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CATALYSTS FOR FINE CHEMICAL SYNTHESIS

Regio- and Stereo-Controlled Oxidations and Reductions

5

Editors: Professor Stan Roberts and Dr John Whittall

Catalysts for Fine Chemical Synthesis

Volume 5

Regio- and Stereo-Controlled Oxidations and Reductions

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Books in this Series

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Catalysts for Fine Chemical Synthesis Series Preface

During the early-to-mid 1990s we published a wide range of protocols, detailing the use of biotransformations in synthetic organic chemistry. The procedures were first published in the form of a loose-leaf laboratory manual and all the protocols have been collected together and published in book form (Preparative Biotransformations, Wiley, Chichester, 1999).

Over the past few years the employment of enzymes and whole cells to carry out selected organic reactions has become much more commonplace. Very few research groups would now have any reservations about using commercially available biocatalysts such as lipases. Biotransformations have become accepted as powerful methodologies in synthetic organic chemistry.

Perhaps less clear to a newcomer to a particular area of chemistry is when to use biocatalysis as a key step in a synthesis, and when it is better to use one of the alternative non-natural catalysts that may be available. Therefore we set out to extend the objective of Preparative Biotransformations, so as to cover the whole panoply of catalytic methods available to the synthetic chemist, incorporating biocatalytic procedures where appropriate.

In keeping with the earlier format we aim to provide the readership with sufficient practical details for the preparation and successful use of the relevant catalyst. Coupled with these specific examples, a selection of the products that may be obtained by a particular technology will be reviewed. In the different volumes of this new series we will feature catalysts for oxidation and reduction reactions, hydrolysis protocols and catalytic systems for carbon–carbon bond formation inter alia. Many of the catalysts featured will be chiral, given the present day interest in the preparation of single-enantiomer fine chemicals. When appropriate, a catalyst type that is capable of a wide range of transformations will be featured. In these volumes the amount of practical data that is described will be proportionately less, and attention will be focused on the past uses of the system and its future potential.

Newcomers to a particular area of catalysis may use these volumes to validate their techniques, and, when a choice of methods is available, use the background

information better to delineate the optimum strategy to try to accomplish a previously unknown conversion.

S. M. ROBERTS
I. KOZHEVNIKOV
E. DEROUANE
Liverpool, 2002

Preface to Volume 5: Regio- and Stereo-Controlled Oxidations and Reductions

In recent years the world has become increasingly energy conscious. For the chemistry arena, this means that old-fashioned, inefficient processes are continually being replaced by modern methods. In turn, this fuels the search for effective catalysts to promote a wide range of transformations.

Across this range there can be no doubt that reactions resulting in either the oxidation or the reduction of a starting material are of paramount importance. In this Volume, a series of new or improved redox catalysts are featured. The catalysts have been disclosed in the recent primary literature (learned Journals) and the respective authors have amplified the disclosure of their catalysts in this Volume. Thus in each report herein, the exact method of preparation of the catalyst is described, the precise method for its use is disclosed and the breadth of substrate range is considered. A description of the equipment required as well as noteworthy safety issues form part of the description of each protocol. Finally, where potentially useful, tips and hints are appended, making these detailed ''recipes'' often more extensive than those found in the experimental sections of most Journals.

In order to place later chapters in proper context, the first chapter offers a comprehensive overview of industrially important catalysts for oxidation and reduction reactions. Chapters 2 and 3 describe the preparation of chiral materials by way of the asymmetric reduction of alkenes and ketones respectively. These two areas have enjoyed a significant amount of attention in recent years. Optically active amines can be prepared by imine reduction using chiral catalysts, as featured in Chapter 4, which also discloses a novel reductive amination protocol.

The remaining chapters deal with a variety of catalysts for effecting oxidation reactions. Chapter 5 describes three simple protocols for the controlled oxidation of primary or secondary alcohols. The importance of stereocontrolled epoxidation and hydroxylation reactions is reflected by the fact that Chapter 6, directed at this field, is one of the most extensive sections of the book. An interesting example of an enantioselective Baeyer-Villiger reaction is featured in Chapter 7, together with an industrially important ketone to enone conversion. Oxidative carbon-carbon

coupling reactions are the focus for Chapter 8, while the controlled oxidation of sulfides and sulfoxides is the topic chosen for the final chapter.

As for the previous volumes in this Series, the Editors are most grateful to the 100+ authors, who have submitted details of their work to the prescribed format for inclusion in this book. We hope that this Volume will increase exposure of their discoveries to the industrial chemical community and so contribute to the expanded employment of their catalysts in fine chemical synthesis.

STANLEY ROBERTS
JOHN WHITTALL
Manchester, 2007

Abbreviations

Ac	Acetyl
ACS	American Chemical Society
Ala	Alanine
API	Active Pharmaceutical Ingredient
aq	Aqueous
Ar	Aryl
ATH	Asymmetric Transfer Hydrogenation
atms	Atmosphere
BARF	*tetrakis*[3,5-Bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
BINAP	2,2′-(Bisdiphenylphosphino)-1,1′-binaphthol
BINOL	1,1′-Binaphthol
tBME	*tert*-Butyl Methyl Ether
Boc	Butoxycarbonyl
Bu	Butyl
BuLi	Butyl Lithium
ca	*circa approxima*
CAL-B	*Candida antarctica* lipase B
CAN	Ceric Ammonium Nitrate
CATHy™	Catalytic Asymmetric Transfer Hydrogenation
CBS	Corey-Bakshi-Shibata
COD	Cyclooctadiene
Cp	Cyclopentadienyl
DBT	Dibenzoyltartaric Acid
DCM	Dichloromethane
de	Diastereomeric Excess
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DKR	Dynamic Kinetic Resolution
DPEN	1,2-Diphenylethylene1,2-diamine
DVB	Divinylbenzene
ee	Enantiomeric Excess
EtOAc	Ethyl Acetate
eq	Equivalent

FID	Flame Ionisation Detector
GC	Gas Chromatography
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IBX	o-Iodoxybenzoic Acid
IR	Infra Red
LDA	Lithium diisopropylamide
LDBB	Lithium di-*tert*-butylbiphenylide
LDH	Layered Double Hydroxide
Me	Methyl
MOM	Methoxymethyl
Ms	Methane Sulfonyl
NAD(H)	Nicotinamide Adenine Dinucleotide (reduced)
NADP(H)	Nicotine Adenine Dinucleotide Phosphate (reduced)
Nbd	Norbornadiene
NK	Neurokinin
NMDA	N-Methyl-(D)-aspartate
NMR	Nuclear Magnetic Resonance
Oxone^{TM}	Potassium Peroxymonosulfate
PDE	Phosphodiesterase
Ph	Phenyl
psi	Pounds Per Square Inch
PTC	Phase Transfer Catalyst
R_f	Retention Factor
R_t	Retention Time
SALEN	Salicylaldehyde Ethylenediamine Imine
SDS	Sodium Dodecylsulfate
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TOF	Turn Over Frequency
TON	Turn Over Number
Ts	Toluene sulfonyl
UV	Ultraviolet

1   Industrial Catalysts for Regio- or Stereo-Selective Oxidations and Reductions. A Review of Key Technologies and Targets

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CONTENTS

1.1   INTRODUCTION

In this volume procedures are documented for selective oxidations and reductions that represent the advances in these fields since Volume 1 of this series was published (in 2002). This introduction highlights some examples from the literature that demonstrates the needs of industry and identifies how some of these requirements were met and illustrates a number of the challenging problems that are still to be overcome.

Since the Nobel Prize-winning pioneering work of Knowles and Noyori for reduction reactions (working with phosphine ligands that have phosphorus chirality and axial chirality, respectively) and Sharpless for epoxidations of allylic alcohols a wide range of chiral oxidation and reduction catalysts have been developed. This book gives an insight into some of the practical uses of these protocols along with more detailed experimental procedures for their use. It also seeks to include other examples of selective reactions which could prove useful in industrial applications and presents detailed procedures to implement these.

From an industrial viewpoint there are several drivers that need to be satisfied before a catalyst can be successfully implemented in production plants. Technically there have been various challenges to be met including the synthesis of the requisite ligands, catalyst sensitivity to the environment in which it is applied, reproducibility in product enantiomeric excess (ee) and yield, feasibility in the use of commercial solvents and IP issues around 'freedom to operate'. All these issues have been factors that have influenced commercial exploitation. An example of how one or more of these factors can decide the selection of a catalyst system was described by Hawkins,[1] where Pfizer's selection of the Degussa DEGUPHOS catalyst system over the technically superior DUPHOS system in the synthesis of a Candoxatril intermediate (shown in Figure 1.1) was decided by royalty payments and freedom to operate issues.

Thus, although Rh–MeDUPHOS gave the desired product in excellent yield and 99 % ee it was not chosen to prepare the two metric tons of Candoxatril intermediate required for phase-III clinical trials. Instead MeOBIPHEP was chosen because it was readily available on large scale (up to 10 kg) and Pfizer needed to have the right to use the catalyst in-house. In the large-scale asymmetric hydrogenation 231 kg batches were hydrogenated in a 4000-L reactor and problems related to olefin isomerization were attenuated by switching the solvent from a methanol/water mixture to a THF/water system. The purity specifications were then met by recrystallization.

The reduction of double bonds using chiral phosphine ligands as the precursors for the appropriate catalysts is a widely used strategy in the asymmetric synthesis of

Figure 1.1   Candoxatril intermediate (Pfizer).
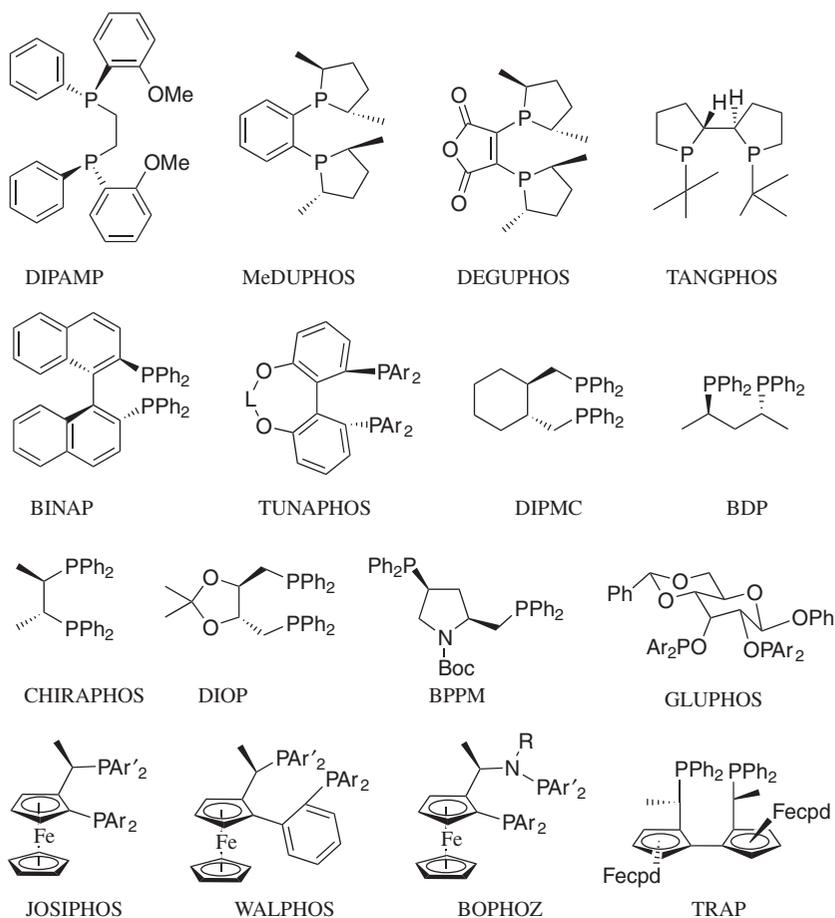
Figure 1.2 Illustrative examples of chiral phosphine ligands.

high value fine chemicals. It is a very powerful tool for introducing chirality into molecules. A large number of different types of chiral phosphines have been investigated for the reduction of a range of unsaturated compounds including alkenes, ketones and imines. Many ligands have been assessed and the structures of some of these that have made a significant impact on industrial processes are shown in Figure 1.2.

1.2 REDUCTION OF CARBON-CARBON DOUBLE BONDS

The chiral phosphines shown in Figure 1.2 represent the typical types of chiral ligands employed to generate those chiral catalysts that have had the most industrial interest in terms of asymmetric reductions. The next section divides these

compounds into groups depending on the substituents on the double bonds that were needed to be reduced and describes some of the challenges that are now being faced by industrial chemists.

The industrial challenges now reside with finding reduction catalyst systems for the emerging drug intermediates for the new classes of pharmaceuticals that are going into clinical application; this introduction intends to give an overview of these pertinent technical issues.

1.2.1   PRIVILEGED STRUCTURES: α-AMINO ACIDS AND ITACONIC ACIDS

The above classes of compounds have the ability to bind to the transition metal of the catalytic species, usually through a carboxylate group, and form the families of chiral reductions that have been the most intensively studied. They also yield products that are key intermediates in a range of active pharmaceutical ingredients (APIs). The catalyst systems for the 'privileged structures' have been well developed and α-amino acids and itaconic acids are routinely synthesized by reduction of unsaturated precursors with high ees and conversions at low catalyst concentrations. Many examples of the reactions shown in Figure 1.3 have been run at industrial scale and a wide range of catalytic systems have been reported that deliver high conversions and greater than 99 % ee.[2]

Perindopril (**A**), an orally active pharmaceutical for the treatment of hypertension, is an important commercial target compound that has a cyclic α-amino acid as an intermediate in its synthetic route. The bicyclic α-amino acid building block is synthesized by reduction of the chiral indoline-2-carboxylic acid (**B**, R=R′=H) shown in Figure 1.4. This chiral cyclic amino acid has so far proven very difficult to synthesize in a highly enantioselective manner using chiral hydrogenation.

Therefore better methods for the chiral reduction of indole-2-carboxylic acid derivatives would provide an elegant synthesis of this intermediate. A study by Kuwano and Kashiwabara[3] of the reduction of indole derivatives into the corresponding indolines found that a range of the more common ligand systems gave almost no enantioselectivity but the TRAP ligand gave the chiral indolines in up to 95 % ee for reduction of the methyl ester (**B**, R=Me, R′=H). Further developments are awaited.
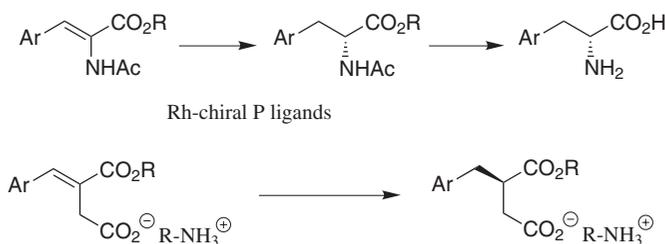
Figure 1.3   Privileged structures for industrial chiral hydrogenation.
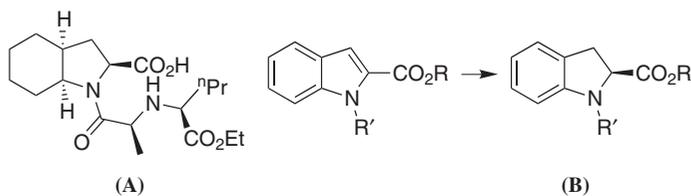
Figure 1.4   Perindopril (**A**) and the key hydrogenation step.

1.2.2   β-AMINO ACIDS

β-Amino acids are key building blocks for several industrial API targets as they form part of the structure of several new potentially commercially important compounds. Although the chiral hydrogenation route has not been investigated as thoroughly as for α-amino acids there is a significant number of published catalyst systems that yield these types of chiral building blocks[4]. β-Amino acids possess several biologically interesting properties including a remarkable stability of their derived amides towards peptidases: when used in the construction of peptidomimetics they confer the ability to fold into distinct secondary structures (similar to α-peptides) such as helices, turns, sheets and tubular structures. Such properties make them powerful tools for medicinal chemistry[5]. β-Homophenylalanine has been a widely reported as an example from this family of compounds. Other structures that use members of this family as their components are exemplified by the 'fiban' compounds (shown in Figure 1.5) which display various β-amino acid residues, including a cyclic constrained structure that forms an important sub-group of the β-amino acids family[6].

The enantioselective synthesis of the β-amino acid ester shown in Figure 1.6 has recently been reported by Kubryk and Hansen[7] (Merck) where good ees were obtained by asymmetric hydrogenation. Using an *in-situ* reaction with diBoc-anhydride to protect the amine group a crystalline product was obtained that was recrystallized to the required 99 % + ee purity very easily.

A recent example from Pfizer reported by Hoge[8] involves the synthesis of the β-amino acid shown in Figure 1.7. Initially the BINAPINE ligand gave the higher diastereomeric excess but only 85 % conversion while the TRICHICKENFOOT ligand was giving incomplete conversion. By running the reaction with the first ligand system until the reaction stalled and then adding a second catalyst based on

X = H SC 54701, X,X = O   Xemilofiban   Elarofiban
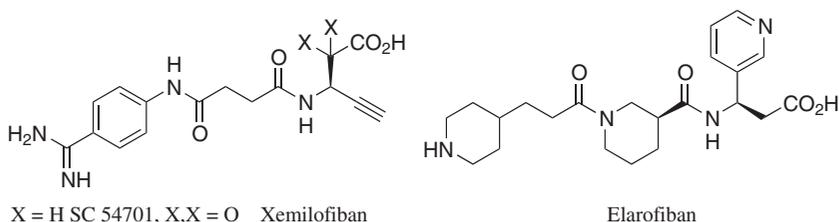
Figure 1.5   Exemplification of β-amino acids as API building blocks.

99 + % ee after recrystallization

Figure 1.6   Merck β-amino acid synthesis.

BINAPINE   TRICHICKENFOOTPHOS
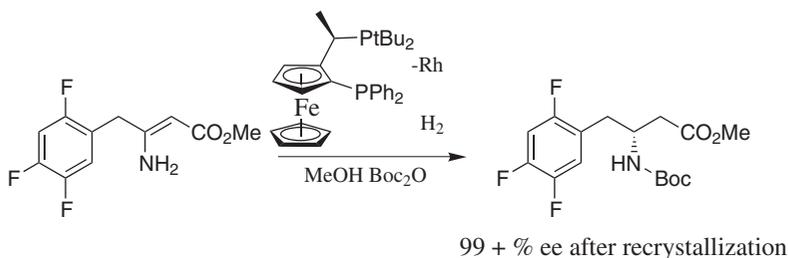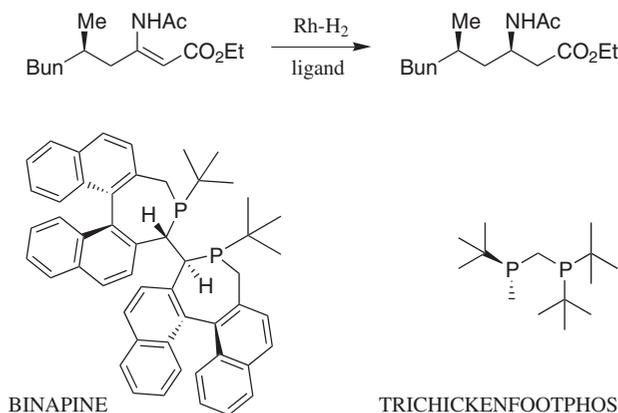
Figure 1.7   Pfizer β-amino acid synthesis.

the other ligand optimum performance was obtained. However, on further optimization by adjusting the solvent mixture and using careful control of water content Pfizer's own TRICHICKENFOOT ligand gave suitable performance and circumvented unwanted IP issues.

1.2.3   α-ALKYL SUBSTITUTED ACIDS

Another important acid derived from the corresponding unsaturated acid family is the α-alkyl substituted acid (**C**). This compound is used in the synthesis of Aliskiren (the active ingredient of Tekturna®) which Novartis has recently been granted FDA approval as the first-in-class renin inhibitor for control of blood pressure. It is estimated that large volumes of this intermediate will be required in the future but the best ee reported so far for production of this intermediate is 95 % as shown in Figure 1.8.[9]

A study by Hoen et al.[10] in collaboration with scientists from DSM indicates that the MONOPHOS derivative (**D**) together with added triphenylphosphine improves both the rate of reaction and enantioselectivity and may offer an improved
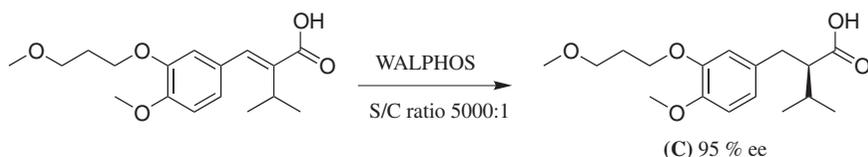
Figure 1.8   Novartis Aliskiren intermediate hydrogenation.
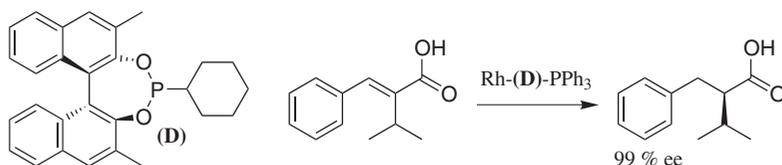
Figure 1.9   DSM MONOPHOS hydrogenation ligand system.

system for this important target as can be seen from the analogous reaction reported by these authors and shown in Figure 1.9.

The drug candidate OPC-51803 is the first nonpeptide vasopressin V$_2$-receptor-selective agonist that is in phase II clinical trials and the best chiral reduction to the intermediate acid (**E**) was with ruthenium acetate-[(*S*)-H8-BINAP] that gave a 77 % ee[11] (Figure 1.10). An improved catalyst system will be needed for large scale production.

Tipranavir is a unique, nonpeptidic protease inhibitor currently in phase III clinical trials for HIV treatment. In this compound a phenolic hydroxyl group behaves as a pseudo carboxylic acid group and the chiral hydrogenation step shown in Figure 1.11 gives reasonable enantioselectivity. Benincori *et al.*[12] have investigated the diastereoselective reduction of the tipranavir intermediate (**F**) using ullaPHOS, a more electron rich variant of DUPHOS, and have found this catalyst system increases the rates of hydrogenation and gives reasonable diastereomeric excesses (de's). Further optimization of this transformation is awaited.
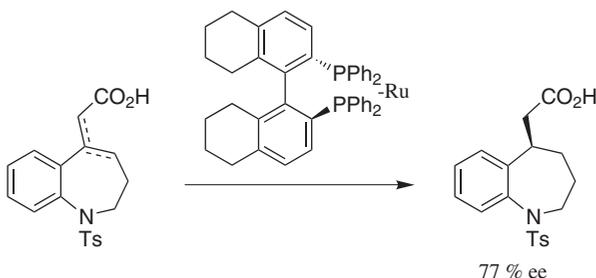
Figure 1.10   OPC-51803 intermediate.
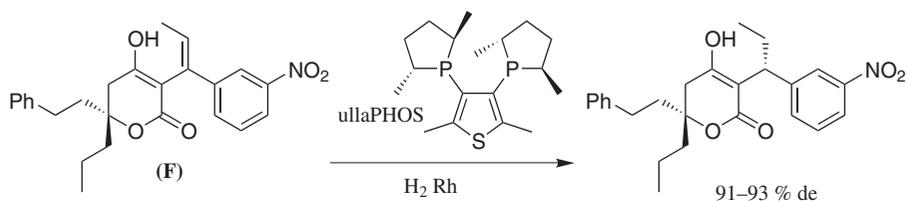
Figure 1.11   Tipranavir intermediate synthesis.

1.2.4   α-ALKOXY SUBSTITUTED ACIDS

Another important family of emerging pharmaceutical substances is the 'glitazar' portfolio of pharmaceuticals. These are peroxime proliferator activated receptor (PPAR) agonists that have attracted significant attention due to their potential usefulness in the treatment of type 2 diabetes and dislepedimia. Several compounds of this class are now in various stages of development and many contain a chiral α-alkoxy carboxylic acid motif (Figure 1.12) that has often been introduced by techniques other than asymmetric hydrogenation.[13]

However, with relevance to this review, Houpis *et al.*[14] screened over 250 ligands and catalysts from the Lilly catalyst libraries (containing representatives from most commercial ligand families) under their standard conditions to synthesize the key intermediate for Naveglitazar synthesis. They obtained the best results (92 % ee) employing WALPHOS as exemplified in Figure 1.13.
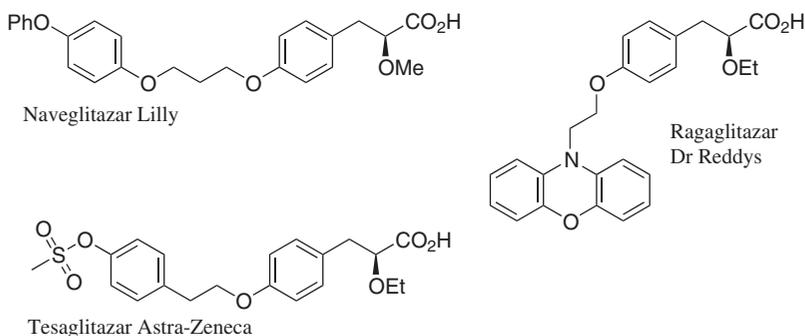
Figure 1.12   Glitazar API structures.
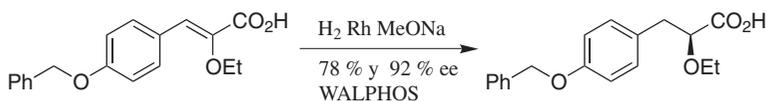
Figure 1.13   Lilly Azar intermediate formed by chiral hydrogenation.

1.2.5   UNSATURATED NITRILES

The asymmetric reduction of unsaturated nitriles to introduce chirality is a very useful process for the synthesis of many pharmaceutical intermediates. An important application of this strategy involves the further reduction of the nitrile group to yield chiral amines. The amine moiety is an important functional group which features in many APIs. As the nitrile group tends to bind 'end on' to rhodium, the high selectivities obtained from acids are not reproduced and the earlier work in this arena tended to concentrate on nitriles which had other functional groups in the molecule. This is exemplified by the synthesis of the Pregabalin intermediate made by hydrogenation of an unsaturated nitrile as shown in Figure 1.14. Hoge *et al.*[15] demonstrated that the three hindered quadrant phosphine TRICHICKENFOOTPHOS catalyst system gave results that were superior to those reported for Rh-MeDUPHOS, in respect to enantioselectivity (98 % ee vs 95 % ee at 100-g scale) using two times more concentrated reaction solutions and a catalyst loading of 27 000:1 substrate to catalyst ratio. These factors could have a profound impact on the cost of goods for producing a pharmaceutical intermediate on a scale required for the industry.

A more challenging example of an unsaturated nitrile reduction that lacks the carboxylate functional group is the asymmetric reduction of the nitrile[16] shown in Figure 1.15. The product was required in the synthesis of chiral
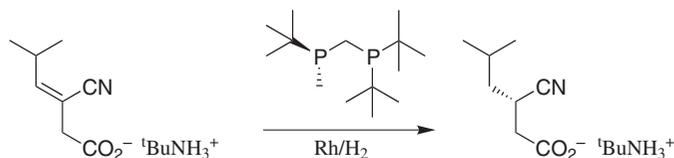
Figure 1.14   Pfizer Pregabalin intermediate synthesis.
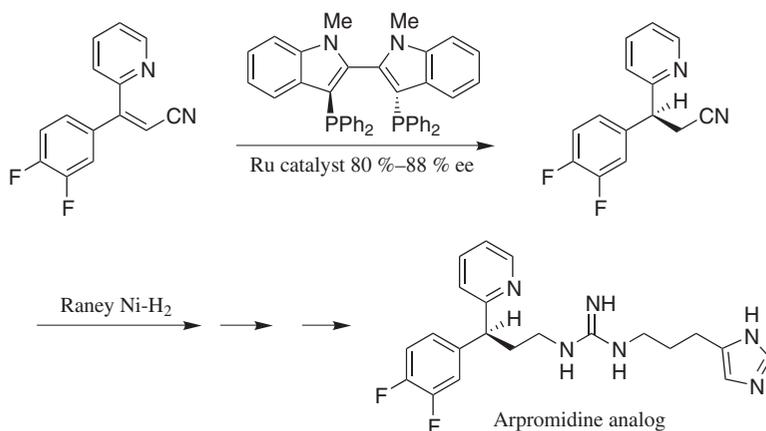
Figure 1.15   Asymmetric unsaturated nitrile reduction.

3,3-diarylpropylamine (**G**) which is an intermediate for the synthesis of the Arpromidines. These compounds are the most potent histamine H_2 receptor agonists known and are promising positive inotropic vasodilators for the treatment of severe congestive heart failure. Note the use of a ruthenium-based catalyst rather than the more usual rhodium catalysts.

The bis-indole diphosphine delivers the best ee and as the heterocyclic units are also electron rich aromatics this also gives the added advantage of the highest activity of the catalyst system. This overcomes one drawback often encountered, that high hydrogen pressures are frequently needed for ruthenium-based catalysts.

1.2.6   ALKENES AND ALLYL ALCOHOLS

Alkenes with no heteroatom functional groups and also allyl alcohols have attracted considerable attention as starting materials for chiral hydrogenation. These are particularly difficult substrates for reduction because a polar group adjacent to the alkene bond is required for the more conventional rhodium-catalyzed highly enantioselective reductions. The most successful class of catalysts for the title substrates has been iridium-based catalysts with substituted oxazoline-phosphine ligands. These relatively air- and moisture-tolerant cationic iridium complexes are efficient catalysts for the asymmetric hydrogenation of olefins; the field has recently been reviewed by Kallstrom et al.[17]

Several variations of these catalyst systems have been investigated and the asymmetric reduction of methylstilbene (Figure 1.16) has been the usual test reaction for new catalysts.

High ees have been obtained for several different catalytic systems for an extended range of substrates.

Lightfoot et al.[18] have developed one of these iridium-based systems for the stereocontrolled synthesis of lilial by asymmetric reduction of an allyl alcohol and subsequent oxidation of the alcohol, as shown in Figure 1.17.

Good methods for the chiral reduction of tetrasubstituted and terminal alkenes have yet to be fully developed.

1.2.7   α,β-UNSATURATED ALDEHYDE REDUCTION

Asymmetric reduction of α,β-unsaturated aldehydes with transition metal catalysts has not yet proven ready for widespread industrial application. One area, namely the chiral reduction of enals to yield chiral alcohols using bakers' yeast has been
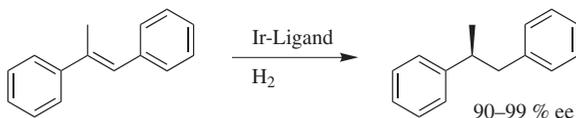
Figure 1.16   Trisubstituted alkene reduction.
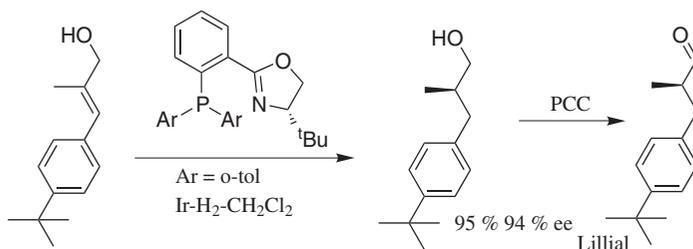
Figure 1.17 Lilial synthesis via iridium catalytic reduction.
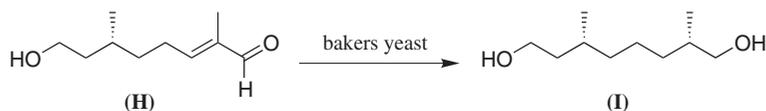
Figure 1.18 Bakers' yeast reduction of unsaturated aldehydes.

known for over 30 years and has attracted considerable attention because, when applied to terpene chemicals, the products can be utilized as chiral building blocks for many pheromones and fragrance chemicals. This is exemplified by the reactions shown in Figure 1.18 where (+)-citronellol was oxidized with selenium dioxide to give the unsaturated aldehyde (**H**), this was reduced by bakers' yeast on a relatively small scale to give the chiral diol (**I**) in high de which is a useful building block for many natural product syntheses.[19]

A recent interesting development in the reduction of carbon-carbon double bonds is the organocatalytic hydride transfer reductions of α,β-unsaturated aldehydes, whereby a Hantzsch ester acts as a good NADH mimic in the hydride-transfer to an iminium ion, formed when the α,β-unsaturated aldehyde reacts with the amine of the organocatalyst. These systems are being developed into metal-free biomimetic transfer hydrogenations. Ouellet and co-workers[20] use salts of chiral amines as organocatalysts, with impressive results as exemplified in Figure 1.19.
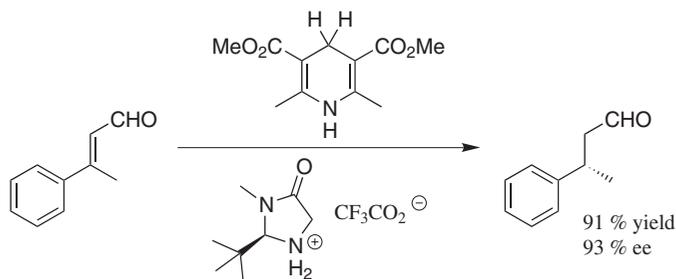
Figure 1.19 Organocatalytic reduction of an unsaturated aldehyde.
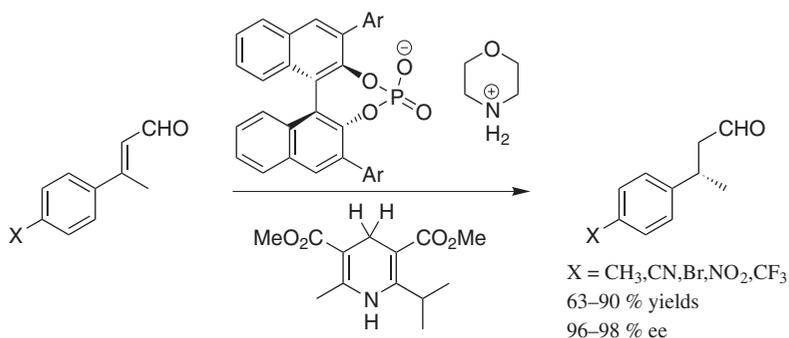
Figure 1.20 Chiral Bronsted acid induced reductions.

Mayer and List[21] used achiral amines and chiral phosphoric acids to form the counter ion and these also induce asymmetry in the process of hydrogen transfer as shown in Figure 1.20.

Adolfsson[22] published an overview of these types of reactions and these systems are also reported to be active for imine reduction (see Section 1.3).

1.3   KETONE AND IMINE REDUCTION

An important field of investigation for new industrial catalysts is the development of improved catalysts for the reduction of ketones and imines to obtain the corresponding chiral secondary alcohols and amines. These are used as key components in many active pharmaceutical intermediates. These heteroatom double bonds can be reduced by conventional hydrogenation with hydrogen gas or by transfer hydrogenation methods that use alcohols or formate as a hydrogen donor. Other significant catalytic reductions used in industry involve the use of chiral borohydride reagents and biocatalytic reductions. These different systems will be discussed in turn.

1.3.1   CATALYTIC HYDROGENATION OF KETONES AND IMINES

A good example of conventional gaseous hydrogenation methodology is the very efficient imine reduction shown in Figure 1.21 using iridium XYLIPHOS catalyst.
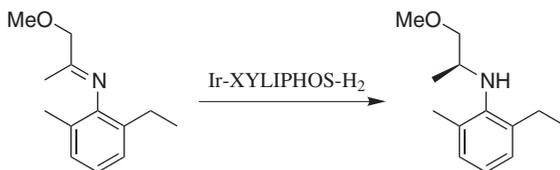
Figure 1.21 Syngenta imine reduction for Dual Magnum[TM] intermediate.
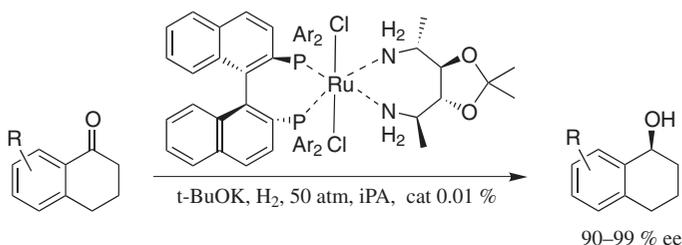
Figure 1.22 Noyori tetralone reduction.

This was developed for Syngenta and was a landmark product for enantioselective industrial catalytic synthesis. The full story behind this remarkable piece of work has been reported by Blaser.[23] Catalyst turnover numbers of 2 000 000 and turnover frequency values of around 600 000 h^{-1} allow highly efficient production of this important intermediate maize crop herbicide (Dual Magnum^{TM}).[23]

Catalysts for ketone hydrogenation continue to be developed but one of the best systems is still the BINAP-DPEN catalyst first reported by Ohkuma *et al.* in 1995.[24] In this system ruthenium is combined with both a chiral diphosphine and a chiral diamine, forming an octahedral complex which gives a high degree of enantioselectivity. This stereoselectivity is considered to be a result of the synergistic effect of the chiral diphosphine and diamine ligands.

More recent developments illustrating the importance of this type of system have been (a) the use of a chiral 1,4-diamine ligand to give a catalyst system that gave high ees for the hydrogenation of tetralones[25] (Figure 1.22) and (b) the use of 2-pyridylmethylamine for the reduction of highly hindered ketones such as t-butylmethylketone[26] (Figure 1.23).

Another recent example of the application of these catalyst systems is the efficient synthesis of the chiral alcohol (**J**) in a route to L-869,298, a potent PDE4 inhibitor, by O'Shea *et al.*[27] at Merck Frost, as shown in Figure 1.24.

During an investigation of transfer hydrogenations with complexes prepared *in situ* from RuCl$_2$(PPh$_3$)$_3$ and chiral phosphine-oxazoline ligand (**K**), Naud *et al.*[28] developed a catalyst for which activity (turnover frequency and turnover number) increased significantly when the reaction was carried out under hydrogen pressure whilst the ees only dropped marginally. This catalytic system is effective for the
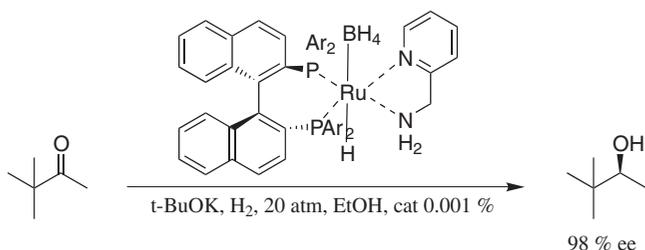
Figure 1.23 Noyori t-butylmethylketone reduction.
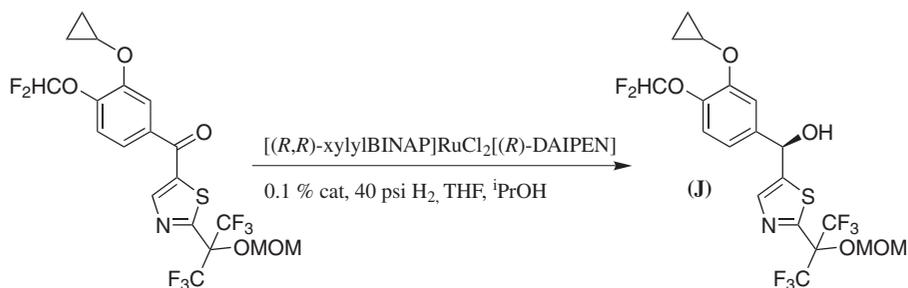
Figure 1.24 L-869,298 intermediate synthesis.

hydrogenation of various aryl ketones with ees up to 99 % and substrate to catalyst ratios of 10 000 – 50 000:1 whilst using high substrate concentrations. This observation makes this protocol attractive for scale-up and a pilot process has already been developed for the hydrogenation of 3,5-bistrifluoromethylacetophenone to produce the Aprepitant intermediate as shown in Figure 1.25.

Tellers *et al.*[29] from Merck optimized this catalyst system for the reduction of an α-substituted ketone that was needed as an intermediate for a drug development candidate. They obtained the best result (93 % ee) with ligand (**L**) in a method using 90 psi hydrogen pressure that was suitable for use at large scale (Figure 1.26).
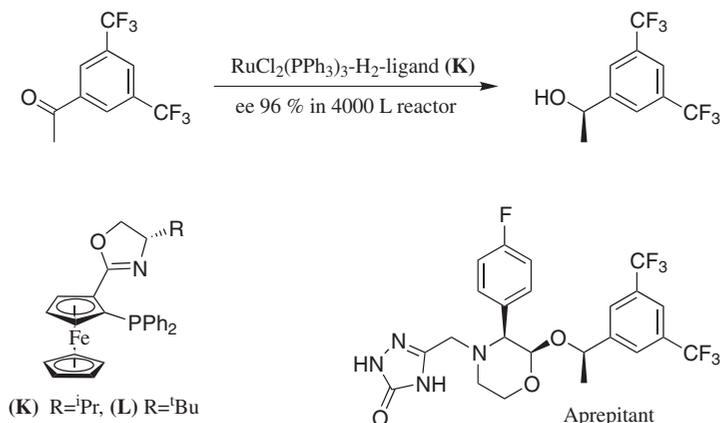
Figure 1.25 Oxazoline ligands for ketone hydrogenation.
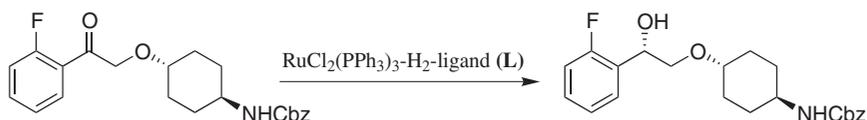
Figure 1.26 Merck process for ketone reduction.
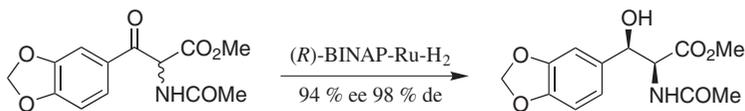
Figure 1.27 *Anti*-selective DKR of an amino keto ester derivative.

The synthesis of β-hydoxy-α-amino acids is important since these compounds are incorporated into the backbone of a wide range of antibiotics and cyclopeptides such as vancomycins. These highly functional compounds are also subject to dynamic kinetic resolution (DKR) processes, as the stereocenter already present in the substrate epimerizes under the reaction conditions and hence total conversions into single enantiomers are possible. These transformations can be *syn*-selective[30] for N-protected derivatives as shown in Figure 1.27 when using a ruthenium-BINAP catalyzed system and *anti*-selective[31] when the β-keto-α-amino acid hydrochloride salts are reduced by the iridium-MeOBIPHEP catalyst as shown in Figure 1.28. One drawback is that both these reductions use 100 atm hydrogen pressure.

1.3.2 ASYMMETRIC TRANSFER HYDROGENATION (ATH) CATALYSTS

A wide range of metals and ligand combinations have been demonstrated to effect the ATH reaction and in this book we concentrate on the systems that have demonstrated high activities and ees that would be the requirement of an industrial application. The initial breakthrough in this area came in 1995 with the report from Ohkuma *et al.*[32] on the use of chiral monotosylated diamine complexes for asymmetric transfer hydrogenation.

From an industrial standpoint the most useful catalysts are those based on transition metal complexes that are neutral and stable 18-electron catalyst precursor complexes that have the following structural elements: (a) an η^6/η^5-aryl complexing group; (b) a metal from Rh, Ir and Ru at the correct oxidation level to give a neutral complex; (c) a chiral bifunctional ligand modifier with an amine group; and (d) an anionic leaving group as shown in Figure 1.29. The most common hydrogen donors are isopropanol which forms an equilibrium mixture with the substrate [therefore these reactions are usually run at high dilutions (typically 0.5 M)] and the 5:2 formic acid–triethylamine azeotrope which makes an irreversible system due to carbon dioxide elimination. This formic acid mixture is incompatible with amino alcohol ligands and is only useful for application with the diamine monosulfonate ligands.
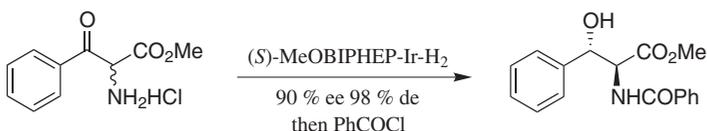
Figure 1.28 *Syn*-selective DKR of an amino keto ester compound.
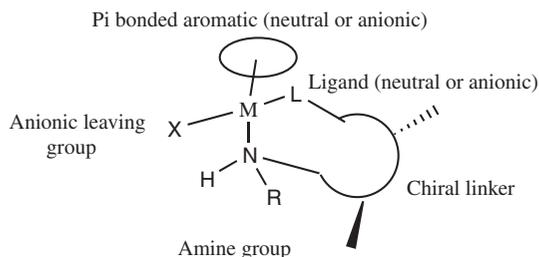
Figure 1.29   General structure for ATH catalysts.

The aromatic complex can be a neutral η^6-benzene derivative or an anionic η^5-cyclopentadienyl ring. Substituents on these aromatic rings can greatly influence the effectiveness of these catalysts. For example, with benzene derivatives the unsubstituted benzene rings give lower ees and the use of hexamethylbenzene results in lower catalytic activities whilst the cumenyl or mesityl rings give optimum catalyst systems. The two types of chiral bifunctional linkers that have been most practical are anionic ones based on monosulfonated diamines and amino alcohols.

Figure 1.30 exemplifies two types of systems that have attracted the most attention for this reaction, namely the Ru(II) complexes (**M**) (originally reported by Ohkuma *et al.*[32]) with monotosyldiphenylethylamine which can reduce arylalkyl ketones with high ees using both 2-propanol or triethylamine-formic acid. Alternatively, the Rh(III) complexes of the type (**N**) have been commercialized as the CATHy[TM] system by Blacker and Mellor[33] (from Avecia now NPIL) using the anionic pentamethylcyclopentadienyl group as the aromatic ligating system. Several case studies describing the scale-up for several processes have been described.[34]

The mechanism of this reaction was fully elucidated by Noyori *et al.*[35] who showed that the relatively stable 18-electron precatalyst complex eliminates HX to give the 16-electron active catalyst complex that then reacts with the hydrogen donor (2-propanol or formic acid) to give the dihydrogen metal complex (and eliminates acetone or carbon dioxide from the hydrogen donor). Transfer of two hydrogens to the substrate in a six-membered ring transition state regenerates the active catalyst (Figure 1.31).

A detailed review of the mechanisms of the hydrogenation of polar double bonds by ruthenium hydride species have been published by Clapham *et al.*[36] The article examines the properties of over 100 catalyst systems for transfer and
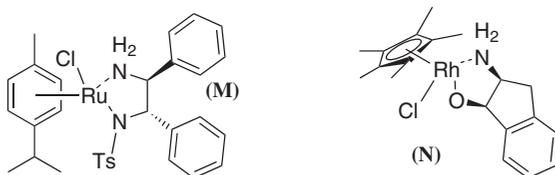
Figure 1.30   Catalytic ATH systems reported for industrial application.
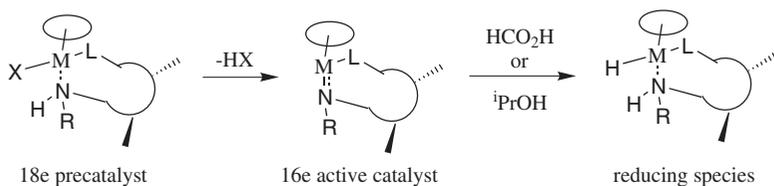
Figure 1.31 Transfer hydrogenation active catalyst species.
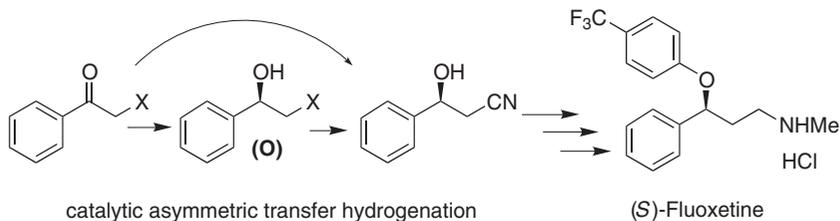
Figure 1.32 Chiral Fluoxetine synthesis using ATH.

gaseous hydrogenation methods to give insights into the critical features of this transformation.

The family of substituted acetophenones shown in Figure 1.32 have been studied in detail as these ketone substrates, on being reduced by ATH, allow the synthesis of the family of chiral phenylalkanols (O) (where X = Br, Cl, CN, CO$_2$R and CONHR) which are used as intermediates in the synthesis of (S)-Fluoxetine and related compounds.[37,38]

The above mentioned catalysts also have the advantage of being robust and they can be attached to scaffolds that allow them to be recycled.[38]

Another field where ATH catalysts have made an industrial impact is in the area of chiral amine synthesis by stereocontrolled reduction of imines. First demonstrated by Uematsu et al.,[39] the reduction of cyclic imines to yield chiral amines has proved to be a highly versatile and successful strategy for the synthesis of chiral tetrahydroisoquinolines and related compounds. This is exemplified in Figure 1.33 which shows the synthesis of the natural product Salsolidine in 95 % ee by the reduction of the precursor cyclic imine. Several other similar types of imines were
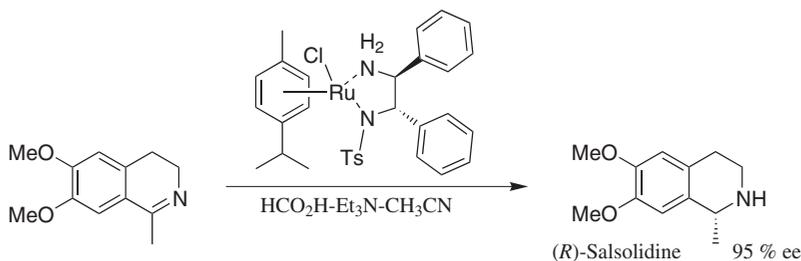
Figure 1.33 ATH chiral imine reduction.
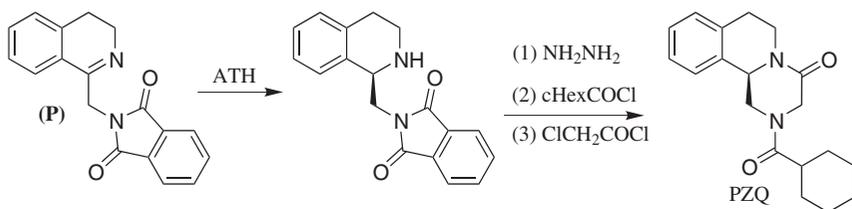
Figure 1.34   ATH as chiral step in PZQ synthesis.

also reduced using these types of catalysts to give cyclic chiral amines that are important structural units in many biologically active pharmaceuticals and alkaloid natural products. These imine reductions require the formic acid–triethylamine reducing hydrogen donor and also an organic cosolvent (acetonitrile, dichloromethane or DMF) to ensure that the reaction is fast enough to be useful, and hence the popular combination of ruthenium(II) with amino alcohol ligands is incompatible with formic acid and therefore not suitable for imine reduction.

Roszkowski et al.[40] have described a method for the enantioselective preparation of Praziquantel (PZQ) a pharmaceutical for the treatment of schistosomiasis and soil-transmitted helminthiasis. Starting with the imine (**P**) (readily available from phenylethyl amine, phthalyl anhydride and glycine) an asymmetric transfer hydrogenation yielded the chiral intermediate in 62 % ee, and the crude product was easily crystallized to the required high ee and converted into the Praziquantel as shown in Figure 1.34.

Williams et al.[41] extended the reaction to produce a range of chiral cyclic amines by reacting an aryl metal species with Boc-lactams to yield Boc-aminoketones which could then be deprotected, cyclized and reduced in a one-pot reaction. However, whilst salsolidine could be made in high ee from this one pot method, the cyclic amines shown in Figure 1.35 could be produced in good yield but these were nearly always produced in racemic form.

For the synthesis of simple amines, including valuable resolving agents such as the (1-naphthyl)ethylamines, ATH can be useful but an N-linked phosphorus-based electron withdrawing group was found to be a necessary addition to the substrate. Blacker and Martin[34] demonstrated that the reduction may be run at very low levels of catalyst when triethylammonium formate was fed into the reactor and nitrogen gas passed into the system as shown in Figure 1.36.

A major impact in the treatment of HIV involves anti-retroviral therapy with APIs that belong to a class known as the 'avir' family of highly active pharmaceuticals. A number of these 'avirs' contain the 1-phenyl-2,4-diamino-butan-3-ol fragment (**Q**).
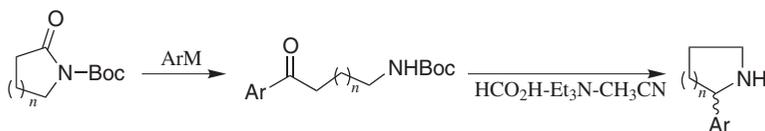
Figure 1.35   Cyclic amine synthesis by transfer hydrogenation.
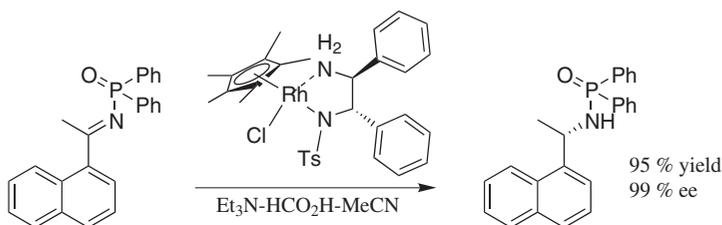
Figure 1.36 ATH of phenylphosphinylimine.

A very good route to these entities is from the protected amino epoxides derived from (L)-phenylalanine shown in Figure 1.37. Economic methods for this conversion have been developed, involving the treatment of the N-protected amino acid with isobutyl chloroformate, then diazomethane and finally hydrochloric acid in industrial continuous reactors that have been designed for this purpose.[42] The (2S,3S)-chloroalcohol has been synthesized in good yield using sodium borohydride reduction or by ATH using the ruthenium TsDPEN catalyst.[43] Recently Pennington and Hodgson[44] have described diastereoselective reduction to give the (2R,3S)-chloroalcohol in 94 % de using MeBOPHOS coordinated to ruthenium catalyst, with 99 % conversion in 20 hours being achieved using a 0.2 % catalyst loading at 10 atm hydrogen pressure. These results are summarized in Figure 1.37. The chloroalcohols
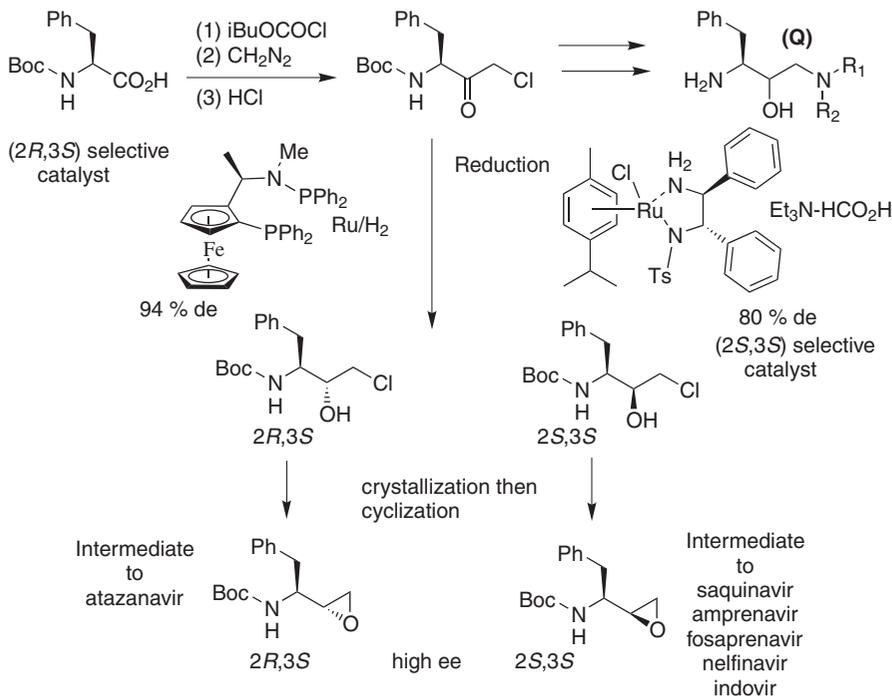
Figure 1.37 Avir intermediate synthesis by ketone hydrogenation.

can be easily crystallized to enhance the ees to the levels needed for pharmaceutical application before conversion into the desired epoxides.

1.3.3   MODIFIED BORANE REAGENTS

One popular method that has been applied to industrial processes for the enantio-selective reduction of prochiral ketones, leading to the corresponding optically active secondary alcohols, is based on the use of chiral 1,3,2-oxazaborolidines. The original catalyst and reagent system [diphenyl prolinol/methane boronic acid (**R**)] is known as the Corey–Bakshi–Shibata (CBS)[45] reagent. Numerous examples describing the application of this method are known, as exemplified by the synthesis of the chiral ferrocene bis-alcohol needed for ligand synthesis described by Schwink and Knochel[46] (Figure 1.38). Although very good enantio- and diastereoselectivities were achieved, high catalyst loadings were required.

Such high catalyst loadings have resulted in polymer supported systems being developed. These higher molecular weight species still give good selectivity but allow the catalyst to be recycled.[47]

The use of CBS-type catalysts has been extended to the reduction of oximes into chiral amines. Chu *et al.*[48] have described the BINOL-proline-borate complex shown in Figure 1.39 that can reduce acetophenone oxime into chiral 1-phenyl-ethylamine with 98 % ee, but the ee drops when the borate complex is used catalytically.
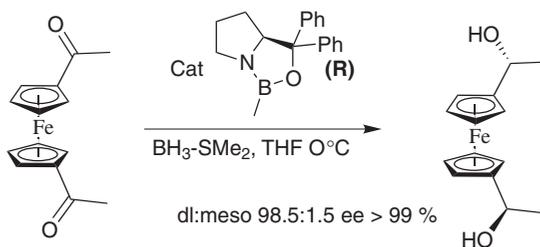
Figure 1.38   CBS catalyzed double ketone reduction.
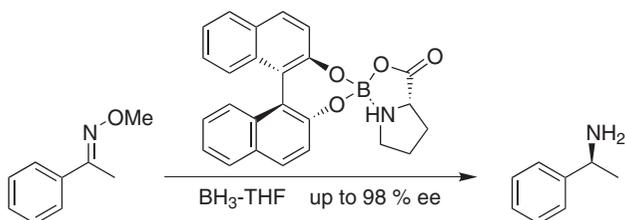
Figure 1.39   Chiral amine synthesis using modified boranes.

1.3.4 BIOCATALYSTS (ALCOHOL DEHYDROGENASES AND KETOREDUCTASES)

The biocatalytic reduction of prochiral ketones, using either whole cell systems or isolated enzymes, shows great potential in terms of mild reaction conditions and good selectivities.[49,50] These attractive properties have resulted in this class of biocatalysts being intensively studied and many potential applications have been identified. Biocatalytic reductions can be accomplished using whole cell systems but these biotransformations can be hampered by low productivity and complicated by the presence of multiple ketoreductases, which can lower the selectivity. The requisite enzymes are commercially available with high activity and the necessary employment of cofactors is no longer an obstacle as they can be efficiently regenerated *in situ* by glucose dehydrogenase (NADPH) and formate dehydrogenase (NADH).[51] Formate dehydrogenase irreversibly oxidizes formate to carbon dioxide process at a rate of about $8000\,h^{-1}$. Both substrate and product are relatively inert with the carbon dioxide being removed as a gaseous by-product; this method has been demonstrated to work on industrial scale for the production of tert-leucine.[52]

Pollard *et al*.[53] from Merck required both enantiomers of 3,5-bistrifluoro-methylphenyl ethanol since the (*R*)-enantiomer can be incorporated into Merck's orally active NK1 receptor antagonist for the treatment of chemotherapy induced emesis, while the (*S*)-enantiomer is used as a chiral synthon for a number of antagonists which the same company currently have under clinical evaluation. Using proteins from a library of commercially available alcohol dehydro-genases both enantiomers were obtained with ees of 99 % (Figure 1.40).

The versatility of these reduction systems are demonstrated by the next few examples, chosen to show that a wide range of functional groups are tolerated by these biocatalysts and how the biotransformations can be applied to synthesize intermediates in API production. Zhu *et al*.[54] from Biocatalytics have devel-oped a library of new recombinant ketoreductases (via genome mining) and have reported their properties, including enantioselectivities and rate of reductions, for a range of β-ketoesters. Stewart *et al*. have reported the reduction of α-chloro-β-ketoesters in good yields and high ees and used these transformations in the elegant syntheses of (−)-bestatin[55] and taxol side chains[56] as shown in Figure 1.41.
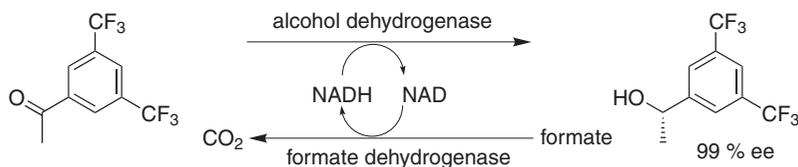
Figure 1.40 (*S*)-3,5-Bis(trifluoromethyl)phenyl ethanol synthesis via bioreduction.
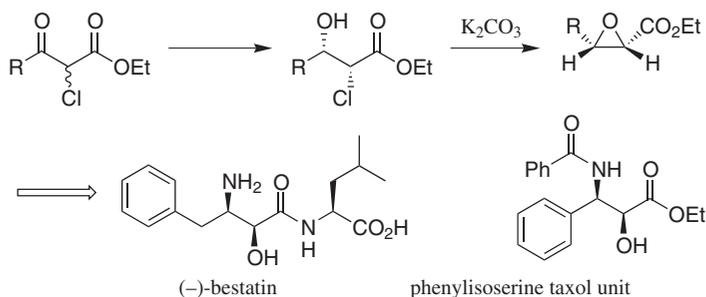
Figure 1.41   α-Chloro-β-ketoester using engineered *Escherichia coli* cells.
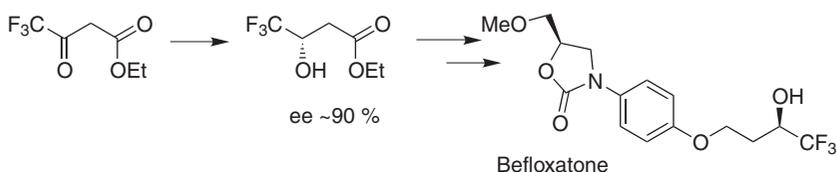
Figure 1.42   Befloxatone fluorinated side chain synthesis.

The reduction of ethyl trifluoroacetoacetate by bacterial alcohol dehydrogenases has been reported by Zhang *et al.*[57] and the product used as an intermediate in the synthesis of Befloxatone as shown in Figure 1.42.

The 'statin' family of pharmaceuticals require a chiral side chain, representing a target that has attracted a great deal of activity focused on preparing various potential intermediates. A number of reports have been published on the reduction of chloroacetoacetate esters for conversion into this target molecule. A method suitable for large-scale production has been published that operates at $36.6\,g\,L^{-1}$ and 95.2 % yield with 99 % ee.[58] This reaction is shown in Figure 1.43.

An elegant approach to address the same need was the double reduction of the diketoester shown in Figure 1.44 reported by Holt *et al.*[59] from Avecia (now NPIL). The chiral triol was produced in a whole cell reduction process and was then selectively protected at the primary alcohol by enzymatic acylation using Novozyme 435 (CAL-B). Finally the key intermediate was produced by protecting the two secondary alcohols as they cleanly reacted with dimethoxypropane to give a crystalline product (>99 % ee, >99 % de, 96 % purity) which was subsequently used for Lipitor production (Figure 1.44).
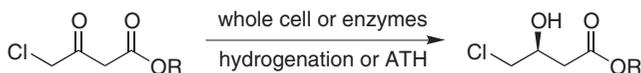
Figure 1.43   Reduction of ethyl chloroacetoacetate.
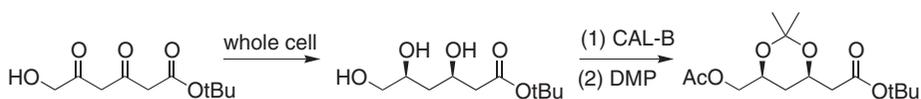
Figure 1.44 Double ketone reduction in a whole cell process.

1.4 OXIDATION

1.4.1 SHARPLESS CHIRAL EPOXIDATION OF ALLYL ALCOHOLS

The original titanium catalyst invented by Sharpless and Katsuki has been used for the epoxidation of an immense number of allylic alcohols to yield high value industrial synthons very effectively, as shown in Figure 1.45.[60]

This transformation has been applied to several chiral production processes, the first being the synthesis of a pheromone (Disparlure) intermediate[61] (**S**) albeit with low turnover numbers and only 91 % ee. Another industrial product is the epoxide of allyl alcohol as developed by PPG-Sipsy,[62] to give a process where catalyst loading was decreased by molecular sieve addition and the safety factors involving peroxide contamination were overcome. These examples are shown in Figure 1.46.

1.4.2 DIOXIRANE CATALYZED EPOXIDATION

Chiral ketone-catalyzed asymmetric epoxidation has received intensive interest since the first reported by Curci *et al.* in 1984.[63] The reaction is performed with oxone[TM] (potassium peroxomonosulfate) as the primary oxidant which generates the chiral dioxirane catalytic species in situ, which in turn, transfers the oxygen
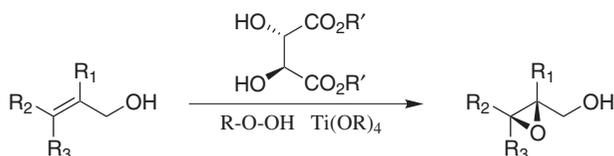
Figure 1.45 The Katsuki–Sharpless epoxidation reaction.
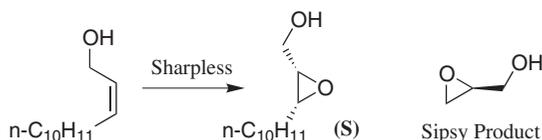
Figure 1.46 Industrial products manufactured using Sharpless epoxidation.
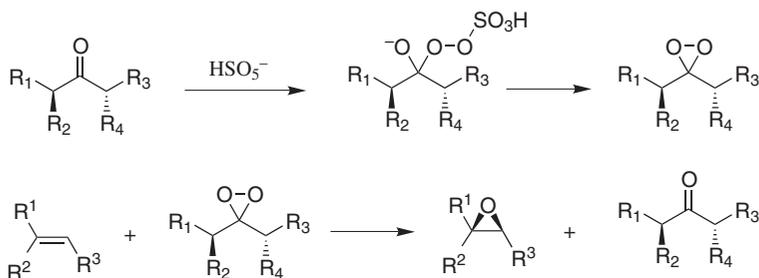
Figure 1.47   The dioxirane catalyzed alkene epoxidation.

atom to the alkene (Figure 1.47). Shi[64] has published an in-depth review of this oxidation method inter alia describing the wide range of substrates that have been successfully epoxidized with these systems.

Discovering highly enantioselective chiral ketone catalysts has proven to be challenging, due to a number of undesired processes that can compete with the catalytic cycle of the epoxidation, including Baeyer–Villiger oxidation of the catalytic ketone into inactive esters. The complication of side reactions has meant fairly high levels of the ketone catalyst are often required. The development of an efficient ketone catalyst thus requires delicately balancing the sterics and electronics of the chiral control elements around the carbonyl group. On the other hand the ketone-catalyzed epoxidation has several positive features including a broad substrate scope. For example, the fructose-derived ketone (**T**) is a highly general and enantioselective catalyst for the epoxidation of *trans* and trisubstituted olefins whilst the ketone (**U**) gives high enantioselectivity for a number of *cis*-olefins and useful levels of enantioselectivity for some terminal olefins (Figure 1.48).

Other advantages include a mechanism that allows one to rationalize and predict the stereochemical outcome for various olefin systems with a reasonable level of confidence utilising a postulated spiro transition state model. The epoxidation conditions are mild and environmentally friendly with an easy workup whereby, in some cases, the epoxide can be obtained by simple extraction of the reaction mixture with hexane, leaving the ketone catalyst in the aqueous phase.
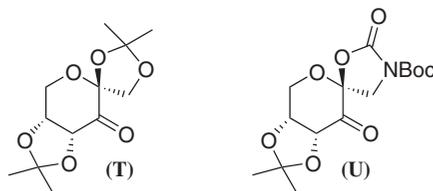
Figure 1.48   Shi epoxidation catalysts.

1.4.3   AMINES AND IMINIUM SALTS

The epoxidation of olefins catalyzed by iminium salts and amines (or ammonium salts) is emerging as a new technique for the functionalization of simple alkenes. These catalysts have relatively simple structures and hence are easily produced at scale; they offer potential as green oxidation catalysts. These organic salts are effective oxygen transfer reagents towards electron-rich unfunctionalized olefins. For the iminium salt systems oxone[TM] oxidizes an iminium salt to the oxaziridinium intermediate,[65] which then transfers oxygen to the olefin and as oxone[TM] reacts readily with iminium ions to regenerate the oxaziridinium species catalytically, efficient oxidation is possible.

Goncalves et al.[66] have compared the amine (**V**) and the iminium salt (**W**) for the enantioselective epoxidation of some prochiral olefins in acetonitrile/water and found that the yields and ees are nearly the same for the epoxidation of a selection of olefins. The amines of type (**X**) are less well developed. Armstrong[67] has summarized the developments in this field and suggested mechanisms based on hydrogen bonded species, one of which is shown in Figure 1.49. Typical yield and ee data for the epoxidation of 1-phenylcyclohexene for these catalysts are also shown in Figure 1.49.

1.4.4   PHASE TRANSFER CATALYSTS

The epoxidation of enones using chiral phase transfer catalysis (PTC) is an emerging technology that does not use transition metal catalysts. Lygo and To[68] described the use of anthracenylmethyl derivatives of a cinchona alkaloid that are capable of catalyzing the epoxidation of enones with remarkable levels of asymmetric control and a one pot method for oxidation of the allyl alcohol directly into

	conv	ee
(**V**)	99 %	76 %
(**W**)	98 %	81 %
(**X**)	93 %	46 %
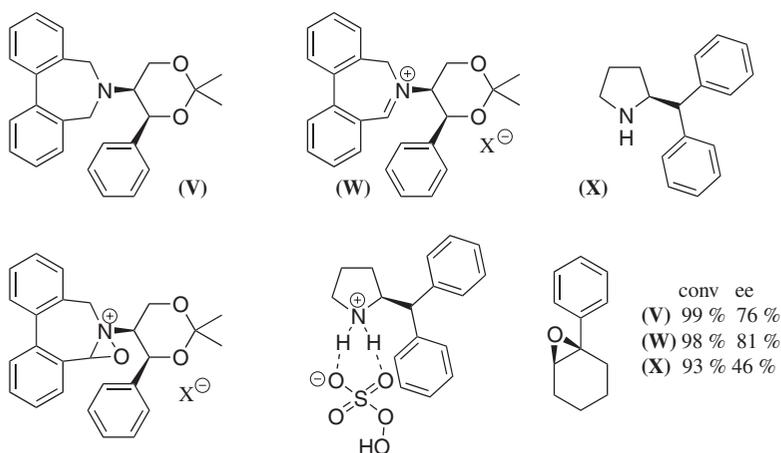
Figure 1.49   Amines and iminium salt epoxidation catalysts.
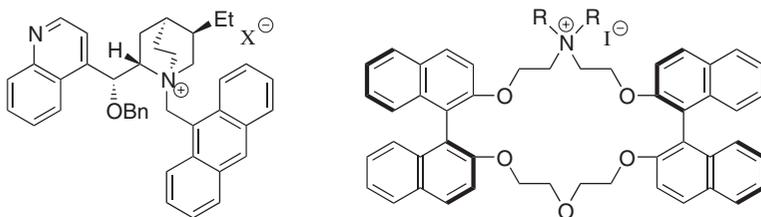
Figure 1.50   Phase transfer catalysts for enone epoxidation.

the epoxide was described. Ye et al.[69] developed an enantioselective epoxidation with similar catalytic chiral quaternary ammonium salts using trichloroisocyanuric acid as the oxidant giving good yields of epoxy ketones from chalcones with enantioselectivities up to 96 %.

Hori et al.[70] have recently reported aza crown ether chiral quaternary ammonium salts for the epoxidation of (E)-chalcone with alkaline hydrogen peroxide as the terminal oxidant. The oxidation proceeded in high yield and good enantioselectivity; the success of the reaction depended on the length of the carbon chain on the nitrogen atom. These PTC catalysts are shown in Figure 1.50.

1.4.5   THE JULIÁ–COLONNA METHOD (POLYLEUCINE OXIDATION)

The oxidation of electron-deficient chalcone-type compounds with hydrogen peroxide and poly-amino acid catalysts is known as the Juliá–Colonna protocol. Optically active epoxides with high ees are obtained from facile processes that use small amounts of catalyst and simple reagents. Gerlach and Geller[71] have reported the process development studies that allow the reaction to be run on pilot plant scale. The resulting epoxides can be converted into a wide range of interesting products,[72] including a Diltiazem intermediate as shown in Figure 1.51.[73]
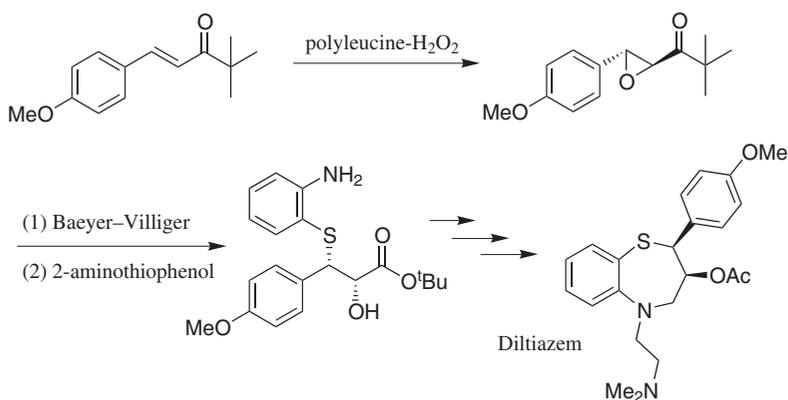
Figure 1.51   Diltiazem synthesis using polyleucine epoxidation.
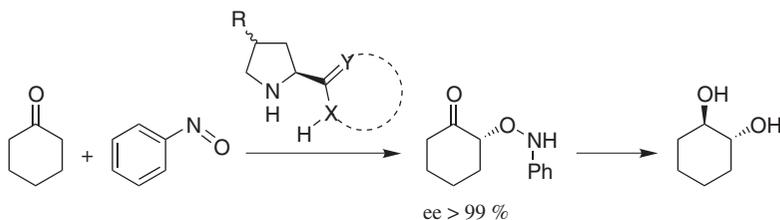
Figure 1.52 Organocatalyst α-hydroxylation of ketones.

1.4.6 ORGANOCATALYTIC α-HYDROXYLATION OF KETONES

A newer method of oxidation that is attracting considerable attention is the reaction of ketones with nitrosobenzene and proline-based organocatalysts (Figure 1.52). Effective hydroxylation of the ketone is achieved in exceptionally high ee.[74–76]

1.4.7 BAEYER–VILLIGER OXIDATION

The Baeyer–Villiger oxidation of ketones represents a powerful synthetic method that breaks carbon-carbon bonds in an oxygen insertion process to deliver lactones. A recent comprehensive review by ten Brink *et al*.[77] describes the different methods used for this reaction and highlights the technical and environmental advantages of the transformation. Symmetrical ketones can be converted into chiral lactones that are frequently used synthons for many target molecules in modern pharmaceuticals. A review by Mihovilovic *et al*.[78] discusses enantioselective Baeyer–Villiger oxidations by chemical and biotransformation approaches, including scope and limitations, the improvement of optical purity and implications upon scale-up.

Figure 1.53 shows the Fluka (kilogram-scale) asymmetric microbial Baeyer–Villiger oxidation of racemic bicyclo[3.2.0]hept-2-en-6-one (**X**) using a 50 L bioreactor as described in a publication by Wohlgemuth *et al*.[79]

High productivity was obtained by a combination of several (bio)chemical engineering techniques including resin-based *in situ* substrate feeding/product removal methodology, a glycerol feed control and an improved oxygenation regime.
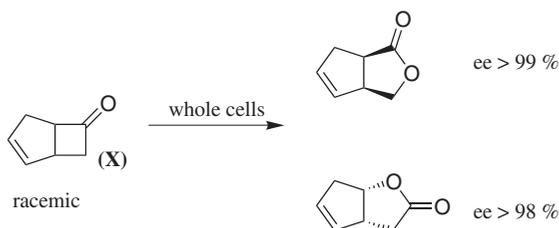
Figure 1.53 Baeyer–Villiger biotransformation of ketones.

Both regioisomeric lactones were obtained in nearly enantiopure form (ee > 98 %) and good yield.

1.4.8   CHIRAL SULFOXIDES

The development of the single enantiomer 'azole' within the family of compounds used for gastrointestinal treatments is exemplified by Astra-Zeneca's Esomeprazole (a potent gastric acid secretion inhibitor) (Figure 1.54). This development gave the impetus for the search for industrial chiral sulfoxidation catalysts.

The development of a large scale manufacturing route to Esomeprazole is described by Federsel and Larsson[80] using the titanium catalyst originally described by Kagan and Luukas.[81] Employment of a tartaric acid derived chiral auxiliary, with the addition of a base such as diisopropylethylamine to the reaction mixture, resulted in a full-scale catalytic process capable of delivering multi-ton quantities of product with optical yields well above 90 %, a figure which could be raised to 99.5 % ee by recrystallization from methyl isobutyl ketone.

The Kagan protocol for asymmetric oxidation of sulfides to sulfoxides has been used for other plant scale processes the structures of which are shown in Figure 1.55. These include the intermediate for Sulindac, a nonsteroidal anti-inflammatory drug for which some other biological effects have been attributed to single enantiomers and a neurokinin antagonist candidate intermediate where the scale-up required the use of cumyl peroxide and careful control of oxidant addition to keep the temperature sufficiently low to achieve very high ees when run on pilot scale process.[82] The Astra-Zeneca candidate drug ZD3638, an atypical antipsychotic agent for the treatment of schizophrenia, was formed from the corresponding
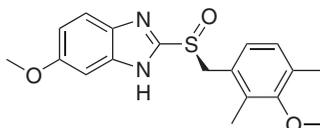
Figure 1.54   Esomeprazole.
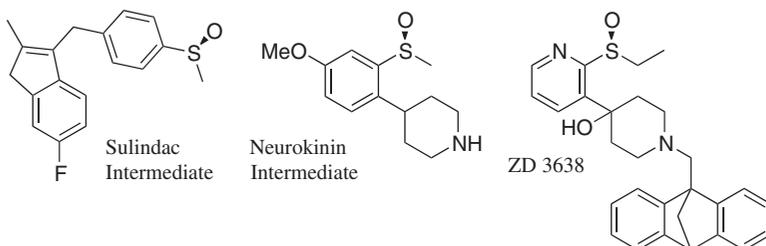
Figure 1.55   Industrial scale chiral sulfoxides from titanium catalyzed asymmetric oxidations.

sulfide with a moderate enantiomeric excess of only 60 % ee when using the standard conditions but addition of Hunig's base improved the results and avoided the formation of the corresponding sulfone by-product.[83] This is one of the rarer examples whereby a side-chain longer than a methyl group has been enantioselectively oxidized.

These reactions may give very high enantioselectivities, particularly for structures such as ArS(O)Me and this approach has been used on a multi-kilogram scale in industry.

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2 Asymmetric Hydrogenation of Alkenes, Enones, Ene-esters and Ene-Acids

CONTENTS

2.1   (*S*)-2,2′-BIS{[DI(4-METHOXYPHENYL)PHOSPHINYL]OXY}-5,5′,6,6′,7,7′,8,8′-OCTAHYDRO-1,1′-BINAPHTHYL AS A LIGAND FOR RHODIUM-CATALYZED ASYMMETRIC HYDROGENATION

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Rhodium-catalyzed asymmetric hydrogenation is one of the most important applications of homogeneous catalysis in industry.[1] High activity, selectivity, and stability, as well as readily accessible ligands and enzyme-like stereocontrol are among the characteristic features of an ideal catalyst for practical asymmetric synthesis.[1,2] Recently, a new chiral ligand (Figure 2.1) based on the 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl atropisomeric backbone, has been synthesized and applied in asymmetric hydrogenation of dimethyl itaconate and methyl (Z)-α-acetamidocinnamate.[3] The effectiveness of this catalyst is manifested by the excellent enantioselectivities and high catalytic activities.
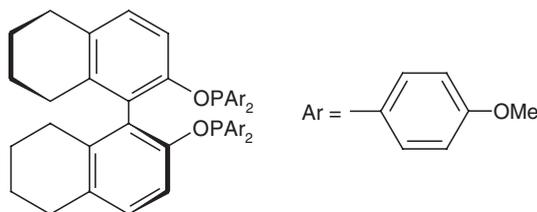
Figure 2.1

2.1.1   SYNTHESIS OF (S)-5,5′,6,6′,7,7′,8,8′-OCTAHYDRO-1, 1′-BI-2-NAPHTHOL[4]
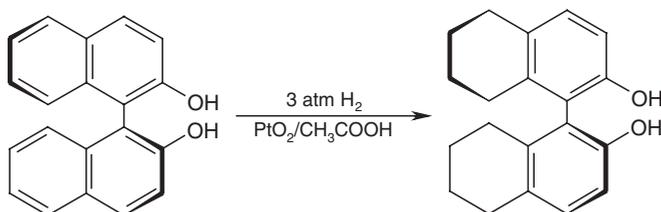
Materials and Equipment

- (S)-1,1′-Bi-2-naphthol (>99 % ee) (10 g, 27.5 mmol)
- PtO$_2$ (1.2 g, 5.3 mmol)
- Glacial acetic acid (250 mL)
- Chloroform (>99 %) (400 mL)
- Solution of 10 % NaHCO$_3$ (1 L)

- Heptane (99%)
- Anhydrous magnesium sulfate
- Celite®, 20 g
- Magnetic stirrer plate
- One 2 L round-bottomed flask with magnetic stirrer bar
- One 500 mL Erlenmeyer flask
- One 2 L separatory funnel
- One 250 mL stainless steel autoclave
- One glass filter funnel, diameter 3 cm

Procedure

1. A mixture of (S)-1,1′-bi-2-naphthol (10 g, 27.5 mmol), PtO$_2$ (1.2 g) and glacial acetic acid (250 mL) was placed in a 250 mL stainless steel autoclave. The autoclave was pressurized with H$_2$ and then shaken under 3 atm of H$_2$ at 25 °C for 7 days. The reaction was monitored by the change in pressure.
2. The mixture was filtered through a Celite pad, and the filtrate was shaken with 400 mL of CHCl$_3$ and 1 L of water. The organic layer was washed with 2×1 L of water and 1 L of 10 % NaHCO$_3$ solution then dried over anhydrous magnesium sulfate and evaporated.
3. The residue was dissolved and crystallized from hot heptane to give 9.2 g (91 %) of (S)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol as white needles (m.p. 165–166 °C).

Note: All operations should be conducted in an efficient fume cupboard.

