structure, of various additives, and of reaction parameters have been reported for both the tartrate modified Ni catalysts [2, 4, 11] as well as for *Cinchona* modified Pt catalysts [2, 3, 7]. In addition, kinetic [2, 4, 12, 13] and molecular modeling studies [8] have been carried out. This experimental basis allows the discussion of their mode of action with some confidence and a mechanistic picture has been developed in the last few years that can explain the major observations, even though it is not accepted universally.

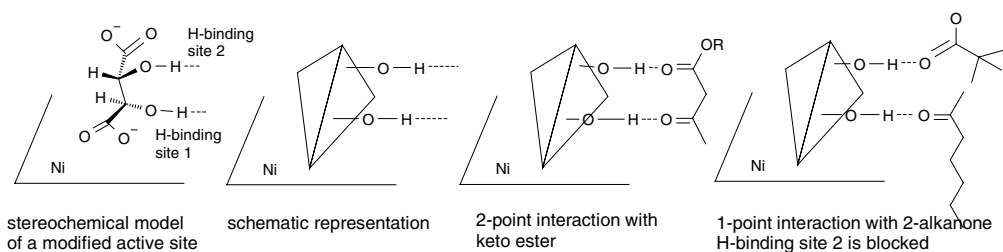


Fig. 1. Ni-tartrate catalyzed hydrogenation of β -keto esters and 2-alkanones. Important interactions between adsorbed tartrate and different ketones [14]

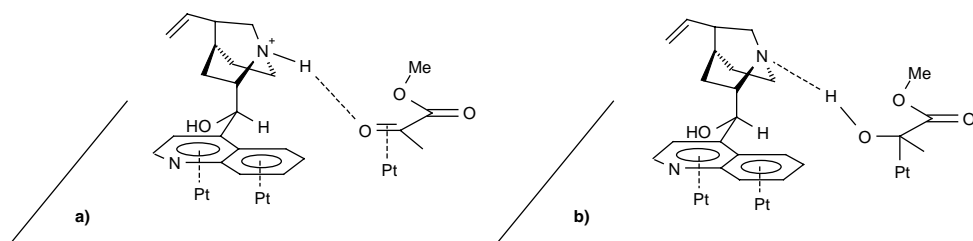


Fig. 2. Two intermediates proposed for Pt-cinchona catalyzed hydrogenation of α -keto esters: a) a protonated cinchonidine-ketone complex [8]; b) a stabilized half-hydrogenated ketone intermediate [3]

It is reasonably certain that a stepwise addition of hydrogen to the keto group takes place in the adsorbed state on the metal surface (Langmuir-Hinshelwood kinetics). While the reaction on an ordinary metal site leads to racemic alcohol, it is assumed that chiral active sites are formed by strong adsorption of a modifier molecule on the metal surface. Hydrogen bonding with the modifier as depicted in Fig. 1 and Fig. 2 not only controls the adsorption of the ketone but also facilitates and controls the addition of hydrogen. According to Sugimura et al. [14], this relatively simple model for the Ni catalysts is able to explain not only the observed absolute configuration of the product but also the steric effect of substituents in β -ketoesters and methyl ketones as well as the blocking effect of bulky organic acids. The Pt-Cinchona system has been modeled extensively, especially by the group of Baiker [8], and the modeling results are in agreement with the observed stereoselectivity for a number of modifier-substrate combinations.

2.2

Tartrate-Modified Nickel Catalysts

The development of the nickel tartrate system and its successful preparative applications for the hydrogenation of β -functionalized and methyl ketones have been reviewed by Tai and Harada [4]. The preferred catalyst is freshly prepared

Raney nickel; the only useful modifier is *d*- or *l*-tartaric acid with bromide as co-modifier. The choice of the Ni alloy, the leaching and impregnation procedure (tartaric acid and NaBr concentrations, pH, T, time, ultrasound [15]) as well as the reaction conditions (solvent, p, T, acid co-modifiers) are crucial for getting good results. In general, the catalysts have relatively low activity and high pressures (up to 100 bar) and temperatures (usually 100 °C) are necessary [4]. Persistent and systematic optimization of the system parameters led to ee's up to 98% [14]. The Ni/SiO₂-tartrate system has recently been investigated in great detail (effect of impregnation and reaction parameters, catalyst characterization) and it looks as if modification by tartaric acid increases the specific activity by a factor of two [16].

2.3

Cinchona Modified Pt, Pd, and Related Catalysts

The *Cinchona* modified platinum catalysts are at the moment among the most selective catalytic systems known for the hydrogenation of α -keto acid derivatives and for other activated keto groups, whereas some Pd-cinchonidine catalysts give reasonable ee's for α,β -unsaturated acids [7, 8, 9]. For α -keto esters, the best catalysts are commercial 5% Pt/Al₂O₃ with low dispersion and a rather large pore volume. Carriers like SiO₂ or BaCO₃ and carbon supports are also suitable. The best modifiers are cinchonidine derivatives but some new types of modifiers [8, 10] also give good optical yields (see Fig. 3). The catalysts have to be pretreated in hydrogen at 300 to 400 °C before the reaction. The modifier can be directly added to the reaction solution but more elaborate modification procedures have also been reported [3]. The reaction conditions (solvent, modifier concentration, p, T) have a strong effect on rate and optical yield. Typical substrate/modifier ratios are in the range of 100 to 10,000, depending on substrate and solvent. Acetic acid is the solvent of choice for the hydrogenation of most α -ketoesters in order to get high enantioselectivity [17]. For the hydrogenation of α -ketoacid derivatives, the modified catalyst is 10 to 100 times more active than the unmodified Pt/Al₂O₃ (modifier accelerated catalysis) [18].

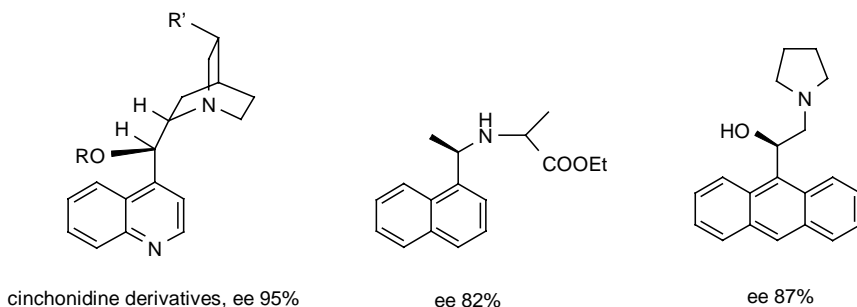


Fig. 3. Structure of modifiers (best ee observed for the hydrogenation of ethyl pyruvate) [7, 8, 10]

2.4

New Catalytic Systems

As already pointed out, several research teams are actively looking for new catalytic systems and/or new applications. Until now, the results confirm the difficulty of this endeavor. In the area of the enantioselective hydrogenation of aromatic rings, Rh colloids stabilized and modified by chiral amines gave low but significant ee's of 3 to 6% for the hydrogenation of *o*-substituted toluenes [19]. A pyrazine derivative was hydrogenated with Pd/C in presence of camphor-10-sulfonic acid with 50% ee [20]. New results were also reported for the hydrogenation of pyruvic acid oxime (Pd/Al₂O₃-ephedrine, ee 26%) [21] and for an α,β -unsaturated ketone (Pd/C-ephedrine, ee 36%) [22]. However, in all cases 0.5 to more than 1 equivalents of modifier were necessary to give good results suggesting that 1:1 modifier-substrate adducts were the reactive species.

2.5

Synthetic Applications

2.5.1

Hydrogenation of Ketones

Enantioselectivities reported in Table 2 for aliphatic ketones and for α - and β -ketoesters as well as for aliphatic methyl ketones are still among the highest for hydrogenation reactions. The most outstanding results are 85% ee for *tert*-butyl methyl ketone [11], 95% ee for ethyl pyruvate [17], and 98% ee for methyl 3-cyclopropyl-3-oxobutanoate [14]. While the preparation of the modified Raney-nickel catalysts is not trivial, the *Cinchona* modified Pt catalysts are easy to use for preparative purposes. Both catalytic systems work well only at rather high pressures, so special autoclaves are needed. Synthetic applications of the Ni-tartrate catalyst have been described for sex pheromones of the pine sawfly [25]; for biologically active C₁₀ to C₁₆-3-hydroxyacids [26]; for a diphosphine ligand [4, 27], and for an intermediate of tetrahydrolipstatin, a pancreatic lipase inhibitor (ee 90 to 92%, 6 to 100 kg scale) [28]. Using a Pt *Cinchona* catalyst, the hydrogenation of ethyl 2-oxo-4-phenylbutyrate, an intermediate for the ACE inhibitor benazepril, has been developed and scaled-up into a production process (10–200 kg scale, chemical yield >98%, ee 79 to 82%) [29].

Several alternative methods with high ee's for various types of ketones are known: reductions catalyzed by enzymes or baker's yeast [30] and microbial reagents [31], homogeneous hydrogenation (cf. Chapter 6.1), and stoichiometric reductions with chiral metal hydrides [32].

2.5.2

Hydrogenation of C=C Bonds

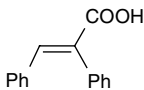
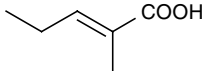
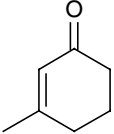
Despite some recent progress as shown in Table 3, heterogeneous hydrogenation of C=C bonds is not ripe for synthetic applications and certainly not competitive

Table 2. Hydrogenation of various ketones, best ee's and turnover frequencies

Substrate	R/R'	Catalyst	Modifier	ee (%)	tof (1/h) ^a	Ref.
CH ₃ COR	<i>n</i> -Alk	Ra-Ni	tartrate/NaBr/PvOH	71–80	<<1	[11]
CH ₃ COR	<i>i</i> -Pr	Ra-Ni	tartrate/NaBr/PvOH	85	<<1	[11]
PhCOCF ₃		Pt/Al ₂ O ₃	cinchonidine (Cd)	56	150	[23]
RCOCOOEt	<i>n</i> -Alk	Pt/Al ₂ O ₃	<i>O</i> -methyl-dihydro-Cd	95	>50,000	[17]
PhCH ₂ CH ₂ COCOOH		Pt/Al ₂ O ₃	<i>O</i> -methyl-dihydro-Cd	85	1000	[7]
CH ₃ COCONHR	var.	Pt/Al ₂ O ₃	Cd	49–60	100	[24]
ketopantolactone		Pt/Al ₂ O ₃	Cd	79	50	[8]
RCOCH ₂ COOCH ₃	<i>i</i> -Pr	Ra-Ni	tartrate/NaBr	96–98	1	[14]
RCOCH ₂ COOR'	<i>n</i> -Alk	Ra-Ni	tartrate/NaBr	83–94	<1	[15]
CH ₃ CO(CH ₂) ₃ COOR	Alk	Ra-Ni	tartrate/NaBr/PvOH	59–61	<1	[15]
CH ₃ COCH ₂ SO ₂ CH ₃		Ra-Ni	tartrate/NaBr	71	n.a.	[4]
CH ₃ COCH ₂ COCH ₃		Ra-Ni	tartrate/NaBr	91 (diol)	1	[15]

^a Average turnover frequencies for complete conversion, rough estimates

Table 3. Hydrogenation of various C=C bonds, best ee's and turnover frequencies

Substrate	Catalyst	Modifier	ee (%)	tof (1/h) ^a	Ref.
	Pd/TiO ₂	cinchonidine	72	400	[9]
	Pd/Al ₂ O ₃	cinchonidine	52	2000	[8]
	Pd black	dihydrovinpocetine	40	–	[7]

^a Average turnover frequencies for complete conversion, rough estimates. Unmodified catalysts usually show higher activity.

with the homogeneous hydrogenation using Rh and Ru diphosphine complexes (cf. Chapter 5).

3

Modified Metal Oxides

Solid acids and bases are being increasingly applied for the catalytic synthesis of fine chemicals. However, chirally modified versions have not yet been developed to the point where their synthetic application seems feasible. Very little is known about their mode of action. In many cases, the preparation of the catalysts is not trivial and not always reproducible. Therefore, only a cursory overview is given here.

Titanium-pillared montmorillonites (Ti-PILC) modified with tartrates were described as heterogeneous Sharpless epoxidation catalysts [33] as well as for the oxidation of aromatic sulfides [34]. Metal oxides modified with histamine showed modest efficiencies for the kinetic resolution of activated amino acid esters ($k_R/k_S \approx 2$) [35]. Silica or alumina treated with diethylaluminium chloride and menthol catalyzed the Diels-Alder reaction between cyclopentadiene and methacrolein with modest enantioselectivities of up to 31% ee [36]. Zeolite HY, modified with chiral sulfoxides had remarkable selectivities for the kinetic resolution of 2-butanol ($k_S/k_R=39$) but unfortunately the catalyst is not very stable [37]. Clearly, this class of chiral catalysts, although of potential interest because of its variability, is not ready for synthetic applications.

4

Chiral Polymers

Because nature has provided us with so many chiral polymeric materials, their use for enantioselective synthesis is obvious. Indeed, some of the first successful attempts at enantioselective catalysis were carried out using aminocellulose by Bredig in 1932, metals on quartz by Schwab in 1932, and Pd supported on silk fibroin by Akabori in 1956 [2]. However, the catalysts were very difficult to reproduce and other strategies were pursued more successfully. In the mean time, impressive progress has been made for the synthetic application of polypeptides and of dipeptide gel catalysts. But even though good enantioselectivities are observed, there is very little understanding of their mode of action. For both systems there are indications that supramolecular interactions inside a polymeric aggregate might be important for catalysis and stereocontrol.

4.1

Polypeptides

Synthetic poly(amino acid) derivatives are highly selective catalysts for the asymmetric epoxidation of electron-deficient olefins with NaOH/H₂O₂ in a two-phase reaction system [38]. Parameters of importance for the catalytic performance are the type of amino acid, the degree of polymerization, the substituent at the terminal amino group (R in Fig. 4), catalyst pretreatments, and the organic solvent. In general, the catalysts are commercially available [39] or seem relatively easy to prepare even in larger quantities (>200 g) [40].

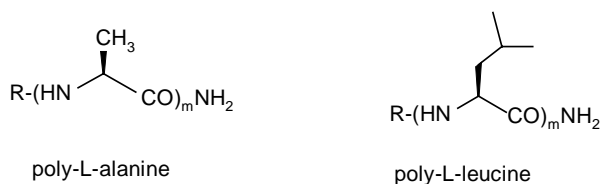
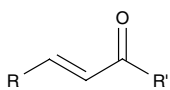
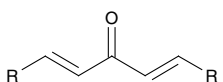
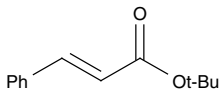
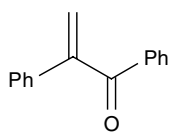


Fig. 4. Structure of most widely use polypeptide catalysts. R can be an alkyl or a polymeric residue

Table 4. Epoxidation of various activated C=C bonds using poly-peptide catalysts [39]

	R	R'	ee (%)
	(subst)-Ph, 2-naphthyl 2'-styryl, cyclopropyl, 2-furyl, pyridyl	Ph, 2-naphthyl, 2-furyl, <i>t</i> -Bu, cyclopropyl	>90
		C(CH ₂) ₂ OH, H	60
	2-furyl, 2'-styryl (both C=C epoxidized)		80–90
			95
			59

Recently, the scope of original Julia epoxidation was extended from the chalcones to a variety of activated C=C bonds and the catalytic system was broadened and extended to other oxidants, bases, and solvents [39]. In Table 4 we have summarized recently published examples that show the present scope and limitations. Generally, chemical yields are high but the activity of the catalysts is rather low (tof's ca. 0.1 h⁻¹) and relatively long reaction times and/or high catalyst loadings are necessary. Poly-L-alanine was used to prepare chiral intermediates for a leukotriene receptor antagonist with very high enantioselectivity [40].

4.2 Cyclic Dipeptides

Cyclic dipeptides, especially cyclo[(*S*)-phenylalanyl-(*S*)-histidyl], are efficient and selective catalysts for the hydrocyanation of aromatic aldehydes (Fig. 5) [41]. The catalysts are not available commercially but can be synthesized by conventional methods and their structure can be varied easily (Fig. 5) [41, 42, 43]. The catalysts are only selective in a particular heterogeneous state, described as a “clear gel” [41, 43]. It seems that their method of precipitation is crucial [41, 44] and that reproducing literature results is not always easy [42]. A recent study confirmed the importance of the aggregate formation and reported a second order rate dependence on the concentration of the cyclic dipeptide [45]. These findings indicate that the enantioselective catalytic species is not monomeric but either a dimer or polymer.

Because cyanohydrins are versatile intermediates, various methods for their asymmetric preparation have been worked out [46] (cf. Chapter 29). The chiral dipeptide catalysts allow the use of HCN but their application is restricted to aromatic aldehydes. Generally, 2% catalyst is needed and best optical yields are obtained at room temperature or below. As summarized by North [46], the pattern and the nature of substitution strongly affects the enantioselectivity (Table 5). Recently, the application to the synthesis of chiral side chains for liquid crystal polymers was described [44].

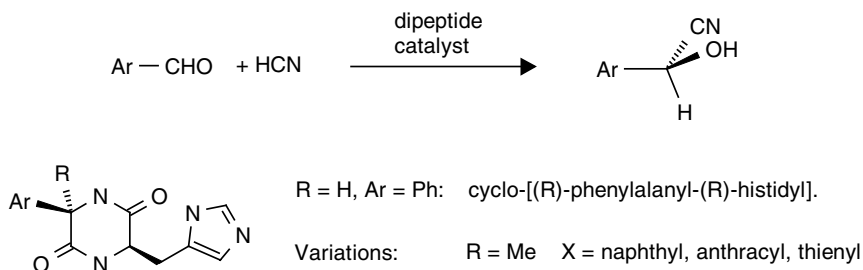


Fig. 5. Reaction scheme and structure of cyclo-[(*R*)-phenylalanyl-(*R*)-histidyl] and analogs

Table 5. Enantiomeric excesses for various aldehydes using cyclo-[(*S*)-phenylalanyl-(*S*)-histidyl]

Ar	ee (%)	Ref.
Ph, <i>m</i> -OR-Ph, <i>m</i> -tol, 2-naphthyl	91–97	[41]
<i>p</i> -OMe-Ph, <i>o</i> -OMe-Ph	78–84	[41]
heteroaromatic, aliphatic aldehydes	40–70	[41]
allyl-O-Ph	>98	[44]
H ₂ C=CH-(CH ₂) _n O-Ph	72–90	[44]

5

Future Trends/Developments

Most groups working in the field of chiral heterogeneous catalysts use an empirical approach in order to expand the scope of known catalytic systems. There are, however, some attempts to try new principles and ideas. Even though the ee's are still low, there are some interesting first results:

- *Chiral metal surfaces.* Inherently chiral Ag metal surfaces were produced by cutting along the (643) surface to give Ag(643)^R and Ag(643)^S and characterization by LEED [47]. Not so surprisingly, no difference was detected for adsorption and decomposition of (*R*) and (*S*)-2-butanol.
- *Grafted auxiliaries.* Smith et al. [48] grafted chiral silyl ethers to a Pd surface through a Pd-Si bond. A borneoxysilyl-Pd catalyst was able to hydrogenate α -methylcinnamic acid with ee's up to 22%. Santini et al. [49] reported the preparation of a menthyl-Sn-Rh catalyst that hydrogenated ketopantolactone with 11% ee.
- *Chiral imprints.* The imprinting of organic [50] and inorganic materials [51] with transition state analog templates should, at least in principle, lead to what could be called artificial catalytic antibodies. Up to now, either the chiral recognition and/or the catalytic properties of such materials are still very poor. Some examples are a zeolite β , partially enriched in polymorph A [51], "chiral footprints" on silica surfaces [52], or several imprinted polymers [50].

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Chapter 38.1

Catalyst Immobilization: Solid Supports

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Keywords: Heterogenization, Immobilization, Support, Grafting, Copolymerization, Adsorption, Entrapment, Site isolation

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1 Introduction

Control of stereoselectivity is easier with homogeneous than with heterogeneous catalysts. On the other hand, these soluble catalysts are more difficult to separate and to handle than the technically well-established heterogeneous catalysts. A promising strategy to combine the best properties of the two catalyst types is the heterogenization or immobilization of active metal complexes on insoluble supports or carriers [1, 2, 3]. Besides easy separation, immobilization opens opportunities like, e.g., the use of continuous flow reactors [4, 5, 6], site isolation [7], or the tuning of the catalyst environment [8, 9, 10] which in some cases can lead to improved catalytic performance. On the other hand, immobilization increases the complexity and the costs of the catalytic system.

To be of practical use, immobilized enantioselective catalysts should meet the following requirements:

- (i) The preparation methods should be versatile, since it is not yet possible to predict which ligand and support will be the most suitable for a given sub-

strate and process. Modular systems that allow combinations of different support and ligand will therefore be preferred.

- (ii) The selectivity, activity, and productivity of an immobilized catalyst should be comparable or better than that of the corresponding free analogs.
- (iii) Separation should be achieved by simple filtration and at least 95% of the catalyst should be recovered.

Re-use is not mandatory, but would be a great advantage from an economic point of view.

First efforts in the field of catalyst immobilization showed the feasibility of the concept with respect to catalyst separation but in most cases lead to immobilized catalysts with very poor performance [1]. In the meantime, further efforts in catalyst preparation and the use of new supports have lead to several catalytic systems that meet these requirements. However, to our knowledge, none is applied on a technical scale yet.

2

Supports

The supports used for catalyst immobilization can be classified as follows:

- *Soluble polymers*: Non-crosslinked, linear polymers are soluble in suitable solvents. In the soluble state, high mobility of the bound catalyst and good mass transport are guaranteed and, therefore, catalytic properties will practically not be affected. However, separation of such catalysts is often problematic and costly since it is done either by ultrafiltration or precipitation.
- *Swellable polymers*: Crosslinked polymers are 3-dimensional networks and can easily be separated by sedimentation or filtration. Slightly crosslinked polymers such as, e.g., polystyrene crosslinked with 0.5–3% 1,4-divinylbenzene have to be used in solvents in which they swell, otherwise mass transport may be completely stopped.
- *Unswellable supports*: Highly crosslinked polymers (e.g., macroreticular polystyrenes or polyacrylates) and inorganic supports (metal oxides) are practically not swellable. In contrast to soluble or swellable polymers, these materials can therefore be used in a large variety of different solvents without changing their texture. To obtain immobilized catalysts with reasonable weights per mole of active sites these supports should have large specific surface areas ($>100 \text{ m}^2/\text{g}$). Also, to avoid mass transport problems, the pore size should be considerable larger than the size of the metal complex catalyst and the substrate [8]. The most frequently used insoluble support is silica gel. Different types, covering a large range of specific areas and pore sizes are commercially available.

3 Approaches for the Immobilization of Metal Complex Catalysts

A schematic view of the most important approaches that have so far been described in the literature is given in Fig. 1.

For all approaches it is important that the metal does not dissociate from the ligand. Since, with a few exceptions [12], the binding to monodentate ligands is usually insufficient [13], most immobilized catalysts are based on bi- or polydentate ligands.

For covalent binding or adsorption, the ligands have either to be attached to a linker or to an adsorbable moiety. In these cases, ligands with an additional function such as an NH or OH group have proven to be particularly useful, since they can be combined in a modular way with different linkers, supports, adsorbable moieties, or water-soluble groups. A highly versatile modular system has been developed that allows to bind various functionalized diphosphines to inorganic supports or to organic polymers via trialkoxysilane-isocyanate or di-isocyanate linkers [11, 14].

3.1 Immobilization via Covalently Bound Ligands

Covalent binding of ligands to supports is by far the most frequently used strategy for the heterogenization of metal complexes and, in general, the successful catalytic systems are sooner or later immobilized by this method. Covalent binding can be effected either by copolymerization or by grafting.

Copolymerization of functionalized ligands with a suitable monomer [e.g., 15, 16, 17] is being more frequently used than grafting. The polymerization is well

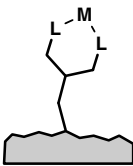
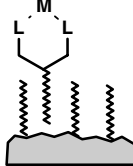
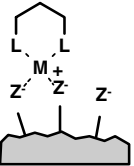
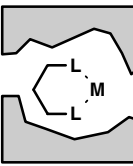
				
Immobilization method	Covalent binding	Adsorption	Ion pair formation	Entrapment or 'Ship in a bottle'
Applicability, versatility	broad	restricted (competition with solvents, substrates)	restricted (competition with ionic substrates, salts)	restricted (size of substrate)

Fig. 1

established, but it is difficult to predict and control the properties of the resulting polymer that is a random sequence of the original monomer units. In addition, the formation of inaccessible immobilized ligands cannot be excluded. Finally, unwanted polymerization could occur during the synthesis or storage of the functionalized ligands.

Grafting, i.e., reacting a functionalized ligand or metal complex with reactive groups of a preformed support [e.g., 11, 14, 18, 19] has several advantages. Different suitable supports are commercially available and many methods for introducing reactive groups onto non-functionalized polymers are described in the literature [20, 21, 22]. Their properties (e.g., solubility or swellability, particle size, separation, purity) can be checked before use. Finally, the ligands will preferentially bind at locations that are also accessible for the substrate during the catalytic reaction. A potential problem of the grafting method is the remaining reactive groups on the support that may interact with the immobilized catalysts.

The choice of the best method seems to depend on the catalytic system. A comparison of immobilized catalysts for enantioselective hydrogenation shows a clear superiority of the catalysts that were prepared by grafting. On the other hand, Itsuno [23] found that immobilized Lewis acid catalysts for Diels-Alder reactions showed better performance when they were prepared by copolymerization.

Table 1 gives some examples for catalysts that were immobilized by covalent binding and that are either typical or are promising with respect to potential future applications.

Most efforts have been made with catalysts for enantioselective hydrogenation and some have now catalytic performances that are of industrial interest.

Table 1. Examples of potentially useful immobilized catalysts prepared by covalent binding

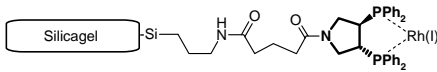
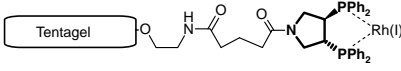
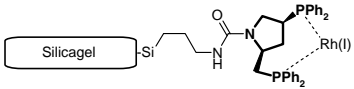
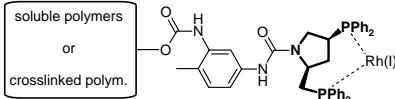
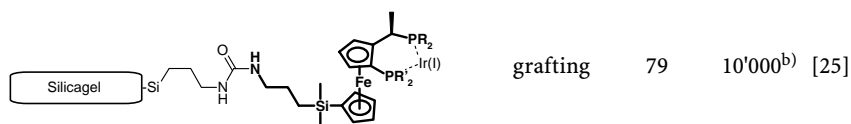
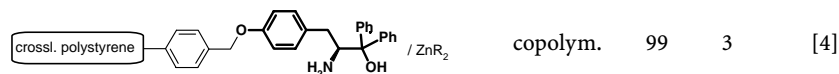
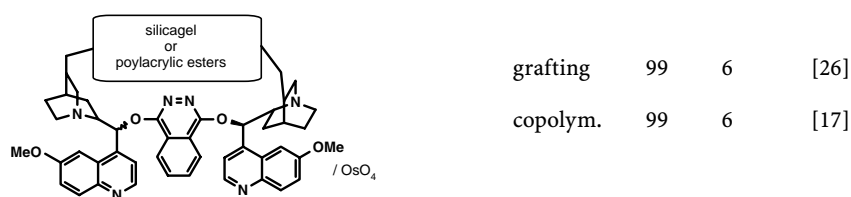
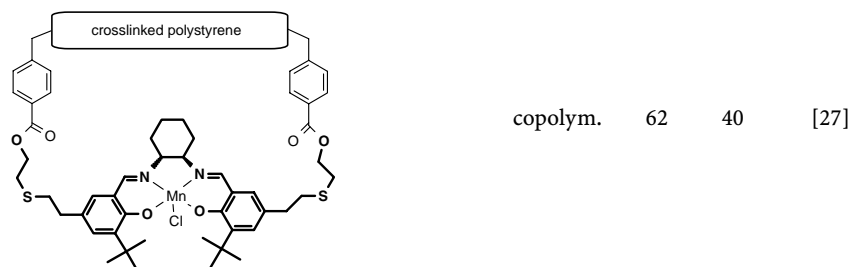
<i>reaction/support-linker-catalyst</i>	preparation	ee ^a	to ^(a)	ref
<i>hydrogenation of enamides</i>				
	grafting	100	400	[18]
	grafting	97	60	[19]
	grafting	94.5	1500	[11, 24]
	grafting	95	2000	[14]
	grafting	97	200	[14]

Table 1. Continued

hydrogenation of iminesaddition of R₂Zn to aldehydesDiels Alderdihydroxylation of alkenesepoxidation of alkenes

^aBest ee and tof; tof=moles of substrate/moles of catalyst per h.

