Asymmetric transfer hydrogenation of ketones
Petra, D.G.I.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE (Digital Academic Repository)
UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 22 Dec 2018
Introduction
1.1 General introduction

The central topic of the research described in this thesis is the development of fast and selective catalysts for the preparation of optically active alcohols. The phenomena of chirality and optical activity were discovered one and a half centuries ago by the pioneering work of Pasteur, Van 't Hoff and Le Bel. Once the significance of optically active compounds was recognised, major efforts were undertaken to find effective routes to obtain optically pure compounds. There are many examples where the chirality of a compound has a determining effect on its interaction with a living organism.  The L-form of asparagine, one of the 20 natural occurring amino acids, tastes bitter, whereas the (R)-isomer is sweet. The (+)-form of estrone is a hormone, whereas the (-)-form has no hormonal activity. There are barbiturates for which one enantiomer has a narcotic effect and its mirror image isomer has a carcinogenic effect. Only one isomer of thalidomide, which was sold as a racemic mixture under the commercial name of Softenon in the Netherlands, proved to have the desired sedative effect, whereas the opposite enantiomer caused severe fetal damage. These examples illustrate that the two enantiomers of a racemic mixture can behave very differently in biological systems. The reason for this is that all living beings contain only single enantiomers of the constituent amino acids and sugars in their proteins, DNA and glycoproteins. The uniform chirality in biological systems results in diastereomeric interactions with the compounds of a racemic mixture. If synthetic compounds are to be used as pharmaceuticals, agrochemicals, human food additives and animal food supplements they should be used in their optically pure form to avoid secondary effects and to ensure that the minimum quantity is sufficient. Examples such as the use of the sweetener aspartame in soft-drinks, that contains only the L-form of phenylalanine, and the use of L-lysine in animal feed demonstrate this strategy. The insight in the effects of chiral compounds on living beings as is described above has had a major impact on the developments in the fine-chemical industries. Some years ago most synthetic drugs were sold as racemates, whereas recently they are more sold as single enantiomers. At the moment, two thirds of the drugs in development are chiral and more than 50% are being developed as single
enantiomer drugs. Also FDA regulations on the marketing of new drugs have become stricter in recent years with respect to chiral compounds. Any company wishing to license a new active ingredient as a racemic mixture has to establish the activity of both enantiomers and show that the unwanted enantiomer does not cause any adverse effects. In the same report it is estimated that the market for dosage forms of single enantiomers will increase from $73 billion in 1996 to above $90 billion by the year 2000.

Nowadays there are several well-established routes for obtaining optically pure compounds (Figure 1.1). Starting from a racemic mixture the optically pure compound can be obtained either by diastereomeric salt formation (i) or by enzymatic or chemical kinetic resolution (ii). A drawback in using these methods is that the undesired enantiomer is always formed in 50%. This unwanted enantiomer should be racemised and recycled to obtain high atom efficiencies. The classical resolution of racemates by diastereomeric crystallisation is, however, still the most important method applied in industry.

In asymmetric synthesis starting from naturally occurring compounds a stoichiometric amount of the chiral material is needed for a reaction (iii). As optically
active material is usually expensive this is not a very economic approach with regard to the amount of chiral information that is required. Furthermore, the lack of availability of both enantiomers of most natural compounds is often a limiting factor.

A more elegant way to prepare chiral compounds is catalytic asymmetric synthesis starting from a prochiral substrate (iv). In this case the chiral information is part of an optically active catalyst. Only a minimum amount of expensive chiral material is required because one chiral catalyst can create up to millions of targeted chiral product molecules. This concept is called asymmetric catalysis. Its application leads to a multiplication of the chiral information contained in the catalyst. The subject of this thesis falls within the field of asymmetric catalysis.

Special attention has been devoted to the topic of asymmetric catalysis during the last decades. A wide variety of highly successful reactions with enantiomeric excesses of over 95% have been reported. In most cases transition metal complexes are used as the catalyst, preferably generated in situ.