2.1.2   SYNTHESIS OF (S)-2,2′-BIS {[DI(4-METHOXYPHENYL)PHOSPHINYL]OXY} -5,5′,6,6′,7,7′,8,8′-OCTAHYDRO-1,1′-BINAPHTHYL
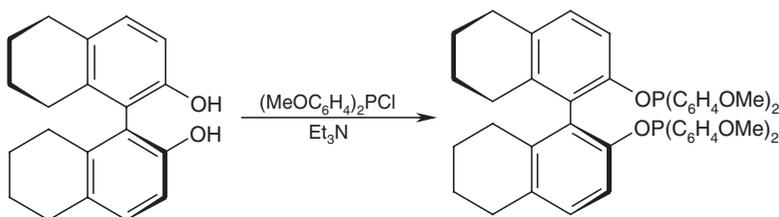
Materials and Equipment

- (S)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-bi-2-naphthol (1.5 g, 5.1 mmol)
- Bis(4-methoxyphenyl)chlorophosphine (3.1 g, 11.2 mmol)

- Dry triethylamine (Et_3N) (1.1 g, 1.5 mL, 11.2 mmol)
- 4-(Dimethylamino)pyridine (DMAP) (99%) (50 mg, 0.41 mmol)
- Dry toluene (90 mL)
- Dry diethyl ether (Et_2O) (110 mL)
- Dry tetrahydrofuran (THF) (10 mL)
- Aluminum oxide, activated, neutral, Brockmann I (30 g)
- One 250 mL three-necked round-bottomed flask, equipped with a magnetic stirrer bar and a glass stopcock
- One 50 mL additional funnel with two glass stopcocks, one on a side-arm
- One filter funnel with glass stopcock on side-arm, diameter 3 cm
- One 100 mL Schlenk tube
- Magnetic stirrer plate

Procedure

1. (S)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-bi-2-naphthol (1.5 g, 5.1 mmol) was placed in a three-necked round-bottomed flask, and dried azeotropically with toluene (3 × 30 mL), and then the solvent was evaporated.

   Note: All operations must be carried out in oven-dried glassware using Schlenk techniques under an atmosphere of argon and conducted in an efficient fume cupboard.

2. The three-necked round-bottomed flask was equipped with an addition funnel. To a solution of (S)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (1.5 g, 5.1 mmol), Et_3N (11.2 mmol, 1.1 g, 1.5 mL) and DMAP (50 mg, 0.41 mmol) in Et_2O (40 mL) was added slowly a solution of bis(4-methoxy-phenyl)chlorophosphine (11.2 mmol, 3.1 g) in mixture of Et_2O/THF=1:1 (20 mL) at ambient temperature. The resulting mixture was vigorously stirred for 1 h at the same temperature.
3. The suspension was filtered and the solvent was removed under reduced pressure.
4. The residue was dissolved in 40 mL of Et_2O and the solution was filtered through a pad of Al_2O_3 and the pad was washed with Et_2O (2 × 10 mL). The solvent was removed under reduced pressure to give the product as a white solid. Yield 2.0 g (50 %); m.p. 50–52 °C; $[\alpha]_D^{20} = -31.0°$ ($c = 1$, CH_2Cl_2).

   $^{31}P\{^1H\}$-NMR (121.42 MHz, $CDCl_3$): $\delta = 108.81$ (s).
   ^1H-NMR (300.15 MHz, $CDCl_3$): $\delta = 1.63$ (m, 8H; CH_2), 2.23 (m, 2H; ArCH_2), 2.36 (m, 2H; ArCH_2), 2.76 (m, 4H; ArCH_2), 3.76 (s, 6H; diast. CH_3O), 3.80 (s, 6H; diast. CH_3O), 6.73 [d, ^3J(H,H) = 8.4 Hz, 4H; diast. H_m], 6.78 [d, ^3J(H,H) = 8.8 Hz, 4H; diast. H_m], 6.98 [d, ^3J(H,H) = 8.4 Hz, 2H; H_3, H_3'], 7.04 [d, ^3J(H,H) = 8.4 Hz, 2H; H_4, H_4'], 7.18 (m, 8H; H_o).
   $^{13}C\{^1H\}$-NMR (75.43 MHz, $CDCl_3$): $\delta = 22.91$ (s, CH_2), 22.96 (s, CH_2), 27.53 (s, ArCH_2), 29.48 (s, ArCH_2), 55.04 (s, diast. CH_3O), 55.12 (s, diast. CH_3O), 113.63 [d, ^3J(P,C) = 5.5 Hz, diast. C_m], 113.71 [d, ^3J(P,C) = 2.2 Hz, diast. C_m], 115.10 (brs, C_3), 115.30 (brs, C_3'), 128.32 (s, C_1, C_1'), 128.62 (s, C_4, C_4'), 131.37

[d, ^2J(P,C)=16.4 Hz, diast. C$_o$], 131.72 [d, ^2J(P,C)=12.1 Hz, diast. C$_o$], 131.96 (s, C$_5$, C$_5$'), 133.53 [d, ^1J(P,C)=5.5 Hz, diast. C$_i$], 133.68 [d, ^1J(P,C)=5.5 Hz, diast. C$_i$], 136.87 (s, C$_{10}$, C$_{10}$'), 152.40 [d, ^2J(P,C)=5.5 Hz, C$_2$], 152.52 [d, ^2J(P,C)=2.2 Hz, C$_2$'], 160.22 (s, diast. CH$_3$OC), 160.35 (s, diast. CH$_3$OC).

Anal. calcd for C$_{48}$H$_{48}$O$_6$P$_2$: C 73.64, H 6.18 %. Found: C 73.33, H 6.41.

2.1.3   ASYMMETRIC HYDROGENATION OF DIMETHYL ITACONATE
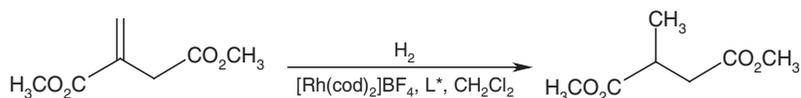
Materials and Equipment

- (S)-2,2'-Bis{[di(4-methoxyphenyl)phosphinyl]oxy}-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (L*) (8.6 mg, 0.011 mmol)
- [Rh(cod)$_2$]BF$_4$ (4.1 mg, 0.01 mmol)
- Dry methylene chloride (10 mL)
- Dimethyl itaconate (0.7 mL, 5 mmol)
- Hydrogen pressure (20 atm)
- Stainless steel autoclave, 20 mL
- One Schlenk tube, 20 mL
- One round-bottomed flask, single neck, 50 mL
- Micro distillation apparatus
- Vacuum pump
- Magnetic stirrer plate
- Hydrogen pressure stirred reactor

Procedure

1. The catalyst was made *in situ* by mixing phosphinite (8.6 mg, 0.011 mmol) with [Rh(cod)$_2$]BF$_4$ (4.1 mg, 0.01mmol) in 10 mL of CH$_2$Cl$_2$ under argon. The solution was stirred for 15 min and then the substrate was added. The mixture was transferred into the autoclave under an argon atmosphere.
2. The autoclave was pressurized with H$_2$ and then shaken at a frequency of 180 min^{-1}, 75 ° from the upright position, with horizontal amplitude of 3 cm. The reaction was monitored by the change in pressure.
3. The reaction mixture was analyzed by gas chromatography (GC) and was distilled under vacuum (1 mmHg) to remove the catalyst. The enantiomeric excess of the distilled product was determined by GC analysis.

   - *For ee determination*: Hewlett-Packard HP 4890 gas chromatograph, split/splitless injector, β-DEX 225, 30 m, internal diameter 0.25 mm, film

Table 2.1 Asymmetric hydrogenation of dimethyl itaconate (**A**) and methyl (*Z*)-α-acetamido cinnamate (**B**)

Entry	Substrate	Reaction time (min)	Pressure (atm)	Conversion (%)	ee (configuration) (%)
1	**A**	5	20	100	92.2 (*R*)
2	**A**	25	1	100	93.9 (*R*)
3	**B**	6	7	100	96.8 (*S*)[5]
4	**B**	25	1	97.5	98.6 (*S*)[5]

General conditions: substrate:catalyst = 500, room temperature, 2 mmol of **B** was used.

thickness 0.25 μm, carrier gas 100 kPa nitrogen, FID detector, 75 °C constant temperature; the retention times of the enantiomers are 30.5 min (*R*) and 32.1 min (*S*).

CONCLUSION

The procedures (2.1.1 and 2.1.2) can be applied to the preparation of a series of (*S*)-H$_8$-BINOL based diphosphinites with varying basicities.

Asymmetric hydrogenation of dimethyl itaconate and methyl (*Z*)-α-acetamido cinnamate with *in situ* formed rhodium(I)-diphosphinite catalyst system gave the desired products with high activity and enantioselectivity (Table 2.1). The asymmetric hydrogenation may be applied to a wide range of substrates.

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5. In the case of methyl (*Z*)-α-acetamido cinnamate (**B**) the reaction mixture was passed through a short silicagel column to remove the catalyst. The ee was determined on CP-CHIRASIL-L-VAL column [25 m, internal diameter 0.25 mm, film thickness 0.12 μm, carrier gas 100 kPa nitrogen, FID detector; the retention times of the enantiomers are 32.5 min (*R*), 34.2 min (*S*)].

2.2   SYNTHESIS AND APPLICATION OF PHOSPHINITE OXAZOLINE IRIDIUM COMPLEXES FOR THE ASYMMETRIC HYDROGENATION OF ALKENES

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Recently, we found that iridium complexes with chiral P,N-ligands are highly versatile catalysts for asymmetric hydrogenation. Exceptionally high ees in combination with good turnover frequencies were obtained in the reduction of different unfunctionalized alkenes and certain functionalized alkenes[1] and imines.[2] Among the various P,N-ligands that were investigated, phosphinite oxazolines derived from serine or threonine were found to comprise one of the most promising ligand classes in this field.[3]

2.2.1   SYNTHESIS OF (4*S*,5*S*)-2-(5-METHYL-2-PHENYL-4,5-DIHYDRO-OXAZOL-4-YL)-1,3-DIPHENYL-PROPAN-2-OL
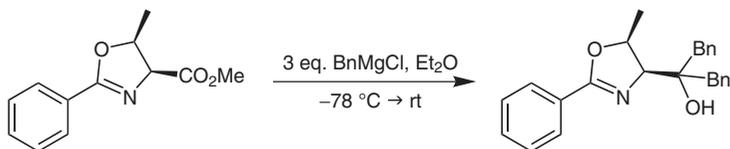
Materials and Equipment

- (4*S*,5*S*)-4-Methyl-2-phenyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester[4] (2.50 g, 11.4 mmol)
- Schlenk flask (100 mL)
- Magnetic stir bar
- Magnetic stirrer
- Dry diethyl ether
- Syringes (50 mL and 5 mL)
- Benzylmagnesium chloride (1.0 M solution in diethyl ether) (34.2 mL, 34.2 mmol)
- Dry ice cooling bath (−78 °C)
- Separating funnel (250 mL)
- Saturated solution of ammonium chloride, ice
- Diethyl ether (3 × 50 mL)
- Saturated solution of sodium chloride
- Anhydrous magnesium sulfate
- Folded filter paper
- Rotary evaporator
- Silica gel (Merck 60, 0.040–0.063 mm, 230–400 mesh ASTM)

- Glass column, diameter 5 cm
- Pentane/diethyl ether (6:1)

Procedure

1. A 100 mL Schlenk flask equipped with a magnetic stir bar was heated under vacuum and flushed three times with argon.
2. The flask was filled with (4*S*,5*S*)-4-methyl-2-phenyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (2.50 g) and 70 mL of dry diethyl ether. The solution was cooled to −78 °C using a dry ice–acetone bath.
3. With good stirring, benzylmagnesium chloride (34.2 mL) was added dropwise using a syringe. When the addition was complete, the stirring was continued for 12 h whilst the mixture warmed slowly to room temperature.
4. A separating funnel was filled with 10 mL of crushed ice and 30 mL of saturated aqueous ammonium chloride solution. The suspension in the Schlenk flask was poured carefully into the separating funnel. The reaction mixture was shaken and the phases separated. After extracting the aqueous phase three times with diethyl ether (50 mL), the combined organic phase was washed with saturated aqueous sodium chloride solution (30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed using a rotary evaporator.
6. The crude product was purified by silica gel column chromatography using pentane/diethyl ether (6:1) as eluent to yield 3.43 g (9.23 mmol, 81 %) of (4*S*,5*S*)-2-(5-methyl-2-phenyl-4,5-dihydro-oxazol-4-yl)-1,3-diphenyl-propan-2-ol as a white foam.

> ^{1}H-NMR (400.1 MHz, CDCl$_3$, 300 K): $\delta = 1.73$ (d, $J = 6.8$ Hz, 3H, CHC*H*$_3$), 2.00 (s, 1H, OH), 2.69 (d, $J = 13.6$ Hz, 1H, CH$_2$Ph), 2.93 (d, $J = 13.9$ Hz, 1H, CH$_2$Ph), 3.11 (d, $J = 13.9$ Hz, 1H, CH$_2$Ph), 3.19 (d, $J = 13.6$ Hz, 1H, CH$_2$Ph), 4.11 (d, $J = 9.6$ Hz, 1H, NCH), 4.84 (dq, $J = 6.8$ Hz, 9.6 Hz, 1H, C*H*CH$_3$), 7.15 – 7.37 (m, 10H, Ar-H), 7.44 (t, $J = 7.3$ Hz, 2H, Ar-H), 7.50 (t, $J = 7.3$ Hz, 1H, Ar-H), 8.05 (d, $J = 7.3$ Hz, 2H, Ar-H) ppm.
> $[\alpha]_D^{20} = +126°$ ($c = 1.4$, CHCl$_3$). $R_f = 0.35$ (pentane/diethyl ether 6:1).

> *Note: Continuous stirring and maintenance of a low temperature during the addition of the Grignard reagent is essential, otherwise partial epimerization could be observed.*

2.2.2 SYNTHESIS OF (4S,5S)-O-[1-BENZYL-1-(5-METHYL-2-PHENYL-4,5-DIHYDRO-OXAZOL-4-YL)-2-PHENYL-ETHYL]-DIPHENYLPHOSPHINITE
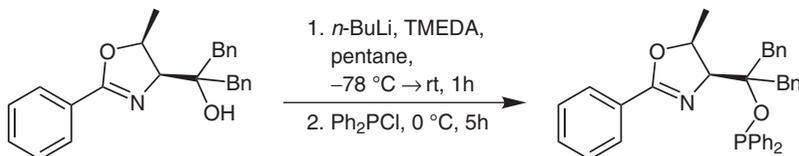
Materials and Equipment

- Schlenk flask (75 mL) equipped with a magnetic stir bar
- (4*S*,5*S*)-2-(5-Methyl-2-phenyl-4,5-dihydro-oxazol-4-yl)-1,3-diphenyl-propan-2-ol (337 mg, 0.91 mmol)
- Magnetic stirrer
- Dry and degassed pentane (15 + 2 mL)
- Dry ice cooling bath (−78 °C)
- Syringes (1 mL, 500 μL and 250 μL)
- *n*-Butyllithium (1.6 M in hexane), 0.70 mL, 1.12 mmol
- *N,N,N′,N′*-Tetramethylethylenediamine[5] (TMEDA) (0.27 mL, 1.8 mmol)
- Chlorodiphenylphosphine, 180 μL, 0.99 mmol
- Cooling trap
- Glass column, diameter 5 cm
- Silica gel (Merck 60, 0.040–0.063 mm, 230–400 mesh ASTM)
- Degassed hexane/ethyl acetate (15:1)
- Rotary evaporator

Procedure

1. A 75 mL Schlenk flask equipped with a magnetic stir bar was heated under vacuum and flushed three times with argon.
2. The flask was filled with (4*S*,5*S*)-2-(5-methyl-2-phenyl-4,5-dihydro-oxazol-4-yl)-1,3-diphenyl-propan-2-ol (337 mg) and 15 mL of dry and degassed pentane. The solution was cooled to −78 °C using a dry ice/acetone bath. Under these conditions the alcohol partially precipitated.
3. *n*-Butyllithium (0.70 mL) was added dropwise followed by *N,N,N′,N′*-tetramethylethylendiamine (0.27 mL). The cooling bath was removed and the mixture stirred for 1 h by which time the reaction mixture had reached room temperature.
4. The reaction mixture was cooled to 0 °C and chlorodiphenylphosphine (180 μL) was added. The cooling bath was subsequently removed.
5. After stirring for 5 h at room temperature the solvent was completely removed using a high vacuum pump and a cooling trap. The residue was suspended in 2 mL of degassed pentane and transferred directly onto a silica gel column. Chromatography with degassed hexane/ethyl acetate (15:1) as the eluent afforded the product (310 mg, 0.56 mmol, 62 %) as a voluminous white powder.

^{1}H-NMR (400.1 MHz, CDCl$_3$, 300 K): $\delta = 1.24$ (d, $J = 6.6$ Hz, 3H, CHCH_3), 3.11 (d, $J = 14.4$ Hz, 1H, CH$_2$Ph), 3.33 (d, $J = 13.4$ Hz, 2H, CH$_2$Ph), 3.72 (d, $J = 12.9$ Hz, 1H, CH$_2$Ph), 4.34 (d, $J = 9.6$ Hz, 1H, NCH), 4.73 (m, 1H, CHCH$_3$), 7.05–7.50 (m, 23H, Ar-H), 8.01 (d, $J = 7.3$ Hz, 2H, Ar-H) ppm.
^{31}P{^{1}H}-NMR (162.0 MHz, CDCl$_3$, 300 K): $\delta = 88.7$ ppm.
$R_f = 0.65$ (hexane/ethyl acetate 15:1).

Note: (a) The column was dry packed under an argon atmosphere and equilibrated carefully with the solvent mixture which was degassed simply by bubbling argon through it for 20 min. For fraction collection, test tubes were used which, prior to use, were filled with argon. The solvent was removed by the use of a rotary evaporator.

(b) Sometimes the product contained a small amount of the corresponding phosphinate ($^{31}P\{^1H\}$-NMR: $\delta = 25.6$). However, the impure phosphinite could be used in the next step without further purification.

2.2.3 SYNTHESIS OF (4S,5S)-[(η^4-1,5-CYCLOOCTADIENE)-{2-(2-PHENYL-5-METHYL-4,5-DIHYDRO-OXAZOL-4-YL)-1,3-DIPHENYL-2-DIPHENYLPHOSPHINITE-PROPANE}IRIDIUM(I)]-TETRAKIS[3,5-BIS(TRIFLUOROMETHYL)PHENYL]BORATE
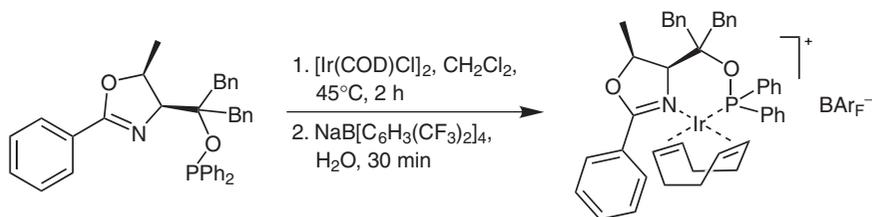
Materials and Equipment

- Schlenk flask (25 mL) equipped with a magnetic stir bar
- [Ir(COD)Cl]$_2$ (83 mg, 0.12 mmol)
- Magnetic stirrer with heating
- Water bath
- Dry dichloromethane (5 + 2 mL)
- Syringe (2 mL)
- (4S,5S)-O-[1-Benzyl-1-(5-methyl-2-phenyl-4,5-dihydro-oxazol-4-yl)-2-phenyl-ethyl]-diphenylphosphinite (125 mg, 0.225 mmol)
- Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr$_F$)[6] (227 mg, 0.243 mol)
- Water (3 mL, degassed)
- Dichloromethane
- Separating funnel (250 mL)
- Anhydrous magnesium sulfate
- Folded filter paper
- Glass column, diameter 4 cm
- Silica gel (Merck 60, 0.040–0.063 mm, 230–400 mesh ASTM)
- Rotary evaporator

Procedure

1. A 25 mL Schlenk flask equipped with a magnetic stir bar was heated under vacuum and flushed three times with argon.
2. The Schlenk flask was charged with [Ir(COD)Cl]$_2$ (83 mg) and 2 mL of dry dichloromethane. (4S,5S)-O-[1-Benzyl-1-(5-methyl-2-phenyl-4,5-dihydro-oxazol-4-yl)-2-phenyl-ethyl]-diphenylphosphinite (125 mg) was dissolved in anhydrous dichloromethane (5 mL) under an argon atmosphere, and added to the metal precursor. The so-formed orange/yellow solution was heated at reflux for 1 h.
3. At room temperature, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr$_F$, 227 mg) was added to the reaction mixture followed after 1 min by degassed water (3 mL). The biphasic system was vigorously stirred for 30 min.
4. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The red/brown residue was purified by column chromatography (eluent: dichloromethane) to give the desired iridium complex (262 mg, 0.15 mmol, 68%) as an orange powder.

> ^{1}H-NMR (400.1 MHz, CDCl$_3$, 300 K): $\delta = 1.73$ (d, $J = 7.0$ Hz, 3H, CHCH_3), 1.75–2.05 [br m, 6H, CH$_2$(COD)], 2.05–2.25 [br m, 1H, CH$_2$(COD)], 2.27–2.33 [br m, 1H, CH$_2$(COD)], 2.95 (dd, $J = 14.9$ Hz, 5.3 Hz, 1H, CH$_2$Ph), 3.04 (d, $J = 14.4$ Hz, 1H, CH$_2$Ph), 3.15–3.38 [br m, 2H, CH(COD)], 3.42 (d, $J = 14.9$ Hz, 1H, CH$_2$Ph), 4.10–4.35 [br m, 2H, CH$_2$Ph und CH(COD)], 4.53 [br m, 1H, CH(COD)], 4.75 (d, $J = 8.1$ Hz, 1H, NCH), 5.35 (m, 1H, CHCH$_3$), 6.93 (m, 2H, Ar-H), 7.08 (m, 4H, Ar-H), 7.18 (m, 2H, Ar-H), 7.23–7.36 (m, 7H, Ar-H), 7.51 (br s, 4H, BAr$_F$-H), 7.52–7.69 (m, 7H, Ar-H), 7.72 (m, 8H, BAr$_F$-H), 7.78 (m, 1H, Ar-H), 8.39 (m, 2H, Ar-H) ppm.
> ^{31}P{^{1}H}-NMR (162.0 MHz, CDCl$_3$, 300 K): $\delta = 93.6$ ppm.
> $[\alpha]_D^{20} = +13.2°$ ($c = 1.0$, CHCl$_3$). $R_f = 0.9$ (dichloromethane). m.p. 121 °C.
> $M_w = 1719.25$ g mol^{-1}.

> *Note: (a) Although these iridium complexes were proven to be stable under ambient atmosphere at room temperature for several months, we recommend prolonged storage under an argon atmosphere at −20 °C.*
> *(b) The synthesis could be scaled up to yield 10 g of iridium complex.*

2.2.4   ASYMMETRIC HYDROGENATION OF *trans*-α-METHYLSTILBENE
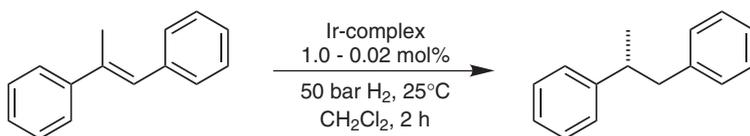
Materials and Equipment

- Autoclave (e.g. 50 ml HPM-005, Premex Reactor AG, Lengnau, Switzerland)
- *trans*-α-Methylstilbene (19.4 mg, 0.1 mmol)
- (4*S*,5*S*)-[(η^4-1,5-Cyclooctadiene)-{2-(2-phenyl-5-methyl-4,5-dihydro-oxazol-4-yl)-1,3-diphenyl-2-diphenylphosphinite-propane}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (1.72 mg, 1.0 µmol). The catalyst is available from Strem Chemicals, Inc. (catalogue no. 77-5020).
- Screw cap vials (2 mL) equipped with magnetic stir bars[7]
- Magnetic stirrer
- Dichloromethane (HPLC quality)
- Hydrogen, pressurized (50 bar)
- Syringes (2 mL and 5 mL)
- Heptane (3 mL, HPLC quality)
- Syringe filter (e.g. 0.2 mm, CHROMAFIL Type O20/15, Macherey-Nagel)

Procedure

1. A 2 mL glass vial equipped with a magnetic stir bar was filled with 1.72 mg of the chiral iridium catalyst and 19.4 mg of *trans*-α-methylstilbene. Subsequently, 0.5 mL of dichloromethane were added and the vial placed in the autoclave.
2. After purging the autoclave with hydrogen the pressure was adjusted to 50 bar and the autoclave sealed. The speed of the stirrer was set to 1000 rpm.
3. After stirring for 2 h, the pressure was released and the solvent was evaporated in a slow stream of nitrogen gas. The residue was extracted with heptane (3 mL) and the resulting suspension filtered through a syringe filter. The filtrate was directly analyzed by GC and chiral HPLC to determine the conversion and enantiomeric excess (for analytical procedures and data, see ref. [1]).

   Note: (a) An inert atmosphere was not needed to be employed while the reactions were being set up.
   (b) On lowering the catalyst loading to 0.02 mol% extension of the reaction time to 4 h was required.
   (c) Depending on the substrate, the reaction can also be performed at ambient hydrogen pressure in an argon flushed Schlenk tube.[1]
   (d) In a preparative experiment on a gram scale, the catalyst was removed by filtration through a short silica column (2 ×1 cm) with hexane as solvent. After evaporation of the solvent, the product was isolated in >94 % yield.

CONCLUSION

The iridium complexes used as precatalysts are air-stable and easy to handle. A further attractive feature is the modular nature of the chiral ligands, which makes it possible to tailor the catalyst structure for a specific substrate. So far several unfunctionalized and functionalized olefins have been hydrogenated with good to

Table 2.2 Enantioselective hydrogenation of *trans*-α-methylstilbene using a phosphinite oxazoline iridium complex at different catalyst to substrate ratios

Entry	Catalyst loading (mol%)	c (substrate) (mol L^{-1})	Yield (%)	ee (%) (configuration)
1	1	0.1	>99	99 (*R*)
2	0.5	0.2	>99	99 (*R*)
3	0.1	1.0	>99	99 (*R*)
4	0.05	1.0	>99	99 (*R*)
5	0.02	2.5	>99	99 (*R*)
6	0.01	2.5	54	99 (*R*)

excellent enantioselectivity using these iridium complexes. Table 2.2 shows the hydrogenation results using different catalyst to substrate ratios.

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4. Commercially available from Aldrich (No. 29217-6).
5. *N,N,N′,N′*-Tetramethylethylenediamine was distilled from *n*-butyllithium prior to use.
6. (a) Taube, R. and Wache, S. *J. Organomet. Chem*. **1992**, *428*, 431–442. (b) Reger, D. L., Wright, T. D., Little, C. A., Lamba, J. J. S. and Smith, M. D. *Inorg. Chem.* **2001**, *40*, 3810–3814. (c) Leaser Jr, J. L., Cvetovich, R., Tsay, F.-R., Dolling, U., Vickery, T. and Bachert, D. *J. Org. Chem.* **2003**, *68*, 3695–3698.
7. The dimensions of these vials were 40×13 mm, and the dimensions of the magnetic stir bar were 3.0×6.5 mm. Four of these vials fit exactly into the Premex HPM-005 50 mL reactor. Identical results were obtained using this 'parallel' reactor compared with reactions performed in isolated vessels.

2.3 SYNTHESIS AND APPLICATION OF HETEROCYCLIC PHOSPHINO OXAZOLINE(HetPHOX) IRIDIUM COMPLEXES FOR THE ASYMMETRIC HYDROGENATION OF ALKENES

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Recently, Pfaltz and co-workers reported that iridium complexes with chiral P,N-ligands are highly selective catalysts for asymmetric hydrogenation of several

unfunctionalized and functionalized alkenes[1] and imines[2]. Among the various P,N-ligands that were investigated, heterocyclic phosphine oxazolines derived from thiophene were shown to be highly versatile ligands, easily accessible in two steps from commercial available starting materials.[3]

2.3.1 SYNTHESIS OF (4S)-tert-BUTYL-2-(THIOPHENE-2-YL)-4,5-DIHYDROOXAZOLE
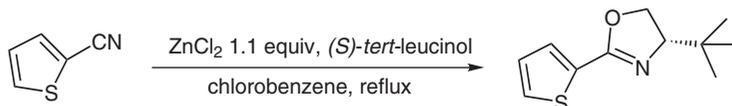
Materials and Equipment

- Schlenk flask (250 mL)
- Magnetic stir bar
- Magnetic stirrer
- Condenser
- Reagent grade chlorobenzene (30 mL)
- Syringes (50 mL and 5 mL)
- (S)-tert-Leucinol 2.24 g, 19.2 mmol
- 2-Cyanothiophene 1.6 mL, 16 mmol
- Anhydrous zinc chloride 2.6 g, 19.2 mmol
- Separating funnel (250 mL)
- Water
- Dichloromethane (3 × 70 mL)
- Saturated aqueous solution of sodium chloride
- Anhydrous sodium sulfate
- Folded filter paper
- Rotary evaporator
- Silica gel (Merck 60, 0.040–0.063 mm, 230–400 mesh ASTM)
- Glass column, diameter 3 cm
- Dichloromethane/diethyl ether (9:1)

Procedure

1. A 250 mL two-stopcock Schlenk flask, equipped with a condenser was charged with anhydrous zinc chloride and heated under vacuum until the salt melted. The flask was cooled under nitrogen. Then a magnetic stir bar was inserted.
2. The flask was filled with (S)-tert-leucinol (2.24 g), 70 mL of chlorobenzene and 2-cyano-thiophene.

3. With stirring, the contents of the flask was heated to reflux for 24 h. The flask was cooled to room temperature and the mixture was transferred into a flask containing water and CH_2Cl_2 (80 mL). The solid residues in the Schlenk flask were quenched with water and CH_2Cl_2 (20 mL) and all contents transferred into the second flask. The mixture was stirred for 30 min with the formation of a white precipitate.

4. The mixture was filtered through a glass frit and transferred in a separating funnel. The phases were separated. After extracting the aqueous phase three times with CH_2Cl_2 (40 mL), the combined organic phase was washed with saturated aqueous sodium chloride solution (50 mL) and dried over anhydrous sodium sulfate. The solvent was removed using a rotary evaporator.

6. The crude product was purified by silica gel column chromatography using dichoromethane/diethyl ether (9:1) as eluent to yield 2.85 g (13.6 mmol, 85%) of (2S)-tert-butyl-2-(thiophene-2-yl)-4,5-dihydrooxazole as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 0.96$ (s, 9H); 3.99–4.39 (m, 3H); 7.05–7.09 (m, 1H); 7.43 (dd, 1H, $J = 2$, 6Hz); 7.60 (d, 1H, $J = 2$Hz).?
$R_f = 0.30$ (dichloromethane/diethyl ether 9:1).

Note: A catalytic amount of ZnCl$_2$ (10 mol%) could be also used in the reaction.

2.3.2   SYNTHESIS OF (4S)-tert-BUTYL-2-(3-DIPHENYLPHOSPHINO-THIOPHENE-2-YL)-4,5-DIHYDROOXAZOLE
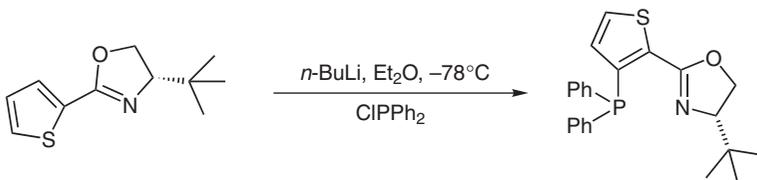
Materials and Equipment

- Schlenk flask (5 mL)
- Magnetic stir bar
- Magnetic stirrer
- Anhydrous ether
- Syringes (1 mL)
- (S)-tert-Butyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (0.420 g, 2 mmol)
- Diphenylchlorophosphine 0.72 mL, (4 mmol)
- n-BuLi 2.5 M in hexane 1.6 mL (4 mmol)
- Dry ice cooling bath ($-78\,°$C)
- Ice-water bath (0 °C)
- Separating funnel (50 mL)

- Water
- Diethyl ether (5 mL)
- Diethyl ether (3 × 10 mL)
- Saturated solution of sodium chloride
- Anhydrous sodium sulfate
- Folded filter paper
- Rotary evaporator
- Silica gel (Merck 60, 0.040–0.063 mm, 230–400 mesh ASTM)
- Glass column, diameter 2 cm

Procedure

1. The flask was filled with (S)-tert-butyl-2-(thiophene-2-yl)-4,5-dihydrooxazole (0.42 g, 2 mmol) and 5 mL of dry diethyl ether. The solution was cooled to −78 °C using a dry ice–acetone bath.
2. With stirring the n-BuLi was added using a syringe. When the addition was complete, stirring was continued for 0.5 h whilst the mixture was maintained at −78 °C.
3. The flask was warmed at 0 °C and stirred at the same temperature for 0.5 h.
4. The flask was cooled again at −78 °C and diphenylchlorophosphine was added by syringe to the reaction mixture; stirring was continued for 20 h whilst the mixture warmed slowly to room temperature.
5. The reaction was quenched with water and the mixture in the Schlenk flask was poured in a separating funnel. The reaction mixture was extracted and the phases separated. After extracting the aqueous phase three times with diethyl ether (50 mL), the combined organic phase was washed with saturated aqueous sodium chloride solution (30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed using a rotary evaporator.
6. The crude product was purified by silica gel column chromatography using cyclohexane/diethyl ether (9:1) as eluent to yield 0.268 g (0.68 mmol, 34 %) of (4S)-tert-butyl-2-(3-diphenylphosphino-thiophene-2-yl)-4,5-dihydrooxazole as an clear oil that slowly transformed into a waxy white solid.

^{1}H-NMR (CDCl$_3$, 200 MHz): $\delta = 0.62$ (s, 9H); 3.91–4.13 (m, 3H); 6.31 (d, 1H, $J = 4.6$ Hz); 7.23–7.30 (m, 11H).
^{13}C-NMR (50 MHz, CDCl$_3$): $\delta = 25.59$, 33.82, 66.82, 76.35, 127.38, 128.26 (d, $J = 4$ Hz), 128.31, 128.61, 131.60 (d, $J = 22.1$ Hz), 132.94, 133.40, 133.50 (d, $J = 11$ Hz), 133.83 (d, $J = 21$ Hz), 137.28 (d, $J = 9$ Hz), 138.40 (d, $J = 12$ Hz), 141.23, (d, $J = 27$ Hz), 158.00 (d, $J = 4$ Hz).
^{31}P-NMR (124 MHz, CHCl$_3$): $\delta = 13.14$.
$[\alpha]_D^{20} = -136°$ ($c = 0.53$, CHCl$_3$). $R_f = 0.30$ (cyclohexane/diethyl ether 9:1).
$M_W = 393.48$ g mol^{-1}.

2.3.3   SYNTHESIS OF (4S)-[(η^4-1,5-CYCLOOCTADIENE)-{4-*tert*-BUTYL-2-(3-DIPHENYLPHOSPHINO-THIOPHENE-2-YL)-4,5-DIHYDROOXAZOLE}IRIDIUM(I)]-TETRAKIS[3,5-BIS(TRIFLUOROMETHYL)PHENYL]BORATE
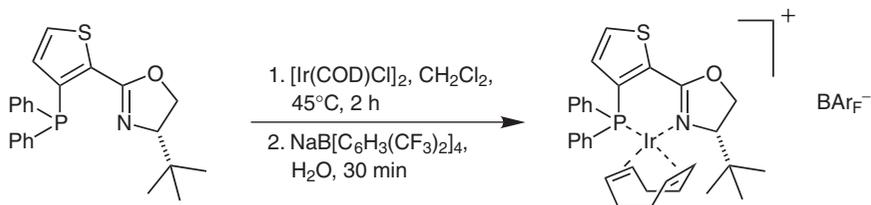
Materials and Equipment

- Schlenk flask (25 mL) equipped with a magnetic stir bar
- [Ir(COD)Cl]$_2$, (9.4 mg, 14 µmol)
- Magnetic stirrer with heating
- Water bath
- Dry dichloromethane (2 + 1 mL)
- Syringe (2 mL)
- (4S)-*tert*-Butyl-2-(3-diphenylphosphino-thiophene-2-yl)-4,5-dihydrooxazole (10 mg, 25 µmol)
- Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr$_F$)[4] (26 mg, 28 µmol)
- Water (3 mL, degassed)
- Dichloromethane
- Separating funnel (250 mL)
- Anhydrous magnesium sulfate
- Folded filter paper
- Glass column, diameter 4 cm
- Silica gel (Merck 60, 0.040–0.063 mm, 230–400 mesh ASTM)
- Rotary evaporator

Procedure

1. A 25 mL Schlenk flask equipped with a magnetic stir bar was heated under vacuum and flushed three times with argon.
2. The Schlenk flask was charged with [Ir(COD)Cl]$_2$ (9.4 mg) and 1 mL of dry dichloromethane. (4S)-*tert*-butyl-2-(3-diphenylphosphino-thiophene-2-yl)-4,5-dihydrooxazole (10 mg) was dissolved in anhydrous dichloromethane (2 mL) under an argon atmosphere, and added to the metal precursor. The orange-red solution was heated at reflux for 2 h.
3. At room temperature, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr$_F$, 26 mg) was added to the reaction mixture followed, after 1 min,

by degassed water (3 mL). The biphasic system was vigorously stirred for 30 min.

4. The layers were separated and the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The red residue was purified by column chromatography (dichloromethane) to give the desired iridium complex (33 mg, 21 µmol, 85 %) as an orange-red powder.

> ^{1}H-NMR (400.1 MHz, CDCl$_3$, 300 K): $\delta = 0.71$ [s, 9H, C(CH$_3$)$_3$], 1.39 [m, 1H, CH$_2$(COD)], 1.61 [m, 1H, CH$_2$(COD)], 1.90–2.07 [m, 2H, CH$_2$(COD)], 2.31–2.62 [m, 4H, CH$_2$(COD)], 2.88 [br m, 1H, CH(COD)], 3.51 [br m, 1H, CH(COD)], 3.89 (dd, $J = 8.6$ Hz, 2.5 Hz, 1H, CH), 4.35 (dd, $J = 9.8$ Hz, 8.8 Hz, 1H, CH$_2$), 4.62 (dd, $J = 9.6$ Hz, 2.5 Hz, 1H, CH$_2$), 4.93 [m, 2H, CH(COD)], 7.02 (dd, $J = 5.0$ Hz, 3.3 Hz, 1H, Ar-H), 7.12–7.17 (m, 2H, Ar-H), 7.43–7.57 (m, 12H, Ar-H, BAr$_F$-H), 7.67–7.73 (m, 9H, Ar-H, BAr$_F$-H) ppm.
> ^{31}P{^{1}H}-NMR (162.0 MHz, CDCl$_3$, 300 K): $\delta = 4.2$ ppm.
> $[\alpha]_D^{20} = -267°$ ($c = 0.095$, CHCl$_3$). $R_f = 0.9$ (dichloromethane). m.p. 183 °C.
> $M_W = 1557.09$ g mol^{-1}.

> *Note: The iridium complexes were kept under an argon atmosphere for prolonged storage.*

2.3.4   ASYMMETRIC HYDROGENATION OF *trans*-α-METHYLSTILBENE
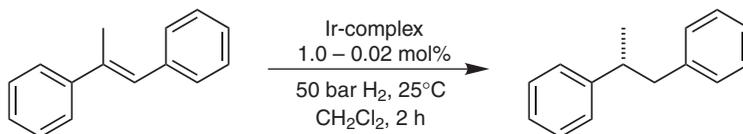
Materials and Equipment

- Autoclave (e.g. 50 ml HPM-005, Premex Reactor AG, Lengnau, Switzerland)
- *trans*-α-Methylstilbene (19.4 mg, 0.1 mmol)
- (4S)-[(η^4-1,5-Cyclooctadiene)-{*tert*-butyl-2-(3-diphenylphosphino-thiophene-2-yl)-4,5-dihidrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (1.6 mg, 1.0 µmol)
- Screw cap vials (2 mL) equipped with magnetic stir bars[5]
- Magnetic stirrer
- Dichloromethane
- Hydrogen, pressurized (50 bar)
- Syringes (2 mL and 5 mL)
- Heptane (3 mL, HPLC quality)
- Syringe filter (e.g. 0.2 mm, CHROMAFIL Type O20/15, Macherey-Nagel)

Procedure

1. A 2 mL glass vial equipped with a magnetic stir bar was filled with 1.72 mg of the chiral iridium catalyst and 19.4 mg of *trans*-α-methylstilbene. Subsequently, 0.5 mL of dichloromethane were added and the vial placed in the autoclave.
2. After purging the autoclave with hydrogen the pressure was adjusted to 50 bar and the autoclave sealed. The speed of the stirrer was set to 1000 rpm.
3. After stirring for 2 h, the pressure was released and the solvent was evaporated in a slow stream of nitrogen gas. The residue was extracted with heptane (3 mL) and the resulting suspension filtered through a syringe filter. The filtrate was directly analyzed by GC and chiral HPLC to determine the conversion and enantiomeric excess (for analytical procedures and data, see ref. [1]).

Note: (a) Employment of an inert atmosphere was not necessary for the reactions.
(b) On lowering the catalyst loading to 0.02 mol%, extension of the reaction time to 4 h was required.
(c) Depending on the substrate, the reaction can also be performed at ambient hydrogen pressure in an argon-flushed Schlenk tube (see ref. [1]).
(d) In a preparative experiment on a gram scale, the catalyst was removed by filtration through a short silica column (2 × 1 cm) with hexane as solvent. After evaporation of the solvent, the product was isolated in >99 % yield and 92 % ee.

CONCLUSION

The iridium complexes used as precatalysts are air-stable and easy to handle. A further attractive feature is the modular nature of the HetPHOX chiral ligands, which makes it possible to tailor the catalyst structure for a specific substrate. Unfunctionalized and functionalized olefins were hydrogenated with good to excellent enantioselectivity using these iridium complexes and it was possible to obtain also high yield and good enantioselectivity (99 % yield, 72 % ee.) in the hydrogenation of (*E*)-phenyl-(1-phenylethylidene)-amine.[3]

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5. The dimensions of these vials were 40 × 13 mm, and the dimensions of the magnetic stir bar were 3.0 × 6.5 mm. Four of these vials fit exactly into the Premex HPM-005 50 mL

reactor. Identical results were obtained using this 'parallel' reactor compared with reactions performed in isolated vessels.

2.4   (R)-2,2′,6,6′-TETRAMETHOXY-BIS[DI (3,5-DIMETHYLPHENYL)PHOSPHINO]-3,3′-BIPYRIDINE [(R)-Xyl-P-Phos] AS A LIGAND FOR RHODIUM-CATALYZED ASYMMETRIC HYDROGENATION OF α-DEHYDROAMINO ACIDS

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Chiral amino acids are attractive targets for enantioselective synthesis on account of their considerable significance in the pharmaceutical industry both as nutritional supplements and as synthetic intermediates. A convenient method for the synthesis of these compounds is through the asymmetric catalytic hydrogenation of prochiral amidoacrylic acids. Rhodium catalysts containing chiral phosphine ligands have been proved to be the most successful for this type of reaction.[1] We have recently developed a highly effective dipyridylphosphine ligand Xyl-P-Phos {1, Figure 2.2, Xyl-P-Phos = 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridine)}[2] for applications in highly stereoselective Ru-catalyzed hydrogenation of β-ketoesters[2] and aromatic ketones.[3] This ligand also exhibited high efficacy in the Rh-catalyzed asymmetric hydrogenation of acetamidoacrylic acids and esters.[4]
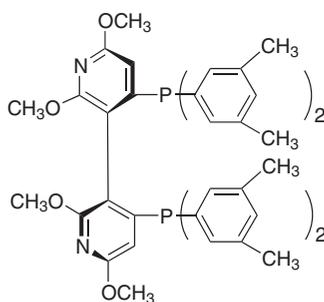
(R)-Xyl-P-Phos, (R)-**1**

Figure 2.2

2.4.1   SYNTHESIS OF 3-BROMO-2,6-DIMETHOXYPYRIDINE (**2**)

(**2**)
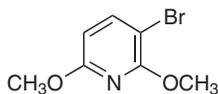
Materials and Equipment

- 2,6-Dimethoxypyridine (98 %), (31.7 mL, 240 mmol)
- Bromine (>99 %), (10.3 mL, 200 mmol)
- Sodium carbonate saturated aqueous solution (50 mL)
- Dry carbon tetrachloride (400 mL)
- Dichloromethane (300 mL)
- Anhydrous sodium sulfate
- Immersion chiller
- Mechanical stirrer
- One 1000 mL three-necked round-bottomed flask
- One 100 mL dropping funnel
- One 1000 mL separatory funnel
- One Bűchner funnel, diameter 10 cm
- One Bűchner flask (1000 mL)
- Filter paper
- Rotary evaporator
- Vacuum distillation equipment

Procedure

1. To a mechanically stirred mixture of 2,6-dimethoxypyridine (31.7 mL, 240 mmol) and carbon tetrachloride (400 mL), a solution of bromine (10.3 mL, 200 mmol) in carbon tetrachloride (50 mL) was slowly added at −30 °C to −40 °C over 12 h.
2. The solution was neutralized to pH = 7.5 with sodium carbonate at 0 °C followed by three-fold extraction with dichloromethane (100 mL each portion).
3. The combined extracts were dried with anhydrous Na_2SO_4 and the solvent was removed with a rotary evaporator to give a crude product which was purified by distillation under vacuum to furnish 30.3 g (70 % of theoretical yield) of pure product as a colorless oil (67–74 °C/0.05 mmHg).

   ^{1}H-NMR (500 MHz, CDCl_3): $\delta = 3.89$ (s, 3H), 3.99 (s, 3H), 6.22 (d, $J = 8.5$ Hz, 1H), 7.62 (d, $J = 8.5$ Hz, 1H).

2.4.2   SYNTHESIS OF BIS(3,5-DIMETHYLPHENYL)PHOSPHINE CHLORIDE (3)

(**3**)
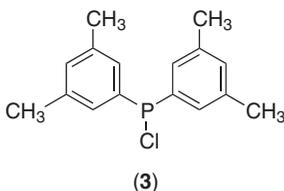
Materials and Equipment

- Magnesium turnings (5.0 g, 206 mmol)
- 5-Bromo-*m*-xylene (35.2 g, 190 mmol)
- Diethylphosphoramidous dichloride (15.0 g, 86 mmol)
- Dry THF (210 mL)
- Dry hexane (280 mL)
- Dry HCl
- One 250 mL three-necked round-bottomed flask equipped with a magnetic stirring bar
- One 500 mL three-necked round-bottomed flask equipped with a magnetic stirring bar
- One condenser
- One 150 mL dropping funnel
- Two-ended needle
- Magnetic stirrer

Procedure

1. To a mixture of magnesium turnings (5.0 g, 206 mmol) and 20 mL of dried THF in a 250 mL three-necked flask equipped with a magnetic stirring bar, a condenser and an addition funnel, a solution of 5-bromo-*m*-xylene (35.2 g, 190 mmol) in 120 mL of dried THF was added slowly at such a rate as to keep the reaction mixture at a gentle reflux. The mixture was allowed to reflux for 1 h upon completion of the addition to facilitate quantitative formation of the Grignard reagent.
2. To a solution of diethylphosphoramidous dichloride (15.0 g, 86 mmol) in 90 mL THF, the Grignard reagent (190 mmol) formed in the previous step was added dropwise via a two-ended needle at 0 °C under a N_2 atmosphere. After 2 h, the mixture was concentrated *in vacuo*. Hexane (250 mL) was added to the residue and the mixture was filtered to provide a solution of bis(3,5-dimethylphenyl)-diethylaminophosphine.
3. Dry HCl was passed through the above solution for 1 h and the solution was degassed to precipitate the amine hydrochloride. The filtrate was collected and the solvent was removed under vacuum to give the semi-solid product (21.0 g, 88.1 % yield on the basis of the Et_2NPCl_2 used).

^{31}P-NMR (202 MHz, CDCl$_3$): $\delta = 85.13$.

2.4.3   SYNTHESIS OF 3-BROMO-2,6-DIMETHOXY-4-DI (3,5-DIMETHYLPHENYL)PHOSPHINOPYRIDINE (4)

(4)
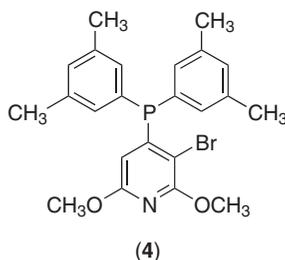
Materials and Equipment

- 2.0 M LDA (lithium diisopropylamide) (47.5 g, 95 mmol)
- 3-Bromo-2,6-dimethoxypyridine (**2**) (15.9 g, 73 mmol)
- Bis(3,5-dimethylphenyl)phosphine chloride (**3**) (21.0 g, 76.0 mmol)
- Dry THF (200 mL)
- Dichloromethane (150 mL)
- Anhydrous sodium sulfate
- Methanol (50 mL)
- One 500 mL three-necked round-bottomed flask equipped with a magnetic stirrer
- One 500 mL separatory funnel
- Two-ended needle
- Magnetic stirrer
- One Bűchner funnel, 5 cm diameter
- One Bűchner flask (500 mL)
- Filter paper
- Rotary evaporator

Procedure

1. To a magnetically stirred solution of 47.5 mL (95 mmol) of ca. 2.0 M LDA (lithium diisopropylamide) at −78 °C, a solution of 3-bromo-2,6-dimethoxypyridine (**2**, 15.9 g, 73 mmol) in dried THF (100 mL) was added by syringe over a period of 20 min.
2. To the resulting red-brown suspension, a solution of bis(3,5-dimethylphenyl)-phosphine chloride (**3**, 21.0 g, 76.0 mmol) in 100 mL THF was added at −78 °C under a N_2 atmosphere. The reaction mixture was allowed to warm to room temperature and stirred at this temperature overnight.
3. The reaction was quenched with 10 mL water and the solvent was removed with a rotary evaporator. The organic product was extracted with CH_2Cl_2 (3 × 100 mL). The combined extract was washed with water (2 × 50 mL) and was dried with anhydrous sodium sulfate and concentrated *in vacuo* to give a crude product which was recrystallized from methanol to provide a white powdery product (18.6 g, 53.4 % yield).

^{1}H-NMR (500 MHz, CDCl₃): $\delta = 2.35$ (s, 6H), 3.83 (s, 3H), 4.00 (s, 3H), 5.73 (d, $J = 2.5$ Hz, 1H), 7.15–7.21 (m, 8H).
^{13}C-NMR (125.7 MHz, CDCl₃): $\delta = 21.59$, 53.81, 54.67, 101.84, 102.06, 106.81, 129.79, 129.85, 131.36, 131.42, 134.32, 134.48, 139.62, 155.06, 155.19, 158.85, 158.89, 161.69.
^{31}P-NMR (202 MHz, CDCl₃): $\delta = -5.78$.

2.4.4   SYNTHESIS OF 3-BROMO-2,6-DIMETHOXY-4-DI(3,5-
DIMETHYLPHENYL)PHOSPHINOYLPYRIDINE (**5**)

(5)
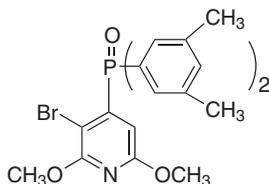
Materials and Equipment

- 3-Bromo-2,6-dimethoxy-4-diarylphosphinopyridine (**4**) (18.0 g, 39.3 mmol)
- ca. 35 % hydrogen peroxide (30 mL)
- Acetone (300 mL)
- 10 % aq. Na_2SO_3
- Dichloromethane (450 mL)
- Anhydrous sodium sulfate
- One 500 mL round-bottomed flask equipped with a magnetic stirring bar
- Magnetic stirrer
- One 1000 mL separatory funnel
- One Bűchner funnel, 5 cm diameter
- One Bűchner flask (1000 mL)
- Rotary evaporator

Procedure

1. To a magnetically stirred solution of 3-bromo-2,6-dimethoxy-4-diaryl-phosphinopyridine (**4**, 18.0 g, 39.3 mmol) in 300 mL acetone, 30 mL of ca. 35 % aqueous hydrogen peroxide was added slowly at 0 °C.
2. The reaction was monitored by thin-layer chromatography and the product was extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were washed with 10 % aq. Na_2SO_3 (3 × 150 mL) and water (3 × 150 mL) and dried with anhydrous sodium sulfate. The filtrate was concentrated *in vacuo* to give a white powder (18.4 g, 99 % yield).

   ^{1}H-NMR (500 MHz, CDCl$_3$): $\delta = 2.26$(s, 12H), 3.83 (s, 3H), 3.95 (s, 3H), 6.19 (d, $J = 13.5$ Hz, 1H), 7.11(s, 2H), 7.20–7.23 (m, 4H).
   ^{13}C-NMR (125.7 MHz, CDCl$_3$): $\delta = 21.52$, 54.13, 54.99, 99.07, 99.12, 108.44, 108.53, 129.67, 129.75, 130.28, 131.13, 134.23, 138.45, 138.55, 146.54, 147.31, 159.92, 160.01, 161.76, 161.89.
   ^{31}P-NMR (202 MHz, CDCl$_3$): $\delta = 31.67$.

2.4.5   2,2′,6,6′-TETRAMETHOXY-BIS[DI(3,5-DIMETHYLPHENYL)PHOSPHINOYL]-3,3′-BIPYRIDINE (6)
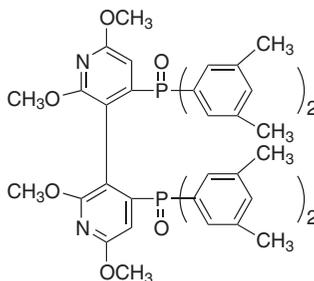
(**6**)

Materials and Equipment

- 3-Bromo-2,6-dimethoxy-4-di(3,5-dimethylphenyl)phosphino-pyridine (**5**) (5.4 g, 11.4 mmol)
- Cu powder, (2.9 g, 45.6 mmol)
- Dried DMF (8 mL)
- Chloroform (250 mL)
- Ethyl acetate (20 mL)
- Anhydrous sodium sulfate
- One 50 mL round-bottomed flask equipped with a magnetic stirrer
- Magnetic stirrer plate
- One Büchner funnel, 5 cm diameter
- One Büchner flask (500 mL)
- Filter paper
- Rotary evaporator

Procedure

1. A mixture of 3-bromo-2,6-dimethoxy-4-di(3,5-dimethylphenyl)phosphino-pyridine (**5**, 5.4 g, 11.4 mmol), Cu powder (2.9 g, 45.6 mmol) and dried DMF (8 mL) was stirred at 140 °C for 14 h.
2. The mixture was evaporated to dryness, then $CHCl_3$ (100 mL) was added and the mixture was refluxed for a few minutes. Insoluble solid was removed by filtration and was washed with $CHCl_3$ (100 mL). The combined filtrate was dried with anhydrous sodium sulfate and the solvent was evaporated. The solid residue was washed with ethyl acetate (20 mL) to give a white, powdery product (3.8 g, 84.6 % yield).

   ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 2.07$ (s , 12H), 2.29 (s, 12H), 3.41 (s, 6H), 3.80 (s, 6H), 6.31 (d, $J = 13.5$ Hz, 2H), 6.93 (s, 2H), 7.07 (d, $J = 13.0$ Hz, 6H), 7.34 (d, $J = 12.0$ Hz, 4H).
   ^{13}C-NMR (125.7 MHz, $CDCl_3$): $\delta = 21.16$, 21.46, 53.20, 53.52, 104.96, 105.06, 113.27, 129.88, 129.95, 130.18, 130.26, 133.32, 133.43, 137.62, 137.72, 137.84, 137.94, 144.20, 144.97, 161.15, 161.27, 161.43, 161.57.
   ^{31}P-NMR (202 MHz, $CDCl_3$): $\delta = 30.65$.

2.4.6   OPTICAL RESOLUTION OF (±)-**6** WITH (−) OR (+)-2,3-*O,O′*-DIBENZOYLTARTARIC ACID MONOHYDRATE [(*R*)-**6** OR (*S*)-**6**]

(*R*)-6-(−)-DBT
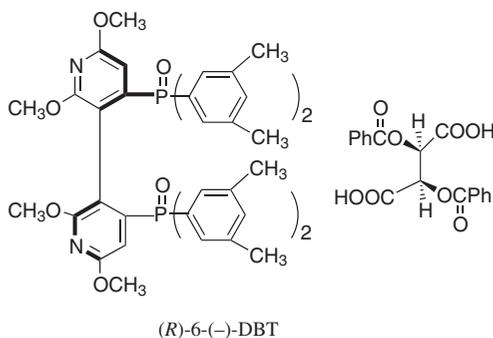
Materials and Equipment

- (±)-2,2′,6,6′-Tetramethoxy-bis[di(3,5-dimethylphenyl)phosphinoyl]-3,3′-bipyridine [(±)-**6**] (4.0 g, 5.1 mmol)
- (−)-2,3-*O,O′*-Dibenzoyltartaric acid monohydrate [L-(−)-DBT], (1.90 g, 5.1 mmol)
- Chloroform (200 mL)
- Ethyl acetate (50 mL)
- 10 % aq. NaOH
- Anhydrous sodium sulfate
- One 250 mL round-bottomed flask equipped with a magnetic stirring bar
- One 100 mL round-bottomed flask equipped with a magnetic stirring bar
- One condenser
- One 100 mL addition funnel
- One glass funnel
- Filter paper
- One 250 mL separatory funnel
- One Bűchner funnel, 5 cm diameter
- One Bűchner flask (250 mL)
- Rotary evaporator
- Magnetic stirrer plate

Procedure

1. To a refluxing solution of racemic 2,2′,6,6′-tetramethoxy-bis[di(3,5-dimethylphenyl)phosphinoyl]-3,3′-bipyridine [(±)-**6**, 4.09, 5.1 mmol] in 30 mL CHCl₃, a solution of (−)-2,3-*O,O′*-dibenzoyltartaric acid monohydrate [L-(−)-DBT, 1.90 g, 5.1 mmol] in 50 mL ethyl acetate was added slowly. The mixture was stirred under reflux for 30 min and then allowed to stand at room temperature overnight.
2. The crystals formed are collected on a glass funnel and the filtrate was stored for recovery of the other enantiomer. The white solid product was dried *in vacuo* at

room temperature (0.1 mm Hg) for 2 h to give a 1: 1 complex (R)-**5**-(−)-DBT as needles [2.36 g, 80.0 % yield based on (±)-**6** initially used, $[\alpha]_D^{20} = +136.1°$ (c = 1.01, CHCl₃)].

^{1}H-NMR (500 MHz, CDCl₃): $\delta = 2.25$ (s, 24H), 3.37 (s, 6H), 3.82 (s, 6H), 6.08(s, 2H), 6.27 (d, J = 12.5 Hz, 2H), 7.07–7.14 (m, 8H), 7.22–7.26 (m, 4H), 7.36–7.39 (m, 4H), 7.50–7.53 (m, 2H), 8.08 (d, J = 10.0 Hz, 4H). Absorptions due to hydroxylic protons could not be observed.

^{13}C-NMR (125.7 MHz, CDCl₃): $\delta = 12$, 21.38, 53.37, 53.73, 72.08, 105.13, 105.23, 112.55, 128.41, 129.65, 129.87, 129.95, 130.09, 130.17, 130.24, 133.25, 133.82, 137.87, 137.98, 138.10, 161.18, 161.31, 161.76, 161.90, 165.38, 167.84.

^{31}P-NMR (202 MHz, CDCl₃,): $\delta = 33.29$.

3. The complex (R)-**6**-(−)-DBT (2.36 g, 2.03 mmol) was dissolved in 15 mL CHCl₃ and treated with 10 % aq. NaOH (40 mL) overnight. The mixture was extracted with three 20 mL portions of CHCl₃. The combined organic phase was washed with 10 % aq. NaOH (10 mL), water (3 × 15 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent furnished white solid (R)-**5** [1.49 g, 75% yield based on the amount of (±)-**6** initially used, $[\alpha]_D^{20} = +253.2°$ (c = 1.01, CHCl₃)].
4. Optical purities of the resolved **6** were determined by HPLC analysis (Diacel-AD column, eluted by hexane:2-propanol = 4:96, flow rate = 1.0 mL min⁻¹, $\lambda_{\text{detection}} = 254$ nm, t_R of (S)-**6** = 9.33 min, t_R of R isomer = 15.25 min). The ee of (R)- or (S)-**6** was found to be over 99.0%.

2.4.7   (R)-2,2′,6,6′-TETRAMETHOXY-BIS[DI(3,5-DIMETHYLPHENYL) PHOSPHINO]-3,3′-BIPYRIDINE [(R)-XYL-P-PHOS, (R)-**1**]
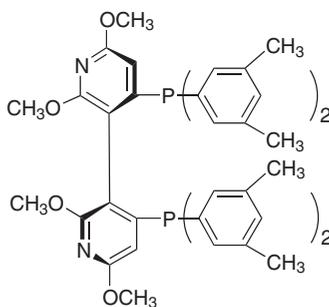
Materials and Equipment

- (R)-2,2′,6,6′-Tetramethoxy-bis[di(3,5-dimethylphenyl)phosphinoyl]-3,3′-bipyridine [(R)-**6**] (1.7 g, 2.16 mmol)
- Triethylamine (2.8 mL, 20.3 mmol)
- Trichlorosilane (2.5 mL, 20.3 mmol)
- Dry, degassed toluene (250 mL)
- Degassed 20 % aqueous sodium hydroxide

- Degassed brine (100 mL)
- Anhydrous sodium sulfate
- Degassed methanol (20 mL)
- 250 mL three-necked flask, fitted with a magnetic stirring bar, a thermometer and a reflux condenser
- Two-ended needle
- Magnetic stirrer plate

Procedure

1. To a 250 mL three-necked flask, fitted with a magnetic stirring bar, a thermometer and a reflux condenser, was added (*R*)-**6** (1.7 g, 2.16 mmol) followed by dry, degassed toluene (50 mL), triethylamine (2.8 mL, 20.3 mmol) and trichlorosilane (2.5 mL, 20.3 mmol). The mixture was stirred and heated at 100 °C for 1 h and finally at reflux overnight.
2. After the solution was cooled to room temperature, 40 mL of 20 % aqueous sodium hydroxide solution was added carefully. The mixture was then stirred at 80 °C until the organic and aqueous layers were clear.
3. The aqueous layer was separated and extracted with two 50 mL portions of warm toluene. The combined organic layer was washed with two 20 mL portions of 10 % sodium hydroxide solution and two 40 mL portions of brine and then dried over anhydrous sodium sulfate.
4. The organic layer was concentrated to dryness under reduced pressure, then degassed methanol (2×10 mL) was added. The precipitate was collected and dried at reduced pressure overnight to give (*R*)-XylP-Phos as a white solid [1.49 g, 91 % yield, $[\alpha]_D^{20} = +122.8°$ (*c*-1.0, CH$_2$Cl$_2$)].

   ^{1}H-NMR (500 MHz, CDCl$_3$): $\delta = 2.20$ (s, 12H), 2.25 (s, 12H), 3.37 (s, 6H), 3.83 (s, 6H), 6.06 (d, $J = 1.5$ Hz, 2H), 6.79–6.92 (m, 12H).
   ^{13}C-NMR (125.7 MHz, CDCl$_3$): $\delta = 21.52$, 21.55, 53.06, 53.43, 105.47, 115.25, 115.39, 115.54, 130.34, 130.61, 131.38, 131.46, 131.54, 132.33, 132.42, 132.50, 137.36, 137.39, 137.43, 137.68, 137.71, 137.74, 154.64, 154.70, 154.75, 160.72, 160.76, 160.81, 162.30.
   ^{31}P-NMR (202 MHz, CDCl$_3$): $\delta = -11.99$.

2.4.8   PREPARATION OF THE STOCK SOLUTION OF [Rh(*R*-Xyl-P-Phos)(COD)]BF$_4$ (**Cat. 1**)
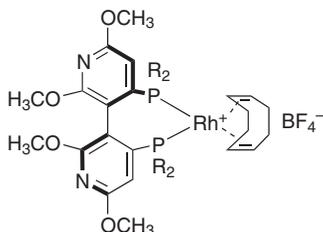
(*R*)-**Cat. 1**, R = 3,5-(CH$_3$)$_2$C$_6$H$_3$

Materials and Equipment

- (*R*)-2,2′,6,6′-Tetramethoxy-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridine [(*R*)-Xyl-P-Phos, (*R*)-**1**] (7.9 mg, 0.0105 mmol)
- [Rh(COD)$_2$]BF$_4$ (4.1 mg, 0.01 mmol)
- Dried and degassed CH$_2$Cl$_2$

Procedure

1. [Rh(COD)$_2$]BF$_4$ (4.1 mg, 0.01 mmol) was dissolved in CH$_2$Cl$_2$ (0.5 mL) under nitrogen. A solution of (*R*)-Xyl-P-Phos [(*R*)-**1**, 7.9 mg, 0.0105 mmol] in CH$_2$Cl$_2$ (0.5 mL) was added dropwise to the above solution with stirring. The reaction mixture was stirred overnight to give a solution of (*R*)-**Cat. 1** (0.01 mol L^{-1}).

   ^{31}P-NMR (202 MHz, CDCl$_3$): $\delta = 21.2$ (d, $J_{Rh-P} = 144.6$ Hz).

2.4.9   A TYPICAL PROCEDURE FOR THE ASYMMETRIC HYDROGENATION OF METHYL (*Z*)-2-ACETAMIDOCINNAMATE

Materials and Equipment

- Methyl (*Z*)-2-acetamidocinnamate (4 mg, 0.0183 mmol)
- Stock solution of [Rh(*R*-Xyl-P-Phos)(COD)]BF$_4$ (**Cat. 1**) (18.3 uL, 1.83×10^{-4} mmol)
- Dried and degassed methanol

Procedure

1. A solution of 0.01 mol L^{-1} **Cat. 1** in CH$_2$Cl$_2$ (18.3 μL, 1.83×10^{-4} mmol), methyl (*Z*)-2-acetamidocinnamate (4 mg, 0.0183 mmol) and methanol (348 μL) were charged into a 25 mL round bottom flask equipped with a magnetic stirring bar under a N$_2$ atmosphere. A stream of H$_2$ was bubbled through the solution while it was magnetically stirred at ambient temperature for 5 min; stirring was continued under 1 atm of H$_2$ for 2 h. The resulting solution was then submitted to analysis for the conversion and ee. Quantitative conversion of the starting material to the hydrogenation product, (*R*)-2-acetamido-3-phenyl-propanoate, with 90 % ee was observed by chiral GC analysis (column, Chrompack Chirasil-L-Val, 25 m × 0.25 mm, carrier gas, N$_2$).

   Table 2.3 summarizes the different substrates that has been reduced with the [Rh(*R*-Xyl-P-Phos)(COD)]BF$_4$ complex in methanol.

Table 2.3 Rh-catalyzed asymmetric hydrogenation of the derivatives of methyl (Z)-2-acetamidocinnamate using **Cat. 1**[a]

R—CH=C(COOR^1)(NHCOCH$_3$) + H$_2$ →[Cat. 1 / Methanol] R—CH$_2$—CH(COOR^1)(NHCOCH$_3$)
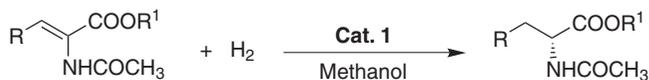
Entry	R	R^1	Temp. (°C)	Time (h)	Conv. (%)[a]	ee (%)[a]
1	C$_6$H$_5$-	CH$_3$	RT	2	>99.9	90
2	C$_6$H$_5$-	CH$_3$	0	18	>99.9	93
3	C$_6$H$_5$-	H	RT	10	>99.9	91
4	2-Cl-C$_6$H$_4$	CH$_3$	0	18	>99.9	92
5	3-Cl-C$_6$H$_4$	CH$_3$	0	18	>99.9	93
6	4-Cl-C$_6$H$_4$	CH$_3$	0	18	>99.9	93
7	4-CH$_3$-C$_6$H$_4$	CH$_3$	0	18	>99.9	94
8	4-CH$_3$O-C$_6$H$_4$	CH$_3$	0	18	>99.9	94

[a]The conversion and ee value were determined by chiral GC with a 25 m × 0.25 mm Chrompack Chirasil-L-Val column. The acids were converted to the corresponding methyl esters with methyl iodide/KHCO$_3$ before GC analysis. Product possessing the R configuration was obtained for all products. The absolute configuration was determined by comparing the retention time with that reported in the literature.[4]

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2.5 (R,R)-2,3-BIS(TERT-BUTYLMETHYLPHOSPHINO)QUINOXALINE (QuinoXP*) AS A LIGAND FOR RHODIUM-CATALYZED ASYMMETRIC HYDROGENATION OF PROCHIRAL AMINO ACID AND AMINE DERIVATIVES

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Rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids and en-amides is an efficient method for the preparation of optically active amino acids and
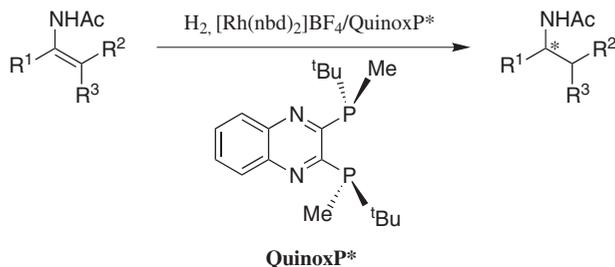
QuinoxP*

Figure 2.3

secondary amines.[1,2] Very recently, a new P-chiral phosphine ligand, (R,R)-2,3-bis(tert-butylmethylphosphino)quinoxaline (QuinoxP*), has been prepared by the reaction of enantiomerically pure (S)-tert-butylmethylphosphine–borane with 2,3-dichloroquinoxaline. This ligand is an air-stable solid and exhibits excellent enantioselectivities in rhodium-catalyzed asymmetric hydrogenation of dehydro-amino acids and related substrates (Figure 2.3).[3]

2.5.1   SYNTHESIS OF (R)-tert-BUTYL(HYDROXYMETHYL)METHYLPHOSPHINE–BORANE
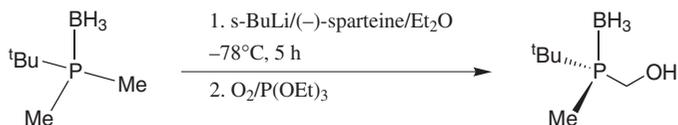
Materials and Equipment

- (−)-Sparteine (18.3 g, 78 mmol)
- Dry diethyl ether (200 mL, 150 mL)
- s-BuLi, 72 mL of 1.0 M cyclohexane solution (72 mmol)
- Nitrogen gas
- tert-Butyl(dimethyl)phosphine–borane (7.92 g, 60 mmol)
- Distilled triethyl phosphite (10 g, 60 mmol)
- Oxygen gas
- 2 M HCl
- Ethyl acetate
- Brine (saturated solution of sodium chloride)
- Anhydrous sodium sulfate
- Hexane
- Silica gel (Cica–Reagent 60N, spherical neutral, 63–220 Ìm), 300 g
- TLC plates, Silica gel F$_{254}$, Merck
- One 1 L three-necked flask with one 200 mL dropping funnel with a magnetic stirrer bar

- Constant temperature bath, MeOH
- Magnetic stirrer plate
- One 3 L balloon
- One 1 L separatory funnel
- One 1 L Erlenmeyer flask
- One funnel, diameter 12 cm
- Filter paper
- One glass column, diameter 5 cm
- One 1 L round-bottomed flask
- Rotary evaporator

Procedure[4]

Note: All operations should be carried out in a well-ventilated hood.

1. To a stirred, cooled ($-78\,°C$) solution of ($-$)-sparteine (18.3 g, 78 mmol) in Et$_2$O (200 mL) was added s-BuLi (72 mL of 1.0 M cyclohexane solution, 72 mmol) under a nitrogen atmosphere. After 15 min, a solution of *tert*-butyl(dimethyl)-phosphine–borane[5] (7.92 g, 60 mmol) in diethyl ether (150 mL) was added dropwise, and the mixture was stirred at $-78\,°C$ for 5 h. Triethyl phosphite (10 g, 60 mmol) was added, and oxygen gas was passed through the solution with vigorous stirring. The mixture was kept at $-78\,°C$ under an oxygen atmosphere with vigorous stirring for 1 h, and the reaction was quenched with ice-cold 2 M aqueous HCl (300 mL).
2. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with 2 M HCl and brine, and dried over Na$_2$SO$_4$. The solvent was removed on a rotary evaporator, and the residue was purified by flash chromatography over silica gel (eluent: hexane/ethyl acetate = 3/1) to give (R)-*tert*-butyl(hydroxymethyl)methylphosphine–borane as a colourless solid (6.48 g, 73 %). $[\alpha]_D^{28}$ $-9.9°$ (92 % ee,[6] $c = 1.0$, CHCl$_3$).

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 0.39$ (br q), 1.21 (d, $^3J_{HP} = 13.5$ Hz, 9H), 1.27 (d, $^2J_{HP} = 10.1$ Hz, 3H), 2.05 (s 1H), 3.96 (d, $J = 13.3$ Hz, 1H), 4.05 (d, $J = 13.3$ Hz, 1H).
^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 3.0$ (d, $J_{CP} = 34.4$ Hz), 25.4 (d, $^2J_{CP} = 10.6$ Hz), 27.2 (d, $J_{CP} = 32.0$ Hz), 57.0 (d, $J_{CP} = 37.7$ Hz).
IR (KBr): 3480, 2970, 2380, 1070, 910 cm^{-1}.

2.5.2 SYNTHESIS OF (R)-BENZOYLOXY(*tert*-BUTYL)METHYLPHOSPHINE–BORANE
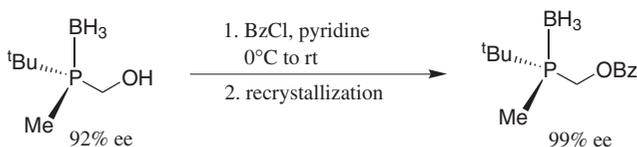
Materials and Equipment

- Nitrogen gas
- (R)-*tert*-Butyl(hydroxymethyl)methylphosphine–borane, 92 % ee (2.22 g, 15.0 mmol)
- Distilled pyridine (10 mL)
- Distilled benzoyl chloride (2.61 mL, 22.5 mmol)
- Diethyl ether
- Brine (saturated solution of sodium chloride)
- Anhydrous sodium sulfate
- Hexane
- Ethyl acetate
- Silica gel (Cica–Reagent 60N, spherical neutral, 63–220 μm) (150 g)
- TLC plates, Silica gel F$_{254}$, Merck
- One 30 mL two-necked flask with a magnetic stirrer bar
- Magnetic stirrer plate
- Ice bath
- One separatory funnel
- One Erlenmeyer flask
- One funnel, diameter 10 cm
- Filter paper
- One round-bottomed flask
- Rotary evaporator
- One glass column

Procedure

1. Benzoyl chloride (2.61 mL, 22.5 mmol) was added to a stirred, cooled (0 °C) solution of (R)-*tert*-butyl(hydroxylmethyl)methylphosphine–borane (92% ee, 2.22 g, 15.0 mmol) in pyridine (10 mL) and the mixture was warmed to room temperature. After 1 h, the reaction mixture was quenched with 2 M aqueous HCl.

2. The mixture was extracted with ether three times, and the combined organic extracts were washed with brine and dried over Na$_2$SO$_4$. The solvent was removed on a rotary evaporator, and the residue was purified by chromatography over silica gel (eluent: hexane/EtOAc = 3/1). The product was recrystallized two times from hexane/ethyl acetate (20:1) to give optically pure (R)-benzoyl-oxy(*tert*-butyl)methylphosphine–borane (2.34 g, 62 %, >99 % ee) as colourless crystals, (m.p. 85–86 °C).

^{1}H-NMR (CDCl$_3$): δ = 0.48 (br q, J_{HB} = 108.6 Hz, 3H), 1.28 (d, J_{HP} = 14.0 Hz, 9H), 1.39 (d, J_{HP} = 9.8 Hz, 3H), 4.74–4.76 (m, 2H), 7.45–8.06 (m, 5H).
^{13}C-NMR: δ = 3.5, 25.5, 27.6, 57.9, 128.6, 129.7, 133.6.
^{31}P-NMR: δ = 28.6 (dd).
MS (FAB): *m/z* 251 (M$^+$-H).

2.5.3 SYNTHESIS OF (*S*)-*tert*-BUTYLMETHYLPHOSPHINE–BORANE
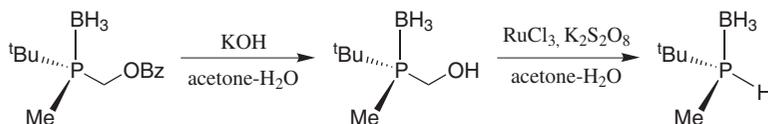
Materials and Equipment

- Benzoyloxy(*tert*-butyl)methylphosphine–borane (99 % ee), (6.05 g, 24.0 mmol)
- Acetone (25 mL, 70 mL)
- Potassium hydroxide (4.0 g, 72 mmol)
- Water
- Diethyl ether
- Brine (saturated solution of sodium chloride)
- Anhydrous sodium sulfate
- Potassium hydroxide (13.5 g, 240 mmol)
- Potassium persulfate (19.4 g, 72 mmol)
- Ruthenium trichloride trihydrate (624 mg, 2.4 mmol)
- 3 M aqueous HCl
- Pentane
- Celite®, 20 g
- Silica gel (Cica–Reagent 60N, spherical neutral, 63–220 μm), 150 g
- TLC plates, Silica gel F$_{254}$, Merck
- One 200 mL Erlenmeyer flask with magnetic stirrer bar
- Magnetic stirrer plate
- One separatory funnel, 300 mL
- One funnel, diameter 10 cm
- Filter paper
- One round-bottomed flask
- Rotary evaporator
- One glass column, diameter 3 cm
- Water aspirator

Procedure

1. To a stirred solution of benzoyloxy(*tert*-butyl)methylphosphine–borane (99% ee, 6.06 g, 24 mmol) in acetone (25 mL) was added a solution of potassium hydroxide (4.0 g, 72 mmol) in water (15 mL) dropwise. After completion of the hydrolysis (ca. 1 h), the reaction mixture was diluted with water (100 mL) and extracted three times with diethyl ether. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. The solvent was evaporated and the resulting crude (*R*)-*tert*-butyl(hydroxymethyl)methylphosphine–borane was dissolved in acetone (70 mL). The solution was added to a vigorously stirred, cooled (0 °C)

solution of potassium hydroxide (13.5 g, 240 mmol), potassium persulfate (19.4 g, 72 mmol) and ruthenium trichloride trihydrate (624 mg, 2.4 mmol) in water (150 mL). The ice bath was removed and stirring was continued for 2 h at room temperature. The reaction mixture was neutralized with 3 M HCl and agitated with diethyl ether (100 mL), and the resultant mixture was passed through a Celite pad to remove insoluble materials. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed on a rotary evaporator with a cold water bath (ca. 0 °C) and the residue was purified by chromatography over silica gel (eluent: pentane/diethyl ether = 8/1) to give (S)-tert-butylmethylphosphine–borane (99% ee,[7,8] 1.77 g, 63 %).[9]

2.5.4   (R,R)-2,3-BIS(tert-BUTYLMETHYLPHOSPHINO)QUINOXALINE (QuinoxP*)
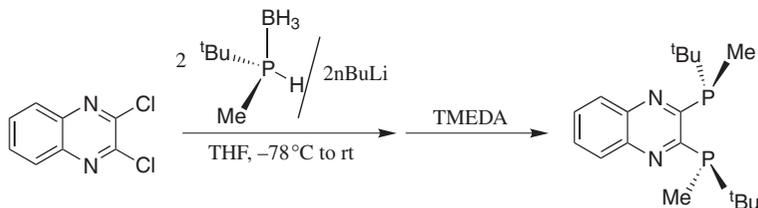
Materials and Equipment

- n-BuLi, 3.8 mL of a 1.60 M solution in hexane (6.0 mmol)
- (S)-tert-Butylmethylphosphine–borane (99 % ee) (708 mg, 6.0 mmol)
- Distilled THF (4 mL, 8 mL)
- Nitrogen gas
- 2,3-Dichloroquinoxaline (398 mg, 2 mmol)
- Tetramethylethylenediamine (3 mL)
- 2 M aqueous HCl
- Hexane
- Brine (saturated solution of sodium chloride)
- Anhydrous sodium sulfate
- Ethyl acetate
- Methanol
- Silica gel (Cica–Reagent 60N, spherical neutral, 63–220 μm), 50 g
- TLC plates, Silica gel F$_{254}$, Merck
- One Schlenk flask with magnetic stirrer bar
- Magnetic stirrer plate
- Dry ice–acetone bath
- Separatory funnel

- One funnel
- Filter paper
- One round-bottomed flask
- Rotary evaporator
- One glass column, diameter 2 cm
- One Erlenmeyer flask, 10 mL

Procedure

1. A solution of *n*-BuLi (3.8 mL of a 1.60 M solution in hexane, 6.0 mmol) was added to a stirred solution of *tert*-butylmethylphosphine–borane (708 mg, 6.0 mmol) in THF (4 mL) at −78 °C under a nitrogen atmosphere. After 15 min, a solution of 2,3-dichloroquinoxaline (398 mg, 2 mmol) in THF (8 mL) was added in one portion. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. Tetramethylethylenediamine (3 mL) was added and, after stirring for an additional 2 h, the reaction was quenched with 2 M aqueous HCl. The reaction mixture was extracted with hexane, and the combined organic extracts were dried over Na_2SO_4. The solvent was removed on a rotary evaporator, and the residue was purified by chromatography over silica gel (eluent: hexane/EtOAc = 30/1) to give (*R,R*)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline (452 mg, 70 %) as an orange solid, which was recrystallized from MeOH (4.5 mL) as orange cubes (358 mg) (m.p. 102–103 °C).

   ^{1}H-NMR: $\delta = 1.02$ (t, 9H), 1.43 (t, 3H), 7.72 (dd, $J_{HH} = 3.7$ Hz, $J_{HH} = 6.4$ Hz, 2H), 8.10 (dd, $J_{HH} = 3.4$ Hz, $J_{HH} = 6.4$ Hz).
   ^{13}C-NMR: $\delta = 4.7, 27.5, 31.9, 129.5, 141.6, 165.1$.
   ^{31}P-NMR: $\delta = 17.7$ (s).
   IR (KBr): 2950, 1470, 780 cm^{-1}.
   MS (FAB): *m/z* 335 (M$^+$H).