^bHydrogenation in presence of acid.

The recent activities directed towards the immobilization of the dihydroxylation and epoxidation catalysts have already led to systems with acceptable catalytic properties [17, 26, 27]. Both, immobilized Zn amino alcohol and oxazaborolidinone catalysts have been applied in continuous flow reactors [4, 6]. Interestingly, these immobilized oxazaborolidinone catalysts give better enantioselectivities than their soluble analogs [6].

3.2

Heterogenization via Adsorption and Ion Pair Formation

This approach has not often been used so far, but seems promising with respect to practical applications. It relies on various adsorptive interactions between a carrier and a metal complex. The advantage is the easy preparation of the heterogenized catalyst by a simple adsorption procedure, very often without the need to functionalize the ligand. Electrostatic forces were used to bind cationic Rh diphosphine complexes to anionic resins [28, 29]. The resulting catalysts could be recycled 20 times with very little leaching. Toth et al. [30] functionalized diphosphine ligands with amino groups and adsorbed the corresponding Rh complexes on Nafion. Another approach by Inoue relied on the interaction of lipophilic ligands with surface methylated silica [31]. Further examples were described by Brunner [32, 33] and Inoue [34]. With few exceptions [28], adsorbed complexes have lower enantioselectivities than covalently bound catalysts. It is to be expected that the applicability of this elegant immobilization strategy is limited by strong solvent and salt effects.

3.3

Heterogenization via Entrapment

This method relies on the size of the metal complex rather than on a specific adsorptive interaction. There are two different preparation strategies: One, often called the 'ship-in-a-bottle' approach, is based on building up catalysts in well defined cages of porous supports. Recently, enantioselective Mn epoxidation catalysts with different salen ligands have been assembled in zeolites. In zeolite EMT [35] ees up to 88% and in zeolite Y [36] ees up to 58% were obtained with *cis*- β -methylstyrene. However, both entrapped catalysts were much less active than their homogeneous counterparts. Rh diphosphine complex were entrapped in the interlayers of Smectite [37]. The resulting catalyst was active for the enantioselective hydrogenation of *N*-acetamidoacrylic acid (ee 75%).

The other approach is to build up a polymer-network around a preformed catalyst. Using this method, Jacobs et al. [38] occluded Jacobsen's Mn-Salen epoxidation catalysts and Noyori's Ru-Binap-catalyst in poly-dimethylsiloxane and demonstrated that leaching strongly depends on the size and the solubility of the metal complex and the swelling of the polymer [39].

4

Effect of Immobilization on Catalytic Performance

Unfortunately, heterogenization of a homogeneous catalyst often leads to a change of its catalytic properties. Most of the time the consequences are negative but sometimes the performance is improved. Even though most effects are poorly understood and ill-defined, several factors may be distinguished.

- (i) Interactions between functional groups on the surface of the support and the metal center can influence the catalytic performance. Stille [8, 9, 10] dem-

onstrated that the enantioselectivity of a chiral hydrogenation catalyst bound to a support with additional chiral groups significantly changes with the change of the configuration of these groups.

- (ii) Restricted conformational flexibility through geometrical confinement can be positive as described by Corma et al. [40, 41, 42] for proline amide Rh complexes that were attached in modified USY zeolites or negative as observed by Pugin and Müller [11] for a diphosphine Rh complex that was immobilized on silica gels with different pore sizes. Itsuno et al. [6] studied an asymmetric oxazaborolidinone Diels-Alder catalysts bound to polystyrene. They were able to raise the enantioselectivity from 65% to 95% by increasing the length and the polarity of the crosslinking agent.
- (iii) Attaching a complex to a rigid support via a covalent bond can lead to so-called site isolation, i.e., different active centers no longer interact with each other. The most remarkable positive effects are observed for complexes that are prone to form inactive dimers [7]. To our knowledge, no example for the alternative situation, the so-called 'site cooperation', where site interactions are important for good catalytic performance, has been described yet.
- (iv) Mass transport can be hindered or even completely stopped if unsuitable solvents are used with swellable supports [43] or if solid supports with too large particle size or with too narrow pores are used. It is conceivable that this may in some cases lead to a large population of highly reactive catalytic intermediates that, instead of reacting with the substrate, deactivate the system by undesired side-reactions.

5

Conclusions and Outlook

Immobilized catalysts are a fascinating topic and currently several research groups both in industry and at university are active. There are many examples demonstrating that efficient separation by filtration or sedimentation can be achieved. In a few cases re-use of the recovered catalysts is possible without loss of performance. Immobilized catalysts can be applied in continuous flow reactors. This technique has advantages in cases where a high concentration of catalyst is required to obtain good selectivities or where degradation of the support particle by stirring is a problem. Also, in a few cases, catalytic properties could be improved by the effect of site isolation or by tuning the catalyst's surroundings.

However, immobilized catalysts are much more complex and expensive than their homogeneous counterparts and immobilization usually goes along with changes of the catalytic property that cannot be predicted. For these reasons there is now a strong tendency to avoid heterogenization and to develop soluble catalysts that can be separated by extraction [44], by ultrafiltration [45], or that can be precipitated by changing the temperature [46] or the pH [47]. Promising results have also been obtained recently with 'supported aqueous phase' (SAP) catalysts [48]. These are based on a thin film of a water-soluble catalyst in water

or another polar solvent that is adsorbed on a hydrophilic support and that reacts with a water-insoluble solution of the substrate. All these approaches have their strong and weak points and all of them require a functionalization of the ligand.

The chances for the application of immobilized catalysts will improve with the number of chiral ligands that have an anchoring group, the number of efficient immobilization methods, better understanding of the interactions between supports and catalysts and the increasing experience in manufacturing well-defined solid supports. Also, in the near future it is to be expected that combinatorial solid phase synthesis and screening of chiral ligands [49] will become an important issue that will give another push to the development of this still young field.

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Chapter 38.2

Catalyst Immobilization: Two-Phase Systems

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Keywords: Biphasic catalysis, Asymmetric phase-transfer catalysis, Micellar catalysis, Vesicles, Microheterogeneous systems

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1 Introduction

Most asymmetric-catalytic reactions are carried out in homogeneous organic media. The well known advantages are high activity and selectivity and a good reproducibility under mild conditions; however, catalyst recycling can be difficult. From a practical point of view it is desirable to separate the catalytic system from the reactants using two immiscible liquid phases. After conversion the phases can be separated and the catalyst phase can be used in the next cycle. In accordance to Southern [1] we will use the following terms for two-phase systems:

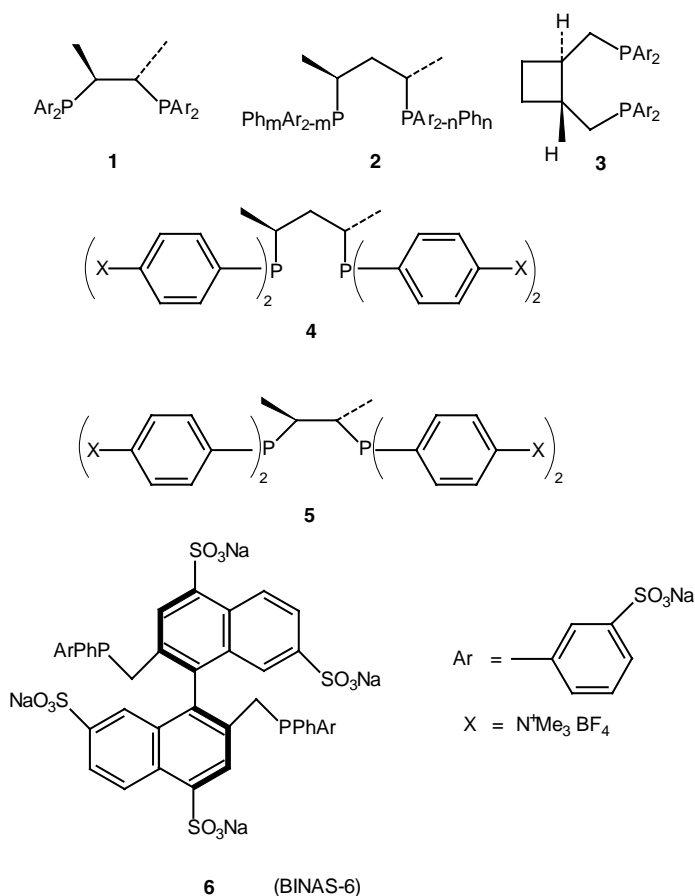
- The term biphasic catalysis will be used for liquid-liquid systems containing two immiscible liquids without any phase-transfer agent,
- the term phase-transfer catalysis will be used for biphasic liquid-liquid systems containing a phase-transfer agent for transportation of a part of catalyst or reactant into one favored phase, and
- thirdly (in a free extension), the term micellar or vesicular catalysis will be used for microheterogeneous liquid-liquid systems containing colloidal assemblies of self-organized amphiphiles. The surfactant simultaneously is the phase-transfer agent and the organic phase [2].

Liquid-solid phase-transfer systems and other systems with immobilized catalysts are not mentioned here.

2 Biphasic Catalytic Systems

Two important industrial processes are based on biphasic systems: the Shell higher olefin process (SHOP) [3] and the hydroformylation developed by Ruhrchemie/Rhône Poulenc [4]. Prerequisite was the synthesis of water-soluble ligands, especially water-soluble phosphines. Scheme 1 shows a selection of optically active phosphines for asymmetric reactions under biphasic conditions.

Some excellent reviews collect the early and recent literature with respect to typical complex-catalyzed reactions [5, 6, 7, 8, 9, 10, 11, 12]. Most of the water-soluble phosphines were synthesized by direct sulfonation of the phenyl group leading to mixtures of products. Sinou et al. [13] investigated the asymmetric hydrogenation of precursors of α -amino acids [14] and even of dehydropetides [15]. In comparison to homogeneous systems in organic solvents activity and

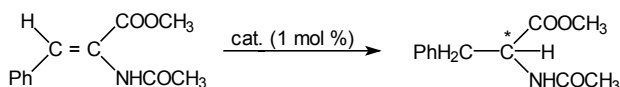


Scheme 1

enantioselectivity decrease in the presence of water [16] and Table 1 shows some characteristic results in biphasic systems.

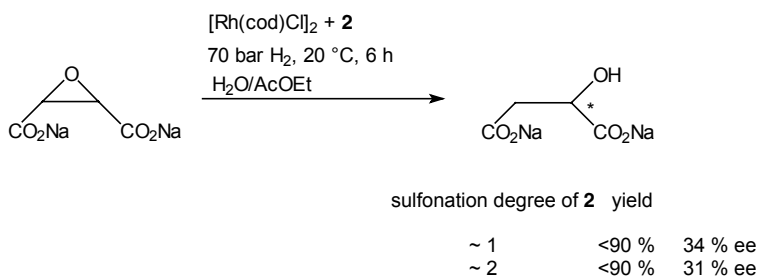
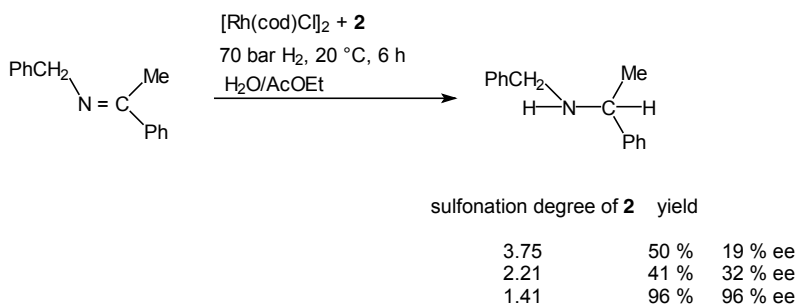
A favored ligand can be derived from BDPP, [(*S,S*)-1.3-bis(diphenylphosphino)pentane]. Bakos [17] showed that two quite different asymmetric catalytic reactions, the hydrogenation of acetophenonbenzylimine and the hydrogenolysis of sodium *cis*-epoxysuccinate [18] by rhodium(I) complexes depend on the degree of sulfonation of the ligand **2** (Scheme 2).

Table 1. Hydrogenation in the biphasic system water/AcOEt (1/1)

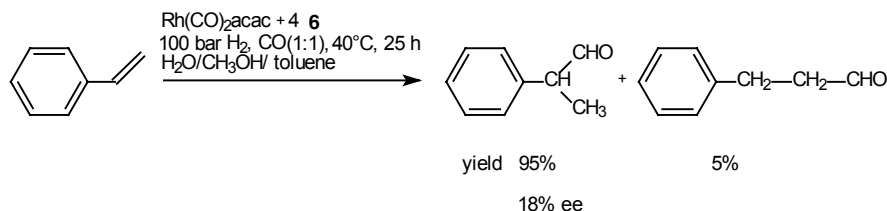


catalyst	pressure in bar	optical yield in % ee	Ref.
Rh(cod)Cl ₂ +2.2 1	10	88 (<i>R</i>)	[14]
[Rh(cod)Cl] ₂ +2.2 2	15	67 (<i>R</i>)	[14]
[Rh(cod)Cl] ₂ +2.2 3	1	67 (<i>S</i>)	[14]
[Rh(nbd) 4] [BF ₄] ₅ ^a	14	44 (<i>R</i>)	[19]

^aBiphasic system water/AcOEt-benzene (2/1-1); cod=*cis,cis*-1.5-cyclooctadiene; nbd = norbornadiene



Scheme 2

**Scheme 3**

Best results were observed with a sulfonation degree between one and two.

Also, outstanding enantioselectivities could be achieved with the rhodium complex of ligand 4 in the hydrogenation of a DOPA precursor [19]. In the case of a H_2O -slurry of the substrate the reaction yielded 95% ee.

A very simple experiment, the adsorption of a water-soluble catalyst on a silica gel prepared with organic solvent or on a controlled pore glass treated with an organic solvent, led to a new generation of catalysts, SAP (supported aqueous phase) catalysts [20,21]. In a comprehensive study Wan and Davis [22] investigated the use of $\text{Ru-BINAP-4 SO}_3\text{Na}$ as catalyst in the homogeneous, biphasic, and SAP asymmetric hydrogenation of the naproxen precursor 2-(6'-methoxy-2'-naphthyl)acrylic acid. The best enantioselectivities were 96% ee for the homogeneous, 83% ee for the biphasic, and 77% ee for the SAP catalysis, the relative activities were 1:0.0026:0.14.

The low activity and enantioselectivity of the biphasic systems seems to be a characteristic feature. Eckl et al. [23] described the use of NAPHOS and its sulfonated derivative BINAS (6) as ligands in the asymmetric hydroformylation of styrene (Scheme 3). NAPHOS yielded 34% ee (in toluene), BINAS 18% ee (in toluene/water) of phenylmethylacetaldehyde.

The achievements in asymmetric biphasic catalysis are not very encouraging except for some hydrogenation reactions. Nevertheless, the simplicity of catalyst-product separation in biphasic systems should be a challenge to improve activity and stereoselectivity. New developments of biphasic systems containing a hydrocarbon and a perfluorinated hydrocarbon which are miscible at slightly enhanced temperature and separable at ambient temperature have not yet been used in asymmetric catalysis [24, 25].

3

Phase-Transfer Catalytic Systems

Phase-transfer catalysis (PTC) has been developed to a very important laboratory method in organic and organometallic chemistry. Numerous books [26, 27, 28, 29, 30] and reviews [31, 32, 33] give a good insight into methods and results. In principle PTC is a two-phase liquid-liquid system with an amphiphilic PT catalyst for equilibration of the reactants between the phases. Actually, the asymmetric potential of PTC is rather low and only a few examples with taylor-made

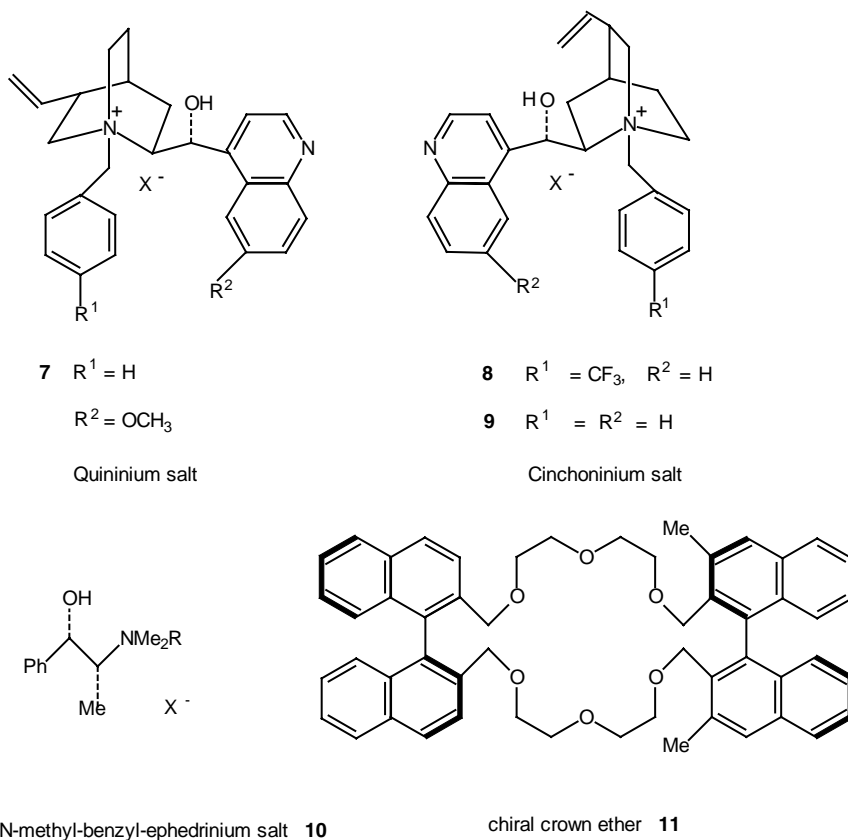
catalysts gave spectacular results. All successful chiral catalysts are ammonium salts or crown ethers. A selection of PT catalysts is summarized in Scheme 4.

Some highlights will be discussed here. Schiff bases of glycine esters were alkylated under PT conditions with benzylated *Cinchona* bases (**9**) as catalysts in the presence of 50% NaOH and dichloromethane with a maximum of 64% ee [34]. Outstanding enantioselectivities could be observed by alkylation of a special phenylindanone with modified benzylcinchoninium salt according to Scheme 5.

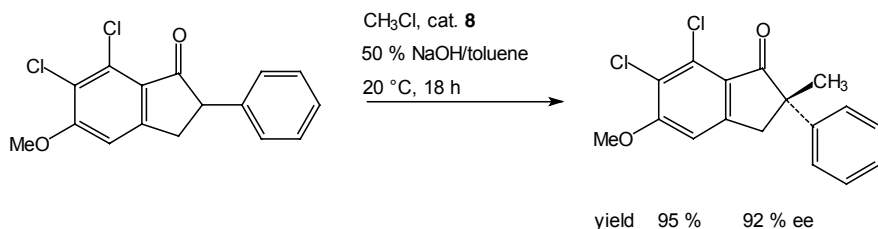
The enantioselectivity of the alkylation depends on the electrophile. Best results were surprisingly obtained with methyl chloride [35].

The Michael addition is one of the favored reactions in enantioselective PTC. For instance, the reaction of an indanone similar to those in Scheme 5 with methyl vinyl ketone in the presence of catalyst **8** in a toluene system (50% NaOH) gave the Michael product in 95% yield and 80% ee [36].

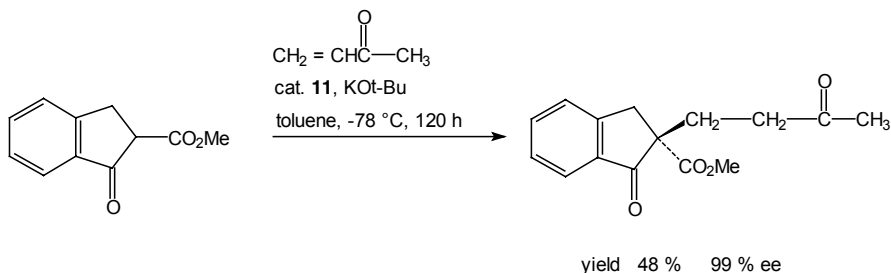
The best result (99% ee) was achieved by Michael addition of an indanone derivative to methyl vinyl ketone in the presence of a chiral crown ether at $-78\text{ }^{\circ}\text{C}$ in toluene (Scheme 6) [37].



Scheme 4



Scheme 5



Scheme 6

In a more recent paper an enhancement of the rate by sonication was reported [38]. Benzylmethylephedrinium bromide **10** was used in this reaction.

Many experiments have been described for the PT reduction of ketones and imines with NaBH_4 as reagent. The catalysts were ammonium salts of *Cinchona* alkaloids and ephedrine and even chiral crown ethers. Only medium enantioselectivities could be achieved.

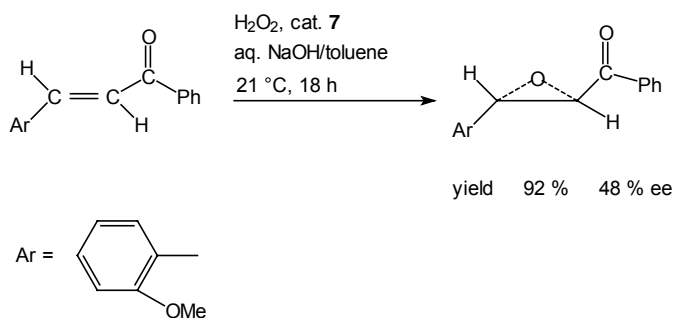
Ding, Hanson, and Bakos [39] used an amphiphilic chiral rhodium-phosphine complex in the catalytic asymmetric two-phase hydrogenation of methyl (*Z*)- α -acetamidocinnamate in ethyl acetate/water and obtained enantioselectivities of up to 69% ee.

In the field of asymmetric oxidation reactions the epoxidation of α,β -unsaturated carbonyl compounds was investigated. In the case of 1,4-naphthoquinone derivatives and *tert*-butyl hydroperoxide as reagents enantioselectivities up to 78% ee were observed with quininium and quinidinium salts as PT catalysts [40].

Important seems to be also the epoxidation of chalcones with hydrogen peroxide as reagent leading to 48% ee for the epoxide [41] (Scheme 7).

Masui et al. [42] reported a high optical yield (up to 79% ee) in the autoxidation of cyclic ketones in the presence of 4-trifluoromethylbenzyl-cinchoninium bromide **8**, 50% NaOH/toluene, oxygen and triethyl phosphite.

With the same type of PT catalyst Aires-de-Sousa et al. [43] described recently an enantioselective synthesis of *N*-arylaziridines starting from *N*-acylarylhydroxylamines in a PT system of NaOH/toluene. High conversion needs highly concentrated NaOH ($\geq 33\%$) and yielded only up to 50% ee. Decreasing the NaOH



Scheme 7

concentration to 9% decreased the conversion from 79% to 12% and enhanced the enantioselectivity to 61% ee.

Only few examples of asymmetric catalytic reactions by PTC are really successful but in all cases it was the result of an acerbic development. The potential of PTC in asymmetric catalytic reactions will be a topic of future application.

4

Catalysis in Micelles and Vesicles

This term is connected with assemblies of typically structured surfactants above a critical micelle concentration (cmc) or a critical vesicle concentration (cvc). The aggregates have colloidal dimensions and are spherically shaped [44].

The core of a micelle and the bilayer of a vesicle are comparable with a liquid-crystalline phase and can influence the stereoregularity of asymmetrically catalyzed reactions. Self-organization and the neighborhood of hydrophilic and hydrophobic regions are close to those of natural systems and we designate this as membrane mimetic or enzyme mimetic chemistry [45]. The large field of artificial enzymes was recently reviewed by Murakami et al. [46].

The enhancement of reaction rate as well as the stereoselectivity of hydrolytic reactions were studied by several authors [47]. Typical substrates were hydrophobized activated esters of amino acids and typical catalysts were surface active peptides with histidine as active component. The kinetic resolution of racemic esters was determined. Brown [48] and Moss [49] gave explanations for the stereoselectivity. Ueoka et al. [50] reported one example where non-functional amphiphiles as cosurfactants can enormously improve the stereoselectivity: the saponification of *D,L-p*-nitrophenyl *N*-dodecanoylphenylalaninate with the tripeptide *Z*-PheHisLeu-OH as catalyst in assemblies of ditetradecyldimethylammonium bromide yielded practically pure *L-N*-dodecanoylphenylalanine upon the addition of between 7 to 20 mol % of the anionic surfactant sodium dodecyl sulfate (SDS).

As models for metalloenzymes, Scrimin, Tonellato, Tecilla and coworkers [51] describe in a series of papers amphiphilic chiral complexes as catalysts for the

hydrolysis of α -amino acid esters. In some cases moderate kinetic resolution of the racemic esters was observed [52]. Best results were obtained with bilayer forming cosurfactants in the gel state [53].

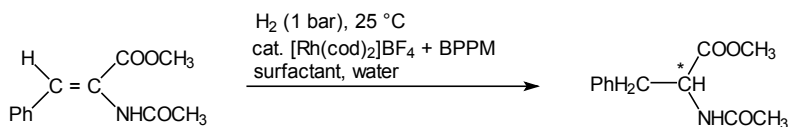
An enantioselective oxidation of 3,4-dihydroxy-L-phenylalanine catalyzed by an *N*-lauroyl-L- or -D-histidine-Cu(II) complex in the presence of cetyltrimethylammonium bromide as cosurfactant was described by Yamada et al. [54].

One of the most successful asymmetric catalytic reactions is the asymmetric hydrogenation of amino acid precursors by means of optically active rhodium(I)phosphine or phosphinite complexes [55]. Usually, the reaction is carried out in methanol as solvent. When water is used the activity and enantioselectivity decrease significantly [16], but the addition of micelle forming surfactants leads to a solubilization of catalyst and substrate and increases activity and enantioselectivity. The results are somewhat better than the ones obtained with methanol as solvent [56]. Table 2 shows the effect with different types of surfactants.

All types of surfactants promote the reaction but only the hydrogen sulfate was active in the case of the cationic amphiphiles. There is no need to work with water-soluble complexes. However, surfactant could be substituted by polymer bound amphiphiles [57, 58].

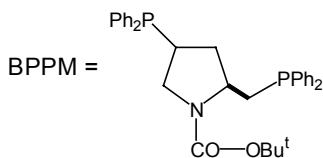
Less successful was the use of achiral catalysts in chiral micelles. The induced enantioselectivity in the resulting α -amino acid derivatives was in all cases below 10% ee depending on the type of amphiphile [59]. Other asymmetric reac-

Table 2. Hydrogenation^a



surfactant	t/2 in min	optical yield in % ee (R)
none in water (methanol)	90 (2)	78 (90)
sodium dodecyl sulfate (SDS)	6	94
cetyltrimethylammonium hydrogen sulfate	5	95
<i>N</i> -dodecyl- <i>N,N</i> -dimethyl-3-ammonio-1-propanesulfonate	5	93
decaoxyethylene-hexadecyl ether	7	95

^aRh : surfactant : substrate = 1:20:100;



cod = cis, cis-1.5-cyclooctadiene

tions in optically active surfactant assemblies gave distinctly higher inductions. Examples are the conversion of aromatic aldehydes with chloroform and ammonia in presence of *N*-hexadecyl-*N*-methylephedrinium bromide [60] (28% ee), the reduction of phenyl ethyl ketone with sodium borohydride in the presence of dodecyl- β -D-glucopyranoside [61] (98% ee) and the hydroxylation of olefins via acetoxymercuration [62] (up to 96% ee) in the presence of *N*-hexadecyl-*N*-methylephedrinium bromide, and finally the Michael addition of nitromethane to chalcone with piperidine as catalyst and *N*-dodecyl-*N*-methylephedrinium bromide as chiral surfactant [63] (17% ee).

Recently, Zhang and Sun [64] reported the reduction of a series of phenyl alkyl ketones with NaBH₄ to optically active alcohols in reverse micelles of different ephedrinium bromides. Addition of sugars like D-fructose and D-glucose enhanced the stereoselectivity up to 27% ee. Other asymmetric catalytic reactions in reverse micelles have been investigated by Nozaki et al. [65] and Buriak and Osborn [66].