The effectiveness of a homogeneous chiral catalyst, involved in a one step process, depends on the difference in the Gibbs free energy between the transition states of the (R)- and the (S)-enantiomer (i.e. $\Delta G^R$ and $\Delta G^S$). Starting from a prochiral substrate the chirality of the product is induced by the catalyst in the enantioselectivity determining step of the reaction. The interaction between the substrate and the chiral catalyst results in an enantiomerically enriched product mixture, or in the ideal situation, an enantiopure compound. The optically active information present in the catalyst differentiates between front side and back side attack (the re-face and si-face of the substrate in Figure 1.2).

The reaction path will proceed by preference via the transition state with the lowest energy gap, $\Delta(\Delta G^\dagger)$, forming either the (R)- or the (S)-enantiomer in excess. Unless the reaction products exhibit enantioselectivities in the high 90's, there is only a small energy difference between these transition states. When the energy gap between the two diastereomeric transition states becomes more than 3 kcal/mol (at room temperature) one enantiomer is formed in over 99%. It should be noted that this value is in the same order of magnitude as the rotation energy of a simple
molecule such as ethane. Predicting product enantioselectivity from the structure of a postulated catalyst-substrate intermediate species is therefore still extremely difficult.

![Diagram](image)

**Figure 1.2** Front side and back side attack of a ruthenium-amino alcohol catalyst.

The first example of homogeneous enantioselective catalysis that appeared in the literature dates back to 1966. In the reaction of styrene with ethyl diazoacetate cis and trans isomeric cyclopropane derivatives were formed, each consisting of a pair of enantiomers. For the trans isomers the observed enantiomeric excess was 6%. Most of the early work in the field of enantioselective catalysis centered around the hydrogenation of prochiral olefins with emphasis on amino acid precursors as unsaturated substrates. A milestone in the development of enantioselective catalysts is Kagan's synthesis of the diphosphine DIOP (Figure 1.3). In this ligand the chirality resides in the backbone rather than in the phosphorus atom. This invention greatly simplified the synthesis of these chiral diphosphines and it became the cornerstone of a massive worldwide effort to create new diphosphine ligands. With rhodium complexes of DIOP, hydrogenation of Z-α-acetamidocinnamic acid gave N-
acetylphenylalanine with an enantiomeric excess 95%.

DIPAMP (Figure 1.3) is the basis of the first commercial application of the concept of enantioselective catalysis.\textsuperscript{19} L-Dopa, a drug for Parkinson’s disease, is produced in the Monsanto amino acid process by rhodium catalysed hydrogenation of the corresponding dehydro amino acid.

![Figure 1.3](image)

Due to the growing demand for optically active compounds the concept of enantioselective catalysis is nowadays applied to many other reactions. The most abundant reactions involved are asymmetric reduction, asymmetric oxidation and asymmetric carbon-carbon bond formation. \textit{Asymmetric reduction} of carbonyl functionalities forming chiral alcohols is among the most essential molecular transformations.\textsuperscript{8} This thesis describes the development of enantioselective catalysts for the reduction of unsymmetrical ketones in order to obtain optically active alcohols. For supplementary information concerning asymmetric organometal catalysed reactions considering different transformations the interested reader is referred to the references throughout this Chapter.

1.2 Routes to optically active alcohols via asymmetric catalysis

The synthesis of chiral non-racemic secondary alcohols by catalytic enantioselective reduction of the corresponding ketone remains a pivotal transformation in organic
synthesis. Chiral alcohols form an important class of intermediates for the pharmaceutical, agrochemical, flavour and fragrance industries.\textsuperscript{8, 12} The synthesis of these types of compounds should proceed in an environmentally benign way. Efficient and clean enantioselective routes to chiral alcohols are well known but hardly developed on an industrial scale. The four major catalytic procedures that have emerged in recent years are: (i) enzymatic catalysed reduction; (ii) enantioselective hydride reduction; (iii) enantioselective hydrogenation; and (iv) enantioselective transfer hydrogenation.