2.5.5 ASYMMETRIC HYDROGENATION OF METHYL (*E*)-3-ACETYLAMINO-2-BUTENOATE CATALYZED BY Rh(I)-(*R,R*)-2,3-BIS(*tert*-BUTYLMETHYLPHOSPHINO)QUINOXALINE
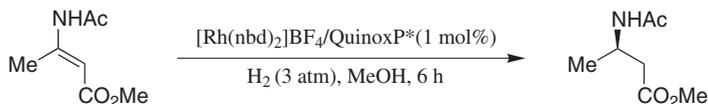
Materials and Equipment

- Methyl (*E*)-3-acetylamino-2-butenoate (157 mg)
- Methanol (3 mL)
- Bis(norbornadiene)rhodium(I) tetrafluoroborate (3.8 mg)

- (*R,R*)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline (4.0 mg)
- Hydrogen gas
- Ethyl acetate
- One hydrogenation tube with magnetic stirrer bar
- Magnetic stirrer plate
- Silica gel (Cica –Reagent 60N, spherical neutral, 63–220 μm), 5 g
- One syringe (5 mL)
- Rotary evaporator
- One glass column, diameter 1 cm

Procedure

1. A 50 mL hydrogenation tube was charged with a magnetic stirrer bar and methyl (*E*)-3-acetylamino-2-butenoate (157 mg, 1 mmol). The tube was connected to a hydrogen tank via stainless steel tubing. The vessel was evacuated and filled with hydrogen gas. A mixture of [Rh(nbd)$_2$]BF$_4$ (3.8 mg, 0.01 mmol), (*R,R*)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline (4.0 mg, 0.012 mmol), and methanol (3 mL) was added via a syringe and the hydrogen pressure was increased to 3 atm. After stirring for 6 h, the solvent was removed on a rotary evaporator and the residue was dissolved in ethyl acetate. The solution was passed through a short column of silica gel using ethyl acetate as the eluent, and the solvent was evaporated to afford methyl (*R*)-methyl 3-acetylaminobutanoate [159 mg (100%), 99.7 % ee (*R*)].[10]

CONCLUSION

The procedure is easy to reproduce and the asymmetric hydrogenation may be applied to a wide range of dehydroamino acids and related substrates. Table 2.4 shows some different substrates than can be hydrogenated in the presence of Rh(I)-*t*-Bu-QuinoxP* in methanol.

Table 2.4 Asymmetric hydrogenation of dehydroamino acid esters and α-enamides catalyzed by Rh(I)-*t*-Bu-QuinoxP* (see Figure 2.3)

Entry	R^1	R^2	R^3	Product ee (%) (configuration)
1	CO$_2$Me	Ph	H	99.9(*R*)
2	CO$_2$Me	4-AcO-3-MeOC$_6$H$_3$	H	99.6(*R*)
3	Me	H	CO$_2$Me	99.7(*R*)
4	Me	CO$_2$Me	H	99.2(*R*)
5	Ph	H	H	99.9(*R*)
6	1-Adamantyl	H	H	96.3(*R*)

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6. The enantiomeric excess of the product was determined by the HPLC analysis of its benzoyl derivative. Chiracel OJ-H, hexane:2-propanol $= 9:1$, flow rate $1.0\,mL\,min^{-1}$, UV detection: 254 nm, (*R*) $t_1 = 9.4$ min, (*S*) $t_2 = 10.3$ min.
7. In order to determine the ee of the product, it was successively reacted with *n*-BuLi and benzyl chloride in dry THF; the product, benzyl(*tert*-butyl)methylphosphine–borane, was analyzed by HPLC. Chiracel OD-H, hexane:2-propanol $= 9:1$, flow rate $0.5\,mL\,min^{-1}$, UV detection 254 nm, (*S*) $t_1 = 14.7$ min, (*R*) $t_2 = 16.4$ min.
8. Pure product was solidified at room temperature.
9. The product gradually evaporated under reduced pressure, and hence low-boiling point solvents such as ether and pentane are most suitable for the extraction and the purification.
10. The ee of the product was determined by GC analysis: DEX-CB, column temperature $135\,°C$, flow rate $24\,mL\,min^{-1}$, (*S*) $t_1 = 7.27$ min, (*R*) $t_2 = 7.66$ min.

2.6 RHODIUM-CATALYZED ASYMMETRIC HYDROGENATION OF INDOLES

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Catalytic enantioselective hydrogenation of heteroaromatics can provide, in an efficient way, heterocyclic skeletons possessing a chiral carbon centre. However, such an asymmetric reaction is not widely reported. Recently, a rhodium complex modified with a chiral bisphosphine PhTRAP[1] (a ligand which forms *trans*-chelate complexes with various transition metals) was found to be a good catalyst for enantioselective hydrogenation of indoles (Figure 2.4).[2,3] A broad range of 2- and 3-substituted indoles was transformed into chiral indolines with high ees.

2.6.1 SYNTHESIS OF (*R*)-2-[(*S*)-1-(DIMETHYLAMINO)ETHYL]-1-IODOFERROCENE
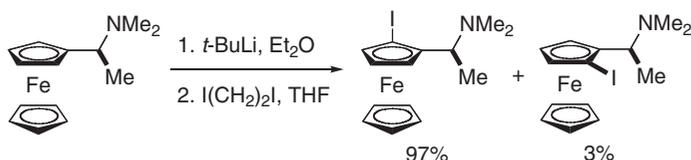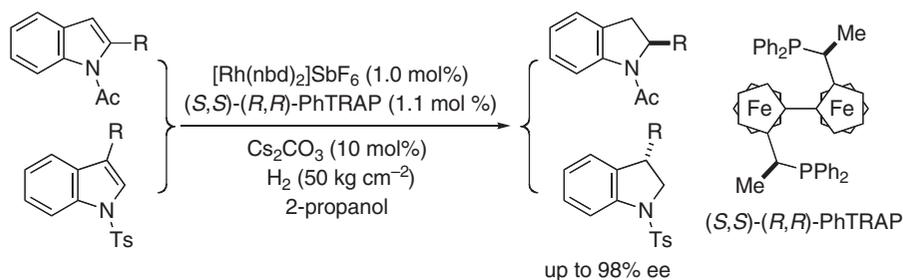
Figure 2.4

Materials and Equipment

- (S)-N,N-Dimethyl-1-ferrocenylethylamine (5.22 g, 20 mmol)
- *tert*-Butyllithium (1.62 M pentane solution) (15.0 mL, 24 mmol)
- Dry diethyl ether (60 mL)
- 1,2-Diiodoethane (>95 %) (7.05 g, 25 mmol)
- Dry THF (12 mL)
- Saturated aqueous sodium thiosulfate (20 mL)
- Ethyl acetate (60 mL)
- Saturated aqueous sodium chloride (20 mL)
- Sodium sulfate (anhydrous)
- Source of dry nitrogen (or argon)
- 200 mL four-necked round-bottomed flask with a Teflon-coated magnetic stirrer bar and a rubber septum
- 20 mL pressure-equalizing dropping funnel with a rubber septum
- Low-temperature thermometer with an adapter
- Three-way stopcock
- 30 mL Schlenk tube with a Teflon-coated magnetic stirrer bar and a rubber septum
- All-glass lure syringes of appropriate volumes with a 15 cm needle
- Cannula
- Dry ice–acetone bath (or acetone bath cooled with NESLAB CC-100II)
- Ice bath
- Magnetic stirrer plate
- 200 mL separating funnel
- Two 200 mL Erlenmeyer flasks
- Büchner funnel, diameter 4 cm
- 250 mL Büchner flask
- Filter paper
- 300 mL round-bottomed flask
- Rotary evaporator
- Diaphragm vacuum pump
- High-vacuum (oil) pump

Procedure

1. (*S*)-*N*,*N*-Dimethyl-1-ferrocenylethylamine[4] (5.22 g, 20 mmol) was placed in the 200 mL four-necked round-bottomed flask equipped with the 20 mL dropping funnel, the thermometer, and a three-way stopcock connecting with a source of dry nitrogen. The apparatus was evacuated and was charged with nitrogen, and then dry diethyl ether (60 mL) was added. After the solution had been cooled below −70 °C with the dry ice–acetone bath, 1.62 M *tert*-butyllithium solution (15.0 ml, 24 mmol) was added dropwise over 20 min. The resulting mixture was stirred for 10 min below −70 °C and then for 2 h at 0 °C.

2. 1,2-Diiodoethane (7.05 g, 25 mmol) was placed in the 30 mL Schlenk tube, and was dried *in vacuo*. After the vessel was charged with nitrogen, the 1,2-diiodoethane was dissolved in dry THF (12 mL). After the ferrocenyllithium solution prepared above had been cooled below −70 °C, the solution of 1,2-diiodoethane was transferred into the dropping funnel through a cannula and was added dropwise over 30 min. The mixture was stirred for 15 min below −70 °C and then for 20 min at 0 °C.

   Note: All glassware used in the above procedure was washed sequentially in soap solution, water, and acetone. The glassware was dried in an electric oven (at 120 °C) for at least 3 h.

3. After saturated aqueous sodium thiosulfate was added, the aqueous phase was extracted twice with ethyl acetate (30 mL × 2). The combined organic phase was washed with brine, dried with sodium sulfate, and then concentrated using a rotary evaporator. The residue was dried *in vacuo* to give a mixture of (*R*)-2-[(*S*)-1-(dimethylamino)ethyl]-1-iodoferrocene and its diastereomer (97/3 ratio) as a brown solid (7.7 g, 97 %).

   ^{1}H-NMR (200 MHz, CDCl$_3$, TMS): $\delta = 1.50$ (d, $J = 6.8$ Hz, 3H), 2.15 (s, 6H), 3.62 (q, $J = 6.8$ Hz, 1H), 4.12 (s, 5H), 4.12–4.17 (m, 1H), 4.24 (t, $J = 2.6$ Hz, 1H), 4.44–4.48 (m, 1H).

   The ^{1}H-NMR peaks sometimes broadened due to a trace of impurities. The impurities can be removed from the NMR sample by passing through alumina (>0.1 g).

   This mixture is usable for the next step without further purification. The mixture often contained (R)-N,N-dimethyl-1-ferrocenylethylamine. However, the starting material scarcely affects the following reactions.

2.6.2   SYNTHESIS OF (*R*)-2-[(*S*)-1-(DIPHENYLPHOSPHINYL)ETHYL]-1-IODOFERROCENE
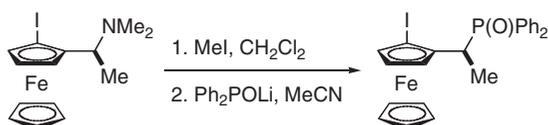
Materials and Equipment

- (*R*)-2-[(*S*)-1-(Dimethylamino)ethyl]-1-iodoferrocene [containing 3 % (*S*)-(*S*)-iso-mer] (3.83 g, 9.7 mmol)
- Iodomethane (99.5%) (7.1 g, 50 mmol)
- Dry dichloromethane (10 mL)
- Diphenylphosphine oxide (4.05 g, 20 mmol)
- Butyllithium (1.54 M hexane solution) (13.5 mL, 21 mmol)
- Dry THF (50 mL)
- Dry acetonitrile (110 mL)
- Water (300 mL)
- Ethyl acetate (400 mL)
- Saturated aqueous sodium chloride (100 mL)
- Magnesium sulfate (anhydrous)
- Ethyl acetate/benzene
- Activated alumina 200 (Nacalai tesque, abt. 200 mesh) (200 g)
- Source of dry nitrogen (or argon)
- 200 mL two-necked round-bottomed flask with a Teflon-coated magnetic stirrer bar, a three-way cock, and a rubber septum
- 300 mL three-necked round-bottomed flask with a Teflon-coated magnetic stirrer bar and a rubber septum
- Dimroth condenser with a three-way stopcock
- 20 mL pressure-equalizing dropping funnel with a rubber septum
- All-glass lure syringes of appropriate volumes with a 15 cm needle
- Cannula
- Magnetic stirrer plate
- Ice bath
- Oil bath
- 1 L separating funnel
- Two 1 L Erlenmeyer flasks
- Büchner funnel, diameter 6 cm
- 1 L Büchner flask
- Filter paper
- 1 L round-bottomed flask
- 300 mL round-bottomed flask
- Glass column, diameter 4 cm
- Rotary evaporator
- Vacuum solvent trap
- Diaphragm vacuum pump
- High-vacuum (oil) pump

Procedure

1. (*R*)-2-[(*S*)-1-(Dimethylamino)ethyl]-1-iodoferrocene [containing 3% (*S*)-(*S*)-iso-mer] (3.83 g, 9.7 mmol) was placed in the 200 mL two-necked round-bottomed

flask. The reaction vessel was evacuated and then charged with nitrogen. After the starting material had been dissolved in dry dichloromethane (10 mL), iodomethane (7.1 g, 50 mmol) was added dropwise over several minutes from a 5 mL syringe at 0 °C. The mixture was stirred for 30 min at room temperature. After the three-way stopcock was removed the apparatus was attached to a rotary evaporator, whereupon the solvent and excess iodomethane were evaporated. The three-way stopcock was re-attached to the two-necked flask and the remaining ammonium salt was dried *in vacuo*. The flask was charged with nitrogen.

2. Diphenylphosphine oxide[5] (4.05 g, 20 mmol) was placed in the 300 mL three-necked round-bottomed flask equipped with the Dimroth condenser and a 20 mL dropping funnel. The reaction vessel was evacuated and charged with nitrogen. The phosphine oxide was dissolved in dry THF (50 mL), and then 1.54 M butyllithium solution (13.5 mL, 21 mmol) was added dropwise over 15 min. The resulting reddish orange solution was stirred for 1.5 h at room temperature, and then the apparatus was connected to a diaphragm vacuum pump through a vacuum solvent trap cooled with a salt–ice bath. The solvent was removed under reduced pressure, and the residue was dried *in vacuo*. The reaction vessel was charged with nitrogen.

Note: All glassware used in the above procedure was washed sequentially in soap solution, water, and acetone. The glassware was dried in an electric oven (at 120 °C) for at least 3 h.

Diphenylphosphine oxide was recrystallized from diethyl ether prior to use and was weighed quickly because of its hygroscopic nature.

3. Under a nitrogen atmosphere, the ammonium salt (prepared in paragraph 1) was dissolved in dry acetonitrile (110 mL). The solution was transferred into the 300 mL three-necked flask containing lithium diphenylphosphinite (paragraph 2) by a cannula. The mixture was stirred under reflux for 1 h.

4. The mixture was then allowed to cool to room temperature. After water was added, the mixture was extracted twice with ethyl acetate (200 mL × 2). The combined organic phase was washed with brine, dried with magnesium sulfate, and then concentrated using a rotary evaporator. The residue was purified by column chromatography over alumina (eluent: ethyl acetate/benzene = 0 /100–1/3). The fractions containing the desired compound was collected in a 300 mL round-bottomed flask and evaporated to give a mixture of (*R*)-2-[(*S*)-1-(diphenylphosphinyl)ethyl]-1-iodoferrocene and its deiodinated compound (ca. 5/1 molar ratio) as a brown viscous oil (5.03 g).

^{1}H-NMR (400 MHz, CDCl$_3$, TMS): $\delta = 1.68$ (dd, $J = 7.3$, 15.4 Hz, 3H), 3.29 (dq, $J = 6.5$, 7.3 Hz, 1H), 4.16 (s, 5H), 4.28 (dd, $J = 1.4$, 2.5 Hz, 1H), 4.31 (dt, $J = 0.5$, 2.5 Hz, 1H), 4.55 (ddd, $J = 1.3$, 1.4, 2.5 Hz, 1H), 7.14–7.25 (m, 4H), 7.31–7.36 (m, 1H), 7.54–7.63 (m, 3H), 7.90–7.97 (m, 2H).

^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 16.13$ (d, $J = 1.8$ Hz), 34.29 (d, $J = 65.9$ Hz), 47.04 (d, $J = 2.4$ Hz), 66.61 (d, $J = 1.9$ Hz), 68.90, 71.34, 73.23, 89.21,

127.69 (d, $J = 11.6$ Hz), 128.66 (d, $J = 11.0$), 130.82 (d, $J = 92.8$ Hz), 131.40 (d, $J = 3.0$ Hz), 131.59 (d, $J = 98.3$ Hz), 131.64 (d, $J = 8.6$ Hz), 131.81 (d, $J = 9.2$ Hz), 131.84 (d, $J = 3.1$ Hz).
^{31}P-NMR (81 MHz, CDCl$_3$): $\delta = 34.40$ (s).

The crude mixture after the extraction can be purified by flash column chromatography over silica gel (Silica gel 60, Merck, 230–400 mesh) with ethyl acetate/hexane elution (1/1–3/1) as the eluent.

This mixture is usable for the next Ullmann coupling without further purification so long as if it contains no diphenylphosphine oxide. The phosphine oxide causes a low yield in the next reaction.

2.6.3   SYNTHESIS OF (R,R)-2,2′-BIS[(S)-1-(DIPHENYLPHOSPHINYL)ETHYL]-1,1″-BIFERROCENE

45% (for 2 steps)
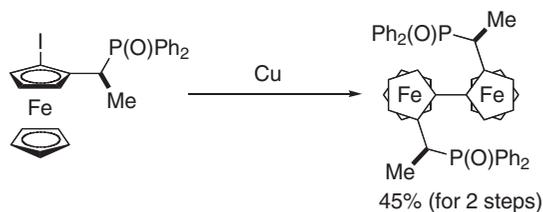
Materials and Equipment

- (R)-2-[(S)-1-(Diphenylphosphinyl)ethyl]-1-iodoferrocene (the mixture obtained from Section 2.6.2) (5.03 g)
- Copper powder (>99 %, 300 mesh, purchased from Lancaster) (36.1 g, 568 mmol)
- Iodine (>99 %) (3.13 g, 12.3 mmol)
- Acetone (100 mL)
- Hydrochloric acid (35–37 %) (10 mL)
- Dry dichloromethane (20 mL)
- Dichloromethane (100 mL)
- Ethyl acetate/benzene
- Toluene
- Celite$^{®}$, 10 g
- Silica gel 60 (Merck, 230–400 mesh) (150 g)
- Source of dry nitrogen (or argon)
- 100 mL Erlenmeyer flask
- Two 300 mL round-bottomed flask
- Three-way stopcock
- Glass stopper
- 20 mL all-glass lure syringe with a 15 cm needle
- Oil bath
- Two Büchner funnels, diameter 4 cm

- Two 200 mL Büchner flasks
- Filter paper
- Glass column, diameter 4 cm
- 50 mL Erlenmeyer flask
- Rotary evaporator
- Diaphragm vacuum pump
- High-vacuum (oil) pump

Procedure

1. Copper powder (36.1 g, 568 mmol) and iodine (3.13 g, 12.3 mmol) were placed in a 100 mL Erlenmeyer flask. Acetone (40 mL) was added, and then the mixture was shaken until the dark brown supernatant turned colourless. Immediately, the copper powder was collected by filtration, was washed sequentially with acetone, acetone/hydrochloric acid (1/1), acetone, and then dried *in vacuo*.

   Note: The 1:1 mixture of acetone and hydrochloric acid was prepared by adding carefully hydrochloric acid (35–37 %) to acetone at 0 °C. When concentrated hydrochloric acid is mixed with acetone at room temperature, a violent exothermic reaction can occur.
   The activated copper powder was used immediately for the following Ullmann coupling.

2. The freshly activated copper powder (31.8 g, 0.50 mol) was added to a 300 mL round-bottomed flask containing (*R*)-2-[(*S*)-1-(diphenylphosphinyl)ethyl]-1-iodoferrocene (5.03 g) (from Section 2.6.2). The flask was evacuated and charged with nitrogen. The organic material was dissolved in dry dichloromethane (20 mL). The resulting suspension was concentrated using a rotary evaporator, and then the residue was dried *in vacuo*. The flask was charged with nitrogen and was capped with a glass stopper. The mixture was heated at 130 °C for 12 h, and then allowed to cool to room temperature.

   When the Ullmann coupling was conducted with copper powder purchased from suppliers other than Lancaster, the reaction gave the desired product in very low yield.
   In order to avoid undue pressurization in the closed reaction vessel, dichloromethane was completely removed from the reaction mixture under vacuum with heating by a hair-dryer.
   We used an oil bath (200 mm ID × 200 mm height) for the Ullmann-coupling in order to heat the reaction mixture homogeneously. The reaction vessel was deeply immersed in the oil bath. The bath temperature was strictly controlled by Thermo Minder DH-12 (TAITEC Co., Ltd, Saitama, Japan).

3. The product was dissolved in dichloromethane, and then the remaining copper powder was filtered off through a Celite pad. The filtrate was concentrated using a rotary evaporator. The residue was purified by flash column chromatography over

silica gel (eluent: ethyl acetate/benzene $= 0/100$–$100/0$) to give a mixture of the desired product and [(S)-1-ferrocenylethyl]diphenylphosphine oxide. The mixture was recrystallized from toluene to give a toluene adduct of (R,R)-2,2″-bis[(S)-1-(diphenylphosphinyl)ethyl]-1,1″-biferrocene as orange crystals (2.09 g, 45 % for the two steps), m.p. 245–250 °C (decomp), $[\alpha]_D^{25} + 130°$ ($c = 1.02$, CHCl$_3$).

^{1}H-NMR (400 MHz, CDCl$_3$, TMS): $\delta = 1.65$ (d, $J = 7.4$, 16.8 Hz, 6H), 3.81 (dq, $J = 11,0$, 7.4 Hz, 2H), 4.01 (m, 2H), 4.08 (t, $J = 2.6$ Hz, 2H), 4.35 (s, 10H), 4.35 (m, 2H), 6.99–7.06 (m, 4H), 7.28–7.33 (m, 2H), 7.40–7.52 (m, 6H), 7.60–7.68 (m, 4H), 7.77–7.84 (m, 4H).

^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 19.14$, 30.23 (d, $J = 69.0$ Hz), 65.39, 68.32 (d, $J = 5.5$ Hz), 69.36, 72.56, 84.48 (d, $J = 6.8$ Hz), 90.58, 128.07 (d, $J = 11.0$ Hz), 128.18 (d, $J = 11.6$ Hz), 130.95 (d, $J = 2.4$ Hz), 131.22 (d, $J = 3.0$ Hz), 131.36 (d, $J = 9.1$ Hz), 132.03 (d, $J = 94.0$ Hz), 132.25 (d, $J = 8.5$ Hz), 133.85 (d, $J = 94.6$ Hz).

^{31}P-NMR (81 MHz, CDCl$_3$): $\delta = 35.59$ (s).

2.6.4   SYNTHESIS OF (R,R)-2,2″-BIS[(S)-1-(DIPHENYLPHOSPHINO)ETHYL]-1,1″-BIFERROCENE [ABBREVIATED TO (S,S)-(R,R)-PhTRAP]
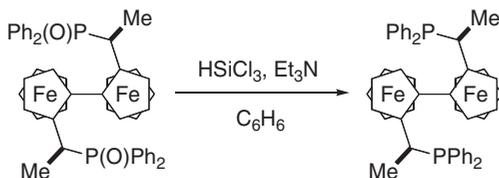
Materials and Equipment

- (R,R)-2,2″-Bis[(S)-1-(diphenylphosphinyl)ethyl]-1,1″-biferrocene (1.5 toluene adduct) (918 mg, 0.95 mmol)
- Trichlorosilane (0.6 mL, 5.9 mmol)
- Triethylamine (1.1 mL, 7.9 mmol)
- Dry benzene (2.5 mL)
- Nitrogen-saturated benzene
- Nitrogen-saturated 15 % aqueous potassium hydroxide (10 mL)
- Sodium sulfate (anhydrous)
- Celite®, 2 g
- Activated alumina 200 (Nacalai tesque, abt. 200 mesh) (15 g)
- Source of dry nitrogen (or argon)
- 17 mL screw-capped test tube
- Rubber septum
- Screw cap
- All-glass lure syringes of appropriate volumes with a 15 cm needle
- Ice bath

- Oil bath
- Dry ice–acetone bath
- Two Büchner funnels, diameter 2 cm
- Two 100 mL Büchner flasks
- Filter paper
- 50 mL separating funnel
- 50 mL Erlenmeyer flask
- Two 50 mL round-bottomed flasks
- Glass column, diameter 2 cm
- Rotary evaporator
- Diaphragm vacuum pump
- High-vacuum (oil) pump

Procedure

1. Recrystallized (R,R)-2,2″-bis[(S)-1-(diphenylphosphinyl)ethyl]-1,1″-biferrocene (1.5 toluene adduct, 918 mg, 0.95 mmol) was placed in a 17 mL screw-capped test tube equipped with a rubber septum. The test tube was evacuated and was charged with nitrogen. After dry benzene (2.5 mL) was added at room temperature, triethylamine (1.1 mL, 7.9 mmol) and trichlorosilane (0.6 mL, 5.9 mmol) were added at 0 °C. The rubber septum was quickly replaced with a screw cap, which was tightened up and sealed with adhesive tape. The screw capped test tube was immersed in the oil bath at 100 °C, and the mixture was heated for 10 h.
2. After the mixture was frozen by a dry ice–acetone bath, the screw cap was opened to air. Nitrogen-saturated 15 % aqueous potassium hydroxide was carefully added to the mixture, and then the white precipitate was filtered off through a Celite pad and washed with nitrogen-saturated benzene. The filtrate was extracted twice with nitrogen-saturated benzene (10 mL × 2). The combined organic phase was dried with sodium sulfate, and evaporated. The residue was quickly passed through a short column of alumina (eluent: nitrogen-saturated benzene) to give (S,S)-(R,R)-PhTRAP (741 mg, 98%) as an orange powder, m.p. 98–103 °C, $[\alpha]_D^{25} + 426°$ ($c = 0.51$, CHCl$_3$).

^{1}H-NMR (400 MHz, CDCl$_3$, TMS): $\delta = 1.35$ (pseudo-t, 6H), 3.49 (q, $J = 6.9$ Hz, 2H), 3.79 (dd, $J = 1.4$, 2.5 Hz, 2H), 4.12 (t, $J = 2.5$ Hz, 2H), 4.29 (s, 10H), 4.55 (dd, $J = 1.4$, 2.5 Hz, 2H), 7.05–7.40 (m, 20H).

^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 17.03$ (t, $|J_{P–C} + J_{P'–C}| = 2.2$ Hz), 29.25 (split into six lines, $|J_{P–C} + J_{P'–C}| = 17.1$ Hz), 65.36, 68.05 (t, $|J_{P–C} + J_{P'–C}| = 6.8$ Hz), 69.32, 71.67 (t, $|J_{P–C} + J_{P'–C}| = 2.3$ Hz), 84.37 (t, $|J_{P–C} + J_{P'–C}| = 4.2$ Hz), 93.08 (quint, $|J_{P–C} + J_{P'–C}| = 20.2$ Hz), 127.19, 127.46 (t, $|J_{P–C} + J_{P'–C}| = 6.7$ Hz), 128.00 (t, $|J_{P–C} + J_{P'–C}| = 4.8$ Hz), 128.33, 132.14 (quint, $|J_{P–C} + J_{P'–C}| = 18.3$ Hz), 135.11 (quint, $|J_{P–C} + J_{P'–C}| = 21.4$ Hz), 136.13 (split into six lines, $|J_{P–C} + J_{P'–C}| = 21.3$ Hz), 139.01 (split into six lines, $|J_{P–C} + J_{P'–C}| = 18.9$ Hz).

^{31}P-NMR (81 MHz, CDCl$_3$): $\delta = 2.19$ (s).

In order to avoid oxidation of PhTRAP, nitrogen-saturated solvent was used for the extraction and the chromatography. These manipulations should be done as quickly as possible.

PhTRAP in solid can be handled in air, and can be stored (with no oxidation) in a freezer under a nitrogen atmosphere for over 1 year.

2.6.5   CATALYTIC ASYMMETRIC HYDROGENATION OF *N*-ACETYL-2-BUTYLINDOLE

92%, 93% ee (*R*)
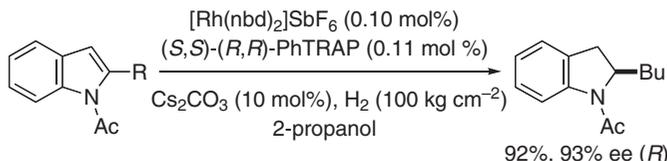
Materials and Equipment

- *N*-Acetyl-2-butylindole (215 mg, 1.00 mmol)
- [Bis(bicyclo[2,2,1]hepta-2,5-diene)rhodium(I)]hexafluoroantimonate (abbreviated to [Rh(nbd)$_2$]SbF$_6$) ($2.6 \times 1/5$ mg, 1.0 µmol)
- (*R*,*R*)-2,2''-Bis[(*S*)-1-(diphenylphosphinyl)ethyl]-1,1'-biferrocene (abbreviated to (*S*,*S*)-(*R*,*R*)-PhTRAP) ($4.3 \times 1/5$ mg, 1.1 µmol)
- Cesium carbonate (99 %) (3.2 mg, 9.8 µmol)
- Dry 2-propanol (0.6 mL $+ 2.0 \times 1/5$ mL)
- Hydrogen pressure (100 kg cm^{-2})
- Ethyl acetate/hexane
- Silica gel 60 (Merck, 230–400 mesh) (20 g)
- 10 mL Schlenk tube with a Teflon-coated magnetic stirrer bar and a rubber septum.
- 50 mL stainless steel autoclave (Figure 2.5)
- 50 mL test tube with a Teflon-coated magnetic stirrer bar and a rubber septum (Figure 2.5)
- 2 mL all-glass lure syringe with a 15 cm needle
- 500 µL or 1 mL gastight syringe
- Magnetic stirrer plate
- Oil bath
- Two 50 mL round-bottomed flasks
- Glass column, diameter 1.5 cm
- Rotary evaporator

Procedure

1. [Rh(nbd)$_2$]SbF$_6$ (2.6 mg, 5.0 µmol) and (*S*,*S*)-(*R*,*R*)-PhTRAP (4.3 mg, 5.4 µmol) were placed in the 10 mL Schlenk tube. The reaction apparatus was evacuated
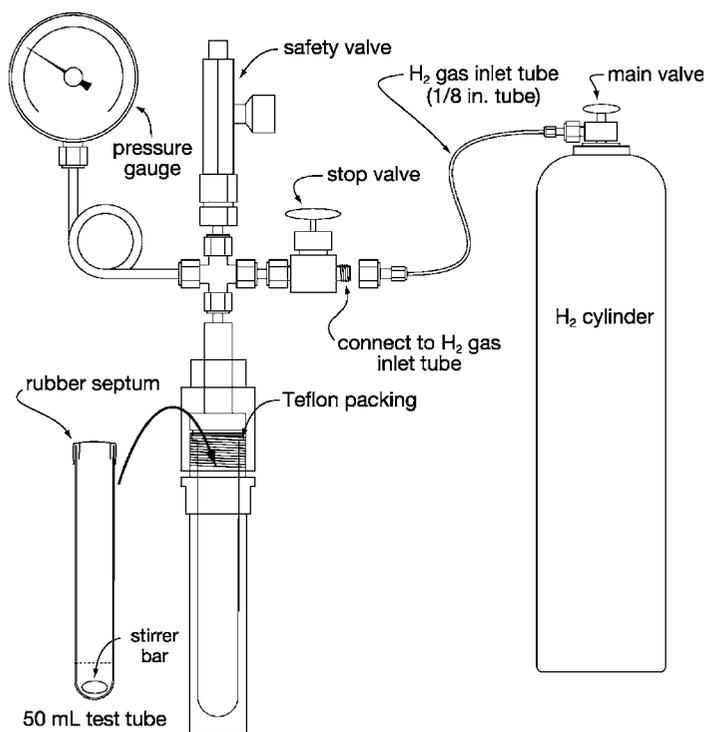
Figure 2.5

and charged with nitrogen. Dry 2-propanol (2.0 mL) was added and the mixture was stirred at room temperature for 10 min. N-Acetyl-2-butylindole (215 mg, 1.00 mmol) and cesium carbonate (3.2 mg, 9.8 μmol) were placed in the 50 mL test tube. The test tube was evacuated and charged with nitrogen. Dry 2-propanol (0.6 mL) was added. By use of a gastight syringe, 0.4 mL of the PhTRAP–rhodium catalyst solution (prepared above) was transferred into the test tube. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-filled stainless steel autoclave, and the autoclave was sealed immediately. The autoclave was connected to a hydrogen cylinder through a 1/8 in. stainless steel tube. The air originally present in the H_2 gas inlet tube was replaced by hydrogen. Hydrogen was introduced into the autoclave until the pressure gauge indicated 100 kg cm^{-2}, and then the pressure was carefully released to 1 kg cm^{-2}. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 100 kg cm^{-2}. After the stop-valve was closed, the gas inlet tube was disconnected. The mixture was stirred at 60 °C for 20 h, and then was allowed to cool to room temperature.

Note: All glassware used in the above procedure was washed sequentially in soap solution, water and acetone. The glassware was dried in an electric oven (at 120 °C) for at least 3 h.

2. Excess hydrogen was carefully released by opening the stop-valve, and then the apparatus was disassembled. The resulting mixture was transferred to a 50 mL round-bottomed flask, and the solvent was removed using a rotary evaporator. The residue was purified by flash column chromatography over silica gel (eluent: ethyl acetate/hexane = 1/20–1/3) to give (R)-N-acetyl-2-butylindoline (201 mg, 92 %, 93 % ee) as a pale yellow oil, $[\alpha]_D^{20}$ −97.5° (c = 1.00, CHCl$_3$).

^{1}H-NMR (300 MHz, CDCl$_3$, TMS): δ = 0.80–0.99 (br, 3H), 1.19–1.41 (br, 4H), 1.51–1.79 (br, 2H), 2.28 and 2.38 (a pair of br s, 3H), 2.57–2.88 (br m, 1H), 3.12–3.40 (br m, 1H), 4.16–4.41 and 4.63–4.90 (a pair of br, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.05–7.28 (m, 2H), 8.14 (br d, J = 6.9 Hz, 1H).

^{13}C-NMR δ (75 MHz, CDCl$_3$): δ = 13.9, 22.5, 23.3 and 24.3 (a pair of s), 27.2, 33.8 and 32.7 (a pair of s), 35.0, 60.6 and 59.8 (a pair of s), 117.8 and 115.1 (a pair of s), 123.8, 124.7 and 126.0 (a pair of s), 127.4, 130.6 and 133.4 (a pair of s), 142.4 and 141.4 (a pair of s), 168.4.

Chiral HPLC: Chirapak AD; 4% 2-propanol in hexane; 0.5 ml min^{-1}; t_R = 24.8 min for R isomer, 27.0 min for S isomer; detecting by UV at 254 nm.

2.6.6 CATALYTIC ASYMMETRIC HYDROGENATION OF 3-METHYL-N-(P-TOLUENESULFONYL)INDOLE

96%, 98% ee (S)
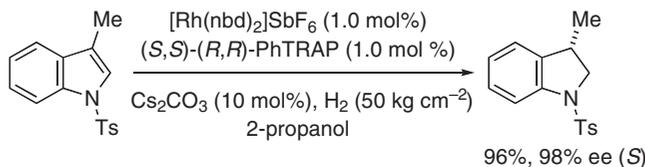
Materials and Equipment

- 3-Methyl-N-(p-toluenesulfonyl)indole (143 mg, 0.50 mmol)
- [Bis(bicyclo[2,2,1]hepta-2,5-diene)rhodium(I)]hexafluoroantimonate {abbreviated to [Rh(nbd)$_2$]SbF$_6$} (2.6 mg, 5.0 μmol)
- (R,R)-2,2″-Bis[(S)-1-(diphenylphosphinyl)ethyl]-1,1″-biferrocene [abbreviated to (S,S)-(R,R)-PhTRAP] (4.0 mg, 5.0 μmol)
- Cesium carbonate (99 %) (16.2 mg, 50 μmol)
- Dry 2-propanol (2.0 mL)
- Hydrogen pressure (50 kg cm^{-2})
- Ethyl acetate/hexane
- Silica gel 60 (Merck, 230–400 mesh) (20 g)
- 10 mL Schlenk tube with a Teflon-coated magnetic stirrer bar and a rubber septum
- 50 mL stainless steel autoclave (Figure 2.5)
- 50 mL test tube with a Teflon-coated magnetic stirrer bar and a rubber septum (Figure 2.5)

- 2 mL all-glass lure syringe with a 15 cm needle
- Cannula
- Magnetic stirrer plate
- Oil bath
- Two 50 mL round-bottomed flasks
- Glass column, diameter 1.5 cm
- Rotary evaporator

Procedure

1. Under a nitrogen atmosphere, dry 2-propanol (2.0 mL) was added to a mixture of [Rh(nbd)$_2$]SbF$_6$ (2.6 mg, 5.0 µmol) and (*S,S*)-(*R,R*)-PhTRAP (4.0 mg, 5.0 µmol). The mixture was stirred at room temperature for 10 min, then the resulting orange suspension was transferred through a cannula into a mixture of 3-methyl-*N*-(*p*-toluenesulfonyl)indole (143 mg, 0.50 mmol) and cesium carbonate (16.2 mg, 50 µmol) in the 50 mL test tube. The test tube was inserted into a nitrogen-filled stainless steel autoclave, and the autoclave was sealed immediately. Hydrogen was introduced into the autoclave until the pressure gauge indicated over 50 kg cm^{-2}, and then the pressure was carefully released to 1 kg cm^{-2}. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 50 kg cm^{-2}. The mixture was stirred at 80 °C for 24 h.

   Note: All glassware used in the above procedure was washed sequentially in soap solution, water and acetone. The glassware was dried in an electric oven (at 120 °C) for at least 3 h.

2. After the autoclave was allowed to cool to room temperature, excess hydrogen was released carefully. The resulting mixture was evaporated, and the residue was purified by flash column chromatography over silica gel (eluent: ethyl acetate/hexane = 1/20–1/5) to give (*S*)-3-methyl-*N*-(*p*-toluenesulfonyl)indoline (138 mg, 96 %, 98 % ee) as a colourless oil, $[\alpha]_D^{20}$ + 29.4° (*c* = 1.06, CHCl$_3$).

   ^{1}H-NMR (300 MHz, CDCl$_3$, TMS): δ = 1.11 (d, *J* = 7.0 Hz, 3H), 2.36 (s, 3H), 3.19 (double quintet, *J* = 8.6, 7.0 Hz, 1H), 3.42 (dd, *J* = 7.0, 10.4 Hz, 1H), 4.08 (dd, *J* = 8.6, 10.4 Hz, 1H), 6.96–7.08 (m, 2H), 7.16–7.26 (m, 3H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H).
   ^{13}C-NMR δ (75 MHz, CDCl$_3$): δ = 19.4, 21.4, 34.6, 57.5, 114.9, 123.8, 124.0, 127.4, 127.9, 129.7, 134.1, 136.9, 141.6, 144.1.
   Chiral HPLC: Chirapak OD-H; 4 % 2-propanol in hexane; 0.5 ml min^{-1}; t_R = 22.4 min for *R* isomer, 25.8 min for *S* isomer; detecting by UV at 254 nm.

CONCLUSION

The present asymmetric hydrogenation using PhTRAP–rhodium catalyst is applicable to the syntheses of various optically active indolines possessing a substituent at

Table 2.5 Asymmetric hydrogenation of indoles using (S,S)-(R,R)-PhTRAP–rhodium complex as catalyst
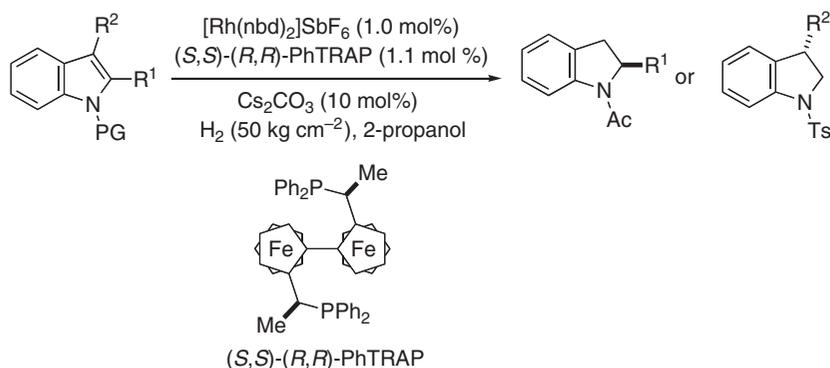
Entry	R^1	R^2	Protective group	Product Yield (%)	ee (%)
1	$CH_2(i\text{-Pr})$	H	Ac	91	91
2	Ph	H	Ac	91	87
3	CO_2Me	H	Ac	95	95
4	H	i-Pr	Ts	94	97
5	H	Ph	Ts	93	96
6	H	$(CH_2)_2OTBS$	Ts	94	98
7	H	$(CH_2)_2CO_2(t\text{-Bu})$	Ts	93	97

either the 2- or 3-position (Table 2.5). The choice of protective group on the nitrogen atom is crucial for achieving the high enantioselectivities. In the case of 2-substituted indoles, acetyl protection provided chiral indolines with the highest ee values.[2] N-Protection with sulfonyl group is required for the highly enantioselective hydrogenation of 3-substituted indoles.[3]

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3 Asymmetric Reduction of Ketones

CONTENTS

3.1 (R,R)-BIS(DIPHENYLPHOSPHINO)-1,3-DIPHENYLPROPANE AS A VERSATILE LIGAND FOR ENANTIOSELECTIVE HYDROGENATIONS

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Chiral trivalent phosphorus compounds play an important role as ligands of late-transition metals in homogeneous catalysis, e.g. enantioselective hydrogenation.[1] Recently, we reported on a three-step synthesis of (R,R)-bis(diphenylphosphino)-1,3-diphenylpropane (Figure 3.1).[2] The chiral diphosphine obtained could be advantageously used as a ligand in the Ru(II)-catalyzed hydrogenation of dibenzoylmethane affording its own enantiopure precursor alcohol with opposite configurations ('cross self-breeding system'). The new ligand could also be successfully applied for the enantioselective hydrogenation of functionalized olefins and ß-amino acid precursors.

3.1.1 SYNTHESIS OF (S,S)-1,3-DIPHENYLPROPANE-1,3-DIOL
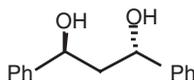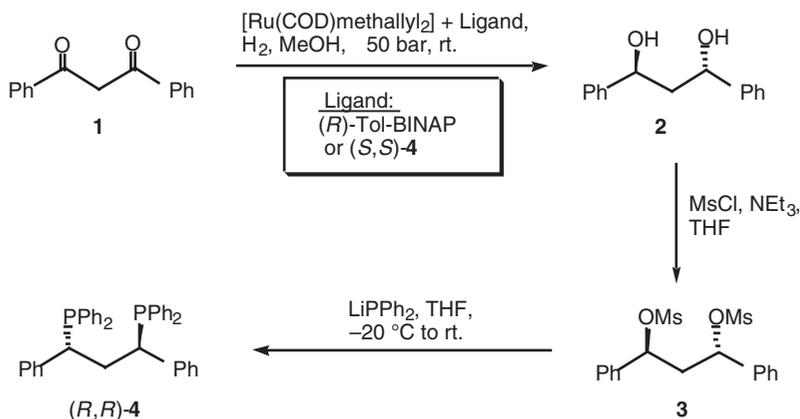
Figure 3.1

Materials and Equipment

- Dibenzoylmethane (98 %) (2.24 g, 10 mmol)
- Benzeneruthenium(II)chloride dimer (0.013 g, 0.026 mmol)
- (R)-(+)-2,2′-Bis(di-p-tolylphosphino)-1,1′-binaphthyl, (R)-Tol-BINAP (98 %) (0.041 g, 0.06 mmol)
- Dry N,N-dimethylformamide (99.8 %) (2 mL)
- Dry methanol (10 mL)
- Hydrogen pressure (50 bar)
- One 50 mL Schlenk vessel with magnetic stirrer bar
- Magnetic stirrer plate
- Vacuum pump
- Hydrogen pressure autoclave, 15 mL
- One glass sintered funnel
- One Büchner flask, 50 mL

Procedure

1. A suspension of $[Ru(C_6H_6)Cl_2]_2$ (0.013 g, 0.026 mmol) and (R)-Tol-BINAP (0.041 g, 0.06 mmol) in DMF (2 mL) was stirred at 100 °C for 10 min. The mixture was cooled to 50 °C and the solvent removed under vacuum to give the catalyst as a red-brown solid. This precatalyst was dissolved in methanol (10 mL).
2. This above solution was directly added to an autoclave containing dibenzoyl-methane (2.24 g, 10 mmol). The hydrogenation was performed at 50 bar initial H_2 pressure.
3. When the hydrogen consumption ceased (ca. 20 h) the enantiopure diol was filtered off and dried to furnish the desired product (1.12 g, 49.5 %) [ee determined by HPLC (CHIRALCEL-OD-H, n-hexane/EtOH 95/5)].

This procedure is very easy and can be scaled up to provide the enantiopure diol on multigram scale

3.1.2 SYNTHESIS OF (*S,S*)-METHANESULFONYLOXY-1,3-DIPHENYLPROPANE-1,3-DIOL
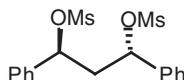
Materials and Equipment

- (*S,S*)-1,3-Diphenylpropane-1,3-diol (>98 % ee/HPLC) (1.12 g, 4.95 mmol)
- Triethylamine (1.63 g, 14.85 mmol)
- Methanesulfonyl chloride (99 %) (1.13 g, 9.90 mmol)
- THF (25 mL)
- Diethyl ether
- Water
- Anhydrous sodium sulfate
- 75 mL and 250 mL round-bottomed flasks with magnetic stirrer bars
- Magnetic stirrer plate
- One Dewar flask
- One 250 mL separatory funnel
- Two 200 mL Erlenmeyer flasks
- Rotary evaporator

Procedure

1. To a solution of (*S,S*)-1,3-diphenylpropane-1,3-diol (1.12 g, 4.95 mmol) and triethylamine (1.63 g, 14.85 mmol) in 25 mL THF at 0 °C was added methanesulfonyl chloride (1.13 g, 9.90 mmol). The mixture was kept at 0 °C for 8 h and then the solvent was removed under reduced pressure at the same temperature. The product was extracted with diethyl ether, washed with water and dried over Na_2SO_4 (1.90 g, quantitative yield). (NMR data.)

Note: Due to the rapid decomposition of methanesulfonyloxy-1,3-diphenylpropane-1,3-diol, it is important to store the material at 0 °C.

3.1.3 SYNTHESIS OF (*R,R*)-BIS(DIPHENYLPHOSPHINO)-1,3-DIPHENYLPROPANE
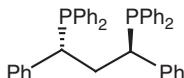
Materials and Equipment

- (*S,S*)-Methanesulfonyloxy-1,3-diphenylpropane-1,3-diol   (>98 % ee)   (1.69 g, 4.40 mmol)

- Chlorodiphenylphosphine (98 %) (3.86 g, 17.6 mmol)
- Lithium (0.74 g, 106 mmol)
- Dry THF (60 mL)
- Dry methanol (70 mL)
- Dry methylene chloride (10 mL)
- Two 100 ml Schlenk vessels with magnetic stirrer bars
- 100 mL round-bottomed flask with magnetic stirrer bar and reflux cooler
- Magnetic stirrer plate
- One Dewar flask
- Vacuum pump

Procedure

1. A solution of LiPPh$_2$ [prepared from chlorodiphenylphosphine (3.89 g, 17.6 mmol) and Li (0.74 g, 106 mmol)] was added with stirring to a solution of 1,3-dimesylate (1.69 g, 4.4 mmol) in 30 ml THF at −20 °C. The resulting solution was allowed to warm to room temperature (5 h) and then the solvent was removed under reduced pressure. The residue was washed with MeOH (30 mL) and recrystallized from MeOH–CH$_2$Cl$_2$ (4:1 mixture) to afford the product as white crystals (1.34 g, 54 % yield).

^{1}H NMR (CDCl$_3$): $\delta = 2.07$ (2H, m, CH$_2$), 3.08 (2H, m, CH), 6.61–7.42 (30 H, m, arom. H).

Table 3.1 Enantioselective hydrogenations of benchmark substrates and β-amino acid precursors using Rh(I)-[(R,R)-bis(diphenylphosphino)-1,3-diphenylpropane] as a catalyst.[a]
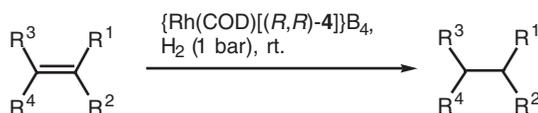
Run	R^1	R^2	R^3	R^4	Solvent	Product ee (%) (configuration)
1	COOH	CH$_2$COOH	H	H	THF	94 (R)
2	COOMe	CH$_2$COOMe	H	H	CH$_2$Cl$_2$	96 (R)
3	H	COOMe	NHAc	Me	CF$_3$CH$_2$OH	97 (S)
4	H	COOMe	NHAc	Me	CH$_2$Cl$_2$	94 (S)
5	H	COOBn	NHAc	Me	CF$_3$CH$_2$OH	96 (S)
6	H	COOBn	NHAc	Me	CH$_2$Cl$_2$	97 (S)
7	H	COOMe	Me	NHAc	CH$_2$Cl$_2$	75 (S)
8	H	COOBn	Me	NHAc	CH$_2$Cl$_2$	82 (S)

[a]Conditions: 0.01 mmol precatalyst, 1.0 mmol of prochiral olefin in 15.0 mL solvent at 25.0 °C, 1.0 atm overall pressure over the solution.

^{13}C-NMR (CDCl$_3$): $\delta = 36.3$ (CH$_2$), 43.2 (CH), 126.7–128.5 (m), 130.2, 131.1, 131.7, 135.5, 137.2.
^{31}P-NMR (CDCl$_3$): $\delta = -0.48$ (s).

Bis(diphenylphosphino)-1,3-diphenylpropane could be advantageously employed for the dibenzoylmethane hydrogenation step [yield of enantiopure diol 1.25 g (55 %) under the same reactions conditions]. Due to this cross self-breeding property and avoiding chromatographic purification large quantities of the chiral ligand can be synthesized in a cheap and convenient manner.

CONCLUSION

The procedure is fast, inexpensive and very easy to reproduce. The chiral diphosphine ligand can be synthesized on a multigram scale. The ligand has been also successfully used in enantioselective Rh(I)-catalyzed hydrogenations (Table 3.1).

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3.2   SYNTHESIS OF BOTH ENANTIOMERS OF 1-PHENYLETHANOL BY REDUCTION OF ACETOPHENENONE WITH *GEOTRICHUM CANDIDUM* IFO 5767

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Microbial reduction of ketones is a useful method for the preparation of optically active secondary alcohols. Recently, both enantiomers of secondary alcohols were prepared by reduction of the corresponding ketones with a single microbe.[1] Thus, reduction of aromatic ketones with *Geotrichum candidum* IFO 5767 afforded the corresponding *S*-alcohols in an excellent ee when Amberlite^{TM} XAD-7, a hydrophobic polymer, was added to the reaction system; the same microbe afforded

R-alcohols also in an excellent ee when the reaction was conducted under aerobic conditions (Figure 3.1).

92 - >99 % ee

77 - 92 % yield

85 - >99 % ee

56 - 99 % yield

R = Ph, *p*-BrPh, 2'-pyridyl, 4'-pyridyl, PhCH$_2$CH$_2$, PhOCH$_2$
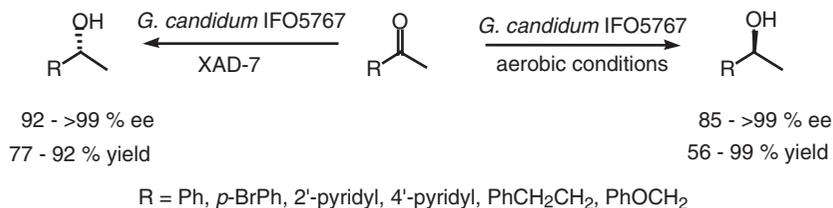
Figure 3.1

3.2.1   CULTIVATION OF *G. CANDIDUM* IFO 5767

Materials and Equipment

- Glycerol (30 g)
- Yeast extract (10 g)
- Polypeptone (5 g)
- Dipotassium hydrogenphosphate (99 %) (11.18 g)
- Potassium dihydrogenphosphate (99 %) (3.12 g)
- Stored culture of *G. candidum* IFO 5767
- Distilled water 1 L
- Filter paper
- One 100 mL test tube with a poromeric silicone plug
- One 2 L Sakaguchi flask with a poromeric silicone plug
- One Bűchner funnel, diameter 10 cm
- One Bűchner flask, 1 L
- Shaker

Procedure

1. Glycerol (30 g), yeast extract (10 g), polypeptone (5 g), potassium dihydrogen-phosphate (11.18 g), and dipotassium hydrogenphosphate (3.12 g) were dissolved with water and the volume was adjusted to 1.0 L with distilled water. A portion of the resulting solution (30 mL) was placed in a 100 mL test tube, and the rest was placed in a 2 L Sakaguchi flask with a poromeric silicone plug and sterilized (121 °C, 20 min). The solution in the test tube was incubated with *G. candidum* IFO 5767 and shaken for 24 h at 30 °C and 130 rpm. The resulting mixture was transferred to the Sakaguchi flask and shaken for 24 h at 30 °C at 130 rpm.
2. The mixture was then filtrated to obtain the cells of *G. candidum* IFO 5767 (about 18 g wet wt).

3.2.2   SYNTHESIS OF (*S*)-1-PHENYLETHANOL

Materials and Equipment

- Distilled water (90 mL)
- Acetophenone (300 mg, 2.50 mmol)
- Amberlite™ XAD-7, (18 g)
- Ethyl acetate
- Anhydrous magnesium sulfate
- Hexane/ethyl acetate
- N_2 gas
- Filter paper
- Silica gel (kieselgel 60 A 63–200 μm), 10 g
- One 100 mL vessel with screw cap
- One Bűchner funnel, diameter 10 cm
- One Bűchner flask, 500 mL
- One 300 mL separatory funnel
- Rotary evaporater
- Kugelrohr distillation equipment

Procedure

1. Acetophenone (305 mg, 2.54 mmol) and Amberlite XAD-7[2] were placed in a 100 mL vessel containing 90 mL distilled water. After 30 min, freshly prepared *G. candidum* IFO 5767 (15 g wet wt) was added to the mixture and the vessel equipped with a screw cap. The mixture was shaken at 130 rpm for 24 h at 30 °C under nitrogen.
2. The mixture was filtered and the resin and the filtrate were extracted with ethyl acetate. The organic layer was collected, dried over anhydrous magnesium sulfate and concentrated using a rotary evaporator. The crude product was purified by column chromatography over silica gel (eluent: hexane:ethyl acetate = 7:1), followed by vacuum distillation using Kugelrohr apparatus (30–33 mbar, 120 °C, cooling the recipient flask with ice)[3] (230 mg, 74% yield).

^{1}H-NMR (200 MHz, CDCl$_3$): $\delta = 1.49$ (3H, d, *J* 6.8Hz), 1.85 (1H, s) 4.90 (1H, q, *J* 6.8 Hz), 7.25–7.37 (5H, m)

3.2.3   SYNTHESIS OF (*R*)-1-PHENYLETHANOL

Materials and Equipment

- Distilled water (180 mL)
- Acetophenone (600 mg, 5.00 mmol)
- Ethyl acetate (100 mL)
- Anhydrous magnesium sulfate
- Hexane/ethyl acetate
- Filter paper
- Silica gel (kieselgel 60 A 63–200 μm), 10 g
- TLC plates (kieselgel 60 F$_{254}$)
- One 500 mL Sakaguchi flask with a poromeric silicone plug
- One Bűchner funnel, diameter 10 cm
- One Bűchner flask, 500 mL
- One 300 mL separatory funnel
- Rotary evaporater
- Kugelrohr distillation equipment

Procedure

1. Acetophenone (608 mg, 5.0 mmol) and freshly prepared *G. candidum* IFO 5767 (30 g wet wt) were placed in a 500 mL Sakaguchi flask containing 180 mL of distilled water and equipped with a poromeric silicone plug. The mixture was shaken at 130 rpm for 1 day at 30 °C.
2. The mixture was filtered and the resin and the filtrate were extracted with ethyl acetate. The organic layer were collected, dried over anhydrous magnesium sulfate and concentrated using a rotary evaporator. The crude product was purified by column chromatography over silica gel (eluent: hexane:ethyl acetate = 7:1), and then vacuum distillation using Kugelrohr apparatus (30–33 mbar, 120 °C, cooling the recipient flask with ice) to afford pure material (450 mg, 73 % yield).

Table 3.2 Microbial reduction of ketones using *G. candidum* IFO 5767 using the procedure in Section 3.2.2.

Entry	R	Product	
		Yield (%)	ee (%)(configuration)
1	*p*-Br-Ph	92	>99 (*S*)
2	PhCH$_2$CH$_2$	>99	96 (*S*)
3	PhOCH$_2$	99	>99 (*S*)
4	*o*-Pyr	98	99 (*S*)
5	*p*-Pyr	99	>99 (*S*)

Table 3.3 Microbial reduction of ketones using *G. candidum* IFO 5767 using the procedure in Section 3.2.3.

		Product	
Entry	R	Yield (%)	ee (%)(configuration)
1	*p*-Br-Ph	99	98 (*R*)
2	PhCH$_2$CH$_2$	56	85 (*R*)
3	PhOCH$_2$	82	95 (*R*)
4	*o*-Pyr	89	99 (*R*)
5	*p*-Pyr	60	>99 (*R*)

CONCLUSION

The procedure is very easy to reproduce and the asymmetric reduction may be applied to a wide range of aromatic ketones and keto esters such as ethyl 3-oxopentanoate.

Tables 3.2 and 3.3 give details of some of the different substrates that can be reduced with *G. candidum* IFO 5767.

REFERENCES

1. Nakamura, K., Takenaka, K., Fujii M. and Ida, Y. *Tetrahedron Lett*. **2002**, *43*, 3629.
2. XAD-7 was washed with 1 M hydrochloric acid, 1 M aq. sodium hydroxide, water and methanol before use.
3. Purification by column chromatography can be omitted when the reaction proceeds to completion. Vacuum distillation using Kugelrohr apparatus is needed to remove fatty acids contained in the biomass.

3.3   TITANOCENE-CATALYZED REDUCTION OF KETONES IN THE PRESENCE OF WATER. A CONVENIENT PROCEDURE FOR THE SYNTHESIS OF ALCOHOLS VIA FREE-RADICAL CHEMISTRY

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The reduction of ketones to secondary alcohols is a reaction of general interest in organic chemistry and, therefore, different methods have been described to achieve this transformation.[1] In this context, we have recently developed a novel procedure

$$Ar\text{—}\underset{R}{\overset{O}{\parallel}} \xrightarrow[\text{THF}]{\substack{\text{Cp}_2\text{TiCl (cat.)} \\ \text{H}_2\text{O or D}_2\text{O}}} Ar\text{—}\underset{R}{\overset{X\quad OH}{\diagup}}$$

X = H or D
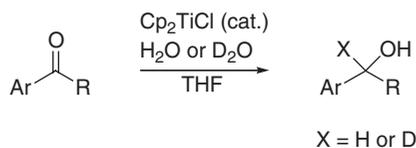
Figure 3.2

for the selective reduction of aromatic ketones and some cycloalkanones using catalytic quantities of commercially available Cp_2TiCl_2, inexpensive Mn or Zn dust, and water as hydrogen source (Figure 3.2).[2] Mechanistically the reaction is presumably initiated by $Cp_2Ti^{III}Cl$ (formed from Cp_2TiCl_2 by metal reduction) and probably proceeds via titanoxy radicals. Significantly, the hydrogen-donor ability of water under these conditions avoids the use of noxious hydrogen-atom donors generally required to reduce free radicals. The process shows an interesting selectivity pattern, takes place under mild conditions, and (obviously) does not require anhydrous solvents. This procedure is also highly convenient for synthesizing deuterium-labeled alcohols employing relatively inexpensive D_2O as the deuterium source.

3.3.1 TITANOCENE-CATALYZED REDUCTION OF ACETOPHENONE IN THE PRESENCE OF WATER

$$Ph\text{—}\underset{CH_3}{\overset{O}{\parallel}} \xrightarrow[\substack{\text{THF} \\ (70\%\ \text{yield})}]{\substack{\text{Cp}_2\text{TiCl}_2\ (20\ \text{mol}\ \%) \\ \text{Mn, H}_2\text{O, C}_8\text{H}_{11}\text{N·HCl}}} Ph\text{—}\underset{CH_3}{\overset{OH}{\diagup}}$$
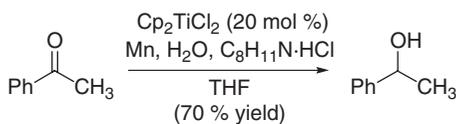
$C_8H_{11}N$ = 2,4,6-collidine

Materials and Equipment

- Acetophenone (100 mg, 0.83 mmol)
- Cp_2TiCl_2 (97 %) (41 mg, 0.16 mmol)
- Mn dust (99.9 %) (364 mg, 6.65 mmol)
- H_2O (44 mg, 2.49 mmol)
- 2,4,6-Collidine hydrochloride (>95 %) (520 mg, 3.32 mmol)
- THF (20 mL)
- t-BuOMe (50 mL)
- HCl (2 N) (5 mL)
- Brine (30 mL)
- Anhydrous Na_2SO_4
- Argon atmosphere

- Vacuum line system
- 50 mL Schlenk flask with a magnetic stirrer bar
- Magnetic stirrer plate
- 10 mL and 50 mL round-bottomed flasks
- One stainless steel cannula (1 mm diameter, 25 cm length)
- One 100 mL separatory funnel
- Silica gel and flash chromatography equipment
- Twenty 100 mL Erlenmeyer flasks
- Filter paper
- One glass funnel
- Rotary evaporator

Procedure

1. Strictly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (41 mg, 0.16 mmol) and Mn dust (364 mg, 6.65 mmol) under an Ar atmosphere, and the suspension was stirred until it turned lime green (after about 15 min). Subsequently, a mixture of acetophenone (100 mg, 0.83 mmol) and H_2O (44 mg, 2.49 mmol) in THF (5 mL), and collidine hydrochloride (520 mg, 3.32 mmol) were added to the green suspension, giving a deep blue mixture which was stirred at room temperature for 48 h. The suspension was then filtered (to recover the excess of Mn) and the solvent was removed from the filtrate; t-BuOMe (50 mL) was added to the residue and the ethereal solution was washed with 2 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed. Flash chromatography (eluent: hexane/t-BuOMe = 4/1) of the residue afforded 1-phenylethanol (71 mg, 70 % yield) and unchanged acetophenone (15 mg).

3.3.2 TITANOCENE-CATALYZED SYNTHESIS OF METHYL 4-DEUTERIO-4-PHENYL-4-HYDROXYBUTANOATE
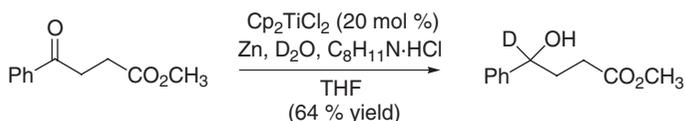
Materials and Equipment

- Methyl 4-oxo-4-phenylbutanoate (70 mg, 0.36 mmol)
- Cp_2TiCl_2 (97 %) (18 mg, 0.072 mmol)
- Zn dust (190 mg, 2.91 mmol)
- D_2O (99.7 %) (50 mg, 2.63 mmol)
- 2,4,6-Collidine hydrochloride (230 mg, 1.45 mmol)
- THF (20 mL)

- *t*-BuOMe (50 mL)
- HCl (2 N) (5 mL)
- Brine (30 mL)
- Anhydrous Na_2SO_4
- Argon atmosphere
- Vacuum line system
- 50 mL Schlenk flask with a magnetic stirrer bar
- Magnetic stirrer plate
- 10 mL and 50 mL round-bottomed flasks
- One stainless still cannula (1 mm diameter, 25 cm length)
- One 100 mL separatory funnel
- Silica gel and flash chromatography equipment
- Twenty 100 mL Erlenmeyer flasks
- Filter paper
- One glass funnel
- Rotary evaporator

Procedure

1. Strictly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (18 mg, 0.072 mmol) and Zn dust (190 mg, 2.91 mmol) under an Ar atmosphere, and the suspension was stirred until it turned lime green. Subsequently, methyl 4-oxo-4-phenylbutanoate (70 mg, 0.36 mmol) and D_2O (50 mg, 2.63 mmol) in THF (5 mL), and collidine hydrochloride (230 mg, 1.45 mmol) treated with D_2O prior to use, were added to the suspension and the mixture was stirred at room temperature for 24 h. The suspension was then filtered and the solvent was removed from the filtrate; *t*-BuOMe (50 mL) was added to the residue and the ethereal solution was washed with 2 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed. Flash chromatography (eluent: hexane/*t*-BuOMe = 1/1) of the residue afforded unchanged starting material (11 mg) and methyl 4-deuterio-4-phenyl-4-hydroxybutanoate (46 mg, 64 % yield).
   GC-MS analysis indicated 55 % deuterium incorporation.
   ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.05$ (2H, br t, J = 8 Hz), 2.42 (2H, t, J = 8 Hz), 3.66 (3H, s), 7.25–7.38 (5H, m).

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1. Larock, R. C. *Comprehensive Organic Transformations*, 2nd edn. John Wiley & Sons, Ltd: New York, **1999**.
2. Barrero, A. F., Rosales, A., Cuerva, J. M., Gansäuer, A. and Oltra, J. E. *Tetrahedron Lett.* **2003**, *44*, 1079–1082.

3.4 XYL-TetraPHEMP: A HIGHLY EFFICIENT BIARYL LIGAND IN THE [DIPHOSPHINE RuCl₂ DIAMINE]-CATALYZED HYDROGENATION OF SIMPLE AROMATIC KETONES

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The ruthenium(II)-dihalide bisphosphine catalyzed asymmetric reduction of functionalized ketones such as ß-keto esters, is one of the best-understood and industrially successful transition metal catalyzed asymmetric transformations due to the high reactivities and selectivities that are observed.[1] The ability to form metal–substrate chelate complexes via a carbonyl group and a second binding site is crucial for both reactivity and enantioselectivity. Until recently no generally applicable and efficient transition metal catalyzed asymmetric hydrogenation protocol existed for simple unfunctionalized ketones without a secondary binding site. In 1995 Noyori described a molecular catalyst system based on [diphosphine RuCl₂ diamine] (**A**) which could effectively reduce unfunctionalized ketones.[2] The chiral version of this technology contains both a chiral diphosphine ligand and a chiral diamine. The chirality of the diphosphine ligand and chiral diamine has to be matched to effect the highest rates and enantioselectivities for any given substrate.[3] In general xylyl-substituted diphosphines such as Xyl-BINAP (**1**)[1b] or Xyl-PhanePhos (**2**)[4] together with the diamines DPEN (**4**) and DIAPEN (**5**) can produce exceptional reactivities and selectivities in the reduction of simple ketones (Figure 3.3). Recently a new xylyl-substituted ligand, Xyl-TetraPHEMP (**3**),[5] prepared via a non-traditional
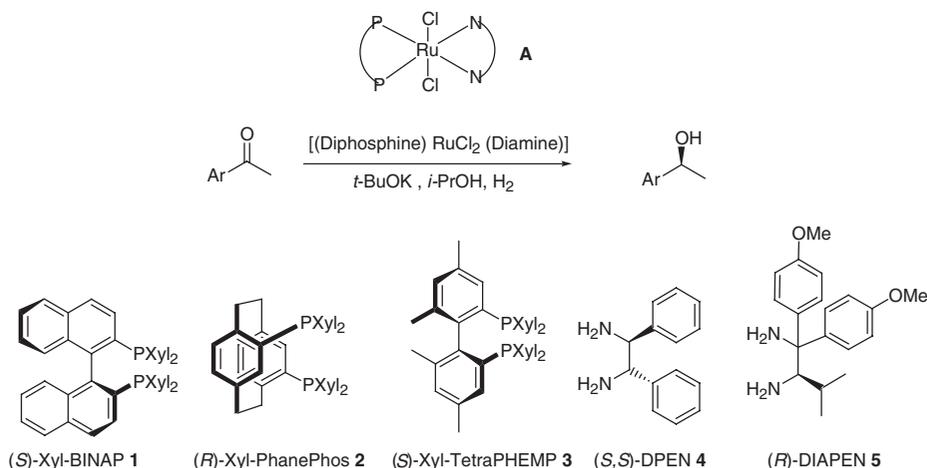
Figure 3.3

route for biaryl-diphosphines, was shown to be a highly efficient ligand in the synthesis of 1-aryl alcohols utilizing the Noyori [diphosphine RuCl$_2$ diamine] hydrogenation protocol. The synthesis of Xyl-TetraPHEMP (**3**) and an example ketone hydrogenation are shown below.

3.4.1 SYNTHESIS OF TRI(3,5-DIMETHYLPHENYL)PHOSPHINE OXIDE
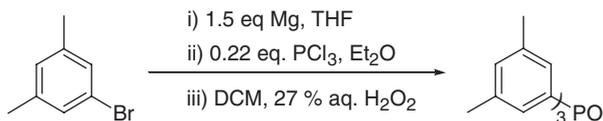
Materials and Equipment

- Magnesium turnings (freshly activated) (13.42 g, 552 mmol)
- 1-Bromo-3,5-dimethylbenzene (68.10 g, 368 mmol)
- Phosphorus trichloride (11.26 g, 82.0 mmol)
- Hydrogen peroxide (27 %) (94.3 mL)
- Anhydrous THF (40 mL and 100 mL)
- Anhydrous diethyl ether (40 mL)
- *tert*-Butyl methyl ether (400 mL and 200 mL)
- Dichloromethane (200 mL)
- Heptane (80 mL)
- Distilled water (100 mL)
- Dilute hydrochloric acid
- Brine solution
- Aqueous sodium metabisulfite
- Anhydrous magnesium sulfate
- Magnetic stirrer plate
- Nitrogen manifold
- Condenser
- 1 L three-necked round-bottomed flask
- 500 mL round-bottomed flask
- 150 mL round-bottomed flask
- Pressure-equalized dropping funnel X3
- Separating funnel X2
- Sinter funnel X2

Procedure

1. To a 1 L three-necked round-bottomed flask with condenser, under a N$_2$ atmosphere, containing 40 mL THF and Mg turnings (13.42 g, 552 mmol) 1-bromo-3,5-dimethylbenzene (13.62 g, 73.6 mmol) was added with stirring at a rate such

that a gentle reflux was maintained. After addition of the neat bromide a solution of 1-bromo-3,5-dimethylbenzene (54.48 g, 294.4 mmol) in THF (100 mL) was added over a 1 h period followed by 1 h stirring. The solution was cooled to 0 °C and a solution of PCl_3 (11.26 g, 82 mmol) in Et_2O (40 mL) was added dropwise and stirred for 20 h. The reaction mixture was quenched with 100 mL H_2O and stirred for 10 min before adding 400 mL t-BME. The organic and aqueous layers were separated. The aqueous layer was acidified with dilute HCl and diluted with 200 mL brine before extracting with 200 mL t-BME. The organic layers were combined and dried with $MgSO_4$. The solution was filtered and the solvent removed *in vacuo* to yield a yellow solid.

2. The yellow solid was dissolved in 200 mL dichloromethane in a 500 mL round-bottomed flask and cooled to 0 °C before cautiously adding 94.3 mL of 27 % aqueous H_2O_2 over 1.5 h. The layers were separated and the organic layer washed with dilute aq. $Na_2S_2O_5$ (100 mL) and brine (100 mL). The organic layer was dried with $MgSO_4$ and filtered before removing the solvent *in vacuo*. The crude product was dissolved in 80 mL of boiling heptane and cooled to room temperature to yield a white crystalline solid. The product was collected by filtration to yield the title compound (77 %, 22.83 g, 62.99 mmol based on PCl_3).

^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (18 H, s, CH_3), 7.15 (3 H, s, ArH), 7.26 (3H, s, ArH), 7.29 (3H, s, ArH).

^{31}P-NMR (162 MHz, $CDCl_3$): $\delta = 30.9$ ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 129.5 (d, $J = 9.8$ Hz), 131.9, 133.0, 133.4 (d, $J = 2.5$ Hz), 137.9 (d, $J = 12.7$).

LCMS (APCi: MeCN/H_2O): 363 (100 %, M + H)$^+$.

3.4.2   SYNTHESIS OF BIS(3,5-DIMETHYLPHENYL)-(2-IODO-3,5-DIMETHYLPHENYL)PHOSPHINE OXIDE
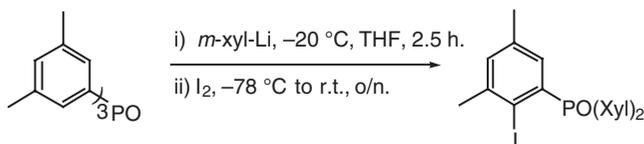
Materials and Equipment

- 1-Bromo-3,5-dimethylbenzene (750 mg, 4.19 mmol)
- *tert*-Butyllithium 1.7 M (4.93 mL, 8.38 mmol)
- Tri(3,5-dimethylphenyl)phosphine oxide (460 mg, 1.27 mmol)
- Iodine (1.17 g, 4.61 mmol)

- Anhydrous THF (6 mL, 4 mL and 7.5 mL)
- Dichloromethane (90 mL)
- Methanol (2 mL)
- Aqueous sodium thiosulfate (20 mL)
- Brine (30 mL)
- Distilled water (100 mL)
- Magnesium sulfate
- *tert*-Butyl methyl ether / heptane
- Silica
- Magnetic stirrer plate
- Nitrogen manifold
- Dewar flask
- Syringe and syringe pump
- 150 mL three-necked round-bottomed flask
- 25 mL round-bottomed flask
- Double ended cannula
- Separating funnel
- Sinter funnel
- 150 mL round-bottomed flask
- Glass chromatographic column and test tubes

Procedure

1. A solution of 1-bromo-3,5-dimethylbenzene (775 mg, 4.19 mmol) in degassed, anhydrous THF (6 mL) at –78 °C in a 25 mL round-bottomed flask under nitrogen was treated dropwise with 1.7 M *t*-BuLi (4.93 mL, 8.38 mmol). The resulting solution was stirred for 40 min at –78 °C before transferring via cannula to a cooled solution (–78 °C) of tri(3,5-dimethylphenyl)phosphine oxide (460 mg, 1.27 mmol) in anhydrous THF in a 150 ml round-bottomed flask. The solution was warmed to –20 °C and stirred for 2 h. The resulting solution was cooled to –78 °C before adding dropwise a solution of I_2 (1.17 g, 4.61 mmol) in 7.5 mL anhydrous THF. The solution was stirred overnight and allowed to warm to room temperature. The reaction was quenched with 2 mL MeOH and diluted with 90 mL dichloromethane before washing with aq. $Na_2S_2O_3$ (20 mL), H_2O (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a brown viscous oil. The crude material was purified via column chromatography using silica gel and eluting with 3:2 *t*-BME/heptane to yield the title compound as a white foam (459 mg, 0.94 mmol, 74 %).

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 2.09$ (3H, s, C*H*$_3$), 2.24 (12H, s, C*H*$_3$), 2.37 (3H, s, C*H*$_3$), 6.72 (1H, appears as two 0.5H finely slip signals at 6.70 and 6.73, Ar*H*), 7.07 (2H, s, Ar*H*), 7.11 (1H, s, Ar*H*), 7.20 (2H, s, Ar*H*), 7.23 (2H, s, Ar*H*).
^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = 36.1$.
LCMS (APCi: MeCN/H$_2$O): 489 (100 %, M + H)$^+$, 490 (30 %).

3.4.3   SYNTHESIS OF *RAC*-4,4′,6,6′-TetraMETHYL-2,2′-BIS[BIS(3,5-DIMETHYLPHENYL)PHOSPHINOYL]-BIPHENYL
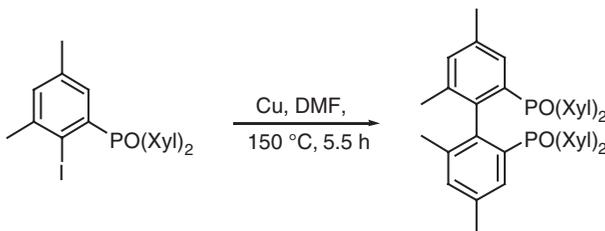
Materials and Equipment

- Bis(3,5-dimethylphenyl)-(2-iodo-3,5-dimethylphenyl)phosphine oxide (2.00 g, 4.1 mmol)
- Activated copper (0.78g, 12.29 mmol)
- Anhydrous *N,N*-dimethylformamide (DMF) (20 mL)
- Dichloromethane (10 mL)
- *tert*-Butyl methyl ether (*t*-BME)/ heptane
- Silica gel
- 150 mL Schlenk tube X2
- Stirrer hot plate and oil bath
- Vacuum pump
- Nitrogen manifold
- Schlenk filter
- Glass chromatographic column and test tubes

Procedure

1. A 150 mL Schlenk tube containing bis(3,5-dimethylphenyl)-(2-iodo-3,5-dimethylphenyl)phosphine oxide (2.00 g, 4.10 mmol), activated Cu powder (0.78 g, 12.29 mmol) and anhydrous DMF (20 mL) under nitrogen was heated (oil bath temperature at 150 °C) for 5.5 h. The product mixture was allowed to cool to room temperature, filtered and evaporated giving an oily residue which was diluted with dichloromethane (10 mL) and filtered. The solvent was evaporated providing an off-white foam (1.66 g). This residue was chromatographed on a column of silica gel eluting with 65:35 t-BME/heptane yielding 1.39 g of the title compound as a white foam (1.92 mmol, 94 %).

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 1.68$ (6H, s, CH_3), 2.03 (12H, s, CH_3), 2.21 (6H, s, CH_3), 2.29 (12H, s, CH$_3$), 6.85 (2H, s, ArH), 6.93 (2H, s, ArH), 7.09 (5H, s, ArH), 7.12 (3H, s, ArH), 7.34 (2H, s, ArH), 7.37 (2H, s, ArH).
^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = 31.1$ ppm.
LCMS (APCi: MeCN/H$_2$O): 723 (100%, M + H)$^+$, 724 (53%).

3.4.4   SYNTHESIS OF *RAC*-4,4′,6,6′-TETRAMETHYL-2,2′-BIS[BIS(3,5-DIMETHYLPHENYL)PHOSPHINO]-BIPHENYL [ABBREVIATED TO (*RAC*)-XYL-TetraPHEMP]
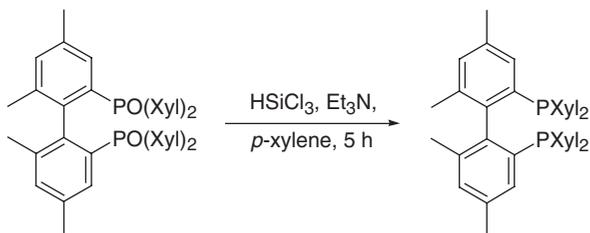
Materials and Equipment

- *rac*-4,4′,6,6′-Tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphinoyl]-biphenyl (1.00 g, 1.38 mmol)
- Triethylamine (3.09 g, 30.57 mmol)
- Trichlorosilane (93 g, 29.05 mmol)
- Anhydrous toluene (15 mL)
- 30 % Aqueous sodium hydroxide (30 mL)
- *tert*-Butyl methyl ether (*t*-BME) (3 × 15 mL)
- Magnesium sulfate
- 100 mL Schlenk tube
- Condenser
- Stirrer hot plate and oil bath
- Vacuum pump
- Nitrogen manifold
- Schlenk filter
- Glass chromatographic column and test tubes

Procedure

1. A solution of 6,6′-bis[bis(3,5-dimethylphenyl)phosphinoyl]-2,4,2′,4′-tetra-methylbiphenyl (1.00 g, 1.38 mmol) in anhydrous toluene (15 mL) in a 100 mL Schlenk flask fitted with a reflux condenser was treated cautiously with Et₃N (3.09 g, 30.57 mmol) and HSiCl₃ (3.93 g, 29.05 mmol). The suspension was heated to reflux (oil bath temperature 120°C) and stirred for 22 h under a nitrogen atmosphere. The reaction was cooled to room temperature and 30 mL of 30 % aq. NaOH was cautiously added and stirred for 15 min. The aqueous and organic layers were separated and the aqueous fraction was extracted with 3 × 15 mL *t*-BME. The combined organic fractions were dried (MgSO₄), filtered under a nitrogen atmosphere and evaporated to give a white foam. The product was chromatographed on a column of silica gel providing the desired product as a white foam (767 mg, 1.04 mmol, 76 %).

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 1.51$ (6H, s, CH_3), 2.12 (12H, s, CH_3), 2.22 (12H, s, CH_3), 2.26 (6H, s, CH_3), 6.77 (2H, s, ArH), 6.80 (4H, m, ArH), 6.86 (4H, m, ArH), 6.89 (2H, s, ArH), 6.92 (2H, s, ArH), 6.95 (2H, s, ArH).
^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = -13.4$ ppm.
LCMS (APCi: MeCN/H$_2$O):691 (100 %, M + H)$^+$, 692 (58 %).

3.4.5 SYNTHESIS OF [(R)-N,N-DIMETHYL(1-METHYL)BENZYLAMINATO-C^2,N]-{RAC-4,4′,6,6′-TETRAMETHYL-2,2′-BIS[BIS(3,5-DIMETHYLPHENYL)PHOSPHINO]-BIPHENYL}-PALLADIUM(II) TETRAFLUOROBORATE AND SEPARATION OF THE DIASTEREOMERS
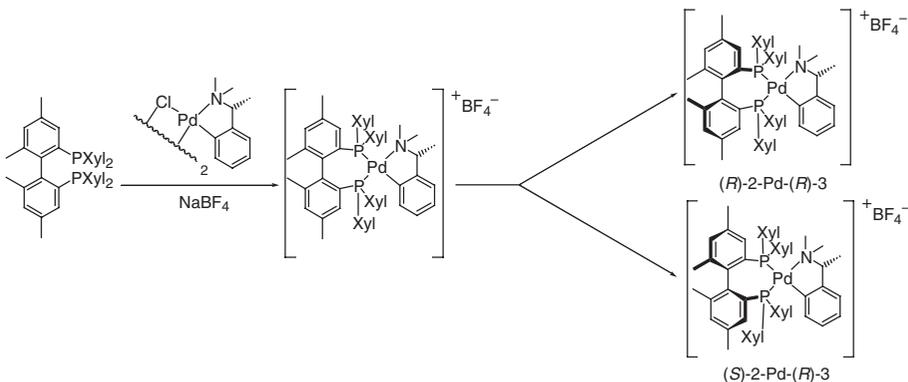
Materials and Equipment

- rac-4,4′,6,6′-Tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl (1.28 g, 1.85 mmol)
- Di-μ-chloro-bis[(R)-dimethyl(1-methyl)benzylaminato-C^2, N]dipalladium(II) (0.63 g, 1 mmol)
- Sodium tetrafluoroborate (0.96 g, 8.7 mmol)
- Methanol (80 mL)
- Deionized water (50 mL)
- Dichloromethane (3 × 50 mL and 50 mL)
- Magnesium sulfate
- tert-Butyl methyl ether/toluene (4/1)
- Silica gel
- Stirrer hot plate and oil bath
- 150 mL Schlenk tube
- Nitrogen manifold
- Glass sinter
- Glass chromatographic column & test tubes

Note: Use only deionized H$_2$O, as anion exchange can take place between BF$_4^-$ and dissolved salts in H$_2$O.

Procedure

1. *rac*-4,4′,6,6′-Tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl (1.28 g, 1.85 mmol) and di-μ-chloro-bis[(R)-dimethyl(1-methyl)benzylaminato-C^2,N]dipalladium(II) (0.63g, 1 mmol) were dissolved in MeOH (80 mL) and stirred at 45 °C for 6 h. The clear solution was stirred at room temperature for a further 2 days, then NaBF$_4$ (0.96 g, 8.7 mmol) was added. The reaction was heated to 45 °C for 2 h, then the solvent was concentrated under reduced pressure to ∼10 mL. Deionized H$_2$O (50 mL) was added. A solid precipitated and was collected by filtration (crop 1). The mother liquor was extracted with dichloromethane (3 × 50 mL). The solid obtained in crop 1 was dissolved in dichloromethane (50 mL) and all the organic fractions combined and dried over magnesium sulfate, filtered and evaporated to produce a pale yellow solid residue (1.69 g, 92 % yield).