In summary, the influence of micellar and vesicular media on asymmetric catalytic reactions could be of general interest in the future.

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Chapter 39

Combinational Approaches

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Keywords: Chiral catalysts, Asymmetric synthesis, High-throughput screening, Ligand diversity, Solid phase chemistry

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1 Introduction

Combinatorial chemistry has emerged as an important and formidable strategy in the search for effective therapeutic agents [1]. The practicality, efficiency, and productivity of diversity-based protocols for drug discovery have already had a notable impact on the pharmaceutical industry. Although the major applications of combinatorial libraries remain in the search for biologically active compounds, it has also been recognized that such methods might be effective in the identification of compounds with any attractive properties. Combinatorial and related strategies have indeed been recently utilized in investigations in materials science [2], molecular recognition [3, 4], polymer chemistry [5], and asymmetric catalysis [6].

This article provides a brief overview of the recently developed diversity-based approaches in the screening and identification of effective metal-based chiral catalysts for enantioselective synthesis. This first wave of reports indicates

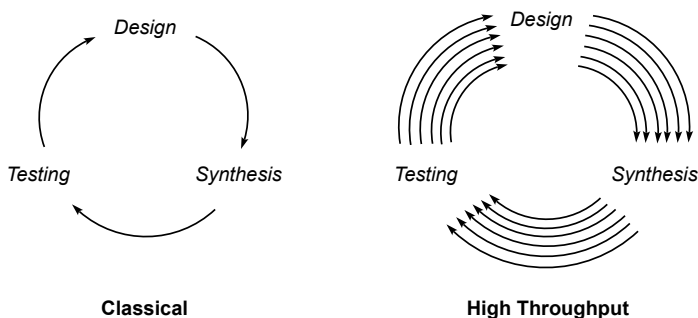
that high throughput technologies might represent a viable and efficient route for the development of useful chiral catalysts. In a few instances, it is likely that the more traditional screening approaches, often based on *a priori* mechanistic bias, would have been less successful, at least within the same time span.

2

Diversity-Based Approach for Drug vs Catalyst Discovery

The searches for therapeutic agents and asymmetric catalysts share a number of facets and can reap similar benefits from diversity-based protocols. Traditionally, both fields have relied on iterative approaches wherein a single compound is designed, synthesized, and tested (Scheme 1). The cycle is repeated until a compound is obtained with the desirable levels of enantioselectivity or activity. In contrast, as illustrated in Scheme 1, a high throughput strategy enables the chemist to simultaneously generate and test notably larger numbers of candidates, potentially reducing the entire search cycle to one or two iterations. A more comprehensive search can thus be completed more efficiently.

Combinatorial chemistry is not an irrational method; rather, it brings together rational design and high throughput evaluation and is rooted in empirical observations and logical deduction. Structure-selectivity observations remain the basis for propagating molecular features from one generation of catalysts to the next. High throughput strategies therefore permit more initial “guesses” and a greater allowance for failure. Combinatorial chemistry is particularly well suited toward optimizing novel and previously unexamined reactions for which little mechanistic data are available. Such strategies can be viewed as the chemist's attempt to address the notion that mechanistic subtleties that often differentiate the selectivity and reactivity from one substrate or catalyst to another may not be generalized – these mechanistic intricacies can vary unpredictably. Such a broad-based approach relieves the chemist from the risk of following a relatively narrow path that is selected on the basis of fickle mechanistic parameters. It is



Scheme 1. The diversity-based approach can provide a wealth of reactivity and selectivity data in an efficient manner

perhaps fair to state that almost all successful asymmetric catalysts have benefited, at some point in their development, from serendipitous observations. Combinatorial chemistry integrates this aspect of catalyst discovery into the overall search process, increasing the rate at which “advantageous mutations” can occur. Nevertheless, a combinatorial approach can significantly promote the mechanistic studies of new asymmetric processes, as it can put forth a large structure-selectivity database from which data can be rapidly generated.

Three important issues need to be addressed for the successful implementation of combinatorial asymmetric catalyst design: (i) sources of diversity, (ii) high throughput synthesis of catalysts, and (iii) high throughput catalyst screening.

- (i) *Sources of diversity.* Two distinct approaches have been adopted in introducing the element of diversity into asymmetric reactions. The first is analogous to that developed for drug design, where a modular catalyst composed of changeable subunits is used. Variation of the modules generates an exponential number of catalysts with myriad steric and electronic attributes. When organometallic complexes are employed as reaction initiators, metal centers can be modified as well. The second route for introducing diversity into asymmetric reactions involves variation of the reaction conditions. Solvent, concentration, temperature, and reaction times are potential parameters that can be altered. These protocols towards introducing diversity are not mutually exclusive.
- (ii) *High throughput catalyst synthesis.* To retain the benefits of a diversity-based method, it is imperative that the catalyst is easily and efficiently synthesized. At the same time, reaction initiators must be of high purity due to the potential deleterious effects of impurities in metal-catalyzed reactions. These stringent requirements can therefore limit the types of catalysts that are amenable to combinatorial and related techniques. Most “combinatorial catalysts” to date have been made through parallel syntheses. The modularity of the chiral ligands has been critical to accelerate their preparation by making the fabrication of each catalyst identical, regardless of structural variations. In many cases, hundreds of compounds can be manually synthesized by a single researcher. A high level of efficiency requires that lengthy separations be avoided by utilizing only high-yielding reactions that join various modules.
- (iii) *High throughput catalyst screening.* Currently, the greatest bottleneck is in assaying each catalyst for asymmetric induction. A successful approach in drug design has been to test mixtures of compounds and then, by means of a deconvolution strategy, to identify the active component. This approach is not easily amenable to asymmetric catalytic processes where two opposing and neutralizing outcomes (*R* and *S* enantiomers) can exist; a mixture of chiral complexes may yield a racemic product even with a mixture of selective catalysts. Accordingly, recent reports generally involve testing individual systems. It merits mention that the parallel screening strategy has also been applied in therapeutic discovery efforts, due to the difficulties involved in the accurate deconvolution of various mixtures and in order to remove

any synergism that may exist between several active compounds. As such, combinatorial chemistry does not necessarily have to involve the generation of mixtures of compounds; it may be better characterized by the modular nature of the constituent compounds that in different combinations provide large numbers of molecular ensembles.

3

Diversity-Based Investigations on the Discovery of Catalysts for Enantioselective Synthesis

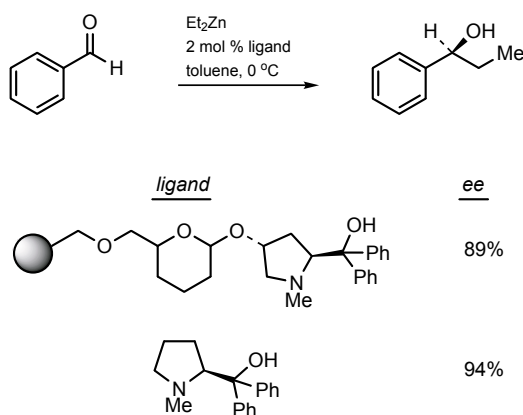
3.1

Catalytic Enantioselective Aldehyde Alkylation

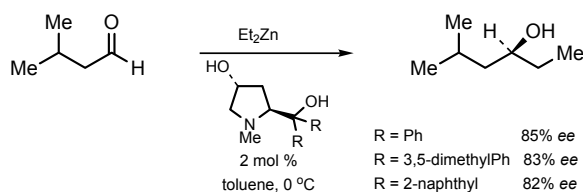
One of the earliest demonstrations of the viability of a combinatorial approach in the discovery of asymmetric reactions was reported by Ellman in 1995 [7]. The Berkeley team's selection of the dialkylzinc addition to aldehydes (Scheme 2) to gauge the potential utility of a combinatorial approach was based on several factors:

- (i) Previous studies had clearly demonstrated a direct correlation between ligand structure and enantioselectivity. Thus, variations of the 2-pyrrolidinemethanol ligand framework could lead to significant improvements in asymmetric induction.
- (ii) Although extensive work had been done with aromatic aldehydes as substrates, the levels of enantioselectivity with aliphatic systems left ample room for improvement.

Thirteen different ligands were synthesized on a solid support from a 4-hydroxyproline precursor and attached to the support (commercially available Merri-



Scheme 2. In catalytic alkylation of aldehydes, similar but slightly lower enantioselectivity is attained when the chiral ligand is anchored to a solid support



Scheme 3. Influence of various chiral ligands on the enantioselective addition of Et_2Zn to an aliphatic aldehyde

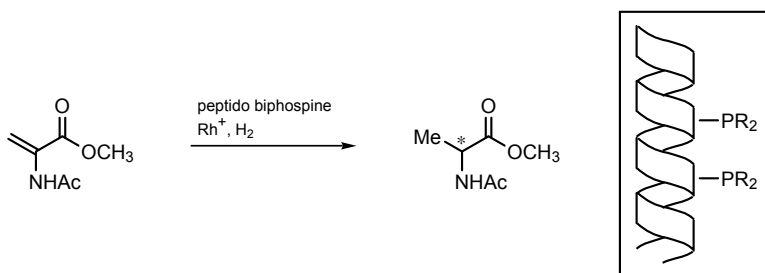
field resin) through the 4-hydroxy substituent. The ligands were initially screened while still covalently anchored to the support. As depicted in Scheme 2, the levels of enantioselectivity for reactions initiated by the resin-bound ligands proved to be high, but slightly lower than those obtained with the free ligands in solution (e.g., 89% vs 94% ee).

Screening was carried out with unbound chiral ligands, synthesized on solid supports and subsequently freed from the resin. Representative data are shown in Scheme 3. It is important to note that, subsequent to cleavage from the solid support, little or no purification of the ligands was required to maintain excellent enantioselectivity. This is a tribute to the efficient multistep synthesis carried out on the Merrifield resin and to the benefits of ligand-accelerated catalysis [8]. The effects of the chiral pyrrolidinone ligand are sufficiently dominant so as not to allow adventitious side products from ligand synthesis to catalyze product formation and thus lower overall selectivity or hinder accurate analysis of the screening process.

3.2

Catalytic Enantioselective Hydrogenation

Chiral phosphines have been used on numerous occasions in conjunction with various transition metals to effect enantioselective bond formation [9]. As with many other metal-catalyzed asymmetric reactions, it is nearly impossible to predict which phosphine ligands or metal centers will afford the most desirable outcomes. Gilbertson and coworkers therefore set out to prepare a sixty-three member library of chiral phosphines that could be screened for catalytic and enantioselective olefin hydrogenation. A particular feature of these phosphines is that they were built within a helical peptide scaffold. Thus, a variable sequence of four to five amino acids was inserted into the peptide Ac-Ala-Aib-Ala-[...]-Ala-Aib-Ala- NH_2 to yield a range of chiral ligands. These researchers argued that folding of the polypeptide backbone would bring together two different donor phosphine units to present effectively a bisphosphine system and an appropriate chiral environment to the transition metal (Scheme 4) [10]. The terminal Ala-Aib-Ala sequences were designed to promote helix formation by bringing the two synthetic amino acids with phosphine side chains in close proximity when they are positioned at spacings of $(i, i+1)$ and $(i, i+4)$.



Scheme 4. Phosphine units attached to helical peptide scaffolds have been screened as catalysts for enantioselective hydrogenation

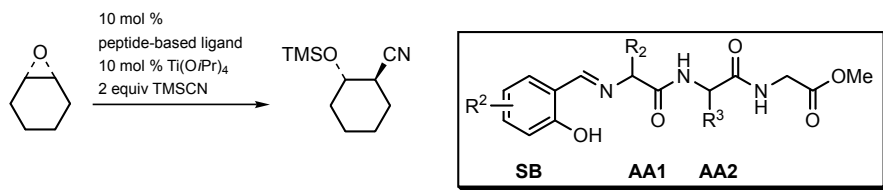
The modular peptidic ligands are amenable to well-established solid-phase synthesis protocols, enabling ready access to a diverse array of structures. Sixty-three different peptides were synthesized in parallel on pins and tested for asymmetric induction while still attached to the solid-phase. As depicted in Scheme 4, Rh(I) was selected as the metal center (based on ample precedence) and the enantioselective hydrogenation of an α -amino acid was examined. Although relatively low levels of enantioselectivity were observed ($\leq 19\%$ ee), this study demonstrated that a combinatorial protocol can efficiently provide the chemist with a wealth of data. It is not clear whether any reliable mechanistic information can be gleaned from these initial results because of the low levels of stereodifferentiation. However, future developments of these ligands, along the lines demonstrated by Gilbertson, could well afford more practical levels of selectivity: the helical peptidic bisphosphines have been recently reported to effect the hydroformylation of styrene with 40% ee [11].

3.3

Catalytic Enantioselective Addition of TMSCN to Meso Epoxides

As part of a program directed towards the development of new catalytic and enantioselective reactions, we have utilized diversity-based protocols to introduce variations within a modular peptide-based ligand as the means to identify effective chiral ligands for enantioselective TMSCN addition to *meso* epoxides (Scheme 5). These peptidic ligands had previously been used in other enantioselective catalytic processes [12] and, as depicted in Scheme 5, are composed of three subunits: Schiff base (SB), amino acid 1 (AA1), amino acid 2 (AA2) [13]. Such peptide-based systems offer various attractive features: (i) A number of chiral amino acids are available in the non-racemic form, thus allowing a gamut of optically pure chiral ligands to be readily accessed. (ii) Peptidic systems can be prepared efficiently, in parallel, and by established solid phase protocols. (iii) There is ample precedent that polypeptides effectively associate with a range of transition metal centers.

In principle, 8000 (20^3) different chiral catalysts could be made from the 20 natural amino acids and 20 different aldehydes. However, to control the num-



Scheme 5. Peptidic Schiff bases may be screened for identification of an effective chiral ligand for catalytic enantioselective addition of TMSCN to *meso*-epoxides

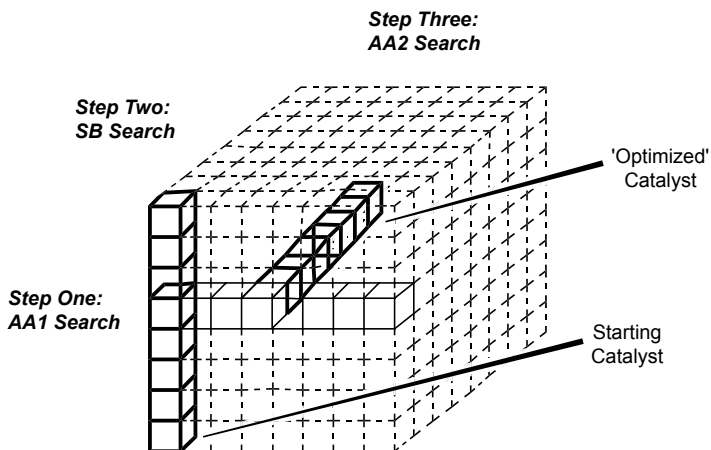

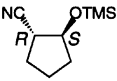
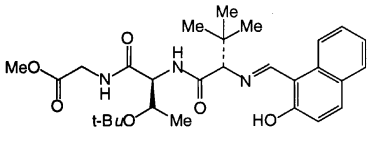

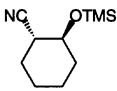
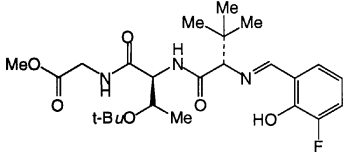

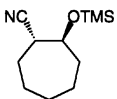
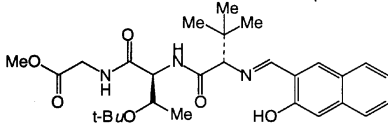
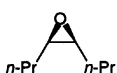
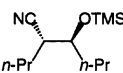
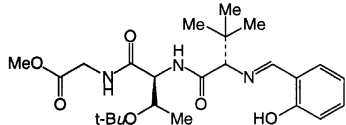


Fig. 1. Representation of a search strategy adopted for catalyst screening that allows identification of effective ligands without examination of all possibilities

bers of compounds synthesized and screened, a representational search strategy was employed (illustrated in Fig. 1). Each of the three subunits in the modular ligand was successively optimized, such that the first amino acid 1 (AA1 - shown in red) was varied and the other two subunits were kept constant. *tert*-Leucine was found to be optimal at position AA1 and this structural element was retained in successive generations. The second position (AA2) was then altered, and *O-tert*-butylthreonine was identified as the best AA2. Finally, from a pool of salicylic aldehydes, 3-fluorosalicylaldehyde was selected as the best Schiff base (SB). In the end, only a representative sampling of sixty (20×3) catalysts was necessary to identify one that affords nearly a 95:5 ratio of enantiomers (89% ee). The initial catalyst provided the addition product with only 26% ee (cyclohexene oxide as substrate); successive modifications of the ligand structure enhanced the level of selectivity in three steps to afford finally a synthetically attractive level of enantioselectivity (with 3-fluorosalicylaldehyde-*tert*-leucine-*O-tert*-butylthreonine-glycine-OMe as the catalyst). It is unlikely that any mechanistic considerations would have pointed to this peptidic complex as being one of the most suitable species.

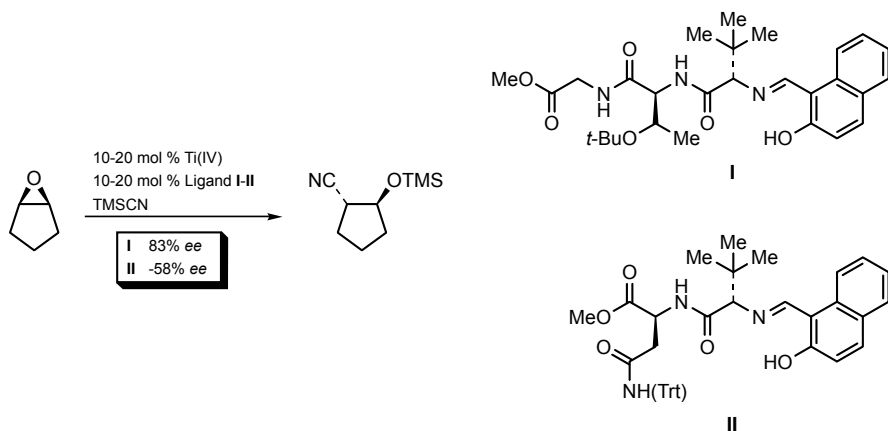
Table 1. Optimized ligands for catalytic enantioselective addition of TMSCN to *meso*-epoxides^[a]

Entry	Substrate	Product	ee [%]	Yield [%]	Optimized Ligand
1			83	72	
2			87	65	
3			84	68	
4			78	69	

^[a]Conditions: 20 mol % Ti(O*i*Pr)₄, 20 mol % ligand, 4 °C, toluene, 6–20 h

The aforementioned strategy for catalyst screening raises an intriguing question: Is the “optimal catalyst” identified by this process truly the very best catalyst? And if it is not, does the attendant improvement in enantioselectivity (>99% ee), assuming there will be no notable difference in efficiency, justify the additional effort that would be required to achieve it? In the approach described above, we have made certain assumptions about the additivity and absence of cooperativity between the three subunits. At least for this small sampling, these assumptions seem to hold true, but without testing every combination we cannot definitively answer this important question. Examination of every possibility would tax and detract from the efficiency of the general screening method. An important practical advantage of the above approach is that, in a relatively short amount of time, it allowed us to identify a selective catalyst for an entirely new asymmetric process. That is, the search strategy is not an open-ended odyssey but a well-structured, program that allows a fairly comprehensive assessment of a ligand framework with respect to a specific asymmetric reaction in a finite and predictable period of time.

When we applied the above search strategy to various other *meso*-epoxide substrates, a number of important observations were made [14]. One significant trend that emerged from these studies was that for each epoxide substrate, as de-



Scheme 6. Subtle modifications in the structure of a peptide ligand may unexpectedly lead to significant variations in selectivity

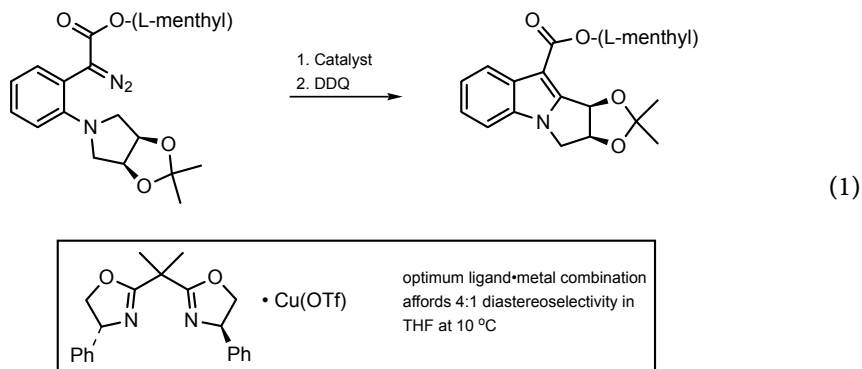
picted in Table 1, a similar but unique chiral catalyst was identified. This type of catalyst/substrate selectivity is akin to that observed in Nature where many reactions have their own unique enzymes. The high levels of selectivity observed with enzymatic reactions are often accompanied by a lack of substrate generality. In this instance, however, because ligand modification is relatively straightforward, substrate specificity does not necessarily imply lack of generality. Another important issue raised by the data in Table 1 is that the search for a “truly general catalyst” is perhaps unrealistic: catalysts that afford exceptional selectivity do so because they associate with specific structures with great fidelity. To expect high specificity and broad range generality may be somewhat contradictory.

An important factor that emerged from our studies is that the above method of catalyst identification increases the frequency with which unexpected observations are made. For example, as illustrated in Scheme 6, a subtle alteration in the structure – and not the stereochemical identity – of the peptide ligand leads to inversion of stereochemistry in the epoxide-opening reaction (compare reaction with ligands I and II). These observations validate our choice of individually synthesizing and testing each catalyst, as mixtures of catalysts can lead to racemic products.

3.4 Catalytic Asymmetric Carbene Insertion

In the above examples, the modularity was contained within the chiral ligand. Burgess and Sulikowski adopted an alternate approach by matching an array of chiral ligands with a range of metal centers [15]. A third dimension of diversity was introduced by changing the reaction conditions through variation of the solvent systems. The approach is thus an amalgamation of the diversity strategies outlined

earlier. All told, five chiral ligands coupled with six different metal salts were examined in four different solvents. Ninety-six of the possible one hundred and twenty different combinations were examined in less than a week for their ability to direct the asymmetric carbene C-H insertion, Eq (1). The most effective catalyst was found to be a Cu(I)-(bis)oxazoline ligand complex which was optimized to give a 3.9:1 diastereomeric ratio, compared to the previously reported 2.3:1 selectivity. The unprecedented catalysis of carbene insertion by Ag(I) was also observed, underlining an additional strength of the high throughput approach.



4

Conclusions and Outlook

The studies discussed in this brief overview represent the chemist's initial attempts to establish a reasonably general protocol for the identification and discovery of metal-based catalysts that effect bond formation in an enantioselective manner. These research activities are perhaps the result of the appreciation of the principle that a "rational" approach has its shortcomings: mechanisms may not be general and can be unpredictable. Such principles can vary with subtle changes in reaction conditions or substrate structure. Development of high throughput protocols is based on the realization that, even within a single class of substrates, the identity of the "optimum catalyst" may change. Perhaps this area of research has its deepest roots in the history of asymmetric catalysis: it is more than often the unanticipated "hit" that becomes the key factor that fuels a successful investigation. If so, why not carry out research in a manner that enhances the probability of making positive chance observations? Combinatorial and related strategies likely arise from the scientist's desire to harness and effectively utilize serendipity, the factor that has been most instrumental in allowing us to achieve our most impressive successes. The interesting and enlightening observation is often the unpredicted; diversity-based approaches allow us to uncover the often convoluted and hidden path to success.

This line of research does not advocate that we abandon rational or rigorous investigations of detailed mechanisms of important processes. Elements of de-

sign and *a priori* decisions are still required in determining what collection of catalysts need be prepared; the framework is simply broader and thus initial bias, that may be based on few initial observations, has less of a chance to direct us in the wrong direction. Diversity-based strategy will allow us to base our mechanistic hypotheses on a much wider pool of data points – it will discourage us from making naive generalities, which are more than often revised soon after a few additional experiments.

The above investigations are the first steps in the exciting road that lies ahead of us. It is likely that we will soon be able to screen significantly larger catalyst collections. A recent report by Jacobsen's group [16] in connection with an impressive library of chiral metal complexes represents an important first step in this direction. The high throughput approach to enantioselective reaction discovery will likely present us with a more complete picture, where the hidden subtleties are highlighted, where the exciting exceptions, as well as the more useful generalities, become more apparent.

Acknowledgments: We are most grateful to our colleagues Dr. Bridget Cole, Mr. Clinton Krueger, Mr. Kevin Kuntz, and Dr. Joseph Harrity for making numerous invaluable intellectual and experimental contributions to the project discussed in this article. Research in our laboratories was generously supported by the National Science Foundation (CHE-9632278 to A. H. H.), Johnson and Johnson (Focused Giving Grant to A. H. H.), Pfizer (Young Faculty Award to A. H. H.), Massachusetts Department of Public Health (Breast Cancer Scholar Award to M. L. S.), and the National Institutes of Health (postdoctoral fellowship to K. D. S.; F32-GM-17821).

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Chapter 40

Catalytic Antibodies

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Keywords: Catalytic antibody, Hapten, Enantiofacial, Enantioselective, Diels-Alder cycloaddition, Cationic reactions, Aldol condensation, Disfavored cyclization

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Abbreviations

ER	Enhancement ratio, equivalent to $k_{\text{cat}}/k_{\text{uncat}}$
IgG	Immunoglobulin-G
K_m	Michaelis-Menten constant, equivalent to the substrate concentration at which an enzyme or catalytic antibody is 50% saturated
k_{cat}	Catalytic rate constant, equivalent to the maximal rate of turnover by an enzyme or catalytic antibody when saturated with substrate
k_{uncat}	The rate constant for a non-catalyzed reaction
TS	transition state

1 Introduction

The *de novo* design and synthesis of new catalysts for organic synthesis and biochemistry has long been the goal of chemists and biochemists alike. This chap-

ter documents the rise of antibodies as a new class of such catalysts and describes their increasing scope and utility in asymmetric chemical processes.

For the purposes of this treatise, the definition of asymmetric synthesis is a modification of that proposed by Morrison and Mosher [1] and as such will be applied to stereospecific reactions in which a prochiral unit in either an achiral or a chiral molecule is converted, by utility of other reagents and/or a catalytic antibody, into a chiral unit in such a manner that the stereoisomeric products are produced in an unequal manner. As such, the considerable body of work devoted to antibody-catalysis of stereoselective reactions including chiral resolutions, isomerizations and rearrangements are considered to be beyond the scope of this discussion. For information regarding these specific topics and more general information regarding the catalytic antibody field the following papers [2,3,4,5,6] and reviews [7,8,9,10] are recommended.

1.1

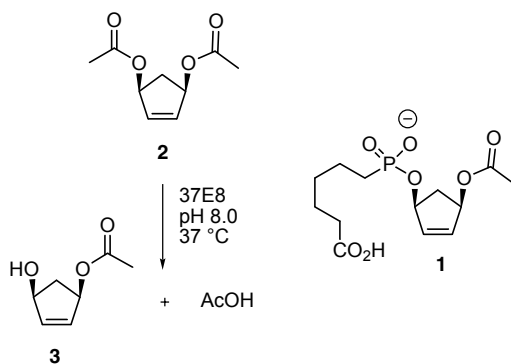
Antibody Structural Features

Antibodies, termed more correctly immunoglobulins, are important components of the mammalian defense mechanism. Structurally, they are symmetrical protein molecules composed of two pairs of polypeptide chains, two heavy chains (M_R 50,000) and two light chain (M_R 25,000), interlinked by disulfide bonds [11]. Sequence comparison of different monoclonal immunoglobulin G (IgG) molecules reveals that the carboxy-terminal half of the light chain and approximately three-quarters of the heavy chain show little sequence variation [12]. By contrast, the *N*-terminal regions of both the antibody light and heavy chains show high degrees of structural variability. These regions of variability compose the binding pockets, or antigen-binding regions, of the antibodies. Antibody recognition of its antigen (hapten) is highly specific and, in general, comprises non-covalent interactions leading to high affinity constants, typically $K_d > 10^{-4}$ to 10^{-14} M^{-1} [13]. If linked to catalysis, this binding may supply up to $20 \text{ kcal} \cdot \text{M}^{-1}$ of free energy, sufficient to catalyze most chemical reactions. The mammalian immune system comprises *ca.* 10^{10} different antibody molecules, each with a distinct variable region sequence and hence binding site specificity, the net result of this vast protein library is that immunoglobulins possess high affinity and unmatched structural specificity towards virtually any molecule. It is this vast library of chiral binding sites and binding energies that the field of catalytic antibodies is perusing in its quest for novel biocatalysts.