In early days, synthesis of enantiomerically pure compounds from prochiral precursors was considered possible only by using biochemical methods. Enzymes in man, animals and plants perform the elegant and valuable concept of asymmetric catalysis to produce all the optically pure substances needed for life. Enzymes are able to catalyse reactions spectacularly fast, however, mainly with their natural substrates. Usually, a remarkable drop in enzymatic turnover and enantioselectivity is observed when different substrates are involved. Furthermore, the use of enzymes as biocatalysts is often limited to the accessibility of only one stereoisomer and is frequently accompanied by the use of complicated co-factor systems. The use of biocatalysts has proven to be economically successful in several cases. However, most of these examples are limited to hydrolytic enzymes, e.g. aminopeptidases, amidases, lipases and esterases, that are used for kinetic resolutions in which 50% of the undesired enantiomer is formed.\textsuperscript{20}

Some of the most successful and general catalysts for hydride reduction are based on the oxazaborolidine structure, developed by Corey \textit{et al.},\textsuperscript{21, 22} following on from initial work by Itsuno \textit{et al.}\textsuperscript{23} Excellent results have been obtained with these materials, however the high level of rather expensive catalyst that is often required (typically 10 mol%), and the non-compatibility of borane with certain functional groups somewhat limits its utility. Furthermore, borane salts are always formed as waste.

Catalytic reduction using molecular hydrogen can be conducted with a cheap reducing reagent on a large scale without producing intrinsic byproducts. Great success has been achieved concerning asymmetric induction and turnover numbers using \textit{e.g.} ruthenium-BINAP, ruthenium-DuPHOS and rhodium-DIPAMP.
More recently, Noyori and coworkers have described a variant system which utilises a chiral diamine and KOH in 2-propanol to activate a BINAP-Ru(II) complex to catalyse the hydrogenation of unfunctionalised aromatic ketones. Remaining problems within the field of hydrogenation are related to the high pressure equipment needed and the often difficult synthesis and handling of the required chiral diphosphine ligands. Furthermore, not all types of substrates can be reduced enantioselectively by classical hydrogenation. In this respect unfunctionalised olefins, simple ketones and imines remained a problem for a long time.

Better techniques are required to overcome these disadvantages. One of the most attractive methods for industrial application is transfer hydrogenation of ketones. Transfer hydrogenation has recently emerged as a powerful, practical and versatile system for the transformation of prochiral ketones to chiral alcohols, and is described in detail below.

1.3 History of asymmetric transfer hydrogenation of ketones

General

The reduction of a multiple bond by the aid of a hydrogen donor in the presence of a catalyst is known as hydrogen transfer or transfer hydrogenation. This process involves hydrogen abstraction from the reagent (hydrogen donor) by means of a catalyst, followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor), as is generalised in Scheme 1.1.

In hydrogen transfer reactions the hydrogen source is different from dihydrogen. The most common reagents employed are 2-propanol and formic acid. Other less frequently used organic molecules are unsaturated hydrocarbons such as
cyclohexene or cyclohexadiene and primary or secondary alcohols like methanol or benzyl alcohol.\textsuperscript{37}

\[
\text{DH}_2 + A \xrightarrow{} D + \text{AH}_2
\]

\(\text{DH}_2 = \text{hydrogen donor}; A = \text{hydrogen acceptor}\)

Scheme 1.1 Transfer hydrogenation

The use of organic hydrogen donors has some advantages over the use of molecular hydrogen. It avoids the risks and the constraints associated with \(\text{H}_2\) and the reaction does not require special high-pressure equipment that is necessary for hydrogenation reactions. Furthermore, the reaction can be favourably affected by selecting the most appropriate hydrogen donor.

Because of the advantages of this method, much effort has been devoted to the development of new chiral catalysts tailored to the transfer hydrogenation of various prochiral substrates. Several substrates have been successfully reduced by transfer hydrogenation in the presence of both heterogeneous and homogeneous catalysts. The list of hydrogen acceptors includes ketones, \(\alpha,\beta\)-unsaturated acids and esters, imines and nitro compounds.\textsuperscript{36, 39-42} While until 1981 the optical yields were not higher than 20\% ee,\textsuperscript{39} and consequently lower than the ones obtained in catalytic hydrogenation, more recently enantioselectivities of over 95\% have been reached.\textsuperscript{38}