^{31}P-NMR (400 MHz, CDCl$_3$): $\delta = 39.8$ (d, $J = 45$ Hz), 39.2 (d, $J = 45$ Hz), 11.8 (d, $J = 45$ Hz), 9.7 (d, $J = 45$ Hz).

2. The diastereoisomers of [(R)-N,N-dimethyl(1-methyl)benzylaminato-C^2,N]-{*rac*-4,4′,6,6′-tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl}-palladium(II) tetrafluoroborate (2.19 g, 2.20 mmol) were separated by chromatography (eluent: *t*-BME/toluene 4/1) to produce 0.925 g of the first diastereoisomer (42 % yield) and 0.94 g of the second eluted diastereoisomer (44 % yield).

First eluted diastereoisomer: [(R)-N,N-dimethyl(1-methyl)benzylaminato-C^2,N]-{(S)-4,4′,6,6′-tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl}-palladium(II) tetrafluoroborate.

^{31}P-NMR (400 MHz, CDCl$_3$): $\delta = 39.8$ (d, $J = 45$ Hz), 39.2 (d, $J = 45$ Hz), 11.8 (d, $J = 45$ Hz), 9.7 (d, $J = 45$ Hz).

^{1}H-NMR (400 MHz, CDCl$_3$) distinctive signal at $\delta = 5.15$ (q, N-C*H*-CH$_3$).
Second eluted diastereoisomer: [(R)-N,N-dimethyl(1-methyl)benzylaminato-C^2,N]-{(R)-4,4′,6,6′-tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl}-palladium(II) tetrafluoroborate.

^{31}P-NMR (400 MHz, CDCl$_3$): $\delta = 39.2$ (d, $J = 45$ Hz), 11.8 (d, $J = 45$ Hz).
^{1}H-NMR (400 MHz, CDCl$_3$): distinctive signal at $\delta = 3.5$ (m, N-C*H*-CH$_3$).

3.4.6 SYNTHESIS OF (S)-4,4′,6,6′-TETRAMETHYL-2,2′-BIS[BIS(3,5-DIMETHYLPHENYL)PHOSPHINO]-BIPHENYL [ABBREVIATED TO (S)-XYL-TetraPHEMP] AND (R)-4,4′,6,6′-TETRAMETHYL-2,2′-BIS[BIS(3,5-DIMETHYLPHENYL)PHOSPHINO]-BIPHENYL [ABBREVIATED TO (R)-XYL-TetraPHEMP]

(R)-2-Pd-(R)-3   (R)-Xyl-TetraPHEMP   (S)-2-Pd-(R)-3   (S)-Xyl-TetraPHEMP
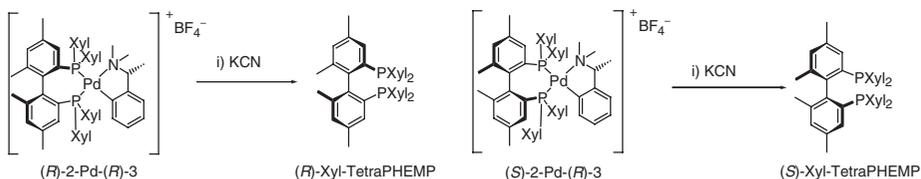
Materials and Equipment

- [(R)-N,N-Dimethyl(1-methyl)benzylaminato-C^2,N]-{(S)-4,4′,6,6′-tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl}-palladium(II) tetrafluoroborate (0.91 g, 0.91 mmol)
- 37 % Hydrochloric acid (1.5 mL)
- Saturated sodium hydrogencarbonate (30 mL)
- Deionized water (30 mL, 3 × 30 mL, 10 mL and 5 × 30 mL)
- Potassium cyanide (0.95 g, 14.6 mmol)
- Anhydrous dichloromethane (30 mL)
- Toluene (3 × 20 mL)
- Sodium sulfate
- Silica gel
- Bleach solution
- Two 250 mL Schlenk tubes
- Magnetic stirrer plate
- Nitrogen manifold
- Schlenk filter

Note: Use of cyanide. Handle in a well-ventilated fume hood and use appropriate disposal procedures. Refer to MSDS.

Procedure

1. [(R)-N,N-Dimethyl(1-methyl)benzylaminato-C^2,N]-{(S)-4,4′,6,6′-tetramethyl-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-biphenyl}-palladium(II) tetrafluoroborate (0.91 g, 0.91 mmol) was dissolved in anhydrous dichloromethane (30 mL). HCl (37 %, 1.5 mL) was added and the reaction was stirred at room temperature for 2.5 h. The dichloromethane solution was washed with degassed, deionized H$_2$O (30 mL), NaHCO$_3$ saturated solution (30 mL) and further deionized H$_2$O (3 × 30 mL). KCN (0.95 g, 14.6 mmol) and degassed, deionized H$_2$O (10 mL) were added and the reaction was stirred for 5 h at room temperature. The aqueous layer was removed and the dichloromethane solution was washed with degassed, deionized H$_2$O (5 × 30 mL) then evaporated to dryness. Anhydrous Na$_2$SO$_4$ was added to the resulting off-white solid residue and the mixture of solids was extracted with anhydrous toluene (3 × 20 mL). The toluene solution was filtered through a 5 cm silica gel plug. Evaporation of the solvent gave 0.38 g of product (60 % yield). All operations were carried out under a N$_2$ atmosphere. All aqueous solutions and contaminated glassware were quenched with bleach.

   The spectroscopic data were identical to the ones observed for the racemic mixture. A sample was oxidized with hydrogen peroxide and analyzed by HPLC for enantiomeric purity (e.e. > 98 %).

(*R*)-Xyl-TetraPHEMP: The title compound was prepared by a reaction analogous to this procedure.

^{1}P-NMR (162 MHz, CDCl$_3$): $\delta = -13.4$.

3.4.7   SYNTHESIS OF [(*R*)-XYL-TetraPHEMP RUCL$_2$ (*R,R*)-DPEN] AND [(*S*)-XYL-TetraPHEMP RuCl$_2$ (*S,S*)-DPEN]
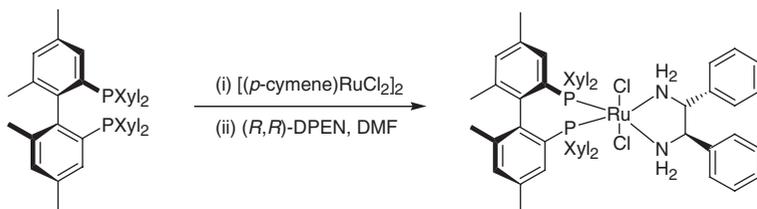
Materials and Equipment

- (*R*)-Xyl-TetraPHEMP (100 mg, 0.14 mmol)
- Di-μ-chlorobis[(*p*-cymene)chlororuthenium (II)] (44.3 mg, 0.072 mmol)
- (*R,R*)-1,2-Diphenylethylenediamine (35 mg, 0.14 mmol)
- Anhydrous *N,N*-dimethylformamide
- Anhydrous acetone
- Silica gel
- Two 25 mL Schlenk tubes
- Schlenk filter
- Vacuum pump
- Magnetic stirrer plate
- Nitrogen manifold

Procedure

1. A Schlenk tube under nitrogen containing 100 mg (0.14 mmol) of (*R*)-Xyl-TetraPHEMP and 44.3 mg (0.072 mmol) of [(*p*-cymene)RuCl$_2$]$_2$ and 5 mL of dry, degassed DMF was heated to 110 °C for 3 h before 35 mg (0.14 mmol) of (*R,R*)-DPEN were added in one portion. The dark red/brown solution turned yellow. The solution was stirred for 1 h while cooling to room temperature. DMF was removed under reduced pressure. The crude product was dissolved in degassed acetone and filtered under nitrogen through a plug of silica to give the product as an orange/yellow solid. The yield was 78 mg, 50 %.

^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = 45.1$ ppm.

[(S)-Xyl-TetraPHEMP RuCl$_2$ (S,S)-DPEN]: The title compound was produced by the same procedure giving identical spectroscopic data.

It is advisable to filter the crude product rapidly to avoid decomposition.

3.4.8   REDUCTION OF ACETOPHENONE USING [(S)-XYL-TetraPHEMP RuCl$_2$ (S,S)-DPEN] AS A PRECATALYST
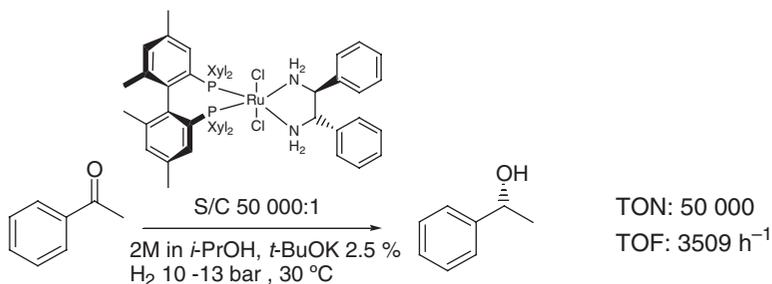
Materials and Equipment

- [(S)-Xyl-TetraPHEMP RuCl$_2$ (S,S)-DPEN] (17.9 mg, 0.0166 mmol, 2×10^{-5} equiv)
- Potassium *tert*-butoxide 1 M in *tert*-butanol (20.75 mL, 20.75 mmol, 0.025 equiv)
- Acetophenone (distilled) (100 g, 832.3 mmol, 1 equiv)
- Isopropyl alcohol, HPLC grade (283.3 mL and 10 mL)
- 600 mL Parr hydrogenation vessel with jacket heater
- Overhead mechanical stirrer
- Water circulator
- Glass liner
- Nitrogen manifold
- 15 mL Schlenk tube
- Magnetic stirrer plate

Procedure

1. A 600 mL Parr hydrogenation vessel equipped with an injection port with a rubber septum for the addition of the solvent via syringe, a pressure gauge, a tightly fitting removable internal glass liner, thermocouple and an overhead mechanical stirrer was assembled and pressure tested to 14 bar with N$_2$ over

60 min. The liner was removed and charged with 100 g of acetophenone (832.3 mmol) and isopropanol (283.3 mL). The vessel was reassembled and purged with nitrogen six times, by pressurizing to 10 bar and releasing the pressure. Then 20.75 mL of the 1 M *t*-BuOK solution was added through the injection port and the vessel was purged twice with N_2. The vessel was heated to 30 °C. A solution of [(*S*)-Xyl-TetraPHEMP RuCl$_2$ (*S,S*)-DPEN] (17.9 mg, 0.0166 mmol) in isopropyl alcohol (10 mL) was prepared under N_2 and was added and the vessel via the injection port was purged five times with hydrogen. The reaction flask was pressurized to 13 bar and maintained between 10 and 13 bar with vigorous stirring until no further hydrogen was consumed (14.5 h). The vessel was depressurized and purged three times with N_2. An aliquot was taken for GC analysis. Conversions and ees were determined using chiral GC analysis [Chirasil DEX-CB column; 100 °C for 7 min, then 15 °C min^{-1} to 200 °C: 9.9 min (*R*), 10.1 (*S*)] analysis. The stereochemistry of 1-phenyl-ethanol was assigned by comparison with commercially available (*R*)-1-phenyl-ethanol (Aldrich). Analysis reveals >99 % conversion and 97 % ee (*R* enantiomer).

CONCLUSION

The non-traditional synthetic route to Xyl-TetraPHEMP is an expedient way to assemble a xylyl-substituted atropisomeric biaryl bisphosphine ligand, introducing both axial chirality and a xylyl-substitution pattern in one synthetic step. When used in conjunction with the matching enantiomer of the chiral diamine DPEN in the Noyori [diphosphine RuCl$_2$ diamine]-catalyzed ketone hydrogenation, the ligand Xyl-TetraPHEMP exhibits the expected high reactivity and selectivity associated with xylyl-substituted biaryl bisphosphine ligands. In the asymmetric reduction of acetophenone an industrially acceptable high substrate to catalyst ratio (50 000:1) can be easily achieved with complete conversion and excellent enantioselectivity.

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3. In the reduction of 1′-acetonaphthone the combinations (*S*)-BINAP/(*S,S*)-DPEN and (*S*)-BINAP/(*R,R*)-DPEN gave enantioselectivities of 97 % and 12 %, respectively (see ref. [2b], p. 52).
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3.5 *N*-ARENESULFONYL- AND *N*-ALKYLSULFAMOYL-1,2-DIPHENYLETHYLENEDIAMINE LIGANDS FOR RUTHENIUM-CATALYZED ASYMMETRIC TRANSFER HYDROGENATION OF ACTIVATED KETONES

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A variety of optically active secondary alcohols could be prepared via ruthenium-catalyzed asymmetric transfer hydrogenation using HCO$_2$H-Et$_3$N 5:2 or 2-propanol. High ees are attained using ruthenium catalysts based on chiral 1,2-diphenylethylenediamine (DPEN) such as Noyori's Ts-DPEN ligand (**1a**) or *N*-arenesulfonyl- (**1b–f**) and *N*-alkylsulfamoyl-DPEN (**2a,b**) ligands (Figure 3.3).[1–3]

3.5.1 SYNTHESIS OF *N*-ARENESULFONYL-1,2-DIPHENYLETHYLENEDIAMINES

Materials and Equipment

- (1*S*,2*S*)-Diphenylethylenediamine (DPEN) (21.23 g, 0.10 mol)
- Arenesulfonyl chloride (0.105 mmol)
- Dichloromethane (180 mL)
- Saturated aqueous sodium carbonate

a: R= *p*-Me-C$_6$H$_4$ (Ts-DPEN)
b: R= *p*-NO$_2$-C$_6$H$_4$
c: R= 2,4,6-Cl$_3$-C$_6$H$_2$
d: R= 2,4,6-(MeO)$_3$-C$_6$H$_2$
e: R= 2,4,6-^{i}Pr$_3$-C$_6$H$_2$
f: R=

(*S*,*S*)-DPEN-SO$_2$

a: R= Me
b: RR= -(CH$_2$)$_5$-
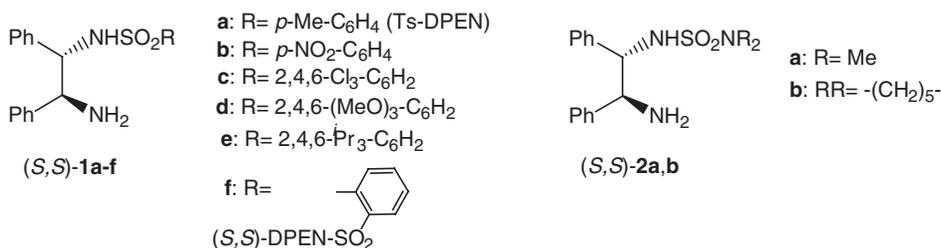
Figure 3.3 Reprinted from reference [1], with permission from Elsevier.

- Anhydrous sodium sulfate
- Silica Gel 60 (Merck), 200 g
- Dichloromethane, ethyl acetate
- Diisopropyl ether
- Standard organic laboratory glassware and equipment

Procedure

1. A 500 mL round-bottomed flask equipped with a magnetic stirring-bar was charged with (1*S*,2*S*)-DPEN (0.10 mmol; in case of **1f**, 0.20 mmol) and CH_2Cl_2 (100 mL). The arenesulfonyl chloride (0.105 mmol) in CH_2Cl_2 (80 mL) was added via cannula over 10 min and the resulting mixture was left to stir at room temperature overnight.
2. The reaction mixture was washed with saturated aqueous Na_2CO_3 (2 × 90 mL), dried over Na_2SO_4, concentrated, and the residue purified by column chromatography (over silica gel, eluent: CH_2Cl_2/EtOAc 20:1). The product was recrystallized from $^iPr_2O$ (yield: **1c**, 66 %; **1e**, 85 %; **1f**, 51 %; **2a**, 55 %).

^{1}H-NMR (300 MHz, $CDCl_3$): $\delta =$ for **1c**: 4.29 (1H, d, $J = 4.2$ Hz), 4.71 (1H, d, $J = 4.2$ Hz), 7.10–7.27 (12H, m); **1e**: 1.08, 1.17 and 1.21 (6H, 3d, $J = 6.6$, 6.9 Hz), 2.83 (1H, hept, $J = 6.6$ Hz), 3.95 (2H, hept, $J = 6.6$ Hz), 3.97 (1H, d, $J = 7.5$ Hz), 4.49 (1H, d, $J = 7.5$ Hz), 6.82, 7.00 and 7.17 (12H, 3m); **1f**: 4.18 (2H, d, $J = 4.6$ Hz), 4.54 (2H, d, $J = 4.6$ Hz), 6.92, 7.12, 7.20 and 7.33 (24H, 4m); **2a**: 2.33 (6H, s), 4.15 (1H, d, $J = 5.9$ Hz), 4.44 (1H, d, $J = 5.9$ Hz), 7.21–7.33 (10H, m).

3.5.2 PREPARATION OF Ru(II)-*N*-ARENESULFONYL-1,2-DIPHENYLETHYLENEDIAMINE COMPLEXES

Materials and Equipment

- *N*-Arenesulfonyl-1,2-diphenylethylenediamine (0.21 mmol)
- Dichloro(*p*-cymene)ruthenium(II) dimer (61 mg, 0.10 mmol)
- *N,N*-Dimethylformamide (30 mL)
- Standard organic laboratory glassware and equipment

Procedure

1. A 100-mL round-bottomed flask equipped with a magnetic stirring-bar was charged with $RuCl_2$(*p*-cymene)$_2$ (61 mg, 0.10 mmol),[4] (1*S*,2*S*)-*N*-arenesulfonyl-1,2-diphenylethylenediamine (0.21 mmol) and DMF (30 mL). The mixture was degassed by back-filling with nitrogen and heated at 80 °C for 30 min. The tinted solution was cooled to room temperature.
2. The complex can be used as such (i.e. in solution) or after evaporation under vacuum.

3.5.3 ASYMMETRIC TRANSFER HYDROGENATION OF ETHYL BENZOYLACETATE

98 % ee
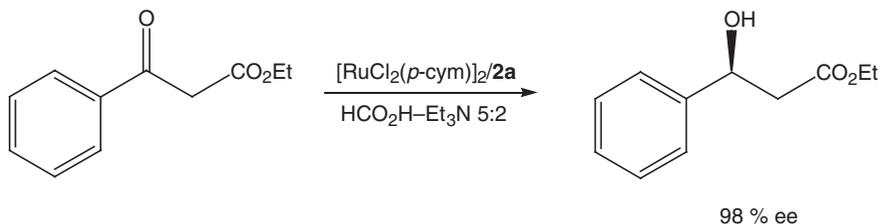
Materials and Equipment

- (1*S*,2*S*)-*N*-(Dimethylsulfamoyl)-1,2-diphenylethylenediamine (55 mg, 172 μmol)
- Dichloro(*p*-cymene)ruthenium(II) dimer (50 mg, 82 μmol)
- *N,N*-Dimethylformamide (20 mL)
- Ethyl benzoylacetate (5.2 mL, 30 mmol)
- HCO_2H–Et_3N (5:2, 15 mL)
- Dichloromethane
- Brine
- Anhydrous magnesium sulfate
- Standard organic laboratory glassware and equipment

Procedure

1. A 100-mL round-bottomed flask equipped with magnetic stirring-bar was charged with [$RuCl_2$(*p*-cymene)]$_2$ (50 mg, 82 μmol), (1*S*,2*S*)-*N*-(dimethylsulfamoyl)-1,2-diphenylethylenediamine (55 mg, 172 μmol) and DMF (20 mL). The mixture was degassed by back filling with nitrogen and heated at 80 °C for 30 min. The dark-orange solution was cooled to room temperature and ethyl benzoylacetate (5.2 mL, 150 mmol) and HCO_2H–Et_3N (5:2, 15 mL) were successively added. The mixture was left to stir at room temperature (25 °C) for 24 h with a continuous nitrogen stream.
2. The reaction mixture was partitioned between diethyl ether (60 mL) and water (30 mL). The organic layer was washed with water (2 × 30 mL), brine (30 mL), and dried over $MgSO_4$. After concentration on a rotary evaporator, the oily residue was distilled using a Kugelrohr apparatus (120°/0.07 mbar) to yield 5.35 g (92 %) of (*S*)-ethyl 3-hydroxy-3-phenylpropanoate with 98 % ee.

Gas chromatography analysis showed total consumption of starting ethyl benzoylacetate and 98 % ee of (*S*)-ethyl 3-hydroxy-3-phenylpropanoate [Chirasil-DEX CB (25 m) column: 140 °C, 22.1 min (*S*), 23.0 min (*R*)].

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 1.27$ (3H, t, $J = 7.2$ Hz), 7.23 and 7.74 (2H, 2d, $J = 4.4$ and 8.2 Hz), 3.27 (1H, br s), 4.19 (2H, q, $J = 7.2$ Hz), 5.14 (1H, dd, $J = 4.6$, 8.2 Hz), 7.26–7.41 (5H, m).

Table 3.4   [RuCl$_2$(*p*-cymene)]$_2$-RSO$_2$-DPEN catalyzed asymmetric transfer hydrogenation of activated ketones R^{1}COR^2.

Entry	R^1	R^2	Ligand	Product	
				Yield (%)	ee (%)
1	Ph	Me	**1e**	100	96
2	2-Furyl	CO$_2$Et	**1c** or **1f**	100	94
3	PhCH$_2$	CF$_3$	**1f**	100	98
4	Ph	CH$_2$CO$_2$Et	**2a**	100	98
5	CF$_3$	CH$_2$CO$_2$Et	**2b**	100	98

CONCLUSION

These ligands and their ruthenium complexes are easy to prepare and are useful in asymmetric transfer hydrogenation of a variety of activated ketones. Table 3.4 shows a selection of substrates that can be reduced with the Ru(II)-RSO$_2$-DPEN complexes using HCO$_2$H–Et$_3$N 5:2.

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3. The equivalent ruthenium complex can be prepared from [RuCl$_2$(η^6-arene)]$_2$ precursors where η^6-arene = benzene, mesitylene, hexamethylbenzene.
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3.6   THE SYNTHESIS AND APPLICATION OF BrXuPHOS: A NOVEL MONODENTATE PHOSPHORUS LIGAND FOR THE ASYMMETRIC HYDROGENATION OF KETONES

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The asymmetric hydrogenation of ketones is one of the most powerful methods for the formation of enantiomerically pure alcohols.[1] The use of the novel monodentate phosphorus ligand, BrXuPHOS (1),[2] in a ruthenium(II) complex (*S, S, SS*)-BrXuPHOS-Ru-DPEN (4), furnishes a catalyst for the asymmetric hydrogenation of simple ketones, giving the corresponding alcohols at a substrate/catalyst ratio of up to 10 000 with enantioselectivities of up to 99 %.[3]
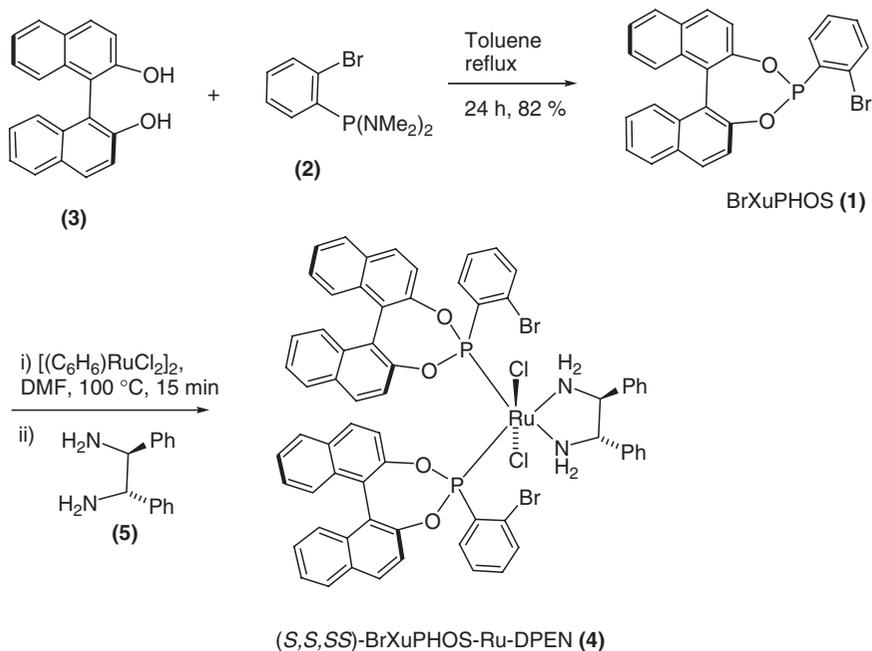
Figure 3.4 Preparation of BrXuPHOS (**1**) and (S, S, SS)-BrXuPHOS-Ru-DPEN (**4**).

BrXuPHOS (1) may be prepared (Figure 3.4) from bis(dimethylamino)phosphine (2), the preparation of which has been described in a previous volume in this series,[4] in a condensation with BINOL (3). The preparation procedure for the ruthenium(II) complex (S, S, SS)-BrXuPHOS-Ru-DPEN (**4**) is a modification of that reported by Noyori.[5] All reactions described below must be carried out under an inert atmosphere of argon or nitrogen. Examples of ketone reductions using (**4**) as the catalyst are given in Figure 3.5 and Table 3.5.

3.6.1   SYNTHESIS OF (S)-BrXuPHOS (1)

Materials and Equipment

- (S)-Bi-2-naphthol (**3**) (0.859 g, 0.003 mol)
- Anhydrous, degassed toluene (50 mL)
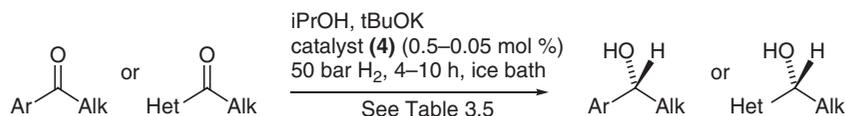
Figure 3.5   Ketone reductions using complex (**4**).

Table 3.5 Asymmetric hydrogenation of ketones catalyzed by ruthenium(II) complex (*S,S,SS*)-(**4**); selected results.

Aryl/Het.	Alkyl	Time (h)	Pressure (bar)	Conv. (%)	ee (%) (configuration)
C_6H_5	CH_3	4	50	95	93 (*R*)
p-ClC_6H_4	CH_3	8	50	99	86 (*R*)
o-ClC_6H_4	CH_3	8	60	97	95 (*R*)
o-BrC_6H_4	CH_3	8	50	93	99 (*R*)
p-IC_6H_4	CH_3	8	50	100	89 (*R*)
o-IC_6H_4	CH_3	8	60	98	99 (*R*)
o-$CH_3C_6H_4$	CH_3	8	60	99	95 (*R*)
o,m-$Cl_2C_6H_3$	CH_3	10	80	100	95 (*R*)
1'-Naphthyl	CH_3	8	50	92	99 (*R*)
C_6H_5	C_2H_5	7	70	97	90 (*R*)
3-Thienyl	CH_3	8	50	100	91 (*R*)
2,5(Cl_2)thienyl	CH_3	8	80	100	92 (*R*)
2,5(Me_2)thienyl	CH_3	8	80	95	97 (*R*)
4-Pyridyl	CH_3	8	55	100	93 (*R*)
Cyclohexyl	CH_3	10	70	99	68 (*S*)

- *ortho*-bis(dimethylamino)phosphino bromobenzene (**2**) (0.822 g, 0.003 mol)
- Two-necked round-bottomed flask (250 mL)
- Magnetic stirrer bar
- Reflux condenser
- Bubbler

Note: The hydrogenation process requires the use of high pressure equipment and an explosive gas. All equipment, i.e. hydrogenation vessel, gas supply and all linking tubing, should be fit for the use and in good condition. Normal precautions for the use of hydrogen gas under pressure should be observed.

Procedure

1. To a solution containing *ortho*-bis(dimethylamino)phosphino bromobenzene (**2**) (0.822 g, 0.003 mol) dissolved in toluene (25 mL) was charged a solution of (S)-bi-2-naphthol (**3**) (0.859 g, 0.003 mol) in toluene (25 mL). The reaction flask was placed in an oil bath and stirring was continued at room temperature for 10 min; the solution was then heated up to reflux for 24 h. The reaction was monitored by ^{31}P-NMR, and the released dimethylamine gas was monitored by pH paper. After the reaction was finished, it was allowed to cool down to room temperature. The solvent was removed to give a yellow oil. Then 30 mL of degassed pentane was added and the mixture stirred overnight. The resulting suspension was filtered and rinsed with further pentane. The off-white solid was left to dry

under high vacuum. The solid was purified by recrystallization with toluene to give slightly yellow crystals of (**1**) (1.17 g, 82 %). m.p. 225–227°C; $[\alpha]_D^{27}$ −58.1° ($c = 0.2$, CH$_2$Cl$_2$).

IR (ν_{max} solid):3053, 1226, 1199, 948, 821, 803, 749 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 8.05$–8.02 (2H, m, Ar-H), 7.82–7.80 (1H, d, Ar-H), 7.62–7.59 (3H, m, Ar-H), 7.47–7.18 (8H, m, Ar-H), 7.03–6.96 (1H, m, Ar-H), 6.82–6.78 (1H, m, Ar-H).

^{13}C-NMR (75 MHz, CDCl$_3$): $\delta = 149.99$ (s), 149.20 (s), 133.35 (s), 133.17 (d, $J_{CP} = 5.75$ Hz), 132.8 (s), 132.1 (s), 131.9 (d, $J_{CP} = 4.60$ Hz), 131.1 (s), 129.87 (s), 128.8 (d, $J_{CP} = 8.62$ Hz), 128.2 (s), 127.2 (d, $J_{CP} = 5.17$ Hz), 126.7 (s), 126.5 (s), 125.5 (s), 125.2 (s), 121.9 (d, $J_{CP} = 5.75$ Hz).

^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = 174.7$.

Anal. calcd α for C$_{26}$H$_{16}$BrO$_2$P: C, 66.26; H, 3.42; N, 16.95. Found: C, 66.58; H, 3.50; N, 14.12.

MS (EI): m/z (%) = 471 ([M+H]$^+$, 100, 286 (90), 268 (30), 239 (40).

HRMS: calcd α for C$_{26}$H$_{16}$BrO$_2$P: 468.9993 ([M-H]$^+$). Found: 468.9977.

3.6.2   SYNTHESIS OF (*S*,*S*,*SS*)-BrXuPHOS-Ru-DPEN (**4**)

Materials and Equipment

- Benzene ruthenium chloride dimer (100 mg, 0.200 mmol)
- (*S*)-BrXuPHOS (**1**) (377 mg, 0.800 mmol)
- Anhydrous DMF (10 mL)
- (*S*,*S*)-DPEN (**5**) (85 mg, 0.400 mmol)
- Dichloromethane
- One-necked round-bottomed flask (50 mL)
- Magnetic stirrer bar
- Oil bath
- Heating plate

Procedure

1. [RuCl$_2$(C$_6$H$_6$)]$_2$ (100 mg, 0.200 mmol) and (*S*)-BrXuPHOS (**1**) (377 mg, 0.800 mmol, 4 equiv) were placed in a 50 mL Schlenk flask. After the air in the flask was replaced with argon, anhydrous DMF (10 mL) was added, the mixture was degassed and the mixture stirred under argon at 100 °C for 10 min to form a reddish-brown solution. After the solution was cooled to 25 °C, (*S*, *S*)-DPEN (**5**) (85 mg, 0.400 mmol) was added and the mixture was degassed again before being stirred for 3 h. The supernatant liquid was removed, and DCM was added in portions into the reaction mixture; each time it was removed under high vacuum and then the residue covered with argon. The resulting dark yellow solid was dried under the high vacuum and recrystallized from hot DMF (100 mg,

3.3 mL) at 100 °C to give bright golden crystals of (**4**) (345 mg, 65 %). m.p. 235–237 °C (dec.); $[\alpha]_D^{19} - 496.8°$ ($c = 0.1$, CH_2Cl_2).

IR (ν_{max} solid): 2927, 2360, 1673, 1224, 954, 809 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 8.43–8.41$ (2H, m, Ar-H), 8.15–8.14 (2H, m, Ar-H), 7.92–7.86 (4H, m, Ar-H), 7.51–7.26 (6H, m, Ar-H), 7.12–7.10 (10H, m, Ar-H), 6.98–6.84 (12H, m, Ar-H), 6.55–6.30 (6H, m, Ar-H), 4.55–4.53 (2H, m, 2NHH), 4.23–4.20 (2H, m, 2NHH), 2.88–2.83 (2H, m, 2NH$_2$CH).

^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = 203.9$.

LSIMS (FAB): m/z (%) = 1291 ([M-Cl]$^+$, 100), 1247 (65), 1196 (50), 1079 (35).

HRMS: calcd for C$_{66}$H$_{48}$Br^{79}Br^{81}Cl$^{35}_2$N$_2$O$_4$P$_2$Ru^{102}: 1291.0168 ([M-Cl]$^+$). Found: 1291.0167.

Anal. calcd for C$_{66}$H$_{48}$Br$_2$Cl$_2$N$_2$O$_4$P$_2$Ru: C, 59.74; H, 3.65; N, 2.11; P, 4.67. Found: C, 59.29; H, 3.60; N, 2.05; P, 4.72.

3.6.3 GENERAL PROCEDURE OF ASYMMETRIC HYDROGENATION OF ACETOPHENONE[5]

Materials and Equipment

- Acetophenone (2.17 g, 18.08 mmol)
- Potassium *tert*-butoxide (10 mg, 0.0904 mmol)
- (S, S, SS)-BrXuPHOS-Ru-DPEN (**4**) (12 mg, 0.00904 mmol, 0.05 mol%)
- Anhydrous *iso*-propanol (120 mL)
- High purity hydrogen gas
- Dichloromethane (6 mL)
- Mixture of ethyl acetate/hexane (50: 50)
- One-necked round-bottomed flask (250 mL)
- Parr hydrogenation autoclave (300 mL)

Procedure

1. In an oven-dried round-bottomed flask (250 mL), acetophenone (2.10 mL, 2.17 g, 18.08 mmol) and (CH$_3$)$_3$COK (10 mg, 0.0904 mmol, 0.5 mol%) were dissolved in dry and degassed 2-propanol (120 mL). (S,S,SS)-BrXuPHOS-Ru-DPEN (**4**) (12 mg, 0.00904 mmol, 0.05 mol%) was dissolved in anhydrous CH$_2$Cl$_2$ (6 mL), and transferred into the above reaction solution under argon. The mixture was degassed by three vacuum/argon cycles and then it was quickly transferred into the autoclave. It was purged with hydrogen for 10 s at 2, 5 and 8 bar, respectively, cooled in an ice bath for 1 h, and hydrogen was introduced to the required pressure. The reaction mixture was stirred vigorously at 0 °C (ice bath temperature) for the required time. The mixture was filtered through a pad of silica gel and the pad was washed with a 50 % solution of ethyl acetate in hexane (150 mL). The filtrate was concentrated under reduced pressure to afford the reduction product. Purification was accomplished by flash chromatography when appropriate. Full details of the

reduction products and HPLC/GC methods for ee determination have been published previously.[2,3]

CONCLUSION

A ruthenium(II) complex (*S*,*S*,*SS*)-BrXuPHOS-Ru-DPEN (**4**) containing BINOL-based monodonor phosphorus ligand BrXuPHOS (**1**) has been prepared and applied as a catalyst (S/C = up to 10 000) for the asymmetric hydrogenation of ketones, providing the enantiomerically pure secondary alcohols with up to 99 % ee.

ACKNOWLEDGEMENT

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3.7 *IN SITU* FORMATION OF LIGAND AND CATALYST: APPLICATION IN RUTHENIUM-CATALYZED ENANTIOSELECTIVE REDUCTION OF KETONES

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The direct, *in situ* formation of highly efficient ruthenium catalysts for the asymmetric reduction of ketones was accomplished by combining chiral ligand

building blocks with a ruthenium precursor. Aryl alkyl ketones were reduced under hydrogen transfer conditions in high conversions with excellent enantiomeric excess (up to >99 % ee).[1]

3.7.1   SYNTHESIS OF (*S*)-3-FLUORO-1-PHENYLETHANOL
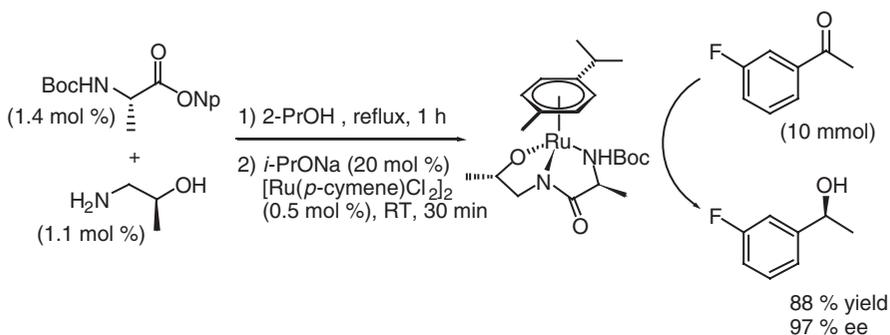
Materials and Equipment

- (*S*)-Boc-Ala-ONp (42.7 mg, 0.13 mmol)
- (*S*)-1-Amino-2-propanol (8.7 μL, 0.11 mmol)
- 2-Propanol, distilled
- Na, for preparation of *i*-PrONa
- 3-Fluoroacetophenone (1.2 mL, 10 mmol)
- [RuCl$_2$(*p*-cymene)]$_2$ (30.6 mg, 0.05 mmol)
- Ethyl acetate
- Diluted brine solution
- Pentane
- 100 mL three-necked round-bottom flask (oven dried)
- Condenser (oven dried)
- Two glass stoppers (oven dried)
- Magnetic stirring plate
- Separatory funnel
- Filter funnel, diameter 6 cm
- Silica gel (Matrex 60 Å, 35–70 μm) (140 g)
- Chromatography column, diameter 7 cm
- 500 mL round-bottomed flask
- Rotary evaporator

Procedure

1. (*S*)-Boc-Ala-ONp (42.7 mg, 0.13 mmol) was placed in a 100 mL three-necked round-bottomed flask (equipped with a stirring bar, two glass stoppers and a condenser) and dried under vacuum for 15 min. (*S*)-1-Amino-2-propanol (8.7 µL, 0.11 mmol) mixed in 10 mL 2-propanol was added to the flask under an inert atmosphere (N$_2$). The yellow mixture was heated at 80 °C for 1 h to form the active ligand. The resulting solution is at this time almost colourless. The mixture was cooled to room temperature and *i*-PrONa (2 mmol in 20 mL 2-propanol) was added. The solution turned bright yellow upon base addition. 3-Fluoroacetophenone (1.2 mL, 10 mmol) was added, followed by [RuCl$_2$ (*p*-cymene)]$_2$ (30.6 mg, 0.05 mmol) and finally an additional 20 mL of 2-propanol. The mixture was stirred for 30 min at which time the reaction was quenched with diluted brine and extracted with ethyl acetate. The organic phase was filtered through a silica-pad (40 g), which was washed with ethyl acetate. The solvents were evaporated before column chromatography was performed over 100 g silica gel in a 7 cm diameter column, using pentane:ethyl acetate 8:1 as eluent (yield 88%). The enantiomeric purity (97 % ee) was analyzed with GLC (CP Chiralsil DEX CB): 110 °C hold 10 min, rate 80 °C min^{-1} to 200 °C and hold for 5 min. t_R (*R*-isomer) = 9.72 min and t_R (*S*-isomer) = 10.29 min.[2]

CONCLUSION

We have previously disclosed that ruthenium-arene complexes modified with *pseudo*-dipeptide ligands are efficient catalysts for the asymmetric reduction of prochiral ketones.[3] The preparation of the ligands is a straightforward process, where a protected amino acid is coupled with a vicinal amino alcohol using an appropriate coupling reagent. Nevertheless, the synthesis of the ligand is a time-consuming step which involves separations and purifications. The one-pot *in situ* formation of both ligand and the catalytically active ruthenium complex prior to the reduction reaction is therefore highly beneficial. The procedure requires no isolation or purification of either ligand or catalyst precursor, and the catalytic reduction is performed in the same reaction vessel where the ligand/catalyst is formed. The small amount of *p*-nitrophenol released in the ligand preparation does not affect the outcome of the ketone reduction. Hence, this direct route provides easy access to optically active secondary aryl alcohols, compounds which can be used as building blocks in the synthesis of various pharmaceuticals. The procedure has successfully been applied in the asymmetric transfer hydrogenation of aryl ketones with varying electronic properties (Table 3.6). Electron-rich as well as electron-poor substrates are reduced in high to excellent enantioselectivity. The structure of the active catalyst is currently unknown, but recent mechanistic studies strongly indicate that alkali cations introduced

Table 3.6   Scope of the transfer hydrogenation reaction.[a]
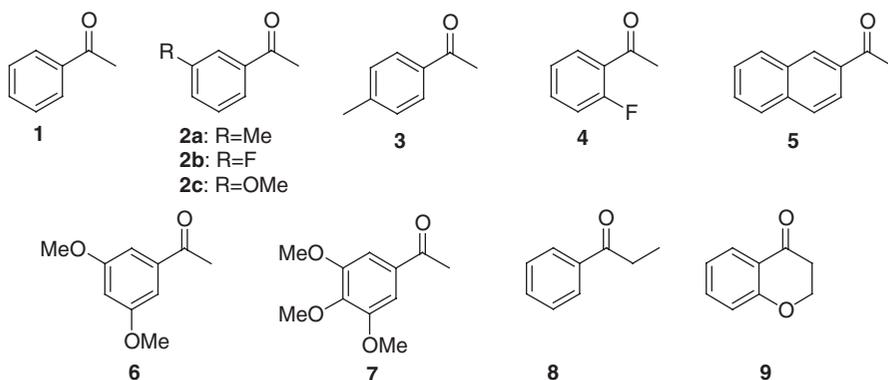
Entry	Ketone	Time (min)	Conv. (%)	ee (%) (configuration)
1	**1**	60	85[b]	97 (S)
2	**2a**	60	83	97 (S)
3	**2b**	30	88[b,c]	97 (S)
4	**2c**	60	86	97 (S)
5	**3**	60	66	96 (S)
6	**4**	60	90	92 (S)
7	**5**	60	64	97 (S)
8	**6**	60	82	97 (S)
9	**7**	60	45	99 (S)
10	**8**	60	64	97 (S)
11	**9**	60	31	>99 (S)

[a]All reactions were performed on a 1 mmol scale, except where indicated.
[b]Isolated yield.
[c]Performed on a 10 mmol scale.

along with the base play an important role in the hydride transfer to the ketone.[4]

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3.8 SYNPHOS AND DIFLUORPHOS AS LIGANDS FOR RUTHENIUM-CATALYZED HYDROGENATION OF ALKENES AND KETONES

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Ruthenium(II) complexes bearing atropisomeric diphosphine ligands have proved to be efficient systems for the hydrogenation of a wide range of prochiral substrates. A new catalytic system has been developed based on ruthenium complexes having SYNPHOS and DIFLUORPHOS as chiral diphosphanes (Figure 3.6).

3.8.1 SYNTHESIS OF [RuCl((*S*)-SYNPHOS)(*P*-CYMENE)]Cl
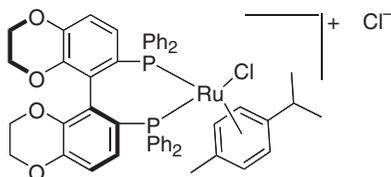
Materials and Equipment

- [Ru(*p*-cymene)Cl$_2$]$_2$ (15 mg, 0.024 mmol)
- (*S*)-SYNPHOS (32 mg, 0.05 mmol)
- Methanol (3 mL)
- Dry methylene chloride (8 mL)
- 50 mL round-bottomed tube with a magnetic stirrer bar
- Magnetic stirrer plate
- Condenser
- Oil bath
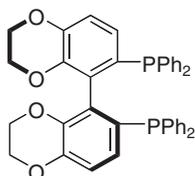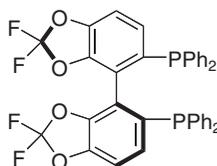
(*S*)-SYNPHOS   (*S*)-DIFLUORPHOS

Figure 3.6

Procedure

1. Commercially available [Ru(*p*-cymene)Cl$_2$]$_2$ (15 mg, 0.024 mmol) and (*S*)-SYNPHOS (32 mg, 0.024 mmol) were placed in a 50 mL round-bottomed tube equipped with a magnetic stirrer bar and a condenser. The mixture was degassed by three vacuum/argon cycles at room temperature. Degassed methanol (3 mL) and dry methylene chloride (8 mL) were added to the solids. The orange mixture was refluxed (50 °C) for 1.5 h and then cooled to room temperature. The solvent was evaporated under vacuum to give a crude orange solid which was used as catalyst for the hydrogenation reaction without further purification.

^{31}P-NMR (CDCl$_3$,162 MHz): $\delta = 27.2$ (d, $J = 63$ Hz), 41.8 (d, $J = 63$ Hz).
MS (ESI): $m/z = 909$ ([RuCl((*S*)-SYNPHOS)(*p*-cymene)]$^+$).

3.8.2 SYNTHESIS OF [RuCl((*S*)-DIFLUORPHOS)(*P*-CYMENE)]Cl
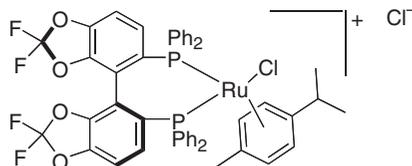
Materials and Equipment

- [Ru(*p*-cymene)Cl$_2$]$_2$ (15 mg, 0.024 mmol)
- (*S*)-DIFLUORPHOS (34 mg, 0.05 mmol)
- Methanol (3 mL)
- Dry methylene chloride (8 mL)
- 50 mL round-bottomed tube with a magnetic stirrer bar
- Magnetic stirrer plate
- Condenser
- Oil bath

Procedure

1. Following the procedure in Section 3.8.1, a crude orange solid was obtained and used as catalyst for the hydrogenation reactions without further purification.

^{31}P-NMR (CDCl$_3$, 162 MHz): $\delta = 28.6$ (d, $J = 62$Hz), 43.9 (d, $J = 62$Hz).
^{19}F-NMR (CDCl$_3$, 376 MHz): $\delta = -50.5$ (d, $J = 91$ Hz), -49.8 (d, $J = 91$ Hz), -49.0 (d, $J = 91$ Hz), -47.4 (d, $J = 91$ Hz).
MS (ESI): $m/z = 953$ ([RuCl((*S*)-DIFLUORPHOS)(*p*-cymene)]$^+$).

3.8.3   SYNTHESIS OF [RUI((S)-DIFLUORPHOS)(P-CYMENE)]I
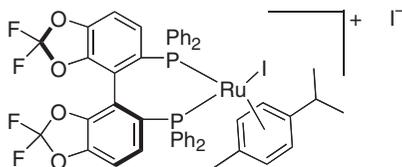
Materials and Equipment

- [Ru(p-cymene)I]$_2$ (23 mg, 0.024 mmol)
- (S)-DIFLUORPHOS (34 mg, 0.05 mmol)
- Methanol (3 mL)
- Dry methylene chloride (8 mL)
- 50 mL round-bottomed tube with a magnetic stirrer bar
- Magnetic stirrer plate
- Condenser
- Oil bath

Procedure

1. Following the procedure in Section 3.8.1, a crude brown solid was obtained and used as catalyst for the hydrogenation reaction without further purification.

^{31}P-NMR (CDCl$_3$, 162 MHz): $\delta = 25.4$ (d, $J = 60$Hz), 42.9 (d, $J = 60$Hz).

^{19}F-NMR (CDCl$_3$, 376 MHz): $\delta = -47.7$ (d, $J = 91$ Hz), -48.8 (d, $J = 91$ Hz), -49.4 (d, $J = 91$ Hz), -51.0 (d, $J = 91$ Hz).

MS (ESI): $m/z = 1045$ ([RuI((S)-DIFLUORPHOS)(p-cymene)]$^+$).

3.8.4   SYNTHESIS OF [NH$_2$R$_2$] [(RuCl(P*P))$_2$(μ-Cl)$_3$] P*P = SYNPHOS OR DIFLUORPHOS AND R = Me OR Et.
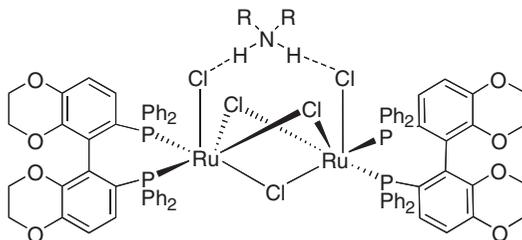
Materials and Equipment

- $[Ru(C_6H_6)Cl_2]_2$ (25 mg, 0.05 mmol)
- (*S*)-SYNPHOS (64 mg, 0.1 mmol)
- $NHR_2.HCl$ (R=Me, 8 mg; R=Et, 11 mg; 0.1 mmol)
- Dry THF (6 mL)
- 50 mL round-bottomed tube with a magnetic stirrer bar
- Magnetic stirrer plate
- Condenser
- Oil bath

Procedure

1. Commercially available $[Ru(C_6H_6)Cl_2]_2$ (25 mg, 0.05 mmol), SYNPHOS (64 mg, 0.1 mmol) and $NHR_2.HCl$ (R = Me or Et) (2 equiv, 0.1 mmol) were introduced into a 50 mL round-bottomed tube equipped with a magnetic stirrer bar and a condenser. The mixture was degassed by three vacuum/argon cycles at room temperature. Then 6 mL of degassed anhydrous tetrahydrofuran was added. The orange mixture was refluxed overnight and then cooled to room temperature. The solvents were evaporated under vacuum and the brown solid was used without further purification as the crude catalyst for the hydrogenation reaction.

R = Me. ^{31}P-NMR (121 MHz, CDCl$_3$): $\delta = 51.1$ (d, $J = 39$ Hz), 52.9 (d, $J = 39$ Hz). [Secondary complex: $\delta = 53.7$ (d, $J = 42$ Hz), 56.6 (d, $J = 42$ Hz), ca. 8 %.]
R = Et. ^{31}P-NMR (162 MHz, CDCl$_3$): $\delta = 52.1$ (d, $J = 39$ Hz), 54.4 (d, $J = 39$ Hz). [Secondary complex: $\delta = 54.6$ (d, $J = 42$ Hz), 58.1 (d, $J = 42$ Hz), ca. 20 %.]

3.8.5 SYNTHESIS OF [NH$_2$ME$_2$][RuCl-(*S*)-DIFLUORPHOS]$_2$[μ-Cl]$_3$
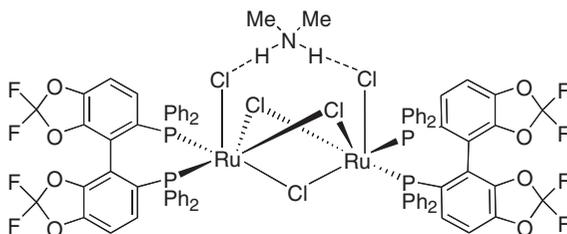
Materials and Equipment

- $[Ru(C_6H_6)Cl_2]_2$ (25 mg, 0.05 mmol)
- (*S*)-DIFLUORPHOS (68 mg, 0.1 mmol)
- $NHMe_2 \cdot HCl$ (8 mg, 0.1 mmol)

- Dry THF (6 mL)
- 50 mL round-bottomed tube with a magnetic stirrer bar
- Magnetic stirrer plate
- Condenser
- Oil bath

Procedure

1. Following the procedure in Section 3.8.4, a crude brown solid was obtained and used as the catalyst for the hydrogenation reaction without further purification.

^{31}P-NMR (121 MHz, CDCl$_3$): $\delta = 51.6$ (d, $J = 38$ Hz), 52.1 (d, $J = 38$ Hz). [Secondary complex: $\delta = 53.5$ (d, $J = 41$ Hz), 56.2 (d, $J = 41$ Hz), ca. 16 %.]
^{19}F-NMR (282 MHz, CDCl$_3$): $\delta = -51.0$ (d, $J = 95$ Hz), -49.5 (d, $J = 95$ Hz), -48.4 (d, $J = 95$ Hz), -45.7 (d, $J = 95$ Hz).

3.8.6 SYNTHESIS OF *IN SITU* GENERATED [RuBr$_2$((*S*)-SYNPHOS)] AND [RuBr$_2$((*S*)-DIFLUORPHOS)]

(*S*)-SYNPHOS   (*S*)-DIFLUORPHOS
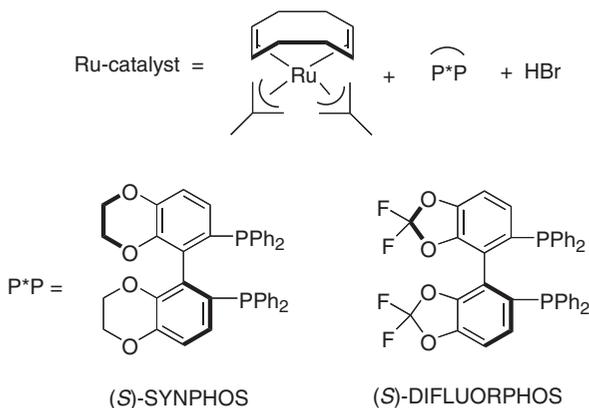
Materials and Equipment

- [Ru(1,5-cyclooctadiene)(2-methylallyl)$_2$] (3.2 mg, 0.01 mmol)
- Diphosphine (P*P) (0.011 mmol):
  (*S*)-SYNPHOS (7.1 mg) or (*S*)-DIFLUORPHOS (7.5 mg)
- Distilled acetone (1 mL)
- Methanolic bromhydric acid (0.2 N) (110 µL, 0.022 mmol)
- Glass tube (10 mL) with a magnetic stirrer bar
- Magnetic stirrer plate

Table 3.7 Asymmetric ruthenium-catalyzed hydrogenations using SYNPHOS-Ru(II) and DIFLUORPHOS-Ru(II) catalysts.

Substrate	(P*P)-[Ru]	ee (%) (configuration)	Product	Ref.
	in situ [RuBr$_2$((S)-SYNPHOS)]	97 (S)		[3]
	in situ [RuBr$_2$((S)-SYNPHOS)]	92 (S)		[6]
	in situ [RuBr$_2$((R)-SYNPHOS)]	97 (S)		[3]
	in situ [RuBr$_2$((S)-DIFLUORPHOS)]	70 (R)		[5]
	[RuCl((S)-DIFLUORPHOS)(p-cymene)]Cl	81 (R)		a
	[NH$_2$Me$_2$][(RuCl((S)-DIFLUORPHOS))$_2$(μ-Cl)$_3$]	97 (R)		a
	in situ [RuBr$_2$((S)-DIFLUORPHOS)]	86 de 98 ee *anti*(2R,4R)		[5]
	in situ [RuBr$_2$ ((S)-SYNPHOS)]	98 de 99 ee *syn(2R,3S)*		[7,8]
	in situ [RuBr$_2$ ((S)-SYNPHOS)]	99 de 97 ee *anti (2S,3S)*		[7,8]
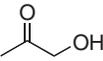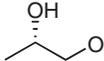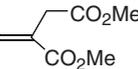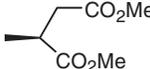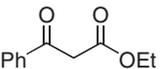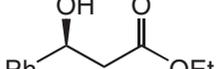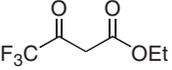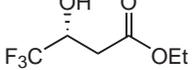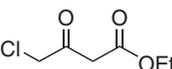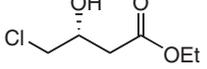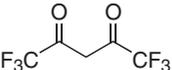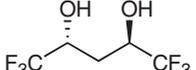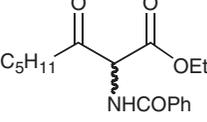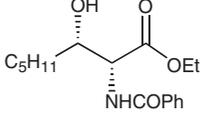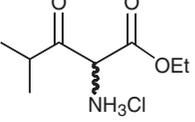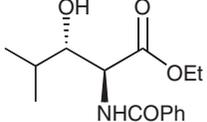
^{a} Unpublished results.

Procedure

1. All reactions were carried out under argon in solution in dry solvents.
2. The ruthenium catalysts were prepared at room temperature by reaction of [Ru(1,5-cyclooctadiene)(2-methylallyl)$_2$] with ligand P*P (1.1 equiv) in acetone (1 mL). Methanolic HBr (2.2 equiv) was added dropwise to the solution which

was subsequently stirred for 30 min at room temperature. An orange precipitate was formed and the solvent was then evaporated under vacuum. The crude catalysts were used in the hydrogenation reaction without further purification.

CONCLUSION

The enantioselective ruthenium-catalyzed hydrogenation reaction using enantiopure SYNPHOS and DIFLUORPHOS diphosphanes has a large scope and has been applied to a wide range of prochiral substrates. We have shown that a number of olefins and functionalized carbonyl compounds can be hydrogenated with an excellent level of selectivities by using SYNPHOS-Ru(II)[1−4] and DIFLUORPHOS-Ru(II)[1,5,6] catalysts. For instance, α- and β-ketoesters, olefins and 1,3-diketones have been reduced to the corresponding saturated compounds in enantiomeric excesses approaching 100 %. Selected results are given in Table 3.7. Dynamic kinetic resolution of α-chloro and α-acetamido-β-ketoesters[7,8] have also been performed by using these new atropisomeric diphosphanes with high levels of enantio- and diastereoselectivities.
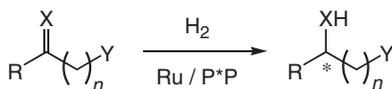
X = C,O
n = 0, 1
R = aryl, alkyl
Y = chelating group
P*P = SYNPHOS or DIFLUORPHOS

All these hydrogenation reactions[9−13] are easy to perform on large scale, in quantitative yield and represent a highly convenient approach to a variety of optically pure compounds. These SYNPHOS-Ru(II) and DIFLUORPHOS-Ru(II) catalysts have been used in the synthesis of natural products of biological interest.[14,15]

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3.9   AN ARENE RUTHENIUM COMPLEX WITH POLYMERIZABLE SIDE CHAINS FOR THE SYNTHESIS OF IMMOBILIZED CATALYSTS

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Since their discovery more than 30 years ago,[1] dimeric [(arene)RuCl$_2$]$_2$ complexes or their corresponding monomeric derivatives [(arene)RuLCl$_2$] and [(arene)Ru(L-L′)Cl] have been frequently employed as catalysts. In view of the potential advantages of heterogeneous as compared with homogenous catalysts, several groups have investigated methods to immobilize (arene)Ru complexes. Usually, the attachment to the support is achieved via mono- or bidentate ligands, which are directly bound to the ruthenium atom.[2] Below, the synthesis of a dimeric ruthenium complex with polymerizable side chains is described. This complex allows one to immobilize (arene)Ru catalysts via the π-ligand (Figure 3.7).[3]
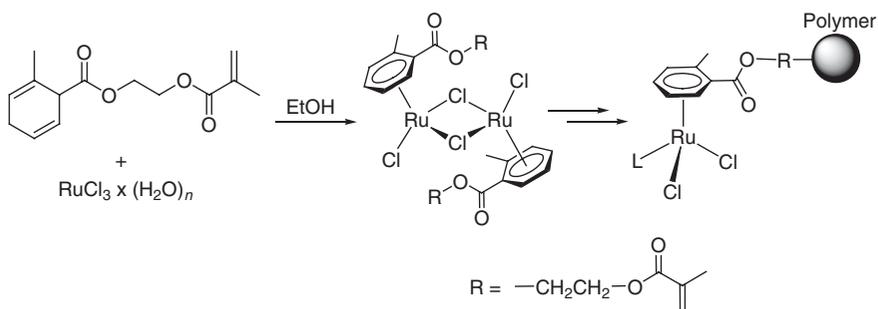
Figure 3.7   Reprinted from reference [3], with permission from Elsevier.

3.9.1 SYNTHESIS OF 2-METHYL-CYCLOHEXA-2,5-DIENECARBOXYLIC ACID 2-(2-METHYL-ACRYLOYLOXY)-ETHYL ESTER
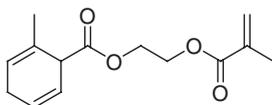
Materials and Equipment

- Dihydromethylbenzoic acid (1.00 g, 7.24 mmol)
- Oxalyl chloride (1.14 mL, 10.86 mmol)
- Dimethylaminopyridine (DMAP) (2 mg)
- Triethylamine (0.10 mL, 0.72 mmol)
- 2-Hydroxyethyl methacrylate (1.06 mL, 0.72 mmol)
- Dry dichloromethane (50 mL)
- Water
- Anhydrous magnesium sulfate
- 100 mL three-necked flask with magnetic stirrer bar
- One dropping funnel
- One reflux condenser
- Magnetic stirrer plate
- One glass sintered funnel
- One 500 mL Erlenmeyer flask
- Filter paper
- One 100 mL separatory funnel
- Rotary evaporator

Procedure

1. Dihydromethylbenzoic acid (1.00 g, 7.24 mmol) was added to degassed dichloromethane (30 mL) containing catalytic amounts of DMAP in a 100 mL three-necked flask (equipped with a magnetic stirrer bar, a reflux condenser, a dropping funnel) under nitrogen. Then oxalyl chloride (1.14 mL, 10.86 mmol) was slowly added to the solution through the dropping funnel. After heating under reflux for 1 h, the solvent and the excess oxalyl chloride were removed under reduced pressure.

2. The resulting dihydromethylbenzoic acid chloride was dissolved in degassed dichloromethane (20 mL) in a three-necked flask equipped with a magnetic stirrer bar, a reflux cooler, a dropping funnel and under nitrogen. After addition of triethylamine (0.10 mL, 0.72 mmol), 2-hydroxyethyl methacrylate (1.06 mL, 8.70 mmol) was added slowly over a period of 15 min through the dropping funnel. The reaction mixture was subsequently heated under reflux for 6 h. The slightly yellow solution was washed with water and dried over magnesium sulfate. After evaporation of the solvent, the product, which contains small amounts of 2-hydroxyethyl methacrylate, was obtained as a slightly yellow oil (1.63 g, 91% yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 1.71 (s, 3 H, CH$_3$), 1.93 (s, 3 H, CH$_3$), 2.72 (m, 2 H, CH$_2$), 3.63 (m, 1 H, CH), 4.36 (m, 4 H, OCH$_2$), 5.58 (s, 1 H, C=CH), 5.70 (m, 2 H, CH), 5.88 (m, 1 H, CH), 6.11 (s, 1 H, C=CH).

^{13}C-NMR (101 MHz, CDCl$_3$): δ (ppm) = 18.20 (CH$_3$), 22.02 (CH$_3$), 26.75 (CH$_2$), 47.08 (C$_q$), 62.31 (CH$_2$), 62.41 (CH$_2$), 122.01 (CH), 122.24 (CH), 126.06 (CH), 129.97 (CH), 132.16 (CH), 135.88 (CH), 167.07 (CO), 172.31 (CO).

3.9.2 SYNTHESIS OF [η^6-(2-METHYL-BENZOIC ACID 2-(2-METHYL-ACRYLOYLOXY)-ETHYL ESTER)RuCl$_2$]$_2$
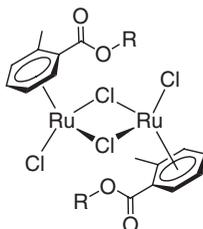
Materials and Equipment

- 2-Methyl-cyclohexa-2,5-dienecarboxylic acid 2-(2-methyl-acryloyloxy)-ethyl ester (1.50 g, 6.00 mmol)
- RuCl$_3 \cdot$3H$_2$O (523 mg, 2.00 mmol)
- Absolute ethanol (99 %) (40 mL)
- Chloroform (30 mL)
- 100 mL Schlenk flask with magnetic stirrer bar
- One reflux cooler
- Magnetic stirrer plate
- One glass sintered funnel
- One 500 mL Erlenmeyer flask
- Filter paper
- Rotary evaporator

Procedure

1. A solution of RuCl$_3 \cdot$3H$_2$O (523 mg, 2.00 mmol) and 2-methyl-cyclohexa-2,5-dienecarboxylic acid 2-(2-methyl-acryloyloxy)-ethyl ester (1.50 g, $\sim$6.00 mmol) in degassed ethanol (40 mL) in a 100 mL Schlenk flask fitted with a reflux condenser was heated under reflux for 6 h. After evaporation of the solvent under reduced pressure, the residue was extracted with chloroform (30 mL). Evaporation of the solvent gave the crude product, which was dissolved in a minimum amount of hot ethanol. Cooling to –4 °C gave orange crystals, which were collected and dried (710 mg, 84 % yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 1.97 (s, 6 H, CH$_3$), 2.48 (s, 6 H, CH$_3$), 4.51 (m, 4 H, OCH$_2$), 4.63 (m, 4 H, OCH$_2$), 5.36 (d, ^3J = 6 Hz, 2 H, CH), 5.60 (s, 2 H, C=CH), 5.73 (t, ^3J = 5 Hz, 2 H, CH), 5.94 (t, ^3J = 5 Hz, 2 H, CH), 6.17 (s, 2 H, C=CH), 6.42 (d, ^3J = 6 Hz, 2 H, CH).

^{13}C-NMR (101 MHz, CDCl$_3$): δ (ppm) = 18.33 (CH$_3$), 19.75 (CH$_3$), 62.24 (OCH$_2$), 64.22 (OCH$_2$), 65.81, 78.81, 80.54, 88.00, 89.57, 102.93 (CH and C), 126.27 (C=CH$_2$), 135.85 (C=CH$_2$), 165.00 (CO), 167.05 (CO).

CONCLUSION

A chloro-bridged (arene)Ru$^{(II)}$ complex with polymerizable side-chains can be easily prepared in two steps using commercially available starting materials. It is possible to immobilize this complex by copolymerization with ethyleneglycol dimethacrylate. The resulting copolymer is of interest for catalytic applications. In combination with the chiral ligand (1R,2R)-(-)-N-p-tosyl-1,2-diphenylethylene-diamine (TsDPEN), for example, the copolymer can be employed as a catalyst in asymmetric transfer hydrogenations using azeotropic NEt$_3$/HCO$_2$H as the reducing agent. When aromatic ketones were used as the substrates, an enantiomeric excess between 87 % and 97 % was observed.[3]

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3.10   SELECTIVE REDUCTION OF CARBONYL GROUP IN β,γ-UNSATURATED α-KETOESTERS BY TRANSFER HYDROGENATION WITH Ru(P-CYMENE)(TsDPEN)

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The transfer hydrogenation of α-keto-β,γ-unsaturated esters, catalyzed by Ru(p-cymene)(TsDPEN) (TsDPEN: monotosylated 1,2-diphenylethylene-1,2-diamine) with 2-propanol as the hydrogen source, has been developed as an efficient method for the preparation of α-hydroxy-β, γ-unsaturated esters or acids.

3.10.1 SYNTHESIS OF DI-μ-CHLORO-BIS[CHLORO(η^6-1-ISOPROPYL-4-METHYL-BENZENE)RUTHENIUM(II)][1]

$$2 \ RuCl_3 \ + \ 2 \ \text{[structure]} \xrightarrow{C_2H_5OH} [RuCl_2(\eta^6\text{-}C_{10}H_{14})]_2$$
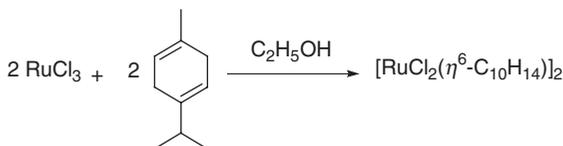
Materials

- RuCl₃●3H₂O (38–39 % Ru), 1.00 g, approximately 3.83 mmol
- γ-Terpinene, available from Acros, 98 %, 5 mL
- Ethanol, 50 mL

Procedure

1. Under the argon atmosphere, a solution of hydrated ruthenium trichloride (approximately RuCl₃●3H₂O, containing 38–39 % Ru) (1.00 g, approximately 3.83 mmol) in 50 mL of ethanol was treated with 5 mL of γ-terpinene and heated under reflux in a 100-mL, round-bottomed flask for 4 h. The hot solution was filtered as quickly as possible to remove the undissolved dark residue. The filtrate was concentrated to 25 mL under reduced pressure and cooled to room temperature and the red-brown microcrystalline product that resulted was collected by filtration. After drying *in vacuo* (approximately 1 mmHg) for 4 h, 0.70 g (59.9 %) of ruthenium complex was obtained.

^{1}H-NMR (300 MHz, CDCl₃):$\delta = 5.33$–5.47 (m, 4 H), 2.96 (hept, $J = 6.7$ Hz, 1 H), 2.19 (s, 3 H), 1.28 (d, $J = 6.7$ Hz, 6 H).

3.10.2 SYNTHESIS OF (±)-MONOTOSYLATE-1,2-DIPHENYL-1,2-ETHYLENEDIAMINE[2]

Materials

- Glacial acetic acid (173 mL)
- Benzil (27.0 g, 0.129 mol)
- Ammonium acetate (67.7 g, 0.87 mol)

- Cyclohexanone (13.5 mL, 0.133 mol)
- Dry THF (400 mL)
- Liquid ammonia (350 mL)
- Lithium (8.0 g, 1.14 mol)
- Ethanol (25 mL)
- Ammonium chloride (60.0 g)
- 2 N aqueous hydrochloric acid (250 mL)
- 2 N aqueous sodium hydroxide (250 mL)
- Triethylamine (2 mL, 14.3 mmol)
- *p*-Toluenesulfonyl chloride (0.91 g, 4.8 mmol)

Procedure

1. Synthesis of 2,2-Spirocyclohexane-4,5-diphenyl-2*H*-imidazole
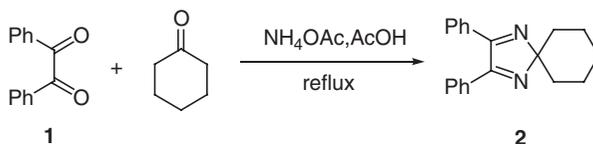
A 250 mL, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser was charged with glacial acetic acid (173 mL), benzil (27.0 g, 0.129 mol), ammonium acetate (67.7 g, 0.87 mol) and cyclohexanone (13.5 mL, 0.133 mol). The mixture was stirred and refluxed for 1.5 h and then poured into 450 mL of ice-cold and vigorously stirred water while hot. The mixture was slowly cooled to ambient temperature and left overnight. The resulting solid was collected by filtration, washed four times with 50 mL of water, crushed in a mortar and dried under reduced pressure to give the imidazole as a yellowish-green solid (35.8 g, 97.3 % yield).

2. Synthesis of (±)-1,2-diphenyl-1,2-ethylenediamine.
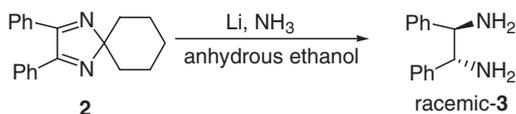
A 2 L, four-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer and dry ice condenser was charged with 2,2-spirocyclohexane-4,5-diphenyl-2*H*-imidazole (61.1 g, 0.212 mol). The flask was flushed with argon, and 400 mL of anhydrous tetrahydrofuran was added. The mixture was stirred until all solids dissolved, cooled to −78 °C (dry ice/acetone bath) and treated with a stream of gaseous ammonia until the volume of liquid increased to about 350 mL. Lithium (8.0 g, 1.14 mol) was then slowly introduced through one of the side-necks by cutting the wire with scissors in a gentle stream of argon. The rate of lithium addition was controlled such that the temperature of the reaction mixture did not rise above −65 °C. Following the addition of lithium, the mixture was stirred for 30 min and 25 mL of

ethanol was slowly added. The mixture was stirred for an additional 20 min and 60.0 g of ammonium chloride was added. The cold bath was removed and the mixture was allowed to warm to 0 °C. Water (30 mL)was carefully introduced and the phases were separated. The aqueous phase was washed three times with 250 mL of ether and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to about 200 mL. The solution was transferred to a 1L, one-necked, round-bottomed flask equipped with a mechanical stirrer, cooled to 0 °C and treated with 250 mL of 2 N aqueous hydrochloric acid. The biphasic mixture was vigorously stirred at ambient temperature for 1 h, 400 mL of water was added and phases were separated. The organic phase was washed with 150 mL of water and the combined aqueous phases were extracted with 300 mL of dichloromethane. The aqueous solution was then carefully treated with 250 mL of 2 N aqueous sodium hydroxide and the mixture was extracted four times with 120 mL of dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. Removal of volatile material under reduced pressure gave racemic diamine as a pale yellow solid, which was purified by crystallization from hexane (38.5 g, 85.7% yield).

3. Synthesis of *N-p*-toluenesulfonyl-1,2-diphenyl-1,2-ethylenediamine
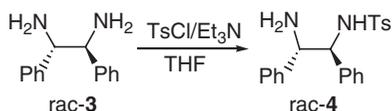
A 100 mL three-necked, round-bottomed flask equipped with magnetic stirrer was charged with racemic 1,2-diphenylethylenediamine (1.02 g, 4.8 mmol), triethylamine (2 mL, 14.3 mmol) and dry tetrahydrofuran (10 mL) followed by dropwise addition of *p*-toluenesulfonyl chloride (0.91 g, 4.8 mmol) dissolved in 10 mL of dry tetrahydrofuran. The reaction mixture was stirred at ambient temperature for 12 h and a white salt was obtained. The salt was filtered and washed with ether. The combined filtrate was concentrated and purified by flash column chromatography (eluent: petroleum ether/ethyl acetate = 1/1) to give *N-p*-toluenesulfonyl-1,2-diphenyl-1,2-ethylenediamine (1.02 g, 58.0 % yield:).

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 6.96$–7.33 (m, 14 H), 4.39 (d, $J = 5.2$ Hz, 1 H), 4.15 (d, $J = 5.2$ Hz, 1 H), 2.33 (s, 3 H), 1.56 (bs, 2 H).

3.10.3   SYNTHESIS OF Ru COMPLEX Ru(*P*-CYMENE)(TsDPEN)[3]
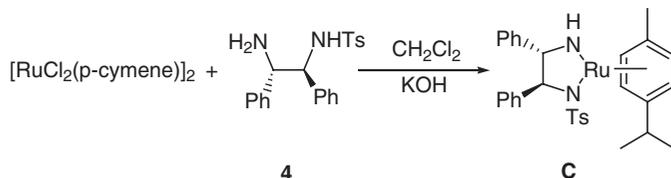
Materials

- KOH (400 mg, 7.1 mmol)
- Dichloromethane, freshly distilled from CaH_2 (20 mL)
- Deoxygenated water (15 mL)
- Calcium hydride, powdered

Procedure

1. A mixture of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (306 mg, 0.5 mmol), TsDPEN (366 mg, 1.0 mmol) and KOH (400 mg, 7.1 mmol) in 7 mL dichloromethane was stirred at room temperature for 5 min. On addition of water (7 mL) to the reaction mixture, the colour changed from orange to deep purple. The purple organic layer was washed with 5 mL of water, dried with calcium hydride and concentrated to dryness to give the deep purple complex Ru(p-cymene)(TsDPEN) (455 mg, 75.8 % yield).

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 6.76$–7.6 (m, 14 H), 5.62 (d, $J = 6.1$ Hz, 1 H), 5.53 (d, $J = 6.1$ Hz, 1 H), 5.40 (d, $J = 6.1$ Hz, 1 H), 5.36 (d, $J = 6.1$ Hz, 1 H), 4.35 (s, 1 H), 3.93 (s, 1 H), 2.73 (m, 1 H), 2.23 (s, 3 H), 2.18 (s, 3 H), 1.27 (d, $J = 7.2$ Hz, 3 H), 1.23 (d, $J = 7.2$ Hz, 3 H).

3.10.4   Ru-TsDPEN CATALYZED TRANSFER HYDROGENATION REACTION OF β,γ-UNSATURATED-α-KETOESTERS
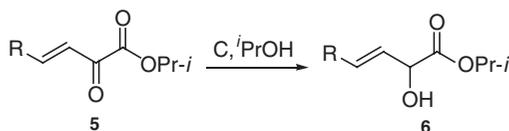
Materials

- Isopropyl alcohol, freshly distilled from magnesium (5 mL)
- β,γ-Unsaturated-α-ketoesters, prepared according to standard procedure[4] (0.5 mmol)
- Ru(p-cymene)(TsDPEN) complex (prepared in Section 3.10.3)

Procedure

1. A degassed Schlenk reaction tube was charged successively with the ketoester (0.5 mmol), isopropyl alcohol (5 mL) under argon atmosphere. The reaction mixture was degassed three times by the circulation of freeze–pump–thaw, then Ru(p-cymene)(TsDPEN) (3 mg, 0.005 mmol) was added under argon atmosphere. The reaction mixture was then stirred at argon atmosphere for about 1 h to effect a complete conversion of the substrate.[5] The solvent was removed

under reduced pressure and the residue was purified by flash chromatography to give the product (**6a**).

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.41–7.26$ (m, 5 H), 6.82 (dd, $J = 15.9$, 1.5 Hz, 1 H), 6.24 (dd, $J = 15.9$, 5.7 Hz, 1 H), 5.13 (hept, $J = 6.0$ Hz, 1 H), 4.81–4.76 (m, 1 H), 3.13 (d, $J = 5.7$ Hz, 1 H), 1.32 (d, $J = 6.0$ Hz, 3 H), 1.28 (d, $J = 6.0$ Hz, 3 H).
^{13}C-NMR (75.4 MHz, CDCl$_3$): $\delta = 172.95$, 136.30, 131.88, 128.55, 127.91, 126.63, 125.57, 71.25, 70.21, 21.73, 21.70.
IR (KBr, cm^{-1}): 3451, 1729, 1201, 1106.
MS (m/z): 220 (M$^+$, 2.88).
HRMS calcd for C$_{13}$H$_{16}$O$_3$: 220.1100. Found: 220.1099.

CONCLUSION

In conclusion, we have found a convenient and practical method for the selective reduction of C=O bond of a wide spectrum of α-keto-β,γ-unsaturated esters with Ru(p-cymene)(TsDPEN) as catalyst. The transition metal catalyzed transfer hydrogenation reaction with good selectivity and high efficiency offers possibilities to provide the optically active α-hydroxy-β,γ-unsaturated esters with chiral catalysts. Table 3.8 gives different substrates that can be reduced with Ru(p-cymene) (TsDPEN) complex in isopropyl alcohol.

Table 3.8 Ru-TsDPEN catalyzed transfer hydrogenation reaction of β,γ-unsaturated-α-ketoesters.[a]
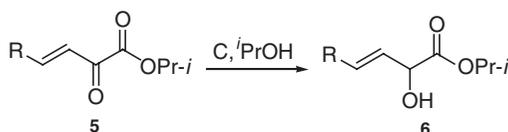
Entry	R(5)	6, yield %[b] (ee %)[c]
1	Phenyl (**5a**)	**6a**, 94 (8)
2	p-CF$_3$C$_6$H$_4$ (**5b**)	**6b**, 95
3	p-MeOC$_6$H$_4$ (**5c**)	**6c**, 93
4	p-BrC$_6$H$_4$ (**5d**)	**6d**, 92 (6)
5	2, 4-dichlorophenyl (**5e**)	**6e**, 91
6	(E)-PhCH=CH (**5f**)	**6f**, 99 (7)
7	2-furanyl (**5g**)	**6g**, 99 (59)
8	2-thiophenyl (**5h**)	**6h**, 95 (65)
9	Et$_2$CH (**5i**)	**6i**+**7i**,[d] 99 (**6i** : **7i** = 4:1)

[a]All reactions were run with ketoester (0.5 mmol), Ru(p-cymene)(TsDPEN) (3 mg, 0.005 mmol) in isopropyl alcohol (5 mL) at room temperature for 1 h under argon atmosphere.
[b]Isolated yields.
[c]ee obtained when enantiopure (1S, 2S)-TsDPEN was employed as ligand.
[d]β, γ-Saturated α-hydroxy esters.

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3. Haack, K.–J., Hashiguchi, S., Fujii, A., Ikariya, A. and Noyori. R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285–288.
4. Schummer, A., Yu, H. and Simon, H. *Tetrahedron* **1991**, *47*, 9019–9034.
5. The reaction process can be monitored by TLC or GC. The unsaturated ketoester is generally consumed within 1 h. Once the starting material is consumed, the reaction can be quenched with 1 N HCl. The double bond in the product will be slowly reduced at elevated temperature (80 °C) and prolonged reaction time. However, it is relatively stable at room temperature under the catalysis of Ru(p-cymene)(TsDPEN); no significant amount ($<1\%$) of double bond reduced product was detected 5 h after the consumption of the starting material.

3.11 PREPARATION OF POLYMER-SUPPORTED RU-TSDPEN CATALYSTS AND THEIR USE FOR ENANTIOSELECTIVE SYNTHESIS OF (S)-FLUOXETINE

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Asymmetric transfer hydrogenation of prochiral ketones is one the most attractive chemical methods to obtain optically active secondary alcohols.[1] Covalent immobilization of the chiral ligand onto a polymer bead allows the simple recovery and reuse of the usually expensive chiral catalyst and decreases the potentially toxic transition metal species contaminating the product, thus rendering the procedure to be green and practical.[2] Recently, we presented the synthesis of two novel polystyrene-bound chiral Ru-TsDPEN catalysts (Figures 3.8 and 3.9), which have been shown to exhibit high activities and enantioselectivities for heterogeneous asymmetric transfer hydrogenation of several functionalized aromatic ketones (Table 3.9).[3] The resulting secondary alcohols are useful in the synthesis of optically active fluoxetine (Figure 3.10),[3] a very important antidepressant.