2

Enantiotopic and Enantiofacial Selective Reactions

One of the first demonstrations of antibodies as chiral determinants in an organic reaction involved the enantioselective perturbation of a *meso*-substrate [14]. For this case phosphonate **1** was used as a hapten and the *meso*-diacetate **2** as the substrate for antibodies elicited to this hapten (Scheme 1). This strategy engages



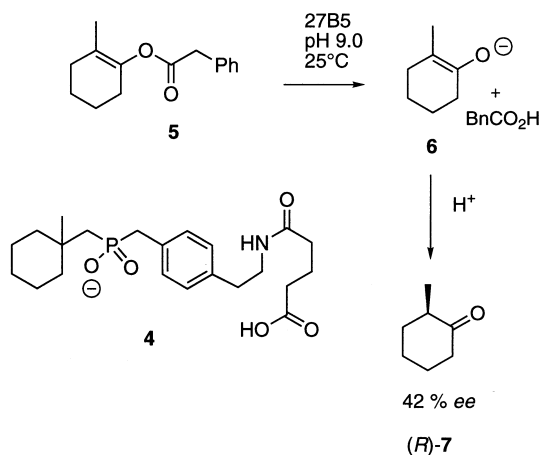
Scheme 1. Antibody 37E8, elicited to the phosphonate hapten **1** catalyzes the enantiotopic hydrolysis of the *meso*-diacetate **2** (>98% ee) at pH 8.0 (ATE [0.1 M *N*-(2-acetamido)-2-aminoethanesulfonic acid (ACES), 0.052 M Tris, 0.052 M ethanolamine] and 37 °C

1 as a transition state (TS) mimic; however, some significant extensions to preceding work were implicit in this study.

First, the lack of an aromatic component in **1** meant that decreased immunogenicity was observed. Second, initial screening assays for highlighting catalytic clones were not readily susceptible to a UV assay. Enantiotopic hydrolysis of **2** to the hydroxyacetate **3** was best accomplished by antibody 37 EB with a turnover number (catalytic rate constant), $k_{\text{cat}}=0.007 \text{ min}^{-1}$, and with excellent enantioselectivity, 86% ee.

One of the first enantiofacially selective processes catalyzed by an antibody involved the hydrolysis of enol esters [15]. Hapten **4** was used to elicit antibodies for the hydrolysis of enol ester **5** (Scheme 2). This reaction proceeds *via* a putative enolate intermediate **6** and the key asymmetric induction step involves antibody-catalyzed enantiofacial protonation of one of the prochiral faces of **6**. Antibody 27B5 catalyzes the hydrolysis of the enol ester **5** with a turnover number $k_{\text{cat}}=0.01 \text{ min}^{-1}$ corresponding to an enhancement ratio (ER), $k_{\text{cat}}/\text{non-catalyzed rate } (k_{\text{uncat}})=300$ and provides an optically enriched mixture of the *R*-ketone product **7** (42% ee). Although the asymmetric induction is lower than that achievable by natural enzymes for certain substrates [16], it was a successful demonstration, at entry level, for catalytic antibodies and asymmetric induction.

The enantioface selective protonation of prochiral enol derivatives is a simple and attractive route for the preparation of optically active carbonyl derivatives. Reports of stoichiometric protonation of metal enolates by a chiral proton source at low temperature leads to optical yields from 20 to 85% ee and yeast esterase catalyzes the hydrolysis of 1-acetoxycycloalkenes with enantioselectivities between 41 and 96% for enol protonation [17,18]. These reactions involve enolates under basic conditions. Hydrolysis of enol ethers under acidic conditions proceeds *via* a rate-determining carbon protonation and is catalyzed by carboxylic acids [19,20]. Raymond et al. [21] reasoned that a complementary



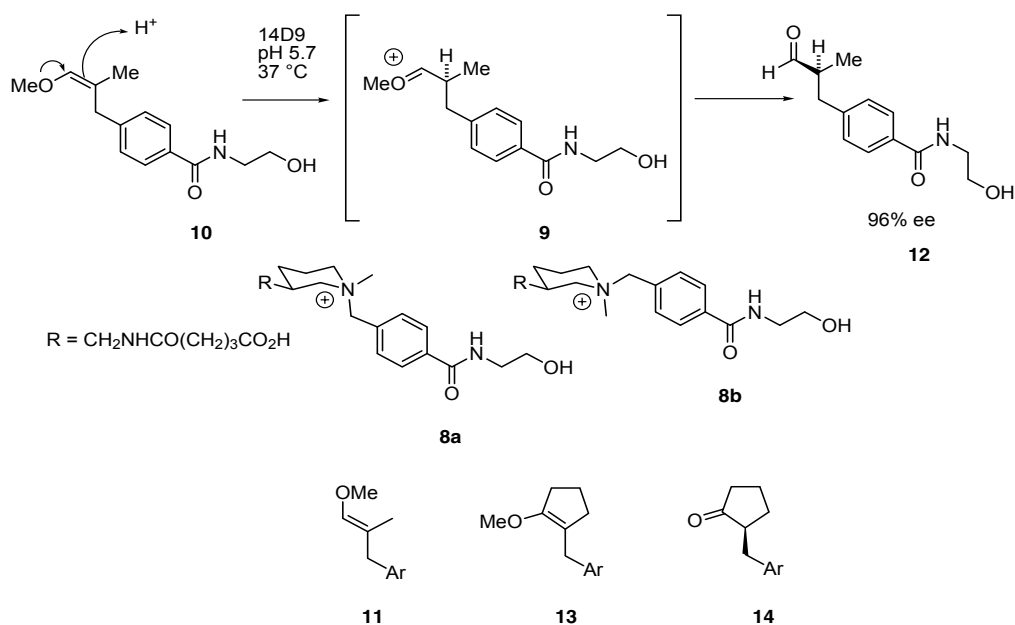
Scheme 2. Antibody 27B5 elicited to the phosphonate hapten **4** catalyzes the enantiofacial protonation of the enolate intermediate **6** during the acid-catalyzed hydrolysis of the enol ester **5** to yield the chiral ketone **7** with 42% ee

carboxylic acid elicited in an antibody binding site to either of the diastereomers of the *N*-methylpiperidinium salt **8a** or **8b**, both of which are ‘bait-and-switch’ haptens, would be in an optimal position for enantiofacial protonation of enol ethers (Scheme 3). Furthermore, in its conjugate base form this carboxylate may subsequently serve to stabilize the intermediate oxocarbenium ion **9**. The tetrahedral geometry of the ammonium ion of **8a** and **8b** was seen as a critical factor for supplying a binding pocket for the asymmetric pyramidalization of the carbon undergoing protonation.

The most active antibody generated, 14D9, elicited to **8a** catalyzes the enantioselective hydrolysis of the enol ether substrates **10** and **11** to the chiral aldehyde **12** and the enol ether **13** to ketone **14** (Scheme 3) [22, 23]. The process is readily scaled up for the cyclic substrate **13** and leads to the ready production of gram quantities of optically active ketone (–)-(*S*)-**14** in 65% yield (based on starting material) and 86% ee, demonstrating the potential of this catalytic antibody in organic synthesis [24].

In an alternative approach, Nakayama and Schultz [25] have successfully achieved the enantiofacial reduction of prochiral ketones. By utilizing the phosphonate hapten **15** catalytic antibodies were elicited which catalyze a highly stereospecific reduction of ketone **16** with sodium cyanoborohydride as a cofactor (Scheme 4). The most active antibody, A5, was found to have a pH optimum at acidic pH, consequently the reductions were performed in aqueous buffer at pH 5.0. The reaction was followed for multiple turnovers (>25) without any decrease in activity or stereoselectivity highlighting the utility of this catalytic system.

Lineweaver-Burke analysis of the steady-state kinetic data for A5 revealed a $k_{\text{cat}}=0.1 \text{ min}^{-1}$, equivalent to a rate enhancement of 290. The background reac-



Substrate ^a (conditions)	conv. [%]	ee [%]	configuration
10 (5 days, 37 °C) ^b	56	97	(S)
11 (7 days, 37 °C)	20	93	(S)
13 (1 h, 20 °C) ^c	100	93	(S)

^aSolutions containing 1 mM substrate and 30 μM antibody

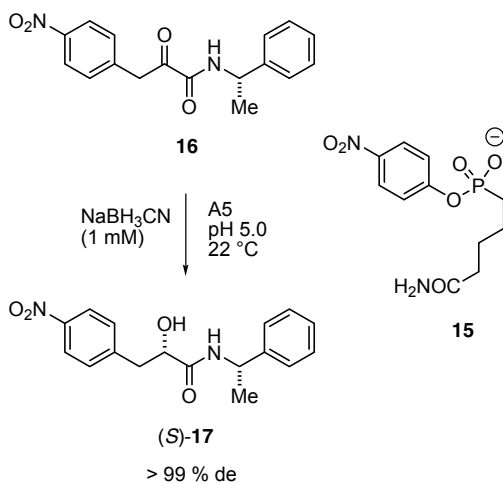
^bIn 50 mM MES buffer, 10 mM NaCN, and 90 mM NaCl, pH 5.5

^cIn 50 mM bis-tris buffer and 100 mM NaCl, pH 7.0

Scheme 3. Enantiofacial protonation of the enol ethers **10**, **11**, **13** by antibody 14D9, elicited to haptens **8a**, yields chiral products **12**, **14** with upto 96% ee

tion yields the α -hydroxy amide (*R*)-**17** with a 56% de. In contrast, the antibody-catalyzed process completely switches the stereospecificity of this reaction by generating the (*S*)-**17** product with a diastereomeric excess of >99%. This result emphasizes the fact that antibodies, even when elicited to achiral haptens, can provide binding pockets which discriminate between enantiomeric transition states with a high degree of selectivity.

Epoxides are key chiral synthetic intermediates and their enantioselective preparation by oxidation of achiral alkenes is a key reaction in many synthetic strategies. Sharpless' asymmetric epoxidation is suitable for most allylic alcohols [26, 27], but few general procedures exist for unfunctionalized olefins. Jacobsen's manganese salen-mediated epoxidation is suitable for and gives good selectivities with *Z*-olefins (85 to 90% ee) [28]. The enzyme chloroperoxidase

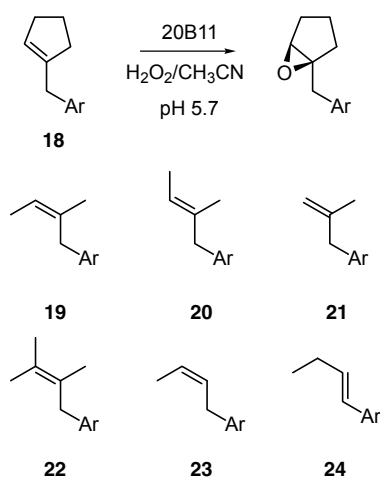


Scheme 4. Antibody A5, elicited to hapten **15**, catalyzes the highly enantiospecific reduction of α -ketoamide **16** (>99% de) with sodium cyanoborohydride (NaCNBH_3) as a cofactor. This is a good example of an achiral hapten generating a catalyst possessing exquisite chiral discrimination

has recently been shown to catalyze the epoxidation of unfunctionalized alkenes with hydrogen peroxide as the oxidant with 66 to 97% ee [29]. Raymond et al. [30] sought to expand the role of antibody-catalysis into the realm of catalytic asymmetric epoxidation. Mechanistic investigations into the origin of the catalytic power of enol ether hydrolysis supplied by antibody 14D9 (*vide supra*) revealed an equal contribution of general acid catalysis supplied by a carboxyl group and pyramidalization of the enol ether's β -carbon by hydrophobic contacts. It was reasoned that antibodies possessing the latter effect, coupled with a suitable oxidizing agent may be capable of catalyzing an enantioselective epoxidation of alkenes.

Based on this reasoning, the library of monoclonal antibodies elicited to the bait-and-switch haptens **8a** and **8b**, *vide supra*, were rescreened for their ability to catalyze the asymmetric epoxidation of the alkene substrate **18** (Scheme 5).

After a survey of oxidizing reagents the previously reported combination of hydrogen peroxide and acetonitrile [31,32] in aqueous buffer, under neutral conditions, effected clean epoxidation without damaging the antibodies. Testament to the successful mimicry of the transition-state for epoxidation by **8a** and **8b**, nine anti-**8a** and six anti-**8b** antibodies were found to catalyze the epoxidation reaction. One antibody, 20B11 elicited to **8a**, was studied in detail for its ability to catalyze the epoxidation of a range of alkenes **18** to **24** (Scheme 5). Alkenes **18** to **22** were indeed substrates, but **23** and **24** were not, revealing the importance both of double substitution at the benzylic carbon and proper localization of the double bond in the binding pocket. As shown in Scheme 5, the asymmetric induction supplied by 20B11 ranges from 67 to >98% ee for alkenes **18**, **19**, and **20**.



Alkene	K_m	$k_{\text{cat}} \times 10^5 \text{ s}^{-1}$	ER	ee ^a , [%]
18	85	5.0	40	>98
19	120	6.4	125	67
20	140	3.0	50	>98
21	260	1.4	60	nr ^b
22	60	3.6	15	nr

^aAbsolute configuration not determined

^bNot recorded

Scheme 5. Alkenes 18 to 24 were utilized as substrates for antibody 20B11 mediated chiral epoxidation. An oxidation system of $\text{H}_2\text{O}_2/\text{CH}_3\text{CN}$ was found to be sufficiently mild so as not to damage the biocatalyst

It should be noted, however, that the competing background reaction (which yields racemic products) is of a sufficient rate to result in optical purities of only 47, 64 and 71%, respectively.

3

C-C Bond Forming Processes

3.1

Diels-Alder Cycloaddition Reaction

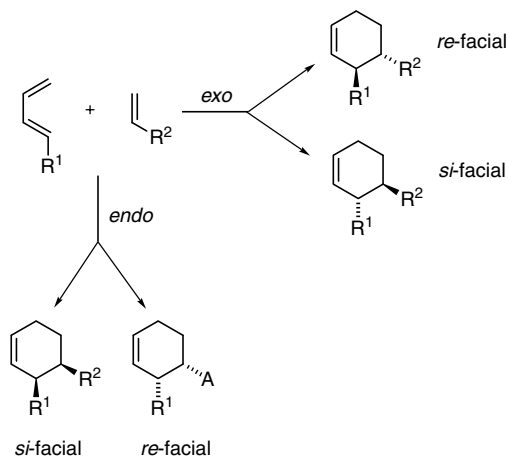
The Diels-Alder reaction is one of the most useful carbon-carbon bond-forming reactions in organic chemistry and can lead to the rapid assimilation of complex molecules containing a high degree of asymmetry. It is a bimolecular process and is a classic example of a reaction that demands control of translational entropy. It is accelerated by both high pressure and ionic solutions (8 M LiCl) and

proceeds through an entropically disfavored, highly ordered transition state, showing large activation entropies: -30 to -40 $\text{cal}\cdot\text{mol}^{-1}\text{K}^{-1}$ [33, 34].

While it is one of the most important and versatile transformations available to the organic chemist, the reaction between an unsymmetrical diene and dienophile can generate up to eight stereoisomers [35]. By increasing the electron-withdrawing character of the substituent on the dienophile Danishefsky [36] has shown that the regioselectivity of the Diels-Alder reaction can be controlled such that only the four *ortho*-adducts are produced (Scheme 6).

However, complete stereochemical control of the Diels-Alder reaction to yield only disfavored *exo*-products in enantiomerically pure form has proven to be very difficult by chemical means. Furthermore, only recently has a potentially enzymatic Diels-Alder reaction been reported [37]. Therefore, attempts to generate antibodies which can catalyze stereoselective Diels-Alder reactions is seen as an ongoing major target in the field.

Of particular difficulty when attempting to elicit catalytic antibodies for a bimolecular reaction, where by necessity the transition-state is very similar to products, is choosing a suitable hapten design that does not lead to strong product recognition and hence inhibition. Three strategies have been developed to circumvent this problem. In the first, the reaction is chosen to generate an unstable bicyclic intermediate which can either spontaneously rearrange or eliminate to furnish the product [38]. A more general strategy engages a highly constrained bicyclic hapten, which elicits a binding pocket that juxtaposes the diene and dienophile in an 'entropic trap', but with the additional feature of locking the developing cyclohexene product into a high energy pseudo-boat conformation [39,40,41,42,43,44]. This product destabilization, while perhaps reducing the turnover number of any catalyst generated, serves to aid the release of the product and minimize product inhibition. The final strategy replaces the rigid

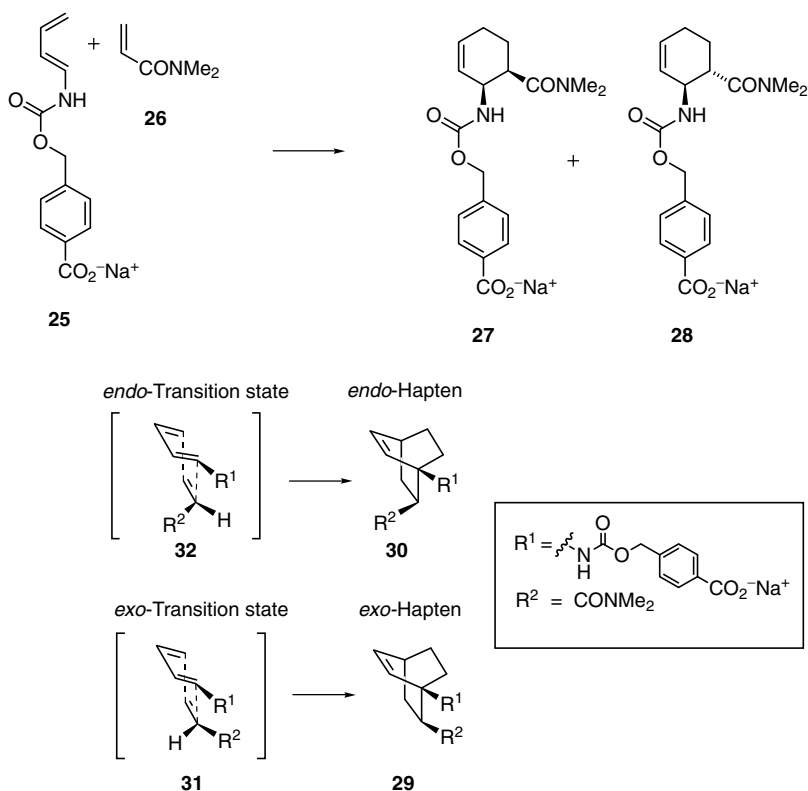


Scheme 6. Diastereo- and enantioselectivity in the Diels-Alder reaction between a substituted diene and dienophile

bicyclic core, common to both of the above strategies, with a freely rotating metallocene. One then relies on the antibodies being able to freeze out a conformer of the hapten which mimics the Diels-Alder transition state during the evolution of the immune response to elicit catalysts [45].

Gouverneur et al. [44] were interested in using catalytic antibodies to control the stereochemical outcome of the reaction between diene **25** and *N,N*-dimethylacrylamide **26** (Scheme 7).

The uncatalyzed reaction leads to the formation of only two diastereomers; the *ortho-endo-27* and the *ortho-exo (trans)-28*, in a ratio of 85:15. Two bicyclic haptens **29** and **30** were designed, one to mimic the *exo-31* and one a mimic of the *endo-32* transition-state structures. Kinetic studies showed that two monoclonal antibodies, 13D4 and 7D4, derived from immunization with hapten **29** and four antibodies, 22C8, 27R4, 14F2, and 8B11 derived from immunizations with hapten **30**, catalyze exclusively the formation of either the *exo-28* or *endo-27* adducts, respectively. Antibodies 7D4 (*exo*) and 22C8 (*endo*) provided the



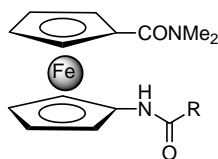
Scheme 7. Highly constrained haptens **30** and **31** were utilized to elicit catalytic antibodies for the diastereo- and enantioselective Diels-Alder reaction between diene **25** and dimethylacrylamide **26**

best rate enhancements and were studied in some detail. The turnover numbers for these antibodies were $k_{\text{cat}}=3.44\times 10^{-3}$ and $3.17\times 10^{-3} \text{ min}^{-1}$, respectively, equivalent to effective molarities ($k_{\text{cat}}/k_{\text{uncat}}$) of 4.8 M (7D4) and 18 M (22C8). These rate enhancements were slightly lower than for previous examples of Diels-Alderase antibody and were rationalized as being a result of a less than ideal transition state representation [38,39]. Both the bicyclic haptens **29** and **30** are mimics of a synchronous cycloaddition transition state, whereas *ab initio* studies had revealed that the reaction between **25** and **26** actually proceeds with considerable asynchronicity [44,46].

Each antibody catalyzes its respective processes not only with high diastereoselectivity (>98% de), but also with excellent enantioselectivity (>98% ee), such that the antibody-catalyzed Diels-Alder reaction gives essentially optically pure *endo*-**27** or *exo*-**28** adducts.

A more recent enterprise has focused on the compounds **33** and **34** perceived as freely rotating haptens for the same Diels-Alder cycloaddition between diene **25** and dienophile **26** (Fig. 1) [45]. Critical to the success of this enterprise is antibody recognition and freezing out of conformers which resemble either the Diels-Alder *exo*-**31** or *endo*-**32** transition states.

From a library of antibodies which recognize hapten **33** seven were found to be catalysts, (1 *endo* and 6 *exo*) and from the antibodies that recognized **34**, eight antibody catalysts (7 *endo* and 1 *exo*) were found. From these sublibraries, the most efficient *endo* (4D5, $k_{\text{cat}}=3.43\times 10^{-3} \text{ min}^{-1}$, EM 5 M) and *exo* (13G5, $k_{\text{cat}}=3.17\times 10^{-3} \text{ min}^{-1}$, EM 18 M) catalysts were studied in detail. Both undergo multiple turnovers without evidence of product inhibition and the reaction occurs with complete regio- and high diastereoselectivity (>98% de) and enantioselectivity (>98% ee). X-Ray crystal structure analysis of antibody 13G5, in complex with a ferrocenyl inhibitor containing the essential haptenic core which elicited it, revealed that the antibody does indeed bind the the hapten with the ring substituents in an eclipsed conformation [47]. In addition, three antibody residues have been implicated as being key, both in terms of the catalytic rate enhancement and the marked stereochemical control. Tyrosine-L36 acts as a Lewis acid activating the dienophile for nucleophilic attack, and asparagine-L91 and aspartic acid-H50 form hydrogen bonds to the carboxylate side chain that substitutes



33 R = $(\text{CH}_2)_3\text{CO}_2\text{H}$

34 R = 4-carboxyphenyl

Fig. 1. The freely rotating metallocenes **33** and **34** were utilized in a new strategy for the elicitation of enantioselective Diels-Alderase antibodies

for the carbamate diene substrate **25**. It is this hydrogen bonding network that is directly responsible for the pronounced stereoselectivity imparted by 13G5.

3.2

Cationic Reactions

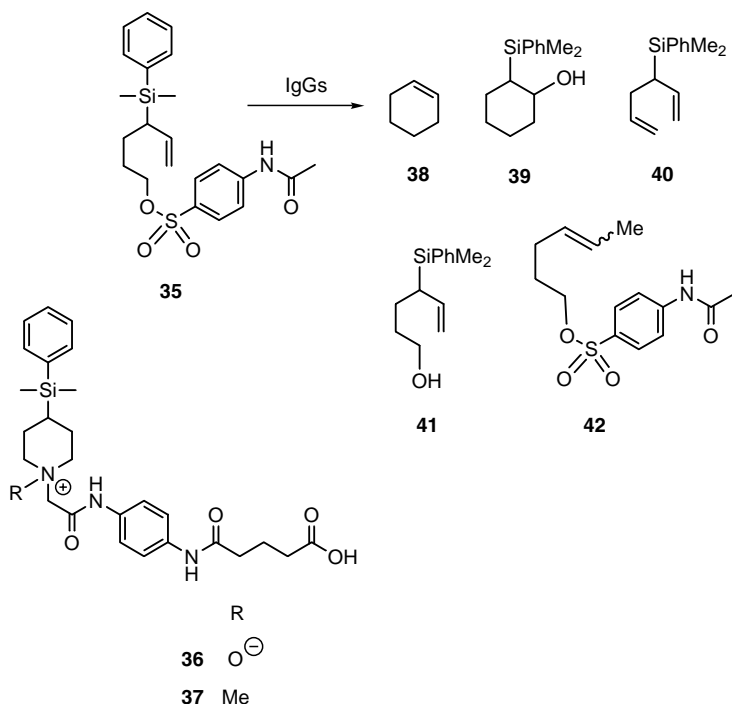
Carbocations can be difficult to generate and are such highly reactive intermediates that it is not easy to predict or control their reaction pathways [48]. This is of particular relevance in biochemical systems where the nucleophilic nature of the carbenium ion makes it susceptible to attack from peptidic side chain residues and/or backbone peptide bond components, thereby nullifying the required activity and essentially alkylating the protein catalyst. Nonetheless, nature has set us an impressive target in the way it deals with these intermediates [49,50,51]. A number of enzymes utilize cationic processes, one of the most remarkable being 2,3-oxidosqualene cyclase which catalyzes the formation of a highly complex tetracyclic triterpenoid with the concurrent generation of seven asymmetric centers [52,53].

For more than three decades chemists have been attempting to mimic cationic cyclization reactions [54,55]. This work has led to the realization that cationic cyclization reactions can be divided into three distinct steps: initiation, propagation and termination. Each of these steps must be rigidly controlled if one wishes to precisely organize the reaction outcome.

For antibodies to be successful catalysts for the initiation and control of cationic cyclization, they must be able to simultaneously stabilize point charges, overcome entropic barriers, and provide a chiral environment to elicit asymmetry [56]. In essence the problem reduces to that of generating a carbocation in an environment that stabilizes its formation and controls its subsequent reaction pathways.

The primary approach was a development of the classical system investigated by Johnson [57], which involves initiation of carbocation formation following solvolysis of a sulfonate ester. In this scenario, once cyclization has occurred, the newly formed carbocation can be captured by either elimination or attack of a nucleophile. At an entry level, in an attempt to catalyze the cyclization of the acyclic sulfonate ester **35** two haptens, **36** and **37**, were utilized in a 'bait-and-switch' strategy (Scheme 8) [58]. HPLC assay revealed that four antibodies (4C6, 16B5, 1C9, and 6H5) elicited to the *N*-oxide hapten **36** and one antibody, 87D7, elicited to the *N*-methylammonium hapten **37** were 'initiation' catalysts, i.e., they catalyzed the solvolysis of the sulfonate ester bond of **35**. A remarkable feature of antibody catalysis of this reaction is the narrow product distribution observed. Of all the possible products **38** to **42** inferred from the work of Johnson, only the cyclized products **38** and **39** were detected, a testimony to the antibodies exquisite binding of a putative cyclic transition state as programmed by the haptens **36** and **37**.

Antibody 4C6, elicited to the *N*-oxide hapten **36** yields cyclohexene **38** (2%) and *trans*-2-(dimethylphenylsilyl)cyclohexanol **39** (98%). Whereas 18G7, elicit-



Scheme 8. Antibodies elicited to the *N*-oxide hapten **36** catalyze the cationic cyclization of the arenesulfonate **35** to cyclohexene **38** and the diastereomeric alcohol **39**. The background reaction generates a much broader product spectrum **38** to **42**

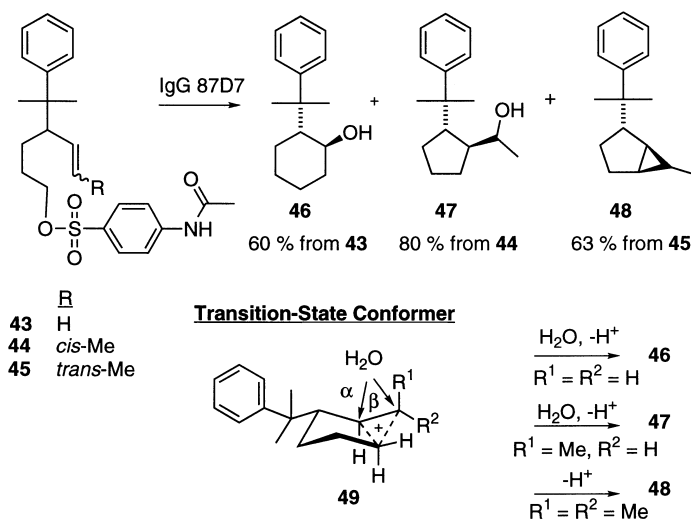
ed to the quaternary ammonium hapten **37**, gives a complete reversal of this product distribution, **38** (90%) and **39** (10%). In terms of the absolute rates, both these are efficient catalysts, for 4C6 $k_{\text{cat}}=0.02 \text{ min}^{-1}$ and $K_{\text{m}}=230 \mu\text{M}$, and for 18G7 $k_{\text{cat}}=0.02 \text{ min}^{-1}$, $K_{\text{m}}=25 \mu\text{M}$. The ratio of cyclohexene to cyclohexanol is entirely a reflection of the antibody's ability to exclude water from the binding site and hence prevent it from acting in the termination step. It is still unclear if the chiral induction at C2, leading to formation of exclusively the *anti*-cyclohexanol derivative **39**, is a result of direct antibody control or simply due to the steric constraints imposed by the bulky C1 moiety, leading to antarafacial quenching by a water molecule [59].