Enantioselective transfer hydrogenation catalysts

Enantioselective transfer hydrogenation reactions have been carried out most commonly using iridium, rhodium or ruthenium catalysts in combination with many ligands. In the following a brief summary of the recent developments in asymmetric transfer hydrogenation is given.
Phosphine ligands in iridium, rhodium and ruthenium catalysed transfer hydrogenation

Chiral phosphines are the most popular ligands in asymmetric catalysis and they have been employed in transfer hydrogenation since the very beginning in iridium, rhodium and ruthenium catalysts. Besides a few tertiary monophosphines, chelating didentate ligands like DIOP, CHIRAPHOS, NORPHOS, BINAP, PROPHOS and BPPM have mainly been used (see Figure 1.4). The common feature of several of these ligands is the $C_2$-symmetry axis. Enantioselective transfer hydrogenation of ketones in the presence of the iridium or rhodium diphosphine catalysts $[\text{M(diene)}(\text{P-P})\text{PF}_6]$ ($\text{P-P} = \text{CHIRAPHOS, DIOP or PROPHOS}$) resulted in good catalyst activities and enantioselectivities of up to 66%.

Very low optical yields (0.3-9.8%) were obtained with $[\text{H}_4\text{Ru}_4(\text{CO})_8(-)-\text{DIOP}]_2$ as preformed catalyst. Better results were obtained by Genêt et al. in the transfer hydrogenation of acetophenone using a series diphosphine$\text{Ru(Br)}_2$ catalysts and
NaOH as promotor. After 2-25 minutes enantioselectivities of up to 52%, with a yield of over 80%, were obtained using CHIRAPHOS, BINAP, PROPHOS or BPPM as the chiral ligand.

Recently, enantioselectivities of up to 72% were obtained using a ruthenium(II) complex of the diferrocene derived (S)-(R)-Pigiphos.

Nitrogen donor ligands iridium, rhodium and ruthenium catalysed transfer hydrogenation

Unlike asymmetric hydrogenation, in the field of asymmetric transfer hydrogenation the most successful chiral auxiliaries contain nitrogen as the donor atom. This may be the consequence of higher catalytic activities displayed in early hydrogen transfer reactions by Rh(I) and Ir(I) complexes containing chelating didentate nitrogen ligands compared to catalysts containing didentate phosphorus ligands.

Iridium catalysed transfer hydrogenation using nitrogen donor ligands

Iridium(I) complexes with chiral phenanthrolines and chiral imines (Figure 1.5) have shown poor to moderate enantioselectivities (i.e. of up to 63%) in the transfer hydrogenation of acetophenone. More recently, much better results have been obtained in asymmetric hydrogen transfer reduction of ketones. This is in part a result of a report by Pfaltz and coworkers in 1991 pointing out that iridium(I) catalysts containing C₂-symmetric 4,4′,5,5′-tetrahydro-2,2′-bioxazoles (Figure 1.5) display a good activity in the hydrogen transfer reduction of ketones in 2-propanol. Aryl-alkyl ketones were readily reduced, affording the corresponding alcohols in 47-91% ee, whereas dialkyl ketones were less reactive and gave low yields of racemic products. In 1995, at the starting point of this project, this was still the best result in the hydrogen transfer reduction of aryl-alkyl ketones that was published in literature.

The use of iridium(I) as a catalyst precursor is limited in examples. The combination of iridium(I) and the diamine ligand depicted in Figure 1.5 gave rise to 78 % ee in the
reduction of acetophenone.\textsuperscript{58} A tosylated diamine ligand developed by Noyori and coworkers (i.e. TsDPEN) proved to be very useful in iridium(I) catalysed hydrogen transfer reactions in 2-propanol, resulting in an enantioselectivity of 92\% in the reduction of acetophenone (TsDPEN = \(N\)-(p-tolylsulfonyl)-1,2-diphenylethlenediamine).\textsuperscript{59} This ligand was initially developed for ruthenium(II) catalysed transfer hydrogenation reactions giving rise to high enantioselectivities and reaction rates.\textsuperscript{60}

![Figure 1.5 Chiral nitrogen donor ligands in iridium catalysed transfer hydrogenation](image)