3.11.1 SYNTHESIS OF THE SUPPORTED LIGAND 9

9
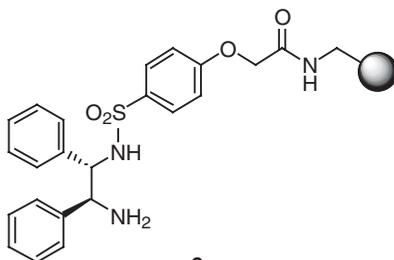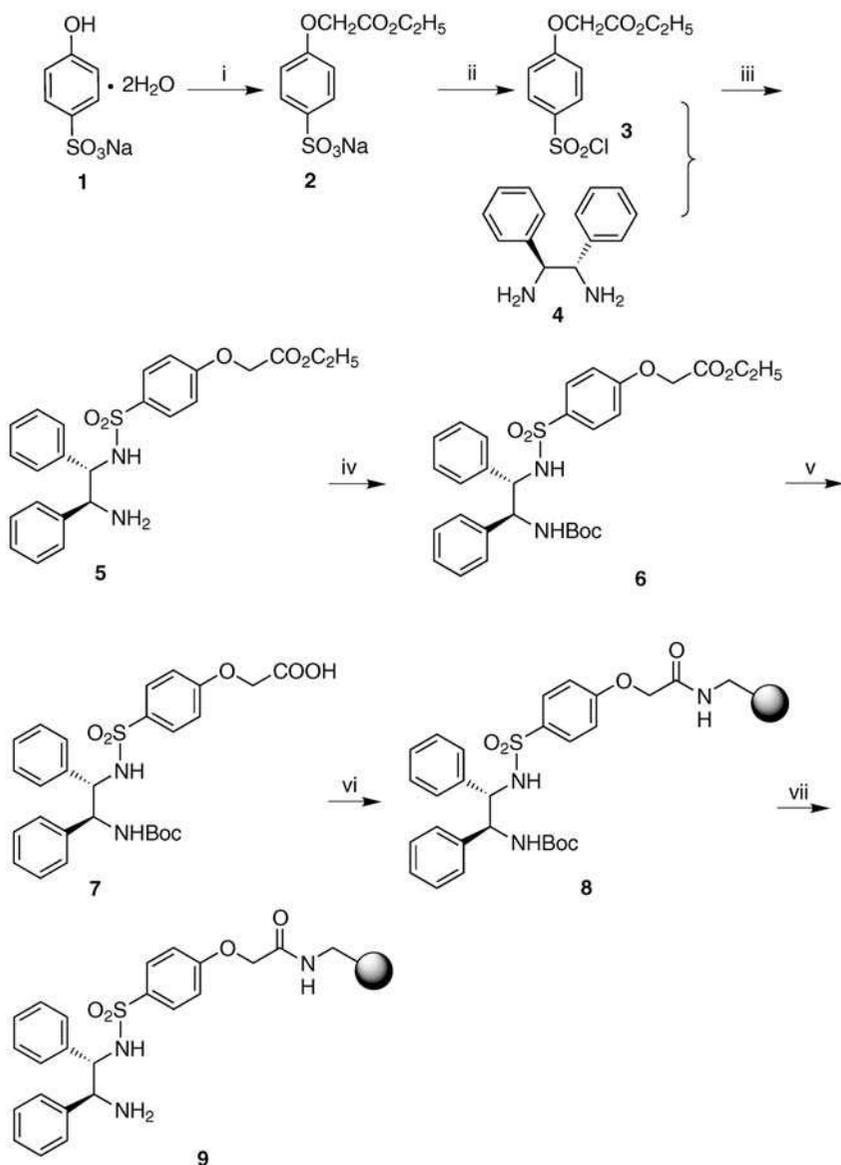
Figure 3.8   Reagents and conditions: (i) Dean–Stark; then $BrCH_2CO_2Et$, K_2CO_3, dibenzo-18-crown-6, acetone, 95 %; (ii) $SOCl_2$, DMF (cat.), 71 %; (iii) Et_3N, CH_2Cl_2, 55 %; (iv) $(Boc)_2O$, DIPEA, CH_2Cl_2, 98 %; (v) NaOH, H_2O, 95 %; (vi) aminomethylated polystyrene, DCC, pentafluorophenol, DMAP; (vii) TFA, CH_2Cl_2. Reprinted from reference [3], with permission from Elsevier.
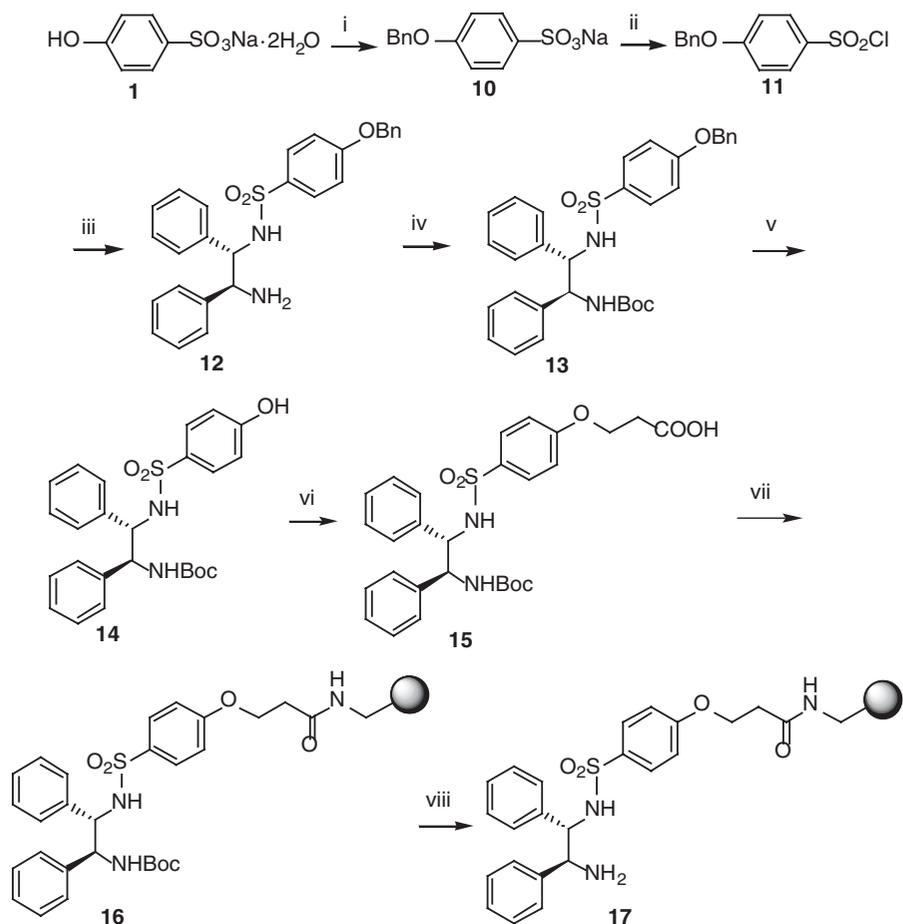
Figure 3.9 Reagents and conditions: (i) Dean–Stark; then BnBr, K₂CO₃, dibenzo-18-crown-6, acetone, 99 %; (ii) SOCl₂, DMF (cat.), 85 %; (iii) **4**, Et₃N, CH₂Cl₂, 65 %; (iv) (Boc)₂O, DIPEA, CH₂Cl₂, 95 %; (v) Pd/C, H₂, CH₃OH, 99 %; (vi) Cs₂CO₃, 3-bromopropionic acid, acetone, 67 %; (vii) aminomethylated polystyrene, DCC, pentafluorophenol, DMAP; (viii) TFA, CH₂Cl₂. Reprinted from reference [3], with permission from Elsevier.

Materials and Equipment

- Sodium 4-hydroxybenzenesulfonate dihydrate (98 %) (2.37 g, 0.010 mol)
- Ethyl bromoacetate (98 %) (2.04 g, 0.012 mol)
- Potassium carbonate (99 %) (2.79 g, 0.02 mol)
- Dibenzo-18-crown-6 (98 %) (74 mg, 0.2 mmol)
- Thionyl chloride (freshly distilled) (15 mL)
- Dry *N,N*-dimethylformamide (69 mg, 0.95 mmol)
- (1*S*,2*S*)-Diphenylethylenediamine (97 %) (219 mg, 1.0 mmol)

Table 3.9 Asymmetric transfer hydrogenation of aromatic ketones **18a-c**[a]
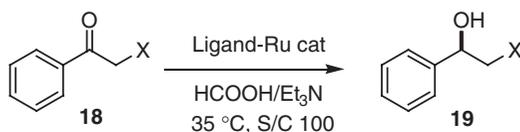
18,19 **a**: X = $CO_2C_2H_5$; **b**: $CONHCH_3$; **c**: CN

Entry	Ketone	Ligand	Time (h)	Conversion[b](%)	ee [c](%)
1	**18a**	**9**	24	97	94
2	**18a**	**17**	20	95	96
3	**18b**	**9**	22	93	86
4	**18b**	**17**	22	95	88
5	**18c**	**9**	17	98	95
6	**18c**	**17**	17	98	97
7	**18c**	**17** (2nd use)	28	92[d]	93
8	**18c**	**17** (3rd use)	60	81[d]	93

[a] Ketone:chiral ligand:[Ru] = 100:1.2:1, ketone = 0.5 mol L^{-1}, acid:triethylamine azeotrope, $CH_2Cl_2 = 1:1$.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by HPLC on a Daciel Chiralcel OD column.
[d] Based on GC analysis. Reprinted from reference [3], with permission from Elsevier.

- Di-*tert*-butyl dicarbonate (98 %) (267 mg, 1.2 mmol)
- *N,N*-Diisopropylethylamine (99 %) (260 mg, 2 mmol)
- Sodium hydroxide (97 %) (165 mg, 4.0 mmol)
- 1,3-Dicyclohexylcarbodiimide (99 %) (1.04 g, 5 mmol)
- Pentafluorophenol (99+ %) (920 mg, 5 mmol)
- 4-(Dimethylamino)pyridine (99 %) cat.
- Aminomethylated polystyrene (DVB 1 %, 1.07 mmol g^{-1}) (930 mg)
- Trifluoroacetic acid / dichloromethane (1/1, v/v) (10 mL)
- Triethylamine
- Benzene
- Acetone
- *N,N*-Dimethylformamide
- Dichloromethane
- Methanol
- Ethyl acetate
- Hexane
- 5 % aq. HCl
- Citric acid
- Ice, water, brine
- Saturated solution of sodium hydrogencarbonate
- Anhydrous sodium sulfate
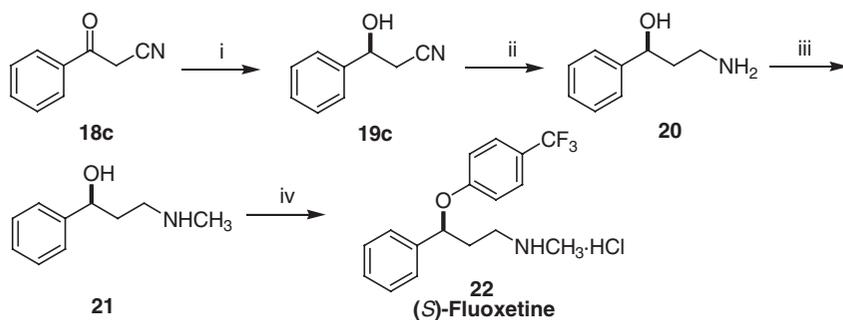
Figure 3.10 Reagents and conditions: (i) ligand **17**, [Ru(η^6-cymene)Cl$_2$]$_2$, HCOOH/Et$_3$N, CH$_2$Cl$_2$, 98 %; (ii) BH$_3$·Me$_2$S, THF, 92 %; (iii) methyl chloroformate, K$_2$CO$_3$, CH$_2$Cl$_2$; then LiAlH$_4$, THF, two steps: 92 %; (iv) NaH, 4-chlorobenzotrifluoride, DMSO, then saturated HCl of Et$_2$O, 90 %. Reprinted from reference [3], with permission from Elsevier.

- Anhydrous magnesium sulfate
- Silica gel (10–40 μm)
- TLC plates, SIL G-60 UV$_{254}$
- Dean–Stark apparatus
- 25 mL, 50 mL and 100 mL round-bottomed flasks
- A 50 mL Schlenk reaction and storage tube
- Magnetic stirring plate
- Several magnetic stir bars
- A stirring bar retriever
- A 250 mL separatory funnel
- A Büchner funnel, diameter 7 cm
- A 250 mL Büchner flask
- Filter paper
- A reflux condenser
- A 50 mL addition funnel with pressure-equalization arm
- Several flash-chromatography columns
- Rotary evaporator

Procedure

1. *Sodium 4-[(ethoxycarbonyl)methoxy] benzenesulfonate (2)*
Sodium 4-hydroxybenzenesulfonate dihydrate (2.37 g, 0.01 mol) was dehydrated by distillation with benzene using Dean–Stark apparatus and then dissolved in 20 mL of acetone in a 100 mL round-bottomed flask with a reflux condenser. Ethyl bromoacetate (2.04 g, 0.012 mol), potassium carbonate (2.79 g, 0.02 mol) and dibenzo-18-crown-6 (74 mg, 0.2 mmol) were added, and the mixture was heated at reflux for 48 h. After cooling to room temperature, the crystals were collected on a Büchner funnel, washed with acetone (2 × 60 mL), and dried under reduced pressure to yield **2** as a white powder (2.68 g, 95 %). m.p. > 300 °C.
IR (KBr): $v = 3070, 2866, 1730, 1598, 1495, 1451\,\text{cm}^{-1}$.

2. *Ethyl (4-chlorosulfonyl)phenoxyacetate* (**3**)

The sodium salt **2** (2.68 g, 0.095 mol) and a magnetic stir bar were placed in a dry 100 mL round-bottomed flask equipped with a 50 mL addition funnel with pressure-equalization arm. A solution of dry *N,N*-dimethylformamide (69 mg, 0.95 mmol) in thionyl chloride (15 mL) was prepared and transferred to the dropping funnel, which was added dropwise to the flask containing **2** with stirring at 0 °C. The resulting mixture was stirred at 60 °C for 2 h. At the end of this time, the mobile, nearly homogeneous reaction mixture was poured over 100 g of ice with vigorous stirring. The aqueous layer was extracted with ethyl acetate (3×50 mL). The organic phases were combined, washed with 50 mL of ice water, then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator. The product was purified by silica gel chromatography (eluent: ethyl acetate/hexane, 1/9, v/v) to provide **3** as a colourless viscous liquid (1.87 g, 67 %). IR (neat): $v = 3093, 2938, 1720, 1586, 1492, 1368, 1262 \, \text{cm}^{-1}$.

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 1.32$ (t, $J = 7.1$ Hz, 3 H, CH$_2$*CH$_3$*), 4.30 (q, $J = 7.1$ Hz, 2 H, *CH$_2$*CH$_3$), 4.74 (s, 2 H, CH$_2$CO), 7.06 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$), 7.99 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$).

3. *(1S,2S)-N-[(4-Ethoxycarbonyl)methoxybenzenesulfonyl]-1,2-diphenylethylene-diamine* (**5**)

In a 100 mL round-bottomed flask equipped with a 50 mL addition funnel with pressure-equalization arm were placed triethylamine (101 mg, 1.0 mmol), *(1S,2S)*-diphenylethylenediamine (219 mg, 1.0 mmol) and dichloromethane (10 mL) and a magnetic stir bar. A solution of **3** (279 mg, 1.0 mmol) in dichloromethane (20 mL) was prepared. The solution was placed in the dropping funnel and added carefully dropwise over 1 h. The mixture was stirred at room temperature for 4 h, and washed with saturated aqueous sodium hydrogencarbonate (20 mL). The organic phase was separated and dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The residue was purified by silica gel chromatography [gradient elution: CH$_2$Cl$_2$ to CH$_2$Cl$_2$/EtOAc/Et$_3$N (1/2/0.01, v/v/v)] to yield **5** as a white powder (250 mg, 55 %). m.p. 121–123 °C.
IR (KBr): $v = 3209, 3010, 2880, 1729, 1589, 1453 \, \text{cm}^{-1}$.

^{1}H-NMR (500 MHz, CDCl$_3$): $\delta = 1.21$ (t, $J = 7.0$ Hz, 3 H, CH$_2$*CH$_3$*), 3.94 (d, $J = 7.5$ Hz, 1 H, CH), 4.17 (q, $J = 7.0$ Hz, 2 H, *CH$_2$*CH$_3$), 4.29 (d, $J = 7.5$ Hz, 1 H, CH), 4.78 (s, 2 H, CH$_2$CO), 6.77 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$), 6.92–7.12 (m, 10 H, $2 \times$ C$_6$H$_5$), 7.33 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$).

4. *(1S,2S)-N-Boc-N'-[(4-ethoxycarbonyl)methoxybenzenesulfonyl]-1,2-diphenyl-ethylenediamine* (**6**)

In a 50 mL round-bottomed flask equipped with a magnetic stir bar were placed **5** (454 mg, 1.0 mmol), di-*tert*-butyl dicarbonate (267 mg, 1.2 mmol), *N,N*-diisopropylethylamine (260 mg, 2 mmol) and dichloromethane (20 mL). The solution was stirred at room temperature for 4 h. The resulting solution was washed with 5 % aq. HCl. The organic phase was separated, dried over anhydrous sodium sulfate and

concentrated on a rotary evaporator. The residue was purified by silica gel chromatography (eluent: CH_2Cl_2/EtOAc, 1/1) to give **6** as a white powder (544 mg, 98 %). m.p. 131–133 °C.

IR (KBr): $v = 3033$, 2934, 1710, 1627, 1593, 1450, 1320 cm^{-1}.

^{1}H-NMR (500 MHz, DMSO-d_6): $\delta = 1.21$ (t, $J = 7.1$ Hz, 3 H, CH$_2$*CH$_3$*), 1.29 (s, 9H, C(CH$_3$)$_3$), 4.20 (q, $J = 7.1$ Hz, 2 H, *CH$_2$*CH$_3$), 4.64 (s, 2 H, 2 × CH), 4.71 (s, 2 H, CH$_2$CO), 6.80 (d, $J = 8.8$ Hz, 2 H, C$_6$H$_4$), 7.08–7.25 (m, 10 H, 2 × C$_6$H$_5$), 7.35 (d, $J = 8.8$ Hz, 2H, C$_6$H$_4$), 8.10 (s, 1 H, NHCO).

5. *(1S,2S)-N*-Boc-*N′-(4-carboxymethoxybenzenesulfonyl)-1,2-diphenylethylenediamine (7)*

In a 25 mL round-bottomed flask equipped with a reflux condenser were placed **6** (555 mg, 1.0 mmol), sodium hydroxide (165 mg, 4.0 mmol) in 4 mL of CH_3OH/H_2O (1:1, v/v) and a magnetic stir bar. The solution was stirred under reflux for 6 h. The resulting mixture was cooled and diluted with 10 mL H_2O and acidified with citric acid, and then extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with 10 mL of brine, then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator. The residue was purified by silica gel chromatography using hexane/EtOAc (1/2, v/v) as the eluent, yielding **7** as colourless crystals (501 mg, 95 %). m.p. 142–143 °C.

IR (KBr): $v = 3390$, 2921, 2851, 1685, 1592, 1316 cm^{-1}.

^{1}H-NMR (500 MHz, DMSO-d_6): $\delta = 1.23$ [s, 9 H, C(CH$_3$)$_3$], 4.61–4.64 (m, 2H, CH$_2$CO and CH), 4.81 (s, 1 H, CH), 6.67 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$), 7.04–7.18 (m, 10 H, 2 × C$_6$H$_5$), 7.30 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$), 8.05 (s, 1 H, NHCO).

6. *The polymer-bound ligand* **8**

A dry 50 mL Schlenk reaction tube was flushed with nitrogen and charged with a mixture of **7** (527 mg, 1.0 mmol), 1,3-dicyclohexylcarbodiimide (1.04 g, 5 mmol), pentafluorophenol (920 mg, 5 mmol), 4-(dimethylamino)pyridine as the catalyst and the aminomethylated polystyrene (930 mg, 1.07 mmol g^{-1}) in dry dichloromethane (20 mL). The mixture was stirred at room temperature for 24 h under a N$_2$ atmosphere. The polymer was filtrated, rinsed sequentially with CH_2Cl_2 and acetone and dried at 50 °C *in vacuo* to yield the polymer-bound ligand **8** as pale yellow beads.

Elemental analysis: Found: N, 2.90 requires N, 2.91 %.

IR (KBr): $v = 3058$, 2922, 2850, 1671, 1601, 1492, 1451, 1366 cm^{-1}.

7. *The polymer-bound ligand* **9**

In a 25 mL round-bottomed flask were placed a solution of trifluoroacetic acid / dichloromethane (1/1, v/v, 10 mL) and a magnetic stir bar. The polymer-bound ligand **8** (500 mg) was added in batches. The mixture was stirred at room temperature for 40 min. The polymer was filtrated, rinsed sequentially with CH_2Cl_2 and CH_2Cl_2/Et$_3$N (1/4, v/v), and dried at 50 °C *in vacuo* to yield the deprotected polymer-bound ligand **9** as pale yellow beads.

Elemental analysis: Found: N, 3.04 requires N, 3.13 %.

IR (KBr): $v = 3025$, 2922, 2851, 1664, 1601, 1493, 1452, 1382 cm^{-1}.

3.11.2 SYNTHESIS OF LIGAND 17
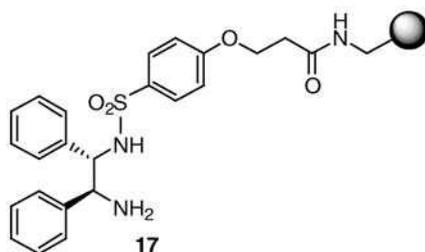
Materials and Equipment

- Sodium 4-hydroxybenzenesulfonate dehydrate (98 %)
- Benzyl bromide (98 %)
- Potassium carbonate (99 %)
- Dibenzo-18-crown-6 (98 %)
- Thionyl chloride
- Dry *N,N*-dimethylformamide
- (*1S,2S*)-Diphenylethylenediamine (97 %)
- Di-*tert*-butyl dicarbonate (98 %)
- *N,N*-Diisopropylethylamine (99 %)
- 10 % Pd/C (11 mg, 0.1 mmol)
- Sodium hydroxide (97 %)
- 1,3-Dicyclohexylcarbodiimide (99 %)
- Pentafluorophenol (99+ %)
- 4-(Dimethylamino)pyridine (99 %)
- Aminomethylated polystyrene (DVB 1 %, 1.07 mmol g^{-1})
- Trifluoroacetic acid / dichloromethane (1/1, v/v), 10 mL
- 3-Bromopropionic acid (97 %) (158 mg, 1 mmol)
- Cesium carbonate (99.9 %) (652 mg, 2 mmol)
- Triethylamine
- Benzene
- Acetone
- *N,N*-Dimethylformamide
- Dichloromethane
- Methanol
- Ethyl acetate, hexane
- 5 % aq. HCl
- Citric acid
- Ice, water, brine
- Saturated solution of sodium hydrogencarbonate
- Anhydrous sodium sulfate

- Anhydrous magnesium sulfate
- Hydrogen (atmosphere pressure)
- Silica gel (10–40 μm)
- TLC plates, SIL G-60 UV$_{254}$
- Dean–Stark apparatus
- 25 mL, 50 mL and 100 mL round-bottomed flasks
- A 50 mL Schlenk reaction and storage tube
- Magnetic stirring plate
- Several magnetic stir bars
- A stirring bar retriever
- A 250 mL separatory funnel
- A Büchner funnel, diameter 7 cm
- A Büchner flask, 250 mL
- Filter paper
- A reflux condenser
- A 50 mL addition funnel with pressure-equalization arm
- Several flash-chromatography columns
- Rotary evaporator
- A hydrogen-volume-measurement burette
- A hydrogen cylinder

Procedure

1. Compounds **10**, **11**, **12** and **13** were prepared as described for **2**, **3**, **5** and **6**, respectively.
2. (1*S*,2*S*)-*N*-Boc-*N'*-(4-hydroxybenzenesulfonyl)-1,2-diphenylethylenediamine (**14**)

    The *N*-boc-*N'*-benzyl protected diamine **13** (559 mg, 1 mmol), 10 % Pd/C (11 mg, 0.1 mmol) and 20 mL methanol were placed in a 50 mL round-bottomed flask equipped with a magnetic stir bar and a hydrogen inlet tube which is connected to a hydrogen volume measurement burette and a hydrogen cylinder. The mixture was degassed with the aid of a water aspirator and hydrogen gas was introduced with caution. The mixture was stirred at room temperature for 24 h under an atmosphere of H$_2$. At completion of the reaction, the mixture was filtered, and the cake was washed with methanol. The combined methanol solutions were evaporated on a rotary evaporator and the residue was purified by silica gel chromatography using CH$_2$Cl$_2$ as eluent to yield a white powder (464 mg, 99 %). m.p. 132 °C (dec.).

IR (KBr): $v = 3381, 3033, 2978, 1688, 1590, 1517, 1452, 1319, 1450 \, cm^{-1}$.
^{1}H-NMR (500 MHz, DMSO-*d$_6$*): $\delta = 1.25$ [s, 9 H, C(CH$_3$)$_3$], 4.60 (m, 1 H, CH), 4.79 (m, 1 H, CH), 6.50 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$), 7.02–7.24 (m, 10 H, 2 × C$_6$H$_5$), 7.25 (s, 1 H, NHCO), 7.95 (d, $J = 8.7$ Hz, 2 H, C$_6$H$_4$), 10.07 (br, 1 H, OH).

3. (1*S*,2*S*)-*N*-Boc-*N'*-(4-carboxyethoxybenzenesulfonyl)-1,2-diphenylethylenediamine (**15**)

The debenzylated *N*-boc-protected diamine (469 mg, 1 mmol), 3-bromopro-pionic acid (158 mg, 1 mmol), cesium carbonate (652 mg, 2 mmol) and 10 mL of acetone were placed in a 50 mL round-bottomed flask equipped with a magnetic stir bar and a reflux condenser. The mixture was heated under reflux for 24 h. The volatiles were removed on a rotary evaporator and the residue was triturated with dichloromethane. The extracts were filtered and dried over anhydrous sodium sulfate; after evaporation of the solvent on a rotary evaporator, a pale yellow foam was obtained which was purified by silica gel chromatography (eluent: CH_2Cl_2/hexane, 1/2, v/v) to yield white crystals (362 mg, 67 %). m.p. 161–163 °C.

IR (KBr): $v = 3381, 2923, 2852, 1687, 1590, 1454, 1318, 1288 \, cm^{-1}$.

^{1}H-NMR (500 MHz, DMSO-d_6): $\delta = 1.27$ [s, 9 H, $C(CH_3)_3$], 2.67 (t, $J = 5.8$ Hz, 2 H, CH_2COOH), 4.14 (t, $J = 5.8$ Hz, 2 H, OCH_2), 4.61 (m, 1 H, CH), 4.79 (m, 1 H, CH), 6.68 (d, $J = 8.6$ Hz, 2 H, C_6H_4), 7.07–7.19 (m, 10 H, $2 \times C_6H_5$), 7.29 (d, $J = 8.6$ Hz, 2 H, C_6H_4), 8.04 (s, 1 H, NHCO), 12.41 (br, 1 H, COOH).

4. *The polymer-bound ligand* **16**

   16 was prepared as described for the polymer **8**.

   Elemental analysis: Found: N, 2.71 requires N, 2.88 %.

   IR (KBr): $v = 3059, 2923, 2853, 1669, 1602, 1494, 1451, 1367, 1165, 1090 \, cm^{-1}$.

5. *The polymer-bound ligand* **17**

   17 was prepared as described for the polymer **9**.

   Elemental analysis: Found: N, 3.01 requires N, 3.06 %.

   IR (KBr): $v = 3058, 2924, 2855, 1671, 1601, 1492, 1450, 1369, 1163 \, cm^{-1}$.

3.11.3   GENERAL PROCEDURE FOR ASYMMETRIC TRANSFER HYDROGENATION

Materials and Equipment

- Polymer-bound ligand (0.012 mmol)
- $[Ru(\eta^6\text{-cymene})Cl_2]_2$ (3.1 mg, 0.005 mmol)
- Dry dichloromethane
- Ketone (1.0 mmol)
- HCOOH–Et_3N azeotrope (1.0 mL)
- Dichloromethane
- Saturated solution of sodium hydrogencarbonate
- Anhydrous magnesium sulfate
- Silica gel (10–40 μm)
- TLC plates, SIL G-60 UV_{254}
- A 50 mL Schlenk reaction and storage tube with a magnetic stir bar
- Magnetic stirring plate
- A Büchner funnel, diameter 3.6 cm
- A Büchner flask, 250 mL
- Filter paper

- Rotary evaporator
- A flash-chromatography column

Procedure

1. A suspension of [Ru(η^6-cymene)Cl$_2$]$_2$ (3.1 mg, 0.005 mmol) and the polymer-bound ligand (0.012 mmol) in dichloromethane (1 mL) was stirred in a dry 50 mL Schlenk reaction tube for 1 h at room temperature under an atmosphere of argon. The appropriate ketone (1.0 mmol) and HCOOH–Et$_3$N azeotrope (1.0 mL) were sequentially added, and the mixture was stirred for an appropriate period of time (as indicated in Table 3.9) at 35 °C. After completion of the reaction, the suspension was diluted with dichloromethane (20 mL) and filtered immediately. The filtrates were washed with a saturated solution of sodium hydrogencarbonate and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator. The residue was purified by silica gel chromatography using CH$_2$Cl$_2$ as eluent.

   The recovered catalyst was washed with dichloromethane four times and reused in the hydrogen transfer reaction by reloading HCOOH–Et$_3$N azeotrope (1.0 mL) and the ketone (1.0 mmol).

Note: Since the catalyst is rather moisture-sensitive, it is a necessity to use dry solvents and equipment. The reaction has to be performed with exclusion of moisture.

3.11.4   PREPARATION OF (S)-FLUOXETINE HYDROCHLORIDE

22
(S)-Fluoxetine
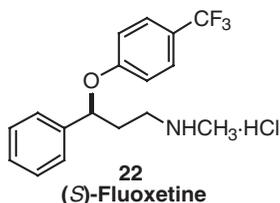
Materials and Equipment

- The polymer ligand **17** (494 mg, 0.36 mmol)
- [Ru(η^6-cymene)Cl$_2$]$_2$ (90 mg, 0.15 mmol)
- 2-Cyanoacetophenone (4.35 g, 30.0 mmol)
- HCOOH–Et$_3$N azeotrope (30 mL)
- BH$_3$·Me$_2$S (1.76 g, 2.2 mL, 23 mmol)
- Methyl chloroformate (99 %) 3.05g, 32 mmol)
- Potassium carbonate (99 %) (15.1 g, 108 mmol)
- Lithium aluminum hydride (95 %) (1.08 g, 27 mmol)

- Sodium hydride (60 %) (1.19 g, 30 mmol)
- 4-Chlorobenzontrifluoride (98 %) (4.59 g, 25 mmol)
- Saturated solution of HCl in Et$_2$O
- Dimethylsulfoxide
- Dichloromethane
- Ethyl acetate, methanol
- Dry THF
- Diethyl ether
- Water, brine
- Saturated solution of sodium hydrogencarbonate
- Anhydrous sodium sulfate
- Anhydrous magnesium sulfate
- Silica gel (10–40 μm)
- TLC plates, SIL G-60 UV$_{254}$
- A 200 mL Schlenk reaction and storage tube
- 100 mL and 250 mL round-bottomed flasks
- Magnetic stirring plate
- Several magnetic stir bars
- A 125 mL separatory funnel
- A Büchner funnel, diameter 7 cm
- A Büchner flask, 250 mL
- Filter paper
- A reflux condenser
- A 50 mL addition funnel with pressure-equalization arm
- Several flash-chromatography columns
- Rotary evaporator

Procedure

1. *(S)-2-Cyano-1-phenyl-1-ethanol* **(19c)**

A suspension of [Ru(η^6-cymene)Cl$_2$]$_2$ (90 mg, 0.15 mmol) and the polymer-bound ligand **17** (494 mg, 0.36 mmol) in dichloromethane (30 mL) was stirred in a 200 mL Schlenk reaction tube for 1 h at room temperature under argon. 2-Cyanoacetophenone (4.35 g, 30.0 mmol) and HCOOH–Et$_3$N azeotrope (30 mL) were added and the mixture stirred for 18 h at 35 °C. After addition of dichloromethane (50 mL), the suspension was filtered immediately. The filtrates were washed with saturated solution of sodium hydrogencarbonate and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator. The residue was purified by silica gel chromatography using CH$_2$Cl$_2$ as eluent to yield a colourless viscous liquid (4.33 g, 98%). $[\alpha]_D^{20}$ – 53.2° ($c = 2.60$, C$_2$H$_5$OH) [lit.,[4] $[\alpha]_D^{20}$ – 52.5° ($c = 2.60$, C$_2$H$_5$OH)].

^{1}H-NMR (500 MHz, CDCl$_3$): $\delta = 2.54$ (br, 1 H, OH), 2.77–2.79 (m, 2 H, CH$_2$CN), 5.07 (t, $J = 6.1$ Hz, 1 H, *CH*OH), 7.33–7.57 (m, 5 H, C$_6$H$_5$).

2. *(S)-3-Amino-1-phenyl-1-propanol* (**20**)

(*S*)-**19** (4.30 g, 29 mmol) and 10 mL dry tetrahydrofuran were placed in a 100 mL round-bottomed flask equipped with a magnetic stir bar and a 50 mL addition funnel with pressure-equalization arm. A solution of $BH_3 \cdot Me_2S$ (1.76 g, 2.2 mL, 23 mmol) in anhydrous tetrahydrofuran (10 mL) was placed in the dropping funnel and added dropwise to the solution of (*S*)-**19** (4.30 g, 29 mmol) in dry tetrahydrofuran (10 mL) at 0 °C with stirring under N_2. The mixture was heated at 70 °C for 4 h. After cooling to 0 °C, 20 mL of water was added carefully to quench the reaction and the product was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated on a rotary evaporator. Purification by silica gel chromatography (eluent: EtOAc/methanol, 1:1) afforded a white solid (4.03 g, 92%). m.p. 53–55 °C (lit.,[5] 56 °C); $[\alpha]_D^{20}$ − 44.1° ($c = 1$, CH_3OH) [lit.,[6] $[\alpha]_D^{20}$ − 43.7° ($c = 1$, CH_3OH)].

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 1.72$–1.85 (m, 2 H, CH_2NH_2), 2.91–3.13 (m, 2 H, CH_2CH), 5.01 (dd, $J = 3.0$, 8.6 Hz, 1 H, $CHOH$), 7.25–7.57 (m, 5 H, C_6H_5).

3. *(S)-3-Methylamino-1-phenyl-1-propanol* (**21**)

In a 100 mL round-bottomed flask equipped with a magnetic stir bar were placed (*S*)-**20** (4.03 g, 27 mmol), methyl chloroformate (3.05 g, 32 mmol) and dichloromethane (15 mL). A solution of potassium carbonate (15.1 g, 108 mmol) in H_2O (15 mL) was added at 0 °C with stirring. The mixture was warmed to room temperature and stirred for a further 30 min. After the reaction was complete, 10 mL of water were added to the mixture, which was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator and then evaporated to dryness *in vacuo*. The residual solid was dissolved in 10 mL of THF, which was used directly in the next reduction step. *Reduction:* To a suspension of lithium aluminum hydride (1.08 g, 27 mmol) in anhydrous THF (20 mL) was added dropwise a solution of the above formamide intermediate in 10 mL of THF at 0 °C with stirring under N_2. Then the mixture was heated at reflux for 8 h. After cooling to 0 °C, 4 mL of degassed water was added carefully to quench the reaction. The resulting mixture was filtered off, and the organic layers were separated, dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. Purification by flash chromatography over silica gel (CH_2Cl_2/methanol, 1:1) yielded **21** as a colourless viscous oil (4.10 g, 92%). $[\alpha]_D^{20}$ − 37.5° ($c = 1$, $CHCl_3$) [lit.,[5] $[\alpha]_D^{20}$ − 38.2° ($c = 1.07$, $CHCl_3$)].

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 1.72 \sim 1.93$ (m, 2 H, CH_2NH), 2.44 (s, 3 H, CH_3), 2.87 (m, 2 H, CH_2CH), 4.92 (dd, $J = 3.0$, 8.5 Hz, 1 H, $CHOH$), 7.31–7.42 (m, 5 H, C_6H_5).

4. *(S)-Fluoxetine hydrochloride* (**22**)

In a 100 mL round-bottomed flask equipped with a magnetic stir bar were placed (*S*)-3-(methylamino)-1-phenylpropan-1-ol **21** (4.10 g, 25 mmol) and dry dimethyl sulfoxide (20 mL). Sodium hydride (60 %) (1.19 g, 30 mmol) was added in three

batches into the solution at 0 °C with stirring. After the mixture was vigorously stirred at 70 °C for 30 min, a solution of 4-chlorobenzotrifluoride (4.59 g, 25 mmol) in 5 mL of dry dimethyl sulfoxide was added to the mixture and then heated at 90 °C for 2 h. The resulting mixture was cooled to 0 °C, 20 mL of water was added carefully and extracted with diethyl ether (2×20 mL). The diethyl ether extracts were combined and dried over anhydrous magnesium sulfate and concentrated to about 10 mL. A saturated solution of HCl in Et_2O was added dropwise into the solution, the crystals were collected on a Büchner funnel, washed with diethyl ether (2×50 mL), and dried under reduced pressure to yield **22** as colorless crystals (7.79 g, 90 %). m.p. 144–145 °C (lit.,[7] 138–140 °C); $[\alpha]_D^{20} + 13.5°$ ($c = 1$, $CHCl_3$) [lit.,[8] $[\alpha]_D^{20} + 13.9°$ ($c = 1.01$, $CHCl_3$)].

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 2.50$ (m, 2 H, CH_2N^+), 2.64 (s, 3 H, CH_3), 3.21 (m, 2 H, CH_2CH), 5.51 (dd, $J = 6.2$ Hz, 1 H, CHC_6H_5), 6.91 (d, $J = 8.5$ Hz, 2 H, C_6H_4), 7.21–7.53 (m, 7 H, $C_6H_5 + C_6H_4$).

CONCLUSION

The procedure for getting the polymer-bound ligands is very easy to reproduce. Three β-functionalized aromatic ketones were successfully reduced to the corresponding alcohols by heterogeneous asymmetric hydrogen transfer reaction with formic acid–triethylamine azeotrope as the hydrogen donor. One of the product alcohols (**19c**) is an intermediate for the synthesis of optically active fluoxetine.

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3.12 POLYMER-SUPPORTED CHIRAL SULFONAMIDE CATALYZED REDUCTION OF β-KETO NITRILES: A PRACTICAL SYNTHESIS OF (R)-FLUOXETINE

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Enantioselective reduction of β-keto nitriles to optically active 1,3-amino alcohols has been carried out in one step using an excess of borane-dimethyl sulfide complex as a reductant and a polymer-supported chiral sulfonamide as a catalyst with moderate to high enantioselectivity (Figure 3.11).[1] The facile and enantioselective method to prepare optically active 1,3-amino alcohols has been used to prepare 3-aryloxy-3-arylpropylamine type antidepressant drugs, for example (R)-fluoxetine.

3.12.1 SYNTHESIS OF (R)-3-AMINO-1-PHENYL-PROPAN-1-OL
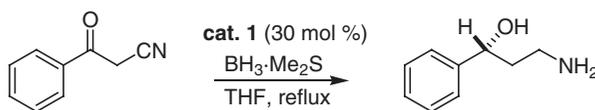
Materials and Equipment

- Polymer-supported chiral sulfonamide[2] (loading $= 2.36$ mmol g^{-1}), (127 mg, 0.30 mmol)
- Tetrahydrofuran (freshly distilled over sodium/benzophenone) (15 mL)
- Borane-dimethyl sulfide complex (2 M in THF) (1.6 mL, 3.2 mmol)
- 3-Oxo-3-phenylpropanenitrile[3] (145 mg, 1.0 mmol)
- Methanol (10 mL)
- Ethyl acetate, methanol, ammonia solution (25–28 %)
- Silica gel (Matrex 60A, 37–70 μm) (100 g)
- TLC plates, SIL G-60 UV$_{254}$
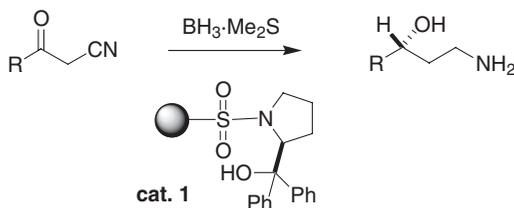
Figure 3.11

- 50 mL three-necked flask with magnetic stirrer bars
- Magnetic stirrer plate
- Syringe pump
- Rotary evaporator
- One glass column, diameter 7 cm

Procedure

1. To polymer-supported chiral sulfonamide (127 mg, 0.3 mmol) in a 50 mL three-necked flask, was added 15 mL dry THF and 1.6 mL borane-dimethyl sulfide complex under an argon atmosphere. The suspension was heated under reflux and stirred for 0.5 h.
2. Then a THF (8 mL) solution of 3-oxo-3-phenylpropanenitrile (1.0 mmol) was added at a rate of 3 mL h^{-1} by a syringe pump. After the addition was complete, the mixture was allowed to cool down and treated with 10 mL methanol and filtered. The solid polymeric catalyst was washed several times with ethyl acetate and methanol.
3. The resulting solution was evaporated and the crude product was used in the next step directly. An analytical sample was acquired by silica gel chromatography employing NH$_4$OH–CH$_3$OH–EtOAc (1:10:90) to give (R)-3-amino-1-phenyl-propan-1-ol as a colourless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.40$–7.23 (m, 5H), 4.93 (dd, $J = 3.3$ Hz, 8.5Hz, 1H), 3.05 (br, 3H), 2.97–2.89 (m, 2H), 1.90–1.69 (m, 2H).

The ee (96 %) was determined by HPLC employing a Chiralcel OB column after the product had been converted into its acetamide.

Note: This procedure has been scaled up to provide 2.0 g of the product.

3.12.2 SYNTHESIS OF (R)-ETHYL 3-HYDROXY-3-PHENYLPROPYLCARBAMATE
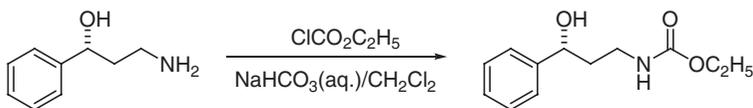
Materials and Equipment

- Ethyl chloroformate (0.4 mL)
- Dichloromethane
- Saturated aqueous NaHCO$_3$ (10 mL)
- Ethyl acetate, *n*-hexane

- Anhydrous sodium sulfate
- TLC plates, SIL G-60 UV$_{254}$
- One 50 mL flask equipped with a magnetic stirrer bar
- One glass funnel (25 mL)
- Magnetic stirrer plate

Procedure

1. To a solution of non-purified (*R*)-3-amino-1-phenylpropan-1-ol which had been prepared from 3-oxo-3-phenylpropanenitrile (1.0 mmol) (see above) in 15 mL dichloromethane was added 10 mL saturated aqueous NaHCO$_3$. Ethyl chloroformate (0.4 mL) in 15 mL dichloromethane was added to the mixture dropwise over 10 min. The mixture was allowed to stir at room temperature overnight.
2. The reaction mixture was extracted with dichloromethane (3 × 10 mL) and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography employing ethyl acetate–hexane (10:90) as the eluent to afford (*R*)-ethyl 3-hydroxy-3-phenylpropylcarbamate as an oil (63% yield over two steps from 3-oxo-3-phenylpropanenitrile).

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.34$–7.24 (m, 5H), 5.23 (br, 1H), 4.76–4.70 (m, 1H), 4.08 (q, $J = 7.0$ Hz, 2H), 3.45–3.17 (m, 3H), 1.89–1.82 (m, 2H), 1.23 (t, $J = 7.0$ Hz, 3H).

3.12.3 SYNTHESIS OF (*R*)-3-(METHYLAMINO)-1-PHENYLPROPAN-1-OL
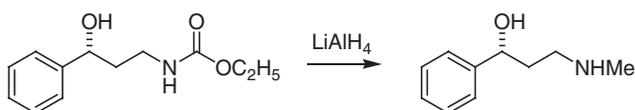
Materials and Equipment

- Lithium aluminum hydride (95 %) (240 mg)
- Tetrahydrofuran (freshly distilled over sodium/benzophenone)
- Distilled water
- Sodium sulfate
- Ethyl acetate, methanol, ammonia solution (25–28 %)
- TLC plates, SIL G-60 UV$_{254}$
- One 50 mL flask equipped with a magnetic stirrer bar
- One glass funnel, 25 mL
- Magnetic stirrer plate

Procedure

1. To a solution of lithium aluminum hydride (190 mg, 5.0 mmol) in dry tetra-hydrofuran (10 mL) under argon at room temperature was added dropwise a solution of (R)-ethyl 3-hydroxy-3-phenylpropylcarbamate (1.0 mmol) in dry tetrahydrofuran (5 mL) and the resulting reaction mixture was heated under reflux for 1 h.
2. After completion of the reaction the mixture was cooled to 0 °C and $Na_2SO_4 \cdot 10H_2O$ was added slowly. The resultant mixture was filtered; the residue was treated with ethyl acetate and filtered three times. The filtrates were combined and evaporated under reduced pressure to leave a residue which was purified by column chromatography employing NH_4OH-CH_3OH-EtOAc (1:10:90) as the eluent to afford (R)-3-(methylamino)-1-phenylpropan-1-ol as an oil (93 % yield).

^{1}H-NMR (300MHz, CDCl$_3$): $\delta = 7.39$–7.24 (m, 5H), 4.94 (dd, $J = 3.3$Hz, 8.7Hz, 1H), 3.58 (br, 2H), 2.94–2.80 (m, 2H), 2.44 (s, 3H), 1.92–1.70 (m, 2H).

3.12.4 SYNTHESIS OF (R)-FLUOXETINE
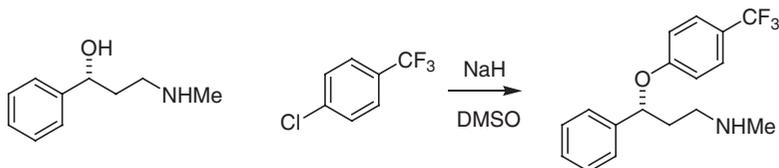
Materials and Equipment

- Sodium hydride (60 % on mineral oil) (80 mg, 2.0 mmol)
- Dry dimethylsulfoxide (8 mL)
- 4-Chlorobenzotrifluoride (330 mg, 1.82 mmol)
- Distilled water
- Diethyl ether
- Sodium sulfate
- Ethyl acetate, methanol, ammonia solution (25–28 %)
- TLC plates, SIL G-60 UV$_{254}$
- One 25 mL flask equipped with a magnetic stirrer bar
- Magnetic stirrer plate

Procedure

1. To a solution of (R)-3-(methylamino)-1-phenylpropan-1-ol (200 mg, 1.21 mmol) in dry dimethylsulfoxide (5 mL) at room temperature was added sodium hydride

(80 mg, 60 %, 2.00 mmol) and heated at 55 °C for 45 min to form the sodium alkoxide of the amino alcohol.

2. To the above-formed alkoxide was added 4-chlorobenzotrifluoride (330 mg, 1.82 mmol) in dimethylsulfoxide (3 mL) and the resulting mixture was heated at 95 °C for 1 h.

3. After the completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool down, diluted with water (8 mL) and then extracted with diethyl ether (3 × 20 mL). The combined ether layers were concentrated to leave a residue, which was purified by column chromatography employing NH_4OH-CH_3OH-EtOAc (1:10:90) as the eluent to afford (*R*)-fluoxetine[4] (92 % yield).

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.42$ (d, $J = 9.0$Hz, 2H), 7.35–7.26 (m, 5H), 6.90 (d, $J = 9.0$Hz, 2H), 5.30 (m, 1H), 2.75 (t, $J = 7.0$Hz, 2H), 2.44 (s, 3H), 2.24–2.15 (m, 2H), 2.02–1.97 (m, 1H), 1.64 (br, 1H).

CONCLUSION

The procedure provides a practical and highly enantioselective methodology for the synthesis of an optically active 1,3-amino alcohol. In respect of the efficiency and high enantioselectivity observed, this method represents a very useful alternative to previously reported procedures. Finally, we applied this method to the enantio-selective synthesis of the antidepressant drug (*R*)-fluoxetine.

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4 Imine Reduction and Reductive Amination

CONTENTS

4.1   METAL-FREE REDUCTION OF IMINES: ENANTIOSELECTIVE BRØNSTED ACID CATALYZED TRANSFER HYDROGENATION USING CHIRAL BINOL-PHOSPHATES AS CATALYSTS

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The enantioselective reduction of imines to the corresponding chiral amines still represents a challenging topic. While many highly enantioselective hydrogenations of ketones and alkenes are known, only less effective reductions of imines are available. Recently, we established that several proton acids catalyze the metal-free reduction[1] of ketimines under hydrogen-transfer conditions with Hantzsch dihydropyridine[2] as the hydrogen source. Additionally, we were able to extend this new methodology to the first organo-catalytic asymmetric hydrogenation[3] by employing chiral BINOL-phosphates as catalysts (Figure 4.1).
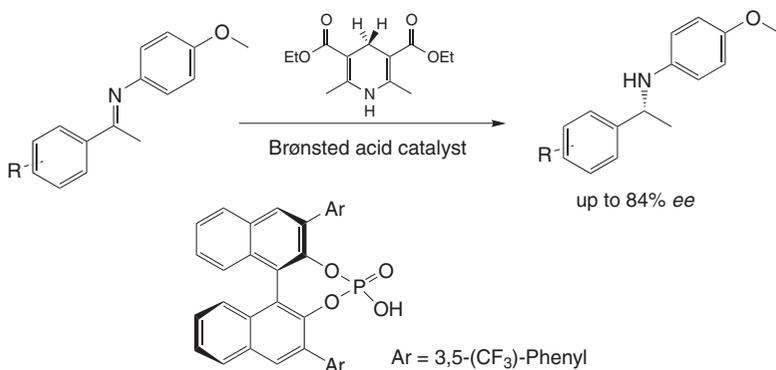
Figure 4.1

4.1.1   SYNTHESIS OF (R)-2,2′-BIS-METHOXYMETHOXY-[1,1′] BINAPHTHALENE (MOM-BINOL)
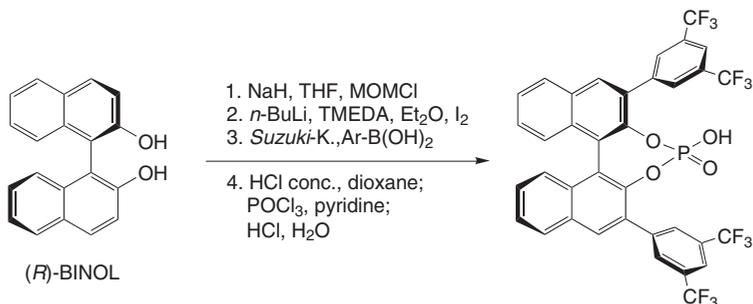
Materials and Equipment

- (R)-1,1-Binaphthalene [(R)-BINOL] (50.0 g)
- Sodium hydride (NaH) (21.0 g)
- Chloromethoxymethane (MOMCl) (36.5 mL)
- Tetrahydrofuran (THF) (1 L)
- Saturated sodium carbonate solution (300 mL)
- Deionized water (100 mL)
- Diethyl ether (400 mL)
- Sodium sulfate (anhydrous) (30 g)
- Argon line
- Ice bath
- 2 L three-necked flask with magnetic stirrer
- Sintered-glass filter, diameter 8 cm
- 2 L round-bottomed flask
- Rotary evaporator
- Column, diameter 7 cm
- Silica gel 60 (0.063–0.2) (Merck) (500 g)
- n-Hexane
- Dichloromethane
- High-vacuum (oil) pump

Note: Chloromethoxymethane is a carcinogen.

Procedure

1. The reaction was carried out under an argon atmosphere using standard Schlenk techniques. To a suspension of NaH (21.0 g, 0.52 mol) in THF (1 L), (R)-BINOL (50.0 g, 0.175 mol) was added. The mixture was stirred for 45 min, cooled down to 0 °C and MOMCl (36.5 mL, 0.44 mol) was injected. The solution was allowed to warm to room temperature, treated with saturated sodium carbonate solution (300 mL) and water (100 mL). The mixture was separated and the aqueous phase extracted with diethyl ether (4 × 100 mL). The combined organic fractions were dried (sodium sulfate) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (500 g silica gel, eluent: n-hexane/ CH_2Cl_2 1:1→CH_2Cl_2) to yield the protected BINOL as a colourless solid (53.0 g, 96 %).

R_f (n-hexane/ ethyl acetate 5:1) = 0.34.
^{1}H-NMR (250 MHz, CDCl$_3$): δ = 3.15 (s, 6 H, 2 OCH$_3$), 4.98 (d, J = 6.8 Hz, 2 H, 2 OCHH), 5.08 (d, J = 6.8 Hz, 2 H, 2 OCHH), 7.11–7.38 (m, 6 H, 6 Ar), 7.58 (d, J = 9 Hz, 2 H, 2 Ar), 7.87 (d, J = 8.5 Hz, 2 H, 2 Ar), 7.95 (d, J = 8.5 Hz, 2 H, 2 Ar).

4.1.2 SYNTHESIS OF (*R*)-3,3′-DIIODO-2,2′-BIS(METHOXYMETHOXY)-1,1′-BINAPHTHALENE

Materials and Equipment

- (*R*)-2,2′-Bis-methoxymethoxy-[1,1′]binaphthalene (MOM-BINOL) (5.00 g)
- *n*-Butyl lithium (*n*-BuLi, 1.6 M in hexane) (25 mL)
- *N, N, N′, N′*-Tetramethylethylenediamine (TMEDA) (5 mL)
- Iodine (41 g)
- Diethyl ether (250 mL)
- Saturated sodium thiosulfate solution (200 mL)
- Ethyl acetate (600 mL)
- Magnesium sulfate (anhydrous) (30 g)
- Argon line
- 500 mL three-necked flask with magnetic stirrer
- Ice bath
- Dewar, liquid nitrogen, isopropanol
- Sintered-glass filter, diameter 8 cm
- 1 L round-bottomed flask
- Rotary evaporator
- Column, diameter 7 cm
- Silica gel 60 (0.063–0.2) (Merck) (350 g)
- *n*-Hexane, 4 L
- Dichloromethane, 4 L
- High-vacuum (oil) pump

Procedure

1. The reaction was carried out under a nitrogen atmosphere using standard Schlenk techniques. A solution of diethyl ether (250 mL), *n*-BuLi (25 mL, 40 mmol) and TMEDA (5 mL, 33 mmol) was stirred for 45 min. The mixture was cooled to 0 °C and MOM-BINOL (5.0 g, 13 mmol) was added in solid form. After stirring for 12 h at room temperature, the light brown suspension was cooled down to −78 °C and iodine (41.0 g, 160 mmol) was added. Under vigorous stirring the mixture was allowed to slowly warm up to room temperature. After 3 h the purple mixture was treated with saturated sodium thiosulfate solution (200 mL). The phases were separated, the aqueous phase was extracted with ethyl acetate (3 × 200 mL) and the combined organic fractions were dried over magnesium sulfate (30 g). The solvent was removed under reduced pressure to give an orange oil. The crude product was purified by column-chromatography (350 g silica gel, gradient: *n*-hexane→*n*-hexane/CH_2Cl_2 1:1→CH_2Cl_2). After evaporation and drying *in vacuo* a colourless solid (4.40 g, 53 %) was obtained.

   R_f (*n*-hexane/ethyl acetate 5:1) = 0.57.
   ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 2.60$ (s, 6 H, 2 OCH_3), 4.69 (d, $J = 5.6$ Hz, 2 H, 2 OC*H*H), 4.81 (d, $J = 5.6$ Hz, 2 H, 2 OCH*H*), 7.14–7.47 (m, 6 H, 6 Ar), 7.78 (d, $J = 8.3$ Hz, 2 H, 2 Ar), 8.54 (s, 2 H, 2 Ar).

4.1.3 SYNTHESIS OF 3,3′-BIS-(3,5′-BIS-TRIFLUOROMETHYL-PHENYL)-2,2′-BISMETHOXYMETHOXY [1,1′-BINAPHTHALENE]

Materials and Equipment

- (*R*)-3,3′-Diiodo-2,2′-*bis*(methoxymethoxy)-1,1′-binaphthalene (2.50 g)
- Barium hydroxide octahydrate [Ba(OH)$_2$•8H$_2$O] (6.50 g)
- 3,5-Bistrifluoromethylphenylboric acid (3.00 g)
- Tetrakis(triphenylphosphine)palladium(0) [Pd(PPh$_3$)$_4$] (0.46 g)
- 1,4-Dioxane (90 mL)
- Deionized water (30 mL)
- Dichloromethane (240 mL)
- Saturated sodium chloride solution (60 mL)
- Magnesium sulfate (anhydrous) (10 g)
- Sintered-glass filter, diameter 6 cm
- 250 mL round-bottomed flask
- 500 mL round-bottomed flask
- Magnetic stirrer with hotplate
- Oil bath
- Liebig condenser
- Argon line
- Vacuum line
- Rotary evaporator
- Column, diameter 3 cm
- Silica gel 60 (0.062–0.2) (Merck), 150 g
- *n*-Hexane
- Ethyl acetate
- High-vacuum (oil) pump

Procedure

1. (*R*)-3,3′-Diiodo-2,2′-*bis*(methoxymethoxy)-1,1′-binaphthalene (2.50 g, 4.0 mmol), Ba(OH)$_2$•8H$_2$O (6.50 g, 21.0 mmol) and 3,5-bistrifluoromethylphenylboric acid (3.00 g, 12.0 mmol) were dissolved in 120 mL dioxane/water (3:1). The mixture was degassed, Pd(PPh$_3$)$_4$ (0.46 g, 0.40 mmol) was added and the reaction mixture was heated at 110 °C for 48 h under an argon atmosphere. Dioxane was removed under reduced pressure and the aqueous residue was extracted with dichloro-methane (3 × 80 mL). The combined organic phases were washed with saturated sodium chloride solution (60 mL), dried over magnesium sulfate and solvent was evaporated. The resulting solid was purified by column chromatography (150 g silica gel, eluent: *n*-hexane/ethyl acetate 15:1). After evaporation and drying *in vacuo* a colourless solid (2.80 g, 88 %) was isolated.

   R_f (*n*-hexane/ethyl acetate 5:1) = 0.74 ; $[\alpha]_D^{20} = -80.1°$ ($c = 1$, CHCl$_3$).
   IR (KBr) (cm^{-1}): 2934, 1621, 1601, 1496, 1470, 1378, 1326, 1280, 1247, 1133, 1083, 1022, 990, 968, 893, 845, 792, 752, 707, 683.

^{1}H-NMR (250 MHz, CDCl3): $\delta = 2.49$ (s, 6 H, 2 OCH3), 4.36 (d, $J = 6.0$ Hz, 2 H, 2 OCHH), 4.42 (d, $J = 6.0$ Hz, 2 H, 2 OCHH), 7.28–7.33 (m, 2 H, 2 Ar), 7.37 (dt, $^3J = 7.5$ Hz, $^4J = 1.3$ Hz, 2 H, 2 Ar), 7.50 (dt, $^3J = 7.5$ Hz, $^4J = 1.3$ Hz, 2 H, 2 Ar), 7.89–8.04 (m, 6 H, 6 Ar), 8.24 (s, 4 H, 4 Ar).

^{13}C-NMR (63 MHz, CDCl3): $\delta = 56.2$, 99.1, 121.0, 125.9, 126.2, 126.4, 127.5, 128.3, 129.9, 130.0, 130.7, 131.1, 131.4, 131.9, 132.7, 134.1, 141.1, 151.2.

MS-MALDI: m/z (%) = 820.59 (100) [M$^+$ + Na$^+$].

4.1.4   SYNTHESIS OF (R)-3,3′-[3,5- BIS(TRIFLUOROMETHYL)PHENYL]-1,1′-BINAPHTHYLPHOSPHATE

Materials and Equipment

- 3,3′-Bis-(3,5-bis-trifluoromethyl-phenyl)-2,2′-bismethoxymethoxy[1,1′]-binaphthalene (2.30 g)
- 1,4-Dioxane (100 mL)
- Concentrated hydrochloric acid (HCl conc.) (20 mL)
- Deionized water (2 × 50 mL)
- Dichloromethane (300 mL, 150 mL)
- Magnesium sulfate (anhydrous) (2 × 10 g)
- 3,3′-Bis-(3,5-bis-trifluoromethyl-phenyl)-[1,1′]binaphthalenyl-2,2′-diol (2.00 g)
- Dry pyridine (50 mL)
- Phosphorus oxychloride (POCl3) (1.31 mL)
- Concentrated hydrochloric acid (HCl conc.)
- Methanol
- 100 mL round-bottomed flask
- 250 mL round-bottomed flask
- 500 mL round-bottomed flask (×2)
- Rotary evaporator
- High-vacuum (oil) pump
- pH paper
- Column, diameter 3 cm
- Silica gel 60 (0.063–0.2) (Merck), (100 g)

Procedure

1. 3,3′-Bis-(3,5-bis-trifluoromethyl-phenyl)-2,2′-bismethoxymethoxy[1,1′]-binaphthalene (2.30 g, 2.90 mmol) was dissolved in dioxane (100 mL). The solution was cooled down to 0 °C and concentrated hydrochloric acid (20 mL) was slowly added. The mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, diluted carefully with purified water (30 mL) and stirred for 45 min at room temperature. The solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic phases were dried over magnesium sulfate and the solvent was evaporated. The diol (2.00 g, 98 %) was isolated without further purification as a colourless solid.

   R_f (n-hexane/ ethyl acetate 5:1) = 0.63

2. 3,3′-Bis-(3,5-bis-trifluoromethyl-phenyl)-[1,1′]binaphthalenyl-2,2′-diol   (2.00 g, 3.00 mmol) was dissolved in pyridine (50 mL). The solution was cooled to 0 °C and POCl$_3$ (1.31 mL, 14 mmol) was slowly added. The mixture was stirred overnight at room temperature under argon atmosphere. The reaction mixture was hydrolyzed with water (50 mL) and stirred for 45 min at room temperature. The mixture was cooled to 0 °C and concentrated hydrochloric acid (20 mL) was slowly added until the solution reached a pH value of 1–2. The mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried with magnesium sulfate and the solvent was evaporated. The resulting residue was purified by column chromatography (150 g silica gel, eluent: dichloromethane/methanol 50:1) to yield the product as a colourless solid (1.80 g, 83 %).

R_f (CH$_2$Cl$_2$/MeOH 20:1) $=$ 0.21; $[\alpha]_D^{20} = -134.2°$ ($c = 1$, CHCl$_3$).

IR (KBr) (cm^{-1}): 1621, 1531, 1474, 1379, 1325, 1281, 1245, 1176, 1134, 1084, 1021, 989, 968, 893, 846, 825, 775, 749, 708, 695, 683.

^{1}H-NMR (250 MHz, CDCl$_3$): $\delta =$ 7.38–7.45 (m, 4 H, 4 Ar), 7.55–7.65 (m, 4 H, 4 Ar), 7.98–8.05 (m, 8 H, 8 Ar).

^{13}C-NMR (63 MHz, CDCl$_3$): $\delta =$ 120.1, 121.6, 122.6, 125.3, 126.7, 127.1, 127.5, 128.7, 129.9, 131.2, 131.4, 131.7, 132.0, 2·132.3, 138.6, 143.5, 143.7.

^{31}P-NMR (400 MHz, CDCl$_3$): $\delta =$ 5.97 (s, 1 P). HRMS-ESI: Exact mass calcd for C$_{36}$H$_{17}$O$_4$F$_{12}$NaP [M+Na]$^+$: 795.0571. Found: 795.0574.

4.1.5   GENERAL PROCEDURE FOR THE TRANSFER HYDROGENATION OF KETIMINES

Imine, catalyst (20 mol %), Hantzsch dihydropyridine (1.4 equiv) and benzene were added to a screw-capped vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was allowed to stir at 60 °C for 3 days or until the solution became colourless. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography to afford the corresponding amine.

Alternatively, the imine, catalyst (5 mol %), Hantzsch dihydropyridine (1.4 equiv), 5 Å molecular sieves and benzene were added to a screw-capped vial and reaction was carried out as described.

4.1.6   SYNTHESIS OF [1-(2,4-DIMETHYL-PHENYL)-ETHYL]-(4-METHOXY-PHENYL)-AMINE
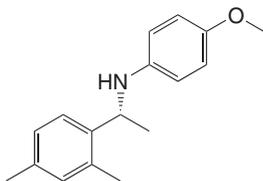
Materials and Equipment

- [1-(2,4-Dimethyl-phenyl)-eth-(E)-ylidene]-phenyl-amine (51.0 mg, 0.20 mmol)
- 2,6-Bis-(3,5-bis-trifluoromethyl-phenyl)-4-oxo-3,5-dioxa-$4\lambda^5$-phospha-cyclo-hepta[2,1-a;3,4-a']dinaphthalen-4-ol (30.90 mg, 20 mol %)
- Hantzsch dihydropyridine (71.0 mg, 0.28 mmol)
- Benzene (3.5 mL)
- Screw-capped vial
- Argon line
- Magnetic stirrer with hotplate
- Oil bath
- Column, diameter 2 cm
- Silica gel 60 (0.063–0.2) (Merck), 15 g
- Rotary evaporator
- High-vacuum (oil) pump

Procedure

Imine (51.0 mg, 0.20 mmol), catalyst (30.90 mg, 20 mol %), Hantzsch dihydropyridine (71.0 mg, 0.28 mmol) and benzene (3.5 mL) were added to a screw-capped vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was allowed to stir at 60 °C for 3 days. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate 40:1 as eluent to afford the amine as an oil (46.5 mg, 91 %, 78 % ee).

$[\alpha]_D^{20} = -28.7°$ (c = 1.8, CH$_2$Cl$_2$).
IR (CDCl$_3$) (cm^{-1}): 2235, 1505, 1241, 908, 735.
^{1}H-NMR (250 MHz, CDCl$_3$): δ = 1.44 (d, J = 6.5 Hz, 3 H, HC-CH$_3$), 2.28 (s, 3 H, Ar-CH$_3$), 2.39 (s, 3 H, Ar-CH$_3$), 3.69 (s, 3 H, O-CH$_3$), 3.73 (bs, 1 H, NH), 4.57 (q, J = 6.5 Hz, 1 H, HCCH$_3$), 6.36–6.46 (m, 2 H, 2 Ar), 6.63–6.73 (m, 2 H, 2 Ar), 6.99 (d, J = 8.0 Hz, 2 H, 2 Ar), 7.32 (d, J = 8.0 Hz, 1 H, 1 Ar).
^{13}C-NMR (63 MHz, CDCl$_3$): δ = 18.9, 21.0, 23.2, 25.4, 50.3, 55.8, 114,2, 114.8, 124.7, 127.2, 131.4, 134.5, 136.1, 140.1, 141.7, 151.8.
MS (FD): m/z (%) = 255.2 (100) [M$^+$].
HPLC conditions: OD-H column, n-hexane/2-propanol = 98/2, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 12.26 min; minor enantiomer: t_R = 15.43 min.

CONCLUSION

The Brønsted acid catalyzed enantioselective reduction of several methyl-aryl ketimines affords the corresponding amines in good yields and enantioselectivities (Table 4.1). The mild reaction conditions and generally good chemoselectivity of this transfer hydrogenation render this transformation an attractive and metal-free approach to optically active amines.

Table 4.1

Entry	R	Amine	Yield (%)	ee (%)
1	PMP		82	70
2	Ph		69	68
3	PMP		71	72
4	Ph		58	70
5	PMP		76	74
6	Ph		71	72
7	PMP		82	84
8	PMP		74	78
9	PMP		91	78
10	PMP		71	74
11	PMP		76	72
12	PMP		62	72
13	PMP		46	82
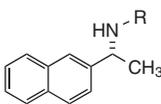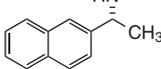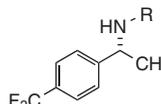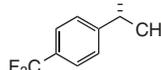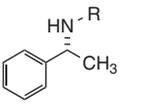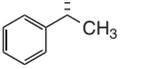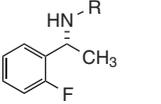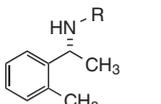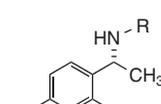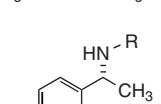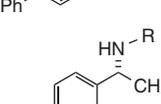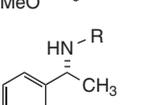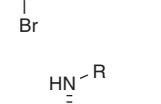
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4.2   METAL-FREE BRØNSTED ACID CATALYZED TRANSFER HYDROGENATION: ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDROQUINOLINES

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The enantioselective hydrogenation of olefins, ketones and imines still represents an important topic and various highly enantioselective processes based on chiral Rh, Ru or Ir complexes have been reported. However, most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of aromatic and heteroaromatic compounds and examples of efficient catalysts are rare. This is especially the case for the partial reduction of quinoline derivatives which provide 1,2,3,4-tetrahydroquinolines, important synthetic intermediates in the preparation of pharmaceutical and agrochemical products. Additionally, many alkaloid natural products consist of this structural key element.

Recently, we established that several proton acids catalyze the metal-free reduction of ketimines under hydrogen-transfer conditions with Hantzsch dihydropyridine as the hydrogen source.[1] Additionally, we were able to demonstrate a catalytic enantioselective procedure of this new transformation by employing a chiral Brønsted acid as catalyst.[2] (see Chapter 4.1).

Herein, we report an extension of this methodology and report the metal-free hydrogenation of quinolines using 1 mol % of diphenyl phosphate (DPP) and the asymmetric variant of this procedure using 1 mol % of a chiral BINOL-phosphate **1** as catalyst (Figure 4.2).

4.2.1   GENERAL PROCEDURE FOR THE TRANSFER HYDROGENATION OF QUINOLINES

Materials and Equipment

- The quinoline (20.0 mg)
- (*R*)-4-Oxo-2,6-diphenanthren-9-yl-3,5-dioxa-4λ^5-phospha-cyclohepta [2,1-α;3,4α′]-dinaphthalin-4-ol, (1.4 mg, 2 mol %)
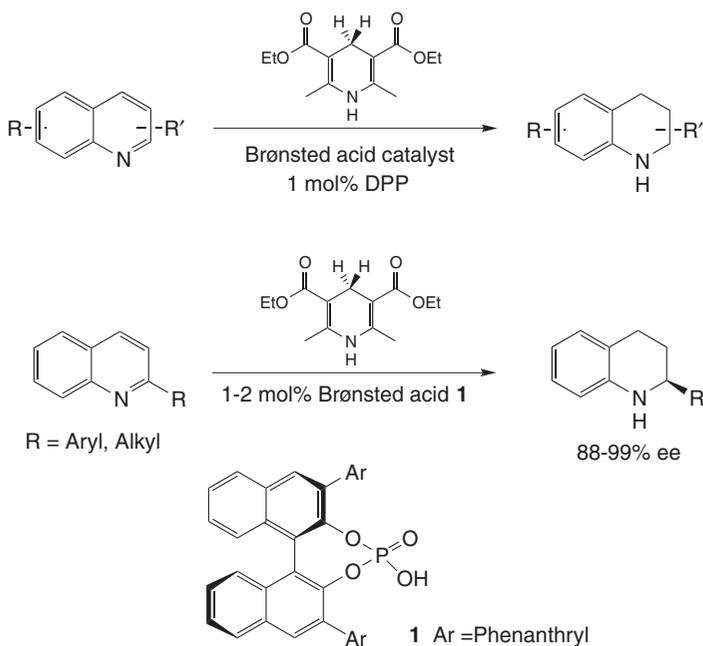
Figure 4.2

- Hantzsch dihydropyridine (59.2 mg, 0.234 mmol)
- Benzene (2.0 mL)
- Screw-capped vial
- Argon line
- Magnetic stirrer with hotplate
- Oil bath
- Column, diameter 2 cm
- Silica gel 60 (0.063-0.2) (Merck), 15 g
- Rotary evaporator
- High-vacuum (oil) pump

Procedure

1. In a typical experiment quinoline (20 mg), catalyst (1–2 mol %) and Hantzsch dihydropyridine (2.4 equiv) were suspended in benzene (2 mL) in a screw-capped vial and flushed with argon. The resulting mixture was allowed to stir at 60 °C for 12 h. The solvent was removed under reduced pressure and purification of the crude product by column chromatography on silica gel afforded the pure 1,2,3,4-tetrahydroquinoline.

4.2.2 SYNTHESIS OF 7-CHLORO-4-PHENYL-1,2,3,4-TETRAHYDROQUINOLINE
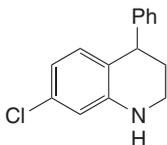
Materials

- 7-Chloro-4-phenylquinoline (20.0 mg, 0.083 mmol)
- Diphenyl phosphate (DPP) (0.2 mg, 1 mol %)
- Hantzsch dihydropyridine (50.7 mg, 0.200 mmol)
- Benzene (2.0 mL)

Procedure

1. 7-Chloro-4-phenylquinoline, (20.0 mg 0.083 mmol), diphenyl phosphate (1 mol %), Hantzsch dihydropyridine (50.7 mg, 0.200 mmol) and benzene (2.0 mL) were added to a screw-capped vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was allowed to stir at 60 °C for 12 h. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography over silica gel to afford the corresponding amine (94 %).

   ^{1}H-NMR (250 MHz, CDCl$_3$): $\delta = 1.88$–2.18 (m, 2 H, C-3H), 3.08–3.28 (m, 2 H, C-2H), 3.94 (br s, 1 H, NH), 4.01 (t, $J = 6.1$ Hz, 1 H, C-4H), 6.39–6.48 (m, 2 H, Ar), 6.56–6.59 (m, 1H, Ar), 6.99–7.07 (m, 2 H, Ar), 7.09–7.27 (m, 3 H, Ar).
   ^{13}C-NMR (62.5 MHz, CDCl$_3$): 30.7, 38.9, 42.4, 113.4, 116.8, 121.7, 126.3, 128.4, 128.6, 131.5, 132.6, 145.9, 146.0.
   IR (KBr): $v = 3412$, 3396, 2919, 1604, 1492, 1089, 700 cm^{-1}.
   MS-ESI: 243.8 (M$^+$), 245.8 (M$^+$).
   Anal. calcd for C$_{15}$H$_{14}$ClN (243.73): C, 73.92; H, 5.79; N, 5.75.
   Found: C, 73.69; H, 5.54; N, 5.74.

4.2.3 SYNTHESIS OF (*S*)-2-PHENYL-1,2,3,4-TETRAHYDROQUINOLINE
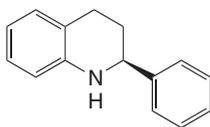
Materials

- 2-Phenylquinoline (20.0 mg, 0.097 mmol)
- (R)-4-Oxo-2,6-diphenanthren-9-yl-3,5-dioxa-$4\lambda^5$-phospha-cyclohepta[2,1-α;3,4α′]-dinaphthalin-4-ol (1.4 mg, 2 mol %)
- Hantzsch dihydropyridine (59.2 mg, 0.234 mmol)
- Benzene (2.0 mL)

Procedure

1. 2-Phenylquinoline (20.0 mg 0.097 mmol), BINOL-phosphate **1** (1.4 mg, 2 mol %), Hantzsch dihydropyridine (59.2 mg, 0.234 mmol) and benzene (2.0 mL) were added to a screw-capped vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was allowed to stir at 60 °C for 12 h. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography over silica gel to afford the amine as yellow oil (92 %, 97 % ee).

> ^{1}H-NMR (250 MHz, CDCl$_3$): δ = 7.40–7.14 (m, 5H, Ph), 7.01–6.86 (m, 2H, 5-H and 7-H), 6.57 [td, J(H,H) = 7.4, 0.9 Hz, 1H, 6-H], 6.46 [dd, J(H,H) = 1.0, 8.0 Hz, 1H, 8-H], 4.36 [dd, J(H,H) = 3.4, 9.2 Hz, 1H, 2-H], 3.96 [br s, 1H, 1-H], 2.94–2.75 [m, 1H, 4-H], 2.66 [dt, J(H,H) = 16.4, 4.8 Hz, 1H, 4-H], 2.12-1.82 ppm [m, 2H, 3-H].
>
> ^{13}C-NMR (62.5 MHz, CDCl$_3$): δ = 144.80, 144.72, 129.29, 128.56, 127.43, 126.89, 126.53, 120.87, 117.15, 113.96, 56.25, 30.97, 26.38 ppm.
>
> IR (KBr): v = 3352, 2945, 2921, 1478, 1309, 1254, 762, 702 cm^{-1}.
>
> MS-ESI m/z (%): 210.1 ([M+H]$^+$). $[\alpha]_D^{20}$ = −37.7° (c = 1.0, CHCl$_3$).
>
> HPLC conditions: n-hexane/2-propanol = 95/5, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 18.98 min; minor enantiomer: t_R = 25.43 min.

4.2.4   SYNTHESIS OF (R)-2-(2-(BENZO[1,3]DIOXOL-5-YL)ETHYL)-1,2,3,4-TETRAHYDROQUINOLINE
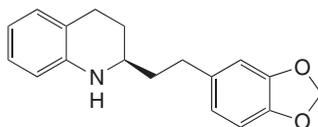
Materials

- 2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-quinoline (20.0 mg 0.072 mmol)
- (R)-4-Oxo-2,6-diphenanthren-9-yl-3,5-dioxa-$4\lambda^5$-phospha-cyclohepta [2,1-α;3,4α′]- dinaphthalin-4-ol (0.5 mg, 1 mol %)

- Hantzsch dihydropyridine (43.8 mg, 0.173 mmol)
- Benzene (2.0 mL)

Procedure

1. 2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-quinoline (20.0 mg 0.072 mmol), BINOL-phosphate **1** (0.5 mg, 1 mol %), Hantzsch dihydropyridine (43.8 mg, 0.173 mmol) and benzene (2.0 mL) were added to a screw-capped vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was allowed to stir at 60 °C for 12 h. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel to afford the amine (94 %, 91 % ee).

   ^{1}H-NMR (250 MHz, CDCl$_3$): δ = 6.93–6.83 (m, 2H, 5-H and 7-H), 6.70–6.47 (m, 4H, Ar), 6.38 [dd, J(H,H) = 8.0, 1.1 Hz, 1H, 8-H], 5.84 (s, 2H, O-CH2-O),3.68 (br s, 1H, 1-H), 3.27–3.14 (m, 1H, 2-H), 2.82–2.53 (m, 4H), 1.97–1.84 (m, 1H), 1.76–1.65 (m, 2H), 1.64–1.49 ppm (m, 1H).

   ^{13}C-NMR (62.5 MHz, CDCl$_3$): δ = 147.67, 145.72, 144.50, 135.64, 129.26, 126.74, 121.29, 121.02, 117.05, 114.14, 108.79, 108.23, 100.82, 50.97, 38.48, 31.87, 27.97, 26.21 ppm.

   IR (KBr): ν = 3408, 2922, 2850, 1502, 1487, 1246, 1038, 748 cm^{-1}. MS-ESI *m/z*: 281.8 ([M]$^+$). $[\alpha]_D^{20}$ + 50.7° (c = 1.0, CHCl$_3$).

   HPLC conditions: *n*-hexane/2-propanol = 80/20, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 18.96 min; minor enantiomer: t$_R$ = 24.20 min.

CONCLUSION

The Brønsted acid catalyzed hydrogenation of quinolines with Hantzsch dihydropyridine as reducing agent provides a direct access to a variety of substituted tetrahydroquinolines[3] (Table 4.2). The mild reaction conditions of this metal-free reduction of heteroaromatic compounds, high yields, operational simplicity and practicability, broad scope, functional group tolerance and remarkably low catalyst loading render this environment-friendly process an attractive approach to optically active tetrahydroquinolines and their derivatives (Table 4.3) (see page 176).[4]

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4. Rueping, M., Antonchick A. P. and Theissmann, T. *Angew. Chem. Int. Ed*. **2006**, *45*, 3683.

Table 4.2

Entry	Tetrahydroquinoline	Yield (%)	Entry	Tetrahydroquinoline	Yield (%)
1	(2-Ph tetrahydroquinoline)	92	7	(4-Ph, 7-Ph tetrahydroquinoline)	91
2	(6-F, 2-methyl tetrahydroquinoline)	88	8	(3-Ph tetrahydroquinoline)	88
3	(2-Bu tetrahydroquinoline)	93	9	(3-methyl, 2-Ph tetrahydroquinoline)	86
4	(2-CH$_2$Cl tetrahydroquinoline)	92	10	(octahydroacridine)	82
5	(2-(2-fluorophenyl) tetrahydroquinoline)	95	11	(4-CO$_2$Me, 2-Ph tetrahydroquinoline)	93
6	(2-(2-furyl) tetrahydroquinoline)	90	12	(2-CH(OMe)$_2$ tetrahydroquinoline)	75
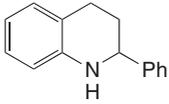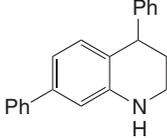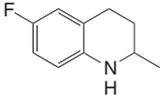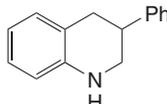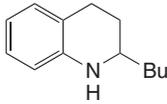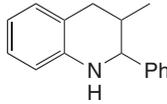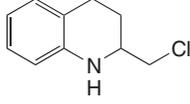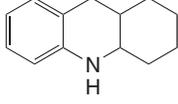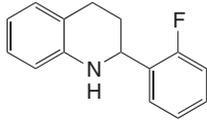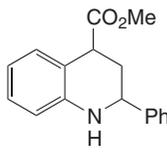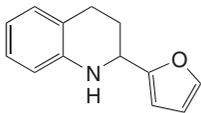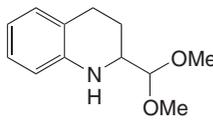
4.3 A HIGHLY STEREOSELECTIVE SYNTHESIS OF 3α-AMINO-23,24-BISNOR-5α-CHOLANE VIA REDUCTIVE AMINATION

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Stereoselective reduction has been a focus of research in synthetic chemistry for many decades. There are numerous examples in the literature which require high

Table 4.3

Entry	Tetrahydroquinoline	Time (h)	Yield (%)	ee (%)
1		12	92	97
2		30	93	98
3		48	54	91
4		18	92	98
5		30	91	99
6		12	93	91
7		12	91	88
8		12	88	90
9		12	90	90
10		12	94	91
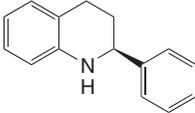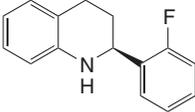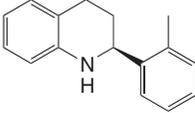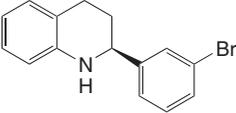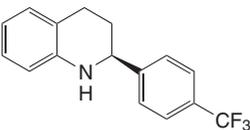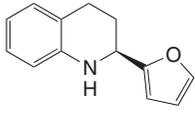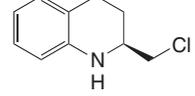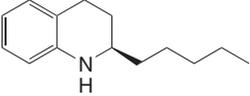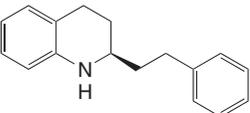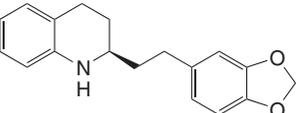
Reprinted from reference [4 in 4.2], with permission from Wiley-VCH.
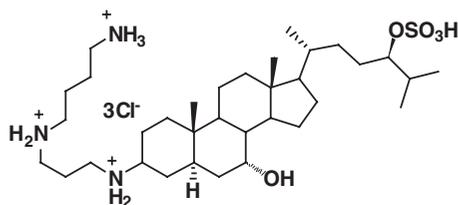
Figure 4.3 Squalamine. Reprinted from reference [1], with permission from National Academy of Science, USA.

degrees of stereoselectivity. One such example is squalamine[1] (Figure 4.3), which is well known for its antibiotic properties against Gram positive and Gram negative bacteria and fungi, and as an anticancer agent which also inhibits angiogenesis. A highly stereoselective reductive amination method was developed based upon *in situ* generated sodium acyloxyborohydride and successfully applied to a steroidal skeleton with various amine sources. A high yield (96 %) and *de* up to 95 % was achieved.[2]

4.3.1 SYNTHESIS OF TRIS[(2-ETHYLHEXANOYL)OXY]BOROHYDRIDE [NaBH(OEh)$_3$][3]

Materials and Equipment

- NaBH$_4$ (98 %) (1.9 g, 50.2 mmol)
- 2-Ethylhexanoic acid (99 %) (28 mL, 175.7 mmol)
- Methylene chloride, 100 mL (dried over CaH$_2$)
- One 250 mL two-necked flask
- Magnetic stirrer plate
- Argon
- Ice bath

Procedure

1. NaBH$_4$ (1.9 g, 50.2 mmol) was mixed with dry methylene chloride (100 mL) in a 250 mL two-necked flask under an argon atmosphere. 2-Ethylhexanoic acid (28 mL, 175.7 mmol) was slowly added by syringe at 0 °C and stirred for 72 h at room temperature. The reagent was stored in a refrigerator.