Subsequent studies with this antibody catalyst have involved discrete substrate modification experiments in order to probe and modify the reaction course and hence product outcome. Thus, the silicon atom of the phenyldimethylsilyl group was replaced with a carbon atom so that a potential β -effect would no longer bias the reaction course. In addition, a methyl group was added to the terminal olefin appendage for the purpose of both eliminating the chemical advantage of a reaction route involving a secondary rather than a primary carbo-

cation and also to increase the potential asymmetry of the products. This led to substrate modification experiments with the olefins **43** to **45** (Scheme 9) [60,61].

When olefin **43** was incubated with antibody 87D7, clean conversion to a single diastereomeric alcohol **46** was observed in 60% yield ($k_{\text{cat}}=0.013 \text{ min}^{-1}$, K_m 58 μM), with no observable product inhibition. With olefin **44**, where the silyl moiety had been replaced with carbon, a single diastereomeric exocyclic alcohol **47** was formed in 80% yield. The most interesting result however, was obtained with *trans*-olefin **45** which lead to the chirally defined cyclopropane **48** in 63% yield ($k_{\text{cat}}=0.021 \text{ min}^{-1}$, K_m 102 μM). Even under harsh Johnson-like conditions (formic acid/sodium formate, 80 °C, 2 h) this product could not be detected in the uncatalyzed reaction, revealing the exquisite power of antibody-catalysis not only to generate optically pure products from cationic cyclizations, but also to reroute cation reactivity to elicit novel homochiral products. Furthermore, the rate accelerations for this antibody catalyst is within an order of magnitude of those of natural enzymes that catalyze similar processes [62].

A unified reaction pathway invoking a protonated cyclopropane **49** was formulated to rationalize formation of the reaction products **46** to **48**. Thus, for substrate **43**, addition of water to **49** at the α -carbon generates the cyclohexanol **46**. For the substrates **44** and **45**, which both contain an electron-donating methyl group, products **47** and **48** are formed by either addition of water to the β -carbon of intermediate **49**, or loss of a proton from **49**. The observed product distribution and asymmetry can thus be ascribed to the direct control of the central carbocation intermediate **49** by the antibody catalyst.

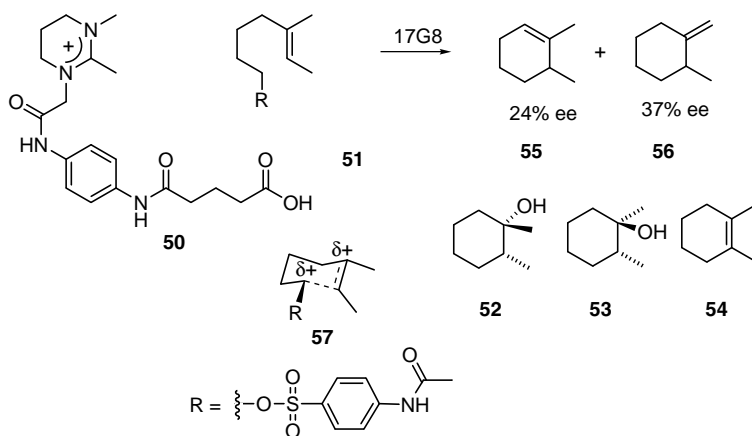


Scheme 9. Substrate modification experiments with alkenes **43**, **44**, **45** and antibody 87D7 revealed the intermediacy of a protonated cyclopropane **49** in the antibody-catalyzed cationic cyclization process

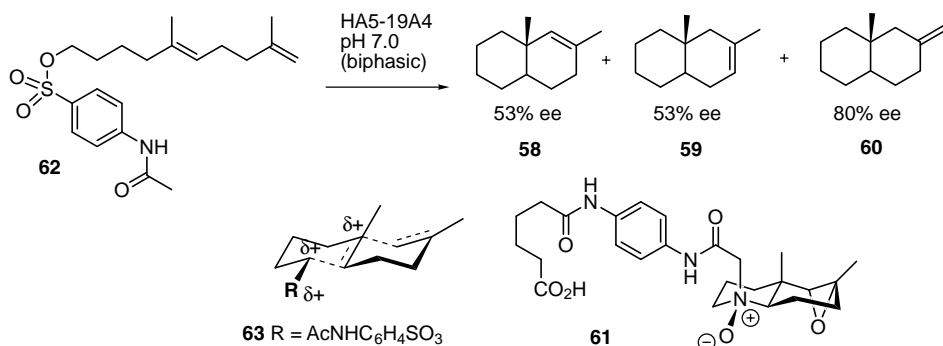
More recent efforts in this area have moved away from bait-and-switch haptens and focused on cationic transition state mimics, such as the amidinium ion species **50**, used to generate antibodies for the cationic cyclization of the arenesulfonate **51** (Scheme 10) [63]. Antibody 17G8, elicited to **50**, catalyzes the solvolysis of the terpenoid **51** (K_m 35 μM , k_{cat} $3.6 \times 10^{-3} \text{ min}^{-1}$) and re-routes the product distribution from the diastereomeric pair of cyclohexanols **52** and **53** and 1,2-cyclohexene **54**, into the cyclic products **55** and **56**. However, the enantioselectivity of the 17G8-catalyzed process is poor, carbocycles **55** and **56** being formed in a 24 and 37% ee, respectively. This poor stereoselectivity is attributed in part to the planar nature of the transition state analog **50** at the 2-position, a critical locus for asymmetric induction by the antibody during cyclization of the chair-like transition structure **57**.

Arguably the most demanding antibody-catalyzed cationic cyclization thus far reported has involved the formation of the decalins **58**, **59**, and **60** (Scheme 11) [64]. The *trans*-decalin epoxide **61** hapten, a TS mimic, was immunized as a diastereomeric mixture. Monoclonal antibody HA5-19A4 emerged as the best catalyst for the cyclization of arenesulfonate **62**. The olefinic fraction (70%) was predominantly a mixture of **58**, **59**, and **60** with an enantiomeric excess of 53, 53, and 80%, respectively, with a significant proportion (30%) of cyclohexanols.

Kinetic investigations revealed that the antibody first catalyzes the ionization of the arenesulfonate **62** to generate the first carbocation, this process has an ER of 3.2×10^3 and a $K_m = 320 \mu\text{M}$. The resulting cation can then either cyclize to decalins **58**, **59**, **60** in a concerted process (as *via* the transition structure **63**) or in a stepwise fashion. The formation of significant amounts of cyclohexanols



Scheme 10. The amidinium **50** was engaged as a transition state analog hapten to generate antibodies for the cationic cyclization of the arenesulfonate **51**. Antibody 17G8 catalyzes this cyclization process to yield two cyclohexene derivatives **55** and **56**, albeit with low enantioselectivity 24 and 37% ee, respectively. The remarkable feature the 17G7-catalyzed process is a complete change in the product outcome from non-catalyzed process which yields **52**, **53**, **54**



Scheme 11. Antibody HA5–19A4, elicited to that transition state analog hapten, diastereomeric epoxide **61**, catalyzed the formation of decalins **58**, **59**, **60** in a tandem cyclization reaction with moderate to good ees from the arenesulfonate **62**

seems to indicate that the latter may be the case. Most interestingly, inhibition studies with **61** strongly suggest that the isomer of the haptenic mixture of that elicited this antibody has an axial representation of the leaving sulfonate group, which would indicate a formal reversal of the Stork–Eschenmoser [65, 66] concept of equatorial leaving groups and presents an interesting challenge for future study.

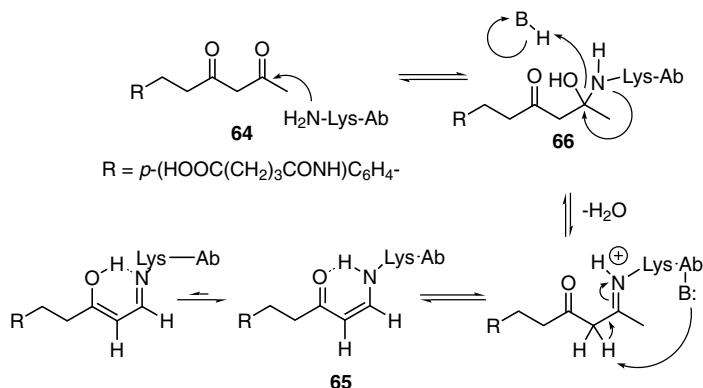
3.3

Aldol Condensation

The aldol condensation is one of the most utilized C–C bond forming reactions in both organic chemistry and nature. A variety of efficient reagents have been developed to control the stereochemical outcome of this reaction, but they are required in stoichiometric amounts and, in general, require preformed enolates and involve extensive protecting group strategies [67,68,69]. More recently, catalytic aldol reactions have been explored [70,71]. In addition a number of enzymes is known to catalyze the aldol condensation and much mechanistic information has been gleaned about their modes of action [72,73].

Class I aldolases utilize the ϵ -amino group of a lysine (Lys) residue in the active site to form a Schiff base with one of the substrates, which thus activates the substrate to an aldol donor. In an attempt to mimic this mechanism, the β -diketone **64** was used as a hapten in the hope of eliciting of a Lys residue in an antibody binding site (Scheme 12) [74].

The hapten was designed to trap the requisite Lys residue in the active site and then form the essential enamine intermediate **65** by dehydration of the tetrahedral carbinolamine intermediate **66**. The trapping of a nucleophile in antibody-binding sites for enhanced efficiency of antibody catalysis had previously been reported by Wirsching and co-workers [75] and has been dubbed ‘reactive immunization’. By utilizing this reactive immunization strategy, two antibodies,



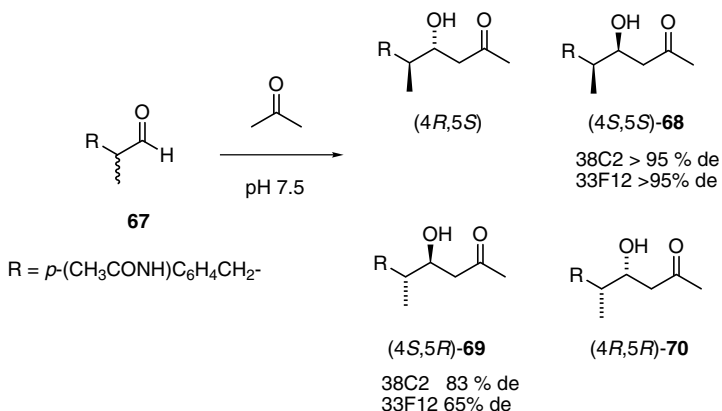
Scheme 12. Diketone hapten **64** was utilized as a reactive immunization hapten and trapped a lysine residue in an antibody binding site by the mechanism outlined

38C2 and 33F12, were found that possessed a Lys residue in their binding sites and that catalyze the aldol reaction between a variety of aliphatic ketones and aldehydes.

Reaction of the branched 3-phenylpropionaldehyde **67** acceptor with acetone is the most efficient process yet observed and shows no product inhibition (Scheme 13). In addition, only 1 mol % of catalyst is required to achieve high conversion of substrate.

The background reaction at pH 7.5 under identical conditions gives a $k_{\text{uncat}} = 2.28 \times 10^{-7} \text{ M}^{-1} \text{ min}^{-1}$ [76]. For antibody 38C2 and 33F12, this gives a $(k_{\text{cat}}/K_{\text{m}})/k_{\text{uncat}}$ of ca. 10^9 . The proficiency [77] of this process was attributed in a large part to the entropic advantage gained from the juxtaposition of the bi-reactant system in the antibody binding site reflected also in the high effective molarity (EM) of this process ($>10^5 \text{ M}$). In fact, the catalytic efficiency of these antibodies is only 3 orders of magnitude lower than that of the most studied type-I aldolase enzyme, 2-deoxyribose 5-phosphate aldolase [78].

The stereoselectivity of the antibody-catalyzed addition of acetone to aldehyde **67** revealed that the ketone was added to the *re*-face of **67** regardless of the stereochemistry at C2 of this substrate. The aldol process follows a classical Cram-Felkin mode of attack on (*S*)-**67** to generate the (4*S*,5*S*)-**68** diastereomer and the anti-Cram-Felkin mode of attack on the (*R*)-**67** to yield the (4*S*,5*R*)-**69** diastereomer. The products are formed at a similar rate and yield, therefore there is no concomitant kinetic resolution of the racemic aldehyde. The two antibodies differ in their diastereofacial selectivity, reflecting the ability of the antibodies to orient the **67** on opposite sides of the prochiral faces of the nucleophilic antibody-enamine complex of acetone. Heathcock and Flippin [79] have shown that the chemical reaction of the lithium enolate of acetone with (*S*)-**67** yields the (4*S*,5*S*)-**68** diastereomer a 5% de for this Cram-Felkin product. The generation of the (4*S*,5*R*)-**69** and (4*R*,5*R*)-**70** products in a ratio of 11:1 by the



Scheme 13. Diastereoselectivity of the aldol reaction between racemic aldehyde **67** and acetone catalyzed by antibodies 38C2 and 33F12

38C2-catalyzed process is a remarkable reversal of this typical Cram-Felkin stereoselectivity of the aldol, to a disfavored and energetically more demanding anti-Cram-Felkin model.

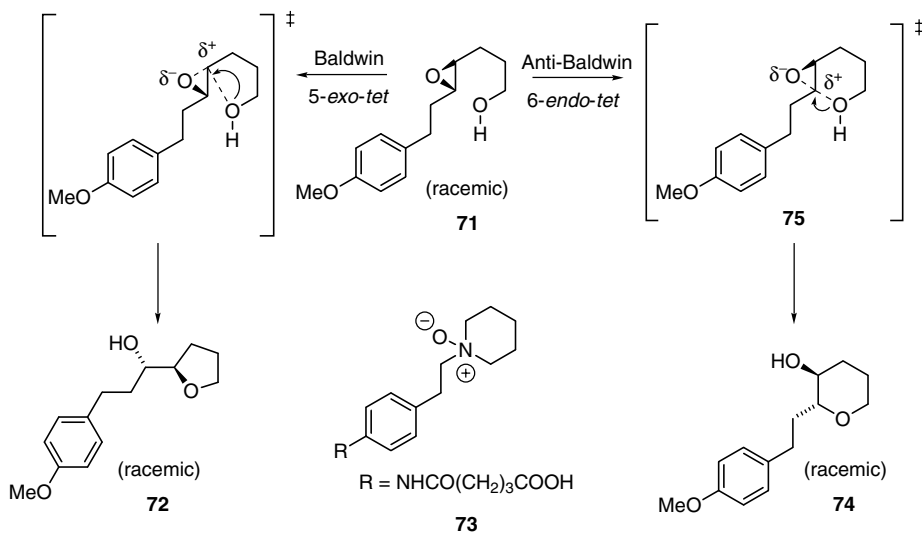
The crystal structure of unliganded 33F12, shows a lysine residue, Lys-H93, at the bottom of a hydrophobic well, but linked *via* a hydrogen-bonded water to a tyrosine moiety, TyrL41 [80]. The high catalytic rates imparted by this catalyst are now rationalized as being a composite of both imine formation with LysH93 and general base catalysis supplied by the TyrL41 residue.

One normally expects antibodies to have a low tolerance to substrate modifications, however an ongoing feature of these aldolase antibodies is their wide scope. They accept a remarkable range of aldol donors and acceptors and perform crossed-, intramolecular- and retro-variants of this reaction, with high yields, rates, and stereospecificities [81,82,83]. Substrate modification experiments have revealed that when acetone is the aldol donor in a ketone-aldehyde crossed aldol reaction, stereoselectivity is linked to attack of the *si*-face of a prochiral aldehyde with typically >95% ee and when hydroxyacetone is the donor substrate, attack occurs preferentially at the *re*-face of the aldehyde leading to a diastereomeric α,β -dihydroxy ketones with the two stereogenic centers having an α -*syn* configuration. This reaction leads to stereospecificities of typically 70 to >99% ee.

4

Disfavored Cyclization

For reactions where there are several possible outcomes, the final product distribution reflects the relative free energies of each transition state when the reaction is under kinetic control, this is in fact the empirical basis behind enantio-



Scheme 14. *N*-Oxide haptent **73** elicited an antibody, 26D9, which re-routes the cyclization of the hydroepoxide **71** to the disfavored product **74**

and diastereospecific reactions [84]. Baldwin's rules predict that for the acid-catalyzed ring closure of the hydroepoxide **71** the tetrahydrofuran **72** arising from 5-*exo-tet* attack will be preferred (Scheme 14) [85,86]. Janda et al. [87] raised antibodies to the cyclic haptent **73** and generated a catalytic antibody, 26D9, which reverses the kinetic outcome of the reaction and produces exclusively the tetrahydropyran product **74** in optically pure form.

The haptent was designed to elicit antibodies which would strategically place a negatively charged amino acid adjacent to the epoxide moiety in a position to selectively stabilize the disfavored the 6-*endo-tet* TS structure **75**. A remarkable feature of 26D9 catalysis of this reaction is its stereoselectivity, accepting only the (*S,S*)-enantiomer of **71** as a substrate and leading to a kinetic resolution of racemic **71**. The turnover number for this catalyst is $k_{\text{cat}}=4.6\times 10^{-6} \text{ min}^{-1}$. The comparison of $k_{\text{cat}}/k_{\text{uncat}}$ was not possible for this process because no 6-*endo-tet* product **74** could be detected. This process is an unprecedented achievement in *de novo* catalyst generation, as catalytic antibodies were elicited to a reaction for which there is no enzymatic or synthetic equivalent.

5 Conclusions

Since the first reports of antibody catalysis appeared just over a decade ago [88, 89], >50 different chemical reactions have been catalyzed by these remarkable proteins and their scope and application is expanding at a rapid pace [7]. Improved haptent design strategies such as reactive immunization and refinements

of the more classical transition state analog and bait-and-switch hapten approaches are resulting in improvements in both the catalytic power and applicability of these remarkable enzyme-mimics. From the perspective of asymmetric catalysis (vide supra), initial attempts focusing on relatively trivial problems have been superseded by more complex systems targeting asymmetric C-C bond forming reactions with real synthetic viability. However, despite these notable successes, many problems still remain to be solved. These include limitations in the scope of the reactions that have been achieved and much more work still remains to optimize catalyst stereospecificity and performance under the rigorous conditions of organic synthesis, especially in large-scale reactions. Nonetheless, continued exploratory approaches with catalytic antibodies is undoubtedly going to bear fruit in the field of asymmetric chemistry for many decades to come.

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Chapter 41.1

The Chiral Switch of Metolachlor

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Keywords: Imine hydrogenation, Ir diphosphine complexes, Ir ferrocenyldiphosphine complexes, Rh diphosphine complexes, Technical process, Industrial application, MEA imine, Ir ferrocenyldiphosphine complexes, (S)-Metolachlor, Chiral switch

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1 Introduction

Up to now, relatively few enantioselective catalysts are used on an industrial scale. One reason for this is the fact that enantioselective catalysis is a relatively young discipline: Up to 1985, only few catalysts affording enantioselectivities up to 95% were known [1]. This has changed dramatically in recent years and now many chiral catalysts are known that catalyze a variety of transformation with ee's >98% [2]. Another reason is that the application of enantioselective catalysts

on a technical scale presents some very special challenges and problems [3]. Some of these problems are due to the special situation for manufacturing chiral products, others are due to the nature of the enantioselective catalytic process.

Enantiomerically pure compounds will be used above all as pharmaceuticals and vitamins [4], as agrochemicals [5], and as flavors and fragrances [6]. Pharmaceuticals and agrochemicals usually are multifunctional molecules that are produced via multistep syntheses. Compared to basic chemicals, they are relatively small scale products with short product lives, produced in multipurpose batch equipment. The time for development of the production process is often very short since “time to market” affects the profitability of the product.

1.1

Critical Factors for the Application of Enantioselective Catalysts

Whether a synthetic route containing an enantioselective catalytic step can be considered for a particular product is usually determined by the answer to two questions:

- Can the costs for the over-all manufacturing process compete with alternative routes?
- Can the catalytic step be developed in the given time frame?

The following critical factors determine the technical feasibility of an enantioselective process:

- The *enantioselectivity* of a catalyst should be >99% for pharmaceuticals unless further enrichment is easy (via recrystallization or at a later stage via diastereomer separation). *Ee*'s >80% are often acceptable for agrochemicals.
- The *catalyst productivity*, given as turnover number (ton) or as substrate/catalyst ratio (s/c), determines catalyst costs. Ton's should be >1,000 for high value products and >50,000 for large scale or less expensive products (catalyst re-use increases the productivity).
- The *catalyst activity* (turnover frequency, *tof*, h^{-1}), affects the production capacity. *Tof*'s should be >500 h^{-1} for small and >10,000 h^{-1} for large scale products.
- *Availability and cost of the catalyst*: chiral ligands and many metal precursors are expensive and/or not easily available. Typical costs for chiral diphosphines are 100 to 500 \$/g for laboratory quantities and 5,000 to >20,000 \$/kg on a larger scale (only few ligands are available commercially). Chiral ligands used for early transition metals are usually cheaper.
- The *development time* can be a hurdle, especially if an optimal catalyst has to be developed for a particular substrate (substrate specificity) and/or when not much is known on the catalytic process (technological maturity).

For most other aspects such as catalyst stability and sensitivity, handling problems, catalyst separation, space time yield, poisoning, chemoselectivity, process sensitivity, toxicity, safety, special equipment, etc., enantioselective catalysts have similar problems and requirements as nonchiral catalysts.

Which of these criteria will be critical for the development of a specific process will depend on the particular catalyst and transformation. In the following section we describe the various steps that were necessary to develop a technical process for the production of (*S*)-metolachlor.

2

(*S*)-Metolachlor: The Problem

Metolachlor was first described in 1972 [7]; it is an *N*-chloroacetylated, *N*-alkoxyalkylated *ortho* disubstituted aniline (Fig. 1). The unusual functionalization pattern renders the amino function extremely sterically hindered. As a consequence, *metolachlor* has two chiral elements: a chiral axis (atropisomerism, due to hindered rotation around the C_{Ar}-N axis) and a stereogenic center, leading to four stereoisomers. In 1982 it was found that the two 1'*S*-stereoisomers provide most of the biological activity [8]. This was the driving force for finding a production process for the biologically active stereoisomers – a formidable task due to the very special structure and properties of this molecule, the large production volume, and also because of the extremely efficient production process for the racemic product [9]. During the course of the development efforts, the following minimal requirements evolved for a technically viable catalytic system: ee ≥80%, substrate to catalyst ratio >50,000 and tof >10,000 h⁻¹.

2.1

Outline of Synthetic Routes

Of the many possible approaches to synthesize enantiomerically pure compounds, enantioselective catalysis is arguably the most elegant method. In such a case, the overall synthesis is usually designed around the enantioselective catalytic transformations. The reason for this is that only a limited number of effective catalytic enantioselective transformations are available. In addition, it is often quite difficult to transfer the results obtained for a particular substrate to even a close analogue due to the high substrate specificity of many catalysts (low tolerance for structure variation even within a class of substrates). Moreover, the assessment of the a technical feasibility of enantioselective catalysts is also hampered because there is little information on catalyst activity or other aspects

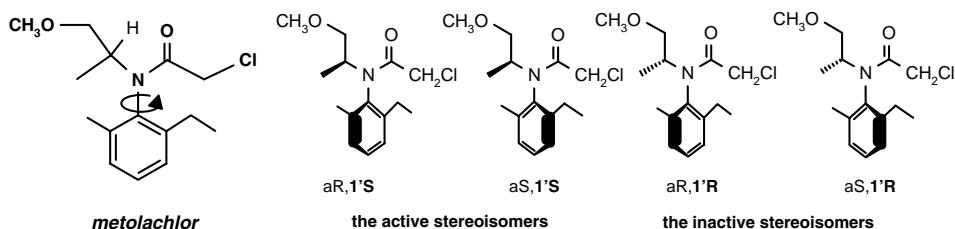


Fig. 1. Structure of metolachlor and its individual stereoisomers

available (in the literature enantioselectivity is the dominant criterion) and because few applications with “real” substrates exist (usually simple model reactions are studied).

Many possibilities exist for the enantioselective preparation of (*S*)-metolachlor, four synthetic routes were considered in some detail:

Enamide hydrogenation (Fig. 2). This idea clearly was inspired by the successful L-dopa process of Monsanto [10]. At that time, little was known on the effects of the substituents at the C=C bond and the amide nitrogen. A selective synthesis of one of the enamides looked difficult.

Nucleophilic substitution of a (*R*)-methoxyisopropanol derivative (Fig. 3). Here, the proposed key step was the enantioselective hydrogenation of methoxyacetone in analogy to the Pt-*Cinchona* catalyzed hydrogenation of α -ketoesters [11] (the Ru-binap system was not yet known at that time). The nucleophilic substitution with clean inversion was expected to be difficult.

Hydrogenation of MEA imine (Fig. 4). Because the racemic metolachlor is produced via a reductive alkylation, it was obvious to try to hydrogenate the imine

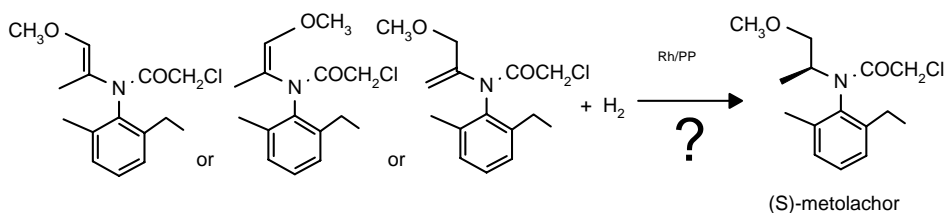


Fig. 2. Enamide hydrogenation: Structures of tested enamides

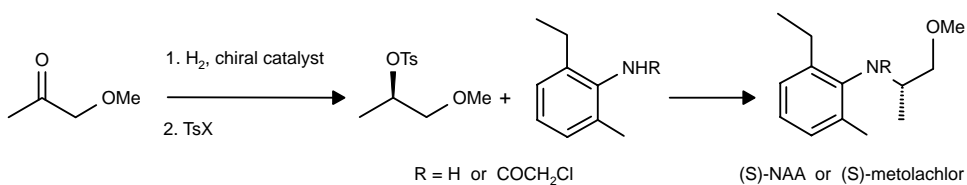


Fig. 3. Enantioselective hydrogenation of methoxyacetone and nucleophilic substitution with a MEA derivative

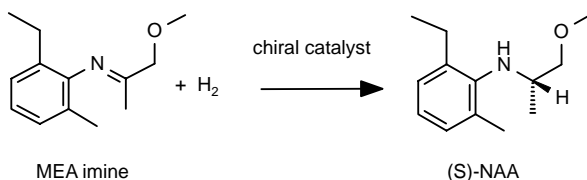


Fig. 4. Imine hydrogenation: Structures of MEA imine and (*S*)-*N*-alkylated aniline

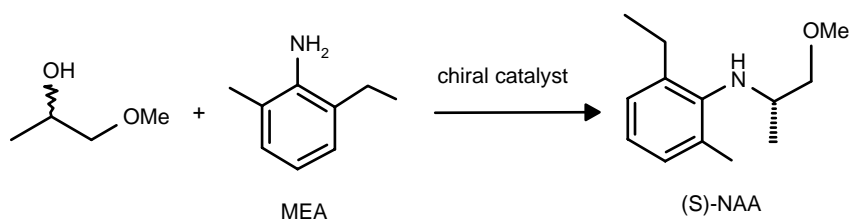


Fig. 5. Alkylation of MEA with methoxyisopropanol

intermediate, either isolated or formed in situ. Unfortunately, at that time only one single imine hydrogenation was described in the literature with 22% ee [12].