Very recently, two papers described the use of similar monotosylated diamines in iridium(III) and rhodium(III) complexes.\textsuperscript{61-63} The Ir(III) and Rh(III) complexes contain pentamethylcyclopentadienyl counterions, which make them isoelectronic with the ruthenium(II)-arene complexes bearing the same monotosylated diamine ligands. The Ir(III) and Rh(III) complexes catalyse the reduction of acetophenone affording enantioselectivities of up to 97\%.
Rhodium catalysed transfer hydrogenation using nitrogen donor ligands

In the field of rhodium(I) catalysed transfer hydrogenation chiral alkyl-2,2′-bipyridines and alkyl-1,10-phenanthrolines (see Figure 1.6) were used by Gladiali et al. giving rise to ee's of up to 63% for acetophenone reduction. Various C₂-symmetric chiral diamines have been used as ligands for rhodium catalysed transfer hydrogenation by Lemaire and coworkers. In general, the enantioselectivities obtained were modest, the best (i.e. 67%) being obtained with the diamine depicted in Figure 1.6. This ligand was incorporated into a polymer backbone, by preparation of the polyurea derivative, which gave rise to higher reaction rates and an enantioselectivity of 43% in the rhodium catalysed reduction of acetophenone.

![Figure 1.6 Chiral nitrogen donor ligands in rhodium catalysed transfer hydrogenation](image)

Ruthenium catalysed transfer hydrogenation using nitrogen donor ligands

The most frequently used metal for the asymmetric transfer hydrogenation of ketones is ruthenium(II). Simple racemic β-amino alcohols have proved to afford one of the highest levels of acceleration in the ruthenium(II) catalysed transfer
hydrogenation of ketones.\textsuperscript{35, 69} The use of chiral amino alcohol ligands in ruthenium(II) catalysed hydrogen transfer reduction of ketones was pioneered by Noyori and coworkers and further developed by Palmer and Andersson (Figure 1.7). Enantioselectivities of up to 95\% were reached in the transfer hydrogenation of acetophenone.\textsuperscript{69-71} A notable feature of the Ru(II)-amino alcohol catalysts is the need for a primary or secondary amine in the ligands to obtain high activities and enantioselectivities.

The tridentate “ambox” ligand developed by Zhang and coworkers proved to be a very good chiral ligand for ruthenium(II) catalysed reduction of aromatic ketones using RuCl\(_2\)(PPh\(_3\)\(_3\)) as the catalyst precursor, giving rise to enantioselectivities of up to 98\%.\textsuperscript{72} The presence of the central amine is considered to be essential for high reactivity and enantioselectivity.

Didentate, tridentate and tetradebate P,N-containing ligands have been applied successfully in the ruthenium(II) catalysed transfer hydrogenation of ketones. Zhang and coworkers prepared and evaluated a series of nitrogen containing phosphine ligands in Ru(II) catalysed transfer hydrogenation in which notable enantioselectivities of up to 92\% were achieved.\textsuperscript{73-75} The tetradebate diphosphine/diamine system, developed by Noyori and coworkers has been applied in the asymmetric transfer hydrogenation of aromatic ketones furnishing products in up to 96\% ee.\textsuperscript{76} Helmchen and coworkers have applied Ru(II) complexes of chiral phosphinoxazolines to the transfer hydrogenation of ketones in 2-propanol.\textsuperscript{77} Enantioselectivities of 86\% were obtained in the reduction of acetophenone, whereas aliphatic ketones could be obtained in up to 60\% ee. Recently, Nishibayashi \textit{et al.} found that the related ruthenium complex RuCl\(_2\)(PPh\(_3\))-(oxazolinyl-ferrocenylphosphine) is an effective catalyst for the reduction of ketones resulting in enantioselectivities of \textgreater{}99\%.\textsuperscript{78} In contrast to the N,O- or N,N-chelates the P,N-containing ligands do not necessarily need a primary or secondary amine functionality in order to obtain high activities and enantioselectivities.
The mono- and dithiourea ligands used by Lemaire and coworkers were a little less successful with ee’s of up to 93\%,\textsuperscript{79} just like the ferrocenyl ligands of Knochel et al.\textsuperscript{80} Noyori and coworkers developed a highly effective monosubstituted diamine ligand, \textit{i.e.} TsDPEN, for ruthenium(II) catalysed transfer hydrogenation using either formic acid or 2-propanol as a hydrogen donor.\textsuperscript{60, 81} The monotosylated TsDPEN ligand can be considered as the most effective and best understood ligand system yet reported. Three different ruthenium(II)-TsDPEN complexes that are involved in the catalytic cycle have been characterised by X-ray diffraction. With chemical yields of up to 100\% and enantioselectivities of over 95\% in the reduction of most aryl-alkyl ketones this system is of great use in organic synthesis.
The use of transfer hydrogenation is a valuable and versatile reaction which is now emerging as one of the very best methods for achieving asymmetric reductions of C=O bonds. The combination of practical simplicity, mild reaction conditions, relatively non-hazardous reagents and high selectivities is unparalleled by most other processes in synthetic organic chemistry.