4.3.2 SYNTHESIS OF 3α-ACETAMINO-23,24-BISNOR-5α-CHOLANE (**2a**) (FIGURE 4.4)

Materials and Equipment

- 22-*tert*-Butyldimethylsilyloxy-23,24-bisnor-5α-chola-3-one (100 mg, 0.2 mmol)
- Ammonium trifluoromethanesulfonate (377 mg, 2.2 mmol)
- NaBH(OEh)$_3$ (2 equiv)
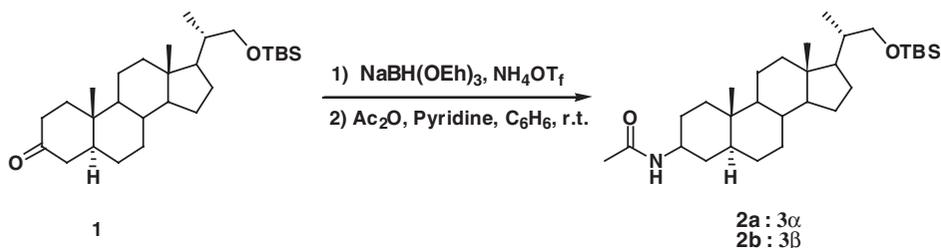
Figure 4.4 Reductive amination of **1** with ammonium trifluoromethanesulfonate followed by acetylation. Reprinted from reference [2], with permission from Elsevier.

- Tetrahydrofuran (10 mL, dried over sodium and benzophenone)
- Acetic anhydride (0.03 mL, 0.24 mmol)
- Pyridine (0.16 mL, 2 mmol)
- Benzene (5 mL)
- Ethyl acetate (60 mL)
- Anhydrous sodium sulfate (2 g)
- TLC plates (Silica gel 60, Merck 5721)
- Büchner funnel with filter paper (Advantec No. 2)
- One 100 mL Erlenmeyer flask
- One 50 mL round-bottomed flask with a magnetic bar
- Magnetic stirrer plate
- Medium pressure liquid chromatography (MPLC) Lobar® Li Chroprep® Si 60 (40–63 μm) column (E.M. Merck)
- Argon
- Rotary evaporator
- Ice bath

Procedure

1. A mixture of **1** (100 mg, 0.2 mmol) and ammonium trifluoromethanesulfonate (377 mg, 2.2 mmol) in THF (10 mL) was reacted with NaBH(OEh)$_3$ (2 equiv) at room temperature under an argon atmosphere. The reaction was monitored by TLC analysis. After the reaction was complete, the solvent was removed by a rotary evaporator, the mixture extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, and concentrated.
2. The crude reaction mixture was dissolved in benzene (5 mL); pyridine (0.16 mL, 3 equiv) and acetic anhydride (0.03 mL, 1.2 equiv) were added. After stirring overnight, the solvent was removed by a rotary evaporator, the mixture extracted with ethyl acetate, then the combined organic extracts dried over anhydrous Na$_2$SO$_4$, and concentrated.
3. Column chromatography on MPLC (eluent: ethyl acetate: hexane, 1:4) yielded the 3α-isomer (95 mg, 90 %) and the 3β-isomer (11 mg, 6 %).

(**2a**) $R_f = 0.19$ (1:1 = EtOAc:hexane).

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 0.63$ (s, 3H, 18-CH$_3$), 0.77 (s, 3H, 19-CH$_3$), 0.86 (s, 9H, t-Bu), 1.98 (s, 3H, acetyl-CH$_3$), 4.09 (bs, 1H, H-3), 5.97 (bs, 1H, H-N).

^{13}C-NMR (100.6 MHz, CDCl$_3$): $\delta = 169.7$, 68.2, 56.7, 54.9, 53.1, 45.3, 43.0, 41.3, 40.2, 39.4, 36.9, 35.8, 33.5, 33.1, 32.3, 28.0, 28.8, 26.3, 26.0, 24.6, 23.9, 21.1, 18.7, 12.5, 11.8, −4.9.

Anal. calcd for C$_{30}$H$_{55}$NO$_2$Si: C, 73.56; H, 11.32; N, 2.86. Found: C, 73.35; H, 11.60; N, 2.96.

(**2b**) $R_f = 0.15$ (1:1 = EtOAc:hexane).

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 0.62$ (s, 3H, 18-CH$_3$), 0.75 (s, 3H, 19-CH$_3$), 0.86 (s, 9H, t-Bu), 1.94 (s, 3H, acetyl-CH$_3$), 3.70 (bs, 1H, H-3), 5.97 (bs, 1H, H-N).

^{13}C-NMR (100.6 MHz, CDCl$_3$): $\delta = 169.8$, 68.2, 56.5, 54.6, 53.1, 49.5, 45.6, 43.0, 40.1, 39.4, 37.7, 35.8, 35.7, 32.3, 29.1, 28.9, 28.0, 26.3, 26.0, 24.7, 23.7, 21.4, 18.75, 17.2, 12.5, −4.9.

Anal. calcd for C$_{30}$H$_{55}$NO$_2$Si: C, 73.56; H, 11.32; N, 2.86. Found: C, 73.30; H, 11.05; N, 2.94.

4.3.3   SYNTHESIS OF 3α-N-1-[N(3-[4-AMINOBUTYL])-1,3-DIAMINOPROPANE]-23,24-BISNOR-5α-CHOLANE (**3a**) (FIGURE 4.5)

Materials and Equipment

- 22-*tert*-Butyldimethylsilyloxy-23,24-bisnor-5α-cholan-3-one
- Spermidine (380 mg, 1.1 mmol)
- NaBH(OEh)$_3$ (2 equiv)
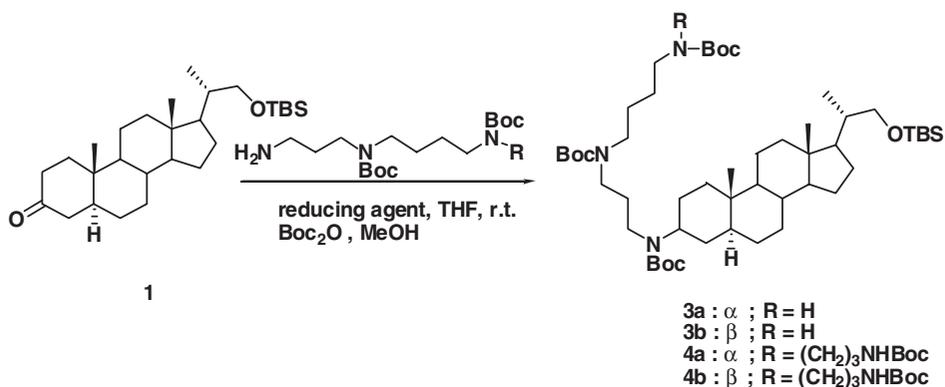
Figure 4.5 Reductive amination of **1** with Boc protected spermidine and spermine. Reprinted from reference [2], with permission from Elsevier.

- Tetrahydrofuran, 10 mL (dried over sodium and benzophenone)
- Di-*tert*-butyldicarbonate, 97 % (121 mg, 0.5 mmol)
- Methanol (5 mL)
- Ethyl acetate (60 mL)
- Anhydrous sodium sulfate (2 g)
- TLC plates (Silica gel 60, Merck 5721)
- Büchner funnel with filter paper (Advantec No. 2)
- One 100 mL Erlenmeyer flask
- One 50 mL round-bottomed flask with a magnetic bar
- Magnetic stirrer plate
- Medium pressure liquid chromatography (MPLC) Lobar® Li Chroprep® Si 60 (40–63 μm) column (E.M. Merck)
- Argon
- Rotary evaporator
- Ice bath

Procedure

1. A mixture of **1** (200 mg, 0.45 mmol) and spermidine **4b** (380 mg, 1.1 mmol) in THF (10 mL) was reacted with $NaBH(OEh)_3$ (2 equiv) at room temperature under an argon atmosphere. The reaction was monitored by TLC analysis. After the reaction was complete, the solvent was removed, the residue extracted with ethyl acetate, and then the combined organic extracts were dried over anhydrous Na_2SO_4, before being concentrated.

2. The crude reaction mixture was further reacted with di-*tert*-butyldicarbonate (1.2 equiv) in MeOH (5 mL) at room temperature for 8 h. The solvent was removed by a rotary evaporator and the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried and evaporated. MPLC (eluent: ethyl acetate: hexane, 1:4) yielded the 3α isomer (361 mg, 88 %) and the 3β isomer (19 mg, 8 %).

  (**3a**) $R_f = 0.36$ (1:4 = EtOAc:hexane).
  ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 0.63$ (s, 3H, 18-CH$_3$), 0.77 (s, 3H, 19-CH$_3$), 0.86 (s, 9H, t-Bu), 1.42 (s, 27H, H-Boc), 4.04 (bs, 1H, H-3).
  ^{13}C-NMR (100.6 MHz, CDCl$_3$): $\delta = 157.5, 157.2, 157.0, 80.8, 80.6, 69.4, 57.7, 54.3, 51.2, 44.2, 43.9, 41.4, 40.6, 37.1, 36.5, 33.4, 31.2, 30.3, 30.1, 29.9, 29.2, 28.9, 27.5, 26.6, 22.4, 19.9, 18.4, 14.8, 13.7, -3.7$.
  Anal. calcd for $C_{50}H_{93}N_3O_7Si$: C, 68.52; H, 10.70; N, 4.79. Found: C, 68.48; H, 10.67; N, 4.77.
  (**3b**) $R_f = 0.33$ (1:4 = EtOAc: hexane).
  ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 0.63$ (s, 3H, 18-CH$_3$), 0.76 (s, 3H, 19-CH$_3$), 0.86 (s, 9H, t-Bu), 1.43 (s, 27H, H-Boc), 4.60 (bs, 1H, H-3).
  ^{13}C-NMR (100.6 MHz, CDCl$_3$): $\delta = 157.5, 157.1, 157.0, 148.2, 86.7, 80.8, 80.6, 69.4, 57.7, 55.7, 54.3, 48.1, 44.2, 41.4, 40.6, 37.0, 33.5, 31.2, 30.3, 30.1, 30.0, 29.2, 28.9, 27.5, 25.9, 22.6, 19.9, 18.4, 14.0, 13.7, -3.7$.

Anal. calcd for $C_{50}H_{93}N_3O_7Si$: C, 68.52; H, 10.70; N, 4.79. Found: C, 68.44; H, 10.72; N, 4.78.

CONCLUSION

We have described a method with high stereoselectivity which will be useful in the synthesis of squalamine analogs.[4] It is promising in synthetic applications and will prove significant in the preparation of 3α-aminosteroids. These results are summarized in Table 4.4.

Table 4.4 Reductive amination of **1** with amines in the presence of various reducing reagents in THF

Entry	Reducing reagent	Amines	Product	Yield (%)	Ratio (3α:3β)
1	NaBH(OEh)$_3$	NH$_4$OTf	**2**	96	9:1
2	NaBH(OAc)$_3$	NH$_4$OTf	**2**	94	1:1
3	NaBH(OEh)$_3$	Spermine	**4**	97	24:1
4	NaBH(OAc)$_3$	Spermine	**4**	95	3:1
4	NaBH(OEh)$_3$	Spermidine	**3**	96	19: 1
6	NaBH(OAc)$_3$	Spermidine	**3**	98	3:1
7	MP-BH(OAc)$_3$^{a}	Spermidine	**3**	92	3:1
8	NaBH$_3$CN	Spermine	**4**	90	0.65:1
9	NaBH$_3$CN	Spermidine	**3**	91	0.60:1

^{a}Polymer bound triacetoxyborohydride. Reprinted from reference [2], with permission from Elsevier.

ACKNOWLEDGEMENTS

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5 Oxidation of Primary and Secondary Alcohols

CONTENTS

5.1 COPPER(II) CATALYZED OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES WITH ATMOSPHERIC OXYGEN

SURIBABU JAMMI AND THARMALINGAN PUNNIYAMURTHY*

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Copper(II) complex **1** selectively catalyzes the oxidation of primary alcohols to aldehydes in high yields by atmospheric oxygen in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[1] This procedure does not require an

additive and the catalyst **1** is readily accessible, soluble in common organic solvents and recyclable without loss of activity.[2]

1
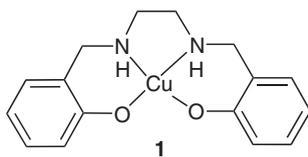
5.1.1   SYNTHESIS OF COPPER(II) COMPLEX **1**
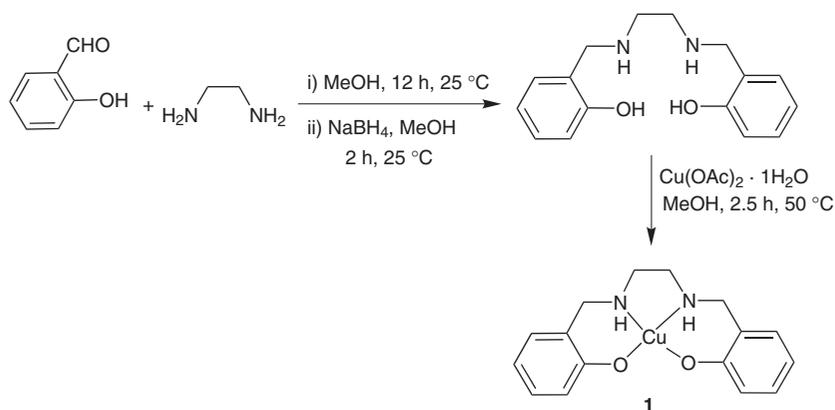
Materials and Equipment

- Salicylaldehyde (98 %) (125 mg, 1 mmol)
- Ethylenediamine (99 %) (30 mg, 0.5 mmol)
- Sodium borohydride (95 %) (40 mg, 1 mmol)
- Methanol (20 mL)
- Copper(II) acetate 1-hydrate (98 %) (204 mg, 1 mmol)
- Ethyl acetate
- Acetonitrile (5 mL)
- Silica gel (60–120 mesh)
- Nitrogen gas
- Magnetic stirrer
- 100 mL round-bottomed flask with magnetic stirrer bar
- Rotary evaporator
- One glass column

Procedure

1. *Synthesis of salen-H$_4$ ligand*

   The reaction of salicylaldehyde (122 mg, 1 mmol) with ethylenediamine (30 mg, 0.5 mmol) in methanol (5 mL) at ambient temperature for 12 h afforded salen-H$_2$ as a lemon-yellow powder (81 % yield, 217 mg), which was further treated with NaBH$_4$ (1 mmol, 37.83 mg) in methanol (5mL) at ambient temperature for 2 h. Removal of the solvent in a rotary evaporator followed by treatment with water afforded salen-H$_4$ as a colourless powder (72 % yield, 162 mg).

   ^{1}H-NMR (90 MHz, CDCl$_3$): δ-6.7–7.2 (m, 8 H), 3.9 (s, 4 H), 2.85 (s, 4 H).
   IR (KBr): v3288, 2909, 2868, 2827, 1608, 1565, 1398, 1260, 999 cm^{-1}.
   Anal. calcd for C$_{16}$H$_{20}$N$_2$O$_2$: C, 70.56; H, 7.40; N, 10.25. Found: C, 70.59; H, 7.38; N, 10.25.

2. *Synthesis of copper(II) complex 1*

   The salen-H$_4$ (150 mg, 0.55 mmol) was treated with Cu(OAc)$_2 \cdot$1H$_2$O (200 mg, 1 mmol) in methanol (10 mL) and stirred at 50 °C for 2.5 h under nitrogen atmosphere. Evaporation of the solvent on a rotary evaporator gave a powder, which was purified on silica gel column chromatography using EtOAc and MeOH (15:5) as eluent to afford complex **1** as a green powder (70 % yield).

   UV/vis (CH$_3$CN): 328, 584 nm.
   FAB-MS: *m/z* 334 ([M$^+$]).
   Anal. calcd for C$_{16}$H$_{18}$CuN$_2$O$_2$: C, 57.55; H, 5.43; N 8.39. Found: C, 57.51; H, 5.42; N, 8.00.

5.1.2 TYPICAL PROCEDURE FOR THE OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES[1]
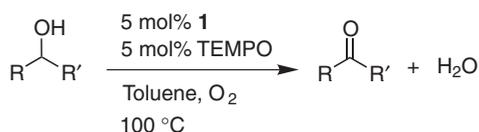
Materials and Equipment

- Alcohols (5 mmol)
- Catalyst **1** (5 mol %, 84 mg)
- 2,2,6,6-Tetramethyl-1-piperidinyloxy (5 mol %, 39 mg)
- Toluene (120 mL)
- Anhydrous sodium sulfate (98 %)
- Ethyl acetate
- Diethyl ether
- Hexane
- Magnetic stirrer
- 100 mL round-bottomed flask

Table 5.1 Copper(II) complex **1** and TEMPO catalyzed oxidation of alcohols with molecular oxygen

Entry	R	R′	Time (h)	Yield (%)
1	C_6H_5	H	10	99^a
2	p-NO_2-C_6H_4	H	14	98
3	p-Br-C_6H_4	H	19	70
4	p-MeO-C_6H_4	H	09	98
5	3,4,5-MeO-C_6H_4	H	13	97
6	C_6H_{11}	H	22	75^b
7	C_5H_4N	H	26	92
8	C_4H_3O	H	19	98
9	C_4H_3S	H	21	94
10	n-C_9H_{19}	H	25	84^b
11	n-C_6H_{13}	H	21	90^b
12	C_6H_5	CH_3	12	2

[a]GC yield.
[b]7 mol % of **1** and TEMPO used.

- Magnetic bar
- Separating funnel
- Silica gel
- One glass column
- Gas chromatograph
- Rotary evaporator

Procedure

1. Alcohol (5 mmol), catalyst **1** (5 mol %, 84 mg) and TEMPO (5 mol %, 39 mg) were stirred at ca. 100 °C in toluene (10 mL) under atmospheric oxygen for the appropriate time (Table 5.1). After completion, the reaction mixture was treated with water (3 mL) and the organic layer, after drying over sodium sulfate and GC analysis, was passed through a short pad of silica gel using ethyl acetate (or diethyl ether) and hexane as an eluent to provide the analytically pure aldehyde which was characterized by NMR, IR and mass analysis.

   For the recyclability of catalyst **1**, after completion of the oxidation of 4-methoxybenzyl alcohol, the reaction mixture was treated with water (3 mL), and the organic layer, after drying (Na_2SO_4) and GC analysis, was passed through a short pad of silica gel using ethyl acetate and hexane as eluent to afford analytically pure 4-methoxybenzaldehyde in quantitative yield. Evaporation of the aqueous layer afforded the copper complex **1** that was subsequently reused for the oxidation of 4-methoxybenzyl alcohol up to three times using fresh TEMPO whereupon no loss of activity was observed.

CONCLUSION

In conclusion, a novel procedure has been described for the oxidation of primary alcohols to aldehydes.[1] This method can be used for the selective oxidation of

primary alcohols in the presence of secondary alcoholic groups and the catalyst **1** is recyclable without loss of activity over three cycles. [2]

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5.2 SOLVENT-FREE DEHYDROGENATION OF SECONDARY ALCOHOLS IN THE ABSENCE OF HYDROGEN ACCEPTORS USING ROBINSON'S CATALYST

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Applying $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ (Robinson's catalyst),[1] secondary alcohols can be dehydrogentated with high selectivity into the corresponding ketones with relatively short reaction times. No solvent is required and hydrogen gas is produced as the sole by-product, leading to a highly effective atom utilization ($\sim$98 %).[2] The catalyst could be prepared *in situ* from commercially available chemicals.

5.2.1 DEHYDROGENATION OF 2-OCTANOL USING $Ru(OCOCF_3)_2(CO)(PPh_3)_2$ AS A CATALYST
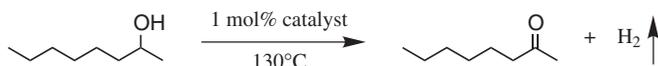
Materials and Equipment

- Carbonyl(dihydrido)tris(triphenylphosphino)ruthenium(II) $[RuH_2(CO)(PPh_3)_3]$ (99 %) (91.8 mg, 0.1 mmol)
- Trifluoroacetic acid (99 %) (138 mg, 1.2 mmol)
- 2-Octanol (98 %) (1.30 g, 10 mmol)
- 1,3,5-Tri-*tert*-butylbenzene (97 %), (85 mg, 0.34 mmol)
- Radley Carousel Reaction System
- One 40 mL Radley Carousel Reaction Tube equipped with a magnetic stirrer bar

Procedure

1. Reactions were performed in a dry, oxygen-free argon atmosphere. An oven-dry 40 mL Radley Carousel Reaction Tube was flushed with argon before it

Table 5.2 Ru(OCOCF$_3$)$_2$(CO)(PPh$_3$)$_2$-catalyzed hydrogen elimination from secondary alcohols

Entry	Substrate	Time (h)	Conv. (%)	Yield (%)	Sel. (%)
1	2-octanol	5	84	81	96
2	2-decanol	5	86	82	95
3	1-phenylethanol	2	94	59	63
	1-phenylethanol^a	5	54	49	91
4	4-*tert*-butylcyclohexanol	5	53	34	64
5	menthol	25	73	51	70
6	cyclohexanol	5	85	80	94

^{a}Reaction in toluene (3.0 M), 5 molar equivalents (with respect to the catalyst) of CF$_3$CO$_2$H, 110 °C.

was charged with the RuH$_2$(CO)(PPh$_3$)$_3$ and trifluoroacetic acid. 2-Octanol and 1,3,5-tri-*tert*-butylbenzene [3] (internal standard) were then added and the mixture was heated to 130 °C and stirred for several hours. Small aliquots of reaction mixture were taken for GC analysis.

CONCLUSION

The procedure presented for the dehydrogenation of secondary alcohols is very easy to reproduce and high atom utilization achieved presents a major benefit over hydrogen-transfer oxidations. Results for the dehydrogenation of various substrates using Ru(OCOCF$_3$)$_2$(CO)(PPh$_3$)$_2$ as a catalyst are presented in Table 5.2.

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3. In other experiments tridecane was used as the internal standard and similar results were obtained.

5.3   2-IODOXYBENZOIC ACID (IBX)/*n*-Bu$_4$NBr/CH$_2$Cl$_2$–H$_2$O: A MILD SYSTEM FOR SELECTIVE OXIDATION OF SECONDARY ALCOHOLS

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The selective oxidation of a single primary or secondary hydroxyl group within the same molecule has been a challenging problem for synthetic organic chemists. Many oxidizing reagents are known to promote selective oxidation of secondary

alcohols to ketones in the presence of primary alcohols.[1,2] Recently, a new alternative system has been developed based on 2-iodoxybenzoic acid[3] (IBX) oxidation in dichloromethane/water mixture in the presence of n-Bu$_4$NBr as a catalyst, which we have shown to be an efficient method for the selective oxidation of secondary hydroxyl groups to ketones in moderate to good yields.[4]

5.3.1   SYNTHESIS OF 1-HYDROXY-5-DECANONE
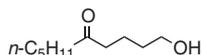
Materials and Equipment

- 2-Iodoxybenzoic acid (840 mg, 3 mmol)
- Tetrabutylammonium bromide (160 mg, 0.5 mmol)
- 1,5-Decanediol (174 mL, 1 mmol)
- Methylene chloride (2 mL)
- Distilled water (2 mL)
- Diethyl ether (20 mL)
- 8 % Aqueous solution of sodium thiosulfate (15 mL)
- Distilled water (30 mL)
- Saturated solution of sodium chloride (brine) (15 mL)
- Anhydrous sodium sulfate
- Silica gel (Merck 60 Å, 0.063–0.200 mm)
- Hexanes, ethyl acetate
- TLC aluminium sheets, SIL G-60 F$_{254}$
- 10 mL and 100 mL Round-bottomed flasks
- Magnetic stirrer bar
- Magnetic stirrer plate
- One glass funnel, diameter 7 cm
- One 125 mL Erlenmeyer flask
- Filter paper
- One 50 mL separatory funnel
- One glass column, diameter 1.5 cm
- Rotary evaporator

Procedure

1. To a stirred suspension of IBX [5] (3.0 equiv) in H$_2$O: CH$_2$Cl$_2$ (v/v = 1: 1, 0.25 M based on starting alcohol) was added n-Bu$_4$NBr (0.5 equiv) followed by the addition of alcohol (1.0 equiv) in one portion. The mixture was stirred at room temperature for 4 h. The residual solids were filtered off and washed thoroughly with diethyl ether. The combined filtrate was washed successively with 8 %

sodium thiosulfate (15 mL), water (2×15 mL) and brine (1×15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated (aspirator). The crude product was subsequently examined by gas chromatography for determining product conversion. Purification of the crude product by column chromatography (SiO_2) provided the isolated yield of the ketone.

2. According to the above procedure, oxidation of 1,5-decanediol (174 mg, 1 mmol) gave 1-hydroxy-5-decanone, after column chromatography over silica gel (18×1.5 cm, 8:2 hexanes/ethyl acetate as eluent), 127 mg (isolated yield, 74 %) as a colourless liquid: analytical TLC on silica gel, 7:3 hexanes/ethyl acetate, $R_f = 0.17$.

IR (neat, cm^{-1}): 3423, O-H; 1712, C=O.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ-3.57 (2H, br s) 2.55–2.10 (4H, m), 1.70–1.10 (11H, m), 0.82 (3H, t, $J = 6.9$ Hz).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ-211.6, 62.1, 42.7, 42.1, 32.0, 31.3, 23.5, 22.4, 19.6, 13.8.

Molecular ion (M+H) calcd for $C_{10}H_{21}O_2$: 173.1542. Found (ESI-TOF): $m/z = 173.1536$, error $= 3$ ppm.

CONCLUSION

A new, selective and efficient alternative method has been developed for the oxidation of secondary alcohols to ketones in moderate to good yields in hydrated media. Table 5.3 shows different substrates that can be selectively oxidized under the reaction conditions.

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5. *Note*: IBX, like other hypervalent iodine oxidants, can explode upon impact or heating. Plum, J. B. and Harper, D. *J. Chem. Eng. News* **1990**, *68*, 3.

Table 5.3 Selective oxidation of secondary hydroxyls using IBX/n-Bu$_4$NBr in 1:1 v/v CH$_2$Cl$_2$–H$_2$O
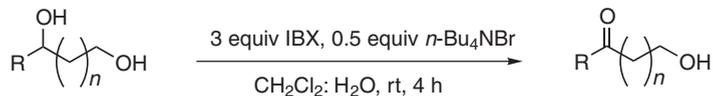
Entry	Substrate	Product (% yield)[a]		
1	OH, n-C$_5$H$_{11}$ ... OH	81 % (74 %)[b]	10 %	3 %
2	OH, n-C$_6$H$_{13}$ ... OH	88 % (70 %)[b]	2 %	5 %
3	OH ... OH	72 % (70 %)[b]	3 %	
4	OH, n-C$_3$H$_7$ ... OH	62 % (56 %)[b]		

5	67 % (58 %)[b]	
6	84 % (71 %)[b]	8 %
7	80 % (72 %)[b]	7 %
8	46 % (38 %)[b]	8 %

[a]GC yields.
[b]% Yields given in parentheses are isolated yields after purification by column chromatography.
Reprinted from reference [4], with permission from Elsevier.

6 Hydroxylation, Epoxidation and Related Reactions

CONTENTS

6.1   PROLINE-CATALYZED α-AMINOXYLATION OF ALDEHYDES AND KETONES

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The direct catalytic enantioselective α-aminoxylation of carbonyl compounds is a synthetically useful method for the preparation of versatile α-hydroxy carbonyl compounds. We have developed the direct catalytic enantioselective α-aminoxyla-

tion of aldehydes[1] and ketones,[2] using nitrosobenzene as the oxygen source and L-proline as a catalyst, affording α-aminoxylated aldehydes and ketones in high yield with excellent enantioselectivities.[3]

6.1.1   SYNTHESIS OF (*R*)-2-ANILINOXYPROPANOL
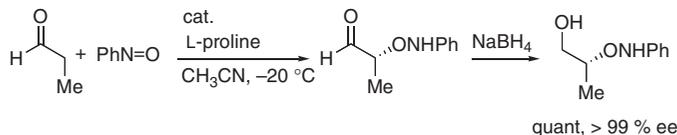
Materials and Equipment

- Propanal (129 μL, 1.8 mmol)
- Nitrosobenzene (64.3 mg, 0.6 mmol)
- L-Proline (21 mg, 0.18 mmol)
- CH$_3$CN (3.6 mL)
- NaBH$_4$ (114 mg, 3.0 mmol)
- MeOH (1 mL)
- pH 7.0 Phosphate buffer solution (5 mL)
- Ethyl acetate (40 mL)
- Hexane (150 mL)
- Anhydrous Na$_2$SO$_4$ (3 g)
- Silica Gel 60N (Spherical, neutral, 63–210 μm, KANTO Chemical Co. Inc.) (13 g)
- TLC plates (Silica gel 60 F$_{254}$, Merck)
- 30 mL Two-necked reaction flask equipped with a magnetic stirrer bar
- Magnetic stirrer plate
- Filter paper
- One 50 mL separatory funnel
- Rotary evaporator
- Equipment for column chromatography
- Cooling equipment

Procedure

1. To a CH$_3$CN (3.6 mL) solution of propanal (129 μL, 1.8 mmol) and nitrosobenzene (64.3 mg, 0.6 mmol) was added L-proline (21 mg, 0.18 mmol) at −20 °C. The reaction mixture was stirred for 24 h at that temperature.
2. The reaction was quenched with addition of MeOH (1 mL) and NaBH$_4$ (114 mg, 3.0 mmol) and the reaction mixture was stirred for 10 min at room temperature. After addition of pH 7.0 phosphate buffer solution, the organic materials were extracted with ethyl acetate three times and the combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* after filtration.

   Note: Due to the instability of 2-anilinoxypropanal, it was isolated and characterized after conversion to 2-anilinoxypropanol by reduction with NaBH$_4$.

3. Purification by silica gel column chromatography (eluent: ethyl acetate:hexane = 1:10–1:5) gave (*R*)-2-anilinoxypropanol (100 mg, 0.6 mmol) quantitatively.

> ^{1}H-NMR (CDCl$_3$): δ = 1.24 (3H, d, *J* = 6.4 Hz), 3.72 (1H, dd, *J* = 12.0, 6.6 Hz), 3.80 (1H, dd, J = 12.0, 2.9 Hz), 4.08–4.15 (1H, m), 6.94–6.99 (3H, m), 7.23–7.28 (2H, m).
> ^{13}C-NMR (CDCl$_3$): δ = 15.3, 65.9, 80.0, 114.4, 122.0, 128.9, 148.5.
> IR (neat): *v* = 3270, 2929, 1600, 1492, 1062, 761, 669 cm^{-1} .
> $[α]_D^{21}$ +1.8° (*c* = 0.57, CHCl$_3$).
> HRMS(FAB) calcd for C$_9$H$_{13}$NO$_2$: 167.0946. Found: 167.0908.

> Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (10:1 hexane:2-propanol), 1.0 mL min^{-1}; major enantiomer t_r = 10.3 min, minor enantiomer t_r = 9.3 min.

6.1.2   SYNTHESIS OF (*R*)-7-ANILINOXY-1, 4-DIOXASPIRO[4.5]DECAN-8-ONE

93 %, > 99 % ee
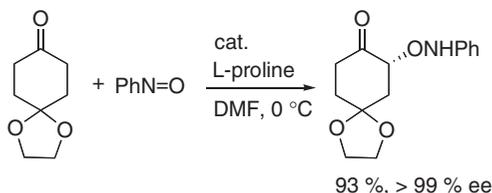
Materials and Equipment

- 1,4-Cyclohexanedione mono-ethylene ketal (187 mg, 1.2 mmol)
- Nitrosobenzene (64.3 mg, 0.6 mmol)
- L-Proline (21 mg, 0.18 mmol)
- DMF (3.6 mL)
- pH 7.0 Phosphate buffer solution (5 mL)
- Ethyl acetate (40 mL)
- Hexane (150 mL)
- Anhydrous Na$_2$SO$_4$ (3 g)
- Silica Gel 60N (Spherical, neutral, 63–210 μm, KANTO Chemical Co. Inc.) (13 g)
- TLC plates (Silica gel 60 F$_{254}$, Merck)
- 30 mL Two-necked reaction flask equipped with a magnetic stirrer bar
- Syringe (1 mL)
- Syringe pump
- Magnetic stirrer plate
- Filter paper
- One 50 mL separatory funnel
- Rotary evaporator
- Equipment for column chromatography

Procedure

1. To a DMF (2.7 mL) solution of 1,4-cyclohexanedione mono-ethylene ketal (187 mg, 1.2 mmol) and L-proline (21 mg, 0.18 mmol) was added a DMF (0.9 mL) solution of nitrosobenzene (64.3 mg, 0.6 mmol) over 12 h at 0 °C via syringe pump and the mixture was stirred for 30 min at that temperature.
2. The reaction was quenched with pH 7.0 phosphate buffer solution and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration.
3. Purification by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:10 – 1:5) gave α-aminoxy ketone (147 mg, 0.56 mmol) in 93 % yield.

   This procedure has been scaled up to provide 15 g of the α-aminoxylated adduct.

   ^{1}H-NMR (CDCl$_3$): δ = 1.88–2.04 (2H, m), 2.16 (1H, t, J = 12.8 Hz), 2.36–2.46 (2H, m), 2.62 (1H, dt, J = 14.0, 6.8 Hz), 4.38–4.21 (4H, m), 4.60 (1H, dd, J = 12.9, 6.5 Hz), 6.87 (2H, d, J = 7.7 Hz), 6.90 (1H, t, J = 7.2 Hz), 7.20 (2H, t, J = 7.2 Hz).
   ^{13}C-NMR (CDCl$_3$): δ = 34.9, 36.0, 39.7, 64.8, 64.9, 82.7, 107.6, 114.5, 122.2, 128.9, 148.0, 208.6.
   IR (neat): v = 2960, 2888, 1728, 1602, 1494, 1305, 1122, 1052 cm^{-1}.
   $[\alpha]_D^{18}$ + 78.7° (c = 1.2, CHCl$_3$).
   HRMS (FAB) calcd for $C_{14}H_{17}NO_4$: 263.1158. Found: 263.1172.

Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (10:1 hexane:2-propanol), 0.5 mL min^{-1}; major enantiomer t_r = 26.5 min, minor enantiomer t_r = 29.1 min.

CONCLUSION

This asymmetric α-aminoxylation can be applied to a wide range of aldehydes (Table 6.1) and six-membered cyclic ketones (Table 6.2). Because of the easy conversion of α-aminoxy moiety to the α-hydroxy group,[4] operational simplicity, and the

Table 6.1 Proline-catalyzed direct asymmetric α-aminoxylation of aldehydes.

Entry	R	Product	
		Yield (%)	ee %
1	Me	quant.	98
2	Et	87	99
3	*n*-Pr	81	95
4	*i*-Pr	77	97
5	Ph	62	99
6	CH$_2$Ph	70	99

Table 6.2   Proline-catalyzed direct asymmetric α-aminoxylation of ketones.

Entry	Ketone	Product	
		Yield (%)	ee %
1		77	>99
2		93	>99
3		84	>99
4		53	96
5		44	99
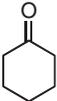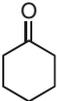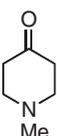
availability and low cost of the catalyst, the present method is one practical approach to the preparation of optically active α-hydroxy aldehydes and ketones. The same α-aminoxylation of aldehydes has been reported by Zhong[3a] and Brown et al.,[3b] while Cordova and colleagues[3c,3d] reported the equivalent reaction of ketones. The α-aminoxylated ketone was successfully employed in the asymmetric total synthesis of fumagillol, RK-805, FR65814, ovalicin and 5-demethylovalicin by our group.[5]

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6.2   Ru/SILIA* CAT*[TM]TEMPO-MEDIATED OXIDATION OF ALKENES TO α-HYDROXYACIDS

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Valuable α-hydroxy acids are conveniently synthesized with relevant selectivity enhancement using a sol-gel hydrophobized nanostructured silica matrix doped with the organocatalyst TEMPO [Silia*Cat*[TM]TEMPO] and bleach as primary oxidant, coupled with rapid RuO_4-mediated olefin dihydroxylation (Figure 6.1).[1,2] The porous structure of the fully methyl-modified organically modified silicate (ORMOSIL) xerogel dictates the accessibility of the diol molecules to the entrapped catalyst limiting oxidative cleavage and at the same time preventing catalyst deactivation.

6.2.1   SYNTHESIS OF SILIA*CAT*[TM]TEMPO

Materials and Equipment

- 3-Aminopropyl-trimethoxysilane (97 %) (0.72 mL, 4 mmol)
- 4-Oxo-2,2,6,6,-tetramethyl-1-piperidinoloxy (189 mg, 1 mmol)
- Sodium cyanoborohydride (95 %) (33 mg, 0.5 mmol)
- Methanol (3.6 mL)
- Methyltrimethoxysilane (98 %) (5.82 mL, 40 mmol)
- Water (Ultra pure Millipore Type 1 quality) (5.8 mL, 322 mmol)
- Sodium fluoride (0.75 mL, 1 M)
- Aqueous hydrochloric acid (7 M) (143 μL, 0.143 mmol)
- Methylene chloride
- Double-neck round-bottomed flask (under N_2 atmosphere)
- Glass vessel (20 mL)
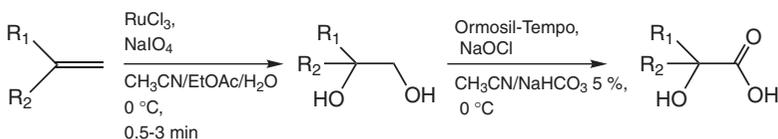
Figure 6.1

- Magnetic stirrer plate
- Vortex agitator
- Filter paper
- Silicon oil bath
- Water reflux condenser
- Oven

Procedure

1. The chemical entrapment of TEMPO moiety in the sol-gel silica hybrid material is performed in two steps: reductive amination of 4-oxo-TEMPO with 3-aminopropyl-trimethoxysilane (APTMS) followed by sol-gel co-poly-condensation of the TEMPO-funcionalized alkoxide thereby obtained with methyl-trimethoxysilane (MTMS) catalyzed by fluoride (Figure 6.2).
2. The molar ratios in the precursor sol was set at Si:MeOH:H_2O:$F^- = 1:3:8:0.017$ Silia*Cat*^{TM}TEMPO was prepared by dissolving APTMS (1.25 mL, 6.9 mmol) in MeOH (2.6 mL) in a double-neck round-bottomed flask bringing the pH
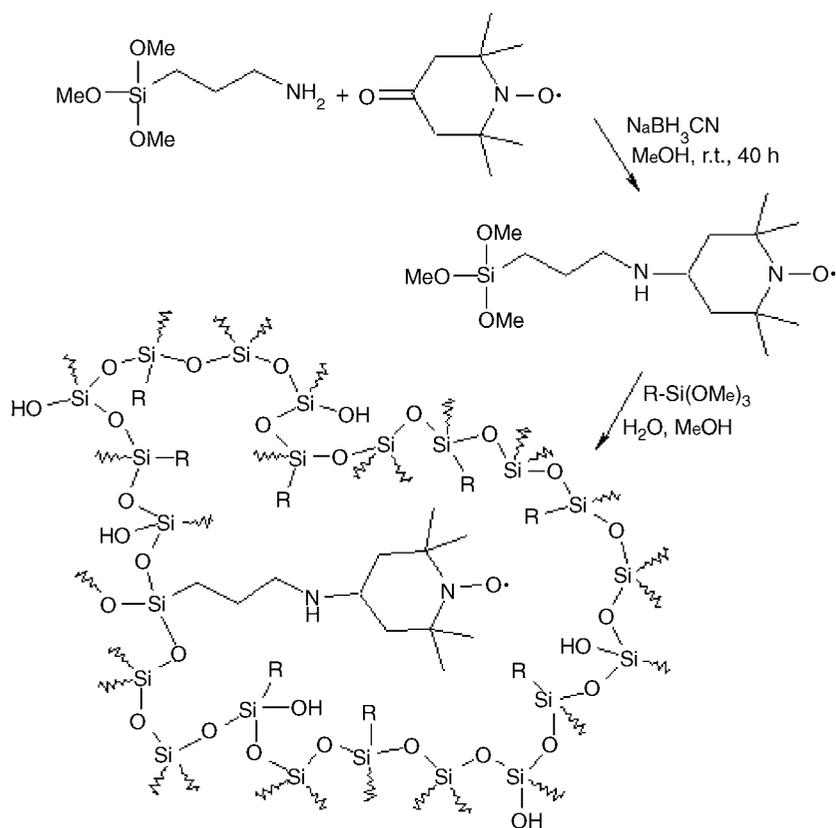
Figure 6.2

at 7 with conc. HCl (10 μL, 1 M) followed by the addition of 4-oxo-TEMPO (189 mg, 1 mmol) and NaBH₃CN (33 mg, 0.5 mmol), keeping the mixture under N_2 atmosphere. After 48 h with rapid stirring at room temperature, excess NaBH₃CN was destroyed by adding aqueous HCl (143 μL, 7 M) followed by MTMS (5.82 mL, 40 mmol), MeOH (1 mL), H_2O (5.8 mL, 322 mmol) and aqueous NaF (0.75 mL, 1M). The mixture was stirred using a Vortex agitator and gelled rapidly. The alcogel obtained was cooled at 0 °C in an ice bath for 30 min, sealed and left to age at room temperature for 24 h after which it was dried in an oven at 60 °C for 5 days. The resulting orange xerogel was washed three times with dichloromethane under reflux, dried again at 60 °C and powdered in a mortar. The catalytic load was 0.67 mmol radical g^{-1}.

6.2.2   SYNTHESIS OF 2-(4-CHLOROPHENYL)-1,2-PROPANEDIOL
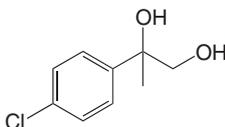
Materials and Equipment

- 4-Chloro-α-methylstyrene (98 %) (0.146 mL, 1 mmol)
- Sodium periodate (321 mg, 1.5 mmol)
- Ruthenium trichloride trihydrate (18.3 mg, 0.07 mmol)
- Water (Ultra pure Millipore Type 1 quality) (1 mL)
- Ethyl acetate (3 mL)
- Acetonitrile (3 mL)
- *n*-Hexane, ethyl acetate
- Anhydrous sodium sulfate
- Chiller
- Mechanical shaker
- Jacketed glass reactor
- Silica gel (Merck silica gel 60, 0063–0.2 nm) (250 g)
- TLC plates, SIL G-60 UV₂₅₄
- 250 mL round-bottomed flask
- One 250 mL separatory funnel
- Rotary evaporator

Procedure

1. NaIO₄ (321 mg, 1.5 mmol) was dissolved under stirring in 1 mL of H_2O. The solution was placed in a jacketed glass reactor thermostated to 0 °C. A 0.1 M solution of RuCl₃·3H₂O (700 μL, 0.07 mmol) was added under mechanical shaking until its colour turned into bright yellow. Ethyl acetate (3 mL) and

acetonitrile (3 mL) were then added, followed by 4-chloro-α-methylstyrene (146 μL, 1 mmol). The reaction mixture was vigorously shaken for 0.5 min after which time the excess periodate was quenched with 5 mL of saturated $Na_2S_2O_3$.

2. The two phases were separated, extracting the aqueous layer with ethyl acetate (3×15 mL). After the combined organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure, the crude product was purified by chromatography over a silica-gel column using a *n*-hexane/ethyl acetate as the mobile phase (yield 74 %).

6.2.3   SYNTHESIS OF 2-(4-CHLOROPHENYL)-1,2-HYDROXYPROPANOIC ACID
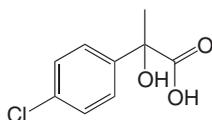
Materials and Equipment

- 2-(4-Chlorophenyl)-1,2-propanediol (373 mg, 2 mmol)
- Silia*Cat*^{TM}TEMPO (300 mg, 0.2 mmol)
- Potassium bromide (2.4 mg, 0.02 mmol)
- Acetonitrile (20 mL)
- 5 wt % Solution of sodium hydrogencarbonate (20 mL)
- 13 wt % Aqueous sodium hypochlorite solution (5 mL, 10.5 mmol)
- L-Tartaric acid solution (10 mL, 1 M)
- Methylene chloride
- Ethyl acetate
- Chiller
- Mechanical shaker
- Glass tube with cooling mantle, equipped at the bottom with a ceramic filter plate to allow easy separation of the catalyst upon reaction, diameter 4 cm
- One 250 mL separatory funnel
- TLC plates, SIL G-60 UV$_{254}$
- Magnetic stirrer plate

Procedure

1. A solution of 2-(4-chlorophenyl)-1,2-propandiol (2 mmol) in acetonitrile (20 mL) was placed in the jacketed reaction vessel followed by 300 mg of Silia*Cat*^{TM}TEMPO (0.2 mmol of TEMPO), potassium bromide (2.4 mg,

0.2 mmol) and 20 mL of a 5 wt % solution of NaHCO₃. Upon cooling the resulting mixture to 0 °C, an aqueous solution of NaOCl (5 mL, 10.5 mmol) (buffered to pH 9.1) was added under vigorous mechanical shaking following the reaction by TLC. Once all the diol substrate was consumed, the mixture was filtered and the filtrate acidified by adding tartaric acid (10 mL, 1 M). The resulting solution was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na₂SO₄ before removing the solvent under reduced pressure. The crude product was purified by column chromatography over silica gel using a CH₂Cl₂/ethyl acetate mixture as eluent (yield 80 %).

Molecular formula: $C_9H_9O_3Cl$.

m.p. (°C): 127–128 °C.

^{1}H-NMR (400 MHz, DMSO): δ (ppm) = 1.64 (s, 3H), 7.39 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H).
^{13}C-NMR (400 MHz, DMSO): δ (ppm) = 27.34 (q), 74.62 (s), 127.58 (d), 127.87 (d), 131.85 (s), 143.42 (s), 176.58 (s).
I.R. (cm^{-1}): v = 3410 (OH), 1732 (CO), 655 (CCl).
GC-MS: t_r 24.3 min; m/z (%) = 156 (9), 154 (26), 141 (33), 139 (100), 113 (16), 111 (48), 75 (17).

Table 6.3 Silia*Cat*^{TM}TEMPO-mediated oxidation of *vic* diols to α-hydroxy acids.

Entry	Product	Yield (%)^a	Ketone (%)
1		24	55
2		60	40
3		80	5
4		79	0
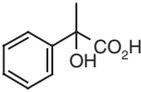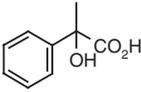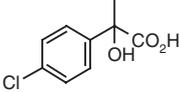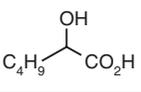
^{a}Isolated yield.

CONCLUSION

The procedure is easily reproduced and can be applied to a variety of readily available olefins to afford valuable α-hydroxyacids (Table 6.3). The method offers a practical alternative to the use of cyanohydrins currently employed in industrial processes and further demonstrates the synthetic benefit of entrapping the TEMPO catalyst inside the nanocages of hydrophobized porous silica,[3] where the radical catalytic molecules are highly protected from degradation.[4] Silia* Cat*[TM] TEMPO is a trademark of SiliCycle Inc., Quebec City, Canada.

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4. This is due to intrinsic prevention of the intermolecular quenching that is commonly observed for nitroxyl radicals heterogenized at a material's external surface. Ciriminna, R., Bolm, C., Fey, T. and Pagliaro, M. *Adv. Synth. Catal.* **2002**, *344*, 159.

6.3   CATALYTIC ENANTIOSELECTIVE EPOXIDATION OF *TRANS*-DISUBSTITUTED AND TRISUBSTITUTED ALKENES WITH ARABINOSE-DERIVED ULOSE

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Chiral dioxiranes, generated *in situ* from chiral ketones and Oxone®, are promising reagents for the asymmetric epoxidation of unfunctionalized alkenes.[1] Chiral ketone catalysts that are easily accessible in both enantiomers are targets for development.

We recently reported our results on the asymmetric epoxidation of *trans*-disubstituted and trisubstituted alkenes, using Oxone® as oxidant, catalyzed by readily available arabinose-derived 4-uloses containing tunable steric blockers that control the enantioselectivity of the epoxidation.[2] Ulose (**3**), containing a 2′,3′-diisobutyl acetal unit, was the most efficient catalyst and displayed good enantioselectivity.[2]

6.3.1   SYNTHESIS OF 2′,3′-DIISOBUTYL ACETAL (2)
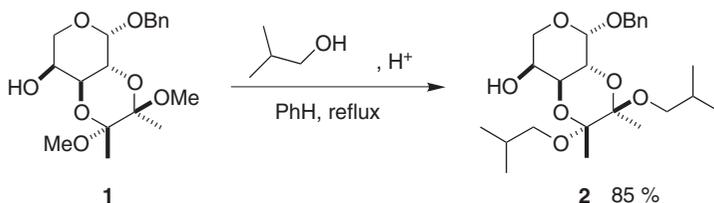
Materials and Equipment

- 2′,3′-Dimethyl acetal (1)[3] (1 g, 2.82 mmol)
- 2-Methyl-1-propanol (1.5 mL, 16.2 mmol)
- p-Toluenesulfonic acid monohydrate (p-TsOH) (97.5 %) (5 mg, 0.03 mmol)
- Dry benzene (99.0 %) (70 mL)
- Diethyl ether (Et$_2$O) (99.9 %)
- Hexane (95.7 %)
- Saturated solution of sodium hydrogencarbonate (NaHCO$_3$)
- Saturated solution of sodium chloride (brine)
- Anhydrous magnesium sulfate (MgSO$_4$)
- One Dean–Stark trap, height 9 cm, diameter 1 cm
- One 100 mL round-bottomed flask with a magnetic stirrer bar
- One 500 mL round-bottomed flask
- Magnetic stirrer plate
- TLC plate, SIL G-60 F$_{254}$
- Silica gel (Macherey-Nagel 60M, 0.04–0.063 mm/230–400 mesh), 20 g for filtration pad; 250 g for column chromatogram
- One 250 mL separatory funnel
- One glass sintered funnel, diameter 3 cm
- One glass column, diameter 4 cm
- Water aspirator
- Rotary evaporator
- Automatic polarimeter, 589 nm
- Automatic FT-IR spectrophotometer
- NMR spectroscopy at 300.13 MHz (^{1}H) and at 75.47 MHz (^{13}C) in CDCl$_3$ solution

Procedure

1. 2-Methyl-1-propanol (1.5 mL, 16.2 mmol) and dry benzene (70 mL) were placed in a 100 mL round-bottomed flask equipped with a magnetic stirrer bar under nitrogen. The solution was dried by heating under reflux with a Dean–Stark trap

for 8 h and cooled to room temperature. 2′,3′-Dimethyl acetal (**1**)[3] (1.0 g, 2.82 mmol) and *p*-TsOH (5.0 mg) were added. The reaction mixture was again heated under reflux with a Dean–Stark trap for 12 h and then cooled to room temperature.

2. The reaction mixture was transferred to a separatory funnel and washed with saturated NaHCO$_3$ solution (40 mL) and extracted with Et$_2$O (3 × 70 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous MgSO$_4$, and filtered through a thin pad of silica gel on a glass sintered funnel into a 500 mL round-bottomed flask with the aid of a water aspirator. The filtrate was concentrated under reduced pressure in a rotary evaporator. The crude residue was purified by flash column chromatography (silica gel, eluent:hexane/Et$_2$O: 2/1) to give 2′,3′-diisobutyl acetal (**2**) as a syrup (1.45 g, 85 %).

$[\alpha]_D^{23}$ + 13.6° (*c*=1.2, CHCl$_3$); R_f 0.22 (hexane/Et$_2$O: 2.5/1).
IR (thin film): 3449 (OH) cm^{-1}.
^{1}H-NMR (CDCl$_3$): δ = 7.40–7.28 (5H, m), 4.98 (1H, d, *J* = 2.1 Hz), 4.77 (1H, d, *J* = 12.3 Hz), 4.62 (1H, d, *J* = 12.3 Hz), 4.24 (2H, m), 3.90 (1H, d, *J* = 1.8 Hz), 3.81 (1H, dd, *J* = 12.6, 1.5 Hz), 3.74 (1H, dd, *J* = 12.6, 1.5 Hz), 3.25–3.15 (4H,m), 1.87–1.82 (2H, m), 1.64 (1H, brs), 1.33 (3H, s), 1.32 (3H, s), 0.95–0.92 (12H, m).
^{13}C-NMR (CDCl$_3$): δ = 138.0, 128.1, 127.2, 127.0, 99.8, 99.7, 97.6, 69.1, 68.2, 66.7, 65.5, 65.2, 63.1, 28.6, 19.6, 19.5, 18.5.
MS (EI): *m/z* (relative intensity)-364 (M$^+$–C$_4$H$_{10}$O, 23), 291 (10).
Anal. calcd for C$_{24}$H$_{38}$O$_7$: C, 65.73; H, 8.73. Found: C, 65.68; H, 9.20.

6.3.2 SYNTHESIS OF ULOSE (3)

2   **3** 95 %
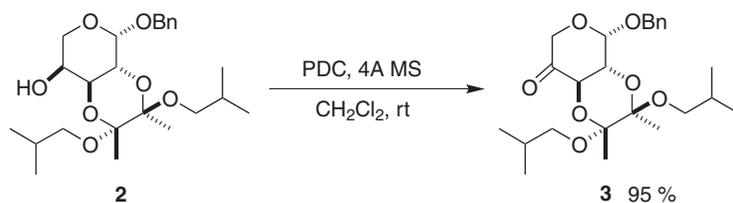
Materials and Equipment

- 2′,3′-Diisobutyl acetal (**2**) (1 g, 2.28 mmol)
- Pyridinium dichlorochromate (PDC) (2.5 g, 6.65 mmol)
- Dry dichloromethane (CH$_2$Cl$_2$) (99.8 %) (60 mL)
- Diethyl ether (Et$_2$O) (99.9 %)
- Hexane (95.7 %)
- Celite®, 6 g

- One 100 mL round-bottomed flask with a magnetic stirrer bar
- 100 mL and 250 mL round-bottomed flasks
- Magnetic stirrer plate
- 4 Å Molecular sieves (Acros, 4–8 mesh), 2 g
- TLC plate, SIL G-60 F$_{254}$
- Silica gel (Macherey-Nagel 60M, 0.04–0.063 mm/230–400 mesh), 20 g for filtration pad; 250 g for column chromatogram
- One glass syringe, 10 mL
- One hypodermic needle, 7G × 4 in.
- Two rubber septa for two 100 mL round-bottomed flasks
- One glass sintered funnel, diameter 3 cm
- One glass column, diameter 4 cm
- Water aspirator
- Rotary evaporator
- Automatic polarimeter, 589 nm
- Automatic FT-IR spectrophotometer
- NMR spectroscopy at 300.13 MHz (^{1}H) and at 75.47 MHz (^{13}C) in CDCl$_3$ solution

Procedure

1. Powdered 4 Å molecular sieves (2.0 g) and PDC (2.5 g, 6.65 mmol) were placed in a 100 mL round-bottomed flask equipped with a magnetic stirrer bar and then stoppered with a rubber septum under nitrogen. A solution of 2′,3′-diisobutyl acetal (**2**) (1.0 g, 2.28 mmol) in dry CH$_2$Cl$_2$ (60 mL) in a 100 mL round-bottomed flask stoppered with a rubber septum was transferred to the above-mentioned 100 mL round-bottomed flask via a glass syringe. The mixture was stirred at room temperature for 12 h.

   Note: *The powdered 4 Å molecular sieves should be flame-dried, and cooled to room temperature, before PDC is added.*

2. The chromium reagent, by-products, and molecular sieves were removed by filtration through a glass sintered funnel containing a thin pad of silica gel topped with packed Celite® into a 250 mL round-bottomed flask with the aid of a water aspirator. The filtrate was concentrated under reduced pressure using a rotary evaporator. The crude residue was purified by flash column chromatography (silica gel, eluent: hexane/Et$_2$O: 4/1) to give ulose (**3**) (1.05 g, 95 %) as a syrup.

   $[\alpha]_D^{23}$ + 12.2°($c = 1.4$, CHCl$_3$); R_f 0.35 (Et$_2$O/hexane: 3/7).
   IR (thin film): 1743, 1736 (C=O) cm^{-1}

   ^{1}H-NMR (CDCl$_3$): δ = 7.43–7.30 (5H, m), 5.10 (1H, d, $J = 3.3$ Hz), 5.00 (1H, d, $J = 11.1$ Hz), 4.83 (1H, d, $J = 12.3$ Hz), 4.75 (1H, d, $J = 12.3$ Hz), 4.15 (1H, d, $J = 15.9$ Hz), 4.09 (1H, dd, $J = 11.1, 3.3$ Hz), 3.90 (1H, d, $J = 15.9$ Hz), 3.29–3.16 (4H, m), 1.86–1.81 (2H, m), 1.40 (3H, s), 1.36 (3H, s), 0.93–0.89 (12H, m).

^{13}C-NMR (CDCl$_3$): $\delta = 200.5, 137.3, 128.3, 127.7, 127.2, 100.1, 99.5, 97.1,$ 70.9, 70.2, 69.9, 67.2, 67.1, 66.9, 28.6, 28.5, 19.6, 19.5, 19.4, 18.3, 18.2.

MS (EI): *m/z* (relative intensity) $= 362$ (M$^+$–C$_4$H$_{10}$O, 100), 288 (8).

Anal. calcd for C$_{24}$H$_{36}$O$_7$: C, 66.03; H, 8.31. Found: C, 66.19; H, 8.38.

6.3.3 ASYMMETRIC EPOXIDATION OF *TRANS*-α-METHYLSTILBENE USING ULOSE (**3**) AS CATALYST AT 0 °C
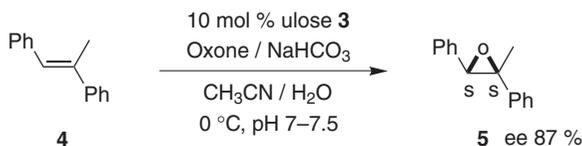
Materials and Equipment

- *trans*-α-Methylstilbene (20 mg, 0.1 mmol)
- Ulose (**3**) (4.36 mg, 10 mol%)
- Oxone$^{®}$ (307 mg, 0.5 mmol)
- Sodium hydrogencarbonate (NaHCO$_3$) (252 mg, 3 mmol)
- Tetrabutylammonim hydrogensulfate (*n*-Bu$_4$NHSO$_4$) (>99 %) (0.5 mg)
- Acetonitrile (CH$_3$CN) (99.9 %)
- Ethylenediaminetetraacetic acid disodium salt dehydrate (EDTA) buffer solution
- Diethyl ether (Et$_2$O) (99.9 %)
- Hexane (95.7 %)
- Europium tris[3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate][Eu(hfc)$_3$] (98 %)
- One two-necked 50 mL round-bottomed flask with a magnetic stirrer bar
- One 100 mL round-bottomed flask
- Two 10 mL dropping funnels
- Magnetic stirrer plate
- TLC plate, SIL G-60 F$_{254}$
- Silica gel (Macherey-Nagel 60M, 0.04–0.063 mm/230–400 mesh), 5 g for filtration pad; 100 g for column chromatogram
- One 100 mL separatory funnel
- One glass sintered funnel, diameter 2 cm
- One glass column, diameter 1 cm
- Water aspirator
- Rotary evaporator
- Automatic pH meter

- Automatic polarimeter operating at 589 nm
- NMR spectroscopy at 300.13 MHz (^{1}H) and at 75.47 MHz (^{13}C) in CDCl$_3$ solution

Procedure

1. *trans*-α-Methylstilbene (**4**) (20 mg, 0.1 mmol), ulose (**3**) (4.36 mg, 10 mol %) and *n*-Bu$_4$NHSO$_4$ (0.5 mg) were placed in a two-necked 50 mL round-bottomed flask with a magnetic stirrer bar. Then CH$_3$CN (10 mL) and aqueous buffer solution (5 mL, 4×10^{-4} M aqueous EDTA) were added and the mixture was cooled to 0 °C (bath temperature).
2. A solution of Oxone® (307 mg, 0.5 mmol) in aqueous EDTA (5 mL, 4×10^{-4} M) and a solution of NaHCO$_3$ (252 mg, 3 mmol) in H$_2$O (5 mL) were added dropwise to the mixture concomitantly via two dropping funnels. The pH of the mixture was maintained at about 7–7.5 over a period of 12 h.
   Note: The pH was monitored using a pH meter.
3. The reaction mixture was transferred to a separatory funnel containing water (10 mL) and extracted with Et$_2$O (3 × 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and filtered through a thin pad of silica gel on a glass sintered funnel into a 100 mL round-bottomed flask with the aid of a water aspirator. The filtrate was concentrated under reduced pressure using a rotary evaporator. The crude residue was purified by flash column chromatography (silica gel, hexane/Et$_2$O: 50/1) to give *trans*-α-methylstilbene oxide (**5**) (23 mg, 93%) as a mixture of enantiomers.
4. The enantioselectivity (ee) was determined by ^{1}H-NMR shift analysis of the chromatographed products directly with Eu(hfc)$_3$. The chromatographed products (**5**) (8 mg) were dissolved in CDCl$_3$ (0.6 mL) and shift reagent Eu(hfc)$_3$ was added until the ^{1}H singlet at δ 3.98 was split into two separate singlets at around δ 4.03 [ratio of products (**5**)/Eu(hfc)$_3$ ≈ 10/1.2 (w/w)]. The enantioselectivity was calculated from the integration of two separate singlets:

$$ee = |(a - b)/(a + b)| \times 100\%$$

where a is the integration value of one of two separated singlets and b is the integration value of the other singlet.

CONCLUSION

The preparation is easy to reproduce and since D- and L-arabinose are commercially available in large quantities, both enantiomers of ulose (**3**) are readily accessible. The enantioselectivity of the asymmetric epoxidation using ulose (**3**) towards *trans*-disubstituted and trisubstituted alkenes is shown in Table 6.4.

Table 6.4 Asymmetric epoxidation of alkenes using ulose (**3**) as catalyst at 0 °C.
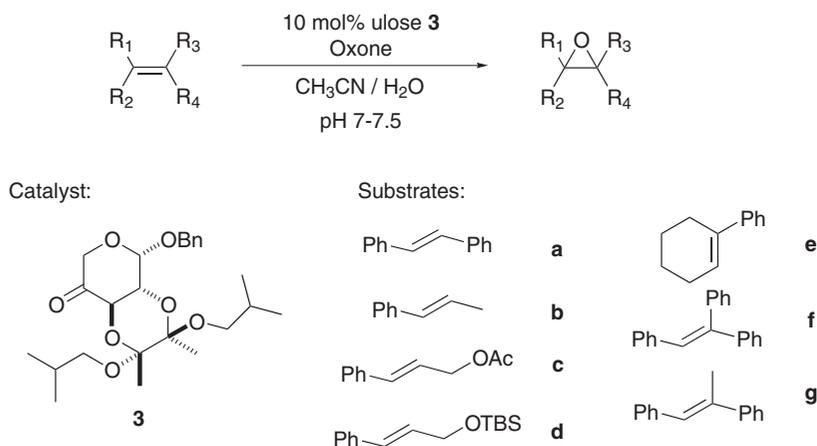
Entry	Substrates	Yield (%)	ee (%)	Config.
1	a	97	76	(−)-(S,S)[4]
2	b	89	69	(−)-(S,S)[5]
3	c	93	77	(−)
4	d	85	75	(−)-(S,S)[7,8]
5	e	92	85	(−)-(S,S)[9,10]
6	f	99	90	(+)-(S)[5]
7	g	93	87	(−)-(S,S)[6]

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6.4   VO(acac)$_2$/TBHP CATALYZED EPOXIDATION OF 2-(2-ALKENYL)PHENOLS. HIGHLY REGIO- AND DIASTEREOSELECTIVE OXIDATIVE CYCLIZATION TO 2,3-DIHYDROBENZOFURANOLS AND 3-CHROMANOLS

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VO(acac)$_2$/TBHP is an extremely useful system for the regio- and stereoselective epoxidation of unsaturated alcohols[1] and widely employed as key-step methodology in many synthetic sequences. We found that the same system is very efficient for the epoxidation of various double-bond substituted 2-(2-alkenyl) phenols, affording the corresponding epoxides in high yields (Figure 6.3, Table 6.5).[2] The phenolic group was found to be necessary for the epoxidation to occur through its coordination to the vanadium catalyst, in analogy to what is reported for the allylic alcohols.[1] The corresponding OH protected phenols were indeed found to be unreactive.

Furthermore, the VO(acac)$_2$/TBHP/TFA system promotes the one-pot highly regio and diastereoselective oxidative cyclization of 2-(2-alkenyl) phenols to 2,3-dihydrobenzofuranols and/or 3-chromanols in good yields, provided the proper C-C double bond substituted 2-(2-alkenyl)phenols are available (Figure 6.4, Table 6.6).
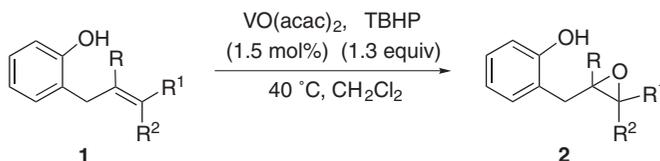
Figure 6.3   Reprinted from reference [2], with permission from Georg Thieme Verlag KG.

Table 6.5   VO(acac)$_2$/TBHP epoxidation of 2-(2-alkenyl) phenols **1**.

Entry	R	R^1	R^2	t (h)	Yield **2** (%)	*trans/cis* ratio
1	H	H	H	5	62	—
2	H	Me	H	2	80	85:15
3	H	Ph	H	2.5	65	*trans*
4	Me	H	H	1.5	92	—
5	H	Me	Me	2.5	81	—
6	H	(alkenyl chain)	Me	1.5	83	*trans*

Reprinted from reference [2], with permission from Georg Thieme Verlag KG.
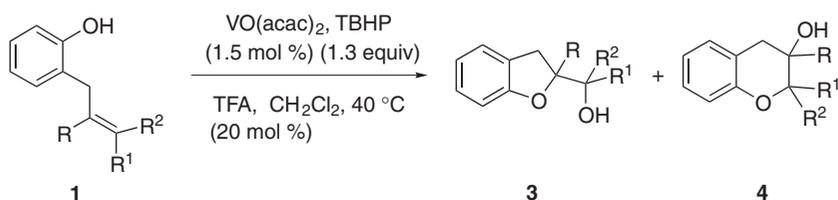
Figure 6.4

Table 6.6 VO(acac)$_2$/TBHP/TFA oxidative cyclization of 2-(2-alkenyl) phenols **1**.

Entry	R	R^1	R^2	Time (h)	Yield **3** %	Yield **4** %	Diasteromeric ratio
1	H	H	H	7	59	—	—
2	H	Me	H	3.5	74	—	85:15
3	H	Ph	H	3	—	58	2S*,3R*
4	Me	H	H	2.5	85	—	—
5	H	Me	Me	3	9	80	—
6	H		Me	3	3	70	2S*,3R*

6.4.1 VO(acac)$_2$/TBHP CATALYZED EPOXIDATION OF 2-(3,7-DIMETHYL-OCTA-2,6-DIENYL)-PHENOL[3]
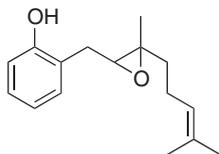
Materials and Equipment

- *t*-Butyl hydroperoxide (TBHP, 5–6 M decane solution) (230 μL, 1.3 mmol)
- 2-(3,7-Dimethyl-octa-2,6-dienyl)-phenol (246 mg, 1 mmol)
- VO(acac)$_2$ (3.9 mg, 0.015 mmol)
- Dry methylene chloride (8 mL)
- Silica gel (Merck, 230–400 mesh) (14 g)
- TLC plates (Merck, silica gel 60, F$_{254}$)
- 25 mL round-bottomed flask with magnetic stirring bar
- Magnetic stirrer plate
- Condenser

- Oil bath
- One glass column, diameter 2 cm
- Rotary evaporator

Procedure

1. To a stirred solution of dry CH_2Cl_2 (5 mL) placed in a 25 mL round-bottomed flask equipped with a magnetic stirrer bar and a condenser under argon was added VO(acac)$_2$ (3.9 mg, 0.015 mmol) and 2-(3,7-dimethyl-octa-2,6-dienyl)-phenol (246 mg, 1 mmol) dissolved in dry CH_2Cl_2 (3 mL) was added using a cannula. After 5 min TBHP was added (230 μL, 1.3 mmol of 5–6 M decane solution). The mixture was warmed at 40 °C. Upon completion, monitoring by TLC (petrol/Et$_2$O 80/20), the solvent was removed *in vacuo*.
2. The epoxide was isolated from the crude reaction mixture by column chromatography (eluent: petrol/Et$_2$O 80/20) (204.2 mg, 83% yield).

   ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.49 (3H, s), 1.61 (3H, s), 1.68 (3H, s), 1.60–1.70 (2H, m), 2.06–2.11 (2H, m), 2.84 (1H, dd, J = 14.6, 9.4 Hz), 2.90 (1H, dd, J = 14.6, 3.3 Hz), 3.04 (1H, dd, J = 9.4, 3.3 Hz), 5.03–5.08 (1H, m), 6.84–6.86 (1H, m), 6.91–6.93 (1H, m), 7.06 (1H, s), 7.10–7.12 (1H, m), 7.15–7.17 (1H, m).
   ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 16.7, 17.6, 23.5, 25.6, 31.6, 38.4, 63.4, 64.5, 117.0, 120.5, 123.1, 124.3, 128.5, 130.6, 132.2, 155.5.

6.4.2   VO(acac)$_2$/TBHP/TFA CATALYZED OXIDATIVE CYCLIZATION OF 2-(3,7-DIMETHYL-OCTA-2,6-DIENYL)-PHENOL
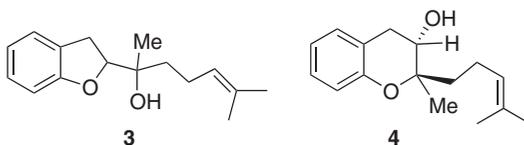
3   **4**

Materials and Equipment

- *t*-Butyl hydroperoxide (TBHP, 5–6 M decane solution) (230 μL, 1.3 mmol)
- 2-(3,7-Dimethyl-octa-2,6-dienyl)-phenol (246 mg, 1 mmol)
- VO(acac)$_2$ (3.9 mg, 0.015 mmol)
- Dry methylene chloride (8 mL)
- TFA (15 μL, 0.20 mmol)
- Silica gel (Merck, 230–400 mesh) (14 g)
- TLC plates (Merck, silica gel 60, F$_{254}$)
- 25 mL round-bottomed flask with magnetic stirring bar
- Magnetic stirrer plate
- Condenser

- Oil bath
- One glass column, diameter 2 cm
- Rotary evaporator

Procedure

1. To a stirred solution of dry CH_2Cl_2 (5 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer bar and a condenser under argon was added $VO(acac)_2$ (3.9 mg, 0.015 mmol) and 2-(3,7-dimethyl-octa-2,6-dienyl)-phenol (246 mg, 1 mmol) dissolved in dry CH_2Cl_2 (3 mL) was added using a cannula. After 5 min TBHP (230 μL, 1.3 mmol of 5–6 M decane solution) and TFA (15 μL, 0.20 mmol) were added. Upon completion, monitoring on TLC (petrol/Et_2O: 90/10–80/20), the solvent was removed *in vacuo*.

2. 3-Chromanol **4** and 2,3-dihydro-benzofuranol **3** were isolated from the crude reaction mixture by column chromatography (petrol/Et_2O: 90/10–80/20).

   3-Chromanol **4** (172.2 mg, 70 % yield).

   ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.34 (3H, s), 1.60 (3H, s), 1.67 (3H, s), 1.50–1.60 (2H, m), 1.95 (1H, bs), 2.16–2.14 (2H, m), 2.78 (1H, dd, J = 16.7, 5.8 Hz), 3.05 (1H, dd, J = 16.7, 4.9 Hz), 3.86–3.89 (1H, m), 5.07–5.11 (1H, m), 6.75–6.95 (2H, m), 7.03–7.20 (2H, m).

   ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.5, 19.3, 21.6, 25.6, 31.1, 37.0, 68.1, 78.5, 117.2, 118.9, 120.5, 123.9, 127.6, 129.9, 131.9, 152.8.

   2,3-Dihydro-benzofuranol **3** (7.4 mg, 3 % yield).

   ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.31 (3H, s), 1.60–1.50 (2H, m), 1.63 (3H, s), 1.69 (3H, s), 1.87 (1H, bs), 2.10–2.16 (2H, m), 3.09 (1H, dd, J = 15.7, 9.5 Hz), 3.22 (1H, dd, J = 15.7, 8.9 Hz), 4.63 (1H, t, J = 9.3), 5.08–5.14 (1H, m), 6.70–6.90 (2H, m), 7.05–7.18 (2H, m).

   ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.6, 21.9, 23.0, 25.7, 30.3, 36.9, 73.5, 88.7, 109.1, 120.5, 124.2, 124.9, 127.1, 127.8, 132.0, 159.5.

CONCLUSION

The procedures are very easy to reproduce and the mild and catalytic conditions are far superior to previously employed *m*-CPBA[4], to perform, respectively, the epoxidation and the oxidative cyclization of 2-(2-alkenyl)phenols.

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6.5   AN OXAZOLIDINONE KETONE CATALYST FOR THE ASYMMETRIC EPOXIDATION OF *cis*-OLEFINS

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Asymmetric epoxidation of prochiral olefins is a powerful strategy for the synthesis of enantiomerically enriched epoxides.[1–10] Previously, we reported a fructose-derived catalyst (**1**) that gives high ee for a wide variety of *trans*- and trisubstituted olefins (Figure 6.5).[11] Recently, we discovered a new catalyst (**2**) derived from D-glucose that can epoxidize many *cis*-olefins with high enantioselectivity and no *cis/trans*-isomerization.[12–14]
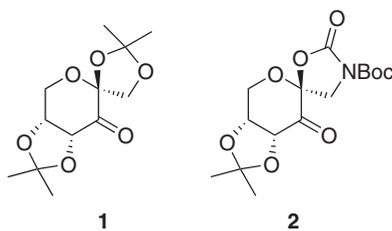
Figure 6.5

6.5.1   AMADORI REARRANGEMENT TO GIVE 1-DIBENZYLAMINO-1-DEOXY-D-FRUCTOSE
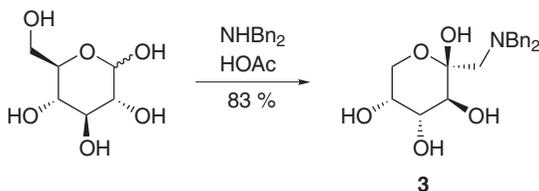
Materials and Equipment

- D-Glucose (ACS) (59.8 g, 332.0 mmol)
- Dibenzylamine (98 %) (64.0 mL, 332.0 mmol)
- Absolute ethanol (350 mL)
- Glacial acetic acid (57.0 mL, 995.7 mmol)
- One 1 L round-bottomed flask with magnetic stirrer bar
- One reflux condenser
- One oil bath

- One filter flask (500 mL)
- One variac
- Water aspirator
- One glass sintered funnel, diameter 8 cm
- One Dewar
- One magnetic stirrer plate

Procedure

1. To a suspension of D-glucose (59.8 g, 332.0 mmol) and dibenzylamine (64.0 mL, 332.0 mmol) in absolute ethanol (350 mL) was added acetic acid (57.0 mL, 995.7 mmol). The mixture was heated to reflux with an oil bath (temperature not exceeding 90 °C) and stirred continuously for 3 h. After cooling to 0 °C, the mixture was filtered, washed to white with ethanol, and dried under vacuum to give the rearranged product as a white solid (98.4 g, 83 %).

6.5.2 ACETAL PROTECTION OF 1-DIBENZYLAMINO-1-DEOXY-D-FRUCTOSE
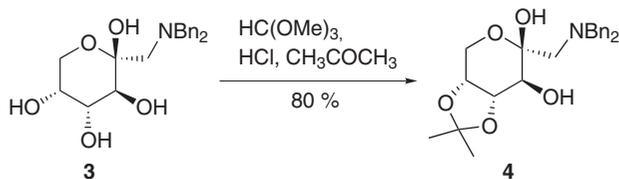
Materials and Equipment

- 1-Dibenzylamino-1-deoxy-D-fructose (**3**) (26.93 g, 75.0 mmol)
- Trimethyl orthoformate (98 + %) (35.0 mL, 320.0 mmol)
- Acetone (700 mL)
- Concentrated hydrochloric acid (9.0 mL, 108.0 mmol)
- One 2 L round bottomed flask with magnetic stirrer bar
- Ammonium hydroxide (28–30 %) (12 mL)
- Silica gel (Whatman, bulk 230–400 mesh), height 2 cm
- TLC plates, Aldrich Si on aluminum, UV (PK=25)
- One filter flask (1000 mL)
- Water aspirator
- One glass sintered funnel, diameter 8 cm
- One Dewar
- One rotary evaporator
- Hexane
- Ethyl acetate
- One magnetic stirrer plate

Procedure

1. To a suspension of 1-dibenzylamino-1-deoxy-D-fructose (**3**) (26.93 g, 75.0 mmol) and trimethyl orthoformate (35.0 mL, 320.0 mmol) in acetone (700 mL) under nitrogen at 0 °C in a 2 L round bottomed flask equipped with a stir bar, was added hydrochloric acid (9.0 mL, 108.0 mmol).

2. The reaction mixture was then carefully monitored by TLC while stirring vigorously at 0 °C for 1.5 h. Immediately upon observing the presence of a by-product that adversely affects the subsequent hydrogenation step [R_f values of the desired product and byproduct in hexane–ethyl acetate (1:1) are about 0.6 and 0.5, respectively], ammonium hydroxide (12 mL) was added to quench the reaction. (Note: Regardless of whether or not the by-product is ever observed by TLC, the reaction time must never be allowed to exceed 2 h.) The mixture was then filtered through a pad of silica gel with suction to remove NH_4Cl, washed with acetone, and concentrated to around 50 mL.

3. A mixture of hexanes–ethyl acetate (3:2, 400 mL) was added, and the undesired starting material was then allowed to precipitate in the freezer for 3 h. The mixture was filtered through a second pad of silica gel with suction to remove any starting material remaining in solution and washed with additional hexanes–ethyl acetate (3:2, 200 mL). The filtrate was concentrated on the rotary evaporator and then dried overnight with high vacuum to give diol **4** as a yellow oil (24.0 g, 80 % yield).

   ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (3 H, s), 1.53 (3 H, s), 2.71 (1 H, d, $J = 13.6$ Hz), 3.08 (1 H, d, $J = 13.6$ Hz), 3.30 (1 H, d, $J = 7.5$ Hz), 3.52–3.48 (2 H, m), 4.22–3.91 (6 H, m), 7.42–7.24 (10 H, m).

6.5.3 HYDROGENATION OF THE DIBENZYLAMINE
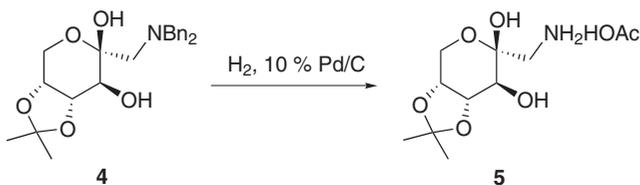
Materials and Equipment

- Compound **4** (26.0 g, 65.0 mmol)
- 10% Pd/C (4.3 g)
- Absolute ethanol (450 mL)

- Glacial acetic acid (4.3 g, 72.0 mmol)
- One 2 L three necked flask with magnetic stir bar
- Hydrogen gas
- Celite®, height 3 cm
- TLC plates, Aldrich Si on aluminum, UV (PK=25)
- One filter flask, 1000 mL
- Water aspirator
- One glass sintered funnel, diameter 8 cm
- One balloon equipped with a syringe and needle
- One rotary evaporator
- Ethyl acetate
- One magnetic stirrer plate

Procedure

1. In a 2 L three-necked flask equipped with a stir bar, compound **4** (26.0 g, ca. 65.0 mmol) was first dissolved in absolute ethanol (450 mL) and then degassed and purged with nitrogen three times. Following addition of acetic acid (4.3 g, 72.0 mmol) and Pd/C (4.3 g), the mixture was degassed and filled with hydrogen three times.
2. After stirring at room temperature under H_2 until the reaction was determined complete by TLC (the starting material and monobenzylated intermediates can be observed by UV with R_f values of 0.8 and 0.2, respectively, in ethyl acetate, while the product stays on the baseline), the mixture was filtered through Celite to remove the catalyst.
3. The filtrate was then concentrated on the rotary evaporator and dried with the high vacuum to give the product (**5**) as a brown solid (17.5 g, 96% crude yield), which was used without further purification. Drying under vacuum is imperative to remove all remaining ethanol, which consumes phosgene in the subsequent step.

Use of active Pd/C catalyst, vigorous stirring, and less solvent frequently resulted in shorter reaction time and better yield.

6.5.4 PHOSGENE CYCLIZATION OF AMINOALCOHOL
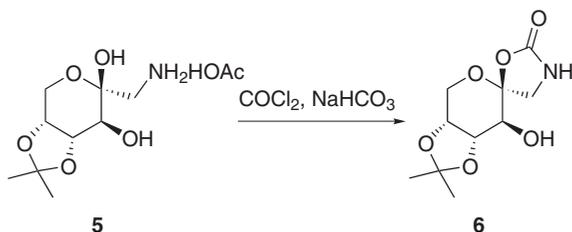
Materials and Equipment

- Aminoalcohol **5** (17.4 g, 62.0 mmol)
- Sodium bicarbonate (ACS) (30.0 g, 360.0 mmol)
- Dry methylene chloride (300 mL)
- Phosgene (20 % solution in toluene) (46.2 mL, 87.0 mmol)
- One 1 L round-bottomed flask with magnetic stir bar
- Methanol (100 mL)
- Silica gel (Whatman, bulk 230–400 mesh), height 8 cm
- One filter flask, 1000 mL
- One addition funnel, 50 mL
- Water aspirator
- One glass column, diameter 5 cm
- One rotary evaporator
- TLC plates, Aldrich Si on aluminum, UV (PK=25)
- Ethyl acetate
- One magnetic stirrer plate

Procedure

1. Aminoalcohol **5** (17.4 g, 62.0 mmol) and sodium bicarbonate (30.0 g, 360.0 mmol) were suspended in methylene chloride (300 mL) at 0 °C under nitrogen.
2. 20 % Phosgene in toluene (46.2 mL, 87.0 mmol) (a reagent which is extremely toxic and requires careful handling), was then added dropwise over a period of 30 min at 0 °C. Vigorous stirring, was mandatory to adequately neutralize HCl.
3. After 6 h of stirring at room temperature, the reaction was assessed to be complete by TLC (the product has an R_f of about 0.5 in ethyl acetate while the starting material remains on the baseline), so the mixture was opened to air.
4. Methanol (100 mL), which hydrolyzes unwanted chloroformate compounds in addition to unreacted phosgene, was then added dropwise over 30 min (very slowly at the beginning by pipette). Furthermore, vigorous stirring during methanol addition is required to ensure HCl does not accumulate in the flask, hence preventing the hydrolysis of the ketal to the undesired alcohol.
5. After an additional 30 min of stirring, the reaction mixture was filtered through a short column of silica gel and washed with additional methanol until no more brown liquid came off the column. Care should be taken to not wash with excess methanol, in order to prevent salts from passing through the silica gel in addition to the desired compound. Solvent evaporation on the rotary evaporator followed by the high vacuum line to remove any residual methanol that could consume oxidant in the following step gave alcohol **6** as a light brown solid (16.4 g, ca. 62.0 mmol).