Direct catalytic alkylation with racemic methoxyisopropanol (Fig. 5). This idea was based on an alternative process developed for the racemic product with heterogeneous catalysts in the gas phase [13] and some results of the *N*-alkylation of aliphatic amines with primary alcohols using homogeneous Ru phosphine catalysts [14].

2.2

Assessment and Screening of Proposed Routes

2.2.1

Assessment Criteria

When assessing proposed routes the following criteria are important:

- chances of success for the catalytic step according to precedents, i.e., is there a closely related, efficient catalytic transformation,
- number and perceived difficulty of the non-catalytic steps, and
- first approximations for costs and ecology of the over-all synthesis

In Table 1 the four proposed routes are classified according to these criteria. The overall ranking was used for setting priorities to carry out practical work. Because the enantioselective catalysis is usually considered to be the most difficult

Table 1. Comparison of possible routes for the synthesis of (S)-metolachlor

Route	Catalytic step	Other steps	Cost (ecology)	Priority
Enamide	close analogy ee >90%	enamide synthesis difficult	high (medium)	1
Substitution	weak analogy ee >80%	substitution difficult	high (bad)	2
Ímine	weak analogy ee <30%	as in current process	medium (good)	3
Direct alkylation	no precedent	as in current process	low (very good)	4

step, its chances of success very often dominate the decision and accordingly, the enamide and the substitution route were tested first.

2.2.2

Screening Results for Routes 1 and 2

Enamide route. The preparation of the three MEA enamides proved to be rather difficult. Disappointingly, we did not succeed to hydrogenate any of the three isomers using seven different Rh diphosphine complexes at normal pressure and temperatures up to 50 °C.

Substitution route. The hydrogenation of methoxyacetone was somewhat more successful: Using a Pt/C catalyst modified with cinchonidine as described by Orieto et al. [14] produced (*R*)-methoxyisopropanol, but ee's were never higher than 12%. The *direct alkylation* was not tested experimentally, because chances for success were considered to be too low.

3

Imine Hydrogenation

The results of the route screening left the hydrogenation of the MEA imine as the only realistic possibility. As a matter of fact, it took more than 10 years (Table 2) and the collaboration of an untold number of research and development chemists, technicians, engineers, and workmen until the production plant for making (*S*)-metolachlor was opened on November 16, 1996. The most time-consuming part was of course to find the right catalyst: metal, ligand, and additives. Many of the classical strategies were used: screening of various metal-diphosphine combinations; use of different metal precursors; synthesis of novel ligands; ligand fine tuning; screening and optimization of solvents, additives and reaction

Table 2. Milestones in the history of *S*-metolachlor

1970	Discovery of the biological activity of <i>rac</i> -metolachlor (patent for product and synthesis)
1978	Full-scale plant for the production of <i>rac</i> -metolachlor in operation (capacity >10,000 t/y)
1982	Synthesis and biological tests of the four stereoisomers of metolachlor
1983	First unsuccessful attempts to synthesize <i>S</i> -metolachlor via enantioselective catalysis
1985	Rhodium/cycphos catalyst gives 69% <i>ee</i> for the imine hydrogenation (UBC Vancouver)
1986	Discovery of new iridium diphosphine catalysts that are more active and selective than Rh catalysts for the hydrogenation of MEA imine
1993	Ir/ferrocenyl-diphosphine catalysts and acid effect are discovered. Process development starts
1993/4	Patents for <i>rac</i> -metolachlor expire
1995/6	Pilot results for <i>S</i> -metolachlor: <i>ee</i> 79%, ton 1,000,000, tof >200,000 h ⁻¹ , first 300 t produced
1996	Full-scale plant for production of >10,000 t/y <i>S</i> -metolachlor starts operation

conditions. The development of the technical process, the design of the high pressure equipment and the construction of the plant were carried out in less than 3 years, a very remarkable achievement in itself.

3.1

Finding the Right Metal-Ligand Combination

The history of the development of a technically feasible catalyst for the enantioselective hydrogenation of MEA imine has been described [15]. Very important were collaborations, initially with a research team of the University of British Columbia at Vancouver [16] and later with the group of J.A. Osborn [17] of the University of Strasbourg.

Screening of Rh diphosphine complexes (Fig. 6). First positive results were obtained by trying to adapt Rh diphosphine catalysts originally developed for the hydrogenation of olefins. An extensive ligand screening led to $[\text{Rh}(\text{kbd})\text{Cl}]_2/\text{cycphos}$ as the best catalyst: 69% ee were achieved at $-25\text{ }^\circ\text{C}$, the best tof was 15 h^{-1} at 65 bar, r.t., far too low for an industrial application [16]. Nevertheless, these results represented a remarkable progress for the enantioselective hydrogenation of *N*-arylimines.

Screening of Ir diphosphine complexes. The next breakthrough was obtained when iridium was used instead of rhodium. This idea was inspired by results of Crabtree et al. [18] who described an extraordinarily active Ir/tricyclohexylphosphine/pyridine catalyst that was able to hydrogenate even tetra-substituted C=C bonds. The highest ee's were observed with an Ir-bdpp catalyst in the presence of additional iodide ions (ee 84% at $0\text{ }^\circ\text{C}$), but the activity was disappointing; ton 's up to 10,000 and tof 's of 250 h^{-1} (100 bar and $25\text{ }^\circ\text{C}$) with somewhat lower ee's were obtained for Ir-diop-iodide catalysts [17, 19]. A major problem of these new Ir diphosphine catalysts was an irreversible catalyst deactivation.

These results, especially the good enantioselectivities, were very promising and represented by far the best catalyst performance for the enantioselective hydrogenation of imines at that time. Nevertheless, it was also clear that we could probably not reach our ambitious goals using Ir complexes with "classical" diphosphine ligands. Even though Ir/diop and Ir/bdpp catalysts showed much higher activities than the best Rh complexes for MEA imine, they were still far below the requirements: A new approach was clearly required.

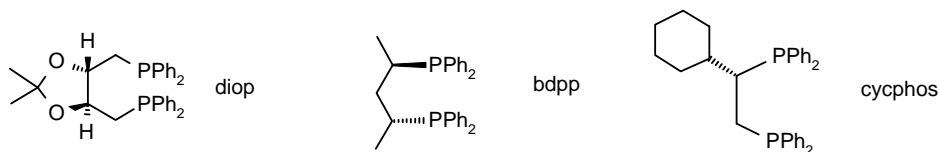


Fig. 6. Imine hydrogenation: Structure of important ligands

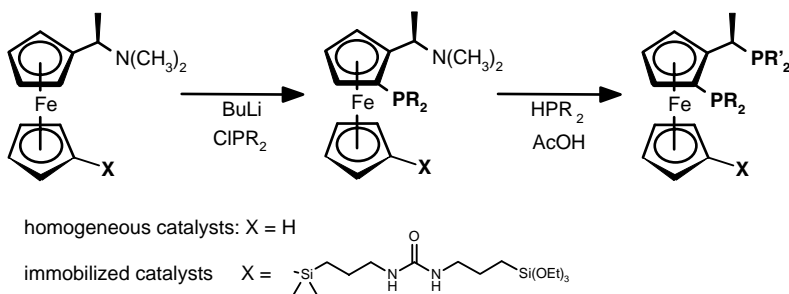


Fig. 7. Preparation and structure of ferrocenyl diphosphine ligands

Synthesis and screening of a new ligand class. Since we could not get stable catalysts with the known diphosphine ligands, new types were tested, among others, novel ferrocenyl-diphosphines (PPF) developed by Togni and Spindler [20]. Their mode of preparation (Fig. 7) allows an efficient fine tuning of the electronic and steric properties of the two phosphino groups, something that is often very difficult with other ligand classes. Indeed, the Ir complexes of such diphosphines proved to be very efficient. Especially PPF-P(3,5-(CH₃)₂C₆H₃)₂ (R=Ph, R'=3,5-xylyl), named xyliphos, turned out to give an exceptionally active catalyst and, even more important, it did not deactivate!

3.2

Optimization of Reaction Medium and Conditions

Using xyliphos as ligand, a screening of solvents and additives as well as an optimization of the reaction conditions were carried out. Most remarkable was the effect observed when 30% of acetic acid were added to the reaction mixture of MEA imine and Ir-xyliphos-NBu₄I: we observed a rate increase by a factor of 5 while the time for 100% conversion was more than 20 times shorter than without additives. The effect of pressure and temperature was investigated in the presence of acid and iodide. The reaction rate was approximately proportional to the hydrogen pressure, ee's decreased from 81% at -10 °C to 76% at 60 °C. Using optimized conditions, the isolated imine can be hydrogenated at a hydrogen pressure of 80 bar and 50 °C with a substrate to catalyst ratio (s/c) of 1,000,000. Complete conversion is reached within 4 h with an enantioselectivity of 79% with an initial tof exceeding 1,800,000 h⁻¹ [21]. These results set a new standard concerning catalyst activity and productivity for a homogeneous enantioselective hydrogenation.

3.3 Ligand Fine Tuning

As described above, the Ir-xylyphos catalysts showed extremely high catalyst activities and productivities. On the other hand, the enantioselectivity to the desired *S*-enantiomer just barely meets the requirement. Therefore, we tried to improve the ee's by tuning of the electronic and steric properties of the new ferrocenyl ligands. As shown in Table 3, we could indeed improve the selectivity of the catalyst [21]. However, as observed before with other ligands, an improvement in selectivity was always offset by a loss in activity and often productivity. In the end, xylyphos was the best compromise regarding activity and selectivity for a technical process.

3.4 Alternative Catalytic Systems

During the course of the development work two alternative variants based on the very active xylyphos were investigated in some detail.

Immobilized Ir diphosphine catalysts. Immobilized catalysts were investigated for two reasons. First, because many Ir catalysts deactivate via dimerization it was attempted to prevent this by site isolation. Indeed, several of immobilized Ir diphosphine complexes showed improved activities and stabilities [21]. Best results were obtained with ferrocenyl diphosphine ligands immobilized on SiO₂ via the X substituent (see Fig. 7): ee 79%, ton up to 120,000. These are at the moment the most active heterogeneous catalysts known. The second reason for immobilization was their expected better separation properties, allowing different work up strategies. Because the catalytic performance of the homogeneous analogs was so much better (see Table 3), this approach was not investigated further.

Reductive alkylation using Ir ferrocenyl diphosphine catalysts. Because the synthesis, isolation, and purification of the MEA imine are cost factors, the most attractive method would be an enantioselective reductive alkylation, in analogy to the existing process for *rac*-metolachlor. At that time, enantioselective reduc-

Table 3. MEA imine hydrogenation with Ir-ferrocenyldiphosphine complexes: Comparison of catalyst performances of (a) homogeneous catalysts, (b) immobilized on silica gel, and (c) for reductive alkylation in a two-phase system (formulas see Fig. 7)

R	R'	ton	tof (h ⁻¹)	ee	type	comments
Ph	3,5-xylyl	1,000,000	>200,000	79	(a)	production process
<i>p</i> -CF ₃ C ₆ H ₄	3,5-xylyl	800	400	82	(a)	ligand screening
Ph	4- <i>t</i> -Bu-C ₆ H ₄	5000	80	87	(a)	low temperature
Ph	4-(<i>n</i> -Pr) ₂ N-3,5-xylyl	100,000	28,000	83	(a)	optimized conditions
Ph	3,5-xylyl	120,000	12,000	79	(b)	optimized conditions
Ph	3,5-xylyl	10,000	700	78	(c)	optimized conditions

tive alkylations were not known. Nevertheless, we tried the direct reductive alkylation of MEA with methoxyacetone using our most active Ir-ferrocenyl diphosphine catalysts. In a two-phase system, we indeed achieved ton's up to 10,000 and ee's up to 78% [21]. Again, due to the superior performance of the MEA imine hydrogenation this approach was abandoned (see Table 3).

3.5

Technical Process

Once a catalyst system with the required performance was found and confirmed, attention was turned to finding a technically feasible overall process. Without going into too much detail, the following aspects had to be dealt with. The technical preparation of methoxyacetone and 2-methyl-6-ethylaniline as well as the chloroacetylation step were already established in the existing process for *rac*-metolachlor. However, the production of the MEA imine in the required quality remained to be worked out. This proved to be not trivial, since most high performance catalysts are quite sensitive to all kinds of impurities. Another problem to be solved was the availability and the technical handling of the ligand and the organometallic catalyst precursor. In the end, a large-scale synthesis for the ligand was developed, while the Ir precursor is supplied by a commercial manufacturer. Scale up from the 50 mL screening autoclave via 6.3 L and 50 L stirred tanks, and a 1,000 L loop reactor to the final 10 m³ production autoclave was carried out without much problems. The catalyst and the process are very well behaved if all starting materials have the required quality. Indeed, the production plant in Kaisten has been producing since about one year without major problems.

4

Conclusions

The case of (S)-metolachlor allows some generalized conclusions.

- The chiral switch from the racemate to an enriched form is attractive not only for pharmaceuticals but also for agrochemicals. Enantioselective hydrogenation is an especially attractive and technically feasible technology to allow this. The activity of the catalyst and not so much its enantioselectivity is often the major problem to be solved.
- The selection of the catalytic system is especially difficult when the required catalyst performance is very high. In addition, every enantioselective catalytic reaction must be treated individually. Besides establishing the technical feasibility of the catalytic key step, it is important to evaluate the entire reaction sequence to the final product.
- The time for process development obviously depends very much on the state of the art of a given catalytic technology. When one has to start almost at point zero as for the enantioselective imine hydrogenation, it may take many years to reach the goal. In our experience, an empirical approach is the fastest

way to find or develop a catalytic system for a problem that has no close precedent. Mechanistic information is especially helpful in later stages of process development or for trouble shooting.

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Chapter 41.2

Process R&D of Pharmaceuticals, Vitamins, and Fine Chemicals

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Keywords: Pantothenic acid, Pantolactone, Dextromethorphan, Cilazapril, Mibefradil, Vitamin E, (*R,R,R*)- α -Tocopherol, Orlistat, Tetrahydropipstatin, β -Ketoester hydrogenation, α -Ketolactone hydrogenation, Enamide hydrogenation, Imine hydrogenation, α,β -Unsaturated acid hydrogenation, Allylic alcohol hydrogenation, γ -Oxo-olefin hydrogenation, Ene reaction, Glyoxylate-ene reaction, Rh(BPPM), Ru(MeOBIPHEP), Raney-Ni/tartaric acid, Ti(BINOL), Enantioselective hydrogenation, Chiral drugs, Ruthenium diphosphine catalysts, Rhodium diphosphine catalysts, Iridium diphosphine catalysts

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List of Additional Abbreviations

s/c	molar substrate to catalyst ratio used in the reaction
TON	turnover number (moles of substrate produced per moles of catalyst used)
TOF	turnover frequency (turnover numbers per time unit (h^{-1}))

tfa	trifluoroacetate
ox	oxidation
res	resolution
cy-Hex	cyclohexyl
aqu	aqueous

1

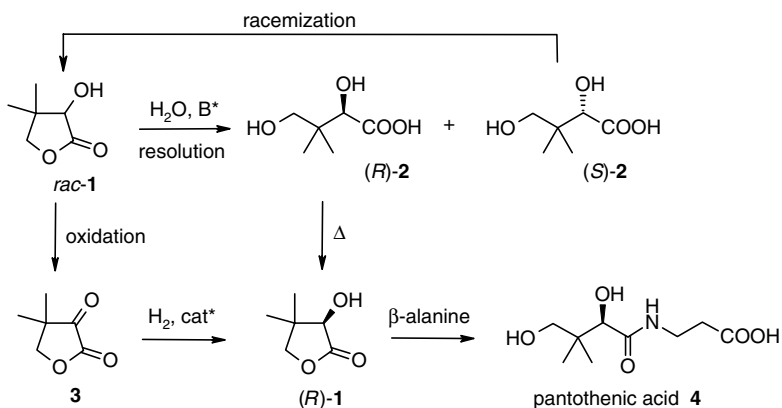
Introduction

Enantioselective catalysis, due to its enormous potential to install the chirality in enantiomerically pure compounds selectively, cost-effectively, and with minimal environmental impact has justifiably attracted great attention in the life-science and related fine chemical industries. At Roche, the evaluation and application of enantioselective catalytic methodology was prompted by the desire to replace labor- and equipment-intensive resolution processes for established commercial products such as, e.g., pantothenic acid and dextromethorphan and to perform chiral switches for commercial racemic products, namely for α -tocopherol (vitamin E). Subsequently, applications towards pharmaceuticals have become more and more important as single enantiomer drugs have predominated. Specifically, the development of short routes to chiral drug building blocks is now the dominant motive. In the following, selected Roche Process R&D examples of enantioselective catalysis applications, most of which have reached pilot or pre-pilot stage in development, are presented and discussed [1].

2

Pantothenic Acid: an α -Ketolactone Hydrogenation

Pantothenic acid (**4**), a water-soluble vitamin, is currently manufactured from (*R*)-pantolactone ((*R*)-**1**) and β -alanine (Scheme 1) Commercial syntheses for



Scheme 1

(*R*)-1 involve resolutions at the stage of pantoic acid (2), the undesired enantiomer being recycled back into *rac*-1. The enantioselective hydrogenation of ketopantolactone (3; easily accessible from *rac*-1 by oxidation) by means of a Rh(BPPM)Cl catalyst to afford (*R*)-1 was discovered by Ojima, Kogure, and Achikawa [2] (Table 1, entry 1). The catalyst, however, due to the low turnover number (TON), appeared not to be sufficiently active for technical application [3].

Table 1. Development and state of the art of the pantolactone hydrogenation, 3→(*R*)-1

Entry	Cat* ^a	s/c	Solvent	T [°C]	p [atm]	t ^b [h]	ee [%]	Ref.
1	Rh(BPPM)Cl	1,000	THF	50	50	>48	72	[2b]
2	Rh(BPPM)Cl	50,000	toluene	70	30	6	83	[4]
3	Rh(<i>m</i> -Tol-POPPM)Cl	50,000	“	45	30	7	81	[5]
4	Rh(<i>m</i> -Tol-POPPM)(tfa)	50,000	“	40	40	1	91	[5]
5	Rh(<i>m</i> -Tol-POPPM)(tfa)	200,000	“	40	40	13	90	[5]
6	Rh(BCPM)Cl	10,000	THF	50	50	45	90	[7b]
7	Rh(Cy-oxoProNOP)(tfa)	70,000	toluene	40	40	48	96	[8]

^a For ligand structures and abbreviations see Fig. 1

^b Time required to achieve complete conversion

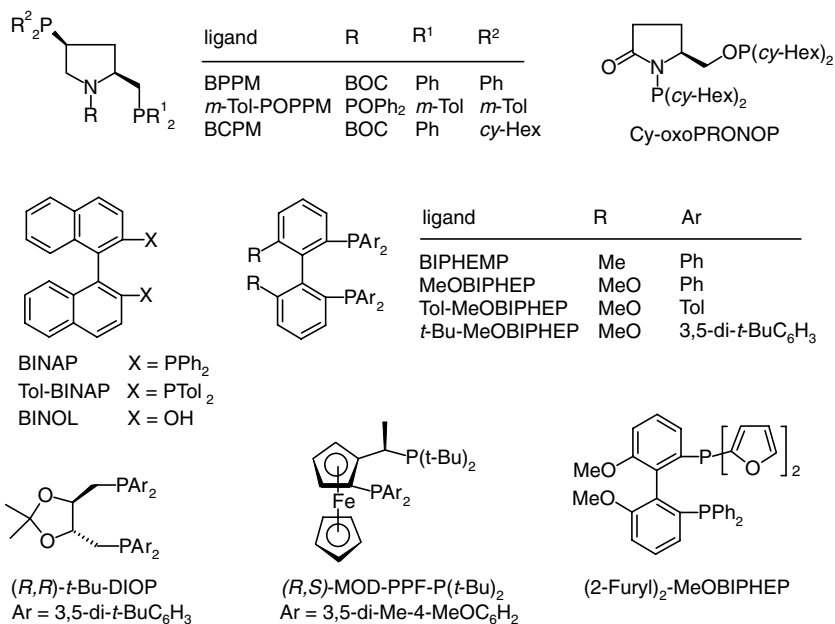


Fig. 1. Ligand structures and abbreviations

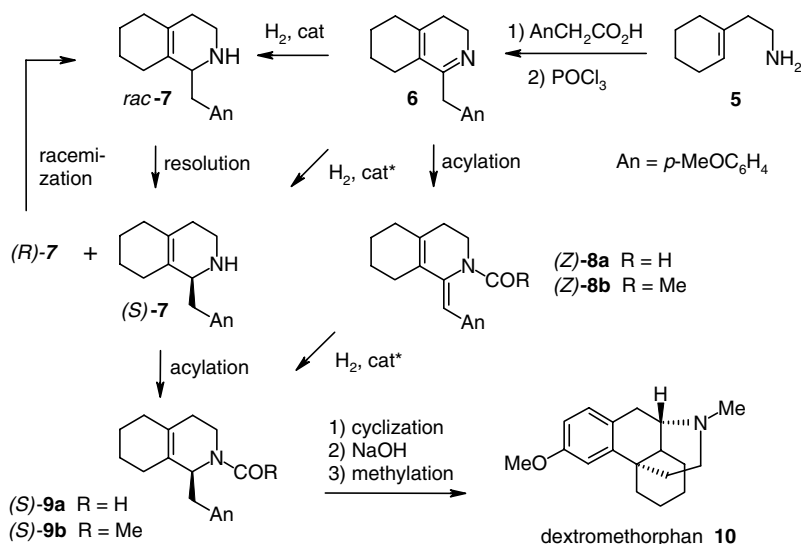
Investigations in our laboratories which included a) elaboration of a suitable purification protocol for **3**, b) solvent screening, and c) optimization of reaction conditions and of experimental techniques demonstrated that molar substrate to catalyst ratios (*s/c*) up to 50,000 and 83% ee could be achieved with the Achiwa catalyst (Table 1, entry 2) [4]. Subsequent ligand fine tuning (cf. Fig. 1) and, even more importantly, variation of the anionic ligand at Rh, led to catalysts with even higher activity and selectivity (Table 1, entries 3–5) [5]. The best catalyst, a Rh(*m*-Tol-POPPM) trifluoroacetato complex, afforded turnover frequencies (TOF) up to 50,000 h⁻¹ and 91% ee. In conjunction with this work, a new continuous gas-phase dehydrogenation of *rac*-**1** was developed to prepare the hydrogenation substrate [6]. In the final process, (*R*)-**1** of 91% ee is isolated by distillation and upgraded to 99.9% ee by crystallization. The almost racemic material from the mother liquor is recycled back into the oxidation step. Rhodium is recovered from the distillation residue. The overall process proved suitable for technical implementation, although optimization of the oxidation step is still required. More recently, Achiwa [7] and Mortreux [8] have reported new highly active and enantioselective catalysts for the pantolactone hydrogenation (Table 1, entries 6 and 7). The potential of these catalysts towards technical application is still to be realized.

3

Dextromethorphan: Enamide and Imine Hydrogenations

Dextromethorphan (**10**), a commercial antitussive agent that is widely used in cough-relieving medications, is manufactured by a resolution/recycling route (Scheme 2: **6** → *rac*-**7** → (*S*)-**7** → (*S*)-**9** → **10**). Noyori and the Takasago group demonstrated that *N*-formyl-enamide (*Z*)-**8a**, accessible by formylation of **6**, can be enantioselectively hydrogenated with Ru(BINAP) type catalysts to provide (*S*)-**9a** of 98% ee (Table 2, entry 1) [9]. Investigation at our laboratories proved the *N*-acetyl-enamide (*Z*)-**8b** to be an even better substrate: its hydrogenation with a Ru(MeOBIPHEP)(*tfa*)₂ catalyst at 120 °C and *s/c* 20,000 afforded (*S*)-**9b** of 98% ee in 97% yield after distillation (entry 2) [10]. Very high space-time yields are possible due to the high substrate concentration of 60%. Both the synthesis of (*Z*)-**8b** and the conversion of (*S*)-**9b** into **10** were developed into efficient processes [11]. Thus, overall an efficient and competitive process is at hand which, however, deviates substantially from the established resolution route by going through new intermediates and therefore would require further process development before full scale-up in the plant.

Recently, the attractive direct enantioselective hydrogenation of **6** to (*S*)-**7** has met with some success. Thus, the Lonza group showed that the dihydrogen phosphate salt of the chemically rather labile imine **6** can be hydrogenated with Ir-ferrocenyldiphosphine catalysts in a two-phase solvent system with up to 89% ee (Table 2, entry 3) [12]. Similar results were achieved in our laboratories with the hydrogen sulfate salt of **6** and an Ir catalyst derived from a sterically bulky *t*-Bu-DIOP ligand in a monophasic solvent system (Table 1, entry 4) [13]. Chemose-



Scheme 2. Resolution and enantioselective hydrogenation routes to dextromethorphan

Table 2. Enantioselective hydrogenation approaches to dextromethorphan (10)

Entry	Substrate	Cat* ^a	s/c	Solvent	T [°C]	p [atm]	ee [%]	Ref.
1	(Z)-8a	[Ru((S)-Tol-BINAP)(SnCl ₆)] ₂ NEt ₃	1,000	MeOH	75	35	98	[9b]
2	(Z)-8b	Ru((S)-MeO-BIPHEP)(tfa) ₂	20,000	MeOH	120	35	98	[10]
3	6-H ₃ PO ₄	Ir((R,S)-MOD-PPF-P(<i>t</i> -Bu) ₂)(cod)BF ₄	1,500	^b	rt	70	89	[12]
4	6-H ₂ SO ₄	Ir((R,R)- <i>t</i> -Bu-DIOP)Cl/NBu ₄ I	1,000	^c	60	100	84	[13]

^a For ligand structures and abbreviations see Fig. 1

^b toluene/aqu NaOH, NBu₄Cl

^c MeOH/toluene/*i*-Pr₂NEt

lectivity problems, in particular overhydrogenation, and the relatively low s/c ratios and ee's are issues which remain to be resolved in this direct approach.

4

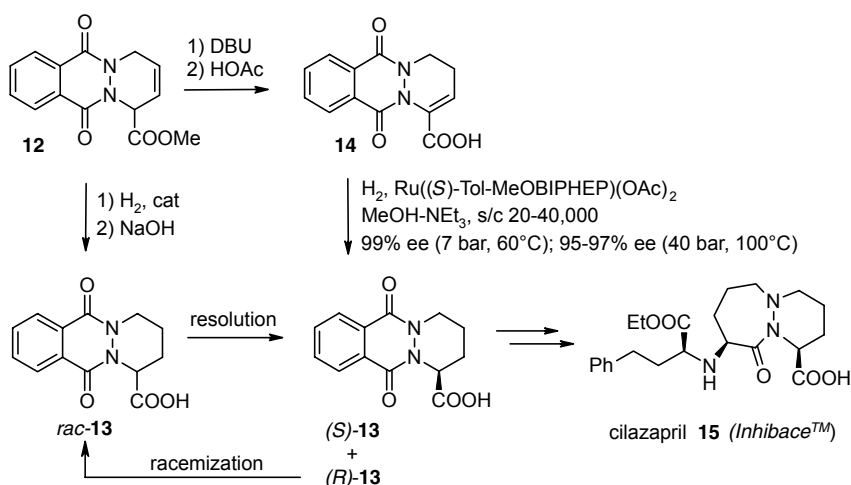
Cilazapril and Mibefradil: α,β -Unsaturated Acid Hydrogenations

Further replacements of resolution by enantioselective hydrogenation routes have been developed in the syntheses of cilazapril (15) [14] (an angiotensin converting enzyme inhibitor; the active ingredient of the antihypertensive *Inhib-*

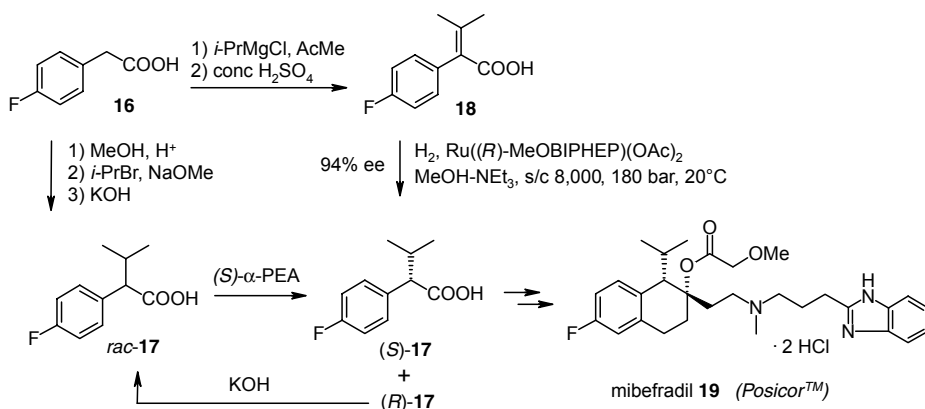
*ace*TM) and in the synthesis of mibefradil (**19**) [15, 16] (a new type of calcium antagonist; the active ingredient of the antihypertensive *Posicor*TM).