Mechanistic aspects

From a mechanistic point of view, two general reaction paths can be envisaged for hydrogen transfer: a stepwise process, called "hydridic route", and a concerted process, called "direct hydrogen transfer" (Figure 1.8). The "hydridic route" involves the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. The "direct hydrogen transfer" implies that hydrogen is transferred to the substrate in a concerted process where both the H-donor and the H-acceptor are held together in close proximity of the catalyst. If the "hydridic route" is operative, enantioface differentiating reactions should be only marginally affected by the use of different hydrogen donors. In contrast, enantiomer discriminating H-transfer reactions that follow the "direct hydrogen transfer" could give rise to different enantioselectivities using various hydrogen donors. It should be noted however, that the hydrogen donor can be a "noninnocent" spectator ligand in the stereodetermining step of the "hydridic route" and that it can therefore influence, albeit moderately, the stereochemistry of the reaction. An example in which the direct hydrogen transfer route is operative is the Meerwein-Pondorf-Verley reduction, involving aluminium or lanthanide catalysts. When transition metal catalysts are involved, however, it is assumed that the hydridic route is preferred.

In ruthenium(II) catalysed transfer hydrogenation Noyori and coworkers isolated a ruthenium hydride complex, that was capable of reducing acetophenone to its corresponding chiral alcohol in high yield and high enantiomeric excess. Also, Lemaire and coworkers postulated that for rhodium(I) catalysed transfer
hydrogenation the active catalyst is a *rhodium hydride* complex, based on both theoretical and experimental data.\textsuperscript{65}

![Diagram of hydrogenation pathways](image)

**Path A: "Hydridic route"**

**Path B: "Direct hydrogen transfer"**

From these results one could rationalise that for transition metal catalysed transfer hydrogenation reactions the active catalyst is most likely a metal hydride, as in path A.

### 1.4 Source of chirality

The success of the use of optically active catalysts for asymmetric synthesis depends highly on the availability of chiral ligands. The possibility of efficient fine-tuning of the ligand systems plays an important role to create selective catalysts.
The optically active catalysts described in this thesis all contain chiral ligands that are directly or indirectly derived from chiral 1,2-amino alcohols. A relatively large number of natural products contain an amino alcohol functionality. Amino sugars can be considered as members of this class of compounds, and nucleosides and nucleotides also fall within the definition. Three types of 1,2-amino alcohols can be distinguished, i.e. 1-substituted, 2-substituted and 1,2-disubstituted 2-amino-1-alcohols (Figure 1.9).

\[
\begin{align*}
\text{1-substituted} & : \quad R \quad \text{HO} \quad \text{NH}_2 \\
\text{2-substituted} & : \quad \text{HO} \quad \text{NH}_2 \\
\text{1,2-disubstituted} & : \quad \text{HO} \quad \text{NH}_2
\end{align*}
\]

1-substituted, 2-substituted and 1,2-disubstituted amino alcohols

\[\text{Figure 1.9}\]