^{1}H-NMR (300 MHz, CD$_3$OD): $\delta = 1.40$ (3 H, s), 1.53 (3 H, s), 3.36 (1 H, d, $J = 9.9$ Hz), 3.64 (1 H, d, $J = 7.8$ Hz), 3.83 (1 H, d, $J = 9.9$ Hz), 4.10 (1 H, d, $J = 13.8$ Hz), 4.27–4.21 (2 H, m), 4.37–4.34 (1 H, m).

6.5.5 ALCOHOL OXIDATION

Materials and Equipment

- Alcohol **6** (16.4 g, 62.0 mmol)
- Molecular sieves (3A) (56 g)
- Dry methylene chloride (300 mL)
- Pyridinium dichromate (35.0 g, 93.0 mmol)
- One 500 mL round bottomed flask with magnetic stir bar
- Glacial acetic acid (5 drops)
- Silica gel (Whatman, bulk 230–400 mesh), height 8 cm
- One filter flask, 1000 mL
- One addition funnel, 50 mL
- Water aspirator
- One glass column, diameter 5 cm
- One rotary evaporator
- TLC plates, Aldrich Si on aluminum, UV (PK=25)
- Ethyl acetate
- Hexane
- One magnetic stirrer plate

Procedure

To a solution of alcohol **6** (16.4 g, 62.0 mmol) and unactivated molecular sieves (56 g) in methylene chloride (300 mL), was added PDC (35.0 g, 93.0 mmol) followed by acetic acid (5 drops). After stirring at room temperature for about 5 h, the reaction was determined complete by TLC (the ketone has an R_f of about 0.8 in ethyl acetate while the hydrate only appears slightly above the starting material at 0.5. The hydrate has a reddish tint when stained with *p*-anisaldehyde, while the starting material is much darker). The mixture was then filtered through a short column of silica gel and washed with ethyl acetate–hexane (3:1), but care must be taken to avoid using too much solvent which would dissolve impurities that adversely affect the recrystallization. The mixture was concentrated on the rotary evaporator and extensively dried under a high vacuum to remove hydrate.

Recrystallization using hexane–methylene chloride (3:1) gave ketone **6** as a white solid (6.0 g, 38 % overall yield from **4**).

^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 1.42$ (3 H, s), 1.46 (3 H, s), 3.38 (1 H, dd, $J = 10.7, 0.6$ Hz), 4.23 (1 H, d, $J = 13.5$ Hz), 4.32 (1 H, d, $J = 10.7$ Hz), 4.64–4.53 (2 H, m), 4.82 (1 H, d, $J = 5.4$ Hz), 5.48 (1 H, brs).

6.5.6   SYNTHESIS OF KETONE **2**
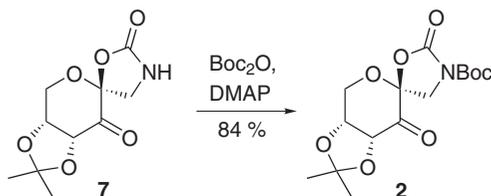
Materials and Equipment

- Compound **7** (2.56 g, 10.5 mmol)
- Di-*tert*-butyl dicarbonate (97 %+) (2.75 g, 12.6 mmol)
- Dry tetrahydrofuran (32 mL)
- 4-Dimethylaminopyridine (99 %) (0.013 g, 0.11 mmol)
- One 50 mL round-bottomed flask with magnetic stir bar
- Oxalic acid (0.01 g, 0.11 mmol)
- Silica gel (Whatman, bulk 230–400 mesh), height 3 cm
- Potassium carbonate (ACS)
- One filter flask, 1000 mL
- One addition funnel, 50 mL
- Water aspirator
- One glass column, diameter 1 cm
- One rotary evaporator
- TLC plates, Aldrich, Si on aluminum, UV (PK=25)
- Ethyl acetate
- Hexane
- One magnetic stirrer plate

Procedure

1. First, a column was prepacked with silica gel, and a solution of ethyl acetate–hexane (1:1) was dried over potassium carbonate.
2. To a solution of ketone **7** (2.56 g, 10.5 mmol) and di-*tert*-butyl dicarbonate (2.75 g, 12.6 mmol) in freshly distilled tetrahydrofuran (32 mL) under nitrogen

was added 4-dimethylaminopyridine (0.013 g, 0.11 mmol). Care must be taken to add the specified amount of di-*tert*-butyl dicarbonate. After 15–20 min, when the reaction was judged complete by TLC [the product has an R_f of about 0.6 in ethyl acetate–hexanes (1:1), while a small amount of impurity that can be removed by the subsequent hexane–ether treatment appears at 0.8], oxalic acid (0.01 g, 0.11 mmol) was *immediately* added to quench the reaction. It is essential to carefully monitor the reaction time. Too much time leads to product decomposition, while not enough time results in a mixture of starting material and product. The mixture was then immediately flushed through the aforementioned prepacked column, eluted with the dried ethyl acetate–hexanes (1:1, 42 mL), and concentrated to give crystals.

3. Hot hexanes–ether (3:1, 27 mL) was then added, and the suspension was allowed to stir without additional heating for 10 min. After filtration with suction, the suspension was washed with cold hexanes–ether (3:1, 20 mL) to give the desired ketone **2** as a white solid (3.02 g, 84%).

Extensive drying under a high vacuum removes the water of the hydrate to provide an uncomplicated NMR spectrum.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.41 (3 H, s), 1.45 (3 H, s), 1.53 (9 H, s), 3.71 (1 H, d, $J = 11.6$ Hz), 4.23 (1 H, d, $J = 13.6$ Hz), 4.51 (1 H, dd, $J = 13.6$, 1.8 Hz), 4.56 (1 H, d, $J = 11.6$ Hz), 4.61 (1 H, dd, $J = 5.6$, 1.8 Hz), 4.79 (1 H, d, $J = 5.6$ Hz).

6.5.7   ASYMMETRIC EPOXIDATION OF *CIS*-β-METHYLSTYRENE
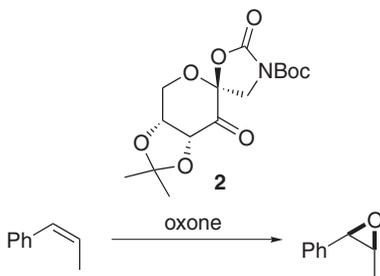
Materials and Equipment

- *cis*-(Methylstyrene (98 %) (0.059 g, 0.5 mmol)
- Ketone **2** (0.026 g, 0.075 mmol)
- Dimethoxymethane (1.9 mL)

- Dimethoxyethane (5.6 mL)
- pH 8 Buffer (AcOH–0.2 M K_2CO_3 in 4×10^{-4} M EDTA) (5 mL)
- Tetrabutylammonium sulfate (97 %) (0.0075 g, 0.02 mmol)
- Oxone (0.212 M in 4×10^{-4} M EDTA) (4.2 mL)
- Potassium carbonate (0.479 M in 4×10^{-4} M EDTA) (4.2 mL)
- One separatory funnel (50 mL)
- Sodium chloride
- Anhydrous sodium sulfate
- Silica gel (Whatman, bulk 230–400 mesh), height 5 cm
- One rotary evaporator
- Triethylamine
- Brine
- Ether
- Pentane
- Filter paper
- Syringe pump
- One glass column, diameter 1 cm
- One magnetic stirrer plate

Procedure

1. To a solution of ketone **2** (0.026 g, 0.075 mmol) and *cis-β*-methylstyrene (0.059 g, 0.5 mmol) in DME–DMM (3:1 v/v, 7.5 mL) in a 50 mL round bottomed flask equipped with a stir bar was added pH 8.0 buffer (5 mL) followed by tetrabutylammonium hydrogen sulfate (0.0075 g, 0.02 mmol). An ice–salt bath was used to cool the mixture to –10 °C. Oxone (0.212 M, 4.2 mL) and K_2CO_3 (0.479 M, 4.2 mL) were then added dropwise and separately over a period of 3.5 h via a syringe pump while stirring at –10 °C. After additions were complete, the reaction mixture was quenched with pentane and extracted with pentane. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated. *cis-β*-Methylstyrene oxide was isolated from the crude reaction mixture by flash chromatography (silica gel was buffered with 1 % triethylamine, pentane–ether: 1/0–50/1) as a colourless oil (0.058 g, 87 % yield, 91 % ee).

CONCLUSION

This experimental procedure in section 6.5.7 can be used to epoxidize certain cyclic as well as acyclic *cis*-olefins with good enantioselectivity and no *cis/trans*-isomerization (Table 6.7). Promising results have also been observed for some terminal olefins with this new glucose-derived catalyst, which complements our previously reported *trans*- and trisubstituted olefin catalyst **1**.

Table 6.7 Asymmetric epoxidation of olefins by ketone **2**.

Entry	Olefin	Yield (%)	ee (%)	Configuration
1		87	91	$(-)$-(1R,2S)
2		91	92	$(-)$-(1R,2S)
3		77	91	$(-)$-(5R,6S)
4		61	97	$(+)$
5		90	85	$(-)$-(R)
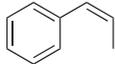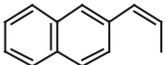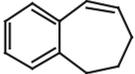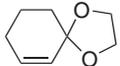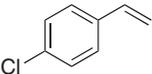
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6.6 α-FLUOROTROPINONE IMMOBILIZED ON SILICA: A NEW STEREOSELECTIVE HETEROGENEOUS CATALYST FOR EPOXIDATION OF ALKENES WITH OXONE®

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Preparation of nonracemic epoxides has been extensively studied in recent years since these compounds represent useful building blocks in stereoselective synthesis,[1] and the epoxide functionality constitutes the essential framework of various naturally occurring and biologically active compounds.[2] The enantiomerically enriched α-fluorotropinone was anchored onto amorphous KG-60 silica (Figure 6.6); this supported chiral catalyst (KG-60-FT*) promoted the stereoselective epoxidation of several *trans-* and trisubstituted alkenes with ees up to 80 % and was perfectly reusable with the same performance for at least three catalytic cycles.

6.6.1   SYNTHESIS OF SILICA KG-60-SUPPORTED ENANTIOMERICALLY ENRICHED α-FLUOROTROPINONE

Materials and Equipment

- KG-60 silica (Merck) (5 g)
- 3-Mercaptopropyl trimethoxysilane (8.5 mL, 45 mmol)
- Toluene (75 mL)
- Dichloromethane (50 mL)
- Diethyl ether (50 mL)
- Degassed chloroform (50 mL)
- α-Fluoro-*N*-carballyloxytropinone (0.7 g, 3 mmol)
- α,α′-Azoisobutyronitrile (AIBN) (0.5 g, 3 mmol)
- 100 mL and 250 mL round-bottomed flasks with magnetic stirrer bars
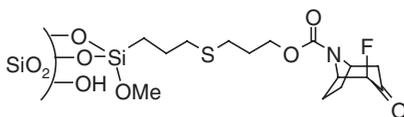
Figure 6.6

- Magnetic stirrer-heating plate
- Liebig's refrigerator
- Two Büchner funnels, diameter 10 cm
- Two Büchner flasks, 500 mL
- Filter paper
- Soxhlet apparatus
- High vacuum pump

Procedure

1. The tethering of enantiomerically enriched α-fluoro-*N*-carballyloxytropinone on the siliceous support was performed following a modification of a procedure reported in the literature.[3]
2. The KG-60 silica (5 g) was treated with 3-mercaptopropyl trimethoxysilane (45 mmol, 8.5 mL) in dry toluene (75 mL) at reflux for 24 h. After cooling the mixture was filtered on Büchner funnel and the solid washed with Soxhlet apparatus for 16 h with a mixture of dichloromethane/diethyl ether (50 mL, 1/1 v/v).
3. The functionalized silica (2 g) was dried under vacuum for 3 h and refluxed, under nitrogen, in degassed chloroform (50 mL) for 15 h with α-fluoro-*N*-carballyloxy-tropinone (3 mmol, 0.7 g) and α,α′-azoisobutyronitrile (AIBN) (3 mmol, 0.5 g) as radical initiator. After filtration, the functionalized solid KG-60-FT* was washed with Soxhlet apparatus for 16 h with a mixture of dichloromethane/diethyl ether (50 mL, 1/1 v/v) and dried under vacuum at room temperature.
   α-Fluorotropinone loading on silica $= 0.58$ mmol g^{-1}.

6.6.2 SYNTHESIS OF ENANTIOMERICALLY ENRICHED EPOXIDES

Materials and Equipment

- Selected alkene (0.1 mmol)
- KG-60-FT*, 69 mg, 4.0×10^{-2} mmol of supported catalyst
- Acetonitrile (3 mL)
- Aqueous ethylenediaminetetraacetic acid disodium salt (4×10^{-4} M) (2 mL)
- Oxone® (0.154 g, 0.25 mmol)
- Sodium bicarbonate (0.033 g, 0.39 mmol)
- Dichloromethane (10 mL)
- Water (10 mL)
- Anhydrous magnesium sulfate
- 50 mL Schlenk tube with magnetic stirrer bar
- Magnetic stirrer-heating plate
- Büchner funnel, diameter 10 cm
- Büchner flask, 100 mL
- Filter paper

- One 100 mL separatory funnel
- Rotary evaporator
- Gas chromatograph

Procedure

1. In a Schlenk tube equipped with a magnetic stirrer the selected alkene (0.1 mmol) was added to a suspension of KG-60-FT* (4.0×10^{-2} mmol of supported catalyst, 69 mg) in acetonitrile (3 mL) and 4×10^{-4} M aqueous Na_2EDTA (2 mL). Then, under vigorous stirring, portions of Oxone$^{\textregistered}$ (0.25 mmol, 0.154 g) and $NaHCO_3$ (0.39 mmol, 0.033 g) were added every 30 min for 1.0–2.5 h.
2. Water (10 mL) and methylene chloride (10 mL) were added, the catalyst was filtered off on a Büchner funnel and the organic phase was dried with $MgSO_4$.
3. The solvent was distilled off under reduced pressure and the product identified by GLC analysis.

CONCLUSION

The preparation of the silica supported α-fluorotropinone is easy to reproduce as a commercially available solid support was employed; the asymmetric epoxidation has been applied to *trans-* and trisubstituted alkenes affording the corresponding

Table 6.8 Enantioselective epoxidation of various alkenes over KG-60-FT*.

Entry	Substrate	Conversion	Product Yield (%)	Product ee (%) (Configuration)
1	Ph (cyclohexenyl)	96	94	58 (*S,S*)
2	Ph⟋Ph	98	97	66 (*S,S*)
3	Ph⟋Ph	95	93	67 (*S,S*)
4	Ph⟋Ph, Ph	93	91	80 (*S*)
5	Ph⟋OH	100	90	50 (*S,S*)
6	Ph⟋OTBS	100	95	48 (*S,S*)
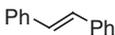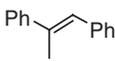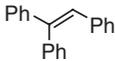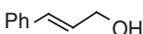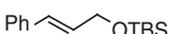
Table 6.9   Recycling of KG-60-FT* in the 1-phenylcyclohexene epoxidation.

			Product	
Entry	Cycle	Conversion	Yield (%)	ee (%) (Configuration)
1	1st	96	94	58 (S,S)
2	2nd	100	97	61 (S,S)
3	3rd	100	96	63 (S,S)

epoxides in high yield, excellent selectivity and ees up to 80% (Table 6.8). The catalyst can be recovered simply by filtration and reused for at least three catalytic cycles without appreciable lowering in activity (Table 6.9).

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6.7   ASYMMETRIC EPOXIDATION CATALYZED BY NOVEL AZACROWN ETHER-TYPE CHIRAL QUATERNARY AMMONIUM SALTS UNDER PHASE-TRANSFER CATALYTIC CONDITIONS

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Asymmetric epoxidation with hydrogen peroxide as the oxidizer promoted by chiral phase-transfer catalysts (chiral PTCs, Figure 6.7) can be performed under mild
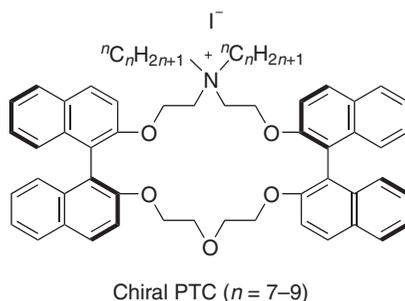
Chiral PTC (n = 7–9)
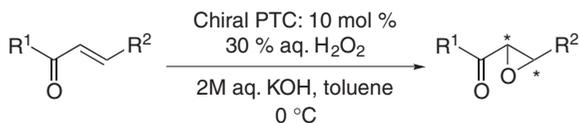
Figure 6.7

Figure 6.8

reaction conditions with aqueous media, which is obviously an ecologically sound synthetic method (Figure 6.8). We have synthesized a new type of chiral PTCs, which are quaternary ammonium salts of azacrown ethers, and have applied it to asymmetric epoxidation of chalcones with alkaline hydrogen peroxide to give the corresponding epoxy compounds in excellent yields with good enantioselectivities.[1]

6.7.1   SYNTHESIS OF PRECURSOR OF THE AZACROWN ETHER
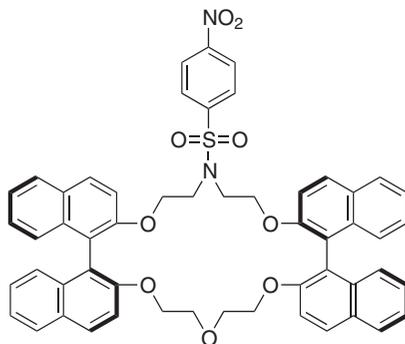
Materials and Equipment

- (*S*,*S*)-Oxybis[2-(ethyleneoxy)-2′-hydroxy-1,1′-binaphthyl][2] (2.32 g, 3.61 mmol)
- Potassium carbonate (1.10 g, 7.96 mmol)
- *N*,*N*-Bis-(2-*p*-nitrobenzenesulfonyloxyethyl)-*N*-*p*-nitrobenzenesulfonamide dichloromethane complex,[3] (3.44 g, 4.32 mmol)
- Dry methyl ethyl ketone (142 mL)
- Dichloromethane (75 mL)
- Brine (ca. 25 mL)
- Anhydrous magnesium sulfate
- Silica gel (Wakogel® C-200, 75–150 μm), 250 g
- One 300 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirrer bar
- Magnetic stirrer plate
- Oil bath
- One Büchner funnel, diameter 8 cm

- One 200 mL Büchner flask
- Filter paper
- One 100 mL separatory funnel
- One glass column, diameter 5 cm
- Rotary evaporator

Procedure

1. (*S,S*)-Oxybis[2-(ethyleneoxy)-2′-hydroxy-1,1′-binaphthyl] (2.32 g, 3.61 mmol) and potassium carbonate (1.10 g, 7.96 mmol) were placed in a 300 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirrer bar. Dry methyl ethyl ketone (142 mL) was then added and the mixture was refluxed on an oil bath for 1 h. To this solution, *N,N*-bis-(2-*p*-nitrobenzenesulfonyloxyethyl)-*N-p*-nitrobenzenesulfonamide dichloromethane complex (3.44 g, 4.32 mmol) was added.

2. After the resulting mixture was heated under reflux for 24 h, the solvent was evaporated under reduced pressure. To the residue was added water (50 mL) and the mixture was extracted with dichloromethane (3 × 25 mL) using a separatory funnel. The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford the crude product.

3. The crude product was purified by flash column chromatography (silica gel, toluene/ethyl acetate 40/1–20/1) to give (*S,S*)-2,3:4,5:13,14:15,16-tetra(1,2-naphtho)-9-(4-nitrobenzenesulfonyl)aza-1,6,12,17,20-pentaoxacyclodocosa-2,4,13,15-tetraene (1.68 g, 52%) as a light yellow crystalline solid. m.p. 132.0–135.0 °C; $[\alpha]_D^{32.5} + 108°(c = 1.0, CHCl_3)$.

   ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 2.86–2.97 (m, 4H), 3.25–3.40 (m, 4H), 3.70–3.73 (m, 2H), 3.77–3.82 (m, 4H), 3.97–4.02 (m, 2H), 7.02–7.10 (m, 6H), 7.17–7.27 (m, 6H), 7.31–7.40 (m, 6H), 7.88 (dd, *J* = 3.3, 8.0 Hz, 4H), 7.97 (dd, *J* = 9.0, 14.2 Hz, 4H).
   ^{13}C-NMR (101 MHz, CDCl$_3$): δ = 46.0, 68.0, 69.4, 69.9, 114.5, 115.3, 119.6, 120.1, 123.6, 123.8, 124.1, 125.3, 125.4, 126.5, 126.8, 127.5, 127.8, 127.9, 129.2, 129.3, 129.4, 133.9, 134.0, 145.7, 149.2, 153.6, 154.0.
   HRMS (FAB) calcd for C$_{54}$H$_{44}$N$_2$O$_9$S: 896.2768 (M$^+$). Found: 896.2770 (M$^+$).

6.7.2   SYNTHESIS OF THE AZACROWN ETHER
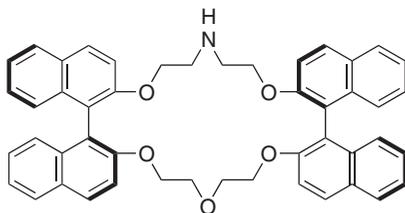
Materials and Equipment

- (*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-9-(4-nitrobenzenesulfonyl)aza-1,6,12,17,20-pentaoxacyclodocosa-2,4,13,15-tetraene (1.68 g, 1.88 mmol)
- Potassium carbonate (0.97 g, 7.00 mmol)
- *p*-Toluenethiol (0.28 g, 2.26 mmol)
- Dry DMF (70 mL)
- 1 M NaOH aqueous solution (50 mL)
- Dichloromethane (75 mL)
- Brine, (ca. 25 mL)
- Anhydrous magnesium sulfate
- Silica gel (Wakogel® C-200, 75–150 μm), 250 g
- One 200 mL round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer plate
- One Büchner funnel, diameter 8 cm
- One 200 mL Büchner flask
- Filter paper
- One 100 mL separatory funnel
- One glass column, diameter 5 cm
- Rotary evaporator

Procedure

1. A mixture of (*S,S*)-2,3:4,5:13,14:15,16-tetra(1,2-naphtho)-9-(4-nitrobenze-nesulfonyl)aza-1,6,12,17,20-pentaoxacyclodocosa-2,4,13,15-tetraene (1.68 g, 1.88 mmol), potassium carbonate (0.97 g, 7.00 mmol), and dry DMF (70 mL) was placed in a 200 mL round-bottomed flask equipped with a magnetic stirrer bar under argon. To this solution, *p*-toluenethiol (0.28 g, 2.26 mmol) was added, and then the resulting mixture was stirred at room temperature for 24 h.
2. The solvent was evaporated under reduced pressure, and to the residue was added 1 M NaOH (50 mL). The mixture was extracted with dichloromethane (3 × 25 mL) using a separatory funnel. The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford the crude product.
3. The crude product was purified by flash column chromatography (silica gel, eluent: ethyl acetate) to give (*S,S*)-2,3:4,5:13,14:15,16-tetra(1,2-naphtho)-9-aza-1,6,12,17,20-pentaoxacyclodocosa-2,4,13,15-tetraene (1.04 g, 78 %) as a light brown crystalline solid. m.p. 126.0–128.0 °C; $[\alpha]_D^{32.5} - 155°$ ($c = 1.0$, CHCl$_3$).

    ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 2.38$–2.47 (m, 4H), 3.08–3.24 (m, 4H), 3.75–3.92 (m, 8H), 7.06–7.09 (m, 4H), 7.16–7.21 (m, 4H), 7.25–7.36 (m, 8H), 7.88 (d, $J = 8.2$ Hz, 4H), 7.94–7.98 (m, 4H).
    ^{13}C-NMR (101 MHz, CDCl$_3$): $\delta = 47.7$, 69.1, 69.2, 69.6, 115.4, 115.6, 120.1, 120.6, 123.6, 123.7, 125.4, 125.5, 126.3, 126.4, 127.8, 127.9, 129.2, 129.3, 129.4, 134.1, 134.2, 154.0, 154.2.

HRMS (FAB) calcd for $C_{54}H_{44}N_2O_9S$: 711.2985 (M^+). Found: 712.3081 (M^++1).

6.7.3 SYNTHESIS OF THE AZACROWN ETHER-TYPE QUATERNARY AMMONIUM SALT
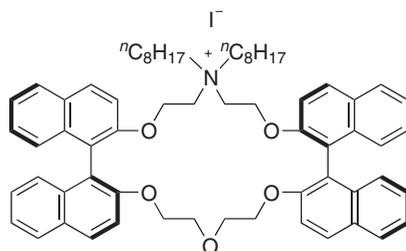
Materials and Equipment

- (S,S)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-9-aza-1,6,12,17,20-pentaoxacyclo-docosa-2,4,13,15-tetraene (0.21 g, 0.30 mmol)
- Potassium carbonate (0.20 g, 1.44 mmol)
- 1-Iodooctane (0.72 g, 3.00 mmol)
- Dry acetonitrile (5 mL)
- n-Hexane (ca. 50 mL)
- Diethyl ether (ca. 50 mL)
- Dichloromethane (50 mL)
- Celite®, ca. 20 g
- Anhydrous magnesium sulfate, ca. 20 g
- One 20 mL round-bottomed flask with a condenser and a magnetic stirrer bar
- Magnetic stirrer plate
- Oil bath
- One glass sintered funnel, diameter 4 cm
- One suction flask, 100 mL
- Filter paper
- Water aspirator
- Rotary evaporator

Procedure

1. (S,S)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-9-aza-1,6,12,17,20-pentaoxacyclo-docosa-2,4,13,15-tetraene (0.21 g, 0.30 mmol) and potassium carbonate (0.20 g, 1.44 mmol) were placed in a 20 mL round-bottomed flask equipped with a reflux condenser and a magnetic stirrer bar. Dry acetonitrile (5.0 mL) was then added

and the mixture was refluxed on an oil bath for 1 h. To this solution, 1-iodooctane (0.72 g, 3.0 mmol) was added.

2. After the resulting mixture was heated under reflux for 24 h, the solvent was evaporated under reduced pressure. To the residue was added *n*-hexane and the resulting precipitate was then filtered through Celite® and anhydrous magnesium sulfate into a glass sintered funnel with the aid of a water aspirator. The precipitate was washed with *n*-hexane and diethyl ether.

3. To the precipitate was added dichloromethane, and then the combined organic extracts were filtered and concentrated *in vacuo* to afford the corresponding azacrown ether-type quaternary ammonium salt (0.27 g, 85%) as a light brown crystalline solid. The purity of the crude product is high enough to be used in the catalysis experiments. m.p. 118–119 °C; $[\alpha]_D^{32.5}$ −71 (*c* = 1.0, CHCl₃).

¹H-NMR (400 MHz, CDCl₃): δ = 0.45–0.55 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 6H), 0.88–1.32 (m, 20H), 2.15–2.32 (m, 4H), 2.47 (dd, *J* = 13.6, 6.2 Hz, 2H), 3.10–3.25 (m, 6H), 3.62 (dd, *J* = 12.3, 6.3 Hz, 2H), 3.82–4.00 (m, 4H), 4.37 (dd, *J* = 12.3, 6.3 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.16–7.39 (m, 4H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.90–7.94 (m, 4H), 8.04 (d, *J* = 9.0 Hz, 2H), 8.17 (d, *J* = 9.0 Hz, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 14.0, 21.8, 22.5, 25.4, 28.7, 28.8, 31.5, 57.6, 59.7, 65.4, 69.1, 69.5, 115.0, 116.9, 119.2, 121.7, 124.0, 124.6, 124.7, 125.4, 126.7, 127.0, 127.9, 128.3, 129.0, 130.0, 130.4, 133.7, 133.8, 152.7, 153.9.

HRMS (FAB) calcd for $C_{64}H_{74}NO_5$: 936.5562 (M⁺). Found: 936.5569 (M⁺).

6.7.4 ASYMMETRIC EPOXIDATION OF (*E*)-CHALCONE CATALYZED BY THE AZACROWN ETHER-TYPE QUATERNARY AMMONIUM SALT AS CHIRAL PTC
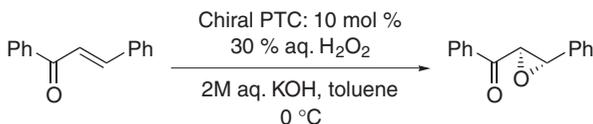
Materials and Equipment

- (*E*)-Chalcone (104.1 mg, 0.50 mmol)
- Azacrown ether-type quaternary ammonium salt (53.2 mg, 0.050 mmol)
- Toluene (1.5 mL)
- 2 M aq. KOH (0.63 mL, 1.25 mmol)
- 30 % aq. H₂O₂ (0.50 mL, 4.93 mmol)
- 10 % aq. NaHSO₃ (20 mL)
- Dichloromethane (60 mL)
- Brine (ca. 25 mL)

- Anhydrous magnesium sulfate
- Silica gel (Wakogel® C-200, 75–150 μm), 20 g
- One 20 mL round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer plate
- Cooling bath
- One Büchner funnel, diameter 8 cm
- One 100 mL Büchner flask
- Filter paper
- One 100 mL separatory funnel
- One glass column, diameter 1 cm
- Rotary evaporator

Procedure

1. A mixture of (*E*)-chalcone (104.1 mg, 0.50 mmol), the azacrown ether-type quaternary ammonium salt (53.2 mg, 0.050 mmol) and toluene (1.5 mL) was placed in a 20 mL round-bottomed flask equipped with a magnetic stirrer bar. To this solution, 2 M aq. KOH (0.63 mL, 1.25 mmol) was added, and then the resultant mixture was stirred vigorously at 0 °C for 10 min.
2. To the mixture was added 30 % aq. H_2O_2 (0.50 mL, 4.93 mmol) after which it was stirred vigorously at 0 °C for 24 h, before being quenched by 10 % aq. $NaHSO_3$ (20 mL) and extracted with dichloromethane (3 × 20 mL) using a separatory funnel. The combined organic extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford the crude product.

   Note: In quenching excess H_2O_2 with 10 % aq. $NaHSO_3$, an exothermic reaction occurred.

3. The crude product was purified by flash column chromatography (silica gel, *n*-hexane/ethyl acetate 20/1) to give the corresponding epoxy compound (89.7 mg, 80 %) as a light yellow crystalline solid.
4. The enantiomeric excess was determined by HPLC analysis (column: Daicel Chiralcel OD-H, eluent: *n*-hexane/2-propanol 98/2, flow rate: 0.5 mL min^{-1}, detector: UV 254 nm, retention time: 32.4 and 34.3 min). Absolute configuration of the epoxy compound was (*αR,βS*), which was determined by comparison of HPLC data with the literature reference.[4]

CONCLUSION

The azacrown ether-type chiral quaternary ammonium salts as chiral PTCs are easily prepared from BINOL in four steps. Remarkably, Table 6.10 shows that the good efficiency of asymmetric epoxidation of various chalcones can be achieved by adjustment of the length of the carbon chains on the nitrogen atom in the quaternary ammonium salts.

Table 6.10 Asymmetric epoxidation of chalcones catalyzed by the azacrown ether-type quaternary ammonium salts as Chiral PTCs (see Figure 6.8).

				Product	
Entry	R^1	R^2	Chiral PTC n^a	Yield^b (%)	ee %
1	Ph	Ph	7	75	54
2	Ph	Ph	8	85	70
3	Ph	Ph	9	42	32
4	Ph	1-Naphthyl	9	90	83
5	Ph	p-Cl-C$_6$H$_4$	7	96	32
6	p-Cl-C$_6$H$_4$	Ph	7	85	71

^{a}denotes the number of carbon atoms in the two alkyl chains on its nitrogen.
^{b}The yields were determined by ^{1}H-NMR.

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6.8   ENANTIOSELECTIVE EPOXIDATION OF OLEFINS USING PHASE TRANSFER CONDITIONS AND A CHIRAL [AZEPINIUM][TRISPHAT] SALT AS CATALYST

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Oxaziridinium cations are effective oxygen-transfer reagents towards electron-rich substrates.[1] They are most often prepared *in situ* by oxidation of iminium ions with Oxone® and react particularly well with unfunctionalized olefins to give access to a broad range of epoxides.[2] The chiral iminum salts developed in our group, available in just three steps from phenanthrene, are the combination of: (i) a *tropos* diphenylazepinium skeleton; (ii) a commercially available enantiopure exocyclic appendage made from (*S*)- or (*R*)-3,3-dimethylbutan-2-amine; and (iii) a lipophilic TRISPHAT counter-ion. The use of this latter anion allows, in combination with
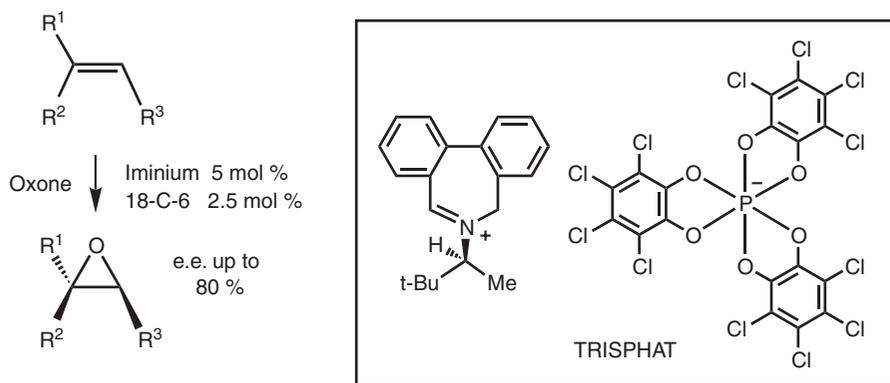
Figure 6.9

18-crown-6, strict biphasic conditions which can increase both conversion and selectivities. This is due – most probably – to the strict partitioning of reagents, substrates and products in separated aqueous and organic phases.[3] Herein a versatile catalytic procedure is thus described for the enantioselective epoxidation of olefins using phase transfer conditions and an iminium TRISPHAT salt as catalyst. It affords epoxides with high conversion and decent levels of enantiomeric excess (Figure 6.9).[4,5]

6.8.1   ENANTIOSELECTIVE EPOXIDATION OF 1-PHENYL-3,4-DIHYDRONAPHTHALENE
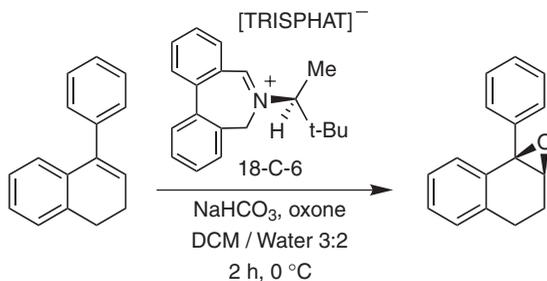
Materials and Equipment

- $NaHCO_3$ (67 mg, 0.80 mmol)
- Oxone® (132.0 mg, 0.21 mmol)

   Note: *Persons handling Oxone® should avoid contact of the oxidant with eyes, skin, or clothing. Avoid breathing dust. Wash thoroughly after handling and*

launder contaminated clothing before reuse. Exposure to Oxone® can be minimized by providing adequate ventilation and by wearing rubber- or plastic-coated gloves and chemical safety goggles. For further information, see: http://www.dupont.com/oxone/techinfo/#safety

- 1-Phenyl-3,4-dihydronaphthalene (41.3 mg, 0.20 mmol)
- [6-*N*-((*S*)-3,3-Dimethylbutan-2-yl)-5*H*-dibenz[*c,e*]azepinium][*rac*-TRISPHAT] (10.5 mg, 10.0 μmol, 5 mol %)[4]
- 18-Crown-6 (1.0 mg, 5.0 μmol, 2.5 mol %)
- Naphthalene (internal standard) (25.6 mg, 0.20 mmol)
- Methylene chloride (1.2 mL)
- Water (0.8 mL)
- One flask (10 mL) equipped with magnetic stirrer bar
- One magnetic stirrer plate
- One Cryostat
- One separatory funnel (25 mL)
- One glass column (1.5 × 25 cm)
- Silica gel (Fluka 60A, 230–400 mesh), 1.5 × 10 cm
- TLC plates, SIL G-60 UV$_{254}$
- Rotary evaporator

Procedure

1. In a one-necked round-bottomed flask (10 mL) equipped with a magnetic stirring bar, NaHCO$_3$ (67.0 mg, 0.80 mmol, 4.0 equiv) was added to water (800 μL). Oxone® (132.0 mg, 0.21 mmol, 1.0 equiv) was then added and the solution stirred for 2 min until effervescence subsided. A solution of 1-phenyl-3,4-dihydronaphthalene (41.3 mg, 0.20 mmol, 1.0 equiv) and naphthalene (internal standard, 25.6 mg, 0.20 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (400 μL, 0.5 M) was added. The flask was cooled to 0 °C by application of an external thermostated bath and a solution of [6-*N*-((*S*)-3,3-dimethylbutan-2-yl)-5*H*-dibenz[*c,e*]azepinium][*rac*-TRISPHAT] salt (10.0 μmol, 5 mol%) in CH$_2$Cl$_2$ (600 μL) was added, followed by a solution of 18-crown-6 (1.0 mg, 5.0 μmol, 2.5 mol %) in CH$_2$Cl$_2$ (200 μL). The reaction was then stirred at 0 °C.
2. The crude mixture was monitored by chiral stationary phase (CSP) HPLC (eluent: hexane/isopropanol 95/5, 0.5 mL min^{-1}, Chiralcel OD-H). After 2 h, (*1R,2S*)-1-phenyl-3,4-dihydronaphthalene oxide (80 % ee) was obtained as the major enantiomer (t_R = 13.9 min) with 100 % conversion (calculated using the internal standard); the minor (*1S,2R*) enantiomer eluting first (t_R = 10.1 min).
3. Water (5 mL) was then added and the product extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic phases were dried (Na$_2$SO$_4$) and evaporated. The pale yellow solid obtained was purified by column chromatography (silica gel, pentane/ethyl acetate 95/5) to afford the desired product (31.1 mg, 70 % yield).

4. This procedure was scaled up starting from 5.0 g of 1-phenyl-3,4-dihydro-naphthalene (24.2 mmol) and 1.27 g of catalyst (5 mol %). It provided 4.7 g of (1R,2S)-1-phenyl-3,4-dihydronaphthalene oxide in a better yield (87 %) and analogous conversion (95 %) and enantiomeric excess (78 % ee).

^{1}H-NMR: $\delta = 7.49–6.97$ (m, 9H), 3.63 (d, $J = 2.6$ Hz, 1H), 2.97 (ddd, $J = 15.1$, 13.8, 6.6 Hz, 1H), 2.70 (dd, $J = 15.7$, 5.5 Hz, 1H), 2.48 (m, 1H), 2.04 (ddd, $J = 14.2$, 13.9, 5.7 Hz, 1H).

CONCLUSION

The enantioselective epoxidation using [diphenylazepinium][TRISPHAT] salts as catalysts is an easily reproducible procedure that requires no particular precautions except in the handling of Oxone[®]. Although moderate levels of enantiomeric excess are observed, this reaction can be applied to a wide range of olefins, and both enantiomers of the catalyst are readily available through the use of the (S) or (R) enantiomers of 3,3-dimethylbutan-2-amine. The results of a small screen using [6-N-((S)-3,3-dimethylbutan-2-yl)-5H-dibenz[c,e]azepinium][rac-TRISPHAT] salt as catalyst are reported in Table 6.11.[5]

Table 6.11 Enantioselective epoxidation of olefins **1** to **5** in the presence of [6-N-((S)-3,3-dimethylbutan-2-yl)-5H-dibenz[c,e]azepinium][rac-TRISPHAT] as catalyst.[a]

Olefin	Conv. (%)[b]	ee (%)[c]	Configuration
1	68[d]	66[e]	(−)-(1S,2S)
2	100	80	(+)-(1R, 2S)
3	61	31	(+)-(S)
4	75	46	(−)-(1S,2S)
5	64	17	(−)-(S,S)
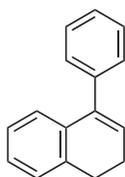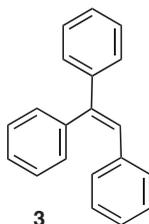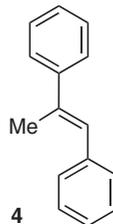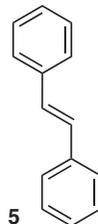
[a]Conditions: catalyst (5 mol %), 18-crown-6 (2.5 mol %), Oxone[®] (1.1 equiv), NaHCO$_3$ (4.0 equiv), CH$_2$Cl$_2$/H$_2$O (3/2), 0 °C, 2 h. Average of at least two runs.
[b]Conversion calculated with naphthalene as an internal standard unless otherwise stated.
[c]Determined by CSP-HPLC (Chiralcel OD-H) unless otherwise stated.
[d]Conversion calculated with dodecane as an internal standard.
[e] Determined by CSP-GC (Chiraldex Hydrodex β–3P).

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6.9   CATALYTIC ASYMMETRIC EPOXIDATION OF α,β-UNSATURATED ESTERS PROMOTED BY A YTTRIUM-BIPHENYLDIOL COMPLEX

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The catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds is
one of the synthetically useful reactions in organic synthesis.[1] The resulting chiral
epoxides are easily converted to various useful chiral compounds. We developed a
new yttrium-(*S*)-6,6′-[oxybis(ethylene)dioxy]biphenyl-2,2′-diol (**1**) (Figure 6.10)

(**1**)
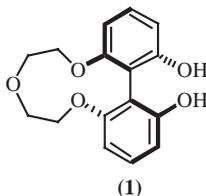
Figure 6.10
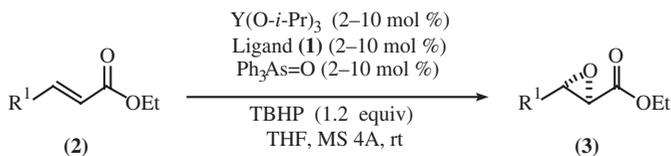
Figure 6.11
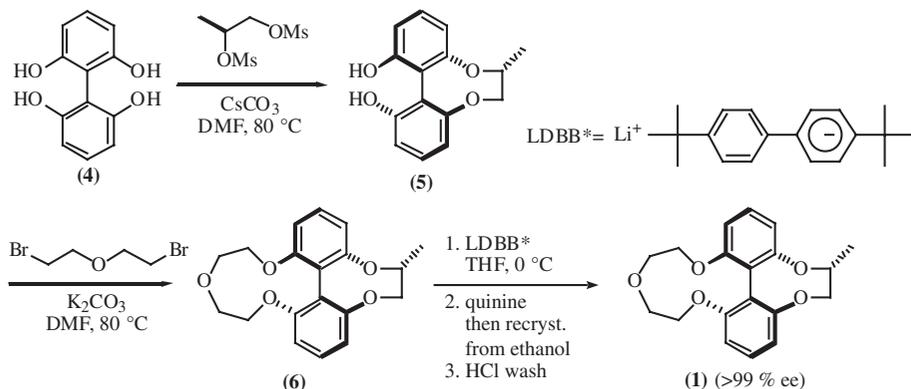
Figure 6.12

complex for catalytic asymmetric epoxidation of α,β-unsaturated esters **2** (Figure 6.11). The catalyst provided α,β-epoxy esters in high yields (up to 97 %), and excellent enantiomeric excesses (up to 99 % ee).[2]

The ligand, (S)-6,6′-[oxybis(ethylene)dioxy]biphenyl-2,2′-diol (**1**), is prepared in three steps from readily available 2,2′,6,6′-tetrahydroxybiphenyl (**4**).[2, 3] The steps involved are firstly asymmetric desymmetrization of **4**[4], secondly bridging of the 6,6′-position by diethylene ether, and finally selective deprotection of the propane diol to afford **1** (Figure 6.12).

6.9.1 SYNTHESIS OF (aS,R)-6,6′-[(PROPYLENE)DIOXY]BIPHENYL-2,2′-DIOL (5)

(5)
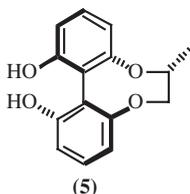
Materials and Equipment

- 2,2′,6,6′-Tetrahydroxybiphenyl (4.4 g, 20.2 mmol)
- (*S*)-1,2-Propanediol bismesylate (2.74 g, 14.5 mmol)
- Cesium carbonate (15.2 g, 46.5 mmol)
- *N*,*N*′-Dimethylformamide (786 mL)
- 1 M aqueous hydrochloric acid
- Diethyl ether, hexane, ethyl acetate
- Saturated aqueous solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel [Merck 60 (230-400 mesh ASTM)]
- TLC plates (Merck Silica Gel 60 F_{254})
- 2 L round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer plate
- One 3-way tap
- One glass funnel, diameter 8 cm
- Two 1 L Erlenmeyer flasks
- One 1 L separating funnel
- One glass column, diameter 4 cm
- Silicon oil bath
- Syringe pump
- Rotary evaporator

Procedure

1. A 2 L round-bottomed flask with a magnetic stirrer bar and a 3-way tap with argon balloon was charged with 2,2′,6,6′-tetrahydroxybiphenyl (4.4 g, 20.2 mmol), cesium carbonate (15.2 g, 46.5 mmol) and *N*,*N*′-dimethylformamide (780 mL). The mixture was heated to 80 °C. To the mixture was slowly added (*S*)-1,2-propanediol bismesylate (2.74 g, 14.5 mmol) in *N*,*N*′-dimethylformamide (6 mL) over 4h, and this was stirred for 1 h at the same temperature (TLC: hexane/ethyl acetate = 1/1, product: R_f = 0.5). After cooling to 0 °C, the reaction mixture was quenched by 1 M aqueous hydrochloric acid (150 mL).

2. Most of the *N*,*N*′-dimethylformamide was removed by distillation under reduced pressure. The solution was extracted with diethyl ether (three times). The combined organic layers were washed with brine, and dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 10/1–3/1) to give (*aS*,*R*)-**5** (2.12 g, 62 %) as a yellow solid.

   ^{1}H-NMR (acetone): δ = 1.31 (d, *J* = 6.5 Hz, 3H), 3.72 (dd, *J* = 12.0, 10.8 Hz, 1H), 4.28 (m, 1H), 4.43 (dd, *J* = 12.0, 3.6 Hz 1H), 6.77–6.84 (m, 4H), 7.24–7.29 (m, 2H), 8.28 (br-s, 2H).
   ^{13}C-NMR (acetone): δ = 17.5, 79.9, 81.9, 113.0, 115.0, 115.0, 117.4, 117.5, 130.3, 130.4, 155.8, 155.8, 161.7, 162.2.

6.9.2   SYNTHESIS OF (*aS*,*R*)-2,2-[OXYBIS(ETHYLENE)DIOXY]-6,6′-[(PROPYLENE)DIOXY]BIPHENYL (**6**)

(6)
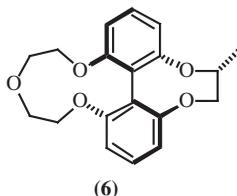
Materials and Equipment

- (*aS*,*R*)-6,6′-[(Propylene)dioxy]biphenyl-2,2′-diol (600 mg, 2.4 mmol)
- 2-Bromoethyl ether (553 μL, 4.8 mmol)
- Potassium carbonate (720 mg, 5.52 mmol)
- *N*,*N*′-Dimethylformamide (154 mL)
- 1 M aqueous hydrochloric acid
- Benzene, hexane, ethyl acetate
- Saturated aqueous solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel [Merck 60 (230–400 mesh ASTM)]
- TLC plates (Merck Silica Gel 60 F$_{254}$)
- 300 mL round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer plate
- One 3-way tap
- One glass funnel, diameter 6 cm
- One 1 L Erlenmeyer flask
- One 500 mL Erlenmeyer flask
- One 500 mL separating funnel
- One glass column, diameter 3 cm
- Syringe pump
- Silicon oil bath
- Rotary evaporator

Procedure

1. A 300 mL dried round-bottomed flask with a magnetic stirrer bar, and a 3-way tap with argon balloon was charged with (*aS*,*R*)-6,6′-[(propylene)dioxy]biphenyl-2,2′-diol (**5**) (600 mg, 2.4 mmol), potassium carbonate (720 mg, 5.52 mmol) and *N*,*N*′-dimethylformamide (150 mL). The mixture was heated to 80 °C. To the mixture was slowly added 2-bromoethyl ether (553 μL, 4.8 mmol) in *N*,*N*′-dimethylformamide (4 mL) over 4 h, and this was stirred for 5 h at the same

temperature (TLC: hexane/ethyl acetate = 1/1, product: R_f = 0.45). After cooling to 0 °C, the reaction mixture was quenched by 1 M aqueous hydrochloric acid (30 mL).

2. The mixture was extracted with benzene three times, and the combined organic layers were washed with brine and dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography to give (hexane/ethyl acetate = 20/1–4/1) (*aS,R*)-**6** (558.0 mg, 70 %) as a colourless solid.

^{1}H-NMR (CDCl$_3$): δ = 1.22 (d, *J* = 6.4 Hz, 3H), 3.62–3.66 (m, 1H), 3.77–3.81 (m, 2H), 3.84–3.88 (m, 2H), 4.08–4.12 (m, 2H), 4.15–4.19 (m, 1H), 4.25–4.29 (m, 3H), 6.61–6.63 (m, 2H), 6.73–6.74 (m, 2H), 7.19–7.23 (m, 2H).
^{13}C-NMR (CDCl$_3$): δ = 17.2, 69.7, 69.7, 72.5, 72.5, 78.9, 80.6, 107.4, 107.5, 114.8, 114.8, 117.8, 117.8, 129.2, 129.3, 156.2, 156.2, 160.0, 160.4.

6.9.3   SYNTHESIS OF (*S*)-6,6′-[OXYBIS(ETHYLENE)DIOXY]BIPHENYL-2,2′-DIOL(**1**)

(1)
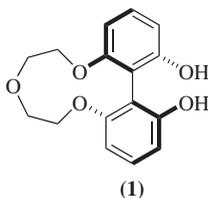
Materials and Equipment

- (*aS,R*)-2,2-[Oxybis(ethylene)dioxy]-6,6′-[(propylene)dioxy]biphenyl, (656 mg, 2.0 mmol)
- Lithium wire in mineral oil (70 mg, 10.0 mmol)
- 4,4′-Di-*tert*-butylbiphenyl (2.25 g, 8.45 mmol)
- Tetrahydrofuran distilled from sodium benzophenone ketyl
- 1 M Aqueous hydrochloric acid
- Diethyl ether, hexane, ethyl acetate
- Saturated aqueous solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel [Merck 60 (230–400 mesh ASTM)]
- TLC plates (Merck Silica Gel 60 F$_{254}$)
- Two 50 mL round-bottomed flasks with a magnetic stirrer bar
- Magnetic stirrer plate
- Two 3-way taps
- One glass funnel, diameter 4 cm

- One 200 mL Erlenmeyer flask
- One 100 mL Erlenmeyer flask
- One 200 mL separating funnel
- One glass column, diameter 3 cm
- Ice bath
- Rotary evaporator

Procedure

1. A 50 mL, flame dried round-bottomed flask equipped with a magnetic stirrer bar and a 3-way tap with argon balloon was charged with lithium wire (70 mg, 10 mmol) and 4,4′-di-*tert*-butylbiphenyl (2.25 g, 8.45 mmol). Distilled tetrahydrofuran (25 mL) was then added at room temperature. After stirring for 10 min at room temperature, the mixture was cooled to 0 °C. The stirring was continued for 1 h at 0 °C to afford di-*tert*-butylbiphenyllithium (LDBB) solution in THF (25 mL).

   Note: (a) Lithium wire should be washed by hexane, and cut into small pieces under argon.
   (b) Lithium wire and 4,4′-di-tert-butylbiphenyl should be charged into the flask under argon.

2. To a dried round-bottomed flask equipped with a magnetic stirrer bar and a 3-way tap with argon balloon containing (*aS,R*)-2,2-[oxybis(ethylene)dioxy]-6,6′-[(propylene)dioxy]biphenyl (**6**) (656 mg, 2.0 mmol) at 0 °C was added the LDBB solution in THF (25 mL). The stirring was continued for 1 h (TLC: hexane/ethyl acetate = 1/1, product: $R_f = 0.3$) and quenched by aqueous 1 M HCl (20 mL).

3. The mixture was extracted with diethyl ether (three times). The combined organic layers were washed with brine and dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 20/1–3/1) to give (*S*)-**1** (426.3 mg, 74%, 98% ee) as a colourless solid. The enantiomeric excess of (*S*)-**1** was determined by chiral stationary-phase HPLC analysis {DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL min^{-1}, t_R 14.0 min [(*R*)-isomer)] and 21.3 min [(*S*)-isomer), detection at 254 nm]}.

6.9.4 ENANTIOMERIC ENRICHMENT OF (*S*)-6,6′-[OXYBIS(ETHYLENE)DIOXY]BIPHENYL-2,2′-DIOL (**1**)

Materials and Equipment

- (*S*)-6,6′-[Oxybis(ethylene)dioxy]biphenyl-2,2′-diol (98% ee) (225.6 mg, 0.78 mmol)
- Quinine (127.0 mg, 0.39 mmol)

- Ethanol (2 mL)
- 1 M aqueous hydrochloric acid
- Diethyl ether, hexane, ethyl acetate
- Saturated aqueous solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel [Merck 60 (230–400 mesh ASTM)]
- TLC plates (Merck Silica Gel 60 F$_{254}$)
- 10 mL round-bottomed flask
- One stopper
- One glass funnel, diameter 4 cm
- One 50 mL Erlenmeyer flask
- One 30 mL Erlenmeyer flask
- One 50 mL separating funnel
- One glass column, diameter 3 cm
- One glass filter
- Water bath
- Rotary evaporator

Procedure

1. A 10 mL round-bottomed flask was charged with (*S*)-6,6′-[oxybis(ethylene) dioxy]biphenyl-2,2′-diol (**1**) (98% ee, 225.6 mg, 0.78 mmol), quinine (127.0 mg, 0.39 mmol) and ethanol (2 mL). The mixture was warmed until the mixture suspension turned to a clear solution, and was allowed to settle for 12 h. The solid residue [crystals of (*S*)-**1**-quinine complex] was collected by filtration. To a mixture of aqueous 1 M HCl and ether was added the obtained crystals of (*S*)-**1**-quinine complex. This was stirred for 15 min at room temperature, and the solution was extracted with ether (twice). The combined organic layers were washed with brine, and dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 20/1–3/1) to give optically pure (*S*)-**1** (167.8 mg, 74%, 99% ee) as a colourless solid. The enantiomeric excess of (*S*)-**1** was determined by chiral stationary-phase HPLC analysis {DAICEL CHIRALCEL OD-H, *i*-PrOH/hexane 1/4, flow rate 1.0 mL min^{-1}, t_R 14.0 min [(*R*)-isomer)] and 21.3 min [(*S*)-isomer], detection at 254 nm. $[\alpha]_D^{22}$ + 136.2° [*c* = 0.89, CHCl$_3$ (99% ee)].

   ^{1}H-NMR (CDCl$_3$): δ = 3.66 (dd, *J* = 12.7, 6.3 Hz, 2H), 3.75 (dd, *J* = 12.7, 5.6 Hz, 2H), 4.08 (dd, *J* = 12.2, 5.6 Hz, 2H), 4.23 (dd, *J* = 12.2, 6.3 Hz, 2H), 5.15 (br-s, 2H), 6.48 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 7.18 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.19 (dd, *J* = 8.3, 8.3 Hz, 1H);
   ^{13}C-NMR (CDCl$_3$): δ = 69.9, 72.0, 105.6, 108.7, 109.1, 130.1, 154.4, 157.4.

6.9.5 CATALYTIC ASYMMETRIC EPOXIDATION OF α,β-UNSATURATED ESTERS (TABLE 6.11)
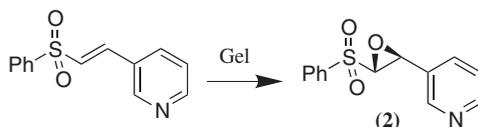
Materials and equipment

- Yttrium tri-*iso*-propoxide (powder) (1.07 g, 4.0 mmol; Kojundo Chemical Laboratory Co., Ltd)
- (S)-6,6′-[Oxybis(ethylene)dioxy]biphenyl-2,2′-diol (7.2 mg, 0.025 mmol)

Table 6.11 Catalytic asymmetric epoxidation of α,β-unsaturated esters using yttrium-biphenyldiol complex.
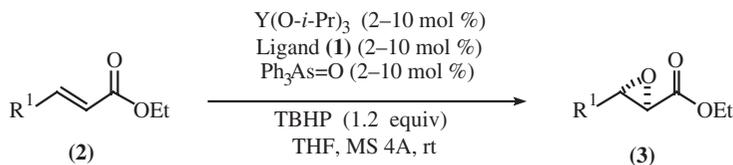
				Product	
Entry	R^1	Catalyst(mol %)	Time(h)	Yield(%)	ee(%)
1	Ph	2	36	89	99
2[a]	p-Me-C_6H_4	5	24	84	98
3[a]	p-MeO-C_6H_4	5	45	74	99
4	m-Cl-C_6H_4	2	20	92	99
5	p-Cl-C_6H_4	2	24	90	99
6	p-Ac-C_6H_4	2	24	89	89
7	1-naphthyl	5	40	62	97
8	2-naphthyl	2	24	89	99
9[a,b]	3-furyl	3	27	78	92
10	3-pyridyl	3	24	93	98
11	3-thiophenyl	3	24	97	93
12	$Ph(CH_2)_2$	10	47	86	91
13	$PhCH=CH(CH_2)_2$	10	71	81	93
14	$Ph(CO)(CH_2)_3$	10	42	78	92
15	$PMBO(CH_2)_2$	10	66	81	96

[a]Work-up with short pad silica gel chromatography and purification using silica gel pretreated with triethylamine were required to avoid decomposition of epoxides.
[b]Freshly distilled substrate was required.

- Triphenylarsine oxide (8.1 mg, 0.025 mmol)
- 4.0 M *tert*-Butyl hydroperoxide solution in toluene (0.375 mL, 1.5 mmol)
- (*E*)-Ethyl cinnamate (220.3 mg, 1.25 mmol)
- Tetrahydrofuran distilled from sodium-benzophenone ketyl
- Molecular sieves 4A (Fluka)
- 2 % Aqueous citric acid
- Hexane, ethyl acetate
- Saturated aqueous solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel [Merck 60 (230-400 mesh ASTM)]
- TLC plates (Merck Silica Gel 60 F$_{254}$)
- One 50 mL round-bottomed flask equipped with a magnetic stirrer bar
- Two 10 mL round-bottomed flasks, one equipped with a magnetic stirrer bar
- Magnetic stirrer plate
- Heat gun
- Three 3-way taps
- One glass funnel, diameter 4 cm
- Two 50 mL Erlenmeyer flasks
- One 50 mL separating funnel
- One glass column, diameter 2 cm
- Silicon oil bath
- Rotary evaporator

Procedure

1. To a 50 mL, flame dried round-bottomed flask equipped with a magnetic stirrer bar and a 3-way tap with argon balloon containing yttrium tri-*iso*-propoxide (1.07 g, 4.0 mmol) at 0 °C was slowly added freshly distilled tetrahydrofuran (20 mL) over 30 min. After stirring for 30 min at 0 °C, the mixture was warmed to room temperature. The stirring was continued for 1 h at room temperature to afford 0.2 M yttrium tri-*iso*-propoxide solution in tetrahydrofuran.

   Note: (a) The quality of the yttrium tri-iso-propoxide solution is important to obtain good reactivity and selectivity. (Yttrium tri-iso-propoxide from Kojundo was used). In addition, yttrium tri-iso-propoxide should be charged into the flask under argon using a glove bag or in a glove box.
   (b) Distilled tetrahydrofuran should be cooled to room temperature before addition to the flask.

2. A 10 mL, flame dried round-bottomed flask equipped with a magnetic stirrer bar and a 3-way tap was charged with molecular sieves 4A (250 mg). The molecular sieves 4A was activated under reduced pressure (ca. 1.0 kPa) at 180 °C for 3 h. After cooling, a solution of (*S*)-6,6′-[oxybis(ethylene)dioxy]biphenyl-2,2′-diol (**1**) (7.2 mg, 0.025 mmol) and triphenylarsine oxide (8.1 mg, 0.025 mmol) in distilled tetrahydrofuran (1.125 mL) was added to the flask. To the mixture was added yttrium tri-*iso*-propoxide (Y(O-*i*-Pr)$_3$) (125 μL, 0.025 mmol, 0.2 M in

tetrahydrofuran) at room temperature. After stirring for 50 min at the same temperature, a solution of *tert*-butyl hydroperoxide (0.375 mL, 1.5 mmol, 4.0 M in toluene) was added. After 10 min, (*E*)-ethyl cinnamate (**2a**) (220.3 mg, 1.25 mmol) was added, and the mixture was stirred at room temperature under argon. The stirring was continued for 36 h (TLC: hexane/ethyl acetate = 5/1, product: $R_f = 0.6$), diluted with ethyl acetate, and quenched by addition of 2% aqueous citric acid (2.5 mL).

Note: (a) The activation of the molecular sieves 4A is essential.

(b) In the case of substrates with electron donating groups on aromatic rings or with a furan ring, a different work-up procedure is required to prevent decomposition of products.

After dilution of the reaction mixture with ethyl acetate, the reaction mixture should be quenched by short pad silica gel chromatography without aqueous work-up.

3. The mixture was extracted with ethyl acetate (twice) and the combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent gave a crude mixture of epoxides. After purification by silica gel flash column chromatography (hexane/ethyl acetate 100/1–50/1), the corresponding α,β-epoxy ester **3a** was obtained (212.7 mg, 1.11 mmol, 89%) as a colourless oil. The enantiomeric excess of **3a** was determined by chiral stationary-phase HPLC analysis {Daicel Chiralpak AD-H, *i*-PrOH/ hexane 2/98, flow rate 0.4 mL min-1, t_R 31.5 min [(*2S,3R*)-isomer] and 38.0 min [(*2R,3S*)-isomer], detection at 254 nm}. $[\alpha]_D^{24}$ −158.8° [*c* = 1.06, CHCl$_3$ (99% ee)].

Note: In the case of substrates with electron donating groups on aromatic rings or with a furan ring, the use of silica gel pretreated with triethylamine is required to prevent decomposition of products.

^{1}H-NMR (CDCl$_3$): δ = 3.66 (t, *J* = 7.2 Hz, 3H), 3.48 (d, *J* = 1.7 Hz, 1H), 4.07 (d, *J* = 1.7 Hz, 1H), 4.22–4.32 (m, 2H), 7.24–7.37 (m, 5H).
^{13}C-NMR (CDCl$_3$): δ = 14.1, 56.8, 57.9, 61.8, 125.8, 128.6, 129.0, 168.2.

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6.10 CATALYTIC ENANTIOSELECTIVE EPOXIDATION OF α,β-ENONES WITH A BINOL-ZINC-COMPLEX

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Asymmetric epoxidation of α,β-unsaturated ketones represents an efficient method for the preparation of optically active α,β-epoxy ketones.[1] Recently, a new and very efficient catalytic system for enantioselective epoxidation of (E)-α,β-enones to the corresponding *trans*-epoxy ketones has been developed based on a BINOL-zinc complex.[2] Very high yields and excellent diastereo- and enantioselectivities are achieved at room temperature using cumene hydroperoxide (CMHP) as the terminal oxidant and performing the reaction in diethyl ether. A combination of enantiomerically pure BINOL and diethylzinc readily affords the active catalyst in situ (Figure 6.13).[3]

1) 20 mol% (R)-BINOL, Et₂O
2) 20 mol% ZnEt₂, 0°C
3) 1.2 eq CMHP, 0 °C to r.t.
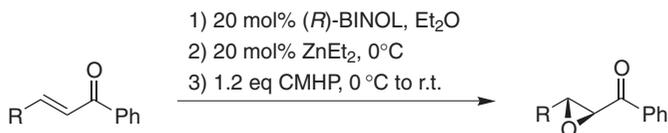
Figure 6.13

6.10.1 SYNTHESIS OF (E)-(2S,3R)-PHENYL-(3-PHENYLOXIRAN-2-YL)METHANONE
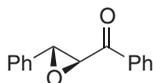
Materials and Equipment

- (R)-1,1'-Bi-2-naphthol (99%, 99% *ee*), (57 mg, 0.2 mmol)
- Diethylzinc (1.1 M solution in toluene), (0.18 mL, 0.2 mmol)
- Cumene hydroperoxide (80% solution in cumene), (0.22 mL, 1.2 mmol)
- (E)-1,3-Diphenyl-2-propenone (98%), (0.21 g, 1 mmol)
- Dry diethyl ether, (4 mL)
- Ethyl acetate, (50 mL)

- Methylene chloride, (500 mL)
- Solution of sodium bisulfite (38–40%)
- Saturated solution of sodium hydrogencarbonate
- Saturated solution of sodium chloride
- Anhydrous magnesium sulfate
- Silica gel (60, 0.063–0.2 mm), 70 g
- TLC plates, Silica gel 60 F_{254}
- 50 mL Schlenk flask with magnetic stirrer bar
- Magnetic stirrer plate
- One glass funnel, diameter 5 cm
- One 250 mL separatory funnel
- Two 100 mL beakers
- One sintered-glass filter, diameter 3.5 cm
- One 100 mL round-bottom flask
- One glass column, diameter 3 cm
- One cold bath
- Rotary evaporator

Procedure

1. (*R*)-BINOL (57 mg, 0.2 mmol) was placed in a 50-ml Schlenk flask equipped with a magnetic stirring bar under an inert atmosphere and dissolved in dry diethyl ether (4 ml). After cooling the solution to 0°C with an ice-bath, diethylzinc (0.18 ml, 0.2 mmol, 1.1 M solution in toluene) was added whilst stirring. After three hours the complete precipitation of an amorphous white solid was observed and (*E*)-1,3-diphenyl-2-propenone (0.21 g, 1 mmol) and cumene hydroperoxide (0.22 ml, 1.2 mmol, 80% solution in cumene) were added; stirring of the reaction mixture at room temperature was maintained for one hour.
2. The reaction was quenched with aq. $NaHSO_3$ (10 ml, 38–40% solution in H_2O) and extracted with EtOAc (20 ml). The organic layer was washed consecutively with aq. sat. Na_2CO_3 (10 ml) and brine (10 ml) and finally dried over $MgSO_4$.
3. Solvent evaporation in a rotary evaporator afforded the crude product, which was further purified by column chromatography (silica gel, CH_2Cl_2) to give the (*E*)-(2*S*,3*R*)-chalcone epoxide (0.23 g, 99% yield, >99% *de*, 90% *ee*). (*R*)-BINOL was recovered almost quantitatively in the last fractions.

CONCLUSION

This procedure, which is based entirely on commercially available reagents, is very easy to reproduce. Table 6.12 shows different aryl- and alkyl-substituted enones that can be epoxidised with high asymmetric induction with the in situ formed (*R*)-BINOL-zinc-catalyst in diethyl ether, with cumene hydroperoxide as the terminal oxidant.

Table 6.12 Enantioselective catalytic epoxidation of aryl- and alkyl-substituted α,β-enones using a (R)-BINOL-zinc catalyst (see Figure 6.13).

Entry	Enone (R)	Yield (%)	Product De (%)	Product Ee (%)
1	Ph	99	>99	90 (2S,3R)
2	p-Br-C$_6$H$_4$	99	>99	92 (2S,3R)
3	p-NO$_2$-C$_6$H$_4$	99	>99	76 (2S,3R)
4	Me	99	>99	68 (2S,3R)
5	Et	99	>99	73 (2S,3R)
6	n-Pr	90	>99	64 (2S,3R)
7	i-Pr	90	>99	68 (2S,3R)
8	t-Bu	83	>99	96 (2S,3R)

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6.11   ASYMMETRIC EPOXIDATION OF PHENYL-2-(3′-PYRIDYLVINYL)SULFONE USING POLYLEUCINE HYDROGEN PEROXIDE GEL

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The Juliá - Colonna[1] asymmetric epoxidation of electron-deficient unsaturated ketones to the corresponding epoxides with high yields and high ee is well known. This technique produces chiral chemical entities from the clean oxidant, hydrogen peroxide, without the use of a toxic or water sensitive transition metal additive.

This procedure describes a recently reported extension of this reagent and catalyst system for the preparation of epoxysulfones (**1**) and exemplifies this with the synthesis of multifunctional epoxy sulfone (**2**) in good ee.[2]
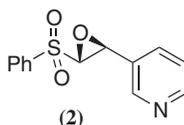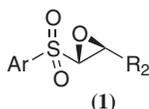
6.11.1   PREPARATION OF POLYLEUCINE-HYDROGEN PEROXIDE GEL

Materials and Equipment

- Poly-(L)-leucine-1,3-diaminopropane (0.74 g)
- Tetrabutylammonium hydrogen sulfate (1.0 g)
- Hydrogen peroxide (30% aqueous solution) (2 × 15 ml)
- Sodium hydroxide (5M aqueous solution) (2 × 30 ml)
- Toluene (30 ml)
- Magnetic stirrer box
- One 100 ml round bottom flask with stirrer bar
- Glass pippette

Procedure

Poly-(*L*)-leucine-1,3-diaminopropane (740 mg, 0.10 mmol, 1.0 mol%) and tetrabutylammonium hydrogen sulfate (1.0 g, 2.95 mmol, 30 mol%) were placed in a flask with a stirrer bar. Toluene (2 ml), sodium hydroxide solution (5M, 30 ml, 10 eq.) and aq. hydrogen peroxide (30%, 15 ml, 10 eq.) were added and stirred for three hours. The aqueous layer was removed and sodium hydroxide solution (5M, 30 ml, 10 eq.) and aq. hydrogen peroxide (30%, 15 ml, 10 eq.) were added and the mixture was stirred overnight. The aqueous layer was removed to leave the activated polyleucine gel.

6.11.2   SYNTHESIS OF PHENYL-2-(3′-PYRIDYLVINYL) SULFONE (2)
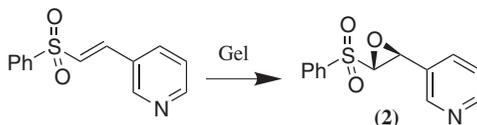
Materials and Equipment

- Polyleucine-hydrogen peroxide gel (*as prepared*)
- Phenyl(3-pyridyl) vinyl sulfone (2.50 g, 10.2 mmol)
- Toluene (5 ml)
- Ethyl acetate
- Hexane
- Magnesium sulfate
- Ceric ammonium nitrate dip

- Celite®, 20 g
- TLC plates, silica G-60 UV$_{254}$
- Magnetic stirrer box
- One 100 ml round bottom flask with stirrer bar
- One glass sintered funnel, diameter 7 cm
- One Bűchner flask, 250 mL
- One glass chromatography column 50 cm × 3.5 cm diameter

Procedure

1. A solution of phenyl(3-pyridyl) vinyl sulfone (2.50 g) in toluene (5 ml) was added to the stirred polyleucine-hydrogen peroxide gel suspension in toluene. The mixture was stirred at room temperature for six hours and the reaction followed by TLC (eluent: 60% ethyl acetate in hexane, vis. CAN). The product was isolated by filtration through Celite® washing with ethyl acetate, drying over magnesium sulfate and concentration *in vacuo*.

2. The crude material was purified by column chromatography (over silica gel (column: 3.5 × 15 cm; eluent: 60% ethyl acetate in hexane) to give the *title compound* (1.62 g, 61%): $[\alpha]_D^{20} = +80$ (c = 1.0 in CHCl$_3$); Found M$^+$ 262.0538, C$_{13}$H$_{11}$NSO$_3$ requires 262.0538; Calculated for C$_{13}$H$_{11}$NSO$_3$: C, 59.8, H, 4.2, N, 5.4, Found: C, 60.1, H, 4.2, N, 5.2; v_{max} (NaCl) 1245 (C–O), 1330 and 1115 (SO$_2$), 1650, (ArC=C) cm^{-1}; δ_H (400 MHz, CDCl$_3$) 4.61 (1H, d, *J* 1.5), 4.68 (1H, d, *J* 1.5), 7.3–7.8 (6H, m, ArH), 7.95 (2H, m, ArH), 8.5 (1H, m, ArH); δ_C (75 MHz, CDCl$_3$) 57.4, 70.1, 123.2, 124.8, 128.3, 129.3, 132.4, 134.3, 137.4, 150.7; HPLC on AD with 70% ethanol in hexane, 220 nm, 0.5 mlmin^{-1} shows an ee of 95%.

The procedure has been used to synthesize the epoxysulfones described in Table 6.13.
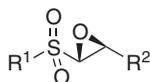
Table 6.13 Selected examples of the epoxidation of vinyl sulfones.

Entry	R^1	R^2	isolated yield (%)	ee %
1	Ph	3-Py	61	95
2	Ph	4-BrPh	49	94
3	Ph	Ph	66	91
4	4-MePh	H	76	70

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3. The absolute configurations of the epoxysulfones are tentative, having been assigned on the basis of the equivalent epoxidation reactions on unsaturated ketones.

7 Oxidation of Ketones to Lactones or Enones

CONTENTS

7.1 SYNTHESIS OF 2-(PHOSPHINOPHENYL)PYRIDINE LIGAND AND ITS APPLICATION TO PALLADIUM-CATALYZED ASYMMETRIC BAEYER–VILLIGER OXIDATION OF PROCHIRAL CYCLOBUTANONES

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7.1.1 SYNTHESIS OF (7R)-2-(2-HYDROXYPHENYL)-7-ISOPROPYL-6, 7-DIHYDRO-5H-1-PYRINDINE
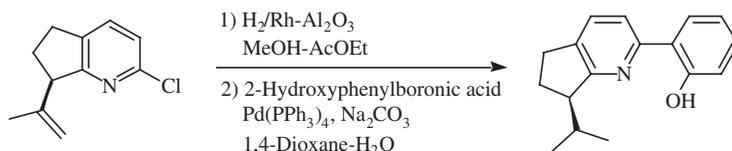
Materials and Equipment

- (7R)-2-Chloro-7-isopropyl-6,7-dihydro-5H-1-pyrindine[1] (1.28 g, 6.6 mmol)
- Distilled methanol (16.5 mL)
- Distilled ethyl acetate (16.5 mL)
- Rhodium on aluminum oxide (64.0 mg)
- Celite® (3.0 g)
- 2-Hydroxyphenylboronic acid (724.2 mg, 5.2 mmol)
- Sodium carbonate (1.52 g, 14.3 mmol)
- Tetrakis(triphenylphosphine)palladium (165.3 mg, 0.14 mmol)
- Distilled 1,4-dioxane (28.5 mL)
- Distilled water
- *n*-Hexane, ethyl acetate
- Magnesium sulfate
- Nitrogen
- Silica gel 60 N (spherical, neutral; 63–210 μm)
- Thermostatically controlled oil-bath and thermometer
- Reflux condenser
- 100 mL round-bottomed flask with a magnetic stirrer bar
- 200 mL round-bottomed flask
- Syringes
- Separating funnel, 100 mL
- Balloon, filled with hydrogen
- Magnetic stirrer
- Glass column
- Rotary evaporator

Procedure

1. In a 100 mL round-bottomed flask equipped with a magnetic stirrer bar were placed (7R)-2-chloro-7-isopropyl-6,7-dihydro-5H-1-pyrindine[1] (1.28 g), distilled methanol (16.5 mL), distilled ethyl acetate (16.5 mL) and rhodium on aluminum oxide (64.0 mg). The flask was connected to a hydrogen balloon and flushed with hydrogen.
2. The mixture was stirred under hydrogen (ca. 1 atm) overnight at room temperature. The reaction was monitored by silica gel TLC (eluent: n-hexane–ethyl acetate, 19:1). The substrate and the product (UV active) having R_f values of 0.26 and 0.34, respectively, were visualized by 10 % ethanolic molybdophosphoric acid dip.
3. The mixture was filtered through a pad of Celite® (3.0 g), washed with ethyl acetate (20 mL) and concentrated on a rotary evaporator. Silica gel chromatography of the residue (hexane–ethyl acetate, 30:1) gave (7R)-2-chloro-7-isopropyl-6,7-dihydro-5H-1-pyrindine (1.14 g, 88 %) as an oil.
4. In a 100 mL round-bottomed flask equipped with a magnetic stirrer bar were placed 2-hydroxyphenylboronic acid (724.2 mg), sodium carbonate (1.52 g) and tetrakis(triphenylphosphine)palladium (165.3 mg); the apparatus was flushed with nitrogen.
5. To the flask was added distilled 1,4-dioxane (19.0 mL), distilled water (4.8 mL) and (7R)-2-chloro-7-isopropyl-6,7-dihydro-5H-1-pyrindine (934.1 mg) in 1,4-dioxane (9.5 mL).
6. The flask was equipped with a reflux condenser and the mixture was heated under nitrogen at 80 °C and stirred overnight at this temperature. The reaction was monitored by TLC (eluent: n-hexane–diethyl ether, 2:1). The substrate and the product (UV active) having R_f values of 0.60 and 0.53, respectively, were visualized by 10 % ethanolic molybdophosphoric acid dip.
7. The mixture was cooled to room temperature and transferred into a separating funnel and water (ca. 20 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated.
8. The residue was purified by silica gel chromatography (hexane–ethyl acetate, 30:1) to give (7R)-2-(2-hydroxyphenyl)-7-isopropyl-6,7-dihydro-5H-1-pyrindine (1.19 g, 99 %) as a colourless solid.

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 14.69$ (s, 1H); 7.78 (d, $J = 1.5$, 8.0 Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.27 (dt, $J = 1.5$ and 8.0 Hz, 1H), 7.01 (dd, $J = 1.5$ and 8.0 Hz, 1H), 6.89 (dt, $J = 1.5$ and 8.0 Hz, 1H), 3.21 (dt, $J = 4.5$ and 8.5 Hz, 1H), 2.98–2.82 (m, 2H), 2.40 (double septet, $J = 4.5$ and 6.5 Hz, 1H), 2.21 (ddt, $J = 5.5$, 8.5 and 13.6 Hz, 1H), 1.97 (ddt, $J = 7.0$, 8.5 and 13.6 Hz, 1H), 1.06 (d, $J = 6.5$ Hz, 3H), 0.82 (d, $J = 6.5$ Hz, 3H).

IR (KBr, cm^{-1}): 2956, 1589, 1462, 1225, 750.

7.1.2   2-[2-(DIPHENYLPHOSPHINOYL)PHENYL]-7-ISOPROPYL-6, 7-DIHYDRO-5*H*-1-PYRINDINE
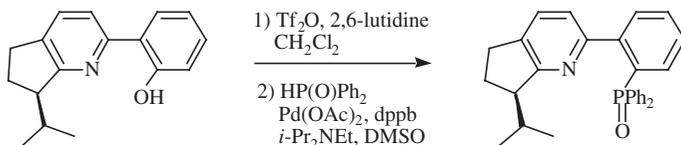
Materials and Equipment

- (7*R*)-2-(2-Hydroxyphenyl)-7-isopropyl-6,7-dihydro-5*H*-1-pyrindine (284.5 mg, 1.12 mmol)
- Anhydrous dichloromethane (5.6 mL)
- 2,6-Lutidine (388 µL, 3.36 mmol)
- Trifluoromethanesulfonic anhydride (262 µL, 1.57 mmol)
- Diphenylphosphine oxide (325.3 mg, 1.60 mmol)
- Palladium(II) acetate (18.1 mg, 0.080 mmol)
- 1,4-Bis(diphenylphosphino)butane (dppb) (34.3 mg, 0.080 mmol)
- Anhydrous dimethylsulfoxide (DMSO) (4 mL)
- Diisopropylethylamine (560 µL, 3.20 mmol)
- Water
- *n*-Hexane, ethyl acetate
- Magnesium sulfate
- Nitrogen
- Silica gel 60 N (spherical, neutral; 63–210 µm)
- Cooling bath
- Thermostatically controlled oil-bath and thermometer
- Reflux condenser
- 25 mL round-bottomed flask with a magnetic stirrer bar
- 10 mL round-bottomed flask with a magnetic stirrer bar
- Syringes
- Separating funnel, 50 mL
- Magnetic stirrer
- Glass column
- Rotary evaporator

Procedure

1. In a 25 mL round-bottomed flask equipped with a magnetic stirrer was dissolved (7*R*)-2-(2-hydroxyphenyl)-7-isopropyl-6,7-dihydro-5*H*-1-pyrindine (284.5 mg) in anhydrous dichloromethane (5.6 mL) under nitrogen, then 2,6-lutidine (388 µL) was added. After the mixture was cooled to 0 °C using a cooling bath, trifluoromethanesulfonic anhydride (262 µL) was added dropwise.
2. The mixture was stirred at the temperature for 3 h. The reaction was monitored by TLC (eluent: *n*-hexane–ethyl acetate, 9:1). The substrate and the product

(UV active), having R_f values of 0.46 and 0.31, respectively, were visualized by 10 % ethanolic molybdophosphoric acid dip.

3. The mixture was transferred into a separating funnel and water (ca. 10 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated on a rotary evaporator.

4. The residue was purified by silica gel chromatography (hexane–ethyl acetate, 30:1) to give the corresponding triflate (310.0 mg, 72 %) as an oil, which was immediately used for the next cross-coupling reaction.

5. In a 10 mL round-bottomed flask equipped with a magnetic stirrer bar were placed the triflate (310.0 mg), diphenylphosphine oxide (325.3 mg), palladium(II) acetate (18.1 mg) and dppb (34.3 mg); the apparatus was flushed with nitrogen.

6. To the flask was added anhydrous DMSO (4.0 mL) and diisopropylethylamine (560 μL). The flask was equipped with a reflux condenser and the mixture was heated under nitrogen at 100 °C and stirred overnight at the temperature. The reaction was monitored by TLC (eluent: *n*-hexane–ethyl acetate, 1:1). The substrate and the product (UV active) having R_f values of 0.90 and 0.19, respectively, were visualized by 10 % ethanolic molybdophosphoric acid dip.

7. The mixture was cooled to room temperature and transferred into a separating funnel and water (ca. 10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed three times with water, then dried over magnesium sulfate, filtered and concentrated on a rotary evaporator.

8. The residue was purified by silica gel chromatography (eluent: *n*-hexane–ethyl acetate, 1:1) to give 2-[2-(diphenylphosphinoyl)phenyl]-7-isopropyl-6,7-dihydro-5*H*-1-pyrindine (307.9 mg, 88 %) as a colourless solid.

^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 7.75$–7.66 (m, 2H), 7.64–7.58 (m, 2H), 7.55–7.20 (m, 12H), 2.83–2.589 (m, 3H), 2.06–1.90 (m, 2H), 1.87–1.76 (m, 1H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.56 (d, $J = 6.5$ Hz, 3H).
IR (KBr, cm^{-1}): 2953, 1582, 1437, 1190, 1109, 698.