In the cilazapril case (Scheme 3), hydrogenation of tetrahydropyridazinecarboxylic acid **14** was realized with a Ru(Tol-MeOBIPHEP)(OAc)₂ catalyst to produce the key chiral building block (*S*)-**13** [17]. The hydrogenation substrate **14** was prepared from **12**, an intermediate in the current resolution route, by isomerization and transesterification. In the optimized process, **14** was hydrogenated at *s/c* 40,000 and at 40 bar/100 °C in MeOH in the presence of 1 equiv of Et₃N, to afford (*S*)-**13** of 95 to 97% ee. A lower pressure/lower temperature version afforded material with 99% ee. In both variants, enantiomerically pure (*S*)-**13** was obtained in >95% yield after a single crystallization. Of critical importance for the high catalyst productivity was the optimization of the **12** to **14** conversion in terms of reaction conditions and purification steps. It is noteworthy that this required far more effort than the demonstration, optimization, and scale-up of the enantioselective hydrogenation itself.

In the mibefradil case, (*S*)-**17**, the key chiral building block for establishing the tetralin skeleton is currently produced by a 5-step resolution/recycling process starting from **16** (Scheme 4). An efficient enantioselective route has been developed which involves a high-yield 2-step conversion of **16** into the trisubstituted acrylic acid **18** and its hydrogenation with a Ru(MeOBIPHEP)(OAc)₂ catalyst [18]. In this process – which constitutes one of the rare examples of a hydrogenation of a tetrasubstituted olefin – the ee increased strongly with pressure (35% at 5 bar, 95% at 250 bar). In the optimized process at 180 bar (*S*)-**17** was obtained with 94% ee. Scale-up was performed in a continuous stirred tank reactor system (CSTR) at 270 bar, *s/c* 1,000 and 30 °C to provide (*S*)-**17** of 93.5% ee [19]. Upgrading to 98% ee was achieved by crystallization of the sodium salt. Compared to batch mode the CSTR system allows for a higher space-time yield and



Scheme 3. Resolution and enantioselective hydrogenation in the synthesis of cilazapril



Scheme 4. Resolution and enantioselective hydrogenation in the synthesis of mibefradil

requires less reactor volume; both are factors which translate into lower investment costs particularly when working at high pressure. Overall, the enantioselective route to (*S*)-17 is shorter (2 vs 5 steps) and higher-yielding (80 vs 70%) than the resolution route. The resulting significant cost advantage renders the new process attractive for implementation in the plant.

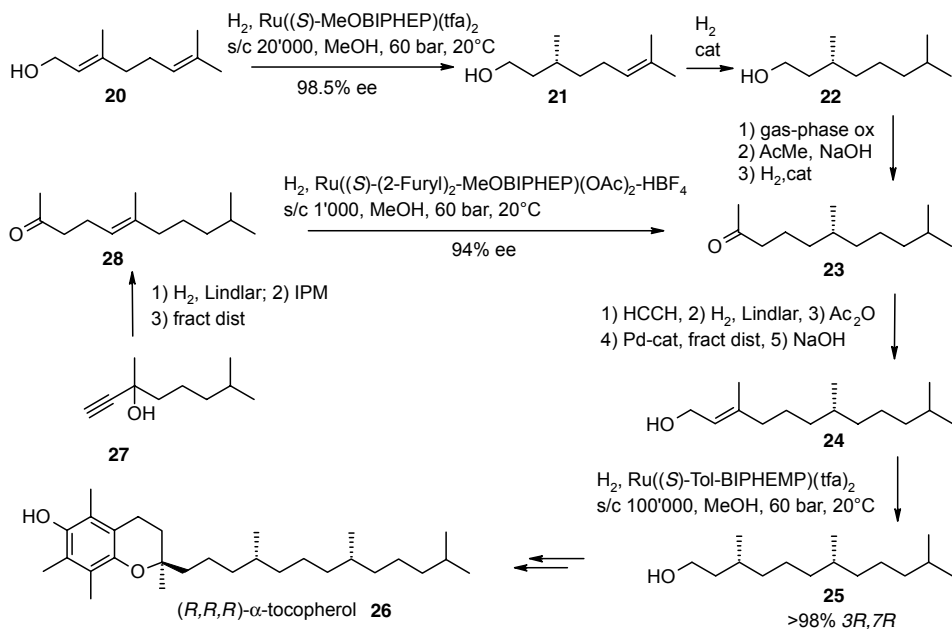
5

Vitamin E: the Quest for an Economic Total Synthesis of (*R,R,R*)- α -Tocopherol

The total synthesis of α -tocopherol in the naturally occurring (*R,R,R*)-configuration (26, Scheme 5) was a potent promoter for establishing enantioselective catalytic methodologies at Roche. Based on the fundamental work of Noyori and Takaya on the Ru(BINAP)-catalyzed hydrogenation of allylic alcohols [20] the synthesis of the C₁₅ side-chain alcohol 25 was realized in our laboratories as outlined in Scheme 5. The hydrogenations of 20 and 24 proceeded extremely well with Ru(MeOBIPHEP)(tfa)₂ catalysts: TON's of 20,000 and 100,000 and ee's of 98.5 and 98%, respectively, were achieved, thus providing 25 of >98% (*R,R*)-content. A major difficulty on the larger scale remains the *E/Z* isomer separation (by fractional distillation) of 24 or its acetate.

The hydrogenation of 28, which is readily accessible from dehydrolinalol (27), was investigated as an alternative entry into the side chain chemistry. Ru(BINAP)- or Ru(MeOBIPHEP)-catalyzed hydrogenation of this γ -oxo-substituted olefin afforded 23 with only 64 and 77% ee, respectively. Remarkably, MeOBIPHEP diphosphines containing P(2-furyl)₂ moieties afforded ee's >90%, the best ligand found so far being the unsymmetrical ligand (2-furyl)₂-MeOBIPHEP [21].

Numerous approaches were pursued to establish the quaternary chroman center in the correct stereochemistry, several of them involving catalytic methodology, e.g. Sharpless asymmetric epoxidation or enantioselective cyclization, but none of them proved economically viable [22]. At present, an economic total



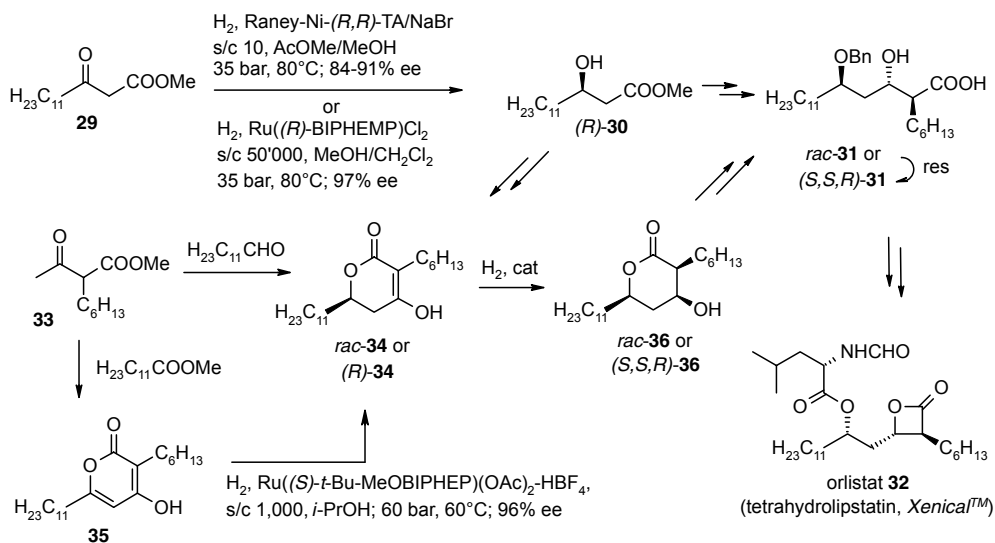
Scheme 5. (*R,R,R*)- α -Tocopherol side-chain building blocks

synthesis of **26** remains elusive. Although enantioselective catalysis was highly successful to establish the stereogenic centers, especially those of the side-chain, the chemistry involved in synthesizing the substrates for the catalytic reactions as well as the coupling of the building blocks is by far too lengthy and expensive. As of today, partial synthesis of **26** by permethylation of mixtures of naturally occurring α -, β -, γ -, and δ -tocopherols remains the only competitive route to produce **26**.

6

Orlistat: a β -Ketoester and an α -Pyrone Hydrogenation

Orlistat (**32**; tetrahydrolipstatin, *Xenical*TM) is a potent inhibitor of pancreatic lipase [23] which has been launched for the treatment of obesity in 1998. Large amounts of **32** required for clinical development were obtained using a route based on the enantioselective reduction of β -ketoester **29** to provide β -hydroxyester (*R*)-**30** followed by diastereoselective elaboration strategies (via (*S,S,R*)-**31**, Scheme 6) [24]. For the reduction a heterogeneous version based on the use of the Raney-Ni/tartaric acid catalyst [25] and a homogeneous process with an Ru(BI-PHEMP)Cl₂ catalyst were investigated. The heterogeneous process, although being less enantioselective, was chosen for scale-up due to its shorter development time. The catalyst could be recycled up to 15 times, whereby the ee slightly dropped, but crystallization afforded enantiomerically pure material in >80% yield.



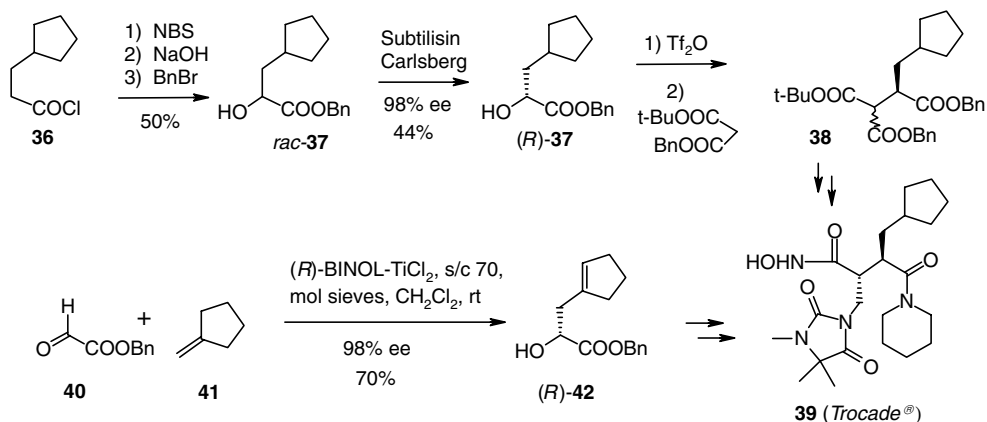
Scheme 6. Enantioselective and resolution routes to orlistat

Subsequently, the enantioselective route was replaced by a resolution process (**33**→**rac-34**→**rac-36**→**rac-31**→(*S,S,R*)-**31**→**32**) [26]. This synthesis proved superior due to the reduced number of steps, although the undesired stereoisomer (*R,R,S*)-**31** could not be recycled. Ecological considerations led to the investigation of another enantioselective approach which is based on the hydrogenation of α -pyrone **35** to dihydropyrone (*R*)-**34** [27]. Ee-values up to 96% were achieved with a cationic Ru catalyst derived from the electron-rich and sterically bulky *t*-Bu-MeOBIPHEP ligand. The relatively low TON of 1,000 calls for further catalyst improvement in this hitherto unprecedented type of reduction.

7

A Glyoxylate-Ene Reaction for a Collagenase Inhibitor Intermediate

The chemical development of the collagenase-selective inhibitor **39** [28] provides an example for a partially concurrent, partially sequential evaluation and scale-up of various conceptual approaches to establish the stereogenic center of an α -hydroxyester building block (Scheme 7). In one approach, hydroxyester **rac-37**, obtained in 3 steps from inexpensive acid chloride **36**, was resolved by enzymatic kinetic resolution to afford (*R*)-**37** in high ee [29]. This approach, although suffering from a low overall yield, served well to produce the first tens-of kg of product rapidly. Another approach to produce (*R*)-**37** or the corresponding ethyl or methyl esters by Ru(MeOBIPHEP)-catalyzed hydrogenation of the corresponding α -ketoesters suffered from the relative inaccessibility of the substrates and insufficient enantioselectivities of 80–90% ee.



Scheme 7. Enantioselective glyoxylate-ene synthesis of an α -hydroxyester intermediate for a collagenase-selective inhibitor

Most remarkably, a Mikami type enantioselective glyoxylate-ene reaction [30] of **40** and **41** catalyzed by (R) -BINOL- TiCl_2 provided the α -hydroxyester (R) -**42** in excellent 98% ee and in good 70% yield [31]. This approach constitutes a very efficient and short entry into the optically active series. It was successfully developed and scaled-up into a reliable process to produce (R) -**42** on a large scale.

8 Concluding Remarks

The enantioselective catalytic processes described above have produced over 10 tons of chiral intermediates in piloting studies and over 4 tons of chiral building blocks for final bulk drug substances. With regard to batch-scale, the largest ones performed so far were 150 kg in the hydrogenation of pantolactone and 250 kg in the glyoxylate-ene reaction. Some of the processes described have served well to produce bulk drug material required for clinical development.

With respect to methodologies, enantioselective hydrogenation has proven to be highly versatile and powerful in our applications. Ee's often were very high, occasionally even at high reaction temperatures. Therefore, the challenges to be met were more frequently: a) to achieve high catalyst productivity (TON) and – sometimes intimately related to that – b) to secure an appropriate quality of the hydrogenation substrate, and finally c) to develop processes within given short time frames. Enantioselective hydrogenation remains the tool most widely applicable to our current problems, but we foresee other methodologies such as enantioselective C-C bond formation and oxidation to gain in importance in the future.

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Chapter 41.3

Cyclopropanation

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Keywords: Cyclopropanation, Diazoacetate, Amino alcohols, Schiff base, Copper complexes

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1

Cyclopropanes in Agro and Pharma Chemicals

Certain kinds of cyclopropanecarboxylic acids are important in the production of pyrethroid, an insecticide with low mammalian toxicity [1]. For example, chrysanthemic acid is an acid component of allethrin (Fig. 1). Various kinds of alcohols have been developed to produce pyrethroids for special application [2]. Chrysanthemic acid has two chiral centers and there are four optical isomers. There is a close correlation between the chirality of a molecule and its biological activity [3]. In the case of chrysanthemic acid, the most effective isomer is shown to be the *d-trans* isomer, which is followed by the *d-cis* isomer whereas

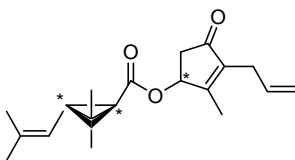


Fig. 1

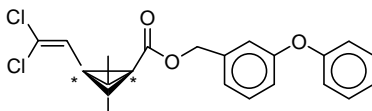


Fig. 2

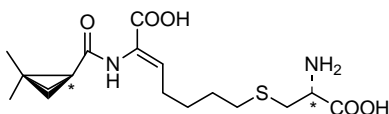


Fig. 3

the *l-trans* and *l-cis* isomers are almost ineffective [4]. The naturally occurring chrysanthemic acid found in the pyrethrum flower also has the *d-trans* or 1*R*,3*R* configuration.

Permethrinic acid, 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid, is another kind of cyclopropanecarboxylic acid producing insecticides of higher performance and stability [5]. The structure of permethrin, a totally synthetic pyrethroid, is shown in Fig. 2. The most effective isomer of permethrinic acid is shown to be the *d-cis* isomer rather than the *d-trans* isomer [6].

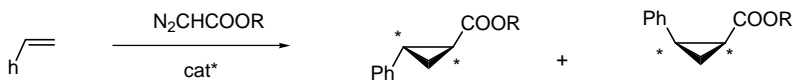
Some cyclopropanes have proved to be useful as pharmaceutical intermediates. The compound, (+)-*S*-2,2-dimethylcyclopropanecarboxylic acid, is a component of cilastatin (Fig. 3), which is administered in combination with imipenem, a carbapenem antibiotic [7]. In spite of its high and wide antibacterial activity, imipenem is found to be easily decomposed in the kidneys. This metabolism is suppressed by cilastatin, an enzyme inhibitor for dehydropeptidase I.

Certain kinds of cyclopropylamines have been developed as a component of so-called new quinolone antibacterials [8].

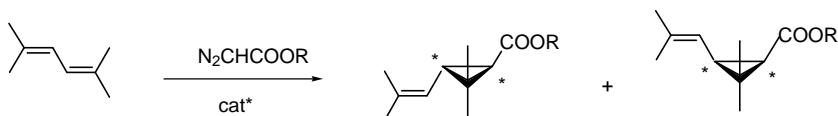
2

Chiral Copper Carbenoid Reaction

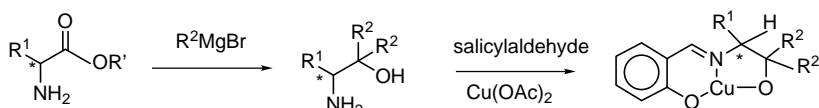
In Kyoto in 1966, Nozaki and Noyori and their coworkers discovered that reaction of ethyl diazoacetate with styrene in the presence of a chiral copper catalyst gives the cyclopropanated product in optically active form (Scheme 1). This experiment showed that the carbene derived from diazoacetate is not free but is



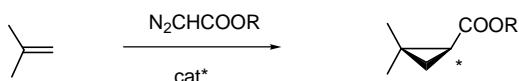
Scheme 1



Scheme 2



Scheme 3



Scheme 4

combined to the catalyst to form a carbene-copper complex, which is responsible for the asymmetric induction [9].

In 1971, Sumitomo started to apply this reaction to the chrysanthemic acid synthesis (Scheme 2). The first problem was how to choose a suitable catalyst which would achieve the highest ee of the product. Here we describe our approach to this problem [10, 11, 12, 13, 14, 15, 16, 17, 18]. Other effective catalysts [19, 20, 21, 22, 23, 24, 25] are discussed by Pfaltz [26].

Reaction of optically active α -amino esters with an excess of Grignard reagent gives optically active amino alcohols with complete retention of configuration [27, 28]. The amino alcohol (Scheme 3) has two substituents, R^1 and R^2 . The R^1 comes from the amino acid and R^2 comes from the Grignard reagent. The amino alcohol was reacted with salicylaldehyde to give a Schiff base, whose treatment with cupric acetate followed by alkaline work-up afforded a copper(II) complex, in which the Schiff base was incorporated as a tridentate ligand [29, 30].

In the chrysanthemic acid synthesis (Scheme 2), the ee of the product increased with the bulkiness of the R^2 group [11]. The highest ee achieved was 70%, when R^1 was methyl (the amino acid was alanine) and R^2 was 2-octyloxy-5-*tert*-butylphenyl. The catalyst with the *R*-configuration (from *D*-amino acid) favored the formation of *d-trans* and *d-cis* isomers to that of *l-trans* and *l-cis* isomers, respectively.

Further improvement of the stereoselectivity was achieved by selection of the alkyl group of the diazoacetate [12]. Both the preference for the *trans* isomer and the ee of the *trans* isomer increased in proportion to the bulkiness of the alkyl

group. Reaction of *l*-menthyl diazoacetate with 2,5-dimethyl-2,4-hexadiene in the presence of the *R*-catalyst gave the product in which the most effective isomer, *d-trans*, predominated by as much as 92%.

The catalyst was successfully applied to the production of *S*-2,2-dimethylcyclopropanecarboxylic acid (Scheme 4). Reaction of ethyl diazoacetate with isobutylene in the presence of the *R*-catalyst gave the corresponding ethyl ester in 92% ee [10, 22, 31].

3

Copper Complexes of *N*-Salicylideneamino Alcohols

The catalyst was a copper(II) chelate having the chiral Schiff base, *N*-salicylideneamino alcohol, as a tridentate ligand. The Schiff base occupies three of the four coordination sites leaving the fourth site vacant. In the absence of another ligand, the coordination number four is satisfied by dimerization. The binuclear structure (Fig. 4) was suggested by measurements of the magnetic susceptibility and confirmed by X-ray crystallography [14]. The two copper atoms are bridged by two phenolic oxygen atoms of salicylaldehyde.

In the presence of donating ligands, the dimer collapses into two equivalents of the mononuclear complex. For example, addition of pyridine gave rise to the pyridine adduct (Fig. 5) in which pyridine occupies the fourth coordination site of copper.

In an attempt to prepare another kind of mononuclear complex (Fig. 6) having the Schiff base as a bidentate ligand, the amino alcohol was reacted with bis(salicylaldehydato)copper [32]. The product was again a mononuclear complex (Fig. 7), in which the same Schiff base resides as a tridentate ligand and the

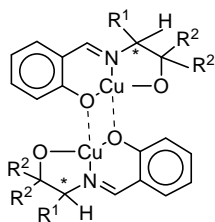


Fig. 4

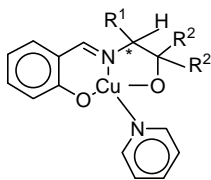


Fig. 5

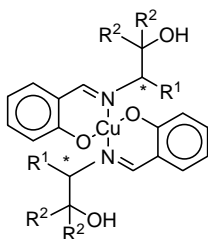


Fig. 6

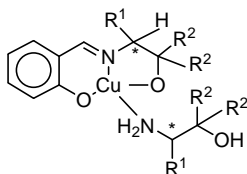


Fig. 7

last coordination site is occupied by the amino group of the amino alcohol. The structure was established by X-ray crystallography [15].

4

Experimental Section

4.1

***R*-2-Amino-1,1-di-(2-methoxyphenyl)-3-phenylpropanol (Scheme 3) [33]**

To a solution of Grignard reagent prepared from 2-bromoanisole (46.8 g, 250 mmol) and magnesium turnings (6.08 g, 250 mmol) in diethyl ether (150 mL), a solution of *D*-phenylalanine ethyl ester (9.66 g, 50 mmol) in ether (50 mL) was added in the course of 5 h. The reaction mixture was heated under reflux for 5 h and was then carefully added to dilute hydrochloric acid under cooling. The precipitate was filtered and treated with an aqueous ammonia to give the amino alcohol as white crystals (yield: 12.4 g, 68%). A sample recrystallized from cyclohexane showed mp 102–103 °C, $[\alpha]_D +42.5^\circ$ (*c* 1.00, chloroform).

4.2

Mononuclear Copper Complex of *R*-*N*-Salicylidene-2-amino-1,1-di(2-methoxyphenyl)-3-phenylpropanol (Fig. 7) [34]

To a suspension of bis(salicylaldehydato)copper [32] (0.43 g, 1.4 mmol) in methanol (10 mL), a solution of *R*-2-amino-1,1-di-(2-methoxyphenyl)-3-phenylpropanol (1.1 g, 3.0 mmol) in methanol (10 mL) was added in the course of 1 h. The addition was carried out with vigorous stirring at room temperature. After the

reaction mixture had been stirred for another 1 h, the solid product was filtered, washed with methanol, and dried in vacuo. Recrystallization from benzene-methanol gave grayish blue crystals (yield: 0.75 g, 58%), mp 205–206 °C (dec), $[\alpha]_{546} +860^\circ$ (c 0.065, benzene). The magnetic susceptibility μ was 1.78 B.M. For X-ray crystallography, see [15].

4.3

Binuclear Copper Complex of *R-N*-Salicylidene-2-amino-1,1-di-(2-butoxy-5-*tert*-butylphenyl)-3-phenylpropanol (Fig. 4) [34]

The corresponding amino alcohol, *R*-2-amino-1,1-di-(2-butoxy-5-*tert*-butylphenyl)-3-phenylpropanol, was prepared by the reaction of a Grignard reagent from 2-bromo-4-*tert*-butylphenyl butyl ether [35] with *D*-phenylalanine ethyl ester. In this case, neither the amino alcohol nor its hydrochloride was crystalline. The reaction mixture was treated with aqueous hydrochloric acid and the inorganic phase was discarded. The separated organic layer was neutralized with aqueous ammonia and concentrated in vacuo to give a crude mixture of the amino alcohol and butyl 4-*tert*-butylphenyl ether, a hydrolysate of the Grignard reagent. The yield was estimated to be 67% (LC) based on a pure sample, $[\alpha]_{\text{D}} +43.5^\circ$ (c 1.00, chloroform), isolated by column chromatography on silica gel.

An equimolar mixture of the crude amino alcohol and salicylaldehyde in toluene was heated under reflux for 2 h. Evaporation of the toluene followed by distillation of butyl *tert*-butylphenyl ether (bp 100 °C/3 torr) gave the corresponding Schiff base as a yellow viscous residue. The yield was estimated to be 65% (LC) based on phenylalanine ethyl ester. A pure sample, $[\alpha]_{\text{D}} -8.00^\circ$ (c 1.00, chloroform), was isolated by column chromatography on silica gel [36].

An equimolar mixture of the Schiff base and cupric acetate monohydrate in ethanol was heated under reflux for 2 h. The ethanol was evaporated in vacuo and the dark green residue was dissolved in toluene. The toluene solution was treated with aqueous sodium hydroxide to complete complex formation. Removal of the toluene followed by trituration in methanol induced crystallization of the copper complex as a bluish green mass. Filtration of the solid followed by drying in vacuo gave a pure sample, $[\alpha]_{546} +1040^\circ$ (c 0.087, benzene), mp 186–188 °C (dec), in 77% yield based on the Schiff base. The magnetic susceptibility μ was 0,86 B.M. For X-ray crystallography, see [14].

4.4

Ethyl *S*-2,2-Dimethylcyclopropanecarboxylate (Scheme 4) [37]

To a solution of the binuclear copper complex of *R-N*-salicylidene-2-amino-1,1-di-(2-butoxy-5-*tert*-butylphenyl)-3-phenylpropanol (0.40 g, 0.55 mmol copper) in toluene (50 mL), was dissolved isobutylene (14 g) under a nitrogen atmosphere. Addition of a toluene solution of phenylhydrazine (10%, 0.30 mL, 0.28 mmol) induced an instant color change of the solution from green to pale yellow indicating the reduction of copper valency from +2 to +1.

Ethyl diazoacetate (purified by distillation, 16.15 g, 142 mmol) in toluene (40 g) was added dropwise at 40 °C in the course of 7 h. During the addition, isobutylene gas (33 g) was continuously blown into the solution. Evolution of nitrogen gas started as soon as the addition was started and, at the end of addition, a quantitative amount of nitrogen gas (3.4 L) was observed.

The reaction mixture was heated to 80 °C to remove an excess of isobutylene. GC analysis of the reaction mixture (105.2 g) showed that the yield of ethyl 2,2-dimethylcyclopropanecarboxylate was 82% based on ethyl diazoacetate. Distillation gave a pure sample, bp 80 °C /60 torr, $[\alpha]_{\text{D}} +105.6^{\circ}$ (*c* 2.0, chloroform). The ee was 92% by GC analysis of the corresponding *d*-octyl ester.

4.5

Binuclear Copper Complex of *R-N*-Salicylidene-2-amino-1,1-di-(5-*tert*-butyl-phenyl)-2-octyloxy)propanol (Fig. 4) [34]

The amino alcohol, *R*-2-amino-1,1-di-(2-octyloxy-5-*tert*-butyl-phenyl)-propanol, was prepared by the reaction of a Grignard reagent from 2-bromo-4-*tert*-butylphenyl octyl ether [35] with *D*-alanine ethyl ester. The copper complex was prepared in the similar manner as above. In this case, neither the amino alcohol, the Schiff base, nor the copper complex was crystalline.

The Schiff base was purified by column chromatography on silica gel (65% yield based on alanine ethyl ester). An equimolar mixture of the Schiff base and cupric acetate monohydrate in ethanol was heated under reflux for 1 h. After evaporation of the ethanol in vacuo, the dark green residue was dissolved in toluene and treated with aqueous sodium hydroxide. Removal of the toluene and drying in vacuo gave the copper complex as a dark green viscous oil, $[\alpha]_{546} +730^{\circ}$ (*c* 0.076, benzene), which is used in the subsequent reaction.