\(\alpha\)-Amino alcohols that contain a chiral centre at the 2-position can easily be obtained from \(\alpha\)-amino acids by reduction. \(\alpha\)-Amino acids are natural compounds that are readily available. Moreover, a wide variety of non-natural amino acids can be synthesised on large scale using an L-specific aminopeptidase, produced by *Pseudomonas putida*, in an enzymatic resolution of a racemic mixture of \(\alpha\)-amino acid amides.\(^{83-87}\) Simple transformations, such as \(\alpha\)-amino acid reductions, allow entry to other classes of compounds that are also useful as chiral source. Various hydride sources have been used to reduce amino acids to form amino alcohols such as lithium aluminium hydride, sodium borohydride, lithium borohydride, etc. Recently other efficient routes from amino acids to amino alcohols have been reported. One approach uses a sodium borohydride-sulphuric acid system\(^{88}\) while a different route employs sodium borohydride-iodine.\(^{89}\) The formed 1,2-amino alcohols can serve as ligands of which the heteroatoms can be used to form an organometal complex, i.e. the chiral catalyst.

\(\alpha\)-Amino alcohols in which the chiral centre is positioned at the 1-position can only be obtained using a different synthetic strategy, since they can not be derived from
natural occurring amino acids. The 1-substituted amino alcohols that are described in this thesis are derived from their corresponding cyanohydrins. An efficient three-step one-pot synthesis to convert optically active cyanohydrins into 1-substituted amino alcohols was developed by Brussee and coworkers (see Figure 1.10).\cite{90,91} The reaction sequence involves a DIBAL reduction of the nitrile to an imine, transamination to a secondary imine and sodium borohydride reduction to the corresponding 1-substituted amino alcohols.

![Figure 1.10](image)

Optically active cyanohydrins are generated using hydroxynitrile lyases. They catalyse the stereoselective addition of hydrocyanic acid to aldehydes and ketones. Enzymes for the synthesis of either (R)- or (S)-cyanohydrins are available.\cite{92} The hydroxynitrile lyase from almonds, *Prunus amygdalus*, provides an easy access to (R)-cyanohydrins. Furthermore, recent advances in cloning and overexpression techniques have provided (S)-Hydroxynitrile lyase enzymes from *Hevea brasiliensis* and *Manihot esculenta* in sufficient quantity for potential application to industrial synthesis of (S)-cyanohydrins.

Chiral cyanohydrins can also be converted into 1,2-disubstituted amino alcohols, as
was shown by Krepski et al. and Brussee et al. Erythro and threo amino alcohols were synthesised by the addition of a Grignard reagent to the O-protected cyanohydrins, followed by reduction of the intermediate imine. In this way (1R, 2S)-norephedrine and (1S, 2R)-2-amino diphenylethanol could be synthesised in good yields.

Other possible ways to obtain 1,2-amino alcohols containing two stereogenic centres include either isolation of the natural product from Ephedrae Herba, which contains norephedrine, ephedrine, pseudoephedrine and methylephedrine, or, among others, oxime reduction, imine reduction, ketone reduction, etc.

The optically active 1,2-amino alcohols that are described in this thesis serve directly or indirectly as chiral auxiliaries in asymmetric transfer hydrogenation reactions to generate a new stereogenic centre in the final product.

1.5 IOP objectives and justification

The research described in this thesis was financed by the Dutch Ministry of Economic Affairs via the Innovation Oriented Research Programmes directed towards Catalysis.

The Innovation Oriented Research Programmes were set up by the Dutch Ministry of Economic Affairs to promote research in a number of promising fields to improve the Dutch competitive position in international trade. These IOP’s provide Dutch universities and research institutes with additional funding for research projects that are specifically aimed at meeting the needs of industry. IOP’s are also intended to encourage stronger relationships between academic research institutes and industry. Catalysis offers the opportunity to steer chemical conversions in a desired direction. The central theme of a four year research programme known as IOP Catalysis is "precision in chemical conversion". This precision is required both to save energy and feedstocks and to avoid the formation of undesired byproducts and waste. Catalytic conversions are involved in the manufacture of more than 80% of the total volume of chemicals. Hence a solid knowledge based on catalysis is of strategic
Introduction

interest to the Dutch chemical industry. Catalysis is extensively applied in petroleum refining and in the manufacture of bulk chemicals. This is far less the case in the manufacture of fine chemicals where classical multi-step chemical conversions play a larger role. These classical procedures often involve lower selectivities, the use of undesirable, toxic, or corrosive reagents, and the formation of side products and large amounts of waste. Therefore, it has been decided to direct the efforts of IOP Catalysis in particular to the introduction of novel catalytic routes in the fine chemical industries.