7.1.3   2-[2-(DIPHENYLPHOSPHANYL)PHENYL]-7-ISOPROPYL-6,7-DIHYDRO-5*H*-1-PYRINDINE
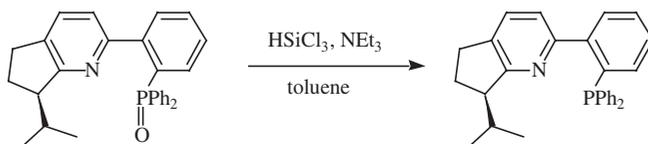
Materials and Equipment

- (*R*)-2-[2-(Diphenylphosphinoyl)phenyl]-7-isopropyl-6, 7-dihydro-5*H*-1-pyrindine (307.0 mg, 0.70 mmol)
- Anhydrous toluene (18.0 mL)
- Triethylamine (710 μL, 5.04 mmol)
- Trichlorosilane (360 μL, 3.57 mmol)

- Saturated sodium hydrogencarbonate aqueous solution (20 mL)
- Dichloromethane, n-hexane, ethyl acetate
- Magnesium sulfate
- Nitrogen
- Silica gel 60 N (spherical, neutral; 63–210 μm)
- Cooling bath
- Thermostatically controlled oil-bath and thermometer
- Reflux condenser
- 25 mL round-bottomed flask with a magnetic stirrer bar
- Syringes
- Separating funnel, 100 mL
- Magnetic stirrer
- Glass column
- Rotary evaporator

Procedure

1. In a 25 mL round-bottomed flask equipped with a magnetic stirrer was dissolved (7R)-2-(diphenylphosphinoyl)phenyl]-7-isopropyl-6,7-dihydro-5H-1-pyrindine (307.0 mg) in anhydrous toluene (18 mL) under nitrogen. After the mixture was cooled to 0°C with the cooling bath, triethylamine (710 μL) and trichlorosilane (360 μL) were successively added.
2. After the mixture was stirred at the temperature for 30 min, the cooling bath was replaced with an oil-bath. The flask was equipped with a reflux condenser and the mixture was refluxed for 48 h. The reaction was monitored by TLC (eluent: n-hexane–ethyl acetate, 1:1). The substrate and the product (UV active) having R_f values of 0.19 and 0.82, respectively, were visualized by 10 % ethanolic molybdophosphoric acid dip.
3. The mixture was cooled to room temperature and transferred into a separating funnel, and then saturated sodium hydrogencarbonate aqueous solution (ca. 20 mL) was added. After the two layers were separated, the aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated.
4. The residue was purified by silica gel chromatography (hexane–ethyl acetate, 30:1–4:6) to give (R)-2-[2-(diphenylphosphanyl)phenyl]-7-isopropyl-6,7-dihydro-5H-1-pyrindine (292.1 mg, 99 %) as an oil.

   ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 7.61$ (ddd, $J = 1.0$, 4.5 and 8.0 Hz, 1H), 7.44–7.39 (m, 2H), 7.30–7.21 (m, 12H), 7.07–7.05 (m, 1H), 3.00 (ddd, $J = 4.0$, 5.5 and 9.0 Hz, 1H), 2.89–2.77 (m, 2H), 2.06 (ddt, $J = 6.5$, 8.5 and 15.1 Hz, 1H), 1.87 (ddt, $J = 6.5$, 8.5 and 15.1 Hz, 1H), 1.80 (double septet, $J = 4.0$ and 6.5 Hz, 1H), 0.84 (d, $J = 6.5$ Hz, 3H), 0.51 (d, $J = 6.5$ Hz, 3H).
   IR (KBr, cm^{-1}): 2953, 1581, 1437, 1190, 1109, 698, 536.
   Mass: calculated for C$_{29}$H$_{29}$NP: m/z 422.2038. Found: 422.2042 ([MH]$^+$).
   The structure of the corresponding Pd(II) dichloride complex was unequivocally determined by X-ray analysis:[2] CCDC 244644.

7.1.4   ASYMMETRIC BAEYER–VILLIGER OXIDATION OF 3-PHENYLCYCLOBUTANONE[3]
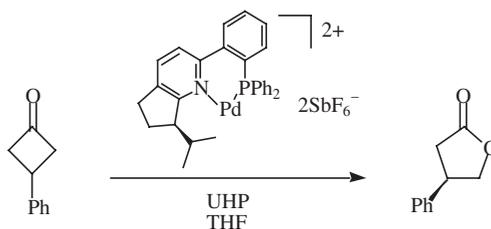
Materials and Equipment

- (R)-2-[2-(Diphenylphosphanyl)phenyl]-7-isopropyl-6,7-dihydro-5H-1-pyrindine (2.3 mg, 5.5 μmol)
- Bis(benzonitrile)palladium(II) chloride (1.9 mg, 5.0 μmol)
- Anhydrous THF (0.4 mL)
- Silver hexafluoroantimonate (3.4 mg, 10 μmol)
- 3-Phenylcyclobutanone (15.2 mg, 0.1 mmol)
- Urea hydrogen peroxide addition compound (UHP) (12.2 mg, 0.13 mmol)
- n-Hexane, ethyl acetate
- Celite®
- Nitrogen
- Silica gel 60 N (spherical, neutral; 63–210 μm)
- Thermostatically controlled cooling bath and thermometer
- Three 5 mL round-bottomed flasks with magnetic stirrer bars
- Syringes
- Magnetic stirrer
- Glass column
- Rotary evaporator

Procedure

1. In a 5 mL round-bottomed flask equipped with a magnetic stirrer was placed bis(benzonitrile)palladium(II) chloride under nitrogen. To this flask was added (R)-2-[2-(diphenylphosphanyl)phenyl]-7-isopropyl-6,7-dihydro-5H-1-pyrindine (2.3 mg) in anhydrous THF (0.4 mL) and the mixture was stirred at room temperature for 1 h.
2. Silver hexafluoroantimonate (3.4 mg) was placed in another flask under nitrogen and to this flask was added the above palladium complex solution. After being stirred for 1 h at room temperature, the mixture was filtered through a short pad of Celite under nitrogen.
3. To the filtrate was added 3-phenylcyclobutanone (15.2 mg) and then the mixture was cooled to −60 °C. To the cooled solution was added UHP (12.2 mg) and the mixture was stirred at this temperature for 214 h.

The reaction was monitored by TLC (eluent: *n*-hexane–ethyl acetate, 8:2). The substrate and the product (UV active) having R_f values of 0.57 and 0.27, respectively, were visualized by 10 % ethanolic molybdophosphoric acid dip.

4. The mixture was directly concentrated using a rotary evaporator and the residue was purified by silica gel chromatography (hexane–ethyl acetate, 9:1) to give (*R*)-dihydro-4-phenylfuran-2(3*H*)-one[4] (14.8 mg, 91 %) as an oil.

The ee (80 %) was determined by HPLC analysis (Daicel Chiralpak AD-H; eluent, hexane–*i*-PrOH 95:5, flow rate 0.5 mL min^{-1}); (*S*)-enantiomer: t_R 39.8 min, (*R*)-enantiomer: t_R 42.2 min.[4]

CONCLUSION

The asymmetric Baeyer–Villiger oxidation using a palladium complex of 2-(phosphinophenyl)pyridine ligand provides a useful procedure for the synthesis

Table 7.1 Asymmetric Baeyer–Villiger oxidation of several cyclobutanones using chiral palladium complex[a]

Entry	Substrate	Time (h)	Yield (%)	% ee	Config.
1		208	76	73	*R*
2		208	52	73	—
3		211	94	83	—
4		211	65	60	—
5[b]		44	89	>99	(1*S*, 4*R*, 7*R*, 10*S*)
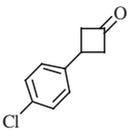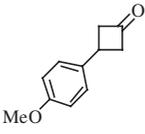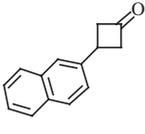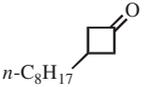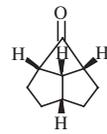
[a]All reactions were carried out in THF at −60°C unless otherwise stated.
[b]Reaction was carried out in THF at −40°C.

of chiral γ–butyrolactones. Palladium complexes of other P-N chelate ligands such as 2-(phosphinophenyl)oxazoline also catalyzed the reaction, but the enantioselectivity was somewhat diminished. The use of UHP as the terminal oxidant is crucial in this procedure. When aqueous hydrogen peroxide or *tert*-butyl hydroperoxide was used in place of UHP, a lower enantioselectivity was observed. Table 7.1 shows some examples of Baeyer–Villiger oxidations of several cyclobutanone derivatives.

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7.2 (D)-CODEINONE FROM (D)-DIYDROCODEINONE VIA THE USE OF MODIFIED Ó-IODOXYBENZOIC ACID (IBX). A CONVENIENT OXIDATION OF KETONES TO ENONES

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The oxidation of saturated ketones to the corresponding enones is a challenging transformation for which the reagents are often not tolerant of other functional groups. The report by Nicolaou *et al.*[1] of the ligand 4-methoxypyridine-*N*-oxide modified IBX that could perform this transformation led us to develop this system as a reagent for the conversion of (D)-dihydrocodeinone into (D)-codeinone (Figure 7.1), the latter being a precursor to the novel NMDA receptor antagonist
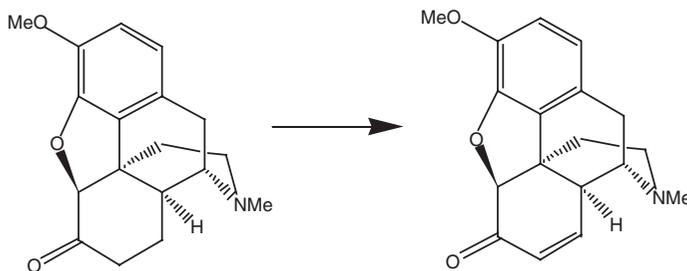
Figure 7.1

(D)-morphine.[2] Previously this transformation had required five steps and no direct route had been identified.[3]

7.2.1   SYNTHESIS OF IBX

Materials and Equipment

- 2-Iodobenzoic acid (5 g, 20 mmol)
- Oxone (37.2 g)
- Water (500 mL)
- Acetone (150 mL)
- 1 L round-bottomed flask with magnetic stirrer bar
- Magnetic stirrer plate and oil bath
- One Büchner flask, 1 L
- One sintered glass funnel, 10 cm diameter

Procedure

1. Oxone was added to a suspension of 2-iodobenzoic acid in water (200 mL) and the mixture was heated at 70°C for 3 h. The mixture was cooled to 0°C, then filtered and washed with water (4 × 75 mL) and acetone (2 × 75 mL) to afford IBX, which was then dried under vacuum and stored in a foil-shielded flask.

7.2.2   SYNTHESIS OF CODEINONE

Materials and Equipment

- (+)-Dihydrocodeinone (0.52 g, 1.74 mmol)
- o-Iodoxybenzoic acid (IBX) (0.58 g, 2.08 mmol)
- 4-Methoxypyridine-N-oxide (0.26 g, 2.08 mmol)
- Dimethylsulfoxide (DMSO) (4.5 mL)
- Dichloromethane (DCM) (1.5 mL)
- 5 % Aqueous sodium hydrogencarbonate (NaHCO$_3$) (60 mL)
- Chloroform (150 mL)
- Celite (10 g)
- Water (50 mL)
- Brine (50 mL)
- Anhydrous magnesium sulfate
- Silica gel
- Dichloromethane / methanol / triethylamine (for chromatography)
- TLC plates, silica gel UV$_{254}$
- Aluminum foil
- 50 mL round-bottomed flasks with magnetic stirrer bar
- Magnetic stirrer plate
- One 250 mL separatory funnel

- One 250 mL Erlenmeyer flask
- One glass sintered funnel, diameter 5 cm
- One Büchner flask, 250 mL
- One glass funnel
- Filter paper
- Rotary evaporator
- One glass column, diameter 4 cm
- One rack of test tubes

Procedure

1. *o*-Iodoxybenzoic acid (IBX) (0.58 g) and 4-methoxypyridine-*N*-oxide (0.26 g) were added to DMSO (3.5 mL) and stirred under nitrogen at room temperature in a foil-shielded flask for 1 h, then (+)-dihydrocodeinone (0.52 g) in DMSO:DCM (1:2.5) added. After stirring overnight (18 h), 5 % aqueous NaHCO$_3$ solution (50 mL) was added and the mixture extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with water and brine (50 mL each), dried (MgSO$_4$) and evaporated. Purification by flash chromatography (eluent: DCM:MeOH, 20:1 + 0.5 % TEA → DCM:MeOH, 10:1 + 0.5 % TEA) afforded (+)-codeinone (150 mg, 29 %) and unreacted (+)-dihydrocodeinone (0.32 g, 62 %). The conversion, based on starting material consumed, is 75%.

The usefulness of this method is further exemplified by the synthesis of the products shown is figure 7.2 that were reported by Nicolaou *et al.* [1]
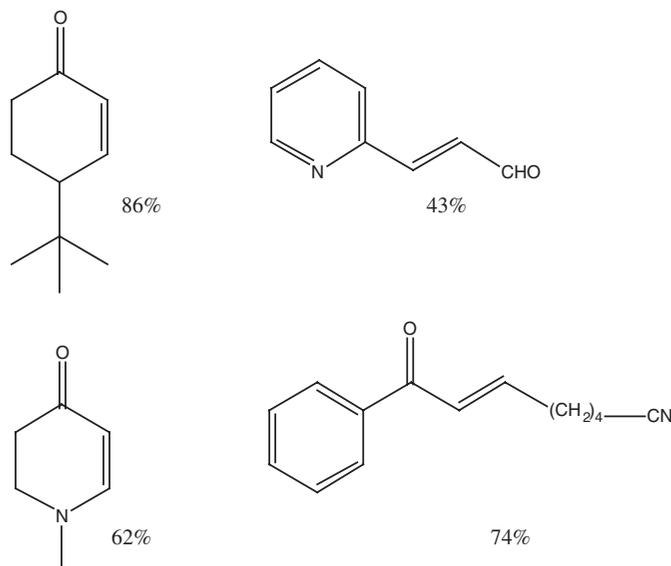
Figure 7.2   Some further examples of the product of oxidation (after Nicolaou *et al.*[1]).

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8 Oxidative C–C Coupling

CONTENTS

8.1 ENANTIOSELECTIVE OXIDATIVE COUPLING OF 2-NAPHTHOLS CATALYZED BY A NOVEL CHIRAL VANADIUM COMPLEX

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Optically pure 1,1′-binaphthol and its derivatives have been evaluated as versatile chiral auxiliaries and ligands in asymmetric transformations. Research in this area has provided many efficient and useful methods for the preparation of key chiral building blocks, some of which have been used for the construction of complex natural products. The wide ranging and important applications of such compounds in organic synthesis have stimulated great interest in developing efficient methods

(1)
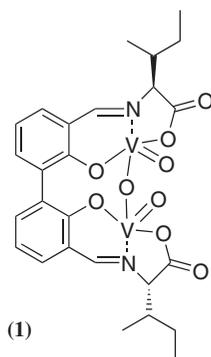
Figure 8.1

for their preparation. Recently, a novel chiral vanadium catalyst system has been developed based on biphenol (Figure 8.1), which has been shown to be an efficient catalyst for the enantioselective coupling of 2-naphthols affording the corresponding binaphthols with high yields and excellent enantioselectivities.[1]

8.1.1 SYNTHESIS OF 3,3-DIFORMYL-2,2′-BIPHENOL
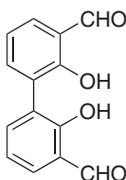
Materials and Equipment

- Biphenol (99 %) (6.0 g, 32 mmol)
- Methoxymethyl chloride (MOMC1) (>85 %) (7 mL, 90 mmol)
- Sodium hydride (60 %, dispersion in mineral oil) (3.6 g, 90 mmol)
- Butyl lithium (99 %) (56 mL, 90 mmol)
- N,N'-Dimethylformamide (DMF) (99 %) (45 mL)
- THF (115 mL)
- Dry diethyl ether (300)
- Sodium hydrogencarbonate (5 % aqueous solution) (50 mL)
- Anhydrous sodium sulfate (100 g)
- Ethyl acetate (700 mL)
- Petroleum (1000 mL)
- 6 N HC1 (60 mL)

- Chloroform (60 mL)
- Brine (600 mL)
- Ethanol (40 mL)
- Saturated aqueous ammonium chloride (150 mL)
- Silica gel 60 µ (150 g)
- TLC plates, UV_{254}
- 250 mL round-bottomed flasks and 500 mL three-necked round-bottomed flasks with magnetic stirrer bars
- Magnetic stirrer plate
- One glass sintered funnel, diameter 7 cm
- One 1000 mL Erlenmeyer flask
- One Büchner funnel, diameter 10 cm
- One 500 mL Büchner flask
- Filter paper
- One 500 mL separatory funnel
- One glass column, diameter 7 cm
- Rotary evaporator

Procedure

1. To a suspension of NaH (3.6 g, 90 mmol) in anhydrous THF (75 mL) and DMF (25 mL) was slowly added a solution of biphenol (6.0 g, 32 mmol) in anhydrous THF (20 mL) at 0 °C. After the mixture was stirred for 10 min at this temperature, MOMC1 (85 %, 7 mL, 90 mmol) was added. The resulting reaction mixture was stirred for about 2 h at room temperature. The reaction was quenched with water (100 mL). The aqueous layer was extracted with ethyl acetate (3×100 mL), the combined organic layer was washed with brine (3×100 mL) and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by column chromatography on silica get (eluent: petroleum/ethyl acetate $= 5:1$) to yield 2,2′-bis (methoxymethoxyl) biphenyl as a colourless oil (8.2 g, 94 %).

2. Under nitrogen, to a solution of 2,2′-bis(methoxymethoxyl)biphenyl (8.2 g, 30 mmol) in diethyl ether (300 mL, distilled from sodium under nitrogen) was slowly added n-BuLi (56 mL, 1.6 M in hexane, 90 mmol) at room temperature. After stirring for about 3 h, the reaction mixture was cooled down to 0 °C and a solution of DMF (20 mL, 260 mmol) in THF (20 mL) was slowly added. After stirring for another 3 h, the reaction was quenched with saturated aqueous ammonium chloride (150 mL). The aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layer was washed with brine (3×100 mL) and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was recrystallized from petroleum–ethyl acetate (3:1) to give 3,3′-diformyl-2,2′-bis(methyloxylmethoxyl) biphenyl as needle-like crystals (2.5 g, 25 %, m.p. 116–118 °C).

3. To a solution of 3,3-diformyl-2,2′-bis(methyloxylmethoxyl) biphenyl (2.5 g, 7.6 mmol) in a solvent mixture of chloroform (60 mL) and ethanol (40 mL)

was added HC1 (6 M, 60 mL). The reaction mixture was refluxed for 14 h. Then the organic layer was separated and washed sequentially with 5 % NaHCO₃ (50 mL) and water (2 × 80 mL). The organic solution was dried over MgSO₄. After removal of the solvent, the residue was recrystallized from petroleum-ethyl acetate (2:1) to give 3,3′-diformyl-2,2′- biphenol as yellow needles (1.65 g, 90 %, M.p. 159–160 °C).

8.1.2   SYNTHESIS OF CHIRAL VANADIUM COMPLEXES

(1)
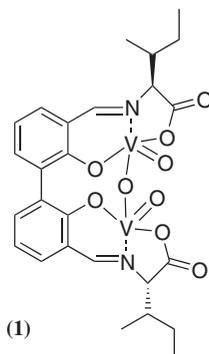
Materials and Equipment

- 3,3-Diformyl-2,2′-biphenol (1.6 g, 6.6 mmol)
- Iso-leucine (2.7 g, 15.8 mmol)
- Sodium acetate (2.59 g, 31.6 mmol)
- Water (51 mL)
- THF (30 mL)
- VOSO₄ (2.439 g, 14.52 mmol)
- Dichloromethane (600 mL)
- Sodium sulfate (50 g)
- 250 mL round-bottomed flasks
- Magnetic stirrer plate
- One 1000 mL Erlenmeyer flask
- One Büchner funnel, diameter 10 cm
- One 500 mL Büchner flask
- Filter paper
- One 500 mL separatory funnel
- Rotary evaporator

Procedure

To a solution of iso-leucine (2.069 g, 15.8 mmol) and sodium acetate (2.591 g, 31.6 mmol) in water (26 mL), a solution of 3,3′-diformyl-2,2′-biphenol (1.6g,

6.6 mmol) in a solvent mixture of ethanol (30 mL) and THF (30 mL) was added at 60 °C. The solution was heated at 90 °C for 1.5 h, and then a solution of VOSO$_4$ (2.439 g, 14.52 mmol) in water (25 mL) was added. After stirring for 3 h at room temperature, the dark green solution was evaporated to remove ethanol and THF, and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layer was washed with water (3 × 250 mL) and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent gave the desired chiral vanadium complex (3.95 g, 97.4 %).

8.1.3   CATALYTIC OXIDATIVE COUPLING OF 7-ALKOXY-1-NAPHTHOLS BY CHIRAL VANADIUM COMPLEXES
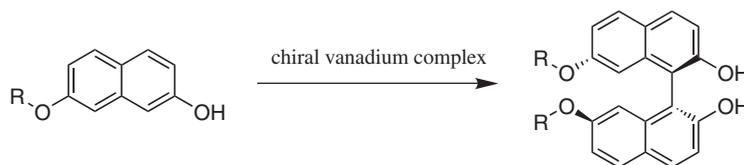
Materials and Equipment

- Chiral vanadium catalyst (892.5 mg, 1.46 mmol)
- 7-Allyloxy-2-naphthol (5.0 g, 25 mmol)
- CCl$_4$, redistilled from calcium hydride (100 mL)
- Ethyl acetate (500 mL)
- Petroleum (1500 mL)
- Silica gel 60 μ (100 g)
- TLC plates, UV$_{254}$
- 150 mL Round-bottomed flask with magnetic stirrer bars
- Magnetic stirrer plate
- One glass sintered funnel, diameter 7 cm
- One 1000 mL Erlenmeyer flask
- One Büchner funnel, diameter 10 cm
- One 500 mL Büchner flask
- Filter paper
- One 500 mL separatory funnel
- One glass column, diameter 7 cm
- Rotary evaporator

Procedure

1. To a solution of chiral vanadium catalyst (892.5 mg, 1.45 mmol) in CCl$_4$ (100 mL) was added 7-allyloxy-2-naphthol (5.0 g, 25 mmol). The resulting

Table 8.1 Oxidative coupling of 2-naphthols using catalyst **1**

Entry	RO	Yield	ee %
1	H	84	90
2	OCH_3	95	95
3	OCH_2CH_3	99	95
4	OBu	99	94
5	OHexyl	99	94
6	OOctyl	99	94
7	ODodecyl	94	97
8	OBn	80	95

mixture was stirred at $0\,°C$ under O_2 for about 4–6 days until the reaction was complete (monitored by TLC). After removal of solvent, the residue was purified by column chromatography on silica gel ($R_f = 0.35$, petroleum–ethyl acetate $= 5:1$) to give crude 7,7-diallyloxy-2,2′-dihydroxy-1,1′-binaphthyl (5.0 g, >99 %) in 95 % ee. The crude product was dissolved in a solvent mixture of ethyl acetate (10 mL) and petroleum (200 mL). After the solution had been set aside at room temperature for 5 h, some precipitate (lower than 10 % ee) formed. Removal of the precipitate and concentration of the mother solution yielded 7,7-diallyloxy-2,2′-dihydroxy-1,1′-binaphthyl (4.7g, 95 %) as a colourless thick oil. $[\alpha]_D^{20} = -234.8°$ ($c = 1.13$, $CHCl_3$), >99 % ee determined by HPLC (Chromasil CHI-TBB column, 10 % IPA in hexane, flow rate $0.25\,mL\,/\,min^{-1}$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) $= 4.25$ (m, 4H), 5.05 (s, 2H), 5.12 (m, 4H), 5.88 (m, 2H), 6.48 (d, $J = 2.1$ Hz, 2H), 7.05 (dd, $J = 8.8$, 2.1 Hz, 2H), 7.22 (d, $J = 8.8$ Hz, 2H), 7.78 (d, $J = 8.8$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 2H).

^{13}C-NMR (75 MHZ, $CDCl_3$): δ (ppm) $= 68.593$, 104.432, 109.936, 115.055, 116.278, 118.009, 124,692, 129.836, 130.939, 130.719, 134.605, 153.180, 157.870.

MS (EI) *m/z*: 398 (M^+).

HRESI-MS (positive ion) calcd for $C_{26}H_{23}O_4$: ($[M+H^+]$) 399.1596. Found: 399.1591.

IR (KBr): $v = 3502$, 3078, 1620, 1512, 1452, 1270, 1214, $1022\,cm^{-1}$.

Anal. calcd. for $C_{26}H_{22}O_4$: C, 78.37. Found: C, 78.45.

Some substrates are listed in Table 8.1.

Note: This procedure has been scaled up to provide 50 g of the optically pure 7,7′-diallyloxy-2,2′-dihydroxy-1,1′ -binaphthyl.

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8.2 CATALYTIC OXIDATIVE CROSS-COUPLING REACTION OF 2-NAPHTHOL DERIVATIVES

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1,1'-Bi-2-naphthol derivatives have been widely used in asymmetric syntheses, catalyses, and resolutions due to their axially dissymmetric structure.[1] The asymmetric oxidative coupling reaction is one of the most facile ways of preparing the 1,1'-bi-2-naphthol framework. Many studies on the homo- or self-coupling reaction leading to a symmetrical binaphthol skeleton are available, whereas there have been only a few reports on the catalytic cross-coupling reaction affording a binaphthol with an unsymmetrical structure. Recently, we found that the cross-coupling reaction between 2-naphthol derivatives (**1**) and 3-hydroxy-2-naphthoates (**2**) effectively proceeds using the CuCl-(*S*)-(−)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) [(*S*)Phbox] catalyst (Figure 8.2).[2–4]
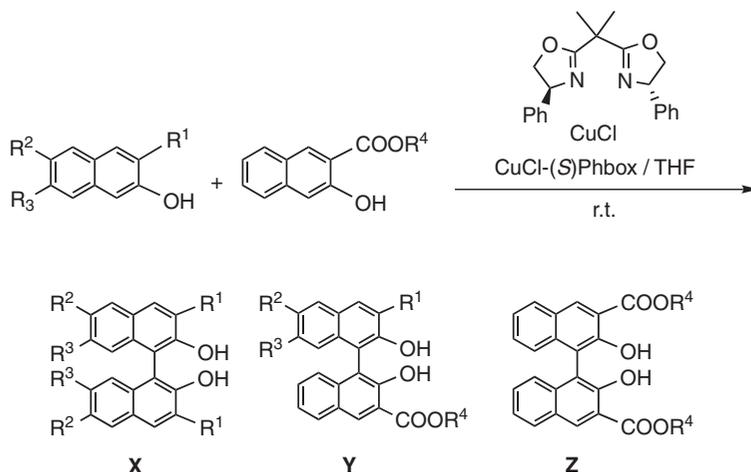
Figure 8.2

8.2.1 SYNTHESIS OF METHYL 2,2'-DIHYDROXY-1, 1'-BINAPHTHALENE-3-CARBOXYLATE [5]
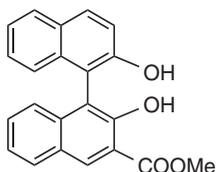
Materials and Equipment

- Methyl 2-hydroxy-3-naphthoate (>99 %) (0.070 g, 0.35 mmol)
- 2-Naphthol (99 %) (0.050 g, 0.35 mmol)
- Copper(I) chloride (>99 %) (0.014 g, 0.14 mmol)
- (*S*)-2,2′-Isopropylidenebis(4-phenyl-2-oxazoline) (97 %) (0.058 g, 0.17 mmol)
- Dry THF (2 mL)
- Chloroform (25 mL)
- 1 N HCl (25 mL)
- Saturated solution of sodium chloride (25 mL)
- Anhydrous magnesium sulfate
- Hexane
- Ethyl acetate
- Silica gel (spherical, neutral, 63–210 μm), 50 g
- TLC plates, Silica gel 60 F_{254}
- One 10 mL Schlenk tube equipped with a magnetic stirrer bar
- One 100 mL round-bottomed flask
- Magnetic stirrer plate
- One 100 mL Erlenmeyer flask
- One funnel
- Filter paper
- One 100 mL separatory funnel
- One glass column, diameter 2 cm
- Rotary evaporator

Procedure

1. A mixture of copper(I) chloride (0.014 g, 0.14 mmol), (*S*)Phbox (0.058 g, 0.17 mmol), and dry THF (2 mL) was stirred for 30 min under an O_2 atmosphere. To this mixture, 2-naphthol (0.050 g, 0.35 mmol) and methyl 2-hydroxy-3-naphthoate (0.070 g, 0.35 mmol) were added. The reaction mixture was stirred at room temperature for 3 h, diluted with $CHCl_3$, and washed with 1 N HCl. The organic layer was dried over $MgSO_4$. Filtration and concentration afforded the crude product.
2. The cross-coupling compound was isolated from the crude product by silica gel column chromatography (hexane/ethyl acetate: 94/6–88/12). (0.104 g, 87 % yield).

CONCLUSION

Table 8.2 shows the results of the cross-coupling reaction between two differently substituted 2-naphthol derivatives using the CuCl-(*S*)Phbox catalyst. In conclusion, the first catalytic asymmetric oxidative coupling with a high cross-coupling selectivity was accomplished under mild conditions.

Table 8.2 Asymmetric oxidative cross-coupling reaction with CuCl-(*S*)Phbox
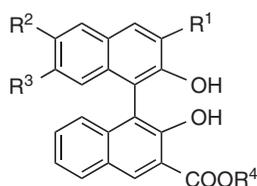
					Coupling ratio	Product Y	
Entry	R^1	R^2	R^3	R^4	(X : Y : Z)	Yield (%)	ee (%) (configuration)
1	H	H	H	Me	0.3: 95.8: 3.9	87	10 (*S*)
2	H	H	H	Ph	5.0: 86.4: 8.6	72	55 (*R*)
3	OBn	H	H	Ph	12.9: 85.2: 1.9	73	65 (*R*)
4	H	OBn	H	Ph	0: 98.7: 1.3	76	3 (*S*)
5	H	H	OBn	Ph	1.3: 93.0: 5.7	63	58 (*R*)

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8.3 OXIDATIVE COUPLING OF BENZENES WITH α, β− UNSATURATED ALDEHYDES BY Pd(OAc)₂/HPMoV /O₂ SYSTEM

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The C−H bond activation of aromatic hydrocarbons is a challenging subject which makes them serve as direct feedstocks for functionalized compounds.[1] Recently, we
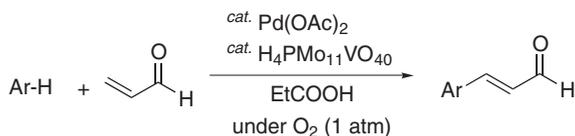
Figure 8.2 Reprinted from reference [2], with permission from American Chemical Society.

have developed the oxidative coupling reaction of benzenes with α,β-unsaturated aldehydes catalyzed by $Pd(OAc)_2$ combined with molybdovanadophosphoric acid (HPMoV) using molecular oxygen as a terminal oxidant (Figure 8.2).[2] Thus, the reaction of benzene with acrolein under dioxygen (1 atm) by the use of catalytic amounts of $Pd(OAc)_2$ and $H_4PMo_{11}VO_{40} \cdot 26H_2O$ [3] in the presence of dibenzoyl-methane as a ligand in propionic acid at 90 °C for 1.5 h afforded cinnamaldehyde in 57 % yield and β-phenyl cinnamaldehyde in 12 % yield.

8.3.1 SYNTHESIS OF CINNAMALDEHYDE
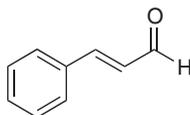
Materials and Equipment

- $Pd(OAc)_2$ (24.6 mg, 0.11 mmol)
- $H_4PMo_{11}VO_{40} \cdot 26H_2O$ (45.2 mg, 0.02 mmol)
- Na_2CO_3 (5.3 mg, 0.05 mmol)
- Dibenzoylmethane (22.4 mg, 0.1 mmol)
- Benzene (2.343 g, 30 mmol)
- Acrolein (84.1 mg, 1.5 mmol)
- Propionic acid (5 mL)
- Balloon filled with O_2 (1 atm),
- Ethyl acetate (10 mL)
- *n*-Hexane (200 mL)
- Saturated sodium hydrogencarbonate (100 mL)
- Anhydrous magnesium sulfate (1 g)
- Silica gel (Merk 60, 0.063–0.200 mm) (100 g)
- 30 mL round bottomed-flask with magnetic stirrer bars
- Magnetic stirrer plate
- One glass sintered funnel, diameter 7 cm
- One 100 mL Erlenmeyer flask
- Filter paper
- One 200 mL separatory funnel
- One glass column, diameter 3 cm
- Rotary evaporator

Procedure

1. $Pd(OAc)_2$ (0.11 mmol), $H_4PMo_{11}VO_{40} \cdot 26H_2O$ (45.2 mg, ca. 0.02 mmol), Na_2CO_3 (0.05 mmol), dibenzoylmethane (0.1 mmol), benzene (30 mmol) and

acrolein (1.5 mmol) were placed in a 30 mL round bottomed-flask equipped with a balloon filled with O_2 and a magnetic stirrer bar. Propionic acid (5 mL) was then added and the mixture was heated at 90 °C, and the resulting mixture was vigorously stirred for 1.5 h under O_2 at the same temperature. Cinnamaldehyde and β-phenyl cinnamaldehyde were formed in 57 % and 12 % yields, respectively, by GLC analysis using *n*-dodecane as an internal standard. After the reaction the reaction mixture was diluted with ethyl acetate (10 mL), and washed with the saturated sodium hydrogencarbonate solution (5 × 20 mL). The organic layer was dried over $MgSO_4$ (1 g) and concentrated by using a rotary vacuum evaporator.

2. The product was easily isolated from the crude reaction mixture by column chromatography (silica gel, hexane/AcOEt: 97/3) (cinnamaldehyde 102 mg, 50 % yield and β-phenyl cinnamaldehyde 32 mg, 10 % yield).

3. $H_4PMo_{11}VO_{40} \cdot 26H_2O$ was purchased from Nippon Inorganic Chemical Co., Ltd. $H_4PMo_{11}VO_{40} \cdot nH_2O$ was prepared by the known method; $Na_2HPO_4 \cdot 26H_2O$ (0.61 g, 5 mmol) was dissolved in 10 mL of water and mixed with $NaVO_3$ (1.79 g, 5 mmol) that had been dissolved by boiling in 10 mL of water. The mixture was cooled and acidified to a red colour with 0.5 mL of concentrated sulfuric acid. To this mixture was added a solution of $Na_2MoO_4 \cdot 2H_2O$ (13.31 g, 55 mmol) dissolved in 20 mL of water. Finally, 8.5 mL of concentrated sulfuric acid was added slowly with vigorous stirring. With this addition the dark red colour changed to a lighter red. The heteropoly acid was then extracted with 100 mL of diethyl ether after the water solution was cooled. In this extraction, the heteropoly etherate was present as a middle layer; the bottom layer (water) was yellow and probably contained vanadyl species. After separation, the middle layer was concentrated by using a rotary vacuum evaporator. The orange solid that remained was allowed to crystallize in water. The orange crystals that formed were filtered, washed with cold water, and dried under vacuum for 2 h.[3]

Table 8.3 Coupling of substituted benzenes with acrolein or methacrolein using the $Pd(OAc)_2/HPMoV/O_2$ system

Entry	Benzenes	Aldehydes	Product	
			GC yield (%)	-Ratio (*o, m, p*)
1	Toluene	Acrolein	59	13:44:43
2	*t*-Butylbenzene	Acrolein	54	0:56:44
3	Anisole	Acrolein	45	17:10:73
4	*t*-Butylbenzene	Methacrolein	66	0:56:44
5	Cumene	Methacrolein	63	9:51:40
6	*p*-Xylene	Methacrolein	52	—

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CONCLUSION

The oxidative coupling may be applied to a wide range of substituted benzenes with acrolein or methacrolein. Table 8.3 gives different substrates that can be coupled with acrolein or methacrolein by the $Pd(OAc)_2$ / HPMoV /O_2 system.

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9 Oxidation of Sulfides and Sulfoxides

CONTENTS

9.1   THE FIRST EXAMPLE OF DIRECT OXIDATION OF SULFIDES TO SULFONES BY AN OSMATE-MOLECULAR OXYGEN SYSTEM

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The oxidation of sulfides to sulfones has been the subject of extensive studies, since sulfones are useful synthons for the construction of various chemically and biologically significant molecules.[1,2] Recently, a new catalytic system has been developed by exchanging potassium osmate onto chloride-saturated layered double hydroxides (Figure 9.1), which we have shown to be an efficient catalyst for the direct oxidation of sulfides to sulfones, using molecular oxygen as the stoichiometric oxidant and with delivery of two oxygen atoms simultaneously to the sulfide, reminiscent of olefin dihydroxylation reactions.[3]

9.1.1   SYNTHESIS OF OSMATE EXCHANGED Mg-Al LAYERED DOUBLE HYDROXIDES (LDH-OsO$_4$)

$$(OsO_4^{2-},\ Cl^-)\text{-}[Mg,Al]LDH$$
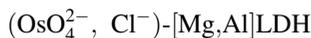
Materials and Equipment

- Potassium osmate dihydrate (0.689 g. 1.87 mmol)
- Magnesium chloride hexahydrate (99 %) (30.49 g, 0.15 mmol)
- Aluminum chloride hexahydrate (99 %) (12.07 g, 0.05 mmol)
- Sodium hydroxide (99 %) (16 g)
- Deionized and decarbonated water (1000 mL)
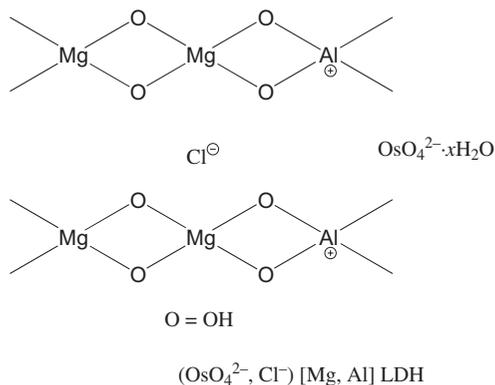
Figure 9.1

- Vacuum pump
- Whatman filter papers (No. 41)
- One 1000 mL round-bottomed flask with magnetic stirrer bar
- Magnetic stirrer plate
- One Büchner flask, 1000 mL
- One Büchner funnel, 500 mL
- One glass sintered (G-3) funnel, 250 mL
- Nitrogen gas cylinder with regulator
- Two glass rods
- Two stainless steel spatulas
- pH paper (range 1–11)
- One oil bath (2 L) equipped with heating coil and temperature regulator
- Glove box equipped with nitrogen gas cylinder
- Hot oven
- One thermometer
- One glass bubbler
- One glass trap filled with oil
- One glass condenser
- One rubber cork

Procedure

1. The preparation of LDH (Mg-Al-Cl)
   TLDH (Mg-Al-Cl) preparation was based on the literature procedure.[4] A mixture of $Mg \cdot Cl_2 \cdot 6H_2O$ (30.49 g, 0.15 mmol) and $AlCl_3 \cdot 6H_2O$ (12.07 g, 0.05 mmol) was dissolved in 200 mL of deionized water. To this aqueous solution was then slowly added, at 25 °C, NaOH (2 M, 100 mL) solution at pH 10 under a nitrogen flow. The pH of the reaction mixture was maintained at this value by the continuous addition of 2 M NaOH. The resulting suspension was stirred overnight under a nitrogen flow at 70 °C. The solid product was isolated by filtration, washed thoroughly with deionized water, and dried overnight at 80 °C. All synthetic steps were carried out using decarbonated water.

2. *The preparation of LDH-OsO₄*
   Mg-Al-Cl LDH (1 g) was suspended in 100 mL (0.689 g, 1.87 mmol) of aqueous potassium osmate solution and stirred at 25 °C for 12 h under nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 mL of water, and vacuum-dried to obtain 1.416 g of LDH-OsO₄ (1.34 mmol of Os per g).

   Note: This procedure has been scaled up to provide 5 g of LDH-OsO₄.

9.1.2 SYNTHESIS OF METHYL PHENYL SULFONE OR METHYLSULFONYLBENZENE
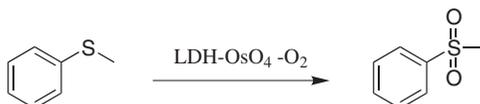
Materials and Equipment

- Methyl phenyl sulfide (99 %) (0.124g. 1 mmol)
- Distilled water (1 L)
- Potassium monohydrogenphosphate (98 %) (0.8709 g in 100 mL distilled water)
- Potassium dihydrogenphosphate (98 %) (0.6804 g in 100 mL distilled water)
- *tert*-Butyl alcohol (99 %) (5 mL)
- Silica gel (60–120 mesh)
- TLC plates, silica gel 60F$_{254}$
- One glass sintered funnel, 250 mL
- One 25 mL two-necked round-bottomed flask, equipped with a magnetic stirrer bar
- Magnetic stirrer plate
- One oil-bath (250 mL) equipped with heating coil and temperature regulator
- One glass condenser
- One rubber septum
- Oxygen gas cylinder with regulator
- Balloons
- Rotary evaporator equipped with water aspirator
- pH meter

Procedure

1. LDH-OsO$_4$ (10 mg. 0.0134 mmol) was added to a round-bottomed flask containing aqueous buffer solution (12.5 mL, pH 10.4) and *tert*-BuOH (5 mL) and stirred at 1 bar O$_2$, 55 °C in an oil bath. Then methyl sulfide (0.124 g, 1 mmol) was added in one portion and the reaction mixture was stirred vigorously. The reaction was completed in 8 h as monitored by TLC.
2. The LDH-OsO$_4$ catalyst was then removed by filtration through a glass sintered funnel with the aid of a water aspirator. The filtration was completed by washing with ethyl acetate (10 mL).

   Note: Due to the high toxic nature of potassium osmate, it should be handled with extreme care in a chemical fume hood using chemical resistant gloves and safety goggles.

3. After solvent was removed by rotavapor, the crude product was chromatographed over silica gel to afford methyl phenyl sulfones (0.154 g, 99 % yield, white solid). Spectral data were comparable with literature values.[2a]

   ^{1}H-NMR (200 MHZ,CDC1$_3$): δ = 3.0 (3H, s, Me), 7.44–7.64 (3H, m, Ph-H), 7.84–7.95 (2H, d, Ph-H, J = 8.1 Hz).

CONCLUSION

The LDH-OsO$_4$ catalyst is successfully employed for oxidation of sulfides to sulfones with excellent yields using molecular oxygen. The simple

Table 9.1 Oxidation of sulfides ArSR to sulfones catalyzed by LDH-OsO$_4$ using molecular oxygen as oxidant.

Entry	Ar	R	Time(h)	Yield (%)
1	p-Cl-C$_6$H$_4$	CH$_3$	5	96
2	p-MeO-C$_6$H$_4$	CH$_3$	5	95
3	C$_6$H$_5$	CH$_3$	16	96
4	p-Cl-C$_6$H$_4$	CH$_3$	15	95
5	p-Br-C$_6$H$_4$	CH$_3$	10	96
6	n-C$_{10}$H$_{21}$	CH$_3$	12	95

ecofriendly procedure employing an easily recoverable and reusable catalytic system as described here, is a potential candidate and practical alternative to the currently practiced process. Table 9.1 gives different substrates that can be oxidized with the LDH-OsO$_4$, using molecular oxygen as oxidant.

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9.2 SELECTIVE OXIDATION OF SULFIDES TO SULFOXIDES AND SULFONES USING HYDROGEN PEROXIDE IN THE PRESENCE OF ZIRCONIUM TETRACHLORIDE

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The oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides and sulfones.[1] During recent years, very useful procedures involving aqueous hydrogen peroxide (H$_2$O$_2$) as the terminal oxidant are noteworthy due to the effective oxygen-content, low cost, safety in storage and operation and

$$R\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}R' \xleftarrow{\text{(ii)}} R{-}S{-}R' \xrightarrow{\text{(i)}} R\overset{\overset{O}{\|}}{S}R'$$
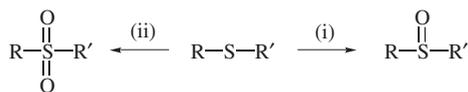
(i): H$_2$O$_2$ (14 equiv), ZrCl$_4$ (4 equiv), CH$_3$OH, r.t.
(ii): H$_2$O$_2$ (20 equiv), ZrCl$_4$ (5 equiv), CH$_3$OH, r.t.

Figure 9.2

environmentally friendly character of H$_2$O$_2$. A Lewis acid activator has been developed to promote this transformation.[2] The activator is essential for the success of the reaction because H$_2$O$_2$ oxidizes sulfides rather slowly. Herein, we describe the successful use of the H$_2$O$_2$/ZrCl$_4$ system as a method to oxidize sulfides efficiently to either sulfoxides or sulfones and selectively oxidize sulfides containing other easily oxidized groups (Figure 9.2).

9.2.1   OXIDATION OF BENZYL 4-BROMOBENZYL SULFIDE TO BENZYL 4-BROMOBENZYL SULFOXIDE USING H$_2$O$_2$ IN THE PRESENCE OF ZIRCONIUM TETRACHLORIDE
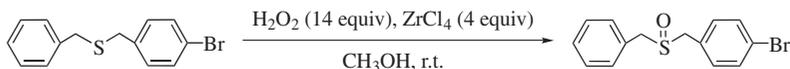
Materials and Equipment

- Benzyl 4-bromobenzyl sulfide (0.590 g, 2 mmol)
- *n*-Hexane (7 mL)
- Ethyl acetate (3 mL)
- Methanol (15 mL)
- Hydrogen peroxide (30 %) (1.4 mL, 20 mmol)
- Zirconium tetrachloride (0.93 g, 4 mmol)
- Chloroform (40 mL)
- Anhydrous magnesium sulfate
- TLC plates, SIL G-60 UV$_{254}$
- 50 mL round-bottomed flasks
- Magnetic stirrer plate
- One Büchner funnel, diameter 7 cm
- One Büchner flask, 250 mL
- Filter paper
- Rotary evaporator

Procedure

1. In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a solution of benzyl 4-bromobenzyl sulfide (0.590g, 2 mmol) in CH_3OH (15 mL) was prepared. 30 % H_2O_2 (14 mmol, 1.4 mL) and $ZrCl_4$ (4 mmol, 0.93 g) were added and the mixture was stirred at room temperature for the time indicated in Table 9.2. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate: 7/3). When the starting sulfide had completely disappeared, the reaction mixture was quenched by adding water (15 mL).

2. The reaction mixture was extracted with chloroform (4×10 mL) and the extract dried with anhydrous $MgSO_4$. The filtrate was evaporated and benzyl 4-bromobenzyl sulfoxide was obtained as the only product (0.598 g, 96 % yield) (Table 9.2). m.p 139–140 °C.

IR (KBr, cm^{-1}): $\nu = 1028$.

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 3.78$ (d, 1H, $J = 13.1$ Hz), 3.89 (d, 1H, $J = 13.09$ Hz), 3.95 (s. 2H), 7.2 (d, 2H, $J = 8.3$ Hz), 7.32–7.33 (m, 2H), 7.40–7.44 (m, 3H), 7.54 (d, 2H, $J = 8.3$ Hz).

Anal. calcd for $C_{14}H_{13}SOBr$: C, 54.38; H, 4.24; S, 10.37%. Found: C, 54.30; H, 4.20; S, 10.47%.

Table 9.2 Oxidation of sulfides RSR′ to sulfoxides using the H_2O_2 (20 mmol)/$ZrCl_4$ (4 mmol) system

Entry	R	R′	Time (min)	Yield (%)
1	C_6H_5	(C_6H_5)	1	96
2	$C_6H_5CH_2$	C_6H_5	2	96
3	$C_6H_5CH_2$	$C_6H_5CH_2$	2	97
4	$4-O_2NC_6H_4CH_2$	C_6H_5	3	95
5	$4-MeC_6H_4$	$C_6H_5CH_2$	2	94
6	$4-ClC_6H_4$	$C_6H_5CH_2$	3	94
7	$4-BrC_6H_4CH_2$	$C_6H_5CH_2$	3	96
8	$4-BrC_6H_4CH_2$	$4-MeC_6H_4$	2	95
9	$4-BrC_6H_4CH_2$	$4-ClC_6H_4$	3	97
10	$4-O_2NC_6H_4CH_2$	$4-ClC_6H_4$	3	93
11	$2-C_6H_4-2-C_6H_4$		3	99
12	$2-C_6H_4-CO-2-C_6H_4$		3	99
13	C_6H_5	Me	1	97
14	$4-MeC_6H_4$	Me	1	95
15	$4-ClC_6H_4$	Me	1.5	94
16	C_6H_5S	$CH_2CH=CH_2$	1	95
17	$CH_2=CHCH_2$	$CH_2=CHCH_2$	1	96
18	$n-C_4H_9$	$n-C_4H_9$	1	94

9.2.2 OXIDATION OF BENZYL 4-BROMOBENZYL SULFIDE TO BENZYL 4-BROMOBENZYL SULFONE USING H_2O_2 IN THE PRESENCE OF ZIRCONIUM TETRACHLORIDE
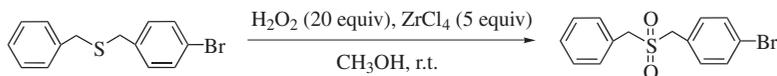
Materials and Equipment

- Benzyl 4-bromobenzyl sulfide (0.590g, 2 mmol)
- *n*-Hexane (7 mL)
- Ethyl acetate (3 mL)
- Methanol (15 mL)
- Hydrogen peroxide (30 %) (2 mL, 20 mmol)
- Zirconium tetrachloride (1.16 g, 5 mmol)
- Chloroform (40 mL)
- Anhydrous magnesium sulfate
- TLC plates, SIL G-60 UV_{254}
- 50 mL round-bottomed flasks
- Magnetic stirrer plate
- One Büchner funnel, diameter 7 cm
- One Büchner flask, 250 mL
- Filter paper
- Rotary evaporator

Procedure

1. In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a solution of benzyl 4-bromobenzyl sulfide (0.590g, 2 mmol) in CH_3OH (15 mL) was prepared. 30 % H_2O_2 (20 mmol, 2 mL) and $ZrCl_4$ (5 mmol, 1.16 g) were added and the mixture was stirred at room temperature for the time indicated in Table 9.3. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate: 7/3). When the starting sulfide had completely disappeared, the reaction mixture was quenched by adding water (15 mL).
2. The reaction mixture was extracted with chloroform (4×10 mL) and the extract dried with anhydrous $MgSO_4$. The filtrate was evaporated and benzyl 4-bromobenzyl sulfone was obtained as the only product (0.628 g, 96 % yield) (Table 9.3). mp 176–178 °C.

    IR (KBr; cm^{-1}): $v = 1116, 1299$.
    ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 4.02$ (s, 2H), 4.14 (s, 2H), 7.17–7.60 (m, 9H).
    Anal. calcd. for $C_{14}H_{13}BrSO_2$: C, 51.70; H, 4.03; S, 9.86 %. Found: C, 51.60; H, 4.15; S, 9.90%.

Table 9.3   Oxidation of sulfides RSR′ to sulfones using the H_2O_2 (20 mmol)/$ZrCl_4$ (5 mmol) system

Entry	R	R′	Time (min)	Yield (%)
1	C_6H_5	(C_6H_5)	1.5	99
2	$C_6H_5CH_2$	C_6H_5	2	98
3	$C_6H_5CH_2$	$C_6H_5CH_2$	2	97
4	$4-O_2NC_6H_4CH_2$	C_6H_5	3.5	99
5	$4-MeC_6H_4$	$C_6H_5CH_2$	2	96
6	$4-ClC_6H_4$	$C_6H_5CH_2$	3.5	95
7	$4-BrC_6H_4CH_2$	$C_6H_5CH_2$	3	96
8	$4-BrC_6H_4CH_2$	$4-MeC_6H_4$	2	95
9	$4-BrC_6H_4CH_2$	$4-ClC_6H_4$	3	97
10	$4-O_2NC_6H_4CH_2$	$4-ClC_6H_4$	4	99
11	$2-C_6H_4-2-C_6H_4$		2	99
12	$2-C_6H_4-CO-2-C_6H_4$		2	99
13	C_6H_5	Me	1	97
14	$4-MeC_6H_4$	Me	1	98
15	$4-ClC_6H_4$	Me	2	95
16	C_6H_5S	$CH_2CH=CH_2$	1	95
17	$CH_2=CHCH_2$	$CH_2=CHCH_2$	1	98
18	$n-C_4H_9$	$n-C_4H_9$	2	97

CONCLUSION

In conclusion, $ZrCl_4$ is an excellent Lewis acid for promoting the highly chemo-selective and rapid oxidation of functionalized sulfides with 30 % H_2O_2 under very mild conditions. It is noteworthy that the reaction tolerates sensitive functional groups and that the sulfur atom is selectively oxidized.

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9.3   WO$_3$–30 % H$_2$O$_2$–CINCHONA ALKALOIDS: A NEW HETEROGENEOUS CATALYTIC SYSTEM FOR ASYMMETRIC OXIDATION OF SULFIDES AND KINETIC RESOLUTION OF RACEMIC SULFOXIDES

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Chiral sulfoxides have emerged as versatile building blocks and chiral auxiliaries in the asymmetric synthesis of pharmaceutical products.[1] The asymmetric oxidation of prochiral sulfides with chiral metal complexes has become one of the most effective routes to obtain these chiral sulfoxides.[2] We have recently developed a new heterogeneous catalytic system (WO$_3$–30% H$_2$O$_2$) which efficiently catalyzes both the asymmetric oxidation of a variety of thioethers (**1**) and the kinetic resolution of racemic sulfoxides (**3**), when used in the presence of cinchona alkaloids such as hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)$_2$–PYR]. Optically active sulfoxides (**2**) are produced in high yields and with good enantioselectivities (Figure 9.3).[3]
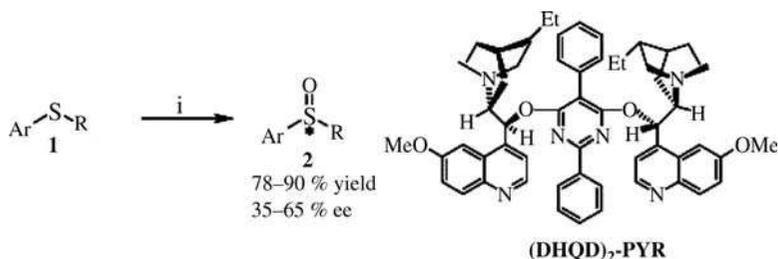
Figure 9.3   (i) WO$_3$ (5 mol %), (DHQD)$_2$-PYR (10 mol %), aq. 30 % H$_2$O$_2$ (1.1 equiv), THF. Reprinted from reference [3], with permission from Elsevier.

ASYMMETRIC OXIDATION OF THIOETHERS

9.3.1   SYNTHESIS OF (*R*)-2-[[[3-METHYL-4-(2,2,2-TRIFLUOROETHOXY)-2-PYRIDYL]METHYL]SULFINYL]-1*H*-BENZIMIDAZOLE {(*R*)-(+)-LANSOPRAZOLE}
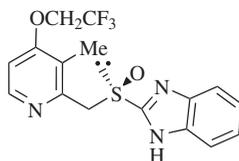
Materials and Equipment

- Tungsten trioxide (>99 %) (0.012 g, 0.05 mmol)
- Hydrogen peroxide 30 wt % solution in water (0.17 mL, 1.5 mmol)
- Hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)$_2$-PYR] (97 %) (0.088 g, 0.1 mmol)
- THF (>99 %) (2.0 mL)
- 2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylthio]-1*H*-benzimidazole (0.353 g, 1 mmol)
- Ethyl acetate (20 mL)
- Petroleum ether (60–80 °C), ethyl acetate
- Saturated solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel (60–120 mesh), 50 g
- TLC plates, SIL G-60 UV$_{254}$
- 25 mL and 50 mL round-bottomed flasks with magnetic stirrer bars
- Magnetic stirrer plate
- One glass sintered funnel, diameter 2 cm
- One glass funnel, diameter 7 cm
- Two 100 mL Erlenmeyer flasks
- One 125 mL separatory funnel
- One glass column, diameter 2 cm
- One Dewar flask
- Rotary evaporator

Procedure

1. A 25 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with WO$_3$ (0.012 g, 0.05 mmol), (DHQD)$_2$-PYR (0.088 g, 0.1 mmol) and 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylthio]-1*H*-benzimidazole[4] (0.353 g, 1 mmol) in tetrahydrofuran (2 mL) and the mixture was cooled to 0 °C. To this was added dropwise aq. 30 % H$_2$O$_2$ (0.17 mL, 1.5 mmol) and the reaction mixture was stirred at 0 °C for 50 h (monitored by TLC).

2. After completion, the reaction mixture was filtered through a sintered funnel to recover the catalyst, the filtrate diluted with EtOAc (20 mL) and washed with water and brine. The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure.

3. The crude reaction mixture was purified by column chromatography by using petroleum ether: EtOAc (6:4–5:5) as eluent to afford (*R*)-lansoprazole (0.312 g, 84 %) as well as (DHQD)$_2$-PYR (0.084 g). Recovered catalyst and ligand were reused without any loss in activity and selectivity.

   (*R*)-(+)-lansoprazole: yield 84%; m.p. 162–165 °C (dec.); $[\alpha]_{25}^{D} = +250.60°$ (*c* = 0.5, acetone).

Table 9.4 Asymmetric oxidation of prochiral sulfides ArSR by aq. H_2O_2 catalyzed by WO_3–cinchona alkaloids at $0\,°C$

					2	
Entry	Ar	R	Chiral ligand	Time (h)	Yield (%)	ee (%) (configuration)
1	Ph	Me	(DHQD)$_2$-PYR	49	88	59 (R)
2		Me	(DHQ)$_2$-PYR	46	83	55 (S)
3		Et	(DHQD)$_2$-PYR	44	82	51 (R)
4		i-Pr	(DHQD)$_2$-PYR	44	83	45 (R)
5		n-Bu	(DHQD)$_2$-PYR	40	90	35 (R)
6		C$_6$H$_{11}$	(DHQD)$_2$-PYR	36	78	46 (R)
7		CH$_2$Ph	(DHQD)$_2$-PYR	24	88	61 (R)
8	p-tolyl	Me	(DHQD)$_2$-PYR	44	81	44 (R)
9		Me	(DHQ)$_2$-PYR	32	87	52 (S)
10		Et	(DHQD)$_2$-PYR	46	86	43 (R)
11		CH$_2$Ph	(DHQD)$_2$-PYR	34	85	65 (R)

HPLC: 88% ee, Chiracel OD-H, $\lambda = 254\,nm$, hexane:2-propanol (9:1), 0.5 ml min^{-1}. Retention time: (R)-enantiomer $= 18.4$ min, (S)-enantiomer $= 21.3$ min.

IR (Nujol, cm^{-1}): $v = 576$, 746, 858, 973, 1037, 1110, 1163, 1263, 1267, 1379, 1444, 1579, 1658, 2852, 2950, 3053, 3200.

^{1}H-NMR (200 MHz, CDCl$_3$): $\delta = 2.18$ (s, 3H), 4.35 (q, $J = 8.14$ Hz, 2H), 4.81 (d, $J = 6.30$ Hz, 2H), 6.64 (d, $J = 6.30$ Hz, 1H), 7.27–7.66 (m, 5H), 8.32 (d, $J = 6.31$ Hz, 1H).

^{13}C-NMR (50 MHz, CDCl$_3$): $\delta = 11.08$, 30.19, 61.11, 66.25 (q, $J = 0.40$ Hz), 107.27, 116.61, 124.66, 148.88, 150.54, 153.52, 163.07.

MS m/z (rel. intensity): 369 (M$^+$, 26), 353 (20), 308 (4), 320 (60), 252 (16), 238 (83), 204 (40), 165 (56), 150 (32), 137 (51), 122 (72), 106 (82), 90 (73), 77 (50), 65 (76), 52 (100).

Analysis C$_{16}$H$_{14}$F$_3$N$_3$SO$_2$ requires: C, 52.03; H, 3.82; N, 11.38; S, 8.68. Found: C, 52.02; H, 3.72; N, 11.31; S, 8.73%.

Table 9.4 presents results of different sulfides that underwent asymmetric oxidation using catalytic WO_3 in the presence of cinchona alkaloids such as hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)$_2$-PYR] with 30 % H_2O_2 as oxidant.

KINETIC RESOLUTION OF RACEMIC SULFOXIDES (FIGURE 9.4)

9.3.2   SYNTHESIS OF (R)-(+)-PHENYL BENZYL SULFOXIDE
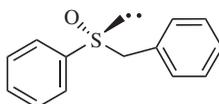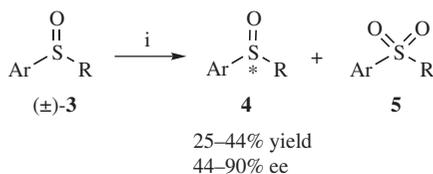
Figure 9.4 (i) WO$_3$ (5 mol %), (DHQD)$_2$–PYR (10 mol %), aq. 30 % H$_2$O$_2$ (1.1 equiv), THF, 25 °C. Reprinted from reference [3], with permission from Elsevier.

Materials and Equipment

- Tungsten trioxide (>99 %) (0.012 g, 0.05 mmol)
- Hydrogen peroxide 30 wt% solution in water (0.17 ml, 1.5 mmol)
- Hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)$_2$-PYR] (97 %) (0.088 g, 0.1 mmol)
- THF (>99 %) (2.0 mL)
- (±)-Benzyl phenyl sulfoxide (0.216 g, 1.0 mmol)
- Ethyl acetate (10 mL)
- Petroleum ether (60–80 °C), ethyl acetate
- Saturated solution of sodium chloride
- Anhydrous sodium sulfate
- Silica gel (60–120 mesh), 25 g
- TLC plates, SIL G-60 UV$_{254}$
- 25 mL and 50 mL round-bottomed flasks with magnetic stirrer bars
- Magnetic stirrer plate
- One glass funnel, diameter 7 cm
- One glass sintered funnel, diameter 2 cm
- Two 100 mL Erlenmeyer flasks
- One 125mL separatory funnel
- One glass column, diameter 2 cm
- One Dewar flask

Procedure

1. A 25 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with WO$_3$ (0.012 g, 0.05 mmol), (DHQD)$_2$-PYR (0.088 g, 0.1 mmol) and racemic (±)-benzyl phenyl sulfoxide (0.216 g, 1 mmol) in THF (2 mL). To this reaction mixture was added aq. 30 % H$_2$O$_2$ (0.17 mL, 1.5 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 20 h.
2. The reaction mixture was filtered through a sintered funnel to recover the catalyst, the filtrate diluted with EtOAc (10 ml) and washed with water and

brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

3. The crude reaction mixture was purified by column chromatography by using petroleum ether: EtOAc (6:2–5:5) as eluent to afford (R)-(+)-phenyl benzyl sulfoxide (0.067 g, 31 %), phenyl benzyl sulfone (0.132 g, 57 %) as well as (DHQD)$_2$-PYR (0.085 g). Recovered catalyst and ligand were reused without any loss in activity and selectivity.

(R)-(+)-Phenyl benzyl sulfoxide: yield 31 %; m.p. 124–125 °C; α_D^{25} 201.0° (c = 1.5, acetone).

HPLC: 79 % ee, Chiracel OD-H, $\lambda = 254$ nm, hexane:2-propanol (9:1), 0.5 ml min^{-1}. Retention time: (R)-enantiomer = 14.82 min, (S)-enantiomer = 17.42 min.

IR (neat, cm^{-1}): $v = 694, 746, 765, 914, 1035, 1149, 1215, 1377, 1442, 1454, 1463, 1494, 2854, 2921, 2958.$

^{1}H-NMR (200 MHz, CDCl$_3$): $\delta = 3.99$ (d, $J = 14.13$ Hz, 1H), 4.11 (d, $J = 14.13$ Hz, 1H), 6.98–7.00 (m, 2H), 7.27–7.45 (m, 8H).

^{13}C-NMR (50 MHz, CDCl$_3$): $\delta = 63.44, 124.31, 128.09, 128.28, 128.72, 129.05, 130.23, 131.0, 142.69.$

MS m/z (rel. intensity): 216 (M$^+$, 5), 200(2), 125(5), 97(6), 91(100), 65(10).

Table 9.5 shows results of different sulfoxides which were kinetically resolved using catalytic WO_3 in the presence of cinchona alkaloids such as hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQD)$_2$-PYR] with 30% H_2O_2 as oxidant.

Table 9.5 WO_3-catalyzed kinetic resolution of aryl alkyl sulfoxides (**3**) in the presence of (DHQD)$_2$-PYR at 25 °C

Entry	Ar	R	Time (h)	Yield (%)		**4** ee (%)
				Sulfoxide (**4**)	Sulfone (**5**)	
1	Ph	Me	12	40	55	69
2		Et	10	39	52	66
3		i-Pr	12	32	60	60
4		n-Bu	10	44	48	44
5		C$_6$H$_{11}$	13	35	62	71
6		C$_6$H$_5$CH$_2$	20	31	57	82
7	p-tolyl	Me	16	29	66	67
8		Et	14	33	67	58
9		i-Pr	12	28	66	62
10		C$_6$H$_5$CH$_2$	18	25	72	90

CONCLUSION

The asymmetric oxidation of thioethers as well as kinetic resolution of sulfoxides with 30 % H_2O_2 catalyzed by a stable, recyclable and commercially avialable solid WO_3 catalyst provides a simple and effective procedure for the preparation of chiral sulfoxides in good enantimeric purity. The procedure is very easy to perform.

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9.4 BENZYL-4,6-*O*-ISOPROPYLIDENE-α-ᴅ-GLUCOPYRANOSIDE, 2-DEOXY-2-[[(2-HYDROXY-3,5-di-*tert*-BUTYLPHENYL)METHYLENE]IMINE] AS A LIGAND FOR VANADIUM-CATALYZED ASYMMETRIC OXIDATION OF SULFIDES

Rᴀꜰꜰᴀᴇʟʟᴀ Dᴇʟ Lɪᴛᴛᴏ, Gɪᴜꜱᴇᴘᴘɪɴᴀ Rᴏᴠɪᴇʟʟᴏ ᴀɴᴅ Fʀᴀɴᴄᴇꜱᴄᴏ Rᴜꜰꜰᴏ*

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Asymmetric oxidation of prochiral sulfides is one of the most effective routes for the preparation of chiral sulfoxides. These latter molecules attract great interest, as they are useful synthons for some drugs. They can also be used as chiral auxiliaries due to their configurational stability. The oxidation can be performed by using complexes of several transition metals, e.g. Ti,[1] Mn,[1] Fe,[2] V,[3] Nb,[4] W,[5] Re.[6] Recently, we have developed vanadium complexes having chiral O,N,O'-tridentate ligands
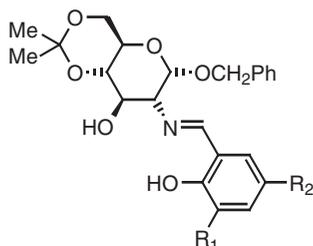
Figure 9.5   Reprinted from reference [7], with permission from Elsevier.

derived from sugars (Figure 9.5), which behaved as efficient catalysts for the enantioselective oxidation of thioanisole.[7]

9.4.1   SYNTHESIS OF BENZYL-4,6-*O*-ISOPROPYLIDENE-α-D-GLUCOPYRANOSIDE, 2-DEOXY-2-[[(2-HYDROXY-3,5-DI-*Tert*-BUTYLPHENYL)METHYLENE]IMINE]
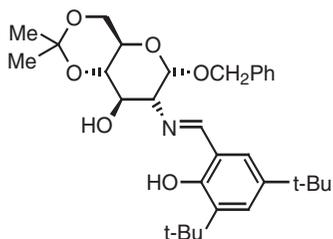
Figure 9.6   Reprinted from reference [7], with permission from Elsevier

Materials and Equipment

- 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (99 %) (0.23 g, 1.0 mmol)
- Benzyl-4,6-*O*-isopropylidene-2-amino-2-deoxy-α-D-glucoside[8] (0.31 g, 1.0 mmol)
- Toluene, ACS reagent (> 99.5 %) (16 mL)
- Hexane, ACS reagent (> 98.5 %) (24 mL)
- 50 mL Round-bottomed flask equipped with a reflux condenser
- 25 mL Beaker
- 25 mL Graduated cylinder
- Magnetic hot plate stirrer
- Rotary evaporator
- Vacuum pump oil
- Pasteur pipette with rubber bulb

- Magnetic stirrer bar
- Spatula

Procedure

A solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (1.0 mmol) in toluene (8 mL) was added to a solution of benzyl-4,6-*O*-isopropylidene-2-amino-2-deoxy-α-D-glucoside[8] (1.0 mmol) in the same solvent (8 mL). The resulting mixture was stirred for 2 h at 80 °C affording a yellow solution. The volume of the solvent was reduced under vacuum to ca. 3 mL and hexane (8 mL) was slowly added to afford the product as a yellow microcrystalline powder, which was washed with hexane (2 × 8 mL) and dried under vacuum (0.45 g, 85 % yield).

- *This procedure has been applied to synthesize other imino sugar derivatives in high yield (Table 9.6).*

9.4.2   OXIDATION OF THIOANISOLE

Materials and Equipment

- Benzyl-4,6-*O*-isopropylidene-α-D-glucopyranoside, 2-deoxy-2-[[(2-hydroxy-3,5-di-*tert*-butylphenyl)methylene]imine] (0.016 g, 0.030 mmol)
- Dichloromethane, ACS reagent (> 99.5 %) (3 mL)
- Vanadyl acetylacetonate (98 %) (0.005 g, 0.02 mmol)
- Thioanisole (99 %) (117 μL, 1.00 mmol)
- Hydrogen peroxide, solution in water (35 %w/w) (100 mL, 1.1. mmol)
- Sodium sulfite, saturated solution in water (5 mL)
- Sodium sulfate anhydrous (> 99.0%)
- 50 mL round-bottomed flasks
- Celite
- 10 mL graduated cylinder

Table 9.6 Asymmetric oxidation of thioanisole using some iminosugar complexes as catalysts

Entry	R^1	R^2	Conversion (%)	Ph(Me)SO/Ph(Me)SO$_2$	ee (%)
1	*t*-Bu	*t*-Bu	99	97/3	60
2	H	H	99	95/5	42
3	H	*t*-Bu	99	90/10	26
4	*t*-Bu	H	99	80/20	26
5	*t*-Bu	NO$_2$	99	90/10	20
6	I	I	99	90/10	18

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- 250 μL Hamilton glass syringes
- 25 mL beaker
- Magnetic hot plate stirrer
- Vacuum pump oil
- Pasteur pipettes with rubber bulb
- Magnetic stirrer bar
- Spatula

Procedure

A solution of benzyl-4,6-*O*-isopropylidene-α-D-glucopyranoside, 2-deoxy-2-[[(2-hydroxy-3,5-di-*tert*-butylphenyl)methylene]imine] (0.03 mmol) in dichloromethane (1.5 mL) was added to a solution of [VO(acac)$_2$] (0.02 mmol) in the same solvent (1.5 mL). After 10 min of stirring, thioanisole (1 mmol) was added followed by hydrogen peroxide (1.1 mmol). After 1 h, the addition of a saturated solution of sodium sulfite quenched the reaction. The organic phase was filtered through a bed of Celite contained in a Pasteur pipette, dried over sodium sulfate and evaporated under vacuum to afford the reaction products (Table 9.6).

- *This procedure has been applied to oxidize thioanisole with other imino sugar derivatives (Table 9.5).*

CONCLUSION

This paper validates the assumption that ligands for asymmetric catalysis can be obtained by simple functionalization of common carbohydrates. Condensation of 2-aminoglucose with substituted-2-hydroxybenzaldehydes affords O,N,O'-tridentate ligands whose activity in the V-catalyzed asymmetric oxidation of thioanisole is reported in Table 9.6.

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9.5 ASYMMETRIC SULFOXIDATION OF ARYL METHYL SULFIDES WITH HYDROGEN PEROXIDE IN WATER

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Catalytic asymmetric sulfoxidation is a well studied reaction; many transition metal catalysts have been reported for such oxyfunctionalization, featuring high conversions and excellent enantioselectivities.[1] Hydrogen peroxide has been implemented recently in asymmetric sulfoxidation due to the environmentally friendly character of this terminal oxidant, which allows the development of more 'green' processes.[2] In asymmetric catalysis, in addition to the classical targets such as high enantioselectivity and yield, easy procedures, use of safe and environmentally friendly reagents and mild conditions, as well as the replacement of organic and especially chlorinated solvents with water,[3, 4] are stringent requirements.[5–7] Last but not least, easy isolation of the enantioenriched product is also advisable.

Recently we presented a new methodological approach for catalytic sulfoxidation which makes use of water as solvent in the presence of anionic surfactant, and hydrogen peroxide as terminal oxidant activated by an easily prepared chiral Pt(II) complex, all under mild conditions (Figure 9.7). Moreover, the enantioenriched sulfoxides are isolated from the catalyst by means of simple diethyl ether extraction (Figure 9.8) which does not dissolve the catalyst.[8]
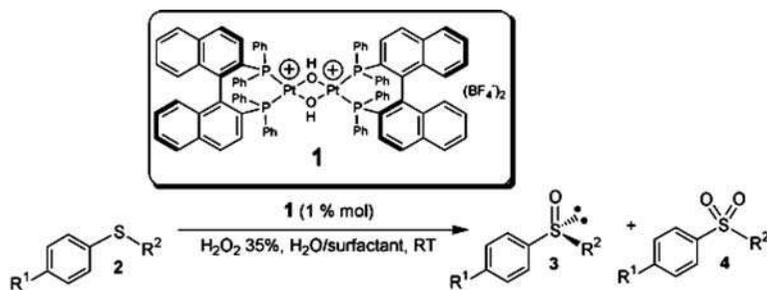
Figure 9.7
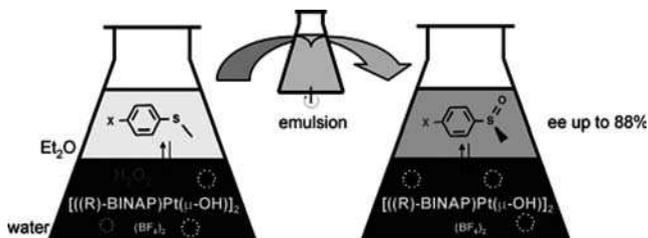
Figure 9.8

9.5.1   SYNTHESIS OF COMPLEX ((*R*)-BINAP)PtCl$_2$ [9] (**5**)

(**5**)
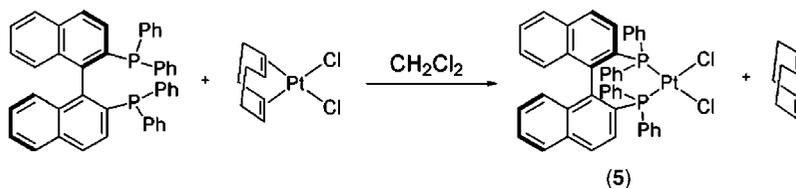
Materials and Equipment

- Dichloromethane (15 mL)
- Toluene (30 mL)
- Hexane (50 mL)
- Diethyl ether (50 mL)
- (COD)PtCl$_2$[10]
- (*R*)-BINAP 99%
- Vacuum line and inert N$_2$ line
- 50 mL round-bottomed flask with magnetic stirrer bar
- Magnetic stirrer plate
- One glass sintered funnel, diameter 5 cm
- Rotary evaporator

Procedure

1. The complex (COD)PtCl$_2$ (COD = 1,5-cyclooctadiene) (0.16 g, 0.43 mmol) was placed in a 50 mL round-bottomed flask equipped with a magnetic stirrer bar, followed by the addition of dichloromethane (15 mL). The solution was degassed and placed under N$_2$ at room temperature.
2. Solid (*R*)-BINAP (0.27 g, 0.43 mmol) was added and the resulting pale yellow solution was stirred overnight.
3. The solution was evaporated to dryness under vacuum and the solid residue was thoroughly washed using small portions of toluene (overall 30 mL).
4. The solid was filtered on a glass sintered funnel, washed with hexane and diethyl ether and dried under vacuum (yield 95%).

   ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 7.81 (t, Ar), 7.57 (d, Ar), 7.51 (d, Ar), 7.40(m, Ar), 7.12 (t, Ar), 6.83 (t, Ar), 6.75 (d, Ar), 6.67 (t, Ar).
   ^{31}P-NMR {^{1}H} NMR (121 MHz, CD$_2$Cl$_2$): δ = 8.56 ($^1J_{\text{Pt-P}}$ = 3661 Hz)

9.5.2   SYNTHESIS OF COMPLEX [((R)-BINAP)Pt(μOH)]₂(BF₄)₂[9] (6)

(6)
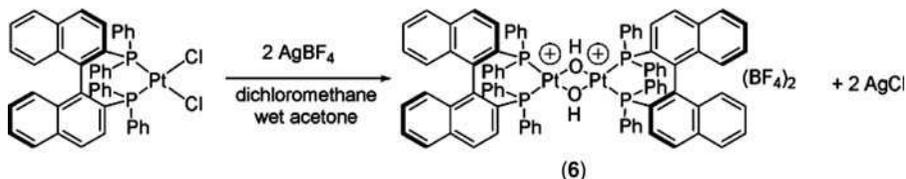
Materials and Equipment

- Dichloromethane (5 mL)
- Acetone (3mL)
- Diethyl ether (20 mL)
- AgBF₄, 1.31 M solution in acetone[11]
- Vacuum line and inert N₂ line
- 50 mL round-bottomed flasks with magnetic stirrer bar
- Magnetic stirrer plate
- Filter paper, diameter 8 cm
- Funnel, diameter 12.5 cm
- One glass sintered funnel, diameter 7 cm
- Rotary evaporator

Procedure

1. The complex ((R)-BINAP)PtCl₂ (0.30 g, 0.33 mmol) was dissolved in dichloromethane (5 mL) and the solution was degassed and placed under N₂ at room temperature.
2. To the solution, acetone (3 mL) was added, followed by a solution of AgBF₄ (1.31 M, 0.51 mL) in acetone.
3. The mixture was allowed to react for 1 h, subsequently filtered through paper and the filtrate was evaporated to dryness in a vacuum.
4. The solid residue was thoroughly washed using a small volume of diethyl ether, then filtered on a glass sintered funnel and dried under vacuum (yield 50 %).

^{1}H-NMR (300 MHz, CD₂Cl₂): δ = 9.03 (dd, Ar), 8.84 (m, Ar), 8.76 (m, Ar), 8.49(m, Ar), 8.36(m, Ar), 7.88 (m, Ar).
^{31}P-NMR {^{1}H} NMR (121 MHz, CD₂Cl₂): δ = 2.85 ($^{1}J_{Pt-P}$ = 3688 Hz).

9.5.3   STEREOSELECTIVE CATALYTIC OXIDATION OF ARYL METHYL SULFIDES

Materials and Equipment

- Sodium dodecyl sulfate, 99 % (SDS)
- MilliQ water (3 mL)
- [(*R*)-(BINAP)Pt(μ-OH)]$_2$ (BF$_4$)$_2$ (**1**)
- Aryl methyl sulfide (0.75 mmol)
- Hydrogen peroxide 35 %[12]
- Diethyl ether, distilled over sodium with benzophenone (5 mL)
- Anhydrous sodium sulfate
- 10 ml round-bottomed flask equipped with a sidearm fitted with a screw-capped silicone septum and equipped with magnetic stirrer bar
- Magnetic stirrer plate
- Thermostat
- One 25 mL separatory funnel
- Filter paper, diameter 8 cm
- Funnel, diameter 12.5 cm
- Rotary evaporator

Procedure

1. Typically, the anionic surfactant SDS (65 mg) was dissolved in milliQ water (3 mL), followed by catalyst **1** (13.8 mg, 0.0075 mmol). Stirring was performed at 700 rpm. Constant temperature (25 °C) was maintained by water circulation through an external jacket connected with a thermostat.
2. After 15 min the substrate (0.75 mmol) was added [if solid with the aid of diethyl ether (3 mL)] and the mixture stirred for 10 min.
3. To this, 35 % hydrogen peroxide was added in one portion (0.75 mmol) and the mixture stirred at room temperature.
4. After 24 or 48 h, diethyl ether (if not present since the beginning) was added to extract the product. The two-phase system was placed in a 25 mL separatory funnel and the organic phase separated and dried with anhydrous sodium sulfate.

CONCLUSION

The procedure is very easy to reproduce and the asymmetric sulfoxidation may be applied to a relatively large range of aryl methyl sulfides (Table 9.7). Remarkable features are: (i) easy isolation of the enantioenriched products from the catalyst by simple diethyl ether/water-SDS two phase separation; (ii) use of green and

Table 9.7 Catalytic enantioselective oxidation of aryl alkyl sulfides **2** with hydrogen peroxide in water-SDS solution mediated by **1**

Entry	R^1	R^2	Time (h)	Yield[a] (%)	[3]/[4] ratio	ee[b](%)	Abs. configuration[c]
1	H **2a**	CH$_3$	24	98	>200	40	R-(+)
2	2-naphthyl **2b**	CH$_3$	24	99	32	34[d]	R-(+)
3	H **2c**	Bn	48	75	19	24[d]	n.d.
4	p-CH$_3$O **2d**	CH$_3$	24	96	97	22[d]	R-(+)
5	p-CH$_3$ **2e**	CH$_3$	24	99	>200	31	R-(+)
6	p-Cl **2f**	CH$_3$	24	87	>200	48	R-(+)
7	p-CN **2g**	CH$_3$	48	68	21	63	R-(+)
8	p-NO$_2$ **2h**	CH$_3$	48	63	90	88[d]	R-(+)

General conditions: substrate:H$_2$O$_2$:**1** = 100:100:1, [substrate] = 0.75 mmol, [H$_2$O$_2$] = 0.75 mmol, [**1**] = 0.0075 mmol, solvent water 3 mL, sodium dodecylsulfate (SDS) (75 mM, 1 mM in micelles), room temperature in air.
[a] Yield of sulfoxide determined by GC (column HP-5, flow 1 mL min^{-1}, 100 °C × 5 min, 15 °C min^{-1} to 200 °C × 20 min).
[b] Enantiomeric excess determined by CSP-GC (column Lipodex-E, flow 1 mL min^{-1}, 100 °C × 60 min, 5 °C min^{-1} to 200 °C × 20 min).
[c] Absolute configuration determined by optical rotations and comparison of the retention orders with known literature data.
[d] Enantiomeric excess determined by integration of the ^{1}H-NMR spectrum with (R)-BINOL at 253 K in CDCl$_3$.
n.d., not determined.

inexpensive hydrogen peroxide as oxidant; (iii) catalyst loading as low as 1 % mol; (iv) good yields, sulfoxide/sulfone selectivities up to 200 and enantioselectivities up to 88 %; (v) use of mild experimental conditions.

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11. The solution was prepared by dissolving AgBF$_4$ in acetone, filtering through paper to remove the insoluble portion and titrating against a solution containing a known amount of KI and K$_2$Cr$_2$O$_7$ as indicator, following the colour change from yellow to orange.
12. The concentration of the commercial 35 % H$_2$O$_2$ solution was checked iodometrically prior to use, titrating with a 0.1 N solution of Na$_2$S$_2$O$_3$ with starch as indicator.

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Page references in *italics* indicate figures, and those in **bold** indicate tables.