4.6

***l*-Menthyl Diazoacetate [38]**

A mixture of *l*-menthyl glycine [39] (19.7 g, 92 mmol), isoamyl nitrite (12.0 g, 100 mmol), and acetic acid (1.6 g, 27 mmol) in chloroform (400 mL) was heated under reflux for 25 min [40]. The reaction mixture was washed with 1M sulfuric acid, with a saturated aqueous solution of sodium bicarbonate, and finally with water. After removal of the solvent, the residue was purified by column chromatography on silica gel (160 g, methylene chloride) to give yellow waxy crystals (15.0 g, 73%), $[\alpha]_{\text{D}} -86.8^{\circ}$ (*c* 1.0, chloroform), IR ν 2125 cm^{-1} (film) and $^1\text{H-NMR}$ δ 5.29 ppm (chloroform-*d*, TMS).

4.7

l-Menthyl *d*-Chrysanthemate (Scheme 2) [38]

To a solution of the binuclear copper complex of *R-N*-salicylidene-2-amino-1,1-di(5-*tert*-butyl-2-octyloxyphenyl)-3-phenylpropanol (0.30 g, 0.40 mmol copper) in 2,5-dimethyl-2,4-hexadiene (17.6 g, 160 mmol), a solution of *l*-menthyl diazoacetate (4.5 g, 20 mmol) in the diene (4.4 g, 40 mmol) was added at 40 °C in the course of 7 h. At the beginning of the addition, the reaction mixture was heated to 70 °C to facilitate decomposition of the diazoacetate and thereafter the temperature was maintained at 40 °C. At the end of the addition, a nearly quantitative amount of nitrogen gas had been evolved.

Removal of the unreacted diene, bp 45 °C/20 torr, followed by distillation, bp 123 °C/0.2 torr, gave *l*-menthyl chrysanthemate (4.7 g, 76%) whose GC analysis showed the following composition: *d-trans*, 89.9%; *l-trans*, 2.7%, and the *cis* isomers, 7.4%. The *cis/trans* ratio was 7/93 and ee of the *trans* isomer was 94%. Complete hydrolysis of the *l*-menthyl ester with potassium hydroxide in aqueous ethanol followed by esterification with *d*-2-octanol in the presence of thionyl chloride and pyridine gave the corresponding *d*-2-octyl ester. GC analysis revealed the following composition: *d-trans*, 90.4%; *l-trans*, 4.7%; *d-cis*, 3.6%, and *l-cis*, 1.3%. The ee was calculated to be 90% for the *trans* isomer and 47% for the *cis* isomer [41].

5

Conclusions

The discovery of the chiral copper carbenoid reaction in Kyoto has led to the introduction of a chiral cyclopropane production in Sumitomo. However, at the present time, the catalysts in our hands are not as selective as those of natural origin. The *Pyrethrum* flower is still much more skillful and beautiful in chrysanthemic acid synthesis. Further endeavors should be exerted to complete the “man-made asymmetric catalysis” [42,43,44,45].

Acknowledgments. The author would like to thank all the people who were involved in the course of this work for their help and encouragement.

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Chapter 41.4

Asymmetric Isomerization of Olefins

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Keywords: Allylamine, BINAP, Catalyst recycle, Citronellal, Enamine, Ene reaction, Isomerization, Menthol, Rhodium complex, Telomerization, Terpenoids

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1 Introduction

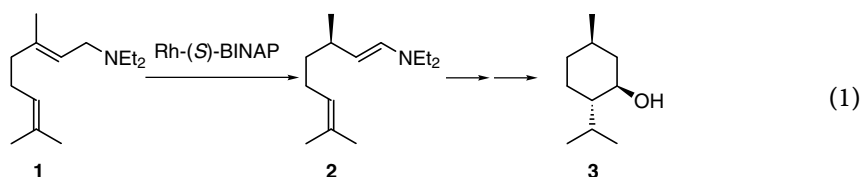
With its characteristic oriental note and cooling effect, (-)-menthol is in daily use among many consumer products including tobacco flavors, mouth-cares, toothpaste, plasters, and in pharmaceuticals. Currently, its world market is approaching 12,000 tons annually, with the selling price in the range of \$30–45/kg. About 70% of the market is supplied from natural products isolated from the essential oil of *Mentha arvensis* cultivated mainly in India and China. Among the eight stereoisomers of menthol, only the (1*R*,3*R*,4*S*)-configuration exhibits genuine biological properties. Thus, the major synthetic problem is the control of stereoisomers. There are two commercialized synthetic processes, one is a resolution method and the other is an asymmetric methodology, equally sharing the remaining 3,500-ton market.

Since 1984 Takasago has been producing (-)-menthol based on Rh-BINAP catalysts (see Chapter 25). The catalysts can convert *N,N*-diethylgeranylamine 1

to citronellal enamine **2** enantioselectively, Eq. (1) [1, 2, 3]. Both chemical and enantioselectivities are extremely high at 99% yield and 98.5% ee, respectively. Besides, the enantioselectivity is independent of the reaction temperature in the range of 25 to 100 °C which is favorable for obtaining a high TON. This article summarizes the process development in the practical use of the Rh-BINAP catalyst for the production of (-)-menthol **3** and related enantiopure terpenoids in a total amount of over 2,300 tons.

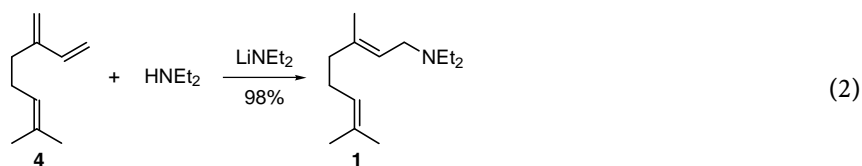
2 Process Development

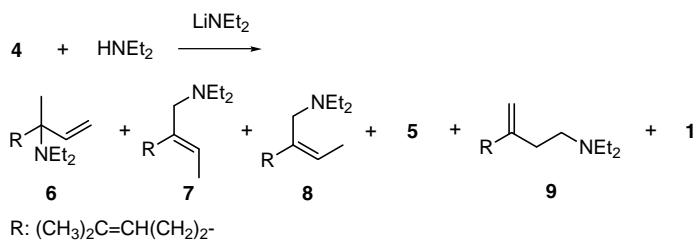
In the practice of homogeneous asymmetric catalysts, we must solve such problems as high cost of chiral auxiliaries and difficulties in the handling of sensitive catalysts. For industrial applications, the consumption of chiral auxiliaries should be kept to a minimum by improving TON as much as possible. When first discovered, the TON of the Rh-BINAP catalysis in Eq. (1) was only 100 as usual laboratory works. A feasibility study indicated that the TON must be more than 100,000 for the profitable manufacturing of **2** on a 2,500-ton scale. It was also necessary to complete the synthetic scheme not only before substrate production but also after the asymmetric process to complete the target molecules. The studies on process development described below have realized this criterion and enabled the commercial operation.



2.1 Substrate Production

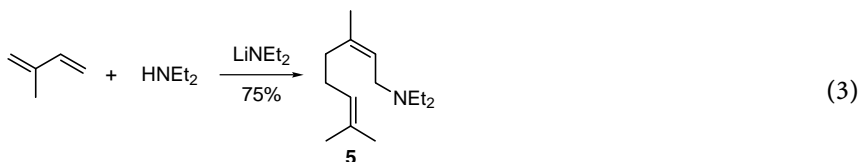
During the 1970's, the lithium diethylamide catalyzed anionic telomerizations of myrcene **4**, Eq. (2) [4] and isoprene, Eq. (3) [5] with secondary aliphatic amines were discovered. These reactions are highly chemo- and regioselective and opened the way for the production of various useful terpenoids. The selective formation of *N,N*-diethylnerylamine **5** from isoprene is noteworthy, because this reaction is only one example hitherto known that can effect isoprene coupling in the natural fashion.





Products	Adduct of	Ratio [%]	Relative volatility
6	3-4	0.03	0.75
7	<i>cis</i> 4-1	0.20	0.80
8	<i>trans</i> 4-1	0.50	0.85
5	<i>cis</i> 1-4	1.20	0.90
9	1-2	0.07	0.98
1	<i>trans</i> 1-4	98.00	1.00

Scheme 1



We are now producing 3,000 tons of *N,N*-diethylgeranylamine **1** annually according to Eq. (2) [6]. In the industrial operation, where drastic conditions such as the higher reaction temperature of 120 °C and the lower catalyst ratio (1 to 100) are required, the regioselectivity drops to 92%. The crude telomer consists of six regioisomers, which were formed by all possible modes of addition between diethylamine and the conjugated diene of **4** (Scheme 1) [3].

It is essential to remove isomers **5** and **9** from **1** for the asymmetric reaction, because the former reduces the enantiomeric purity while the latter acts as a strong catalyst poison (see Chapter 23). As the volatility of **9** is very close to that of **1**, a distillation column with 80 theoretical plates is applied to furnish **1** in the purity of 99.98% for the Rh-BINAP catalysis.

2.2 Catalyst Preparation

Industrially, we have been using Tol-BINAP **10** instead of the prototype BINAP (Fig. 1). The merit is its higher crystallization properties both in the resolution and as rhodium complexes.

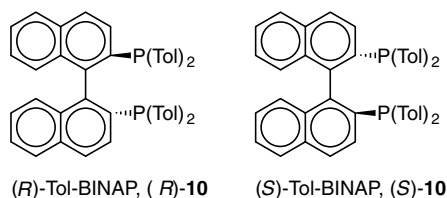
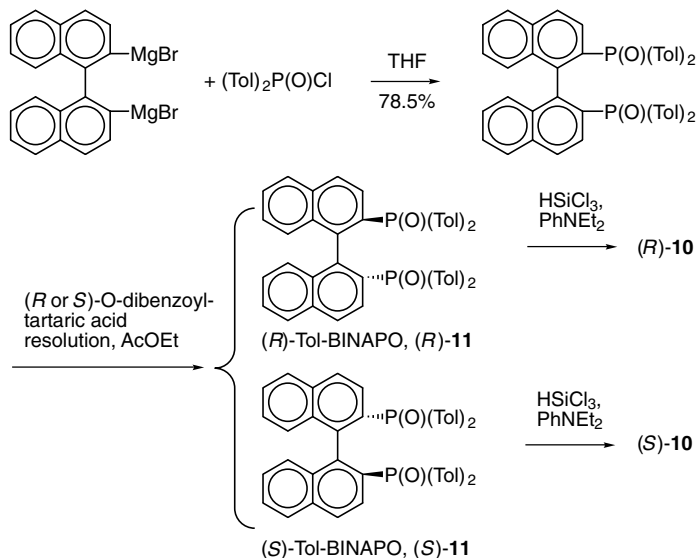
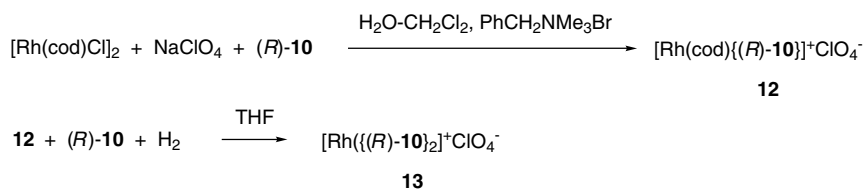


Fig. 1



Scheme 2

Compared to the recent publication [7], our synthetic scheme consists of a sequence of classical organic syntheses suitable for 100 kg scale production (Scheme 2) [8, 9]. Generally, it is difficult to introduce diphenylphosphino groups at the sterically hindered 2,2'-positions of binaphthyl in a high yield. The combination of organomagnesium bromide with diphenylphosphinyl chloride gives Tol-BINAPO 11 in a yield of 87.5%, the value is much higher than that obtained from the organolithium and diphenylphosphinous chloride (37%). The resolution of 11 can be carried out perfectly according to the following procedure. When 45% mol equivalent of (*R*)-*O*-dibenzoyltartaric acid is added to racemic 11 in ethyl acetate at 15 °C, the (*R,R*)-diastereomeric salt precipitates quantitatively. The optical purity of (*R*)-11, liberated by sodium hydroxide, is sufficient for the trichlorosilane reduction to 10 without further purification. Similarly, the (*S*)-isomer is obtainable by applying 45% mol equivalent of (*S*)-*O*-dibenzoyltartaric acid to the mother liquor containing (*S*)-rich 11.



Scheme 3

In our asymmetric process development, the discovery of the thermally stable rhodium bis-BINAP complex was outstanding as it enabled the repeated use of catalyst [10]. In Scheme 3, the synthesis of the cationic rhodium bis-Tol-BINAP complex 13 is illustrated. Its precursor 12 can be prepared quantitatively using cheap sodium perchlorate in a binary system in the presence of a phase transfer catalyst. It is possible to convert 12 to 13 by monitoring the reaction either by the volume of hydrogen absorbed or the color change from orange (12) to deep red (13).

2.3

Improvement of TON

In the sense of coordination chemistry, almost all catalyst inhibitors were removed to attain high a TON. First, we introduced the treatment of substrate 1 by distillation over Vitride, a toluene solution of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, to remove donor substances such as oxygen, moisture, carbon dioxide, and in particular sulfur-containing impurities which originated from turpentine. Thus, the TON was raised to 1,000 from the original 100. Second, the removal of an amine isomer, 9 in Scheme 1, by fractional distillation increased the TON to 8,000. The coordination order of substrates and products to a rhodium complex is supposed to be proportional with the basicity order of the simple tertiary amine 9, the allylic amine 1, and the enamine 2. This phenomenon enables the fast replacement of the enamine formed from the metal by a substrate molecule that allows the smooth catalytic cycle. As the coordination of 9 to rhodium is too strong, it acts as a strong catalyst poison even in a small amount.

2.4

Catalyst Recycle System

Finally, we have established the practical asymmetric isomerization process as follows: In a 15-m³ batch reactor, a mixture of 7 tons of 1 and 6.71 kg of the catalyst 13 (the molar ratio of catalyst to substrate is 1 to 8,000) in THF (3 m³) are charged. The isomerization is completed in 18 h at 100 °C, providing 2 in 99% yield and 98.5% ee [3, 11, 12]. After the reaction, the whole products (THF, enamine, and catalyst) are subjected for distillation under reduced pressure (initially 400 torr, finally 2 torr) to recover THF and 2. The distillation residue is an

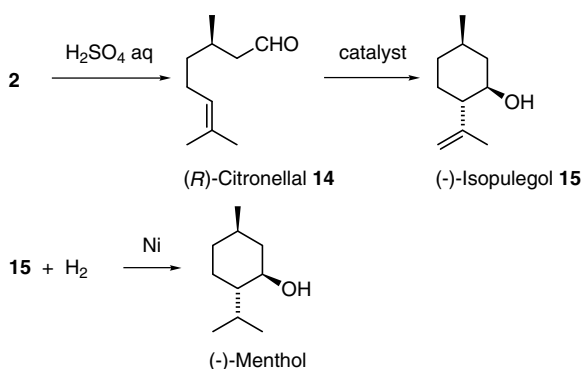
orange-brown solid mass containing mainly **12** and free ligand **10**. The reverse coordination of these two components to **13** is slow in the solid, however, the complex **13** can be precipitated in a pure form by the addition of *n*-heptane to the residue.

During the early stage of the manufacturing, the recovery of **13** was 90%, by which we assumed 10% of the catalyst was decomposed during the reaction. Hence the additional 0.671 kg of fresh catalyst **13** was required for the following batch to keep the same operation. Thus, the total TON was 80,000. Now, as a result of total quality control, the catalyst recovery has become 98%. Consequently the next batch requires 2% of the fresh catalyst in addition to the recovered amount thus exemplifying the total TON of 400,000. It is also possible to recover rhodium metal and **11** from the *n*-heptane solution, thus making the total mass balance of precious materials higher than 99.9%.

2.5

Enamine to Menthol

After the isomerization, the production of (-)-menthol is carried out according to Scheme 4. On usual hydrolysis, **2** gives (*R*)-citronellal **14** quantitatively in 98.5% ee. The cyclization of **14** to (-)-isopulegol **15**, an intramolecular ene reaction, is promoted by various acid catalysts. Whereas ordinary Lewis acid gives a



Catalyst	Conversion [%]	15 [%]
SiO ₂	100	62
Rh(PPh ₃) ₃ Cl	25	85
ZnCl ₂	15	70
ZnBr ₂	12	99
ZnI ₂	8	100
ZnBr ₂ , calcined at 160 °C	97	98

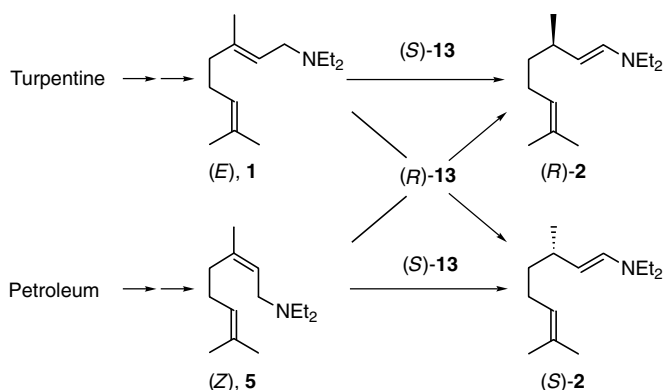
Scheme 4

mixture of conformers of **15**, zinc bromide (calcined at 160 °C) catalyzed the reaction stereoselectively. The 100% enantiomeric purity of **15** can be accomplished by the crystallization of isopulegol (98.5% ee) at -50 °C from *n*-heptane solution. Finally, the last step is a simple hydrogenation.

3 Application

In the isomerization, one favorable feature is the desirable stereochemical correlation between substrate geometries, product configurations, and ligand chiralities, as shown in Scheme 5. Since both enantiomers of the ligand as well as the substrates are easily obtainable, this stereochemical relation provides economical advantages in the option of taking the starting material either from natural resource (renewable turpentine) or petroleum. It is also possible to produce both enantiomers of citronellal from a single intermediate only by changing the ligand chirality.

The present asymmetric technology has enabled the manufacturing of enantiomeric pairs of aroma chemicals that is a strategically powerful means in the fragrance business. Both enantiomers of citronellol **16** (Fig. 2) are precious fragrances inaccessible before this technology. We are supplying a pair of isomers



Scheme 5

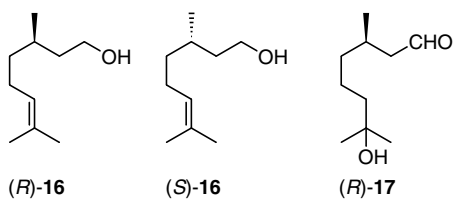


Fig. 2

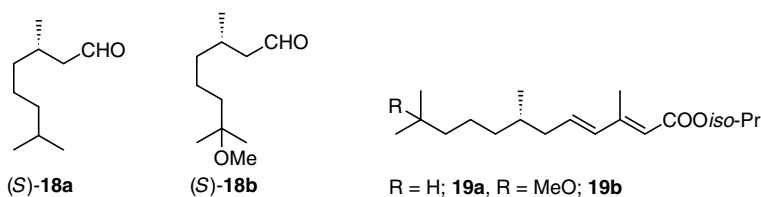


Fig. 3

of **16** on a 200 ton scale, produced by the copper-chromite catalyzed hydrogenation of **14**. A lily of the valley fragrance, 7-hydroxycitronellal **17**, where the (*R*)-form is less skin irritant compared to its (*S*)-enantiomer, is produced for the perfumery industry in 300 ton amounts.

Besides aroma chemicals, we are supplying key intermediates for the synthetic insect growth regulators, (*S*)-3,7-dimethyl-1-octanal **18a** and (*S*)-7-methoxy-citronellal **18b**, on 100 ton scales each. Hydropren **19a** is effective for mosquitoes and Methopren **19b** is used for controlling cockroach, where only (*S*)-forms are active (Fig. 3).

4

Conclusion

As a pioneer, Takasago started the synthesis of menthol in the early 1960's. Originally, our raw material was citronellal obtained from Indonesian and Taiwanese citronella oil. The enantiomeric purity of natural citronellal was only 82%. On a glance at the formula of *N,N*-diethylnerylamine in the literature, an idea of asymmetric isomerization spontaneously came to me that was driven by the major need for enantiopure citronellal. Besides, the first synthesis of BINAP by the late Prof. Takaya was quite timely to realize this idea. We believe that our menthol process has become a milestone in the progress of homogeneous asymmetric catalysis. The rhodium-BINAP catalysts, though using very extensive components, have become one of the cheapest catalysts in the chemical industry by extensive process development. During the period 1983 to 1996, we have produced 22,300 tons of menthol, for which the consumption of Tol-BINAP was only 125 kg. Thus one part of the chiral ligand has multiplied its chirality to 180,000 parts of the product. This value has enabled the precious metal catalyst to become an economically feasible reagent.

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Chapter 42

Future Perspectives in Asymmetric Catalysis

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1	Introduction	1
2	New Reaction Design.	2
3	Development of Practical Catalyst Systems	3
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1

Introduction

Taken together, the chapters in this collection highlight the remarkable progress made in asymmetric catalysis since the inception of the field three decades ago. Indeed, it is difficult to think of a transformation that involves the reaction of achiral starting materials to give chiral products that has *not* been subjected to asymmetric catalysis with some degree of success. And the progress continues at an accelerating pace: during the period that this collection was being written and edited (1998-Spring 1999), significant breakthroughs were made in many topics that were too poorly developed to merit coverage at the beginning of the project. For example, several enantioselective catalytic systems were developed for the venerable Strecker reaction [1–5] – the addition of hydrogen cyanide to imines – whereas only one example had been described prior to 1998 [6]. Important progress was also made during 1998–9 in conjugate addition catalysis [7], and significant breakthroughs were achieved with asymmetric catalysis of the brand-new ring-closing metathesis reaction [8]. As such, this collection is clearly just a snapshot of a rapidly growing field. It is due to this fact that the publishers at Springer have committed themselves to keeping *Comprehensive Asymmetric Catalysis* current by regular updates in a CD-ROM format, and we hope that this will make this collection most useful.

Given this high level of ongoing activity in the field, it is interesting to consider what new advances are likely during the coming years. This exercise, of course, requires a notion of what it is that remains to be done. If one defines the

ultimate goal of the field to be the successful development of general and practical asymmetric catalysts for every synthetically interesting transformation, then much future effort will need to be directed not only toward new reaction discoveries, but also to process research and development. From a more fundamental perspective, one could add the goal of the elucidation of the mechanism of action of every one of those catalyst systems, including stereochemical models with complete predictive values. An even more ambitious goal would be the attainment of a level of mechanistic understanding that would allow rational design of new chiral catalyst systems. Regardless of which of those is set as the ideal, it is quite clear that the field is still in its relative infancy, and a great deal of work remains ahead.

2

New Reaction Design

Only partial solutions have been provided thus far to many of the most important transformations amenable to asymmetric catalysis. For example, no generally effective methods exist yet for enantioselective epoxidation or aziridination of terminal olefins, or for hydroxylation of C-H bonds of any type. Despite the enormous advances in asymmetric hydrogenation catalysis, highly enantioselective reduction of dialkyl ketones remains elusive [9]. And as far as asymmetric C-C bond-forming reactions are concerned, the list of successful systems is certainly shorter than the list of reactions waiting to be developed.

The methods by which new asymmetric catalytic reactions will be discovered in the future will most likely be as interesting as the reactions themselves. Certainly, we will continue to see the tried-and-true method of taking a known metal-catalyzed reaction and rendering it asymmetric by incorporating either known or new chiral ligands and optimizing enantioselectivity through a combination of design, intuition, persistence, and good fortune. However, the recognition that an effective asymmetric catalyst relies on the successful combination of a large number of interrelated variables – not all of which are necessarily well-understood – renders this exercise largely empirical. As a result, the possibility of using high-throughput screening methods in asymmetric catalysis research has been widely recognized to be extremely desirable. The challenge of identifying enantioselective catalysts from mixtures of possible catalysts is significant to say the least, and many obstacles must be overcome before the full potential of combinatorial chemistry can be realized. Nonetheless, at the time of writing in 1999, nearly all of the leading research laboratories in the field make use of GC and HPLC autosamplers for screening asymmetric reactions, and it is certain that the level of automation will only increase. Perhaps of even greater significance, we are already seeing the first successes in the application of combinatorial strategies to the discovery and/or optimization of new chiral catalysts [1, 10–11].

3 Development of Practical Catalyst Systems

The very first genuine success in the field of asymmetric catalysis, the hydrogenation of dehydroamino acids developed by Knowles at Monsanto [12], helped set an awesome standard for future work. The Knowles reaction became a commercial process for the synthesis of an important pharmaceutical, and it found continuous use in that context for decades. The Monsanto L-dopa process made it clear that the ultimate test of practicality – commercialization – was an attainable standard for asymmetric catalysis, and this has colored subsequent research in the field ever since. In that light, it has become clear that it takes more than just high yields and ee's in a catalytic reaction to attain practicality, and some of the very best process research in the world has been done in the context of asymmetric catalysis. Especially notable examples can be found in the Takasago menthol process (Chapter 23), the CIBA-Geigy (Novartis) imine hydrogenation [13], and the Sharpless epoxidation (Chapter 18.1). In the first two cases, extremely precious metals and relatively complex synthetic ligands are required for the synthesis of high-volume, low-margin chiral products. In the case of the Sharpless epoxidation, an inherently unstable catalyst system is employed that is sensitive to moisture, concentration, temperature, and aging. The fact that such obstacles have been overcome and that these processes have each been used for manufacture on a multi-ton scale is a testament to how concerted effort in process research can be rewarded with dramatic success, and it certainly bodes well for the future development of commercial processes using asymmetric catalysis.

Yet, as noted in the introduction, the number of truly useful enantioselective catalysts is still limited, and there are only a handful of systems that have been used in a commercial context. With notable exceptions, even the number of asymmetric catalytic reactions that have seen application in academic target-oriented synthesis research is relatively small. There is no doubt that a major emphasis in future research will be placed on rendering known reactions more practical.

This is of course more easily said than done, and the factors that determine practicality vary greatly according to the system at hand. One of the most obvious is the issue of catalyst turnover number. Loadings of 5 mol % of a non-recyclable catalyst are acceptable in the commercial process for the Sharpless epoxidation, whereas millions of turnovers are needed to render the CIBA-Geigy imine hydrogenation system viable. The difference, in this case, is that the Sharpless reaction employs inexpensive titanium with tartrate ester ligands, while the CIBA-Geigy Josiphos catalyst uses precious iridium and an expensive phosphine ligand. Other issues are less straightforward yet. For example, the need for high dilution or low reaction temperature in a catalytic process can render scale-up extremely difficult or expensive. The seemingly simple problem of catalyst removal from the product can prove critical, especially in the case of toxic heavy-metal-catalyzed reactions. Given that many of these issues fall outside the scope of what is generally considered “academic” research, there is no doubt that at least part of the responsibility for advancing the field will continue to be assumed

by the industrial sector. It is certainly noteworthy in that context that several companies (e.g. ChiRex, Chirotech, Catalytica) are committing increasing resources to commercialization of asymmetric catalytic technologies discovered in academic laboratories.

4 Mechanism

It is easy to forget that the first publication on the topic of asymmetric catalysis described a mechanistic study [14]. From the very origins of the field, it was recognized that enantioselectivity can provide useful insights into a catalytic process that are otherwise difficult to attain. Ultimately, the degree and sense of asymmetric induction in a reaction can help shed light on the most difficult and important mechanistic questions, including the precise geometry of the selectivity-determining transition state.

However, the now-classic work on the mechanism of the Rh-catalyzed asymmetric hydrogenation of dehydroamino acids ended up serving a dual role [15]. On one hand, it helped establish that some of the very best work in mechanistic chemistry could be done in the context of asymmetric catalysis. On the other, it provided a stark example of the Curtin-Hammett Principle at work, and thereby highlighted the dangers associated with trying to devise stereochemical models for even the most selective reactions. While “Halpern’s Law” (various versions exist, but all follow along the lines of “if you can detect an intermediate, it probably is not an intermediate!”) may be a somewhat cynical view of the situation, it is a simple fact that even a very highly enantioselective reaction requires only a small (<5 kcal/mol) difference in activation barrier energies leading to the enantiomeric products. As a result, the construction of stereochemical models is typically more art than science, and very few reactions are understood at the level of detail that allows complete predictability, much less rational design.

Will research in asymmetric catalysis always be an empirical endeavor, such that it will never be possible to carry out completely rational design of new systems? It is likely that one might get as many different answers to this question as there are researchers in the field. However, no one would argue that research activity in asymmetric catalysis will continue to grow, and the collection of more and more information about selectivity in catalysis will certainly help guide future work and facilitate the discovery of more effective systems.

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