The work described in this thesis involves the development of novel catalytic routes to chiral alcohols in the fine chemical industries.

The objective of the project described in this thesis is the development of fast and selective transfer hydrogenation catalysts for the synthesis of chiral alcohols. Enantioselective transfer hydrogenation is one the most attractive methods for the synthesis of chiral alcohols as has been outlined in section 1.2. So far, asymmetric transfer hydrogenation using various aryl-alkyl ketones has been applied successfully. However, substrates of industrial interest carry functional groups that, in general, have a dramatic effect on both the activity and the selectivity of the catalyst. Therefore, it will be necessary to tailor catalysts for the transfer hydrogenation of functionalised model substrates (e.g. 1-3).

![Chemical Structures](image)

These substrates have the advantage that successful transfer hydrogenation may lead directly to commercial application. The product alcohol of chloroacetophenone (1) can be converted into chiral epoxides. Asymmetric reduction of chloropropiophenone (2) results in a precursor for the homochiral form of fluoxetine, an anti-depressant. The product of α-keto-ester 3 is a potential building block for “Angiotensin Converting Enzyme inhibitors”, blood regulating
compounds. The latter product is an oil, which makes purification by crystallisation impossible. Hence, the enantioselectivity of the reaction needs to be high. Also, asymmetric reduction of dialkyl ketones, ketones containing an alkyne functionality, α-keto esters and α,β-unsaturated ketones will lead to industrial interesting products and have therefore also been taken into account in this project.

1.6 Outline of this thesis

The development of fast and selective transfer hydrogenation catalysts for the synthesis of chiral alcohols was the main objective in the research project of which the results are described in this thesis. A variety of ruthenium(II)-amino alcohol and iridium(I)-amino sulf(ox)ide catalysts were studied and used in the asymmetric transfer hydrogenation of several ketones.

Chapter 2 describes the asymmetric transfer hydrogenation of prochiral ketones using ruthenium(II)-amino alcohol catalysts and 2-propanol as the hydrogen donor. The ligand coordination fashion was studied and the amino alcohol structure was optimised in terms of activity and enantioselectivity. The enantioselective outcome of the ruthenium(II)-amino alcohol catalysed reaction was studied in more detail in chapter 3. The actual process of the transfer of a hydride from the metal to the substrate was calculated on the density functional level of theory. Comparison of two proposed mechanistic pathways showed that the pathway of choice proceeds through hydrogen bond formation between the substrate and the catalyst. The steric interactions between the ketone and the catalyst were discussed resulting in a better understanding of the observed enantioselectivities.

A completely different and new catalytic system for the asymmetric transfer hydrogenation of ketones is described in chapter 4. A series of amino sulf(ox)ides was synthesised from amino alcohols and was used in the iridium(I) catalysed reduction of ketones. Both formic acid and 2-propanol were successfully used as hydrogen donors. Aryl-alkyl ketones were reduced to the corresponding alcohols in high
enantiomeric excess.

With the active and enantioselective catalysts described in chapters 2-4 the scope of the reaction was studied in order to synthesise functionalised chiral alcohols. The results of substrate variations are presented in chapter 5. High chemoselectivities and moderate to high enantioselectivities were obtained in the reduction of various substituted ketones.

In chapter 6 a high throughput screening method for the enantioselective transfer hydrogenation of ketones is presented. On using IR-spectroscopy the performance of ruthenium(II)-amino alcohol catalysts was determined by monitoring the reverse reaction.

1.7 References

1. L. Pasteur, C.R. Acad. Sci. 1848, 26, 535.
5. T. Eriksson, S. Björkman, B. Roth, Å Fyge, P. Höglund, Chirality 1995, 7, 44.
Introduction

Introduction
